# HHS Public Access

Author manuscript

*J Autism Dev Disord*. Author manuscript; available in PMC 2022 October 31.

Published in final edited form as:

*J Autism Dev Disord*. 2022 October ; 52(10): 4301–4310. doi:10.1007/s10803-021-05305-0.


# Association Between Exposure of Children to General Anesthesia and Autism Spectrum Disorder


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## Abstract

This study tested the hypothesis that exposure of children prior to their third birthday to procedures requiring general anesthesia is associated with an increased incidence of autism spectrum disorder (ASD) in later life. This study employed a nested, 1:2 matched-case control study design using ASD cases identified in a population-based birth cohort of children born in Olmsted County, MN from 1976 to 2000. Matching variables included sex, date of birth, and mother's age in conditional logistic regression including 499 ASD cases and 998 controls. After adjusting for birth weight and health status, there was no significant association between exposure and ASD (OR 1.27 [95% CI 0.92–1.76]), indicating that general anesthesia is not associated with an increased risk of ASD.



### Keywords

Autism; Anesthesia; ASD; Childhood; Neurodevelopmental disorders



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**Author Contributions** Drs JS and DOW led the study team, conceptualized and designed the study, supervised the data collection, led the interpretation of the data, drafted the initial manuscript, and reviewed and revised the manuscript. Dr MLL participated in the design of the study, designed the data collection instruments, collected data, supervised the initial analyses, interpreted the data, and reviewed and revised the manuscript. Mr. DTH and Ms. CAF collected data, interpreted the data, and critically reviewed the manuscript for important intellectual content. Ms. ALW and Mr. DRS and ACH designed the data collection instrument, carried out the analyses, and critically reviewed the manuscript for important intellectual content. Drs SMM, RGV, TNW, and RPF participated in the design of the study, helped interpret the data, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

**Conflict of interest** The authors have no conflict of interest to disclose.

Autism spectrum disorder (ASD) is a neurodevelopmental disability characterized by deficits in social communication and restricted/repetitive behaviors (Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR, 2000). Although a specific genetic etiology can be identified in a substantial minority of individuals, most cases are currently considered idiopathic and a complex interplay between genomic and environmental factors likely plays an important role (de la Torre-Ubieta et al., 2016; Modabbernia et al., 2017; Muhle et al., 2018). In many countries the estimated prevalence of ASD has increased (Baxter et al., 2015), which may reflect in part improved diagnostics and increased availability of medical care (Hansen et al., 2015; Lundstrom et al., 2015; Myers et al., 2019). However, this increase may also suggest the potential importance of environmental factors (Lyall et al., 2017), such as birth complications and exposure to toxins, infections, and drugs (Christensen et al., 2019; Currenti, 2010; Doja & Roberts, 2006; Modabbernia et al., 2017; Newschaffer et al., 2007).

Exposure of young animals to general anesthetics causes neurodegenerative changes associated with long-term changes in learning, memory, and behavior (Coleman et al., 2016; Jevtovic-Todorovic et al., 2003). In studies of children residing in Olmsted County, MN, multiple (but not single) exposures of young children to anesthesia were associated with an increased incidence of attention-deficit hyperactivity disorder (ADHD) and learning disabilities (Flick et al., 2012; Hu et al., 2017; Sprung et al., 2012; Wilder et al., 2009). Some, but not all, other investigators have found that single exposures to anesthesia at a young age are also associated with ADHD (Ing et al., 2017; Ko et al., 2014; Sedighnejad et al., 2020). Many children with ADHD have difficulties with social interactions, and many children with ASD also meet criteria for ADHD (Antshel & Russo, 2019; Kushki et al., 2019; Llanes et al., 2020; van der Meer et al., 2012). This interaction raises the question of whether the association between undergoing procedures requiring general anesthesia and ADHD may also exist for ASD if there is a similar underlying biology for the social deficits in the two conditions. Two studies find that the use of general anesthesia during caesarean delivery is associated with a higher likelihood of ASD compared with the use of regional anesthesia, with the authors suggesting peripartum anesthesia exposure as a possible cause (Chien et al., 2015; Huberman Samuel et al., 2019). Two other studies have not found a relationship between post-natal exposure to anesthesia and ASD ascertained via clinical diagnosis (Creagh et al., 2016; Ko et al., 2015). Thus, the relationship between exposure to procedures requiring anesthesia and ASD remains unclear.

This study tested the hypothesis that exposure of children prior to their third birthday to procedures requiring general anesthesia is associated with an increased likelihood of ASD. We tested this hypothesis using a population-based birth cohort of children from Olmsted County, MN, taking advantage of prior work in this cohort that ascertained ASD cases using research criteria (Myers et al., 2019).

## Methods

The population-based study cohort was assembled as described in prior work (Myers et al., 2019) using birth certificate data for Olmsted County, Minnesota, obtained from the Minnesota Department of Health, and the resources of the Rochester Epidemiology Project

(REP), a medical records linkage system that includes records of all outpatient and inpatient medical care in the community, including Mayo Clinic, Olmsted Medical Center, their 3 affiliated hospitals, and several smaller practices. The REP provides centralized longitudinal medical data, including clinical documentation from primary care and specialty clinic visits, emergency department visits, hospitalizations, laboratory and imaging results, and birth and death certificate data. The study was approved by the institutional review boards at Olmsted Medical Center and Mayo Clinic. Access to cumulative school records was made possible through contractual agreement of Mayo Clinic, the Independent School District No. 535 school board, and equivalent authorities governing private schools.

### Study Population

All children born between January 1, 1976 and December 31, 2000 to mothers residing in Olmsted County ($n$ = 43,215) at the time of delivery were considered. Among these children, 39,890 had authorized the use of their medical records for research. A total of 31,220 children who still lived in the Olmsted County at or after the age of 3 years were followed from birth until age 21, emigration or death.

### Identification of Individuals with ASD

ASD case status was determined retrospectively using data from the REP and school documentation and an operational research definition based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria, as describe in detail previously (Myers et al., 2019). First, a group of individuals with neurodevelopmental or psychiatric disorders was identified based on diagnostic codes in their medical records or educational disability classification codes in their school records. The codes included were conditions with signs and symptoms that overlap with the core social, communicative, and behavioral features of ASD or that commonly coexist with ASD. Among the 31,220 eligible individuals in the population-based birth cohort, 4301 were identified as having one or more of these neurodevelopmental/psychiatric disorder or educational disability codes. Of these, 1766 individuals were determined to have potential ASD based on the presence of certain codes or combinations of codes and screening of prioritized relevant parts of the medical records, as described elsewhere (Myers et al., 2019). Records of all 1766 individuals with potential ASD were then manually reviewed to abstract specific data through a systematic, multistage process. The abstractors carefully reviewed all medical record documentation through 21 years of age to identify pertinent descriptive phrases, based on an extensive data dictionary developed by the research team, that mapped to any of the 58 ASD signs or symptoms that contributed to the 12 core criteria (4 social interaction, 4 communication, and 4 restricted, repetitive behavior) in the DSM-IV-TR. Finally, the research team applied the DSM-IV-TR–based criteria to the abstracted information to identify individuals meeting the research definition of ASD. Likely false-positive results were excluded by a manual review process that identified individuals whose signs and symptoms were attributed to other conditions, such as adolescent-onset psychosis, bipolar disorder, or major depression. Cases in the original work (Myers et al., 2019) were ascertained using two research definitions: (1) a broader, more inclusive definition requiring that at least 3 criteria were met (including 2 of the 4 social interaction criteria and at least 1 of the communication criteria or 1 of the restricted, repetitive behavior criteria), based on the DSM-IV-TR criteria for pervasive developmental disorder not otherwise specified and encompassing autistic disorder and Asperger's disorder), and (2) a more narrow, higher-confidence definition requiring that at least 6 criteria were met (including at least 2 of 4 social interaction criteria, 1 of 4 communication criteria, and 1 of 4 restricted, repetitive behavior criteria), based on DSM-IV-TR criteria for autistic disorder. For the current analysis, the latter definition was used (Myers et al., 2019). Because ADHD is frequently diagnosed in children with ASD and has been associated with early exposure to anesthesia in other studies, we also identified the presence of ADHD in cases and controls by searching the medical records for ICD-9 codes 314.X (Gruschow et al., 2019; Shi et al., 2020).

## Identification of Matched Controls

A nested, 1:2 matched case–control design was employed. The date that there was sufficient information in the medical records for a case to meet research criteria for ASD is herein referred to as the "index date". Case–control matching variables included sex, date of birth (± 90 days), and the mother's age at the time of the birth (± 2 years). For each ASD case, 2 controls were randomly selected from the birth cohort who (1) met the matching criteria, (2) were still residing in Olmsted County at the time of the index date, and; (3) did not themselves meet ASD criteria prior to the index date.

## Identification of Exposure to Procedures Requiring General Anesthesia

All cases and controls who underwent any procedure requiring general anesthesia prior to their 3rd birthday (or prior to the index date if the index date was before their 3rd birthday) at Mayo Clinic Rochester or Olmsted Medical Center, the two facilities that provide medical care in Olmsted County, were identified. Any exposures during cesarean delivery were not included. Anesthesia and surgical information were abstracted and entered manually into the web-based Research Electronic Data Capture (REDCap®) system (Version 9.1.15, 2020 Vanderbilt University, Nashville, Tennessee).

## Statistical Analysis

Analyses were performed using conditional logistic regression taking into account the 1:2 matched case–control study design. The explanatory variable of interest was exposure to general anesthesia under the age of 3 years. Exposure was defined using a binary variable (any vs none), a categorical variable defined based on the number of exposures (0, 1, 2 or more), and also using a continuous and categorical variable (< 60 min or ≥ 60 min) representing the cumulative duration of exposure to general anesthesia.

As in our prior work (Flick et al., 2012; Gleich et al., 2014; Hu et al., 2016; Warner et al., 2018) the health status of each child up to age 3 years (or prior to the index date if the index date was before age 3) was quantified using the Johns Hopkins Adjusted Clinical Groups ACG® Case–Mix System (ACG® System Version 12.0, John Hopkins, Baltimore, MD) (Weiner et al., 1991, 1996). This method utilizes International Classification of Diseases, 9th Revision diagnosis codes (ICD-9). Codes for each child were converted to ICD-9 if necessary and assigned to one of 32 unique morbidity clusters (aggregated diagnostic groups [ADGs]).

Since birth weight and health status were not included as matching variables, additional analyses were performed with birth weight (treated as a continuous variable) and 28 ADG indicator variables included as covariates. These indicators represent all ADGs with the exception of those included in the psychosocial category (which maps to the diagnosis of ASD and other behavioral disorders) and pregnancy. Findings are summarized using the odds ratio and corresponding 95% confidence interval (CI). For all continuous variables initial models were fit using restricted cubic splines to assess for evidence of non-linearity. After verifying the lack of significant non-linearity, continuous variables were modeled using linear terms for all subsequent analyses. In all cases, two-tailed P-values < 0.05 are considered statistically significant (Version 9.4, SAS Institute, Inc, Cary, NC).

ASD and ADHD frequently co-exist (Antshel & Russo, 2019; Kushki et al., 2019; Llanes et al., 2020; van der Meer et al., 2012). As a supplemental analysis, cases were categorized into those with ASD only and those with both ASD and ADHD. A supplemental covariate adjusted conditional logistic regression analyses was performed to assess the association between anesthesia exposure and autism for each of these case categories. An additional supplemental analysis was performed to assess whether the association of anesthesia with autism differed based on the age of ASD diagnosis (before vs after 7th birthday). The purpose of this analysis was to approximately the method used in a prior analysis of the association between anesthesia exposure and ASD (Ko et al., 2015) which sought earlier diagnoses (within 3 years of exposure, corresponding approximately to a diagnosis prior to the 7th birthday in the current analysis).

All analyses were performed using the original case–control sets in which two controls for a given case were selected from the pool of all undiagnosed individuals residing in Olmsted County on the date the case was diagnosed. Using this approach, some controls could later be diagnosed with ASD, and therefore included in the study as both a control and as a case. A sensitivity analysis was performed in which the controls that later became cases were replaced with new controls who were never diagnosed with ASD.

At the time of study design, we estimated that there would be approximately 500 cases and 1000 controls. Under the assumption that 15% of the underlying population would be exposed to anesthesia prior to their 3rd birthday (Shi et al., 2018), this sample size provided statistical power of 80% to detect an odds ratio of 1.5.

## Results

There were 533 research defined ASD cases identified in the 1976–2000 birth cohort. After excluding 34 cases who denied authorization for the use of their medical records for research, 499 ASD cases and 998 matched controls were analyzed (Table 1). The median age when cases first met research criteria for ASD was 6.9 years [25th, 75th percentile: 4.5, 9.5]; 55 cases (11%) met criteria prior to age 2 years, and 474 cases (95%) prior to age 14 years. Among the 499 individuals with research defined ASD, 194 (39%) had received an ASD diagnosis as part of their clinical care.

Among cases there were 132 children who underwent 194 procedures requiring general anesthesia under the age of 3 years, and among controls there were 155 children who underwent 230 procedures. Among those who received anesthesia, the median [25th, 75th percentile] age at the first exposure was 14 [7, 24] months for cases and 14 [7, 23] months for controls (rank sum test $p = 0.811$). The median duration of anesthesia for each procedure was 60 [35, 115] minutes for cases and 61 [30, 105] minutes for controls (rank sum test $p = 0.162$) and the median total cumulative anesthesia duration was 76 [40, 155] minutes for cases and 70 [30, 119] minutes for controls (rank sum test $p = 0.123$).The most frequent types of procedures were ear, nose and throat, general and urologic (Table 2). Most procedures included the use of a halogenated inhalational agent.

From the matched analysis that did not include additional covariates, anesthesia exposure was significantly associated with ASD when exposure was quantified as a dichotomous variable (any exposure vs. none), an ordinal variable of the number of exposures (0, 1, or ≥ 2), or the cumulative or categorical duration of exposure (all $p < 0.001$) (Table 3). However, after adjusting for birth weight and health status, no significant association was detected when exposure was quantified as a dichotomous variable (OR 1.27, [95% CI 0.92–1.76]), the number of exposures (OR 1.39 [0.98–1.98] and 0.93 [0.53–1.64] for 1 and ≥ 2 exposures, respectively, compared to no exposure) or by the cumulative duration of exposure (OR 0.99 [0.95–1.04] per 30 min increase) (Table 3).

In supplemental analyses, among the 499 ASD cases, 305 (61%) children also had a diagnosis of ADHD prior to age 19 years. For covariate adjusted analysis, with anesthesia exposure defined using a dichotomous variable (any exposure vs none), there was no significant association between exposure to anesthesia and ASD without co-existent ADHD (n = 194 cases and 388 controls, OR 1.21 [0.74–1.97]) or ASD with co-existent ADHD (n = 305 cases and 610 controls, OR 1.31 [0.88–1.95]). There was also no significant association between exposure to anesthesia and ASD diagnosed under the age of 7 years (OR 1.32 [0.84–2.08]) or over the age of 7 years (OR 1.23 [0.81–1.87]).

Finally, of the 998 controls included in the primary analyses, 19 subsequently met research criteria for ASD when they were older. From the supplemental analysis that replaced these individuals with alternative controls who never met research criteria for ASD, the pattern of results remained unchanged (covariate adjusted OR 1.30 [0.94–1.80] for any exposure to anesthesia under the age of 3 years versus no exposure; $p = 0.114$).

## Discussion

The main finding of this study is that receiving procedures requiring general anesthesia before the age of 3 years is not associated with an increased incidence of later ASD.

The present report defines ASD cases according to research criteria based on the work of Myers et al. (Myers et al., 2019), who utilized these criteria to determine secular tends in autism incidence. In contrast, most investigators employ the clinical diagnosis of autism according to DSM criteria to analyze prevalence and to examine associations with anesthesia. The latest edition of DSM (DSM-5) combined three diagnostic categories in DSM-IV-TR (ASD, Asperger's disorder, and pervasive developmental disorder not otherwise specified) into the single category of ASD. We utilize the more narrow, "restricted" definition of ASD described by Myers et al. (which were based on DSM-IV-TR autistic disorder criteria), chosen (1) to be more conservative in our analysis by using the stricter criteria, (2) to reflect diagnostic conventions over the bulk of the time period examined, and; (3) to make the manual review of records for anesthesia exposure more feasible. Prevalence estimates based on this narrower, higher-confidence research definition, were similar to those reported in other studies that used active ascertainment strategies when comparable data (based on ages and calendar years) were examined.

One important finding of Myers et al. relevant to the current analysis is that the clinical diagnosis of ASD was attached to fewer than half of the cases that met research criteria for ASD (Myers et al., 2019). Because other studies of the association between anesthesia and exposure and ASD discussed in the following section use clinical diagnosis to ascertain ASD cases, our results are not strictly comparable with these other studies.

The etiology of ASD is uncertain and likely multifactorial, including genetic factors as well as perinatal,and postnatal environmental factors (Currenti, 2010; Freitag, 2007; Gardener et al., 2011; Modabbernia et al., 2017). The evidence for the importance of genetic and perinatal factors is considerable; examples of risk factors include family history, birth complications, pre-term birth, and advanced paternal age (Gardener et al., 2011). Evidence for the role of postnatal exposure to other environmental factors is not as well-developed, with evidence supporting the association between ASD and exposures to toxins such as inorganic mercury and lead (Modabbernia et al., 2017), and infectious processes such as encephalitis (Atladottir et al, 2010; Marques et al, 2014).

Of potential relevance to anesthesia exposure, some studies suggest that Cesarean delivery (CD) is associated with an increased likelihood of autism (Curran, et al., 2015a, 2015b; Zhang et al., 2019). Two studies suggest specifically that this association is present for CD conducted with general, but not regional, anesthesia (Chien et al., 2015; Huberman Samuel et al., 2019). Peripartum exposure to general anesthetic drugs was suggested as a possible cause, based on pre-clinical studies showing neurotoxic effects of prenatal and perinatal exposure to general anesthesia, including those in non-human primates (Coleman et al., 2016; Currenti, 2010; Freitag, 2007). However, as noted by others, confounding by indication (i.e., parturients requiring CD differ from those who do not) is difficult to address in these observational studies (Sagi-Dain et al., 2020). Indeed, a recent study using a sibling-matched cohort design found that ASD was not associated with CD, highlighting the importance of confounding (Curran, et al., 2015a, 2015b). In addition, the fetus is exposed only briefly to low concentrations of general anesthetic drugs during CD, as best exemplified by the fact that the neonate is awake at delivery, making it implausible that these drugs would contribute to any such association.

Our results also affirm the potential for confounding to affect conclusions. Despite the use of a matched case–control design, it appears that factors related to differences in health status between children who did and did not receive anesthesia account for the significant association observed in univariate analysis. We noted a similar pattern of results in our prospective matched cohort study (Mayo Anesthesia Safety in Kids) using neuropsychological tests as outcomes. The primary outcome of full-scale intelligence quotient was significantly decreased in children exposed to multiple anesthetics compared to children not exposed to anesthesia, but this association was no longer significant when other cofactors, including health status assessed using the ACG methodology, were included in the analysis (Warner et al., 2018).

Other studies have also examined the association between ASD and exposure to procedures requiring general anesthesia. Two studies utilized Medicare datasets and created a composite outcome of developmental and behavioral disorders that included autism (DiMaggio et al., 2009, 2011). They found associations between exposures and this composite outcome, but did not separately analyze autism as an outcome. A study using a sibling cohort design involving children from Puerto Rico found in univariate analysis no difference in exposures to anesthesia prior to the age of diagnosis, ascertained by parent interview, between children diagnosed with ASD and their non-affected siblings (Creagh et al., 2016). A matched cohort study of children in Taiwan examined the relationship between exposure to procedures requiring anesthesia prior to age 2 years and the clinical diagnosis of ASD within 3 years of exposure, finding no association in adjusted analysis (hazard ratio = 0.93 [95% CI 0.57–1.53]) (Ko et al., 2015). We performed a sensitivity analysis to approximate their criteria of earlier ASD diagnosis (seeking ASD prior to the 7th birthday), which did not change our pattern of results.

Other analyses using a subset of this Olmsted County birth cohort (children born from 1976 to 1982 and from 1996 to 2000) found a significant association between the incidence of ADHD and receiving multiple, but not single, procedures requiring general anesthesia prior to age 3 years (Hu et al., 2017; Sprung et al., 2012). There is considerable overlap between symptoms of ADHD and ASD (Kushki et al., 2019; Llanes et al., 2020); approximately 15% of youth with ADHD are diagnosed with comorbid ASD, and ADHD is the most common comorbidity in children with ASD (diagnosed in up to 70% of children, a rate consistent with our results) (Antshel & Russo, 2019). However, a sensitivity analysis segregating those children with ASD with and without ADHD did not affect the pattern of results, suggesting the specificity of the previously-noted association between multiple anesthesia exposures and ADHD.

In addition to the potential for confounding shared by all observational designs and extensively discussed in this field of investigation (Davidson et al., 2015; Hansen, 2015; Wilder et al., 2009), this analysis has other notable limitations. Although most characteristics of Olmsted County residents are similar to the rest of Minnesota, some differ from the United States population as a whole (St Sauver et al., 2012), such that the results may not apply to other populations. The number of cases may be insufficient to detect a small odds ratio. However, the fact that there was no evidence of any dose–response relationship between exposure intensity and incidence (e.g., the OR for multiply-exposed children was numerically less than the OR for singly-exposed children) makes any significant association unlikely. If the biological processes causing ASD are operative prior to anesthesia exposure, this would bias towards not finding an association between exposure and ASD, even if exposure was a factor in some children. Finally, compared with our prior analyses using subsets of this birth cohort (Flick et al., 2012; Hu et al., 2017; Sprung et al., 2012; Warner et al., 2018; Wilder et al., 2009), some potentially relevant covariates such as parental education and socio-economic status were not available for all cohort members, and thus were not included as adjustors in this analysis.

In conclusion, these findings add to the evidence that exposure of young children to procedures requiring general anesthesia is not itself associated with an increased likelihood of developing ASD in later life, a finding reassuring for both families and physicians.

## Acknowledgments

We are grateful to Drs. Slavica Katusic, MD, Emeritus Consultant, Mayo Clinic, Rochester, MN who is now retired and conducted earlier studies to identify incident autism cases in the Olmsted County. We also thank Jenna Steege, APRN, CRNA, Mayo Clinic, Rochester, MN for support in this research project.

### Funding

This study used the resources of the Rochester Epidemiology Project (REP) medical records-linkage system, which is supported by the National Institute on Aging (NIA; AG 058738), by the Mayo Clinic Research Committee, and by fees paid annually by REP users. The content of this article is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health (NIH) or the Mayo Clinic. The funders had no role in the design and conduct of the research.

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## Table 1

Sex, birth weight, maternal age, and health status as measured by Adjusted Clinical Groups (ACG)® Case-Mix System of cases and controls

| Variable | Cases (N = 499) | Controls (N = 998) |
|---|---|---|
| Sex, n (%) | | |
| Female | 124 (25%) | 248 (25%) |
| Male | 375 (75%) | 750 (75%) |
| Birth weight, grams, n (%) | | |
| < 2500 | 40 (8%) | 45 (5%) |
| ≥ 2500 | 459 (92%) | 953 (95%) |
| Mother's Age, years | 28 (6) | 28 (6) |
| ACG® Case-Mix System-ADG codes | | |
| Acute Minor | | |
| Time limited:minor, n (%) | 361 (72%) | 635 (64%) |
| Time limited:minor-primary infections, n (%) | 427 (86%) | 814 (82%) |
| Injuries/adverse effects:minor, n (%) | 215 (43%) | 356 (36%) |
| Signs/symptoms:minor, n (%) | 237 (47%) | 382 (38%) |
| Acute major | | |
| Time limited:major, n (%) | 122 (24%) | 153 (15%) |
| Time limited:major-primary infections, n (%) | 150 (30%) | 216 (22%) |
| Injuries/adverse effects:major, n (%) | 177 (35%) | 282 (28%) |
| Signs/symptoms:uncertain, n (%) | 299 (60%) | 535 (54%) |
| Signs/symptoms:major, n (%) | 284 (57%) | 365 (37%) |
| Likely to recur | | |
| Allergies, n (%) | 52 (10%) | 86 (9%) |
| Likely to recur:discrete, n (%) | 193 (39%) | 311 (31%) |
| Likely to recur:discrete_infections, n (%) | 427 (86%) | 806 (81%) |
| Dermatologic, n (%) | 97 (19%) | 181 (18%) |
| Discretionary, n (%) | 303 (61%) | 581 (58%) |
| Asthma | | |
| Asthma, n (%) | 77 (15%) | 92 (9%) |
| Chronic medical: unstable | | |

| Variable | Cases (N = 499) | Controls (N = 998) |
|---|---|---|
| Likely to recur:progressive, n (%) | 4 (0%) | 4 (1%) |
| Chronic medical:unstable, n (%) | 63 (13%) | 44 (4%) |
| Malignancy, n (%) | 2 (0%) | 1 (0%) |
| Chronic medical: stable | | |
| Chronic medical:stable, n (%) | 110 (22%) | 98 (10%) |
| See and reassure, n (%) | 112 (22%) | 175 (18%) |
| Chronic specialty: stable | | |
| Chronic specialty:stable-orthopedic, n (%) | 13 (3%) | 15 (2%) |
| Chronic specialty:stable-ear, nose, throat, n (%) | 52 (10%) | 58 (6%) |
| Eye/dental | | |
| Chronic specialty:stable-eye, n (%) | 205 (41%) | 369 (37%) |
| Dental, n (%) | 13 (3%) | 20 (2%) |
| Chronic specialty unstable | | |
| Chronic specialty:unstable-orthopedic, n (%) | 33 (7%) | 17 (2%) |
| Chronic specialty:unstable-ear, nose, throat, n (%) | 41 (8%) | 36 (4%) |
| Chronic specialty:unstable-eye, n (%) | 40 (8%) | 28 (3%) |
| Psychosocial | | |
| Psychosocial:time limited:minor, n (%) | 106 (21%) | 130 (13%) |
| Psychosocial:persistent/recurrent, stable, n (%) | 163 (33%) | 61 (6%) |
| Psychosocial:persistent/recurrent,cunstable, n (%) | 19 (4%) | 1 (0%) |
| Preventive/administrative | | |
| Prevention/administrative, n (%) | 467 (94%) | 978 (98%) |
| Pregnancy | 0 (0%) | 0 (0%) |

N (%), number and percentage of patients. Analyses were performed using 28 ADG indicator variables included as covariates, a method employed in our prior work where further details may be found (Flick et al., 2012; Gleich et al., 2014; Hu et al., 2016; Warner et al., 2018). These indicators represent all ADGs with the exception of those included in the psychosocial category (which maps to the diagnosis of ASD and other behavioral disorders) and pregnancy

## Table 2

Surgeries performed among cases and controls

| Procedure type | Cases (N = 499) | Controls (N = 998) |
|---|---|---|
| Ear, nose and throat | 74 (15%) | 85 (9%) |
| General | 25 (5%) | 32 (3%) |
| Urologic | 18 (4%) | 25 (3%) |
| Ophthalmology | 8 (2%) | 8 (1%) |
| Orthopedic | 3 (1%) | 7 (1%) |
| Neurologic | 3 (1%) | 4 (0%) |
| Oral/Maxillofacial | 6 (1%) | 6 (1%) |
| Cardiovascular | 6 (1%) | 1 (0%) |
| Other | 10 (2%) | 8 (1%) |

Values represent the number (%) of children among cases or controls who had at least 1 of the designated types of surgery. Among cases, 132 children underwent 194 procedures requiring general anesthesia and among controls, 155 children underwent 230 procedures

## Table 3

Association between exposure to procedures requiring anesthesia before age 3 and incidence of autism spectrum disorder

| Anesthetic characteristics | Matched analysis without additional covariates | | Matched analysis, covariate adjusted | |
|---|---|---|---|---|
| | **Odds ratio (95% CI)** | **p** | **Odds ratio (95% CI)** | **p** |
| Any anesthetic exposure | | < .001 | | 0.149 |
| No | 1.00 | | 1.00 | |
| Yes | 1.94 (1.49–2.52) | | 1.27 (0.92–1.76) | |
| Number of anesthetic exposures | | < .001 | | 0.144 |
| No exposure | 1.00 | | 1.00 | |
| 1 exposure | 1.88 (1.39–2.54) | | 1.39 (0.98–1.98) | |
| ≥ 2 exposures | 2.09 (1.33–3.31) | | 0.93 (0.53–1.64) | |
| Cumulative duration, per 30 min[a] | 1.08 (1.03–1.12) | < .001 | 0.99 (0.95–1.04) | 0.772 |
| Categorical duration | | < .001 | | 0.337 |
| No exposure | 1.00 | | 1.00 | |
| < 60 min | 1.62 (1.10–2.39) | | 1.25 (0.79–1.98) | |
| ≥ 60 min | 2.19 (1.58–3.05) | | 1.29 (0.87–1.91) | |

Analysis performed using conditional logistic regression taking into account the 1:2 matched set study design (matched on sex, date of birth (± 90 days), and mother's age at the time of birth (± 2 years)). Additional covariates in the adjusted analysis include birth weight and health status as measured using the Adjusted Clinical Groups (ACG)® Case-Mix System

[a]Cumulative duration of exposure to anesthetic before age 3 was analyzed as a continuous variable, with the odds ratio presented for a 30 min increase