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Original Research Article

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Quality of life associated with chronic cough in the multinational Burden of Obstructive Lung Disease (BOLD) study: A cross-sectional study

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SUMMARY

Background. Chronic cough (CC) can impact daily life and persist for years. Its prevalence varies globally, but whether quality of life in CC also varies across regions is unknown. This study investigates the association of CC with mental and physical component scores of the 12-item Short Form Health Survey (SF-12) reflecting health-related quality of life in a multinational study.

Methods. We analysed data from 19,642 adults (≥40 years), recruited between Jan 2, 2003 and Dec 26, 2016 in 31 sites (25 countries) from the Burden of Obstructive Lung Disease (BOLD) study, who provided information on quality of life and CC. We assessed associations using linear regression, adjusted for confounders, and used random-effects meta-analysis to examine differences by sex and gross national income.

Findings. Overall, lower mental (-1.42, 95%CI -2.11 to -0.73; I^2 = 32.7%) and physical (-2.59, 95%CI -3.22 to -1.96; I^2 = 40.1%) health scores were associated with chronic cough. The association between physical health score and CC did not materially differ between sexes or gross national income. In males, physical health seems to be more affected by CC amongst those living in low- and middle-income countries (LMICs). In females, mental health also seems to be more affected by CC amongst those living in LMICs.

Interpretation. CC impairs health-related quality of life globally. However, it appears that physical health in males and mental health in females living in LMICs may be particularly affected by CC. These findings support the need to consider CC as a target for specific interventions to attenuate its burden on health and the economy.

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KEYWORDS: chronic cough; epidemiology; quality of life; health status

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RESEARCH IN CONTEXT

Evidence before this study: We searched PubMed, from database inception to 19 December 2024, using terms such as "chronic cough," "epidemiology," "quality of life," "SF-12," "adult," and "general population". A global and systematic assessment of the relationship of quality of life and chronic cough is limited to certain world regions and affected by use of different definitions and assessment tools.

Added value of this study: This study provides population-based estimates of the association of CC with quality of life for 31 sites, across 25 countries in several world regions, using the same protocol and definition. This provides a more comprehensive overview about chronic cough and its impact on health-related quality of life.

Implications of all the available evidence: The findings indicate the need for increased awareness about chronic cough and its association with reduced quality of life, particularly in low- and middle-income countries. This evidence can inform public health policies, improve diagnostic approaches, and guide treatment strategies to alleviate the burden of chronic cough globally.

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INTRODUCTION

Chronic cough (CC) is a debilitating condition that impacts daily life and has been associated with poor quality of life (QoL) outcomes in some populations.[1–3] It has been associated with several other conditions including depression, anxiety, sleep disorders, urinary incontinence and social disability.[4–9] CC is also linked with high healthcare utilization and costs.[10–13] In a European Lung Foundation internet survey conducted between 2012 and 2013, 96% of 1066 respondents said that their cough has an impact on their QoL.[14] Recent data from the population-based Respiratory Health in Northern Europe (RHINE) cohort show that participants with CC have lower work ability and are more likely to take more days of sick leave compared to those without CC.[15]

Most reports on QoL associated with CC are from countries in Europe[12, 16–23] and North America,[13, 24–28] as well as from China, Japan, and South Korea.[2, 11, 29–34] With the exception of China, these are all high-income countries. In addition, different instruments to assess QoL, including generic scores as the SF-36 questionnaire[34, 35] and cough-specific tools like the Leicester Cough Questionnaire (LCQ), have been used.[19, 22] Therefore, the aim of this study was to investigate the association of CC with QoL across several world regions, including low- and middle-income countries (LMIC), using data from the multinational Burden of Obstructive Lung Disease (BOLD) study using the same tool across study sites.[36]

METHODS

Study design

A detailed description of the BOLD study has been published elsewhere.[36] In brief, non-institutionalized adults (≥40 years old) were identified and recruited between 2003 and 2016 from the general population in 41 sites with more than 150,000 inhabitants. In each site, the aim was to recruit a minimum of 600 participants, with an equal number of males and females. Information on respiratory symptoms, health status, and exposure to potential risk factors was collected by trained fieldworkers, who administered standardised questionnaires translated into the local language. All sites received approval from their local ethics committee, and participants provided written informed

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consent. The study was conducted as per good clinical practice (GCP) as well as local ethics regulations.

Chronic cough

CC was defined as a cough, without having a cold, on most days for at least three months each year. It was assessed using two questions: "Do you usually cough when you don't have a cold?" and "Do you cough on most days for as much as three months each year?", and participants who affirmatively responded to both were classified as reporting CC.[37]

Quality of life

QoL was measured using the 12-item Short Form Health Survey (SF-12) in 31 of the 41 study sites. The SF-12 form includes questions on 12 items covering eight health-related QoL domains. Answers to the SF-12 form are scored and the results are reported in terms of a physical component score and a mental component score, which range from 0 to 100, with 100 representing the highest level of QoL.[38]

Statistical analysis

We used multivariable logistic regression models to assess the association of the SF-12 component scores with CC in each study site. These models were adjusted for age (years), sex (male, female), smoking status (never, former, current), passive smoking (yes, no), body mass index (BMI; underweight: <18.5 $kg.m^{-2}$, normal weight: 18.5 to 24.9 $kg.m^{-2}$, overweight: 25.0 to 29.9 $kg.m^{-2}$, obese: ≥30.0 $kg.m^{-2}$), exposure to dust in the workplace (years), education (years), a history of tuberculosis (yes, no), hypertension (yes, no), chronic airflow obstruction (post bronchodilator ratio of the forced expiratory volume in the first second to the forced vital capacity below the lower limit of normal (FEV1/FVC < LLN)), diabetes (yes, no), heart disease (yes, no), and dyspnoea (grade 2 or above on the modified Medical Research Council dyspnoea scale[39]). Site specific estimates were pooled using random effects meta-analysis,[40] and stratified by sex and smoking status. We used

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the I^2 statistics to summarize heterogeneity across sites. Results were considered significant if p value < 0.05. Analyses were conducted using Stata v.17 (Stata Corp., College Station, TX, USA).

RESULTS

Population characteristics

Data on 19,642 participants who completed the core questionnaire and had data on CC and QoL were included in this study (Tables 1 and 2). The mean age of participants ranged from 47 years in Mysore (India) to 59 years in Tartu (Estonia) and Salzburg (Austria). The lowest proportion of male participants was found in Tartu (Estonia) at 40.5% while the highest proportion was in Mumbai (India) at 62.9%. Mean BMI ranged from 21.6 kg/m² in Nampicuan-Talugtug (Philippines) to 30.9 kg/m² in Riyadh (Saudi Arabia). The prevalence of ever smokers ranged from 9.6% in Mysore (India) to 69.6% in Uitsig-Ravensmead (South Africa).

The prevalence of CC (Table 2) varied widely, ranging from 0.4% in Ife (Nigeria) to 18.1% in Lexington, KY (USA). For other respiratory conditions, dyspnoea was most frequently reported in Nampicuan-Talugtug (Philippines) at 28.8%, while chronic airflow obstruction was most common in Uitsig-Ravensmead (South Africa) at 18.8%. Regarding cardiometabolic comorbidities, heart disease had the highest prevalence in Tartu (Estonia) at 32.4%, diabetes was most prevalent in Riyadh (Saudi Arabia) at 27.4%, and arterial hypertension was most common in the Lexington (KY, USA) at 43.8%.

Table 3 provides the mean QoL component scores for each study site. For physical component scores, Krakow (Poland) had the lowest (43.9) while Blantyre (Malawi) had the highest (53.9) mean score. In terms of mental health, the lowest mean score (41.8) was found in Fes (Morocco), whereas the highest mean score (58.4) was found in Mysore (India).

Physical health and chronic cough

The physical component score in people with CC was lower than that of people without CC (-2.59, 95%CI -3.22 to -1.96) (figure 1). The heterogeneity across sites was low (I^2 = 40.1%) and mainly driven by stronger associations in Kashmir (India) with a difference of -7.43 (95%CI -9.47 to -5.39) and Mumbai (India) with -6.06 (95%CI -10.89 to -1.22). There was no material difference in the

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association of physical health with CC between high-income country sites (-2.17, 95%CI -2.80 to -1.53) and LMIC sites (-2.94, 95%CI -4.08 to -1.81). The magnitude of the association between physical component score and CC was approximately the same in females (-2.44, 95%CI -3.27 to -1.61) (supplementary figure 1) and in males (-2.93, 95%CI -4.02 to -1.83) (supplementary figure 2). Although not statistically significant, physical scores in association with CC were lower among males from LMIC sites than in high income sites.

Mental health and chronic cough

The mental component score in people with CC was lower than that of people without CC (-1.42, 95%CI -2.11 to -0.73) (figure 2). The heterogeneity across sites was low (I^2 = 32.7%) and mainly driven by Mumbai (India) with difference of -6.78 (95%CI -13.67 to 0.12), London (England) with -6.58 (95%CI -9.71 to -3.44), Maastricht (Netherlands) with -4.65 (95%CI -9.35 to 0.05), as well as Mysore (India) with 6.30 (95%CI -1.50 to 14.10) and Khartoum (Sudan) with 4.58 (95%CI 0.00 to 9.16). There was no difference in the association of mental health with CC between high-income country sites (-1.37, 95%CI -2.27 to -0.46) and LMIC sites (-1.49, 95%CI -2.62 to -0.35).

The magnitude of the association between mental component score and CC was approximately the same in females (-1.19, 95%CI -2.22 to -0.16) (supplementary figure 3) and in males (-1.71, 95%CI -2.79 to -0.64) (supplementary figure 4). Although not statistically significant, mental health scores were lower among females from LMIC sites than in high income sites.

DISCUSSION

In this multinational population-based study, CC was associated with worse physical and mental health-related QoL. These associations were independent of chronic airflow obstruction, dyspnoea, history of tuberculosis, and cardiometabolic comorbidities.

We report lower physical and mental health scores in individuals with CC compared to those without. One of the key findings was that CC has a particularly greater impact on the physical component, which can also be observed in other respiratory conditions.[41–45] For CC, similar findings of studies

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that also used SF-12, lower physical component scores have been reported from China[2], Germany [21] and Norway [46], while data reporting a stronger association with the SF-12 mental component score are from Japan[11], South Korea and Taiwan[47], the United Kingdom[12], France[20], and Spain.[23] The use of other cough-specific tools like the LCQ also reflects this variability: a study from the Netherlands[22] reported lower physical domain scores, while a Finnish employee study [19] found slightly lower psychological scores. Using the SF-36 questionnaire also showed different directions where lower physical scores were reported in Australia[35] and Korea[48], but lower mental health scores in China.[34]

The association with physical and mental QoL was significant and relatively of the same magnitude in both sexes. This contradicts prior studies suggesting that females may experience a greater impact of CC on health-related QoL[30] because they have a heightened cough reflex sensitivity[49, 50] and are more likely to seek medical attention due to other to physical complaints like urinary stress incontinence.[22, 51, 52] Our results are supported by findings from primarily Asian studies stating that females did not have a greater impact on physical health scores[2, 34] despite reporting more frustration and sleep disturbance compared to men.[34] It is also reported that females are more adversely affected as the duration of a cough increases.[53] Considering this, previous studies that reported a stronger negative impact on females may have experienced potential selection bias by including females with a higher frequency of coughing.[34] However, slight sex differences without statistical significance were observed in LMIC sites, where lower physical QoL scores were reported in males and lower mental QoL scores in females.

To our knowledge, no study has compared the effect of CC on QoL by national income levels. Our study provides strong evidence that CC is a significant global health issue with a substantial negative impact on both physical and mental QoL without a clear pattern indicating that CC has a stronger impact in either high-income sites or LMIC sites. However, the above mentioned sex-related differences were more pronounced in LMICs where healthcare resources are commonly more limited and chronic respiratory symptoms are among the most prevalent and increasing health complaints.[54–56]

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The strengths of this population-based study include its large sample size and wide geographical coverage, the use of a standardised protocol for data collection across study sites, and the rigorous training of all staff involved in the study. Our study also has limitations. Our definition of CC (i.e. three month cut-off for cough duration) is not in line with the most recent guidelines[5, 57–59], but it agrees with the majority of epidemiological studies on CC. [60] This difference should be considered when comparing our findings with studies with more recent data collection. The cross-sectional design of this study limits the ability to establish causality. However, it is unlikely that low health-related QoL would cause CC. The wide variation in prevalence of CC across our study sites is likely explained by varying exposure to risk factors, [37, 61–63] and because information on CC was self-reported, it may also be influenced by culture, health literacy and different thresholds for reporting cough.[64] However, this is unlikely to have had much of influence in our findings as there was little evidence of heterogeneity in the association between QoL and CC across sites. CC can present with co-morbidities such as gastroesophageal reflux, rhinosinusitis and depression,[8, 17, 18, 65] for which we do not have information. We did, however, adjust our models for chronic airflow obstruction, which is a key characteristic of COPD. These conditions should be considered as potential confounders when assessing the relationship of CC with QoL in future studies. In addition, this study is limited to adults aged 40 years and above.

In conclusion, our study found that CC significantly impacts both physical and mental health-related QoL with a stronger effect on the physical component across world regions independently of other respiratory or cardiometabolic conditions. It also suggests that the strength of these associations may differ by sex depending on the gross national income of the country of residence. Our findings emphasize the need for further research into these associations and their underlying mechanisms so that interventions can be tailored accordingly and supports further research into the treatment of cough.

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CONTRIBUTORS

HA, EFMW, and AFSA conceived the analyses. AFSA accessed, verified and analysed the data. Under the supervision of EFMW and AFSA, HA prepared the initial draft. All authors provided critical revision of the manuscript, as well as read and approved the final manuscript. All authors had full access to the data and accept responsibility for the decision to submit for publication.

DATA SHARING

De-identified participant data and questionnaires may be shared, after publication, on a collaborative basis upon reasonable request made to Dr Amaral (a.amaral@imperial.ac.uk). Requesting researchers will be required to submit an analysis plan.

ROLE OF THE FUNDING SOURCE

The funders had no role in the conduction of the study.

DECLARATION OF INTERESTS

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TABLE LEGENDS

Table 1. Characteristics of study participants in the Burden of Obstructive Lung Disease study at baseline.

Table 2. Prevalence of chronic cough and other conditions in the Burden of Obstructive Lung Disease study at baseline.

Table 3. SF-12 mental and physical component scores in the Burden of Obstructive Lung Disease study at baseline.

FIGURE LEGENDS

Figure 1: Association of physical health score with chronic cough in the BOLD participants. ES (95% CI) is the adjusted odds ratio and 95% confidence interval.

Figure 2: Association of mental health score with chronic cough in the BOLD participants.

Supplementary Figure 1: Association of physical health score with chronic cough among females.

Supplementary Figure 2: Association of physical health score with chronic cough among males.

Supplementary Figure 3: Association of mental health score with chronic cough among females.

Supplementary Figure 4: Association of mental health score with chronic cough among males.

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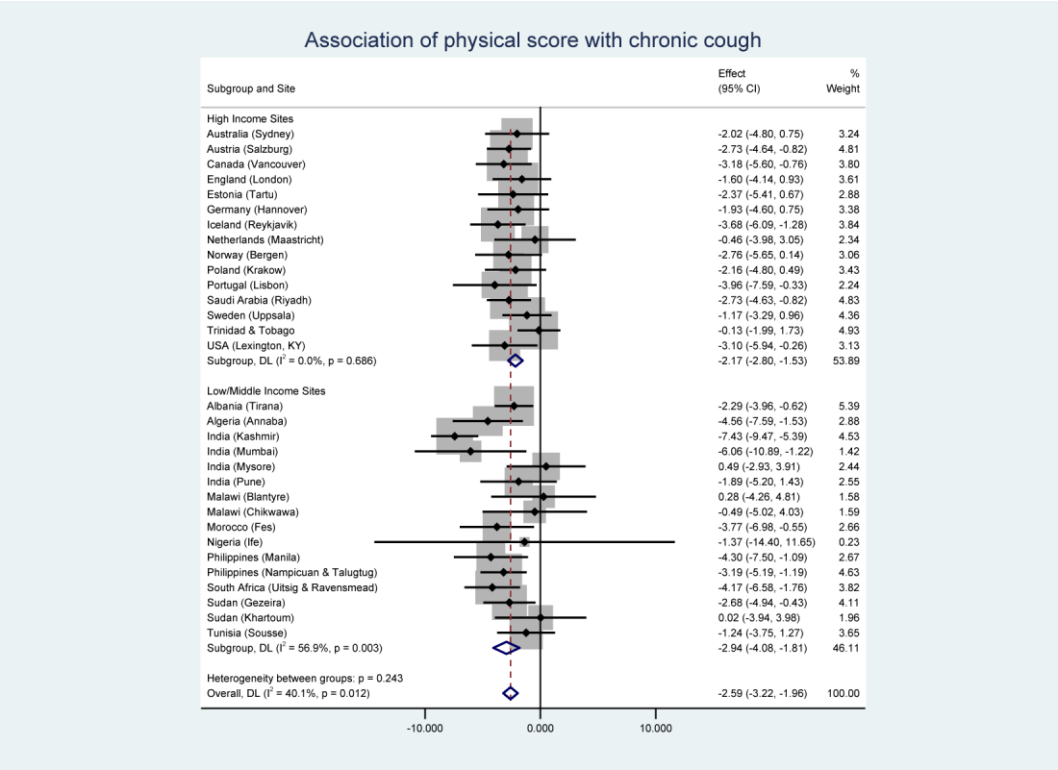


Figure 1

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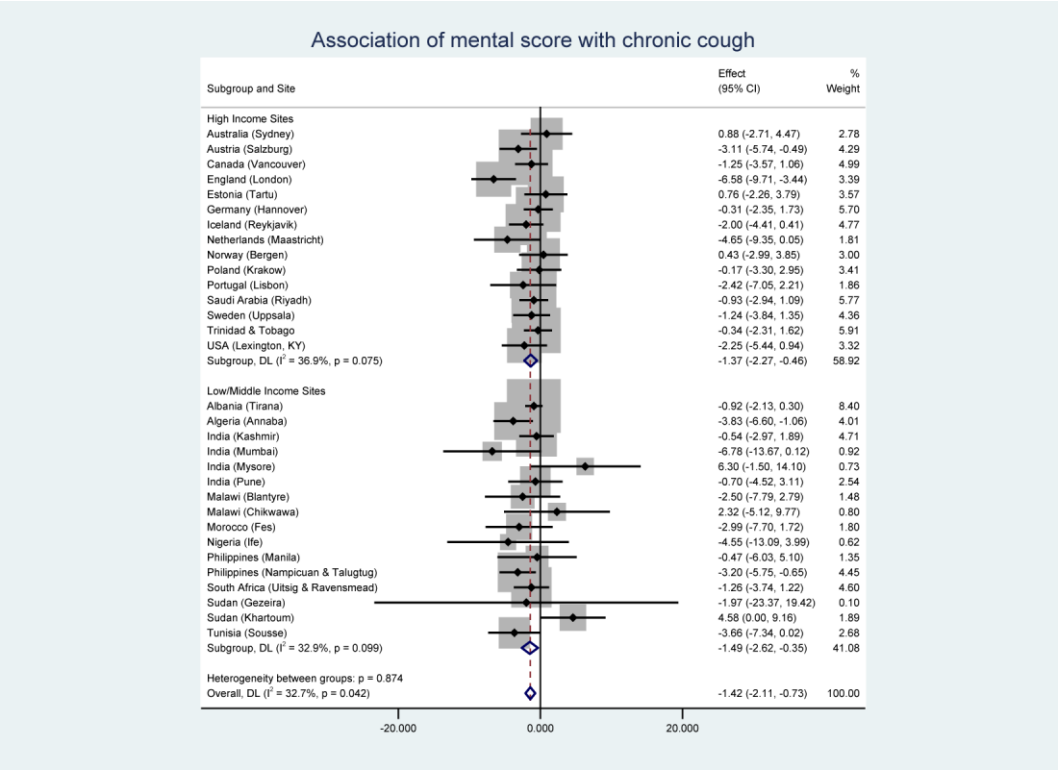


Figure 2

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Table 1. Characteristics of study participants in the Burden of Obstructive Lung Disease study

	N	Males (%)	Age (year), mean (SD)	BMI (kg/m^2), mean (SD)	Ever smokers (%)	Passive smoking (%)	Education (years), mean (sd)	Dust in workplace (years), mean (sd)
Albania (Tirana)	887	49.5	55 (12)	27.5 (4.1)	36.5	37	10 (5)	15 (14)
Algeria (Annaba)	828	51.0	53 (11)	28.1 (5.6)	39.7	10.5	8 (6)	6 (10)
Australia (Sydney)	474	46.0	58 (13)	27.7 (5)	52.3	11.1	11 (3)	4 (9)
Austria (Salzburg)	1202	46.8	59 (12)	26.2 (4.1)	53.3	21.6	10 (2)	5 (12)
Canada (Vancouver)	793	47.9	56 (12)	26.7 (5)	57.3	5.6	16 (3)	3 (8)
England (London)	642	45.6	57 (12)	27.1 (4.9)	65.5	17.3	14 (4)	4 (10)
Estonia (Tartu)	565	40.5	59 (12)	28.3 (5.3)	45.6	15.3	14 (4)	5 (10)
Germany (Hannover)	529	47.0	57 (11)	26.6 (4.3)	60.4	17.8	11 (2)	3 (9)
Iceland (Reykjavik)	726	52.0	57 (12)	27.8 (4.9)	66.3	16.7	13 (4)	4 (10)
India (Kashmir)	751	51.6	51 (11)	22.6 (3.7)	52.2	64.1	2 (4)	0 (1)
India (Mumbai)	434	62.9	53 (10)	23.9 (4.1)	10.0	0.9	9 (5)	1 (6)
India (Mysore)	592	42.3	47 (7)	24.7 (3.8)	9.6	0	9 (6)	1 (4)
India (Pune Rural)	828	60.0	52 (10)	22.1 (3.9)	12.5	11	4 (4)	2 (6)
Malawi (Blantyre)	359	54.4	50 (9)	24.4 (5)	16.2	3.3	9 (4)	3 (7)
Malawi (Chikwawa)	381	56.9	51 (10)	21.8 (3.8)	29.2	2.7	4 (4)	3 (7)
Morocco (Fes)	474	60.3	53 (12)	27.2 (4.9)	35.3	8.1	5 (6)	9 (13)
Netherlands (Maastricht)	572	47.4	58 (12)	27.4 (4.5)	64.3	18.2	15 (5)	3 (9)
Nigeria (Ife)	841	55.1	53 (11)	25 (5.1)	14.6	1.7	10 (6)	5 (10)
Norway (Bergen)	574	49.0	57 (12)	26.4 (4.2)	64.6	22	13 (3)	7 (12)
Philippines (Manila)	825	46.5	52 (11)	24.5 (4.7)	56.8	49.4	10 (4)	7 (11)
Philippines (Nampicuan & Talugtug)	715	49.3	54 (11)	21.6 (4.1)	55.2	47.2	8 (4)	6 (12)
Poland (Krakow)	477	49.9	55 (11)	27.6 (4.7)	61.7	40.8	11 (3)	10 (13)
Portugal (Lisbon)	563	47.8	57 (12)	27.7 (4.5)	44.9	19.8	9 (5)	10 (14)
Saudi Arabia (Riyadh)	609	54.9	50 (8)	30.9 (5.7)	27.0	5.4	10 (5)	3 (8)
South Africa (Uitsig/Ravensmead)	763	44.2	53 (10)	27.5 (7.3)	69.6	49.9	8 (3)	7 (10)
Sudan (Gezeira)	372	57.2	52 (10)	26.9 (17.6)	27.7	11.1	6 (5)	5 (11)
Sudan (Khartoum)	479	53.1	53 (11)	26.3 (6.3)	21.7	7.5	7 (6)	3 (8)
Sweden (Uppsala)	488	47.5	58 (11)	26.7 (4.3)	59.0	5.8	13 (4)	5 (11)
Trinidad and Tobago	1051	50.0	55 (11)	28.7 (9.3)	29.8	22	11 (4)	7 (11)
Tunisia (Sousse)	433	60.7	51 (9)	27.8 (5.2)	52.8	30.4	9 (5)	11 (13)
USA (Lexington, KY)	415	46.3	56 (12)	30.4 (6.3)	61.0	26.6	13 (3)	8 (12)

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Table 2. Prevalence of chronic cough and other conditions in the Burden of Obstructive Lung Disease study.

	N	Chronic cough (%)	Dyspnoea (%)	Chronic airflow obstruction (%)	History of tuberculosis (%)	Heart disease (%)	Hypertension (%)	Diabetes (%)
Albania (Tirana)	887	9.8	9.2	7.4	0.7	2.7	22.1	6.9
Algeria (Annaba)	828	2.8	12.3	6.2	2.4	6.1	22.2	14.2
Australia (Sydney)	474	6.4	7.2	9.7	0.8	11.1	31.4	8.2
Austria (Salzburg)	1202	5.4	8	16.9	2.6	12.7	29.9	5.9
Canada (Vancouver)	793	10.6	6.7	12.7	3.1	11.9	20.2	7.4
England (London)	642	14.3	14.2	17	1.8	6.2	33.7	6.3
Estonia (Tartu)	565	6.7	13.5	5.9	6.2	32.4	36.5	6.3
Germany (Hannover)	529	7.7	3.8	8.2	3.6	12.7	33.2	4.8
Iceland (Reykjavik)	726	11.1	8.7	11.1	4.9	13.7	31.7	4.2
India (Kashmir)	751	5.6	4.9	16	0.4	1.1	26.7	2.6
India (Mumbai)	434	1.6	9.8	6.5	0.5	2	10.6	5.2
India (Mysore)	592	1.4	0.0	7.9	0	0.2	17	16.9
India (Pune Rural)	828	1.7	6.6	5.9	0.8	0.8	5.2	2.2
Malawi (Blantyre)	359	2.1	1.9	6.4	5.2	1.9	16.1	5.9
Malawi (Chikwawa)	381	1.2	1.4	12.2	4	0.9	1.6	1.3
Morocco (Fes)	474	6.4	14.8	6.8	0.9	2.9	22	9.1
Netherlands (Maastricht)	572	5.3	10.3	18.4	1.5	16.4	30	7.2
Nigeria (Ife)	841	0.4	3.2	7	0.4	0.1	1.4	0.6
Norway (Bergen)	574	7.2	5.3	11.1	0.1	8.7	25.2	4
Philippines (Manila)	825	6.1	22.9	8.6	10.3	7.6	23.6	6.1
Philippines (Nampicuan & Talugtug)	715	8	28.8	15	3.5	7.4	20.4	2.6
Poland (Krakow)	477	7	24.1	13.9	2	29.8	40.2	10
Portugal (Lisbon)	563	9.1	12.2	7.8	5	9.3	28.9	8.9
Saudi Arabia (Riyadh)	609	10.9	22.5	2.8	1.8	5	24	27.4
South Africa (Uitsig/Ravensmead)	763	11.4	28.7	18.8	15.2	7.3	34.9	11.4
Sudan (Gezeira)	372	1.3	8.2	5.8	0.3	0	9.7	6.7
Sudan (Khartoum)	479	3.3	6.8	10.1	0.9	1.9	20.6	8.7
Sweden (Uppsala)	488	6.7	5.5	7.8	1.1	9.6	26.6	3
Trinidad and Tobago	1051	7.1	8.6	5.9	0	5.3	27.9	14.8
Tunisia (Sousse)	433	8.2	15.4	5.2	0	4	14.1	7
USA (Lexington, KY)	415	18.1	19.5	12.4	2.3	22.8	43.8	15.7

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Table 3. SF-12 mental and physical component scores in the Burden of Obstructive Lung Disease study.

	N	Mental component score, mean (sd)	Physical component score, mean (sd)
Albania (Tirana)	887	51.4 (5.9)	51.5 (6.8)
Algeria (Annaba)	828	49.3 (7.2)	49.7 (8.8)
Australia (Sydney)	474	51.8 (9.3)	51.1 (8.5)
Austria (Salzburg)	1202	54.2 (8.6)	50.4 (7.5)
Canada (Vancouver)	793	50.8 (9.6)	51.6 (9)
England (London)	642	48.8 (11)	49 (10.3)
Estonia (Tartu)	565	52 (8.7)	47.3 (9.2)
Germany (Hannover)	529	55.9 (7.5)	48.6 (7.9)
Iceland (Reykjavik)	726	53.6 (8.9)	50.5 (9.3)
India (Kashmir)	751	51.7 (6.3)	51.2 (6.6)
India (Mumbai)	434	58 (6.6)	52.3 (7.1)
India (Mysore)	592	58.4 (7.1)	53.3 (4.1)
India (Pune Rural)	828	49.3 (7.4)	50.1 (6.6)
Malawi (Blantyre)	359	54 (8.2)	53.9 (3.9)
Malawi (Chikwawa)	381	56 (7.9)	52.3 (4.1)
Morocco (Fes)	474	41.8 (8.4)	50.8 (9.2)
Netherlands (Maastricht)	572	53.5 (9.4)	50.2 (9)
Nigeria (Ife)	841	55.2 (9.7)	45.5 (8.3)
Norway (Bergen)	574	54.2 (8.9)	50.8 (8.7)
Philippines (Manila)	825	53.2 (9.4)	46.4 (7.6)
Philippines (Nampicuan & Talugtug)	715	50.1 (7.2)	45.7 (7.6)
Poland (Krakow)	477	47.8 (10.2)	43.9 (10.7)
Portugal (Lisbon)	563	50.3 (11.4)	49.7 (8.6)
Saudi Arabia (Riyadh)	609	50.2 (7.8)	48.5 (8.6)
South Africa (Uitsig/Ravensmead)	763	49 (9.8)	46.5 (9.4)
Sudan (Gezeira)	372	53.1 (10.1)	47.3 (7.6)
Sudan (Khartoum)	479	47.6 (9.2)	48.8 (7.4)
Sweden (Uppsala)	488	43.5 (6.8)	48.8 (6.6)
Trinidad and Tobago	1051	54.9 (8.4)	48.2 (7.1)
Tunisia (Sousse)	433	50.5 (9.7)	47.4 (8.6)
USA (Lexington, KY)	415	50.4 (11.1)	45.8 (11.4)

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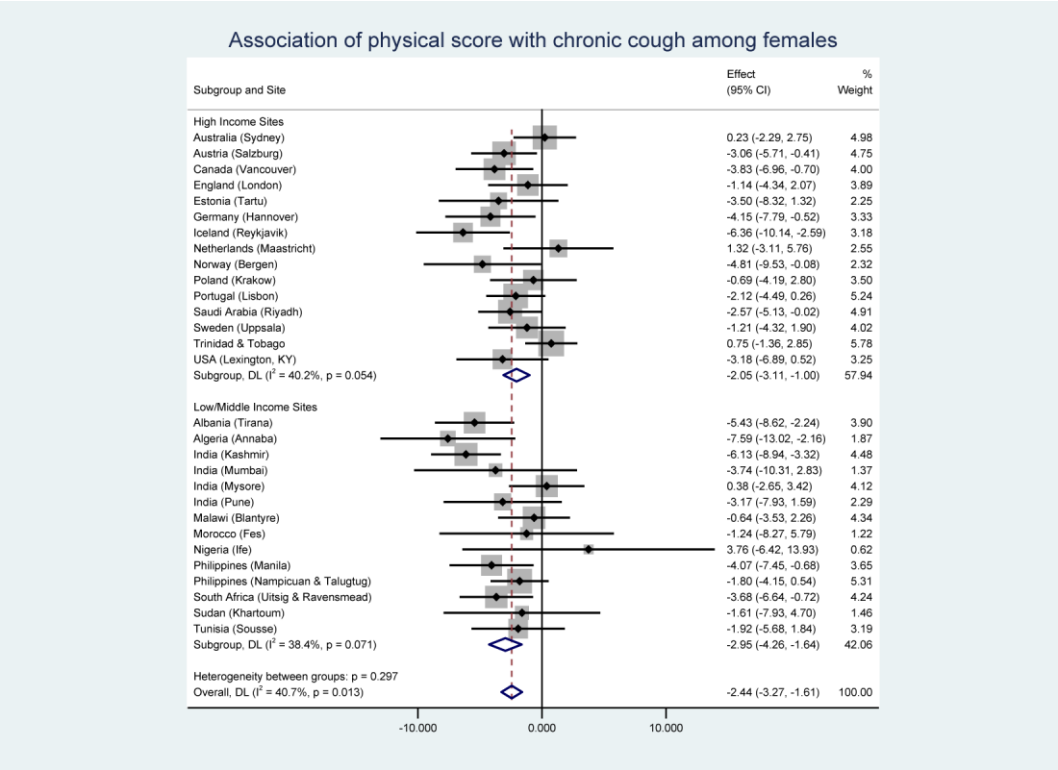


Figure S1

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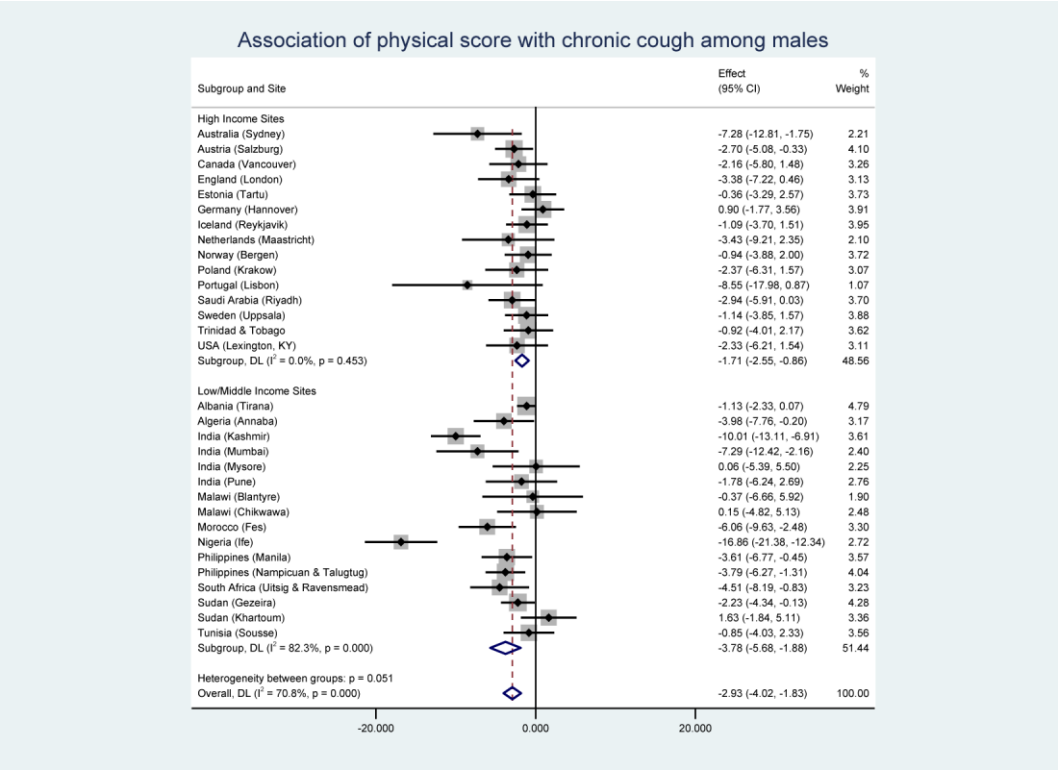


Figure S2

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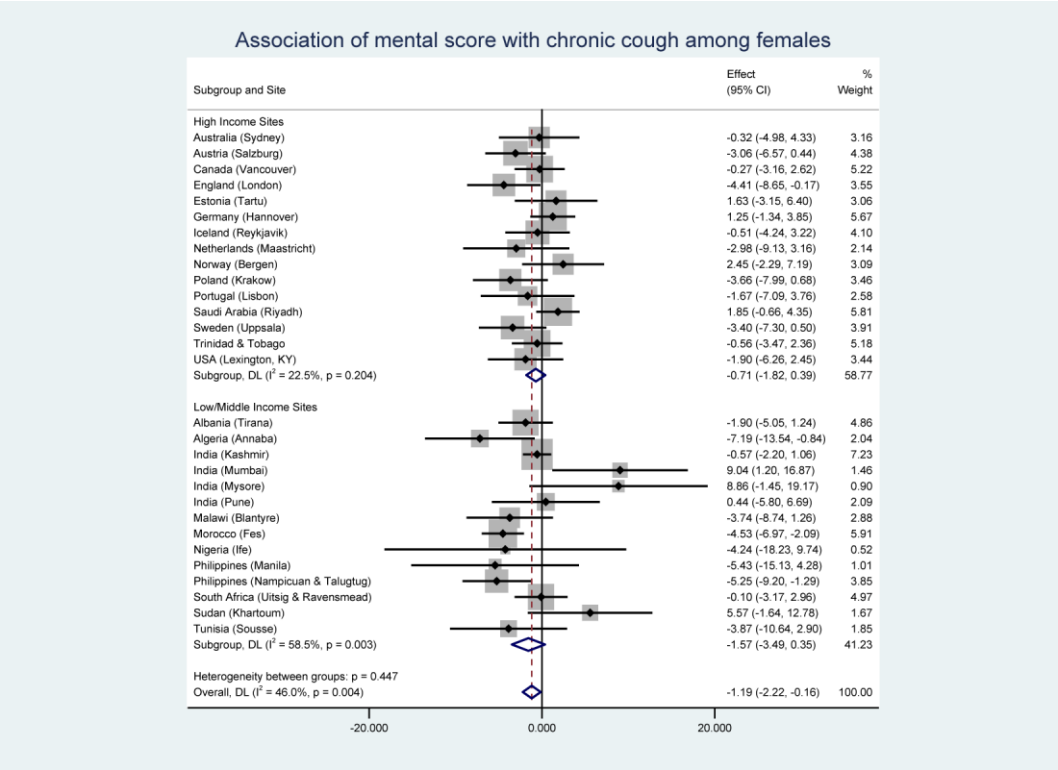


Figure S3

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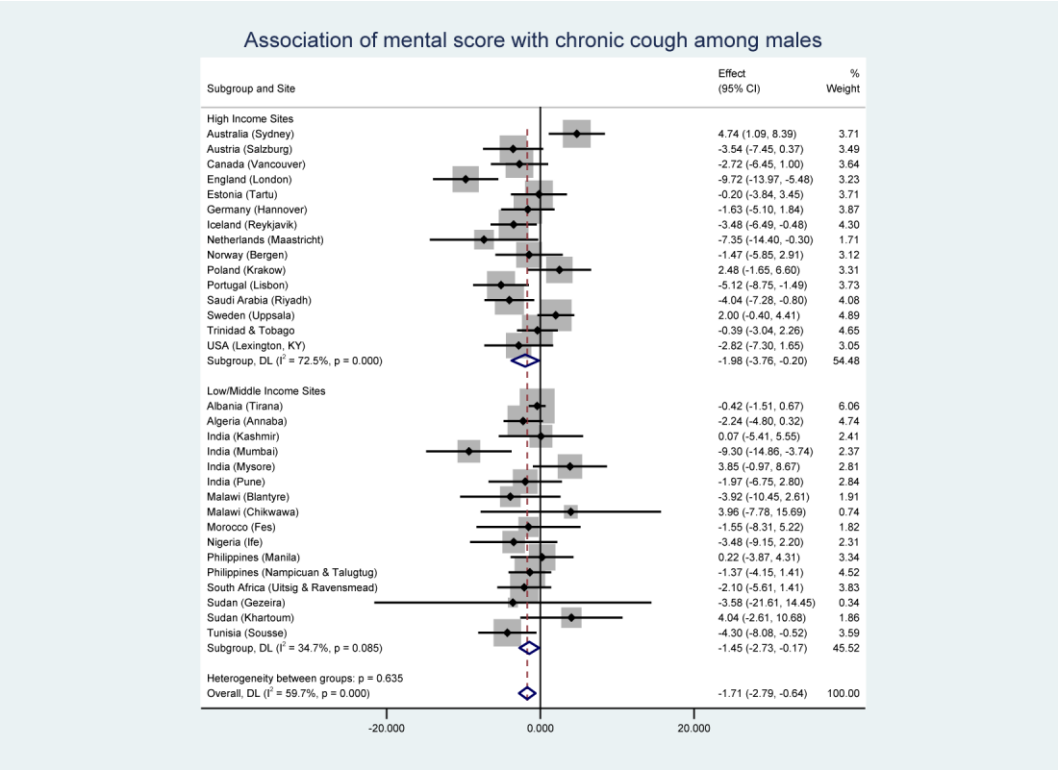


Figure S4

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