

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Symptoms of anxiety and depression in patients with persistent asthma: a cross-sectional analysis of the INSPIRERS studies
AUTHORS	Simões Cunha, Mafalda; Amaral, Rita; Pereira, A. M.; Almeida, Rute; Alves-Correia, Magna; Loureiro, Cláudia Chaves; Lopes, Cristina; Carvalho, Joana; Ribeiro, Carmelita; Vidal, Carmen; Antolín-Amérigo, Dario; Pinto, Diana; Ferreira-Magalhães, Manuel; Vasconcelos, Maria João; Lozoya, Carlos; Santos, Natacha; Cardia, Francisca; Taborda-Barata, Luís; Ferreira, Rosário; Morais Silva, Pedro; Ferreira, Tania; Câmara, Raquel; Silva, Eurico; Bordalo, Diana; Guimarães, Cristina; Calix, Maria José; da Silva, Sofia; Marques, Maria; Morete, Ana; Nunes, Carlos; Vieira, Cláudia; Páscoa, Rosália; Alves, Adelaide; Marques, José; Reis, Bruno; Monteiro, Luís; Monteiro, Rosário; Cepa, Margarida; Valentim, Bruno; Coelho, Daniela; Fernandes, Sara; Meireles, Patrícia; Aguiar, Margarida; Mourão, Ana; Fonseca, Joao A.; Jácome, Cristina

VERSION 1 – REVIEW

REVIEWER	Carvalho, Celso University of Sao Paulo
REVIEW RETURNED	21-Oct-2022

GENERAL COMMENTS	<p>This is an interesting secondary analysis of a multicentric study that recruited adults and adolescents with asthma. The study aimed to assess the frequency of anxiety and depression using the Hospital Anxiety and Depression Scale (HADS) and the European Quality of Life Five Dimension Questionnaire (EQ-5D); the level of agreement between these questionnaires and the factors associated with these symptoms in 614 patients with asthma, a large population. The study is clinically relevant; the methodology is adequate to answer the objectives and the study is well written. The study presents the following strong points: the expressive sample size; its a multicentric study; a comprehensive set of individual-level characteristics was analyzed to explore the impact of sociodemographic factors on the presence of anxiety/depression symptoms. As limitations: the fact that the sample was for convenience; another limitation is related to its cross-sectional nature, which does not allow inferring the presence of symptoms over time. Moreover, some clarifications and adjustments are required:</p> <p>Abstract</p> <ul style="list-style-type: none">- The abstract's conclusion does not respond to the study's aim, regarding the level of agreement between the questionnaires. I strongly suggest it be reworded. In addition, some mention should be made regarding the main factors associated with the frequency of anxiety and depression. (page 3, line 112)- It is also suggested to reduce the number of keywords. (page 4, line 127)
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	<p>Introduction</p> <ul style="list-style-type: none"> - A reference is required to support the frequency of anxiety and depression in asthma (page 5, line 139). <p>Methods</p> <ul style="list-style-type: none"> - Please inform the relevance of applying questionnaires to Physicians answer? (Global Initiative for Asthma (GINA) assessment of symptom control, the asthma treatment plan, and comorbidities). This needs to be clarified. (page 7, line 199) - Why did the authors not assess clinical control using a validated and widely used questionnaire for this population (eg. Asthma Control Questionnaire (ACQ)? <p>Discussion</p> <ul style="list-style-type: none"> - The description of the EQ-5D seems unnecessary and repetitive. (page 15, line 351) - The study's conclusion needs to be rewritten to include the main factors associated/or not with the presence of anxiety and depression in the studied population. (page 17, line 396)
REVIEWER	García-San, María-Teresa SERGAS, Primary Care
REVIEW RETURNED	31-Dec-2022
GENERAL COMMENTS	It is convenient to update the references, there is a predominance of old citations

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 - Dr. Celso Carvalho, University of Sao Paulo

Initial Comment: This is an interesting secondary analysis of a multicentric study that recruited adults and adolescents with asthma. The study aimed to assess the frequency of anxiety and depression using the Hospital Anxiety and Depression Scale (HADS) and the European Quality of Life Five Dimension Questionnaire (EQ-5D); the level of agreement between these questionnaires and the factors associated with these symptoms in 614 patients with asthma, a large population. The study is clinically relevant; the methodology is adequate to answer the objectives and the study is well written. The study presents the following strong points: the expressive sample size; its a multicentric study; a comprehensive set of individual-level characteristics was analyzed to explore the impact of sociodemographic factors on the presence of anxiety/depression symptoms. As limitations: the fact that the sample was for convenience; another limitation is related to its cross-sectional nature, which does not allow inferring the presence of symptoms over time.

Response: We greatly appreciate the comment. Thank you.

Comment #1: The abstract's conclusion does not respond to the study's aim, regarding the level of agreement between the questionnaires. I strongly suggest it be reworded. In addition, some mention should be made regarding the main factors associated with the frequency of anxiety and depression. (page 3, line 112)

Response: We thank the reviewer for the comment, indeed the abstract's conclusion does not respond to the study's aims and it has been rewritten.

Please see page 3, lines 113-117 "At least 1/3 of the patients with persistent asthma experience symptoms of anxiety/depression, showing the relevance of screening these disorders in patients with asthma. EQ-5D and HADS questionnaires showed a moderate agreement in the identification of

anxiety/depression symptoms. The identified associated factors need to be further investigated in long-term studies.”

Comment #2: It is also suggested to reduce the number of keywords. (page 4, line 127)

Response: We thank the reviewer for the comment. We agree that the keywords can be reduced and the ones related to epidemiology were removed.

Please see page 4, line 129 “Key Words: Asthma; Anxiety Disorders; Depression Disorder; Surveys and Questionnaires.”

Comment #3: A reference is required to support the frequency of anxiety and depression in asthma (page 5, line 139).

Response: We thank the reviewer for the comment. We agree that a reference was missing to support the reference of anxiety and depression as comorbidities in asthma. We have now included the reference: Homętowska, H., et al., Fatigue, Depression, and Anxiety in Patients with COPD, Asthma and Asthma-COPD Overlap. *J Clin Med*, 2022. 11(24).

Please see page 5, line 138 “(...) anxiety and depression [6].”

Comment #4: Please inform the relevance of applying questionnaires to Physicians answer? (Global Initiative for Asthma (GINA) assessment of symptom control, the asthma treatment plan, and comorbidities). This needs to be clarified. (page 7, line 199).

Response: We thank the reviewer for the comment. We applied questionnaires directly to the recruiting physicians to improve the quality of the information obtained about the active treatment plan and identified comorbidities. This data collection procedure was mainly linked with the main aim of the INSPIRERS studies, which was to address the topic of adherence to asthma inhalers among adolescents and adults with persistent asthma, and we wanted to check if a higher number of comorbidities and/or complex treatment plans were associated with specific adherence patterns. Regarding asthma control, we aimed to obtain data both from physicians and patients. For physicians, we used the worldwide recognized GINA classification of assessment of symptom control. We included this information in the Data Collection sub-section.

Please, see pages 7-8 lines 197-208 “During the baseline face-to-face visit, data were collected from both physicians and patients in an attempt to improve the quality of the information obtained.

Physicians answered a questionnaire including the asthma treatment plan and comorbidities. (...)

Two asthma control questionnaires were used to gather the perspectives of the physician and the patient. Physicians answered the Global Initiative for Asthma (GINA) assessment of symptom control [26], which is recommended to be used at every opportunity in adolescents and adults.”

Comment #5: Why did the authors not assess clinical control using a validated and widely used questionnaire for this population (eg. Asthma Control Questionnaire (ACQ))?

Response: We thank the reviewer for the comment. We used the Control of Allergic Rhinitis and Asthma Test (CARAT), which has a main advantage, the assessment of both upper and lower airway symptoms. A recent systematic review and meta-analysis of CARAT's measurement properties[28], the first systematic review of measurement properties for asthma and/or AR and following the COSMIN (COnsensus-based Standards for the selection of health status Measurement Instruments) guidelines, has demonstrated that CARAT, overall, has good internal consistency, reliability, construct validity and responsiveness. Moreover, all COSMIN recommendations for the development of patient reported outcome measures (PROM) were met, except for concept elicitation and assessment of comprehensibility, as reported in other systematic reviews assessing PROM measurement properties in specialties (Beelen LM, et al. Patient-reported outcome measures in lymphedema: a systematic review and COSMIN analysis. *Ann Surg Oncol*. 2021;28(3):1656-1668; and Wang Y, et al. Patient-reported outcome measures used in patients undergoing total knee arthroplasty. *Bone Joint Res*. 2021;10(3):203-217).

In addition, when compared with ACQ, it has similar reliability (CARAT: 0.91; ACQ: 0.90) and correlation with clinician impression of disease control (CARAT 0.57, ACQ 0.67). Since its

development, CARAT has been widely used in clinical practice and in scientific research. It is now translated/culturally adapted in >27 languages, used in clinical research in >15 different countries and is currently integrated into a mHealth app (MASK-air) with users from 27 different countries [28]. Please see page 8 lines 209-214 “Patients answered the Control of Allergic Rhinitis and Asthma Test (CARAT). CARAT is a self-report questionnaire with a total score (CARAT-T) calculated by summing up the score of each of the 10 questions, resulting in a range of 0–30 points. A score >24 indicates good disease control [27]. This questionnaire has been widely used in clinical practice and in scientific research, being translated/culturally adapted in >27 languages and used in >15 different countries [28].”

Comment #6: The description of the EQ-5D seems unnecessary and repetitive (page 15, line 351).

Response: We thank the reviewer for the comment. We agree that the description of the EQ-5D seems unnecessary and repetitive, so we removed the phrase in the discussion section, and we now start the paragraph this way (please see page 16, line 357) “EQ-5D questionnaire could be useful in clinical practice [52]. The EQ-5D anxiety or depression domain had a greater agreement with the HADS score in identifying cases with both symptoms, as expected, than in identifying anxiety or depressive symptoms.”

Comment #7: The study's conclusion needs to be rewritten to include the main factors associated/or not with the presence of anxiety and depression in the studied population. (page 17, line 396)

Response: We thank the reviewer for the comment. We have now rewritten the study's conclusion with the main factors associated/or not with the presence of anxiety and depression. We have also included the level of agreement between HADS and EQ-5D questionnaires.

Please see page 18, lines 401-408 “This study shows that more than 30% of the patients with persistent asthma experience symptoms of anxiety/depression, which supports the relevance of emotional distress screening in patients with asthma. EQ-5D and HADS questionnaires showed a moderate agreement in the identification of anxiety/depression symptoms. Late asthma diagnosis, presence of comorbidities and female gender were positively associated with the presence of emotional distress, while better asthma control, health-related quality of life and perception of better health presented a negative association. These factors need to be further investigated in future long-term studies.”

Reviewer 2 - Dr. María-Teresa García-San, SERGAS

Comment #1: It is convenient to update the references, there is a predominance of old citations

Response: We thank the reviewer for the comment. We updated some citations, please see some examples below:

Introduction (page 5, lines 134-137): “Yet, this disease is often accompanied by multiple associated comorbidities, (...), and also anxiety and depression [6].”

Reference: Homętowska, H., et al., Fatigue, Depression, and Anxiety in Patients with COPD, Asthma and Asthma-COPD Overlap. *J Clin Med*, 2022. 11(24).

Methods – Data collection (page 8, lines 211-213): “This questionnaire has been widely used in clinical practice and in scientific research, being translated/culturally adapted in >27 languages and used in >15 different countries [28]”

Reference: Vieira, R.J., et al., Control of Allergic Rhinitis and Asthma Test: A systematic review of measurement properties and COSMIN analysis. *Clin Transl Allergy*, 2022. 12(9): p. e12194.

Discussion (page 17, lines 371-373): “Actually, emotional distress screening is very important in clinical practice because physicians can use targeted interventions to improve patients' symptoms [56].” Reference: Cooley, C., et al., Impact of interventions targeting anxiety and depression in adults with asthma. *J Asthma*, 2022. 59(2): p. 273-287.

Moreover, currently less than 35% of the references are older than 10 years and most of those concern manuscripts describing the study questionnaires (EQ-5D, HADS, CARAT), including their measurement properties, and systematic reviews and other studies assessing the relationship

between asthma and anxiety/depression symptoms. Over one-fourth of the references were published less than 5 years ago.