

Incidence of IBS in a Cohort of People with Asthma

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Abstract We conducted a study to examine the relation of asthma and its treatment to irritable bowel syndrome (IBS). We identified cohorts of members with and without asthma from January 1996 through June 2002 and calculated rates of IBS in both cohorts. In a nested case-control study, we calculated odds ratios for oral steroid dispensings before IBS onset. To address differential IBS detection, we conducted a quantitative sensitivity analysis. We identified 91,237 people with asthma and sample of 24,518 people without asthma.

There was a 20% increase in the incidence of IBS among people with asthma (standardized morbidity ratio = 1.2; 95% CI, 1.0–1.5), and no association between oral steroids and IBS among people with asthma (OR = 1.0; 95% CI, 0.9–1.1.) Misclassification of IBS would have biased the rate ratio toward the null. We observed a small increase in IBS among people with asthma, and no association between oral steroids and IBS onset among asthma patients.

Keywords Irritable bowel syndrome · Asthma · Oral steroids · Epidemiology · Cohort · Case-control

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Introduction

Asthma is a chronic disease of unknown etiology characterized by recurrent airway obstruction, hyperresponsiveness, and inflammation [1, 2]. Its prevalence in the United States during 2001 was estimated at 7.2% and has been increasing since 1980 [3–5]. People with asthma are frequent consumers of health services, with about 10.8 million office visits associated with asthma in 1999 [5]. Asthma patients are typically classified through pulmonary function studies into symptom severity categories of mild intermittent, mild persistent, and moderate-severe persistent. Recent theories about the cause of asthma have focused on an allergic response that may manifest when mild as allergic rhinitis and when severe as asthma [1].

Irritable bowel syndrome (IBS) is a functional disorder of the gastrointestinal tract which results in the clinical symptoms of altered bowel habits and abdominal pain [6, 7]. It is characterized by three specific forms: diarrhea-predominant, constipation-predominant, and alternating between diarrhea and constipation. While there is no diagnostic instrument to screen and diagnose people with the condition, the Rome

criteria represent the established standard for diagnosis [8]. The Rome criteria are used in clinical trials of IBS, but not routinely by clinicians.

Because of the relatively high prevalence of asthma and IBS, there may be a considerable number of people who have both diseases. The relation between asthma and IBS has not been well studied, although it has been hypothesized that both diseases result from an underlying inflammatory process [9, 10]. A cohort study of this possible association using data from the General Practitioner Research Database in the United Kingdom found a rate ratio of 1.3 (95% CI, 1.1–1.5) of IBS incidence among asthma patients compared with people without asthma, after controlling for age and sex [11]. In that study, asthma patients who were current users of oral steroids had a 50% reduced incidence of IBS compared with nonusers of steroids (risk ratio, 0.5; 95% CI, 0.2–1.2) [11]. An earlier study from the United Kingdom based on survey data found a rate ratio of 1.6 (95% CI, 1.2–2.1) for the prevalence of IBS among people with asthma compared with those without [9]. Although both of these studies provide support for a hypothesis that an underlying disorder could produce both respiratory and gastrointestinal symptoms, the evidence has not been consistent. A recent study of asthma patients found little association between methacholine challenge test results (a test used to assess bronchial hyperresponsiveness) and IBS [12].

To examine further the occurrence of IBS among people with asthma, we conducted a record-based cohort study of two cohorts, one with asthma and another without. To examine the relation between oral steroid use and IBS, we also conducted a case-control study within the asthma cohort.

Methods

Data source

The data came from UnitedHealthcare, a large, national health insurance plan. Coverage through the plan is typically available as an employment benefit. Plan members either are employed or are spouses or dependents of the employed subscriber. A research database contains automated insurance claims for medical services, including those provided by a physician or hospital, along with claims for prescriptions filled at an outpatient pharmacy. For this research, we used data from eight geographically diverse states with the largest number of health plan members.

Study population

We identified all people with a diagnosis of asthma in association with a physician visit between January 1, 1996, and June 30, 2002. The ICD-9 CM code corresponding to

a diagnosis of asthma is 493 [13]. We restricted the cohort to people with at least two or more visits for asthma, with at least 30 days between two of the asthma visits. The start date of follow-up for people in this cohort was the later of the second diagnosis code for asthma or the date marking 1 year of continuous health plan enrollment. For a comparison cohort, we identified a 5% simple random sample of all health plan enrollees who sought routine medical care with a physician between January 1, 1995, and June 30, 2002. The ICD-9-CM diagnosis code corresponding to a diagnosis of routine medical care is V70.0 [13]. The start date of follow-up for people in this cohort was the later of the first diagnosis of routine medical care or the date marking a year of continuous health plan enrollment.

We created datasets of all medical claims for people in the asthma and comparison cohorts, including those related to physician and hospital services, along with all outpatient pharmacy dispensing claims and all dates of health plan enrollment. We excluded any cohort members who were under 5 years old as of their start date. People who were identified in both the asthma cohort and the comparison cohort were kept only in the asthma cohort.

IBS identification

We identified the first date of an IBS diagnosis among people in each of the two cohorts. We excluded people with their first IBS diagnosis occurring before their follow-up start date. We also excluded any people who, before their follow-up start date, had diagnoses that share symptoms with IBS. These diagnoses were Crohn's disease, colon or rectal cancer, ulcerative colitis, chronic pancreatitis, pancreatic cancer, liver cirrhosis, celiac disease, sprue and other intestinal malabsorption, and ovarian cancer. We also excluded people who had, before the start date, a diagnosis of gastroesophageal reflux, other related gastrointestinal conditions, prescription dispensings of drugs to treat constipation or diarrhea, or medical care by a gastroenterologist.

Person-time of follow-up for each subject began on the follow-up start date and continued through the earliest of the following dates: the first IBS diagnosis, the first date of a diagnosis sharing symptoms similar to IBS, or June 30, 2002. We calculated incidence rates in the asthma and comparison cohort as the number of people with IBS divided by the person-time at risk.

Covariates

We searched the database during the year before each person's start date to record information relating to other possible confounding variables. In addition to age and sex, these variables included medical services for obesity, smoking-related medical services, dispensings of oral contraceptives,

and dispensings of estrogen replacement therapy. We used the total cost of medical and pharmacy services reimbursed by the health plan in the year before the follow-up start date as a proxy measure for severity of underlying disease. We classified people according to quintile of total medical costs.

Data analysis

We calculated crude incidence rates and the incidence rate difference between the asthma and the nonasthma cohorts. We then stratified the cohorts according to each covariate and calculated the standardized morbidity ratio (SMR) using the asthma cohort as the exposed cohort to quantify the magnitude and direction of possible confounding bias [14].

Case-control analysis

To assess the rate of IBS among oral steroid recipients with asthma, we conducted a case-control study nested within the asthma cohort. In this analysis, all people within the asthma cohort identified with IBS served as cases. We randomly sampled 1 of 1000 of those in the asthma cohort who were at risk for IBS at the time corresponding to the diagnosis date for each IBS case, thus sampling a set of controls matched to each case. In this analysis, the IBS date among the IBS cases was termed the *index date*. The index date for each control was the index date for the case to whom the control was matched.

We used the pharmacy claims to classify cases and controls according to dispensing of oral steroids within a year before the index date. The odds ratio for IBS was calculated for any dispensing of oral steroids within a year before the index date, compared with those without an oral steroid dispensing. To examine the relation between the proximity of the most recent oral steroid dispensing and IBS, we created indicator variables for cases and controls according to the most recent oral steroid dispensing during windows of time before the index date. These windows were 0–30, 31–90, 91–180, and 181–365 days. We also created indicator variables for cases and controls according to the number of oral steroid dispensings in the year before the index date (1, 2, 3, 4, and 5 or more). As possible confounders, we considered age, sex, quintile of total medical cost, and dispensing of other asthma drugs (inhaled steroids, oral β -agonists, inhaled β -agonists, xanthines, and leukotriene modifiers) in the year before the index date. We calculated odds ratios pooled across confounders using conditional logistic regression to account for the matched sampling of controls.

Sensitivity analysis

To assess the magnitude of possible bias due to differential ascertainment of IBS cases in the study cohorts, and to deter-

mine the effect that it could have on the observed incidence rate ratio, we conducted a quantitative sensitivity analysis based on simple methods [15]. In the first analysis, we assumed the sensitivity of IBS identification in the asthma cohort was 100%. The sensitivity of IBS identification in the nonasthma cohort was hypothesized at varying levels and the simulated incidence rate ratio was calculated. In a second analysis, we assumed there was no under ascertainment of IBS cases (i.e., the sensitivity was 100%), and we varied the level of hypothesized specificity of IBS detection in the two cohorts.

Privacy and confidentiality

All analyses and reporting for this research were performed using de-identified data with respect to Protected Health Information. Under the Health Insurance Portability and Accountability Act (HIPAA) of 1996, this research, using encrypted automated data, did not require approval by a Privacy Board or Institutional Review Board.

Results

Study population

We identified 97,237 people in the asthma cohort and 24,518 people in the nonasthma comparison cohort, yielding 149,312 and 40,464 person-years of follow-up, respectively. The number of people in the asthma cohort and the nonasthma comparison cohort is shown in Table 1. Of the 97,237 people in the asthma cohort, 51,137 (56%) were women, whereas the nonasthma cohort had about equal numbers of women and men. Children comprised a greater proportion of the asthma cohort compared with the nonasthma cohort. In the asthma cohort, 16% (14,148) were between 5 and 9 years of age, and 23% (20,736) were ages 10 to 19. Only 3% (713) of the nonasthma cohort were between 5 and 9 years of age, and 20% (4,769) were ages 10 to 19.

The distribution of characteristics examined as potential confounding variables is shown in Table 2. Both use of medical services related to obesity and use of medical services related to smoking in the year before the start date were rare, occurring in 1–2% of the asthma and comparison cohorts. Among women, dispensing of estrogen replacement therapy in the year before the start date occurred in 7% of the asthma cohort and 8% of the comparison cohort. Somewhat more women were dispensed oral contraceptives in the year before the start date, occurring in 8 and 11% of the asthma and comparison cohorts, respectively. Median total medical costs in the year preceding cohort entry were \$1067 among people in the asthma cohort. In contrast, median total medical costs among people in the comparison cohort were \$326.

Table 1 Number of people in the asthma and nonasthma cohorts by age and sex, January 1996 through June 2002

Age	Asthma		Nonasthma	
	Number	(%)	Number	(%)
Female				
5–9	5,318	(10.4)	344	(2.8)
10–19	9,245	(18.1)	2,285	(18.6)
20–29	6,591	(12.9)	1,779	(14.5)
30–39	9,669	(18.9)	2,470	(20.1)
40–49	10,661	(20.8)	2,805	(22.9)
50–64	8,881	(17.4)	2,437	(19.9)
65 +	772	(1.5)	143	(1.2)
Total	51,137	(100.0)	12,263	(100.0)
Male				
5–9	8,830	(22.0)	369	(3.0)
10–19	11,491	(28.7)	2,484	(20.3)
20–29	3,816	(9.5)	1,222	(10.0)
30–39	5,493	(13.7)	2,255	(18.4)
40–49	5,167	(12.9)	2,980	(24.3)
50–64	4,675	(11.7)	2,756	(22.5)
65 +	628	(1.6)	189	(1.5)
Total	40,100	(100.0)	12,255	(100.0)
Total				
5–9	14,148	(15.5)	713	(2.9)
10–19	20,736	(22.7)	4,769	(19.5)
20–29	10,407	(11.4)	3,001	(12.2)
30–39	15,162	(16.6)	4,725	(19.3)
40–49	15,828	(17.3)	5,785	(23.6)
50–64	13,556	(14.9)	5,193	(21.2)
65 +	1,400	(1.5)	332	(1.4)
Total	91,237	(100.0)	24,518	(100.0)

Incidence of IBS in relation to asthma

We identified 1451 people with an IBS diagnosis in the asthma cohort during follow-up. There were 276 people with an IBS diagnosis within the nonasthma cohort during follow-up. The incidence rate of IBS in the asthma cohort was 9.7 per 1000 person-years in the asthma cohort, compared with 6.8 per 1000 person-years in the nonasthma cohort. The incidence rate difference of IBS was 2.9 per 1000 person-years (95% CI, 2.0–3.8), and the crude incidence rate ratio was 1.4

Table 3 Incidence rate and rate ratio of IBS, January 1996 through June 2002

	Asthma	Nonasthma
IBS cases	1,451	276
Person-years (PY)	149,312	40,464
Incidence rate per 1000 PY	9.7	6.8
Rate difference per 1000 PY (95% CI)	2.9 (2.0–3.8)	
Crude incidence rate ratio (95% CI)	1.4 (1.3–1.6)	
Standardized morbidity ratio (95% CI) ^a	1.2 (1.0–1.5)	

^aStandardized morbidity ratio adjusted for age category and quintile of total medical costs in the year before the follow-up start date.

(95% CI, 1.3–1.6) (Table 3). After stratification by both cost quintile and age, there was a 20% increase in the rate of IBS in the asthma cohort relative to the nonasthma comparison cohort (SMR = 1.2; 95% CI, 1.0–1.5) (Table 3). Figure 1 shows a Kaplan-Meier plot of the time to IBS in the two cohorts.

Incidence of IBS in relation to oral steroids

The results of the case-control analysis of oral steroid dispensing among people with asthma are shown in Tables 4 and 5. Through sampling, we identified 41,812 controls of the 91,237 people in the asthma cohort. The number of controls per case ranged from 1 to 38. The crude odds ratio of IBS comparing people with at least one oral steroid dispensing to people with no oral steroid dispensing was 1.1 (95% CI, 1.0–1.2). Following adjustment for quintile of cost, there was no association between IBS and any oral steroid dispensings in the preceding year (pooled odds ratio, 1.0; 95% CI, 0.9–1.1).

There was little heterogeneity in the odds ratios across the time windows of the most recent oral steroid dispensing (Table 4). In the analysis stratified by the number of oral steroid dispensings (Table 5), there were weak associations between those with a single dispensing (pooled odds ratio, 1.0; 95% CI, 0.8–1.1) and with two dispensings (pooled odds

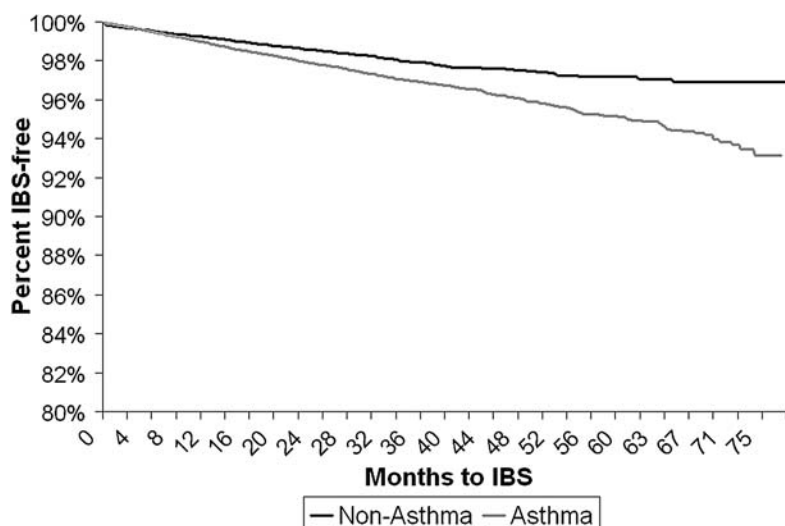
Table 2 Distribution of selected characteristics in the year before the follow-up start date, asthma and nonasthma cohorts, January 1996 through June 2002

^aAmong 51,137 women in the asthma cohort and 12,263 women in the nonasthma cohort.

^bReported as mean (SD) [25th, 50th, 75th percentiles].

	Asthma (<i>n</i> = 91,237)		Nonasthma (<i>n</i> = 24,518)	
	No. of people	(%)	No. of people	(%)
Medical claim for obesity	1,414	(1.6)	302	(1.2)
Medical claim for smoking cessation	1,732	(1.9)	341	(1.4)
Dispensing of estrogen replacement therapy among women ^a	3,346	(6.5)	988	(8.1)
Dispensing of oral contraceptives among women ^a	3,925	(7.7)	1,285	(10.5)
Total medical cost in the year preceding follow-up start date ^b	\$2,092 (\$4,372) [548, \$1,067, \$2,171]		\$912 (\$2,374) [145, \$326, \$811]	

Fig. 1 Kaplan-Meier plot of time to IBS in the asthma and nonasthma cohorts, January 1996 through June 2002



ratio, 0.9; 95% CI, 0.7–1.1) in the previous year and those with no dispensing. People with five or more dispensings in the preceding year had a 10% increase in the risk of IBS (pooled odds ratio, 1.1; 95% CI, 0.8–1.5).

Sensitivity analysis

Figures 2 and 3 shows the results of the sensitivity analysis of differential IBS classification. The curve indicates that the observed excess of IBS in the asthma cohort in the crude incidence rate ratio would have been biased in the opposite direction if the true sensitivity for IBS detection was below 70% in the nonasthma cohort (Fig. 2). The effect of non-differential imperfect specificity of IBS detection is shown in Fig. 3. Error in the specificity of IBS detection would have biased the observed result toward the null. A greater than 10% change between the simulated rate ratio and the observed rate occurs when the hypothesized specificity is below 99.6%. Correcting for the imperfect specificity of IBS detection would result in a simulated rate ratio farther away from the null than the observed rate ratio.

Discussion

In this retrospective study, we observed a 20% increase in the incidence rate of IBS among people with asthma in compar-

ison with people without asthma. The case-control analysis showed little overall association with oral steroid dispensings in the preceding year, with a 10% increase in the risk of IBS among those dispensed five or more oral steroids. The results of this study, showing an increase in the incidence rate of IBS among people with asthma, are in the same direction as other published epidemiologic studies of this relation that showed relative risks ranging from 1.3 to 1.6 [9, 11]. The findings from the case-control analysis, which did not indicate a reduced risk of IBS, differ from other published studies showing relative risks of IBS of between 0.5 and 0.6 among recent oral steroid users [11, 16].

The elevation in the incidence rate of IBS among people with asthma has been thought to support the hypothesis that an underlying disorder resulting in an inflammatory condition could produce respiratory and gastrointestinal symptoms. There are, however, alternative hypotheses that we explored. The sensitivity analysis examined the effect of differential IBS detection on the observed crude incidence rate ratio. Although differential disease classification to the extent that would have been necessary to produce a null rate ratio may not have been likely, this analysis provides a quantitative assessment of the degree of bias that could have been affected the study. Depending on the extent of the differential sensitivity of IBS detection, the study's results could be compatible with a null association, or a protective

Table 4 Case-control analysis of oral steroid dispensing in relation to IBS in the asthma cohort, January 1996 through June 2002

Days before index date	Cases	Controls	Crude OR	(95% CI)	Pooled OR ^a	(95% CI)
Any dispensing within 365 days	504	13,098	1.1	(1.0–1.2)	1.0	(0.9–1.1)
0–30 days	67	1,816	1.0	(0.8–1.4)	0.9	(0.7–1.2)
31–90 days	96	2,702	1.0	(0.8–1.3)	0.9	(0.7–1.1)
91–180 days	149	3,343	1.3	(1.1–1.6)	1.1	(1.0–1.4)
181–365 days	192	5,237	1.1	(0.9–1.3)	1.0	(0.8–1.1)
No dispensing	947	28,714	Ref	—	Ref	—
Total	1,451	41,812				

^aOdds ratio from conditional logistic regression pooled across quintile of total medical costs in the year before the follow-up start date.

Table 5 Case-control analysis of number of oral steroid dispensings in relation to IBS in the asthma cohort, January 1996 through June 2002

Number of dispensings in previous year	Cases	Controls	Crude OR	(95% CI)	Pooled OR ^a	(95% CI)
One or more	504	13,098	1.1	(1.0–1.2)	1.0	(0.9–1.1)
1	274	7,582	1.1	(0.9–1.2)	1.0	(0.8–1.1)
2	109	2,996	1.1	(0.9–1.3)	0.9	(0.7–1.1)
3	56	1,138	1.4	(1.0–1.9)	1.2	(0.9–1.6)
4	23	579	1.1	(0.7–1.7)	0.9	(0.6–1.4)
≥ 5	42	803	1.4	(1.0–2.0)	1.1	(0.8–1.5)
None	947	28,714	Ref	—	Ref	—
Total	1,451	41,812				

^aOdds ratio from conditional logistic regression pooled across quintile of total medical costs in the year before the follow-up start date.

effect of asthma on occurrence of IBS. Considerably different sensitivity of IBS detection (100% in the asthma cohort and 70% in the nonasthma cohort) would be required for the association to be changed from a modest elevation of IBS in the asthma cohort to a null association. On the other hand, non-differential specificity of IBS detection below 99.6% could have also resulted in bias toward the null. A small change in specificity, not substantially different from 100%, would induce bias because of the relative infrequency of an IBS diagnosis among people with asthma. Correcting for a small number of false-positive IBS cases would result in a measure of association away from the observed rate ratio. Without undertaking primary data collection to validate the IBS diagnosis through patient interview or exam, we cannot know the degree to which information bias affected the results. Our assumption is that sensitivity of IBS detection was similar in the two cohorts and that specificity of IBS detection was near 100%.

The case-control analysis showed little association between any dispensing of oral steroids in the preceding year and IBS onset. Although this finding may reflect a lack of effect of oral steroids, it is also plausible that this apparent null association with IBS could result from the combination

of an increased risk of IBS from oral steroids coupled with discontinuation of oral steroid use in the presence of premonitory signs and symptoms of IBS. As people develop gastrointestinal pain and changing bowel patterns, it is likely that their medication regimens may change if there is any suspicion that the medications are aggravating the symptoms. Through the health insurance claims data, it is difficult to identify further evidence to support either hypothesis. Additional data sources, such as patient interview or medical record review, could provide evidence for or against these competing hypotheses.

Since asthma severity cannot be directly measured, we used medical costs as a proxy measure for severity instead. Although clinical measures of asthma severity, such as FEV₁, were not available, the results of this stratified analysis indicated that people who incurred a high level of health care service utilization, measured by the cost of medical care, had the highest incidence rate of IBS. If there is a correlation between cost of medical care and asthma symptom severity, this analysis would suggest that severe asthma patients would have the highest incidence of IBS.

We were unable to assess the severity of gastrointestinal symptoms among the IBS cases. For instance, it is

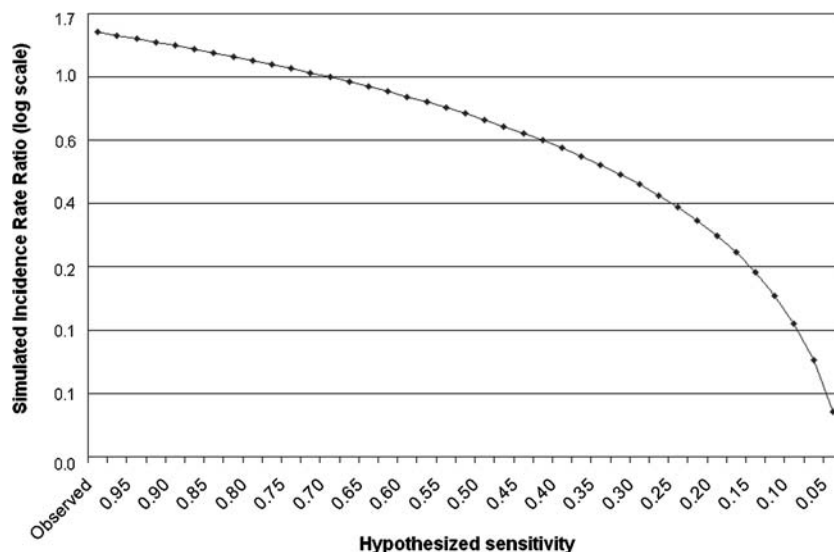
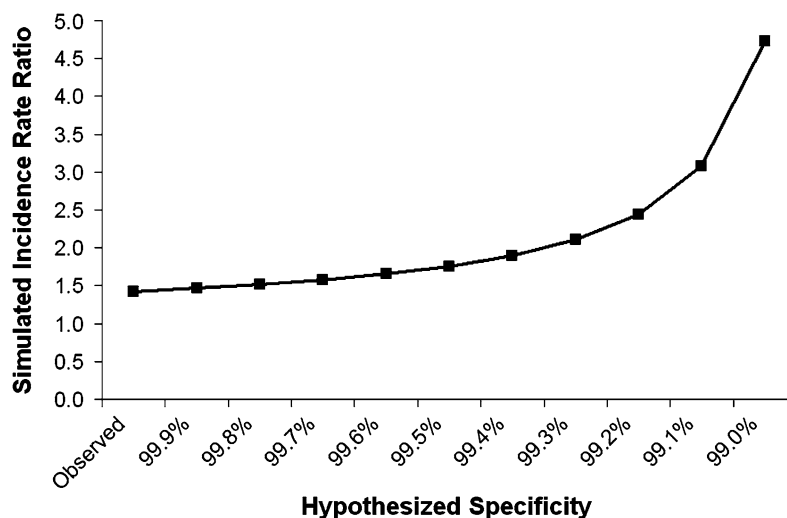
Fig. 2 Simulated incidence rate ratios for varying levels of hypothesized sensitivity of IBS detection in the nonasthma cohort. Ratios assume a sensitivity of IBS classification in the asthma cohort of 100%

Fig. 3 Simulated incidence rate ratios for varying levels of hypothesized levels of nondifferential specificity of IBS detection



possible that in the asthma cohort, diarrhea tends to be the predominant symptom among IBS cases, whereas constipation is the predominant symptom in the nonasthma cohort. Furthermore, we were unable to identify whether each case would have fulfilled the Rome criteria for IBS.

In conclusion, we observed a small increase in the incidence of IBS among people with asthma. We observed no association between oral steroids and IBS onset among asthma patients.

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