

# **Literacy interventions in asthma – a cost-effectiveness study and a perspective in Portugal**

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Dissertação para obtenção do Grau de Mestre em  
**Medicina**  
(Mestrado Integrado)

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Janeiro de 2024



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## **Dedicatória**

À Medicina, para que este trabalho sirva de inspiração e base científica para serem desenvolvidos novos projetos, gerando mais conhecimento e inovação nesta área tão admirável e apaixonante.



## **Agradecimentos**

Ao meu orientador, Prof. Dr. Tiago Maricoto, que foi o principal pilar para este trabalho ser desenvolvido e concluído com sucesso. Toda a sua dedicação, empenho, disponibilidade e prestabilidade foi incansável, facilitando todo este processo, sendo, por isso, merecedor de um agradecimento especial.

Ao meu co-orientador, Prof. Dr. Luís Taborda-Barata, pelo seu conhecimento, experiência e profissionalismo, essenciais ao desenvolvimento desta dissertação.

Ao meu namorado, pela sua resiliência ser uma fonte de inspiração para ser mais e melhor, pelo seu apoio incondicional, motivação e auxílio ao longo de todo este processo.

Aos meus pais, por serem um exemplo a seguir em todos os momentos da minha vida, pela prontidão para me aconselharem da forma mais acertada e pelo apoio a todas as horas. E, por fim, por tornarem este sonho de 6 anos possível.

À minha irmã, pelo seu testemunho e conselhos, mostrando-me a determinação e persistência necessárias para o sucesso.

Aos meus quatro avós, que olham por mim aqui e no Céu, por serem uma fonte de motivação, para que os possa orgulhar de todo o meu percurso.

Aos meus restantes familiares, que, de um modo ou de outro, contribuíram de uma forma especial para a concretização deste trabalho.

Aos meus amigos da Covilhã e aos meus amigos da faculdade, que fazem com que este caminho seja mais bonito.



# Resumo

## Introdução

A asma é uma doença crónica, não transmissível, que se estima afetar até 7% da população portuguesa. A maioria dos pacientes não está clinicamente controlada, o que pode ser parcialmente atribuível à baixa literacia em saúde. Vários ensaios testaram a eficácia de intervenções de literacia nos *outcomes* em asma, contudo, a sua custo-efetividade continua por esclarecer.

## Objetivo

Realizar uma análise de custo-efetividade em intervenções de literacia em pacientes com asma e estimar o custo-benefício da aplicação de um programa desse tipo em Portugal.

## Métodos

Desenvolvemos uma modelo de análise em árvore na perspectiva de um prestador de saúde, de acordo com vários *outcomes* (mau controlo clínico, idas ao serviço de urgência (SU), hospitalizações, uso de medicação em SOS) e custos descritos em ensaios clínicos anteriores, e de acordo com os custos de intervenção. A análise de sensibilidade dos piores e melhores cenários foi realizada para estimar limiares para limites acessíveis de intervenção, bem como estimativas de poupança de custos e Rácio Custo-Efetividade Incremental (ICER) para um cenário português.

## Contexto

Estimámos os limites de custo-efetividade aplicáveis em todos os contextos e realizámos uma análise de sensibilidade de um modelo teórico de intervenção em todos os pacientes, incluindo o aprimoramento da literacia numa consulta anual com um médico e um enfermeiro.

## Resultados

Dados de 8 ensaios clínicos aleatorizados foram incluídos. No melhor cenário possível, o orçamento acessível da intervenção por paciente, por ano, foi estimado em: 107,38€ para evitar mau controlo clínico num paciente, 3,20€ para evitar uma ida ao SU, 10,35€ para evitar uma hospitalização e 1,13€ para evitar o uso de medicação em SOS ou corticóides orais. As poupanças de custos para o cenário português foram mais pronunciadas para evitar um mau controlo clínico, em 100,68€ por paciente, por ano. O ICER para Portugal, para o melhor cenário possível, foi estimado em: 55,83€ para mau controlo clínico, 134,00€ para idas ao SU, 111,67€ para hospitalizações e 55,83€ para uso de medicação em SOS ou corticóides orais; cada valor por evento de *outcome* evitado. A análise de subgrupos mostra que, para estudos com acompanhamento de 12 meses e incluindo pacientes com asma leve a moderada, as estimativas de custo-efetividade são mais favoráveis para evitar mau controlo clínico, idas ao SU e hospitalizações.

### Conclusão

As intervenções de literacia podem ser potencialmente custo-efetivas de acordo com os custos e cenários portugueses, embora com uma ampla gama de incertezas. Isto verifica-se mais na redução do risco de mau controlo clínico, idas ao SU e hospitalizações, particularmente em doentes com asma ligeira a moderada e com um seguimento mais longo (12 meses).

## **Palavras-chave**

Asma; Literacia; Hospitalização; Custo-Efetividade



# Abstract

## Introduction

Asthma is a chronic, non-communicable, respiratory disease which is estimated to affect up to 7% of the Portuguese population. Most patients are clinically uncontrolled, and that may be partially due to low health literacy. Several trials have tested the efficacy of literacy interventions on asthma outcomes, but their cost-effectiveness is still unclear.

## Objective

To perform a cost-effectiveness analysis of literacy interventions in patients with asthma and estimate the cost-benefit of applying such a programme in Portugal.

## Perspective and Methods

We developed a decision tree analysis from a healthcare perspective, according to several outcomes (poor clinical control, emergency department (ED) visits, hospitalisations, use of rescue medication) rates and costs described in previous clinical trials, and according to intervention costs. Sensitivity analysis of worst and best-case scenarios was performed to estimate thresholds for intervention affordable limits, as well as cost-saving estimations and Incremental Cost-Effectiveness Ratio (ICER) for a Portuguese scenario.

## Setting

We estimated cost-effectiveness thresholds applicable in all settings and performed a sensitivity analysis of a theoretical intervention model in all patients, including literacy enhancement at an annual appointment with a doctor and a nurse.

## Results

Data from 8 RCTs was included. In the best-case scenario, intervention affordable budget per patient per year were estimated at: 107,38€ to avoid one patient with poor clinical control, 3,20€ to avoid an ED visit, 10,35€ to avoid a hospitalisation and 1,13€ to avoid the use of rescue medication or OCS. Cost savings for Portuguese scenario were more pronounced to avoid poor clinical control, at 100,68€ per patient per year. ICER for Portugal were estimated for best-case scenarios at: poor clinical control 55,83€, ED visits 134,00€, hospitalisations 111,67€ and use of rescue medication or OCS 55,83€; each per outcome event avoided. Subgroup analysis show that for studies with 12-month follow-up and including mild to moderate asthma patients, the estimates for cost-effectiveness are more favourable to avoid poor clinical control, ED visits and hospitalisations.

### Conclusions

Literacy interventions may be potentially cost-effective according to Portuguese costs and scenarios, although with a wide range of uncertainty. This is more pronounced in reducing the risk for poor clinical control, emergency room visits and hospitalisations, particularly in patients with mild to moderate asthma severity and with longer follow-up (12 months).

## **Keywords**

Asthma; Literacy; Hospitalisation; Cost-Effectiveness

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## **Lista de Acrónimos**

SU	Serviço de Urgência
ED	Emergency Department
ICER	Incremental Cost-Effectiveness Ratio
RCT	Randomized Control Trial
OCS	Oral Corticosteroids

# Chapter 1 - Introduction

## Definition and epidemiology of asthma

Asthma is a chronic, non-communicable, respiratory disease, characterized by inflammation and narrowing of the small airways of the lungs, and whose main symptoms are cough (mostly at night), wheezing, shortness of breath and chest tightness (1). It is one of the most prevalent diseases worldwide, affecting around 262 million people (1). In Portugal, it is estimated that 695.000 people have asthma, approximately 7% of the population (2).

However, only 57% have good clinical control of their symptoms, and most of these patients (88%) have a poor perception of their asthma control (3). This may be associated with low literacy, and several studies have assessed the impact of literacy interventions in the clinical outcomes of asthma, such as symptoms control, emergency department visits, hospitalisations, use of rescue medication, etc. Nevertheless, a recent systematic review concluded that the results are inconclusive and vary significantly, highlighting the need for additional research (4).

## Costs associated with asthma in Portugal

Recently, a Portuguese study (5) evaluated the costs associated with asthma for adults, in Portugal. It was concluded that the total cost is over 386€ million, and that direct costs only are responsible for 359€ million, which represents 2.04% of the total Portuguese health-care expense for 2010. On average, each adult represents a cost of 708,16€ per year, with 93% of this amount being direct costs. In addition, these estimates vary according to the patient's clinical control, ranging from 425,44€ per patient per year for well-controlled patients, up to 894,86€ for uncontrolled patients.

Considering this, it is of paramount importance to perform cost-effectiveness studies to assess interventions that may improve asthma control. Thus, we performed a cost-effectiveness analysis of literacy interventions in patients with asthma, and estimated the cost-benefit of applying such programmes in Portugal.



## Chapter 2 – Methods and Materials

### Study design and framework

We developed a standard cost-effectiveness analysis, based on a decision tree approach (6) and in accordance with CHEERS recommendations (7). Our aims were to perform estimations of treatment affordable thresholds and according to the following adverse outcome costs in adolescents and adults with asthma: poor clinical control, emergency department visits, hospitalisations and use of rescue medication or oral corticosteroids (OCS). In addition, we performed estimations of cost-savings and Incremental Cost-Effectiveness Ratio (ICER) for a Portuguese scenario, according to local costs of a theoretical intervention programme.

### Sources of data

We used data from previously published studies on outcome costs (5), outcome rates, and local costs for interventions in literacy, to try to determine cost-effectiveness ratios. We performed a thorough but non-systematic search for controlled clinical trials, aiming to address the effect of literacy interventions in adolescents and adult patients with asthma. Searches were made in MEDLINE, EMBASE and CENTRAL using “asthma” and “literacy” as key-terms. Eight studies were included, reporting data for the following outcomes: poor clinical control, emergency department visits, hospitalisations and use of rescue medication or OCS. According to those (8–15), interventions that include literacy enhancement in adolescents and adult patients with asthma, show diverging results. Considering poor clinical control, risk ratios vary between 0.12 and 4.47; considering emergency department visits, risk ratios vary between 0.07 and 15.86; for hospitalisations between 0.00 and 33.64, and for the use of rescue medication or OCS between 0.31 and 5.79. Table 1 shows the collected data from the included trials, regarding control group and intervention group risk estimations, and according to the outcomes of interest.

Table 1 - Data collected from included clinical trials, regarding control group and intervention group risk estimations, according to the outcomes of interest.

Study	Outcomes of interest (n° of participants with outcome)			
	Poor clinical control (n° of participants)	Emergency department visits	Hospitalisations	Use of rescue medication or OCS
Apter AJ et al 2011	<i>No clinical improvement at 6 months:</i>	<i>At 6 months:</i> Control: 20/168	<i>At 6 months:</i> Control: 11/168	No data

	Control: 134/168 Intervention: 147/165	Intervention: 29/165	Intervention: 10/165	
Apter AJ 2020	No data	At 12 months: Control: 21/156 Intervention: 33/156	At 12 months: Control: 23/156 Intervention: 19/156	No data
Gallefoss F et al 2001	<i>Symptoms impacting on daily life, at 12 months:</i> Control: 15/39 Intervention: 4/32	No data	No data	No data
Goeman D et al 2013	No data	No data	No data	At 12 months: Control: 13/56 Intervention: 9/58
Guendelman S et al 2002	<i>Coughing or wheezing at 12 weeks:</i> Control: 39/60 Intervention: 39/62	At 12 weeks: Control: 11/60 Intervention: 6/62	At 12 weeks: Control: 1/60 Intervention: 4/62	No data
Guner UC et al 2015	<i>Total day symptoms variation at 2 months:</i> Control: 30/40 Intervention: 14/40	At 2 months: Control: 16/40 Intervention: 6/40	No data	At 2 months: Control: 6/40 Intervention: 15/40
Kauppinen R et al 1998	No data	No data	At 12 months: Control: 2/82 Intervention: 0/80	No data
Sundberg R et al 2005	<i>Total day symptoms variation at 12 months:</i> Control: 4/49 Intervention: 5/48	At 12 months: Control: 1/49 Intervention: 1/48	No data	No data
<b>Global group risk estimations [n° pax; RR(95%CI)]*</b>				
Control group	222/356 0.62 (0.57, 0.67)	69/473 0.15 (0.12, 0.18)	37/466 0.08 (0.06, 0.11)	19/96 0.20 (0.13, 0.29)
Intervention group	209/347 0.60 (0.55, 0.65)	75/471 0.16 (0.13, 0.20)	33/463 0.07 (0.05, 0.10)	24/98 0.25 (0.17, 0.34)
OCS – Oral corticosteroids; RR – risk ratio				
* Estimated according to total number of accumulated participants and reported events among all included studies.				

Risk estimations for each outcome were calculated, both for the intervention group and the control group (herein considered “usual care” for cost-effectiveness analysis). For that, the absolute number of events for each outcome were considered within each study, and gathered as a total amount among all eligible studies. 95%CI were used to perform sensitivity analysis.

Costs for each of the analysed outcomes were also collected from a previously published study, reporting data from Portugal (5). Considering poor clinical control, the mean annual costs per patient are estimated at 894,86€; considering emergency department visits, the

mean annual costs per patient vary between 31,42€ and 64,02€; for hospitalisations between 28,91€ and 172,42€, and for the use of rescue medication or OCS between 3,69€ and 9,69€. Due to the wide range of values, we used all these references to estimate scenarios for the best-case and worst-case estimation.

## **Best-case definition**

The base-case population of our analysis are adolescents and adult patients with asthma. This is a healthcare payer's perspective study, where only direct costs were considered, because indirect costs and patient's own costs were not reliably available. We did not consider medication costs in the different stages of disease management either. Two types of costs were calculated, the intervention costs and outcome costs, which were assigned to the decision tree analysis. This model assumes the previously reported risk reduction for the outcomes of interest, as well as their associated costs. We also performed sensitivity analysis to assess uncertainty regarding thresholds of intervention cost-effectiveness, using reported 95%CI limits in order to estimate worst and best-case scenarios.

## **Intervention**

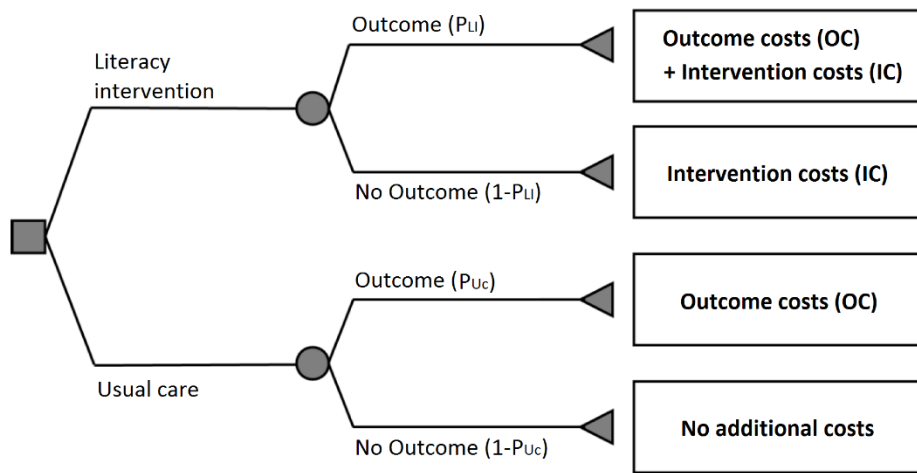
Different intervention programmes were tested in these patients in previous studies, with a wide variety of aspects being addressed. Nevertheless, most interventions included nurses or doctors, with 30-60 minutes duration, and addressing mostly educational strategies, without relevant logistic assets (that would significantly increase intervention costs), and almost all studies performed it only at baseline of the follow-up period. For that reason, we developed a conceptual intervention programme with annual control appointments by a doctor and a nurse. Each appointment would require a 20 min evaluation (40 min both).

## **Setting**

Due to inherent difficulties in specifying different aspects of interventions, the costs of such programme were calculated as a whole, considering health professionals' salaries in 2017 that are based on the official values defined by the Portuguese Central Administration of Health System (ACSS). All costs and outcomes were expressed as additional factors to the main comparator, which in most studies was equivalent to Usual Care. The time frame in the base-case analysis was one year, because most studies reported the outcomes as such. No discount rates were considered in cost estimation.

## Outcome measures

We used a synthesis-based estimate to define outcome measures, which included outcome rates, cost per outcome unit and thresholds of cost-effectiveness for the designed intervention programme. All cost estimations were used according to 2017 references, in euros (€). Outcome costs were considered as a whole in the estimations, regardless of the type of treatment or management that is usually provided to patients. For that reason, some types of clinical interventions provided for the management of asthma could be the same as those provided in our theoretical intervention program. However, that would not hamper the ability to compare them as a conceptual framework for the cost-effectiveness analysis. Figure 1 shows the decision tree used in the model.



$$EV(\text{Literacy intervention}) = EV(\text{Usual care})$$

$$[(OC + IC) * P_{LI}] + [IC * (1 - P_{LI})] = (OC * P_{UC}) + [0 * (1 - P_{UC})]$$

$$IC = OC * (P_{UC} - P_{LI})$$

Figure 1 - Decision tree model to compare Usual care versus Literacy intervention. OC – Outcome costs; IC- Intervention Costs; PLI – Probability of exacerbation under Literacy interventions; PUC – Probability of exacerbation under Usual Care.

The resulting equation for cost-effectivity balance is as follows (OC – Outcome costs; IC- Intervention Costs; PLI – Probability of outcome under Literacy Interventions; PUC – Probability of outcome under Usual Care):

(1)

$$\text{Expected Value (Literacy Intervention)} = \text{Expected Value (Usual Care)}$$

$$[(OC + IC) \times P_{LI}] + [IC \times (1 - P_{LI})] = (OC \times P_{UC}) + [0 \times (1 - P_{UC})]$$

$$IC = OC \times (P_{UC} - P_{LI})$$

Table 2 summarises all data considered in parameters assigned to cost estimations. Using the model assumptions presented in figure 1, we estimated the affordable limits for intervention costs at worst and best-case scenarios. Worst-case scenario was estimated using the 95%CI lower limit of probability of outcome under Usual Care, and 95%CI upper limit of probability of outcome under Literacy Intervention. Best case scenario was estimated using the 95%CI upper limit of probability of outcome under Usual Care, and 95%CI lower limit of Probability of outcome under Literacy intervention.

Table 2 - Input parameters used in the model.

Parameter	Best-case estimation / CI95% lower limit	Worst-case estimation / CI95% upper limit	Source
<b>Outcome rates (annual) *</b>			
• Poor clinical control	Usual care: 0.57 Intervention: 0.55	Usual care: 0.67 Intervention: 0.65	(8–11,14)
• Emergency department visits	Usual care: 0.12 Intervention: 0.13	Usual care: 0.18 Intervention: 0.20	(8–11,13)
• Hospitalisations	Usual care: 0.06 Intervention: 0.05	Usual care: 0.11 Intervention: 0.10	(8,10,13,15)
• Use of rescue medication or OCS	Usual care: 0.13 Intervention: 0.17	Usual care: 0.29 Intervention: 0.34	(9,12)
<b>Outcome Costs (€/patient/year)</b>			
• Poor clinical control	894,86€	894,86€	(5)
• Emergency department visits	31,42€	64,02€	
• Hospitalisations	28,91€	172,42€	
• Use of rescue medication or OCS	3,69€	9,69€	
<b>Intervention Costs (€/patient/year)</b>			
• Doctor (20 min/year)*	4,10€	10,40€	‡
• Nurse (20 min/year)†	2,60€	6,30€	‡
CI: Confidence Interval; €: 2017 Portuguese euro. * Mean salary of a Doctor for each hour ranges from 12,22€ to 31,13€.			
† Mean salary of a Nurse for each hour ranges from 7,90€ to 18,80€.			
‡ based on official values defined by the Portuguese Central Administration of Health System (ACSS).			
‡ Estimated according to total number of accumulated participants and reported events among all included studies.			

Cost-saving estimation for Portugal was also obtained according to worst and best-case scenarios. In the worst-case scenario, we used the lower limit of reported outcome costs, the

worst-case estimation of intervention cost and worst-case estimation of risk difference (the difference between outcome risk of Literacy Intervention group and Usual Care group). In the best-case scenario, we used the upper limit of reported outcome costs, the best-case estimation of intervention cost and the best-case estimation of risk difference.



## Chapter 3 - Results

### Cost-effectiveness estimation and sensitivity analysis

Our analysis estimated the cost-effectiveness thresholds for intervention costs affordable limits per patient per year. Figure 2 presents these results in the range of costs for each outcome of interest.

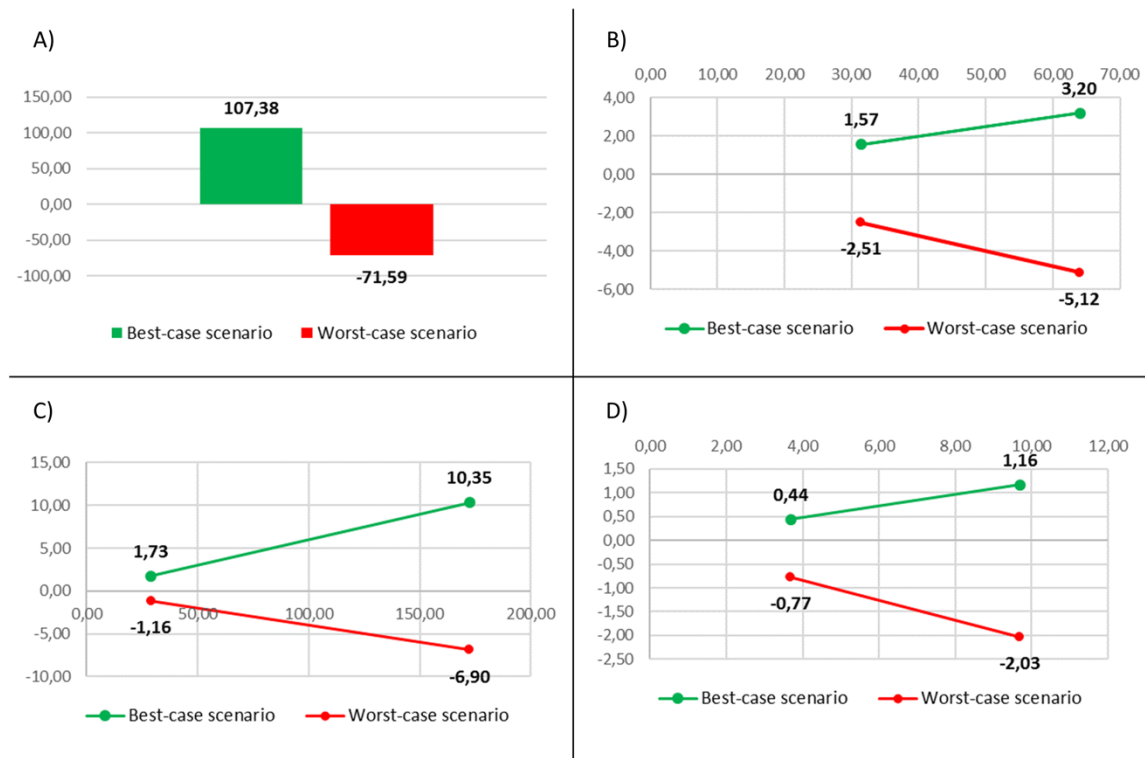


Figure 2 - Cost-effectivity thresholds according to outcomes costs. Lines represent the intervention costs affordable limit scenarios according to outcome proportions of 95%CI lower and upper limits. A - Clinical control. B - Emergency department visits. C - Hospitalisations. D - Use of rescue medication or oral corticosteroids. Y-axis: intervention affordable limits. X-axis - range for outcome costs in Portugal.

The respective estimation equations are (OC – Outcome costs; IC- Intervention Costs; PLI – Probability of outcome under Literacy Interventions; PUC – Probability of outcome under Usual Care):

(2)

Best-case scenario: [CI95% upper limit of P<sub>UC</sub> and lower limit of P<sub>LR</sub>]

$$IC = OC \times (\text{Risk difference for each outcome, at Best - case scenario})$$

$$\Leftrightarrow IC = OC \times (\text{Best-case risk for Usual care group} - \text{Best-case risk for Intervention group})$$

Worst-case scenario: [CI95% lower limit of  $P_{UC}$  and upper limit of  $P_{LI}$ ]

$$IC = OC \times (\text{Risk difference for each outcome, at Worst - case scenario})$$

$$\Leftrightarrow IC = OC \times (\text{Worst-case risk for Usual care group} - \text{Worst-case risk for Intervention group})$$

In the best-case scenario of intervention effectiveness and with outcome costs at the reported upper limit, the intervention affordable budget per patient per year were estimated at: 107,38€ to avoid one patient with poor clinical control, 3,20€ to avoid one patient with an emergency department visit, 10,35€ to avoid a hospitalisation and 1,16€ to avoid one patient from using rescue medication or OCS.

### Cost-saving estimations for a Portuguese scenario

Cost-saving estimations for Portugal were obtained considering worst and best-case scenarios and according to variations of annual costs for each outcome (Figure 3).

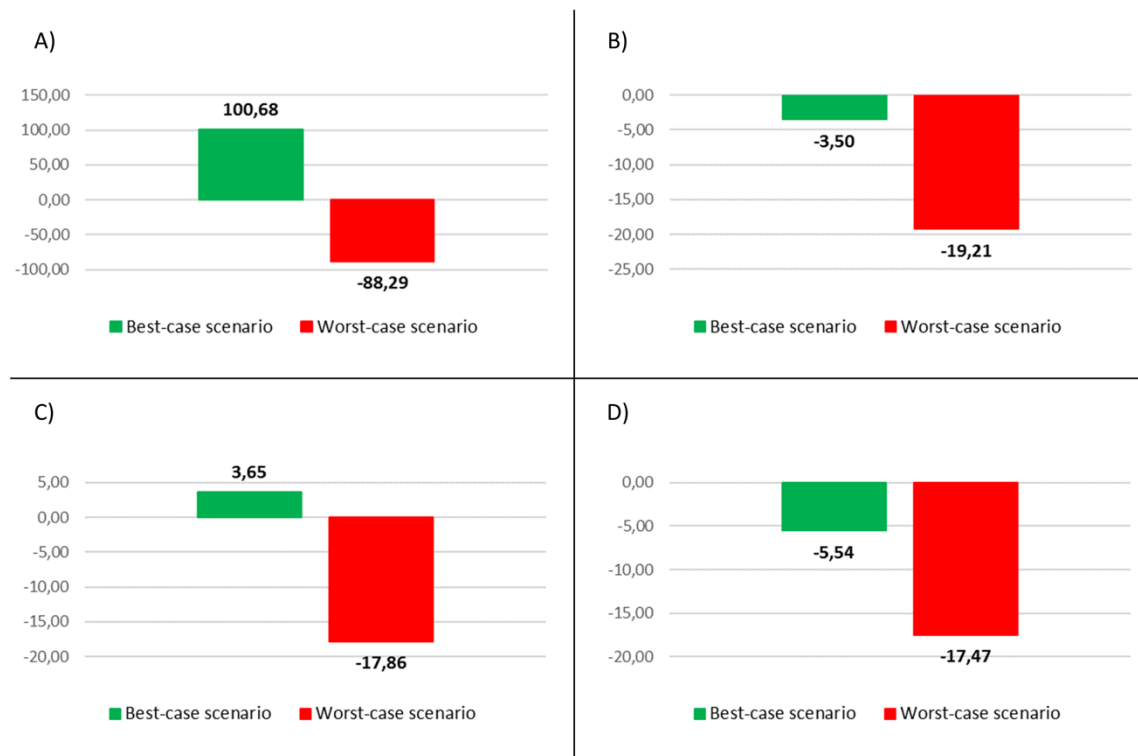


Figure 3 - Cost-saving estimations for a Portuguese scenario, considering worst-case (right bar) and best-case (left bar) scenarios and according to variations of annual costs for each outcome. A - Clinical control. B - Emergency department visits. C - Hospitalisations. D - Use of rescue medication or oral corticosteroids.

These reported costs concern the global population, but were used here to estimate savings for adolescents and adult patients only. The main equations used to estimate cost-savings were (OC: Outcome costs; IC: Intervention costs; RD: risk difference between Usual Care and Literacy Intervention group):

(3)

$$\text{Best-case scenario: Estimation Savings}_{best-case} = (OC_{worst-case} \times RD_{best-case}) - IC_{best-case}$$

$$\text{Estimation Savings}_{best-case} \text{ for Poor Clinical Control} = 100,68\text{€}$$

$$\text{Estimation Savings}_{best-case} \text{ for Emergency Department Visits} = (-)3,50\text{€}$$

$$\text{Estimation Savings}_{best-case} \text{ for Hospitalizations} = 3,65\text{€}$$

$$\text{Estimation Savings}_{best-case} \text{ for Use of Rescue Medication or OCS} = (-)5,54\text{€}$$

$$\text{Worst-case scenario: Estimation Savings}_{worst-case} = (OC_{best-case} \times RD_{worst-case}) - IC_{worst-case}$$

$$\text{Estimation Savings}_{worst-case} \text{ for Poor Clinical Control} = (-)88,29\text{€}$$

$$\text{Estimation Savings}_{worst-case} \text{ for Emergency Department Visits} = (-)19,21\text{€}$$

$$\text{Estimation Savings}_{worst-case} \text{ for Hospitalizations} = (-)17,86\text{€}$$

$$\text{Estimation Savings}_{worst-case} \text{ for Use of Rescue Medication or OCS} = (-)17,47\text{€}$$

Clinical control presents the most pronounced potential saving of up to 100,68€ per patient per year with the intervention; while the remaining outcomes presented most pronounced negative results, resulting in no potential savings for those.

## **Incremental cost-effectiveness ratio (ICER) estimations for a Portuguese scenario**

ICER was estimated for worst and best-case scenarios, and according to upper and lower limits of intervention costs and risk difference. Incremental effectiveness was estimated according to the number of prevented outcome events. Figure 4 represents ICER for Portugal at worst-case and best-case scenarios, which, for each outcome event prevented, vary between: (-)208,75€ and 55,83€ to avoid one patient with poor clinical control, (-)208,75€ to 134,00€ to avoid an emergency department visit, (-)417,50€ to 111,67€ to avoid a hospitalisation and (-)79,52€ to 55,83€ to avoid the use of rescue medication or

OCS. All presented predominant negative intervals, which means a net negative affordable incremental cost per patient per year with intervention.

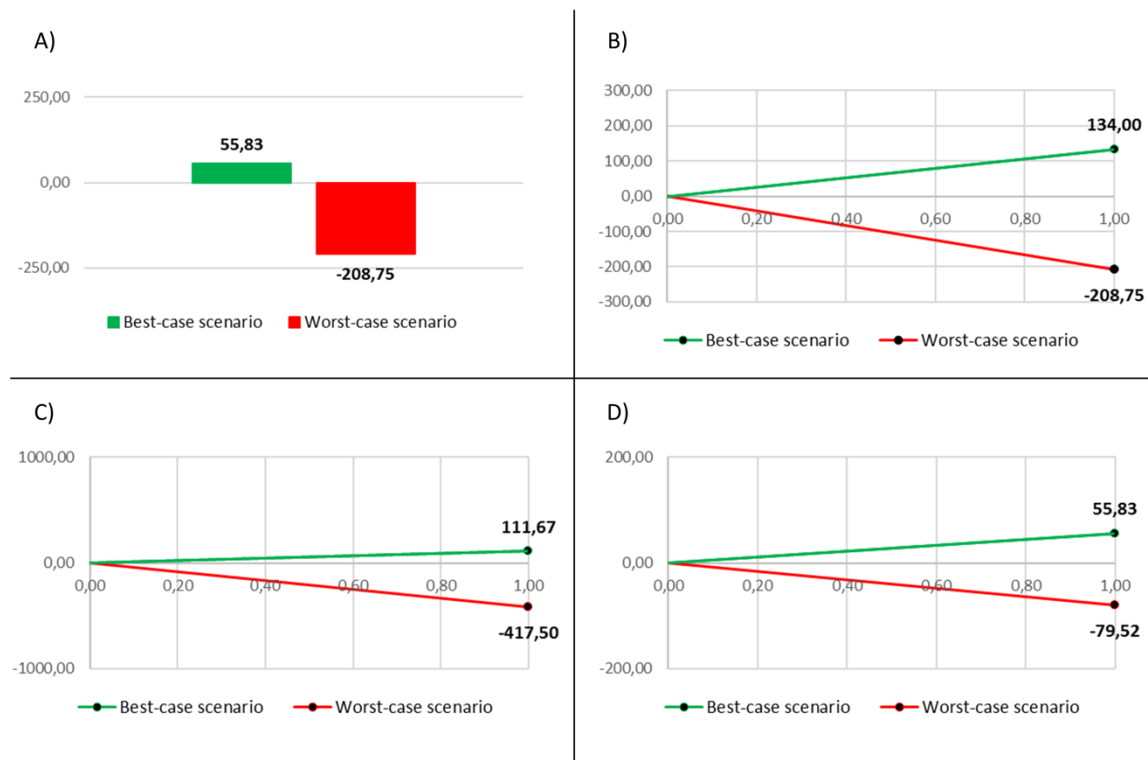


Figure 4 - Incremental cost-effectiveness ratio (ICER) for Portugal at worst-case and best-case scenarios according to lower and upper limits of Intervention Costs and Risk Difference. Incremental effectiveness was estimated according to number of prevented outcome events. A - Clinical control. B - Emergency department visits. C – Hospitalisations. D - Use of rescue medication or oral corticosteroids. Y-axis: intervention incremental cost. X-axis – range for number of outcome events prevented.

The equations used were (IC: Intervention costs; RD: risk difference between Usual Care and Literacy Intervention group):

(4)

$$\text{At best-case scenario: } ICER_{best-case} = \frac{IC_{best-case}}{RD_{best-case}}$$

-

$$ICER_{best-case} \text{ for Poor Clinical Control} = 55,83\text{€}$$

$$ICER_{best-case} \text{ for Emergency Department Visits} = 134,00\text{€}$$

$$ICER_{best-case} \text{ for Hospitalizations} = 111,67\text{€}$$

$$ICER_{best-case} \text{ for Use of Rescue Medication or OCS} = 55,83\text{€}$$

$$\text{At worst-case scenario: } ICER_{worst-case} = \frac{IC_{worst-case}}{RD_{worst-case}}$$

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$$ICER_{worst-case} \text{ for Poor Clinical Control} = (-)208,75\text{€}$$

$$ICER_{worst-case} \text{ for Emergency Department Visits} = (-)208,75\text{€}$$

$$ICER_{worst-case} \text{ for Hospitalizations} = (-)417,50\text{€}$$

$$ICER_{worst-case} \text{ for Use of Rescue Medication or OCS} = (-)79,52\text{€}$$

## Subgroup analysis

Additional analyses were performed according to several subgroups, such as: n<sup>o</sup> of follow-up interventions delivered (1 only versus 2 or more); follow-up duration (12 months versus less than 12 months) and asthma severity (mild or moderate versus severe). Supplementary analysis file presents the estimations for control group and intervention group risks, according to the outcomes of interest, as well as the cost-effectiveness estimations for the most relevant findings.

Overall, we found that studies including patients with mild to moderate asthma only, and studies with 12-month follow-up found a more pronounced benefit of literacy interventions in reducing poor asthma control, emergency department visits and hospitalisations.

In the best-case scenario of intervention effectiveness and with outcome costs at the reported upper limit, the intervention affordable budget per patient per year were estimated at: to avoid one patient with poor clinical control, between 223,72€ up to 456,38€ (studies with 12-month follow-up and mild to moderate patients, respectively); to avoid one patient with an emergency department visit, 30,73€ (studies with mild to moderate patients); and to avoid a hospitalisation, 17,24€ (studies with 12-month follow-up).

Regarding potential savings for the Portuguese scenario, by improving clinical control we estimated of up to 217,02€ and 449,68€ per patient per year with the intervention (studies with 12-month follow-up and mild to moderate patients, respectively); by avoiding emergency department visits, up to 24,03€ per patient per year with the intervention (studies with mild to moderate patients); and by avoiding hospitalisations, up to 10,54€ per patient per year with the intervention (studies with 12-month follow-up).

ICER for Portugal at best-case scenario, for each outcome event prevented, were estimated at: 26,80€ and 167,00€ to avoid one patient with poor clinical control (studies with 12-month follow-up and mild to moderate patients, respectively); 13,96€ to avoid an emergency department visit (studies with mild to moderate patients); and 67,00€ to avoid a hospitalisation (studies with 12-month follow-up).



## Chapter 4 - Discussion

To our knowledge, this is the first study in Portugal to estimate the cost-effectiveness of asthma literacy interventions in major clinical outcomes.

After pooling data from all relevant clinical trials, our results show that literacy interventions have a considerable potential benefit when it comes to decreasing the risk of poor clinical control, as well as some potential benefit reducing the risk for emergency room visits and hospitalisations. These benefits were particularly higher in studies including patients with mild to moderate asthma severity (compared to severe ones) (9,12,14) and whose follow-up was longer (at least 12 months) (11–15), although the estimates for the risk for intervention and comparator (usual care) groups were wide and with range values from negative to positive outcome results. According to our cost-effectiveness analysis, in those subgroups of patients, and considering the best-case scenario, literacy interventions may be designed with affordable budgets up to 456,38€; 30,73€ or 17,24€, per patient per year, to improve each outcome of interest (poor clinical control, emergency department visits and hospitalisations, respectively) within cost-effectiveness limits. Also, considering the intervention costs designed for Portugal (yearly sessions with a doctor/nurse for literacy education), for those subgroups of patients, it may generate savings up to 449,68€ per patient per year, by improving clinical control, up to 24,03€ per patient per year, by avoiding emergency department visits; and up to 10,54€ per patient per year with the intervention, by avoiding hospitalisation).

However, in the sensitivity analysis, and considering all patients included in the selected trials (which includes severe asthma and short follow-ups), the worst-case scenario reveals negative estimations for all outcomes of interest. This is particularly relevant, and can be explained by the fact that mild to moderate asthma patients are less presumed to experience an exacerbation or loss of symptom control. Those patients are, thus, more likely to benefit clinically with the interventions, whereas in patients with severe asthma, it might not be enough to only invest in health literacy. Many external factors may be involved in asthma control in severe patients. Some key examples are the older age (associated with global frailty) (16–18), comorbidities (such as diabetes mellitus, obstructive sleep apnea, obesity, COPD, rhinitis, depression, congestive heart failure, etc). All those are associated with higher severity of the disease and increased risk for exacerbations (19–26), but were not fully evaluated and controlled in clinical trials, since none of them was double-blinded. Also, trials with short follow-up (less than 12 months) may have failed to evaluate some of the

outcomes realistically, such as the risk of hospitalisation and the need to use medication during exacerbations (8–10).

Literacy in respiratory diseases is a complex phenomenon, that significantly exceeds mere patients' health education, and includes other crucial aspects, such as medication adherence and compliance, good inhaler technique and disease self-management strategies, namely regarding treatment adjustments whenever needed, symptom control, trigger avoidances, etc (24,27).

Health literacy also requires the capacity of the patients to apply this knowledge daily, to benefit the most out of it when it comes to their health. However, that can be influenced by cultural factors, beliefs, myths, relationships, socioeconomic and educational levels or even the time availability of the patient (28,29). This means that literacy interventions may not be as effective at preventing exacerbation, emergency rooms visits and hospitalisations as at improving symptoms and clinical control.

Accordini S et al (30) performed a study where they evaluated the correlation between the economic cost and severity of asthma in 11 European countries (Belgium, Estonia, France, Germany, Iceland, Italy, Norway, Spain, Sweden, Switzerland and United Kingdom). The authors found that the estimated mean total cost per adult patient was 1.583€, where 37,5% of this value was due to direct costs, of which 53,1% corresponded to costs associated with pharmacological treatment and the use of hospital services was responsible for 25,0%. The expected total cost of asthma in patients aged 30–54 years of the 11 countries was 4.3€ billion, values that quickly rise to 7.9€ billion if the sample considered is extended to 15-64 years, and even to 19.3€ billion if we consider all the European nations. This is particularly relevant, considering that, for instance, the mean cost of an emergency department visits per year in Portugal, according to Barbosa JP et al (5), is 46,29€ (2010), whereas in the study carried out by Accordini S et al (30), in the rest of the Europe, ranges from 19€ to 44€, with a mean value of 27€ (2012). Accordini S et al (30) also found that the mean total cost per patient was inversely proportional to the degree of disease control: yearly, values ranged from 509€ (95% CI: 366–675) in controlled patients to 702€ (95% CI: 412–1.112) among partly controlled patients to 2.281€ (95% CI: 1.702– 2.983) in uncontrolled patients. In Portugal, these values are slightly lower, ranging from 425,44€ in controlled patients to 894,86€ in uncontrolled patients, with the total mean being 708,16€ (5).

In the study carried out by Accordini S et al (30), other determinants were found to increase the costs related to asthma, such as chronic symptoms and overweight, which supports the

rationale we previously mentioned to explain our sub-group analysis. They found, however, positive results regarding literacy interventions in more severe patients, contrary to our findings, but that may be due to other external factors, such as comorbidities, which deserves future research.

Another relevant aspect is that our results may not apply to the most vulnerable populations, such as children and elderly, where the costs associated to adverse outcomes may be higher, due to drug interactions and comorbidities, for example (929,35€ in children vs 708,16€ in adults) (17,31). The benefit of literacy interventions in these vulnerable populations may also be higher, particularly in children, comparing to adults and adolescents. Parents' health literacy is proven to be related to the outcomes in their children's asthma: parents with low health literacy seem to have children with poorer clinical control, higher asthma severity, increased use of healthcare resources, such as emergency department visits, hospitalisations and receiving care from a specialist, and less disease prevention (32–34). In addition, other studies assessing children's health literacy revealed that higher reading abilities are less related to emergency visits (32). Bearing that in mind, we may consider the potential cost-effectiveness in these cases, as long as families recognise the importance of adhering and complying with the recommendations given by the healthcare provider (33). When it comes to older people, the context is similar. The health literacy of older-age patients is more likely to be low (28), which leads to poor outcomes similar to what is seen in children, as already mentioned: low health literacy patients are more likely to report asthma-related hospitalisations, emergency department visits and, consequently, worse quality of life (33,35).

There are some other limitations in our study: it only evaluates direct costs, excluding the indirect costs; it does not assess the impact on quality of life and impairment, particularly in Quality-Adjusted Life Years (QALY), which would be a valuable cost-utility analysis. Lastly, the heterogeneity of the trials, mostly in terms of interventions given to the patients, the low sample size and the short follow-up in some trials, could have introduced some biases, contributing for the wide range of plausible values found in our sensitivity analysis, and thus, lowering the confidence of our findings.

Future studies may be designed to assess the real efficacy of literacy interventions in different subsets of patients, such as children, old-age patients, and more severe ones. However, it is important to standardise the different intervention types found, as well as to properly control for potential confounders that may affect the final results, such as

comorbidities of other patient's related and phenotypic features. Finally, studies assessing indirect costs are also needed, as they play a relevant role in total asthma related costs.

## **Chapter 5 - Conclusion**

According to the Portuguese costs and the designed intervention scenario, health literacy interventions have potential to be cost-effective at reducing costs associated with poor clinical control, as well as in reduction of emergency department visits or hospitalisations in Portuguese adults. This potential is more pronounced in patients with mild to moderate asthma severity and with timeframes of at least 12 months, whereas in patients with severe asthma, health literacy interventions may not be enough to achieve significant risk reductions and being cost-effective.

Future studies are warranted to assess the real efficacy of health literacy interventions in children, old-age patients, and patients with severe asthma.



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