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Prevalence of Comorbidities in Asthma and Nonasthma Patients

A Meta-analysis

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Abstract: This study compares the prevalence rates of comorbidities between asthma and nonasthma control patients reported in the literature.

Literature was searched in several electronic databases. After the selection of studies by following précised eligibility criteria, metaanalyses of odds ratios were carried out with subgroup and sensitivity analyses.

Eleven studies studying 117,548 asthma patients compared with 443,948 non-asthma controls were included in the meta-analysis. The prevalence of cardiovascular comorbidities (odds ratio (OR): [95% CI] 1.90 [1.70, 2.14]; P < 0.00001), cerebrovascular comorbidities (OR 1.44 [1.29, 1.60]; P < 0.00001), obesity (OR 1.51 [1.14, 2.01]; P < 0.00001), hypertension (OR 1.66 [1.47, 1.88]; P < 0.00001, diabetes (OR 1.25 [1.08, 1.44]; P < 0.00001), other metabolic and endocrine comorbidities (OR 1.60 [1.40, 1.83]; P < 0.00001), gut and urinary comorbidities (OR 1.61 [1.47, 2.49]; P < 0.00001), cancer (OR 1.17 [1.10, 1.25]; P < 0.00001), and respiratory comorbidities (OR 5.60 [4.22, 7.44]; P < 0.00001) were significantly higher in the asthma patients in comparison with nonasthma controls.

Asthma is associated with significantly higher comorbidities including cardio-/cerebrovascular diseases, obesity, hypertension, diabetes, psychiatric and neurological comorbidities, gut and urinary conditions, cancer, and respiratory problems other than asthma. Respiratory comorbidities are found 5 times more prevalent in asthma than in non-asthma patients.

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Abbreviations: AIDS = acquired immunodeficiency syndrome, CI = confident interval, OR = odds ratios, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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INTRODUCTION

A sthma is a common inflammatory disorder of the respiratory tract, which is characterized by the obstruction and hyper-responsiveness of the tracheo-broncheal system.¹ Repeated episodic shortness of breath with variable expiratory flow, wheezing, recurrent cough, excessive mucus production by the lining of air passage and chest tightness are the major symptoms of this disease.² Asthma is recognized as a heterogeneous disease as multiple subtypes of this disease with distinct pathophysiologic mechanisms are identified.³

Estimates of asthma in elderly patients (>60 years of age) indicate 4% to 13% prevalence.⁴ Asthma is an important cause of morbidity and disability in individuals over 65 years of age as control of this disease worsens in later age, which is also associated with increased emergency medicine as well as hospitalizations.⁵

Comorbidities are increasingly recognized as important determinants of asthma management and prognosis as these are associated with inadequate disease control, higher health care use, and poor quality of life.⁶ Moreover, the recurrent exacerbations in asthma are associated with specific co-morbidities that require additional therapeutic interventions.⁷ In elderly, especially, the comorbidities are associated with higher mortality, poor adherence to therapeutic interventions, and reduced quality of life.⁸

Although a considerable number of studies have documented the prevalence of comorbidities in asthma patients, comparative controlled studies are relatively less in number. The aim of the present study was to undertake a systematic literature search and to perform a meta-analysis of the studies which compared the prevalence of comorbidities in asthma and nonasthma patients in order to examine the significance of difference in the prevalence of various comorbidities between asthma patients and nonasthma controls.

METHODS

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines⁹ are followed while performing this meta-analysis and associated systematic review. As this study is a meta-analysis research with the published data as materials, it does not need the approval from the institutional review board.

Literature Search

Several electronic databases including Embase, Google Scholar, Ovid SP, Pubmed/Medline, and Web of Science were searched for the relevant articles. The major medical subject headings (MeSH) and keywords used in different logical combinations and phrases included asthma, comorbidity/comorbidities, prevalence, cardiovascular, heart disease, stroke, myocardial infarction,

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FIGURE 1. A flowchart of the literature search, study screening, and selection process.

thrombosis, atherosclerosis, hypertension, diabetes, obesity, thyroid disease, skin disease, cancer, malignancy, psychiatric disorders, depression, neurological disorders, psychosis, respiratory conditions, gastrointestinal diseases, and musculoskeletal disorders. The search encompassed original research papers published before November 2015.

Inclusion and Exclusion Criteria

The inclusion criterion was: studies reporting the prevalence of the comorbidities in asthma patients by comparing with suitable nonasthma control patients. The exclusion criteria were: (a) studies providing comorbidity prevalence data in asthma patients without control data or studies utilizing asthma/chronic obstructive pulmonary disease controls; studies utilizing indirect data such as medical claims; study reports with data in forms that were unable to be utilized in the metaanalyses of odds ratios.

Data Extraction, Synthesis, and Statistical Analysis

Required data and corresponding demographics were obtained from the selected research articles and synthesized on spreadsheets for use in the meta-analyses. Meta-analyses were carried out with RevMan (Version 5.3; Cochrane Collaboration) software under fixed effects as well as random effects models. For the meta-analyses, the prevalence data were used to calculate the odds ratios of each study data and the overall effect sizes were generated, which was a weighted average of the inverse variance adjusted effect sizes of individual studies (odds ratios [OR] along with 95% CI). Between studies consistency was tested by the I^2 index. Subgroup analyses were carried out and sensitivity analyses performed in order to explore the authenticity of results and sources of higher heterogeneity. Publication bias assessment was made by the visual examination of the funnel plot symmetry.

RESULTS

Eleven studies^{10–20} were selected by following the eligibility criteria (Figure 1). Overall, these studies analyzed 117,548 asthma patients and 443,948 nonasthma control patients. Average age (mean \pm standard deviation; range) of asthma patients was 57.23 \pm 11.65 (18.4 \pm 17.8 to 76 \pm 4.7) years. Gender distribution in the overall population was: 47 \pm 7.1 % males and 52.3 \pm 7.1 % females). A considerable publication bias was evident from the visual examination of the funnel plots (Figure 2).

Cardiovascular and cerebrovascular comorbidities included arrhythmia, atrial fibrillation, congenital heart disease, congestive heart failure, coronary artery disease, ischemic heart disease, heart failure, myocardial infarction, peripheral artery disease, valve disease, and stroke. Metabolic comorbidities included diabetes mellitus, dyslipidemia, hyperlipidemia, hypertension, hyperthyroidism, hypothyroidism, obesity, and



FIGURE 2. A funnel plot of the overall meta-analysis of metabolic and endocrine comorbidities reflecting publication bias.

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	Asthma	atics	Cont	rols		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	I IV, Random, 95% CI
1.1.1 Cardiovascular como	orbidities			10000		MACESING AND	
Balkrishnan 2000 CVD	455	647	3017	4874	7.0%	1.46 [1.22, 1.74]	-
Bellia 2007 CVD	45	210	149	1027	4.5%	1.61 [1.11, 2.33]	
Ben-Noun 2001 Arrythmia	4	141	10	423	0.9%	1.21 [0.37, 3.91]	
Ben-Noun 2001 CHD	16	141	43	423	2.5%	1.13 [0.62, 2.08]	
Cheng 2015 IHD	1345	10455	3331	41820	8.2%	1.71 [1.59, 1.82]	-
Chung 2014 Atrial fibril.	329	31356	731	125157	7.6%	1.80 [1.58, 2.06]	-
Chung 2014 CVD	3019	31356	8902	125157	8.3%	1.39 [1.33, 1.45]	-
Chung 2014 Heart failure	1334	31356	2073	125157	8.2%	2.64 [2.46, 2.83]	-
Oyer 1999 Heart dis.	15	60	8	43	1.2%	1.46 [0.56, 3.83]	
Patel 2014 Cong. HD	32	6350	121	60298	4.3%	2.52 [1.70, 3.72]	
Patel 2014 HD	108	6350	543	60298	6.6%	1.90 [1.55, 2.34]	
Sapra 2005 Arrythmia	311	27493	140	27493	6.7%	2.24 [1.83, 2.73]	
Sapra 2005 CHF	487	27493	184	27493	7.1%	2.68 [2.26, 3.17]	
Sapra 2005 MI	165	27493	82	27493	5.8%	2.02 [1.55, 2.63]	
Sapra 2005 Periph. dis	338	27493	146	27493	6.8%	2.33 [1.92, 2.83]	
Sapra 2005 Valve dis.	192	27493	99	27493	6.1%	1.95 [1.53, 2.48]	
Shen 2015 CAD	11828	38840	30901	155347	8.4%	1.76 [1.72, 1.81]	
Subtotal (95% CI)		294727		837489	100.0%	1.90 [1.70, 2.14]	•
Total events	20023		50480				
Heterogeneity: Tau ² = 0.04;	Chi ² = 291	.83, df =	16 (P < 0	0.00001);	$^{2} = 95\%$		
Test for overall effect: Z = 1	0.99 (P < 0	0.00001)					
1.1.2 Cerebrovascular con	norbidities	S					
Bellia 2007 CeVD	10	210	72	1027	2.4%	0.66 [0.34, 1.31]	
Ben-Noun 2001 CeVD	1	141	9	423	0.3%	0.33 [0.04, 2.62]	• • • • • • • • • • • • • • • • • • • •
Cheng 2015 CeVD	1410	10455	4304	41820	37.0%	1.36 [1.27, 1.45]	
Oyer 1999 Stroke	5	60	2	43	0.4%	1.86 [0.34, 10.09]	
Sapra 2005 CeVD	377	27493	223	27493	21.1%	1.70 [1.44, 2.01]	
Shen 2015 Stroke	2071	38840	5740	155347	38.9%	1.47 [1.39, 1.55]	
Subtotal (95% CI)		77199		226153	100.0%	1.44 [1.29, 1.60]	•
Total events	3874		10350				
Heterogeneity: Tau ² = 0.01;			(P = 0.0)	1); $I^2 = 66$	%		
Test for overall effect: Z = 6.	.64 (P < 0.0	00001)					
							7 7
							0.1 0.2 0.5 1 2 5

FIGURE 3. Forest plots showing significantly higher prevalence of cardiovascular and cerebrovascular comorbidities in asthma patients. CAD = coronary artery disease, CeVD = cerebrovascular disease, CHD = coronary heart disease, CHF = congestive heart failure, Cong.HD = congenital heart disease, CVD = cardiovascular disease, dis = disease/disorder, MI = myocardial infarction.

fluid/electrolyte disorders. Neurological and psychiatric comorbidities included autism, anxiety, cerebral palsy, dementia, depression, cognitive impairment, hemipelgia, ottitis, and psychosis.

Gastrointestinal and urinary comorbidities included gastroesophegeal reflux disease, hernia, liver disease, ulcer, and renal disease/failure. Respiratory comorbidities included chronic bronchitis, respiratory infections, allergy rhinitis, chronic obstructive pulmonary disease, and sinusitis. Other comorbidities included cataract, alcohol/drug abuse, dermatitis, anemia, coagulopathy, and acquired immunodeficiency syndrome (AIDS).

The odds ratios of the prevalence of comorbidities including cardiovascular and cerebrovascular comorbidities (Figure 3), hypertension, diabetes mellitus, obesity, other metabolic, and endocrine comorbidities (Figure 4), neurological and psychiatric comorbidities, gastrointestinal and urinary comorbidities, respiratory comorbidities, cancer, and other some other disease were significantly higher in asthma patients than in nonasthma control patients (Table 1; Figures 5–8). Arthritis was the only disease which was not statistically significantly differently prevalent between asthma and nonasthma patients under the random effects model.

DISCUSSION

The present study has compared asthma patients with nonasthma control patients and has found that asthma is associated with significantly higher comorbidities. Almost all types respiratory, cardiovascular, cerebrovascular, metabolic, gastrointestinal, urinary, neurological, and psychiatric, were significantly higher in asthma patients. Only rheumatoid arthritis was found to be statistically indifferent between asthma and nonasthma patients.

Chronic inflammatory conditions appear to be an important factor for the development of comorbidities, for example, asthma is associated with an increased the risk of cardiovascular disease which is attributed to systemic inflammation.²¹ Moreover, in poorly controlled respiratory obstructive conditions, the use of systemic steroids, reduced activity/exercise, and poor sleep can promote comorbidities such as obesity, diabetes, depression, osteoporosis, and pneumonia.¹

A comorbid condition can also develop or promote other comorbidities. While comparing the comorbid patterns of 292 obese and 383 nonobese asthmatic patients, Shah and Yang²² found that the prevalence of diabetes, lipid disorders, and hypertension was significantly higher in obese asthmatics. Moreover, obese patients are found to have about 2.5 times higher risk of developing asthma, asthma is found more severe in obese individuals, and obesity is associated with poor asthma control.^{23–25} Bariatric surgery of morbidly obese patients with asthma has been found to significantly improve airway function and airway hyper-responsiveness

	Asthm		Cont			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
1.2.1 Hypertension							
Ben-Noun 2001	32	141	106	423	5.6%	0.88 [0.56, 1.38]	
Cheng 2015	5903	10455	19807	41820	24.8%	1.44 [1.38, 1.50]	
Pakhale 2010 None-obese	14	181	5	73	1.2%	1.14 [0.40, 3.29]	
Pakhale 2010 Obese	43	165	19	77	3.3%	1.08 [0.58, 2.01]	
Patel 2014	146	6350	482	60298	15.8%	2.92 [2.42, 3.52]	
Sapra 2005	2642	27493	1611	27493	23.9%	1.71 [1.60, 1.82]	
Shen 2015	15898	38840	46377	155347	25.4%	1.63 [1.59, 1.67]	
Subtotal (95% CI)	0.000	83625		285531	100.0%	1.66 [1.47, 1.88]	•
Total events	24678		68407				
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 77.2$		2 < 0.000		22%			
Test for overall effect: $Z = 8.28$ (P < 0.0		- 0.000	01),1 =	52 70			
1.2.2 Diabetes mellitus							
Balkrishnan 2000	83	647	638	4874	13.5%	0.98 [0.76, 1.25]	
Bellia 2007	23	210	126	1027	6.5%	0.88 [0.55, 1.41]	
Ben-Noun 2001	23	141	53	423	5.5%	1.36 [0.80, 2.32]	
Cheng 2015	2751	10455	9204	41820	21.6%	1.27 [1.20, 1.33]	
Pakhale 2010 None-obese	4	165	2	77	0.7%	0.93 [0.17, 5.20]	
Pakhale 2010 Obese	13	181	9	73	2.3%	0.55 [0.22, 1.35]	
Patel 2014	25	6350	121	60298	7.4%	1.97 [1.28, 3.03]	
Sapra 2005	1801	27493	1130	27493	20.8%	1.64 [1.52, 1.77]	+
Shen 2015	3672	38840	12982		21.8%	1.15 [1.10, 1.19]	
Subtotal (95% CI)	0012	84482	12002	291432		1.25 [1.08, 1.44]	•
Total events	8395		24265			the first start	
Heterogeneity: Tau ² = 0.02; Chi ² = 81.0 Test for overall effect: Z = 3.05 (P = 0.0 1.2.3 Obesity							
Bellia 2007	67	210	236	1027	19.6%	1.57 [1.14, 2.17]	
Ben-Noun 2001	18	141	59	423	12.9%	0.90 [0.51, 1.59]	
Pakhale 2010	165	346	77	150	17.8%	0.86 [0.59, 1.27]	
Sapra 2005	437	27493	220	27493	24.2%		
Shen 2005	675	38840	1269	155347	25.6%	2.00 [1.70, 2.36]	
Subtotal (95% CI)	675	67030	1209	184440	100.0%	2.15 [1.95, 2.36] 1.51 [1.14, 2.01]	
and the second	1362	01030	1861	104440	100.078	1.51 [1.14, 2.01]	
Total events Heterogeneity: Tau² = 0.08; Chi² = 30.2 Test for overall effect: Z = 2.85 (P = 0.0	5, df = 4 (l	P < 0.000		37%			
1.2.4 Other metabolic/endocrine							
Ben-Noun 2001 HYPLIP	11	141	29	423	3.0%	1.15 [0.56, 2.37]	
Ben-Noun 2001 THY dis.	9	141	29	423	2.7%	0.93 [0.43, 2.01]	
Cheng 2015 DYSLIP	3493	10455	11598	41820	19.9%	1.31 [1.25, 1.37]	-
Chung 2014 HYPLIP	5036	31356	15065	125157	20.1%	1.40 [1.35, 1.45]	
Sapra 2005 Fluid/Electrolyte disorder	1311	27493	498	27493	18.2%	2.71 [2.44, 3.01]	-
Sapra 2005 THY dis.	415	27493	239	27493	15.9%	1.75 [1.49, 2.05]	
Shen 2015 HYPLIP	8781	38840	25921	155347	20.2%	1.46 [1.42, 1.50]	
Subtotal (95% CI)		135919		378156	100.0%	1.60 [1.40, 1.83]	•
Total events	19056		53379				125
Heterogeneity: Tau ² = 0.02; Chi ² = 169. Test for overall effect: Z = 6.78 (P < 0.0	03, df = 6	(P < 0.00		96%			
Test for subgroup differences: Chi ² = 9.	76. df = 3	(P = 0.02), $ ^2 = 69$	3%			0.2 0.5 1 2 5 Higher in controls Higher in asthmatics

FIGURE 4. Forest plots showing significantly higher prevalence of metabolic comorbidities in asthma patients. dis. = disease/disorder, DYSLIP = dyslipidemia, HYPLIP = hyperlipidemia, THY = thyroid.

besides improving asthma control and systemic inflammation markers. $^{\rm 26}$

With aging, the number of comorbid conditions in asthma patients increase. Tsai et al^{27} in a sample population of 1,195,109 asthma patients found that the overall prevalence of 10 selected comorbidities was <1% in patients with under 18 years of age, 3.4% in 18 to 54 years age group, and 12% in patients over 55 years of age. In young individuals, the percentage of asthmatic patients with one kind of comorbidity was 34% and with >1 kinds of comorbidity was 11%.^{28,29} Other studies have also reported significantly higher prevalence of comorbidities in elderly in comparison with nonelderly asthma patients.^{30,31} Recently, Zein et al³² have found that after adjusting comorbidities and asthma duration, severity of asthma was significantly higher in individuals >45 years of age.

It is now agreed that asthma in late age is common and relatively less-recognized, underdiagnosed, and undertreated health problem that affects the quality of health and life. It is also speculated that asthma in elderly is causally and phenotypically different from young-age asthma with impact on the diagnosis, assessment, and management.³³ Although Wardzynska et al³⁰ who reported that in elderly asthmatics comorbidities are more prevalent than in nonelderly patients, but apparently this was not having direct impact on asthma control in patients under specialist care, other authors are concerned about potential impacts of comorbidities and their management such as issues related to drug interactions and adverse events resulting from polypharmacy and adherence to therapy.³⁴ Gershon et al⁶ who also observed significantly higher comorbidity in asthmatics than in controls, noted that asthma comorbidities

TABLE 1. Results of the Meta-Analyses

			Odds ratios [95% C	I]; Significance level	
Comorbidities	Studies/ Datasets	Asthma Patients	Fixed Effects	Random Effect	I^2
Cardiovascular	16	294,727	1.75 [1.72, 1.78]; <i>P</i> < 0.00001	1.90 [1.70, 2.14]; <i>P</i> < 0.00001	95%
Cerebrovascular	6	77,199	1.43 [1.38, 1.49]; <i>P</i> < 0.00001	1.44 [1.29, 1.60]; <i>P</i> < 0.00001	66%
Hypertension	7	83,625	1.60 [1.57, 1.63]; P < 0.00001	1.66 [1.47, 1.88]; <i>P</i> < 0.00001	92%
Diabetes mellitus	9	84,482	1.24 [1.21, 1.28]; <i>P</i> < 0.00001	1.25 [1.08, 1.44]; <i>P</i> < 0.00001	90%
Obesity	5	67,030	1.95 [1.81, 2.11]; P < 0.00001	1.51 [1.14, 2.01]; <i>P</i> < 0.00001	87%
Endocrine/metabolic	7	371,056	1.45 [1.42, 1.48]; <i>P</i> < 0.00001	1.60 [1.40, 1.83]; <i>P</i> < 0.00001	96%
Psychiatric and neurological	17	175,784	1.83 [1.78, 1.89]; <i>P</i> < 0.00001	1.62 [1.44, 1.82]; <i>P</i> < 0.00001	91%
Gastrointestinal and urinary	9	132,402	1.81 [1.71, 1.91]; <i>P</i> < 0.00001	1.91 [1.47, 2.49]; <i>P</i> < 0.00001	93%
Respiratory comorbidities	9	165,224	5.15 [5.07, 5.24]; <i>P</i> < 0.00001	5.60 [4.22, 7.44]; <i>P</i> < 0.00001	99%
Cancer	4	59,637	1.17 [1.10, 1.25]; <i>P</i> < 0.00001	1.17 [1.10, 1.25]; <i>P</i> < 0.00001	0%
Arthritis	4	34,550	2.17 [1.89, 2.48]; <i>P</i> < 0.00001	2.73 [0.96, 7.72]; P = 0.06	97%
Other diseases	11	69,747	1.67 [1.55, 1.81]; $P < 0.00001$	1.71 [1.49, 1.98]; <i>P</i> < 0.00001	61%

Asthmatics **Odds Ratio Odds Ratio** Controls Total Weight M-H, Random, 95% Cl Study or Subgroup **Events Total Events** M-H, Random, 95% Cl Balkrishnan 2000 DEP 162 647 985 4874 6.9% 1.32 [1.09, 1.60] Bellia 2007 COGN 210 1027 3.9% 0.93 [0.60, 1.45] 27 140 Bellia 2007 DEP 84 210 337 1027 5.4% 1.36 [1.01, 1.85] Ben-Noun 2001 ANX 6 141 31 423 1.5% 0.56 [0.23, 1.38] Ben-Noun 2001 DEP 141 9 423 0.3% 0.33 [0.04, 2.62] 1 Cheng 2015 DEM 516 10455 1570 41820 7.9% 1.33 [1.20, 1.47] Cheng 2015 DEP 811 10455 1828 41820 8.0% 1.84 [1.69, 2.00] de Miguel Diez 2011 ANX 160 1650 1803 27316 7.1% 1.52 [1.28, 1.80] de Miguel Diez 2011 DEP 149 1650 1502 27316 7.1% 1.71 [1.43, 2.03] Dyer 1999 DEP 0.7% 2.05 [0.51, 8.23] 60 43 8 3 Patel 2014 Autism 95 6350 543 60298 6.5% 1.67 [1.34, 2.08] Patel 2014 Cereb. plasy 57 6350 241 60298 5.6% 2.26 [1.69, 3.02] Sapra 2005 DEP 2.06 [1.88, 2.26] 1342 27493 668 27493 7.9% Sapra 2005 Hemipelgia 27493 1.93 [1.64, 2.27] 421 220 27493 7.2% Sapra 2005 Neurol. dis. 1034 27493 632 27493 7.9% 1.66 [1.50, 1.84] Sapra 2005 Ottitis 5394 27493 2730 27493 8.2% 2.21 [2.11, 2.33] Sapra 2005 Psychosis 1138 27493 1.41 [1.29, 1.54] 817 27493 8.0% Total (95% CI) 175784 404150 100.0% 1.62 [1.44, 1.82] 14059 Total events 11405 Heterogeneity: Tau² = 0.04; Chi² = 176.80, df = 16 (P < 0.00001); I² = 91% 0.1 0.2 0.5 10 ż Ś Test for overall effect: Z = 7.93 (P < 0.00001) Higher in controls Higher in Asthmatics

FIGURE 5. Forest plots showing significantly higher prevalence of neurological and psychiatric comorbidities in asthma patients. ANX = anxiety, COGN = cognitive impairment, DEM = dementia, DEP = depression, dis. = disease/disorder.

	Asthm	atics	Cont	rols		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Ben-Noun 2001 Hernia	19	141	11	423	6.6%	5.83 [2.70, 12.59]	
Ben-Noun 2001 Ulcer	9	141	11	423	5.5%	2.55 [1.04, 6.30]	
Cheng 2015 Renal dis.	631	10455	1992	41820	15.0%	1.28 [1.17, 1.41]	+
Pakhale 2010 GERD	33	181	16	73	7.7%	0.79 [0.41, 1.55]	
Pakhale 2010 Ob. GERD	58	165	26	77	8.9%	1.06 [0.60, 1.88]	
Sapra 2005 Liver dis.	157	27493	74	27493	13.1%	2.13 [1.61, 2.81]	
Sapra 2005 Peptic ulcer	324	27493	157	27493	14.1%	2.08 [1.71, 2.51]	
Sapra 2005 Renal failure	399	27493	159	27493	14.2%	2.53 [2.10, 3.04]	-
Shen 2015 GERD	752	38840	1360	155347	15.0%	2.24 [2.04, 2.45]	-
Total (95% CI)		132402		280642	100.0%	1.91 [1.47, 2.49]	•
Total events	2382		3806			an a	
Heterogeneity: Tau ² = 0.12	Chi ² = 10	9.02, df =	8 (P < 0.	00001); F	= 93%	-	05 0.2 1 5 20
Test for overall effect: $Z = 4$			1993 N. 1993		10000	0	1.05 0.2 1 5 20 Higher in controls Higher in Asthmatics

FIGURE 6. Forest plots showing significantly higher prevalence of gastrointestinal and urinary comorbidities in asthma patients. dis = disease/disorder, GERD = gastro-esophageal reflex disease.

	Asthr	atics	Cont	rols		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Ben-Noun 2001 Ch Bronch	17	141	9	423	6.3%	6.31 [2.74, 14.50]	
Ben-Noun 2001 Sinusitis	8	141	4	423	3.9%	6.30 [1.87, 21.26]	
Cheng 2015 Ch Resp Infect.	3551	10455	1431	41820	13.7%	14.52 [13.58, 15.51]	
Cheng 2015 Rhinitis	3256	10455	4003	41820	13.8%	4.27 [4.05, 4.50]	
Dyer 1999 Ch Bronch	17	60	3	43	3.5%	5.27 [1.44, 19.36]	
Sapra 2005 Resp infect	16001	27493	5554	27493	13.8%	5.50 [5.30, 5.71]	
Sapra 2005 Rhinitis	17	100	3	100	3.7%	6.62 [1.87, 23.39]	
Shen 2015 COPD	3786	38840	2653	155347	13.8%	6.22 [5.91, 6.54]	
Shen 2015 Rhinitis	13525	38840	16262	155347	13.8%	4.57 [4.45, 4.69]	
Shen 2015 Sinusitis	1507	38840	2171	155347	13.7%	2.85 [2.66, 3.04]	•
Total (95% CI)		165365		578163	100.0%	5.60 [4.22, 7.44]	+
Total events	41685		32093				
Heterogeneity: Tau ² = 0.15; Ch	ni ² = 1428.	28, df = 9	(P < 0.00	0001); I ² =	99%		0.05 0.2 1 5 20
Test for overall effect: Z = 11.9	3 (P < 0.00	0001)					0.05 0.2 1 5 20 Higher in controls Higher in Asthmatics

FIGURE 7. Forest plots showing significantly higher prevalence of respiratory comorbidities in asthma patients. Bronch = bronchitis, ch = chronic, COPD = chronic obstructive pulmonary disease, Infect = infection/s, Resp = respiratory.

were associated with poor asthma control, increased health care utility, and decreased quality of life, but the management of comorbidities could significantly improve the outcomes. Thus, comorbidity should be considered with more emphasis in asthma control strategies and should be an important component of covariate analyses in studies with subjective health outcomes.³⁵ Among the foremost limitations of the present study, high statistical heterogeneity representing lower consistency between studies in some comparisons is an important consideration. However, because of the epidemiological nature of the present study, the impact of higher statistical heterogeneity may be less on the overall outcomes. Thus, the availability of more

	Asthm	atics	Cont	rols		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
1.6.1 Cancer							
Balkrishnan 2000	86	647	580	4874	6.8%	1.13 [0.89, 1.45]	
Ben-Noun 2001	5	141	13	423	0.4%	1.16 [0.41, 3.31]	
Chung et al 2014	1171	31356	4005	125157	90.8%	1.17 [1.10, 1.25]	
Sapra 2005	47	27493	36	27493	2.1%	1.31 [0.85, 2.02]	
Subtotal (95% CI)		59637		157947	100.0%	1.17 [1.10, 1.25]	•
Total events	1309		4634				
Heterogeneity: Tau ² = 0.00;	Chi ² = 0.3	1, df = 3	(P = 0.96); I ² = 0%			
Test for overall effect: Z = 4.	96 (P < 0.0	00001)					
1.6.2 Arthritis							
Balkrishnan 2000	347	647	2227	4874	26.4%	1.37 [1.17, 1.62]	+
Dyer 1999	31	60	21	43	23.1%	1.12 [0.51, 2.45]	
Patel 2014	19	6350	42	60298	24.8%	4.31 [2.50, 7.41]	
Sapra 2005	258	27493	33	27493	25.7%	7.88 [5.48, 11.33]	
Subtotal (95% CI)		34550		92708	100.0%	2.73 [0.96, 7.72]	
Total events	655		2323				
Heterogeneity: Tau ² = 1.06;	Chi ² = 86.	95, df = 3	3 (P < 0.0	0001); I ² =	= 97%		
Test for overall effect: $Z = 1$.	89 (P = 0.0)6)					
1.6.3 Other diseases							
Ben-Noun 2001 Cataract	8	141	13	423	2.2%	1.90 [0.77, 4.68]	
Cheng 2015 Alcohal dis.	87	10455	277	41820	12.5%	1.26 [0.99, 1.60]	-
Cheng 2015 Dermititis	133	10455	365	41820	14.1%	1.46 [1.20, 1.79]	
Cheng 2015 Drug abuse	15	10455	49	41820	4.6%	1.22 [0.69, 2.18]	
Patel 2014 Anemia	32	6350	121	60298	7.9%	2.52 [1.70, 3.72]	
Sapra 2005 AIDS	18	6350	72	60298	5.5%	2.38 [1.42, 3.99]	
Sapra 2005 Alcohal dis.	109	6350	663	60298	13.9%	1.57 [1.28, 1.93]	-
	283	6350	1459	60298	16.8%	1.88 [1.65, 2.14]	+
Sapra 2005 Anemia			157	60298	9.1%	2.49 [1.76, 3.51]	
Sapra 2005 Anemia Sapra 2005 Coagulopathy	41	6350	157				
Sapra 2005 Coagulopathy Sapra 2005 Drug abuse		6350 6350	591	60298	13.5%	1.57 [1.26, 1.95]	
Sapra 2005 Coagulopathy	41			60298 487671		1.57 [1.26, 1.95] 1.71 [1.49, 1.98]	•
Sapra 2005 Coagulopathy Sapra 2005 Drug abuse	41	6350					•
Sapra 2005 Coagulopathy Sapra 2005 Drug abuse Subtotal (95% Cl)	41 97 823	6350 69606	591 3767	487671	100.0%		•
Sapra 2005 Coagulopathy Sapra 2005 Drug abuse Subtotal (95% CI) Total events	41 97 823 Chi ² = 23.	6350 69606 17, df = 9	591 3767	487671	100.0%		•

Test for subgroup differences: Chi² = 24.86, df = 2 (P < 0.00001), l² = 92.0%

FIGURE 8. Forest plots showing significantly higher prevalence of cancer and other comorbidities in asthma patients. However, the prevalence of arthritis was not significantly different between asthma and nonasthma patients.

data in future can refine these findings. Another constraint is that majority of the included studies reported selected comorbidities so not all comorbid conditions could be studied here and some comparisons remained underpowered.

CONCLUSION

Asthma is associated with significantly higher comorbid conditions including cardiovascular and cerebrovascular comorbidities, obesity, hypertension, diabetes, metabolic and endocrine conditions, psychiatric and neurological comorbidities, gut and urinary comorbidities, cancer, and respiratory problems other than asthma. Respiratory comorbidities are found 5 times more prevalent in asthma than in nonasthma patients. Management of comorbidities in asthma control strategies can improve outcomes.

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