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Symptoms of anxiety and depression in patients with persistent asthma: agreement between HADS and EQ-5D

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Complete List of Authors:	<p>Simões Cunha, Mafalda; CINTESIS Amaral, Rita; University of Porto, CINTESIS; Faculty of Medicine of University of Porto, Portugal Pereira, A. M.; CUF-Porto Hospital and Institute, Immunoallergy; CINTESIS Almeida, Rute; CINTESIS, MEDCIDS Alves-Correia, Magna; CINTESIS; Hospital CUF, Allergy Unit Loureiro, Cláudia Chaves; Coimbra University Hospital,, Pneumology Lopes, Cristina; FMUP, Basic and Clinic Immunology; Hospital Pedro Hispano, immuno-allergy Carvalho, Joana; Unidade Local de Saúde de Matosinhos EPE, Serviço de Pediatria Ribeiro, Carmelita; Centro Hospitalar e Universitário de Coimbra EPE, Serviço de Imunoalergologia, Hospital Universitário de Coimbra Vidal, Carmen; Complejo Hospitalario Universitario, Department of Medicine Antolín-Amérigo, Dario; Hospital Universitario Ramón y Cajal, Servicio de Alergia Pinto, Diana; Centro Hospitalar Universitário do Porto EPE Centro Materno-Infantil do Norte Dr Albino Aroso, Serviço de Pediatria Ferreira-Magalhães, Manuel; CINTESIS, MEDCIDS; Centro Hospitalar Universitário do Porto EPE Centro Materno-Infantil do Norte Dr Albino Aroso, Serviço de pediatria Vasconcelos, Maria João; Hospital São João, immuno-allergy Lozoya, Carlos ; Hospital Amato Lusitano, Allergy Santos, Natacha; Centro Hospitalar do Algarve EPE, immuno-allergy Cardia , Francisca; Unidade de Saúde Familiar Terras de Azurara Taborda-Barata, Luís; CICS - Health Sciences Research Centre; NuESA - Environment & Health Study Group, Faculty of Health Sciences, University of Beira Interior; Department of Allergy & Clinical Immunology, Cova da Beira University Hospital Centre Ferreira, Rosário ; Centro Hospitalar de Lisboa Norte, Serviço de Pediatria Morais Silva, Pedro ; Grupo HPA Saúde, Immuno-Allergy Ferreira, Tania; Agrupamento de Centros de Saúde Baixo Mondego Câmara, Raquel; Centro Hospitalar Barreiro Montijo EPE Silva, Eurico; Agrupamento de Centros de Saúde de Baixo Vouga Bordalo, Diana; Centro Hospitalar do Médio Ave EPE, Serviço de Pediatria Guimarães , Cristina; Agrupamento de Centros de Saúde Pinhal Litoral Calix, Maria José; Centro Hospitalar Tondela Viseu EPE da Silva, Sofia; Unidade Local de Saúde do Alto Minho EPE</p>

	<p>Marques, Maria; Senhora da Oliveira Hospital Guimaraes, Serviço de Imunoalergologia</p> <p>Morete, Ana; Hospital CUF, Allergy Unit; Baixo Vouga Hospital Centre</p> <p>Nunes, Carlos; Centro de Imunoalergologia do Algarve</p> <p>Vieira, Cláudia; Agrupamento de Centros de Saúde Douro I - Marão e Douro Norte</p> <p>Páscoa, Rosália; Faculty of Medicine, University of Porto, Department of Community Medicine, Information and Health Decision Sciences (MEDCIDS) and Centre for Health Technology and Services Research (CINTESIS), University of Porto, Porto, Portugal.</p> <p>Alves, Adelaide; Vila Nova de Gaia Espinho Hospital Center, Serviço de Pneumologia</p> <p>Marques, José ; Agrupamento de Centros de Saúde do Dão Lafões</p> <p>Reis, Bruno; Agrupamento de Centros de Saúde Pinhal Litoral</p> <p>Monteiro, Luís; CINTESIS, ; USF Esgueira +,</p> <p>Monteiro, Rosário; CINTESIS, MEDCIDS; ACeS Porto Ocidental</p> <p>Cepa, Margarida; ACES Pinhal Litoral</p> <p>Valentim, Bruno; ACES Baixo Mondego</p> <p>Coelho, Daniela; ACES Tâmega I - Baixo Tâmega</p> <p>Fernandes, Sara; ACES Cávado I</p> <p>Meireles, Patrícia; ACES Douro II - Douro Sul</p> <p>Aguiar, Margarida; ACES Grande Porto III - Maia / Valongo</p> <p>Mourão, Ana; ACES Grande Porto VIII - Espinho / Gaia</p> <p>Fonseca, Joao A.; CINTESIS, MEDCIDS; Instituto and Hospital CUF, Allergy Unit</p> <p>Jácome, Cristina; University of Porto, Faculty of Medicine</p>
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1 **Title**2 **Symptoms of anxiety and depression in patients with persistent**3 **asthma: agreement between HADS and EQ-5D**

4 Mafalda Simões Cunha 1; Rita Amaral 2,3,4,5; Ana Margarida Pereira 1,2,6; Rute Almeida 3; Magna
 5 Alves-Correia M 1,2; Cláudia Chaves-Loureiro 7; Cristina Lopes 8,9; Joana Carvalho 10; Carmelita
 6 Ribeiro 11; Carmen Vidal 12, Darío Antolín-Amérigo 13, Diana Pinto 14; Manuel Ferreira-Magalhães
 7 3,14; Maria João Vasconcelos 15; Carlos Lozoya 16; Natacha Santos 17; Francisca Cardia 18; Luís
 8 Taborda-Barata 19,20; Rosário Ferreira 21; Pedro Morais Silva 22; Tania Monteiro Ferreira 23; Raquel
 9 Camara 24; Eurico Silva 25; Diana Bordalo 26; Cristina Guimarães 27; Maria José Cálix 28; Sofia da Silva
 10 29; Maria Luís Marques 30; Ana Morete 2, 31; Carlos Nunes 32; Cláudia Vieira 33; Rosália Páscoa
 11 1,6,34; Adelaide Alves 35; José Varanda Marques 36; Bruno Reis 37; Luís Monteiro 1,38; Rosário
 12 Monteiro 3,34; Margarida Cepa 39; Bruno Valentim 40; Daniela Sousa Coelho 41; Sara Fernandes 42;
 13 Patrícia Meireles 43; Margarida Abreu Aguiar 44; Ana Rita Mourão 45; João Almeida Fonseca 2,3,46;
 14 Cristina Jácome 3, INSPIRERS group

- 15 1. Center for Health Technology and Services Research (CINTESIS), Faculty of Medicine, University
 16 of Porto, Porto , PT
- 17 2. Allergy Unit, Instituto and Hospital CUF , Porto , PT
- 18 3. CINTESIS@RISE, MEDCIDS, Faculty of Medicine of the University of Porto, Porto, Portugal
- 19 4. Department of Cardiovascular and Respiratory Sciences, Porto Health School, Polytechnic
 20 Institute of Porto, Porto , PT
- 21 5. Department of Women's and Children's Health, Paediatric Research, Uppsala
 22 University, Uppsala , SE
- 23 6. Department of Community Medicine, Information and Health Decision Sciences
 24 (MEDCIDS), Faculty of Medicine, University of Porto, Porto , PT
- 25 7. Pulmonology Department, Hospitais da Universidade de Coimbra, Centro Hospitalar e
 26 Universitário de Coimbra, Coimbra, Portugal; Clinical Academic Center of Coimbra, Portugal.
- 27 8. Imunologia Básica e Clínica, Faculdade de Medicina, Universidade do Porto, Porto , PT
- 28 9. Unidade de Imunoalergologia, Hospital Pedro Hispano, Unidade Local de Saúde de
 29 Matosinhos, Matosinhos , PT
- 30 10. Serviço de Pediatria, Hospital Pedro Hispano, Unidade Local de Saúde de
 31 Matosinhos, Matosinhos , PT
- 32 11. Serviço de Imunoalergologia, Centro Hospitalar e Universitário de Coimbra , Coimbra , PT
- 33 12. Servicio de Alergia, Complejo Hospitalario Universitario de Santiago, Santiago de Compostela,
 34 Spain
- 35 13. Servicio de Alergia, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación
 36 Sanitaria, Madrid, Spain
- 37 14. Serviço de Pediatria, Centro Materno Infantil do Norte, Centro Hospitalar Universitário do
 38 Porto, Porto , PT
- 39 15. Serviço de Imunoalergologia, Centro Hospitalar Universitário de São João , Porto , PT
- 40 16. Serviço de Imunoalergologia, Hospital Amato Lusitano, Unidade Local de Saúde de Castelo
 41 Branco, Castelo Branco , PT
- 42 17. Serviço de Imunoalergologia, Centro Hospitalar Universitário do Algarve , Portimão , PT
- 43 18. Unidade de Saúde Familiar Terras de Azurara, Agrupamento de Centros de Saúde Dão
 44 Lafões , Mangualde , PT
- 45 19. Department of Allergy & Clinical Immunology, Cova da Beira University Hospital
 46 Centre , Covilhã , PT

- 1
2
3 47 20. CICS-UBI Centro de Investigação em Ciências da Saúde - Health Sciences Research Centre &
4 48 UBI Air – Clinical & Experimental Lung Centre, University of Beira Interior, Covilhã , PT
5 49 21. Departamento de Pediatria, Hospital de Santa Maria, Centro Hospitalar de Lisboa Norte, Lisboa,
6 50 PT
7 51 22. Imunoalergologia, Grupo HPA Saúde , Portimão , PT
8 52 23. Unidade de Saúde Familiar Progresso e Saúde, Agrupamento de Centros de Saúde Baixo
9 53 Mondego , Tocha , PT
10 54 24. Serviço de Pneumologia, Hospital Nossa Senhora do Rosário, Centro Hospitalar Barreiro
11 55 Montijo, Barreiro , PT
12 56 25. Unidade de Saúde Familiar João Semana, Agrupamento de Centros de Saúde Baixo
13 57 Vouga , Ovar , PT
14 58 26. Serviço de Pediatria, Unidade Hospitalar de Famalicão, Centro Hospitalar do Médio Ave, Vila
15 59 Nova de Famalicão , PT
16 60 27. Unidade de Cuidados de Saúde Personalizados Norte (Arnaldo Sampaio), Agrupamento de
17 61 Centros de Saúde Pinhal Litoral, Monte Redondo, PT
18 62 28. Serviço de Pediatria, Hospital de São Teotónio, Centro Hospitalar Tondela–Viseu, Viseu , PT
19 63 29. Unidade de Saúde Familiar Cuidarte, Unidade Local de Saúde do Alto Minho , Portuzelo , PT
20 64 30. Serviço de Imunoalergologia, Hospital da Senhora da Oliveira, Guimarães, PT
21 65 31. Serviço de Imunoalergologia, Hospital Infante D Pedro, Centro Hospitalar Baixo
22 66 Vouga, Aveiro , PT
23 67 32. Imunoalergologia, Centro de Imunoalergologia do Algarve , Portimão , PT
24 68 33. Unidade de Saúde Familiar Corgo, Agrupamentos de Centros de Saúde Douro I - Marão e Douro
25 69 Norte , Vila Real , PT
26 70 34. Unidade de Saúde Familiar Homem do Leme, ACeS Porto Ocidental, Porto, Portugal
27 71 35. Serviço de Pneumologia, Unidade I, Centro Hospitalar Vila Nova de Gaia/Espinho, Vila Nova de
28 72 Gaia , PT
29 73 36. Unidade de Saúde Familiar Viseu-Cidade, Agrupamento de Centros de Saúde do Dão
30 74 Lafões , Viseu , PT
31 75 37. Unidade de Cuidados Saúde Personalizados Sicó, Agrupamento de Centros de Saúde Pinhal
32 76 Litoral , Leiria , PT
33 77 38. Unidade de Saúde Familiar Esgueira+, ACES Baixo Vouga, Esgueira, Portugal
34 78 39. Unidade de Saúde Familiar Marquês, ACES Pinhal Litoral, Pombal, Portugal
35 79 40. Unidade de Saúde Familiar Condeixa, ACES Baixo Mondego, Condeixa-a-Nova, Portugal
36 80 41. Unidade de Cuidados de Saúde Personalizados de Amarante, ACES Tâmega I – Baixo Tâmega,
37 81 Amarante, Portugal
38 82 42. Unidade de Saúde Familiar Bracara Augusta, ACES Cávado I – Braga, Braga, Portugal
39 83 43. Unidade de Saúde Familiar Almedina, ACES Douro II - Douro Sul, Lamego, Portugal
40 84 44. Unidade de Saúde Familiar Valongo, ACES Grande Porto III - Maia / Valongo, Valongo, Portugal
41 85 45. Unidade de Saúde Familiar Canelas, ACES Grande Porto VIII - Espinho / Gaia, Vila Nova Gaia,
42 86 Portugal
43 87 46. MEDIDA – Medicina, Educação, Investigação, Desenvolvimento e Avaliação, Porto, Portugal
44 88

48 89 **Corresponding author:** Cristina Jácome, Center for Health Technology and Services Research

49 90 (CINTESIS), Department of Community Medicine, Information and Health Decision Sciences

50 91 (MEDCIDS), Faculty of Medicine, University of Porto, Portugal; e-mail:

51 92 cristinajacome.ft@gmail.com

52 93

94 **Abstract**

95 **Objectives:** Anxiety and depression are relevant comorbidities in asthma, but, in
96 Portugal and Spain, data on this topic are scarce. We assessed, in patients with asthma, the
97 frequency of anxiety and depression using the Hospital Anxiety and Depression Scale (HADS)
98 and the European Quality of Life Five Dimension Questionnaire (EQ-5D); the level of
99 agreement between these questionnaires, and the factors associated with these symptoms.

100 **Methods:** This is a secondary analysis of the INSPIRERS studies. A total of 614
101 adolescents and adults with persistent asthma (32.6 ± 16.9 y, 64.7% female) were recruited
102 from 30 primary care centres and 32 allergy, pulmonology and pediatric clinics. Demographic
103 and clinical characteristics, HADS and EQ-5D were collected. A score ≥ 8 on HADS-A/HADS-D
104 or a positive answer to EQ-5D item 5 indicated the presence of these symptoms. Agreement
105 was determined by Cohen's kappa. Two multivariable logistic regressions were built.

106 **Results:** According to HADS, 36% of the participants had symptoms of anxiety and 12%
107 of depression. According to EQ-5D, 36% of the participants had anxiety/depression. The
108 agreement between questionnaires in identifying anxiety/depression was moderate ($k=0.55$,
109 95%CI 0.48-0.62). Late asthma diagnosis, comorbidities and female gender were predictors
110 of anxiety/depression, while better asthma control, health-related quality of life and
111 perception of health were associated with lower odds for anxiety/depression.

112 **Conclusion:** At least 1/3 of the patients with persistent asthma experience symptoms
113 of anxiety/depression, showing the relevance of screening these disorders in patients with
114 asthma. Our results support the complementary use of these questionnaires.

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4 116 **Strengths and limitations of this study**
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7 117 This study is a secondary analysis of a multicentric study that recruited both adults and
8
9 118 adolescents with asthma from primary and secondary care.
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12 119 A comprehensive set of individual-level characteristics was analysed, which allowed us to
13
14 120 explore the impact of sociodemographic factors and cofactors such as quality of life and
15
16 121 asthma control on the presence of anxiety/depression symptoms.
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20 122 A possible source of bias was the recruitment strategy based on convenience sampling.
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22

23 123 The frequency of distressing symptoms and the relationships with associated factors could
24
25 124 not be established overtime.
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28
29 125 **Word count:** 3094
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35 127 **Key Words:** Asthma; Anxiety Disorders; Anxiety Disorders/epidemiology; Depression
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37 128 Disorder; Depressive Disorder/epidemiology; Surveys and Questionnaires;
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39 129 Portugal/epidemiology; Spain/epidemiology.
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131 **Introduction**

132 Asthma affects approximately 300 million people worldwide [1]. In Portugal, asthma
133 affects 695 000 Portuguese, with a general prevalence of 6.8% [2]. In Spain, asthma affects
134 more than three million people, with an estimated prevalence of 5% in adults [3]. Asthma is
135 primarily related to chronic inflammation of the lower respiratory tract, variable airflow
136 obstruction, and bronchial hyperresponsiveness [4]. Yet, this disease is often accompanied by
137 multiple associated comorbidities, such as chronic rhinosinusitis, nasal polyposis, allergic
138 rhinitis, gastroesophageal reflux disease, obstructive sleep apnea syndrome [5], and also
139 anxiety and depression.

140 In two systematic reviews, the average of the reported prevalence of any anxiety
141 disorder among patients with asthma was 24% [6] and 34% [7]. Regarding depression, a
142 pragmatic literature review found that 1% to 45% of patients with asthma suffer from
143 depression or depressive symptoms [8]. In severe asthma, a study reported an average
144 prevalence of 27% for emotional distress (mainly due to anxiety and depression) [9].
145 Currently, most studies about emotional distress focus essentially on adult patients with more
146 severe asthma [10]. There is a lack of data regarding other asthma sub-groups, namely
147 adolescents and those with mild or moderate persistent asthma.

148 Anxiety and depression are associated with significantly lower quality of life, poor
149 asthma control, higher frequency of exacerbations and increased use of healthcare resources
150 [11]. Moreover, anxiety is associated with greater perceived dyspnea intensity and may shape
151 the quality and intensity of this symptom at a given respiratory load [12]. However, it is still
152 uncertain whether other factors can affect the patient's psychological state. It is important to
153 have a more sophisticated understanding of the interplay between emotional distress and
154 asthma [13].

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3 155 Despite these negative impacts, anxiety and depression in patients with asthma is not
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5
6 156 routinely assessed during clinical visits and thus there is a lack of information about its real-
7
8 157 world frequency. One of the most used tools for psychological screening is the Hospital
9
10 158 Anxiety and Depression Scale (HADS). HADS is a self-report questionnaire designed to screen
11
12
13 159 anxiety and depression symptoms [14] and it was already used in adolescents and adults with
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15 160 asthma in previous studies [15, 16]. However, this scale has 14 items and although it takes
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17
18 161 around 5 minutes to complete [17], it is not always feasible to administer in a busy clinic
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20 162 setting [18, 19]. European Quality of Life Five Dimension Questionnaire (EQ-5D) is a generic
21
22
23 163 measure of health status that provides a simple descriptive profile and a single index value
24
25 164 that can be used for the clinical and economic evaluation of healthcare [20], but also
26
27
28 165 emotional distress screening [21]. Currently, EQ-5D is being widely used in a variety of
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30 166 conditions, where asthma is integrated [22]. Some studies compared HADS and EQ-5D in
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32
33 167 patients with other diseases and showed that EQ-5D can be responsive to different degrees
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35 168 of HADS-assessed distress [23]. Yet, there is no published data comparing HADS and EQ-5D in
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38 169 patients with asthma.

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40 170 With the present study, we aimed to assess i) the frequency of symptoms of anxiety
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42 171 and depression in patients with asthma as assessed by HADS and EQ-5D questionnaires; ii)
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44
45 172 the level of agreement between the two questionnaires and iii) the factors associated with
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47
48 173 the presence of these symptoms

49 174 **Methods**

50 175 **Patient and public involvement**

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53
54
55 176 No patient involved

56 57 58 177 **Study design**

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3 178 Data from the baseline face-to-face visit from 5 prospective observational studies of
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6 179 the INSPIRERS project were analysed [24]. This project addresses the topic of adherence to
7
8 180 asthma inhalers among adolescents and adults with persistent asthma. Convenience samples
9
10
11 181 were recruited between November 2017 and October 2020 at 32 allergy, pulmonology and
12
13 182 paediatric secondary care outpatient clinics (30 from Portugal and 2 from Spain) and 30
14
15 183 primary care centres from Portugal. The studies were approved by the ethics committees of
16
17
18 184 all participating centres. Eligible patients were approached by physicians during medical visits.
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20
21 185 Adult patients signed a consent form. Adolescents signed an assent form, and a parental
22
23 186 consent form was also obtained. The studies had similar inclusion criteria and methods. The
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25 187 study is reported according to Strengthening the Reporting of Observational Studies in
26
27
28 188 Epidemiology (STROBE) guidelines [25].

30 189 **Patients**

31
32
33 190 Patients were included in the analysis if they had a previous medical diagnosis of
34
35 191 persistent asthma, were at least 13 years old (13–17 years adolescents; ≥ 18 years adults) and
36
37
38 192 had an active prescription for an inhaled controller medication for asthma. All inhaled
39
40 193 controller treatments were allowed, and there was no change in any prescribed medication
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42
43 194 regarding the participation in these studies. Patients were excluded if they had a diagnosis of
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45 195 a chronic lung disease other than asthma or a diagnosis of another significant chronic
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47
48 196 condition with possible interference with the study aims.

50 197 **Data collection**

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52
53 198 During the baseline face-to-face visit, data were collected from both physicians and
54
55 199 patients. Physicians answered a questionnaire including the Global Initiative for Asthma
56
57
58 200 (GINA) assessment of symptom control [25], the asthma treatment plan and comorbidities.
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3 201 Information about the healthcare setting (primary, secondary) was obtained based on the
4
5
6 202 centre where patients were recruited.
7

8 203 Demographic data (age, gender, educational level, marital status and current
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10 204 occupation) and clinical data (weight, height, smoking habits, and age of asthma diagnosis)
11
12
13 205 were collected from patients. Asthma control was also assessed using the Control of Allergic
14
15 206 Rhinitis and Asthma Test (CARAT). CARAT is a self-report questionnaire with a total score
16
17
18 207 (CARAT-T) calculated by summing up the score of each of the 10 questions, resulting in a range
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20 208 of 0–30 points. A score >24 indicates good disease control [26].
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22

23 209 The Portuguese version of the Hospital Anxiety and Depression Scale (HADS) was used
24
25 210 to assess the presence of symptoms of anxiety and depression [27]. HADS contains 14 items
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27
28 211 related to the past week, 7 of which assess anxiety symptoms (HADS-A) and the other 7
29
30 212 depression symptoms (HADS-D). HADS-A and HADS-D are scored separately. The item
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32
33 213 response scale varies between 0 and 3 points, with total scores ranging from 0 (minimum
34
35 214 symptomatic load) up to 21 (maximum symptomatic load) for HADS-A and HADS-D. A score
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37 215 ≥ 8 on HADS-A or HADS-D was considered as the presence of symptoms of anxiety or
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40 216 depression, respectively [28].
41

42 217 The European Quality of Life Five Dimension Questionnaire (EQ-5D) three-level
43
44
45 218 version was filled in by the patients to assess their overall quality of life. The item 5 “Anxiety
46
47 219 and Depression” could be a useful tool in screening for anxiety and depressive symptoms in
48
49
50 220 hospital and community settings [29]. Therefore, this item, with its 3 response options (“I am
51
52 221 not anxious or depressed”, “I am moderately anxious or depressed”, “I am extremely anxious
53
54 222 or depressed”) was additionally used to assess the presence of these symptoms [30]. Patients
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56
57 223 were considered to have anxiety/depression when answering “I am moderately anxious or
58
59 224 depressed” or “I am extremely anxious or depressed”. The EQ-5D summary index score was
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1
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3 225 calculated to characterize the sample. It ranges from less than 0 (where 0 is a health state
4
5 226 equivalent to death) to 1 (perfect health) [31]. The EQ-5D VAS was also used to assess
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8 227 patients' perception of their general health (from 0 'the worst health you can imagine' to 100
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10 228 'the best health you can imagine').

13 229 **Statistical Analyses**

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16 230 Descriptive statistics were used to characterize the sociodemographic variables,
17
18 231 clinical characteristics, the HADS score and EQ-5D responses. Absolute and relative
19
20 232 frequencies were used to characterize the categorical variables. Means and standard
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22
23 233 deviations or medians and interquartile ranges were used, according to data distribution, to
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25 234 characterize the numerical variables.

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27
28 235 To determine the agreement between HADS and EQ-5D questionnaires for the
29
30 236 presence of symptoms of anxiety/depression, the percentage of agreement and weighted
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33 237 Cohen's kappa were used. Cohen's kappa values were interpreted as follows: <0, no
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35 238 agreement; 0–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial and
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37
38 239 0.81–1.0, almost perfect agreement [32].

39
40 240 To explore associations between variables related to the presence of symptoms of
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42 241 anxiety and depression, patients with and without symptoms of anxiety and depression were
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45 242 compared using independent t-tests for normally distributed data, Mann-Whitney U tests for
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47 243 non-normally distributed continuous data and ordinal data, and Chi-square tests for
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49
50 244 categorical data. In the case of Chi-square tests, when a statistically significant difference was
51
52 245 found for a categorical variable with more than two categories, chi-square multiple
53
54
55 246 comparison tests with Bonferroni correction were performed to explore which categories
56
57 247 differed from each other. The variables that were statistically different ($p < 0.05$) between the
58
59 248 two groups were selected to further explore their relationship with the presence of anxiety

249 and depression and to adjust for possible confounders in two stepwise multivariable logistic
 250 regression models. The dependent variable in each multivariable logistic regression was the
 251 presence of symptoms of anxiety or depression based on HADS (0 = absent, 1 = present). The
 252 overall models were evaluated using the goodness-of-fit tests and Nagelkerke's R-square and
 253 the final model was selected based on the best combination of these results. The level of
 254 significance considered was 0.05. Statistical analyses were performed using IBM SPSS
 255 Statistics version 26.0 (IBM Corporation, Armonk, NY, USA).

256 **Results**

257 **Patient's Characteristics**

258 A total of 614 participants with asthma (mean age 32.6 ± 16.9 years) were included in
 259 this study. There were 447 (72.8%) adults and 397 (64.7%) females. Forty percent of the
 260 participants had completed primary school (n=244), 47.4% were employed (n=289) and 65.1%
 261 were prescribed only 1 inhaler (n=396). According to the GINA assessment of symptom
 262 control, 296 (48.7%) patients had well controlled asthma. Table 1 shows the socio-
 263 demographic and clinical characteristics of the study participants.

264 TABLE 1. Socio-demographic and clinical characteristics of the participants (n=614).

Characteristics	
Age (years) M \pm SD ^a	32.6 \pm 16.9
Age group n (%)	
Adolescent	167 (27.2)
Adult	447 (72.8)
Gender n (%)	
Female	397 (64.7)
Male	217 (35.3)
Educational level n (%)^b	
No education completed	4 (0.7)
Primary school	244 (40.4)
High school	177 (29.3)

Qualification above high school (but not university)	23 (3.8)
University	156 (25.4)
Other	1 (0.2)
Marital status n (%)^c	
Single	348 (56.7)
Married/Living as a couple	223 (36.3)
Separated/divorced	33 (5.4)
Widowed	9 (1.5)
Current occupation n (%)^d	
Employed	289 (47.1)
Student	235 (38.3)
Unemployed	41 (6.7)
Retired	36 (5.9)
Other	9 (1.5)
BMI Kg/m², M ± SD^e	24.7 (5.3)
Smoking Status n (%)^d	
Never smoker	457 (74.4)
Ex-smoker	106 (17.3)
Current smoker	47 (7.7)
Setting	
Secondary care	475 (77.4)
Primary care	139 (22.6)
Age of asthma diagnosis (years) M ± SD^f	16.2 ± 14.8
Number of prescribed inhalers n (%)^g	
1	396 (64.5)
2	193 (31.4)
≥3	19 (3.1)
GINA assessment symptom control n (%)^g	
Well controlled	296 (48.2)
Partly controlled	188 (30.6)
Uncontrolled	124 (20.2)
Number of physician-reported comorbidities Median (P25-P75)	1 [0-2]
CARAT-T Median (P25-P75)	21 [16-25]
CARAT-T Classification	
Controlled n (%)	156 (25.4)
Uncontrolled n (%)	458 (74.6)
EQ-5D-3L Median (P25-P75)	
Total	0.91 [0.81-1.0]
VAS	80.0 [70.0-90.0]

M = Mean; SD= Standard Deviation; BMI=body mass index; GINA = Global Initiative for Asthma; P25= 25th percentile; P75= 75th percentile; CARAT-T=Control of Allergic Rhinitis and Asthma Test total score; EQ-5D-3L= European Quality of Life Five Dimension Questionnaire-three-level version; VAS= Visual analogue scale.

^a 8 missing values. ^b 9 missing values. ^c missing value. ^d 4 missing values. ^e 28 missing values. ^f 22 missing values. ^g 6 missing values.

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270 **Symptoms of anxiety and depression**

271 According to HADS, 221 (36.0%) participants had symptoms of anxiety, 73 (11.9%) had
272 symptoms of depression, 59 (9.6%) both symptoms and 235 (38.3%) participants had
273 symptoms of anxiety or depression. Both anxiety (41.4% vs 21.6%) and depression (14.1% vs
274 6%) symptoms were more frequent in adults than adolescents. According to EQ-5D, 223
275 (36.3%) participants had anxiety or depression problems, 32.6% were moderately anxious or
276 depressed and 3.7% extremely anxious or depressed. The agreement between these two
277 questionnaires was moderate for anxiety ($k=0.54$ (95%CI 0.47-0.61)); sufficient for depression
278 ($k=0.23$ (95%CI 0.17-0.30)) and moderate for anxiety/depression ($k=0.55$ (95% CI 0.48-0.62)).

279 **Predictors of anxiety and depression**

280 In the multivariable logistic regression (Table 2), being an adolescent (OR 0.43, 95% CI
281 0.27-0.68), having a better asthma control (CARAT-T score) (OR 0.98, 95% CI 0.94-1.00) and a
282 perception of better health (OR 0.97, 95% CI 0.95-0.98) were significantly associated with
283 lower odds for the presence of anxiety symptoms. In contrast, being a female was significantly
284 associated with a higher odd for the presence of anxiety symptoms (OR 1.75, 95% CI 1.56-
285 2.64). Having better health-related quality of life (OR 0.97, 95%CI 0.95-0.99) and perception
286 of better health (OR 0.97, 95% CI 0.96-0.99) were associated with a lower odd for the
287 presence of depression. While asthma diagnosis at a later age (OR 1.03, 95% CI 1.01-1.05) and
288 the presence of a higher number of comorbidities (OR 1.31, 95% CI 1.05-1.64) were associated
289 with an increase in the likelihood of exhibiting symptoms of depression. The univariate
290 analyses are presented in Supplementary Table 1.

291 Table 2 – Multivariable logistic regression analyses to explain anxiety and depression.

	Anxiety	Depression
	adjusted OR (95% CI)*	adjusted OR (95% CI)**
Age group		
Adolescent	0.43 (0.27-0.68)	-
Adult	Reference	-
Gender		
Female	1.75 (1.56-2.64)	-
Male	Reference	-
Age of asthma diagnosis	-	1.03 (1.01-1.05)
Number of physician-reported comorbidities	1.17 (0.99-1.37)	1.31 (1.05-1.64)
CARAT T	0.98 (0.94-1.00)	-
Quality of life (EQ-5D total)	-	0.97 (0.95-0.99)
Perception of better health (EQ-5D VAS)	0.97 (0.95-0.98)	0.97 (0.96-0.99)
R²	22%	23%
Hosmer-Lemeshow test - p-value	.435	.449

292 OR = Odds ratio; CI = Confidence interval; BMI = body mass index; CARAT-T = Control of Allergic Rhinitis and Asthma Test total score; EQ-5D
 293 = European Quality of Life Five Dimension Questionnaire; VAS= Visual analogue scale.

294 *Age, current occupation, setting, age of asthma diagnosis, GINA assessment of symptom control and quality of life (EQ-5D total) were also
 295 tested but not included in the final adjusted model.

296 **Age, age group, educational level, marital status, current occupation, BMI, GINA assessment of symptom control and CARAT T were also
 297 tested but not included in the final adjusted model.

298 Discussion

299 This study showed that more than 1/3 of participants with asthma experienced
 300 symptoms of anxiety and/or depression. Asthma diagnosis at a later age, presence of
 301 comorbidities and female gender were predictors of anxiety/depression, while better asthma
 302 control, health-related quality of life and perception of better health were factors associated
 303 with lower odds for anxiety/depression. In this study, the agreement between HADS and EQ-
 304 5D questionnaires in identifying anxiety and depression was sufficient to moderate.

305 According to HADS and EQ-5D questionnaires, more than 1/3 of the patients with
 306 persistent asthma experience symptoms of anxiety/depression (38.3% and 36.3%
 307 respectively). Therefore, the percentages of participants with one of these symptoms
 308 detected by HADS and EQ-5D were similar. With HADS, it was possible to detect the

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3 309 percentages of patients with persistent asthma that had only symptoms of anxiety (36.0%) or
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6 310 had only symptoms of depression (11.9%). The proportions found in the present study were
7
8 311 similar to the ones found among patients with asthma in previous reviews [7, 8], analysing
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10 312 studies that included only, or mostly, adults with asthma. A study from the UK found similar
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13 313 frequencies of anxiety and depression using HADS, although a slightly higher cut-off has been
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15 314 used (HADS-A/HADS-D \geq 10) [33]. We found a lower frequency for depression as compared
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18 315 with a study in patients with severe asthma, where 25% reported depression [34]. This
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20 316 difference might be explained by the role of poorer physical functioning on symptoms of
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23 317 depression [35]. Patients with severe asthma experience more physical disability. Other
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25 318 studies reported that patients with severe asthma have more often emotional distress as
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28 319 compared to patients with mild-moderate asthma [36, 37].

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31 320 This study includes both adolescents and adults with persistent asthma, which is rarely
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33 321 found in previous articles. However, anxiety and depression were only assessed at one time
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35 322 point. Analysing emotional distress in the long run could be important as suggested in
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38 323 previous cohort studies that followed adolescents with asthma to young adulthood, showing
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40 324 that there was a persistence or recurrence of anxiety and depression in adulthood [38, 39]. In
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43 325 our study, adults with persistent asthma presented an increased frequency of
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45 326 anxiety/depression symptoms (vs adolescents), which is in accordance with a population-
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48 327 based study that reported that having asthma and older age were independent risk factors
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50 328 for the presence of anxiety disorders, in participants above the age of 15 years [40].
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53 329 Therefore, emotional distress seems to be associated with age differences in patients with
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55 330 persistent asthma.

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3 331 Age at asthma onset has emerged as a critical factor in distinguishing the phenotypes
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6 332 of asthma [41]. Adult-onset asthma differs from asthma that first occurs in childhood since it
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8 333 usually is less well controlled, is associated with a faster decline in lung function and with
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10 334 more comorbidities [42, 43]. Moreover, worse asthma control and the presence of more
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12 335 comorbidities might be associated with an increased risk of emotional distress [44]. These
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14 336 results contribute to explaining our finding that asthma diagnosis at a later age and number
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16 337 of physician-reported comorbidities were associated with a higher frequency of depression.
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18 338 Female patients were more likely to have anxiety symptoms. This was previously observed in
19
20 339 other studies in asthma but also other respiratory diseases, such as COPD. Possibly these
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22 340 gender differences are more than a specificity of respiratory diseases, but a reflection of the
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24 341 known gender differences in the general population [45, 46].
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31 342 In our study, the perception of better health was associated with a lower odd for the
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33 343 presence of anxiety symptoms. In a previous study with patients with chronic obstructive
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35 344 pulmonary disease (COPD), the perceived severity of COPD symptoms was predictive of
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37 345 depression and anxiety [47]. These findings are in line with our study, although coming from
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39 346 a different disease. The close correlation between asthma control, quality of life, anxiety, and
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41 347 depression has been also confirmed in other studies [48, 49]. Consequently, in patients with
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43 348 poor asthma control, physicians should ask about the symptoms of anxiety/depression or
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45 349 screen it using simple tools like EQ-5D or HADS before making adjustments on asthma
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47 350 treatment strategy [16].
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53 351 EQ-5D questionnaire is a common generic tool used to evaluate health interventions.
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55 352 This questionnaire could be useful in clinical practice [50]. The EQ-5D anxiety or depression
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57 353 domain had a greater agreement with the HADS score in identifying cases with both
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3 354 symptoms, as expected, than in identifying anxiety or depressive symptoms. In general, the
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6 355 percentages of patients with anxiety/depression detected by HADS and EQ-5D were similar.
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8 356 Furthermore, it is expected that remarkably less time consumption is needed for the EQ-5D
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11 357 item 5 assessment compared with HADS [17, 51]. Therefore, EQ-5D score appears to have
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13 358 value as a screening tool for anxiety or depression in patients with asthma. In a previous
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16 359 study, this questionnaire also seemed to be reasonably valid and moderately responsive in
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18 360 patients with anxiety disorders [52]. This could be important in clinical practice because a
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21 361 generic health instrument like the EQ-5D, with few and quick questions, could be used to
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23 362 easily raise awareness of a possible emotional distress in patients with asthma. A limitation
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25 363 of EQ-5D is that anxiety and depression are two separate emotional disorders and their
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28 364 combination in a single item in this questionnaire could lead to inconsistencies in responses
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30 365 [53]. Nevertheless, EQ-5D could be used as a first screening questionnaire and, in patients
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33 366 reporting anxiety or depression symptoms, a more specific questionnaire, such as HADS,
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35 367 could be used to better characterize their symptoms. Actually, emotional distress screening
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38 368 is very important in clinical practice because physicians can use targeted interventions to
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40 369 improve patients' symptoms. Studies about psychological interventions in adults with asthma
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43 370 suggest that education and simple psychological interventions namely relaxation techniques
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45 371 and biofeedback or a stepped care approach could produce significant positive healthcare
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47 372 outcomes [54, 55].

50 373 This study has some strengths that should be acknowledged: it is a multicentric study
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52
53 374 that recruited both adults and adolescents with asthma from primary and secondary care. A
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55 375 comprehensive set of individual-level characteristics was collected and analysed, which
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58 376 allowed us to explore the impact of a range of sociodemographic factors, health literacy and
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60 377 cofactors such as quality of life and asthma control. Therefore, includes a sample from

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3 378 different health care contexts and with different clinical presentations, contributing to the
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6 379 robustness of these findings.
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9 380 Nevertheless, it also has some limitations. A possible source of bias was the
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11 381 recruitment strategy of using a convenience sampling. Future studies using other sampling
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13 382 strategies could be important to generalise the results of our study. A control group of healthy
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16 383 individuals with similar socio-demographic characteristics should also be included in further
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18 384 research to increase the validity of these findings. In the absence of a control group it would
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21 385 have been useful to compare anxiety/depression frequencies with normative data from
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23 386 Portugal and Spain, but we did not find it neither for HADS nor EQ-5D. Moreover, the impact
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26 387 of the presence of specific comorbidities, such as rhinitis, which is closely associated both
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28 388 with asthma and anxiety/depression, was not assessed [56]. Another limitation of the present
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31 389 study is related to its cross-sectional nature. The frequency of distressing symptoms and the
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33 390 relationships with associated factors could not be established along the progression of the
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36 391 disease. Also, patients were not recruited at the same time point, as recruitment in the
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38 392 Inspirers studies occurred across 4 different years (from 2017 to 2020), and the last 15% of
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41 393 the sample was recruited during COVID-19 pandemic. Longitudinal studies following a cohort
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43 394 of patients with asthma would address these issues and identify other predictors of symptoms
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45 395 of anxiety and depression.
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48 396 This study shows that more than 30% of the patients with persistent asthma
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51 397 experience symptoms of anxiety/depression, which supports the relevance of emotional
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53 398 distress screening in patients with asthma. The study also showed that for screening
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56 399 purposes, it is possible to use either EQ-5D and HADS questionnaires.
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401 **a. Contributorship statement**

402 All authors contributed to the selection of bibliography, revision and final approval of the
403 manuscript. AMP, RA, MAC, RAlmeida, JAF and CJ were responsible for study conception and
404 design; RA, AMP, RAlmeida, MAC, CCL, CL, JC, CR, CV, DAA, DP, MFM, MJV, CLozoya, NS, FC,
405 LTB, RF, PMS, TMF, RC, ES, DB, CG, MJC, SS, MLM, AM, CN, CVieira, RP, AA, JVM, BR, LM, RM,
406 MC, BV, DSC, SF, PM, MAA, ARM, JAF and CJ participated in the data collection; CJ and AMP
407 performed the data analysis and MSC prepared the first draft. All authors contributed to the
408 interpretation of data, to the critical revision of the manuscript for important intellectual
409 content.

410 **b. Competing interests**

411 None

412 **c. Funding**

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417 FEDER-029130).

418 **d. Data sharing statement**

419 The data sets generated during and/or analysed during the current study are not publicly available.

420 **Ethics approval**

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3 421 The studies were approved by the ethics committees of all participating centres. For example, the
4
5 422 study was approved by the Ethics Committee of Centro Hospitalar de S. João—EPE (protocol code 258-
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7 423 17 and date of approval: 5th of January 2018).

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1 Supplementary table 1 – Univariate analyses to explain anxiety and depression symptoms.

	Anxiety	Depression
	crude OR (95% CI)	crude OR (95% CI)
Age	1.02 (1.01-1.03)	1.05 (1.03-1.06)
Age group		
Adolescent	0.39 (0.26-0.59)	0.39 (0.19-0.78)
Adult	Reference	Reference
Gender		
Females	2.44 (1.68-3.53)	1.64 (0.95-2.85)
Males	Reference	Reference
Educational level		
No education completed/Primary school	0.99 (0.71-1.39)	1.67 (1.01-2.74)
High school/Qualification above high school (but not university)/University/Other	Reference	Reference
Marital status		
Single/ Separated/Divorced/Widowed	0.72 (0.52-1.02)	0.45 (0.27-0.74)
Married/Living as a couple	Reference	Reference
Current occupation		
Employed/Student/Other	0.55 (0.35-0.87)	0.25 (0.14-0.43)
Unemployed/Retired	Reference	Reference
BMI	1.03 (0.99-1.06)	1.08 (1.04-1.13)
Smoking status		
Non-smokers	0.56 (0.31-1.02)	0.92 (0.37-2.24)
Smokers	Reference	Reference
Setting		
Primary care	1.60 (1.09-2.35)	1.04 (0.58-1.86)
Secondary care	Reference	Reference
Age of asthma diagnosis	1.02 (1.01-1.03)	1.04 (1.03-1.06)
Number of physician-reported comorbidities	1.32 (1.14-1.53)	1.55 (1.29-1.87)
Number of prescribed inhalers	1.29 (0.97-1.71)	1.29 (0.87-1.91)
GINA assessment symptom control		
Well controlled	0.61 (0.44-0.85)	0.51 (0.30-0.85)
Partly controlled/Uncontrolled	Reference	Reference
CARAT T	0.93 (0.91-0.96)	0.91 (0.88-0.95)
Quality of life (EQ-5D total)	0.94 (0.92-0.95)	0.94 (0.93-0.96)
Perception of better health (EQ-5D VAS)	0.96 (0.95-0.97)	0.96 (0.95-0.97)

2 OR = Odds ratio; CI= Confidence interval; BMI=body mass index; GINA = Global Initiative for Asthma; CARAT-T=Control of Allergic Rhinitis
3 and Asthma Test total score; EQ-5D= European Quality of Life Five Dimension Questionnaire.

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	3 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	8 NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	10 10 10 NA NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	11 NA NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	11, table 1 Table 1 NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
2			(b) Report category boundaries when continuous variables were categorized	11-12
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
4	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
5	Discussion			
6	Key results	18	Summarise key results with reference to study objectives	12
7	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
8	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-15
9	Generalisability	21	Discuss the generalisability (external validity) of the study results	16
10	Other information			
11	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	4

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

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Symptoms of anxiety and depression in patients with persistent asthma: a cross-sectional analysis of the INSPIRERS studies

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Complete List of Authors:	<p>Simões Cunha, Mafalda; CINTESIS Amaral, Rita; University of Porto, CINTESIS; Faculty of Medicine of University of Porto, Portugal Pereira, A. M.; CUF-Porto Hospital and Institute, Immunoallergy; CINTESIS Almeida, Rute; CINTESIS, MEDCIDS Alves-Correia, Magna; CINTESIS; Hospital CUF, Allergy Unit Loureiro, Cláudia Chaves; Coimbra University Hospital,, Pneumology Lopes, Cristina; FMUP, Basic and Clinic Immunology; Hospital Pedro Hispano, immuno-allergy Carvalho, Joana; Unidade Local de Saúde de Matosinhos EPE, Serviço de Pediatria Ribeiro, Carmelita; Centro Hospitalar e Universitário de Coimbra EPE, Serviço de Imunoalergologia, Hospital Universitário de Coimbra Vidal, Carmen; Complejo Hospitalario Universitario, Department of Medicine Antolín-Amérigo, Dario; Hospital Universitario Ramón y Cajal, Servicio de Alergia Pinto, Diana; Centro Hospitalar Universitário do Porto EPE Centro Materno-Infantil do Norte Dr Albino Aroso, Serviço de Pediatria Ferreira-Magalhães, Manuel; CINTESIS, MEDCIDS; Centro Hospitalar Universitário do Porto EPE Centro Materno-Infantil do Norte Dr Albino Aroso, Serviço de pediatria Vasconcelos, Maria João; Hospital São João, immuno-allergy Lozoya, Carlos ; Hospital Amato Lusitano, Allergy Santos, Natacha; Centro Hospitalar do Algarve EPE, immuno-allergy Cardia , Francisca; Unidade de Saúde Familiar Terras de Azurara Taborda-Barata, Luís; CICS - Health Sciences Research Centre; NuESA – Environment & Health Study Group, Faculty of Health Sciences, University of Beira Interior; Department of Allergy & Clinical Immunology, Cova da Beira University Hospital Centre Ferreira, Rosário ; Centro Hospitalar de Lisboa Norte, Serviço de Pediatria Morais Silva, Pedro ; Grupo HPA Saúde, Immuno-Allergy Ferreira, Tania; Agrupamento de Centros de Saúde Baixo Mondego Câmara, Raquel; Centro Hospitalar Barreiro Montijo EPE Silva, Eurico; Agrupamento de Centros de Saúde de Baixo Vouga Bordalo, Diana; Centro Hospitalar do Médio Ave EPE, Serviço de Pediatria Guimarães , Cristina; Agrupamento de Centros de Saúde Pinhal Litoral</p>

	<p>Calix, Maria José; Centro Hospitalar Tondela Viseu EPE da Silva, Sofia; Unidade Local de Saúde do Alto Minho EPE Marques, Maria; Senhora da Oliveira Hospital Guimaraes, Serviço de Imunoalergologia</p> <p>Morete, Ana; Hospital CUF, Allergy Unit; Baixo Vouga Hospital Centre Nunes, Carlos; Centro de Imunoalergologia do Algarve Vieira, Cláudia; Agrupamento de Centros de Saúde Douro I - Marão e Douro Norte</p> <p>Páscoa, Rosália; Faculty of Medicine, University of Porto, Department of Community Medicine, Information and Health Decision Sciences (MEDCIDS) and Centre for Health Technology and Services Research (CINTESIS), University of Porto, Porto, Portugal.</p> <p>Alves, Adelaide; Vila Nova de Gaia Espinho Hospital Center, Serviço de Pneumologia</p> <p>Marques, José ; Agrupamento de Centros de Saúde do Dão Lafões Reis, Bruno; Agrupamento de Centros de Saúde Pinhal Litoral Monteiro, Luís; CINTESIS, ; USF Esgueira +, Monteiro, Rosário; CINTESIS, MEDCIDS; ACeS Porto Ocidental Cepa, Margarida; ACES Pinhal Litoral Valentim, Bruno; ACES Baixo Mondego Coelho, Daniela; ACES Tâmega I - Baixo Tâmega Fernandes, Sara; ACES Cávado I Meireles, Patrícia; ACES Douro II - Douro Sul Aguiar, Margarida; ACES Grande Porto III - Maia / Valongo Mourão, Ana; ACES Grande Porto VIII - Espinho / Gaia Fonseca, Joao A.; CINTESIS, MEDCIDS; Instituto and Hospital CUF, Allergy Unit Jácome, Cristina; University of Porto, Faculty of Medicine</p>
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Title

Symptoms of anxiety and depression in patients with persistent asthma: a cross-sectional analysis of the INSPIRERS studies

Mafalda Simões Cunha 1; Rita Amaral 2,3,4,5; Ana Margarida Pereira 1,2,6; Rute Almeida 3; Magna Alves-Correia M 1,2; Cláudia Chaves-Loureiro 7; Cristina Lopes 8,9; Joana Carvalho 10; Carmelita Ribeiro 11; Carmen Vidal 12, Darío Antolín-Amérigo 13, Diana Pinto 14; Manuel Ferreira-Magalhães 3,14; Maria João Vasconcelos 15; Carlos Lozoya 16; Natacha Santos 17; Francisca Cardia 18; Luís Taborda-Barata 19,20; Rosário Ferreira 21; Pedro Morais Silva 22; Tania Monteiro Ferreira 23; Raquel Camara 24; Eurico Silva 25; Diana Bordalo 26; Cristina Guimarães 27; Maria José Cálix 28; Sofia da Silva 29; Maria Luís Marques 30; Ana Morete 2, 31; Carlos Nunes 32; Cláudia Vieira 33; Rosália Páscoa 1,6,34; Adelaide Alves 35; José Varanda Marques 36; Bruno Reis 37; Luís Monteiro 1,38; Rosário Monteiro 3,34; Margarida Cepa 39; Bruno Valentim 40; Daniela Sousa Coelho 41; Sara Fernandes 42; Patrícia Meireles 43; Margarida Abreu Aguiar 44; Ana Rita Mourão 45; João Almeida Fonseca 2,3,46; Cristina Jácome 3, INSPIRERS group

1. Center for Health Technology and Services Research (CINTESIS), Faculty of Medicine, University of Porto, Porto , PT
2. Allergy Unit, Instituto and Hospital CUF , Porto , PT
3. CINTESIS@RISE, MEDCIDS, Faculty of Medicine of the University of Porto, Porto, Portugal
4. Department of Cardiovascular and Respiratory Sciences, Porto Health School, Polytechnic Institute of Porto, Porto , PT
5. Department of Women's and Children's Health, Paediatric Research, Uppsala University, Uppsala , SE
6. Department of Community Medicine, Information and Health Decision Sciences (MEDCIDS), Faculty of Medicine, University of Porto, Porto , PT
7. Pulmonology Department, Hospitais da Universidade de Coimbra, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; Clinical Academic Center of Coimbra, Portugal.
8. Imunologia Básica e Clínica, Faculdade de Medicina, Universidade do Porto, Porto , PT
9. Unidade de Imunoalergologia, Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos, Matosinhos , PT
10. Serviço de Pediatria, Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos, Matosinhos , PT
11. Serviço de Imunoalergologia, Centro Hospitalar e Universitário de Coimbra , Coimbra , PT
12. Servicio de Alergia, Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, Spain
13. Servicio de Alergia, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria, Madrid, Spain
14. Serviço de Pediatria, Centro Materno Infantil do Norte, Centro Hospitalar Universitário do Porto, Porto , PT
15. Serviço de Imunoalergologia, Centro Hospitalar Universitário de São João , Porto , PT
16. Serviço de Imunoalergologia, Hospital Amato Lusitano, Unidade Local de Saúde de Castelo Branco, Castelo Branco , PT
17. Serviço de Imunoalergologia, Centro Hospitalar Universitário do Algarve , Portimão , PT
18. Unidade de Saúde Familiar Terras de Azurara, Agrupamento de Centros de Saúde Dão Lafões , Mangualde , PT
19. Department of Allergy & Clinical Immunology, Cova da Beira University Hospital Centre , Covilhã , PT

- 1
2
3 48 20. CICS-UBI Centro de Investigação em Ciências da Saúde - Health Sciences Research Centre &
4 49 UBI Air – Clinical & Experimental Lung Centre, University of Beira Interior, Covilhã , PT
5 50 21. Departamento de Pediatria, Hospital de Santa Maria, Centro Hospitalar de Lisboa Norte, Lisboa,
6 51 PT
7 52 22. Imunoalergologia, Grupo HPA Saúde , Portimão , PT
8 53 23. Unidade de Saúde Familiar Progresso e Saúde, Agrupamento de Centros de Saúde Baixo
9 54 Mondego , Tocha , PT
10 55 24. Serviço de Pneumologia, Hospital Nossa Senhora do Rosário, Centro Hospitalar Barreiro
11 56 Montijo, Barreiro , PT
12 57 25. Unidade de Saúde Familiar João Semana, Agrupamento de Centros de Saúde Baixo
13 58 Vouga , Ovar , PT
14 59 26. Serviço de Pediatria, Unidade Hospitalar de Famalicão, Centro Hospitalar do Médio Ave, Vila
15 60 Nova de Famalicão , PT
16 61 27. Unidade de Cuidados de Saúde Personalizados Norte (Arnaldo Sampaio), Agrupamento de
17 62 Centros de Saúde Pinhal Litoral, Monte Redondo, PT
18 63 28. Serviço de Pediatria, Hospital de São Teotónio, Centro Hospitalar Tondela–Viseu, Viseu , PT
19 64 29. Unidade de Saúde Familiar Cuidarte, Unidade Local de Saúde do Alto Minho , Portuzelo , PT
20 65 30. Serviço de Imunoalergologia, Hospital da Senhora da Oliveira, Guimarães, PT
21 66 31. Serviço de Imunoalergologia, Hospital Infante D Pedro, Centro Hospitalar Baixo
22 67 Vouga, Aveiro , PT
23 68 32. Imunoalergologia, Centro de Imunoalergologia do Algarve , Portimão , PT
24 69 33. Unidade de Saúde Familiar Corgo, Agrupamentos de Centros de Saúde Douro I - Marão e Douro
25 70 Norte , Vila Real , PT
26 71 34. Unidade de Saúde Familiar Homem do Leme, ACeS Porto Ocidental, Porto, Portugal
27 72 35. Serviço de Pneumologia, Unidade I, Centro Hospitalar Vila Nova de Gaia/Espinho, Vila Nova de
28 73 Gaia , PT
29 74 36. Unidade de Saúde Familiar Viseu-Cidade, Agrupamento de Centros de Saúde do Dão
30 75 Lafões , Viseu , PT
31 76 37. Unidade de Cuidados de Saúde Personalizados Sicó, Agrupamento de Centros de Saúde Pinhal
32 77 Litoral , Leiria , PT
33 78 38. Unidade de Saúde Familiar Esgueira+, ACES Baixo Vouga, Esgueira, Portugal
34 79 39. Unidade de Saúde Familiar Marquês, ACES Pinhal Litoral, Pombal, Portugal
35 80 40. Unidade de Saúde Familiar Condeixa, ACES Baixo Mondego, Condeixa-a-Nova, Portugal
36 81 41. Unidade de Cuidados de Saúde Personalizados de Amarante, ACES Tâmega I – Baixo Tâmega,
37 82 Amarante, Portugal
38 83 42. Unidade de Saúde Familiar Bracara Augusta, ACES Cávado I – Braga, Braga, Portugal
39 84 43. Unidade de Saúde Familiar Almedina, ACES Douro II - Douro Sul, Lamego, Portugal
40 85 44. Unidade de Saúde Familiar Valongo, ACES Grande Porto III - Maia / Valongo, Valongo, Portugal
41 86 45. Unidade de Saúde Familiar Canelas, ACES Grande Porto VIII - Espinho / Gaia, Vila Nova Gaia,
42 87 Portugal
43 88 46. MEDIDA – Medicina, Educação, Investigação, Desenvolvimento e Avaliação, Porto, Portugal
44 89

48 90 **Corresponding author:** Cristina Jácome, Center for Health Technology and Services Research

49 91 (CINTESIS), Department of Community Medicine, Information and Health Decision Sciences

50 92 (MEDCIDS), Faculty of Medicine, University of Porto, Portugal; e-mail:

51 93 cristinajacome.ft@gmail.com

52 94

95 **Abstract**

96 **Objectives:** Anxiety and depression are relevant comorbidities in asthma, but, in
97 Portugal and Spain, data on this topic are scarce. We assessed, in patients with asthma, the
98 frequency of anxiety and depression using the Hospital Anxiety and Depression Scale (HADS)
99 and the European Quality of Life Five Dimension Questionnaire (EQ-5D); the level of
100 agreement between these questionnaires, and the factors associated with these symptoms.

101 **Methods:** This is a secondary analysis of the INSPIRERS studies. A total of 614
102 adolescents and adults with persistent asthma (32.6 ± 16.9 y, 64.7% female) were recruited
103 from 30 primary care centres and 32 allergy, pulmonology and pediatric clinics. Demographic
104 and clinical characteristics, HADS and EQ-5D were collected. A score ≥ 8 on HADS-A/HADS-D
105 or a positive answer to EQ-5D item 5 indicated the presence of these symptoms. Agreement
106 was determined by Cohen's kappa. Two multivariable logistic regressions were built.

107 **Results:** According to HADS, 36% of the participants had symptoms of anxiety and 12%
108 of depression. According to EQ-5D, 36% of the participants had anxiety/depression. The
109 agreement between questionnaires in identifying anxiety/depression was moderate ($k=0.55$,
110 95%CI 0.48-0.62). Late asthma diagnosis, comorbidities and female gender were predictors
111 of anxiety/depression, while better asthma control, health-related quality of life and
112 perception of health were associated with lower odds for anxiety/depression.

113 **Conclusion:** At least 1/3 of the patients with persistent asthma experience symptoms
114 of anxiety/depression, showing the relevance of screening these disorders in patients with
115 asthma. EQ-5D and HADS questionnaires showed a moderate agreement in the identification
116 of anxiety/depression symptoms. The identified associated factors need to be further
117 investigated in long-term studies.

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3 118 **Strengths and limitations of this study**
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7 119 This study is a secondary analysis of a multicentric study that recruited both adults and
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9 120 adolescents with asthma from primary and secondary care.
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12 121 A comprehensive set of individual-level characteristics was analysed, which allowed us to
13
14 122 explore the impact of sociodemographic factors and cofactors such as quality of life and
15
16 123 asthma control on the presence of anxiety/depression symptoms.
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20 124 A possible source of bias was the recruitment strategy based on convenience sampling.
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23 125 The frequency of distressing symptoms and the relationships with associated factors could
24
25 126 not be established overtime.
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29 127 **Word count:** 3661
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35 129 **Key Words:** Asthma; Anxiety Disorders; Depression Disorder; Surveys and Questionnaires.
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130 **Introduction**

131 Asthma affects approximately 300 million people worldwide [1]. In Portugal, asthma
132 affects 695 000 Portuguese, with a general prevalence of 6.8% [2]. In Spain, asthma affects
133 more than three million people, with an estimated prevalence of 5% in adults [3]. Asthma is
134 primarily related to chronic inflammation of the lower respiratory tract, variable airflow
135 obstruction, and bronchial hyperresponsiveness [4]. Yet, this disease is often accompanied by
136 multiple associated comorbidities, such as chronic rhinosinusitis, nasal polyposis, allergic
137 rhinitis, gastroesophageal reflux disease, obstructive sleep apnea syndrome [5], and also
138 anxiety and depression [6].

139 In two systematic reviews, the average of the reported prevalence of any anxiety
140 disorder among patients with asthma was 24% [7] and 34% [8]. Regarding depression, a
141 pragmatic literature review found that 1% to 45% of patients with asthma suffer from
142 depression or depressive symptoms [9]. In severe asthma, a study reported an average
143 prevalence of 27% for emotional distress (mainly due to anxiety and depression) [10].
144 Currently, most studies about emotional distress focus essentially on adult patients with more
145 severe asthma [11]. There is a lack of data regarding other asthma sub-groups, namely
146 adolescents and those with mild or moderate persistent asthma.

147 Anxiety and depression are associated with significantly lower quality of life, poor
148 asthma control, higher frequency of exacerbations and increased use of healthcare resources
149 [12]. Moreover, anxiety is associated with greater perceived dyspnea intensity and may shape
150 the quality and intensity of this symptom at a given respiratory load [13]. However, it is still
151 uncertain whether other factors can affect the patient's psychological state. It is important to
152 have a more sophisticated understanding of the interplay between emotional distress and
153 asthma [14].

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3 154 Despite these negative impacts, anxiety and depression in patients with asthma is not
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6 155 routinely assessed during clinical visits and thus there is a lack of information about its real-
7
8 156 world frequency. One of the most used tools for psychological screening is the Hospital
9
10 157 Anxiety and Depression Scale (HADS). HADS is a self-report questionnaire designed to screen
11
12
13 158 anxiety and depression symptoms [15] and it was already used in adolescents and adults with
14
15 159 asthma in previous studies [16, 17]. However, this scale has 14 items and although it takes
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17
18 160 around 5 minutes to complete [18], it is not always feasible to administer in a busy clinic
19
20 161 setting [19, 20]. European Quality of Life Five Dimension Questionnaire (EQ-5D) is a generic
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22
23 162 measure of health status that provides a simple descriptive profile and a single index value
24
25 163 that can be used for the clinical and economic evaluation of healthcare [21], but also
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27
28 164 emotional distress screening [22]. Currently, EQ-5D is being widely used in a variety of
29
30 165 conditions, where asthma is integrated [23]. Some studies compared HADS and EQ-5D in
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33 166 patients with other diseases and showed that EQ-5D can be responsive to different degrees
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35 167 of HADS-assessed distress [24]. Yet, there is no published data comparing HADS and EQ-5D in
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38 168 patients with asthma.

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40 169 With the present study, we aimed to assess i) the frequency of symptoms of anxiety
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42 170 and depression in patients with asthma as assessed by HADS and EQ-5D questionnaires; ii)
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44
45 171 the level of agreement between the two questionnaires and iii) the factors associated with
46
47
48 172 the presence of these symptoms

49 173 **Methods**

50 174 **Patient and public involvement**

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55 175 No patient involved
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177 **Study design**

178 Data from the baseline face-to-face visit from 5 prospective observational studies of
179 the INSPIRERS project were analysed [25]. This project addresses the topic of adherence to
180 asthma inhalers among adolescents and adults with persistent asthma. Convenience samples
181 were recruited between November 2017 and October 2020 at 32 allergy, pulmonology and
182 paediatric secondary care outpatient clinics (30 from Portugal and 2 from Spain) and 30
183 primary care centres from Portugal. The studies were approved by the ethics committees of
184 all participating centres. Eligible patients were approached by physicians during medical visits.
185 Adult patients signed a consent form. Adolescents signed an assent form, and a parental
186 consent form was also obtained. The studies had similar inclusion criteria and methods. The
187 study is reported according to Strengthening the Reporting of Observational Studies in
188 Epidemiology (STROBE) guidelines [26].

189 **Patients**

190 Patients were included in the analysis if they had a previous medical diagnosis of
191 persistent asthma, were at least 13 years old (13–17 years adolescents; ≥ 18 years adults) and
192 had an active prescription for an inhaled controller medication for asthma. All inhaled
193 controller treatments were allowed, and there was no change in any prescribed medication
194 regarding the participation in these studies. Patients were excluded if they had a diagnosis of
195 a chronic lung disease other than asthma or a diagnosis of another significant chronic
196 condition with possible interference with the study aims.

197 **Data collection**

198 During the baseline face-to-face visit, data were collected from both physicians and
199 patients in an attempt to improve the quality of the information obtained. Physicians

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3 200 answered a questionnaire including the asthma treatment plan and comorbidities.
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6 201 Information about the healthcare setting (primary, secondary) was obtained based on the
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8 202 centre where patients were recruited.
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10 203 Demographic data (age, gender, educational level, marital status and current
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13 204 occupation) and clinical data (weight, height, smoking habits, and age of asthma diagnosis)
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15 205 were collected from patients.
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18 206 Two asthma control questionnaires were used to gather the perspectives of the
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20 207 physician and the patient. Physicians answered the Global Initiative for Asthma (GINA)
21
22 208 assessment of symptom control [26], which is recommended to be use at every opportunity
23
24
25 209 in adolescents and adults. Patients answered the Control of Allergic Rhinitis and Asthma Test
26
27 210 (CARAT). CARAT is a self-report questionnaire with a total score (CARAT-T) calculated by
28
29 211 summing up the score of each of the 10 questions, resulting in a range of 0–30 points. A score
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31 212 >24 indicates good disease control [27]. This questionnaire has been widely used in clinical
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34 213 practice and in scientific research, being translated/culturally adapted in >27 languages and
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36 214 used in >15 different countries [28].
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40 215 The Portuguese version of the Hospital Anxiety and Depression Scale (HADS) was used
41
42 216 to assess the presence of symptoms of anxiety and depression [29]. HADS contains 14 items
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44 217 related to the past week, 7 of which assess anxiety symptoms (HADS-A) and the other 7
45
46 218 depression symptoms (HADS-D). HADS-A and HADS-D are scored separately. The item
47
48 219 response scale varies between 0 and 3 points, with total scores ranging from 0 (minimum
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50 220 symptomatic load) up to 21 (maximum symptomatic load) for HADS-A and HADS-D. A score
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52 221 ≥ 8 on HADS-A or HADS-D was considered as the presence of symptoms of anxiety or
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55 222 depression, respectively [30].
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3 223 The European Quality of Life Five Dimension Questionnaire (EQ-5D) three-level
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6 224 version was filled in by the patients to assess their overall quality of life. The item 5 “Anxiety
7
8 225 and Depression” could be a useful tool in screening for anxiety and depressive symptoms in
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11 226 hospital and community settings [31]. Therefore, this item, with its 3 response options (“I am
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13 227 not anxious or depressed”, “I am moderately anxious or depressed”, “I am extremely anxious
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15 228 or depressed”) was additionally used to assess the presence of these symptoms [32]. Patients
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17
18 229 were considered to have anxiety/depression when answering “I am moderately anxious or
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20
21 230 depressed” or “I am extremely anxious or depressed”. The EQ-5D summary index score was
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23 231 calculated to characterize the sample. It ranges from less than 0 (where 0 is a health state
24
25 232 equivalent to death) to 1 (perfect health) [33]. The EQ-5D VAS was also used to assess
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28 233 patients’ perception of their general health (from 0 ‘the worst health you can imagine’ to 100
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30 234 ‘the best health you can imagine’).

32 33 235 **Statistical Analyses**

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35 236 Descriptive statistics were used to characterize the sociodemographic variables,
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38 237 clinical characteristics, the HADS score and EQ-5D responses. Absolute and relative
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40 238 frequencies were used to characterize the categorical variables. Means and standard
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43 239 deviations or medians and interquartile ranges were used, according to data distribution, to
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45 240 characterize the numerical variables.

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48 241 To determine the agreement between HADS and EQ-5D questionnaires for the
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50 242 presence of symptoms of anxiety/depression, the percentage of agreement and weighted
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53 243 Cohen’s kappa were used. Cohen’s kappa values were interpreted as follows: <0, no
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55 244 agreement; 0–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial and
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57 245 0.81–1.0, almost perfect agreement [34].
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3 246 To explore associations between variables related to the presence of symptoms of
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6 247 anxiety and depression, patients with and without symptoms of anxiety and depression were
7
8 248 compared using independent t-tests for normally distributed data, Mann-Whitney U tests for
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10 249 non-normally distributed continuous data and ordinal data, and Chi-square tests for
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12
13 250 categorical data. In the case of Chi-square tests, when a statistically significant difference was
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15 251 found for a categorical variable with more than two categories, chi-square multiple
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17 252 comparison tests with Bonferroni correction were performed to explore which categories
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19
20 253 differed from each other. The variables that were statistically different ($p < 0.05$) between the
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22
23 254 two groups were selected to further explore their relationship with the presence of anxiety
24
25 255 and depression and to adjust for possible confounders in two stepwise multivariable logistic
26
27 256 regression models. The dependent variable in each multivariable logistic regression was the
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30 257 presence of symptoms of anxiety or depression based on HADS (0 = absent, 1 = present). The
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33 258 overall models were evaluated using the goodness-of-fit tests and Nagelkerke's R-square and
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35 259 the final model was selected based on the best combination of these results. The level of
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37 260 significance considered was 0.05. Statistical analyses were performed using IBM SPSS
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39
40 261 Statistics version 26.0 (IBM Corporation, Armonk, NY, USA).

41 42 262 **Results**

43 44 45 263 **Patient's Characteristics**

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48 264 A total of 614 participants with asthma (mean age 32.6 ± 16.9 years) were included in
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51 265 this study. There were 447 (72.8%) adults and 397 (64.7%) females. Forty percent of the
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53 266 participants had completed primary school ($n=244$), 47.4% were employed ($n=289$) and 65.1%
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56 267 were prescribed only 1 inhaler ($n=396$). According to the GINA assessment of symptom
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268 control, 296 (48.7%) patients had well controlled asthma. Table 1 shows the socio-
 269 demographic and clinical characteristics of the study participants.

270 TABLE 1. Socio-demographic and clinical characteristics of the participants (n=614).

Characteristics	
Age (years) M ± SD^a	32.6 ± 16.9
Age group n (%)	
Adolescent	167 (27.2)
Adult	447 (72.8)
Gender n (%)	
Female	397 (64.7)
Male	217 (35.3)
Educational level n (%)^b	
No education completed	4 (0.7)
Primary school	244 (40.4)
High school	177 (29.3)
Qualification above high school (but not university)	23 (3.8)
University	156 (25.4)
Other	1 (0.2)
Marital status n (%)^c	
Single	348 (56.7)
Married/Living as a couple	223 (36.3)
Separated/divorced	33 (5.4)
Widowed	9 (1.5)
Current occupation n (%)^d	
Employed	289 (47.1)
Student	235 (38.3)
Unemployed	41 (6.7)
Retired	36 (5.9)
Other	9 (1.5)
BMI Kg/m², M ± SD^e	24.7 (5.3)
Smoking Status n (%)^d	
Never smoker	457 (74.4)
Ex-smoker	106 (17.3)
Current smoker	47 (7.7)
Setting	
Secondary care	475 (77.4)
Primary care	139 (22.6)
Age of asthma diagnosis (years) M ± SD^f	16.2 ± 14.8
Number of prescribed inhalers n (%)^g	

1	1	396 (64.5)
2	2	193 (31.4)
3	≥3	19 (3.1)
4	GINA assessment symptom control n (%)^g	
5	Well controlled	296 (48.2)
6	Partly controlled	188 (30.6)
7	Uncontrolled	124 (20.2)
8	Number of physician-reported comorbidities Median (P25-P75)	
9	CARAT-T Median (P25-P75)	
10	1 [0-2]	
11	CARAT-T Classification	
12	Controlled n (%)	156 (25.4)
13	Uncontrolled n (%)	458 (74.6)
14	EQ-5D-3L Median (P25-P75)	
15	Total	0.91 [0.81-1.0]
16	VAS	80.0 [70.0-90.0]

M = Mean; SD= Standard Deviation; BMI=body mass index; GINA = Global Initiative for Asthma; P25= 25th percentile; P75= 75th percentile; CARAT-T=Control of Allergic Rhinitis and Asthma Test total score; EQ-5D-3L= European Quality of Life Five Dimension Questionnaire-three-level version; VAS= Visual analogue scale.

^a 8 missing values. ^b 9 missing values. ^c missing value. ^d 4 missing values. ^e 28 missing values. ^f 22 missing values. ^g 6 missing values.

275 Symptoms of anxiety and depression

276 According to HADS, 221 (36.0%) participants had symptoms of anxiety, 73 (11.9%) had
 277 symptoms of depression, 59 (9.6%) both symptoms and 235 (38.3%) participants had
 278 symptoms of anxiety or depression. Both anxiety (41.4% vs 21.6%) and depression (14.1% vs
 279 6%) symptoms were more frequent in adults than adolescents. According to EQ-5D, 223
 280 (36.3%) participants had anxiety or depression problems, 32.6% were moderately anxious or
 281 depressed and 3.7% extremely anxious or depressed. The agreement between these two
 282 questionnaires was moderate for anxiety (k=0.54 (95%CI 0.47-0.61)); fair for depression
 283 (k=0.23 (95%CI 0.17-0.30)) and moderate for anxiety/depression (k=0.55 (95% CI 0.48-0.62)).

284 Predictors of anxiety and depression

285 In the multivariable logistic regression (Table 2), being an adolescent (OR 0.43, 95% CI
 286 0.27-0.68), having a better asthma control (CARAT-T score) (OR 0.98, 95% CI 0.94-1.00) and a
 287 perception of better health (OR 0.97, 95% CI 0.95-0.98) were significantly associated with

288 lower odds for the presence of anxiety symptoms. In contrast, being a female was significantly
 289 associated with a higher odd for the presence of anxiety symptoms (OR 1.75, 95% CI 1.56-
 290 2.64). Having better health-related quality of life (OR 0.97, 95%CI 0.95-0.99) and perception
 291 of better health (OR 0.97, 95% CI 0.96-0.99) were associated with a lower odd for the
 292 presence of depression. While asthma diagnosis at a later age (OR 1.03, 95% CI 1.01-1.05) and
 293 the presence of a higher number of comorbidities (OR 1.31, 95% CI 1.05-1.64) were associated
 294 with an increase in the likelihood of exhibiting symptoms of depression. The univariate
 295 analyses are presented in Supplementary Table 1.

296 Table 2 – Multivariable logistic regression analyses to explain anxiety and depression.

	Anxiety adjusted OR (95% CI)*	Depression adjusted OR (95% CI)**
Age group		
Adolescent	0.43 (0.27-0.68)	-
Adult	Reference	-
Gender		
Female	1.75 (1.56-2.64)	-
Male	Reference	-
Age of asthma diagnosis	-	1.03 (1.01-1.05)
Number of physician-reported comorbidities	1.17 (0.99-1.37)	1.31 (1.05-1.64)
CARAT T	0.98 (0.94-1.00)	-
Quality of life (EQ-5D total)	-	0.97 (0.95-0.99)
Perception of better health (EQ-5D VAS)	0.97 (0.95-0.98)	0.97 (0.96-0.99)
R²	22%	23%
Hosmer-Lemeshow test - p-value	.435	.449

297 OR = Odds ratio; CI = Confidence interval; BMI = body mass index; CARAT-T = Control of Allergic Rhinitis and Asthma Test total score; EQ-5D
 298 = European Quality of Life Five Dimension Questionnaire; VAS= Visual analogue scale.

299 *Age, current occupation, setting, age of asthma diagnosis, GINA assessment of symptom control and quality of life (EQ-5D total) were also
 300 tested but not included in the final adjusted model.

301 **Age, age group, educational level, marital status, current occupation, BMI, GINA assessment of symptom control and CARAT T were also
 302 tested but not included in the final adjusted model.

303

304 **Discussion**

305 This study showed that more than 1/3 of participants with asthma experienced
306 symptoms of anxiety and/or depression. Asthma diagnosis at a later age, presence of
307 comorbidities and female gender were predictors of anxiety/depression, while better asthma
308 control, health-related quality of life and perception of better health were factors associated
309 with lower odds for anxiety/depression. In this study, the agreement between HADS and EQ-
310 5D questionnaires in identifying anxiety and depression was sufficient to moderate.

311 According to HADS and EQ-5D questionnaires, more than 1/3 of the patients with
312 persistent asthma experience symptoms of anxiety/depression (38.3% and 36.3%
313 respectively). Therefore, the percentages of participants with one of these symptoms
314 detected by HADS and EQ-5D were similar. With HADS, it was possible to detect the
315 percentages of patients with persistent asthma that had only symptoms of anxiety (36.0%) or
316 had only symptoms of depression (11.9%). The proportions found in the present study were
317 similar to the ones found among patients with asthma in previous reviews [8, 9], analysing
318 studies that included only, or mostly, adults with asthma. A study from the UK found similar
319 frequencies of anxiety and depression using HADS, although a slightly higher cut-off has been
320 used (HADS-A/HADS-D \geq 10) [35]. We found a lower frequency for depression as compared
321 with a study in patients with severe asthma, where 25% reported depression [36]. This
322 difference might be explained by the role of poorer physical functioning on symptoms of
323 depression [37]. Patients with severe asthma experience more physical disability. Other
324 studies reported that patients with severe asthma have more often emotional distress as
325 compared to patients with mild-moderate asthma [38, 39].

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3 326 This study includes both adolescents and adults with persistent asthma, which is rarely
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6 327 found in previous articles. However, anxiety and depression were only assessed at one time
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8 328 point. Analysing emotional distress in the long run could be important as suggested in
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10 329 previous cohort studies that followed adolescents with asthma to young adulthood, showing
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13 330 that there was a persistence or recurrence of anxiety and depression in adulthood [40, 41]. In
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15 331 our study, adults with persistent asthma presented an increased frequency of
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17 332 anxiety/depression symptoms (vs adolescents), which is in accordance with a population-
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20 333 based study that reported that having asthma and older age were independent risk factors
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23 334 for the presence of anxiety disorders, in participants above the age of 15 years [42].
24
25 335 Therefore, emotional distress seems to be associated with age differences in patients with
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28 336 persistent asthma.

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30 337 Age at asthma onset has emerged as a critical factor in distinguishing the phenotypes
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32 338 of asthma [43]. Adult-onset asthma differs from asthma that first occurs in childhood since it
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35 339 usually is less well controlled, is associated with a faster decline in lung function and with
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37
38 340 more comorbidities [44, 45]. Moreover, worse asthma control and the presence of more
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41 341 comorbidities might be associated with an increased risk of emotional distress [46]. These
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43 342 results contribute to explaining our finding that asthma diagnosis at a later age and number
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45 343 of physician-reported comorbidities were associated with a higher frequency of depression.
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48 344 Female patients were more likely to have anxiety symptoms. This was previously observed in
49
50 345 other studies in asthma but also other respiratory diseases, such as COPD. Possibly these
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53 346 gender differences are more than a specificity of respiratory diseases, but a reflection of the
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55 347 known gender differences in the general population [47, 48].
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3 348 In our study, the perception of better health was associated with a lower odd for the
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6 349 presence of anxiety symptoms. In a previous study with patients with chronic obstructive
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8 350 pulmonary disease (COPD), the perceived severity of COPD symptoms was predictive of
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10 351 depression and anxiety [49]. These findings are in line with our study, although coming from
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12
13 352 a different disease. The close correlation between asthma control, quality of life, anxiety, and
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15 353 depression has been also confirmed in other studies [50, 51]. Consequently, in patients with
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17 354 poor asthma control, physicians should ask about the symptoms of anxiety/depression or
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19 355 screen it using simple tools like EQ-5D or HADS before making adjustments on asthma
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22 356 treatment strategy [17].
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26 357 EQ-5D questionnaire could be useful in clinical practice [52]. The EQ-5D anxiety or
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28 358 depression domain had a greater agreement with the HADS score in identifying cases with
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30 359 both symptoms, as expected, than in identifying anxiety or depressive symptoms. In general,
31
32 360 the percentages of patients with anxiety/depression detected by HADS and EQ-5D were
33
34 361 similar. Furthermore, it is expected that remarkably less time consumption is needed for the
35
36 362 EQ-5D item 5 assessment compared with HADS [18, 53]. Therefore, EQ-5D score appears to
37
38 363 have value as a screening tool for anxiety or depression in patients with asthma. In a previous
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40 364 study, this questionnaire also seemed to be reasonably valid and moderately responsive in
41
42 365 patients with anxiety disorders [54]. This could be important in clinical practice because a
43
44 366 generic health instrument like the EQ-5D, with few and quick questions, could be used to
45
46 367 easily raise awareness of a possible emotional distress in patients with asthma. A limitation
47
48 368 of EQ-5D is that anxiety and depression are two separate emotional disorders and their
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50 369 combination in a single item in this questionnaire could lead to inconsistencies in responses
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52 370 [55]. Nevertheless, EQ-5D could be used as a first screening questionnaire and, in patients
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54 371 reporting anxiety or depression symptoms, a more specific questionnaire, such as HADS,
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3 372 could be used to better characterize their symptoms. Actually, emotional distress screening
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6 373 is very important in clinical practice because physicians can use targeted interventions to
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8 374 improve patients' symptoms [56]. Studies about psychological interventions in adults with
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10 375 asthma suggest that education and simple psychological interventions namely relaxation
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13 376 techniques and biofeedback or a stepped care approach could produce significant positive
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15 377 healthcare outcomes [57, 58].
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18 378 This study has some strengths that should be acknowledged: it is a multicentric study
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20
21 379 that recruited both adults and adolescents with asthma from primary and secondary care. A
22
23 380 comprehensive set of individual-level characteristics was collected and analysed, which
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25
26 381 allowed us to explore the impact of a range of sociodemographic factors, health literacy and
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28 382 cofactors such as quality of life and asthma control. Therefore, includes a sample from
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30 383 different health care contexts and with different clinical presentations, contributing to the
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33 384 robustness of these findings.
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36 385 Nevertheless, it also has some limitations. A possible source of bias was the
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38 386 recruitment strategy of using a convenience sampling. Future studies using other sampling
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41 387 strategies could be important to generalise the results of our study. A control group of healthy
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43 388 individuals with similar socio-demographic characteristics should also be included in further
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45
46 389 research to increase the validity of these findings. In the absence of a control group it would
47
48 390 have been useful to compare anxiety/depression frequencies with normative data from
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51 391 Portugal and Spain, but we did not find it neither for HADS nor EQ-5D. Moreover, the impact
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53 392 of the presence of specific comorbidities, such as rhinitis, which is closely associated both
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56 393 with asthma and anxiety/depression, was not assessed [59]. Another limitation of the present
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58 394 study is related to its cross-sectional nature. The frequency of distressing symptoms and the
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3 395 relationships with associated factors could not be established along the progression of the
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6 396 disease. Also, patients were not recruited at the same time point, as recruitment in the
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8 397 Inspirers studies occurred across 4 different years (from 2017 to 2020), and the last 15% of
9
10 398 the sample was recruited during COVID-19 pandemic. Longitudinal studies following a cohort
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12
13 399 of patients with asthma would address these issues and identify other predictors of symptoms
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15 400 of anxiety and depression.

17
18 401 This study shows that more than 30% of the patients with persistent asthma
19
20 402 experience symptoms of anxiety/depression, which supports the relevance of emotional
21
22 403 distress screening in patients with asthma. EQ-5D and HADS questionnaires showed a
23
24 404 moderate agreement in the identification of anxiety/depression symptoms. Late asthma
25
26 405 diagnosis, presence of comorbidities and female gender were positively associated with the
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28 406 presence of emotional distress, while better asthma control, health-related quality of life and
29
30 407 perception of better health presented a negative association. These factors need to be further
31
32 408 investigated in future long-term studies.

38 39 409 **a. Contributorship statement**

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42 410 All authors contributed to the selection of bibliography, revision and final approval of the
43
44 411 manuscript. AMP, RA, MAC, RAlmeida, JAF and CJ were responsible for study conception and
45
46 412 design; RA, AMP, RAlmeida, MAC, CCL, CL, JC, CR, CV, DAA, DP, MFM, MJV, CLozoya, NS, FC,
47
48 413 LTB, RF, PMS, TMF, RC, ES, DB, CG, MJC, SS, MLM, AM, CN, CVieira, RP, AA, JVM, BR, LM, RM,
49
50 414 MC, BV, DSC, SF, PM, MAA, ARM, JAF and CJ participated in the data collection; CJ and AMP
51
52 415 performed the data analysis and MSC prepared the first draft. All authors contributed to the
53
54 416 interpretation of data, to the critical revision of the manuscript for important intellectual
55
56 417 content.

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3
4 418 **b. Competing interests**

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6
7 419 None

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9
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12
13
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22 425 FEDER-029130).

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27 426 **d. Data sharing statement**

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31 427 The data sets generated during and/or analysed during the current study are not publicly available.

32
33
34 428 **Ethics approval**

35
36
37 429 The studies were approved by the ethics committees of all participating centres. For example, the
38
39 430 study was approved by the Ethics Committee of Centro Hospitalar de S. João—EPE (protocol code 258-
40
41 431 17 and date of approval: 5th of January 2018).

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45 432 **References**

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1 Supplementary table 1 – Univariate analyses to explain anxiety and depression symptoms.

	Anxiety	Depression
	crude OR (95% CI)	crude OR (95% CI)
Age	1.02 (1.01-1.03)	1.05 (1.03-1.06)
Age group		
Adolescent	0.39 (0.26-0.59)	0.39 (0.19-0.78)
Adult	Reference	Reference
Gender		
Females	2.44 (1.68-3.53)	1.64 (0.95-2.85)
Males	Reference	Reference
Educational level		
No education completed/Primary school	0.99 (0.71-1.39)	1.67 (1.01-2.74)
High school/Qualification above high school (but not university)/University/Other	Reference	Reference
Marital status		
Single/ Separated/Divorced/Widowed	0.72 (0.52-1.02)	0.45 (0.27-0.74)
Married/Living as a couple	Reference	Reference
Current occupation		
Employed/Student/Other	0.55 (0.35-0.87)	0.25 (0.14-0.43)
Unemployed/Retired	Reference	Reference
BMI	1.03 (0.99-1.06)	1.08 (1.04-1.13)
Smoking status		
Non-smokers	0.56 (0.31-1.02)	0.92 (0.37-2.24)
Smokers	Reference	Reference
Setting		
Primary care	1.60 (1.09-2.35)	1.04 (0.58-1.86)
Secondary care	Reference	Reference
Age of asthma diagnosis	1.02 (1.01-1.03)	1.04 (1.03-1.06)
Number of physician-reported comorbidities	1.32 (1.14-1.53)	1.55 (1.29-1.87)
Number of prescribed inhalers	1.29 (0.97-1.71)	1.29 (0.87-1.91)
GINA assessment symptom control		
Well controlled	0.61 (0.44-0.85)	0.51 (0.30-0.85)
Partly controlled/Uncontrolled	Reference	Reference
CARAT T	0.93 (0.91-0.96)	0.91 (0.88-0.95)
Quality of life (EQ-5D total)	0.94 (0.92-0.95)	0.94 (0.93-0.96)
Perception of better health (EQ-5D VAS)	0.96 (0.95-0.97)	0.96 (0.95-0.97)

OR = Odds ratio; CI= Confidence interval; BMI=body mass index; GINA = Global Initiative for Asthma; CARAT-T=Control of Allergic Rhinitis and Asthma Test total score; EQ-5D= European Quality of Life Five Dimension Questionnaire.

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	3 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	8 NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	10 10 10 NA NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	11 NA NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	11, table 1 Table 1 NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12
2			(b) Report category boundaries when continuous variables were categorized	11-12
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
4	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
5	Discussion			
6	Key results	18	Summarise key results with reference to study objectives	12
7	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
8	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-15
9	Generalisability	21	Discuss the generalisability (external validity) of the study results	16
10	Other information			
11	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	4

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.