Prevalence of Inflammatory Bowel Disease Among Patients with Autism Spectrum Disorders

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Background: The objective of this study was to measure the prevalence of inflammatory bowel disease (IBD) among patients with autism spectrum disorders (ASD), which has not been well described previously.

Methods: The rates of IBD among patients with and without ASD were measured in 4 study populations with distinct modes of ascertainment: a health care benefits company, 2 pediatric tertiary care centers, and a national ASD repository. The rates of IBD (established through *International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] codes) were compared with respective controls and combined using a Stouffer meta-analysis. Clinical charts were also reviewed for IBD among patients with *ICD-9-CM* codes for both IBD and ASD at one of the pediatric tertiary care centers. This expert-verified rate was compared with the rate in the repository study population (where IBD diagnoses were established by expert review) and in nationally reported rates for pediatric IBD.

Results: In all of case–control study populations, the rates of IBD-related *ICD-9-CM* codes for patients with ASD were significantly higher than that of their respective controls (Stouffer meta-analysis, $P < 0.001$). Expert-verified rates of IBD among patients with ASD were 7 of 2728 patients in one study population and 16 of 7201 in a second study population. The age-adjusted prevalence of IBD among patients with ASD was higher than their respective controls and nationally reported rates of pediatric IBD.

Conclusions: Across each population with different kinds of ascertainment, there was a consistent and statistically significant increased prevalance of IBD in patients with ASD than their respective controls and nationally reported rates for pediatric IBD.

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Key Words: autism spectrum disorders, inflammatory bowel disease

Gastrointestinal (GI) symptoms are commonly reported in children with autism spectrum disorders (ASD), and there is increasing interest in understanding possible gut–brain connections.[1–4] Valicenti-McDermott et al[5] report increased feeding disorders and abnormal stool patterns, White et al[6] report inflammation of the ileum, and D'Eufemia et al[7] report an altered lactulose to mannitol recovery ratio. GI symptoms are more prevalent in children with ASD compared with their siblings[8] and children with other developmental delays.[5] GI symptoms are more common among children with more severe ASD (e.g., language regression).[9] However, critics note these studies often suffer from referral bias: participants were often recruited based on a history of GI disorders.[10,11] Black et al[12] found no significant difference in the GI symptoms of typical children and children with ASD before the presentation of ASD symptoms. Thus, it is challenging to distinguish whether these GI symptoms are due to a comorbid disease process or due to behaviors associated with ASD (e.g., limited diets).

In this article, we focus specifically on associations between ASD and inflammatory bowel disease (IBD). As IBD can be aggravated by, but is not caused by, dietary choices, such an association could provide additional evidence for gut–brain connections. A recent study across 4 hospitals found individuals with *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes for ASD were more likely to have *ICD-9-CM* codes for IBD.[13] Krigsman et al[14] report increased rates of chronic colitis among patients with ASD. Molecular studies have found a significant overlap in the differential gene expression profile of GI mucosal biopsy tissue between patients with ASD, ulcerative colitis, and Crohn's disease (compared with healthy individuals).[15] Individuals with ASD

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also have an enrichment of copy number variations in the autophagy pathway,[16] which has been implicated in IBD.[17] Understanding whether there is an association between IBD and ASD could also have important public health implications given the increasing incidence of both diseases.[18–20]

The objective of this study was to compare the prevalence of IBD among patients with ASD to those without ASD; we hypothesized that patients with ASD would have an increased prevalence of IBD. To address concerns of ascertainment, we draw data from 3 different kinds of sources—a health care benefits company, 2 tertiary care hospitals, and a national repository—to determine if we could find reproducible differences in IBD rates in ASD populations. To our knowledge, this work comprises the largest group of ASD patient studies for IBD prevalence.

MATERIALS AND METHODS

We describe our selection criteria, case definitions, and analysis procedures. While a consistent signal across these different study populations, as described in the results, provides evidence for an association between IBD and ASD, using such varied sources also complicates direct comparisons. Thus, we first compared patients with and without ASD within each study population (Fig. 1 for a summary) and then combined those comparisons with a meta-analysis. Thus, we could be rigorous within each study population.

Study Populations and Patient Selection

This study used data from 4 sources (summarized in Table 1). The Aetna database contained nationwide claims data between 2009 and 2013 ($N_{ASD} = 52{,}270$; $N_{Control} = 7{,}151{,}925$). The Boston Children's Hospital (BCH; $N_{ASD} = 7201$; $N_{Control} = 594{,}684$) and Wake Forest Baptist Medical Center (WFBMC; $N_{ASD} = 1555$; $N_{Control} = 203{,}084$) study populations were tertiary care pediatric centers in the northeastern and southeastern United States. WFBMC is also a fully integrated academic medical center. The Simons Simplex Consortium (SSC; $N_{ASD} = 2728$) is an ASD registry from 12 North American medical centers.

Although the SSC patients were regularly monitored by the registry, patients in the Aetna, BCH, and WFBMC study populations had less consistent interactions with their providers. We only included patients who met both of the following criteria:

1. At least 3 (inpatient or outpatient) interactions with the health care system on different dates.
2. Born after 1970.

The visit criterion excluded patients who had limited interactions (such as a single visit for second opinion). The second criterion was excluded earlier, often less-complete records.

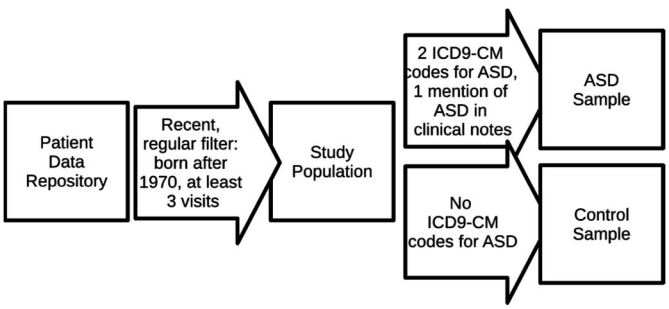

FIGURE 1. Selection criteria and case definitions used in the records databases.

ASD Case Definitions

The SSC required its individuals be aged in 4 to 18 years; meet the standard cutoffs on ADI-R, ADOS, and cognitive measures; and receive a clinical "Best Estimate Diagnosis" of Autistic Disorder, Asperger's Disorder, or PDD-NOS according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision. Because all SSC individuals had ASD, no respective controls were available for this study population.

The remaining study populations (Aetna, BCH, WFBMC) included patients with and without ASD. Because of the large sizes of these study populations, whether a patient had ASD could not be ascertained by expert review. Instead, we defined our ASD cohort as patients with at least 2 primary or secondary diagnoses of ASD (*ICD-9-CM* codes 299.00, 299.01, 299.80, 299.81, 299.90, or 299.91) on at least 2 different dates. The control sample was defined to be the set of individuals who had no *ICD-9-CM* diagnosis codes for ASD. Patients with only 1 *ICD-9-CM* diagnostic code were excluded. As *ICD-9-CM* billing codes have known biases,[21,22] sensitivity to these criteria as assessed in the Supplemental Digital Content 1, http://links.lww.com/IBD/A986.

Finally, in the BCH study population, positive and negative mentions of concepts in the clinical notes had been extracted using natural language processing. The natural language processing system, cTAKES,[23] is capable of not only automatically extracting concepts from the clinical notes but also determining additional factors such as whether a particular term is being negated, refers to a patient's current status, or past or family history. Clinical notes were not available for the Aetna and WFBMC study populations. For the BCH study population, we required both 2 *ICD-9-CM* codes and at least 1 positive current mention of ASD in the clinical notes.

IBD Case Definitions

Individuals in the SSC study population had their IBD diagnosis verified assessed as part of their prospective data collection. For the remaining study populations, we required at least 1 *ICD-9-CM* code for IBD in the patient record. Sensitivity to this criterion is assessed in the Supplemental Digital Content 1, http://links.lww.com/IBD/A986.

Comparison of Prevalence in Case–Control Study Populations

Within the Aetna, BCH, and WFBMC population, Kaplan–Meier curves were computed to estimate the prevalence of IBD by

TABLE 1. Descriptions of the Study Populations, Including Characteristics Relating to ASD and IBD

Study Population	Aetna	BCH	WFBMC	SSC
Description	Health care benefits company	Pediatric tertiary care hospital	Fully integrated academic medical center with pediatric tertiary care services	12 medical centers across North America
ASD cohort size	52,270	7201	1555	2728
Age, mean (SD), yr	12.4 (5.2)	12.3 (5.9)	13.5 (5.2)	9.0 (3.6)
No. individuals with *ICD-9-CM* codes for IBD	210	32	7	NA
No. individuals with confirmed IBD	NA	16	NA	7
Control cohort size	7,151,925	594,684	203,084	NA
Age, mean (SD), yr	12.9 (6.8)	14.2 (6.5)	12.9 (6.7)	NA
No. individuals with *ICD-9-CM* codes for IBD	14,109	2886	602	NA

BCH, Boston Children's Hospital; SSC, Simons Simplex Consortium; WFBMC, Wake Forest Baptist Medical Center.

age. The age of the patient at the time of the study was extracted from the health record. The patient's first IBD diagnosis was used as the age of onset. Because of the differing nature of the study populations, the prevalence of IBD among individuals with ASD was first compared with their respective control populations using a log-rank test with Yates correction. The *P* values from each of the 3 log-rank tests were then combined using Stouffer's method for meta-analysis. Finally, age-adjusted prevalences of IBD were computed for all study populations with respect to the 2010 Census[24] using the direct method.[25] All analyses were computed using Matlab 2012 and the R 2.15.2 package epiTools.

Comparison of Prevalence in Expert-verified Study Populations

The SSC study population lacked a respective control cohort, but unlike other study populations, all diagnoses had been verified by experts. Two SSC individuals lacked an age of the IBD onset; the age at the time of study was used to most conservatively estimate the prevalence. We could also verify IBD diagnoses in the BCH study population because clinical notes were available. Here, we extracted the charts for individuals, which met our ASD case definition and had at least 1 *ICD-9-CM* code for IBD (555.*,556.*). The clinical, laboratory, endoscopic, surgical, and pathology reports were reviewed by an expert in IBD diagnosis (A.B.) until the diagnosis could be confirmed or all relevant reports had been exhausted. If a conclusive diagnosis could not be made, we coded the subject as not having IBD. We used the diagnostic criteria for IBD established by North American and European pediatric gastroenterology societies to confirm the initial screen with *ICD-9-CM* codes.[26,27] This process resulted in 2 study populations, SSC and BCH verified, with expert-verified IBD diagnoses.

The prevalence of IBD for the SSC and BCH-verified study populations were computed using Kaplan–Meier estimates and compared using a log-rank test with Yates correction. The age-adjusted prevalences of the SSC and BCH-verified study populations were compared with the age-adjusted prevalences reported in surveys of pediatric IBD.[19,28]

Sensitivity of Results to Cohort and Case Definition Criteria

Several decisions were required in selecting the patient cohort and determining the ASD and IBD case definitions. In the Supplemental Digital Content 1, http://links.lww.com/IBD/A986, we assess the robustness of our results to these definitions by repeating the analyses above with a minimum visit threshold of 3, 5, and 7; analyzing male and female patients separately; and considering a variety of ASD and IBD case definitions, such as those using additional procedure information proposed by Benchimol.[29]

ETHICAL CONSIDERATIONS

The Institutional Review Boards of Harvard Medical School, BCH, and WFBMC reviewed this study and deemed that it met the regulatory requirements to be granted a waiver of informed consent.

RESULTS

Comparison of Prevalence in Case–Control Study Populations

Table 1 summarizes the number of patients with and without ASD and IBD in the Aetna, BCH, and WFBMC study populations. The prevalence of IBD (as determined by *ICD-9-CM* codes) by age is summarized in Figure 2, and age-adjusted prevalences are listed in Table 2. Although the rate of IBD varied

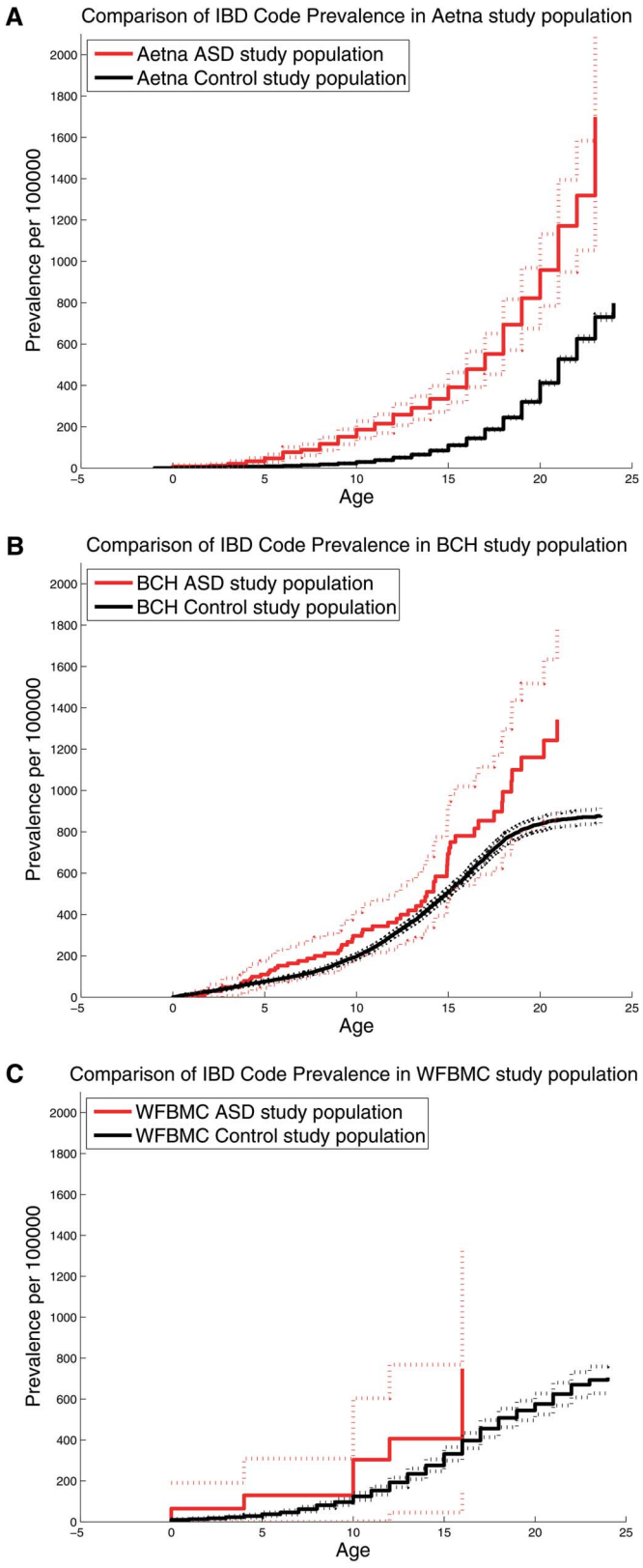

FIGURE 2. Kaplan–Meier curve for the prevalence of *ICD-9-CM* codes for IBD for patients with (red) and without (black) IBD in the Aetna, BCH, and WFBMC study populations with 95% CIs.

TABLE 2. Age-adjusted Prevalence per 100,000 (with 95% CI) of Patients with *ICD-9-CM* Codes for IBD in the 3 Large Study Populations Comparing Those with ASD with Their Respective Baselines

Study Population	Control	ASD
Aetna	186.4 (183.3–189.5)	446.0 (376.8–529.8)
BCH	433.4 (417.5–449.9)	630.6 (462.1–859.9)
WFBMC	282.9 (260.7–306.7)	361.9 (140.0–1824.8)

between study populations, in all cases, the prevalence of IBD among patients with ASD was higher than their respective controls. The difference was significant overall (combined Stouffer z-score, $z = 5.527$, $P < 0.001$) and for the Aetna (one-tailed log-rank test, $P < 0.001$) and BCH (one-tailed log-rank test, $P = 0.010$) study populations individually. The difference in the smaller WFBMC study population was not significant on its own (one-tailed log-rank test, $P = 0.198$).

Finally, Table 3 summarizes additional statistics for each study population. Patients with ASD have a younger mean age of IBD diagnosis. The mean age of patients with IBD tends to be older than the rest of the population, both for patients with and without ASD. As expected, the mean number of diagnoses (*ICD-9-CM* codes) per year is higher for patients with ASD compared with the rest of the population.

Comparison of Prevalence in Expert-verified Study Populations

In the previous section, we found that the rate of IBD, as established by *ICD-9-CM* codes, among patients with ASD was higher than that of their respective controls. We now compare the prevalence of IBD, as established by expert review, in the SSC and BCH-verified study populations with rates published in national surveys.

In the SSC study population, the diagnosis of IBD had already been verified by a research team as part of prospective data collection; 7 of the 2725 SSC individuals had IBD. Full clinical records were available for the BCH study population, and after expert chart review, 16 of the 32 patients with codes for IBD and ASD were verified to have IBD (9 CD, 8 UC; 1 patient had both diagnoses) from a total of 7201 individuals with ASD. Most individuals who failed to meet the formal criteria for IBD did have some form of active or chronic colitis. The mean age for patients verified to have IBD was 15.5 (confidence interval [CI], 13.0–18.0) compared with 12.3 (CI, 12.1–12.4) for the remaining ASD study population. Of note, 18.5% (CI, 17.6%–19.4%) of individuals with both ASD and IBD were female compared with 12.5% (CI, 0%–28.7%) with ASD but not IBD. Patients with ASD but not IBD averaged 11.3 (CI, 10.5–12.2) *ICD-9-CM* codes per year compared with 19.8 (CI, 6.7–32.8) with ASD and IBD. Finally, 4 of the 16 individuals with IBD received their first (BCH) diagnosis of IBD before their first diagnosis of ASD.

TABLE 3. ASD and IBD Characteristics of Each of the 3 Study Populations (with 95% CI)

Statistic	ASD, No IBD	ASD and IBD	Control	IBD, No ASD
Proportion male				
Aetna	0.79 (0.78–0.81)	0.87 (0.69–1.04)	0.50 (0.50–0.50)	0.50 (0.83–0.53)
BCH	0.81 (0.80–0.82)	0.75 (0.64–0.87)	0.52 (0.52–0.53)	0.54 (0.74–0.55)
WFBMC	0.80 (0.78–0.82)	1.00 (1.00–1.00)	0.52 (0.52–0.52)	0.50 (0.96–0.54)
Mean age, yr				
Aetna	12.36 (12.31–12.40)	14.75 (13.94–15.56)	12.92 (12.92–12.93)	18.70 (14.67–18.78)
BCH	12.81 (12.70–12.92)	16.31 (14.90–17.72)	14.22 (14.20–14.24)	17.53 (16.13–17.71)
WFBMC	13.52 (13.26–13.78)	16.14 (13.46–18.83)	12.88 (12.85–12.90)	17.86 (15.76–18.24)
Mean age of IBD diagnosis				
Aetna	NA	12.59 (11.79–13.40)	NA	16.65 (12.51–16.73)
BCH	NA	10.80 (9.40–12.21)	NA	11.37 (10.62–11.55)
WFBMC	NA	9.71 (5.32–14.11)	NA	12.44 (9.29–12.87)
Mean *ICD-9-CM* codes per year				
Aetna	25.75 (25.55–25.96)	54.04 (49.20–58.89)	12.38 (12.36–12.39)	19.19 (53.69–19.54)
BCH	5.25 (5.15–5.34)	14.75 (11.91–17.60)	2.45 (2.45–2.46)	5.69 (14.54–5.91)
WFBMC	9.37 (8.97–9.78)	21.06 (12.43–29.70)	5.37 (5.35–5.40)	7.62 (20.47–8.22)

Figure 3 plots the prevalence of IBD regarding age for both the SSC and BCH-verified study populations (see Supplemental Digital Content 1, http://links.lww.com/IBD/A986 for the rates of CD and UC individually). The CIs are wider for the smaller SSC study population, but the prevalences are on the same scale as the BCH study population. There was no evidence for a statistical difference between the 2 study populations (2-tailed log-rank test, $P = 0.841$). The rates reported in other U.S. studies[19,28] are shown for reference. The expert-verified age-adjusted prevalence from the BCH and SSC study populations, as well as other U.S. studies,[19,28] are also summarized in Table 4. The age-adjusted prevalence of IBD in the BCH-verified and SSC study populations is significantly greater than nationally reported rates ($P < 0.001$, $P < 0.0219$).

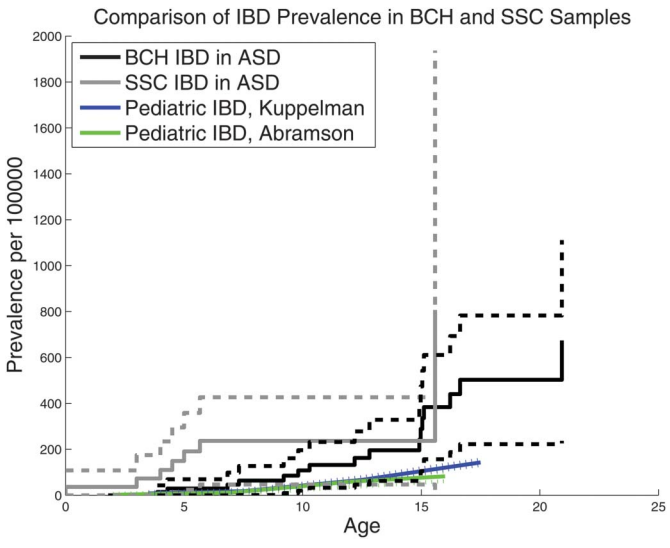

FIGURE 3. Kaplan–Meier curve for prevalence of IBD among patients with ASD with 95% CIs. The prevalence of IBD in the BCH and SSC study populations are on similar scales and higher than the prevalence of pediatric IBD reported in other studies.

Finally, to better understand the clinical context of the enrichment of IBD in ASD, we profiled the *ICD-9-CM*–derived comorbidities of the BCH ASD population (summarized in Table 5) (see Supplemental Digital Content 1, http://links.lww.com/IBD/A986, for *ICD-9-CM* codes used to define each of the comorbidities). No significant difference was observed between the prevalence of intellectual disability and specific developmental disorders in the 2 study populations, suggesting that the severity of the ASDs of the patients with and without IBD could be comparable. Although not significant after multiple hypothesis correction, patients with IBD had higher rates of other diseases with inflammatory components such as rheumatoid arthritis (2-tailed z-test, $P = 0.029$) and asthma (2-tailed z-test, $P = 0.051$).

TABLE 4. Age-adjusted Prevalence per 100,000 (with 95% CI) of Patients with IBD in our 2 Expert-verified Study Populations with ASD in the First 2 Rows and Previously Reported National Statistics

Study Population	Age-adjusted IBD Prevalence
BCH (ASD)	292.2 (149.8–392.9)
SSC (ASD)	425.5 (134.2–1063.3)
Kappelman	71.0 (66.0–45.0)
Abramson	31.5 (26.1–14.4)

TABLE 5. Prevalence per 100 of Other Comorbidities in the BCH Study Population with 95% CIs, for Patients with ASD and IBD

Comorbidity	Prevalence in ASD + IBD Study Population	Prevalence in ASD-only Study Population	*P*
IBD	100.0 (100.0–100.0)	0.3 (0.1–0.4)	0.000
Intellectual disability	18.8 (0.0–37.9)	18.2 (17.3–19.1)	1.000
Rheumatoid arthritis	6.2 (0.0–18.1)	0.2 (0.1–0.3)	0.029
Asthma	25.0 (3.8–46.2)	9.0 (8.4–9.7)	0.051
Celiac disease	0.0 (0.0–0.0)	1.7 (1.4–2.0)	1.000
Specific delays in development	56.2 (31.9–80.6)	62.2 (61.1–63.3)	0.615
Speech or language disorder	18.8 (0.0–37.9)	33.9 (32.8–35.0)	0.291

DISCUSSION

Each of our study populations, Aetna, BCH, WFBMC, and SSC, had different methods of ascertainment and included different statistics. The Aetna, BCH, and WFBMC study populations included patients with and without ASD. For these study populations, we relied largely on *ICD-9-CM* billing codes for diagnoses; complete health records were only available for the BCH study population. As hospitals, BCH and WFBMC were biased toward higher morbidity patients and limited to particular regions of the country. In contrast, the Aetna study population was a nationwide sample without the morbidity bias of a hospital population. However, patient data were only available from 2009 to 2013. The SSC study population drew patients from (nationwide) medical centers; all diagnoses had been previously verified by experts. Given the variation between these study populations, it is remarkable that the rates of IBD among patients with ASD were higher than their respective controls and/or nationally reported pediatric IBD rates in all cases.

Many studies have tracked the prevalence of pediatric IBD across different regions and times. Most relevant to our study are the rates reported by Abramson et al[19] and Kappelman et al.[28] Abramson et al[19] reviewed medical records to confirm the diagnosis of IBD among members of Kaiser Permanente Northern California aged 0 to 17 years. They reported an age-standardized prevalence of 12.0 per 100,000 for Crohn's disease (CI, 9.6–14.4) and 19.5 per 100,000 (CI, 16.5–22.6) for ulcerative colitis. Kappelman et al[28] performed a much larger national survey of 9 million Americans from 87 health plans in 33 states. Patients were identified with IBD if they had 3 *ICD-9-CM* codes for IBD on different visits. The rate of IBD among individuals younger than 20 years based on codes was 43 (95% CI, 40–45) and 28 (95% CI, 26–30) per 100,000, respectively. Lower rates were reported in the South, compared with the Northeast, Midwest, and West.

More generally, rates of pediatric IBD are affected by complex factors, including the local environment, genetics, infection exposures, diet, and socioeconomic factors.[30] Swedish rates of pediatric IBD are 21.5 per 100,000,[31] whereas reported rates in Libya are only 0.9 per 100,000.[32] A study among Israeli adolescents reports prevalences ranging from 100 to 149 per 100,000.[33] The rate of pediatric IBD in the BCH-verified and SSC study populations were higher than the rates reported in all of these studies.

The consistent increased rate of IBD among patients with ASD across all of our large varied study populations provides evidence for a potential association between IBD and ASD. Our study provides impetus for exploring molecular and microbiome measurements for common etiologies underlying both diseases. Common mechanisms to both diseases could inform both treatment and early diagnosis, especially as symptoms of ASD typically present at a younger age than IBD.

Finally, observations made during our chart reviews suggest that many patients with ASD who fail to meet the formal diagnostic criteria for IBD have active chronic colitis. This observation was interesting given the debate about whether there exists a manifestation of IBD, autistic enterocolitis, unique to ASD.[4,10] Walker et al[15] found a significant overlap in the differential gene expression profile of GI mucosal biopsy tissue between patients with ASD, ulcerative colitis, and Crohn's disease (compared with normal patients). Similarly, Torrente et al[3] compared gastric antral biopsies in children with ASD with children with Crohn's disease, *Helicobacter pylori* infection, and histologically normal controls. They found that many of the lesions in patients with ASD were distinct from the focal gastritis of Crohn's disease. White et al[6] provide a review of several studies that describe intestinal abnormalities among individuals with ASD.

Limitations

The BCH, WFBMC, and SSC study populations are biased by the specialties available at their respective medical centers.[34,35] In particular, BCH is recognized for its excellence in both ASD and IBD, and it also had the highest overall rates of IBD. Cohorts ascertained from medical centers are also biased toward higher morbidity patients. We found no significant difference in the rates of intellectual disability or specific developmental delays between individuals with IBD with and without ASD. In contrast, previous studies have found that patients with more severe ASDs have more GI complaints. Valicenti-McDermott et al[9] found that children with ASD and language regression were more likely to have abnormal stool pattern than those without (40% versus 12%), and children with language regression and a family history of autoimmune disease had the highest rates of abnormal stool pattern (78% versus 15%). Future studies should examine these correlations across a broader spectrum of health care facilities.

The Aetna study population only included data from 2009 to 2013. Thus, patients with diagnoses of ASD or IBD before that

period would not have been included. As both ASD and IBD are lifelong diseases, patients with prior diagnoses should have continued to have diagnoses in the study period. However, variables such as the age of first diagnosis must be treated with caution.

Finally, we were unable to review the charts for the thousands of patients with codes for ASD in our 3 larger study population (BCH, WFBMC, Aetna). We mitigated this factor by repeating our analysis for many case definition criteria; other studies, such as Kappelman et al[28] and Bernstein et al,[36] have used similar approaches. It is also compelling that across these very different study populations, the rates of *ICD-9-CM* codes for IBD were higher among patients with ASD compared with individuals without ASD in their respective controls.

CONCLUSIONS

Across each population with different kinds of ascertainment, there was a consistent and statistically significant increased prevalance of IBD in patients with ASD than their respective controls and nationally reported rates for pediatric IBD. These results lend further evidence for an association between IBD and ASD. Of course, future studies will be needed to validate these numbers in other populations, ideally where diagnoses of IBD and ASD can be verified through chart review and where the study population is drawn from sources with low referral bias (e.g., schools or insurers). Finally, molecular and microbiome characterizations will be needed to determine whether IBD and ASD do indeed share common etiologies.

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