Universitat Autònoma de Barcelona

Treatment Safety, Adherence and Health-Related Quality of Life in patients with asthma

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Presented by

María Gimena Hernández Pombo

Under the direction of doctors

Montserrat Ferrer Forés and **Olatz Garin Boronat**

Barcelona, November 2018

Certificate of thesis supervision

Montserrat Ferrer Forés, PhD, MD, researcher of the Health Services Research Group of the IMIM (Hospital del Mar Medical Research Institute), and Professor of the Department of Paediatrics, Obstetrics and Gynecology and Preventive Medicine of the School of Medicine of the Universitat Autónoma de Barcelona, Spain, and

Olatz Garín Boronat, PhD, researcher at the Health Services Research Group of the IMIM (Hospital del Mar Medical Research Institute), and Professor of Epidemiology at Pompeu Fabra University.

CERTIFY:

That **María Gimena Hernández Pombo** has carried out under our supervision the thesis entitled **"Treatment Safety, Adherence and Health-Related Quality of Life in patients with asthma",** which meets the necessary conditions for its presentation as a doctoral thesis.

Montserrat Ferrer, PhD, MD
Thesis Director

Olatz Garin, PhD
Thesis Co-director

María Gimena Hernández Pombo
PhD Candidate

Barcelona, 14 de Noviembre de 2018.

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Parece mentira que ha llegado el día de entregar mi tesis doctoral. Esa palabra que al principio sonaba tan lejana, distante e irreal y que al fin va concretándose y tomando forma. Esa palabra, a la vez tan deseada y tan sufrida, ha traído consigo un montón de personas y experiencias que nunca podré olvidar y que no puedo dejar de agradecer.

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Abstract

The general aim of this doctoral thesis was to evaluate the health-related quality of life (HRQoL) in patients with asthma, and the socio-demographic and clinical factors which contributed to its impairment. Also, to assess the safety of long-acting beta-agonists (LABAs) combined with inhaled corticosteroids (ICs), and the determinants of treatment adherence.

Evidence from observational studies (systematic search in MEDLINE and EMBASE, period 1990-2013, including 19 studies with sample sizes from 50 to 514,216) shows that the combined treatment of LABAs and ICs is not associated with a higher risk of serious adverse events, compared to ICs alone. Major gaps identified were: prospective design, paediatric population and inclusion of mortality as a primary outcome. The systematic review of observational studies on determinants of asthma inhaler adherence identified 51 studies (search performed in EMBASE, Medline, PsychInfo and PsychArticles from 1990 to 2014) which mainly examined patient-related factors and found consistent links between adherence and stronger beliefs in inhaler necessity, and possibly with older age. The need of a broader adoption of common conceptual and methodological standards was detected.

The project entitled "Assessment of the Safety of LABAs in asthma in routine care by combining health care data bases and direct patient-follow-up" (ASTRO-LAB) was a prospective longitudinal study (n= 908 patients). Patients were enrolled in primary care in France and United Kingdom by their general practitioner. Inclusion criteria were: subjects aged 6-40 years old, with persistent asthma, defined as more than 6 months of prescribed ICs and/or LABAs during 12 months before inclusion. Analysis of the 290 patients who completed the EQ-5D-5L in the baseline online survey demonstrated acceptable ceiling effect, good construct validity, and high reliability, supporting the adequacy of this new EQ-5D version for assessing HRQoL in asthma patients.

Finally, French patients (n= 222) were compared with the EQ-5D reference norms from France to estimate the impact of asthma on patients' HRQoL. Persistent asthma has a moderately negative HRQoL impact on patients of both genders, and the youngest women have been identified as a high risk group which merits further research. We identified asthma control as the major factor associated to impaired HRQoL in patients, regardless of their gender, suggesting that asthma HRQoL impact could be alleviated by achieving a good symptom control.

Resumen

El objetivo general de esta tesis doctoral fue evaluar la calidad de vida relacionada con la salud (CVRS) en pacientes con asma y los factores sociodemográficos y clínicos que contribuyen a su deterioro. Asimismo, evaluar la seguridad de los broncodilatadores de acción larga (BAL) combinados con corticosteroides inhalados (CI) y los determinantes de la adherencia al tratamiento.

La evidencia obtenida en los estudios observacionales (búsqueda sistemática en MEDLINE y EMBASE, período 1990-2013, incluyó 19 estudios de tamaños muestrales entre 50 y 514.216) demuestra que el tratamiento combinado de BAL y CI no se asocia con un mayor riesgo de eventos adversos graves, en comparación con el tratamiento sólo con CI. Los principales déficits identificados fueron la falta de diseño prospectivo, de población pediátrica y de mortalidad como resultado primario. La revisión sistemática de estudios observacionales sobre determinantes de la adherencia a los inhaladores para el asma identificó 51 estudios (búsqueda realizada en EMBASE, Medline, PsychInfo y PsychArticles entre 1990 y 2014) que examinaron principalmente los factores relacionados con el paciente y encontraron una relación consistente entre la adherencia y las creencias más arraigadas en la necesidad de inhaladores, y posiblemente con una edad más avanzada. Se detectó la necesidad de una adopción más amplia de estándares conceptuales y metodológicos comunes.

El proyecto titulado "Assessment of the Safety of LABAs in asthma in routine care by combining health care data bases and direct patient-follow-up" (ASTRO-LAB) fue un estudio longitudinal prospectivo (n = 908 pacientes). Los pacientes fueron reclutados en centros de atención primaria en Francia y Reino Unido. Los criterios de inclusión fueron: individuos cuyas edades estaban comprendidas entre los 6 y 40 años con asma persistente, definido como más de 6 meses de prescripción de CI y/o BAL durante los 12 meses anteriores al reclutamiento. El análisis de los 290 pacientes que completaron el EQ-5D-5L en la encuesta basal por internet demostró un efecto techo aceptable, una buena validez de constructo y una alta fiabilidad, lo cual apoya la idoneidad de esta nueva versión del EQ-5D para evaluar la CVRS en pacientes con asma.

Finalmente, comparamos los pacientes franceses (n = 222) con las normas de referencia del EQ-5D en Francia para estimar el impacto del asma en la CVRS de los pacientes. El asma

persistente tiene un impacto en la CVRS moderadamente negativo en pacientes de ambos sexos, y las mujeres más jóvenes fueron identificadas como un grupo de alto riesgo que merece más investigación. Identificamos el control del asma como el principal factor asociado al deterioro de la CVRS en los pacientes, independientemente de su sexo, lo que sugiere que el impacto del asma en la CVRS se podría mitigar logrando un buen control de los síntomas.

Resum

L'objectiu general d'aquesta tesi doctoral va ser avaluar la qualitat de vida relacionada amb la salut (QVRS) en pacients amb asma i els factors sociodemogràfics i clínics que contribueïxen al seu deteriorament. També, avaluar la seguretat dels broncodilatadors d'acció llarga (BAL) combinats amb corticosteroides inhalats (CI) i els determinants de l'adherència al tractament.

L'evidència obtinguda en estudis observacionals (recerca sistemàtica en MEDLINE i EMBASE, període 1990-2013, incloent 19 estudis amb graandàries mostrals entre 50 i 514.216), mostren que el tractament combinat de LABA i CI no està associat a un major risc d'esdeveniments adversos greus, en comparació amb només CI. Els principals dèficits identificats van ser la mancança de disseny prospectiu, de població pediàtrica i de inclusió de la mortalitat com a resultat primari. Una revisió sistemàtica dels estudis observacionals sobre els determinants de l'adherència als inhaladors per a l'asma va identificar 51 estudis (cerca realitzada a EMBASE, Medline, PsychInfo i PsychArticles de 1990 a 2014) que van examinar principalment els factors relacionats amb el pacient, i van trobar associacions consistents entre l'adherència i creences més arralades en la necessitat dels inhaladors, i possiblement amb una edat més avançada. Es va detectar la necessitat d'una amplia adopció d'estàndards conceptuals i metodològics comuns.

El projecte titulat "Assessment of the Safety of LABAs in asthma in routine care by combining health care data bases and direct patient-follow-up" (ASTRO-LAB) va ser un estudi prospectiu longitudinal (n = 908 pacients). Els pacients es van reclutar en els centres d'atenció primària a França i el Regne Unit. Els criteris d'inclusió eren: individus de 6 a 40 anys d'edat amb asma persistent, definit com més de 6 mesos de prescripció de CI i/o BAL durant els 12 mesos previs al seu reclutament. L'anàlisi dels 290 pacients que van completar l'EQ-5D-5L en l'enquesta basal per internet va demostrar un efecte sostre acceptable, una bona validesa de constructe i una alta fiabilitat, donant suport a la idoneitat d'aquesta nova versió del EQ-5D per avaluar la QVRS en pacients amb asma.

Finalment, vam comparar els pacients francesos (n = 222) amb les normes de referència EQ-5D procedents de França per estimar l'impacte de l'asma en la QVRS del pacient. L'asma persistent té un impacte moderadament negatiu en els pacients d'ambdós sexes, i les

dones més joves van ser identificades com un grup d'alt risc que mereix més recerca. Hem identificat el control de l'asma com a principal factor associat de la reducció de la QVRS en els pacients, independentment del seu gènere, el que suggereix que l'impacte de l'asma en la QVRS es podria mitigar aconseguint un bon control dels símptomes.

Preface

The thesis "TREATMENT SAFETY, ADHERENCE, AND HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH ASTHMA", presented as a compendium of publications, is the result of the project entitled *"Assessment of the safety of LABAs in asthma in routine care by combining health-care databases and direct patient follow-up"* (ASTRO-LAB), funded by the VII Framework Program of the European Commission (EC HEALTH-F5-2011-282593).

The thesis comprises 5 published articles that are part of the abovementioned project's publication plan, and 1 other published article as an annex:

1) G. Hernandez, M. Avila, A. Pont, O. Garin, J. Alonso, L. Laforest, C. J. Cates, and M. Ferrer. *Long-acting beta-agonists plus inhaled corticosteroids safety: a systematic review and meta-analysis of non-randomized studies.* Respir.Res. 15 (1):83, 2014. IF: 3.093; Q2 (18 of 58, Respiratory System).

2) A. L. Dima, G. Hernandez, O. Cunillera, M. Ferrer, and M. de Bruin. *Asthma inhaler adherence determinants in adults: systematic review of observational data.* Eur.Respir.J. 45 (4):994-1018, 2015. IF: 8.332; D1,Q1 (3 of 58, Respiratory System)

3) Van Ganse E., N. Texier, A. L. Dima, L. Laforest, M. Ferrer, G. Hernandez, S. Schuck, S. Herbage, D. Vial, and Bruin M. de. *Assessment of the safety of long-acting beta2-agonists in routine asthma care: the ASTRO-LAB protocol.* NPJ.Prim.Care Respir.Med. 2015; 25:15040-15044. IF: 1.447; Q3 (11 of 20, Primary Health Care); Q4 (47 de 58, Respiratory System)

4) G. Hernandez, A, L. Dima, A. Pont, O. Garin, M. Martí-Pastor, J. Alonso, E. Van Ganse, L. Laforest, M. de Bruin, K. Mayoral, M. Ferrer. *Validity of the EuroQol (EQ-5D-5L) in assessing Quality of Life in Adults with Asthma.* In press in Journal of Medical Internet Research. IF; 4,671, Q1 (6 of 94, Health Care Sciences & Services)

5) G. Hernandez, AL. Dima, A. Pont, O. Garin, M. Martí-Pastor, J. Alonso, E. Van Ganse, L. Laforest, M. de Bruin, K. Mayoral, M. Ferrer. *Impact of asthma on women and men: Comparison with the general population using the EQ-5D-5L questionnaire).* PLoS One. 2018 Aug 23;13(8):e0202624. IF: 2.766, Q1 (15 of 64, Multidisciplinary Sciences)

ANNEX: G.Hernandez, Garin O, Pardo Y, Vilagut G, Pont A, Suárez M, Neira M, Rajmil L, Gorostiza I, Ramallo-Fariña Y, Cabases J, Alonso J, Ferrer M. *Validity of the EQ-5D-5L and reference norms for the Spanish population.* Qual Life Res. 2018 May 16. doi: 10.1007/s11136-018-1877-5. IF: 2.392, Q1 (15 of 88, Health Policy & Services).

The first two articles describe the systematic reviews carried out to prepare the protocol of the ASTRO-LAB project, the 1st one focusing on the safety of long-acting bronchodilators evaluated by observational studies, and the 2nd article on the determinants of adherence to inhalers in adult patients with asthma. These two issues were crucial, the safety of long-acting beta-agonists because it was the main objective of the European study, and that of adherence because one of the main hypotheses regarding the safety of the combined administration of long-acting beta-agonists with inhaled corticosteroids was based on a differential adherence.

The 3rd article describes the protocol of the ASTRO-LAB project. The ASTRO-LAB consortium comprises 7 multidisciplinary research teams from four European countries: France (University Claude Bernard Lyon, Kappa Santé SAS and Lyon Ingenierie Projets); United Kingdom (University of Nottingham and CEGEDIM Strategic Data Medical Research Limited); Holland (Universiteit van Amsterdam); and Spain (IMIM).

The 4th article describes the study of the validity of the new EuroQol version with 5 levels of response in patients with asthma. The traditional version with 3 response levels had limitations in these patients, and it was necessary to evaluate the validity of the new version before applying it to measure the impact of asthma on health-related quality of life.
Finally, the 5th manuscript describes the assessment of the impact of asthma on the patients' health-related quality of life.

Moreover, the article included as ANNEX, shows the validity of the new EQ–5D–5L in the Spanish-speaking population, and provides representative population-based norms to allow to estimate the impact of different conditions on patients' health-related quality of life in Spain.

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Abbreviations

95% CI - 95% Confidence Interval

ACQ-5 - Asthma Control Questionnaire

EQ-5D - EuroQol

FDA - Food and Drug Administration

GINA - Global Initiative for Asthma

HRQoL – Health-Related Quality of Life

ICs - Inhaled Corticosteroids

LABAs - Long-acting Beta-agonists

LTRA - Leukotriene receptors antagonists

OR - Odds Ratio

PRO - Patient Reported Outcomes

QALYs - Quality of Life Adjusted Years

RCT - Randomized Clinical Trials

RR - Risk Ratio

SABAs - Short-acting Beta-agonists

SD - Standard Deviation

SF-12 - Short-Form Health Survey 12

SF-36 - Short-Form Health Survey 36

UK - United Kingdom

USA - United States of America

VAS - Visual Analogue Scale

WHO - World Health Organization

1. INTRODUCTION

Asthma is a common life-long chronic inflammatory disorder of the airways that affects adults and children of all ages. It is defined by 'the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation' [1].

1.1. ASTHMA EPIDEMIOLOGY

There are many gaps in asthma epidemiology, partly because the last global surveys to estimate the prevalence of asthma were carried out about 15 years ago, and also because of the lack of a precise and universally accepted definition of asthma, which makes it problematic to carry out a reliable comparison of reported prevalence from different parts of the world. It is estimated that the global prevalence of asthma ranges from 1 to 16% of the population in different countries, and that 8.6% of young adults (aged 18-45) experience asthma symptoms [1, 2]. Asthma prevalence is higher than 9% in western European countries such as Ireland, France, the Netherlands, Denmark, Norway, Sweden and Finland, where it has increased in the latter part of the 20th century, but it now appears to be levelling off [3].

The Global Asthma Network [2], led by an 11-member international Steering Group worldwide, estimated that the number of people with asthma in the world may be as high as 339 million.

Asthma places a huge burden on society in terms of disability: the World Health Organization Global Burden of Disease Study estimates that 15,898 Years Lived with Disability are lost annually due to asthma, occupying the 11th cause of Years Lived with Disability for non-communicable diseases in 2015 [4]. Asthma, along with Chronic Obstructive Pulmonary Disease (COPD), account for the greatest economic burden of respiratory diseases on health services and lost production in the European Union. The expected total cost in the population aged 15-64 years was 19.3 billion, with a mean total cost per patients ranged from Euros 509 (controlled disease) to 2,281 (uncontrolled disease) [5].

The fundamental causes of asthma are still not known. Various genes have been associated with an increased risk of developing asthma. Environmental influences are also likely to play part in the initiation of asthma by interacting with genetic predisposing factors. These may be changing patterns of microbial exposure and of diet, exposure to allergens and to environmental pollutants [3].

1.2. ASTHMA TREATMENT

There is now good evidence that the clinical manifestations of asthma, such as symptoms, sleep disturbances, limitations of daily activity, lung function impairment and use of rescue medications, can be controlled with appropriate treatment [1]. 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 [1], 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 it 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 [6]. In control-based asthma management, pharmacological and non-pharmacological treatment is adjusted in a continuous cycle that involves assessment, treatment and review. This approach has shown to improve asthma outcomes and is essential for asthma management [7].

Asthma medication therapy is divided into 3 main categories [1]:

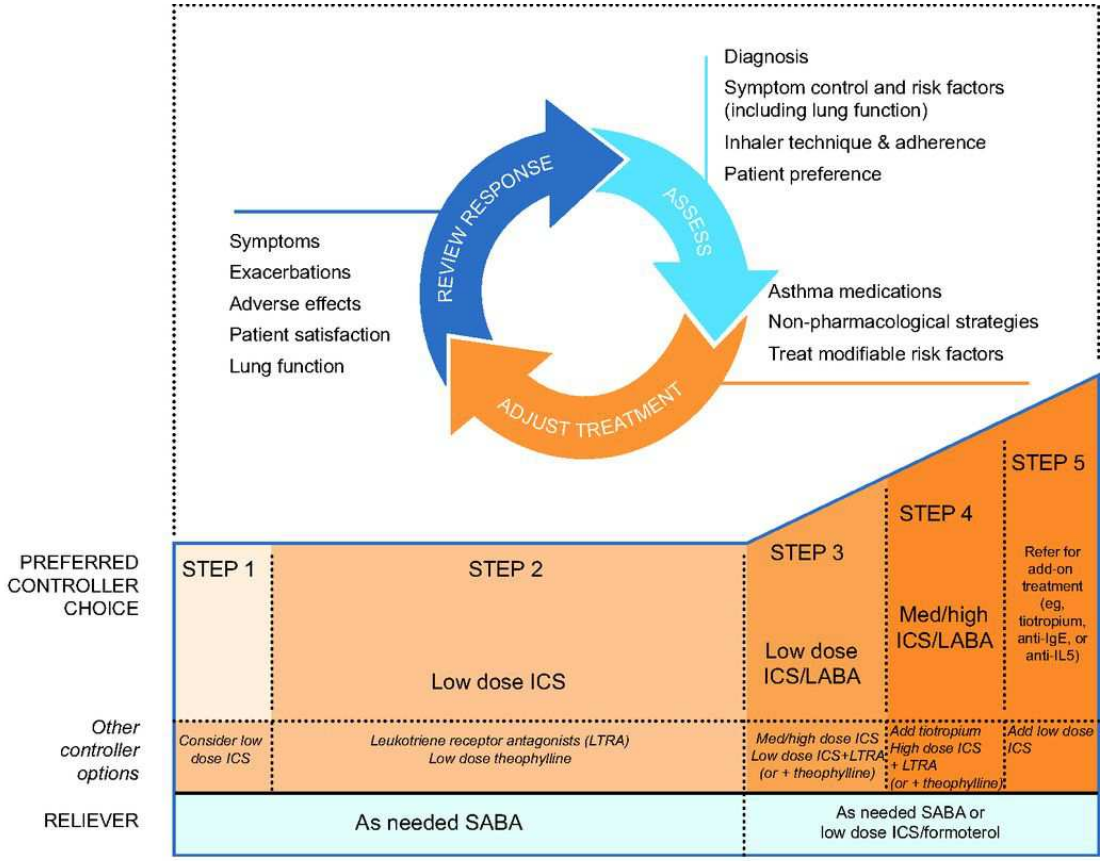
Controller medications for daily management of asthma are used to control symptoms and to reduce airway inflammation and future risks (exacerbations and lung function decline); they include inhaled corticosteroids (ICs) and long-acting beta-agonists (LABAs).

Reliever (rescue) medication, provided for relief as needed to treat acute symptoms and exacerbations, includes short-acting beta-agonists (SABAs), anticholinergics, and systemic corticosteroids.

Add-on therapy for patients with severe asthma with persistent symptoms despite using controller medication includes leukotriene receptors antagonists (LTRA), methylxanthines, and immunomodulators.

Pharmacotherapy is based on 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 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 risk proposed by GINA [1] is illustrated in **Figure 1**.

Figure 1. Stepwise approach to control symptoms and minimize future risks proposed by GINA in 2018 [1].



Treatment in step 1 considers only *reliever medication* as needed, while step 2 includes *controller medication* administered daily. The steps 3 and 4 are characterized by adding a controller and/or increasing dose of ICs. Finally, in the step 5 *add-on therapy* is required.

In clinical practice, the choice of medication, device and dose should be based on assessment of symptom control, risk factors, patient preference, and practical issues (cost, ability to use the device, and adherence). Once good symptom control has been maintained for 3 months, the ICs dose should be carefully titrated to the minimum dose, taken regularly, that will maintain good symptom control and minimize exacerbation risk, while reducing the potential for side-effects.

1.2.1. LONG-ACTING BETA-AGONISTS

Up until the early 1990s, only short-acting beta-agonists (SABAs) were available. As they relieved shortness of breath for about four hours per use, beta-agonists were recommended on an as-needed basis to complement controller therapy. An important change came with the introduction of the long-acting beta-agonists (LABAs), salmeterol and formoterol, to the European market in the early 1990s. LABAs are potent bronchodilators, and have effects lasting for approximately 12 hours. Because of the long duration of their action, the LABAs came to be recommended as controller treatment in the management of asthma, with a systematic review showing significant improvements in reducing symptoms and use of rescue medication [8].

Safety concerns about LABAs started in the mid-1990s when the Serevent Nationwide Surveillance Study, a large Randomized Clinical Trial (RCT) looking into the safety of salmeterol compared with regular salbutamol, reported a threefold but non-significant increased risk of death amongst patients taking salmeterol [9]. In the period following salmeterol's commercialization in the United States of America (USA), post-marketing reports of adverse events also suggested increased risk of serious asthma events [10]. Subsequently, the Salmeterol Multicenter Asthma Research Trial, a large RCT undertaken in response to these concerns, was stopped in 2003 after an interim analysis showed a statistically significant, fourfold increased mortality risk amongst patients randomized to salmeterol, with a sevenfold mortality risk amongst African-American participants [11]. Similar concerns about formoterol

were raised at around the same time by a reanalysis of three RCTs which suggested a higher, non-significant rate of severe asthma exacerbations in the high-dose formoterol arms of the study [12].

1.2.1.1. Synthesis of evidence about LABAs safety from Randomized Clinical Trials

Meta-analyses of LABAs as a monotherapy indicate an increased mortality risk, while the risk of serious adverse events was not consistently observed [13-15]. A significantly increased risk of mortality amongst patients randomized to LABAs, compared with those randomized to placebo or SABAs, was reported in two out of three meta-analyses [13, 14]. The third meta-analysis reported almost no increase in mortality risk, with a low precision [15]. The risk of serious adverse events, which are largely driven by hospitalizations, was increased in one meta-analysis [14] and slightly reduced in another [15] without achieving significance.

Several meta-analyses of RCT have examined the risk of asthma exacerbations associated with the use of **LABAs in combination with ICs**, finding different results [13, 16, 17]. A systematic review found no significant differences in the risk of asthma-related hospitalizations and asthma-related mortality in patients treated with LABAs in combination with ICs, compared with patients treated with ICs alone [16]. Other meta-analyses have shown a lower risk of asthma exacerbations in the group treated with the combination of ICs plus LABAs [13, 17].

An overview of Cochrane Reviews [18] published in 2014 aimed to assess the risk of serious adverse events in adults and adolescents with asthma treated with formoterol or salmeterol: four reviews (89 trials with 61,366 adults) of trials evaluating regular formoterol or salmeterol as a monotherapy (compared to placebo) or as a combination with regular ICs (compared with the same dose of ICs); and two reviews of trials in which patients were randomly assigned to formoterol versus salmeterol (13 trials with 9,614 participants). None of the reviews found a significant increase in death of any cause, and yet none of them could exclude either the possibility of a twofold increase in mortality on regular formoterol or salmeterol (as monotherapy or combination therapy).

The **pooled mortality Odds Ratios** (OR) obtained were [18]: 4.49 (95% CI 0.24 to 84.80, 13 trials, n = 4824) for formoterol monotherapy; 1.33 (95% CI 0.85 to 2.08, 10 trials, n = 29,128) for salmeterol monotherapy; 3.56 (95% CI 0.79 to 16.03, 25 trials, n = 11,271) for formoterol combination; and 0.90 (95% CI 0.31 to 2.6, 35 trials, n = 13,447) for salmeterol combination. It was not possible to assess in this overview whether the risks of mortality on regular combination therapy were different from the risks on regular monotherapy, because study designs were not the same for combination therapy and monotherapy trials.

This overview [18] showed that **non-fatal serious adverse events** were more commonly reported on patients treated with salmeterol monotherapy (OR 1.14, 95% CI 1.01 to 1.28, I2 = 0%,13 trials, n = 30,196), but this OR was not significant in any of the other reviews: 1.26 for formoterol monotherapy (95% CI 0.78 to 2.04, I2 = 15%, 17 trials, n = 5758), 0.99 for formoterol combination (95% CI 0.77 to 1.27, I2 = 0%, 25 trials, n = 11,271), and 1.15 for salmeterol combination (95% CI 0.91 to 1.44, I2 = 0%, 35 trials, n = 13,447).

While evidence was being obtained, the Food and Drug Administration (FDA) required in 2003 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 inhaled corticosteroids. It was therefore unknown whether the use of ICs in combination with LABAs - now considered the standard of care - would mitigate the risk of serious asthma outcomes. Consequently, the FDA required in 2010 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 [19].

Furthermore, in 2011, the FDA mandated that the four companies marketing LABAs for asthma in the USA to perform trials comparing safety of a regimen of LABAs plus ICs, as compared with ICs alone [20]. Therefore, four clinical trials were conducted targeting a total enrolment of 36,010 adolescents and adults with persistent asthma into a 26 week, multicentre, parallel, randomized, double blind, noninferiority trial. AztraZeneca, GlaxoSmithKline, and Merck completed the trials and reported the results [21-23], whereas Novartis interrupted its trial at an early stage, as the company removed its drug from the USA market. In order to assess the relatively rare severe events (asthma-related deaths, asthma-

related intubations) as the primary outcome, and to analyse the frequency of serious asthma-related events (asthma-related deaths, asthma-related intubations, asthma-related hospitalization) as a secondary outcome, the manufacturers harmonized their trial methods to allow that an independent joint oversight committee could perform a final combined analysis of the four trials [24]. Results of this combined analysis, published in 2018, showed that therapy with LABAs plus ICs did not result in a significantly higher risk of serious asthma-related events than treatment with an ICs alone, but resulted in significantly fewer asthma exacerbations (RR 0.83; 95% CI: 0.78-0.89) [24].

1.2.1.2. Synthesis of evidence about LABAs safety from Observational Studies

Respiratory clinicians have access to a wide range of effective therapies. RCTs have repeatedly demonstrated the efficacy of asthma treatment in terms of their ability to minimize symptom burden, improve asthma control and health-related quality of life, and maintain or slow down disease progression [1]. Yet reports of numerous asthma exacerbations persist [2]. This apparent disagreement could be explained by the gap between efficacy results derived from well-controlled, short-term RCTs involving highly selected populations and effectiveness evaluations conducted in every day, real-life settings, typically involving diverse patient populations, across a wide range of care settings and patient characteristics and evaluated over longer time intervals than those used in RCTs [25]. Furthermore, even RCT meta-analyses presented a low precision when evaluating rare safety outcomes.

Observational studies can provide valuable and complementary information to RCT, but observational prospective studies are scarce, and most of them were based on claims databases, providing only a partial assessment of drug exposure. To the best of our knowledge, there is only one systematic review of observational studies published in 2010 [26] which aimed to assess the safety of the concurrent use of LABAs and ICs in adults, compared with those receiving ICs alone. Seven studies, all of them with retrospective design, were included and meta-analysis showed that the combined treatment was associated with a lower risk of asthma-related hospitalizations and/or emergency room visits. Concerns about the sources of these studies are remarkable, as almost half of the studies included were unpublished and came from a pharmaceutical company research register. In addition, this meta-analysis excluded studies on children.

In this context, the lack of systematic reviews of non-randomized studies draws attention. There is a need to explore potential risks associated with LABAs in real life, with more extensive assessments of patterns of use, including ICs concomitant therapy, asthma control and exacerbations over time. To provide answers for these issues, first we planned a new systematic review of the literature published until 2013 [27] and, second, results of this systematic review were applied to design a new project entitled "Assessment of the Safety of LABAs in asthma in routine care by combining health care data bases and direct patient-follow-up" (ASTRO-LAB) in order to overcome the limitations of previous observational studies.

1.2.2. SAFETY CONCERNS ABOUT THE USE OF LABAs IN CHILDREN

Evidence about LABAs safety in children is particularly weak. It is based on few studies, with a relatively small number of children, for rare safety outcomes, again leading to a low precision of risk estimates. However, the existing evidence in children does raise two concerning trends. First, analyses specifically examining children have suggested an increased risk of hospitalizations related to LABAs monotherapy exposure, combined with a possibly lesser impact in reducing severe exacerbation risk [28, 29]. Second, in contrast to adult patients, they suggested that concomitant use of ICs with LABAs do not tend towards a reduction in the rate of severe exacerbations, evoking concerns about different efficacy and safety profiles for LABAs in children from adults [30].

Data on LABAs safety in children was available from the meta-analysis completed internally by the FDA for its safety review meeting in 2008 [10]. This analysis showed a trend in risk difference point estimates across age groups, with the youngest patients estimated to be most at risk. However, as for the meta-analyses published in the medical literature, the precision of the estimates was low-particularly in the youngest age groups.

An overview of Cochrane Reviews in children with asthma was unable to detect any significant differences between the safety of regular formoterol and salmeterol as monotherapy and combination therapy [31]. Results of LABAs monotherapy showed an increase in serious adverse events which was statistically significant when analyzed using Peto Odds Ratio (OR 1.60; 95% CI 1.10 to 2.33). Although OR was similar for LABAs in

combination therapy, the fewer events in these trials drove to a wider confidence interval that was not statistically significant (OR 1.50; 95% CI 0.82 to 2.75).

To address the questions raised by meta-analyses and the limited clinical-trial experience in children, the FDA requested that GlaxoSmith-Kline, the only USA manufacturer of LABAs with a paediatric asthma indication, perform a large safety trial with the primary objective of determining whether fluticasone propionate–salmeterol was noninferior to fluticasone alone with respect to the risk of serious asthma-related events (death, endotracheal intubation, and hospitalization). This clinical trial that included 6,208 children (4-11 years old) comparing patients using LABAs/ICs versus ICs alone was published in 2016 [32], showing that the risk of a fixed-dose combination was not significantly different from the risk with ICs alone: a Hazard Ratio of 1.28 (95% CI: 0.73 to 2.27).

This finding, together with that obtained in the abovementioned overview of Cochrane Reviews [31], highlights concerns on the higher LABAs risk of serious asthma-related events in children. The shortage of data in this important age group still needs to be addressed providing new evidence.

1.2.3. MECHANISMS OF SERIOUS ADVERSE EVENTS ASSOCIATED WITH LABAs

The state-of-the-art knowledge about the mechanisms by which LABAs may increase the risk of serious asthma events is weak. Numerous mechanisms have been proposed, but studies have so far failed to elucidate which pathways are the most likely. Briefly, the main hypothesized mechanisms under debate are:

- Direct toxicity, presumably through cardiac stress owing to β2- stimulation of cardiac β2-receptors, residual stimulation of β1-receptors, tendency to induce hypokalaemia, and peripheral vascular dilatation. This is nonetheless considered an improbable explanation for the findings of increased risk at recommended β2-agonist doses [33, 34].
- Increased bronchial hyper-reactivity in response to allergen challenge, despite maintenance of some degree of bronchodilation [35].

- Tolerance to bronchodilatory effects because of β2-adrenoreceptor tachyphylaxis [36], possibly leading to loss of the β2-agonists' protective effects against allergen-induced bronchoconstriction [34, 37, 38].
- Delay in seeking care despite worsening airway inflammation, since prolonged bronchodilation may mask the symptoms of deteriorating disease control, leading to a later presentation for medical care than in the absence of LABAs treatment [39, 40].
- Reduced adherence to ICs and other controller medications, again related to LABA-induced bronchodilation, which may reduce patients' symptoms and therefore lead to a reduced use of preventative treatments [38].

The two latter mechanisms are related more to patients' behaviour than to a physiological effect of LABAs [39]. Under these hypotheses, patients reducing or stopping ICs treatment would lose the anti-inflammatory effects of ICs, leading to worsening airway inflammation [41]. In parallel, patients may delay seeking treatment as LABAs mask the symptoms of worsening airway inflammation. It should be noted that this mechanism is plausible whether LABAs independently increase the risk of serious asthma events or not.

Following these hypotheses, treatment safety needs to be assessed by taking into account adherence and asthma control, which therefore were considered key aspects in the ASTRO-LAB project.

1.3. TREATMENT ADHERENCE

Although a wealth of research has been conducted to understand causes of medication non-adherence, variations in definitions have led to ambiguity in study findings. There is a wide consensus on the lack of a standard taxonomy for treatment adherence that has led to confusion and misunderstanding, and impeded comparisons among scientific research results. To overcome these difficulties, the European Society for Patient Adherence, Compliance and Persistence (ESPACOMP) [42] has worked on the development of the ABC (Ascertaining Barriers to Compliance) project, an international collaboration of European research groups, in order to propose adherence consensus taxonomy.

The ABC taxonomy defines the overarching concept of "medication adherence" as the process by which patients take their medication as prescribed, and divides it into 3 essential elements: (A) initiation; (B) implementation, and (C) persistence. This division outlines the sequence of events that have to occur for a patient to experience the optimal benefit from his or her prescribed treatment regimen. Step "A" in the process, "initiation"—when the patient takes the first dose of a prescribed medication—is typically a binary event (patients either start taking their medication or not in a given time period). In contrast, step "B," "implementation"— the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose is taken—is a longitudinal description of patient behaviour over time, that is, their dosing history. The final step defined within the taxonomy as "C", "persistence," is the time elapsed from initiation until the eventual treatment discontinuation (ie, time to event); after discontinuation, a period of nonpersistence may follow until the end of the prescribing period [43, 44].

1.3.1. MEDICATION ADHERENCE MEASUREMENT METHODS

Methods to measure medication adherence differ substantially in nature, from self-reporting to electronic medical devices, without forgetting the obtention of information from routine health registers.

Table 1. Strengths and limitations of each adherence measurement method among different phases of adherence: initiation, implementation and persistence [43].

	1. Initiation	2. Implementation	3. Discontinuation
Routine EHR*			
Granularity/Precision†	Granularity in days, if the prescription database is also available	Imprecise—tends to average usage of a time interval of ≥3 months	Granularity in weeks or months
Validity‡	Relatively high (if first use follows dispensation)	Relatively high (if standard dosing regimen or if prescription details are available)	Relatively high (if all sources of dispensation are known) Allows identification of changes in a same class of medications
Ease of Access	Few linked datasets to compare prescribed and collected medication dates	Easy to access if available in health system	Easy to access if available in health system
Patient reports			
Granularity/Precision†	Granularity in days/weeks (depends on the time window of the tool used)	Imprecise due to recall bias	Granularity in days/weeks (depends on patient memory)
Validity‡	Subject to desirability bias	Subject to desirability bias	Subject to desirability bias
Ease of Use	Easy to implement. May require an additional contact with the patient after prescription	Easy to implement at point of care Adds burden to the patient	Easy to implement at point of care
Electronic monitoring			
Granularity/Precision†	Granularity in minutes	Granularity in minutes	Granularity in minutes
Validity‡	High (if first device use is followed by inhalation)	High (especially if inhaler technique is also assessed)	High (if medication is only used with the device)
Ease of Use	Easy to implement in clinical trials In medical practice, can be used as a good start program but requires activation and patient engagement	Easy to implement in clinical trials In medical practice, can be used at specific time of care (when a problem is suspected, at treatment failure, or to support a behavioral intervention, etc.) for a defined period of time	Easy to implement in clinical trials Not feasible for long-term treatments in large-scale populations—limited use due to complexity, costs, patient burden, limited availability, and fatigue

EHR, Electronic health records.
*Electronic Health Records, e.g. prescription (prescribing and/or dispensing) data, and health insurance (or 'claims') data.
†Granularity: the sampling rate at which it is possible to assess changes in the dynamic process of adherence (particularly relevant to objective measures); Precision: degree of reproducibility, that is, ability to measure the same value repeatedly (particularly relevant to patient reports).
‡Degree of potential systematic error in the measurement, that is, difference between the estimated and real value.

Electronic Health Records includes electronic medical records, which are primary or secondary care prescribing data, health insurance "claims" data and pharmacy dispensing databases. For example, a medical prescription event followed by a dispensation event for the same treatment is used in research to infer therapy initiation. Dispensing data can provide information to measure medication adherence and has been demonstrated to be useful and reasonably accurate [45, 46]. It is often the only data source available in large-scale assessments, but it can only estimate implementation over long time intervals based on the ratio of days of medication dispensed versus the number of days of a given period of evaluation. There are some commonly used algorithms for estimating medication implementation, known as "continuous multiple-interval measures of medication availability" or medication possession ratio. Data to calculate medication possession ratio have the

advantage of being easily accessible and inexpensive, but details about devices and day-to-day patterns of adherence are not recorded [47].

Patients Reports: Self-reported measures are the most cost-effective method, but their reliability is questionable [48] as it could be affected by recall bias. Some studies also have shown that patients trend to over-report adherence [49, 50], even in a clinical trial setting [51]. Nonetheless, the quality of patient-reported adherence can be improved by the use of validated questionnaires.

Electronic monitoring: Electronic monitoring devices have the capacity to record the administration, but also to capture the quality of therapy delivery [52, 53]. These objective measures are considered to be more reliable and accurate than the subjective ones [54]. Unfortunately, such monitoring is expensive and often prone to device failure [53].

1.3.2. TREATMENT ADHERENCE-RELATED FACTORS.

Reasons for non-adherence to asthma medication are varied and complex. According to the report developed by the World Health Organization (WHO) [55] entitled "Adherence to long-term therapies - Evidence for action", adherence is a multidimensional phenomenon determined by the interplay of five sets of factors, called "dimensions": social and economic factors, healthcare team and system-related factors, condition-related factors, therapy-related factors and patient-related factors. The common belief that patients are solely responsible for taking their treatment is misleading and most often reflects a misunderstanding of how other factors affect people's behaviour and capacity to adhere to their treatment. Therefore, patient-related factors are only one of the five determinants.

This WHO report [55] provided a critical review of what is known about adherence to long-term therapies. It proposed common issues in need of being addressed among most chronic conditions, such as the conceptual model of adherence. It also developed 9 disease-specific reviews, one of which is for asthma. The factors affecting adherence to asthma are briefly described below.

1.3.2.1. Social and economic factors in asthma

Socioeconomic factors identified by WHO to have a negative effect in asthma medication adherence are [55]: vulnerability of the adolescent to not taking medications; family conflict and a denial of the severity of disease in adolescents; memory difficulties in older patients; polypharmacy in older patients; cultural and lay beliefs about illness and treatment; alternative medicine; fear of the health care system; poverty; inner-city living; lack of transport; and family dysfunction.

1.3.2.2. Healthcare team and system-related factors in asthma

Relatively little research has been conducted on the effects of the health care team and system-related factors on adherence. Whereas a good patient-provider relationship may improve adherence [56], there are many factors that have a negative effect, such as the following ones mentioned in the WHO report [55]: lack of knowledge and training of health care providers in treatment management; inadequate understanding of the disease by health professionals; short consultations; and lack of health care providers' training in changing behaviours of nonadherent patients.

1.3.2.3. Condition-related factors in asthma

Condition-related factors that may negatively affect medication adherence are those particular illness-related demands faced by the patient. In the case of asthma, inadequate understanding of the disease is the only factor highlighted by the WHO report [55].

1.3.2.4. Therapy-related factors in asthma

There are many therapy-related factors that affect adherence. Factors described by the WHO report are [55]: complex treatment regimens; long duration of therapy; frequent doses and adverse effects of treatment.

1.3.2.5. Patient-related factors in asthma

Patient-related factors represent the resources, knowledge, attitudes, beliefs, perceptions and expectations of the patient. The only factor to improve adherence in asthma described in the adherence report [55] was the patient's perception of vulnerability to illness, while several factors affecting adherence were identified [55]: forgetfulness; misunderstanding of instructions about medications; poor parental understanding of children's asthma medications; patients' lack of perception of their own vulnerability to illness; patients' lack of information about the prescribed daily dosage/misconception about the disease and treatments; persistent misunderstandings about side-effects and drug abuse.

1.3.3. MEDICATION ADHERENCE IN ASTHMA

The introduction of inhaled medication as the primary treatment for asthma has led to substantial improvements in asthma control [17, 57]. However, uncontrolled asthma is still common and represents a considerable burden to patients and society [58, 59]. Medication regimens for asthma care are particularly vulnerable to adherence problems because of their duration, the use of multiple medications, and the periods of symptom remission. As stated before, one important reason for poor asthma control is suboptimal adherence to the prescribed regimen [60-62]. Poor adherence has been associated with outcomes like mortality [63] and asthma symptoms [64], as well as direct and indirect costs of care [62] and decreased quality of life [65]. [66]

In asthma, adherence to treatment tends to be poor, with rates of <50% in children [49] and 30–70% in adults [62], depending on country, age, sex and ethnicity [67]. A systematic review published in 2015 [68] showed an overall adherence to ICs of 20–33.9% in children, and of 15% to 54% in adults. Another systematic review of 2018 [69] found that the pooled mean of the overall percentage of adherence was 48% (SD=18) among 23 studies supplying this data.

One of the important differentiating factors between the RCT assessing efficacy and the real-world observational studies assessing effectiveness is medication adherence: it is optimized in the first ones, but commonly suboptimal in everyday routine care. The WHO's adherence report [55] stated that increasing adherence may have a greater effect on health than any

improvement in specific medical treatments. For this reason, a comprehensive systematic review of factors related to adherence to inhaled medication in adults with asthma was planned in order to take them into account adequately in the design of the ASTRO-LAB project.

1.4. PATIENT-REPORTED OUTCOME MEASURES

The patient experience 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 [70, 71]. Moreover, taking into account the patients' views has other advantages, further than avoiding observer bias (inevitable if asking clinicians): 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) [70].

1.4.1. DEFINITIONS

Patient-Reported Outcomes Measures (PROs) is an umbrella term that covers any outcome based on data provided by the patient or patient proxy [72]. According to the Food and Drug Administration'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"[73]. PROs 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. [66]

Different types of outcomes (**Figure 2**) [66] are covered by the term PRO, from symptoms to Health-Related Quality of Life (HRQoL); and are usually measured either by different

instruments or by those that combine several concepts. In general, PROs can be used to help in decision making in clinical practice, but they also are widely used in research to evaluate an intervention's effect. Even PROs that only assess symptoms or functional limitations are of primary interest to the clinician as indicative of disease severity. Most PROs administered nowadays assess Health-Related Quality of Life (**Figure 3**)

Figure 2. An integrate model for health outcomes [66].

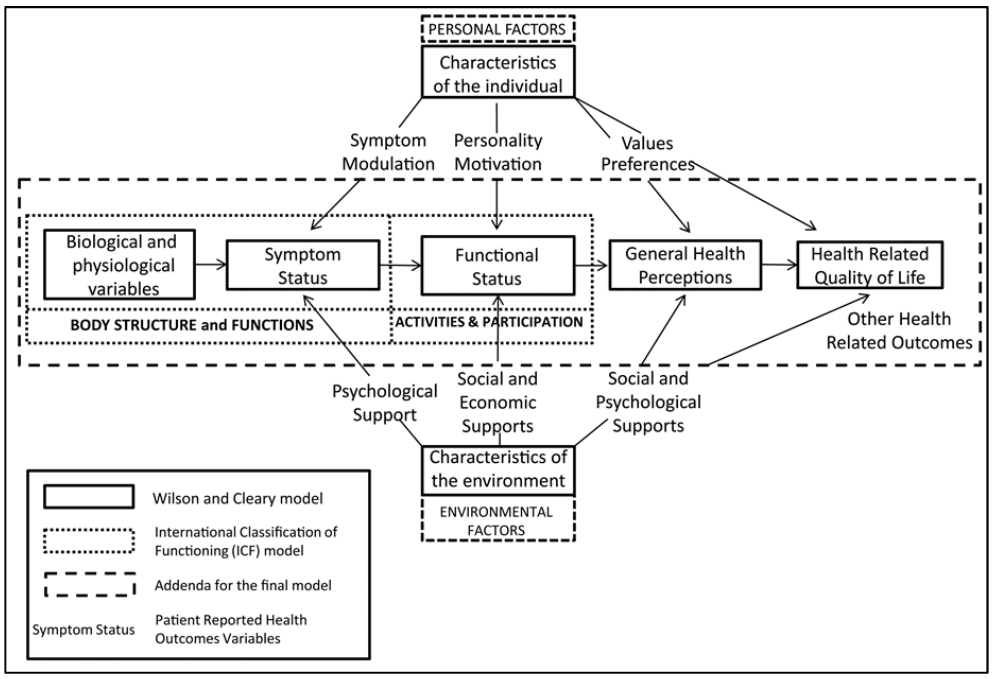
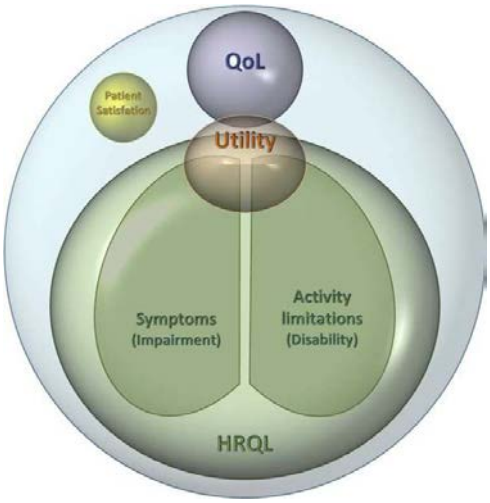


Figure 3. Types of PROs currently used in medical research [74].



In 1948, the World Health Organization (WHO) defined health as being not only the absence of disease and infirmity, but also the presence of physical, mental and social well-being [75]. Since then, the definition of HRQoL and related concepts such as quality of life (for many researchers—limited to what is of primary concern to the patient [76]) health status and perceived health—has been disputed, without reaching a consensus [72, 77]. In 1993 Patrick and Erickson [78] defined HRQoL 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 [79], the definitions for HRQoL in published articles are often not clearly provide or differ in their content. In general, it is accepted that HRQoL measures refer to the physical, psychological and social domains of health seen as distinct areas that are influenced by a person's experience, beliefs, expectations, and perceptions.

Since the early 70s, HRQoL instruments have been developed to assess a person's interpretation of their own health status in comparison to how they might hope to be [80, 81]. However, and despite its frequent use nowadays [75] and the relevance that PROs have acquired due to FDA recommendations [73], for many clinicians the assessment of HRQoL seems more art than science. This belief is due in part to the lack of formal training available for clinicians regarding HRQoL measurement and interpretation.

1.4.1. METRIC PROPERTIES

HRQoL instruments must have adequate measurement properties to be useful in their extense potential applications. **Table 2** shows a modified version of the eight attributes and the main criteria for each of them proposed by the Scientific Advisory Committee of the Medical Outcome Trust [82]: conceptual and measurement model, reliability, validity, responsiveness, interpretability, respondent and administrative burden, alternative forms, and cultural and language adaptations.

Table 2. Attributes and criteria for evaluating PROs [82].

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

1.4.2. GENERIC VS SPECIFIC INSTRUMENTS

HRQoL measures 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 [83]. Their broad applicability is in general derived from their coverage of the complete spectrum of function, disability and distress that is relevant to HRQoL (symptoms, emotional function, or social relations). Generic instruments allow to determinate the effects of the intervention on different aspects of HRQoL without the use of multiple instruments. Also, using them one can compare the effects on HRQoL of similar interventions in different diseases. However, they may not focus on aspects of specific interest

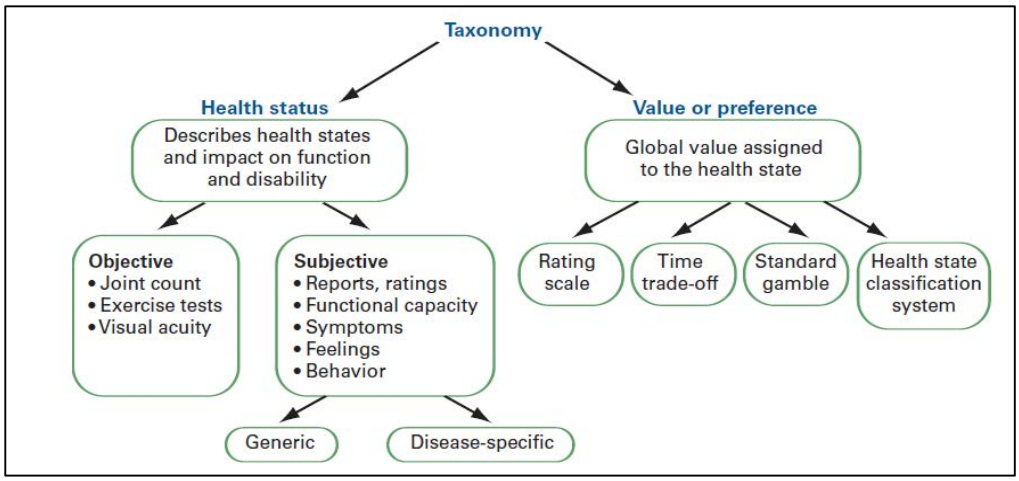
to the investigator. Inadequate focus on specific issues is likely to result in an unresponsive instrument that may miss small but still clinically important changes in HRQoL.

On the other hand, specific measures focus on HRQoL 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 sub-populations 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 [84].

1.4.3. PSYCHOMETRIC VS ECONOMETRIC INSTRUMENTS

The growing interest in HRQoL 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 [80, 81]. It has originated from two fundamentally different approaches: Health status and value/preference (**Figure 4**).

Figure 4. Health-Related Quality of Life Taxonomy [85].



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, health value/preference/utility measures assess the desirability of a state of health against an external metric and summarize HRQoL as a single index value(utility) [85].

Health status profiles are instruments that attempt to measure all the important aspects of HRQoL. The Sickness Impact Profile[86] is a relevant example of this approach and includes a physical dimension (with categories of ambulation, mobility, body care and movement); a psychosocial dimension (with categories including social interaction, alertness behaviour, communication, and emotional behaviour); and five independent categories including eating, work, home management, sleep and rest, and recreation. One of the most popular generic HRQoL profiles is a collection of instruments developed as part of the Medical Outcomes Study [82], such as the Short-Form Health Survey 36 (SF-36) which measures eight dimensions: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health.

Utility measures are derived from economic and decision theory; they reflect the preferences of patients for treatment process and outcome [76]. The key elements of utility measures are that they incorporate preference measurements and relate health states to death. Hence, they can combine duration and quality of life allowing cost-utility analyses. In utility measures, HRQoL is summarized as a single number along a continuum that usually extends from death (0.0) to full health (1.0) (although scores lower than zero, representing states worse than death, are possible) [87]. The preferences in utility measurements may come directly from individual patients who are asked to rate the value of their health state. Alternatively, patients can rate their health status using a multi-attribute, health status classification system. A previously estimated preference, elicited from groups of other patients or from the community, is then used to convert health status into a utility score [76, 88].

1.5. HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH ASTHMA

Traditionally, asthma severity and symptom control have been assessed by objective measures such as lung function tests, rescue short-acting beta-agonists (SABAs) use and number of hospitalizations due to asthma, among others. It has been assumed that if these objective clinical indicators improve, then the patient's symptoms and HRQoL must improve as well. However, although objective clinical indicators provide valuable information, they may be unable to fully assess whether patients feel better and can function better (physically, socially, and emotionally) in everyday life. In the last decades the International guidelines for asthma [1], as well as National Health Services [57], have emphasized the need to include patients´ HRQoL improvement in treatment goals.

1.5.1. PROs INSTRUMENTS FOR PATIENTS WITH ASTHMA

The Patient-Reported Outcomes Measurement Group of the Oxford University published in 2009 a report on the available evidence of PROs for people with asthma [89], which aimed to provide recommendations for the Department of Health of those instruments that could potentially be used on a large-scale population basis to assess the health status of people with asthma and to provide evidence relevant to determining the quality of the services provided in the National Health Service. The authors of this review, which included 6 generic and 22 asthma-specific instruments [89], recommended the SF-36 measure and the EQ-5D (preferably used in combination with the Mini Asthma Quality of Life Questionnaire) as generic measures, as well as four asthma-specific questionnaires (see **table 3**).

A systematic review published in 2014 [90] identified 68 disease-specific and 28 generic PRO instruments that had been evaluated for use in people with asthma. **Table 3** lists, ordered by year of publication, asthma-specific PROs which were found to be well validated and to warrant a full-quality appraisal: 8 designed for adults, 4 for children, and 1 for the children's caregivers. They also identified four generic instruments to apply in asthma patients.

Table 3. Disease-specific and generic PRO instruments for adults and children with asthma [90].

Asthma-Specific PROs

	Asthma-specific PROs for adults	Acronym	Author (Year of publication)
1	Living With Asthma Questionnaire [91]	LWAQ	Hyland (1991)
2	St George's Respiratory Questionnaire [92]	SGRQ	Jones (1992)
3	Asthma Quality of Life Questionnaire [93]	AQLQ*	Juniper (1992)
4	Marks Asthma Quality of Life Questionnaire [94]	M-AQLQ*	Marks (1992)
5	Mini Asthma Quality of Life Questionnaire [95]	mini-AQLQ*	Juniper (1999)
6	Asthma Control Questionnaire [96]	ACQ	Juniper (1999)
7	Rhinasthma [97]	-	Biardini (2003)
8	Asthma Control Test [98]	ACT	Nathan (2004)
	Asthma-specific PROs for children		
1	Childhood Asthma Questionnaire [99]	CAQ	Christie (1993)
2	Paediatric Asthma Quality of Life Questionnaire [100]	PAQLQ	Varni (1999)
3	Pediatric Quality of Life Inventory-asthma module [101]	PedsQL-AM	Varni (2004)
4	Childhood Asthma Control Test [102]	C-ACT	Liu (2007)
	Asthma-specific PROs for child´s caregiver		
1	Paediatric Asthma Caregiver's Quality of Life Questionnaire[103]	PACQLQ	Juniper (1996)

Generic PROs evaluated for patients with asthma

1	EuroQol [104]	EQ-5D*	EuroQol Group (1990)
2	The 36-item Short Form Health Survey [105]	SF-36*	Ware (1992)
3	Sickness Impact Profile [86]	SIP	Gilson (1975)
4	The 12-item Short Form Health Survey [106]	SF-12	Jenkinson (1997)

* Instruments recommended also by the Patient-Reported Outcomes Measurement Group [89], who additionally proposed another asthma-specific PRO not included in this table: Asthma Quality of Life Questionnaire(S) [93, 107].

The great interest in measuring PROs in patients with asthma is reflected in the development of a large number of specific questionnaires for this disease. In the 90s the interest was focused on HRQoL, and that decade was when the majority of asthma-specific instruments measuring this construct were developed, which are still used nowadays, including their reduced versions. The 21st century has involved a change of interest that has turned to other constructs such as asthma control, first with the Asthma Control Questionnaire and then the Asthma Control Test, published in 1999 and 2004, respectively. The children version of this latter instrument was published in 2007.

Two generic PROs were selected by the above mentioned report [89]: the SF-36 and the EQ-5D. However, regarding this latter, it is necessary to remark that only the traditional version of EQ-5D has been validated in asthma patients [108-110]. The EuroQol Group developed a new EQ-5D version in 2009 to improve its sensitivity; by increasing the number of responses from 3 to 5 levels (no problems, slight problems, moderate problems, severe problems, unable to perform/extreme problems). This new EQ-5D-5L has already been tested in other chronic conditions [111-113], showing a better discrimination capability and lower ceiling effects than the traditional 3-level version. However, to date there are no studies evaluating metric properties of the new 5-level EQ-5D in asthma patients.

1.5.2. FACTORS RELATED WITH HRQoL IN ASTHMA

A retrospective analysis of 27 randomized, double-blind, double dummy, parallel group studies of adolescents and adults with persistent asthma suggested that the impact of asthma on patients´ HRQoL is correlated moderately with asthma symptoms and only weakly with objective measures such as lung function [114]. A study that focused on the relation of objective asthma severity with specific and generic HRQoL measures [115] found that association was high with symptom scores, but poor with objective measures.

A multinational, prospective, cohort study of 8,111 participants [116] showed that patients with well-controlled asthma reported a better HRQoL: the difference between those with well-controlled and not well-controlled asthma was around 2 points of the Mini Asthma Quality of Life Questionnaire, which is substantially higher than the +/-0.5 minimal important difference established for this instrument. Another study [117] has also found that asthma control has a substantial effect on HRQoL by using both an asthma-specific measure and a generic one: the Mini Asthma Quality of Life Questionnaire and the EQ-5D, respectively. Finally, yet another study [118] used the traditional EQ-5D to compare the HRQoL between asthma control groups; the EQ-5D index means were 0.88 for patients with well-controlled asthma, and 0.61 for those with not well-controlled asthma.

Studies on clinical samples of asthma have consistently reported worse HRQoL in women than men [119-122]. Significant gender differences in lifespan among people with asthma have also been documented, and asthma-related hospitalizations were found to be most prevalent

among middle-aged women [123]. Worse HRQoL was reported in women as compared to men, both in mental and physical summary components measured with the SF-12 [120]. A study [122] with 914 patients with asthma indicated that women report more symptoms and experience poorer HRQoL than men, as measured by a specific and a generic instrument: all four subscales of the Marks Asthma Quality of Life Questionnaire (p values ranging from 0.001 to 0.006); and all the SF-36 dimensions, except "role emotional" and "mental health".

1.5.3. IMPACT OF ASTHMA ON HRQoL

There are few studies that have evaluated the impact of asthma on HRQoL from National Health Surveys. The 2000 Behavioral Risk Factor Surveillance System [124] included 12,270 individuals with self-reported asthma and 151,503 individuals without asthma. Participants with asthma were more likely than those without to have poor or fair health (OR: 2,41; 95% CI: 2.21 to 2.63), to report having >14 days of impaired physical health (OR: 2,26; 95% CI: 2.06 to 2.49), impaired mental health (OR: 1,55; 95% CI: 1.40 to 1.72), activity limitations (OR: 1,96; 95% CI: 1.73 to 2.21), and impaired physical or mental health (OR: 1,99 95% CI: 1.84- to 2.15). The 2008 European National Health and Wellness Survey in five European countries (France, Germany, Italy, Spain and the UK) included 3,619 individuals with self-reported physician diagnosis of asthma, showing that those with well-controlled symptoms were close to the general population norms, according to the 12-item SF-12 [125].

Self-reporting asthma might have led to under- or over-estimating the impact of asthma on HRQoL from National Health Surveys. For the estimation of asthma HRQoL impact, the comparison of the clinical sample with counterparts from the general population, as reference norms, is needed. Even though this approach has been successfully applied in other chronic conditions [126-129], to our knowledge there are no studies that have assessed asthma impact on HRQoL using reference norms.

2. THESIS RATIONALE

The important gap of knowledge regarding long-acting beta-agonists (LABAs) safety in asthma, with both theoretical arguments and limited empirical evidence that inhaled corticosteroids (ICs) may mitigate LABAs-associated risk [130-132], led the FDA to mandate in 2011 four large randomized clinical trials on adolescents and adults [20], and one specifically on children [32], comparing a regimen of LABAs plus ICs with ICs alone. As randomized trials are the most likely to provide unbiased information regarding the different effects of alternative treatment options, systematic reviews or pooled analyses have been centred on studies with this design.

Non-randomized studies need to be taken into account when there is a need to provide evidence of effects (benefit or harm) on rare and long-term outcomes [133]. Randomized trials cannot adequately assess them because they may not reflect the actual patterns of use of medications, mainly for treatment duration and adherence. All these aspects are specially relevant in this case, since it has been hypothesized that treatment with LABAs could enhance patients to reduce or quit inhaled corticosteroids, leading to worsening airway inflammation [41]; and also that LABAs could mask the symptoms of worsening and could delay seeking treatment. Despite these arguments, the synthesis of evidence from observational studies has been neglected. In this context, there is a need to explore potential risks associated with LABAs in real life, with more extensive assessments of patterns of treatment and adherence to inhalers. To provide answers for these issues, we planned firstly two systematic reviews of observational studies, one focused on LABA safety and another on determinants of adherence to inhalers.

Secondly, to overcome the limitations of observational studies, the review of the available evidence was addressed to generate recommendations to design a real-word study that could include a suitable measure of adherence as a part of the medication safety evaluation. The design of the project entitled "Assessment of the Safety of LABAs in asthma in routine care by combining health care data bases and direct patient-follow-up" (ASTRO-LAB) was based on the synthesis of the evidence provided by the abovementioned systematic reviews. This project was designed as a prospective longitudinal study of primary care asthmatic patients in France and the United Kingdom.

Finally, to take into account the patient's perspective, health-related quality of life has been gaining importance in research, clinical practice and health planning. It aims to understand the symptoms experienced and the impact of illness, as well as providing a picture of the patients' day-to-day concerns and capturing changes that may occur as a result of clinical treatment and care. In this line, a research question emerges from studies on patients with asthma showing worse health-related quality of life in women than men [119-121]: Could these differences imply gender inequalities in asthma impact? We hypothesised that this does not occur, because the worse results in women are mainly explained by gender differences external to asthma, such as other chronic conditions, disease-related behaviours, or socio-economic backgrounds. Understanding factors contributing and deteriorating health-related quality of life is crucial to improve the evaluation, monitoring and clinical management of patients with asthma, as well as to facilitate shared clinical decision-making processes between patients and physicians.

3. OBJECTIVES OF THE DOCTORAL THESIS

3.1. GENERAL OBJECTIVE

To evaluate the health-related quality of life in patients with asthma and the socio-demographic and clinical factors which contribute to its impairment. Also, to assess the safety of long-acting beta agonists combined with inhaled corticosteroids, and the determinants of treatment adherence.

3.2. SPECIFIC OBJECTIVES

- To assess the risk of serious adverse events in patients with asthma treated with long-acting beta-agonists (LABAs) and inhaled corticosteroids (ICs), in comparison to patients treated only with inhaled corticosteroids (ICs), by synthesizing the available evidence from non-randomized studies through a systematic review and meta-analysis.
- To synthesise the current observational evidence on determinants of inhaler adherence in asthmatic adults through a systematic review.
- To develop the protocol of the project entitled "Assessment of the Safety of LABAs in asthma in routine care by combining health care data bases and direct patient-follow-up" (ASTRO-LAB).
- To examine the distribution, construct validity, and reliability of the new EQ-5D-5L in a European sample of patients with asthma.
- To evaluate the impact of asthma on patients' health-related quality of life by comparing asthmatic women and men with EQ-5D reference norms, to examine the factors which contributed to an impaired health-related quality of life, and to identify specific groups at higher risk.

4. PUBLICATIONS

4.1. ARTICLE 1:

Gimena Hernandez, Mónica Avila, Àngels Pont, Olatz Garin, Jordi Alonso, Laurent Laforest, Christopher J Cates, Montserrat Ferrer and ASTRO-LAB group. ***"Long-acting beta-agonists plus inhaled corticosteroids safety: a systematic review and meta-analysis of non-randomized studies"*** Respir Res. 2014 Jul 19;15:83 (IF 3.093-Q2; 18/58, Respiratory System)

RESPIRATORY RESEARCH

RESEARCH Open Access

Long-acting beta-agonists plus inhaled corticosteroids safety: a systematic review and meta-analysis of non-randomized studies

Gimena Hernández[1,2], Mónica Avila[1,3], Àngels Pont[1,3], Olatz Garin[1,3], Jordi Alonso[1,3,4], Laurent Laforest[5], Christopher J Cates[6], Montserrat Ferrer[1,2,3*] and ASTRO-LAB group

Abstract

Background: Although several systematic reviews investigated the safety of long-acting beta–agonists (LABAs) in asthma, they mainly addressed randomized clinical trials while evidence from non-randomized studies has been mostly neglected. We aim to assess the risk of serious adverse events in adults and children with asthma treated with LABAs and Inhaled Corticosteroids (ICs), compared to patients treated only with ICs, from published non-randomized studies.

Methods: The protocol registration number was CRD42012003387 (http://www.crd.york.ac.uk/Prospero). Literature search for articles published since 1990 was performed in MEDLINE and EMBASE. Two authors selected studies independently for inclusion and extracted the data. A third reviewer resolved discrepancies. To assess the risk of serious adverse events, meta-analyses were performed calculating odds ratio summary estimators using random effect models when heterogeneity was found, and fixed effect models otherwise.

Results: Of 4,415 candidate articles, 1,759 abstracts were reviewed and 220 articles were fully read. Finally, 19 studies met the inclusion criteria. Most of them were retrospective observational cohorts. Sample sizes varied from 50 to 514,216. The meta-analyses performed (69,939-624,303 participants according to the outcome considered) showed that odds ratio of the LABAs and ICs combined treatment when compared with ICs alone was: 0.88 (95% CI 0.69-1.12) for asthma-related hospitalization; 0.75 (95% CI 0.66-0.84) for asthma-related emergency visits; 1.02 (95% CI 0.94-1.10) for systemic corticosteroids; and 0.95 (95% CI 0.9-1.0) for the combined outcome.

Conclusions: Evidence from observational studies shows that the combined treatment of LABAs and ICs is not associated with a higher risk of serious adverse events, compared to ICs alone. Major gaps identified were prospective design, paediatric population and inclusion of mortality as a primary outcome.

Keywords: Asthma, Long-acting beta-agonists, Inhaled corticosteroids, LABAs, Serious adverse events, Exacerbations

Background

Long-Acting Beta-Agonists (LABAs) -salmeterol and formoterol- were introduced in the '90s when they demonstrated reducing symptoms and use of rescue medication [1]. Concerns about their safety appeared in 1993 when Castle et al. reported a threefold mortality in a randomized clinical trial (RCT) comparing LABAs with SABAs [2]. Post-marketing reports of adverse events showed an increased risk of death and serious asthma events [3]. The Salmeterol Multicenter Asthma Research Trial was stopped in 2003 after an interim analysis showed a fourfold increased mortality amongst patients randomized to salmeterol vs. placebo [4]. Similar concerns about formoterol were raised by a reanalysis of three RCTs. Meta-analyses of RCTs with LABAs as a monotherapy indicated an increased mortality risk [5,6].

Meta-analyses of RCTs examining the safety of LABAs in combination with inhaled corticosteroids (ICs) showed inconsistent results. Most of them found no significant

* Correspondence: mferrer@imim.es
[1]Health Services Research Group. IMIM (Hospital del Mar Medical Research Institute), Barcelona Biomedical Research Park, office 144. Doctor Aiguader, 88 | 08003, Barcelona, Spain
[2]Universitat Autònoma de Barcelona, Bellaterra, Spain
Full list of author information is available at the end of the article

differences in asthma-related hospitalizations and asthma-related mortality compared with patients treated with ICs alone [7-11]. But a statistically significant increase of catastrophic asthma events for LABAs plus ICs was shown by the update of a meta-analysis [12]. In 2010, the Federal Drug Administration (FDA) required label changes to indicate contraindication of use of LABAs without concomitant ICs, recommending only fixed-dose LABAs plus ICs combination, and calling for new studies to address this issue [13].

Nevertheless, there is still a lack of knowledge regarding LABAs' safety with concomitant ICs use, with both theoretical arguments and limited empirical evidence that ICs may mitigate LABA-associated risks [14-16]. Most of the systematic reviews currently available are based on RCTs, which may present limitations to assess long-term and rare outcomes [5,8-11]. Moreover, RCTs may not reflect the actual patterns of use of these medications in asthma patients' day-to-day regarding treatment duration and adherence. To our knowledge, there is only one systematic review of observational studies [17]. Its meta-analysis showed that the combined treatment was associated with a lower risk of asthma-related hospitalizations and/or emergency room visits.

Since year 2008, end date of the above mentioned review, many non-randomized studies have been published, especially due to the FDA's 2010 call for further evidence. The aim of this study was to assess the risk of serious adverse events in patients with asthma treated with LABAs and ICs in comparison to patients treated only with ICs, by synthesizing the available evidence from non-randomized studies through systematic review and meta-analysis.

Methods

The protocol registration number was CRD42012003387 (http://www.crd.york.ac.uk/Prospero). We searched MEDLINE and EMBASE databases with a specific strategy (see Additional file 1) from 1990, when LABAs were commercialized, to January 20th, 2013.

We looked for non-randomized studies in all languages (non-randomized controlled trials, controlled before-after studies, prospective or retrospective cohorts, case-control studies) on adults, adolescents or children with asthma diagnosis. Studies assessing treatment with LABAs plus ICs (either as two separate inhalers or as a single inhaler) compared with ICs monotherapy were considered, regardless of the dose (see Additional file 1). Co-therapy such as immunomodulators and leukotriene modifiers were not excluded. We defined 'severe exacerbation' following the American Thoracic Society/European Respiratory Society statement [18] which was based on urgent health care utilization: asthma-related emergency department (ED) visits, hospitalizations, intubations, intensive care unit (ICU) admissions, and use of systemic corticosteroids were considered either specific or combined outcomes.

Two members of the study team, a physician (GH) and a pharmacist (MA), independently reviewed studies found in the literature search by examining titles, abstracts, and full text articles. A third reviewer (MF) resolved discrepancies. A pilot test was performed to homogenize criteria among reviewers. Finally, the selected articles' reference lists were reviewed to identify other possible studies that could be included.

Data were extracted by agreement of two reviewers using a standardized, predefined data collection form, including: study and participants characteristics, interventions, comparator, outcomes, asthma severity, co-medication, and ethics consideration of each study. Authors were contacted if clarification was needed.

The risk of bias in the identified studies was assessed using a checklist developed by members of the Cochrane Non-Randomised Studies Methods group [19]. We assessed 4 categories of potential biases: groups of comparison, reasons for allocation in groups, parts of the study that were prospective, and group comparability (Additional file 1).

Analytic strategy

Reported adjusted OR and 95% confidence intervals (95% CI) for the comparison of ICs plus LABAs versus ICs alone were considered. Where adjusted ORs were not reported, unadjusted ORs were held. To assess the risk of severe exacerbation in patients with asthma treated with LABAs plus ICs, compared to those treated only with ICs, meta-analyses were carried out for individual specific adverse events and combined outcomes. Subgroup analyses for children and administration mode were planned. The summary OR and 95% CI estimated in the meta-analyses, together with ORs from individual studies, were presented in forest plots.

Heterogeneity among studies was evaluated using Galbraith plot and I^2 statistic categorized as follows: <30% not important; 30%-50% moderate; 50%-75% substantial; and 75%-100% considerable [19]. If significant heterogeneity was identified among studies, further examination of the individual studies was conducted, and random effects models (Dersimonian-Laird Method) were used to obtain the summary OR estimates. Otherwise, fixed effects models were used (Mantel-Haentzel Method). Publication bias was assessed by Egger regression asymmetry test and funnel plots. The meta-analytic software program used was STATA.12.

Results

Literature search results

The literature search identified 4,415 articles (Figure 1). After excluding 195 duplicates, 4,220 titles and 1,759

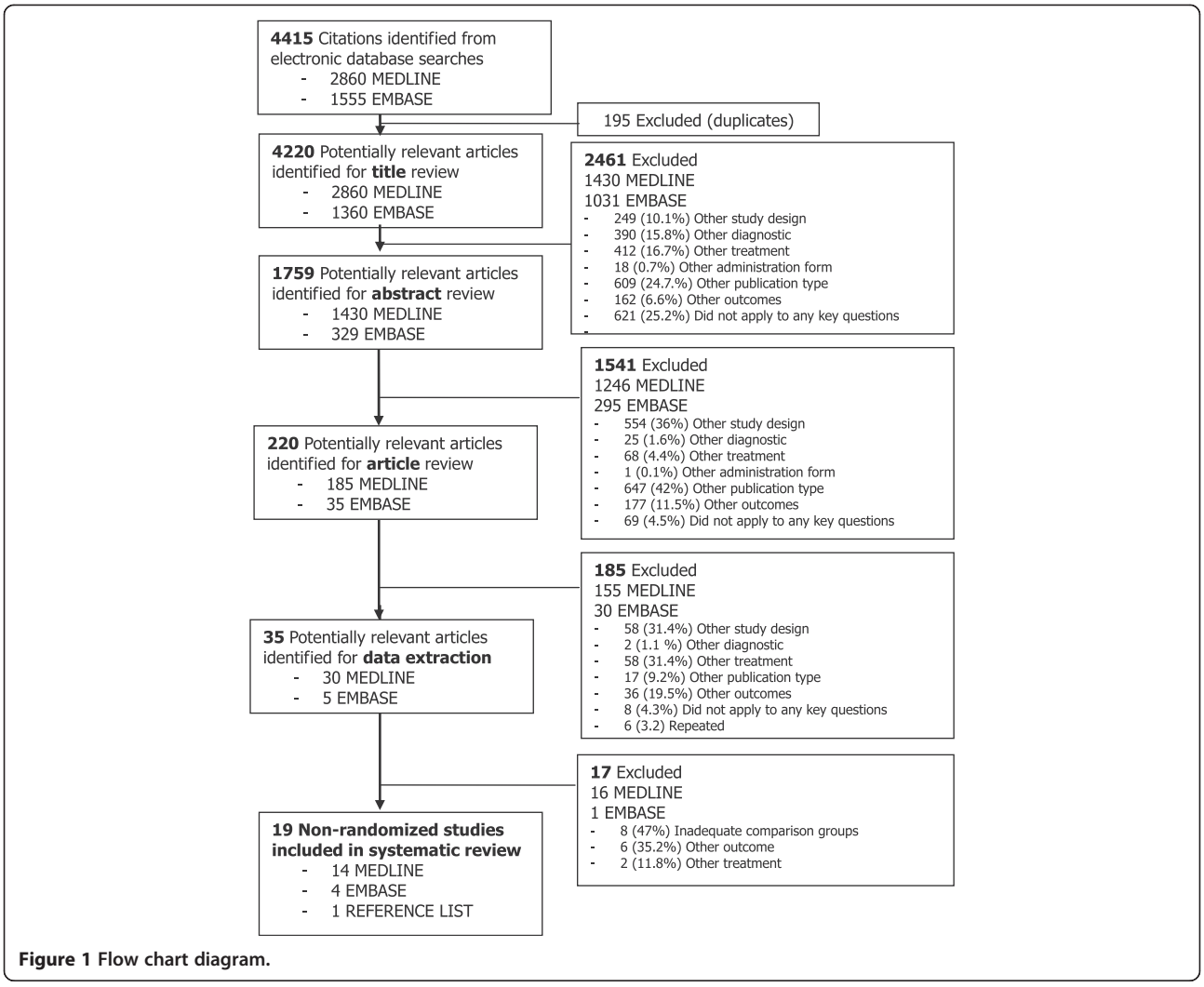


Figure 1 Flow chart diagram.

abstracts were reviewed, reading fully 220 articles. The most frequent reason for exclusion during title and abstract review was "did not apply to any key question" (25.2%), and "other publication type" (42%), respectively; and during full text review, presenting "other study designs" (31.4%) or evaluating "other treatments" (31.4%). Detailed reasons for excluding manuscripts at each step are displayed in Additional file 1. Seventeen of the potentially relevant articles were excluded after full text reading (characteristics are shown in Additional file 1). Finally, 19 studies met the inclusion criteria.

Characteristics of included studies

Main characteristics of included studies are displayed in Table 1. The majority (16/19) were retrospective observational cohorts based on pharmacy claims from insurance databases. These studies analysed patients with asthma who had initiated an inhaled treatment with LABAs plus ICs or ICs alone. There was also 1 prospective observational cohort, 1 case-control study and 1 before-after study. All the articles described studies carried out in either USA (16/19) or UK (3/19). Regarding sample size, number of participants varied from 50 (Nguyen WT et al. 2005) [20] to 514,216 (Guo JJ et al. 2011) [21]. All articles included have been approved by their Ethics Committee

Assessment of risk of bias in individual studies

An overview of the risk of bias in individual studies is shown in Figure 2. First, all studies compared the LABAs plus ICs group with the ICs alone group, as this was an inclusion criterion. Therefore, risk of bias in this item was not identified. Second, risk related to allocation was intermediate since patients were allocated by treatment decisions and not by location differences, participant's preferences, or based on outcomes. Third, we considered the risk related to retrospective design as intermediate, because the outcomes assessment was retrospective and the generation of hypothesis was prospective. Fourth, risk of bias related to groups' comparability was

Table 1 Characteristics of included studies

Author and publication year	Study design	Sample size (n)	Age (years)	Administration mode	Follow-up period	Ascertainment of asthma	Outcomes		Endpoint measure
							Specific	Combined	
Wells et al., 2012 [22]	RC	1,828	12-56	Single inhaler	*2.1(2.0) years	Asthma treatment	————————	1- Asthma-related hospitalization OR asthma-related ED visit OR Systemic Corticosteroid use	aHR
Jacobs et al., 2012 [23]	C-C	181	4-18	Not stated	NA	Clinical diagnosis	1- ICU admission	————————	aOR OR
							2- Deaths		
							3- Intubation		
							4- Positive air pressure use		
Stanford et al., 2012 [24]	RC	10,837	65-79	Single inhaler	12 months	Claims for asthma	1- Asthma-related hospitalization	1- Asthma-related hospitalization OR asthma-related ED visits	aHR
							2- Asthma-related ED visits		
							3- Systemic Corticosteroid use		
Guo et al., 2011 [21]	RC	514,216	0-40	Single & Separate inhalers	-	Claims for asthma	————————	1- Asthma-related hospitalization OR asthma-related ED visits OR Asthma-related intubations	aHR
Stanford et al., 2010 [25]	RC	50,428	> 4	Single inhaler	*290.4 (102.8) days	Claims for asthma	1- Asthma-related hospitalization	1- Asthma-related hospitalization OR asthma-related ED visits	aHR
							2- Asthma-related ED visits		
Hagiwara et al., 2010 [26]	RC	894	12-64	Single inhaler	3-12 months	Claims for asthma	1-Asthma-related hospitalization	1- Hospitalization OR ED visits	aOR
							2-Asthma-related ED visits	2- Hospitalization OR ED visits OR Systemic Corticosteroid use	
							3-Use of SABAs		
Delea et al., 2010 [27]	RC	1,744	> 12	Single inhaler	3-12 months	Claims for asthma	1- ED visits	1- ED visits OR Hospitalization	aOR
								2- ED visits OR hospitalization OR Systemic Corticosteroid use	
de Vries et al., 2010 [28]	RC	467,639	>18	Not stated	5 years	Claims for asthma	1- All mortality;	————————	aRR
							2- Asthma-related mortality		
							3-Asthma-related hospitalization		
							4-GP visits for exacerbation		
Lee et al., 2010 [29]	RC	28,074	18-56	Single & Separate inhalers	12 months	Claims for asthma	1- Asthma-related hospitalization	————————	OR
							2-Asthma-related ED visits		
							3-Systemic Corticosteroid use		
							4- SABAs use		

Table 1 Characteristics of included studies *(Continued)*

Thomas et al., 2009 [30]	RC	64,348	10-58	Single & Separate inhalers	12 months	Claims for asthma and asthma treatment	1- Respiratory Hospitalization 2- Systemic Corticosteroid use 3- SABAs use	1- Asthma-related hospitalization OR asthma-related ED visits OR > 2 prescription of Systemic Corticosteroid uses OR SABA prescription	aOR
Stanford et al., 2008 [31]	RC	58,270	> 12	Single inhaler	12 months	Claim for asthma	1-Asthma-related Hospitalization 2- Asthma-related ED visits	1- Asthma-related ED visits OR asthma-related Hospitalization	aOR aHR
Campbell et al., 2008 [32]	PC	684	> 18	Single inhaler	24 months	Severe asthma	————————	1- Asthma-related hospitalization OR asthma-related ED visit OR Systemic Corticosteroid use	aOR OR
Colice et al., 2008 [33]	RC	1,283	6-64	Not stated	12 months	Claims for asthma	1- Asthma-related hospitalization 2- Asthma-related ED visits	————————	OR
Delea et al., 2008 [34]	RC	2,269	> 5	Single & Separate inhalers	12 months	Claims for asthma	1- Asthma-related hospitalization 2- Asthma-related ED visits 3- Oral corticosteroids use	1- Asthma-related hospitalization OR ED visits OR Systemic Corticosteroid use OR alternative study medication 2- Asthma-related hospitalizations OR ED visits OR oral corticosteroid 3- Asthma-related hospitalization OR ED visits hospitalization	aOR
Friedman et al., 2007 [35]	RC	5,503	12-65	Single inhaler	12 months	Claims for asthma	1-Asthma-related hospitalization 2-Asthma-related ED visits 3- Any ED visits	————————	aOR
Zhang et al., 2007 [36]	RC	2,596	15-55	Single & Separate inhalers	12 months	Claims for asthma	1- Oral corticosteroid use 2- SABA use	1- Asthma-related hospitalization OR asthma-related ED visits	OR
Stempel et al., 2006 [37]	RC	9,192	4-17	Single inhaler	12 months	Claims for asthma	1- SABA use 2-Corticosteroids use	1- Asthma-related hospitalization OR asthma-related ED visit	aRR
O'Connor et al., 2005 [38]	RC	2,414	> 15	Single & Separate inhalers	12 months	Claims for asthma	————————	1- Asthma-related hospitalization OR ED visits	aOR aHR
Nguyen et al., 2005 [20]	B-A	50	4-17	Single inhaler	12 months	Enrolled patients	1- Asthma-related hospitalization 2- Asthma-related ED visits	————————	aRR

RC: Retrospective Cohort; *C-C*: Case-control study; *PC*: Prospective cohort; *B-A*: Before-after study; * = Mean (SD); *SABA* = Short- Acting Beta-Agonist; *ED* = Emergency Department; *HR* = Hazard Ratio; *OR* = Odds Ratio; *aHR* = Adjusted HR; *aOR* = Adjusted OR.

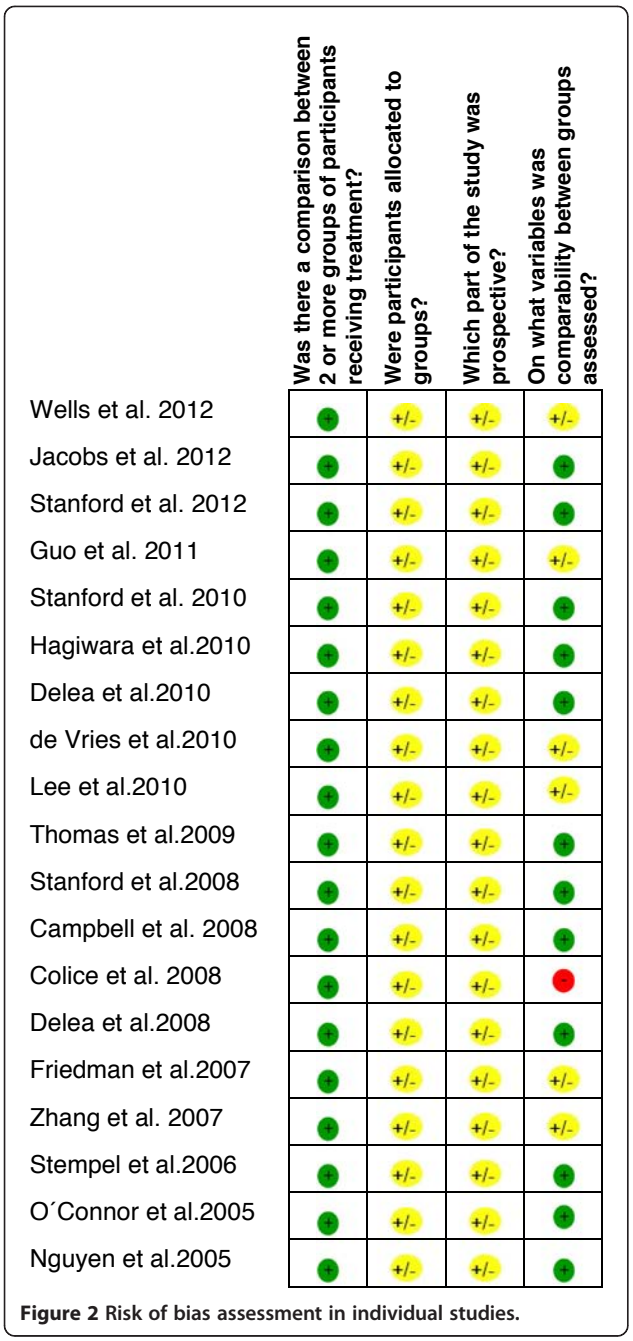


Figure 2 Risk of bias assessment in individual studies.

not identified in most cases because ORs were adjusted for potential confounders and studies compared outcome variables at baseline. Only the study of Colice et al. [33] had not done either of these two procedures (red mark on Figure 2).

Meta-analyses results

Of the 19 studies identified, 6 were not included in the meta-analyses performed (4 retrospective cohorts, the case-control, and the before-after study) because they did not provide any of the specific estimators assessed. The most commonly reported outcomes were emergency department (ED) visit and asthma-related hospitalization (reported in 9 and 8 studies, respectively), followed by systemic corticosteroid use (4 studies). There were also two commonly combined outcomes: asthma-related hospitalizations, asthma-related ED visits or systemic corticosteroid (5 studies); and asthma-related hospitalizations or asthma-related ED visits (9 studies). The latter meta-analysis was not reported because it presented considerable heterogeneity (I^2 = 93%).

Subgroup analyses concerning age and administration mode (single or separate inhalers) could not be performed due to the lack of studies providing disaggregated information for these groups. The three studies focused on children and adolescents had different designs (case-control, before-after and retrospective), and only two of the four retrospective cohorts which included adults and children stratified their analysis by age subgroups. Regarding administration mode, 10 studies included only users of fixed-dose LABAs plus ICs in a single inhaler, three studies did not provide this information, and only three of the six studies which included LABAs plus ICs both as single or two separate inhalers performed disaggregate analysis (Guo et al. [21], Delea et al. [34], and O'Connor et al. [38]).

Asthma-related hospitalizations

Figure 3 shows the Forest plot (Figure 3a), Galbraith plot (Figure 3b), and Funnel plot (Figure 3c) of the asthma-related hospitalization meta-analysis. Estimators of this outcome were provided by 8 of the retrospective cohorts. Overall, these studies included 624,303 patients. Results from the study by Delea et al. [34] were included as 2 different estimators because specific ORs for single and separate inhalers (instead of an overall OR) were provided. The ORs of the individual studies ranged from 0.72 (95% CI 0.55-0.95) reported by Stanford et al. [24] to 4.52 (95% CI 0.28-72.53) reported by Delea et al. [34]. The summary OR was 0.88 (95% CI 0.69-1.12). Random effect models were used due to substantial heterogeneity (I^2 = 66%). The Galbraith plot (Figure 3b) showed that all points except the study corresponding to deVries et al. [28] fell within the confidence limits. However, this has a considerable weight due to the large sample size (n = 467,639). The Funnel plot (Figure 3c) seems symmetric and Egger's test was non-significant, which suggests that there was no publication bias.

Asthma-related ED visits

The forest plot of the risk of asthma-related ED visits was constructed from 9 studies including 153,799 patients (Figure 4). All the ORs of the individual studies were lower than 1 and the overall summary OR was 0.75 (95% CI 0.66-0.84). A fixed effect model was used

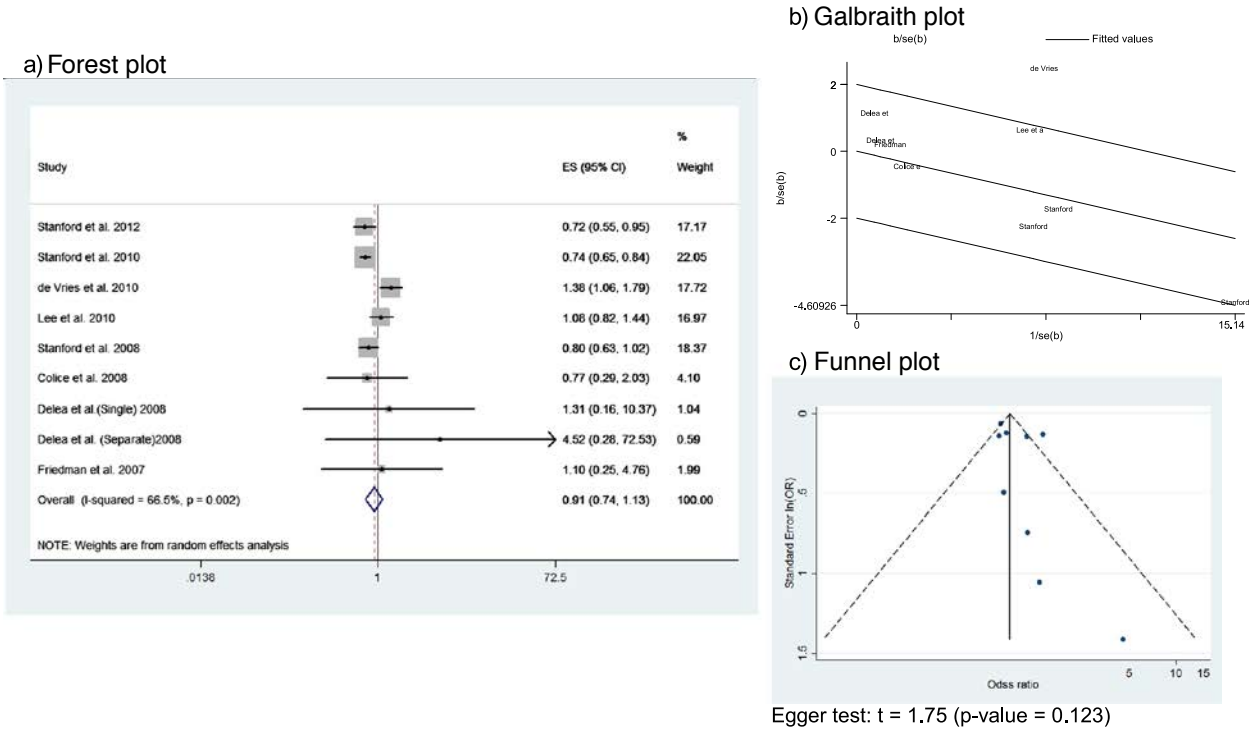


Figure 3 This figure includes Forest plot (a), Galbraith plot (b), and Funnel plot (c) of the asthma-related hospitalization meta-analysis.

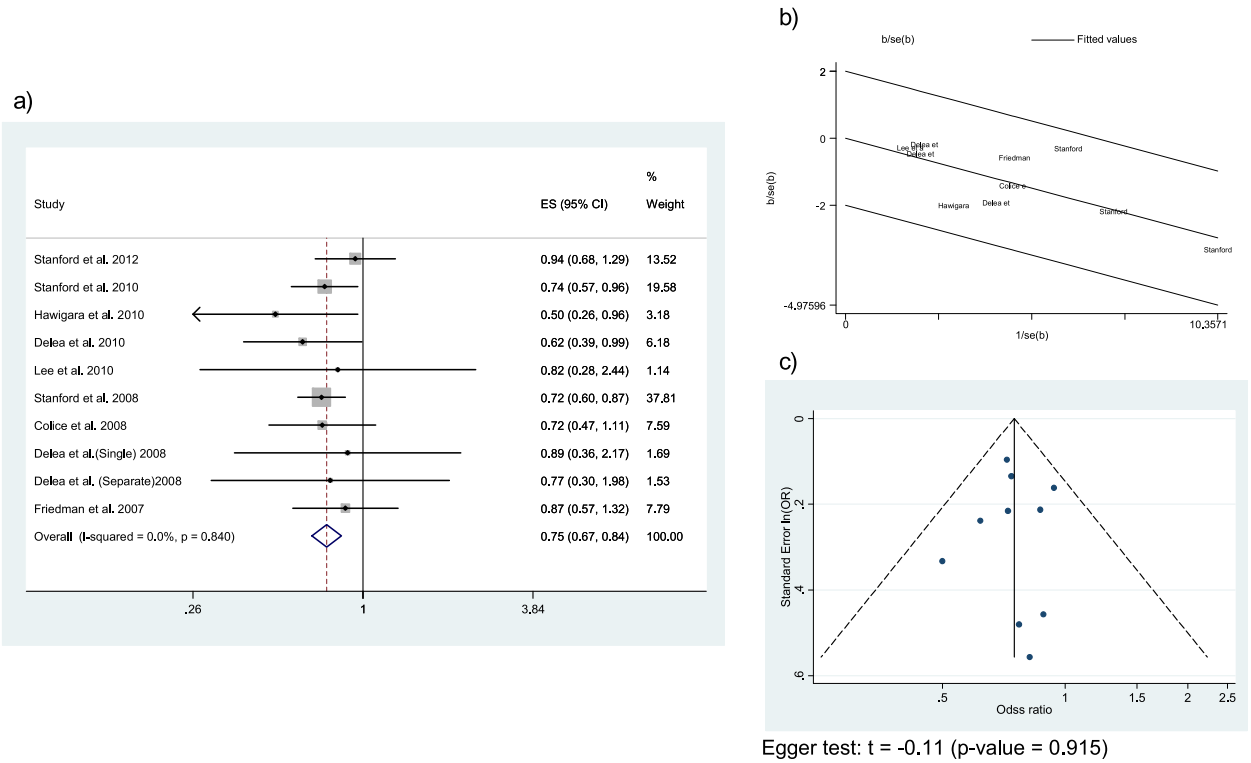


Figure 4 This figure includes Forest plot (a), Galbraith plot (b), and Funnel plot (c) of the asthma-related emergency department visits.

because there was no heterogeneity. Galbraith plot showed that most studies fell within the confidence limits, and the Funnel plot suggested no publication bias.

Asthma-related systemic corticosteroid use

Four studies (105,855 patients in total) provided estimators of asthma-related systemic corticosteroid use risk (Figure 5). Results from the study by Thomas et al. [30] were included as four separate estimators because ORs were provided for each age group. The summary OR was 1.02 (95% CI 0.94-1.10), calculated with a fixed effects model as no heterogeneity was found. All studies fell inside the confidence limits of Galbraith plot, and the funnel plot appeared symmetric.

Combined outcome of asthma-related hospitalizations, asthma-related ED visits or systemic corticosteroid use

Data from 5 studies were available for severe asthma exacerbations meta-analysis (Figure 6), defined as asthma-related hospitalizations, asthma-related ED visits or systemic corticosteroid use. Overall, these studies included 69,939 patients and the summary OR was 0.95 (95% CI 0.9-1). Results from the study by Campbell et al. [32] were included as two separate estimators because ORs were provided for both low and high corticosteroid doses. The latter is the only individual estimator above 1 (OR = 1.42; 95% CI 0.92-2.19). A random effects model was used, as substantial heterogeneity was found (I^2 = 70%). Figure 6b shows that estimators provided by Campbell et al. [32], Hagiwara et al. [26], and Delea et al. [34] fell just outside the confidence limits. Similarly, three estimators are placed outside the triangle in the funnel plot. As there are only 5 studies included in this meta-analyses, Egger's test cannot be interpreted.

Discussion

To date, less than 10% of all systematic reviews have adverse events' assessment as a primary objective [39]. Our findings support the relevance and suitability of performing systematic reviews of harms to provide valuable information on these risks. This systematic review identified 19 studies which met the inclusion criteria: 16 retrospective cohorts, 1 prospective cohort, 1 case-control, and 1 before-after study (1,165,342 participants). The meta-analyses performed (69,939-624,303 participants according to the outcome considered) showed that the LABAs/ICs combined treatment was not associated to a higher risk of adverse events, when compared with ICs alone. The OR ranged from 0.75 to 1.02 for the different outcomes explored, which is congruent with findings from meta-analyses of RCTs assessing asthma-related serious

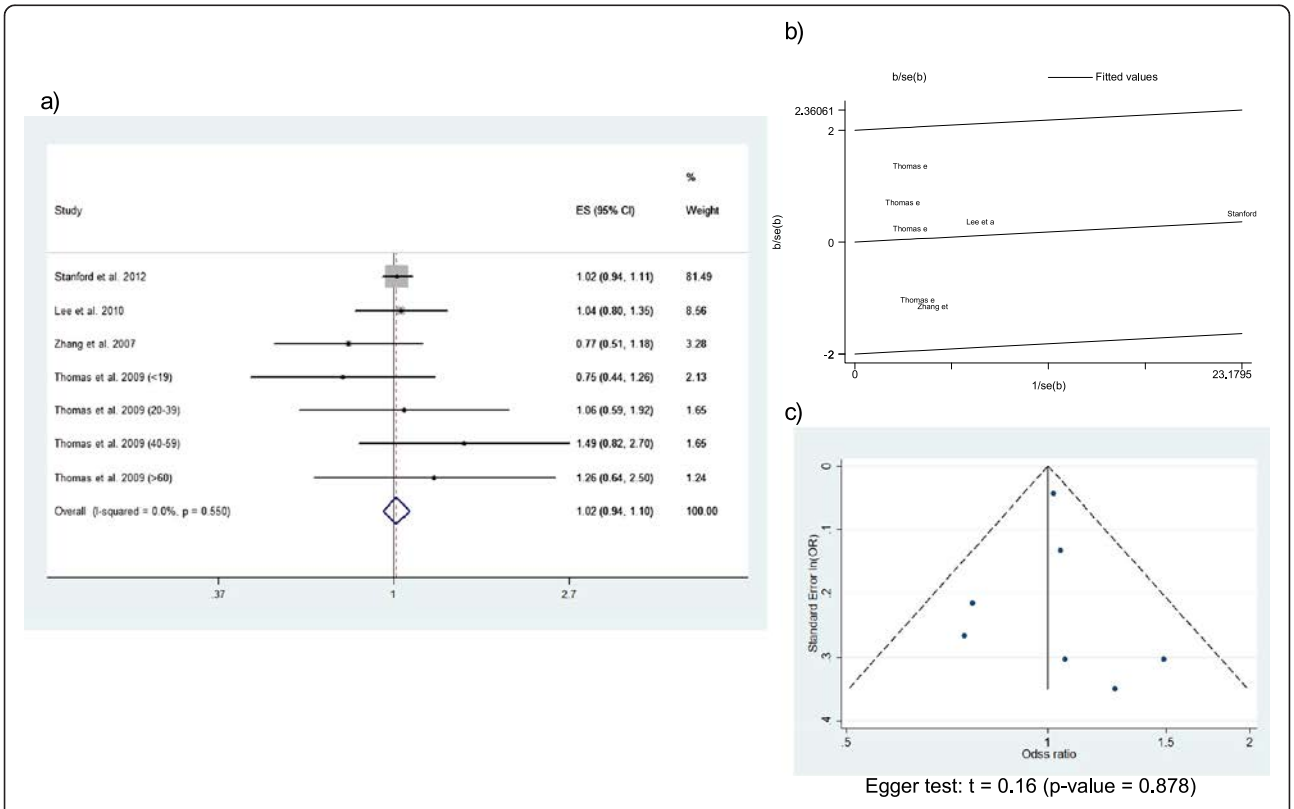


Figure 5 This figure includes Forest plot (a), Galbraith plot (b), and Funnel plot (c) of the asthma-related systemic corticosteroid use.

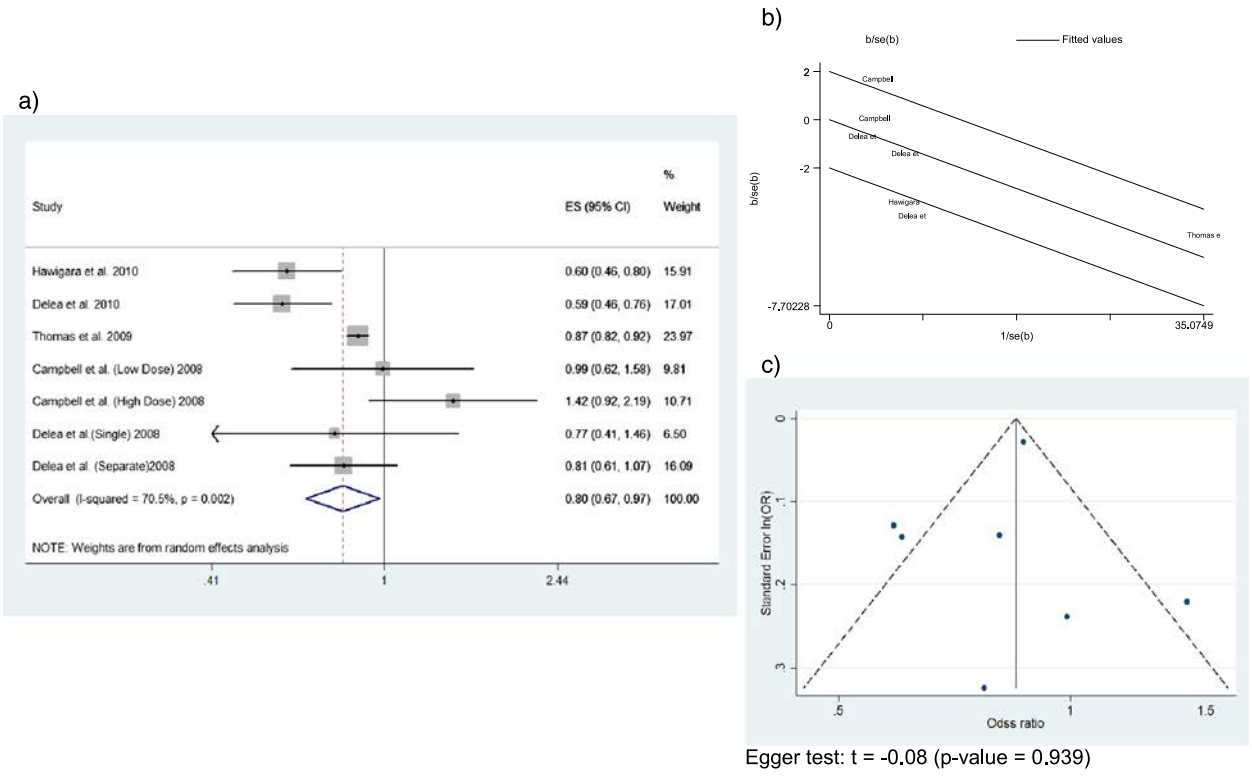


Figure 6 This figure includes Forest plot (a), Galbraith plot (b), and Funnel plot (c) of the asthma-related hospitalization or emergency department visits or systemic corticosteroid use.

adverse events for salmeterol (0.95; 95% CI 0.52-1.73) [8] and formoterol (0.53; 95% CI 0.28-1.0) [10].

This consistency between our results and those from meta-analyses of RCTs reinforces the evidence available on this topic. It is well known that RCTs are the gold standard in evaluating efficacy and safety of emerging therapies. However, their poor external validity [40] is a particular concern for long term chronic conditions that affect large and heterogeneous patient populations, such as asthmatics. In fact, it has been estimated that only 1.2% [41] or 5% [42] of the usual care asthma population could have been eligible for a typical asthma RCT. In this context, despite potential issues regarding observational studies' internal validity, they are gaining widespread recognition [43,44] providing valuable information on treatment effectiveness and safety, especially in long-term outcomes.

To our knowledge, this is the first systematic review of non-randomized studies including children and adults with asthma to assess adverse events of LABAs, as the only systematic review of observational studies previously published was limited to adult patients (asthma-related hospitalizations OR = 0.85; 96%CI 0.74-0.97) [17]. It included mainly unpublished studies identified from a pharmaceutical company's research register. Since then, the publication of 12 observational studies permitted the inclusion of a larger number of patients. In comparison with systematic reviews of salmeterol and formoterol RCTs (with 15,309 and 13,366 patients, respectively), synthesis of non-randomized studies provides results from larger representative asthma samples, more accurate reflection of the usual clinical practice, and longer follow-up periods. The follow-up periods of studies included in our systematic review ranged from 3 months to 5 years, being in most cases 1 year (12 studies), an adequate frame of time for the assessment of adverse events [19].

We identified several limitations on our review process. First, four retrospective cohorts could not be included in any of the meta-analyses performed due mainly to the lack of the specific estimator needed, but their results were consistent with our findings [21,22,37,38]. Second, outcomes of these retrospective cohorts varied substantially, from systemic corticosteroids use to deaths. Related to this wide range of clinical outcomes, there was a limitation for synthesizing them by meta-analysis – mortality, a primary outcome of interest, was reported only by one study [28]. Furthermore, the use of composite endpoints could give misleading conclusions because the components have different relevance [45]. However, not only the composite endpoints, but also the individual adverse events which compose them have been considered in the meta-analyses. Third, internal validity of the summary provided by a

meta-analysis depends on the quality of primary studies. Confounding and selection bias could distort the findings from observational studies and therefore meta-analyses including them would produce biased estimates also. In our systematic review, sensitivity analysis by quality assessment was not performed as risk of bias was homogeneous among studies. Quality assessment was considered moderate for most of them because the studies were mainly comparative, allocation was based on treatment decisions, and adjusted by potential confounders. In fact, only few unadjusted estimators were included in the meta-analysis, and the sensitivity analyses carried out to assess the impact of excluding them, showed similar summary ORs: 0.89 (95% CI 0.69-1.15) for asthma-related hospitalization and 0.75 (95% CI 0.67-0.85) for asthma-related ED visits.

Most of the retrospective cohort studies identified in this systematic review obtained data from administrative medical claims and electronic health records, with definitions based on medication prescriptions and ICD-9 diagnosis (i.e. asthma codes for inclusion and other respiratory conditions for exclusion). The main limitations derived from designs of this nature include: a) presence of a prescription claim does not necessarily indicate that the medication was taken; and b) asthma severity criteria were not applied in most studies, and in those that did, severity definitions were based on medication use instead of spirometry or clinical parameters. To balance treatment groups, most of the studies made adjustments on baseline risk factors and socioeconomic variables by using regression models and propensity score matching. Nevertheless, possible confounding factors such as severity and adherence could still remain.

The planned subgroup analysis for children and administration mode (as single or two separate inhalers) could not be conducted, and merits further comments. Stanford et al. [25] performed an analysis stratified by age groups with similar results for adults and children aged 4-18 years: OR was 0.917 (95% CI 0.85-0.98) for ED visit and 0.88 (95% CI 0.7-1.11) for hospitalization. The case-control study by Jacobs et al. [23] showed that paediatric LABA use in combination with ICs did not increase the likelihood of intensive care unit admission among hospitalized children, compared to ICs alone. Regarding administration mode, the little available evidence is controversial. The largest retrospective cohort identified in this review [21] is remarkable because it showed higher risk for single inhalers compared with separate inhalers on a combined outcome composed of asthma-related hospitalizations, intubations or asthma-related ED visits: OR of 1.13 (95% CI 1.09-1.16) among newly diagnosed patients, and OR of 1.12 (95% CI 1.10-1.12) among those with pre-existing asthma. On the contrary, in the study by O'Connor et al. [38] patients receiving LABAs plus ICs in a single inhaler were less likely to have an ED visit or to be hospitalized, compared with patients receiving the same treatment in separate inhalers (OR 0.69, 95% CI 0.51-.95). Delea et al. [34] showed similar results in both administration modes.

Heterogeneity was substantial (66.5% and 70.5%) in two of the four meta-analyses reported. In those conducted with asthma-related hospitalization risk, the only study out of the confidence limits in the Galbraith plot was deVries et al. [28]. This study differs from the other ones in having a follow-up period of 5 years, but many other possible reasons could explain such heterogeneity. In the meta-analysis conducted with the combined outcome, the only estimator that fell outside the Galbraith plot limits was the group with high dose of corticosteroids and salmeterol in Campbell et al. [32], with an OR higher than 1. This might reflect that despite the adjustments, patients taking high corticosteroid doses represented a more severe group.

Almost two thirds of the studies were performed by Glaxo Smith Kline Beecham, while others received industry support without describing the extent of involvement of their sponsors. Usually, publication bias refers to the journals' rejection of studies with negative results. Yet safety studies sponsored by the pharmaceutical industry could suffer from publication bias in the opposite direction, as it is more likely to publish negative results and to select the most favourable outcomes. We have found no evidence of publication bias in the meta-analyses reported, but Egger's test has limited power when the number of studies is low, and funnel plots may have subjective interpretation.

Conclusions

The current evidence from non-randomized studies shows that combined treatment of LABAs and ICs is not associated with higher risk of serious adverse events. Our systematic review identified major gaps in the available literature; accordingly our key recommendations for further research are to conduct prospective cohort studies, to perform studies among the paediatric population, and to include mortality as a primary outcome. Accumulative valid data is needed to allow evidence-based decisions taking into account safety of LABAs plus ICs in asthma treatment.

Additional file

Additional file 1: The additional file contains the search strategy, the inclusion and exclusion criteria, the risk of bias assessment tool and information regarding the articles excluded at each step of the Systematic Review.

Abbreviations

ICs: Inhaled corticosteroids; LABAs: Long-acting beta2–agonists; SABAs: Short acting beta agonists; RCT: Randomized clinical trial; FDA: Federal Drug Administration; ED: Emergency department; ICU: Intensive care unit admissions; CI: Confidence intervals; HR: Hazard ratio.

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

Authors' contributions
GH contributed to the conception and design of the article, conceptualized and oversaw analyses, contributed to the interpretation of data, and wrote the article. MA contributed to the reviewing and web search of included and excluded articles. AP contributed to the analysis and gave statistical support. OG, JA, CC, LL oversaw all aspects and reviewed the article for important intellectual content. 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 co-authors critically revised the manuscript and approved the final draft before submission.

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Author details
[1]Health Services Research Group. IMIM (Hospital del Mar Medical Research Institute), Barcelona Biomedical Research Park, office 144. Doctor Aiguader, 88 | 08003, Barcelona, Spain. [2]Universitat Autònoma de Barcelona, Bellaterra, Spain. [3]CIBER en Epidemiología y Salud Pública, CIBERESP, Madrid, Spain. [4]Pompeu Fabra University (UPF), Barcelona, Spain. [5]UCBL Unité de Pharmacoépidémiologie - UMR 5558 CNRS - Université Claude Bernard, Lyon, France. [6]St George's University of London, Population Health Sciences and Education, London, UK.

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4.2. ARTICLE 2:

Alexandra L. Dima, Gimena Hernandez, Oriol Cunillera, Montserrat Ferrer, Marijn de Bruin and the ASTRO-LAB group. ***"Asthma inhaler adherence determinants in adults: systematic review of observational data"*** Eur Respir J. 2015 Apr;45(4):994-1018. (IF 8.332-Q1; 3/58 Respiratory System)

ORIGINAL ARTICLE
ASTHMA

Asthma inhaler adherence determinants in adults: systematic review of observational data

Alexandra L. Dima[1], Gimena Hernandez[2,3], Oriol Cunillera[2], Montserrat Ferrer[2,3], Marijn de Bruin[1,4] and the ASTRO-LAB group

Affiliations: [1]Dept of Communication Science, ASCoR, University of Amsterdam, Amsterdam, The Netherlands. [2]Health Services Research Unit, IMIM (Hospital del Mar Research Institute), Barcelona, Spain. [3]Dept of Paediatrics, Obstetrics and Gynaecology and Preventative Medicine, Universitat Autónoma de Barcelona, Barcelona, Spain. [4]Aberdeen Health Psychology Group, Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, UK.

Correspondence: Alexandra L. Dima, Dept of Communication Science, ASCoR, University of Amsterdam, Nieuwe Achtergracht 166 1018 WV, PO Box 15791, 1001NG Amsterdam, The Netherlands.
E-mail: a.dima@uva.nl

ABSTRACT Nonadherence to inhaled medication leads to poor asthma control and increased healthcare utilisation. Many studies exploring adherence determinants have been conducted, but summaries of the evidence are scarce. We performed a systematic review of observational research on determinants of asthma inhaler adherence among adults.

We searched for articles in English reporting quantitative observational studies on inhaler adherence correlates among adults in developed countries, published in EMBASE, Medline, PsychInfo and PsychArticles in 1990–2014. Two coders independently assessed eligibility and extracted data, and assessed study quality. Results were summarised qualitatively into social and economic, and healthcare-, therapy-, condition- and patient-related factors.

The 51 studies included mainly examined patient-related factors and found consistent links between adherence and stronger inhaler-necessity beliefs, and possibly older age. There was limited evidence on the relevance of other determinants, partly due to study heterogeneity regarding the types of determinants examined. Methodological quality varied considerably and studies performed generally poorly on their definitions of variables and measures, risk of bias, sample size and data analysis.

A broader adoption of common methodological standards and health behaviour theories is needed before cumulative science on the determinants of adherence to asthma inhalers among adults can develop further.

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Introduction

The introduction of inhaled medication as the primary treatment for asthma has led to substantial improvements in asthma control [1, 2]. However, uncontrolled asthma is still common and represents a considerable burden to patients and society [3, 4]. An important reason for poor asthma control and, consequently, increased healthcare expenditure is suboptimal adherence to the prescribed regimen [5–7]. To date, few adherence interventions evaluated in asthma treatment have been found to be (cost-)effective [8–10]. A systematic review of observational evidence on adherence determinants could help identify the patients most at-risk for nonadherence and the key drivers of nonadherence that can be modified in adherence interventions.

Although several narrative reviews on determinants of adherence to asthma medication have been conducted [11–18], only two systematic reviews on observational research are available. Both examined adherence to inhaled corticosteroids (ICS): one focused on children [19], the other exclusively evaluated the role of illness and treatment perceptions in adults [20]. Neither examined the quality of the methodology of included studies, which is important in interpreting empirical evidence [21–23]. To our knowledge, no comprehensive systematic review of factors related to adherence to inhaled medication in adults with asthma has been published to date.

The objective of this study was to synthesise the current observational evidence on determinants of inhaler adherence in asthmatic adults through a systematic review, including a critical appraisal of the methodological quality of the studies, and develop recommendations for future research in this domain.

Methods

Literature search and study selection

EMBASE, Medline, PsychInfo and PsychArticles were searched for manuscripts published between January 1, 1990 and June 26, 2014 with keywords on asthma, adherence, persistence, compliance, concordance, determinant, cause, influence, barrier and facilitator (Supplementary material 1). Eligibility was determined using the following criteria: peer-reviewed article in English; reporting an empirical quantitative observational study (cross-sectional or longitudinal designs); presenting results on adult (aged >18 years) asthma patients living in developed countries [24]; investigating one or more predictor of adherence to inhaled asthma medication; and describing the adherence measurement procedure. The selection was initially based on the information in the title and abstract; if inconclusive, the entire manuscript was examined. Two reviewers (A.L. Dima and O. Cunillera) examined the search results independently. Disagreements were reconciled by a third reviewer (M. de Bruin) and through consensus.

Data extraction

Two coders (A.L. Dima and O. Cunillera) extracted information on: study characteristics (objectives, methodology, country, language, setting, sample size, age, sex, asthma severity and type of inhaled medication studied); adherence behaviours and determinants (definition, measurement and psychometrics); and statistical data (type of analysis and results reported). The data extraction procedure was piloted on articles not included in the review. Each coder extracted data from 50% of the papers. The accuracy of the recorded information was verified by the other coder, and disagreements were discussed and reconciled.

Quality rating

Two coders (A.L. Dima and G. Hernandez) rated methodological quality based on six criteria adapted from the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, which are considered key requirements for observational studies [25, 26]. Scoring was performed on a four-level response format, from no information reported to adequate reporting of appropriately used methodology (Supplementary material 2). The studies were judged on clarity of methods and pertinence in six domains: 1) selection of participants (*e.g.* sampling strategy, eligibility criteria and methods for assessing eligibility); 2) definition of variables (*i.e.* outcomes, determinants and confounders); 3) description of data sources and measurement procedures for all variables; 4) addressing potential sources of bias (*e.g.* medical surveillance, recall, or response bias); 5) sample size justification (*e.g.* power analysis, multiple comparisons correction); and 6) data analysis (*e.g.* data preparation, controlling for confounding and data collection, and sensitivity analyses). Disagreements were discussed and reconciled.

Data analysis

The data on study characteristics and adherence measurement were summarised descriptively. The results on the relationships between adherence determinants and behaviours were grouped separately for reliever (*e.g.* short-acting β_2-agonists (SABA)) and controller (*e.g.* ICS) medication as they relate to different recommendations (daily *versus* as needed use). Controller adherence was examined separately for the three

stages of adherence [27]: 1) starting treatment (initiation); 2) accuracy of medication use (implementation); and 3) continuing treatment (persistence). Determinants were classified using the five dimensions of the World Health Organization (WHO) taxonomy [26, 27]: 1) social and economic factors, 2) healthcare team and system-related factors, 3) condition-related factors, 4) therapy-related factors, and 5) patient-related factors; each with additional sub-dimensions. We summarised results regarding the statistical significance and direction of relationships for all studies. Adjusted results obtained by multivariate analyses were prioritised over unadjusted when available.

Metric properties of the six study quality items were investigated. Reliability was assessed by estimating inter-rate agreement with weighted kappa, considered appropriate for ordinal scores [28], and interpreted based on established thresholds for poor, fair, moderate, good and excellent agreement (0.20, 0.40, 0.60 and 0.80) [29]. A Mokken scaling and correlational analyses were performed on consensus scores to evaluate structural validity and examine the relationships between criteria. Total quality scores were computed adding scores on the criteria with adequate metric properties; studies were classified as higher *versus* lower quality *via* median split. Statistical analyses were performed with SPSS version 21 (IBM Corp., Armonk, NY, USA) and the R-project (www.R-project.org) *mokken* package [30, 31].

Results

Study selection

The database search identified 2878 unique articles (fig. 1). The two coders agreed on the selection of 213 articles as potentially relevant (Cohen's κ=0.60). The third coder reviewed 235 disagreements and selected 86 additional articles. Thus, 299 articles were reviewed to confirm they fulfilled all inclusion criteria. 213 articles were excluded based on title and abstract, and a further 35 articles were excluded after full manuscript examination. Finally, 51 studies were included in the review. The reasons for exclusion are presented in figure 1.

Study characteristics

Characteristics of studies are showed in table 1. Most studies were conducted in European countries (n=22) or the USA (n=19). Settings of studies were diverse, and included: primary and secondary care; pharmacies; general population; and various prescription and insurance claims databases. 11 studies used existing databases, while 40 studies collected data directly from patients. 32 studies focused solely on adults (aged >18 years), while 19 studies included adults and children. Sample sizes ranged from 34 to 292 738 participants (median (interquartile range) 204 (906)). Most studies included more females than males. Asthma severity was reported in 16 studies and ranged from mild to severe asthma.

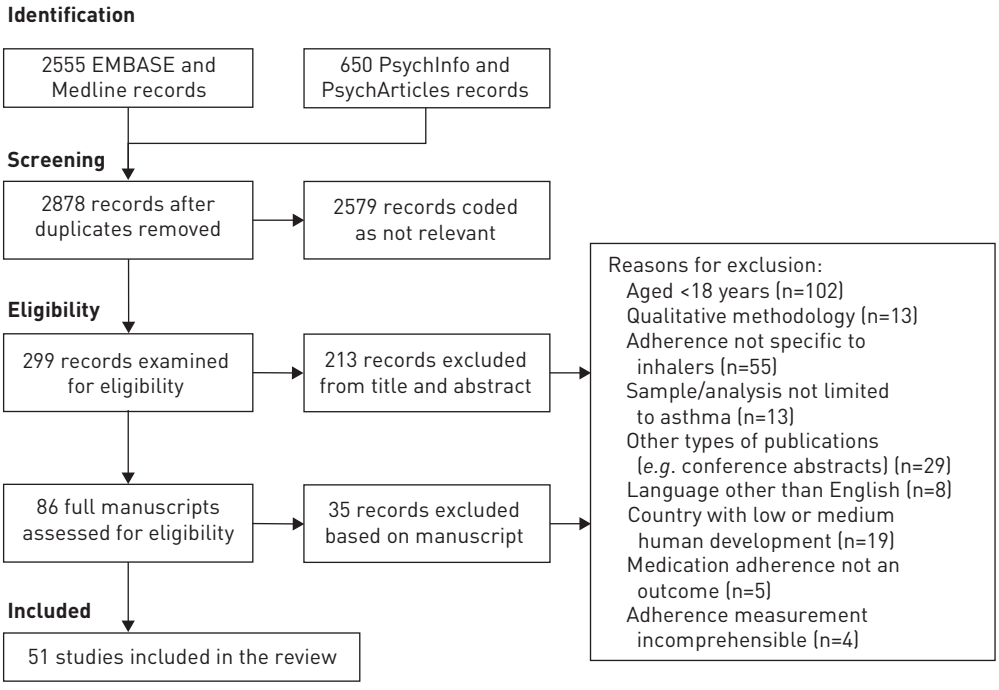

FIGURE 1 Flow diagram of article selection process.

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TABLE 1 Study characteristics of empirical studies on inhaled medication adherence in adults with asthma

First author [ref.]	Country	Year	Objectives	Study design	Data sources	Sample size n	Age years	Females	Asthma severity: FEV_1 %	Inhaled medication
Tettersell [32]	UK	1993	Relationship between knowledge and treatment adherence	Cross-sectional (ASD)	Primary care	100	50.1±20.6	9%	Moderate to severe	NR
Bosley [33]	UK	1995	Psychological factors related to asthma self-reported care and compliance	Prospective (DPA)	Primary care and outpatient clinic	72	45±15	n=62	NR	ICS+LABA, ICS/LABA
Apter [34]	USA	1998	Patient characteristics related to adherence to twice daily ICS treatment	Prospective (DPA and ASD)	Outpatient clinics	50	46±14	n=37 (74%)	75±21	ICS
Bennett [35]	UK	1998	Associations between protection motivation theory factors (health threat, outcome, self-reported efficacy) and adherence to preventive ICS use	Cross-sectional (ASD)	Primary care	71	47±19.25	n=40	NR	ICS
Chambers [36]	USA	1999	Factors associated with regular ICS use	Cross-sectional (ASD)	Primary care	394	Median: 36	75%	NR	ICS
Schmaling [37]	USA	2000	Development of measures to assess psychological factors important to adherence with medication regimens	Cross-sectional (ASD)	Private asthma clinic and hospital	53	36.1±9.6	62.3%	NR	ICS, LABA, SABA
Horne [38]	UK	2002	Relationship between reported adherence to preventer medication and perceptions and asthma medication	Cross-sectional (ASD)	Primary care	100	49.3±18.1	61%	NR	NR
Van Schayck [39]	Netherlands	2002	Influence of inhalation device, patients' inhaler perceptions, daily frequency, and duration of treatment on medication compliance	Prospective (DPA and ASD)	Primary care	34	37±13	n=19	NR	LABA or SABA
Apter [40]	USA	2003	Barriers to adherence as explanations of racial-ethnic differences in adherence	Prospective (DPA and ASD)	Primary and secondary care	85	47±15	n=61 (72%)	65±19	ICS
Jessop [41]	UK	2003	Relationship between cognitive and emotional representations of asthma and adherence to inhaled preventative asthma medication	Cross-sectional (ASD)	Primary care	330	57.2±17.9	n=204 (61.8%)	NR	NR
Labrecque [42]	Canada	2003	Assess compliance to asthma guidelines and influence of age on SABA utilisation	Retrospective (ASD)	Health insurance database claims	987	Range: 5–45	NR	Severe asthma excluded	SABA (with or without ICS)

Continued

TABLE 1 Continued

First author [ref.]	Country	Year	Objectives	Study design	Data sources	Sample size n	Age years	Females	Asthma severity: FEV_1 %	Inhaled medication
Nishiyama [43]	UK	2003	Determine if the Jones Morbidity Index can be used in community pharmacy to identify those who have poor control	Cross-sectional (ASD)	Pharmacy database	306	38.5±20.6	54.5%	NR	ICS and SABA
Balkrishnan [44]	USA	2005	Asthma-related healthcare costs, medication adherence, ICS and newly started on MON *versus* SAL	Retrospective (DPA)	Health insurance database claims	198	22±19.5 MON 24±18.2 SAL	52.5% MON 59.8% SAL	NR	ICS+LABA *versus* ICS +MON
Lacasse [45]	Canada	2005	Describe patterns of compliance and identify factors determining the compliance to ICS in adults	Prospective (DPA and ASD)	NR	124	47±15	n=73	Mild–moderate	ICS
Stempel [46]	USA	2005	Patient adherence with several medication regimens: FP/SAL, FP+SAL, FP+MON, FP, MON	Retrospective (ASD)	Health insurance database claims	3503	38.7±17	64.5%	NR	ICS, LABA, MON
Bender [47]	USA	2006	Factors related to refill adherence to FP/SAL	Retrospective (ASD)	Pharmacy database	5504	54±22	60.2%	NR	ICS/LABA
Chatkin [48]	Brazil	2006	Rate of compliance with preventive treatment for moderate and severe persistent asthma	Prospective (DPA)	Primary care	131	44.4±16.6	71%	Severe persistent	ICS/LABA
Hasegawa [49]	Japan	2006	Comparison between compliance to FP diskus *versus* FP diskhaler	Retrospective (ASD)	Pharmacy database	337	54.2±16.8 FP diskhaler 57.7±18.2 FP diskus	56.3% FP diskhaler 57% FP diskus	NR	ICS
Marceau [50]	Canada	2006	Compare persistence, adherence and effectiveness between patients with asthma starting combination or concurrent therapies (ICS and LABA)	Prospective (DPA and ASD)	Health insurance database claims	5118	32.6±8.2	63.3%	NR	ICS/LABA *versus* ICS +LABA
Ohm [51]	USA	2006	Explore asthma symptom perception and its relationship with adherence to asthma treatment	Cross-sectional (ASD)	Asthma/allergy clinics	120	44.8±9.27	78%	Mild to severe	ICS
Tavasoli [52]	Ireland	2006	Factors related to patients' compliance with prescribed metered dose inhaler drugs	Cross-sectional (ASD)	Outpatient department	160	47.67±12.78	n=105 (65.6%)	NR	ICS, LABA, SABA
Ulrik [53]	Denmark	2006	Patient-related aspects of adherence among adult asthmatics	Cross-sectional (ASD)	Community (web-based panel for market research)	509	Range: 18–45	n=317 (62%)	Mild: 77% Moderate: 12% Severe: 11%	ICS, ICS +LABA

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TABLE 1 Continued

First author [ref.]	Country	Year	Objectives	Study design	Data sources	Sample size n	Age years	Females	Asthma severity: FEV_1 %	Inhaled medication
Williams [54]	USA	2007	Factors associated with ICS adherence among patients with asthma, and among African–American and white patients separately	Retrospective (ASD)	Health maintenance organisation	176	40.8±7.7	n=115 (68.1%)	NR	ICS
Williams [55]	USA	2007	Estimate rates of primary nonadherence and explore associated factors	Retrospective (ASD)	Health maintenance organisation	1064	31.9±16.5	59.8%	NR	ICS
Breekveldt-Postma [56]	Netherlands	2008	Determinants of persistence with ICS	Prospective (DPA)	Pharmacy database	5563	Range: 0–34	51.5–57.2%	NR	ICS, ICS +LABA
Janson [57]	USA	2008	Describe asthma medication adherence, identify predictors of ICS underuse and SABA or LABA overuse	Cross-sectional (DPA and ASD)	Primary and secondary care (random-digit dialling)	158	48.7±7.4 ICS adherent, 46.7±8.5 ICS non-adherent, 46.5±8.8 SABA adherent, 46.2±7.3 SABA over use	68%	NR	ICS and SABA or LABA
Martínez-Moragón [58]	Spain	2008	Relationship between failure to perceive dyspnoea associated with bronchial obstruction and treatment nonadherence in asthmatic patients	Cross-sectional (ASD)	Outpatient respiratory clinics	48	45: range 30–60	50%	Moderate	ICS/LABA
McGann [59]	USA	2008	Relationship between denial of illness and compliance with inhaled controller asthma medications	Prospective (DPA)	Asthma clinics, advertisements, local college	51	42±14.99; range: 18–68	82.3%	NR	NR (controller)
Menckeberg [60]	Netherlands	2008	Relationship between beliefs about ICS (necessity and concerns) and adherence	Cross-sectional/ retrospective (ASD)	Pharmacy database	238	36.2±6.3	67%	NR	ICS
Wells [61]	USA	2008	Factors that contribute to ICS adherence among African–American and white adults with asthma	Retrospective (ASD)	Health maintenance organisation	1006	43.1±10.4	n=716 (71.2%)	NR	ICS
Axelsson [62]	Sweden	2009	Personality traits related to asthma control, health-related quality of life and adherence to regular asthma medication	Cross-sectional (ASD)	Epidemiological study	109	Range: 21–23	61.6%	NR	ICS/LABA, ICS, LABA, SABA

Continued

TABLE 1 Continued

First author [ref.]	Country	Year	Objectives	Study design	Data sources	Sample size n	Age years	Females	Asthma severity: FEV_1 %	Inhaled medication
Bae [63]	South Korea	2009	Baseline information about ICS adherence in Korea, factors related to ICS adherence, clinical implications of ICS adherence for asthma control	Cross-sectional/ retrospective (ASD)	Clinical centres in university hospitals	185	NR	NR	NR	ICS or ICS/ LABA
Laforest [64]	France	2009	Characteristics of patients with interruptions of ICS, intentional or accidental	Cross-sectional (ASD)	Primary care database	204	53.8±19.6	59.3%	All ranges	ICS only or in combination
Ponieman [65]	USA	2009	Impact of potentially modifiable medication beliefs on adherence with ICS therapy across time	Prospective (DPA and ASD)	General internal medicine clinics	261	48±13; range 20–87	82%	Persistent asthma	ICS
Friedman [66]	USA	2010	Adherence and asthma control in adolescents and young adults with mild asthma who began treatment with MF or FP	Retrospective (ASD)	Health insurance claims database	1384	Mean: 16.3 MF; 16.5 FP; range: 12–25	51.3% MF 55.3% FP	Mild	ICS
Takemura [67]	Japan	2010	Assess factors and mechanisms that contribute to and clinical outcomes relating to adherence	Cross-sectional (ASD)	Respiratory clinic	176	57±15	n=89	NR	ICS, ICS/ LABA
Bolman [68]	Netherlands	2011	Explain ICS adherence by the attitude, social influence and self-efficacy model and habit strength (moderation and mediation relationships)	Cross-sectional (ASD)	Pharmacy	139	31.5±5.6	n=98 (70.5%)	NR	ICS
Emilsson [69]	Sweden	2011	Influence of personality traits and beliefs about medicines on asthma medication adherence	Cross-sectional (ASD)	NR	35	52.8±14.7	n=25	NR	ICS/LABA, ICS+LABA, ICS, LABA
Small [70]	UK	2011	Relationship between inhaler satisfaction and patient compliance Influence on health and patient-reported outcomes	Cross-sectional (ASD)	Specialists' and primary care	2135	NR in adults	NR	NR	NR
Suzuki [71]	Japan	2011	Associations between several factors of asthma therapy (patients adherence, asthma severity)	Retrospective (ASD)	University hospital	50	36.3±7.9	46%	NR	ICS

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TABLE 1 Continued

First author [ref.]	Country	Year	Objectives	Study design	Data sources	Sample size n	Age years	Females	Asthma severity: FEV_1 %	Inhaled medication
Foster [72]	Australia	2012	Identify potentially modifiable beliefs and behaviours that predict ICS/LABA adherence	Prospective (ASD)	Community pharmacies, advertising, primary care, volunteer database	99	47.6±15.8	n=57	83%±23%	ICS/LABA
Ahmedani [73]	USA	2013	Relationships between locus of control factors (God, doctors, other people, change and internal) and ICS adherence	Cross-sectional (ASD)	Primary care	1025	37.6±14.8	n=675 (65.9%)	NR	ICS
Axelsson [74]	Sweden	2013	To determine the mediating effects of medication beliefs between personality traits and adherence	Cross-sectional (ASD)	Community	516	47.4±15.6	60%	NR	ICS/LABA, ICS, LABA, SABA
Price [75]	UK	2013	Identify characteristics of patients who prefer once-daily controller regimen	Retrospective (ASD)	Primary care database	3731	45.6±15; range: 2–94	n=2174 (58.3%)	NR	ICS, ICS +LABA
Price [76]	UK	2013	Compare real life effectiveness of extra-fine and larger particle beclometasone	Case–control (DPA)	Primary care databases	30354	Range: 12–80	n=17808 (58.7%)	NR	ICS
Schatz [77]	USA	2013	Develop a questionnaire that reflects nonadherence risk and identifies adherence barriers	Prospective (DPA and ASD)	Health maintenance organisation	420	41.6±9.1	n=280 (66.7%)	NR	ICS, SABA
Wells [78]	USA	2013	Determine whether once daily dosing is associated with higher ICS adherence at least twice daily	Retrospective (DPA)	Health maintenance organisation	1302	28.2±15.8 once daily 31.6±16.0 ⩾twice daily	n=113 (51.1%) once daily n=656 (60.7%) ⩾ twice daily	Low to severe	ICS
Baddar [79]	Oman	2014	Relationships between patient compliance, inhaler technique and asthma control level	Cross-sectional (ASD)	University hospital	218	Range: 12–72	65.1%	NR	ICS, ICS/LABA, ICS +LABA
Federman [80]	USA	2014	Associations of self-management behaviours (*e.g.* medication adherence and inhaler technique) with health literacy	Prospective (DPA)	Outpatient clinics	433	Mean: 67; 45% aged 60–64, 39% aged 65–74, 16% aged ⩾75	83.8%	Moderate or severe	ICS only or in combination

Continued

TABLE 1 Continued

First author [ref.]	Country	Year	Objectives	Study design	Data sources	Sample size n	Age years	Females	Asthma severity: FEV_1 %	Inhaled medication
Taylor [81]	UK	2014	To develop an annual measure of ICS adherence from prescribing data and statistically model ICS adherence controlling for patient factors	Retrospective (DPA)	Primary care database	292738	38.7± 15.4	NR	BTS/SIGN step 2–5	ICS
Van Steenis [82]	Netherlands	2014	Relationship between ICS necessity and concerns, beliefs and subjectively and objectively measured adherence and the agreement between these measures	Cross-sectional (ASD)	Pharmacy	93	43.7±14.5; range: 18–77	n=55 (59.1%)	NR	ICS only or in combination

Data are presented as mean±SD, unless otherwise stated. FEV_1: forced expiratory volume in 1 s; ASD: adherence simultaneous with determinants measurement; NR: not reported; DPA: determinants preceding adherence measurement; ICS: inhaled corticosteroids; LABA: long-acting β_2-agonists; SABA: short-acting β_2-agonists; MON: montelukast; SAL: salmeterol; FP: fluticasone proprionate; MF: mometasone furoate; BTS: British Thoracic Society; SIGN: Scottish Intercollegiate Guidelines Network.

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20 studies focused on adherence to ICS only, eight assessed adherence to inhaled asthma medication as a generic treatment category and 23 studies focused on various types of medication, including ICS and long-acting β_2-agonists (LABA) or SABA, either in monotherapy or in fixed (ICS/LABA) or free (ICS +LABA) combinations. Two studies analysed repeated measures of adherence in longitudinal cohort designs, prospectively [65] or retrospectively [81]. All other studies collected data cross-sectionally, retrospectively or prospectively (n=22, n=16 and n=12 studies, respectively) and analysed relationships between determinants and single adherence measures.

There were substantial differences between studies in operationalisation and measurement of both adherence determinants and behaviours (Supplementary material 3). Of the 68 adherence behaviour assessments (several studies used multiple measures) (table 2), 31 relied on patient reports, 24 accessed medical records (prescription and refill data), seven employed electronic monitoring, four used canister weighting, one used dose counters and one requested physician reports. 15 of the patient-reported adherence assessments applied validated questionnaires, such as the Medication Adherence Rating Scale [38] and Revised Asthma Adherence Scale [83], while the remainder used self-constructed nonvalidated questionnaires.

As most results focused on implementation of controller medication, we chose to summarise these both graphically and in the text (figs 2 and 3). The results on controller initiation and persistence and on reliever use were limited and, therefore, are only described textually.

Determinants of controller medication adherence

Initiation

Determinants of controller initiation were examined in one study that reported a higher probability of non-initiation for younger patients, females, African–American ethnicity (*versus* white), and with fewer SABA fills in the preceding year [55]. No associations were found with socioeconomic status, comorbidity, costs of treatment and various healthcare utilisation indicators.

Implementation

We identified 544 results in 47 studies, of which 457 relationships between a determinant and an adherence measure could be assessed in terms of significance and direction of relationship. Figure 2 provides details on the WHO determinant sub-dimensions with at least three results. As different measures of adherence may lead to different associations with determinants, we distinguished between objective measures, medical records and subjective reports with each type of measurement. Results from higher quality studies are presented in figure 3. Determinants with less than three results are only described briefly in the text.

Social and economic factors were investigated in 15 studies. Adherence was related to higher income in three out of eight reported results [34, 40, 53–55, 57–59]; more prescription coverage in one out of four results [34, 40, 45, 59]; lower treatment costs in two out of seven results [47, 54, 55, 61, 77]; and lower perceptions of social norms in one out of three results [68, 72, 77]. Several other variables were identified in fewer than three results and were found to be unrelated to adherence: geographical area [47]; urban location [59]; immigration status [52]; crime rate in area of residence [54]; social modelling [68]; and social support [40, 68]. Minority status was related to adherence in one result [34], and employment status in one out of two results [52, 59].

Eight studies examined healthcare team and system factors, with education provision relating to adherence in three out of four results [32, 45, 67]. Several other variables were examined in fewer than three results: lower adherence was linked to inability to get an appointment when needed in one result [61], to patient–provider communication in one out of two results [34, 40], and to the time interval being registered with the same prescriber in one result [81], while receiving a prescription from a specialist *versus* a generalist was unrelated to adherence [59].

Therapy-related factors were investigated in 18 studies. Adherence was mostly unrelated to the number of drugs in the treatment regimen (three out of four results; [63, 70, 78]), the number of daily doses (five out of seven results; [39, 47, 64, 67, 78]), and having reliever inhalers prescribed (four out of five results [34, 47, 48, 64]). Using dry-powder inhalers (DPIs) *versus* metered-dose inhalers (MDIs) was linked to adherence in two out of four results [66, 67]. Some variables examined in a single result were unrelated to adherence: prescribed use of peak flow meter or action plan [45]; treatment duration [67]; using various other drugs [44, 48, 52, 57, 64]; using autohalers *versus* other MDIs [39]. Other single result variables were related to higher adherence: using diskus DPIs *versus* diskhaler DPIs [49]; using ultrafine *versus* large-particle formulation [76]; not using a spacer [52]; and receiving more refills in a prescription [47]. Three studies compared ICS/LABA regimens with different types of alternative regimens and reported

TABLE 2 Definition and measurement of adherence behaviours in the studies reviewed

First author [ref.]	Year	Adherence definition/term	Assessment method	Details	Validity/ reliability
Tettersell [32]	1993	Taking inhalers as prescribed	Patient-reported, single item	One item: "do you take your inhalers as prescribed?"; four response options: "always", "majority of the time (8 out of 10 doses)", "about half of the time", "only during or following an attack"	NR
Bosley [33]	1995	Noncompliance; taking <70% of prescribed doses or omitting all doses for ⩾1 week	Electronic monitoring	Turbuhaler Inhalation Computer; computed for two 6-week periods as (no. of doses taken)/(no. of doses prescribed)×100	NR
Apter [34]	1998	Use of ICS in the last 35 days	Electronic monitoring	MDI_{log}, last 35 of 42 days considered, computed for 12-h periods as (recorded − prescribed actuations)×100; mean truncated adherence computed per subject; dichotomised (<or>70%)	NR
Bennett [35]	1998	Adherence to preventive ICS use	Patient-reported, published scale	RAAS [83]	α=0.75
Chambers [36]	1999	Frequency of ICS use	Patient-reported, single item	Item content not specified, four response options: "I use it at least twice a day almost every day", "some days I use it at least twice, but on other days I don't use it at all", I used to use it, but now I don't", "I never used it"; dichotomised into "regular, twice daily" and "less than regular"	NR
Schmaling [37]	2000	As-needed medication use	Canister weighting	Total number of medication inhalations for each day in the prescription period	NR
		Daily medication adherence	Canister weighting	Predicted use (no. days × no. puff per day) compared to actual use; computed as percent of prescribed medication used	NR
Horne [38]	2002	Medication adherence	Patient-reported, published scale	MARS [38]	α=0.85
van Schayck [39]	2002	Medication compliance rate	Canister weighting	Medication used as a percentage of medication prescribed	NR
Apter [40]	2003	Use of ICS in the last 42 days	Electronic monitoring	MDI_{log}, 42 days, computed for 12-h periods as (recorded − prescribed actuations)×100; mean truncated adherence computed per subject; divided into four categories (<20%, 20–<50%, 50–<75%, 75–100%)	NR
Jessop [41]	2003	Adherence to preventative inhaled medication in the last 3 months	Patient-reported, published scale (adapted)	RAAS [83] and two extra items on accidental nonadherence	α=0.92
Labrecque [42]	2003	Conformity of SABA prescription use with accepted good use criteria	Medical (refill) records	Dichotomous, good use criteria: for SABA with no ICS use, the interval between the targeted SABA prescription and the following refill corresponds to a maximum daily use of two inhalations; for SABA with ICS use, the criterion above, and a daily ICS dose below a fixed threshold	NR

Continued

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TABLE 2 Continued

First author [ref.]	Year	Adherence definition/term	Assessment method	Details	Validity/ reliability
Nishiyama [43]	2003	Reliever compliance	Patient-reported, interview	Patients were required to state the drugs and dosage regimens they used; their reports were compared with prescription information; three values were coded: "good"; "overused"; "underused" (first two also applied to reliever)	NR
		Preventer compliance	Patient-reported, interview		NR
Balkrishnan [44]	2005	Adherence to controller pharmacotherapy	Medical (refill) records	Computed as: (days of prescription supply dispensed)/(days between prescription refills − number of days person was hospitalised); dichotomised as compliant (0.5–1.5) or not	NR
Lacasse [45]	2005	Non-compliance	Electronic monitoring	MDI_{log}; calculated for 12 weeks daily as proportion of prescribed daily dose actually inhaled; dichotomised as compliant (>75%) or not	NR
Stempel [46]	2005	Asthma medication refill rate	Medical (refill) records	Number of 1-month supply during the 12-month post-index period	NR
		Number of treatment days	Medical (refill) records	For monotherapy: total days supplied of medication For combination: total days supplied of ICS	NR
		SABA refill rates	Medical (refill) records	Number of 1-month supply during the 12-month post-index period	NR
Bender [47]	2006	Adherence to ICS/LABA	Medical (refill) records	Total days supplied during follow-up period	NR
		Persistence	Medical (refill) records	Time to discontinuation computed as number of days from index date to date preceding the pre-specified gap when supply was exhausted	NR
Chatkin [48]	2006	Compliance	Canister weighting	(Total quantity of medication used)/(quantity prescribed, *i.e.* three canisters in 3 months); dichotomised as compliant (>85%) or not	NR
Hasegawa [49]	2006	Drug compliance	Medical (prescription and refill) records	Computed for 6 months as (number of medicines dispensed)/(number of medicines prescribed)×100; capped at 100%	NR
Marceau [50]	2006	Persistence *versus* discontinuation: having prescriptions continuously renewed within the period	Medical (refill) records	Computed as the sum of three times the duration of the current prescription (in days) plus all overlaps accumulated since therapy start; discontinuation date was the end date of the last filled prescription plus all overlaps	NR
Ohm [51]	2006	Use of ICS+LABA	Electronic monitoring	Advair diskhaler; computed as (number of counted doses)/(number of prescribed doses)×100; dichotomised as good adherence (⩾80%) or not	NR
		Medication adherence	Patient-reported, published scale	MARS [38]	NR

Continued

TABLE 2 Continued

First author [ref.]	Year	Adherence definition/term	Assessment method	Details	Validity/ reliability
Tavasoli [52]	2006	Compliance to prescribed MDI drugs	Patient-reported, interview	Four items: "do you use your prescribed spray (MDI drug) regularly?", "have you ever had any history of not using your spray?", "do you still use your last prescribed spray?", "how do you use your spray? Show me"; response scales from 0 to 4	NR
Ulrik [53]	2006	Intentional nonadherence	Patient-reported, single item	One item: "how often do you decide not to take your controller medication?"; five response options: "almost every day", "a couple of times every week", "a couple of times every month", "a couple of times every year", "hardly ever"	NR
		Adherence	Patient-reported, single item	Item not specified; responses reported on a three-level scale: taking controller therapy as prescribed, less, or more than prescribed	NR
Williams [54]	2007	ICS adherence	Medical (refill) records	(Cumulative days supplied)/ (total number of days between refills for 1-year study period); analyses performed also with adherence stratified (0%, 0%–80%, ⩾80%)	NR
Williams [55]	2007	Primary non-adherence	Medical (refill) records	No prescription fill information recorded for 3 months after index prescription	NR
		ICS adherence	Medical (refill) records	Computed as (total days supplied)/ (number of days of observation)×100; adherence stratified (0%, 0–80%, ⩾80%)	NR
Breekveldt-Postma [56]	2008	Persistence during the first year	Medical (refill) records	Computed as number of days from start to time of first failure to continue renewal of initial prescription, based on (number of units dispensed)/(number of units to be used per day as defined in pharmacy)	NR
Janson [57]	2008	ICS nonadherence during the last 14 days	Patient-report, interview	Nursing home assessment of ICS prescription and use, based on inspection of current asthma medication and two questions: "How many puffs and how many times per day did your doctor tell you to use this?", "During the past 14 days, how many puffs and how many times per day have you used this?"; dichotomised as adherent (⩾7 days of use in previous 14 days) or not	NR
		SABA or LABA overuse	Patient-reported, interview	Nursing home assessment on SABA and LABA prescription and use, dichotomised as overuse (average >8 puffs of SABA or >2 puffs of LABA -single or combination- per day) or adherent	NR

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TABLE 2 Continued

First author [ref.]	Year	Adherence definition/term	Assessment method	Details	Validity/ reliability
Martínez-Moragón [58]	2008	Frequency of ICS use	Patient-reported, single item	One item, not specified, adapted after (37); four response options, from "never" to "at least twice a day almost every day", dichotomised into "almost every day" *versus* "rarely if ever"	NR
McGann [59]	2008	"How closely an individual's medication taking behaviours, as measured by the DOSER, approximated prescribed use instructions provided by the healthcare provider"	Electronic monitoring	DOSER; ratio of the number of observed correct prescribed use days between day 3 and 14	Agreement with other measures (not specified) 84.32%
Menckeberg [60]	2008	Medication acquisition	Medical (refill) records	(Total days supplied)/(total number of days from first and last refill date)×100	
		Medication adherence	Patient-reported, published scale	MARS [38]	α=0.81
Wells [61]	2008	ICS adherence; the proportion of time that the patient had medication available during last 6 months	Medical (refill) records	(Total days supplied)/(number of days of observation)×100	NR
Axelsson [62]	2009	Medication adherence	Patient-reported, published scale	MARS [38]	α=0.71
Bae [63]	2009	Prescription refill adherence	Medical (refill) records	(Number of ICS refills)/12×100; categorised as appropriate use (>80%), underuse (50–80%), or extreme underuse (<50%)	NR
		Subjective self-reported adherence	Patient-reported, single item	One item: "how often did you take your ICS as prescribed for last 1 year?"; response on a visual analogue scale from 0% to 100%; categorised as appropriate use (>80%), underuse (50–80%), and extreme underuse (<50%)	NR
Laforest [64]	2009	Intentional interruption	Patient-reported, single item	Six items included: 1) accidental interruption, 2) intentional interruption when feeling better, 3) intentional interruption when feeling worse, 4) reduced use when feeling better, 5) more frequent use of ICS in case of preliminary signs of asthma attack, and 6) intentional changes of doses independently of physician; analyses performed on intentional (when feeling better) and accidental interruption	NR
		Accidental interruption	Patient-reported, single item		
Ponieman [65]	2009	Medication adherence	Patient-reported, published scale	MARS [38]; dichotomised as good adherence ($\geq$4.5) or not	α=0.86
Friedman [66]	2010	Prescription fills	Medical (refill) records	Total number of prescription refills during the post-index period	NR
		Percentage of days covered	Medical (refill) records	(Number of days patients had medication on hand)/(total number of post-index days=365)×100	NR

Continued

TABLE 2 Continued

First author [ref.]	Year	Adherence definition/term	Assessment method	Details	Validity/ reliability
Takemura [67]	2010	Self-reported adherence to inhalation regimen	Patient-reported, published scale (adapted)	Modification of RAAS [83] concerning the use of inhaled controller medications; mean adherence score computed; dichotomised as good adherence (⩾4.0) or not	NR
Bolman [68]	2011	Medication adherence	Patient-reported, published scale	MARS [38]	α=0.89
Emilsson [69]	2011	Medication adherence	Patient-reported, published scale	MARS [38]	α=0.77
Small [70]	2011	Physician-perceived compliance; "the extent to which the patients are perceived to follow their physician's prescribing instructions and advice"	Physician-reported, bespoke scale	Two items (not specified) on physician-perceived patients' compliance regarding frequency of use and inhaler use; five response options from "not at all compliant" to "fully compliant"	α=0.92
Suzuki [71]	2011	ICS adherence	Medical (prescription and refill) records	Ratio of doses dispensed in the pharmacy divided by prescribed doses documented in medical charts	NR
Foster [72]	2012	Adherence with ICS/LABA	Electronic monitoring	Smart inhaler; daily adherence calculated as (no. recorded actuations/no puffs prescribed)×100, capped at 100% and averaged for the last 4 weeks of 2 months monitored	NR
			Patient-reported, published scale	Morisky adherence scale [84]	NR
			Patient-report, single item	Estimation of own inhaler use (days/week and puffs per day) in the last 4 weeks	NR
Ahmedani [73]	2013	ICS adherence	Medical (prescription and refill) records	(Total days supplied)/(3-month observation period)×100	NR
Axelsson [74]	2013	Medication adherence	Patient-reported, published scale	MARS [38]	α=0.75
Price [75]	2013	ICS adherence	Patient-reported, published scale	MARS [38], categorised as "low"("often" or "always" response to any question), "borderline" (´sometimeś responses to > 1 question), and "good" (any other answer)	NR
Price [76]	2013	ICS adherence	Medical (prescription) records	(Total days supplied)/(365-day observation period)×100	NR
Schatz [77]	2013	Questionnaire low adherence	Patient-reported, published scale	Response to "how often are you actually taking your ICS medication now" compared to response to "based on your doctor's most recent instructions, how often were you advised to be taking your ICS medication now" (less frequently)	NR
		Percent of days covered	Medical (refill) records	Days' supply of dispensed canisters over the follow-up at 3, 6, and 12 months	NR
Wells [78]	2013	ICS adherence	Medical (prescription and refill) records	Continuous multiple-interval measure of medication availability equals number of days' supply for each fill/total number of days between the present and next fill; averaged for the observation period	NR

Continued

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TABLE 2 Continued

First author [ref.]	Year	Adherence definition/term	Assessment method	Details	Validity/ reliability
Baddar [79]	2014	Compliance with controller treatment	Interview cross-checked with electronic patient records	Good equals taking 100% of daily prescribed medication and ⩽2 missed doses/administrations per week; partial equals taking more or less than their daily prescribed medication; poor equals any other inhaler use patterns	NR
Federman [80]	2014	ICS adherence	Dose count	Review of dose counters for all dry powder inhaler devices during the first 3 months and 30 days after each new prescription; dichotomised as <80% and ⩾80%	NR
Taylor [81]	2014	Adherence to ICS prescriptions	Medical (prescription) records	Prescription possession ratio: (number of days prescribed during calendar year)/(number of days in the interval)×100	NR
van Steenis [82]	2014	ICS adherence	Patient-reported, published scale (adapted)	Morisky adherence scale [84], adapted	NR
		ICS adherence	Medical (refill) records	Proportion of days covered: (number of days' supply)/(365 or truncated if medication gap ⩾182)×100; dichotomised as <80% and ⩾80%	NR

NR: not reported; ICS: inhaled corticosteroids; RAAS: Revised Asthma Adherence Scale; MARS: Medication Adherence Rating Scale; MDI: metered-dose inhaler; SABA: short-acting β_2-agonists; LABA: long-acting β_2-agonists; α: Cronbach's α test.

better adherence to ICS/LABA compared to ICS and/or LABA and/or SABA [62], and compared with ICS in monotherapy or in combination with LABA or montelukast [46], but no differences in intentional or accidental nonadherence between ICS/LABA and ICS+LABA regimens [64].

Condition-related factors were investigated in 26 results, with nonsignificant results regarding asthma duration (nine results [34, 35, 38, 41, 45, 52, 61, 67]), pulmonary function (six out of eight results [34, 40, 45, 51, 57, 58]), and presence of current symptoms (19 out of 22 results [34, 35, 41, 43, 45, 48, 52, 57, 58, 61, 62, 64, 70, 79, 82]). Asthma exacerbations showed 13 nonsignificant [34, 40, 48, 55, 57, 67, 73, 81], but also five positive [36, 55, 73, 81] and six negative associations [52, 67, 70] with adherence. Higher health-related quality of life was associated with better adherence in four out of 11 results [45, 57, 62, 64, 67, 70], and higher asthma severity was linked to better adherence in five results [48, 68, 71, 78, 81], compared to one negative [81] and six nonsignificant results [40, 52, 64, 70, 71].

Patient-related factors were investigated in 40 studies. Patient demographics such as age and sex were included in numerous studies. Older age related to better adherence in 16 out of 28 results [32, 34, 35, 38, 40, 41, 45, 47, 52–55, 57, 58, 61, 63, 64, 67, 69, 70, 72, 73, 78, 81, 82]. Sex showed 24 nonsignificant results [34, 38, 40, 45, 48, 52, 54, 55, 57–59, 62–64, 67, 68, 70, 71, 73, 79, 82], with females showing better adherence in three results [41, 47, 53] and males in another three [61, 72, 78]. Being of white ethnicity was linked with better adherence in five out of 10 results [40, 48, 54, 55, 57, 59, 61, 70, 73, 78], while participants with higher education levels were more adherent in four out of 10 results [34, 38, 40, 45, 48, 52, 53, 57–59].

Few studies found significant roles of variables related to patients' general health status. Smoking status was consistently unrelated to adherence [40, 48, 52, 57, 58, 63, 64, 71], as was depression [40, 45, 57, 58]. Higher comorbidity was associated with better adherence in two out of eight results [47, 48, 54, 55, 57, 63], while less healthcare utilisation was linked to better adherence in two out of 11 results [34, 38, 40, 55, 70]. Asthma knowledge was found to be unrelated to adherence [32, 53], while medication knowledge was reported to be related to adherence in only one out of five results [34, 40, 61, 77]. Asthma beliefs (*i.e.* perceptions of the asthma impact in terms of severity, consequences, timeline, *etc.*) showed inconsistent relationships with adherence, with eight positive results [35, 36, 41, 53, 72], 10 nonsignificant results [35, 38, 41, 53, 57, 58], and one negative result [38].

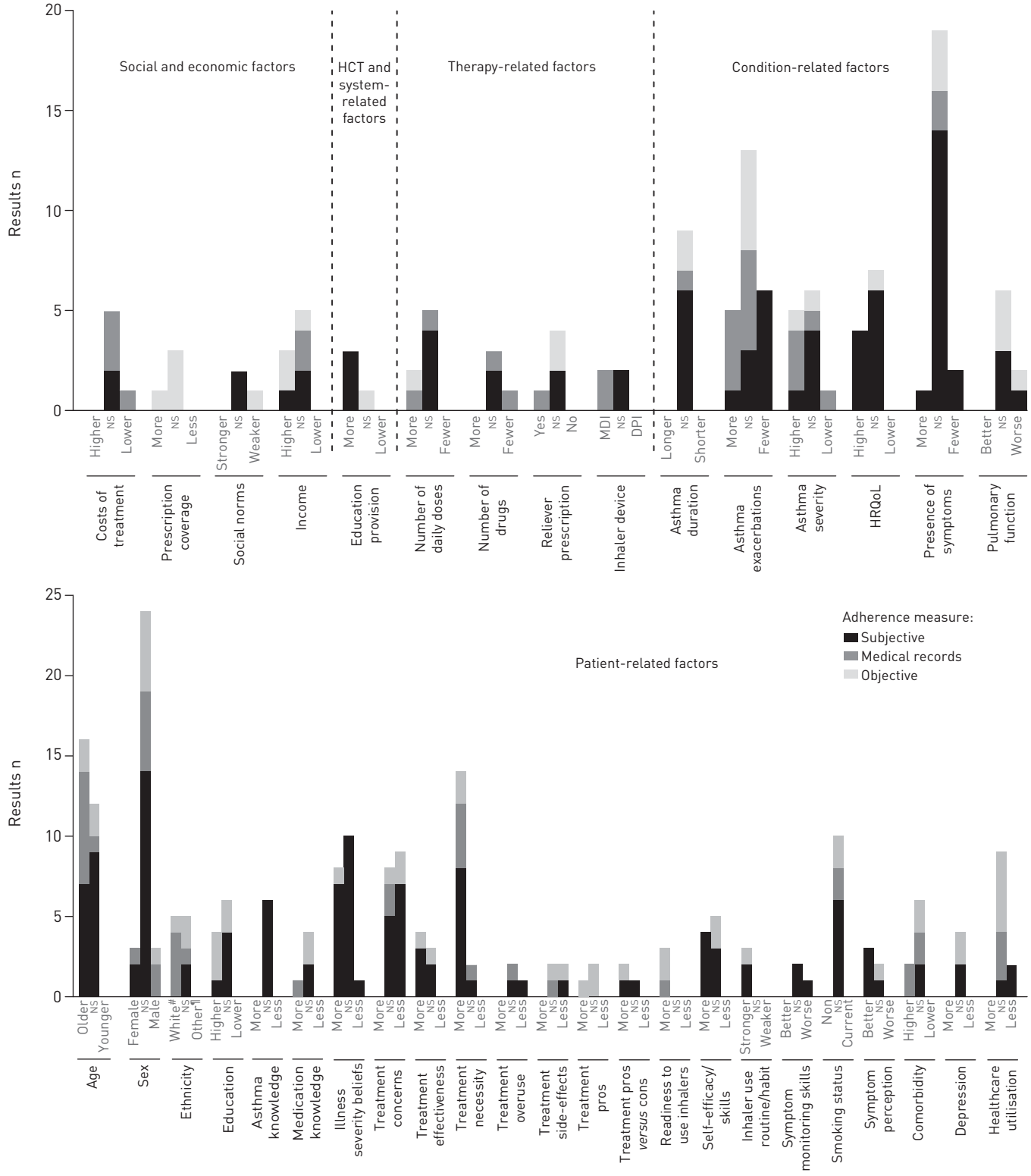

FIGURE 2 Determinants of controller implementation. Number of positive, nonsignificant and negative relationships with adherence indicators for determinants with three or more results identified. HCT: healthcare team; NS: nonsignificant; MDI: metered-dose inhalers; DPI: dry-powder inhalers; HRQoL; health-related quality of life. #: *versus* other; ¶: *versus* white.

The role of treatment beliefs was studied extensively. Stronger beliefs in the necessity of using inhalers were associated with better adherence in 14 out of 16 results [38, 40, 53, 60, 61, 65, 69, 74, 77, 82], beliefs in their effectiveness in four out of seven results [35, 40, 52, 53, 77], and more broadly-framed positive

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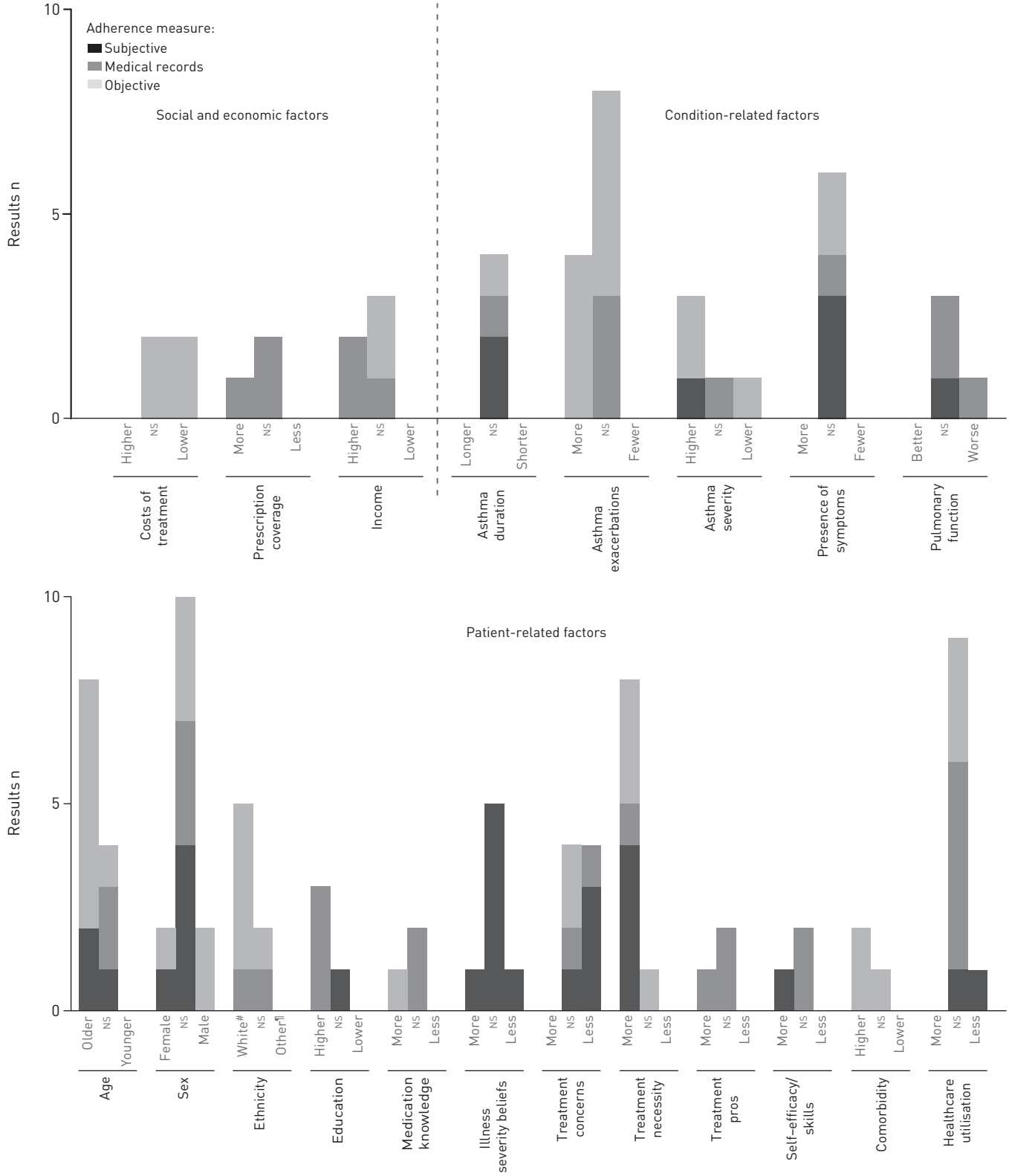

FIGURE 3 Determinants of controller implementation (results from higher quality studies). Number of positive, nonsignificant and negative relationships with adherence indicators for determinants with three or more results identified. NS: nonsignificant. #: *versus* other; ¶: *versus* white.

beliefs in inhaler usefulness or benefits in one out of three results [34]. Having fewer concerns about medication was related to better adherence in nine out of 17 results [38, 40, 60, 64, 65, 68, 72, 74], lower perceived side-effects in two out of four results [72, 77], lower beliefs that medication in general is

overused in one out of three results [60, 77], and stronger beliefs in inhaler necessity relative to concerns in two out of three results [68, 69, 72]. Readiness to use inhalers showed positive associations to adherence in three results [37, 61], indicators of self-efficacy in four out of nine results [32, 35, 40, 57, 65, 68], and stronger adherence routines in three results [53, 68, 72]. A better ability to perceive changes in asthma symptoms was related to adherence in three of five results [51, 58], while lower confidence in the ability to monitor symptoms was related to adherence in one of three results [41, 53].

Numerous other patient-level variables were examined in fewer than three analyses, most with nonsignificant results: general health status and body mass index [57]; marital status [48]; number of causal attributions for asthma [38]; extent of attributing asthma to internal causes [41]; general health self-efficacy [65]; self-control [45]; and various personality and medical history characteristics [34, 39, 45, 52, 58, 62, 68, 69, 71, 73, 74]. Several exceptions referred to better adherence in people who consider medication as less harmful (two results [60]), display lower neuroticism, higher agreeableness and conscientiousness (one out of two results [69, 74]), and believe more strongly that their asthma can be controlled [38, 41]. Several single results showed better adherence in people with a family history of asthma [71], asthma onset at younger age [58], lower impulsivity [62] and high literacy [80]. Other single findings suggested that more adherent people attribute their asthma more to external factors [41], believe that God is less in control of their health and attribute more control to physicians [73], perceive themselves less vulnerable to side-effects, report higher intention to use inhalers [72], have better inhaler use skills [79], are more satisfied with the device [70], prefer to use inhalers rather than pills [32], have no preferences regarding daily inhaler dosage [75], believe more strongly in participating actively in care [36], and report no symptom improvement due to herbal drugs [52].

Persistence

Controller-persistence determinants were investigated in three studies, and results are presented below. Patients receiving prescriptions from a specialist, using MDIs, having a lower recommended dose, having once-daily dosing frequency, having used LABAs in the previous year, and having had previous asthma-related hospitalisations were more likely to persist using single ICS treatment during 1 year, while adolescents and patients with more than twice daily dosing frequency were more likely to discontinue [56]. For ICS/LABA therapy, persistence was less likely for adults compared to children, for people with longer therapy duration, higher daily dose, and having used antibiotics in the previous year [56]. Patients using ICS/LABA were more likely to persist with therapy compared to those using ICS+LABA, as were male patients, older patients, those receiving social assistance, those with lower daily dosage, those receiving prescriptions from a specialist, and those using more medications currently and in the previous year [50]. Time to discontinuation of ICS/LABA therapy was longer for male patients, older patients, those paying moderately for treatment, having more refills included in the first prescription, having prescriptions for other conditions, and having had relievers prescribed before the start of the study [47].

Determinants of reliever use

Reliever use recommendations were examined in three studies. Reliever overuse (as indicator of nonadherence to reliever recommendations) was linked to increased symptoms in two out of three results [43, 57], to older age in one out of two results [42, 57], and to lower education, higher self-perceived asthma severity and lower general health status in one result [57]. Other factors were unrelated to overuse (*e.g.* sex, ethnicity, socioeconomic status, smoking status and various health status indicators).

Study quality

The 51 studies received relatively good quality scores regarding participant selection methods and measurement of variables, with 19 and 14 studies receiving the maximum score, respectively (table 3, Supplementary material 4). Scores were considerably lower on appropriateness of data analysis, measures taken to protect against bias, study size justification and clarity of definitions for the variables included. Common limitations in reporting patient selection were omitting methods of sampling and checking eligibility, and not specifying response rates. The concept definitions often overlapped with the description of measurement methods, or only variable labels were reported. Many studies did not describe measurement methods for all main variables. The majority of studies did not mention any source of bias, and none gave a clear sample size justification or reported optimally on study size decisions. Some studies reported power computations for unspecified analyses, did not correct for multiple comparisons, dichotomised adherence scores without giving a valid rationale, did not control for potential confounders, and offered unclear descriptions of statistical procedures. Inter-rater agreement for the six quality rating criteria (table 3) was poor to moderate, but all discrepancies were resolved through discussion between the two coders. Participant selection methods, measurement of variables, clarity of variable definitions and appropriateness of analyses formed a homogenous scale, with a homogeneity±SE of 64±0.07. Performance

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TABLE 3 Study quality: frequencies and inter-rate agreement for quality criteria[#]

Quality criterion	Unknown[¶]	Low[+]	Medium[§]	High[f]	Inter-rate agreement weighted κ
Participant selection	0	10	22	19	0.41
Definition of variables	2	11	35	33	0.31
Measurement of variables	0	16	21	14	0.38
Addressing sources of bias	27	14	8	2	0.38
Study size	29	19	5	0	0.17
Data analysis	0	24	19	8	0.33

[#]: n=51. [¶]: no description available; [+]: unclear and/or not appropriate; [§]: mostly clear and appropriate, with a few omissions; [f]: clear and appropriate.

on the two remaining criteria (addressing bias and justifying sample size) was only weakly related to the quality scores on the other four criteria (item properties not shown for brevity).

Discussion

This systematic review aimed to qualify and synthesise the observational evidence on determinants of inhaled medication adherence in adults with asthma. In the 51 studies included, patient-related factors associated with controller implementation were the most frequently studied, and healthcare team and system factors the least. The more robust evidence linked stronger treatment necessity beliefs to better implementation. The few studies assessing controller initiation and persistence mainly suggest a possible influence of therapy-related factors and patient demographics. Studies on reliever use were scarce, with reliever overuse related to several patient-related factors. This limited evidence offers only provisional guidance for developing inhaler adherence interventions. Furthermore, the findings regarding each adherence determinant and behaviour should be interpreted with caution and within each study context due to the heterogeneity among studies. Our review reveals important knowledge gaps that need to be addressed in the future, and also highlights crucial methodological limitations that can inform researchers regarding concrete steps to take for accumulating sound evidence in future studies.

Regarding the results on determinants of controller use implementation, the substantial focus on patient-related determinants was noted in previous reviews in asthma [19, 20] and in other chronic conditions [85–87], and reflects an interest in both identifying at-risk groups and understanding patient perspectives as proximal determinants of patient behaviours. Demographic and clinical characteristics and patients' knowledge of asthma and of medication were generally unrelated to controller use, except a possible higher risk of nonadherence in younger adults. Treatment necessity beliefs were consistently related to better controller implementation but moderate evidence exists on the role of other positive treatment beliefs and concerns. These results confirm a previous review on treatment beliefs [20] and support the relevance of addressing patients' views regarding their condition and treatment in adherence interventions.

Determinant categories not related to patients were studied substantially less and should be prioritised in future research. Condition- and therapy-related factors seemed unrelated to controller implementation behaviours or showed inconsistent results. Among these factors, several medical outcomes, such as asthma exacerbations, severity or symptoms, showed contradictory results, suggesting that their relationships with adherence might vary depending on other parameters, which would need careful examination. Despite the relevance of social and economic factors identified in previous reviews [85–87], only financial information was examined more extensively but showed inconsistent results. Limited data were available on the influence of the social environment in adults with asthma, despite the key role of social factors identified in children's asthma management [19] and in adherence to other long-term treatments for chronic conditions in general [85, 88]. Healthcare team and system factors were rarely studied, although the improvement of health services for chronic conditions is currently a priority [89] and adherence-enhancing interventions usually include changes in the structure of healthcare delivery [10]. This highlights the need for further research on the structure and content of adherence support in routine clinical care, which can have a major impact on patient behaviours and treatment success rates [90, 91]. Future studies could also benefit from adopting broader theoretical approaches that also explore factors beyond the individual patient level, such as the Precede-Proceed framework, which would facilitate behaviour change intervention design [92].

The barriers to evidence consolidation identified during the present review raise an important question: what methodological standards would future studies apply to obtain quality evidence on determinants of inhaler adherence? Table 4 summarises nine main barriers and several recommendations for improvement, formulated considering the existing methodological advice for observational research [26] and adherence

TABLE 4 Barriers and recommendations for a solid evidence base on asthma inhaler adherence determinants

Current limitations	When conducting a new study
Heterogeneity in variable selection, definition and measurement, study design and statistical analyses	Consider previous similar studies when selecting determinants and behaviours Clarify variable definitions in relation to previous studies Consider using established measures of adherence behaviours and determinants if available Consider using established study designs and data analysis methods if appropriate
Limited theoretical basis for variable selection and lack of an integrated theoretical approach	Use existing behavioural theory to select variables Focus on testing multi-determinant models instead of a few preferred determinants If testing new models, clarify the choice and relationships with existing theories
Lack of robust study designs for causal inferences in most studies	Prioritise the use of repeated measure longitudinal designs Assess adherence determinants prior to behaviours Choose time lags in which causal influence is likely Control for other possible causal influences
Low or medium quality participant selection in some studies	Use prior literature to decide on clear inclusion criteria that allow comparisons with other studies Employ systematic procedures for participant selection Report participant selection procedures clearly and completely
Insufficient description of variable definitions and measurement	Provide a clear rationale and description for included variables Provide comprehensive descriptions of measurement tools or methods in the manuscript or supplementary materials
Low quality of measurement	Select or develop psychometrically sound measures Examine psychometrics as preliminary analyses Report results of psychometric evaluation
Sources of bias rarely addressed	Reflect on possible sources of bias (*e.g.* response, recall, surveillance bias) and take steps to minimise their effect
Study size rarely addressed	Consider the probability of type I and type II errors given the research question, population and resources available
Low or medium quality data analysis procedures in most studies	Consult methodological literature relevant for the intended analyses Perform and report on preparatory analyses (*e.g.* missing data) Do not group continuous data unless solid justification exists and analyses are performed with both continuous and grouped data Control for possible confounders and justify their selection Adjust for sampling strategy and hierarchical data structures

research [93] in order to invite further dialogue on this topic. The first barrier identified was the substantial study heterogeneity, not only in sample characteristics but also in variable selection, definition, measurement, study design and statistical analyses. Secondly, the studies lacked a unifying theoretical approach which led to differences in variable selection and, thus, to many determinants being examined only in single studies, often without a theoretical justification. Finally, the results gave limited insight regarding causal influences, as only two studies involved repeated measures of adherence [65, 81] and only 17 studies measured determinants before adherence. Moreover, many studies showed limitations in the six quality criteria assessed, although several studies performed well (Supplementary material 4). To address these barriers, we endorse the practical recommendations provided in STROBE [26] and provide brief advice based on STROBE and our experience in this review. Theoretical frameworks and taxonomies of adherence behaviours and determinants are available [27, 94, 95] and should be used more extensively. Conducting research on common theoretical and measurement foundations would allow the field to progress from identifying bivariate or multivariate associations in heterogeneous prediction models towards testing more homogeneous and comprehensive causal models.

Beyond the practical recommendations for future inhaler adherence studies, our review also highlighted the need to develop consensus on several methodological aspects. The fact that few studies reported on variable

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definitions, sources of bias and study size suggests that many researchers might not be aware of their importance for observational studies. The latter two aspects were unrelated to the overall study quality, suggesting that even in higher quality studies, bias and sample size are not systematically considered. More discussion is needed among methodologists and researchers to establish their relevance and specify concrete steps to implement them. These results add to previously expressed concerns regarding the lack of validated tools to evaluate quality in observational studies [23], and highlight a general need for further detailing and clarifying methodological guidelines in this area. Our experience with coding quality exposed the difficulties of assessing these broad criteria given the diversity of designs and brief descriptions permitted by space constraints. We would, therefore, encourage adherence-specific methodological guidelines that can be reported in a standard format as supplementary material in published studies.

Our review has several limitations. First, interpreting the summary based on both adjusted and unadjusted results requires caution, as multivariate analyses control for different sets of confounders, while bivariate analyses ignore any additional influences and may reflect biased relationships. We chose to prioritise adjusted over unadjusted data to avoid this, but we acknowledge that the findings may be biased and we recommend the use of theory-based models to provide more valid and replicable results. Secondly, inter-rate reliability for quality scores was low, which may reflect suboptimal study reporting, difficulty of applying the criteria based on the given definitions, or insufficient training of coders. Although the coders were able to reach consensus, these difficulties illustrate the need for more concrete definitions applicable across studies by coders with diverse research backgrounds. Thirdly, we focused our review on developed nations, as the contribution of determinant dimensions on adherence may be different in developing nations, particularly regarding access to care [86], but only 19 studies were excluded based on this criterion. Finally, meta-analyses were not possible due to the substantial heterogeneity; therefore, we opted for a qualitative summary and for identifying methodological improvements that would make future studies more amenable to meta-analytic approaches.

Our findings suggest that adults with asthma implement controller use recommendations better if they believe more strongly in the necessity of using inhalers, and possibly if they hold other positive beliefs and less concerns about using inhalers. Younger adult patients may be more at risk of nonadherence. Other patient-, condition- and therapy-related factors are either mostly unrelated to adherence or partly studied, and little is known about the role of social, economic and healthcare factors. Initiation and discontinuation of controller use and reliever use behaviours were scarcely explored. Moreover, the methodological limitations identified diminish the strength of current evidence. Our key recommendations for further research are to improve methodology and use established theoretical frameworks, which should enable the development of a cumulative evidence base of causes of nonadherence to asthma inhalers among adults.

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4.3. ARTICLE 3:

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PROTOCOL OPEN

Assessment of the safety of long-acting β_2-agonists in routine asthma care: the ASTRO-LAB protocol

Eric Van Ganse[1,2], Nathalie Texier[3], Alexandra L Dima[4], Laurent Laforest[1], Montserrat Ferrer[5], Gimena Hernandez[5,6], Stéphane Schuck[3], Sandrine Herbage[1], Delphine Vial[7], Marijn de Bruin[4,8] and the ASTRO-LAB group

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BACKGROUND

The safety of long-acting β_2-agonists (LABAs) remains controversial in asthma, particularly in children, which led regulators to contraindicate LABAs as a single agent in asthma treatment.[1] Current evidence regarding the safety of LABAs in combination with inhaled corticosteroids (ICs), based on meta-analyses of randomised clinical trials (RCTs), is less consistent. Recently updated meta-analyses for formoterol and salmeterol failed to reassure on safety.[2,3] Despite the absence of evidence of serious risk with LABAs associated with ICs, the precision of results was low owing to infrequent outcomes. Furthermore, RCTs include highly selected populations, and they are not properly designed to assess infrequent and/or long-term adverse events in actual conditions of drug use.[4]

Evidence is also limited in the observational context. A recent systematic review assessing the risk of LABAs associated with ICs, compared with ICs alone, did not indicate any increased risk for emergency visits or hospital admissions.[5] However, no reliable conclusions could be drawn neither in children, nor on potential differences between LABAs associated with ICs, in fixed-dose combinations, and in two separate canisters, due to the lack of published data for these specific issues. This review also highlighted the scarcity of prospective studies and the lack of data on drug adherence. Most of the observational studies were based on claims databases, providing only a partial assessment of drug exposure. There is an evidence gap, as detailed and valid exposure data are needed. For instance, irregular use of ICs in persistent asthma is a well-known source of exacerbations.[6] Thus, there is a need to explore potential risks associated with LABAs in real life, with more extensive assessments of patterns of use, including ICs concomitant therapy, asthma control and exacerbations over time.

AIMS

The ASTRO-LAB project aims to provide new evidence about the safety of LABAs in children and adults in routine clinical care. Its main objective is to investigate with prospective data whether asthma patients receiving LABAs are at a higher risk of severe asthma exacerbations (SAEx), taking into account baseline differences in severity. Potential variations of respective drug exposures to LABAs and ICs over time, using complementary data sources will also be investigated. In addition, it will be verified whether differential adherence to LABAs and to ICs is a possible mechanism of increased risk of SAEx and other asthma outcomes in patients using these drugs in two separate canisters. A key question that ASTRO-LAB aims to explore is whether the potential LABA-associated risk can be explained by suboptimal adherence to ICs.

METHODS

ASTRO-LAB is a 24-month prospective observational study in asthma, conducted in France and in the United Kingdom (UK).

Participants

ASTRO-LAB will include persistent asthma patients treated in primary care, equally distributed between children (6–17 years) and adults (18–40 years). Inclusion of patients will be performed between May 2013 and February 2015 in the three steps described hereunder (Figure 1).

Patient pre-selection. British patients aged 6–40 years with at least one LABA and/or IC prescription during the past 12 months will be pre-selected from The Health Improvement Network, which is a collection of pseudo-anonymised electronic primary care medical records[7] collected in approximately 550 general practices in the UK, with 3.6 million active patients.

In France, more than 700 general practitioners will perform a preliminary selection of asthma patients aged 6–40 years, with at least two prescriptions of LABAs and/or ICs during the past 12 months, regardless of associations with other controllers. General practitioners will record all asthma-related prescriptions during the past 12 months. A similar pre-selection will be conducted in community pharmacies: pharmacists will record all asthma-related prescriptions available during this time interval for patients aged 6–40 years, with at least one dispensing of LABAs and/or ICs and two pharmacy visits during these past 12 months.

Patient eligibility. From the pre-selection database, the research team will select, in both countries, patients on the basis of an additional inclusion criterion, i.e., $\geqslant$6 months of prescribed coverage of one of the following therapy patterns during the past 12 months: ICs without LABAs, LABAs without ICs, LABAs and ICs as separate inhalers (LABAs+ICs) or fixed-dose combinations (figures available in the Supplementary Information). No change of therapy pattern will be allowed during the last 12 months.

The following exclusion criteria will be checked in pre-selection databases (for the UK) or during enrolment visit by a general practitioner or a pharmacist (for France): chronic oral corticosteroid use ($\geqslant$15 consecutive days during the past 3 months), history of omalizumab therapy and/or any other concomitant respiratory disease (chronic obstructive pulmonary disease, cystic fibrosis, pulmonary fibrosis, bronchiectasis and tuberculosis). In case of SAEx within 2 months before inclusion, patients will be re-contacted 4 months later, so that they will be free of recent SAEx when entering the cohort.

[1]Lyon Pharmaco-Epidemiology Unit- UMR 5558 CNRS-Claude Bernard Lyon 1 University, Lyon, France; [2]Respiratory Medicine, Croix-Rousse University Hospital, Lyon, France; [3]Kappa Santé, Paris, France; [4]Amsterdam School of Communication Research ASCoR, University of Amsterdam, Amsterdam, The Netherlands; [5]IMIM—Hospital del Mar Medical Research Institute, Barcelona, Spain; [6]Universitat Autónoma de Barcelona, Barcelona, Spain; [7]Cegedim Strategic Data Medical Research Limited, London, UK and [8]Aberdeen Health Psychology Group, University of Aberdeen, Aberdeen, UK.
Correspondence: E Van Ganse (eric.van-ganse@univ-lyon1.fr)
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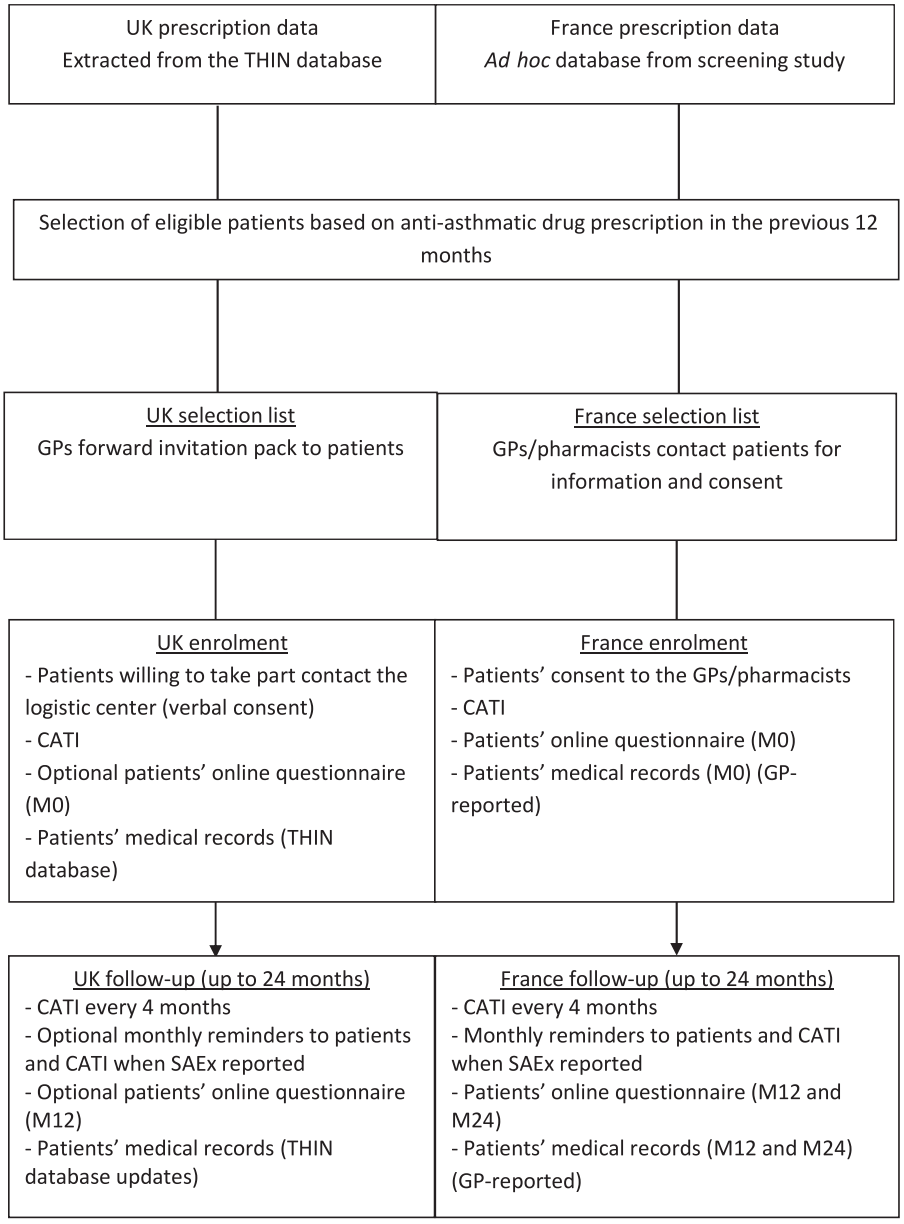

Abbreviations: CATI, Computerised Assisted Telephone Interview; GP, general practitioner; SAEx, severe asthma exacerbation; THIN, The Health Improvement Network.

Figure 1. Study flowchart for patient enrolment and follow-up.

Patients' enrolment. In France, general practitioners and pharmacists will invite eligible patients to participate in the study during a general practitioner or pharmacy visit. In the UK, practices will forward postal invitation packs to eligible patients, who will be invited to contact the logistic centre by phone or online. A consent acknowledgement will be collected before any data collection.

Data collection

Data collection schedule for patient-, caregiver- and health care professionals (HCP)-reported data is summarised in Figure 2.

Patient-reported data

Computerised-assisted telephone interviews and text messages: Trained interviewers will administer computerised-assisted telephone interviews (CATIs) to patients aged 12–40 years (parents/caregivers of patients aged 6–11 years) immediately after inclusion and every 4 months, to assess asthma control, asthma medication used during the past 4 months and SAEx occurrence. If a SAEx is reported, the asthma control- and medication-related questions will be repeated for the period before the SAEx, followed by additional questions (triggers, management). Patients will also receive monthly text messages inquiring about potential new SAEx; a positive answer will be followed by an additional CATI including the above-mentioned SAEx-related questions.

Online surveys: Patients and/or parents/caregivers will be requested to complete online surveys (adapted to age-specific requirements) at 12-month intervals on determinants of medication adherence, self-monitoring of symptoms, triggers and exacerbations management, quality of inhaler technique, quality of life, demographic and other background characteristics.

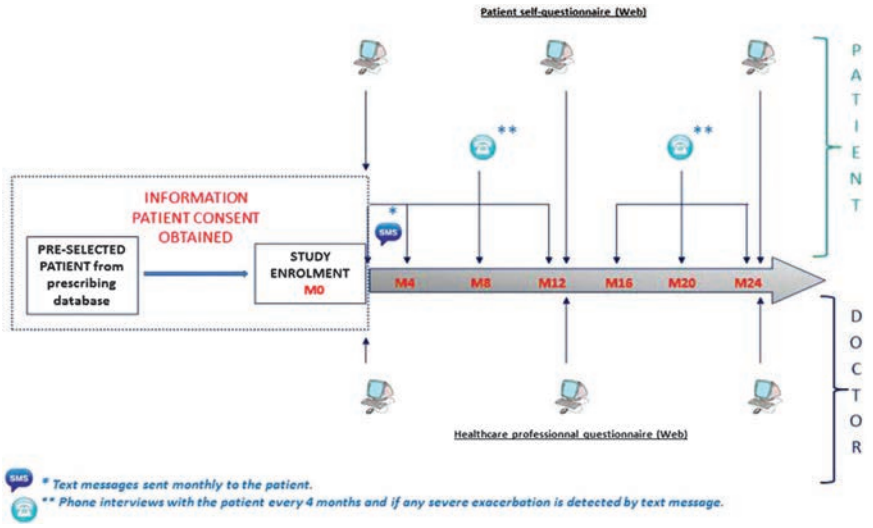

Figure 2. Summary of patient- and physician-reported data at inclusion and during follow-up.

HCP-reported data. HCPs will complete online surveys on their routine asthma care and determinants of adherence support.

Electronic medical records/claims data. The Health Improvement Network data will be available in the UK, whereas refill and hospitalisation data will be obtained from the National Health Insurance System (SNIIRAM) in France.

Measures

We present the main characteristics of the measures relevant to the primary research question regarding the safety of LABAs.

Outcomes. The primary outcome will be the occurrence of SAEx,[8–10] operationalised as occurrence of patient-reported courses of oral corticosteroids (⩾3- day duration), unscheduled asthma-related medical contacts, emergency room visits, hospital admissions and death.

The secondary outcomes will be asthma control, measured with validated questionnaires—symptoms only Asthma Control Questionnaire (ACQ-5)[11] and the Royal College of Physicians three questions,[12,13] as well as the five-level European Quality of Life—5 Dimensions (http://www.euroqol.org/about-eq-5d/publications.html (25 November 2013)). For the latter, French and UK valuation set will be applied to estimate utilities in French and English participants, respectively.

Medication use and adherence. Medication use will be assessed via CATIs for each daily inhaled medication separately, with questions referring to different time intervals and behaviours: number of doses used the day before the interview, number of days with 0% and 100% adherence during the previous 7 days, number of days of non-use during the previous 4 weeks, treatment interruptions longer than a week in the previous 4 months, and medication overuse (for a specific time interval or occasional) in the previous 4 months. Patient/caregiver-reported drug exposure and adherence will be computed via algorithms developed in preliminary analyses.

Therapy patterns, sample size and planned analyses

Studied exposure groups will be based on four initial therapy patterns. Preliminary results on pre-selected populations revealed that, for instance, only 2.4% of patients were prescribed LABAs without ICs in France, and virtually none in the UK. Given these low frequencies, patients under LABA monotherapy would be merged with those receiving ICs and LABAs as separate canisters, after having preliminarily verified their comparability. Hence, three groups have been considered for sample size power computation: LABAs with ICs in separate canisters or in monotherapy, LABA/ICs fixed-dose combinations and ICs without LABAs.

Sample size. Sample size computation for required power was based on differences in binomial proportions of SAEx between the reference ICs without LABAs group and LABAs with ICs in separate canisters or in monotherapy group. The hypothesis for the outcome frequency (24%) was based on asthma-related oral corticosteroid courses reported by patients during a 12-month period in a pharmacy-based study conducted in 2007 in ICs-treated patients.[14] This hypothesis is conservative, as it may underestimate the true frequency of SAEx, which not only consider oral corticosteroid courses but also hospitalisations, unplanned medical contacts and death. Sample size calculations were based on the expected 1.3-fold higher frequency SAEx between the ICs without LABAs group and the other two groups. Considering a bilateral approach and balanced counts between groups, it was calculated that a total of 2,200 patients would be required given a statistical power of 80%, at a significance level of 5%, with a potential 20% loss to follow-up.

Planned analyses

Safety analyses: *Between-group comparisons*. As first approach, the time to the occurrence of the first SAEx will be compared between the initial exposure groups (ICs without LABAs group as reference) with survival analyses (Kaplan–Meier, Cox Model). The total number of SAEx per patient during a 12-month period will be also compared using Poisson regression.

Cohort analyses with time-dependent variables. Patients' actual exposure to LABAs and ICs may change over follow-up owing to the prescriber or patient. In these analyses, such changes will be taken into account. Time-dependent variables, reflecting LABAs or ICs exposure over follow-up, will be constructed. The association between exposure to LABAs over time and the occurrence of SAEx will be investigated, after adjusting in particular for concomitant exposure to ICs. Survival analyses and hierarchical longitudinal models will be applied. Different markers of drug exposure and adherence will be successively explored.

Case–crossover study and nested case–control study approaches. As in a case–crossover design patients are their own controls, LABAs and ICs studied drug exposure patterns occurring just before a SAEx (case period) will be compared with those observed during a preceding regular CATI with no SAEx reported (control period), thus eliminating any potential influence of patients fixed characteristics. A nested case–control study approach will be also considered.

Adjustment for asthma baseline severity. Analyses will be adjusted for the different markers of asthma baseline severity, as it is a potential confounding factor when assessing LABA-related risk, except for the case–crossover approach.

Complementary analyses will be considered with the French patients, using claims data.

Adherence analyses: The relationships between medication adherence determinants and behaviours and asthma-related outcomes will be investigated based on a theoretical model of asthma management.

These analyses will further examine the hypothesis that LABA risk in asthma may be partly owing to suboptimal adherence to ICs, with initial symptoms masked by concomitant LABA use, leading to severe and sudden SAEx. Moreover, they also aim to identify important and changeable causes of nonadherence from a patient, caregiver and HCP perspective, with a view to improving adherence support in primary care.

Ethics

ASTRO-LAB study has been approved by Ethics and Regulatory Boards in both countries.

DISCUSSION

ASTRO-LAB presents several innovative aspects that will allow a unique perspective on LABA safety and asthma management, in real-life conditions. Data will be collected from complementary sources to assess patients' drug exposure. This will allow assessing more elaborated markers of drug exposure and adherence to check the robustness of our findings.

The direct assessment of patients' adherence to therapy, including potential changes over time, will enable us to distinguish the confounding role of inadequate adherence to ICs from LABA-specific risk, as differential adherence between LABAs and ICs may contribute to the occurrence of SAEx for patients receiving both classes in separate canisters.

Methodological limitations and practical difficulties must be acknowledged. The scarcity of patients prescribed LABAs in monotherapy may prevent any reliable conclusion for this non-recommended therapy pattern.[6,15] Pre-selection process between countries will differ: pre-existing prescribing database in the UK versus an *ad hoc* prescription register collected by physicians themselves purposely for the study. This difference is owing to practical access to existing prescribing data (possible in the UK only, in the context of ASTRO-LAB). Nevertheless, the same inclusion/exclusion criteria will be eventually applied to all patients in both countries. A potential bias inherent to prospective studies will be that patients' interaction with field study procedures (for example, questionnaires and CATIs) may modify their behaviours and beliefs regarding medication intake. Nonetheless, this potential bias will influence all treatment groups equally.

Practical difficulties have to be addressed in this multifaceted project. Different national regulatory requirements and health care systems between France and the United Kingdom compelled us to consider specific recruitment processes for each country, while attempting to maintain the two processes as similar as possible to minimise bias.

Given its unique perspective on asthma care, ASTRO-LAB will provide new information on LABA safety of substantial interest to regulators, HCPs, patients and the scientific community. Moreover, developing new methods of assessing drug exposure and adherence will make a valuable contribution beyond the field of asthma care. The investigation of multifaceted insight into asthma management in two different medical systems may be informative for the improvement of asthma care.

Further information can be found in the Supplementary Information.

CONTRIBUTIONS

All the authors have been actively involved in the study at different capacities. EVG (guarantor) was involved in the development of ASTRO-LAB. He is responsible for the scientific coordination of the project and has been involved in all methodological and practical aspects. He participated in the drafting of the manuscript. NT and SS are in charge of ASTRO-LAB patient and general practitioner (GP) recruitments in France, data collection via CATI, online questionnaires and text messages and data management. They took part in the creation of the project. They participated in the drafting of the protocol. MdB was involved in the design, and ALD in refining, of ASTRO-LAB study design. MdB and ALD developed and managed the procedures for assessing patient-reported outcomes, self-management behaviours and quality of care. MdB and ALD contributed to drafting the manuscript. MF and GH contributed to study conception by summarising and updating published evidence. They participated in study design, being specially involved in the ASTRO-LAB analyses strategy and health-related quality of life measurement. They also critically revised the protocol. LL drafted the manuscript and participated in the development of the study protocol, with contributions on methodological aspects. SH coordinates the ASTRO-LAB project at a management level and contributes to methodological and practical aspects. DV is in charge of the management of UK patients and practices recruitment and The Health Improvement Network (THIN) data set extractions for ASTRO-LAB analyses. All the authors critically reviewed the manuscript.

COMPETING INTERESTS

During the past 5 years, EVG has received funds for research, participations to congresses and consulting from ALK-ABELLO, BIF, MSD, ASTRA-ZENECA and CHIESI. During the past 5 years, EVG has been the main investigator of epidemiologic studies sponsored by GSK, MSD, CHIESI and PFIZER. The other authors declare no conflict of interest.

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REGISTRATION

The project is registered in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) registry.

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4.4. ARTICLE 4:

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Original Paper

Validity of the EuroQol (EQ-5D-5L) in assessing Quality of Life in Adults with Asthma

Gimena Hernandez[1,2,3], M.D., M.P.H.; Olatz Garin[1,3,4], MPH, PhD; Alexandra L Dima[5], PhD; Angels Pont[1,3], BSc; Marc Martí Pastor[1,2,3], MD, MPH; Jordi Alonso[1,3,4], MD, PhD; Eric Van Ganse[5,6,7], PhD; Laurent Laforest[6], MD, PhD; Marijn de Bruin[8], PhD; Karina Mayoral[1,2], MPH; Vicky Serra-Sutton[3,9], Ph.D.; Montse Ferrer[1,2,3], MD, PhD; ASTRO-LAB Group[10]

[1]IMIM - Hospital del Mar Medical Research Institute, Health Services Research Group, Barcelona, Spain
[2]Universitat Autònoma de Barcelona, Department of Paediatrics, Obstetrics and Gynaecology and Preventive Medicine, Barcelona, Spain
[3]Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain
[4]Pompeu Fabra University (UPF), Barcelona, Spain
[5]Group author, see list of collaborators, ,
[6]Pharmaco-Epidemiology Lyon (PEL), Claude-Bernard University Lyon1, Lyon, France
[7]Respiratory Medicine, Croix-Rousse Hospital, CHU-Lyon, France
[8]Institute of Applied Health Sciences, University of Aberdeen, Scotland, United Kingdom
[9]Agència de Qualitat i Avaluació Sanitàries de Catalunya (AQuAS), Barcelona, Spain
[10]See list of ASTRO-LAB collaborators, France, United Kingdom, Spain

Corresponding Author:
Montse Ferrer, MD, PhD
IMIM - Hospital del Mar Medical Research Institute
Health Services Research Group
Dr. Aiguader 88
Barcelona, 08003
Spain
Phone: 34 933160763
Email: mferrer@imim.es

Abstract

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KEYWORDS

Health Related Quality of Life, Asthma, Validity, EQ-5D-5L, EuroQol

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Abstract

Background: The EQ-5D, developed in 1990 by the EuroQoL group, is one of the most widely employed generic tools to measure Health-Related Quality of Life (HRQoL) and considered suitable for asthma patients. In 2009, the EuroQol Group developed a new EQ-5D version to overcome limitations related to its consistently reported high ceiling effect. To become more sensitive for assessing HRQoL in further patient populations, the number of responses was increased from 3 to 5 levels (EQ-5D-5L). Moreover, the availability of well-defined requirements for its online administration allows the use of EQ-5D-5L to monitor HRQoL in e-Health programs. To date, there are no studies evaluating metric properties of the new EQ-5D-5L in asthma patients.

Objective: To examine the distribution, construct validity, and reliability of the new EQ-5D-5L questionnaire administered online to adults with asthma.

Methods: Evaluation of asthma patients (18-40 years) from primary care setting in France and England, who self-completed the EQ-5D-5L questionnaire online. Inclusion criteria were persistent asthma defined as ≥6 months of prescribed drug of Inhaled Corticosteroids (ICs) and/or Long-Acting Beta-Agonists (LABAs) during the 12 months prior to inclusion. The EQ-5D index was obtained by applying the English preference value set for the new EQ-5D-5L and the French 3L-5L crosswalk value set. Both value sets produced single preference-based indices ranging from 1 (best health state) to negative values (health states valued as worse than death), where 0 is equal to death, allowing the calculation of Quality-Adjusted Life-Years (QALYs). Responses to dimensions and index distribution, including ceiling and floor effects, were examined. Construct validity was assessed by comparing means of known groups by analyses of variance and calculation of effect sizes.

Results: Of the 312 patients answering the baseline online survey, 290 completed the EQ-5D-5L (93%). The floor effect was null and the ceiling effect was 26.5%. Mean EQ-5D-5L index was 0.88 (SD 0.14) with English value set and 0.83 (SD 0.19) with French 3L-5L crosswalk value set. In both indices large effect sizes were observed for known groups defined by Asthma Control Questionnaire (1.06 and 1.04, $P<0.001$). Differences between extreme groups defined by chronic conditions ($P=0.003$ and $P=0.002$), Short-Acting Beta-Agonists (SABA) canisters in the last 12 months ($P=0.05$), or SABA use during the previous 4 weeks ($P=0.034$ and $P=0.007$) were of moderate magnitude with effect sizes around 0.5.

Conclusions: The new EQ-5D-5L questionnaire has an acceptable ceiling effect, a good construct validity based on discriminant ability for distinguishing among health-related known groups, and a high reliability, supporting its adequacy for assessing HRQoL in asthma patients. The completion of the EQ-5D-5L by most of the online respondents supports the feasibility of this administration form.

Keywords: Health-Related Quality of Life; Asthma; Validity; EQ-5D-5L; EuroQol.

Introduction

The impact of asthma on the patient´s health has been traditionally assessed by either clinical markers or functional tests [1]. Patient-reported outcome measures (PROMS) such as symptom control or health-related quality of life (HRQoL) have shown to be useful for clinical management, understanding disease impact on patients' functional status and well-being, and cost-effectiveness analyses [2]. Due to these reasons, international guidelines for asthma diagnosis and treatment have emphasized that treatment goals should include the improvement of the patients´ HRQoL [3].

In asthma, disease-specific HRQoL measures have been more widely used than generic ones, since they could be more sensitive. Adding generic HRQoL domains important to people with asthma has been proposed [4], because asthma-specific HRQoL instruments measure similar contents to those covered by asthma control questionnaires [5, 6] such as symptoms and activity limitations. Generic HRQoL instruments are broad measures that can be applied in patients with various conditions and in the general population. The EQ-5D, developed in 1990 by the EuroQoL group, is one of the most widely employed generic tools due to its low respondent burden, good psychometric properties and econometric development [7, 8, 9]. In addition, the availability of well-defined requirements for its online administration by multiple devices such as personal computer, tablet or smartphones, makes this instrument adequate for monitoring HRQoL in e-Health programs [10].

The EQ-5D was considered a suitable generic measure in a systematic review [11] of PROMS for asthma patients. This health status measure allows the calculation of Quality-Adjusted Life-Years (QALYs) when society preferences are applied, and cost-utility analysis in economic evaluations [12-14]. However, to the best of our knowledge, there are only three studies that evaluated its psychometric properties in patients with asthma [15-17]. Garrath et al. [16] showed a moderate EQ-5D association with asthma-specific HRQoL instruments and external variables, such as smoking status and education level. Oga et al. [15] and McTaggart-Cowan et al. [17] reported a high ceiling effect (59% and 50% of the sample with the maximum score, respectively) questioning the usefulness of the EQ-5D in asthmatic patients. In fact, limitations related to the high ceiling effect have also been consistently reported for the EQ-5D in other chronic conditions, such as COPD [18], osteoarthritis [18], diabetes [19] and coronary heart disease [20].

The traditional EQ-5D descriptive system, composed of five dimensions with three levels of severity, defines 243 distinct health states resulting from all the possible combinations (i.e. 3^5). This is a low number compared with other generic preference-based instruments, such as the Health Utilities Index [21] or the SF-6D [22] with 972,000 and 18,000 possible combinations, respectively. To improve its sensitivity, the EuroQol Group developed a new EQ-5D version, by increasing the number of responses from 3 to 5 levels, known as EQ-5D-5L with 3,125 health states (i.e. 5^5) [23].

The new EQ-5D-5L has already been tested in some disease-specific samples, such as patients with cancer [24, 25] and with hepatitis [26], showing a better discrimination capability and lower ceiling effects than the traditional 3-level version (11% vs 17% [24], 9.7% vs 16.8% [25], and 21.6% vs 38.3% [26].) However, to date, there are no studies evaluating metric properties of the new 5-level EQ-5D in asthma patients. The aim of this study was to examine the distribution, construct validity, and reliability of the new EQ-5D-5L administered online to adults with asthma.

Methods

Setting and study population

For this study, we analyzed baseline data of adults (aged 18-40 years) enrolled in the ASTRO-LAB cohort who completed the EQ-5D-5L questionnaire. The ASTRO-LAB project is a prospective longitudinal study of asthmatic patients designed to provide new evidence regarding the safety of Long Acting Beta Agonists (LABAs) in routine primary care in France and the United Kingdom (UK). Details of the study were described elsewhere [27].

Inclusion criteria were: persistent asthma and age lower than 40 years. Patients were considered to have persistent asthma when they had ≥6 months of prescribed treatment with Inhaled Corticosteroids (ICs) and/or LABAs during the 12 months prior to inclusion. Persistent asthma requires controller therapy on a regular basis, while intermittent asthma can be treated with rescue medication as needed. The ASTRO-LAB persistent asthma definition was based on a minimal prescription duration level of anti-asthmatic drugs because this method is considered less biased than the practitioner's classification of asthma, and it is frequently used in database studies [28]. The ASTRO-LAB project's age limit was chosen to minimize the recruitment of patients with other comorbid conditions frequent at older ages, most importantly COPD, often overlapped and difficult to exclude without specific tests.

Exclusion criteria were: chronic oral corticosteroid use (≥15 consecutive days 3 months before inclusion), history of omalizumab therapy, and/or any other concomitant chronic respiratory disease (chronic obstructive pulmonary disease, cystic fibrosis, pulmonary fibrosis, bronchiectasis or tuberculosis). Due to ASTRO-LAB's main focus being LABAs safety, the abovementioned criteria based on administration of other medications aimed at avoiding confounding with their adverse effects, but this meant that most patients with severe persistent asthma were excluded.

The ASTRO-LAB study has been approved by the Ethics and Regulatory Boards in France and the UK, and was conducted in accordance with the Declaration of the World Medical Association. In France, approval was obtained from CCTIRS (Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine dela santé) on November 21st, 2012 (Dossier N°12702); and the authorization from CNIL (Commission Nationale d'Informatique et Liberté) was obtained in May 17th, 2013 (DR-2013-264). In UK, according to the UK Research Governance Framework, the study was submitted to The West London Research Ethics Committee (REC) and final approval was obtained on the 15th April 2013 (REC Reference 12/LO/20139). Following the UK regulatory process, ASTRO-LAB consortium submitted the protocol to National Institute for Health Research Clinical Research Network (NIHR CRN) in order to launch the review by PCT (Primary Care Trust) local sites. The first local approval was granted by the West London Primary Care Consortium (WLPC) on May the 22nd 2013. Informed consent was obtained from all participants prior to inclusion.

Measurement instruments

Clinical data were extracted from medical records, and patient-reported information was obtained by two administration modes: 1) patient-completed online survey, and 2) telephone interviews with patients performed by trained interviewers. The EQ-5D-5L was only administered in the online survey.

Clinical data

Information on age, gender, body mass index (BMI), comorbidity and treatment prescribed was obtained: in France, general practitioners completed an online survey at patient inclusion, while in the UK this information was directly extracted from medical records. The history of four associated pathologies (allergic rhinitis, nasal polyps, anxiety/depression, and gastro esophageal reflux), was registered and transformed into a count variable. The total number of Short-Acting Beta Agonist (SABA) canisters prescribed in the 12 months prior to inclusion was transformed into a variable of three categories: 0, 1-4, and 5 or more canisters.

Patient-completed online survey

Patients received instructions during the recruitment contact to self-complete an online survey, which included the EQ-5D-5L to measure HRQoL, and socio-demographic data such as their highest level of education and current work situation, among others. A sample screen shot of the online survey completed by the patients is available in the supplementary material.

The EQ-5D-5L is a brief, multi-attribute, generic, health status measure composed of five questions with Likert response options (descriptive system) and a visual-analogue scale (EQ-VAS). The latter asks patients to rate their own health from 0 to 100 (the worst and best imaginable health, respectively). The descriptive system covers five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with five levels of severity in each dimension (no problems, slight problems, moderate problems, severe problems, unable to perform/extreme problems).

Preference value sets used to obtain the index of the EQ-5D-5L were: the 3L-5L crosswalk from the French 3L version [29], and the new EQ-5D-5L value set from England [30]. In both cases, single preference-based indices were produced ranging from 1 (the best health state) to negative values (health states valued as worse than death), where 0 is equal to death. The minimal important difference for the EQ-5D index was estimated as 0.07 [31].

Telephone Interviews

The telephone interviews were computer-assisted to standardize the process. Trained interviewers administered questions to patients about their asthma control and treatment use, among others. Asthma control is defined as the extent to which the manifestations of asthma can be observed in the patient, or have been reduced or removed by treatment [32, 33]. It reflects the suitability of the asthma treatment.

The Asthma Control Questionnaire (ACQ) is composed of 7 items: the top scoring 5 symptoms, FEV_1% predicted, and daily rescue bronchodilator use. A shorter version called ACQ–symptoms only [34] was developed to use when it is not feasible to collect data about the last two items, as in ASTRO-LAB. It assesses the frequency of the five asthma symptoms during the previous week on a 7-point Likert scale (0=no impairment, 6= maximum impairment). The overall score, calculated as the mean of item responses, ranges from 0 to 6. A score <0.75 was defined as well controlled; 0.75–1.5 as intermediate control; and >1.5 as not well-controlled asthma [35]. The results generated by the short versions have shown to be very similar to those of the complete ACQ, as well as its measurement properties (reliability, responsiveness, internal consistency, construct validity and interpretability) [34].

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”.

Analytic Strategy

Sample characteristics were described by calculating percentages, or means and standard deviations, according to the variable type (detailed in tables and figures). To examine the non-response bias, subjects who completed the online survey were compared to those subjects that had not completed this survey by T test and Chi square.

We calculated percentages of responses to each EQ-5D-5L dimension. To examine the distribution of EQ-5D index, we calculated statistics of central tendency, dispersion, asymmetry, and tail extremity, as well as the proportion and 95% Confidence Intervals (95% CI) of the individuals in the best possible (ceiling) and the worst possible (floor) health states [36]. To assess reliability based on internal consistency, the Cronbach’s alpha coefficient was estimated.

Construct validity examines whether the instrument adequately assesses the concept that it intends to measure [37], in this case HRQoL. The strategy to evaluate construct validity based on known groups consists of testing the ability of the instrument to discriminate among groups previously hypothesized as differing in the concept measured. The following variables were chosen to test the instrument’s capacity to discriminate, as it has been consistently shown that there are differences in HRQoL among groups defined by them [1, 15, 38,

39]: the number of chronic conditions (as an indicator of general health), number of SABA canisters prescribed in the previous year, frequency of SABA inhaler use during the previous 4 weeks, and ACQ scores (as three indicators of asthma control). Our hypotheses are that asthma patients with worse general health or less asthma control report worse HRQoL.

To evaluate the discriminative capacity of the EQ-5D index and EQ-VAS among the above mentioned known groups, mean scores were compared using one-way analysis of variance and the Tukey studentized range (honestly significant difference) test for post hoc comparisons; α was set at 0.05. To assess the magnitude of the differences Cohen's effect sizes were calculated. General guidelines define an effect size of 0.2 as small, 0.5 as moderate, and 0.8 as large [40]. Analyses were conducted using the statistical package SPSS12.

Results

Study sample

Of the 581 subjects with asthma aged 18-40 years composing the ASTRO-LAB cohort, 312 filled in the baseline online survey (53,7% online participation rate), but 22 of these did not complete the EQ-5D-5L questionnaire (7% of questionnaire non-response rate). Of the 290 who fulfilled the EQ-5D-5L, 11 were excluded because they had missing data on all the variables selected to define known groups; hence 279 patients were finally included in this analysis. Table 1 shows patients' baseline characteristics, comparing the included subjects with excluded ones (mainly due to not responding the online survey). Most of the included subjects were from France and had been treated with fixed-dose combinations of LABA and IC. More than half of them had completed a bachelor degree (66.9%) and 72.6% were employed in their usual jobs. These two variables were only available for patients included in the analysis, since they were recorded in the online questionnaire. Non-respondents were younger (29.8 vs 31.0 years old, $P = 0.029$), and presented higher ACQ mean scores (worse control) in comparison to respondents, but did not differ in BMI, treatment, number of other chronic conditions, SABA canisters prescribed last year, and frequency of SABA used in the previous 4 weeks.

Table 1: Characteristics of included and excluded subjects

		Included patients (n = 279)	Excluded patients (n = 302)	P
Age. mean (SD)		31.0 (6.7)	29.8 (6.7)	0.029
	< 25 years	62 (22.2%)	85 (28.1%)	0.103
	25 to 34 years	119 (42.7%)	133 (44.0%)	
	35 years or more	98 (35.1%)	84 (27.8%)	
Gender				
	Male	110 (39.4%)	128 (42.4%)	0.469
	Female	169 (60.6%)	174 (57.6%)	
Country				
	France	222 (79.6%)	264 (87.7%)	0.008
	UK	57 (20.4%)	37 (12.3%)	
	Missing	*0 (0.0%)*	*1 (0.3%)*	
Body Mass Index. mean (SD)		25,2 (6,2)	25.4 (5.8)	0.788
	Missing	*127 (45.5%)*	*107 (35.4%)*	
Treatment				
	Long-Acting Beta-Agonist (LABA)	11 (3.9%)	9 (3.0%)	0.180
	Inhaled Corticosteroids (ICs)	71 (25.4%)	60 (19.9%)	
	LABA + ICs in separate inhalers	37 (13.3%)	33 (10.9%)	
	Fixed LABA and ICs combination	160 (57.3%)	200 (66.2%)	
Other chronic conditions				

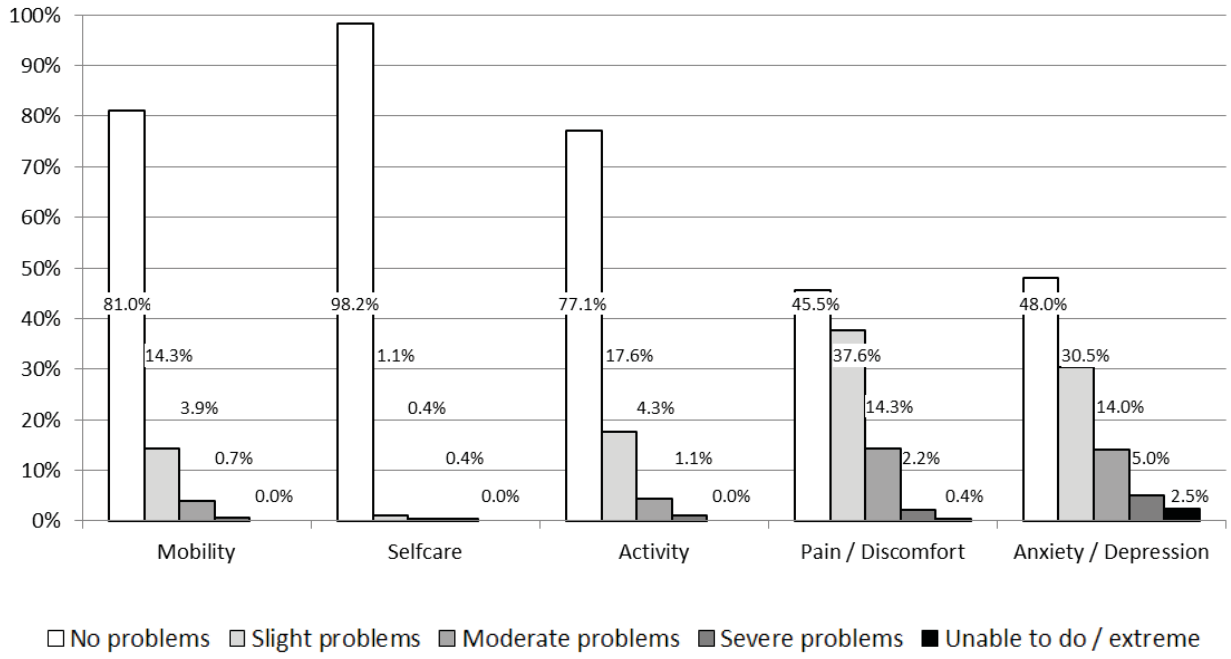
0 conditions	66 (41.5%)	80 (39.2%)	0.511
1 conditions	62 (39.0%)	91 (44.6%)	
2 conditions or more	31 (19.5%)	33 (16.2%)	
Missing	*120 (43.0%)*	*98 (32.5%)*	
Number of SABA canisters prescribed (last year)			
0 canisters	119 (53.6%)	133 (50.2%)	0.754
1 – 4 canisters	78 (35.1%)	100 (37.7%)	
5 canisters or more	25 (11.3%)	32 (12.1%)	
Missing	*57 (20.4%)*		
Frequency of SABA use reported by patient (last 4 weeks)			
Less than once a week	166 (61.9%)	171 (65.5%)	0.631
Once or twice every week	71 (26.5%)	60 (23.0%)	
Almost every day / Every day	31 (11.6%)	30 (11.5%)	
Missing	*11 (3.9%)*	*41 (13.6%)*	
Control of symptoms measured with ACQ, mean (SD)	1,01 (0,92)	1.35 (1.01)	< 0.001
Well-controlled (< 0.75)	119 (44.6%)	89 (34.1%)	< 0.001
Intermediate (0.75 – 1.5)	82 (30.7%)	63 (24.1%)	
Not well-controlled (> 1.5)	66 (24.7%)	109 (41.8%)	
Missing	*12 (4.3%)*	*41 (13.6%)*	
Highest education			
Secondary school or less	13 (4.7%)		
Sixth form or college	41 (14.9%)		
Bachelor degree	184 (66.9%)		
Postgraduate	37 (13.5%)		
Missing	*4 (1.4%)*		
Work status			
Employed at usual job	201 (72.6%)		
On light duty or some restricted work assignment	1 (0.4%)		
Paid leave/sick leave	4 (1.4%)		
Unemployed because of other reason	23 (8.3%)		
Student (school. college. university)	35 (12.6%)		
Keeping house/homemaker	7 (2.5%)		
Retired	0 (0.0%)		
On disability	6 (2.2%)		
Missing	*2 (0.7%)*		

SABA: Short-Acting Beta Agonist; ACQ: Asthma Control Questionnaire.

EQ-5D-5L distribution

Percentages of responses to each EQ-5D-5L dimension are shown in Figure 1. Most subjects reported 'no problems' in mobility (81%) and self-care (98.2%) dimensions, while only around half of the subjects endorsed this category in pain/discomfort (45.5%) and anxiety/depression (48.0%) dimensions. The 'extreme problems' category was endorsed by 1 subject for pain and 7 for anxiety/depression.

Figure 1. Percentage of patients' responses to each dimension



The distribution characteristics of EQ-5D-5L indices are shown in Table 2. In our sample, the EQ-5D-5L index constructed with the English value set ranged from 0.16 to 1, and from -0.074 to 1 when constructed with the French 3L-5L crosswalk value set. The mean was 0.88 (SD 0.14) for the English index and 0.83 (SD 0.19) for the French one. The Kurtosis statistics of 5.62 and 3.26, with skewness of -2.06 and -1.63, indicated that the asymmetry to the right part of the distribution and the tail extremity were greater in the index constructed with the English EQ-5D-5L value set. The floor effect was null and the ceiling effect was 26.5%. Cronbach's alpha coefficient was 0.69, achieving the recommended standard [36, 37].

Table 2. Distribution of EQ-5D-5L indices (n=279)

	EQ-5D-5L (English value set)	EQ-5D-5L (French 3L – 5L crosswalk value set)
Theoretical range	-0.28097 , 1	-0.530 , 1
Observed range	0.160 , 1	-0.074 , 1
Mean (SD)	0.88 (0.14)	0.83 (0.19)
Median [IQ range]	0.92 [0.84, 1.00]	0.91 [0.71, 1.00]
Kurtosis (SE)	5.62 (0.29)	3.26 (0.29)
Skewness (SE)	-2.06 (0.15)	-1.63 (0.15)
Floor effect	0%	0%
Ceiling effect	26.5%	26.5%
Cronbach´s α	0.69	

EQ-5D-5L Construct Validity

Results on construct validity of EQ-5D-5L based on known groups are shown in Table 3. Both EQ-5D-5L indices showed significantly different means for all known groups evaluated, while EQ-VAS only showed statistically significant differences among groups defined by ACQ scores. The mean EQ-5D-5L index for asthmatic patients decreased significantly with the increase in number of other chronic conditions from 0.91 to 0.82 with the English value set, and from 0.86 to 0.75 with the French 3L-5L crosswalk. The effect size between patients with none and those with 2 or more other chronic conditions were 0.62 and 0.60 (moderate) with EQ-5D-5L indices. Effect sizes were also moderate between extreme groups defined by SABA canisters prescribed in the previous year (0.58 and 0.46), and by SABA frequency during the last 4 weeks (both 0.5). Finally, among groups defined by ACQ scores, the effect size between well-controlled and intermediately-controlled asthma was moderate (0.44 and 0.47), and large between well- and not well-controlled asthma (1.06 and 1.04).

Table 3. Construct validity of EQ-5D-5L

	EQ-5D-5L index (English value set)		EQ-5D-5L index (French 3L-5L crosswalk)		EQ-VAS	
	Mean (SD)	**Effect Size [95% CI]**	**Mean (SD)**	**Effect Size [95% CI]**	**Mean (SD)**	**Effect Size [95% CI]**
Other chronic conditions						
0 chronic conditions	0.91 (0.11)	Ref.	0.86 (0.14)	Ref.	78.91 (14.85)	Ref.
1 chronic condition	0.89 (0.10)	0.14 [-0.21 , 0.48]	0.85 (0.15)	0.05 [-0.26 , 0.36]	79.08 (13.23)	0.06 [-0.25 , 0.37]
2 or more chronic conditions	0.82 (0.13)	0.62 [0.18 , 1.06]	0.75 (0.20)	0.60 [0.18 , 1.02]	72.94 (17.22)	0.37 [-0.04 , 0.79]
P-value	.002 [b.c]		.003 [b.c]		.125	
Number of SABA canisters prescribed (last year)						
0 canisters	0.89 (0.11)	Ref.	0.85 (0.15)	Ref.	78.84 (12.90)	Ref.
1 - 4 canisters	0.87 (0.14)	0.11 [-0.18 , 0.39]	0.82 (0.19)	0.19 [-0.07 , 0.45]	76.64 (17.93)	0.21 [-0.06 , 0.47]
5 or more canisters	0.81 (0.17)	0.58 [0.14 , 1.01]	0.76 (0.22)	0.46 [0.05 , 0.86]	72.00 (24.52)	0.47 [0.07 , 0.88]
P-value	.019 [b]		.031 [b]		.153	
Frequency of SABA use reported by patient (last 4 weeks)						
Less than once a week	0.82 (0.19)	Ref.	0.74 (0.23)	Ref.	71.45 (19.85)	Ref.
Once or twice a week	0.87 (0.15)	0.17 [-0.11 , 0.44]	0.81 (0.21)	0.29 [0.03 , 0.55]	78.08 (12.92)	0.07 [-0.19 , 0.32]
Almost every day / Every day	0.89 (0.12)	0.50 [0.11 , 0.89]	0.85 (0.16)	0.50 [0.15 , 0.84]	78.61 (16.26)	0.37 [0.03 , 0.71]
P-value	.034 [b]		.007 [b]		.070	
Asthma control measured with ACQ						
Well-controlled (< 0.75)	0.93 (0.10)	Ref.	0.91 (0.13)	Ref.	81.65 (13.80)	Ref.
Intermediate (0.75 – 1.5)	0.87 (0.11)	0.44 [0.15 , 0.72]	0.81 (0.15)	0.47 [0.22 , 0.73]	79.18 (11.92)	0.15 [-0.11 , 0.40]
Not well-controlled (> 1.5)	0.78 (0.19)	1.06 [0.74 , 1.38]	0.69 (0.24)	1.04 [0.75 , 1.32]	68.39 (20.23)	0.79 [0.51 , 1.08]
P-value	<.001 [a.b.c]		<.001 [a.b.c]		<.001 [b.c]	

a: First category (reference) vs second category
b: First category(reference) vs third category
c: Second category vs third category

Discussion

Principal Results

To the best of our knowledge, this is the first study evaluating metric properties of the new EQ-5D-5L in patients with asthma. In our study, this generic preference-based instrument showed an adequate distribution and reliability, with 26.5% of patients reporting the best possible health state (ceiling effect). It also showed good construct validity, given its capacity of discriminating among groups differing in the number of chronic conditions and symptom control. The distribution of the EQ-5D-5L index was less skewed than the previously-published one for the 3-level version due to its lower ceiling effect [15, 17].

Comparison of Online Participation Rate with Prior Work

In our study 53.7% of the participants completed the online baseline survey, and almost all of these completed the EQ-5D-5L (93%). The internet era has led to implementing online surveys, in order to take advantage of the known benefits such as completeness [41, 42], low expenses [43], and better data management. Nevertheless, there are still some barriers to online self-completion which could produce low response rates and selection bias. Although the reported participation rate varied a lot across online surveys [41, 44, 45], the 53.7% in our study is similar to those by other authors comparing between different modes of data collection, such as 64.2% and 53.3% participation rates reported by Kongsved [41] and Hohwu [46] studies. Remarkably, both studies showed a slightly better response rate with the paper mode: 73.2% versus 64.2% [41] and 56.2% versus 53.4% [46]. In the ASTRO-LAB cohort, the high overall respondent burden (participants were asked to respond to yearly online surveys, 4-monthly telephone interviews, and monthly text messages) could have affected the response rate.

Comparison with Prior Studies evaluating the EQ-5D in patients with asthma

This 26.5 % of patients with mild-to-moderate persistent asthma in the best possible health state in our sample, despite being higher than the 15% [36] established for ceiling effect, was considerably lower than that reported in prior studies using the traditional EQ-5D-3L in paper-and-pencil administration [15, 17]. A ceiling effect of 59% was described in Japanese patients with mild-to-severe asthma treated with inhaled corticosteroids [15], and 50% in Canadian ones with mainly mild-to-moderate self-reported asthma [17]. Our findings also showed a lower proportion of patients with no problems in most dimensions than those reported by the 3-level version: [15] 81.0% vs 90.7% in mobility, 77.1% vs 85.2% in activity, 45.5% vs 74.1% in pain/discomfort, and 48.0% vs 77.8% in anxiety/depression. The other two studies on EQ-5D-3L in asthma [16, 17] did not report percentage distributions for each dimension. This lower endorsement of the top response option when compared to results from previous studies with EQ-5D-3L suggests that the ‘no

problems' category (level 1 out of 3) is partially redistributed to the following intermediate category, 'slight' problems (level 2 out of 5), in the new 5-level version. However, head-to-head studies are needed to ensure that the new 5L version's better properties we have observed, compared to results from previous EQ-5D-3L studies [15,17], are not explained by differences in patients' characteristics or design issues.

Studies that directly elicit preferences from representative general population samples to derive value sets for the new EQ-5D-5L, using a harmonized protocol, have already been published for several countries [30, 47, 48, 49, 50, 51], but they are not yet developed in many others, including France. The EuroQol Group developed the 3L-5L crosswalk value sets as a temporary solution to estimate the EQ-5D-5L in such a situation [29]. The difference between both indices in the negative extreme of the theoretical range (-0.28 and -0.53) is explained by the method used for the elicitation of the societal preference values to derive the value set: time trade-off in French general population for the 3L version [52], and the composite method of time trade-off with discrete choice experiments in the UK general population for the new 5L version [23, 30]. Our findings show that the mean EQ-5D-5L indices obtained with both value sets is quite similar (0.88 and 0.83), supporting that the 3L-5L crosswalk is a good interim solution to calculate the EQ-5D-5L index, until definitive EQ-5D-5L value sets are available.

The EQ-5D-5L index was able to discriminate among different known groups in the hypothesized direction. In all the variables evaluated, differences between extreme groups ranged from 0.07 to 0.2, therefore being equal or higher than the minimal important difference, previously estimated as 0.07 [31]. Magnitude was moderate for differences among groups defined by the presence of other chronic conditions and SABA use or prescription, and large for differences between patients with well and not well-controlled asthma measured with the ACQ. The study by McTaggart-Cowan et al. [17] with the traditional EQ-5D-3L in patients with asthma had also shown differences between extreme groups >0.07, ranging from 0.07 to 0.18. It was not possible to make direct comparisons of effect sizes with this study [17], since the variables to define known groups were different. Mc Taggart-Cowan et al. reported a correlation of 0.37 for ACQ with the EQ-5D-3L index [17], similar to the 0.43 found in our study with the EQ-5D-5L index. These findings indicate a good construct validity for the EQ-5D-5L index, which in general presented a greater discriminant capacity than the EQ-VAS among the known groups evaluated.

Limitations and Strengths

Some potential limitations of the current study need to be considered. First, a direct comparison with EQ-5D-3L was not possible. Although previous EQ-5D-3L studies in asthma patients[15,16,17] showed higher ceiling effects and lower discriminatory properties than ours with the EQ-5D-5L, differences among studies regarding patients' and design characteristics cannot be discarded. Second, since no asthma-specific HRQoL measure was included in this study, we were unable to compare the generic EQ-5D-5L with them. Studies

evaluating the EQ-5D-3L in comparison to the Asthma Quality of Life Questionnaire [15-17] or to the Newcastle Asthma Symptoms Questionnaire [16] showed that these disease-specific instruments were more sensitive to change. Further head-to-head studies comparing the EQ-5D-5L with disease-specific instruments are needed, mainly to compare responsiveness. Third, the usability of online vs other methods of survey administration could not be evaluated because all patients completed the online EQ-5D-5L. Fourth, because the ASTRO-LAB 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. Generalizability is also uncertain to patients older than 40 years. Finally, it is important to note that 46.3% of participants in the ASTRO-LAB project did not answer the online survey. No differences in socio-demographic characteristics, treatment, and comorbidity were found between respondents and non-respondents, and differences detected in asthma control were minor. However, there could be differences in other characteristics which have not been measured, such as personality or other psychological traits.

Our study has several strengths that need to be highlighted. First, embedding this study in an observational cohort in routine care allowed us to select several appropriate known groups for evaluating the EQ-5D-5L's construct validity in asthma patients. The relationship between comorbid chronic conditions and health is well established, and the associations of symptoms control [53] with HRQoL have been extensively studied in this population. Furthermore, the ACQ, validated in 50 languages, is one of the most widely accepted instruments for measuring asthma control [54].

Conclusions

In summary, our results provide support to the construct validity of EQ-5D-5L administered online to patients with asthma, based on its discriminant ability for distinguishing among health-related known groups, as well as its lower ceiling effect than previously reported for the traditional 3-level version [15,17]. The completion of the EQ-5D-5L by most of the online survey respondents supports the feasibility of this administration form. Since it was developed as a preference-based health status measure, the EQ-5D-5L index allows combining both length and quality of life, and calculates Quality-Adjusted Life-Years to measure health outcomes in economic evaluations. All these findings suggest that the new EQ-5D with 5 levels is a promising instrument to compare the efficiency of different programs or treatment strategies for asthma patients. Nevertheless, further studies are recommended to evaluate the responsiveness over time of the EQ-5D-5L among asthma patients.

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Authors' contributions

GH contributed to the conception and design of the article, conceptualized and oversaw analyses, contributed to the interpretation of data, and wrote the article. AP contributed to the analysis and gave statistical support. AD, OG, MM, JA, EVG, LL, MB and KM oversaw all aspects and reviewed the article for important intellectual content. VSS revised 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 co-authors critically revised the manuscript and approved the final draft before submission.

Collaborating author names

Members of the ASTRO-LAB group are: Marijn de Bruin, Alexandra L. Dima (ASCoR, University of Amsterdam, The Netherlands); Eric Van Ganse, Laurent Laforest, Sandrine Herbage, Manon Belhassen, Marine Ginoux (LBBE, University Claude Bernard Lyon 1, France); Stéphane Schück, Nathalie Texier, Sandy Leproust, Hélène Le Cloarec (Kappa Santé, France); Richard Hubbard (University of Nottingham, England); Alison Bourke, Mary Thompson, Delphine Vial, David Ansell (Cegedim Strategic Data, England); Javier Olaiz, Ana Valcarcel Orti (Lyon Ingénierie Projet, France); and Montse Ferrer, Olatz Garin, Gimena Hernandez (IMIM - Hospital del Mar Medical Research Institute, Spain).

Conflicts of interest

None declared.

Supplementary Material: Sample screenshot of EQ5D questions in the online survey

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Abbreviations

ACQ: Asthma Control Questionnaire

BMI: body mass index

EQ-VAS: visual-analogue scale

HRQoL: Health-Related Quality of Life

ICs: Inhaled Corticosteroids

LABAs: Long-Acting Beta-Agonists

PROMS: Patient-reported outcome measures

QALYs: Quality-Adjusted Life-Years

SABA: Short-Acting Beta-Agonists

UK: United Kingdom

4.5. ARTICLE 5:

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PLOS ONE

RESEARCH ARTICLE

Impact of asthma on women and men: Comparison with the general population using the EQ-5D-5L questionnaire

Gimena Hernandez[1,2,3], Alexandra L. Dima[4], Àngels Pont[1,3], Olatz Garin[1,3,5]*, Marc Martí-Pastor[1,2,3], Jordi Alonso[1,3,5], Eric Van Ganse[6,7], Laurent Laforest[6,7], Marijn de Bruin[4,8], Karina Mayoral[1,5], Montse Ferrer[1,2,3]*, the ASTRO-LAB group[¶]

1 Health Services Research Group, IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain, **2** Dept of Paediatrics, Obstetrics and Gynaecology and Preventive Medicine, Universitat Autònoma de Barcelona, Bellaterra, Barcelona, Spain, **3** CIBER en Epidemiología y Salud Pública, CIBERESP, Madrid, Spain, **4** Amsterdam School of Communication Research ASCoR, University of Amsterdam, Amsterdam, The Netherlands, **5** Pompeu Fabra University (UPF), Barcelona, Spain, **6** PharmacoEpidemiology Lyon (PEL), HESPER Unit, Claude-Bernard University-Lyon1, Lyon, France, **7** Respiratory Medicine, Croix-Rousse Hospital, CHU-Lyon, Lyon, France, **8** Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, Scotland, United Kingdom

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* mferrer@imim.es (MF); ogarin@imim.es (OG)

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Abstract

Background

The aim was to evaluate the impact of asthma on patients' Health-Related Quality of Life (HRQoL) by comparing asthmatic women and men with reference norms, to examine the factors which contributed to an impaired HRQoL, and to identify groups at higher risk.

Methods

Cross-sectional evaluation of 222 primary care patients with persistent asthma (18±40 years old). HRQoL impact was estimated with the EuroQol-5 Dimensions (EQ-5D), which allows calculating Quality-Adjusted Life-Years (QALYs) by applying society preferences. Participants self-completed the EQ-5D questionnaire online. Telephonic interviews collected information on medication and adherence, and administered the Asthma Control Questionnaire. Severity markers included asthma-related comorbidity, previous oral corticosteroids course prescription, and inhaled corticosteroids daily dose. After bivariate analyses, multiple linear regression models were constructed to examine the relations between HRQoL asthma impact and socio-demographic and clinical variables, using as dependent variable the deviation from general population-based EQ-5D reference norms.

Results

Deviation from the EQ-5D index norms was moderate in most age/gender groups (-0.1, which corresponds to 0.6 standard deviations), while it was large in women aged 18±24 years (-0.18, corresponding to 1.1 standard deviations). In regression models, a poor asthma control was the only factor independently associated to HRQoL impact in both

independence in designing the study, interpreting the data, writing and publishing the report.

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

women and men: β -0.18 (p<0.001) and -0.15 (p = 0.01) respectively. Translating these β coefficients to QALYs, they are interpretable as 66 fewer days of full health per year in women with uncontrolled asthma and 55 for men, compared with those with controlled asthma.

Conclusion

Persistent asthma has a moderately negative HRQoL impact on patients of both genders, and the youngest women have been identified as a high risk group which merits further research. We identified asthma control as the major contributor to impaired HRQoL in patients, regardless of their gender, suggesting that asthma HRQoL impact could be alleviated by achieving a good control of symptoms.

Introduction

International guidelines for asthma have emphasized the need to include patientsÂHealth-Related Quality of Life (HRQoL) [1] improvement in treatment goals. Studies on clinical samples have reported worse HRQoL in women with asthma, compared with men [2±4]. Significant gender differences in lifespan among people with asthma have also been documented, and asthma-related hospitalizations were found to be most prevalent among middle-aged women [5]. Could these differences imply gender inequalities in HRQoL asthma impact? Clinical studies offer limited information on this topic because they lack a comparison with the general population, where women were also found to have worse HRQoL than men [6±8]. Therefore, to answer this question, we need to know how far the HRQoL of asthma patients is from the general population, by comparing them with controls or reference norms.

The instruments used to assess HRQoL can be roughly divided into disease-specific and generic ones [9]. While the former are very useful, they do not usually allow the evaluation of asthma impact in comparison with that of other diseases or with the general population. Reference norms have been mainly developed to interpret generic HRQoL questionnaires, permitting comparisons of a disease-specific sample with counterparts from the general population. This approach has been successfully applied in diseases such as fibromyalgia and rheumatoid arthritis [10], thalassemia [11], epilepsy [12], and type 2 diabetes [13]. To our knowledge, there are no studies that have assessed asthma impact on HRQoL using reference norms.

There are some studies based on National Health Surveys, but they usually evaluate individuals who self-reported having asthma and, thus, the lack of a reliable diagnosis might have led to under- or over-estimating asthma impact on their HRQoL. The 2000 Behavioral Risk Factor Surveillance System included 12,270 individuals with self-reported asthma who perceived worse HRQoL than those who had never had asthma [14], administering four HRQoL questions but without any standardized instrument. The 2008 European National Health and Wellness Survey, with the 12-item Short-Form Health Survey (SF-12) [15], showed worse results among the 3,619 individuals with self-reported asthma than among general population.

The EuroQol 5 Dimensions (EQ-5D), one of the most widely employed generic tools due to its low respondent burden and good psychometric properties [16±19], has reference norms for 24 countries [20]. Furthermore, the EQ-5D allows the calculation of Quality-Adjusted Life-Years (QALYs) when society preferences are applied [21]. The aim of this study was to evaluate the impact of asthma on patients' HRQoL by comparing asthmatic women and men with EQ-

5D reference norms, to examine the factors which contributed to an impaired HRQoL, and to identify specific groups at higher risk.

We hypothesised that worse HRQoL in women with asthma compared with men [2±4] does not imply gender inequalities in asthma impact, because their worse HRQoL is mainly explained by gender differences external to asthma, such as other chronic conditions, disease-related behaviours, or socio-economic background. In this sense, we expected that when asthma impact on HRQoL is defined as the deviation from general population-based reference norms, differences between women and men with asthma would disappear. According to the available evidence [22±27], we also hypothesised that the main factors related to the HRQoL of asthmatic patients were age, socio-economic characteristics (education, work status,. . .), smoking status, asthma control, controller and reliever medication, adherence to inhalers, comorbidities, and severity.

Materials and methods

Setting and study population

We analysed baseline data from French adult patients (18±40 years old) with persistent asthma who completed the EQ-5D questionnaire with 5 levels (EQ-5D-5L) in the ASTRO-LAB project, approved by the Ethics and Regulatory Boards, and conducted in accordance with the Declaration of the World Medical Association. CCTIRS (Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine dela santé) approval was obtained on November 21st, 2012 (Dossier NÊ12702);and CNIL (Commission Nationale d'Informatique et Liberté) the authorization was obtained in May 17th, 2013 (DR-2013-264). Written informed consent was obtained from all French participants prior to inclusion.

The ASTRO-LAB project was designed as a prospective longitudinal study to evaluate the safety of long-acting beta-agonists (LABAs). Patients were enrolled in primary care in France and United Kingdom by their general practitioner, based on 12-month prescription data. Inclusion criteria were: subjects aged 6±40 years with persistent asthma defined as more than 6 months of prescribed inhaled corticosteroids and/or LABAs during 12 months before inclusion. Exclusion criteria were: chronic oral corticosteroid use ($\geq$15 consecutive days during 3 months before inclusion), history of omalizumab therapy, and/or any other concomitant chronic respiratory disease (chronic obstructive pulmonary disease, cystic fibrosis, pulmonary fibrosis, bronchiectasis or tuberculosis). In addition to clinical records, the main information sources of ASTROLAB were: computer-assisted telephone interviews (CATIs), mobile text messages, and online surveys.

Trained interviewers administered CATIs to patients after inclusion, and then every four months during a follow-up of 24 months at maximum. CATIs assessed asthma medications prescribed, their patient-reported use, control of symptoms, and the occurrence of asthma exacerbations during the previous 4 months. Patients received monthly mobile text messages inquiring whether they had experienced a new asthma exacerbation since the last study contact. Positive responses motivated an extra CATI to characterize the exacerbation. Patients were also requested to complete an online survey at inclusion and at 12-month intervals on socio-demographic characteristics, determinants of medication adherence, triggers, exacerbations management, quality of inhaler technique, and EQ-5D questionnaire. The complete ASTRO-LAB protocol is available in a previous publication [28].

Measurement instruments

General practitioners completed an online survey at patient recruitment with information on age, commonly asthma-associated conditions, and medications prescribed during the 12

months before inclusion. The history of allergic rhinitis, nasal polyps, infectious sinusitis, anxiety/depression, and gastro-esophageal reflux was registered and transformed into a count variable as a summary indicator of asthma-related comorbidity, as well as the number of prescribed oral corticosteroids courses 12 months before inclusion. These two variables, together with the daily dose of inhaled corticosteroids, were used as severity markers.

Patient-reported data collected by computer-assisted telephonic interviews (CATI). We used data from the first (baseline) CATI, which included the Asthma Control Questionnaire-symptoms only (ACQ), and questions on type and adherence to daily controller medication, reliever medication, and the daily dose of inhaled corticosteroids prescribed at the time of inclusion (beclomethasone equivalent). The latter was categorized following clinical guidelines [29] into high (>1,000μg), medium (500 to 1,000 μg), and low (≤500 μg).

The ACQ±symptoms only [30] assesses the frequency of five asthma symptoms during the previous week through Likert scales with 7 response options. The overall score, calculated as the mean of item responses, ranges from 0 to 6. A score <0.75 is defined as well-controlled asthma; 0.75±1.5 as intermediate asthma control; and >1.5 as not well-controlled asthma [31].

Adherence to daily controller medication was measured with the Medication Intake Survey-Asthma (MIS-A) [32], a count-based recall measure of medication implementation. MIS-A 1-week adherence was estimated by the proportion of prescribed medication that the patient had used the previous week. It was categorized into complete (100%), intermediate, and low (≤50%) adherence.

Reliever medication in the past month was measured with the following question: `How often have you usually taken your (brand name) in the past 4 weeks? Every day; almost every day; once or twice every week; or less than once a week'. Responses were dichotomized according to the cut-off point of more than twice per week [29].

EQ-5D-5L and socio-demographic variables. At study enrollment, patients were invited to self-complete an online survey, which included among others the EQ-5D-5L to measure HRQoL, smoking status, and socio-demographic data on highest education and work status.

The EQ-5D-5L is a brief, multi-attribute, generic, health status measure composed of a descriptive system and a visual-analogue scale (EQ-VAS) asking individuals to rate their own health from 0 to 100 (worst and best imaginable health, respectively). The descriptive system covers five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with five response options in each dimension (no problems, slight problems, moderate problems, severe problems, unable to perform/extreme problems). The EQ-5D-5L therefore defines 3125 distinct health states from all the possible combinations of dimensions and response options (i.e. 5^5). Each of these combinations was converted into a single health index ranging from 1 (the best health state) to negative values (health states valued as worse than death) where 0 is equal to death. This conversion was performed applying a formula that attaches societal preference values (weights) to each response. The index was calculated with the crosswalk 3L-5L French value set of preferences [33,34].

Analytic strategy

We calculated the statistical power to estimate the mean of the EQ-5D health index with a 95% confidence interval precision of +/-0.07, which was the Minimal Important Difference (MID) previously established [35]. Given a standard deviation of 0.16, statistical power was 0.80 for the smallest group of our sample (18±25 years old men, n = 19).

Reference norms published by the EuroQol group [20] for France were obtained from a representative sample of non-institutionalized adults [36]. Deviation from reference norms for the EQ-5D-5L index and the EQ-VAS were calculated by subtracting the patients' mean from

the mean of their corresponding age and gender group, and negative values indicate worse health than counterparts from the general population.

All the analyses were carried out separately for women and men. Comparisons among groups were made using chi-squared tests for categorical variables and ANOVA for continuous variables. Multiple linear regression models were constructed to examine the relation of asthma HRQoL impact with socio-demographic and clinical variables, using EQ-5D-5L index and EQ-VAS deviation from reference norms as dependent variables. The covariates were chosen a priori, based on knowledge about determinants of HRQoL in asthma. Analyses were conducted using the statistical package SPSS12, and α was set at 0.05.

Results

Of the 487 French subjects with asthma aged 18±40 years from the ASTRO-LAB cohort, 245 (50.3%) filled in the baseline online survey; 23 did not complete the EQ-5D-5L questionnaire, hence 222 participants were included in the analysis.

Patients had a mean age of 30.3 years (SD 6.7), 61.3% were women, 72% were currently employed, and 63% were non-smokers (Table 1). The means of the EQ-5D-5L index and EQ-VAS were 0.83 and 77.3, respectively, and deviations from reference norms were -0.11 and -4.9. Asthma control was evenly distributed among the three categories. Most patients were prescribed ICs/LABA fixed-dose-combinations, and 43% reported complete adherence. Severity markers showed that 58.5% presented one or more asthma-related comorbidities, around 25% used a high inhaled corticosteroids dose, and 30% was prescribed at least one oral corticosteroid course during the previous 12 months. Statistically significant differences between genders were observed for education ($p = 0.019$), inhaled corticosteroids daily dose prescription ($p = 0.005$) and the number of oral corticosteroids courses prescribed ($p = 0.002$), which indicated more severe asthma for women than men. All EQ-5D results showed a worse HRQoL in women.

French reference population norms and EQ-5D results in women and men with asthma are shown in (Fig 1A and 1B respectively). Mean EQ-5D index in asthmatic women (Fig 1A) was 0.77 (95%CI 0.71±0.84) for those aged 18±24, 0.81 (95%CI 0.76±0.85) for those aged 25±34, and 0.83 (95%CI 0.78±0.88) for those aged 35±40. All these means were significantly different from norms, as the 95% CI didnÂtinclude the mean of the reference norm in any age group. For example, the mean value for women aged 18±24 in the general population was 0.95 [20], which was clearly outside of the 95% CI found in asthmatic women of this age (mean = 0.77, 95%CI 0.71±0.84). The differences between reference norms and the results obtained among women with asthma were markedly greater in the youngest, and they diminished with age (Fig 1A): -0.18, -0.13, and -0.075, respectively. In contrast to the women's pattern, differences on EQ-5D index between men with asthma and reference norms increased slightly with age (-0.05, -0.08, and -0.085, respectively), and were statistically significant for the two oldest groups (Fig 1B). EQ-VAS showed that younger women (18±24 years) perceived significantly worse health than their counterparts, while men with asthma were very close to reference norms.

Fig 2 shows that the proportion of women and men with asthma reporting problems is higher than reference norms in usual activities, pain/discomfort, and anxiety/depresion. The youngest women also reported more problems in mobility.

Deviations from reference norms for EQ-5D-5L index and EQ-VAS in socio-demographics and clinical groups are presented in Table 2. Negative values indicate that all asthmatic groups presented worse health than their counterparts from the general population. These negative values were always larger in women than men. Among women the biggest deviation from

Table 1. Characteristics of study subjects.

	Total (n = 222)	Women (n = 136)	Men (n = 86)	p-value
Age, mean (SD)	30.3 (6.7)	29.7 (6.6)	31.3 (6.7)	0.079
18±24 years	55 (24.8%)	36 (26.5%)	19 (22.1%)	0.124
25±35 years	97 (43.7%)	64 (47.1%)	33 (38.4%)	
35 or more years	70 (31.5%)	36 (26.5%)	34 (39.5%)	
Highest education				
Sixth form or college, Secondary or less	30 (13.8%)	11 (8.2%)	19 (22.6%)	0.019
Bachelor Degree	59 (27.1%)	40 (29.9%)	19 (22.6%)	
Bachelor Degree +2 or +3	98 (45.0%)	61 (45.5%)	37 (44.0%)	
Bachelor Degree +5 or more	31 (14.1%)	22 (16.4%)	9 (10.7%)	
Work status				
Employed at usual job	158 (71.8%)	91 (67.4%)	67 (78.8%)	0.168
Paid sick leave, restricted work, light duty due to disability	9 (4.1%)	7 (5.2%)	2 (2.4%)	
Not working for other reason	53 (24.1%)	37 (27.4%)	16 (18.8%)	
Smoking status				
Non Smoker	137 (62.8%)	88 (66.2%)	49 (57.6%)	*0.204*
Smoker	81 (37.2%)	45 (33.8%)	36 (42.4%)	
Patient-Reported Outcomes				
EuroQol-5 Dimensions-5 Levels (EQ-5D-5L), mean (SD)				
EQ-5D-5L Index	0.83 (0.17)	0.81 (0.18)	0.86 (0.15)	0.016
EQ-5D-5L index deviation from Reference norms	-0.11 (0.17)	-0.13 (0.19)	-0.07 (0.15)	0.015
EQ- VAS	77.3 (16.5)	76.1 (18.5)	79.2 (12.4)	0.137
EQ-VAS deviation from Reference norms	-4.9 (16.8)	-6.7 (18.8)	-2.0 (12.5)	0.045
Asthma Control Questionnaire (ACQ), mean (SD)	1.1 (1.0)	1.2 (1.0)	1.0 (0.9)	0.076
Well controlled (< 0.75)	67 (37.9%)	36 (33.3%)	31 (44.9%)	0.281
Intermediate (0.75±1.5)	61 (34.5%)	39 (36.1%)	22 (31.9%)	
Not well controlled (> 1.5)	49 (27.7%)	33 (30.6%)	16 (23.2%)	
Asthma medication				
Type of controller medication				
Inhaled corticosteroids (ICs)	39 (17.6%)	23 (16.9%)	16 (18.6%)	0.781
Long-acting beta-agonists (LABA) with/out ICs	30 (13.5%)	17 (12.5%)	13 (15.1%)	
ICs/LABA Fixed-dose combination	153 (68.9%)	96 (70.6%)	57 (66.3%)	
Adherence (MIS-A 1-week)				
Low (≤ 50%)	57 (30.3%)	*36 (30.3%)*	21 (30.4%)	0.687
Intermediate	50 (26.6%)	34 (28.6%)	16 (23.2%)	
Complete (100%)	81 (43.1%)	*49 (41.2%)*	32 (46.4%)	
Reliever medication use				
Never	56 (26.5%)	36 (27.9%)	20 (24.4%)	0.395
Less than once a week	79 (37.4%)	51 (39.5%)	28 (34.1%)	
Once or twice every week	54 (25.6%)	32 (24.8%)	22 (26.8%)	
Almost every day	22 (10.4%)	10 (7.8%)	12 (14.6%)	
Severity Markers				
Asthma-related comorbidities				
0	66 (41.5%)	38 (38.4%)	28 (46.7%)	0.443
1	62 (39.0%)	39 (39.4%)	23 (38.3%)	
2 or more	31 (19.5%)	22 (22.2%)	9 (15.0%)	
Inhaled Corticosteroids daily dose[1], mean (SD)	929.8 (866.2)	1051.2 (960.9)	728.4 (637.2)	0.005

(*Continued*)

Table 1. (Continued)

	Total (n = 222)	Women (n = 136)	Men (n = 86)	p-value
≤ 500 μcg	89 (44.1%)	50 (39.7%)	39 (51.3%)	0.094
500±1000 μcg	65 (32.2%)	40 (31.7%)	25 (32.9%)	
> 1000 μcg	48 (23.8%)	36 (28.6%)	12 (15.8%)	
Oral Corticosteroids courses[2], mean (SD)	0.4 (0.8)	0.6 (0.9)	0.3 (0.6)	0.004
0 courses	152 (70.4%)	82 (62.6%)	70 (82.4%)	0.002
1 or more courses	64 (29.6%)	49 (37.4%)	15 (17.6%)	

1 Inhaled corticosteroids prescribed at the time of inclusion (beclomethasone equivalent)

2 Oral corticosteroids courses prescribed during the 12 months before inclusion

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reference norms was found in those using reliever medication almost or every day (mean = -0.31), followed by those with not well-controlled asthma (mean = -0.28), those with 2 or more asthma-related comorbidities (mean = -0.22), and those with inhaled corticosteroids daily dose >1000 μcg (mean = -0.21). Among men, EQ-5D-5L index deviation from norms only showed statistically significant differences regarding asthma control and reliever medication use. The EQ-VAS deviations from reference norms were significantly associated with age, asthma control, and severity markers in women, but only with asthma control in men.

Table 3 presents linear regression models with deviations from reference norms for EQ-5D index and EQ-VAS as dependent variables. Among women, a significant relationship with

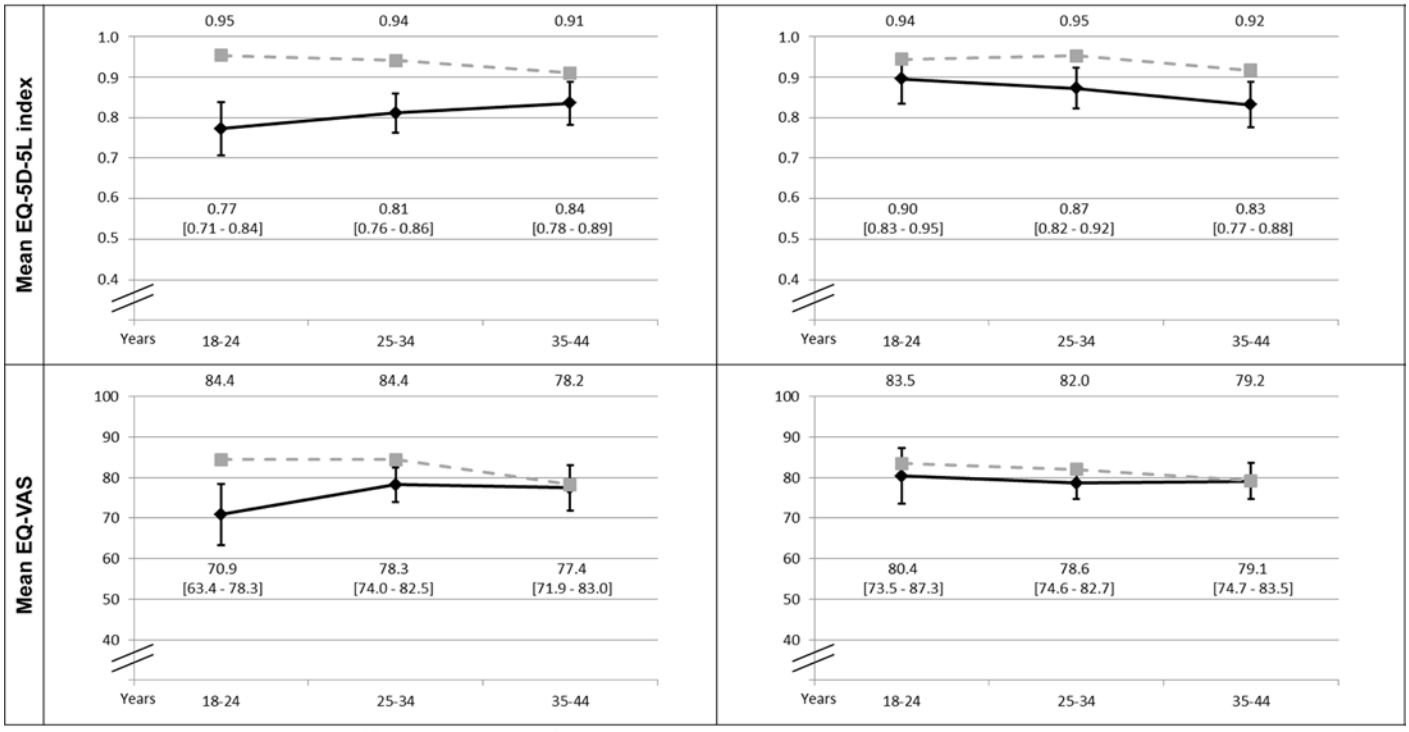

Fig 1. EQ-5D index and EQ-VAS: comparison between patients with asthma and French general population-based reference norms. Mean and 95% Confidence Interval (95%CI) of EQ-5D index and EQ-VAS in patients with asthma stratified by age and gender (in black). Grey dotted line represents the mean in French general population-based reference norms [20].

https://doi.org/10.1371/journal.pone.0202624.g001

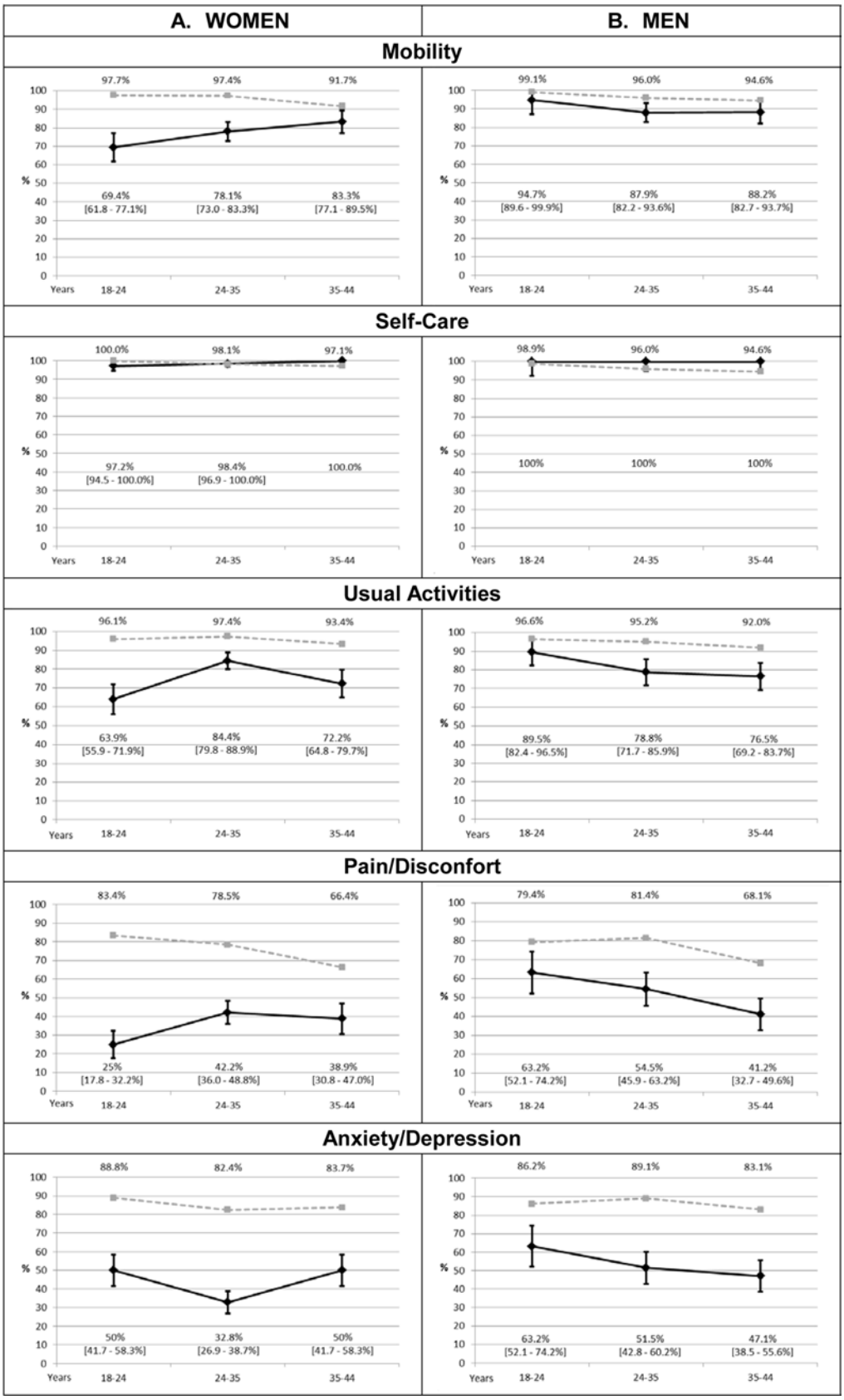
A. WOMEN
B. MEN
Mobility
97.7%
97.4%
91.7%
69.4%
[61.8 - 77.1%]
78.1%
[73.0 - 83.3%]
83.3%
[77.1 - 89.5%]
99.1%
96.0%
94.6%
94.7%
[89.6 - 99.9%]
87.9%
[82.2 - 93.6%]
88.2%
[82.7 - 93.7%]
Self-Care
100.0%
98.1%
97.1%
97.2%
[94.5 - 100.0%]
98.4%
[96.9 - 100.0%]
100.0%
98.9%
96.0%
94.6%
100%
100%
100%
Usual Activities
96.1%
97.4%
93.4%
63.9%
[55.9 - 71.9%]
84.4%
[79.8 - 88.9%]
72.2%
[64.8 - 79.7%]
96.6%
95.2%
92.0%
89.5%
[82.4 - 96.5%]
78.8%
[71.7 - 85.9%]
76.5%
[69.2 - 83.7%]
Pain/Disconfort
83.4%
78.5%
66.4%
25%
[17.8 - 32.2%]
42.2%
[36.0 - 48.8%]
38.9%
[30.8 - 47.0%]
79.4%
81.4%
68.1%
63.2%
[52.1 - 74.2%]
54.5%
[45.9 - 63.2%]
41.2%
[32.7 - 49.6%]
Anxiety/Depression
88.8%
82.4%
83.7%
50%
[41.7 - 58.3%]
32.8%
[26.9 - 38.7%]
50%
[41.7 - 58.3%]
86.2%
89.1%
83.1%
63.2%
[52.1 - 74.2%]
51.5%
[42.8 - 60.2%]
47.1%
[38.5 - 55.6%]
%
Years
18-24
24-35
35-44

Fig 2. EQ-5D dimensions: Comparison between patients with asthma and French general population-based reference norms. Percentage and 95% Confidence Interval (95%CI) of problems in each EQ-5D dimension reported by patients with asthma (in black). Grey dotted line represents the percentage in French general population-based reference norms [20].

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asthma control (β -0.18 for not well-controlled, $p<0.001$) and adherence (β -0.10 for low adherence, $p = 0.03$) was found. In men, only those with not well-controlled asthma presented higher deviation from norms (indicating worse health), compared with well-controlled asthma ($\hat{u} = -0.15$, $p = 0.01$). Regression models with EQ-VAS only showed a significantly worse perceived health in women with uncontrolled asthma ($p = 0.028$), and with inhaled corticosteroids daily dose $\leq$ 500 μg ($p = 0.012$).

Discussion

This is the first study to examine the impact of asthma on HRQoL considering population reference norms, which allows to estimate asthma burden and to identify high risk groups, incorporating a gender perspective. We found that asthmatic patients consistently reported worse HRQoL than subjects of the same age and gender from the general population, with younger women being the most affected. We identified asthma control as the major contributor to impaired HRQoL in both women and men, while education, medication, and severity markers did not contribute significantly. Translating these differences from reference norms to QALYs, they are interpretable as a mean of 40 fewer days of full health per year experienced by persons with asthma: ranging from 68 in the youngest women (18±24 years) to 27 in the oldest (35±40 years), and from 18 to 31 in men within the same age groups.

Our findings are in agreement with studies based on National Health Surveys, showing that subjects self-reporting asthma have worse HRQoL than those without this condition [14] or the general population [15]. The impact of asthma refers to **how much** patients' symptoms, functional status and associated diseases matter to them and adversely affect their HRQoL. Beyond statistical significance, there are a number of approaches to interpret the magnitude of differences (`howmuch'), such as the Minimum Important Difference (MID) and effect size (difference of means/SD of total sample). The MID is instrument-specific (established in +/-0.07 units for the EQ-5D [35]), while the effect size is not (0.2 SD small, 0.5 SD moderate, and 0.8 SD large [37]). In this study, the negative deviations from reference norms in all the groups evaluated (ranging from -0.075 to -0.181) were equal or higher than the MID, except for men aged 18±24 years, with a deviation of -0.05. In terms of effect size, the magnitude of the difference between women with asthma aged 18±24 years and their counterparts was large (1.1 SD), small in men of this age group (0.29 SD), and moderate in the rest of age/gender groups.

Our results highlight that asthma control is the most relevant factor to explain impact on HRQoL. Fig 3 shows the distance between our sample and reference norms according to asthma control. These findings are in agreement with the 2008 European National Health and Wellness Survey [15] and a randomly selected cohort with clinical examination [38], in which well-controlled asthma patients presented similar SF-12 scores to the general population.

In our sample subjects with well-controlled asthma also presented a negligible deviation in the EQ-5D index. In contrast, EQ-5D index of patients with uncontrolled asthma was markedly lower than normative values with regression β coefficients of -0.18 in women and -0.15 in men, both far from the MID of +/-0.07 and indicating large impact (effect sizes of 0.88 SD and 1.17 SD, respectively). Translating these regression β coefficients into QALYs, they are

Table 2. Mean (SD) of deviations from reference norms: EQ-5D-5L index and EQ-VAS.

	EQ-5D-5L deviation from reference norm		EQ-VAS deviation from reference norm	
	Women	**Men**	**Women**	**Men**
Age				
18±24 years	-0,18 (0,20)	-0,05 (0,13)	-13,54 (22,11)	-3,13 (14,30)
25±35 years	-0,13 (0,19)	-0,08 (0,14)	-6,12 (17,02)	-3,36 (11,33)
35 or more years	-0,08 (0,16)	-0,08 (0,16)	-0,76 (16,43)	-0,11 (12,71)
p-value	0.055	0.690	0.014	0.523
Highest education				
Not Universitary	-0,14 (0,19)	-0,09 (0,16)	-6,09 (21,37)	-1,75 (14,46)
Universitary	-0,12 (0,19)	-0,06 (0,14)	-7,20 (17,39)	-2,22 (11,14)
p-value	0.589	0.366	0.744	0.866
Smoking status				
Non-Smoker	-0,13 (0,18)	-0,05 (0,14)	-7,15 (19,33)	-1,77 (12,96)
Smoker	-0,12 (0,17)	-0,10 (0,15)	-4,77 (15,78)	-2,38 (12,25)
p-value	0.728	0.128	0.477	0.825
Patient-Reported Outcomes				
Asthma control Questionnaire (ACQ)				
Well controlled (< 0.75)	-0,04 (0,13)	-0,01 (0,07)	-2,53 (15,02)	-0,94 (10,98)
Intermediate (0.75±1.5)	-0,14 (0,15)	-0,10 (0,15)	-4,15 (11,26)	0,02 (14,33)
Not well controlled (> 1.5)	-0,28 (0,22)	-0,18 (0,17)	-16,23 (21,73)	-9,85 (13,38)
p-value	< 0.001	< 0.001	0.001	0.041
Asthma medication				
Type of controller medication				
Inhaled Corticosteroids (ICs)	-0,11 (0,15)	-0,05 (0,18)	-4,18 (16,89)	-3,81 (13,42)
Long-acting beta-agonist (LABA) with/out ICs	-0,12 (0,16)	-0,09 (0,16)	-7,76 (22,90)	1,94 (13,18)
ICs/LABA fixed combination	-0,14 (0,20)	-0,08 (0,14)	-7,06 (18,63)	-2,43 (12,16)
p-value	0.853	0.753	0.781	0.435
Adherence (MIS-A 1-week)				
Low (≤50%)	-0,14 (0,20)	-0,07 (0,16)	-6,55 (16,13)	-3,58 (15,95)
Intermediate	-0,15 (0,17)	-0,13 (0,17)	-3,84 (13,61)	-4,63 (10,70)
Complete (100%)	-0,09 (0,15)	-0,07 (0,12)	-7,91 (22,43)	-1,36 (13,16)
p-value	0.274	0.345	0.611	0.700
Reliever medication use				
Twice a week or less	-0,12 (0,17)	-0,06 (0,13)	-6,54 (16,10)	-1,51 (12,08)
More than twice a week	-0,31 (0,30)	-0,17 (0,18)	-15,56 (25,68)	-8,36 (16,68)
p-value	0.002	0.010	0.155	0.065
Severity markers				
Asthma-related comorbidities				
0	-0,09 (0,16)	-0,05 (0,12)	-4,57 (17,54)	-0,80 (9,97)
1	-0,11 (0,15)	-0,06 (0,14)	-3,46 (12,90)	-3,25 (14,70)
2 or more	-0,22 (0,22)	-0,11 (0,13)	-11,73 (19,57)	-4,76 (11,27)
p-value	0.013	0.460	0.149	0.631
Inhaled Corticosteroids daily dose[1]				
≤ 500 μcg	-0,11 (0,18)	-0,05 (0,12)	-6,60 (17,45)	-0,17 (10,69)
500±1000 μcg	-0,09 (0,18)	-0,10 (0,17)	-1,44 (16,96)	-2,60 (13,67)
> 1000 μcg	-0,21 (0,20)	-0,11 (0,16)	-13,89 (21,74)	-5,75 (13,53)
p-value	0.011	0.338	0.016	0.362
Oral Corticosteroids courses[2]				

(*Continued*)

Table 2. (Continued)

	EQ-5D-5L deviation from reference norm		EQ-VAS deviation from reference norm	
	Women	Men	Women	Men
0	-0,11 (0,17)	-0,07 (0,14)	-3,81 (14,18)	-1,95 (12,96)
1 or more	-0,16 (0,21)	-0,10 (0,18)	-10,68 (23,47)	-2,91 (10,89)
p-value	0.177	0.454	0.039	0.789

1 Inhaled corticosteroids prescribed at the time of inclusion (beclomethasone equivalent)

2 Oral corticosteroids courses prescribed during the 12 months before inclusion

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interpretable as 66 and 55 fewer days of full health per year in women and men with uncontrolled asthma, respectively, compared with those with controlled asthma.

Previous clinical studies with the traditional EQ-5D reported a very similar mean index to ours: 0.91 vs 0.88 [26] and 0.91 [39] for patients with well-controlled asthma, 0.69 vs 0.61 [26] and 0.73 [39] for those with not well-controlled. Furthermore, a cohort of 8,111 asthmatic patients reported a difference of around 2 points of the Mini Asthma Quality of Life Questionnaire (MiniAQLQ) between those with well-controlled and not well-controlled asthma; this is substantially higher than the +/-0.5 points MID established for the MiniAQLQ [25]. Significant associations between severity markers and HRQoL disappeared after introducing asthma control in the multivariate models. This supports that control could be a mediator factor between severity and HRQoL. These consistent results suggest that the impact of asthma on HRQoL could be alleviated by achieving a good asthma control, reinforcing the relevance of its close follow-up.

Women in the general population have consistently presented worse HRQoL than men despite [40,41], paradoxically, having a higher life expectancy. Studies in clinical samples of asthma patients also reported that HRQoL impairment is greater among women than men [2±4]. Nevertheless, this is the first study confirming that the impact of asthma on HRQoL is higher in women during early adulthood (18±24 years), as deviations from general population-based reference norms indicated a large impact for women (1.1 SD) and small for men (0.29 SD). In this sense, it is important to highlight that, compared to men, this group of very young women had more severe asthma (mean inhaled corticosteroids daily dose 1302.9 vs 835.7 μcg, and number of oral corticosteroids courses 0.61 vs 0.26, p = 0.179 and 0.096 respectively), worse asthma control (mean ACQ score 1.4 vs 1.1, p = 0.449) and lower medication adherence (66.5% vs 56.1%, p = 0.349), but differences were not statistically significant due to the small sample size (36 women and 19 men). Impact of asthma in the youngest women (18±24 years) merits further research to identify explanatory factors (e.g. hormonal, physical activity) underlying this large asthma HRQoL impact at this first stage of women's adult life.

Our study showed that the impact of asthma on patients' HRQoL is moderate in most age-gender groups studied. This impact is greater than other chronic conditions previously evaluated with this approach, such as type 2 diabetes mellitus [13], epilepsy [12], and thalassemia [11], but lower than that of rheumathoid arthritis in the physical component of health [10]. The impact of type 2 diabetes mellitus was small, deviation of EQ-5D index from general population only reached the MID of +/-0.07 units in patients aged 55±64 years (-0.085) [13], while the youngest presented lower deviations. Similarly, the 36-item Short-Form Health Survey (SF-36) indicated that the impact of epilepsy on HRQoL was small in role physical and emotional (effect sizes of 0.29 and 0.42) [12], and that of thalassemia was small on the physical and mental health components [11] (effect sizes of 0.32 and 0.20). Rheumatoid arthritis presented

Table 3. Regression models of EQ-5D-5L and EQ-VAS deviation from norms regarding gender.

	EQ-5D Deviation				VAS Deviation			
	Women		Men		Women		Men	
	β (95% CI)	P	β (95% CI)	P	β (95% CI)	p	β (95% CI)	P
(Constant)	-0.05 (-0.21, 0.10)	0.490	0.04 (-0.20, 0.28)	0.760	-5.61 (-19.84, 8.63)	0.434	-13.96 (-37.50, 9.58)	0.237
Age								
18–24 years	*Reference*		*Reference*		*Reference*		*Reference*	
25±35 years	0.03 (-0.05, 0.11)	0.466	-0.04 (-0.19, 0.12)	0.624	3.74 (-4.01, 11.49)	0.339	7.15 (-8.19, 22.49)	0.351
35 or more years	0.03 (-0.07, 0.14)	0.547	-0.05 (-0.19, 0.10)	0.517	7.24 (-2.67, 17.16)	0.149	10.23 (-3.72, 24.17)	0.146
Highest education								
Not Universitary	*Reference*		*Reference*		*Reference*		*Reference*	
Universitary	0.00 (-0.07, 0.08)	0.926	0.02 (-0.07, 0.10)	0.653	-4.87 (-12.15, 2.41)	0.186	1.70 (-6.67, 10.08)	0.683
Smoking status								
Non smoker	*Reference*		*Reference*		*Reference*		*Reference*	
Smoker	0.04 (-0.04, 0.11)	0.366	0.03 (-0.06, 0.12)	0.524	2.32 (-4.95, 9.59)	0.526	1.25 (-7.77, 10.28)	0.780
Patient-Reported Outcomes								
Asthma Control Questionnaire (ACQ)								
Well controlled	*Reference*		*Reference*		*Reference*		*Reference*	
Intermediate	-0.09 (-0.18, 0.00)	0.055	-0.06 (-0.17, 0.05)	0.261	0.10 (-8.20, 8.40)	0.981	5.41 (-5.02, 15.84)	0.300
Not well controlled	-0.18 (-0.28, -0.09)	<0.001	-0.15 (-0.26, -0.04)	0.011	-9.83 (-18.47, -1.19)	0.026	-6.68 (-17.77, 4.40)	0.230
Asthma medication								
Type of controller medication								
Inhaled Corticosteroids (ICs)	*Reference*		*Reference*		*Reference*		*Reference*	
LABA with/out ICs	-0.04 (-0.20, 0.11)	0.583	-0.05 (-0.22, 0.11)	0.496	-3.18 (-17.87, 11.51)	0.667	1.10 (-14.73, 16.93)	0.889
ICs/LABA Fixed-dose combination	-0.02 (-0.13, 0.10)	0.765	0.02 (-0.11, 0.16)	0.738	-1.27 (-11.64, 9.09)	0.807	7.63 (-5.73, 20.98)	0.254
Adherence (MIS-A 1-week)								
Complete (100%)	*Reference*		*Reference*		*Reference*		*Reference*	
Intermediate	-0.04 (-0.13, 0.05)	0.402	-0.02 (-0.13, 0.09)	0.708	-0.88 (-9.37, 7.62)	0.838	3.23 (-7.76, 14.21)	0.555
Low (≤50%)	-0.10 (-0.19, -0.01)	0.033	0.04 (-0.06, 0.14)	0.440	-4.93 (-13.47, 3.61)	0.253	6.13 (-3.90, 16.16)	0.223
Reliever medication use								
Twice a week or less	*Reference*		*Reference*		*Reference*		*Reference*	
More than twice a week	-0.04 (-0.17, 0.09)	0.552	-0.10 (-0.21, 0.01)	0.074	0.65 (-11.38, 12.68)	0.914	-7.05 (-17.83, 3.73)	0.193
Severity markers								
Asthma-related comorbidities								
0	*Reference*		*Reference*		*Reference*		*Reference*	
1	0.03 (-0.07, 0.14)	0.542	0.01 (-0.11, 0.13)	0.845	2.39 (-7.27, 12.05)	0.623	-6.57 (-18.28, 5.13)	0.262
2 or more	-0.08 (-0.19, 0.03)	0.153	-0.02 (-0.14, 0.09)	0.677	-2.07 (-12.32, 8.18)	0.688	-3.44 (-15.05, 8.17)	0.552
Inhaled Corticosteroids daily dose[1]								

(*Continued*)

Table 3. (Continued)

	EQ-5D Deviation				VAS Deviation			
	Women		Men		Women		Men	
	β (95% CI)	P	β (95% CI)	P	β (95% CI)	p	β (95% CI)	P
≤ 500 µcg	*Reference*		*Reference*		*Reference*		*Reference*	
500±1000 µcg	0.08 (-0.02, 0.18)	0.127	-0.08 (-0.18, 0.01)	0.082	12.20 (2.87, 21.52)	0.011	-3.43 (-12.71, 5.86)	0.459
> 1000 µcg	0.01 (-0.10, 0.11)	0.920	-0.08 (-0.21, 0.05)	0.222	3.06 (-6.72, 12.85)	0.534	-7.00 (-19.50, 5.50)	0.264
Oral Corticosteroids courses[2]								
0 courses	*Reference*		*Reference*		*Reference*		*Reference*	
1 or more courses	0.01 (-0.07, 0.08)	0.839	-0.05 (-0.16, 0.06)	0.353	-2.48 (-9.57, 4.60)	0.486	-2.38 (-13.13, 8.37)	0.656

1 Inhaled corticosteroids prescribed at the time of inclusion (beclomethasone equivalent)

2 Oral corticosteroids courses prescribed during the 12 months before inclusion

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a large impact on physical health and a moderate one on mental health [10], as measured with SF-36 component summaries (effect sizes of 1.8 and 0.6).

It is important to remark that the real impact of asthma on HRQoL could be even higher than described here. Since general population includes a proportion of patients with asthma (as well as other diseases), the differences between our asthma sample and EQ-5D reference norms would have been greater than observed if we strictly compared with subjects without asthma. The most prevalent chronic conditions reported by French individuals aged 15±39 years in the European Health Interview SurveyÐ`Enquête SantéÂet Protection Sociale' (EHIS-ESPS) 2014 [42] were: low back pain (19.8%), allergies (15.9%), cervical pain (9.0%), asthma (8.4%), diabetes (4.2%) and depression (4.1%). As expected, the prevalence of asthma-related chronic conditions was higher in our sample (allergic rhinitis 48.4% and depression 15.3%), but for those non-related to asthma such as musculo-skeletal conditions and diabetes

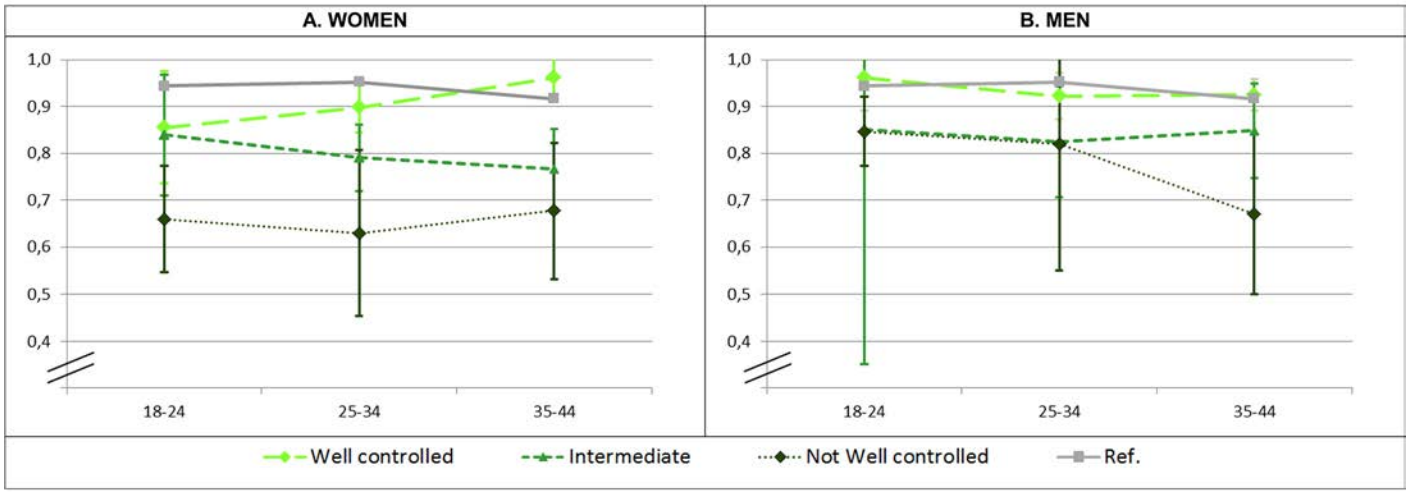

Fig 3. EQ-5D index in patients with asthma, stratified by level of control as measured with ACQ. ACQ = Asthma Control Questionnaire. Well controlled asthma defined as a ACQ score <0.75; intermediate asthma control as ACQ 0.75±1.5; and not well controlled as ACQ score >1.5 [31]. Green dotted lines represent mean and 95% Confidence Interval (95%CI) of EQ-5D index in patients with asthma. Grey continuous line represents the mean in French general population-based reference norms [20].

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Table 4. Characteristics in respondents and non-respondents to the EQ-5D-5L.

	EQ-5D respondents (n = 222)	EQ-5D non-respondents (n = 265)	p
Gender			
Women	136 (61.3%)	150 (56.6%)	
Men	86 (38.7%)	115 (43.4%)	0.298
Age. mean (SD)	30.3 (6.7)	29.5 (6.6)	0.179
18±24 years	55 (24.8%)	78 (29.4%)	0.387
25±35 years	97 (43.7%)	116 (43.8%)	
35 or more years	70 (31.5%)	71 (26.8%)	
Patient-reported outcomes			
Asthma control Questionnaire (ACQ), mean (SD)	1.1 (1.0)	1.3 (1.0)	0.048
Well-controlled (< 0.75)	67 (37.9%)	83 (35.6%)	0.010
Intermediate (0.75±1.5)	61 (34.5%)	55 (23.6%)	
Not well-controlled (> 1.5)	49 (27.7%)	95 (40.8%)	
Missing	45	32	
Asthma medication			
Type of controller medication			
Inhaled Corticosteroids (ICs)	39 (17.6%)	43 (16.2%)	0.666
Long-acting beta-agonist (LABA) with/out ICs	30 (13.5%)	30 (11.3%)	
ICs/LABA fixed combination	153 (68.9%)	192 (72.5%)	
Adherence (MIS-A 1-week)			
Low (≤50%)	57 (30.3%)	52 (28.1%)	0.192
Intermediate	50 (26.6%)	65 (35.1%)	
Complete (100%)	81 (43.1%)	68 (36.8%)	
Missing	34	80	
Reliever medication use			
Twice a week or less	189 (89.6%)	209 (89.7%)	0.965
More than twice a week	22 (10.4%)	24 (10.3%)	
Missing	11	32	
Severity Markers			
Asthma-related comorbidities			
0	66 (41.5%)	80 (39.2%)	0.511
1	62 (39.0%)	91 (44.6%)	
2 or more	31 (19.5%)	33 (16.2%)	
Inhaled Corticosteroids daily dose[1], mean (SD)	929.8 (866.2)	942.0 (823.9)	0.883
≤ 500 μg	89 (44.1%)	88 (41.5%)	0.674
500±1000 μg	65 (32.2%)	77 (36.3%)	
> 1000 μg	48 (23.8%)	47 (22.2%)	
Oral Corticosteroids courses[2], mean (SD)	0.4 (0.8)	0.5 (1.0)	0.905
0	152 (70.4%)	186 (72.9%)	0.537
1 or more	64 (29.6%)	69 (27.1%)	

1 Inhaled corticosteroids prescribed at the time of inclusion (beclomethasone equivalent)

2 Oral corticosteroids courses prescribed during the 12 months before inclusion

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prevalence was not expected to differ from EHIS-ESPS 2014. Although information on non-asthma-related comorbidity was not collected in ASTRO-LAB project, the young age of participants in our study (18±40 years) makes less likely confounding the impact of asthma on HRQoL with other comorbid conditions. For example, prevalence of arthritis in the

EHIS-ESPS 2014 [42] was 1.7% in the age group of 15±39 years old, 20.0% in the group of 40± 64 years, and 49.5% in the group of 65 or more years.

Some potential limitations of the current study need to be considered. First, our findings cannot establish causality between asthma control and HRQoL because of its cross-sectional nature; therefore, we cannot rule out reverse causality. In this sense, when we use the term `asthmaimpact' we are referring to the impairment associated with asthma, we are not suggesting causality. Second, even though we adjusted for severity with three markers, two of them based on drug prescription and one on asthma-related comorbidity, there still might be a residual confounding. Third, although the online survey participation rate was low (49%), the only significant difference between respondents and non-respondents was found in the asthma control questionnaire: non-respondents reported less symptom control; therefore, our results might underestimate the impact of asthma on HRQoL (see Table 4). Finally, because our study only included 18±40 year-old adults receiving daily treatment with inhalers, the generalisability of our results to those older than 40 years and/or with intermittent treatment is uncertain.

Conclusions

Findings confirm our hypothesis that the worse HRQoL in women with asthma compared with men [2±4] seems not to imply real gender inequalities in asthma impact, except for the youngest age group. Our results support considering very young women (18±24 years old) a high-risk group. Therefore, the large HRQoL impact of asthma in this group calls for closer monitoring of symptoms control, asthma self-management programs and adequate medical therapy. In general, persistent asthma has a moderately negative HRQoL impact on patients of both genders at an adult age (25±40 years old). Our study identifies asthma control as the main factor associated to HRQoL, suggesting that its improvement could alleviate the large HRQoL impairment found in women and men with uncontrolled asthma. Effective support options need to be explored for groups at high risk of suffering a large negative asthma impact on HRQoL.

Supporting information

S1 Dataset. Study anonymized dataset.
(XLSX)

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Author Contributions

Conceptualization: Gimena Hernandez, Olatz Garin, Montse Ferrer.

Data curation: Àngels Pont, Laurent Laforest.

Formal analysis: Gimena Hernandez, Àngels Pont.

Funding acquisition: Jordi Alonso, Eric Van Ganse, Montse Ferrer.

Investigation: Alexandra L. Dima, Eric Van Ganse, Laurent Laforest, Montse Ferrer.

Methodology: Gimena Hernandez, Àngels Pont, Jordi Alonso, Laurent Laforest, Montse Ferrer.

Project administration: Alexandra L. Dima, Àngels Pont, Laurent Laforest, Montse Ferrer.

Resources: Montse Ferrer.

Supervision: Olatz Garin, Montse Ferrer.

Validation: Marc MartÂPastor.

Writing ± original draft: Gimena Hernandez.

Writing ± review & editing: Alexandra L. Dima, Olatz Garin, Marc MartÂPastor, Jordi Alonso, Eric Van Ganse, Laurent Laforest, Marijn de Bruin, Karina Mayoral, Montse Ferrer.

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5. CLINICAL IMPLICATION AND FUTURE RESEARCH LINES

The results of the studies presented in the current doctoral thesis have provided an important cumulative of evidence focused on LABA safety, treatment adherence and asthma impact on patients´ health-related quality of life. On one hand, this evidence may enhance clinical management of patients by applying the results obtained and, on the other hand, it also allowed the identification of important knowledge gaps in this field which could be useful to plan future research lines.

Regarding clinical implications in the management of patients with asthma, our results indicate that it would be necessary to focus on two important aspects: adherence and asthma control. Adherence to asthma therapy has been shown to be an integral part of an effective disease management. Furthermore, adherence may play a key role on the stepwise approach recommended by GINA guidelines, based on the lowest dose of appropriate therapy, to optimize symptoms and risk, but stepped up as required to improve control. Monitoring adherence is basic to decide if therapy step-ups are necessary in order to avoid unnecessary treatment escalations and, therefore, possibly avoidable adverse effects of medication. As in other chronic conditions, nonadherence to treatment is highly prevalent and must be identified and addressed accordingly by physicians and caregivers with a patient-orientated view.

The understanding of the multifactorial nature of the determinants of nonadherence is essential, and it must be assimilated and taken into account by health professionals to avoid falling into the common belief that patients are solely responsible for taking their treatment as prescribed. Knowledge of the underlying processes and determinants that affect adherence can be very useful for clinical practice by developing intervention programs for the detection of patients at risk and the establishment of appropriate measures to improve patient patterns of medication administration. Since it is clear that patients implement controller use recommendations better if they believe more strongly in the necessity of using inhalers, and if they hold other positive beliefs and less concerns about using them, it is necessary to highlight the importance of coordinating efforts to provide counselling and education about the disease itself, its recommended treatment and feasible goals. Efforts to improve asthma outcomes

should include educational strategies for both patients and health care providers that target the promotion of adherence, such as more suitable care, self-monitoring, reinforcement, reminders, and other forms of additional attention or supervision.

Good symptom control is the main long-term goal in asthma management to allow developing life without limitations. Our results highlight asthma control as being the most relevant factor to explain impact of this disease on health-related quality of life, suggesting that its improvement could alleviate the large disease impairment found in patients with uncontrolled asthma. This cross-sectional finding needs to be confirmed with longitudinal data. Asthma control, inhaler technique and adherence should be assessed at every opportunity by the different health care professionals and settings, such as routine prescribing or dispensing. This control-based management implies that treatment should be adjusted in a continuous cycle of assessment, treatment and review of patient response. A regular and structured assessment will allow identifying patients with poor asthma control, to optimise outcomes and minimise costs and risks for the patient and the community.

An important gap of knowledge consistently detected in this doctoral thesis was evidence about childhood asthma. This gap has already been underpinned by many other investigators in the field, as the difficulties associated with the research in this particular age are well known. In our case, the observational systematic review on safety of long-acting beta-agonists could not perform a specific analysis in children as planned, because there was a lack of studies providing information on them. Furthermore, during the implementation of the ASTRO-LAB project we found a special difficulty in including children in the cohort recruited in France and the United Kingdom. Considering this relevant gap and that the ASTRO-LAB project did not include Spanish patients, we have planned a new project entitled ARCA (Asthma Research in Children and Adolescents) to create a Spanish cohort of children with asthma following the methodology of the ASTRO-LAB study. This new project aims to assess the risk of severe asthma exacerbations in children with asthma treated with long-acting beta-agonists, compared with those treated only with inhaled corticosteroids, and also to assess the health-related quality of life of children with asthma in Spain and its relationship with treatment adherence and symptom control, according to their type of treatment and age.

ARCA is a prospective multicentre observational study, with 2 years of follow-up on children with persistent asthma in Spain. Recruitment is taking place in primary care offices of

paediatricians from the Paediatric Primary Care Spanish Association Airways Group and collaborators. Inclusion and exclusion criteria of ASTRO-LAB project were applied, except for age - which was limited to 6-14 years old. Assessments include computer-assisted telephone interviews every 6 months, and monthly questionnaires administered through a smartphone app. Similarly to ASTRO-LAB, outcomes evaluation includes occurrence of severe asthma exacerbations, asthma control and health-related quality of life. The ARCA Spanish cohort would make possible the evaluation of LABA safety specifically in children in conjunction with the ASTRO-LAB children sample, as well as to give answers to important research questions about childhood asthma in Spain.

Finally, it is important to remark that principal results on the ASTRO-LAB project will be described in a manuscript under preparation entitled "Assessing LABA safety in routine asthma care: results from the longitudinal ASTRO-LAB cohort study". Preliminary results presented in the final ASTRO-LAB symposium, celebrated together with the Respiratory Effectiveness Group in 2016 in Lyon, were consistent with those obtained in the large randomized clinical trials mandated by the FDA that indicate that LABAs are safe to use in combination with ICs.

6. CONCLUSIONS

The current evidence from non-randomized studies shows that combined treatment of long-acting beta-agonists and inhaled corticosteroids is not associated with higher risk of serious adverse events. Our systematic review identified major gaps in the available literature; accordingly our key recommendations for further research are to conduct prospective cohort studies, to perform studies among the paediatric population, and to include mortality as a primary outcome. Accumulative valid data is needed to allow evidence-based decisions taking into account safety of long-acting beta-agonists plus inhaled corticosteroids in asthma treatment.

Our findings suggest that adults with asthma implement controller use recommendations better if they believe more strongly in the necessity of using inhalers, and possibly if they hold other positive beliefs and less concerns about using inhalers. Younger adult patients may be more at risk of nonadherence. Other patient-, condition- and therapy-related factors are either mostly unrelated to adherence or partly studied, and little is known about the role of social, economic and healthcare factors. Initiation and discontinuation of controller use and reliever use behaviours were scarcely explored. Moreover, the methodological limitations identified diminish the strength of current evidence. Our key recommendations for further research are to improve methodology and use established theoretical frameworks, which should enable the development of a cumulative evidence base of causes of nonadherence to asthma inhalers among adults.

Given its unique perspective on asthma care, the ASTRO-LAB project (Assessment of the Safety of long-acting beta-agonists in asthma in routine care by combining health care data bases and direct patient-follow-up) will provide new information on safety of substantial interest to regulators, health care practitioners, patients and the scientific community. Moreover, developing new methods of assessing drug exposure and adherence will make a valuable contribution beyond the field of asthma care. The investigation of multifaceted insight into asthma management in two different medical systems may be informative for the improvement of asthma care.

Our results provide support to the construct validity of EQ-5D-5L administered online to patients with asthma, based on its discriminant ability for distinguishing among health-related known groups, as well as its acceptable ceiling effect. The completion of the EQ-5D-5L by most of the online survey respondents supports the feasibility of this administration form. Since it was developed as a preference-based health status measure, the EQ-5D-5L index allows combining both length and quality of life, and calculates Quality-Adjusted Life-Years to measure health outcomes in economic evaluations. All these findings suggest that the new EQ-5D with 5 levels is a promising instrument to compare the efficiency of different programs or treatment strategies for asthma patients. Nevertheless, further studies are recommended to evaluate the responsiveness over time of the EQ-5D-5L among asthma patients.

Findings confirm our hypothesis that the worse health-related quality of life in women with asthma compared with men seems not to imply real gender inequalities in asthma impact, except for the youngest age group. Our results support considering very young women (18-24 years old) a high-risk group. Therefore, the large health-related quality of life impact of asthma in this group calls for closer monitoring of symptoms control, asthma self-management programs and adequate medical therapy. In general, persistent asthma has a moderately negative impact on patients of both genders at an adult age (25-40 years old). Our study identifies asthma control as the main factor associated to health-related quality of life, suggesting that its improvement could alleviate the large impairment found in women and men with uncontrolled asthma. Effective support options need to be explored for groups at high risk of suffering a large negative asthma impact on health-related quality of life.

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8. ANNEX

Gimena Hernández, Olatz Garin O, Yolanda Pardo, Gemma Vilagut, Angels Pont, Mónica Suárez, Montse Neira, Luis Rajmil, Iñigo Gorostiza, Yolanda Ramallo-Fariña, Juan Cabases, Jordi Alonso, Montse Ferrer. ***Validity of the EQ-5D-5L and reference norms for the Spanish population.*** Qual Life Res. 2018 May 16. doi: 10.1007/s11136-018-1877-5. IF: 2.392, Q1 (15 de 88 Health Policy & Services)

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Validity of the EQ–5D–5L and reference norms for the Spanish population

Gimena Hernandez[1,2,3] · Olatz Garin[1,3,4] · Yolanda Pardo[1,2,3] · Gemma Vilagut[1,3] · Àngels Pont[1,3] · Mónica Suárez[5] · Montse Neira[5] · Luís Rajmil[1] · Inigo Gorostiza[6,7] · Yolanda Ramallo-Fariña[7,8] · Juan Cabases[9] · Jordi Alonso[1,3,4] · Montse Ferrer[1,2,3]

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Abstract

Background and objective The EuroQol 5 dimensions 5 levels (EQ–5D–5L) is the new version of EQ–5D, developed to improve its discriminatory capacity. This study aims to evaluate the construct validity of the Spanish version and provide index and dimension population-based reference norms for the new EQ–5D–5L.

Methods Data were obtained from the 2011/2012 Spanish National Health Survey, with a representative sample ($n = 20{,}587$) of non-institutionalized Spanish adults (≥ 18 years). The EQ–5D–5L index was calculated by using the Spanish value set. Construct validity was evaluated by comparing known groups with estimators obtained through regression models, adjusted by age and gender. Sampling weights were applied to restore the representativeness of the sample and to calculate the norms stratified by gender and age groups. We calculated the percentages and standard errors of dimensions, and the deciles, percentiles 5 and 95, means, and 95% confidence intervals of the health index.

Results All the hypotheses established a priori for known groups were confirmed ($P < 0.001$). The EQ–5D–5L index indicated worse health in groups with lower education level (from 0.94 to 0.87), higher number of chronic conditions (0.96–0.79), probable psychiatric disorder (0.94 vs 0.80), strong limitations (0.96–0.46), higher number of days of restriction (0.93–0.64) or confinement to bed (0.92–0.49), and hospitalized in the previous 12 months (0.92 vs 0.81).

Conclusions The EQ–5D–5L is a valid instrument to measure perceived health in the Spanish-speaking population. The representative population-based norms provided here will help improve the interpretation of results obtained with the new EQ–5D–5L.

Keywords EuroQol · EQ–5D–5L · Health-related quality of life · Health status · Utilities · Questionnaires · Reference values · Validity

Introduction

Patient-reported outcomes (PROs) have increasingly gained relevance in research, clinical practice, and health planning. Perceived health, health-related quality of life (HRQL), and other PRO constructs provide complementary information to traditional health indicators based on morbidity and mortality [1, 2]. PROs are essential to describe health in countries after the epidemiological transition, where life expectancy has been steadily increasing and indicators related to mortality may not be sensitive to the expected results of new treatments and public health interventions.

Psychometric HRQL instruments generate scores on several health dimensions (profiles), while econometric instruments generate a single global score or index, which incorporates society's preferences for health states (utilities). This feature makes econometric instruments suitable for cost–utility analysis by calculating quality-adjusted life years (QALYs). The most widely used econometric instrument in the world is the EuroQoL which, since its development in 1991, has been adapted into more than 170 languages and

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✉ Olatz Garin
ogarin@imim.es

✉ Montse Ferrer
mferrer@imim.es

Extended author information available on the last page of the article

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countries [3]. It is a generic instrument, applicable both in the general population and in patients with different conditions. There is no doubt that its econometric nature, its low administration burden, and its contrasted metric properties are the main reasons for its wide use. However, the high percentage of individuals with the best health state in the EQ–5D has been repeatedly highlighted as a limitation, since this may reduce its capacity to discriminate within good health [4, 5] and its responsiveness in some health areas [6–8].

The EQ–5D–3L is a brief multi-attribute health status measure composed of five questions with Likert response options (descriptive system) and a visual analogue scale (EQ-VAS). The descriptive system covers five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with three levels of severity in each dimension (no problems, some problems, and extreme problems). To improve the instrument's sensitivity and to reduce ceiling effects, the EuroQol group has developed a new version with more response options, the EuroQol 5 dimensions 5 levels (EQ–5D–5L). This change from 3 to 5 levels [9] implies an increase in the number of possible health states from 243 (3^5) to 3125 (5^5). The studies assessing its metric characteristics suggest that the new EQ–5D–5L version decreases the ceiling effect [10–17], improves its discrimination capacity [9, 11, 14] without reducing its reliability [9, 12, 14, 15], and provides more precise measurement at individual and group levels [18].

The difficulty in interpreting HRQL scores has been identified as one of the main barriers to the widespread use of this type of outcomes [19]. One strategy used to help interpret scores, especially in generic questionnaires, has been providing reference norms based on general population [20–22]. These indicate a standard value that facilitates the interpretation of the questionnaire scores in comparison to what would be expected, according to age and gender [23]. The EuroQol group has published a book with the population reference norms of the EQ–5D original three-level version from 18 countries [24] including the Spanish standards [25]. Reference norms of the five-level version have also been published [26] for Spain. However, as the development of the Spanish value set needed to calculate the EQ–5D–5L index is quite recent, there are neither studies on its validity nor reference norms for our country with this index [27]. The existing publications covering these issues [26, 28] showed results on the five dimensions and the health index constructed with the 3L–5L crosswalk value set.

Moreover, a multistage sampling process, such as that applied in the Spanish National Health Survey (Spanish NHS) [29] with which the EQ–5D–5L Spanish norms were developed, requires the use of weights to obtain representative estimations of the population, and a specific method for complex sample survey designs to estimate associate errors. Weights assign to each individual their corresponding proportion in the population, to avoid biased estimators. For example, individuals older than 55 years, those retired, and people with a higher number of chronic conditions are over represented when these sample weights are not applied in the 2011–2012 Spanish NHS. Further to weights, as the associated errors for estimators in studies with a multistage sampling process differ from those with a simple random sample, it is necessary to apply a complex sample survey design method to calculate them correctly. However, the already published EQ–5D–5L Spanish norms [26] were calculated without these sample weights from the Spanish NHS nor with any specific method to estimate associated errors for complex sample survey designs. Therefore, these norms may not be representative of the Spanish population.

The main objectives of this study were to evaluate the construct validity and to obtain the reference norms for the dimensions and health index of the EQ–5D–5L in a representative sample of the non-institutionalized Spanish adults.

Methods

Sample selection and design

Data came from the 2011/2012 Spanish NHS. It is a 3-stage sampling, with a first random selection of 2000 census tracts in each autonomous community (stratifying according to the population size of the municipalities), then a random selection of 24,000 households, and a final selection of an individual aged 15 or older and one below this age per home. Information was collected through a computer-assisted personal interview, held in the homes between July 2011 and June 2012. Non-response rate was 33.8% after adding the homes reserved for replacement. Detailed information on the survey and sample construction can be consulted online from the Spanish Ministry of Health, Social Services and Equality [29].

In the 2011/2012 edition, the survey included for the first time the EQ–5D–5L questionnaire, together with the usual battery of questions to evaluate different health-related aspects and socio-demographic characteristics (age, gender, level of studies, marital status, and work situation) among other. For the current study focused on adults, individuals under 18 years of age have been excluded.

The EQ–5D–5L

The EQ–5D–5L's descriptive system is composed of the EuroQol's 5 original dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The new 5-level Likert-type scales have the following answer options: No problem, slight problems, moderate problems,

severe problems, and extreme problems or unable to perform. The instrument also includes a visual analogue scale (VAS) on general health: "We would like to know how good or bad your health is today." The descriptive system for the new version was tested in the United Kingdom (UK) and Spain in 2005, as well as the evaluation of the semantic equivalence [30].

Social preference values of the EQ–5D–5L were obtained in parallel in the UK, Canada, Holland, and Spain, using a standardized protocol designed by the EuroQol group [31] to try to reduce heterogeneity to its minimum, since it was widely highlighted in the social preference estimations of the previous 3-level version [32]. The general population studies carried out to elicit the EQ–5D–5L social preferences combine the techniques of time trade-off and discrete choice [31]. Following this protocol, the definitive social preferences were obtained for the Spanish general population [27]. Applying the social preferences to the individual descriptive system answers, a health index was obtained with a range from 1 (perfect health) to negative values (for those health states considered worse than death), 0 being the value assigned to death.

Variables selected to evaluate construct validity

Based on the Spanish NHS content, the following health indicators were selected to evaluate the construct validity through known groups: education, self-reported chronic conditions, mental health measured by the General Health Questionnaire (GHQ), the restrictions of usual activities due to health reasons, and hospitalization in the previous 12 months. Education degree was transformed into a variable with 4 levels according to the number of years of study: less than compulsory secondary education, finished compulsory secondary education, higher secondary or equivalent, and university studies.

In order to have groups with a balanced number of individuals, a 4-category variable was created with the number of self-reported chronic conditions experienced in the last 12 months (out of a list of 30 included in the survey): none, 1 chronic condition, 2–3, and 4 or more. The GHQ mental health questionnaire [33] measures symptoms of anxiety, depression, and/or insomnia [34]. The GHQ short form has 12 items with response options in a 4-point Likert-type scale. To calculate the global score, responses are dichotomized by assigning value 0 to answer options 1–2, and value 1 to options 3–4. A global score ≥ 3 is associated with a high probability of presenting a psychiatric disorder.

The Spanish NHS includes two questions related to activity restriction due to health reasons in the 2 weeks prior to the interview, and one on limitations in the previous 6 months. The first ones gathered information on having had to reduce or limit usual activities during at least half a day, and having been forced to stay in bed (or in hospital) for more than half a day. Those individuals who answered positively were asked about the total number of days affected, which was dichotomized into 1–7 days and more than 1 week. The self-perceived limitation question, known as the "Global Activity Limitation Indicator" (GALI), was: *For at least the last 6 months, have you been limited because of a health problem in activities people usually do? Strongly limited; limited; not limited* [35]. The NHS also includes a question about the number of days hospitalized in the previous 12 months. This variable has been dichotomized for known groups' validity evaluation into having been hospitalized or not.

Data analysis

To describe the characteristics of the sample, the crude frequencies and crude and weighted percentages were calculated. The construct validity of the EQ–5D–5L was assessed by comparing known groups, testing the hypotheses established a priori which were derived from the existing literature [17, 20, 21, 36]. Poorer health (reporting problems at dimensions, or lower values in the EQ–5D–5L index and VAS) was expected in those groups with lower education level, as well as a greater number of chronic conditions, a high probability of presenting psychiatric disorder (evaluated with the GHQ), more limitation in daily activities, higher number of days with restriction or in bed, and hospitalization in previous 12 months. It was specifically hypothesized that individuals with a high probability of presenting a psychiatric disorder would more frequently report problems in the anxiety/depression dimension. Strongly limited individuals, people with a higher number of days with restriction or in bed, and those hospitalized in the previous 12 months, were hypothesized to more frequently report problems in mobility, usual activities, and pain dimensions. To test the differences among known groups, general linear models were applied to the health index and VAS score, and a multinomial logit model to the dimensions, in order to adjust by age and gender.

To graphically show the health differences according to age and gender, figures were created with the different results obtained through the EQ–5D–5L for men and women in each age group (in 10-year intervals): percentage of individuals with no problem in each dimension, and boxplots for the health index and the VAS score. Reference norms based on the Spanish population were estimated stratifying by gender and age groups, calculating the percentage and standard error for each level in the dimensions and the deciles, percentiles 5 and 95, mean, standard deviation (SD), and its 95% confidence interval (95% CI) for both the health index and the VAS score.

The analyses were carried out with the statistic package R. In all analyses, sampling weights were applied to guarantee the sample's representativeness. The standard errors were estimated by the Taylor series linearization method for complex sample survey designs.

Results

Table 1 shows the characteristics of the sample of individuals aged 18 years or older from the Spanish NHS ($N = 20{,}587$), both raw and applying sample weights. Half of the sample were women, and the mean age was 48 (SD = 18) years. More than half of the respondents were married (57.6%) and 46.0% were working at the time of the survey. Regarding studies, 32% had completed compulsory secondary education, 13% higher secondary education, 15.5% vocational training, and 16% university studies. Approximately one-third of the sample stated they had presented no chronic conditions in the last 12 months, and most of them had not suffered any restriction from usual activity (88.4%) nor been confined to bed (94.4%) in the previous 2 weeks, or had not been hospitalized (91.3%) in the previous 12 months. According to the GHQ, 20.8% of individuals were likely to present a psychiatric disorder.

The most marked differences between the crude and weighted data were observed in the distribution by age groups, for example, 18.2 versus 13.4% in the 25–34 year-old group and 34.6 versus 44.1% among those over 55 years of age. In this sense, the differences in the proportion of retired individuals (20.7 vs 28.6%) and of those with 3 or more chronic conditions (38.9 vs 33.3%) also stand out.

Figure 1 shows the percentage of individuals with no problems in each dimension of the EQ–5D–5L, according to gender and age group. The dimensions of mobility, self-care, and activities presented a similar distribution: ≥ 90% of individuals without problems up to 45–54 years of age, and from then on the percentage diminishes as the group's age increases, especially in women. In the pain dimension, there was a higher percentage of individuals with no problems in the younger groups and the gender differences were larger. The dimension of anxiety/depression, however, was the one that showed the fewest differences among age groups and highest differences according to gender.

Figure 2 shows the boxplots with the medians, percentiles 25 (Pc25) and 75 (Pc75), and extreme values of both the EQ–5D–5L health index and the VAS score. For instance, for the group of women aged 75–84 the index median was 0.82, the Pc25 0.62, Pc75 0.95, and the interquartile range (IQR) 0.33. The outliers are those values from the sample located between Pc25-3*IQR and Pc25-1.5*IQR, while extreme outliers are those which differ considerably from the rest of the set (lower than Pc25-3*IQR). In this example, the outliers are those between 0.17 and − 0.38 (represented by circles) and the extreme outliers are placed below − 0.38 (represented by stars). In both genders, the index clearly showed differences according to age, with values diminishing in the groups with older individuals. When assessing the general health with the VAS, gender differences were less marked and the relationship with age was more linear.

Table 2 shows the percentage of individuals reporting problems by dimension and means of EQ–5D–5L index and VAS, adjusted by age and gender. These construct validity results based on known groups confirmed the a priori hypotheses, with EQ–5D–5L estimators worsening as the variables' categories indicate lower education or more severe health status. All contrasts were statistically significant ($P < 0.001$). The pattern of dimensions presented the expected results, 12.66% of individuals with a high probability of psychiatric disorder reported problems in the anxiety/depression dimension, while only 1.44% reported them in the rest of the sample ($P < 0.001$). Strongly limited individuals, people with a higher number of days with restriction or in bed, reported problems in the mobility dimension (4.20, 1.41, and 2.53%) more frequently than those who were not limited (0.10, 0.11, and 0.13%). This pattern was also observed for usual activities (8.55, 1.75, and 2.63% vs a negligible percentage among non-limited individuals) and pain dimensions (20.38, 11.34, and 13.06 vs < 2%).

The utility index showed the highest differences between extreme groups in the limitation of daily activities in the 6 months prior to the interview (mean: 0.96 vs 0.46) and in the number of days confined to bed (mean: 0.92 vs 0.49). In contrast, the education level showed the smallest differences (mean: 0.94 vs 0.87). The VAS score, similarly to the health index, showed a worse perceived health in the groups with a lower education level (from 79.09 to 71.78), higher number of chronic conditions (84.31–63.16), probable psychiatric disorder (79.09 vs 63.78), strong limitations (79.65–48.66), a higher number of days of restriction (77.46–55.48) or confinement to bed (76.53–47.38), and with hospitalization in the previous 12 months (76.30 vs 67.14).

The EQ–5D–5L reference norms are presented in the annex, including each of the 5 dimensions, the health index, and the VAS score, for the whole sample and separately for women and men, stratified by age groups (18–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, and 85 or older).

Discussion

This is the first study to evaluate the construct validity and to obtain the Spanish reference norms of the EQ–5D–5L health index calculated with the new country-specific value set. Until now, publications assessing construct validity and estimating reference norms of the Spanish version of the

Table 1 Socio-demographic characteristics of adult individuals from the 2011–2012 Spanish National Health Survey ($N = 20,587$)

	n (Raw%)	Wt%	Standard error
Gender			
Men	9412 (45.7%)	48.6	0.412
Women	11,175 (54.3%)	51.4	0.412
Age			
18–24	1236 (6.0%)	8.8	0.283
25–34	2757 (13.4%)	18.2	0.376
35–44	3951 (19.2%)	20.6	0.364
45–54	3574 (17.4%)	17.8	0.337
55–64	3173 (15.4%)	13.7	0.283
65–74	2731 (13.3%)	10.5	0.243
75–84	2350 (11.4%)	7.8	0.210
85 or more	815 (4.0%)	2.6	0.120
Marital status			
Single	5490 (26.7%)	29.9	0.434
Married (or living with a partner)	10,979 (53.4%)	57.6	0.463
Widow/er	2746 (13.4%)	7.6	0.189
Divorced or separated	1351 (6.6%)	4.9	0.169
Work status			
Employed	8736 (42.5%)	46.0	0.474
Unemployed	2623 (12.8%)	14.9	0.357
Retired	5877 (28.6%)	20.7	0.349
Student	753 (3.7%)	5.6	0.231
Disabled	438 (2.1%)	2.1	0.130
Household chores	2083 (10.1%)	10.2	0.272
Other	51 (0.2%)	0.3	0.069
Level of education			
Cannot read nor write	490 (2.4%)	1.9	0.129
Has attended school for at least 5 years	2563 (12.5%)	9.8	0.296
Attended school for 5 or more years without reaching the last course	2596 (12.6%)	10.9	0.309
Compulsory secondary education	6372 (31.0%)	32.2	0.493
Higher secondary education	2403 (11.7%)	13.3	0.333
Intermediate vocational training or equivalent	1753 (8.5%)	9.1	0.262
Higher vocational training or equivalent	1246 (6.1%)	6.4	0.228
University degree/studies	3137 (15.3%)	16.3	0.406
HEALTH STATUS			
Number of chronic conditions, previous 12 months			
None	5530 (26.9%)	31.6	0.492
1 chronic condition	4142 (20.2%)	21.3	0.362
2 chronic conditions	2909 (14.2%)	13.8	0.291
3 chronic conditions	2199 (10.7%)	9.6	0.245
4 chronic conditions	1588 (7.7%)	6.7	0.204
5 or more chronic conditions	4192 (20.4%)	17.1	0.351
Mental health (GHQ-12)			
Not probable	15,779 (77.8%)	79.3	0.408
Probable psychiatric disorder	4499 (22.2%)	20.7	0.408
Limitation in daily activities, previous 6 months			
Strongly limited	887 (4.3%)	3.6	0.154
Limited, but not strongly	3797 (18.4%)	16.5	0.354
Not limited	15,896 (77.2%)	79.9	0.383

Table 1 (continued)

	n (Raw%)	Wt%	Standard error
Number of days with restriction, previous 2 weeks			
0	18,055 (87.9%)	88.4	0.299
1–7	1556 (7.6%)	7.4	0.230
8–14	924 (4.5%)	4.2	0.176
Number of days in bed, previous 2 weeks			
0	19,384 (94.2%)	94.4	0.210
1–7	935 (4.5%)	4.5	0.188
8–14	252 (1.2%)	1.1	0.086
Hospitalization, previous 12 months			
No	18,650 (90.7%)	91.3	0.237
Yes	1910 (9.3%)	8.7	0.237

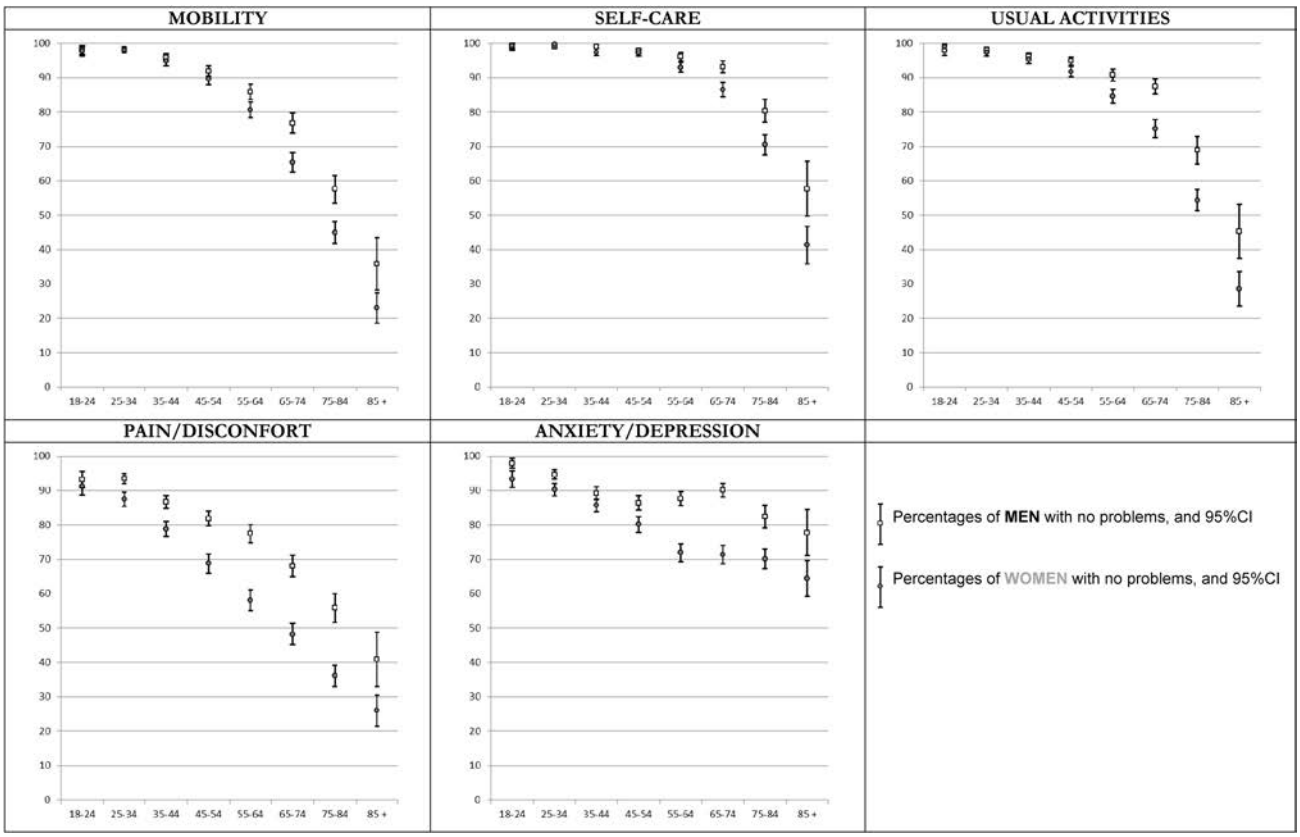

Fig. 1 Percentages of individuals reporting no problems by dimension of EQ–5D–5L index regarding age and gender

EQ–5D–5L showed results regarding the five dimensions and the health index which had been constructed with the 3L–5L crosswalk value set. Moreover, the EQ–5D–5L Spanish population norms are shown for the first time applying sampling weights and methods for complex sample survey designs, and presented with their associated measure of error and percentiles for the EQ–5D–5L index and VAS. As mentioned above, reference norms help to interpret results in instruments that reflect complex and multidimensional constructs by comparing them to a control group. Having population reference norms in Spain is of fundamental importance, as they will permit estimating the impact of a specific disease, monitoring this impact's evolution through time, identifying populations that need special attention, and carrying out comparisons among different countries.

The results obtained confirmed the a priori defined hypotheses to evaluate the construct validity of the EQ–5D–5L according to known groups. The magnitudes

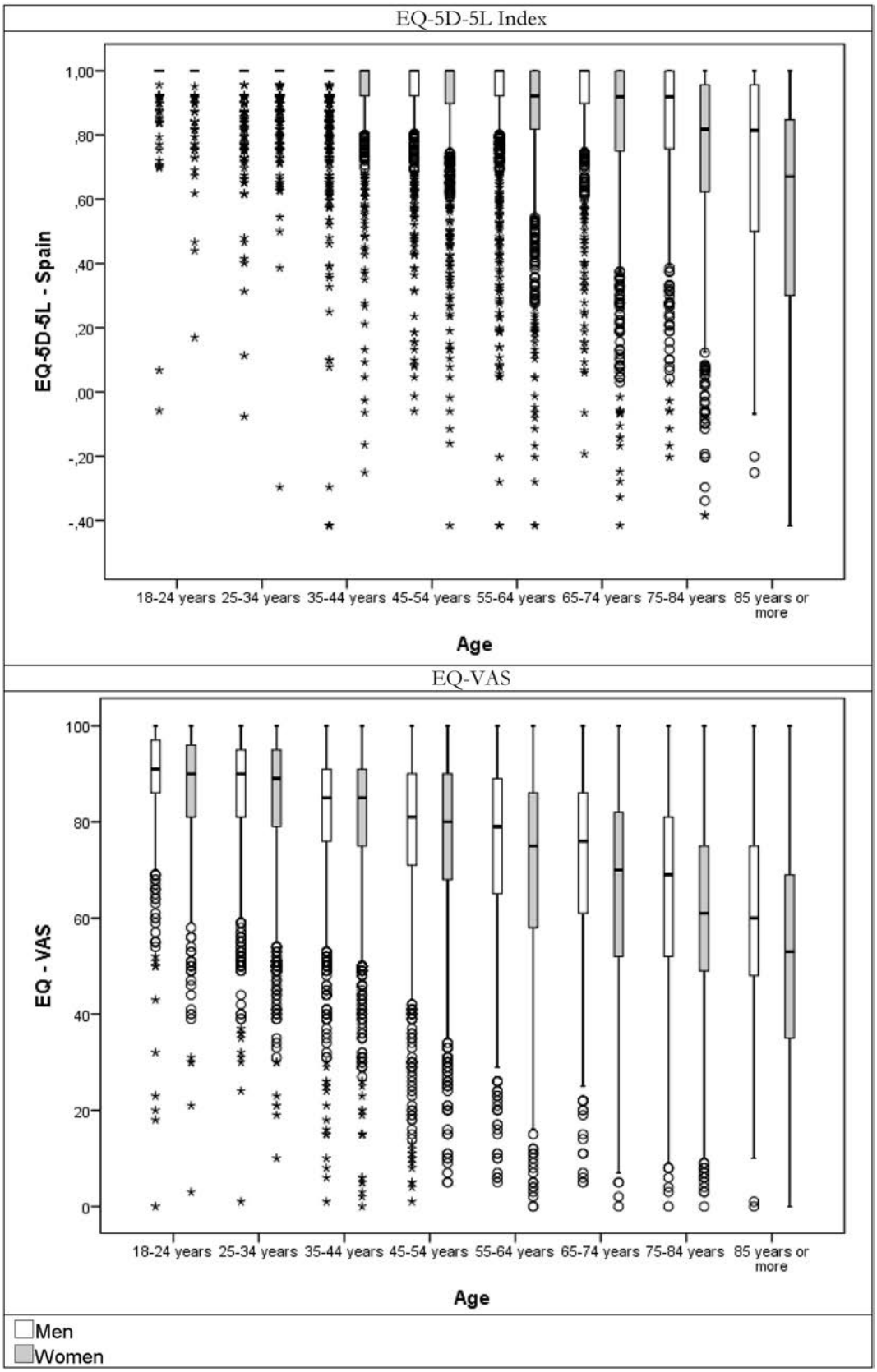

Fig. 2 EQ–5D–5L index and EQ-VAS boxplot, regarding age and gender

Table 2 EQ–5D–5L construct validity based on known groups: percentages of individuals reporting problems by dimension, and means [95% CI] of EQ–5D–5L health index and VAS score

Unweighted *n* (wt%)	% of individuals reporting problems					Health index	VAS score
	Mobility 3650 (14.2%)	Self-care 1635 (6.1%)	Activity 2839 (11.0%)	Pain 5904 (25.4%)	Anxiety 3407 (14.96%)	Adjusted mean [95% CI]	Adjusted mean [95% CI]
Level of education							
Less than compulsory secondary	0.41%	0.08%	0.43%	3.44%	5.09%	0.87 [0.87–0.88]	71.78 [71.28–72.28]
Compulsory secondary education	0.32%	0.05%	0.29%	2.97%	4.50%	0.91 [0.90–0.91]	75.26 [74.84–75.67]
Higher secondary or equivalent	0.20%	0.04%	0.22%	2.14%	3.30%	0.92 [0.92–0.93]	77.32 [76.85–77.78]
University	0.13%	0.03%	0.13%	1.52%	2.28%	0.94 [0.94–0.95]	79.09 [78.49–79.69]
P value	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*
Number of chronic conditions, previous 12 months							
None	0.11%	0.01%	0.08%	1.26%	2.77%	0.96 [0.96–0.97]	84.31 [83.88–84.75]
1 chronic conditions	0.25%	0.04%	0.26%	4.72%	6.16%	0.96 [0.95–0.96]	80.40 [79.92–80.88]
2–3 chronic conditions	0.42%	0.07%	0.44%	7.87%	11.48%	0.93 [0.93–0.94]	75.55 [75.12–75.98]
4 or more chronic conditions	1.54%	0.24%	1.80%	26.55%	31.47%	0.79 [0.79–0.80]	63.16 [62.72–63.60]
P value	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*
Mental health (GHQ-12)							
Not probable	0.10%	0.02%	0.08%	1.33%	1.44%	0.94 [0.94–0.94]	79.09 [78.85–79.34]
Probable psychiatric disorder	0.43%	0.09%	0.46%	4.95%	12.66%	0.80 [0.80–0.81]	63.78 [63.32–64.24]
P value	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*
Limitation in daily activities, previous 6 months							
Not limited	0.10%	0.02%	0.08%	1.76%	3.62%	0.96 [0.96–0.96]	79.65 [79.41–79.88]
Limited, but not strongly	1.15%	0.27%	1.42%	13.13%	14.21%	0.80 [0.80–0.80]	63.69 [63.20–64.19]
Strongly limited	4.20%	1.88%	8.55%	20.38%	25.15%	0.46 [0.45–0.47]	48.66 [47.62–49.70]
P value	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*
Number of days with restriction, previous 2 weeks							
0 days	0.11%	0.02%	0.09%	1.45%	2.79%	0.93 [0.93–0.93]	77.46 [77.23–77.70]
1–7 days	0.51%	0.10%	0.58%	7.96%	8.64%	0.81 [0.80–0.82]	64.49 [63.68–65.29]
8–14 days	1.41%	0.29%	1.75%	11.34%	10.56%	0.64 [0.63–0.65]	55.48 [54.43–56.54]
P value	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*
Number of days in bed, previous 2 weeks							
0 days	0.13%	0.03%	0.12%	1.62%	2.77%	0.92 [0.92–0.92]	76.53 [76.30–76.77]
1–7 days	0.70%	0.14%	0.92%	9.04%	10.32%	0.76 [0.75–0.77]	60.48 [59.43–61.54]
8–14 days	2.53%	0.42%	2.63%	13.06%	15.79%	0.49 [0.47–0.51]	47.38 [45.28–49.49]
P value	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*
Hospitalization, previous 12 months							
No	0.15%	0.03%	0.14%	1.81%	2.90%	0.92 [0.91–0.92]	76.30 [76.05–76.54]
Yes	0.49%	0.10%	0.56%	4.15%	5.36%	0.81 [0.81–0.82]	67.14 [66.58–67.90]
P value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Percentages and means are adjusted by age and gender

Italics indicates the Confidence Interval

of the differences between extreme groups are quite similar (both in direction and magnitude) to those published for the EQ–5D–3L with data from the 2006 Catalan Health Interview Survey (CHIS) [17]. In our study, the difference between the group with no chronic conditions and the one with 5 or more was 0.17 (0.31 in the CHIS), and the difference between no days and more than 1 week of restriction was 0.30 and 0.43 for bed rest (0.25 in the CHIS for any type of restriction). All these results support the construct validity of the EQ–5D–5L for the Spanish population. Moreover, the majority of the differences identified are greater than 0.061 ± 0.008, which has been described as the EQ–5D–5L's minimum important difference (MID), indicating their clinical relevance [37].

Reference norms allow the comparison of the observed results in individuals or groups with the general population by identifying in the table of norms the most appropriate gender and age group. The difference between the observed score and the value found in the table provides the deviation from the reference population. For example, the EQ–5D–5L index mean value for women is higher than 0.90 for those under 55 years of age, and below 0.60 for those who are 85 or older. The VAS mean score for men is between 90 and 80 for those under 45 years old, and below 60 for those at the older group (detailed norms are available at the annex).

According to the abundant available evidence on the effect of age and gender on health [38–41], the results of our study (worse HRQL in women and better in younger groups) confirm the need to generate reference norms stratified by these characteristics, such as the ones in this article's annex. In addition, taking into account the relevant precautions due to the cross-sectional nature of the study, the age distribution reflects the worsening of health associated with aging (more pronounced in the dimension of pain/discomfort) except for the mental component, which remains relatively stable throughout life [41].

Our results show lower percentages of individuals with no problems in all dimensions, compared to the Spanish population reference norms of the EQ–5D–3L [24]: 82.5 versus 86.3% in mobility; 92.1 versus 95.9% in self-care; 86.3 versus 88.3% in usual activities; 71.7 versus 77.1% in pain/discomfort; and 83.6 versus 92.2% in anxiety/depression. The EQ–5D–3L norms were obtained from a representative sample of the Spanish population (2001–2003) with a similar sampling approach and characteristics, but with a lower sample size (5473 vs 20,587) and a slightly lower response rate (66.2 vs 78.5%) than the Spanish NHS. Although the lower proportion of individuals without problems is likely due to the expansion from 3 to 5 levels (which allows reporting slight problems), we cannot discard other reasons related to time point or sampling procedures. The distribution in the five EQ–5D–5L dimensions continues to show a marked aggregation of individuals in the best response option (no problems), but this was expected in the non-institutionalized population.

The smaller ceiling effect obtained with the EQ–5D–5L index has also been described in studies that have compared the two EQ–5D versions in other countries: a 12.5% decrease of ceiling effect in Germany [5, 42], 8.6% in England [10], 5.9% in Italy [16], and 4.5% in South Korea [15]. Focusing on the EQ–5D–5L comparison between countries, our results are closer to the South Korean [15] population than to the German [42], United States [43], or Polish [44] populations. South Korea is the country with the highest prevalence of people answering 'no problems' in mobility (88%), self-care (97%), and usual activities (90%), while Spain is the country showing the highest proportion of individuals without problems in pain (74.6%) and anxiety/depression (85.4).

This is the first time that there are results from the health index of the new EQ–5D–5L in a representative sample of the Spanish population. The means obtained from the EQ–5D–5L health index are very similar to the reference norms of the EQ–5D–3L index [24], and the differences for each age group are very small (below ± 0.02). For instance, the highest difference is observed in the age group of 64–75 years, with means of 0.87 in 5L and 0.89 in 3L reference norms. These differences could be due to the 10-year lapse between both studies [45], the increase in the number of levels in the new version, or the method used to obtain the social preferences: time trade-off [46] in the EQ–5D–3L index and a mixed method in the EQ–5D–5L index [27, 31].

However, the general health VAS results are substantially higher in our study than in the EQ–5D–3L reference norms [24]. The differences are of a larger magnitude in the younger groups (means of 88.2 vs 82.0, in the 18–24-year-old group) and diminish as age increases (means of 69.8 vs 69.0 in the group aged 65–74). As the general health question and the VAS are identical in both versions of the EQ–5D VAS, differences between studies could only be due to the time lapse. In addition, this question on general health is much more global than the EQ–5D descriptive system. Given that it depends on personal values and expectations, social references, and other context factors, it is more probable for the response to vary considerably among generations and groups within the same society, than in the descriptive system with 5 dimensions or the health index.

The previously published reference norms for the EQ–5D–5L [26] offer raw estimators (unweighted) using the 3L–5L crosswalk value set and, even though they are similar, they are not the same as what was obtained using the new EQ–5D–5L Spanish value set, sample weights, and adequate associated errors. For example, the mean of the EQ–5D–5L index in women was 0.855 [26] versus 0.868 (95% CI 0.860–0.876) in the group that was 60–69 years old; 0.780 [26] versus 0.794 (95% CI 0.785–0.803) in the 70–79 years old group; 0.624 [26] versus 0.658 (95% CI

0.647–0.670) in the group aged 80–89; and 0.418 [26] versus 0.523 (95% CI 0.496–0.549) in the group of 90 or more years old.

When interpreting our results, the study's limitations should be considered. The Spanish NHS only includes the non-institutionalized population, thus leaving out of the study those individuals hospitalized, imprisoned, or in senior citizen homes, who have a worse health state and, therefore, resulting in an overestimation of the population's health. This needs to be taken into account when applying the norms in such groups or individuals. Furthermore, the whole Spanish NHS—including the EQ–5D–5L questionnaire—was administered through computer-assisted personal interviews, while self-administration is recommended for the EuroQol. However, a study comparing the interview and the self-completed EQ–5D–3L questionnaire showed little difference between both administration methods [47].

In conclusion, the study has confirmed the construct validity of the new Spanish version of the EQ–5D–5L, and has provided easy-to-use tables with reference norms for all stakeholders (e.g., healthcare planners, researchers, clinicians, patients) in order to interpret results for different purposes, such as establishing optimal goals in clinical management or evaluating changes at the individual and group level. The population norm tables in the annexes reflect granular reporting of descriptive statistics (estimators and their associated error) that facilitate the comparison of EQ–5D–5L results for individuals or specific groups with data for the average person in the general population with a similar age and/or gender.

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Author contributions GH analyzed and interpreted the data, drafted, and critically revised the manuscript and did the statistical analysis. OG provided supervision, conceived, and designed the study, and critically revised the manuscript. YP and GV analyzed and interpreted the data, and critically revised the manuscript. AP analyzed and interpreted the data, and did the statistical analysis. MS, MN, LR, IG, YR, and JC interpreted the data and critically revised the manuscript. JA provided supervision, conceived and designed the study, interpreted the data, and critically revised the manuscript. MF obtained funding, provided supervision, conceived and designed the study, interpreted the data, and critically revised the manuscript.

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Data availability The Spanish National Health Survey is an official statistic included in the National Statistical Plan. The agency responsible for the survey is the Ministry of Health, Social Services and Equality. The anonymized microdata of the Spanish National Health Survey can be requested for purposes of scientific research.

Compliance with ethical standards

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

Ethical approval The Spanish National Health Survey is a statistical operation included in the National Statistical Plan. The agency responsible for the survey is the Ministry of Health, Social Services and Equality and it is performed jointly with the National Statistics Institute according to the 2000 revision of the Helsinki Declaration.

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Affiliations

Gimena Hernandez[1,2,3] · Olatz Garin[1,3,4] · Yolanda Pardo[1,2,3] · Gemma Vilagut[1,3] · Àngels Pont[1,3] · Mónica Suárez[5] · Montse Neira[5] · Luís Rajmil[1] · Inigo Gorostiza[6,7] · Yolanda Ramallo-Fariña[7,8] · Juan Cabases[9] · Jordi Alonso[1,3,4] · Montse Ferrer[1,2,3]

Gimena Hernandez
gimenahernandez@gmail.com

Yolanda Pardo
ypardo@imim.es

Gemma Vilagut
gvilagut@imim.es

Àngels Pont
apont@imim.es

Mónica Suárez
msuarez@msssi.es

Montse Neira
mneira@msssi.es

Luís Rajmil
lrajmil@imim.es

Inigo Gorostiza
inigo.gorostizahormaeche@osakidetza.eus

Yolanda Ramallo-Fariña
yolanda.ramallofarina@sescs.es

Juan Cabases
jmcabases@unavarra.es

Jordi Alonso
jalonso@imim.es

1 Health Services Research Group, IMIM (Hospital del Mar Medical Research Institute), Doctor Aiguader, 88, 08003 Barcelona, Spain

2 Universitat Autónoma de Barcelona, Barcelona, Spain

3 Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain

4 Experimental and Health Sciences Department, Universitat Pompeu Fabra (UPF), Barcelona, Spain

5 Subdirección General de Información Sanitaria e Innovación, Spanish Ministry of Health, Social Services and Equality, Madrid, Spain

6 Unidad de Investigación, Hospital Universitario Basurto - Osakidetza, Bilbao, Spain

7 Red de Investigación en Servicios de Salud en Enfermedades Crónicas (REDISSEC), Madrid, Spain

8 Fundación Canaria de Investigación Sanitaria (FUNCANIS), Tenerife, Spain

9 Departamento de Economía, Universidad Pública de Navarra, Pamplona, Spain