

Determining factors associated with inhaled therapy adherence on Asthma and COPD treatment: a systematic review

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A todos os que estiveram ao meu lado durante esta caminhada e permitiram
concretizar um sonho.

Eles não sabem, nem sonham

Que o sonho comanda a vida

E que sempre que um homem sonha

O mundo pula e avança

Como bola colorida

Entre as mãos de uma criança

António Gedeão

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O meu sincero obrigada!

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Resumo

Introdução / Objetivos:

A adesão à terapêutica inalatória tem sido relatada como um grande problema a nível mundial, sendo particularmente relevante no tratamento da Asma e da Doença Pulmonar Obstrutiva Crônica (DPOC), considerando as suas barreiras e características. Realizou-se uma revisão sistemática da literatura mundial sobre os principais determinantes da adesão nesses pacientes.

Métodos:

A pesquisa foi realizada nas plataformas de dados *Cochrane Library*, *MEDLINE*, *EMBASE* e *ISI Web of Science*. Foram incluídos estudos epidemiológicos observacionais (estudos de coorte, caso-controle e transversais) que relataram a associação entre qualquer tipo de determinante e a adesão à terapêutica inalatória na Asma ou DPOC. Foi ainda realizada meta-análise de efeitos aleatórios de forma a resumir as associações de risco.

Resultados:

Foram incluídos 47 estudos, dando um total de 54.765 participantes. Nas meta-análises, foram apurados como determinantes significativos da adesão à terapêutica inalatória: a idade avançada [RR = 1,07 (1,03-1,10); I² = 94; p < 0,0001]; conhecimento acerca da doença / literacia em saúde [RR = 1,37 (1,28-1,47); I² = 14; p = 0,33]; obesidade [RR = 1,30 (1,12-1,50); I² = 0; p = 0,37]; bom desempenho cognitivo [RR = 1,28 (1,17-1,40); I² = 0; p = 0,62]; maior rendimento familiar [RR = 1,63 (1,05-2,56); I² = 0; p = 0,52]; estar empregado [RR = 0,87 (0,83-0,90); I² = 0; p = 0,76] e no uso de múltiplos fármacos / inaladores [RR = 0,81 (0,79-0,84); I² = 0; p = 0,80]. Na restante avaliação, a força da evidência subjacente às associações de risco foi baixa a moderada.

Conclusão:

Verificou-se que muitos determinantes podem estar associados a uma boa adesão, como os fatores idade, bom conhecimento / literacia sobre a doença, obesidade, bom desempenho cognitivo e maior rendimento familiar; associados a uma fraca adesão, identificou-se os seguintes fatores: estar empregado ou usar múltiplos inaladores.

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Intervenções personalizadas devem ser efetivadas na prática clínica de forma a abordar a adesão do paciente de acordo com as características evidenciadas.

Palavras-chave

Asma;DPOC;Terapêutica Inalatória;Adesão à terapêutica

Resumo Alargado

A adesão à terapêutica é um conceito complexo que inclui o cumprimento efetivo da medicação prescrita, bem como, a compreensão da necessidade da sua toma e o seu resultado.

Duas patologias do foro respiratório muito frequentes na população mundial são a Asma e a DPOC, nas quais a terapêutica inalatória é o principal tratamento e a adesão é crucial neste processo. A adesão à terapêutica inalatória tem sido relatada como um grande problema e desafio a nível mundial. A não adesão à terapêutica inalatória tem tido taxas elevadas e está associada a vários fatores, sejam estes intencionais, ligados por exemplo às crenças do paciente, ou não intencionais, como a incapacidade de usar o inalador adequadamente sem erros de utilização. Estes fatores irão comprometer a eficácia e, conseqüentemente, um controlo clínico inadequado da doença. Devido aos poucos estudos realizados neste âmbito e muitos com resultados inconsistentes, sem análise da magnitude de associação, esta revisão sistemática pretende analisar os determinantes que influenciam a adesão nos pacientes com estas patologias, tendo sido sintetizada a literatura mundial relatando os principais preditores de adesão da terapêutica inalatória.

Foi realizada uma pesquisa inicial nas plataformas de dados *Cochrane Library*, *MEDLINE*, *EMBASE* e *ISI Web of Science* com as seguintes palavras-chave: Asma, DPOC, terapêutica inalatória e adesão terapêutica. Foram selecionados 2306 artigos. Destes, após o processo de exclusão dos que não reuniram critérios, foram incluídos 47 estudos epidemiológicos observacionais (estudos de coorte, caso-controle e transversais) que relataram a associação entre qualquer tipo de determinante e a adesão à terapêutica inalatória na Asma ou DPOC. Foi ainda realizada meta-análise de 33 artigos, com modelos de efeitos aleatórios, de forma a resumir as associações de risco significativas.

Foram incluídos 47 estudos para investigação, com um risco global moderado a alto de avaliação de viés de acordo com uma adaptação da escala GRADE, obtendo um total de 54.765 participantes. Dos quais, apenas 33 estudos continham dados para meta-análise, onde foram apurados como determinantes significativos da adesão à terapêutica inalatória, a idade avançada [RR = 1,07 (1,03-1,10); I² = 94; p < 0,0001], o conhecimento acerca da doença / literacia em saúde [RR = 1,37 (1,28-1,47); I² = 14; p = 0,33], a obesidade [RR = 1,30 (1,12-1,50); I² = 0; p = 0,37], um bom desempenho

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cognitivo [RR = 1,28 (1,17-1,40); I² = 0; p = 0,62], um maior rendimento familiar [RR = 1,63 (1,05-2,56); I² = 0; p = 0,52], o facto de estar empregado [RR = 0,87 (0,83-0,90); I² = 0; p = 0,76] e o uso de múltiplos fármacos e/ou inaladores [RR = 0,81 (0,79-0,84); I² = 0; p = 0,80]. Na restante avaliação, a força da evidência subjacente às associações de risco foi baixa a moderada.

Esses resultados destacam a importância de uma abordagem e avaliação médica dos fatores-chave que podem influenciar a adesão do paciente à terapia inalatória. Além disso, recomenda-se a revisão das orientações GINA e GOLD, de forma a que estes fatores sejam incluídos em novas *guidelines* e seja conferido um foco relevante sobre tais determinantes para a otimização da gestão da Asma e da DPOC na prática clínica.

Verificou-se que muitos preditores podem estar associados a uma boa adesão, tais como a idade, um bom conhecimento / literacia sobre a doença, a obesidade, um bom desempenho cognitivo e maior rendimento familiar. Associados a uma fraca adesão, identificou-se os seguintes fatores: estar empregado ou usar múltiplos inaladores. Intervenções personalizadas devem ser efetivadas na prática clínica de forma a abordar a adesão do paciente de acordo com as características evidenciadas.

Esta revisão é a primeira a determinar e quantificar a magnitude da associação entre os principais determinantes e a adesão à terapêutica inalatória, compilando os dados da literatura mundial.

Abstract

Background:

Adherence to therapy has been reported worldwide as a major problem, and that is particularly relevant on inhaled therapy for Asthma and Chronic Obstructive Pulmonary Disease (COPD), considering its barriers and features. It was synthesized the global literature reporting the main determinants for adherence on these patients.

Methods:

Searches were made in Cochrane Library, MEDLINE, EMBASE and ISI Web of Science databases. Analytical observational epidemiological studies (cohort, case-control and cross-sectional studies) were included, reporting association between any type of determinant and the adherence for inhaler therapy on Asthma or COPD. Random-effects meta-analysis were used to summarize the numerical effect estimates.

Findings:

47 studies were included, giving a total of 54.765 participants. In meta-analyses, the significant determinants of adherence to inhaled therapy were: higher age [RR=1.07 (1.03-1.10); I²=94; p<0.0001] good disease knowledge/literacy [RR=1.37 (1.28-1.47); I²=14; p=0.33]; obesity [RR=1.30 (1.12-1.50); I²=0; p=0.37]; good cognitive performance [RR=1.28 (1.17-1.40); I²=0; p=0.62]; higher income [RR=1.63 (1.05-2.56); I²=0;p=0.52]; being employed [RR=0.87 (0.83-0.90); I²=0; p=0.76] and using multiple drugs/inhalers [RR=0.81 (0.79-0.84); I²=0; p=0.80]. Overall, the strength of the underlying evidence was only low to moderate.

Interpretation:

Many determinants may be associated, either to better adherence, such as age, good disease knowledge/literacy, obesity, good cognitive performance and higher income; either to poor adherence, such as being employed or using multiple inhalers. Personalized interventions should be taken in clinical practice to address patient's adherence according to such features.

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Keywords

Asthma;COPD;Inhaled therapy;Therapy adherence

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List of Abbreviations

CI	Confidence Interval
COPD	Chronic Obstructive Pulmonar Disease
DPOC	Doença Pulmonar Obstrutiva Crónica
GINA	Global Iniciative for Asthma
GOLD	Global Iniciative for Chronic Obstructive Lung Disease
GRADE	Grading of Recommendations Assessment, Development and Evaluation
OR	Odds Ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RR	Risk Ratio

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Chapter 1

Introduction

Asthma and Chronic Obstructive Pulmonary Disease (COPD) are chronic inflammatory disorders of the airways characterized by airway obstruction, and affect about 10% of the global population (1,2). The most recent recommended therapy according to major guidelines is through inhalers therapy.

According to previous reports (3) the concept of adherence emphasizes the need for agreement and can be defined as the extent to which the patient's behavior matches the agreed recommendations from the prescriber and the prescription. Adherence to pharmacological treatment is, therefore, a fundamental factor in the control of chronic respiratory diseases. However, many studies reveal poor adherence to the therapy in all pathways, either oral or inhaled, which leads to poor disease control, particularly on asthma and COPD patients, to an increased misuse of inhalers (4). These patients are at higher risk for adverse outcomes and for significant morbidity and mortality.

Nonadherence to inhaled therapy may be associated with several factors, either intentional (linked to patients willing to take it or even to patients' beliefs) or unintentional (such as the inability to use inhaler properly without maneuver errors). Some studies have pointed out main factors of therapeutic adherence, such as the associated costs, the educational level of patients, age, adverse side effects of the therapy, social and economic problems, satisfaction with treatment, symptomatic control and improvement in lung function, complexity of inhaler functioning, among others (5).

Inhaled therapy presents significant levels of nonadherence (6) leading to increased exacerbations and consequently hospital admissions. There is still an ongoing discussion and controversy upon which predictors are most relevant to inhaler adherence (7), and therefore there is a need to further address this topic, in order to better understand this phenomenon and thus plan adequate strategies for improvement (8). A systematic review was performed aiming to assess the most relevant determining factors associated with poor inhaler adherence in such patients.

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Chapter 2

Methods and Analysis

A protocol for this study was developed, registered with the International prospective register of systematic reviews (PROSPERO) (registration number CRD42020167249) (9). This review is reported in accordance with the PRISMA guidelines for systematic reviews and MOOSE guidelines for meta-analysis of observational epidemiological studies (10,11). No modifications were made, compared with the initial protocol.

Eligibility criteria for study selection

Participants and study types

Were included all studies that had participants of any age, with diagnosed of Asthma and/or COPD, designed as observational and analytical epidemiological studies, including cohort, case-control and cross-sectional studies. Were excluded discussion papers, non-research letters and editorials, randomized controlled trials, clinical case studies and case-series, and animal studies.

Exposure

Studies that include any demographic, individual, psychosocial and environmental predictors of inhaled therapy adherence were eligible for inclusion.

Study outcomes

The outcome was the effective adherence to the inhaled therapy, measured either on a validated scale or by other mean that the authors may find suitable.

Search strategy

A comprehensive search strategy was developed for retrieving published and unpublished studies on the topic (online supplementary Appendix S1 - "Search strategy"). Searches were made in the Cochrane Library, MEDLINE, EMBASE and ISI Web of Science. Search dates were from inception up to October 2020. The references in all eligible studies were reviewed to identify additional studies. No language restrictions were imposed in the searches and translations were made where necessary.

Selection process

Papers retrieved from the databases were exported to the online reference management software Rayyan® (available at rayyan.qcri.org). Two reviewers (Constança Monteiro and Tiago Maricoto) independently selected the articles according to the defined criteria and applied the following screening stages: cleaning of duplicated articles, selection of articles according to eligibility criteria and by reading the title and abstract, and selection of articles according to full text reading. All disagreements were resolved through discussion or arbitrated by a third review author (José Augusto Simões).

Reasons for excluding articles during the full text screening were noted and indicated in PRISMA diagram (Figure 1)(12) .

Data collection process

Two authors (Constança Monteiro and Tiago Maricoto) collected data from included articles in their original presentation and recorded them in a spreadsheet made in Microsoft Excel software and tailored to the current systematic review. Indirect data from figures and charts was collected, adapting their interpretation by consensus, and contacted authors of original articles for further information and data when necessary. Any disagreement in data collection was resolved through discussion or arbitrated by a third review author (José Augusto Simões).

Type of data collected

The following information from all included studies was collected: study design, number of participants and their characteristics (such as sociodemographic variables, smoking and lifestyle habits, environmental exposures, cognitive performance and other psychosocial determinants, inhaler type used, inhaler performance, previous inhaler performance education received, comorbidities, asthma or COPD stage/grade, type of drugs used, clinical control, exacerbation history, etc.), follow-up (in case of cohort studies), country of study, year of publication; Estimates of the association between parameters of the main determinants/predictors identified and the study outcome (measured as hazard ratio, risk ratio, odds ratio, 95% confidence intervals, mean and standard deviation). One author (Tiago Maricoto) inserted data into Review Manager Software (RevMan) (available at <http://community.cochrane.org>), and data were double-checked for correct entry by a second author (Constança Monteiro).

Quality assessment

Two authors (Constança Monteiro and Tiago Maricoto) appraised the quality of included studies using an adaptation of the GRADE quality assessment tool (13,14). Different components of each study were appraised, including confounding, selection, measurement of exposure, departures from exposure, missing data, measurement of outcomes and reported results. For each study, the grading of each individual components and the global study rating were assigned categories of risk of bias: low, moderate, severe, and critical. The global grading involved taking an average and relative weight of all individual components. Any disagreements not resolved by discussion were arbitrated by a third reviewer (José Augusto Simões).

Data synthesis

A descriptive summary of all included studies is presented in order to summarize literature. All studies were judged to be reasonably, clinically and methodologically heterogeneous, thus, it was performed meta-analyses using random-effects models. The heterogeneity between studies was quantified using the I² statistic. Sensitivity analyses were made on the basis of risk of bias in the studies in order to assess the robustness of these findings to different assumptions. Publication bias was assessed using funnel plots. The meta-analyses were performed using Cochrane Review Manager Software© (available at <http://community.cochrane.org>). The PRISMA checklist was followed for reporting of the systematic review.

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Chapter 3

Results

Description of studies

From the research 2306 articles were obtained, from which, after elimination of duplicates, remained 1931. From these articles, 1848 were excluded after reading title and/or abstract. Thus, 83 studies were obtained, from which, after reading the full text, 36 were excluded for several reasons (Figure 1).

Of the 47 eligible studies (3,15–60), 21 (44.7%) were cross-sectional and 26 (55.3%) were cohort studies. A total of 54.765 individuals were studied and most (n=41; 87.2%) were studies in adults.

Twenty-eight studies (59.6%) included only Asthma patients, and 11 (23.4%) only COPD patients. Although the majority of studies did not report data about disease severity, those that did, included participants with moderate and poorly controlled Asthma or COPD.

Detailed information for all selected studies is available at supplementary Appendix S3 – “Complete data of selected studies”.

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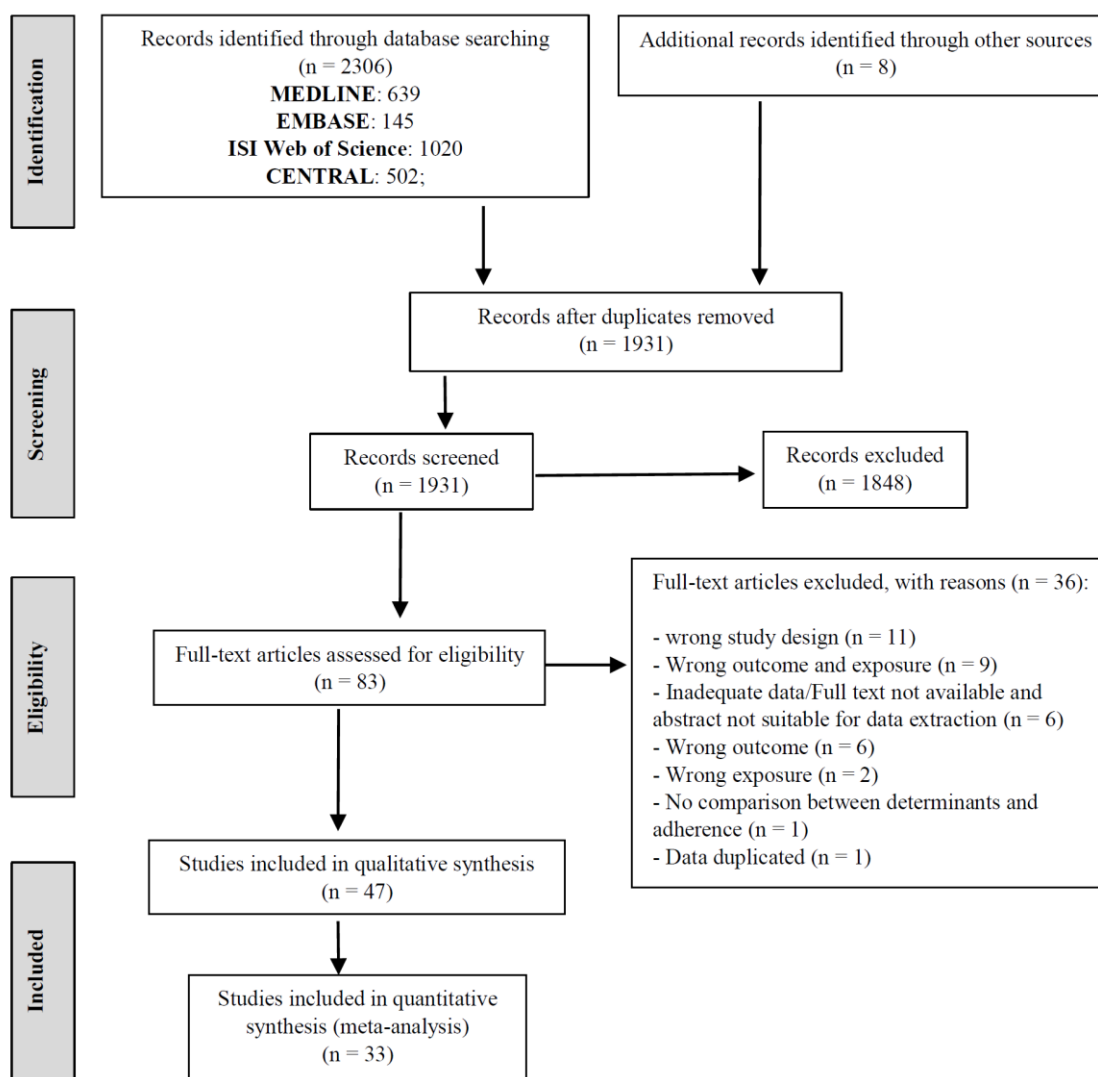


Figure 1 – Flow diagram on search and article inclusion, according to PRISMA statement.(12)

Risk of bias in included studies

Two reviewers (Constança Monteiro and Tiago Maricoto) independently evaluated the risk of bias of the included studies, reaching consensus in all evaluations (Figure 2). Most studies showed a predominance of moderate to serious risk of bias in their risk assessment. Among 47 studies included in quality assessment, only 5 (10.6%) had a global low risk of bias and 7 (14.9%) were considered critical. The dimension found to have the highest risk of bias concerned measurement of outcomes and missing data (detailed evaluation in supplementary Appendix S2 – “Quality Assessment and Risk of Bias of included studies”).

	Risk of Bias adapted from GRADE Evaluation							Overall risk of bias
	1	2	3	4	5	6	7	
Aggarwal D. 2017								MODERATE
Andres J. 2014				NA				SERIOUS
Apter A. 2013								MODERATE
Barja-Martinez E. 2019								MODERATE
Bender B. 1998								MODERATE
Celano M.P. 2010								MODERATE
Chiu K.-C. 2014				NA				SERIOUS
Darbà J. 2015								MODERATE
De Smet B. 2006				NA				CRITICAL
Emilio C. 2019								MODERATE
Erdogan, T. 2020								SERIOUS
D. Federman A. 2014								MODERATE
Foster J. 2012								CRITICAL
George J. 2005								SERIOUS
Plaza V. 2016								LOW
Huetsch J. 2012								LOW
Humenberger M. 2018								MODERATE
Ierodiakonou D. 2020					NA			SERIOUS
Kardas G. 2020								LOW
O'Conor R. 2019								MODERATE
O'Conor R. 2015								MODERATE
Olszanecka-Glinianowicz M. 2015								MODERATE
Plaza V. 2018								MODERATE
Plaza V. 2019								SERIOUS
Price D. 2018								SERIOUS
Sleath B. 2018				NA				SERIOUS
Smith A. 2006								MODERATE
Sriram K. 2016								CRITICAL
Sulaiman I. 2017								LOW
Takemura M. 2010								MODERATE
Takemura M. 2011								SERIOUS
Takemura M. 2017								SERIOUS
Tavasoli S. 2006								CRITICAL
Turan O. 2017								SERIOUS
van Dellen Q. M. 2008								SERIOUS
Vasbinder E. 2013								CRITICAL
Voorham J. 2017								MODERATE
Yu, Andrew P. 2011								MODERATE
Zucchelli A. 2020								LOW
Apter A. J. 1998								SERIOUS
Chambers C. V. 1999				NA				CRITICAL
Lacasse Y. 2005								SERIOUS
Williams L. K. 2007								SERIOUS
Janson S. L. 2008								MODERATE
Wells K. 2008								MODERATE
Ponieman D. 2009								SERIOUS
Emilsson M. 2011								CRITICAL

1 – CONFOUNDING; 2 - SELECTION OF PARTICIPANTS; 3 - CLASSIFICATION OF EXPOSURES; 4 - DEPARTURES FROM INTENDED EXPOSURES; 5 - MISSING DATA; 6 - MEASUREMENT OF OUTCOMES; 7 - SELECTION OF REPORTED RESULTS; NA – NOT APPLICABLE

Figure 2 – Risk of Bias assessment in included studies according to an adaptation of the GRADE quality assessment tool (13).

Determinants of adherence

The determinants of adherence mostly addressed were: age, gender, smoking habits, professional situation, disease knowledge/literacy, education, time since diagnosis, outpatient clinic visits, comorbidities (such as obesity, diabetes or cancer), history of past exacerbations, drugs and inhalers used, cognitive performance, disease severity and family income.

Several tools were used to measure adherence to inhaled therapy. Most studies (n=23; 48.9%) used a dose counting or electronic monitored systems, while 9 studies (19.2%) used an interspecific self-reported measure; 5 (10.6%) used the Morisky Medication Adherence Scale (MMAS) and other 5 (10.6%) used the Test of Adherence to Inhalers (TAI).

Thirty-three studies were eligible for data extraction, reporting data from 44908 participants, and allowing the conduction of meta-analysis of the association between determinants and the risk good adherence to inhaled therapy. Detailed information on meta-analysis for each main determinant of interest is available at supplementary Appendix S4 – “Complete data meta-analysis”.

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Overall, significant trends were observed towards an increased or decreased risk for adherence. Figure 3 reports the main findings from the performed meta-analysis. Therefore, the following determinants revealed to be significantly associated to good adherence on the pooled estimations: higher age [RR=1.07 (1.03-1.10); I²=94; p<0.0001]; having good disease knowledge/literacy [RR=1.37 (1.28-1.47); I²=14; p=0.33]; obesity [RR=1.30 (1.12-1.50); I²=0; p=0.37]; having a good cognitive performance [RR=1.28 (1.17-1.40); I²=0; p=0.62] and having a higher income [RR=1.63 (1.05-2.56); I²=0; p=0.52]. On the other hand, the following determinants were associates to a poor predictive adherence: being employed [RR=0.87 (0.83-0.90); I²=0; p=0.76] and using multiple drugs/inhalers [RR=0.81 (0.79-0.84); I²=0; p=0.80].

Subgroup analysis revealed that smoking exposure (active, past or passive) is associated with good adherence on European studies only [RR=1.32 (1.10-1.59); I²=0; p=0.50]. Previous exacerbations revealed to be associated with better adherence on one single studies with Asthma patients, developed on North America [RR= 1.52 (1.16-1.98)], but with poor adherence in two studies performed in Europe with COPD patients [RR=0.60 (0.36-0.99); I²=88; p=0.003].

Additional sensitivity analysis revealed no significant changes of the risk estimates regarding other variables of interest, such as for publication year, study design, risk of bias assessment, study dimension/sample size, diagnosis included or types of instruments used to measure adherence.

No data were available to perform subgroup analysis according to different types of inhalers or therapies used, or between Asthma versus COPD patients.

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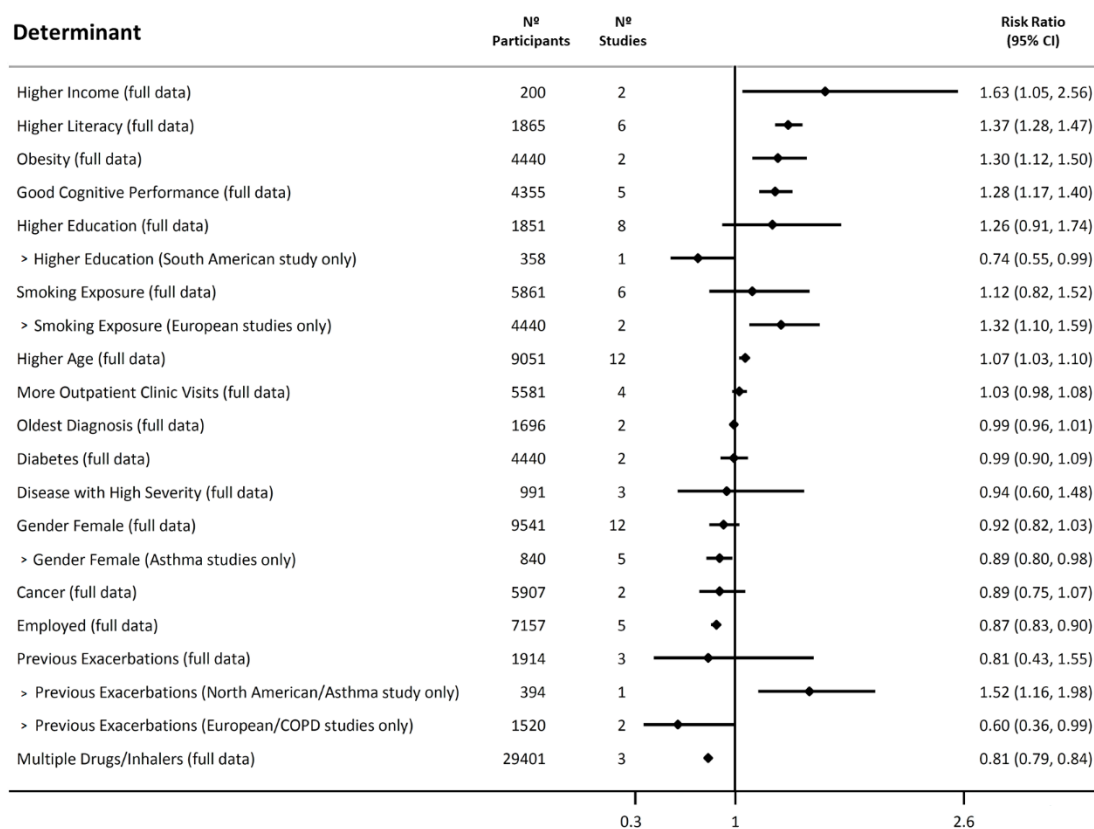


Figure 3 – Forest plot of results on the risk of good adherence to inhaled therapy according to the reported determinants and the most relevant sub-group analysis.

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Chapter 4

Discussion

Summary of key findings

Adherence to therapy has been a challenge for many years, and several factors have been reported to affect adherence on chronic conditions (61,62). This systematic review is the first to address, at a global, comprehensive, and integrated level, the main determinants of adherence to inhalation therapy in patients with COPD and /or Asthma, and to quantify the associated risks.

These results show that the major determinants associated with better adherence were higher income (63% in mean relative risk increase), high degree of literacy (37% increase), obesity (30% increase), good cognitive performance (28% increase), and higher age (7% increase). On the other hand, being employed was associated with a decreased risk for adherence (23% in mean relative risk decrease) as well as using multiple drugs/inhalers (29% decrease). In addition, subgroup analysis revealed that smoking habits are also associated with an increased risk for adherence in European countries (32% increase), and the gender female with lower adherence in Asthma (21% decrease). Regarding the presence of previous exacerbations, in Asthma it might be associated with better adherence, while in COPD it might be associated with lower adherence.

One study reported a greater adherence in dry powder inhaler users compared to pressurized metered dose inhaler users, however, it was not sufficient to be included in the meta-analysis (47).

Nevertheless, no relevant influence on the risk for better adherence was found considering professional situation, education, time since diagnosis, number of outpatient clinic visits, having comorbidities (such as obesity, diabetes, or cancer) or disease severity stage.

Strengths and limitations of the review

Throughout this review no significant inequalities between most of the studies were found, despite the high methodological heterogeneity and the diversity of applied scales among them. Most included studies have poor methodological quality and a high risk of

bias, thus limiting the confidence in the reported results. This means that the reported risk estimations may, at some extent, not faithfully represent the environment in the "real world". Another major limitation was the heterogeneity present in the scales and instruments used to measure adherence, as well as to report and measure the determinants. As an example, age was reported by several studies as a dichotomous variable using different cutoffs, such as 50, 60 or 65 years; therefore, a single cutoff for the pooled risk estimation can not be established. The same limitation may be applied to family income, where most studies used the national mean family income as the main cutoff, but this may differ significantly across different countries. Nevertheless, other determinants were reported with a better homogeneity, such as higher education, which was defined in almost every study with the cutoff in the secondary school level; and cognitive performance, defined in most studies as the presence/absence of cognitive impairment according to the most used scales for cognitive assessment.

Additionally, many studies did not assess the association between determinants and adherence with multivariate analysis techniques, nor were adjustments made to confounding factors, leading to a large bias in the obtained results. For this reason, the estimations resulted in a combination of adjusted and unadjusted risk ratios.

However, the methodological quality applied throughout the review must be highlighted, in accordance with the PRISMA recommendations (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) (12) and compelling on a well-structured method. A broad, but concrete, study inclusion criteria (PICO) was designed, reaching consensus among all reviewers on a rigorous way, and achieving a careful final approach to the results. The inclusion of broad criteria allowed to develop a highly comprehensive review with a significant diversity of determinants included, and therefore, with more generalizable results. In addition, and regardless of the limitations pointed out, some of the pooled results revealed significant risk associations, either with precise confidence intervals, but also of great magnitude of effect, which reinforces the confidence of such estimates. Studies in different languages were also included, to prevent the imposition of a linguistic barrier and bias.

Comparison with previous studies:

Inhaled therapy adherence is a topic with limited available studies so far (63). Thus, this timely and relevant review arises to fill this gap.

In the scope of inhalation therapy, a previous work focused on aspects related to users' "beliefs" (psychological and subjective determinants). However, it does not address all other sociodemographic determinants considered key issues to affect patient's adherence (64). In the present review, there were also several studies addressing aspects of a more subjective character, such as beliefs about medications and patients' perceptions about diseases. Yet, their characteristics and the data reported hampered the ability to include them in the meta-analysis. One study demonstrated that perceptions of behavior are better predictors than sociodemographic ones, reinforcing the paramount diversity of factors that should be considered in this type of reviews (65).

Another review, on Asthma patients, ended up detecting only age as a relevant determinant of adherence. Authors point out the significant heterogeneity of the included studies as the main limitation (66). This limitation is also highlighted in the present review. Nevertheless, its scope is broader because it included studies on Asthma and COPD and reported approximate risk estimations. In fact, in COPD, the patients' characteristics and the used medication are also considered to be key factors of adherence to therapy, as revealed by previous works (67).

Some interventional studies (with ICS only) tried to improve adherence, but without effective results. This might be due to external barriers and other key determinants (68) as highlighted by this work.

GINA and GOLD guidelines have been, since many years, pointing out the importance of patients' determinants on the risk for inhaled therapy adherence (1,2). However, they are not specific and do not consider such determinants in a global way, regardless the inhaler technique used. Some of those highlighted determinants are the type and regimen of medication, the difficulty in handling the device due to pathologies such as arthritis, the frequency of intake on the same day, and the use of different/multiple devices. They also mention the importance of unintended factors (e.g. the poor understanding of the instructions given to patient, forgetfulness, the absence of a daily routine and the cost), but also intentional factors (e.g. the perception that treatment is not necessary, the denial of asthma or its treatment, inappropriate expectations, concerns about adverse effects, dissatisfaction of caregivers, stigma, cultural and religious issues and costs). GOLD also points out the older age as a key factor for COPD inhaled poor adherence (contrary to the results on this review), as well as the use of multiple devices and the lack of education on inhaler performance.

Interpretation and implications of the findings

Further research must be carried out to clarify the influence of sociodemographic and psychological determinants on adherence to inhaled therapy, mainly to assess their synergic or collinear effects on a long-term scope.

These results highlight the need to improve clinical guidelines and practice, in order to address such determinants in patients with Asthma and COPD, thus, increasing the rates of adherence to inhalation therapy. This review brings new evidence to be considered and, possibly, to be included in an upcoming review of GINA and GOLD guidelines, where new sociodemographic determinants should be considered.

Further studies should be carried out in developing countries. The scarcity of research in these countries is delaying the implementation of effective interventions and adherence measures, where poor adherence prevails due to the fact that the determinants in these populations are not certainly known (69).

Subsequently, it would be important to assess other specific adherence determinants, such as the type of inhaler used (dry powder inhaler versus pressurized devices) (47), or even different patterns between Asthma and COPD patients.

At the methodological level, previous studies have also pointed out the need for an harmonization and patronization of the exposure and outcome assessment, namely the tools used to measure adherence, but also the way that all determinants are measured and reported (66). This will allow future systematic reviews to carry out more accurate pooled risk estimations. Several methods may be used to measure adherence, such as through pill counting, self-report, pharmacy refill accounting, electronic monitoring, measurement of blood levels of drugs and even frequent observation by healthcare professionals (70). Nevertheless, some of them are complex or have significant costs, and therefore, there is the need for a more global, uniform, and consensual method.

Future studies should be designed on a longitudinal cohort base, with long-term follow-up, in order to assess these causal relationships over time, to control for potential confounders, and to assess the risk of synergic or collinear effects. Finally, psychological and cultural factors must be addressed in future studies, considering their important dimensions in the holistic approach to patients adherence (71).

Chapter 5

Conclusions

Adherence to inhaled therapy is the cornerstone of Asthma and COPD clinical control and some determinants may be significantly associated with better adherence, such as higher income, high degree of literacy, obesity, good cognitive performance and higher age. On the other hand, being employed and using multiple drugs/inhalers was associated with a decreased adherence. Smoking patterns and gender may also play an important role, but with uncertainty remaining.

Asthma and COPD guidelines should give a reinforced attention to these determinants, recommending their assessment in every appointment. Further longitudinal, well-designed cohorts with long-term follow-up should be developed in order to clarify such causal effects.

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Supplementary data

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Supplementary Appendix S1 - Search strategy used

Search strategy for Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Methodology Register)

- #1 : MeSH descriptor: [Nebulizers and Vaporizers] explode all trees
- #2 : Nebulizers and Vaporizers
- #3 : Inhaler
- #4 : MeSH descriptor: [Asthma] explode all trees
- #5 : Asthma
- #6 : MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees
- #7 : Pulmonary Disease, Chronic Obstructive
- #8 : MeSH descriptor: [Treatment Adherence and Compliance] explode all trees
- #9 : Adherence
- #10: #1 or #2 or #3
- #11: #4 or #5 or #6 or #7
- #12: #8 or #9
- #13: #10 and #11 and #12

Search strategy for ISI Web of Science (Science and Social Science Index),

(Nebulizers or Vaporizers or Inhaler) AND (asthma or COPD or (Chronic Obstructive Pulmonary Disease)) And (adherence)

Search strategy for EMBASE

'nebulizer'/exp AND ('asthma'/exp OR 'chronic obstructive lung disease'/exp) AND adherence

Search strategy for MEDLINE Pubmed

("Nebulizers and Vaporizers"[Mesh]) AND ("Asthma"[Mesh] OR "Pulmonary Disease, Chronic Obstructive"[Mesh]) AND ("Treatment Adherence and Compliance"[Mesh])

Supplementary Appendix S2 - Quality assessment and risk of bias table

Study	Weaknesses/ Limitations	Strengths	Risk of Bias adapted from GRADE Evaluation							Final Classification (overall risk of bias)
			1	2	3	4	5	6	7	
Aggarwal D. 2017	<ul style="list-style-type: none"> Small sample size; Potential bias in the adherence measure; Potential bias by the unevaluated determinants "income status and belief and behaviours about asthma"; 	<ul style="list-style-type: none"> Correct exposure measures and outcomes; Large magnitude of risk association effect; 	?	+	?	?	?	+	+	moderate
Andres J. 2014	<ul style="list-style-type: none"> Potential bias on objective assessment of adherence; Measures of determinants that are not objective; Bias in reported results; 	<ul style="list-style-type: none"> Large sample size; 	?	?	?	NA	+	-	-	Serious
Apter A. 2013	<ul style="list-style-type: none"> Potential bias on objective assessment of adherence; Potential bias in the selection of participants; Potential bias in the exposure measure; 	<ul style="list-style-type: none"> Good sample size; Good adjustment to confounding variables; 	+	?	?	?	?	?	?	moderate
Barja-Martínez E. 2019	<ul style="list-style-type: none"> Low sample size; Potential biases in the characteristics of the population; Missing data; 	<ul style="list-style-type: none"> Correct outcome measures; 	?	?	+	+	-	+	?	moderate
Bender B. 1998	<ul style="list-style-type: none"> Very small sample size; Bias in the selection / characteristics of the population; Potential bias on objective assessment of adherence; 	<ul style="list-style-type: none"> Correct outcome measures; 	+	-	?	?	+	+	?	moderate
Celano M.P. 2010	<ul style="list-style-type: none"> Bias in the selection / characteristics of the population; Small sample size; Potential bias in the exposure measure; 	<ul style="list-style-type: none"> Correct outcome measures; 	?	?	?	?	+	+	?	moderate
Chiu K.-C. 2014	<ul style="list-style-type: none"> Bias in the selection / characteristics of the population; Bias in the measure of exposure; Objective bias in the control of control variables; Potential bias in assessing adherence; 	<ul style="list-style-type: none"> Good sample size; Correct outcome measure; • 	?	?	?	NA	?	+	?	Serious
Darbà J. 2015	<ul style="list-style-type: none"> Bias in the control of control variables; Potential bias in the exposure measure; Potential bias on objective assessment of adherence; 	<ul style="list-style-type: none"> Good sample size; Correct selection / characteristics of the population; 	?	+	?	?	+	-	+	moderate
De Smet B. 2006	<ul style="list-style-type: none"> Bias in the control of control variables; Potential bias in the exposure measure; Potential bias on objective assessment of adherence; Biases in the selection / characteristics of the population; Generalization of all results; 	<ul style="list-style-type: none"> Good sample size; 	?	-	-	NA	-	?	-	critical
Emilio C. 2019	<ul style="list-style-type: none"> Small sample size; Bias in the selection / characteristics of the population; Potential bias in the exposure measure; 	<ul style="list-style-type: none"> Correct objective measurement of outcome adherence; Good control of risk factors; 	+	?	?	?	?	+	?	moderate
Erdogan, T. 2020	<ul style="list-style-type: none"> Very small sample size; Bias in the control of control variables; Potential bias on objective assessment of adherence; Generalization of all results; 	<ul style="list-style-type: none"> Population suited to the problem; Correct exposure measure; 	?	+	+	?	-	-	?	serious

D. Federman A. 2014	<ul style="list-style-type: none"> Bias in the control of control variables; Potential bias on objective assessment of adherence; Potential bias in the exposure measure; Bias in the selection / characteristics of the population; 	<ul style="list-style-type: none"> Good sample size; 	?	?	?	?	+	?	+	moderate
Foster J. 2012	<ul style="list-style-type: none"> Small sample size; Potential bias on objective assessment of adherence; Potential bias in the exposure measure; 	<ul style="list-style-type: none"> Correct selection / characteristics of the population; 	?	+	?	-	-	?	-	critical
George J. 2005	<ul style="list-style-type: none"> Bias in the control of control variables; Potential bias on objective assessment of adherence; Potential bias in the exposure measure; Bias in the selection / characteristics of the population; 	<ul style="list-style-type: none"> Good sample size; 	?	?	?	-	?	?	-	Serious
Plaza V. 2016	<ul style="list-style-type: none"> Bias in the control of control variables; 	<ul style="list-style-type: none"> Good sample size; Correct objective assessment of adherence; Correct exposure measure; Correct and random selection of participants; 	?	+	+	?	+	+	+	low
Huetsch J. 2012	<ul style="list-style-type: none"> Potential bias in the exposure measure; 	<ul style="list-style-type: none"> Good sample size; Correct objective assessment of adherence; Correct and random selection of participants; Data consistent with previous studies; Great magnitude of the effect of the risk association; 	+	+	?	?	?	+	+	low
Humenberger M. 2018	<ul style="list-style-type: none"> Bias in the control of control variables; Potential bias on objective assessment of adherence; Potential bias in the exposure measure; 	<ul style="list-style-type: none"> Good sample size; 	?	+	?	?	?	?	+	Moderate
Ierodiakonou D. 2020	<ul style="list-style-type: none"> Bias in the selection / characteristics of the population; Bias in the control of control variables; Potential bias on objective assessment of adherence; Potential bias in the exposure measure; 	<ul style="list-style-type: none"> Good sample size; 	?	?	?	?	NA	?	?	Serious
Kardas G. 2020	<ul style="list-style-type: none"> Potential bias in the exposure measure; 	<ul style="list-style-type: none"> Good sample size; Correct objective assessment of adherence; Correct and random selection of participants; Data consistent with previous studies; 	+	+	?	+	+	+	?	low
O'Conor R. 2019	<ul style="list-style-type: none"> Potential bias on objective assessment of adherence; Potential bias in the exposure measure; 	<ul style="list-style-type: none"> Good sample size; Correct and random selection of participants; Data consistent with previous studies; 	?	+	?	?	+	?	+	moderate
O'Conor R. 2015	<ul style="list-style-type: none"> Potential bias on objective assessment of adherence; Potential bias in the exposure measure; 	<ul style="list-style-type: none"> Good sample size; Correct and random selection of participants; Data consistent with previous studies; 	?	+	?	?	+	?	+	moderate

Olszanecka-Glinianowicz M. 2015	<ul style="list-style-type: none"> Potential bias on objective assessment of adherence; Potential bias in the exposure measure; Change in the state exposed during the study; 	<ul style="list-style-type: none"> Good sample size; Correct and random selection of participants; Data consistent with previous studies; 	?	+	?	?	?	?	+	moderate
Plaza V. 2018	<ul style="list-style-type: none"> Potential bias on objective assessment of adherence; Potential bias in the exposure measure; 	<ul style="list-style-type: none"> Good sample size; Correct and random selection of participants; 	?	+	?	?	+	?	+	moderate
Plaza V. 2019	<ul style="list-style-type: none"> Potential bias in the exposure measure; 	<ul style="list-style-type: none"> Good sample size; Correct and random selection of participants; Correct exposure measure; 	?	+	?	+	?	?	?	moderate
Price D. 2018	<ul style="list-style-type: none"> Potential bias on objective assessment of adherence; Potential bias in the exposure measure; Bias in the selection / characteristics of the population; Bias in the control of control variables; 	<ul style="list-style-type: none"> Good sample size; 	?	?	?	?	?	?	-	serious
Sleath B. 2018	<ul style="list-style-type: none"> Potential bias on objective assessment of adherence; Potential bias in the exposure measure; Bias in the selection / characteristics of the population; Bias in the control of control variables; Missing data; 	<ul style="list-style-type: none"> Good sample size; 	?	?	?	?	-	?	-	serious
Smith A. 2006	<ul style="list-style-type: none"> Potential bias in the exposure measure; Bias in the selection / characteristics of the population Bias in the control of control variables; Missing data; Small sample size; 	<ul style="list-style-type: none"> Correct outcome measure; 	?	?	?	NA	-	+	?	moderate
Sriram K. 2016	<ul style="list-style-type: none"> Small sample size. Missing data; Bias in the selection / characteristics of the population; potential bias on objective assessment of adherence; Bias in the control of control variables; 	<ul style="list-style-type: none"> Correct exposure measure; 	?	?	+	?	-	-	-	critical
Sulaiman I. 2017	<ul style="list-style-type: none"> Small sample size. Bias in the control of control variables; 	<ul style="list-style-type: none"> Correct exposure measure; Correct outcome measure; Correct selection / characteristics of the population; 	+	+	+	?	+	+	?	low
Takemura M. 2010	<ul style="list-style-type: none"> Small sample size. Bias in the control of control variables; Potential bias on objective assessment of adherence; Missing data; 	<ul style="list-style-type: none"> Correct selection / characteristics of the population; Correct exposure measure; 	?	+	+	?	-	?	+	moderate
Takemura M. 2011	<ul style="list-style-type: none"> Small sample size; Bias in the control of control variables; Potential bias on objective assessment of adherence; 	<ul style="list-style-type: none"> None of relevance; 	?	?	?	?	-	?	?	serious

	<ul style="list-style-type: none"> Missing data; Bias in the selection / characteristics of the population; Bias in the exposure measure; 									
Takemura M. 2017	<ul style="list-style-type: none"> Small sample size; Bias in the control of control variables; Potential bias on objective assessment of adherence; Missing data; Bias in the selection / characteristics of the population; Bias in the exposure measure; Generalization of results; 	<ul style="list-style-type: none"> None of relevance; 	?	?	?	?	-	?	?	serious
Tavasoli S. 2006	<ul style="list-style-type: none"> Small sample size; Bias in the control of control variables; Bias on objective assessment of adherence; Bias in the selection / characteristics of the population; Bias in the exposure measure; 	<ul style="list-style-type: none"> None of relevance; 	?	-	-	?	?	-	?	critical
Turan O. 2017	<ul style="list-style-type: none"> Small sample size; Bias on objective assessment of adherence; Bias in the selection / characteristics of the population; Bias in the exposure measure; 	<ul style="list-style-type: none"> None of relevance; 	?	?	-	?	?	?	?	Serious
van Dellen Q. M. 2008	<ul style="list-style-type: none"> Bias on objective assessment of adherence; Bias in the exposure measure; Bias in the control of control variables; Small sample size; Missing data; 	<ul style="list-style-type: none"> None of relevance; 	?	?	?	?	-	?	?	serious
Vasbinder E. 2013	<ul style="list-style-type: none"> Bias in the exposure measure; Bias in the control of control variables; Small sample size; Missing data; Bias in the selection / characteristics of the population; 	<ul style="list-style-type: none"> Correct outcome measure; 	-	?	?	-	-	+	-	critical
Voorham J. 2017	<ul style="list-style-type: none"> Bias in the exposure measure; Bias in the control of control variables; Bias on objective assessment of adherence; 	<ul style="list-style-type: none"> Good sample size; 	?	+	?	?	?	?	?	moderate
Yu, Andrew P. 2011	<ul style="list-style-type: none"> Bias in the control of control variables; Bias on objective assessment of adherence; 	<ul style="list-style-type: none"> Correct exposure measure; Good sample size; Correct selection / characteristics of the population; 	?	+	+	?	?	?	?	moderate
Zucchelli A. 2020	<ul style="list-style-type: none"> Bias in the control of control variables; Bias on objective assessment of adherence; 	<ul style="list-style-type: none"> Correct exposure measure; Good sample size; Correct selection / characteristics of the population; 	?	+	+	?	+	+	?	low

Apter A. J. 1998	<ul style="list-style-type: none"> Bias in the exposure measure; Bias in the control of control variables; Small sample size; Bias in the selection / characteristics of the population; Bias in the adhesion measure; 	<ul style="list-style-type: none"> None of relevance; 	?	?	?	?	?	?	?	?	Serious
Chambers C. V. 1999	<ul style="list-style-type: none"> Bias in the exposure measure; Bias in the control of control variables; Bias in the selection / characteristics of the population; Bias in the adhesion measure; Missing data; 	<ul style="list-style-type: none"> Good sample size; 	?	?	?	?	-	-	-		critical
Lacasse Y. 2005	<ul style="list-style-type: none"> Bias in the exposure measure; Bias in the selection / characteristics of the population; Bias in the adhesion measure; Missing data; Small sample size; 	<ul style="list-style-type: none"> None of relevance; 	?	?	?	NA	-	?	?		serious
Williams L. K. 2007	<ul style="list-style-type: none"> Bias in the exposure measure; Bias in the adhesion measure; Missing data; Small sample size; 	<ul style="list-style-type: none"> None of relevance; 	?	?	?	?	?	-	?		serious
Janson S. L. 2008	<ul style="list-style-type: none"> Bias in the exposure measure; Bias in the control of control variables; Bias in the adhesion measure; Small sample size; 	<ul style="list-style-type: none"> Correct selection / characteristics of the population; 	?	+	?	?	?	?	?		moderate
Wells K. 2008	<ul style="list-style-type: none"> Bias in the exposure measure; Bias in the selection / characteristics of the population; Bias in the adhesion measure; Missing data; 	<ul style="list-style-type: none"> Large sample size; 	+	?	?	+	?	?	?		moderate
Ponieman D. 2009	<ul style="list-style-type: none"> Bias in the exposure measure; Bias in the control of control variables; Bias in the selection / characteristics of the population; Bias in the adhesion measure; Missing data; 	<ul style="list-style-type: none"> Good sample size; 	?	?	?	?	?	?	?		serious
Emilsson M. 2011	<ul style="list-style-type: none"> Bias in the exposure measure; Bias in the control of control variables; Bias in the selection / characteristics of the population; Bias in the adhesion measure; Missing data; Very small sample size; 	<ul style="list-style-type: none"> None of relevance; 	?	?	-	?	-	-	-		critical
1 - CONFOUNDING 2 - SELECTION OF PARTICIPANTS	5 - MISSING DATA 6 - MEASUREMENT OF OUTCOMES	+ → Low risk of bias	- → Critical risk of bias NA → Not enough information to judge the risk of bias								

3 - CLASSIFICATION OF EXPOSURES	7 - SELECTION OF REPORTED RESULTS	? → Moderate risk of bias
4 - DEPARTURES FROM INTENDED EXPOSURES		? → Serious risk of bias

Supplementary Appendix S3 - Complete data of selected studies.

Study				Sample Size (n ^o)	AGE (mean±SD or median+range)	GENDER (%M, %F)	Diagnosis		EXPOSURE reported		Presence of confounding factors		Primary OUTCOME reported (Adherence)		Measures of association for the Primary OUTCOME (RR, HR, OR with IC95% or ±SE) [Exposed over Non-exposed to the determinant]	Parameters estimates for the Primary OUTCOMES (% of adherent pax OR score at: mean±SD or median+range) [Exposed VS Non-exposed to the determinants]
Author	Year	Country	Design				Type	Disease Stage	Types of Determinants/Characteristics evaluated	Measure (mean±sd; %)	Therapy/Inhalers used	Others	Types of measures	% of Cases (adherent) vs % of Controls (non-adherent) OR Global score of adherence (at mean±SD or median+range)		
Aggarwal D.	2017	India	Cohort	103	41.9±16	42%M 58%F	Asthma	clinically controlled: 56%	Age (mean) Female Smoking Literate Employed Asthma knowledge	41.9±16 58% 31% 53% 34% 56%	No relevant information	- income status and belief and behaviours about asthma	Dose counting check on inhaler	72,7% vs 27,3%	OR for GOOD adherence: Age: 1.72 (0.62-4.7) Female: 0.82 (0.29-2.3) Smoking: 0.92 (0.60-1.15) Employed: 1.31 (0.43-4.0) Literate: 4.4 (1.1-20) (multivariate analysis of objective adherence) Asthma Knowledge: 7.3(1.6-32.2) (multivariate analysis of objective adherence)	No information
Andres J.	2014	Germany	Cohort	3827	>18yr	NA	Asthma	no information	<49 yr 50 yr or more employed no employed	data not available	No relevant information	-	patient reporting	49% vs 51%	No reported information by authors. DATA MANUALLY ESTIMATED/RETRIEVED: OR for GOOD adherence: >50yr: 2.25 (1.977-2.561) Employed: 0.4439 (0.3889-0.5066)	<49yr: 39% >50yr: 59% Employed: 41% Unemployed: 61%
Apter A.	2013	USA	Cohort	284	48±14	29%M 71%F	Asthma	clinically controlled: 1.66± 1.07	Literacy	Adequate literacy: 87%	fluticasone and beclomethasone	- observation of participants limited duration - measurements of literacy - electronic monitoring for adherence - Hawthorne effect: behavior was changed by observation	electronic monitored	with mean baseline adherence of 62% 6 28%	Adjusted OR for GOOD adherence: Asthma-related numeracy (ANQ): 1.86 ± 1.22 Print literacy (5-TOFHLA): 8.00 ± 4.47	No information
Barja-Martínez E.	2019	Spain	Cross-sectional	124	63.2 (IQR 12.6)	50%M 50%F	Asthma: 48.4% COPD: 51.6%	no information	Age education: No education Basic level education Secondary education Vocational training University studies Other studies	63.2 (IQR 12.6) - 10.5% 51.6% 13.7% 14.5% 8.9% 0.8%	No relevant information	-	Test of Adherence to Inhalers' (TAI) questionnaire	38,7% good adherence 37,9% intermediate 23,4% bad	No reported information by authors. DATA MANUALLY ESTIMATED/RETRIEVED: OR for GOOD adherence: a61yr: 2.075 (0.917-4.697) Education: 6.913 (3.056-15.64)	>61yr: 43,8% 41-60yr: 28% <40yr: 20% No education: 61.5% Education: 18.2%
Bender B.	1998	USA	Cohort	24	10±1.9	54%M 46%F	Asthma	no information	Socioeconomic status Parent education level Asthma knowledge score Child Behavior Checklist: - internalizing score - Externalizing score - Total score Family Assessment Device: - Problem solving - Communication - Roles - Affective responsiveness - Affective involvement - Behavior control - General family functioning	no data available	inhaled beta-agonists and corticosteroids	-	electronic device: metered-dose inhaler chronolog (MDIC)	Days with all doses: Days with at least one dose: 58.2%	Spearman Correlations with Adherence: Socioeconomic status: 0.03 Parent education level: 0.31 Asthma knowledge score: 0.42	No information
Celano M.P.	2010	USA	Cohort	143	8,5 yr	64%M36%F	Asthma	mild, moderate or severe by global initiative for Asthma guidelines	Carregivers: African-American (%),Mother of index child (%),Separated, divorced, or widowed (%),Mean age (years, range),Mean age at birth of first child (years, range) Highest educational level- Less than 12th grade (%), High school diploma (%), Some college (%),Children- African American (%), Male (%), Mean age (years), Receiving Medicaid or SCHIP (%),Families- At or below federal poverty level (%)	-- 97886836 (21-79) 20.5 (14-45)26 56 1899 64 8.5 8475	Fluticasone and montelukast	participants' knowledge of the monitoring function of the electronic devices- Families were paid a small honorarium for each of the data collection visits, and an additional small honorarium for returning the electronic monitoring devices- the internal consistency of the asthma knowledge questionnaire was low	Electronically:T1 and T2 A: Fluticasone MDI per MDIlog II B: MontelukastC: Fluticasone MDI and montelukast	Adherence mean values at different visits and Therapies:18: 70 ± 31 TIC: 59 ± 25 T2A: 45 ± 32 T2B: 66 ± 30 T2C: 47 ± 32	Correlation index for GOOD adherence:Caregiver asthma knowledge: -.05Caregiver reported family cohesion cohesion: -.17Child Report of Parent Behavior Inventory limit-setting: .25Limit-setting loss task: .01Limit-setting conflict task: -.12Responsiveness loss task: -.03Responsiveness conflict task: .05Child depressive symptoms: -.08	No information

Study				Sample Size (n ^e)	AGE (mean±SD or median+range)	GENDER (%M, %F)	Diagnosis		EXPOSURE reported		Presence of confounding factors		Primary OUTCOME reported (Adherence)		Parameters estimates for the Primary OUTCOMES (% of adherent pax OR score at: mean±SD or median+range) [Exposed VS Non-exposed to the determinants]	
Author	Year	Country	Design				Type	Disease Stage	Types of Determinants/Characteristics evaluated	Measure (mean±sd; %)	Therapy/Inhalers used	Others	Types of measures	% of Cases (adherent) vs % of Controls (non-adherent) OR Global score of adherence (at mean±SD or median+range)		Measures of association for the Primary OUTCOME (RR, HR, OR with IC95% or ±SE) [Exposed over Non-exposed to the determinant]
Chiu K.-C.	2014	China Korea Malaysia Taiwan Thailand Vietnam	Cross-sectional	1054	53.0 ± 14.4 yrs	61.8%F 38.2%M	Asthma	no information	Age (years), mean (SD) 61.8% 24.6 ± 4.4 - Gender: Female 26.1% BMI (kg/m ²), mean (SD) 24.2% Occupation: - Office work 48.4% - Physical labor 1.3% - Unemployed/retired/housewife 73.7% - Student 4.9% Smoking status: - Never smoker 21.3% - Current smoker 34.9% - Former smoker 80.7% 59% - Exposed to passive smoking 33.9% Any comorbidity: - Any allergic disorder 22.1% - Any cardiovascular disorder 8.9% - Any endocrine and metabolic disorder 3.2% - Gastro-esophageal reflux disease - Chronic obstructive pulmonary disease	53±14.4 61.8% 24.6 ± 4.4 - 26.1% 24.2% 48.4% 1.3% - 73.7% 4.9% 21.3% 34.9% 80.7% 59% 33.9% 22.1% 8.9% 3.2%	ICS and LABA	data on medication adherence, asthma control, and QoL were self-reported and were collected at a single visit;	8-item Morisky Medication Adherence Scale (MMAS-8)	53% adherent vs 47% non-adherent MMAS-8 mean score: 5.53 (±2.03)	RR for POOR adherence (≥ OR for GOOD adherence): Age (yr): 0.99 (0.98–1.00) [->1.01 (1.0–1.02)] Physical labor (vs office work): 0.87 (0.74–1.03) [-> 1.15 (0.97–1.35)] Unemployed/retired/housewife (vs office work): 0.74 (0.62–0.88) [->1.35 (1.34–1.61)] Student: 1.09 (0.78–1.52) [->0.92 (0.66–1.28)] Exposure to passive smoking: 1.17 (1.02–1.34) [->0.85 (0.75–0.98)] Asthma onset at 40–59yr (vs <40): 1.24 (1.03–1.51) [->0.81 (0.66–0.97)] Asthma onset at ≥60yr: 1.15 (0.81–1.63) [->0.87 (0.61–1.23)] Inhaler usage time (yr): 0.99 (0.97–1.00) [->1.01 (1.00–1.03)] N ^e of clinic visits/past 22M: 0.98 (0.96–1.00) [->1.02 (1.00–1.04)] Oral β2 agonist: 0.66 (0.47–0.92) [->1.52 (1.09–2.13)] Allergic rhinitis: 1.17 (1.01–1.36) [->0.85 (0.74–0.99)]	No information
Darbà J.	2015	Spain	Cohort	1263	71 yrs	16.55%F 83.45%M	COPD	mild, moderate or severe	Male, %Age: 39-50 51-61 62-7172-8384-97 retired status Comorbid conditions:ObesitysmokingAlcoholism cardiovascular event hypertensionDiabetesDyslipidemia osteoarthritisarthritisstrokeischemic heart disease Organ failures DementiaDepressionneoplasm 83.45%-4.20%13.22%33.02%40.46%9.11%88.44% 39.98%20.19%6.41%35.15%60.30%28.50%50.75%7.17%2 0.73%24.78%15.60%26.37%6.73%25.73%	study was conducted in a single health system; the assumption that obtaining a prescription was equivalent to taking the medication might not be completely accurate.	3 Month:pMDI- 90% adherent vs 10% non-adherentDPI- 85% adherent vs 15% non-adherent6 Month:pMDI- 85% adherent vs 15% non-adherentDPI- 80% adherent vs 20% non-adherent12 Month:pMDI- 70% adherent vs 25% non-adherentDPI- 65% adherent vs 30% non-adherent18 Month:pMDI- 65% adherent vs 35% non-adherentDPI- 58% adherent vs 42% non-adherent	OR for GOOD adherence:Time since diagnosis: 0.95 (0.923–0.981)Women: 1.21 (0.816–1.782)Age (yr): 0.96 (0.887–0.966)Retirement: 1.37 (0.736–2.563)N ^e of comorbidities:2: 0.95 (0.662–1.374)3 : 0.49 (0.282–0.864)Obesity: 1.47 (0.975–2.231)Smoking: 2.248 (1.105–5.887)Hypertension: 1.48 (1.085–2.018)Diabetes: 1.36 (0.981–1.902)acute exacerbation: 0.59 (0.378–0.933)Additional visit to the doctor: 1.14 (1.122–1.165)	No information			
De Smet B.	2006	USA	Cross-sectional	573	40.5 ± 12.4 yrs	71.0% F 29.0% M	Asthma	no information	Age, y (567) 40.5 ± 2.4 Gender (527) - female 406 (77.0) Race (569) - white 509 (89.5) Years since asthma diagnosis (552) 18.4 ± 14.2 Comorbidities (571) 0 1 272 (47.6) 22 151 (26.4) People in the home (573) 148 (25.9) Health beliefs - benefit—perceived benefits of using medications (548) 3.2 ± 1.6 - barriers—perceived barriers to taking care of asthma (548) 3.8 ± 1.0 3.7 ± 0.7 4.1 ± 0.8 - avoidance—tries to avoid situations that trigger asthma (548) - Highest level of education (571) - not a college graduate 240 (42) 331 (58) - college graduate 48 (9.0) Annual household income, \$ (535) - <20 000 127 (23.7) - 20 000–39 999 130 (24.3) - 40 000–59 999 107 (20.0) - 60 000–79 999 123 (23.0) - ≥80 000	Participants selection (by gender); recall bias (self-administered questionnaire)	Authors used a 4 item questionnaire, not defined, and scored as the mean of the responses	15.4% adherent vs 84.6% non-adherent	Adjusted Beta coefficients for GOOD adherence: Predisposing trigger avoidance: 0.298 (±0.057) Perceived benefit: 0.222 (±0.045) Years since diagnosis: 0.109 (±0.003) Enabling number of MDI instructors: 0.087 (±0.044) Need perceived severity: 0.150 (±0.063) General health-status (SF-36 MCS score): 0.096 (±0.004)	No information		
Emilio C.	2019	Brazil	Cross-sectional	358	49 (19-63) yrs	63.4%F 36.6% M	Asthma	no information	years of schooling more than 10 years: 35.2% less than 10 years: 64.8%	inhaled corticosteroids and long- and short-acting β2 agonists	-	6-Item Asthma Control Questionnaire and The Morisky et al. Questionnaire	85% vs 15%	No reported information by authors. <u>DATA MANUALLY ESTIMATED/RETRIEVED:</u> OR for GOOD adherence: >10 years of schooling: 0.5431 (0.3032-0.973)	>10 years of schooling: 80% <10 years of schooling: 88%	
Erdogan, T.	2020	Turkey	Cross-sectional	29	47.2 ± 12.99 yrs	75.9%F 24.1% M	Asthma	Poorly controlled - 27.6% Not well controlled - 34.5% Well controlled - 37.9%	Age (years)/Sex (F/M)Body mass index (kg/m ²) 47.2 ± 12.99 (23-74)/75.9/24.1%29.9 ± 5.16	ICS and LABA	sample small size- single center experience- self-reported treatment adherence before omalizumab treatment was not evaluated and all patients were considered to be adherent to inhaler treatment.	pharmaceutical and medical device institution records and Turkish Modified Morisky Scale	66% vs 34%	No significant difference was found in the characteristics of the patients (age, sex, additional allergic disease, asthma control status, duration of asthma, duration of omalizumab treatment, blood eosinophil count and ratio, total IgE level, FEV1 and FEV1/FVC) that might affect the adherence to inhaler therapy.	No information	

Study				Sample Size (n ^e)	AGE (mean±SD or median+range)	GENDER (%M, %F)	Diagnosis		EXPOSURE reported		Presence of confounding factors		Primary OUTCOME reported (Adherence)		Measures of association for the Primary OUTCOME (RR, HR, OR with IC95% or ±SE) [Exposed over Non-exposed to the determinant]	Parameters estimates for the Primary OUTCOMES (% of adherent pax OR score at: mean±SD or median+range) [Exposed VS Non-exposed to the determinants]
Author	Year	Country	Design				Type	Disease Stage	Types of Determinants/Characteristics evaluated	Measure (mean±sd; %)	Therapy/Inhalers used	Others	Types of measures	% of Cases (adherent) vs % of Controls (non-adherent) OR Global score of adherence (at mean±SD or median+range)		
Ierodiakonou D.	2020	Greece	Cross-sectional	257	65 ± 12.3 yrs	79.4%M 20.6%F	COPD	GOLD criteria	Age, mean (SD) BMI, mean (SD) Males: n (%) Occupational status; n (%) Employed Unemployed/housewife Retired Smoking status; n (%) Current Ex Never	65 (12.3) 29 (5.3) 204 (79.4) - 74 (33.3) 25 (11.3) 123 (55.4) - 143 (55.6) 83 (32.3) 31 (12.1)	No relevant information	-	Test of Adherence to Inhalers (TAI)	Good adherence: 18.9% Intermediate adherence: 7.0% poor adherence: 74.1%	OR for POOR adherence [-> OR for GOOD adherence]: CAT210: 4.86 (1.61-14.69) [-> 0.21 (0.07-0.62)] mMRC2: 2.93 (1.51-5.71) [-> 0.34 (0.18-0.66)] ≥2 Exacerbations: 4.68 (1.51-4.44) [-> 0.21 (0.23-0.66)]	No information
Kardas G.	2020	Poland	Cohort	1973	65.8 ± 18.0 yrs	50.4%M/49.6%F	Asthma and COPD	GINA and GOLD criteria	Age : - 1-18- 19-39- 40-64- 65-74- 75+ Gender : - Female- male	- 2.6%8.3%26.0%29.9%33.2%- 49.6%50.4%	ICS + LABA	the new e-healthcare system in Poland was a pilot solution; patients aged 75+, the common perception of a possible technological barrier of an e-prescription system for the eldest cannot be proven.	Data base of nationwide e-Health solutions in Poland	84.7% vs 15.3%	No reported information by authors DATA MANUALLY ESTIMATED/RETRIEVED OR for GOOD adherence:DPI (vs MDI): 1.328 (1.032-1.707)Female: 1.243 (0.9716-1.589)	Male: 83.3% Female: 86.1%<19yr: 88.2% 19-39yr: 82.2% 40-64yr: 82.5% 65-74yr: 82.0% >75yr: 89.2%NDP: 17.0% MDI: 13.4%—ICS: 86.63% ICS+LABA: 81.14% LABA: 83.18% LAMA: 86.08% LAMA+LABA: 90.24% LAMA+SABA: 100% SABA: 85.36% SABA+LAMA: 86.57%
O'Connor R.	2019	USA	Cohort	388	68 years	58.3%F 41.7%M	COPD	no information	Age, Mean (SD) Female, % Race, % - White, non-Hispanic - African-American, non-Hispanic - Hispanic - Other Education, % - Some High School or less - High School Graduate - Some College - ≥ College Graduate Household Income, % - < \$1350 per month Limited Health Literacy, % Low MMSE Score, % No. Chronic Conditions, Mean (SD)	68.0 (8.3) 58.3 - 37.1 43.8 16.5 2.6 - 25.8 21.9 24.2 28.1 - 48.2 28.5 37.7 3.7 (1.8)	No relevant information	-	Self-report using the Medication Adherence Reporting Scale (MARS)	38.9% vs 61.1%	Adjusted OR for GOOD adherence: Adequate health literacy: 1.46 (1.02, 2.08) Global cognitive ability: 1.31 (0.92, 1.85)	Health Literacy: 46.0% Global Cognitive Ability: 45.5%
O'Connor R.	2015	USA	Cross-sectional	425	67.4 ± 6.8 years	83.5%F 16.5%M	Asthma	no information	Age, Mean (SD) Female, % Race, % - non-Hispanic black - non-Hispanic white - Hispanic - Other Education, % - less than High School - High School Graduate - Some College - College Graduate Household Income, % < \$1350 per month Limited Health Literacy, %	67.4 ± 6.8 83.5 - 30.8 22.1 38.1 9.0 - 32.8 17.7 20.2 29.3 53.7 35.8	No relevant information	-	Self-report using the Medication Adherence Reporting Scale (MARS)	38% vs 62%	OR for GOOD adherence: Adequate Health Literacy: 2.30 (1.29- 4.08) Fluid cognitive abilities: 1.89 (1.30-2.75) Crystallized cognitive abilities: 1.05 (1.00-1.10)	No information
Olszanecka-Glinianowicz M.	2015	Poland	Cohort	6220	Asthma: 46.7 ± 15.0 yrs COPD: 60.0 ± 13.5 yrs	Asthma: 56.9%F and 43.1%M COPD: 42.7%F and 52.3%M	Asthma: 3618 and COPD: 2602	no information	Age, n (%) [years]: -18-30- 31-40- 41-50- 51-60 +> 60Women, n (%)Men, n (%)Education, n (%): - Primary - Vocational - Secondary - HigherLabour activity, n (%) - Mental work - Manual work - Pensioner - Retired - UnemployedPlace of residence, n (%) - Rural areas-City	Asthma: 117 (4.5)601 (16.6) 96/37905 (25.0) 300 (11.5)839 (23.2) 749 (28.8)622 (17.2). 1340 (51.5)2059 (56.9) 1111 (42.7)1559 (43.1). 1491 (52.3)- 318 (8.8) 528 (20.3)1631 (45.1) 932 (35.8)720 (19.9). 221 (8.5)- 1346 (37.2) 356 (13.7)821 (22.7) 533 (20.5)380 (10.5) 526 (20.2)474 (13.1) 982 (37.7)597 (16.5). 205 (7.9)- 995 (27.5) 1241 (47.7)2623 (72.5). 1361 (52.3)	Asthma: COPD:Currently used pharmacotherapy, n (%) - Short-acting β-agonist adrenergic receptor:1910 (52.8). 1702 (65.4)- Long-acting β-agonist adrenergic receptor:3618 (100). 2602 (100)- Inhaled glucocorticosteroids:3618 (100). 2602 (100)	the lack of a control group treated with fluticasone propionate and formoterol fumarate without using the Fantasma inhaler; self-reported assessment of adherence; the patient's education during observation and the level of knowledge about disease before enrollment; the differences in duration of disease and therapy with the Fantasma inhaler	Morisky 8-item medication adherence questionnaire (MMAS-8)	COPD visit 1: 61.5% COPD visit 2: 73.0%; Asthma visit 1: 72.0% Asthma visit 2: 70.5%;	Correlation index for GOOD adherence: Brief Illness Perception Questionnaire (BIPQ): Asthma: -0.15 COPD: -0.24	Asthma: Visit 1: 72% Visit 2: 70.5% 18-30 yrs: 60.3% >60 years: 84.6% Disease duration >5 years: 56.1% Mild disease severity: 83.4% COPD: Visit 1: 61.5% Visit 2: 73.0% 33-40 years: 43.5% 41-50 years: 68.1% Disease duration <1 year: 56.5% Very severe disease: 64.7%
Plaza V.	2018	Spain	Cross-sectional	778	46.76 ± 16.98 yrs	64.4%F 35.6%M	Asthma	GINA criteria	Age, mean ± SD, y - Age at asthma diagnosis - Age at asthma therapy onset Asthma severity, no. (%) - Moderate - Severe Asthma control, no (%) - Good (ACT score > 20) - Poor (ACT score < 20) Current therapy, no. (%) - Maintenance inhaled therapy - Oral therapy - Rescue inhaled therapy Combination of therapies, no. (%) Only maintenance inhaled therapy - Maintenance inhaled therapy + rescue inhaler - Oral therapy + inhaled therapy (maintenance or maintenance and rescue)	46.76 ± 16.98 29.84 ± 19.00 31.61 ± 18.80 - 635 (81.6) 143 (18.4) - 424 (57.7) 311 (42.3) 777 (99.9) 160 (20.6) 331 (42.6) 395 (50.8) 223 (28.7) 159 (20.5)	Maintenance inhaler, no. (%) pMDI : 68 (8.8) DPI: 707 (91.2) - Easyhaler : 446 (63.1) - Turbuhaler : 93 (13.2) - Diskus/Accuhaler : 66 (9.4) - Ellipta: 25 (3.5) - Spiromax : 11 (1.6) - Nexthaler: 7 (1.0) - Brexhaler : 1 (0.1) - Unspecified: 2 (0.3)	self-report of adherence	Test of Adherence to Inhalers (TAI), the Morisky-Green questionnaire	High satisfaction with inhaler: - TAI mean score: 47.3 (±4.21) - Morisky-green: 3.13 (±0.98) Low satisfaction with inhaler: - TAI mean score: 45.83 (±5.37) - Morisky-green: 2.93 (±1.09)	OR for GOOD adherence: High satisfaction with an inhaler 1.546 (1.025-2.332)	TAI score: High Satisfaction with an Inhaler: 47.30 (±4.21) Low satisfaction: 45.83 (±5.37) Morisky-Green score: High Satisfaction with an Inhaler: 3.13 (±0.98) Low satisfaction: 2.93 (±1.09)

Study				Sample Size (n ^e)	AGE (mean±SD or median+range)	GENDER (%M, %F)	Diagnosis		EXPOSURE reported		Presence of confounding factors		Primary OUTCOME reported (Adherence)		Measures of association for the Primary OUTCOME (RR, HR, OR with IC95% or sE) [Exposed over Non-exposed to the determinant]	Parameters estimates for the Primary OUTCOMES (% of adherent pax OR score at: mean±SD or median+range) [Exposed VS Non-exposed to the determinants]
Author	Year	Country	Design				Type	Disease Stage	Types of Determinants/Characteristics evaluated	Measure (mean±sd; %)	Therapy/Inhalers used	Others	Types of measures	% of Cases (adherent) vs % of Controls (non-adherent) OR Global score of adherence (at mean±SD or median+range)		
Plaza V.	2019	Spain	Cross-sectional	816	60 ± (18-94) yrs	54.5%M 45.5%F	Asthma: 49.8% and COPD: 50.2%	GINA and GOLD criteria	Age, years Sex, male; n (%) Never smoker, n(%)	17.2 54.5 37	corticosteroids and long-acting bronchodilators	self-report; the low cost of these medications in Spain	the Test of Adherence to Inhalers (TAI) and prescription refill data TAI total score: 46.0 (6.0) Non-adherence pattern: - Erratic: 45.6% - Deliberate: 30.1% - Unwitting: 24.3%	No information available	TAI score>50: COPD: 51.5% Asthma: 32.3% TAI mean score: COPD: 47.0 (5.2) Asthma: 45.1 (6.6) Previous inhaler technique training: 3.73 (0.51) No training: 3.44 (0.70)	
Price D.	2018	Germany, The Netherlands, Brazil, Japan, France, Italy, UK, USA, Canada	Cross-sectional	764	56 ± 9.8 yrs	51%M 49%F	COPD	GOLD criteria	sex Male Female age, years 40-49 50-59 60-69 70-75	- 51% 49% 31% 33% 26% 10%	bronchodilators and corticosteroids	self-report	Self reported by telephone visit 70.5% adherent vs 29.5% non-adherent	No reported information by authors. DATA MANUALLY ESTIMATED/RETRIEVED: OR for GOOD adherence: Female: 1.029 (0.754-1.405) >65yr: 1.639 (1.085-2.475) Mild stage: 1.079 (0.7513-1.55)	Male: 70.2% Female: 70.9% Age <65 years: 68.6% Age >65 years: 77.9% -Severity: Mild: 71.6% Moderate: 68.4% Severe: 72.9% Very severe: 85.7% --Time since diagnosis: -<12M: 64.3% >12M: 71.8% Breezhaler: 90% Ellipta: 65%	
Sleath B.	2018	USA	Cross-sectional	359	13.1 ± 1.9 (range: 11-17) yrs	58.9%M 41.1%F	Asthma	no information	Youth gender MaleFemaleYouth race/ethnicityWhiteAfrican American HispanicNative American OtherAsthma severity MildModerateSevereCaregiver gender MaleFemaleCaregiver race WhiteNonwhitePrimary language spoken at homeEnglishSpanishHousehold total annual incomeLess than \$10 000\$10 000-\$19 999\$20 000-\$29 999\$30 000-\$49 999\$50 000-\$69 999\$70 000 or morePositive screen for caregiver depression using PHQ-2 YesNoCharacteristics - Mean (SD), RangeYouth ageYears living with asthmaCaregiver ageCaregiver education (in years)	58.9 (188) 41.1 (131)36.1 (115) 36.7 (117) 12.5 (40) 12.2 (39)2.5 (8)43.6 (139) 56.4 (180)13.8 (44) 86.2 (275)45.5 (145) 54.5 (174)91.5 (292) 8.5 (27)- (17.2) (55) 15.4 (49) 18.2 (58) 12.5 (40) 13.5 (43) 23.2 (74)9.1 (29) 90.6 (289)- 13.1 (1.9), 11-17 9.7 (4.0), 1-17 42.3 (8.4), 19-7013.6 (3.3) 4.26	No relevant information	self-report	Self-reported patient adherence was measured using a Visual Analog Scale (VAS) Youth reported 60% average adherence, whereas caregivers reported 69%	Adjusted Beta coefficients for Youth-Reported GOOD adherence: Youth gender: male: -3.2 (-9.8, 3.4) Youth age: -1.7 (-3.5, 0.29) Race/ethnicity white: 1.6 (-6.0, 9.1) Asthma moderate/severe: 0.51 (-4.5, 7.5) Years living with asthma: -0.29 (-1.2, 0.62) No of controller medications: 7.9 (2.3, 13.6) Positive screen for caregiver depression: -4.2 (-16.1, 7.7) Family speaks Spanish at home: 0.57 (-11.9, 13.0) Household income: 0.67 (-1.5, 2.8) Youth self-efficacy in asthma management: -0.14 (-0.56, 0.28) Youth asthma outcome expectations: 0.63 (0.05, 1.2) Hard to use inhaler correctly: -9.9 (-17.7, -2.2) Hard to remember when to take the medicine: -7.8 (-14.4, -1.2) Hard to use at school: -1.0 (-8.2, 6.2) Adjusted Beta coefficients for Caregiver Reports of Their Child's GOOD adherence: Youth gender: male: -0.07 (-6.2, 6.1) Youth age: -2.27 (-4.06, -0.49) Youth race/ethnicity white: 6.4 (-0.73, 13.5) Asthma moderate/severe: -4.0 (-10.8, 2.8) Years living with asthma: -0.09 (-0.97, 0.80) No of controller medications: 3.4 (-2.1, 8.9) Positive screen for caregiver depression: -1.4 (-12.3, 9.5) Caregiver years of schooling: -0.04 (-1.15, 1.06) Family speaks Spanish at home: -5.6 (-17.6, 6.4) Household income: -1.05 (-3.32, 1.23) Caregiver self-efficacy in asthma management: 2.59 (4.72, 9.91) Caregiver asthma outcome expectations: 1.03 (0.26, 1.8) Hard to understand directions on medication: -9.6 (-26.0, 6.9) Hard to read print on the package: 0.51 (-11.9, 12.9) Hard to get refills on time: -4.25 (-14.7, 6.2) Hard for youth to use inhaler correctly: -3.71 (-11.3, 3.9) Hard to remember when to take the medicine: -11.4 (-17.7, -5.0) Hard to pay for: -0.35 (-8.75, 8.05)	Youth: 60% Caregivers: 69%	
Smith A.	2006	USA	Cohort	59	43.2 ± 10.9 yrs	64%F 36%M	Asthma	no information	Sociodemographics Age, yr - Female gender Race - African American - White - Other Education - Less than high school - High school and beyond Employment - Full/part time - Unemployed - Disabled - Other Marital status - Single - Married - Divorced, separated, or widowed	43.2 (±) -10.9 38 (64) - 47 (80) 10 (17) 2 (3) - 22 (37) 37 (62) - 18 (31) 23 (39) 11 (19) 7 (12) - 33 (56) 8 (14) 18 (31)	corticosteroids	-	electronically monitored adherence to therapy after discharge: 68%	OR for POOR adherence [-> OR for GOOD adherence]: High depressive symptoms: 11.4 (2.2-58.2) [-> 0.09 (0.02-4.5)] Age: 0.9 (0.9-1.0) [-> 1.11 (1.0-1.11)] Female gender: 4.8 (0.8-29.2) [-> 0.21 (0.03-1.25)] Lower education: 0.3 (0.1-1.7) [-> 3.33 (0.59-10.0)]	High levels of depressive symptoms: 60 ± 26% Low/low of depressive symptoms: 74 ± 21%	
Sriram K.	2016	Australia	Cohort	150	70.3 ± 9.8 years	52%M 48%F	COPD	GOLD criteria	Age (mean + SD) Males, n (%) Education, n (%) --- Less than high school High school Technical college/University Marital status, n (%) --- Single/ Never married Married Divorced/separated Widowed BMI (kg/m ²) (mean + SD) Smoking status, n (%) --- Current smoker Former smoker/never smoker Cigarette pack years (mean + SD)	70.3 ± 9.8 years 52% - 65.329.35.3 - 284614.711.326.3 ± 7.1- 21.3% 78.748.5 ± 30.3	ICS and LABA	-	the Medication Adherence Report Scale (MARS) 42% high adherence	Patients who self-reported high adherence were older than those who reported suboptimal adherence. No other significant differences were observed between patients who self-reported high adherence and those who reported suboptimal adherence in their demographic and clinical features. No reported information by authors for Risk Estimations. DATA MANUALLY ESTIMATED/RETRIEVED. OR for GOOD adherence: High School: 1.297 (0.6577-2.557) Smoking exposure: 0.4638 (0.1979-1.087)	<high school: 39.7% High school: 45.5% Technical college/University: 50% Single: 38% Married: 42% Divorced: 45.5% Widowed: 47% GOLD I: 50% GOLD II: 35.3% GOLD III: 50% GOLD IV: 39.1% Current smoker: 29% Former/never smoker: 45.8%	

Study				Sample Size (n ^e)	AGE (mean±SD or median+range)	GENDER (%M, %F)	Diagnosis		EXPOSURE reported		Presence of confounding factors		Primary OUTCOME reported (Adherence)		Measures of association for the Primary OUTCOME (RR, HR, OR with IC95% or ±SE) [Exposed over Non-exposed to the determinant]	Parameters estimates for the Primary OUTCOMES (% of adherent pax OR score at: mean±SD or median+range) [Exposed VS Non-exposed to the determinants]
Author	Year	Country	Design				Type	Disease Stage	Types of Determinants/Characteristics evaluated	Measure (mean±sd; %)	Therapy/Inhalers used	Others	Types of measures	% of Cases (adherent) vs % of Controls (non-adherent) OR Global score of adherence (at mean±SD or median+range)		
Sulaiman I.	2017	Ireland	Cohort	244	70.6 ± 9.7 years	53%F 47%M	COPD	GOLD criteria	Demographics - Mean age - Sex, % female - BMI - Median (IQR) pack-years smoked - Currently smoking, % - Salmeterol/fluticasone dose, % 500 mg - Inhaler Proficiency Score (range, 0-10) Personal factors - Charlson Comorbidity Index - Median (IQR) regular medications, n - Median (IQR) nebulized treatment, n - MoCA score (range, 0-30) - HADS total score (range, 0-14) - Anxiety component of HADS (range, 0-7) - Depression component of HADS (range, 0-7) - European Health Literacy Survey score (range, 15-80) - Beliefs in Medicine Questionnaire (range, 18-90) - Median (IQR) Isolation score - Patients with government-sponsored health insurance, % - Median (IQR) Frailty score	70.6 (9.7) 53 27.5 (6.6) 48.0 (43.5) 22 74 7.5 (1.6) 5.9 (1.7) 15 (7) 1 (1) 22 (9) 12.3 (7.5) 6.9 (4.6) 5.6 (4.1) 33.5 (10.8) 52.0 (10.7) 2 (1) 98 2 (2)	ICS and LABA	-	electronic audio recording device (INCA), separated in 3 clusters: Cluster 1: Poor Adherence attempt + Poor Technique Cluster 2: Good Adherence attempt + Poor Technique Cluster 3: Good Adherence attempt + Good Technique	Adherence mean values: 1.78 (±2.86) 11.2 (±11.8) 53.1 (±26.6)	Adjusted RR for POOR adherence (Cluster 1 vs Cluster 3) [-> RR for GOOD adherence]: MoCA score: 0.598 (±0.157) [->1.672 (1.325-2.268)] Cough PEF: 0.381 (±0.129) [->2.625 (1.963-3.968)] FEV1: 1.442 (±0.373) [->0.693 (0.551-0.935)] Age: 1.216 (±0.308) [->0.822 (0.656-1.101)]	No information
Takemura M.	2010	Japan	Cross-sectional	146	57 ± 15 years	39% M 61%F	Asthma	GINA criteria	Patients, no. Age (years) Gender (male:female %) Repeated instruction (presence:absence)	146 57 ± 15 years 39%:61 % 17.1%: 82.9%	ICS and LABA	repeated instruction was neither randomized nor controlled; self-reported; selection of periodic instruction for each patient.	self-reported adherence questionnaire Mean adherence score: 4.0 ± 0.7 Good adherence: 54.1%	OR for GOOD adherence: Age: 1.02 (0.99-1.04) Gender (male): 1.38 (0.69-2.78) Repeated instructions on inhaler use: 2.90 (1.07-7.88)	No information	
Takemura M.	2011	Japan	Cross-sectional	55	69 ± 8 years	27.3%F 72.7%M	COPD	GOLD criteria	Patients, no. Age (years) Gender (male:female %) Repeated instruction presence	55 69 ± 8 years 27.3%:72.7 % 40%	anticholinergic, β2 agonist, or inhaled corticosteroid	repeated instruction was neither randomized nor controlled; self-reported; selection of periodic instruction for each patient.	self-reported adherence questionnaire 54.5% good adherence Mean adherence score: 4.1 ± 0.7	Adjusted Beta coefficients for GOOD adherence: Age: 0.22 Gender: -0.06 Frequency of clinic visits: -0.01 Frequency of inhaler use: 0.19 Type of inhaler device: -0.02 Comorbidities: -0.11 Antipsychotic drugs: 0.06 Stage of COPD: 0.12 Repeated instruction: 0.28	Adherence mean value: With repeated inhaler instruction: 4.4 ± 0.5 Without instruction: 3.9 ± 0.8	
Takemura M.	2017	Japan	Cohort	114	53 ± 18 years	30.7%M 69.3%F	Asthma	GINA criteria	Age, mean ± SD, (years) Gender (male : female) Current smoking (yes : no) Presence of comorbidities (%)	53±18 35:79 13:101 73 (64.0)	ICS and LABA	-	Pharmacy-refill data and The Japanese version of the ASK-20 54.4% adherent vs 45.6% non-adherent	Adjusted OR for POOR adherence [-> OR for GOOD adherence]: Non-elderly: 2.67 [->0.37] Current smoker: 2.53 [->0.42] Mild asthma: 2.13 [->0.47]	No information	
Tavasoli S.	2006	Iran	Cross-sectional	160	47.67 ± 12.78 years	65.6%F 34.4% M	Asthma	GINA criteria	Mean age (min-max) ± SD Female:Male:Literacy level---Illiterate:Low-literate:Elementary school education:Guidance school(pre-high) education:High school:University education:Family history of asthma:Mean time asthma diagnosis (months) (min-max) ± SD Employment--- Immigrant:Native:living in other cities:Smoking status ---Active:Passive:None smoker:Ex-smoker:History of other chronic disease:History of taking medication for other chronic disease	47.67 (16-83) ± 12.78---105 (65.6%) 55 (34.4%)---32 (20%) 19 (11.9%) 38 (23.8%) 28 (17.5%) 33 (20.6%) 10 (6.3%) 66 (41.3%)102.05 (0-600) ± 103.34---64 (40%) 96 (60%)---97 (60.6%) 51 (31.9%) 12 (7.5%) 5 (3.1%) 25 (15.6%) 104 (65%) 26 (16.3%) 61(38.1%) 63(39.4%)	ICS and LABA	all of the participants were chosen from two clinics; self-reported	questionnaire by self-report compliance score: 2.56± 1.06	Correlation index for GOOD compliance:Age (years): -0.046:Literacy level: 0.199:Length of time having diagnosis of Asthma: 0.043:Immigration status: -0.069 Smoking status: 0.002:Asthma severity (grade): 0.029:Attitude: 0.330 Attitude towards using drugs: 0.530:Attitude towards asthma control: 0.029:symptom contrl: -0.270:Asthma knowledge: 0.227	Compliance Median (IQR) values:Female: 3 (2-3) Male: 3 (1.25-3.75)Family history of asthma: 3 (2.75-3) No: 2.5 (2-3.25)Employed: 3 (2-3) Unemployed: 3 (2-3)History of other chronic disease: Yes: 3 (1-3) No: 3 (2-3)Medication for other chronic disease: Yes: 3 (1-3) No: 3 (2-3.25)Cough: Yes: 3 (2-3) No: 3 (2-4)Wheeze: Yes: 3 (2-3) No: 2 (1-3)Difficult breathing: Yes: 3 (2-3) No: 2 (1-4)Self-reported improvement by herbal drugs: Yes: 3 (2-3) No: 3 (2-3.5)Antihistamines Use: 3 (2-4) Not use: 3 (2-3)Different types of MDIa drugs Use: 3 (2.25-3.75) Not use: 3 (2-3)Antibiotics Use: 3 (2-4) Not use: 2 (1-3)Expectorants Use: 3 (2-3) Not use: 2 (2-3)Theophylline Use: 3 (1.75-3.25) Not use: 3 (2-3)Spacer using Use: 2 (1.75-3) Not use: 3 (2-4)	
Turan O.	2017	turkey	Cross-sectional	121	70.4 ± 5.5 years	65.3%M 34.7%F	COPD: 72.7% and Asthma: 27.3%	GINA and GOLD criteria	COPD: 70.24 ± 5.85 (65-88) 76/12 (86.4/13.6) 6 (6.8) 56 (63.6) 16 (18.2) 8 (9.1) Literate 2 (2.3) Primary school Middle school High school University Smoking (pack-years)	70.24 ± 5.85 (65-88) 76/12 (86.4/13.6) 6 (6.8) 56 (63.6) 16 (18.2) 8 (9.1) 2 (2.3) 46.54 ± 17.67 Asthma: 70.88 ± 4.56 (65-80) 3/90 (9.1/ 90.9) 1 (3) 28 (84.8) 1 (3) 3 (9.1)	No relevant information	the scale for measuring adherence to therapy was developed according to local guidelines, which have not been formally validated; Sex bias: As an arterial blood gas analyzer was not present in all of the centers participating the study, we could measure the level of oxygen by pulse oximetry.	the Morisky Medication Adherence Scale-4 61.2% adherent vs 38.8% non-adherent	Correlation index for GOOD adherence: FEV1%: -0.182 FVC%: -0.233 MRC: 0.012 O2 saturation (%): -0.070 Duration of disease (years): -0.134 Cigarette (pack-years): 0.281 No. hospitalizations (last year): 0.143 Admission to emergency service (last year): 0.153 SGRQ score: -0.006 MMSE score: -0.266	Cognitive dysfunction: 53.1% Normal cognitive function: 66.7%	

Study				Sample Size (n ^e)	AGE (mean±SD or median+range)	GENDER (%M, %F)	Diagnosis		EXPOSURE reported		Presence of confounding factors		Primary OUTCOME reported (Adherence)		Measures of association for the Primary OUTCOME (RR, HR, OR with IC95% or ±SE) [Exposed over Non-exposed to the determinant]	Parameters estimates for the Primary OUTCOMES (% of adherent pax OR score at: mean±SD or median+range) [Exposed VS Non-exposed to the determinants]	
Author	Year	Country	Design				Type	Disease Stage	Types of Determinants/Characteristics evaluated	Measure (mean±sd; %)	Therapy/Inhalers used	Others	Types of measures	% of Cases (adherent) vs % of Controls (non-adherent) OR Global score of adherence (at mean±SD or median+range)			
van Dellen Q. M.	2008	the Netherlands	Cross-sectional	232	7-12 years: 63% 13-17 years: 37%	61%M 39%F	Asthma	no information	Total no. of participants - Dutch - Moroccan - Turkish - SurinameseChildren characteristicsGender - Boys - GirlsAge- 7-12 years - 13-17 yearsAsthma control - Well-controlled- Not well-controlled - MissingParent characteristicsSingle-parent family - Yes-NoEducation - Yes- None or primary education onlyOccupation: Skilled labourer - Manual labourer - HomemakerHousehold income (net per month) < 1600 euro - >1600 euro-MissingLevel of asthma knowledge - Sufficient-Insufficient- MissingComprehension of Dutch(Moroccan and Turkish parents n 1/4 112)- Sufficient - Insufficient	10033292018- 6139- 6337- 61381- 1882- 6832- 5328 19- 513118- 4356 1-3961	ICS	interviewed in a face-to-face; The questionnaire used during the interview was translated backward and forward into Turkish and Arabic language	Self-report and pharmacy record data	74.6% adherent vs 25.4% non-adherent	OR for POOR adherence [-> OR for GOOD adherence]: Well-controlled asthma: 4.12 (1.50-11.3) [->0.24 (0.09-0.67)](positive subjective view of parents: 0.45 (0.25-0.81) [->2.22 (1.23-4.0)]Self-efficacy : 0.51 (0.35-0.75) [->1.96 (1.33-2.86)]	Dutch: 65% Moroccan: 86% Turkish: 73% Surinamese: 77%Girls: 80.3% Boys: 70.9%Well-controlled Asthma: 64.2% Not well-controlled: 87.8%Parent educated: 73.6% No educated: 77.1%Households <1600Euro: 77.1% >1600Euro: 73.5%Single-parent family: 74.2% No: 74.6%Sufficient asthma knowledge: 75% Insufficient: 73.7%	
Vasbinder E.	2013	the Netherlands	Cohort	87	1-11 years	62%M 38% F	Asthma	no information	- Age(months)Sex - boys ICS medication- Fluticasone - Fluticasone/salmeterolDosing frequency- Once daily- Twice dailyParental level of education- None- Primary school - Secondary school - Vocational education- UniversityQuality of housing- Poor- Insufficient- Sufficient- GoodSmoking at home - yesYear family income- <1 x average - low- 1-2 x average - intermediate- >2 x average - highBMIQ groups- Skeptical (nec <15, conc >15)- Indifferent (nec <15, conc <15)- Ambivalent (nec >15, conc >15) - Accepting (nec >15, conc <15)BMIQ necessity- <15 - >15BMIQ concerns- <15 - >15Use of a spacer during inhalations- yesN ^e of annual hospital admissionsN ^e of annual visits to clinic	Dutch children: 53.0±23.032 (72.7) 39 (90.7) (15.9) 4(14.0)36 (81.8) 3(7.0)2 (4.5) 14(32.6)15 (34.1) 8(18.6)- 2 (4.5) 7(16.3)14 (31.8) 12 (27.9)4 (9.1)- 11 (25.0) 28(65.1)26 (59.1) 1 (2.3)- 1 (2.3) 6 (14.0)3 (6.8) 11(25.6)- 14 (31.8) (68.2) 32(74.4)- 40 (90.9) 17(39.5)4 (9.1) (88.6) 0.5±0.83.8±2.8 4.1±2.4	Moroccan children 64.7±35.7 22 (51.2)- 37 (84.1) 4 (9.3)- 8 (18.2) 37(86.0)- 0 (0.0) 6(14.0)7 (15.9) 12 (27.9)20 (45.5) 16(37.2)4 (9.1) 8(18.6)12 (27.9) 11 (25.0) 14(32.6) 7 (15.9) 5 (11.6)13 (29.5) 21(48.8)27 (61.4) 11(25.6)30 (68.2) 40 (90.9) 26(60.5)- 39 (88.6) 35 (81.4) 0.3±0.6 4.1±2.4	ICS	Selection bias (upon diagnosis and treatment)	electronic monitored: Real Time Medication Monitoring (RTMM) system	49.3% adherent vs 50.7% non-adherent	No reported information by authors. DATA MANUALLY ESTIMATED/RETRIEVED, OR for GOOD adherence: Higher education: 1.742 (0.483-6.214)Intermediate/High family income: 1.625 (0.6887-3.834)Higher outpatient clinic visits: 1.513 (0.6483-3.532)	Dutch ethnicity: 55.9% ±30.4 Moroccan ethnicity: 42.5% ±30.8Vocational/lower Parental education: 44.9% ±30.2 College/University: 58.7% ±31.7Poor/insuf. quality of housing: 42.8% ±28.3 Sufficient/good 52.6% ±32.2Family income low: 42.9% ±32.5 intermediate: 52.6% ±29.5 high: 64.3% ±28.3 visits to outpatient clinic: 43.7% ±28.8 >3 visits: 55.9% ±32.9BMIQ-Skeptical: 22.2% ±29.5 BMIQ-Indifferent: 51.4% ±37.4 BMIQ-Ambivalent: 47.8% ±30.4 BMIQ-Accepting: 53.5% ±29.0BMIQ-concerns <15: 52.8% ±30.7 BMIQ-concerns >15: 42.7% ±31.5Use of a spacer: 53.4% ±30.5 No spacer: 26.1% ±25.0
Voorham J.	2017	UK	Cohort	2259 - matched	Age, mean (SD)- Payment cohort: 44.0 (11.1) years- No- Payment cohort: 44.4 (11.2)	Payment cohort: 47.3%M and 52.7%F- No- Payment cohort: 48.1%M and 51.9%F	COPD and Asthma	no information	Payment - 879 (53.6) 322 (52.0)509 (31.0) 191(30.9)231 (1.3) 90 (14.5)21 (1.3) 16 (2.6)44.0 (11.1) 44.4 (11.2)775 (47.3) 298 (48.1)- 762 (46.5) 275(44.4)469 (28.6) 184(29.7)409 (24.9) 160(25.8)- 15 (0.9) 11 (1.8)557 (34.0) 206 (33.3)478 (29.1) 186(30.0)590(36.0) 216 (34.5)- 114 (7.0) 41 (6.6)37 (2.3) 13 (2.1)219 (13.3) 80 (12.9)142 (8.7) 70 (11.3)176 (4.6) 36 (5.8)469 (28.6) 191(30.9)191 (11.6) 81(13.1)166(10.1) 73 (11.8)121(7.4) 49 (7.9)486 (29.6) 170 (27.5)31 (1.9) 14 (2.3)72 (4.4) 24 (2.3)15(0.9) 7 (1.1)	fluticasone propionate/salmeterol xinafoate (FP/SAL)	Medication-taking behavior:geographical biasexposure bias (treatment swich)	Medication possession ratio (MPR)	Adherent with MPR>80%: 34.5%	OR for GOOD adherence: Payment cohort: 1.04 (0.85-1.27)	Payment cohort adherence: 34.3%No payment cohort adherence: 34.9%		
Yu, Andrew P.	2011	USA	Cohort	23494	66.0 ± 9.8 years	53.1% F 46.9% M	COPD	GOLD criteria	Multiple-inhaler users n = 11747 Single-inhalers users n = 11747	23.6% 76.4%	LAMA, LABA and ICS	-	filled prescriptions	Average proportion of days covered (=adherence rate): 0.55±0.279	OR for GOOD adherence: Multiple inhaler user (vs single): 0.66 (0.62-0.70)	Discontinuation rates: Single inhaler users: 78.6% Multiple inhaler users: 86.7%	
Zucchelli A.	2020	Italy	Cohort	3177	more than 40 years	30.9%F 69.1% M	COPD	GOLD criteria	Sex - Males - FemalesAge- 40-49- 50-59- 60-69- 70-79 ->80Smoking habit - Never- Current- PreviousObesity- No- Yes	- 69.130.9- 16.623.439.729.3- 11.527.729.2- 16.710.5	ICS, LAMA and LABA	medical prescriptions	15.0% adherent vs 85% non-adherent	OR for POOR adherence [-> OR for GOOD adherence]: Females (vs males): 1.2 (0.96-1.49) [->0.83 (0.67-1.04)]- Age (vs 40-49): Age 50-59: 1.12 (0.4-3.13) [->0.89 (0.32-2.5)]Age 60-69: 0.84 (0.32-2.24) [->1.19 (0.45-3.13)]Age 70-79: 1.11 (0.42-2.92) [->0.9 (0.34-2.38)]Age >80: 1.35 (0.51-3.58) [->0.74 (0.28-1.96)]Current smoker (vs never): 0.61 (0.41-0.93) [->1.64 (1.08-2.44)]Previous smoker (vs never): 0.52 (0.34-0.78) [->1.92 (1.28-2.94)]Obesity: 1.23 (0.82-1.84) [->1.92 (0.54-1.22)]Visit to GP's office: 1.18 (0.89-1.56) [->0.85 (0.64-1.12)]- Chronic conditions (vs none): Heart failure: 1.78 (1.19-2.65) [->0.56 (0.38-0.84)]ischemic heart disease: 1.44 (1.1-1.88) [->0.69 (0.53-0.91)]Peripheral vascular disease: 1.32 (1.01-1.74) [->0.76 (0.57-0.99)]Cerebrovascular disease: 1.3 (0.99-1.72) [->0.77 (0.58-1.01)]Cardiac arrhythmias: 1.26 (0.97-1.65) [->0.79 (0.61-1.03)]Asthma: 1.27 (0.89-1.81) [->0.79 (0.55-1.12)]Other pulmonary chronic diseases: 0.9 (0.71-1.13) [->1.11 (0.88-1.41)]Peptic ulcer: 0.82 (0.61-1.11) [->1.22 (0.90-1.64)]Diabetes: 1.21 (0.95-1.54) [->0.83 (0.65-1.05)]Chronic kidney disease: 1.25 (1.03-1.51) [->0.8 (0.66-0.97)]Cancer: 1.15 (0.88-1.51) [->0.87 (0.66-1.14)]Depression: 1.41 (1.06-1.88) [->0.71 (0.53-0.94)]Dementia: 2.44 (0.75-7.9) [->0.41 (0.13-1.33)]Polypharmacy: 1.47 (1.17-1.85) [->0.68 (0.54-0.85)]	No information		
Apter A. J.	1998	USA	Cohort	50	46 ± 14 years	26%M 74%F	Asthma	no information	Formal education less than 12 yr Spanish as primary language Household income less than \$20,000 Ethnic-racial-group membership - African-American - Hispanic - Caucasian Type of health insurance - Commercial - Medicaid - Medicare only - Self-pay (none)	32% 36% 46% 22% 36% 42% 52% 32% 6% 10%	ICS	electronically monitored	Mean adherence rate: 63±38%	OR for POOR adherence [-> OR for GOOD adherence]: Formal education <12 yr: 6.72 (1.10-41.0) [->0.15 (0.02-0.91)] Poor patient-clinician communication: 1.20 (1.01-1.55) [->0.83 (0.65-0.99)]	Female: 46% male: 76.9% Household income <\$20,000: 21.2% income >\$20,000: 74% With health insurance: 61.5% Without: 45.8% Formal education <12 yr: 18.8% Education >12yr: 70.6% Minority patients: 37.9% No minority: 76.2% With previous hospitalizations: 58.6% Without: 47.6%		

Study				Sample Size (n ^e)	AGE (mean±SD or median+range)	GENDER (%M, %F)	Diagnosis		EXPOSURE reported		Presence of confounding factors		Primary OUTCOME reported (Adherence)		Measures of association for the Primary OUTCOME (RR, HR, OR with IC95% or ±SE) [Exposed over Non-exposed to the determinant]	Parameters estimates for the Primary OUTCOMES (% of adherent pax OR score at: mean±SD or median+range) [Exposed VS Non-exposed to the determinants]
Author	Year	Country	Design				Type	Disease Stage	Types of Determinants/Characteristics evaluated	Measure (mean±sd; %)	Therapy/Inhalers used	Others	Types of measures	% of Cases (adherent) vs % of Controls (non-adherent) OR Global score of adherence (at mean±SD or median+range)		
Chambers C. V.	1999	USA	Cross-sectional	394	36 years	75%F 25%M	Asthma	no information	Gender (%) - Female 75 - Male 25 Race (%) - African-American 51 - White 40 - Hispanic 4 - Asian 3 - Other 3 Marital Status (%) - Single, never married 47 - Married 39 - Divorced 11 - Other 3 Educational level(%) - Graduate school 18 - College graduate 20 - Some college 28 - High school graduate 22 - Other 12	40.8 ± 7.7	ICS	the instructions that physicians gave to their patients about how to take ICS were not available.	Self-reported % of pax answering "I use it at least twice a day almost every day": 38%	OR for GOOD adherence: "Active health believe": 4.6 (2.8-7.5) "Serious health believe": 2.3 (1.4-3.7) Hospitalization: 2.3 (1.6-4.6)	No information	
Lacasse Y.	2005	Canada	Cohort	124	47 ± 15 years	41.1% M 58.9% F	Asthma	no information	Sex distribution (M:F)Age, years (mean ± SD)Level of education, years (mean ± SD)Public drug insurance plan (%)	51:73 47:15 13±444	ICS	This process involved two translations of the questionnaire from English to French	electronically monitored Self-recorded mean compliance: 88±24%Measured mean adjusted compliance index:72±24%-Compliance mean index:1A - Regular compliers: 91%1B - Irregular compliers: 90% 2A - Regular noncompliers:49%2B - Irregular noncompliers: 51%	OR for noncompliance [-> OR for GOOD compliance]:Age(yr): 0.95 (0.93 -0.98) [->1.05 (1.02-1.08)]	No information	
Williams L. K.	2007	USA	Cohort	176	40.8 ± 7.7 years	68.1% F 31.9% M	Asthma	no information	Age (mean ± SD) Female sex (%) Race-ethnicity (%) - African American 44.4 - White 55.6 Estimated household income (\$; mean 6 SD) Index crime rate in area of residence (events per 1000 population)	40.8 ± 7.7 68.1 - 44.4 55.6 52,701 ± 20,8 65 ± 55	ICS	the study population consisted of patients with health insurance and pharmaceutical coverage; socioeconomic variables were derived from census data; pharmacy claims data to estimate adherence.	prescription - fill data Mean global adherence rate: 0.50 ± 0.37	No information available	Change in adherence rate: Age (each 10yr): +4.1 ± 4.0 Female sex: -12.5 ± 6.4 African American race: -20.8 ± 6.6 Median household income: - 9.7 6± 9.3 Index crime rate in area of residence: 5.2 ± 10.9 Crude adherence rate: African American patients: 0.40 ± 0.26 White patients: 0.58 ± 0.42	
Janson S. L.	2008	USA	Cohort	113	48.7 ± 7.4 years	68%F 32%M	Asthma	no information	Age (y) Female sex Ethnicity: White, non-Hispanic Education - High school graduate or less - Some college - College graduate or higher Income % \$40K \$40K to \$80K % \$80K Ever smoked BMI ≥ 30	48.7 ± 7.4 68% 72% - 14 38 58 - 20 27 53 32 44	ICS	-	electronic monitored and pharmacy refill records 75%adherence vs 15% non-adherent	OR for POOR adherence for inhaled corticosteroid [-> OR for GOOD adherence]: Income (vs ≤\$40K): \$40K to \$80K: 0.75 (0.24-2.40) [->1.33 (0.42-4.17)] ≥\$80K: 0.30 (0.10-0.93) [->3.33 (1.08-10.0)] Oral steroid use: 0.32 (0.04-2.78) [->3.13 (0.36-25.0)] FEV1% predicted: 1.41 (1.08-1.85) [->0.71 (0.54-0.93)] OR for POOR adherence for inhaled beta-agonist [-> OR for GOOD adherence]: Education (vs high school graduate): Some college: 0.32 (0.10-1.03) [->3.13 (0.97-10.0)] College or greater: 0.27 (0.08-0.88) [->3.7 (1.14-12.5)] FEV1% predicted (10% change): 1.89 (0.70-1.13) [->0.53 (0.88-1.43)] Self-perceived high severity: 4.47 (1.56-12.89) [->0.22 (0.08-0.64)] AQOL score: 1.00 (0.97-1.03) [->1.00 (0.97-1.03)] Occasional/nighttime symptoms: 1.37 (0.51-3.69) [->0.73 (0.27-1.96)]	No information	
Wells K.	2008	USA	Cohort	1006	43.1 ± 10.4 years	71.2%F 28.8%M	Asthma	no information	Age, yr, mean SD Female, no. (%) Race-ethnicity, no. (%) - African American - White - Other	43.16 ± 10.4 71.2% - 33.4% 61.0% 5.6%	ICS	-	electronic monitored and pharmacy refill records Mean adherence score: 36.6 ± 34.4	Adjusted Beta coefficients for GOOD adherence: Age (yr): 4.0 (1.7) Female:-10.8 (3.6) African American race-ethnicity: -4.7 (4.7) Duration of asthma: -0.1 (0.1) Asthma control: -0.9 (0.5)	No information	
Poniaman D.	2009	USA	Cohort	261	48 ± 13 years	82%F 18%M	Asthma	no information	Age, mean (SD), y Female sex, % Ethnicity, % Hispanic - Black - White Insurance status, % Medicaid (with or without Medicare) - Medicare alone Commercial insurance - Uninsured Income ≤\$30,000/y, % Education level ≥ high school, % Necessity (%) - Important to use ICS when asymptomatic - Important to use ICS when symptomatic Concerns (%) - Worried about side effects of ICS - Worried about getting addicted to ICS - If use ICS all the time they will stop working Self-efficacy (%) - Confident in ability to use ICS as prescribed - Confident in ability to control asthma - Confident can control future health Regimen complexity (%) - ICS regimen was hard to follow	48 (13) 82- 57 3013- 66 18 142 64 39- 8882- 493732- 8257 75- 7	ICS	-	Medication Adherence Reporting Scale (MARS); self-reported Self reported adherence: 70% Mean MARS score: 4.3	OR for GOOD adherence:"Feeling that using ICS when asymptomatic was important": 4.15 (2.54-6.77)"Being confident in using ICS": 2.23 (1.42-3.52)"Having worries about side effects": 0.52 (0.36-0.74)"Feeling the regimen was hard to follow": 0.48 (0.23-0.99)	No information	

Study				Sample Size (n ^o)	AGE (mean±SD or median+range)	GENDER (%M, %F)	Diagnosis		EXPOSURE reported		Presence of confounding factors		Primary OUTCOME reported (Adherence)		Measures of association for the Primary OUTCOME (RR, HR, OR with IC95% or ±SE) [Exposed over Non-exposed to the determinant]	Parameters estimates for the Primary OUTCOMES (% of adherent pax OR score at: mean±SD or median+range) [Exposed VS Non-exposed to the determinants]
Author	Year	Country	Design				Type	Disease Stage	Types of Determinants/Characteristics evaluated	Measure (mean±sd; %)	Therapy/Inhalers used	Others	Types of measures	% of Cases (adherent) vs % of Controls (non-adherent) OR Global score of adherence (at mean±SD or median+range)		
Emilsson M.	2011	Sweden	Cross-sectional	35	52.8 ± 14.7 years	28,6%M 71,4%F	Asthma	no information	Age Mean (SD): 52.85 (14.72) Level of Education: - Compulsory school 9 - Grammar/High school 17 - College/University 8 - Missing data 1 - Employee/Self-employed 23 - Pensioner 10 - Student 1 - Other 1 Personality traits- total (SD) - Neuroticism 14.91 (9.10) - Extraversion 31.28 (6.21) - Openness 26.63 (6.17) - Agreeableness 34.98 (5.85) - Conscientiousness 35.30(6.29) - MARS 21.17 (3.22) - Specific-Necessity 18.26 (4.60) - Specific-Concerns 10.49 (4.21) - NC/diff2 7.77 (5.66)	ICS and LABA	-	Medication Adherence Reporting Scale (MARS); self-reported	MARS mean score: 21.17 (±3.22)	Pearson's R index for GOOD adherence: Age: -0.06 (-0.39 - 0.29) Neuroticism: -0.34 (-0.61 - -0.01) Extraversion: 0.19 (-0.15 - 0.49) Openness: -0.14 (-0.45 - 0.20) Agreeableness: 0.00 (-0.34 - 0.33) Conscientiousness: 0.25 (-0.08 - 0.54) Specific-Necessity: 0.38 (0.05 - 0.63) Specific-Concerns: -0.16 (-0.47 - 0.19)	No information	

Supplementary Appendix S4 - Complete data meta-analysis.

(results presented with forest-plots and their respective funnel-plots for each specific analysis)

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Summary of main findings of all meta-analysis

(measures of associations reported for determinants of adherence and subgroup analysis. Statistically significant results highlighted as: positive effects on green shadow and negative effects on yellow shadow)

DETERMINANT OF ADHERENCE OR SUBGROUP	PAX	STUDIES	RISK RATIO (IV, RANDOM, 95% CI)	I ²	I ² P value
1. META-ANALYSIS FOR "AGE"					
Full data analysis	9051	12	1.07 (1.03-1.10)	94	<0.0001
• Subanalysis on Publication year	-	-	-	-	-
○ Old studies (≤2010)	329	3	1.03 (1.01-1.05)	78	0.01
○ Recent studies (>2020)	8722	9	1.13 (1.04-1.23)	95	<0.0001
• Subanalysis on Continental region	-	-	-	-	-
○ Asia	1303	3	1.01 (1.00-1.01)	0	0.44
○ Europe	7132	6	1.21 (0.97-1.51)	97	<0.0001
○ North America	616	3	1.04 (1.01-1.06)	44	0.17
• Subanalysis on Study design	-	-	-	-	-
○ Cross-sectional	2998	5	1.02 (0.99-1.04)	78	0.001
○ Cohort	6053	7	1.08 (1.00-1.16)	96	<0.0001
• Subanalysis on Risk of Bias assessment	-	-	-	-	-
○ Low	1154	2	1.11 (0.74-1.67)	92	0.0005
○ Moderate	2128	6	1.02 (0.98-1.05)	77	0.0005
○ Serious	5769	4	1.15 (1.07-1.23)	98	<0.0001
• Subanalysis on Study dimension/size	-	-	-	-	-
○ Small studies	800	6	1.02 (1.00-1.05)	69	0.007
○ Big studies	8251	6	1.16 (1.06-1.27)	97	<0.0001
• Subanalysis on Diagnosis type	-	-	-	-	-
○ Asthma	5746	7	1.08 (1.04-1.12)	96	<0.0001
○ COPD	2271	3	1.01 (0.89-1.15)	75	0.02
○ Asthma or COPD	1034	2	1.39 (1.16-1.65)	0	0.84
• Subanalysis on Types of instruments to measure adherence	-	-	-	-	-
○ Dose counting or Eletronic monitored	1793	5	1.01 (0.98-1.05)	83	<0.0001
○ Inespecific self-reported measure	5170	4	1.19 (0.92-1.55)	98	<0.0001
○ Morisky Medication Adherence Scale (MMAS-8)	1054	1	1.01 (1.00-1.01)	-	-
○ Test of Adherence to Inhalers (TAI)	1034	2	1.39 (1.16-1.65)	0	0.84
2. META-ANALYSIS FOR "GENDER FEMALE"					
Full data analysis	9541	12	0.92 (0.82-1.03)	74	<0.0001
• Subanalysis on Publication year	-	-	-	-	-
○ Old studies (≤2010)	205	2	0.86 (0.62-1.19)	0	0.87
○ Recent studies (>2020)	9336	11	0.92 (0.82-1.04)	78	<0.0001

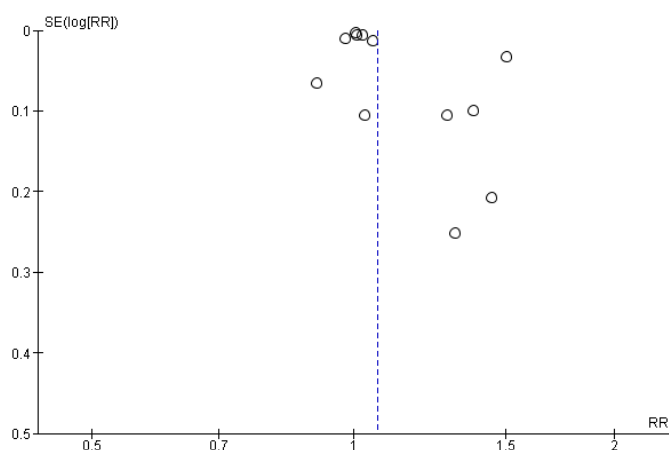
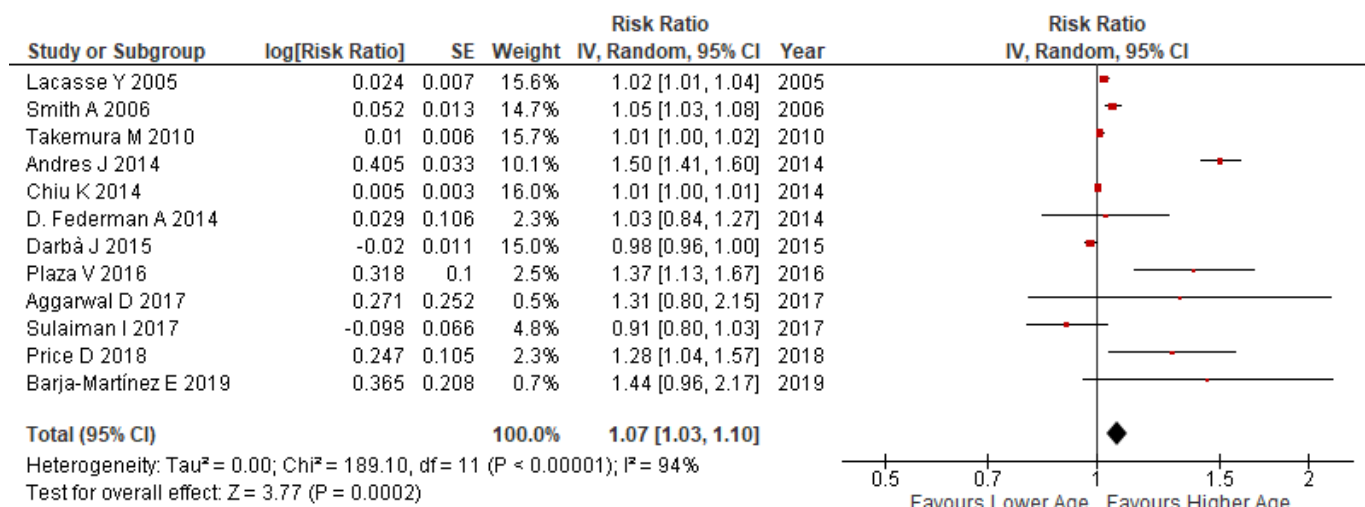
• Subanalysis on Continental region	-	-	-	-	-
○ Asia	249	2	0.87 (0.65-1.16)	0	0.84
○ Europe	8701	7	0.93 (0.79-1.09)	85	<0.0001
○ North America	492	2	0.89 (0.69-1.15)	0	0.94
○ Oceania	99	1	0.89 (0.79-1.00)	-	-
• Subanalysis on Study design	-	-	-	-	-
○ Cross-sectional	2176	5	0.82 (0.66-1.03)	86	<0.0001
○ Cohort	7365	7	1.00 (0.92-1.09)	21	0.27
• Subanalysis on Risk of Bias assessment	-	-	-	-	-
○ Low	6060	3	1.00 (0.88-1.14)	65	0.06
○ Moderate	2361	6	0.99 (0.88-1.22)	0	0.75
○ Serious	1021	2	0.69 (0.32-1.50)	96	<0.0001
○ Critical	99	1	0.89 (0.79-1.00)	-	-
• Subanalysis on Study dimension/size	-	-	-	-	-
○ Small studies	664	5	0.75 (0.54-1.05)	81	0.0003
○ Big studies	8877	7	1.01 (0.94-1.08)	20	0.28
• Subanalysis on Diagnosis type	-	-	-	-	-
○ Asthma	840	5	0.89 (0.80-0.98)	0	1.0
○ COPD	5818	5	0.88 (0.70-1.10)	88	<0.0001
○ Asthma or COPD	2883	2	1.07 (0.95-1.19)	20	0.26
• Subanalysis on Types of instruments to measure adherence	-	-	-	-	-
○ Dose counting or Electronic monitored	7031	7	0.99 (0.90-1.08)	41	0.12
○ Inespecific self-reported measure	1343	3	0.96 (0.85-1.09)	0	0.53
○ Test of Adherence to Inhalers (TAI)	1167	2	0.68 (0.32-1.44)	96	<0.0001
3. META-ANALYSIS FOR “SMOKING EXPOSURE”					
Full data analysis	5861	6	1.12 (0.82-1.52)	98	<0.0001
• Subanalysis on Continental region	-	-	-	-	-
○ Asia	1271	3	1.12 (0.73-1.73)	99	<0.0001
○ Europe	4440	2	1.32 (1.10-1.59)	0	0.50
○ Oceania	150	1	0.68 (0.45-1.04)	-	-
• Subanalysis on Risk of Bias assessment	-	-	-	-	-
○ Low	3177	1	1.28 (1.04-1.57)	1	1
○ Moderate	1366	2	1.15 (0.75-1.77)	75	0.05
○ Serious	1168	2	1.21 (0.71-2.07)	100	<0.0001
○ Critical	150	1	0.68 (0.45-1.04)	-	-
• Subanalysis on Study dimension/size	-	-	-	-	-
○ Small studies	367	3	1.05 (0.66-1.67)	96	<0.0001
○ Big studies	5494	3	1.16 (0.86-1.57)	85	0.001
• Subanalysis on Diagnosis type	-	-	-	-	-
○ Asthma	1271	3	1.12 (0.73-1.73)	99	<0.0001
○ COPD	4590	3	1.11 (0.75-1.66)	76	0.02

• Subanalysis on Types of instruments to measure adherence	-	-	-	-	-
○ Dose counting or Electronic monitored	4657	4	1.30 (0.97-1.73)	93	<0.0001
○ Morisky Medication Adherence Scale (MMAS-8)	1054	1	0.92 (0.86-0.99)	■	■
○ Medication Adherence Reporting Scale (MARS)	150	1	0.68 (0.45-1.04)	-	-
4. META-ANALYSIS FOR “EMPLOYED”					
Full data analysis	7157	5	0.87 (0.83-0.90)	0	0.76
5. META-ANALYSIS FOR “LITERACY”					
Full data analysis	1865	6	1.37 (1.28-1.47)	14	0.33
6. META-ANALYSIS FOR “HIGHER EDUCATION”					
Full data analysis	1851	8	1.26 (0.91-1.74)	80	<0.0001
• Subanalysis on Continental region	-	-	-	-	-
○ South America	358	1	0.74 (0.55-0.99)	■	■
○ Europe	1121	3	1.53 (0.82-2.87)	88	0.0002
○ North America	222	3	1.37 (0.55-3.45)	79	0.008
○ Oceania	150	1	1.14 (0.81-1.60)	-	-
• Subanalysis on Study design	-	-	-	-	-
○ Cross-sectional	1392	3	1.24 (0.71-2.18)	92	<0.0001
○ Cohort	459	5	1.28 (0.84-1.96)	60	0.04
• Subanalysis on Diagnosis type	-	-	-	-	-
○ Asthma	667	5	1.16 (0.68-1.96)	76	0.003
○ COPD	150	1	1.14 (0.81-1.60)	-	-
○ Asthma or COPD	1034	2	1.64 (0.67-3.99)	94	<0.0001
7. META-ANALYSIS FOR “OLDEST DIAGNOSIS”					
Full data analysis	1696	2	0.99 (0.96-1.01)	89	0.002
8. META-ANALYSIS FOR “MORE OUTPATIENT CLINIC VISITS”					
Full data analysis	5581	4	1.03 (0.98-1.08)	94	<0.0001
9. META-ANALYSIS FOR “OBESITY”					
Full data analysis	4440	2	1.30 (1.12-1.50)	0	0.37
10. META-ANALYSIS FOR “DIABETES”					
Full data analysis	4440	2	0.99 (0.90-1.09)	82	0.02
11. META-ANALYSIS FOR “CANCER”					
Full data analysis	5907	2	0.89 (0.75-1.07)	20	0.26
12. META-ANALYSIS FOR “PREVIOUS EXACERBATIONS”					
Full data analysis	1914	3	0.81 (0.43-1.55)	95	<0.0001
• Subanalysis on Continental region	-	-	-	-	-
○ Europe	1520	2	0.60 (0.36-0.99)	88	0.003
○ North America	394	1	1.52 (1.16-1.98)	■	■
• Subanalysis on Diagnosis type	-	-	-	-	-
○ Asthma	394	1	1.52 (1.16-1.98)	■	■
○ COPD	1520	2	0.60 (0.36-0.99)	88	0.003
13. META-ANALYSIS FOR “MULTIPLE DRUGS/INHALERS”					
Full data analysis	29401	3	0.81 (0.79-0.84)	0	0.80

14. META-ANALYSIS FOR "GOOD COGNITIVE PERFORMANCE"					
Full data analysis	4355	5	1.28 (1.17-1.40)	0	0.62
15. META-ANALYSIS FOR "DISEASE WITH HIGH SEVERITY"					
Full data analysis	991	3	0.94 (0.60-1.48)	95	<0.0001
16. META-ANALYSIS FOR "HIGHER INCOME"					
Full data analysis	200	2	1.63 (1.05-2.56)	0	0.52

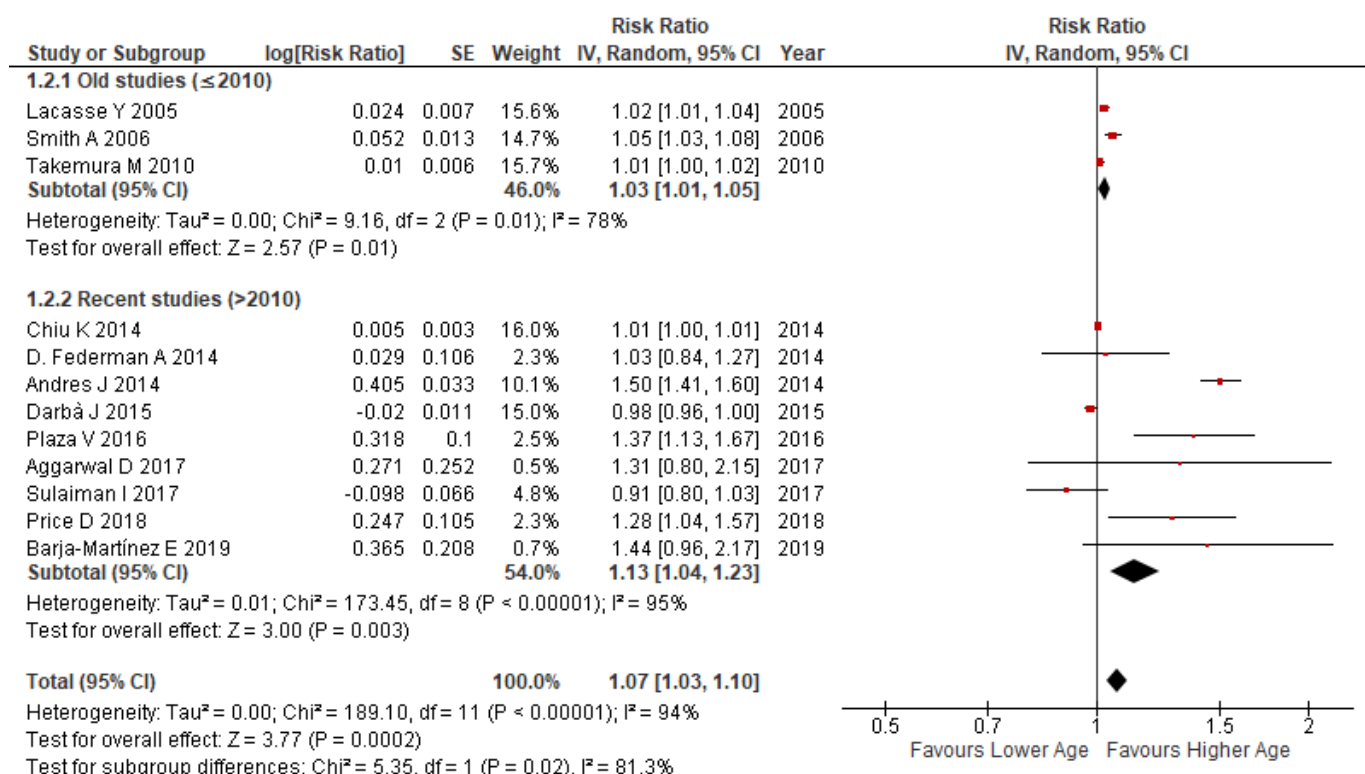
1. Meta-analysis for the determinant "Age"

FULL DATA ANALYSIS

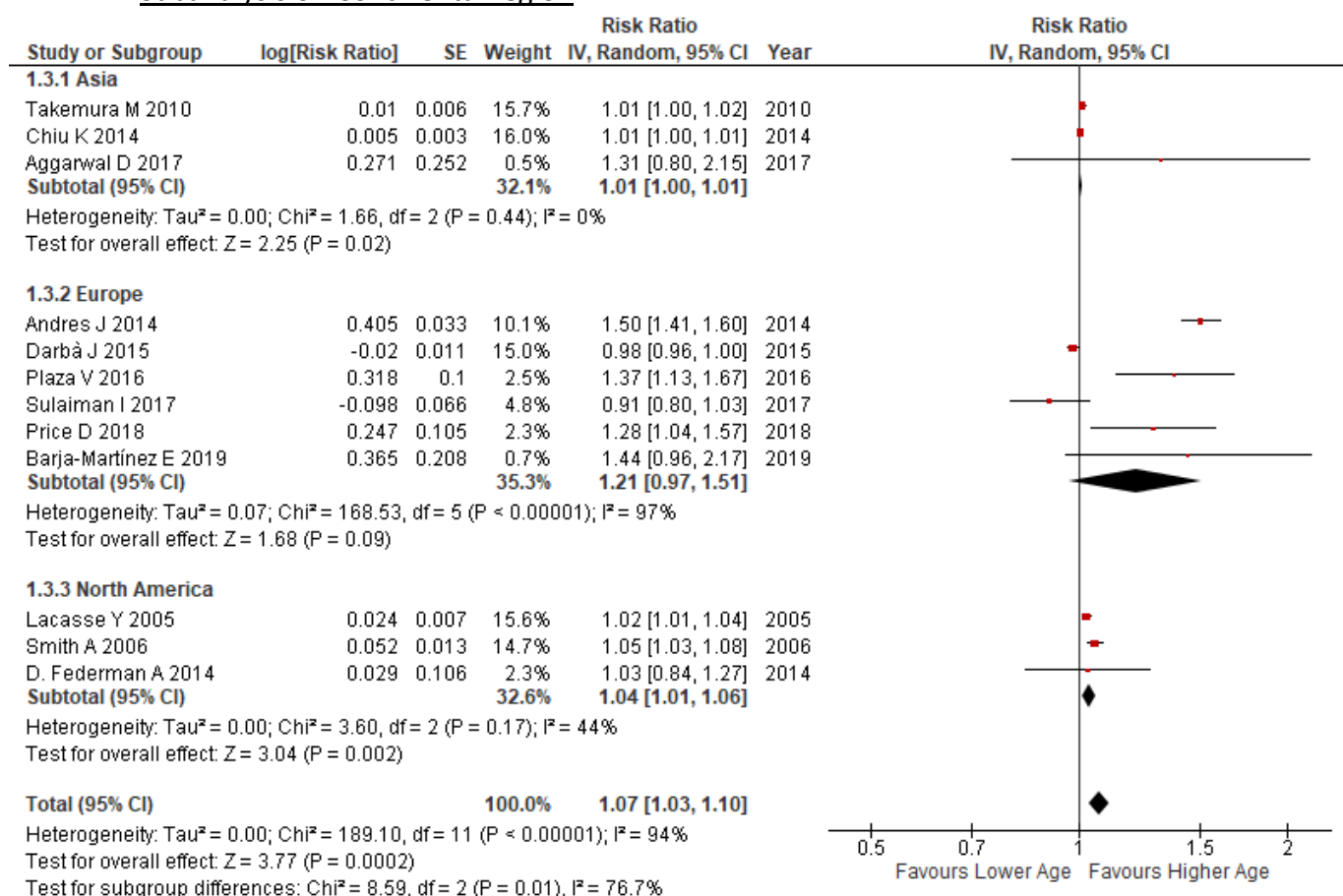


DISAGGREGATED ANALYSIS ACCORDING TO:

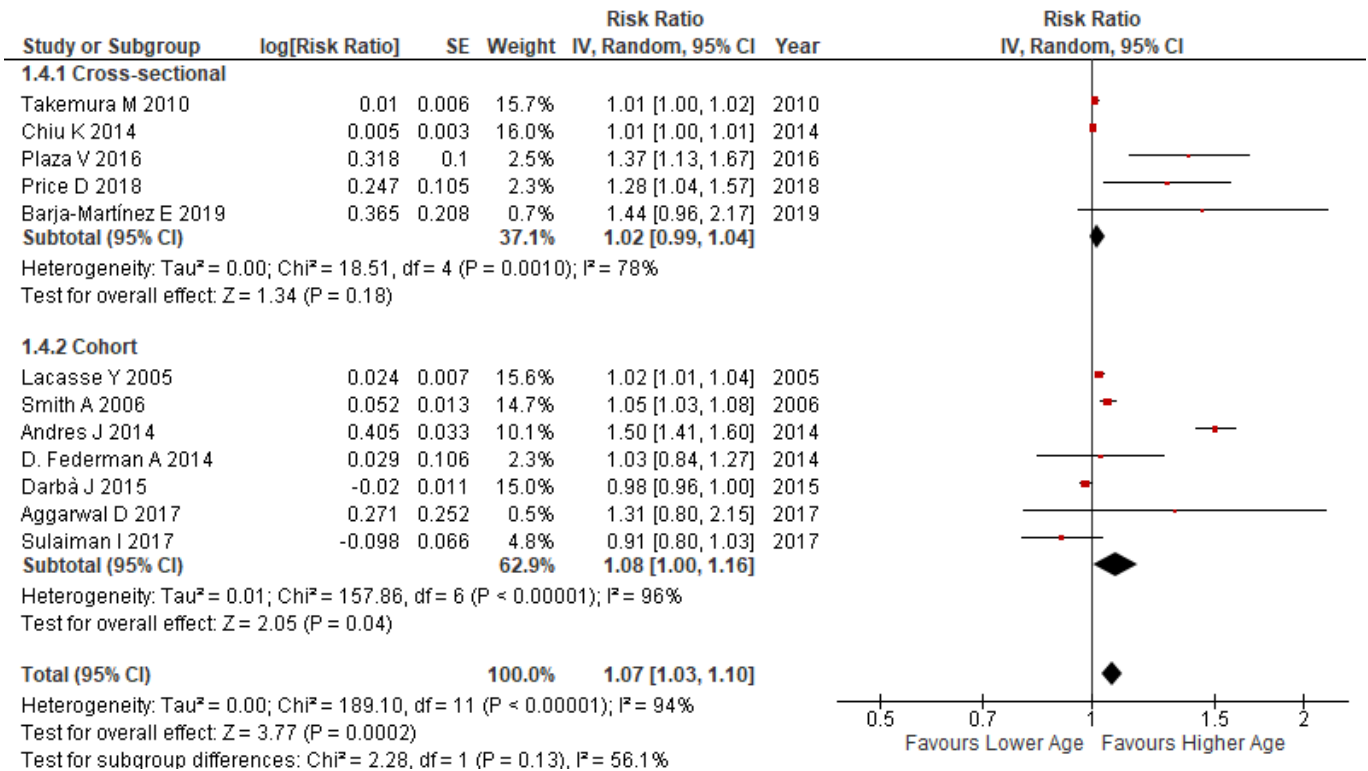
1.1. Subanalysis on Publication year (≤ 2010 VS >2010)



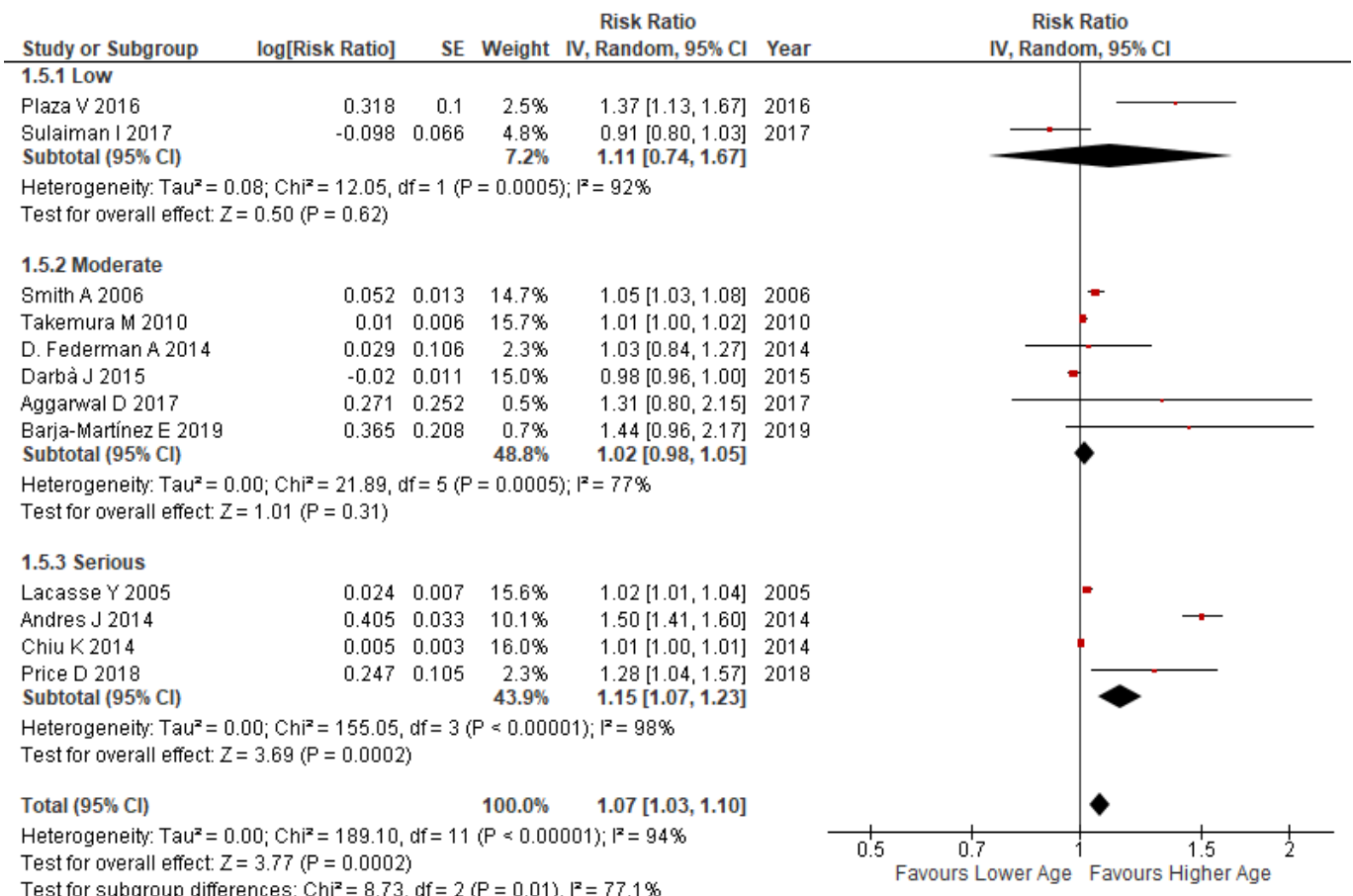
1.2. Subanalysis on Continental region



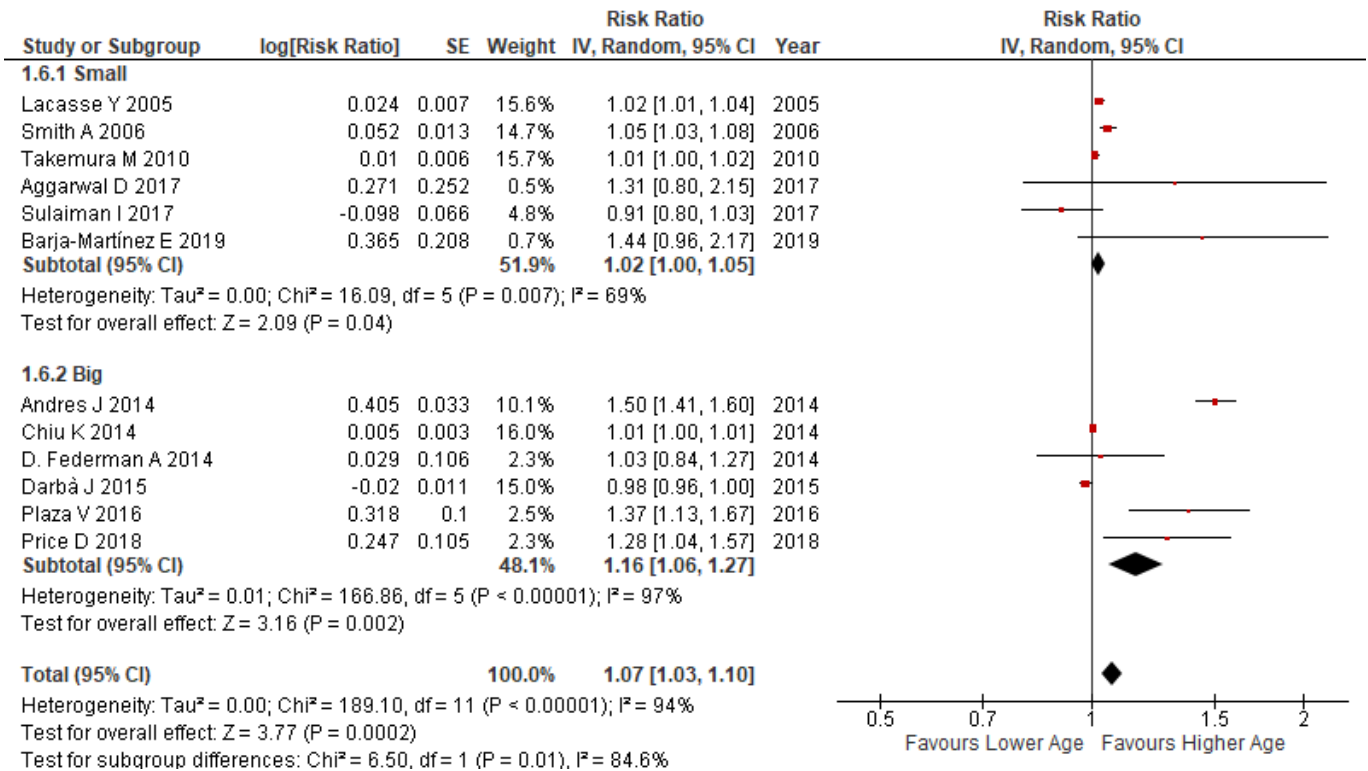
1.3. Subanalysis on Study design



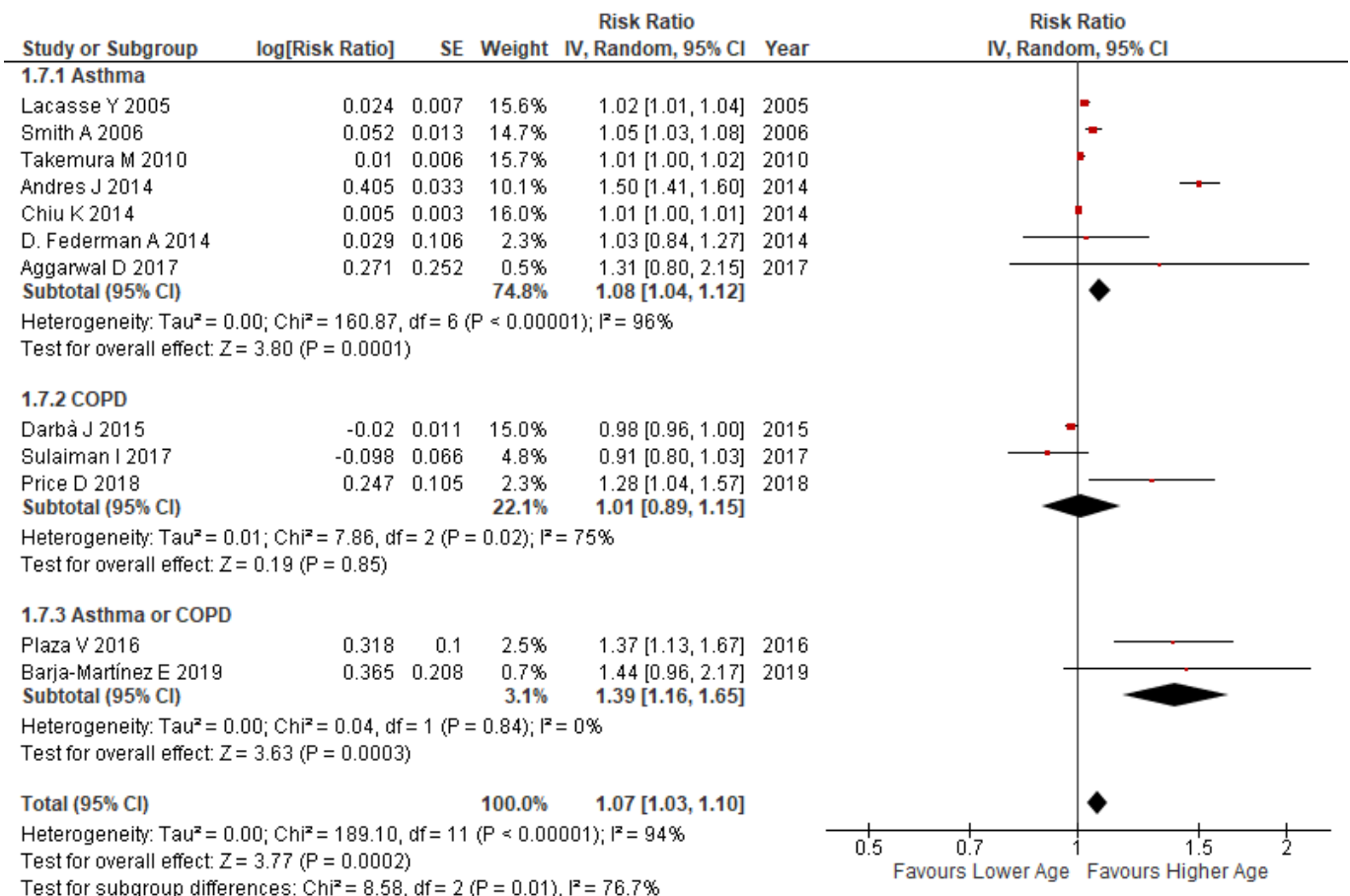
1.4. Subanalysis on Risk of Bias assessment



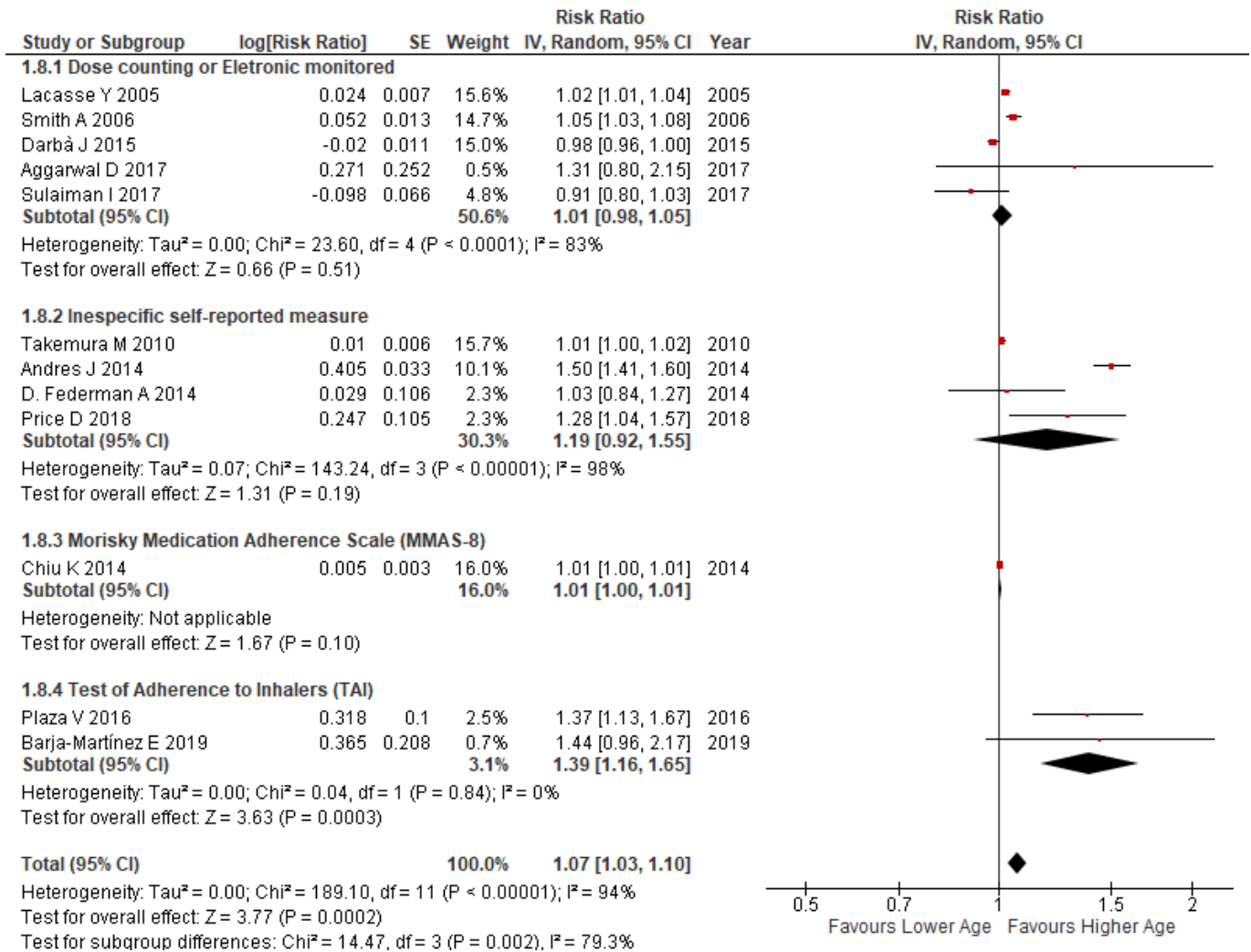
1.5. Subanalysis on Study dimension/size



1.6. Subanalysis on Diagnosis type

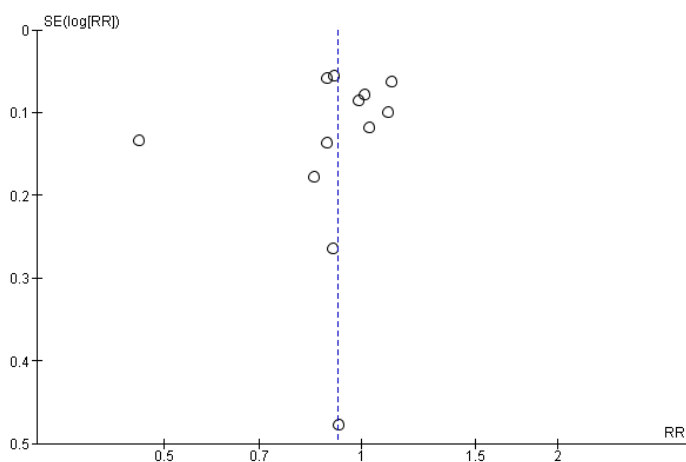
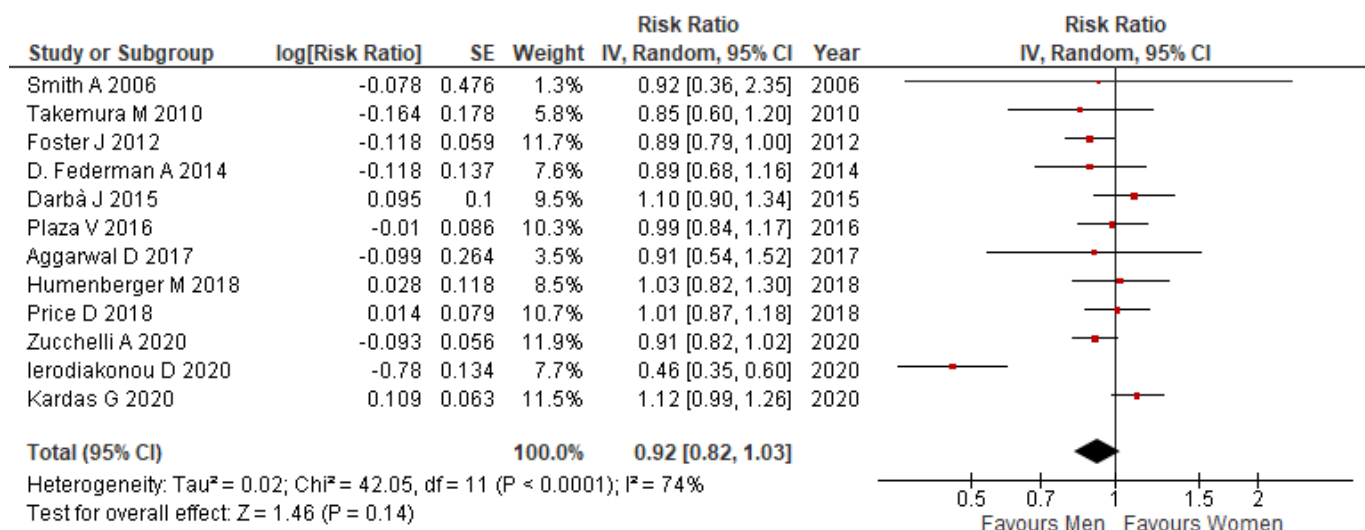


1.7. Subanalysis on Types of instruments to measure adherence



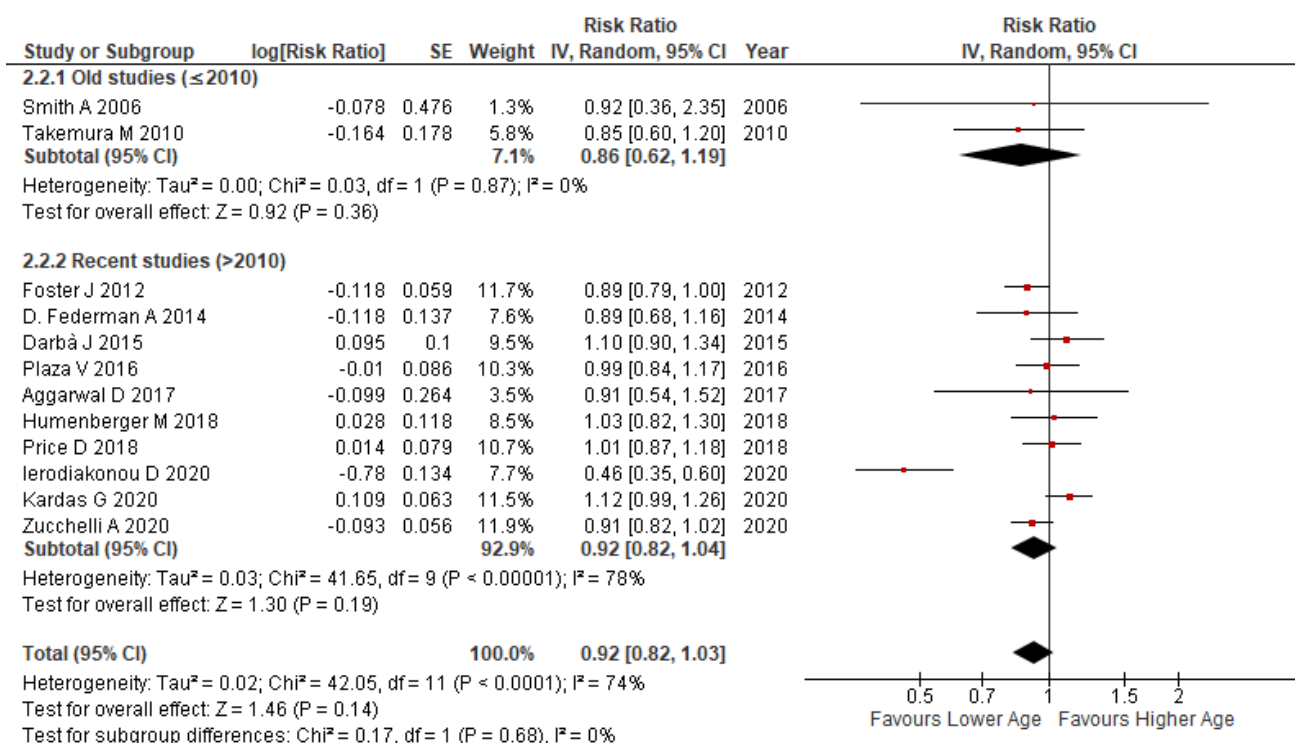
2. Meta-analysis for the determinant "Gender female"

FULL DATA ANALYSIS

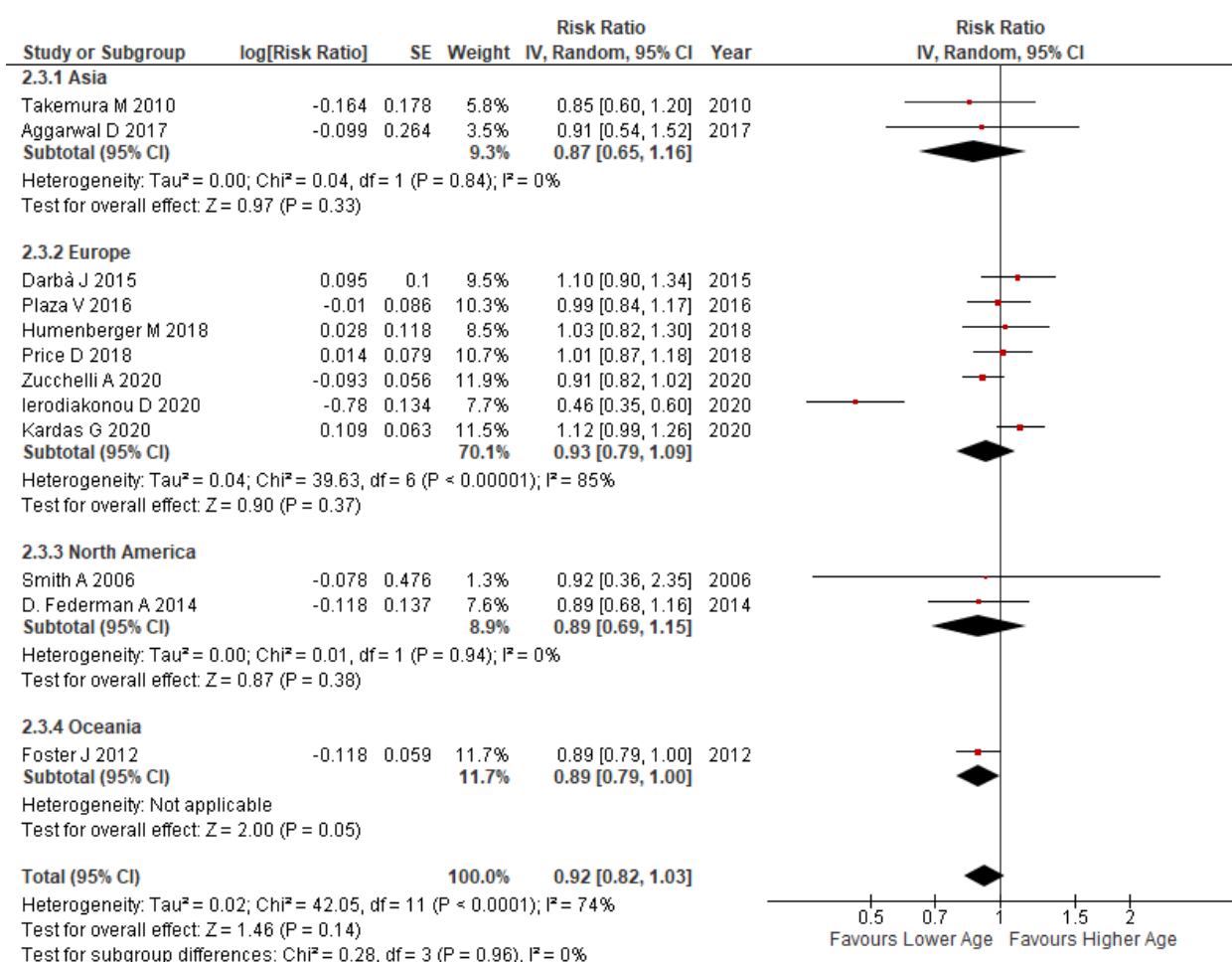


DISAGGREGATED ANALYSIS ACCORDING TO:

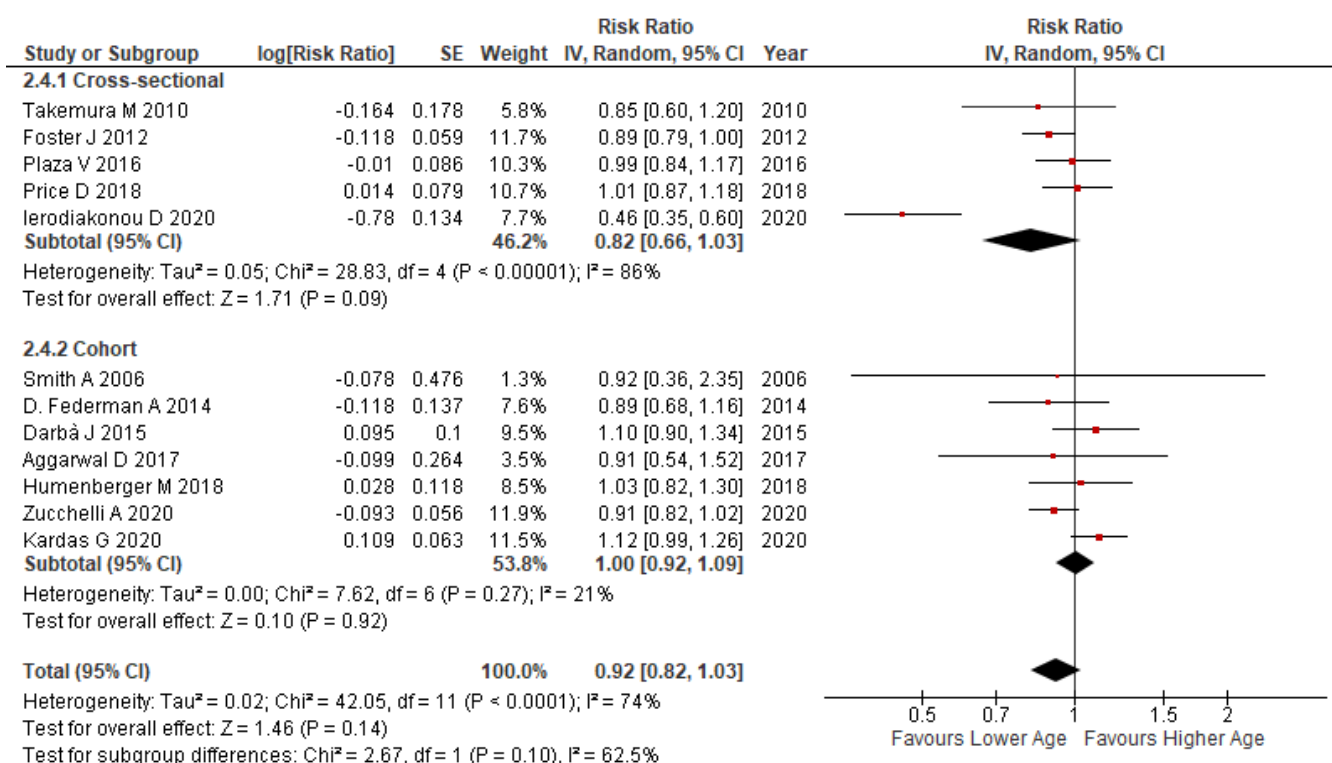
2.1. Subanalysis on Publication year (≤ 2010 VS >2010)



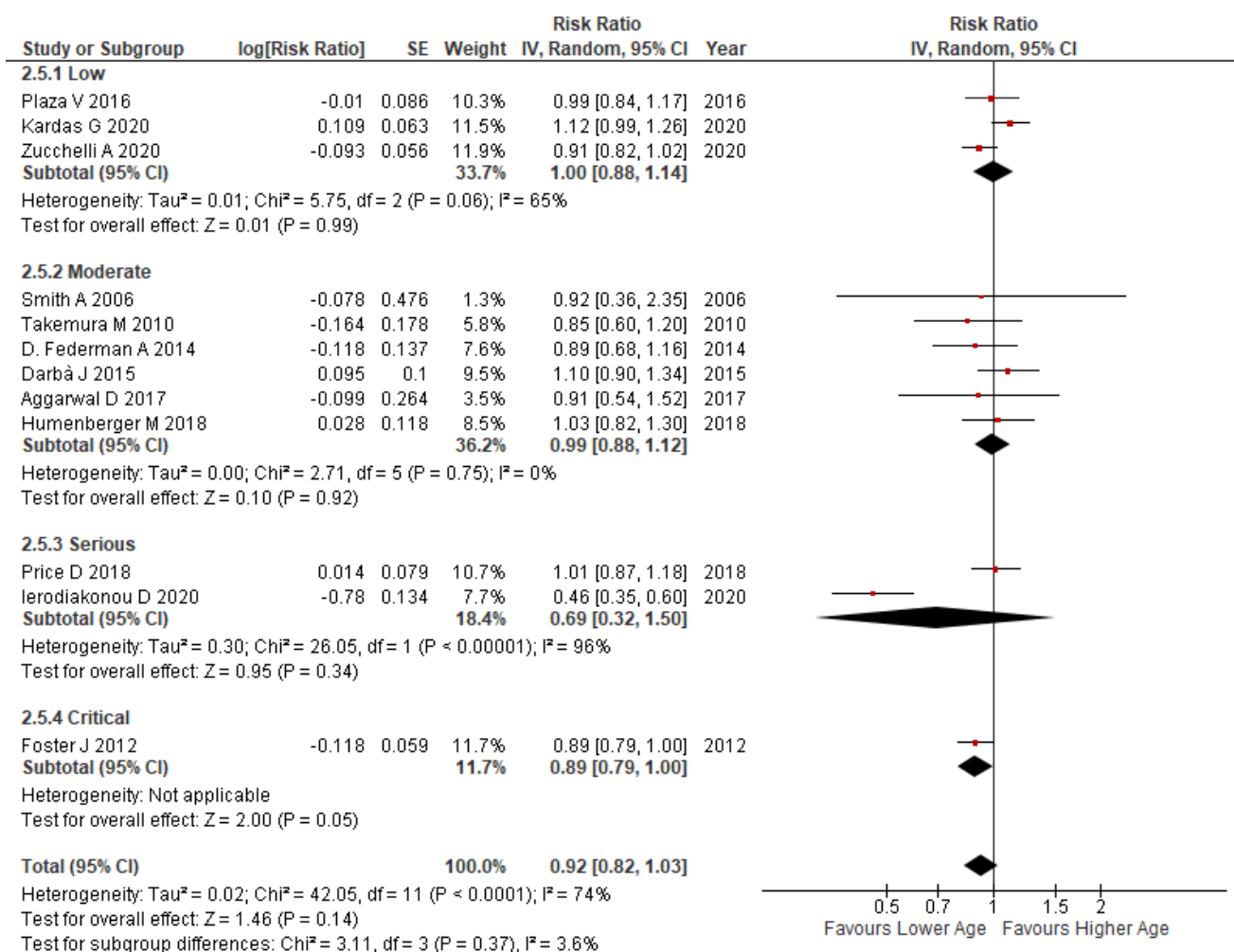
2.2. Subanalysis on Continental region



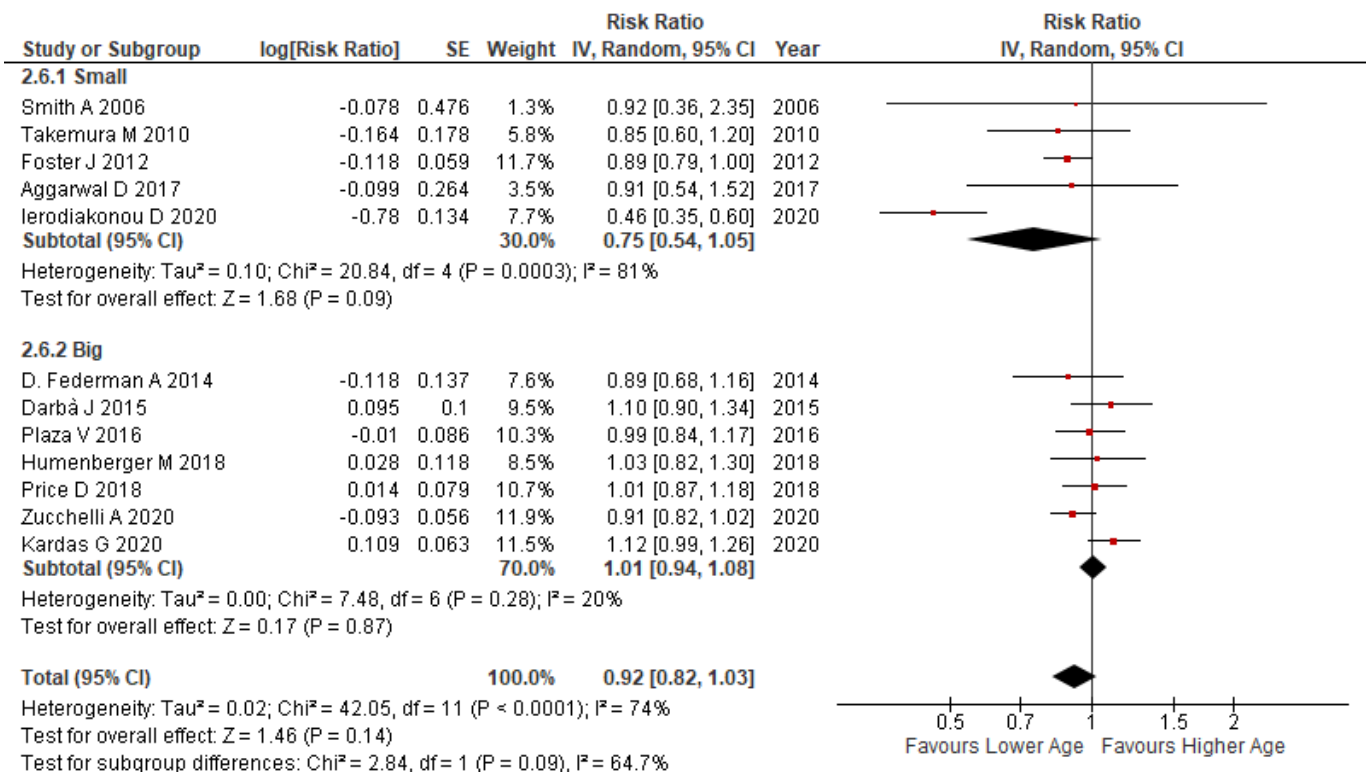
2.3. Subanalysis on Study design



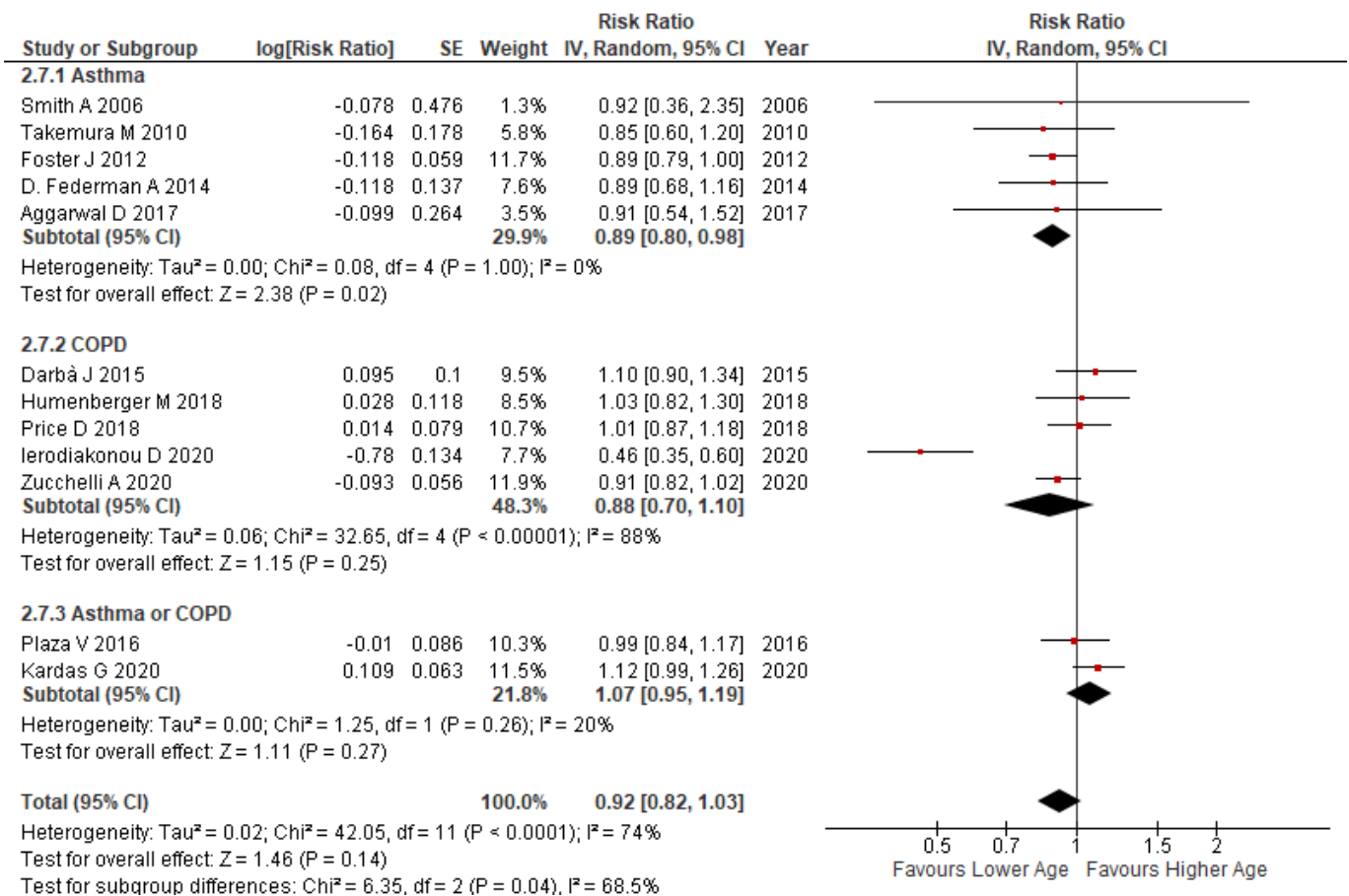
2.4. Subanalysis on Risk of Bias assessment



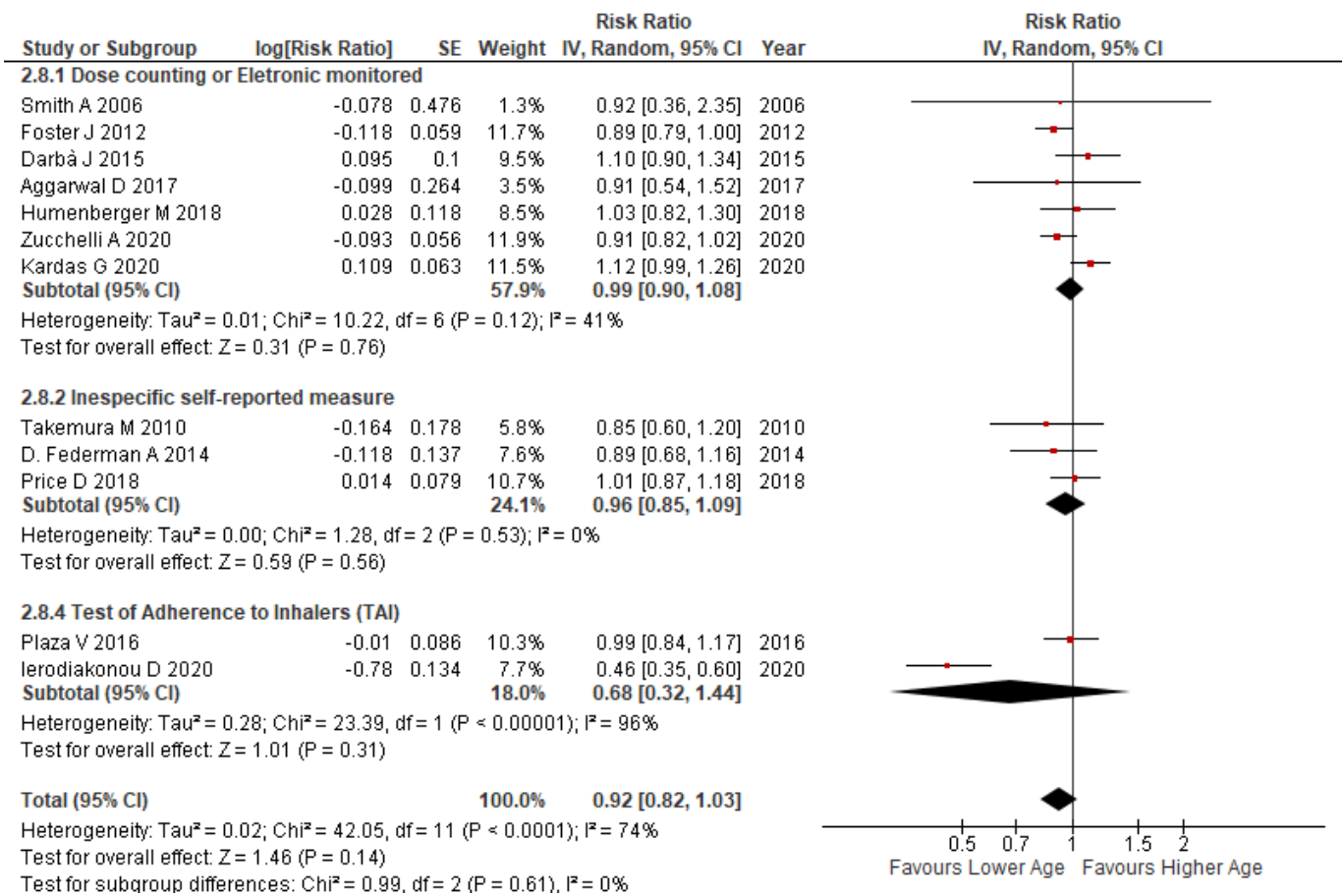
2.5. Subanalysis on Study dimension/size



2.6. Subanalysis on Diagnosis type



2.7. Subanalysis on Types of instrumentss to measure adherence



3. Meta-analysis for the determinant “Smoking exposure”

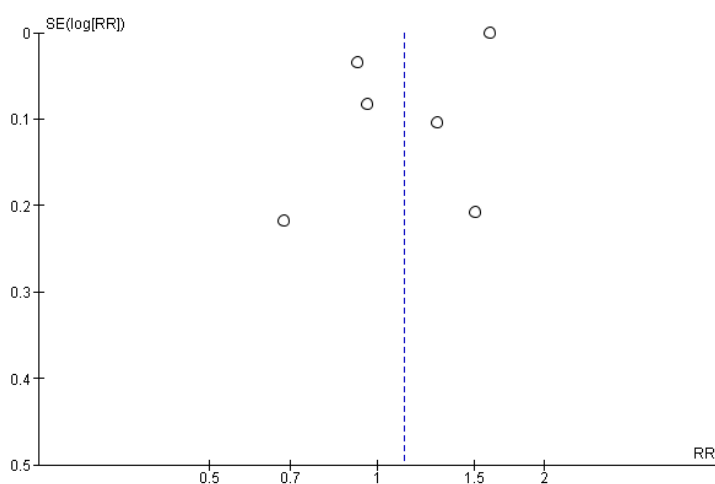
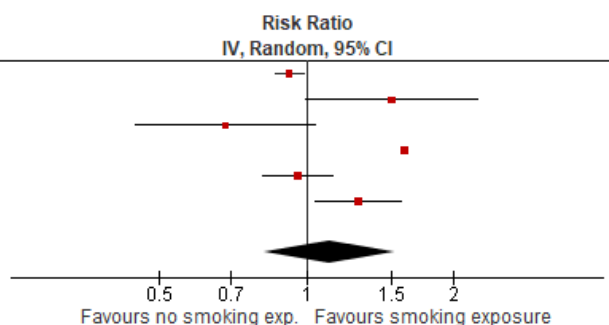
FULL DATA ANALYSIS

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio		Year
				IV, Random, 95% CI	95% CI	
Chiu K 2014	-0.081	0.034	18.5%	0.92	[0.86, 0.99]	2014
Darbà J 2015	0.405	0.207	14.1%	1.50	[1.00, 2.25]	2015
Sriram KB 2016	-0.384	0.217	13.8%	0.68	[0.45, 1.04]	2016
Takemura M 2017	0.464	0.001	18.6%	1.59	[1.59, 1.59]	2017
Aggarwal D 2017	-0.042	0.083	17.7%	0.96	[0.81, 1.13]	2017
Zucchelli A 2020	0.247	0.104	17.2%	1.28	[1.04, 1.57]	2020

Total (95% CI) 100.0% 1.12 [0.82, 1.52]

Heterogeneity: Tau² = 0.13; Chi² = 313.47, df = 5 (P < 0.00001); I² = 98%

Test for overall effect: Z = 0.70 (P = 0.48)

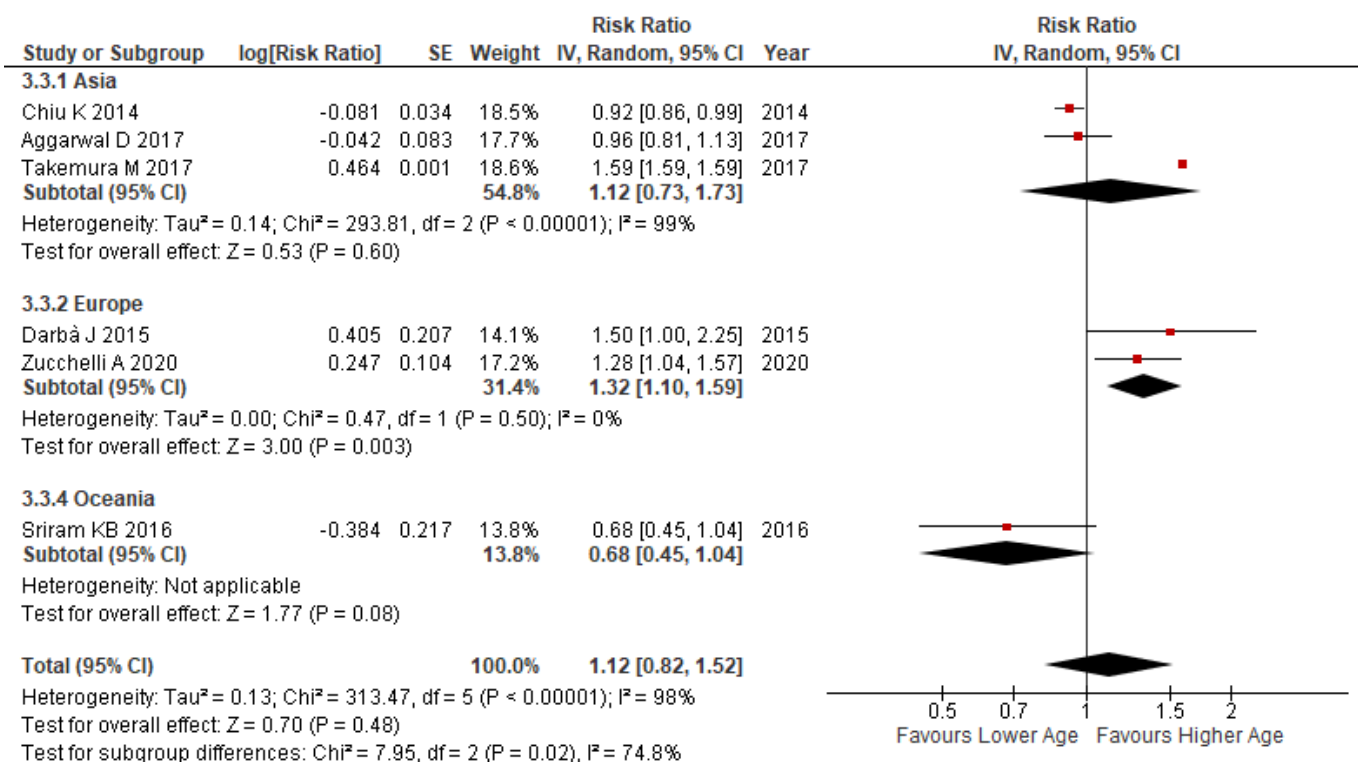


DISAGGREGATED ANALYSIS ACCORDING TO:

3.1. Subanalysis on Publication year

Subanalysis not performed due to insufficient studies available or irrelevance regarding the results obtained in full data analysis.

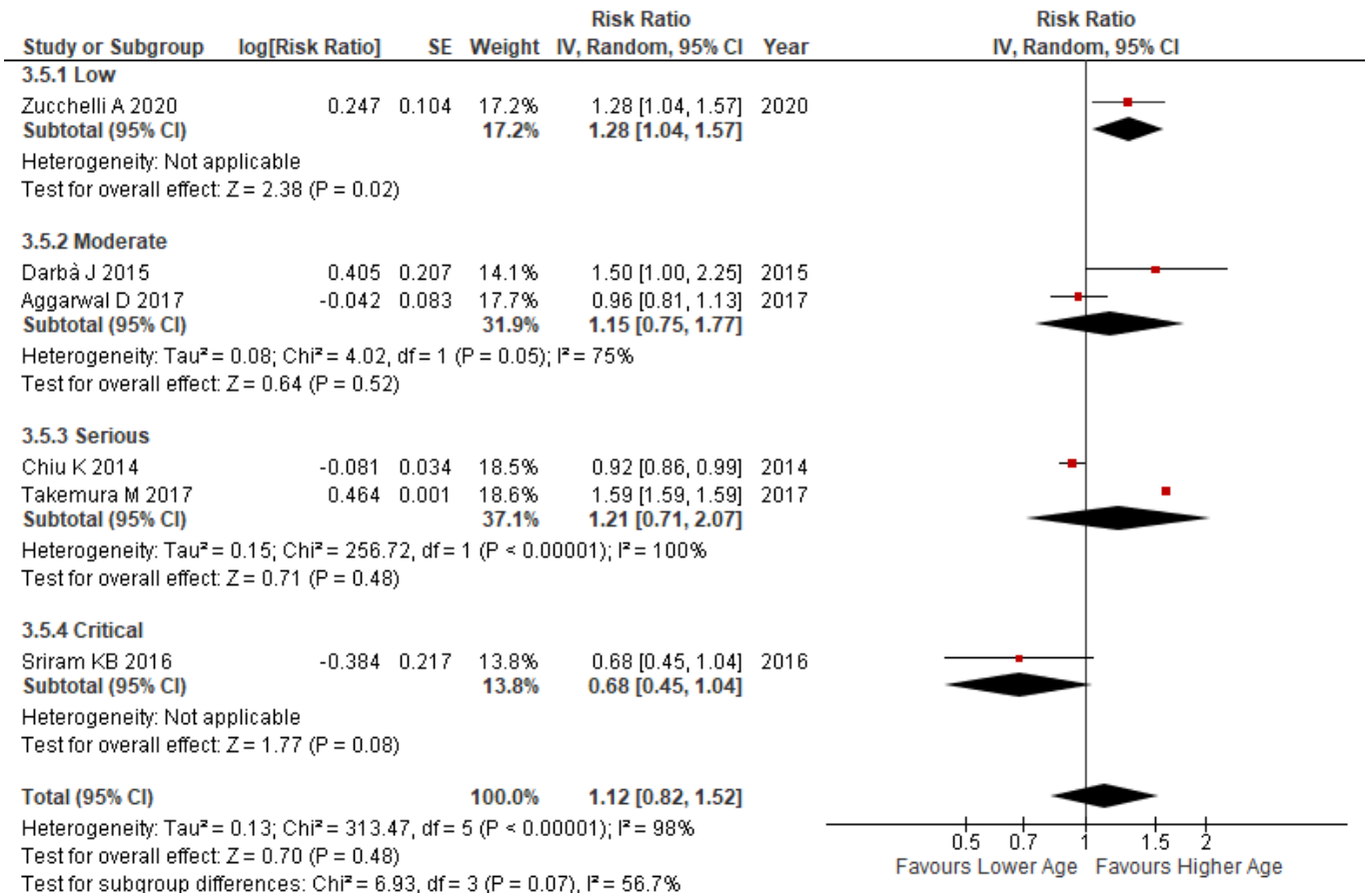
3.2. Subanalysis on Continental region



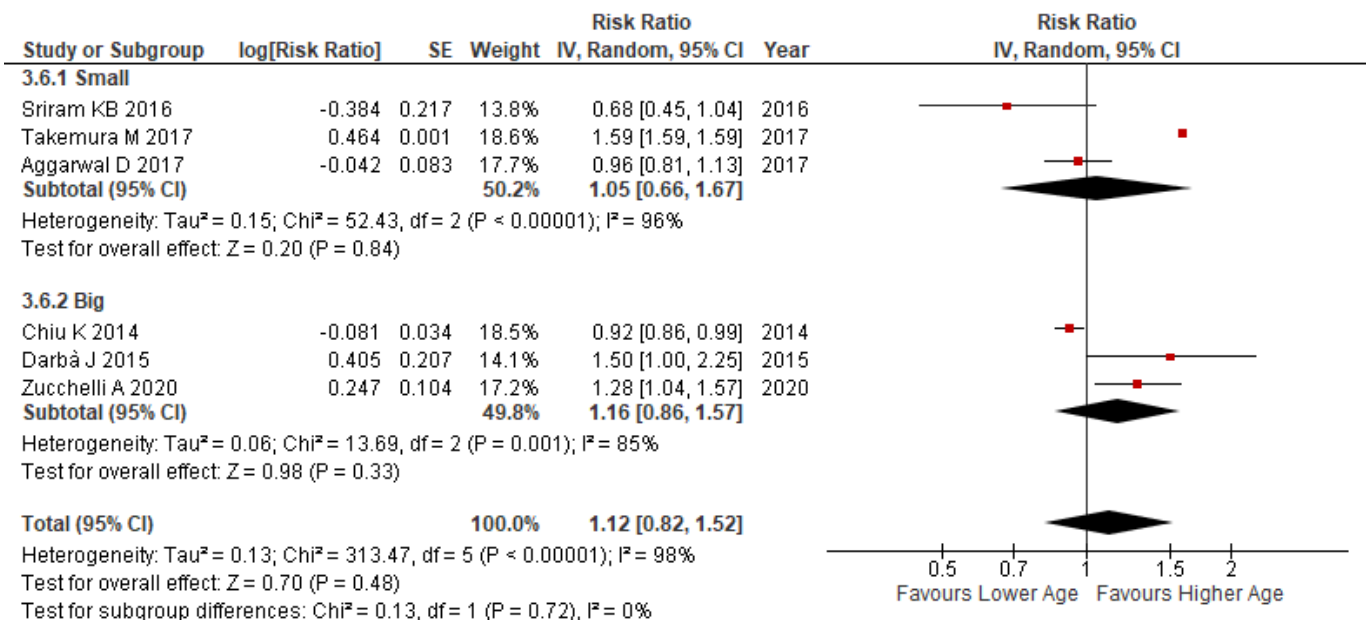
3.3. Subanalysis on Study design

Subanalysis not performed due to insufficient studies available or irrelevance regarding the results obtained in full data analysis.

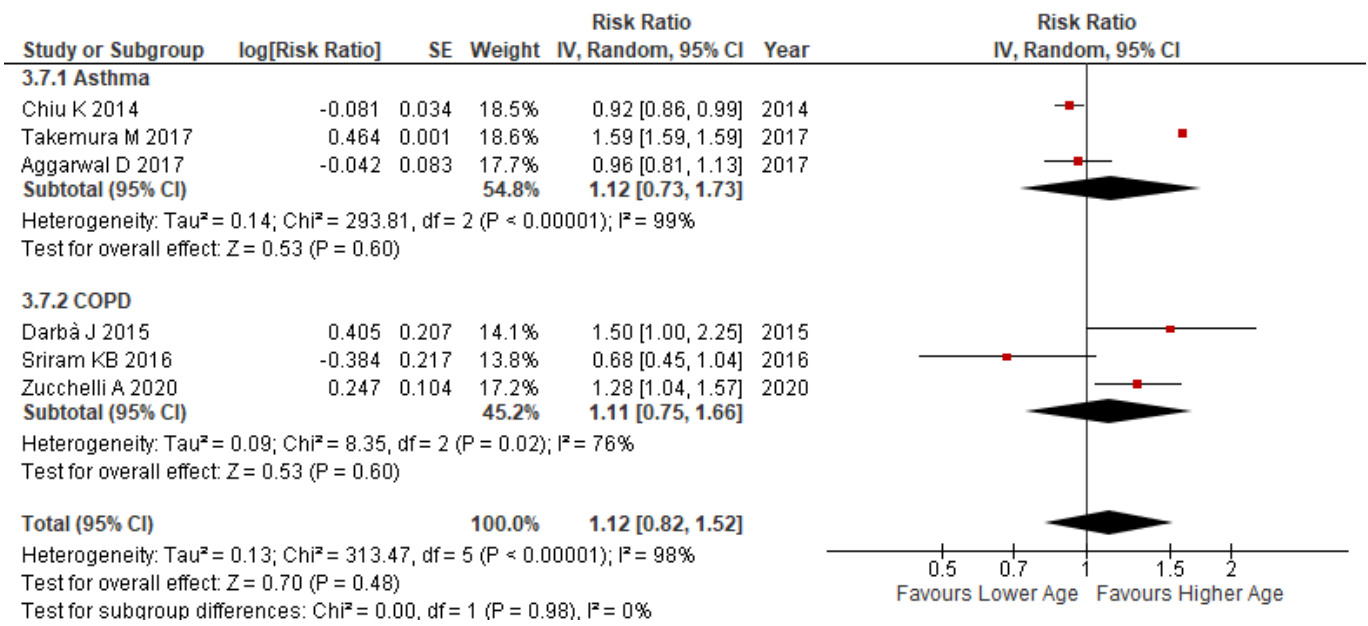
3.4. Subanalysis on Risk of Bias assessment



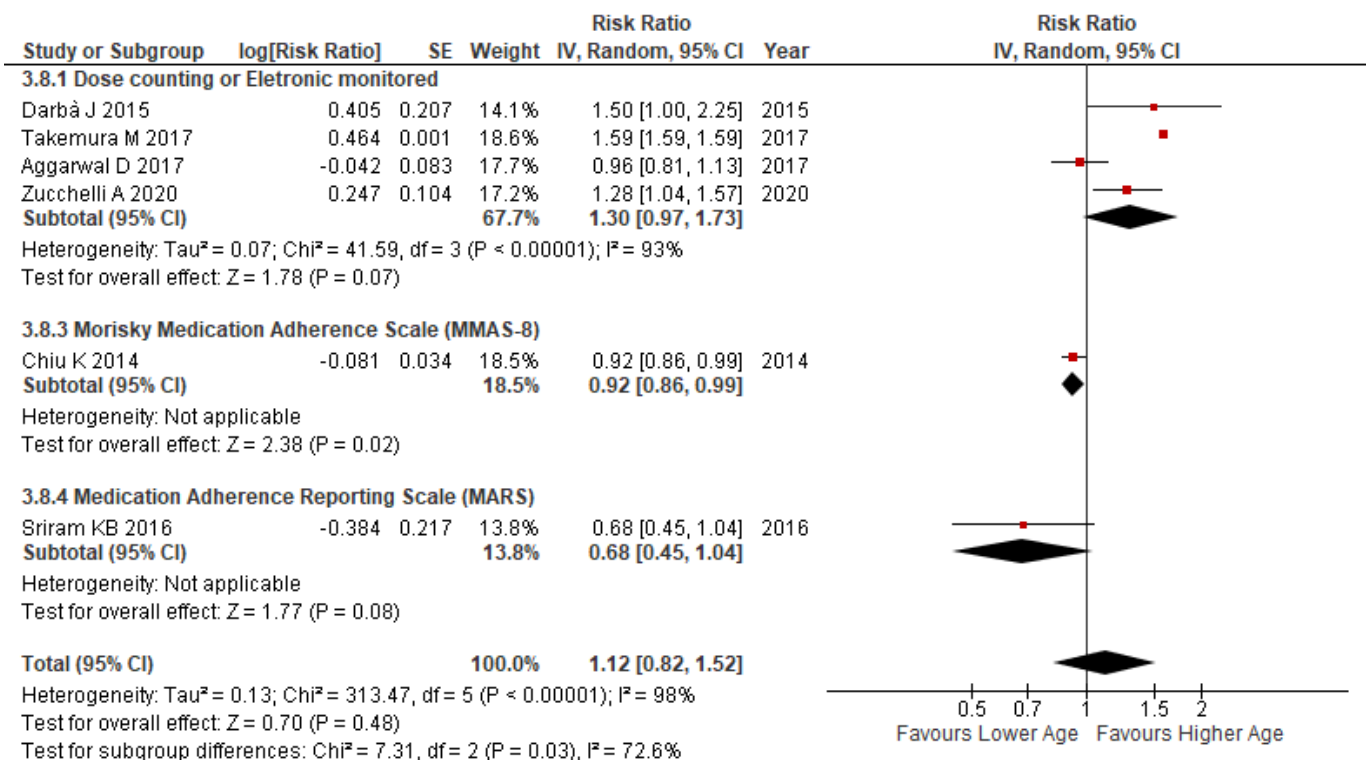
3.5. Subanalysis on Study dimension/size



3.6. Subanalysis on Diagnosis type



3.7. Subanalysis on Types of instruments to measure adherence

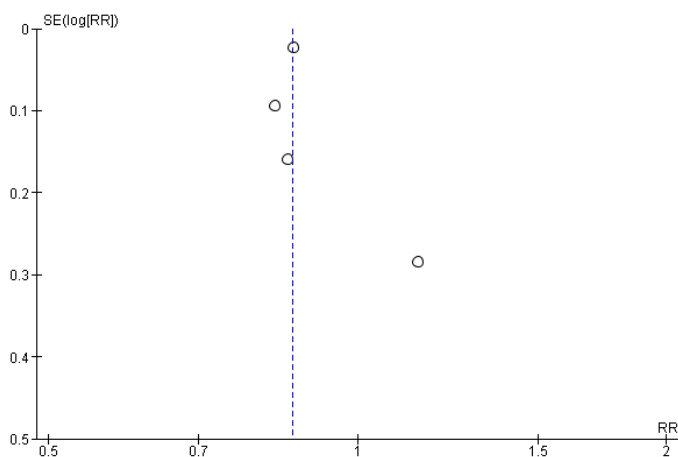


4. Meta-analysis for the determinant “Employed”

FULL DATA ANALYSIS

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio		Year
				IV, Random, 95% CI	95% CI	
Chiu K 2014	-0.144	0.023	92.0%	0.87	[0.83, 0.91]	2014
Darbà J 2015	-0.157	0.159	1.9%	0.85	[0.63, 1.17]	2015
Plaza V 2016	-0.186	0.094	5.5%	0.83	[0.69, 1.00]	2016
Aggarwal D 2017	0.135	0.284	0.6%	1.14	[0.66, 2.00]	2017
Total (95% CI)			100.0%	0.87	[0.83, 0.90]	

Heterogeneity: Tau² = 0.00; Chi² = 1.17, df = 3 (P = 0.76); I² = 0%
 Test for overall effect: Z = 6.57 (P < 0.00001)



DISAGGREGATED ANALYSIS ACCORDING TO:

- 4.1. Subanalysis on Publication year*
- 4.2. Subanalysis on Continental region*
- 4.3. Subanalysis on Study design*
- 4.4. Subanalysis on Risk of Bias assessment*
- 4.5. Subanalysis on Study dimension/size*
- 4.6. Subanalysis on Diagnosis type*
- 4.7. Subanalysis on Types of instruments to measure adherence*

**Subanalysis not performed due to insufficient studies available or irrelevance regarding the results obtained in full data analysis.*

5. Meta-analysis for the determinant “Literacy”

FULL DATA ANALYSIS

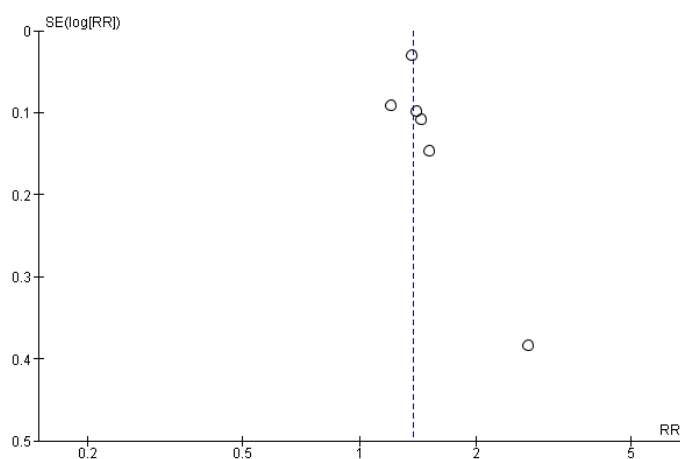
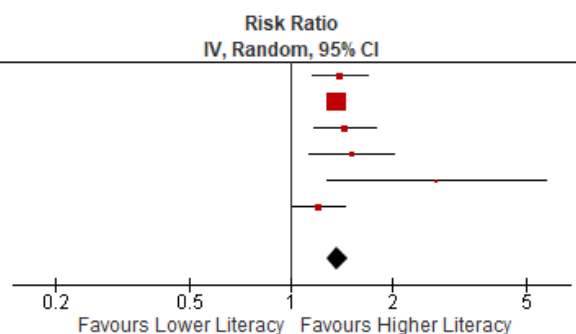
Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio		Year
				IV, Random, 95% CI	95% CI	
van Dellen QM 2008	0.336	0.098	11.9%	1.40	[1.15, 1.70]	2008
Apter A 2013	0.31	0.03	58.3%	1.36	[1.29, 1.45]	2013
D. Federman A 2014	0.366	0.109	9.8%	1.44	[1.16, 1.79]	2014
O’Conor R 2015	0.416	0.147	5.6%	1.52	[1.14, 2.02]	2015
Aggarwal D 2017	0.994	0.383	0.9%	2.70	[1.28, 5.72]	2017
O’Conor R 2019	0.189	0.091	13.5%	1.21	[1.01, 1.44]	2019

Total (95% CI)

100.0% 1.37 [1.28, 1.47]

Heterogeneity: Tau² = 0.00; Chi² = 5.81, df = 5 (P = 0.33); I² = 14%

Test for overall effect: Z = 8.73 (P < 0.00001)



DISAGGREGATED ANALYSIS ACCORDING TO:

- 5.1. Subanalysis on Publication year*
- 5.2. Subanalysis on Continental region*
- 5.3. Subanalysis on Study design*
- 5.4. Subanalysis on Risk of Bias assessment*
- 5.5. Subanalysis on Study dimension/size*
- 5.6. Subanalysis on Diagnosis type*
- 5.7. Subanalysis on Types of instruments to measure adherence*

**Subanalysis not performed due to insufficient studies available or irrelevance regarding the results obtained in full data analysis.*

6. Meta-analysis for the determinant “Higher education”

FULL DATA ANALYSIS

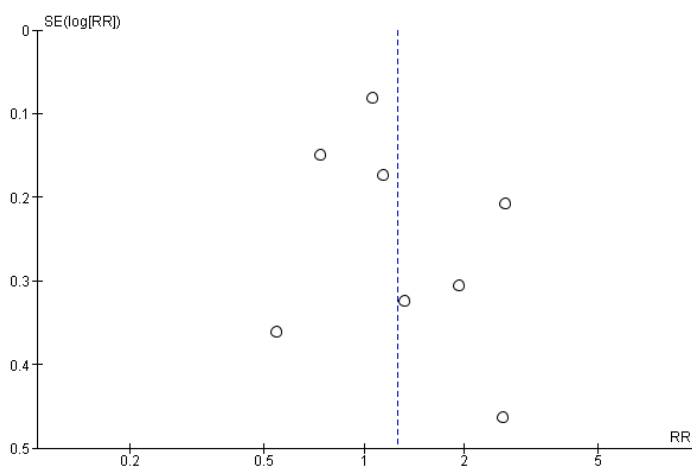
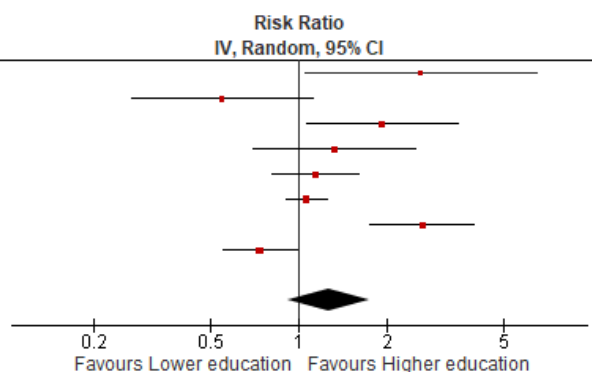
Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio		Year
				IV, Random, 95% CI		
Apter AJ 1998	0.953	0.462	7.4%	2.59	[1.05, 6.41]	1998
Smith A 2006	-0.602	0.361	9.6%	0.55	[0.27, 1.11]	2006
Janson SL 2008	0.654	0.305	11.0%	1.92	[1.06, 3.50]	2008
Vasbinder E 2013	0.278	0.324	10.5%	1.32	[0.70, 2.49]	2013
Sriram KB 2016	0.13	0.173	14.9%	1.14	[0.81, 1.60]	2016
Plaza V 2016	0.057	0.082	17.1%	1.06	[0.90, 1.24]	2016
Barja-Martínez E 2019	0.967	0.208	13.9%	2.63	[1.75, 3.95]	2019
Emilio C 2019	-0.305	0.149	15.6%	0.74	[0.55, 0.99]	2019

Total (95% CI)

100.0% 1.26 [0.91, 1.74]

Heterogeneity: $\text{Tau}^2 = 0.15$; $\text{Chi}^2 = 35.83$, $\text{df} = 7$ ($P < 0.00001$); $I^2 = 80\%$

Test for overall effect: $Z = 1.40$ ($P = 0.16$)



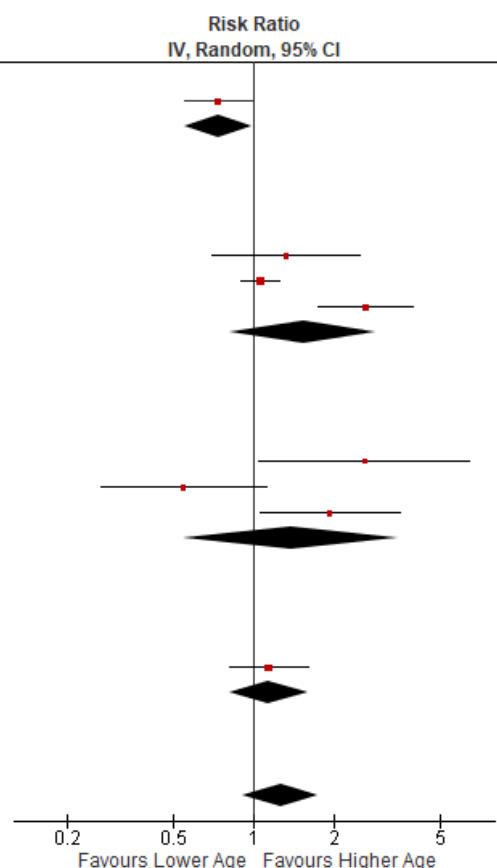
DISAGGREGATED ANALYSIS ACCORDING TO:

6.1. Subanalysis on Publication year

Subanalysis not performed due to insufficient studies available or irrelevance regarding the results obtained in full data analysis.

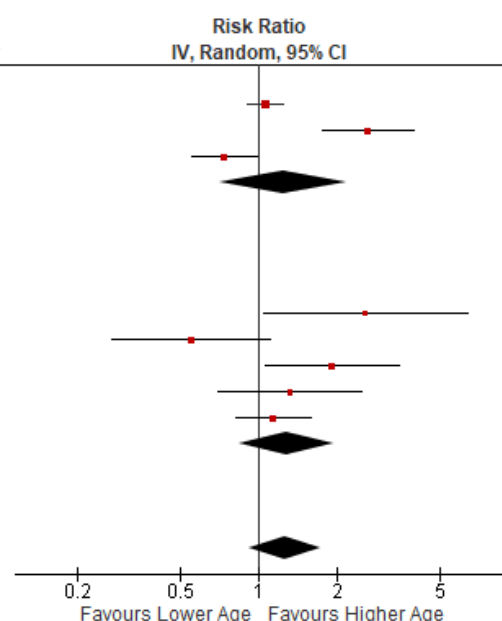
6.2. Subanalysis on Continental region

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio		Year
				IV, Random, 95% CI	Year	
6.3.1 South America						
Emilio C 2019	-0.305	0.149	15.6%	0.74	[0.55, 0.99]	2019
Subtotal (95% CI)			15.6%	0.74	[0.55, 0.99]	
Heterogeneity: Not applicable Test for overall effect: Z = 2.05 (P = 0.04)						
6.3.2 Europe						
Vasbinder E 2013	0.278	0.324	10.5%	1.32	[0.70, 2.49]	2013
Plaza V 2016	0.057	0.082	17.1%	1.06	[0.90, 1.24]	2016
Barja-Martínez E 2019	0.967	0.208	13.9%	2.63	[1.75, 3.95]	2019
Subtotal (95% CI)			41.5%	1.53	[0.82, 2.87]	
Heterogeneity: Tau ² = 0.26; Chi ² = 16.65, df = 2 (P = 0.0002); I ² = 88% Test for overall effect: Z = 1.33 (P = 0.18)						
6.3.3 North America						
Apter AJ 1998	0.953	0.462	7.4%	2.59	[1.05, 6.41]	1998
Smith A 2006	-0.602	0.361	9.6%	0.55	[0.27, 1.11]	2006
Janson SL 2008	0.654	0.305	11.0%	1.92	[1.06, 3.50]	2008
Subtotal (95% CI)			28.0%	1.37	[0.55, 3.45]	
Heterogeneity: Tau ² = 0.52; Chi ² = 9.59, df = 2 (P = 0.008); I ² = 79% Test for overall effect: Z = 0.68 (P = 0.50)						
6.3.4 Oceania						
Sriram KB 2016	0.13	0.173	14.9%	1.14	[0.81, 1.60]	2016
Subtotal (95% CI)			14.9%	1.14	[0.81, 1.60]	
Heterogeneity: Not applicable Test for overall effect: Z = 0.75 (P = 0.45)						
Total (95% CI)			100.0%	1.26	[0.91, 1.74]	
Heterogeneity: Tau ² = 0.15; Chi ² = 35.83, df = 7 (P < 0.00001); I ² = 80% Test for overall effect: Z = 1.40 (P = 0.16) Test for subgroup differences: Chi ² = 6.82, df = 3 (P = 0.08), I ² = 56.0%						



6.3. Subanalysis on Study design

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio		Year
				IV, Random, 95% CI	Year	
6.4.1 Cross-sectional						
Plaza V 2016	0.057	0.082	17.1%	1.06	[0.90, 1.24]	2016
Barja-Martínez E 2019	0.967	0.208	13.9%	2.63	[1.75, 3.95]	2019
Emilio C 2019	-0.305	0.149	15.6%	0.74	[0.55, 0.99]	2019
Subtotal (95% CI)			46.5%	1.24	[0.71, 2.18]	
Heterogeneity: Tau ² = 0.22; Chi ² = 24.94, df = 2 (P < 0.00001); I ² = 92% Test for overall effect: Z = 0.76 (P = 0.45)						
6.4.2 Cohort						
Apter AJ 1998	0.953	0.462	7.4%	2.59	[1.05, 6.41]	1998
Smith A 2006	-0.602	0.361	9.6%	0.55	[0.27, 1.11]	2006
Janson SL 2008	0.654	0.305	11.0%	1.92	[1.06, 3.50]	2008
Vasbinder E 2013	0.278	0.324	10.5%	1.32	[0.70, 2.49]	2013
Sriram KB 2016	0.13	0.173	14.9%	1.14	[0.81, 1.60]	2016
Subtotal (95% CI)			53.5%	1.28	[0.84, 1.96]	
Heterogeneity: Tau ² = 0.13; Chi ² = 10.02, df = 4 (P = 0.04); I ² = 60% Test for overall effect: Z = 1.15 (P = 0.25)						
Total (95% CI)			100.0%	1.26	[0.91, 1.74]	
Heterogeneity: Tau ² = 0.15; Chi ² = 35.83, df = 7 (P < 0.00001); I ² = 80% Test for overall effect: Z = 1.40 (P = 0.16) Test for subgroup differences: Chi ² = 0.01, df = 1 (P = 0.93), I ² = 0%						



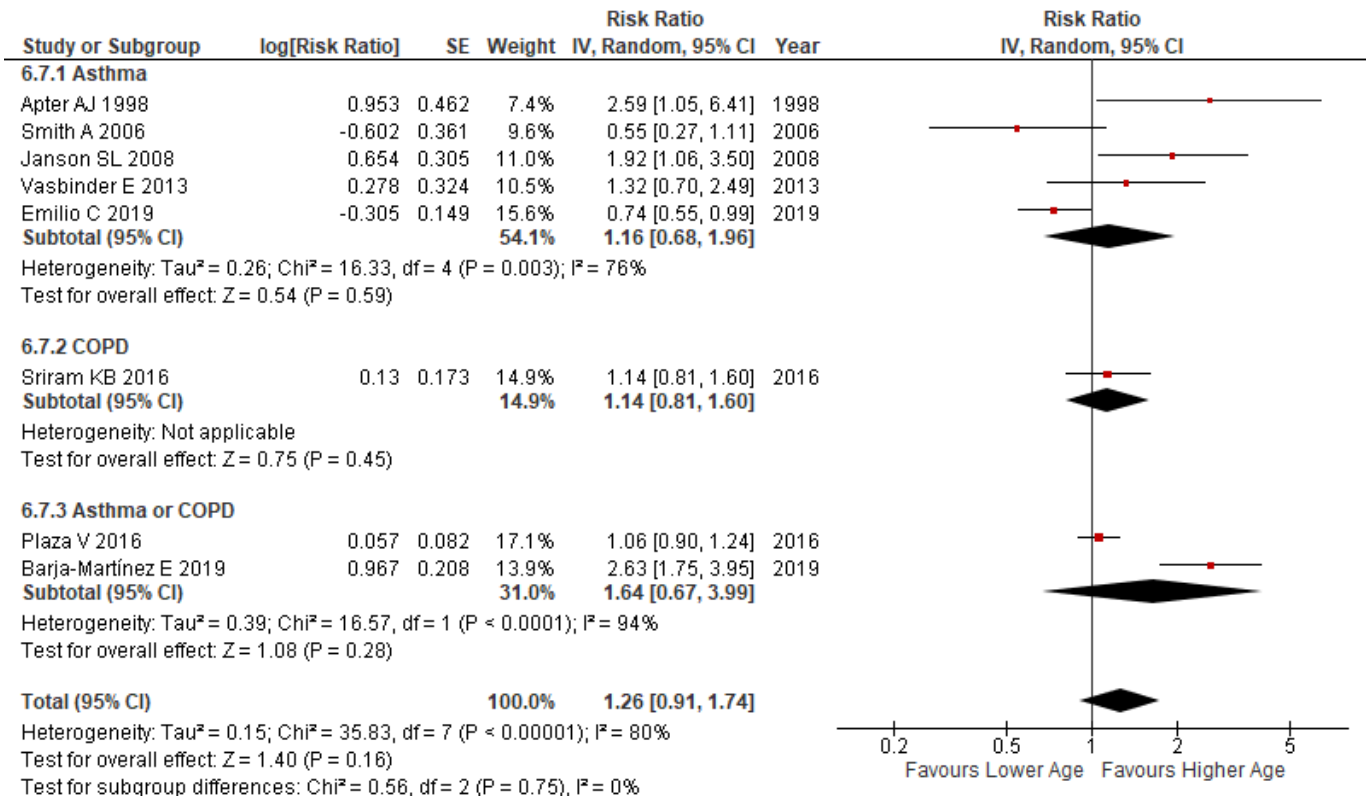
6.4. Subanalysis on Risk of Bias assessment

Subanalysis not performed due to insufficient studies available or irrelevance regarding the results obtained in full data analysis.

6.5. Subanalysis on Study dimension/size

Subanalysis not performed due to insufficient studies available or irrelevance regarding the results obtained in full data analysis.

6.6. Subanalysis on Diagnosis type



6.7. Subanalysis on Types of instruments to measure adherence

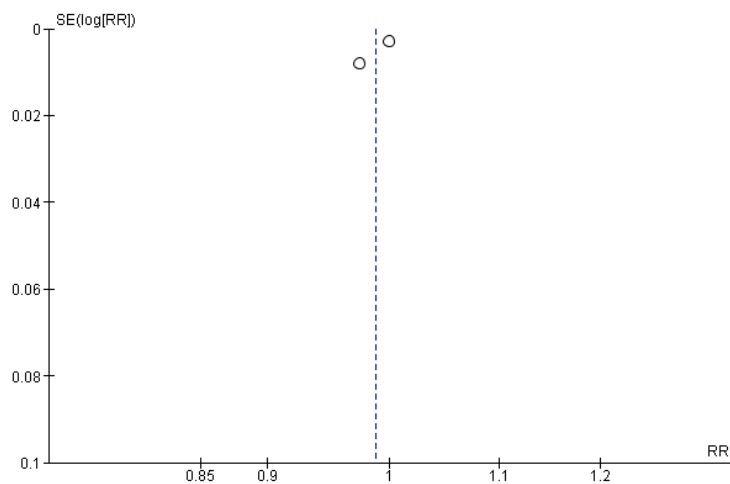
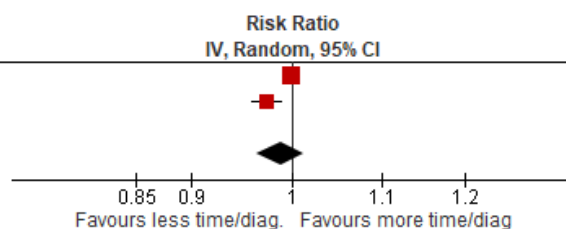
Subanalysis not performed due to insufficient studies available or irrelevance regarding the results obtained in full data analysis.

7. Meta-analysis for the determinant “Oldest diagnosis”

FULL DATA ANALYSIS

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI	Year
D. Federman A 2014	0	0.003	54.1%	1.00 [0.99, 1.01]	2014
Darbà J 2015	-0.026	0.008	45.9%	0.97 [0.96, 0.99]	2015
Total (95% CI)			100.0%	0.99 [0.96, 1.01]	

Heterogeneity: Tau² = 0.00; Chi² = 9.26, df = 1 (P = 0.002); I² = 89%
 Test for overall effect: Z = 0.92 (P = 0.36)



DISAGGREGATED ANALYSIS ACCORDING TO:

- 7.1. Subanalysis on Publication year*
- 7.2. Subanalysis on Continental region*
- 7.3. Subanalysis on Study design*
- 7.4. Subanalysis on Risk of Bias assessment*
- 7.5. Subanalysis on Study dimension/size*
- 7.6. Subanalysis on Diagnosis type*
- 7.7. Subanalysis on Types of instruments to measure adherence*

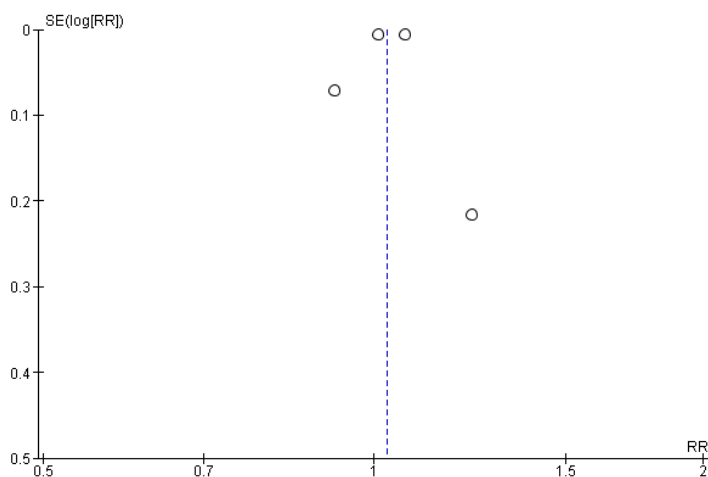
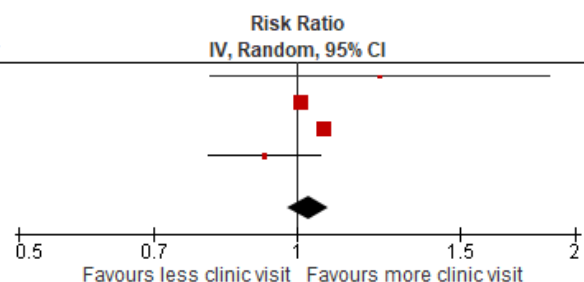
**Subanalysis not performed due to insufficient studies available or irrelevance regarding the results obtained in full data analysis.*

8. Meta-analysis for the determinant “More outpatient clinic visits”

FULL DATA ANALYSIS

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio		Year
				IV, Random, 95% CI		
Vasbinder E 2013	0.207	0.216	1.5%	1.23	[0.81, 1.88]	2013
Chiu K 2014	0.01	0.006	43.9%	1.01	[1.00, 1.02]	2014
Darbà J 2015	0.066	0.006	43.9%	1.07	[1.06, 1.08]	2015
Zucchelli A 2020	-0.081	0.071	10.6%	0.92	[0.80, 1.06]	2020
Total (95% CI)			100.0%	1.03	[0.98, 1.08]	

Heterogeneity: Tau² = 0.00; Chi² = 46.97, df = 3 (P < 0.00001); I² = 94%
 Test for overall effect: Z = 1.05 (P = 0.29)



DISAGGREGATED ANALYSIS ACCORDING TO:

- 8.1. Subanalysis on Publication year*
- 8.2. Subanalysis on Continental region*
- 8.3. Subanalysis on Study design*
- 8.4. Subanalysis on Risk of Bias assessment*
- 8.5. Subanalysis on Study dimension/size*
- 8.6. Subanalysis on Diagnosis type*
- 8.7. Subanalysis on Types of instruments to measure adherence*

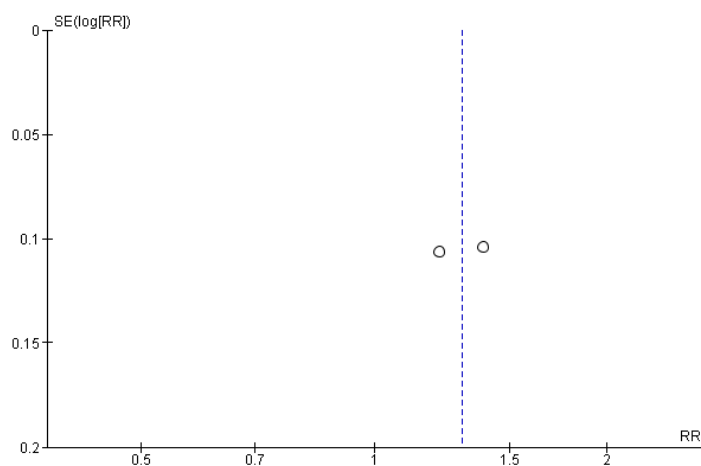
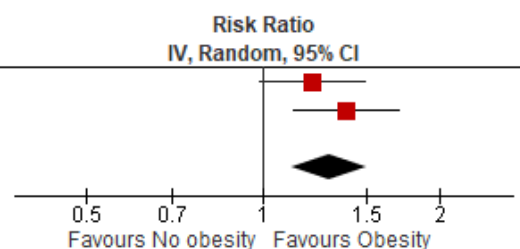
**Subanalysis not performed due to insufficient studies available or irrelevance regarding the results obtained in full data analysis.*

9. Meta-analysis for the determinant “Obesity”

FULL DATA ANALYSIS

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio		Year
				IV, Random, 95% CI	95% CI	
Darbà J 2015	0.193	0.106	49.0%	1.21	[0.99, 1.49]	2015
Zucchelli A 2020	0.326	0.104	51.0%	1.39	[1.13, 1.70]	2020
Total (95% CI)			100.0%	1.30	[1.12, 1.50]	

Heterogeneity: Tau² = 0.00; Chi² = 0.80, df = 1 (P = 0.37); I² = 0%
 Test for overall effect: Z = 3.51 (P = 0.0004)



DISAGGREGATED ANALYSIS ACCORDING TO:

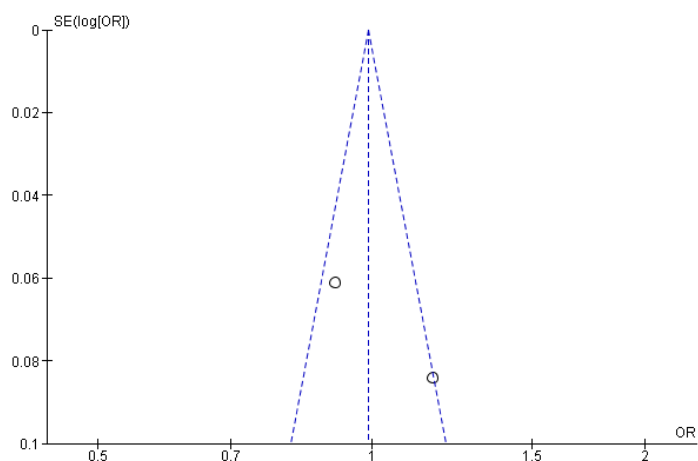
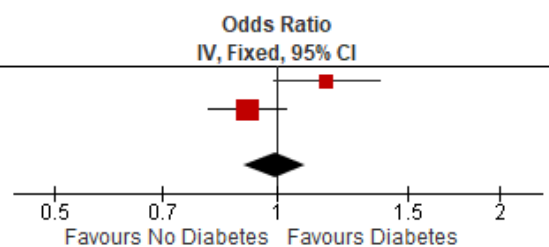
- 9.1. Subanalysis on Publication year*
- 9.2. Subanalysis on Continental region*
- 9.3. Subanalysis on Study design*
- 9.4. Subanalysis on Risk of Bias assessment*
- 9.5. Subanalysis on Study dimension/size*
- 9.6. Subanalysis on Diagnosis type*
- 9.7. Subanalysis on Types of instruments to measure adherence*

**Subanalysis not performed due to insufficient studies available or irrelevance regarding the results obtained in full data analysis.*

10. Meta-analysis for the determinant “Diabetes”

FULL DATA ANALYSIS

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio		Year
				IV, Fixed, 95% CI		
Darbà J 2015	0.154	0.084	34.5%	1.17	[0.99, 1.38]	2015
Zucchelli A 2020	-0.093	0.061	65.5%	0.91	[0.81, 1.03]	2020
Total (95% CI)			100.0%	0.99	[0.90, 1.09]	
Heterogeneity: Chi ² = 5.66, df = 1 (P = 0.02); I ² = 82%						
Test for overall effect: Z = 0.16 (P = 0.88)						



DISAGGREGATED ANALYSIS ACCORDING TO:

- 10.1. Subanalysis on Publication year*
- 10.2. Subanalysis on Continental region*
- 10.3. Subanalysis on Study design*
- 10.4. Subanalysis on Risk of Bias assessment*
- 10.5. Subanalysis on Study dimension/size*
- 10.6. Subanalysis on Diagnosis type*
- 10.7. Subanalysis on Types of instruments to measure adherence*

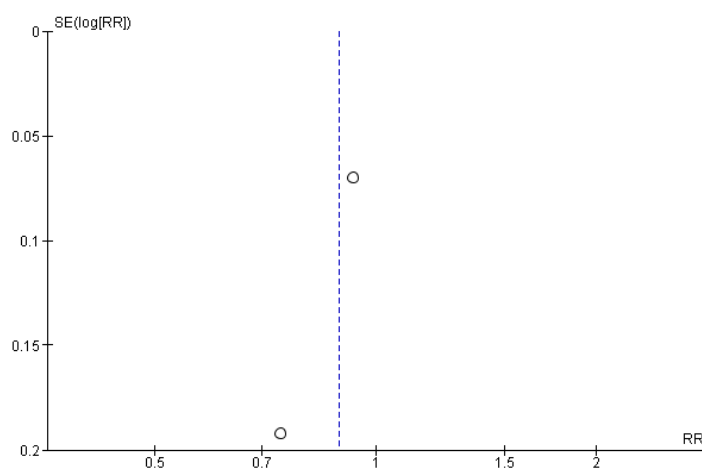
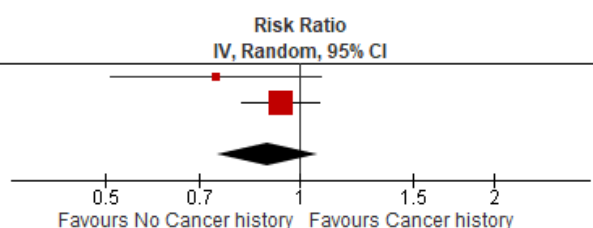
**Subanalysis not performed due to insufficient studies available or irrelevance regarding the results obtained in full data analysis.*

11. Meta-analysis for the determinant “Cancer”

FULL DATA ANALYSIS

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio		Year
				IV, Random, 95% CI	95% CI	
Huetsch J 2012	-0.299	0.192	19.5%	0.74	[0.51, 1.08]	2012
Zucchelli A 2020	-0.07	0.07	80.5%	0.93	[0.81, 1.07]	2020
Total (95% CI)			100.0%	0.89	[0.75, 1.07]	

Heterogeneity: Tau² = 0.01; Chi² = 1.26, df = 1 (P = 0.26); I² = 20%
 Test for overall effect: Z = 1.26 (P = 0.21)



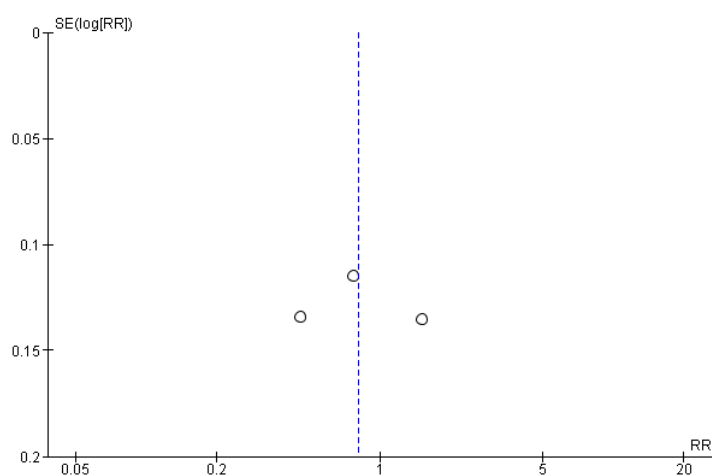
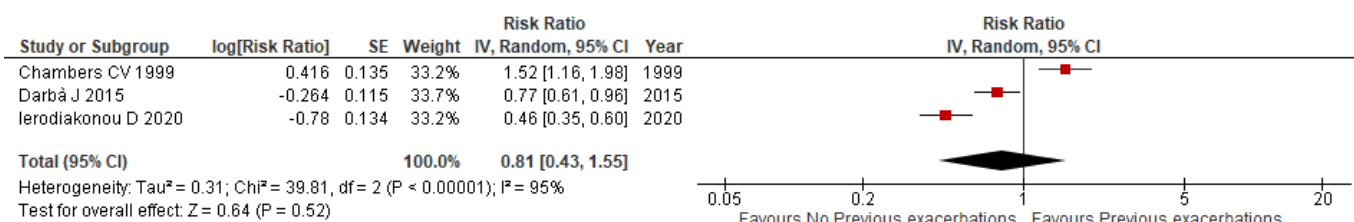
DISAGGREGATED ANALYSIS ACCORDING TO:

- 11.1. Subanalysis on Publication year*
- 11.2. Subanalysis on Continental region*
- 11.3. Subanalysis on Study design*
- 11.4. Subanalysis on Risk of Bias assessment*
- 11.5. Subanalysis on Study dimension/size*
- 11.6. Subanalysis on Diagnosis type*
- 11.7. Subanalysis on Types of instruments to measure adherence*

**Subanalysis not performed due to insufficient studies available or irrelevance regarding the results obtained in full data analysis.*

12. Meta-analysis for the determinant “Previous exacerbations”

FULL DATA ANALYSIS

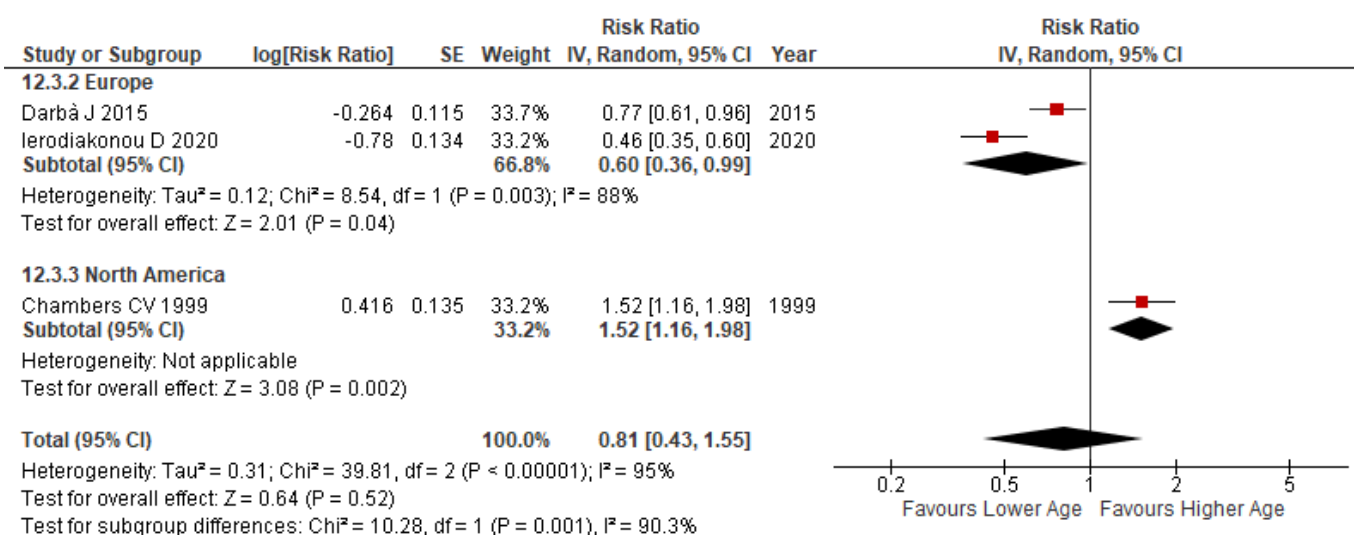


DISAGGREGATED ANALYSIS ACCORDING TO:

12.1. Subanalysis on Publication year

Subanalysis not performed due to insufficient studies available or irrelevance regarding the results obtained in full data analysis.

12.2. Subanalysis on Continental region



12.3. Subanalysis on Study design

Subanalysis not performed due to insufficient studies available or irrelevance regarding the results obtained in full data analysis.

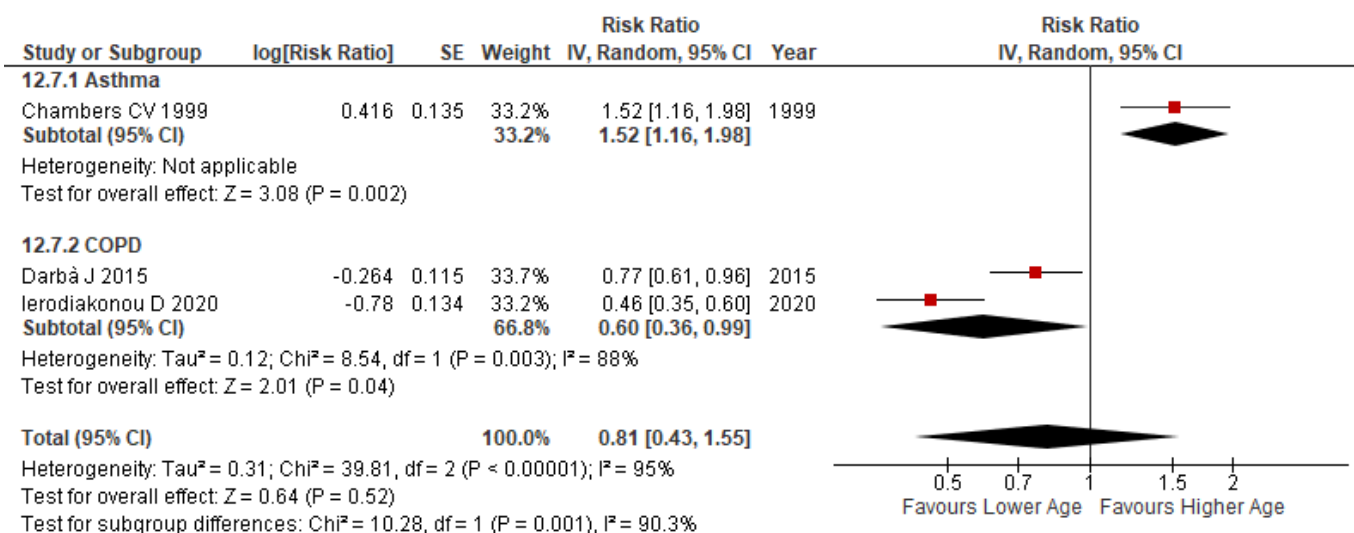
12.4. Subanalysis on Risk of Bias assessment

Subanalysis not performed due to insufficient studies available or irrelevance regarding the results obtained in full data analysis.

12.5. Subanalysis on Study dimension/size

Subanalysis not performed due to insufficient studies available or irrelevance regarding the results obtained in full data analysis.

12.6. Subanalysis on Diagnosis type

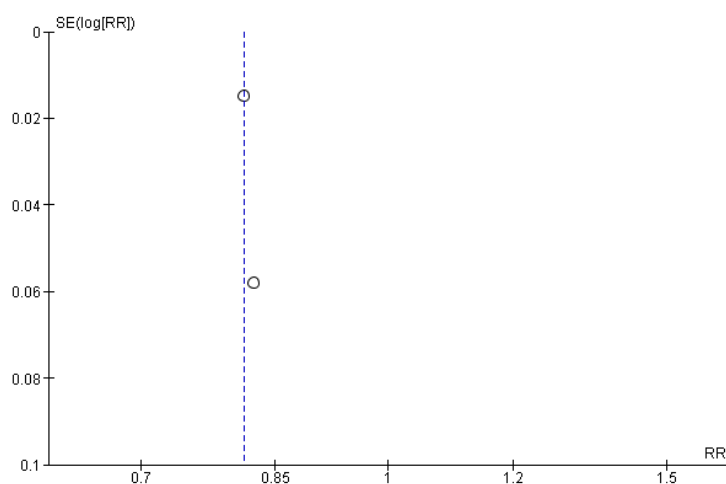
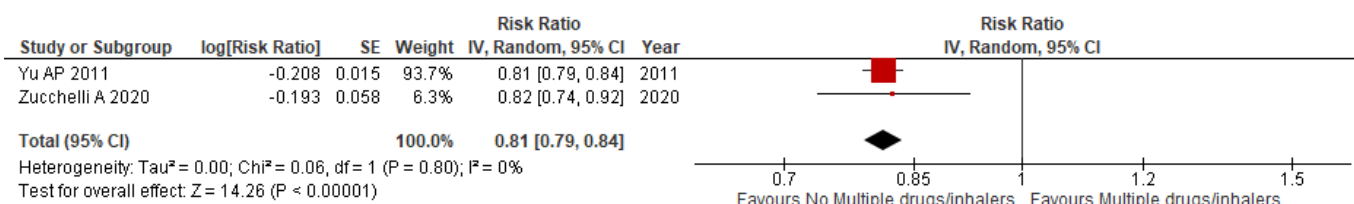


12.7. Subanalysis on Types of instruments to measure adherence

Subanalysis not performed due to insufficient studies available or irrelevance regarding the results obtained in full data analysis.

13. Meta-analysis for the determinant “Multiple drugs/inhalers”

FULL DATA ANALYSIS



DISAGGREGATED ANALYSIS ACCORDING TO:

- 13.1. Subanalysis on Publication year*
- 13.2. Subanalysis on Continental region*
- 13.3. Subanalysis on Study design*
- 13.4. Subanalysis on Risk of Bias assessment*
- 13.5. Subanalysis on Study dimension/size*
- 13.6. Subanalysis on Diagnosis type*
- 13.7. Subanalysis on Types of instruments to measure adherence*

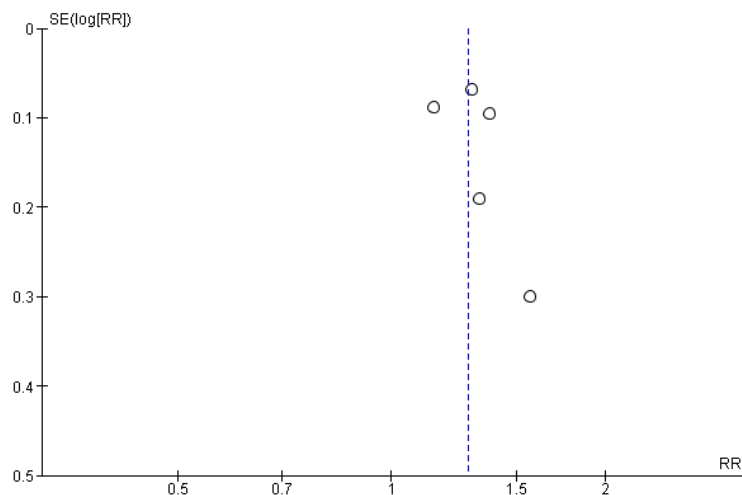
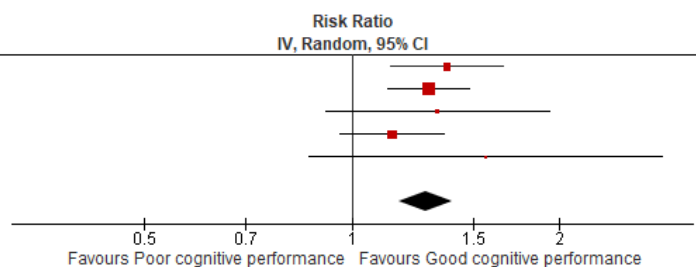
**Subanalysis not performed due to insufficient studies available or irrelevance regarding the results obtained in full data analysis.*

14. Meta-analysis for the determinant “Good cognitive performance”

FULL DATA ANALYSIS

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio		Year
				IV, Random, 95% CI		
O'Connor R 2015	0.318	0.096	22.4%	1.37	[1.14, 1.66]	2015
Sulaiman I 2017	0.257	0.069	43.4%	1.29	[1.13, 1.48]	2017
Turan O 2017	0.285	0.19	5.7%	1.33	[0.92, 1.93]	2017
O'Connor R 2019	0.135	0.089	26.1%	1.14	[0.96, 1.36]	2019
Zucchelli A 2020	0.446	0.3	2.3%	1.56	[0.87, 2.81]	2020
Total (95% CI)			100.0%	1.28	[1.17, 1.40]	

Heterogeneity: Tau² = 0.00; Chi² = 2.63, df = 4 (P = 0.62); I² = 0%
 Test for overall effect: Z = 5.38 (P < 0.00001)



DISAGGREGATED ANALYSIS ACCORDING TO:

- 14.1. Subanalysis on Publication year*
- 14.2. Subanalysis on Continental region*
- 14.3. Subanalysis on Study design*
- 14.4. Subanalysis on Risk of Bias assessment*
- 14.5. Subanalysis on Study dimension/size*
- 14.6. Subanalysis on Diagnosis type*
- 14.7. Subanalysis on Types of instruments to measure adherence*

**Subanalysis not performed due to insufficient studies available or irrelevance regarding the results obtained in full data analysis.*

15. Meta-analysis for the determinant “Disease high severity”

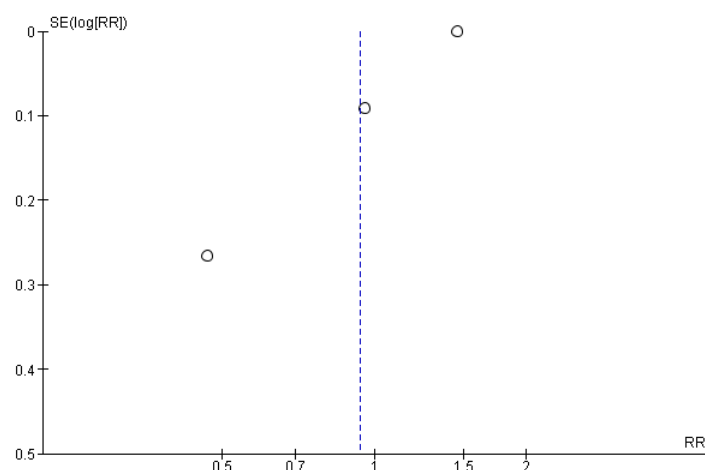
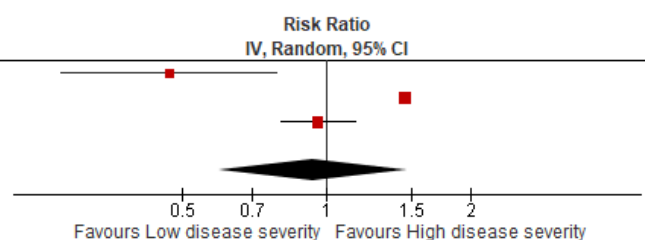
FULL DATA ANALYSIS

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio	Year
				IV, Random, 95% CI	
Janson SL 2008	-0.757	0.265	25.5%	0.47 [0.28, 0.79]	2008
Takemura M 2017	0.378	0.001	38.3%	1.46 [1.46, 1.46]	2017
Price D 2018	-0.042	0.091	36.2%	0.96 [0.80, 1.15]	2018

Total (95% CI) 100.0% 0.94 [0.60, 1.48]

Heterogeneity: Tau² = 0.14; Chi² = 39.64, df = 2 (P < 0.00001); I² = 95%

Test for overall effect: Z = 0.27 (P = 0.78)



DISAGGREGATED ANALYSIS ACCORDING TO:

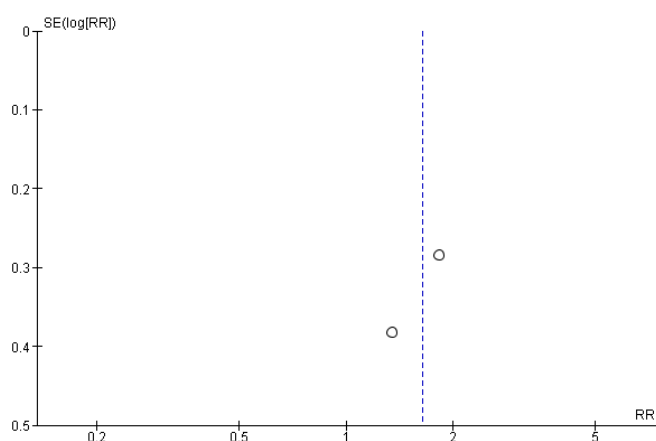
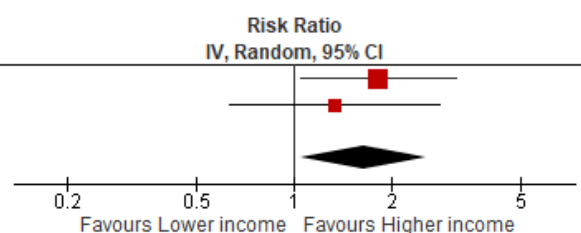
- 15.1. Subanalysis on Publication year*
- 15.2. Subanalysis on Continental region*
- 15.3. Subanalysis on Study design*
- 15.4. Subanalysis on Risk of Bias assessment*
- 15.5. Subanalysis on Study dimension/size*
- 15.6. Subanalysis on Diagnosis type*
- 15.7. Subanalysis on Types of instruments to measure adherence*

**Subanalysis not performed due to insufficient studies available or irrelevance regarding the results obtained in full data analysis.*

16. Meta-analysis for the determinant “Higher income”

FULL DATA ANALYSIS

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio		Year
				IV, Random, 95% CI		
Janson SL 2008	0.601	0.284	64.4%	1.82	[1.05, 3.18]	2008
Vasbinder E 2013	0.293	0.382	35.6%	1.34	[0.63, 2.83]	2013
Total (95% CI)			100.0%	1.63	[1.05, 2.56]	
Heterogeneity: Tau ² = 0.00; Chi ² = 0.42, df = 1 (P = 0.52); I ² = 0%						
Test for overall effect: Z = 2.16 (P = 0.03)						



DISAGGREGATED ANALYSIS ACCORDING TO:

- 16.1. Subanalysis on Publication year*
- 16.2. Subanalysis on Continental region*
- 16.3. Subanalysis on Study design*
- 16.4. Subanalysis on Risk of Bias assessment*
- 16.5. Subanalysis on Study dimension/size*
- 16.6. Subanalysis on Diagnosis type*
- 16.7. Subanalysis on Types of instruments to measure adherence*

**Subanalysis not performed due to insufficient studies available or irrelevance regarding the results obtained in full data analysis.*