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The detection, assessment and clinical evolution of interstitial lung abnormalities identified through lung cancer screening.

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Abstract

Introduction

Interstitial lung abnormalities (ILAs) are common incidental findings in lung cancer screening however their clinical evolution and longer-term outcomes are less clear. The aim of this cohort study was to report five-year outcomes of individuals with ILA identified through a lung cancer screening programme. In addition, we compared patient reported outcome measures (PROMs) in patients with screen-detected ILA to newly diagnosed interstitial lung disease (ILD) to assess symptoms and health-related quality of life (HRQOL).

Methods

Individuals with screen-detected ILA were identified and five-year outcomes, including ILD diagnoses, progression-free survival and mortality, were recorded. Risk factors associated with ILD diagnosis were assessed using logistic regression and survival using Cox proportional hazard analysis. PROMs were compared between a subset of patients with ILA and a group of ILD patients.

Results

1,384 individuals underwent baseline low-dose computed tomography (LDCT) screening with 54 (3.9%) identified as having ILA. 22 (40.7%) were subsequently diagnosed with ILD. 14 individuals (25.9%) died, and 28 (53.8%) suffered disease progression within five years. Fibrotic ILA was an independent risk factor for ILD diagnosis, mortality, and reduced progression-free survival. Patients with ILA had lower symptom burden and better HRQOL in comparison to the ILD group. Breathlessness visual analogue score (VAS) was associated with mortality on multivariate analysis.

Conclusions

Fibrotic ILA was a significant risk factor for adverse outcomes including subsequent ILD diagnosis. Whilst screen-detected ILA patients were less symptomatic, breathlessness VAS was associated with adverse outcomes. These results could inform risk stratification in ILA.

Introduction

Screening for lung cancer with low dose computed tomography (LDCT) identifies early-stage disease and reduces lung cancer-specific mortality.[1, 2] Whilst not the primary aim of screening, LDCT scans can also identify other incidental findings including parenchymal lung changes. These changes have been recognised as a distinct clinical entity, termed interstitial lung abnormalities (ILAs), by the Fleischner Society and defined as an incidental finding of non-dependent abnormalities involving at least 5% of a lung zone.[3] ILA detection in screening is common, ranging between 4-20% across lung cancer screening studies.[4-7] The detection of ILAs is associated with disease progression and mortality[8-10] and radiological pattern, especially the presence of traction bronchiectasis, is an important predictor of adverse outcomes.[8, 11] Three subtypes of ILA have been described: non-subpleural non-fibrotic, subpleural non-fibrotic and subpleural fibrotic.[3] Subpleural fibrotic ILA is characterised by the presence of traction bronchiectasis and is most likely to progress.

The presence of ILA increases the likelihood of a subsequent diagnosis of ILD up to five times.[6] Identifying which individuals with ILA will evolve into clinically significant ILD is of key importance given the increased utility of lung cancer screening programs. A recent report from a UK screening population identified that 65% of patients with ILA were diagnosed with ILD on initial clinical assessment.[12] However, there is a lack of longitudinal data describing the evolution of ILA to ILD, with associated risk factors, within the context of lung cancer screening.

The aim of this study is to report the five-year clinical outcomes of individuals with ILA identified during the Manchester Lung Health Check (MLHC) lung cancer screening pilot. We describe the proportion of patients with subsequent disease progression, ILD diagnosis and mortality. We also explore potential risk factors associated with adverse outcomes. In addition, in a smaller sub-study, we compare patient reported outcome measures (PROMs in a subset of patients with screen-detected ILA to a cohort of patients with newly diagnosed ILD to assess symptoms and health-related quality of

life (HRQOL burden. Finally, we also examine if baseline PROMs predict subsequent adverse outcomes in ILA.

Methods

MLHCs and recruitment: Individuals were recruited from the MLHC pilot, which evaluated the impact of implementing LDCT screening in three socially disadvantaged areas of Manchester, United Kingdom. The design of the MLHC pilot has previously been described. [13] In brief, ever-smokers aged 55-74 were invited to attend a community-based LHC where 6-year lung cancer risk, respiratory symptoms and spirometry were assessed. Those at high risk of lung cancer, defined as having a 'Prostate Lung Colorectal and Ovarian' lung cancer risk prediction model ($PLCO_{M2012}$) score of ≥1.51%, were offered annual LDCT screening over two rounds, starting with an immediate LDCT in a co-located mobile unit.

Radiology reporting, ILA diagnosis and five-year clinical outcomes: All participants who underwent a baseline LDCT scan were included in this study. Individuals with ILA, as defined by the Fleischner Society[3], were identified. All screening LDCT scans with reported ILA were reviewed centrally as part of a specialist ILD multi-disciplinary team (MDT) meeting. Participants with respiratory bronchiolitis-interstitial lung disease (RB-ILD) or features not in keeping with ILA were excluded. In those with confirmed ILA, all relevant CT scans were retrospectively reviewed to determine ILA subtypes.

Clinical outcomes over a five-year period from the point of ILA identification were retrospectively collected from electronic patient records. This included subsequent radiology reports, lung function tests, diagnoses, and all-cause mortality. Disease-progression was defined using one of the following three criteria adapted from guidelines defining progressive pulmonary fibrosis[14]: (1) death, (2) absolute decline in forced vital capacity (FVC) % predicted >10% from baseline or (3) two of symptom progression, absolute decline in FVC % predicted 5-10% from baseline and radiological progression from baseline. Baseline spirometry for all screening participants was performed on the community-

based mobile unit whilst subsequent lung function, when clinically indicated, was performed in the hospital lung function laboratories.

The *ILD in Screening Study*: A subset of patients with ILA were prospectively recruited to a sub-study, The *ILD in Screening Study*, to assess baseline PROMs. These were compared to a control group of consecutive ILD patients attending a new patient clinic at a tertiary ILD centre. Recruited patients completed the following questionnaires: University of California San Diego Shortness of Breath Questionnaire (UCSD-SOBQ),[15] Fatigue Severity Scale (FFS),[16] Leicester Cough Questionnaire (LCQ),[17] Kings Brief Interstitial Lung Disease (KBILD) questionnaire,[18] Medical Outcomes 36-item Short Form Survey (SF-36),[19] and visual analogue scales (VAS) to cough, breathlessness, and fatigue.[20] Further details can be found in table S1 of the supplementary material.

Ethical approval: The MLHC pilot and the *ILD in Screening Study* (REC reference 17/WM/0365) were both approved by the North West-Greater Manchester West Research Ethics Committee. Clinical data from screening were recorded on an ethically approved database (REC ref: 16/NW/0013).

Statistical analysis: Continuous data were tested for normality using the Shapiro-Wilk test and analysed using independent t-test (parametric data) or Mann-Whitney U test (non-parametric data). Categorical data were analysed using Chi-squared test. Associations between baseline characteristics and subsequent diagnosis of ILD were tested using binary logistic regression. Univariable analysis was performed to identify significant associations using a p-value threshold of 0.05. Variables included were baseline demographics (age, sex, smoking status, pack years, body mass index [BMI], indices of multiple deprivation (IMD) rank, $PLCO_{M2012}$ score), FVC % predicted, ILA subtype, Medical Research Council (MRC) dyspnoea score and comorbidities and medications reported in >10% of the cohort. A multivariate model was then constructed using forward selection which included all significant variables, to identify those which were independently associated with a subsequent ILD diagnosis. For ease of analysis, non-subpleural non-fibrotic and subpleural non-fibrotic subtypes were merged into one group (non-fibrotic ILA) and subpleural fibrotic was renamed “fibrotic ILA”. MRC dyspnoea score

was also split into two groups, MRC score <3 and ≥3. ILA survival analysis was performed using Cox proportional hazard model to identify risk factors for mortality. Univariable analysis was performed initially using the same variables included in logistic regression. Significant variables ($p<0.05$) were then selected for multivariate analysis using forward selection to identify independent risk factors for mortality. The same analysis was performed for progression-free survival, which was measured in months from ILA identification to disease-progression as defined above. Statistical analysis was performed using SPSS version 25 (IBM, Armonk, NY, USA).

Results

Screening outcomes and ILA diagnosis: A total of 1,384 individuals underwent baseline LDCT screening as part of the MLHC pilot between June 2016 and October 2016. Interstitial changes were reported in 87 (6.3%) initial LDCT reports. 33 were deemed not to have ILA (31 RB-ILD; two interstitial oedema) and were excluded, leaving 54 individuals with ILA. This equates to 3.9% of the screened cohort at baseline. Screening participants with identified ILA were older (67.5±4.8 vs. 64.7±5.5 years; p= 0.0002), had a higher proportion of men (68.5% vs. 48.7%, p=0.005) and a lower proportion of current smokers (38.9% vs. 53.5%, p=0.04) than those without ILA (table 1). Baseline FVC % predicted was lower in the ILA cohort (89.9%±21.3 vs. 99.9%±24.4; p=0.002) and fewer individuals had obstructive spirometry (33.3% vs. 51.0%, p=0.01). Figure 1 describes the distribution of ILA subtypes and the most common radiological features identified.

Evolution to ILD diagnosis: All 54 individuals with ILA were offered an assessment at a tertiary ILD clinic. 15 chose not to attend and were managed in primary care. A significantly higher proportion of those seen in tertiary care had fibrotic ILA compared to those managed in primary care (46.6% vs 13.3%, p=0.03, table S3). Overall, 22 (40.7%) patients with ILA were formally diagnosed with ILD (Figures 2 and 3), equating to 1.6% of the population screened. Idiopathic pulmonary fibrosis (IPF) was the most common diagnosis (n=7/22, 31.8%). In 15 (68.2%) of those diagnosed with ILD, the diagnosis was made at the first clinic visit. Amongst individuals diagnosed with ILD at subsequent

visits, the median time to diagnosis from the first clinic visit was 14 months (interquartile range [IQR] 17). All diagnoses were clinico-radiological. Four patients were initiated on treatment with medication: three with IPF received antifibrotic therapy (one pirfenidone; two nintedanib) and one with hypersensitivity pneumonitis received oral corticosteroids.

Univariate logistic regression identified that a fibrotic ILA subtype (odds ratio [OR] 3.6, 95% confidence interval [CI] 1.1-11.5, p=0.03) and an MRC score ≥3 (OR 5.6, 95% CI 1.0-31.2, p=0.04)) were predictors of subsequent diagnosis of ILD. All other variables tested were not significant. After multivariate analysis, fibrotic ILA remained independently associated with progression to ILD (OR 3.6, 95% CI 1.1-11.5, p=0.03). Of patients with fibrotic ILA, 60.0% (n=12/20) were subsequently diagnosed with ILD compared to 39.4% (n=10/34) of non-fibrotic ILA (p=0.03).

Survival: 14 individuals (25.9%) died within five years of ILA identification. Cox proportional hazard analysis identified fibrotic ILA (hazard ratio [HR] 13.7, 95% CI 3.0-61.3, p=0.001), hypertension (HR 6.0, 95% CI 1.3-26.2, p=0.002), self-reported breathlessness (HR 3.9, 95% CI 1.2-12.4, p=0.02), history of cancer (HR 3.4, 95% CI 1.0-11, p=0.04), MRC score ≥3 (HR 3.1 95% CI 1.0-9.9, p=0.04) and use of ACE inhibitors (HR 3.0, 95% CI 1.0-9.0, p=0.04) as predictors of mortality on univariate analysis. In the multivariate model, fibrotic ILA was identified as the sole independent predictor of mortality (HR 27.1, CI 3.5-209.3, p=0.002). Figure 4 shows survival curves for fibrotic and non-fibrotic ILA subtypes.

Disease Progression: 22 individuals (40.7%) reported increased symptoms of breathlessness or cough within five years of ILA identification. 43 (79.8%) individuals had repeat lung function tests within five years of ILA identification. There was a general increase in FVC at one year with mean absolute change in FVC % predicted of 6.3 (±12.1) followed by subsequent decline over time with a mean change of 0.1 (±17.1) at five years. There was a larger decline in fibrotic ILA (-3.7±15.1) compared to non-fibrotic (2.7±18.1), although not statistically significant. Further details are provided in Table S4 and Figure S1.

Of 46 patients who had a repeat CT scan at one year, 17 (37.0%) demonstrated radiological progression. Almost all the ILA cohort (n=52/54, 96.3%) had at least one further CT within five years. Half of these (n=26/52, 50.0%) had evidence of radiological progression.

Just over half of individuals (n=28/52, 53.8%) with five years follow up data met the criteria for disease progression (table S5). The median progression-free survival was 51 months (IQR 47). Cox proportional hazard analysis was performed and fibrotic ILA subtype (HR 3.4, CI 1.6-7.3, p=0.002), male sex (HR 3.7, CI 1.3-10.6, p=0.02) and the presence of hypertension (HR 2.5, CI 1.1-5.5, p=0.03) were identified as risk factors for reduced progression-free survival on univariate analysis. Fibrotic subtype was again identified as the sole independent risk factor following multivariate analysis (HR 3.8, CI 1.7-8.2, p=0.001). Figure 5 shows survival curves for progression-free survival stratified by ILA subtype.

PROMs: Nineteen individuals with ILA were recruited to the *ILD in Screening* sub-study and completed PROMs at baseline. A further sixteen consecutive new attendees at the ILD clinic were recruited for the control group. Table 2 shows the baseline demographics of these two groups. There were a higher proportion of current smokers in the screening ILA group and a significantly higher pack year history, but the groups were otherwise well matched. There were no differences in the total number and frequency of common co-morbidities and medications between the two groups (table S6).

The results of the PROMs are summarised in table 3. All outcome measures except for the VAS for breathlessness and four domains of the SF-36 questionnaire were significantly different between the two groups. All the results indicated a lower symptom burden and better HRQOL in the screen-detected ILA group in comparison to the clinically detected ILD group. The results that did not reach statistical significance also followed this trend. We compared PROMs between individuals with fibrotic and non-fibrotic ILA subtypes. Individuals with fibrotic ILA had significantly higher UCSD-SOBQ scores (mean 42.4±26.6 vs 16.3±26.6) and breathlessness VAS scores (54.2±33.1 vs 16.4±19.9)

compared to those with non-fibrotic ILA, indicating significantly increased symptoms of breathlessness. There were no significant differences in any of the other outcome measures reported.

We assessed whether PROMs predicted subsequent mortality and reduced progression-free survival in the ILA group using Cox hazard proportional analysis. UCSD-SOBQ score (HR 1.1, CI 1.0-1.1, p=0.04), cough VAS score (HR 1.1, CI 1.0-1.1, p=0.03), breathlessness VAS score (HR 1.1, CI 1.0-1.1, p=0.003) and fatigue VAS score (HR 1.1, CI 1.0-1.1, p=0.04) were all significantly associated with mortality on univariate analysis. Breathlessness VAS score remained significantly associated with mortality after inclusion in a multivariate model (HR 1.1, CI 1.0-1.1, p=0.003), and remained significant after controlling for ILA subtype. None of the PROMs were associated with progression-free survival.

Discussion

In this study, we report clinical outcomes for individuals five years after identification of ILA in a lung cancer screening program. We found an ILA prevalence rate of 3.9% of which 40.7% were subsequently diagnosed with ILD within five years. This was equivalent to 1.6% of the total population screened, supporting recent findings from another UK screening study.[12] We observed a mortality rate of approximately 25% at five years. Previous mortality estimations have varied, being reported to be as high as 56% in the AGES-Reykjavik study (median follow-up 8.9 years),[10] however data from lung cancer screening populations are limited.

Amongst patients diagnosed with ILD, IPF was most common and DIP the second most common diagnosis. DIP is considered to be a rare form of ILD although the true incidence is unknown.[21] Tobacco smoke exposure is a strong risk factor for the development of DIP which may explain an increased incidence in this cohort with high tobacco consumption.

The identification of ILA could offer the potential for early diagnosis and intervention of ILD, which may be life-prolonging. Incorporation of smoking-cessation within lung cancer screening programmes is recommended and may benefit not only smoking related-ILD but also IPF, in which tobacco smoke is associated with pathogenesis and disease progression.[22] IPF diagnosis is hampered by delays in diagnosis and treating disease at an early stage with antifibrotics may slow the trajectory of decline.[23]

Another potential benefit of screening is the identification of early ILD in high-risk populations with reduced access to health care. The MLHCs were designed to target populations in areas of high social deprivation at higher risk of lung cancer and in whom access to health services is low.[13] This is also an important issue in fibrotic lung disease where reduced socio-economic status has been associated with reduced survival.[24, 25] The reasons for this are likely to be multifactorial but may include increased exposure to atmospheric air pollution.[26] This has been identified as a risk factor for the presence of ILA and development and progression of ILD.[27-29]

The incidental detection of ILA through screening risks placing additional burden on already overstretched healthcare resources. There is a clear need to risk-stratify ILA to identify individuals at highest risk of progression. Fibrotic ILA, as defined by the presence of traction bronchiectasis, appears to be the strongest risk predictor for adverse outcomes. In this study it was an independent risk factor for both disease progression and all-cause mortality, consistent with previous observations.[8, 11] We also found that individuals with fibrotic ILA were three times more likely to be subsequently diagnosed with ILD. Limiting criteria for follow-up to patients with a fibrotic subtype would appear to be a simple method of managing healthcare resources. However, a recent large population-based study identified no difference in radiological progression between subpleural fibrotic and non-fibrotic subtypes of ILA, with reticulation being an independent risk factor for radiological progression.[30]

The inclusion of symptom assessment in risk stratification models may be useful. Symptoms may be present in up to 60% of individuals with ILA.[31] We found individuals with ILA were significantly less symptomatic and had better HRQOL scores than patients with ILD. We found that breathlessness scores were higher in individuals with fibrotic ILA and the breathlessness VAS score was an independent predictor of mortality. A simple objective measure of breathlessness may therefore be a useful addition in ILA assessment.

There are several limitations to this study. A lung cancer screening cohort may not provide an accurate representation of the true prevalence of ILA or the natural evolution of changes due to a higher smoking prevalence. A high incidence of DIP diagnosis may be testament to this. However, the anticipated implementation of lung cancer screening suggests that this will provide a significant proportion of ILA referrals into respiratory services. All baseline lung functions were performed in a community-based mobile unit whilst subsequent tests were performed in a hospital lung function laboratory. This may explain some of the variation in FVC results and the trend towards higher values on initial repeat assessment. Spirometry values may be influenced by multiple factors and even in the context of a randomised control trial, significant variability in repeated FVC values is observed in IPF.[32]

The definition for disease progression that we used in this study was modified from the recently published guidelines for progressive pulmonary fibrosis (PPF) which limits assessment of progression to a one-year period.[14] We applied these criteria over the broader timeframe of five years since progression of disease in ILA is not clearly defined, however modest changes in physiology or radiological features over a prolonged period may not be of clinical importance. We did not include measurements of transfer factor as these were not performed at baseline. We did not include a negative control group in the sub-study assessing PROMs. It is therefore difficult to fully estimate the symptom and HRQOL burden associated with ILA.

In conclusion, we found an ILA prevalence rate of 3.9% in our lung cancer screening population, of which 40.7% were subsequently diagnosed with ILD within five years. Fibrotic ILA is a significant risk factor for progression to ILD, reduced progression-free survival and mortality at five years. Individuals with screen-detected ILA have less symptom burden and HRQOL in comparison to patients newly diagnosed with ILD, however increased breathlessness VAS was associated with increased risk of mortality in ILA. Such data could help inform risk stratification and management of screening-detected ILA as implementation is expanded.

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Table 1. Baseline demographics for individuals with screen-detected ILA and those with no ILA.

Demographics	ILA (n=54)	Non-ILA (n=1330)	p=
Mean Age (±SD)	67.5 (±4.8)	64.7 (±5.5)	0.0002
Male Gender (%)	37 (68.5)	648 (48.7)	0.005
Smoking status Current smoker (%) Ex-smoker (%)	 21 (38.9) 33 (61.1)	 711 (53.5) 619 (46.5)	0.04
Mean Pack years (±SD)	46.8 (±24.6)	51.6 (±26.8)	n/s
Mean BMI (±SD)	29.0 (±4.2)	28.4 (±5.5)	n/s
Mean $PLCO_{M2012}$ score (±SD)	4.5 (±3.6)	5.0 (4.0)	n/s
Median IMD rank (IQR)	2868 (3476)	2866 (4033)	n/s
Asbestos exposure	16 (29.6%)	335 (25.2%)	n/s
Self-reported breathlessness	24 (44.4%)	461 (34.7%)	n/s
Self-reported cough	17 (31.5%)	561 (42.2%)	n/s
MRC 1 2 3 4 5	 32 (59.3%) 14 (25.9%) 6 (11.1%) 2 (3.7%) 0	 869 (65.3%) 281 (21.1%) 112 (8.4%) 66 (5.0%) 2 (0.2%)	n/s
Baseline FVC	3.26 (±1.02)	3.19 (±1.00)	n/s
Baseline FVC % predicted	89.5 (±21.3)	99.9 (±24.4)	0.002
FEV_1/FVC <0.7	18 (33.3%)	678 (51.0%)	0.01
Radiological evidence of emphysema	37 (68.5%)	843 (63.4)	n/s

ILA=interstitial lung abnormality; SD=standard deviation; BMI=body mass index; $PLCO_{M2012}$='Prostate Lung Colorectal and Ovarian' lung cancer risk prediction model; IMD=indices of multiple deprivation; IQR=interquartile range; MRC=medical research council dyspnoea score; FVC=forced vital capacity; FEV_1=forced expiratory volume in 1 second; n/s=non-significant.

Table 2. Baseline demographics of the *ILD in Screening* Sub-study participants, comparing those with screen-detected ILA and clinically detected ILD. The proportion of diagnoses within the ILD group is listed.

Demographics	Screen-detected ILA (n=19)	Clinically detected ILD (n=16)	p=
Mean Age (±SD)	67.6 (±5.2)	68.7 (±8.0)	n/s
Male sex (%)	11 (57.9)	11 (68.8)	n/s
Smoking status *Current (%)* *Ex-smoker (%)* *Never smoker (%)*	 8 (42.1) 11 (57.9) 0	 1 (6.3) 13 (81.3) 2 (12.5)	0.02
Mean Pack years (±SD)	44.2 (±25.6)	21.6 (±18.9)	0.004
Mean BMI (±SD)	28.7 (±3.5)	30.3 (±4.9)	n/s
Asbestos exposure (%)	4 (21.1)	6 (37.5)	n/s
Mean FVC (±SD)	3.2 (±1.1)	3.1 (±1.2)	n/s
Mean FVC % predicted (±SD)	89.9 (±23.0)	86.0 (26.2)	n/s
Mean TLCO (±SD)	5.1 (±1.6)	4.7 (±2.7)	n/s
Mean TLCO % predicted (±SD)	67.9 (±17.7)	58.8 (±25.8)	n/s
Individuals with FEV_1/FVC <0.7 (%)	5 (26.3)	4 (25.0)	n/s
ILA subtype *Fibrotic (%)* *Non-fibrotic (%)*	 8 (42.1) 11 (57.9)	-	-
ILD diagnosis *IPF (%)* *iNSIP (%)* *CTD-ILD (%)* *Unclassifiable (%)* *HP (%)* *DIP (%)*	 - - - - -	 8 (50.0) 2 (12.5) 2 (12.5) 2 (12.5) 1 (6.25) 1 (6.25)	-

ILA=interstitial lung abnormality; ILD=interstitial lung disease; SD=standard deviation; BMI=body mass index; FVC=forced vital capacity; FEV_1=forced expiratory volume in 1 second. TLCO=transfer factor of the lung for carbon monoxide; IPF=idiopathic pulmonary fibrosis; iNSIP=idiopathic nonspecific interstitial pneumonia; CTD-ILD=connective tissue disease related interstitial lung disease; HP=hypersensitivity pneumonitis; DIP=desquamative intestitial pneumonia.

Table 3. Summary of results of PROMs between ILA and ILD groups. Mean (±standard deviation) reported.

PROM	ILA (n=19)	ILD (n=16)	p-value
Fatigue Severity Score	3.3 (±2.0)	5.1 (±1.3)	0.01
University California San Diego Shortness of breath questionnaire	27.3 (±29.8)	52.7 (±29.5)	0.02
Visual Analogue Score			
Cough	22.6 (±9.6)	52.7 (±12.2)	0.04
Breathlessness	32.3 (±31.9)	60.3 (±46.6)	n/s
Fatigue	32.2 (±41.3)	67.0 (±50.5)	0.008
Leicester Cough Questionnaire			
Total	18.2 (±3.3)	13.4 (±1.3)	0.003
Physical	5.5 (±1.1)	4.4 (±2.2)	0.01
Psychological	6.3 (±1.4)	4.2 (±2.0)	0.004
Social	6.4 (±1.1)	4.8 (±1.8)	0.005
Kings Brief Interstitial Lung Disease questionnaire			
Total	79.1 (±22.4)	59.2 (±19.6)	0.003
Breathlessness and activities	73.3 (±26.1)	51.3 (±24.4)	0.02
Psychological	83.7 (±22.3)	60.2 (±19.7)	0.001
Chest symptoms	80.2 (±24.2)	65.9 (±19.2)	0.04
Medical Outcomes 36-item Short Form Survey (SF-36)			
Physical Functioning	61.7 (±32.5)	38.4 (±26.4)	0.04
Role limitations due to physical health	62.5 (±46.2)	21.9 (±40.7)	0.03
Role limitations due to emotional problems	58.2 (±46.8)	45.8 (±48.5)	n/s
Energy/fatigue	56.8 (±22.1)	39.3 (±6.1)	0.03
Emotional well-being	66.3 (±24.1)	70.5 (±25.2)	n/s
Social functioning	81.6 (±26.8)	53.9 (±7.4)	0.004
Pain	75.3 (±36.4)	64.5 (±27.2)	n/s
General Health	51.1 (±22.9)	38.1 (±26.6)	n/s

PROM=patient reported outcome measure; ILA=interstitial lung abnormality; ILD=interstitial lung disease

Online Data Supplement

Title: Variation in asthma care, exacerbations and mortality by ethnicity: A systematic review and meta-analysis.

Authors: AbdulQadr Akin-Imran, PhD[1,2], Achint Bajpai, BSc[3], Dáire McCartan[1], Liam G Heaney, MD[4], Frank Kee, MD[1], Charlene Redmond, BSc[1], John Busby, PhD[1]

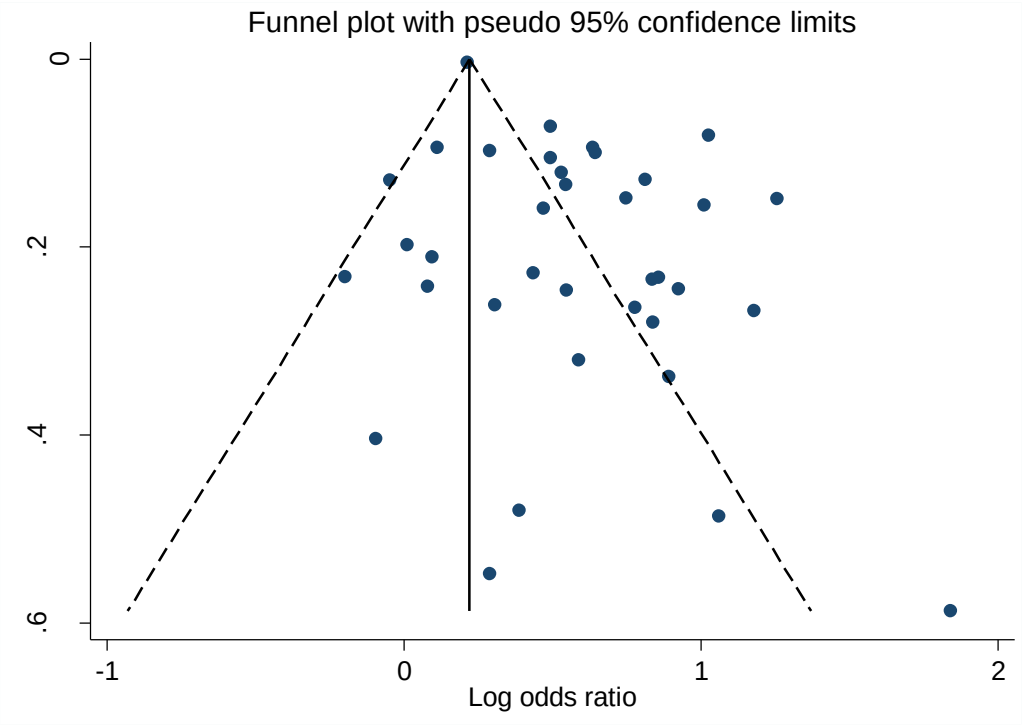

Figure S1: Funnel plot for studies reporting emergency department visits by different ethnic minority groups

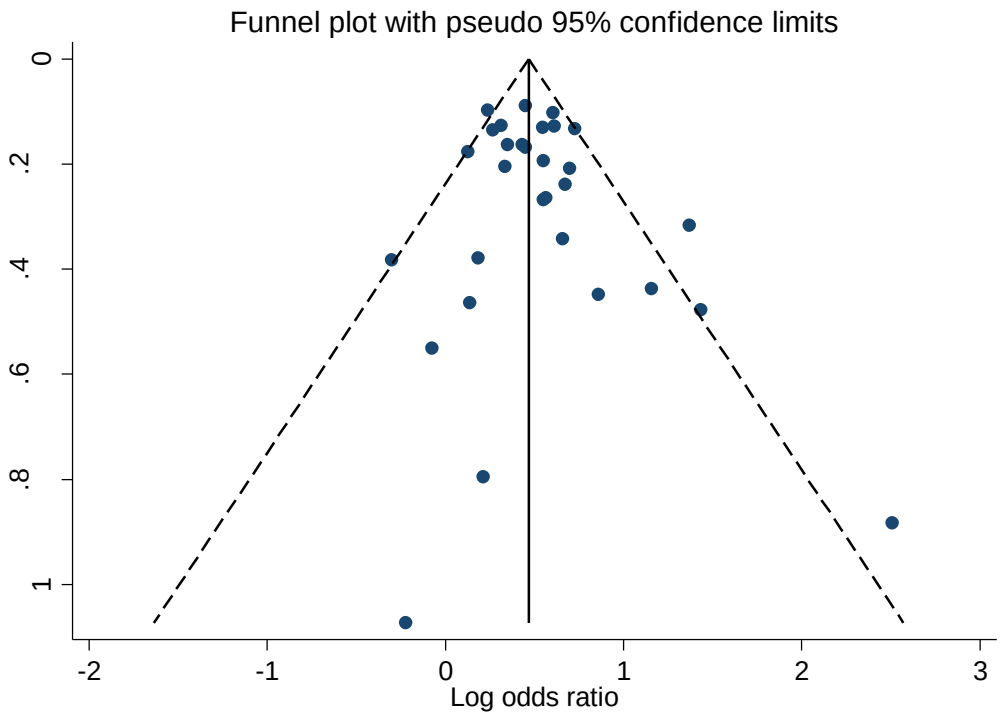

Figure S2: Funnel plot for studies reporting hospitalisations by different ethnic minority groups

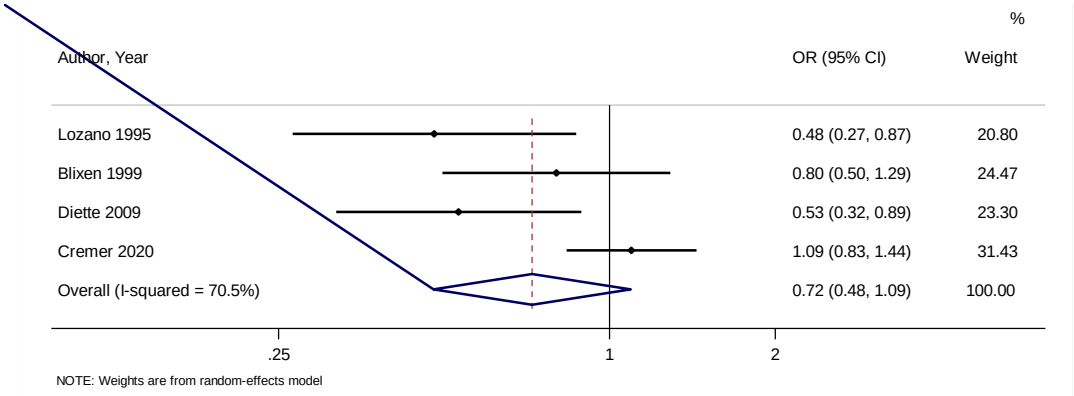

Figure S3: Forest plot of odds ratio of asthma-related primary care attendance

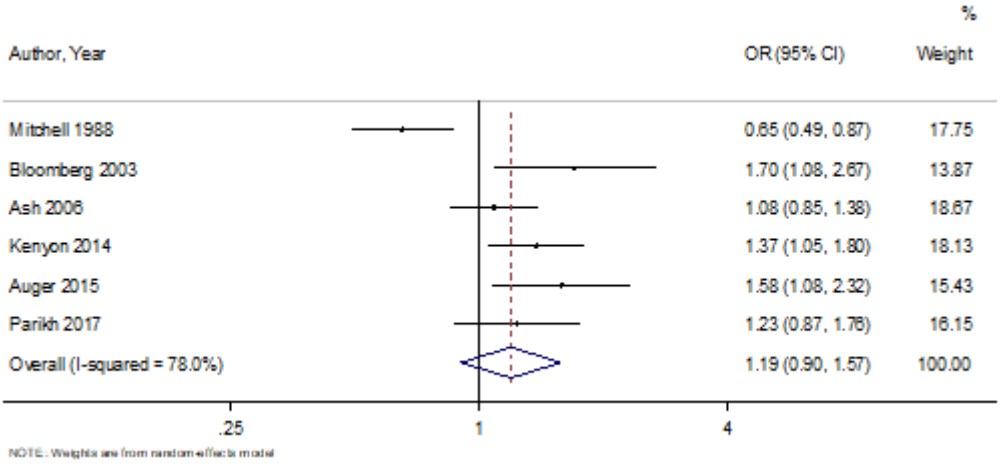

Figure S4: Forest plot of odds ratio of asthma-related hospital readmission

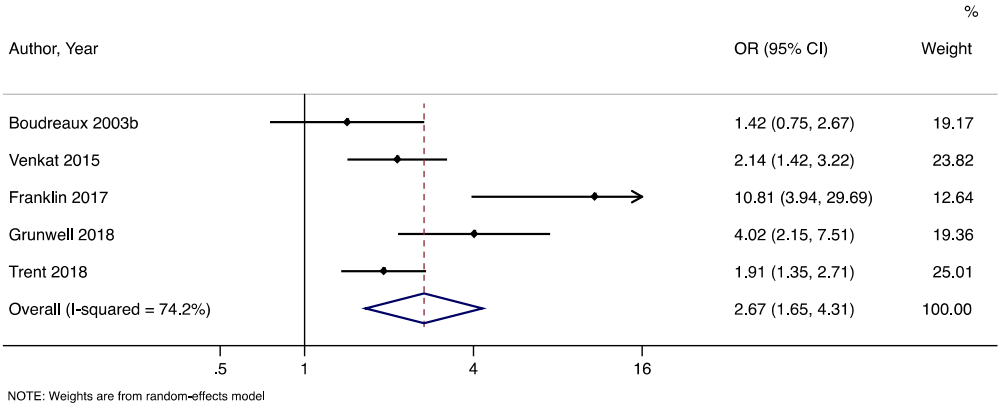

Figure S5: Forest plot of odds ratio of asthma-related ventilation / intubation

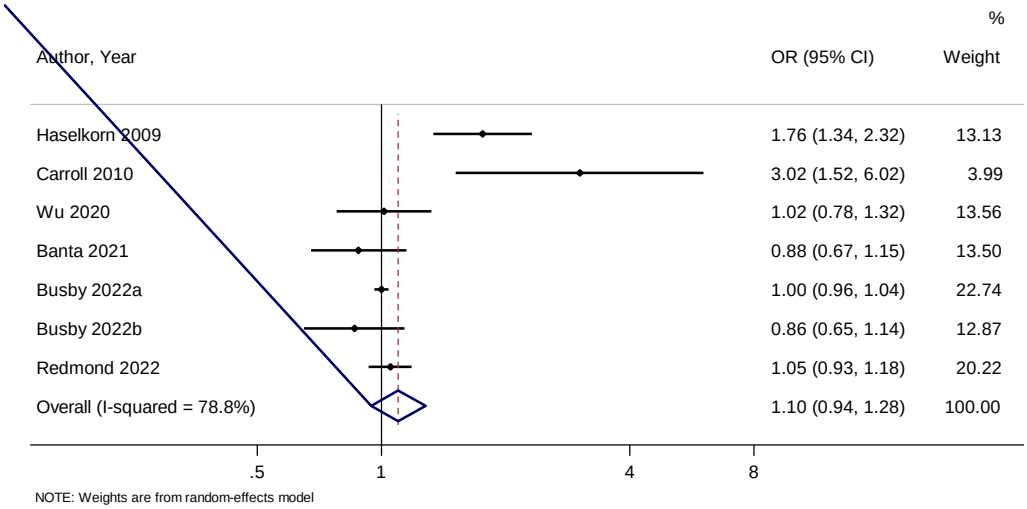

Figure S6: Forest plot of odds ratio of asthma-related exacerbation

Online Data Supplement

Title: Variation in healthcare utilisation, exacerbations and mortality by ethnicity: A systematic review and meta-analysis.

Authors: AbdulQadr Akin-Imran, PhD[1,2], Achint Bajpai, BSc (Hons)[3], Dáire McCartan[1], Liam G Heaney, MD[4], Frank Kee, MD[1], Charlene Redmond, BSc[1], John Busby, PhD[1]

Table S1: Search domains and terms used in MEDLINE and EMBASE database

MEDLINE and EMBASE search strategy: Ovid <inception to July 2020>

Domain	Search Terms
Asthma	Asthma/ or asthma.mp. OR wheeze.mp. **AND**
Ethnic/race	Ethnic Groups/ or ethnic*.mp. OR race*.mp. OR racial group.mp. OR migration.mp. OR emigrant*.mp. OR migrant*.mp. OR "Emigrants and Immigrants"/ or "Emigration and Immigration"/ OR Minority Groups/ or minorit*.mp. OR Minority Health/ OR Refugees/ or refug*.mp. OR Refugee Camps/ OR asylum.mp. OR Indian.mp. OR Pakistani.mp. OR Bangladeshi.mp. OR Asian.mp. OR Black.mp. OR Afro*.mp. OR African Americans/ OR African.mp. OR Chinese.mp. OR BAME.mp. OR Eastern Europe.mp. OR Europe, Eastern/ OR Eastern Europe*.mp. OR Europe, Eastern/ OR Irish.mp. OR Non?White*.mp. OR Arabs.mp. or Arabs/ OR Gyps*.mp. OR Gips*.mp. OR Jews/ OR Jew*.mp. OR Hispanic Americans/ OR Hispanic*.mp. OR Latin America/ or Latin*.mp. OR white.mp. OR mixed.mp. OR Caribbean.mp. OR American Indian.mp. or Indians, North American/ OR Alaska Native.mp. or Alaska Natives/ OR Native Hawaiian.mp. OR Pacific Islander.mp. **AND**
Outcome	Mortality/ or mortality.mp. OR Death/ or death*.mp. OR morbidity.mp. or Morbidity/ OR exacerbat*.mp. OR vent*.mp. OR emergency department.mp. or Emergency Service, Hospital/ OR ED.mp. OR A&E.mp. OR (accident and emergency).mp. OR accident & emergency.mp. OR emergency room.mp. OR emergency ward.mp. OR Patient Readmission/ or readmission*.mp. OR hospitali?ation.mp. OR Patient Admission/ or admission*.mp. OR General Practice/ or general pract*.mp. or Primary Health Care/ or General Practitioners/ OR primary care.mp. OR attend*.mp. OR consult*.mp. OR utili*.mp. OR Intensive Care Units/ or ICU.mp. OR (High Dependency Unit* or HDU).mp. OR critical care.mp. or Critical Care/

Table S2: Search domains and terms used in Web of Science database

Web of Science search strategy: <Inception to July 2020>

Domain	Search Terms
Asthma	TS= (asthma OR wheeze) **AND**
Ethnic/race	TS= (ethnic* OR ethnic groups OR race* OR racial group OR migration OR migrant* OR minorit* OR minority group OR minority health OR emigrant* OR immigrant* OR immigrant OR refug* refugee camp OR asylum OR Indian OR Pakistani OR Bangladeshi OR Asian OR Black OR Afro* OR African OR African American OR Chinese OR BAME OR Eastern Europe* Irish OR Non white* OR arabs/ or gypsies/ or jews* OR Hispanic* OR Latin* OR Gyps* OR Gips*) **AND**
Outcome	TS= (mortality OR death* OR morbidity OR exacerbat* OR vent* OR "emergency department" OR ED OR (accident near/2 emergency) OR A&E OR readmission* OR hospitali?ation OR admission* OR "primary care" OR GP OR "general pract*" OR *attend* or consult* or utili*)

Table S3: List of data fields collected during data extraction

Study details	**Categorical variable options**
Title	
Lead author contact details	
Cohort description	
Country in which the study was conducted	
Study design	Case control, cohort, cross-sectional
Data collection setting	General practice, hospitalization records, ED records, secondary care, tertiary care, insurance database, general population, other
Study year / Data collection period	
Total number of participants	
Mean Age (SD/SE)	
Female (%)	
Age range	
Inhaled Corticosteroid (%)	
Oral Corticosteroid (%)	
Severe asthma (%)	
Asthma severity	Not specified, mild, moderate, severe, other
FEV1 Average	

Study comparison data	**Categorical variable options / examples**
Exposure	Race, Ethnicity, Race/Ethnicity
Group compared	e.g., White vs Hispanic
Reference group summary	i.e., White
Estimate group summary	e.g., Black
How outcomes were compared	e.g., the probability of ED visit (odds ratio) or counting the number of admissions (rate ratio)
Outcomes	primary care attendance, exacerbations, ED visit, hospitalisation, ventilation / intubation, readmission, Mortality
Ratio type	Odds ratio, risk ratio, hazard ratio, chi squared
Ratio	
Lower CI	
Upper CI	
Confidence level (%)	
P value	
Standard error	
Are estimates adjusted?	Yes, no
Variables adjusted for	
Were estimates calculated manually?	Yes, no
Outline how estimate was calculated	

Table S4: Quality assessment criteria, based on Newcastle - Ottawa Quality Assessment Scale Cohort Studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection
1) Representativeness of the exposed cohort
a) truly representative of the average **(i.e. ethnic minority asthma patients)** in the community ✵ b) somewhat representative of the average **(i.e. ethnic minority asthma patients)** in the community ✵ c) selected group of users e.g. nurses, volunteers d) no description of the derivation of the cohort
2) Selection of the non exposed cohort
a) drawn from the same community as the exposed cohorts (i.e. **White / Caucasian / non-minority asthma patients)** ✵ b) drawn from a different source c) no description of the derivation of the non exposed cohort
3) Ascertainment of exposure
a) secure record (e.g. **medical, insurance, health records)** ✵ b) structured interview ✵ c) written self report d) no description
4) Demonstration that outcome of interest was not present at start of study
a) yes ✵ b) no
Comparability
1) Comparability of cohorts on the basis of the design or analysis
a) study controls for (**asthma severity**) ✵ b) study controls for any additional factor (**e.g. sex, age, socioeconomic status, comorbidity)** ✵
Outcome
1) Assessment of outcome
a) independent blind assessment (e.g. **health records**) ✵ b) record linkage (e.g. **health records**) ✵ c) self report (i.e. **no reference to original health records or documented source to confirm the outcome**) d) no description
2) Was follow-up long enough for outcomes to occur
a) yes (**3 months and over)** ✵ b) no
3) Adequacy of follow up of cohorts
a) complete follow up - all subjects accounted for ✵ b) subjects lost to follow up unlikely to introduce bias - small number lost **(<5%)** follow up, (or description provided of those lost) ✵ c) follow up rate **< 80%** and no description of those lost

d) no statement

Threshold between good and poor-quality studies

Studies were rated poor-quality if:

- They did not adjust, by design or analysis, any factor
- They had less than 2 stars in the outcome section
- They had less than 3 stars in the selection section
- They had an overall rating of less than 6 stars

NOTE: The above quality assessment criteria were adapted for case-control and cross-sectional studies. However, regarding cross-sectional studies, studies were assigned a single star for ascertainment of the exposure, if they had used a validated tool, or described the measurement tool within the study or in their study protocol.

Table S5: Methodological quality assessment of the included studies using Newcastle-Ottawa Scale

Cohort Study

Study	Selection				Comparability	Outcomes			Quality Rating
	Representativ e-ness	Selection	Exposure Ascertainment	Outcome not present at start of study	Comparability	Outcome Assessment	Sufficient follow-up period	Adequacy of follow-up	
Mitchell 1988[1]	*	*	-	*	*	*	*	*	Good
Lozano 1995[2]	*	*	*	*	*	*	*	*	Good
Sarpong 1997[3]	*	*	-	*	*	*	*	*	Good
Joseph 1998[4]	*	*	*	*	*	*	*	*	Good
Blixen 1999[5]	*	*	*	*	*	*	*	*	Good
Eisner 2001[6]	*	*	-	*	*	-	*	-	Poor
Ortega 2001a[7]	*	*	-	*	-	-	*	*	Poor
Ortega 2001b[8]	*	*	-	*	-	-	*	*	Poor
Amre 2002[9]	*	*	*	*	*	-	*	*	Good
Diette 2002[10]	*	*	-	*	*	-	*	-	Poor
Lafata 2002[11]	*	*	*	*	*	*	*	*	Good
Weber 2002[12]	*	*	*	*	*	-	*	-	Poor
Bloomberg 2003[13]	*	*	*	*	-	*	*	*	Poor
Boudreaux 2003a[14]	*	*	-	*	-	*	*	*	Poor
Boudreaux 2003b[15]	*	*	-	*	*	-	*	-	Poor
Shields 2004[16]	*	*	-	*	*	*	*	*	Good
Carroll 2005[17]	*	*	*	*	*	*	*	*	Good
Griswold 2005[18]	*	*	-	*	*	*	*	*	Good
Ash 2006[19]	-	*	*	*	*	*	*	*	Good
Erickson 2007[20]	*	*	-	*	*	*	*	-	Good
Haselkorn 2008[21]	*	*	-	*	*	-	*	*	Good
Chandra 2009[22]	*	*	*	*	-	*	*	*	Poor
Haselkorn 2009[23]	*	*	-	*	*	-	*	*	Good
Carroll 2010[24]	*	*	*	*	-	*	-	*	Poor
Hasegawa 2014[25]	*	*	*	*	-	*	*	-	Poor

Kenyon 2014[26]	*	*	*	*	*	*	*	-	Good
Auger 2015[27]	*	*	*	*	*	*	*	-	Good
Venkat 2015[28]	*	*	*	*	-	*	-	*	Poor
Hull 2016[29]	*	*	-	*	*	*	*	*	Good
Mitchell 2016[30]	*	*	-	*	-	-	*	*	Poor
Franklin 2017[31]	*	*	-	*	-	*	*	*	Poor
Parikh 2017[32]	*	*	-	*	*	*	*	*	Good
Grunwell 2018[33]	*	*	-	*	*	-	*	*	Good
Trent 2018[34]	*	*	*	*	-	*	*	*	Poor
Aratani 2019[35]	*	*	*	*	*	*	*	*	Good
Fitzpatrick 2019[36]	*	*	-	*	-	*	*	*	Poor
Zein 2020[37]	*	*	*	*	-	*	*	*	Poor
Kraft 2021[38]	*	*	*	*	-	*	*	*	Poor
Sheikh 2021[39]	*	*	-	*	-	-	*	*	Poor
Adejare 2022[40]	*	*	*	*	-	*	*	*	Poor
Beuther 2022[41]	*	*	-	*	*	*	*	*	Good
Busby 2022[42]	*	*	*	*	*	*	*	*	Good
Lugogo 2022[43]	*	*	*	*	-	*	*	*	Poor
Redmond 2022[44]	*	*	*	*	*	*	*	*	Good

Cross-sectional Study

Study	Selection				Comparability	Exposures		Quality Rating
	Representative-ness	Sample size	Response rate	Exposure Ascertainment	Comparability	Outcome Assessment	Statistical test	
Zoratti 1998[45]	*	*	*	*	-	**	*	Poor
Meurer 2000[46]	*	*	-	*	*	*	*	Good
Krishnan 2001[47]	*	*	*	*	-	*	*	Poor
Grant 2005[48]	*	*	*	*	*	*	*	Good

Meng 2006[49]	*	*	-	*	*	*	*	Good
DeWalt 2007[50]	*	*	-	*	*	*	*	Good
Forester 2008[51]	*	*	*	*	-	*	*	Poor
Crocker 2009[52]	*	*	-	*	*	*	*	Good
Diette 2009[53]	*	*	-	*	*	*	*	Good
Gorman 2009[54]	*	*	-	*	-	*	-	Poor
Kim 2009[55]	*	*	-	*	*	*	*	Good
Wright 2009[56]	*	*	*	*	-	*	*	Poor
Canino 2012[57]	*	-	*	-	-	*	*	Poor
Lee 2014[58]	*	*	-	*	*	*	*	Good
Hughes 2017[59]	*	*	*	*	*	*	*	Good
Zhang 2017[60]	*	*	-	*	*	*	*	Good
Deshpande 2018[61]	*	*	-	*	*	*	*	Good
Cremer 2020[62]	*	*	-	*	*	*	*	Good
Urquhart 2020[63]	*	*	-	*	*	*	*	Good
Banta 2021[64]	*	*	*	*	*	*	*	Good

Case control Study

Study	Selection				Comparability	Outcomes			Quality Rating
	Case Definition	Representative-ness	Control Selection	Control Definition	Comparability	Exposure Ascertainment	Consistent between cases and controls	Non-Response rate	
Wells 2015[65]	-	*	-	*	-	*	*	-	Poor

Table S6: Adjustment factors reported from studies reporting asthma-related healthcare use by ethnicity

Study ID	Age	Sex	SES	Income	Insurance	Education	BMI	Asthma severity	Asthma drug	Smoking status	Comorbidity	Health status	Location	Literacy
Mitchell 1988[1]	×	×	✓	×	×	×	×	×	×	×	×	×	×	×
Lozano 1995[2]	✓	✓	×	×	×	×	×	×	×	×	×	×	✓	×
Sarpong 1997[3]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Joseph 1998[4]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Zoratti 1998[45]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Blixen 1999[5]	✓	✓	×	✓	×	×	×	×	×	×	×	×	×	×
Meurer 2000[46]	✓	✓	×	×	×	×	×	✓	×	×	×	×	×	×
Eisner 20011[6]	✓	✓	×	✓	×	✓	×	✓	×	✓	×	✓	×	×
Krishnan 2001[47]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Ortega 2001a[7]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Ortega 2001b[8]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Amre 2002[9]	✓	✓	×	×	×	×	×	×	✓	✓	×	×	×	×
Diette 2002[10]	✓	✓	×	×	×	✓	×	✓	×	✓	✓	✓	×	×
Lafata 2002[11]	✓	✓	×	✓	×	×	×	×	×	×	×	×	×	×
Weber 2002[12]	✓	✓	×	×	×	×	×	✓	✓	×	×	×	×	×
Bloomberg 2003[13]	✓	✓	×	×	✓	×	×	×	×	×	×	×	×	×
Boudreaux 2003a[14]	✓	✓	×	✓	✓	×	×	×	✓	×	×	×	×	×
Boudreaux 2003b[15]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Shields 2004[16]	✓	✓	×	×	✓	×	×	×	×	×	×	×	✓	×
Carroll 2005[17]	✓	×	×	×	×	✓	×	×	×	✓	×	×	✓	×
Grant 2005[48]	✓	✓	×	✓	×	×	×	×	✓	×	×	×	×	×
Griswold 2005[18]	✓	✓	×	×	✓	✓	×	×	✓	×	×	×	×	×
Ash 2006[19]	✓	✓	×	×	×	×	×	×	×	×	✓	×	×	×
Meng 2006[49]	✓	✓	×	✓	✓	✓	×	✓	×	✓	×	✓	✓	×
DeWalt 2007[50]	✓	×	×	✓	×	×	×	✓	✓	✓	×	×	×	✓
Erickson 2007[20]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Forester 2008[51]	✓	×	×	×	×	×	×	×	✓	×	×	×	×	✓
Haselkorn 2008[21]	×	×	×	×	×	×	×	×	×	×	×	×	×	×

Chandra 2009[22]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Crocker 2009[52]	✓	✓	×	✓	✓	×	✓	✓	×	✓	×	×	✓	×
Diette 2009[53]	✓	✓	×	✓	✓	✓	✓	×	×	×	×	×	×	×
Gorman 2009[54]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Haselkorn 2009[23]	✓	✓	×	✓	×	×	✓	×	✓	✓	×	×	×	×
Kim 2009[55]	✓	✓	×	×	×	×	×	×	×	×	×	×	✓	×
Wright 2009[56]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Carroll 2010[24]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Canino 2012[57]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Hasegawa 2014[25]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Kenyon 2014[26]	✓	✓	×	✓	×	×	×	×	✓	×	×	×	×	×
Lee 2014[58]	×	✓	×	×	✓	×	×	✓	✓	✓	×	✓	×	×
Auger 2015[27]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Venkat 2015[28]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Wells 2015[65]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Hull 2016[29]	✓	✓	✓	×	×	×	×	✓	✓	✓	✓	×	×	×
Mitchell 2016[30]	×	×	×	×	×	✓	×	×	×	×	×	×	×	×
Franklin 2017[31]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Hughes 2017[59]	✓	✓	×	✓	×	✓	×	×	×	×	×	×	✓	×
Parikh 2017[32]	✓	×	×	×	✓	×	×	✓	×	×	✓	×	×	×
Zhang 2017[60]	✓	✓	×	✓	✓	✓	×	×	×	✓	×	×	×	×
Deshpande 2018[61]	✓	✓	×	×	×	✓	×	×	✓	×	×	✓	×	×
Grunwell 2018[33]	✓	×	×	✓	×	×	×	✓	×	×	✓	×	×	×
Trent 2018[34]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Aratani 2019[35]	×	✓	×	×	×	×	×	×	×	×	×	×	×	×
Fitzpatrick 2019[36]	×	×	×	✓	×	✓	×	×	×	✓	×	×	×	×
Cremer 2020[62]	×	×	×	×	✓	×	×	×	✓	✓	✓	×	×	×
Urquhart 2020[63]	✓	✓	×	✓	✓	✓	×	×	×	×	×	✓	✓	×
Zein 2020[37]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Banta 2021[64]	✓	✓	×	×	×	×	✓	×	×	×	×	×	×	×
Kraft 2021[38]	×	×	×	×	×	×	×	×	×	×	×	×	×	×

Sheikh 2021[39]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Adejare 2022[40]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Beuther 2022[41]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Busby 2022[42]	✓	✓	×	×	×	×	×	✓	×	×	×	×	×	×
Lugogo 2022[43]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Redmond 2022[44]	✓	✓	×	×	×	×	×	✓	✓	×	×	×	✓	×

NOTE: SES, socioeconomic status; BMI, body mass index; Smoking; smoking status, exposure, environmental tobacco smoke; Location, urban or rural area of residence; √, Yes; ×, No

TABLE S7 - Subgroup Analyses: pooled effect on asthma-related healthcare utilisation by various factors

Subgroup	ED Visit				Hospitalisation				Hospital Readmission			
	N	OR (95% CI's)	I^2	*P*	N	OR (95% CI's)	I^2	*P*	N	OR (95% CI's)	I^2	*P*
Race				0.001				0.068				<0.001
Black	33	1.86 (1.68, 2.06)	90.6		30	1.69 (1.40, 2.06)	86.1		5	1.76 (1.61, 1.91)	65.4	
Hispanic	22	1.52 (1.35, 1.71)	89.6		13	1.33 (1.09, 1.62)	61.2					
Asian	5	0.97 (0.59, 1.61)	81.8		4	1.42 (0.85, 2.38)	88.8					
Other	8	1.13 (0.86, 1.48)	73.3		6	1.23 (0.88, 1.72)	30.8		4	1.05 (0.97, 1.13)	0.0	
Age				0.942				0.840				
Paediatric	18	1.72 (1.45, 2.04)	89.3		13	1.63 (1.37, 1.94)	36.9					
Other	18	1.79 (1.45, 2.18)	85.8		17	1.62 (1.44, 1.83)	49.1					
Time period				0.745								
Pre-2010	30	1.79 (1.54, 2.08)	90.7									
Post-2010	6	1.58 (1.29, 1.94)	74.2									

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