Childhood appendectomy and adult mental disorders: A population-based cohort study

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Abstract

Background: Recent studies suggest that disruption of the colonic microbiota homeostasis is associated with low-grade systemic inflammation and mental disorders. The cecal appendix may influence the homeostasis of the colonic microbiota. In this large population-based study, we investigated whether early removal of the appendix is associated with an increased risk of mental disorders later in life.

Materials and Methods: All Swedish individuals born between 1973 and 1992 (N = 1,937,488) were included and followed prospectively until December 31, 2016 for any psychiatric International Classification of Disease diagnosis from age 14 or later in life. The main exposure was defined as having a history of appendectomy before age 14 (N = 44,259); the second exposure, appendicitis before age 14 but without appendectomy (N = 1,542), and the third exposure studied was a history of hernia surgery before age 14 (N = 35,523). Control groups for each respective exposure were all unexposed individuals in the study population.

Results: Individuals exposed to appendectomy before age 14 had a 19% increased risk of depressive disorder (adjusted hazard ratio [aHR] = 1.19; 95% confidence interval [95% CI]: 1.15–1.23), 27% increased risk of bipolar affective disorder (aHR = 1.27; 95% CI: 1.17–1.37), and a 20% increased risk of an anxiety disorder (aHR = 1.20; 95% CI: 1.16–1.23) compared to individuals unexposed to childhood appendectomy. We found no association between appendectomy and increased risk of obsessive–compulsive disorder and schizophrenia and there was no association between appendicitis without appendectomy and mental disorders. The association between childhood hernia surgery and mental disorders later in life was small but significant.

Conclusion: Childhood appendectomy, but not appendicitis without appendectomy, was associated with a significantly increased risk of mood and anxiety disorders in adulthood.

Keywords
appendectomy, appendix vermiformis, colonic bacterial diversity, human gut-brain axis, mental disorders, microbiota, population-based cohort study, Sweden
1 | INTRODUCTION

Recent data suggest that low-grade systemic inflammation may contribute to the development of mental disorders, particularly depression and other mood disorders. In support of this notion, patients diagnosed with depressive disorder and bipolar affective disorder have been found to have significantly increased serum levels of proinflammatory cytokines (Bai et al., 2015; Barnes, Mondelli, & Pariante, 2017; Dantzer, O’Connor, Freund, Johnson, & Kelley, 2008; Leonard & Maes, 2012; Liu, Ho, & Mak, 2012; Miller, Maletic, & Raison, 2009; Moylan et al., 2014; Reichenberg et al., 2001; Stein, Naude, & Berk, 2018).

The human vermiform appendix is a secondary lymphatic organ rich in secretory immunoglobulin A (IgA). Prone to inflammation, the current standard of care for children with acute appendicitis is surgical removal (Gonzalez, Deans, & Minneci, 2016). Up until recently, the appendix was considered a physiologically redundant vestige of evolution but growing evidence suggests that the appendix may, in fact, serve as a bacterial reservoir with the ability to reinoculate the colon and regulate microbiota homeostasis and biodiversity. We investigated the possible association between childhood appendectomy and risk of adult mental disorders in a large population-based retrospective cohort study. This has, to our knowledge, never been studied before.

2 | MATERIALS AND METHODS

2.1 | Study design

We conducted a population-based retrospective cohort study including all individuals born in Sweden between 1973 and 1992. The study population was followed until December 31, 2016 for diagnoses of mental disorders according to the International Classification of Diseases (ICD) at ≥14 years of age using linked register data. The study was approved by the Stockholm ethical review board (2010/1185-31/5). Informed consent was not required for the analysis of anonymized register data.

2.2 | Data sources

Data were acquired through linkage of several national registers held by Statistics Sweden and the National Board of Health and Welfare. The Swedish National Patient Register (NPR) was used to follow the study population with regard to the defined diagnoses of mental disorders and surgical procedures. The NPR has registered close to 100% of medical in-patient data in Sweden since 1973, and all outpatient specialist care since 2001 and is considered highly reliable and valid (Ludvigsson et al., 2011). The Swedish Medical Birth Register contains data on nearly 100% of deliveries in Sweden since 1973 and was used to collect data on individual births and biological parents (Cnattingius, Ericson, Gunnarskog, & Kallen, 1990). The Swedish Total Population Register (founded 1968) with almost complete coverage, provided information on marital status, migration, and other demographics. Socioeconomic variables were obtained through the Income and Taxation Register (founded 1968) and the longitudinal integration database for health insurance and labor market studies (founded 1990). Lastly, we used the Cause of Death Register with information on all deaths of Swedish residents since 1952 coded according to ICD syntax, to censor those who died before the end of follow-up.

2.3 | Study population

Data obtained from the above-mentioned registers on all Swedes born between 1973 and 1992 (n = 2,086,232) was back-end linked through the unique Swedish personal identity number and anonymized through a conversion key held by Statistics Sweden that was unavailable to the research team. The following were excluded: Individuals where one or both biological parents were unidentified at the time of birth (n = 26,176, 1.25%), those who emigrated or died before age 14 years (n = 83,525, 4.00%) and individuals with a mental disorder diagnosis that preceded any of our three defined exposures (n = 39,043, 1.87%). The final study population (n = 1,937,488) was prospectively followed until December 31, 2016 for any diagnosis of mental disorders in the NPR. To explore the role of familial confounding on mental disorders in adulthood, we performed within-family analyses where we compared exposed individuals in our study cohorts with unexposed biological siblings. To this end, we identified a subset of 588,897 families in the study population with at least two children born between 1973 and 1992 (n = 1,371,841) of which 28,842 families had one exposed child and 1,281 families had two to four exposed children who underwent appendectomy before age 14. Among them, there were n = 29,569 families that had at least two children that were discordant for appendectomy before age 14 and were included in the sibling comparison analyses.
2.4 | Exposures and controls

Three childhood exposures (<14 years of age) were defined using diagnostic codes in ICD-8, -9, and -10 and the nordic medico-statistical committee syntax (Table S1). Main exposure (childhood appendectomy) was defined as all individuals who had undergone appendectomy surgery before age 14 years (n = 44,259) and these individuals were compared to all individuals unexposed to appendectomy surgery before age 14 years (n = 1,893,229). Exposure 2 (childhood appendicitis without appendectomy) was defined as all individuals with appendicitis diagnosis before age 14 years who did not receive subsequent appendectomy surgery during the study period (n = 1,542). These individuals were compared to all individuals in the study population unexposed to appendicitis before age 14 and appendectomy during the study period (n = 1,827,909). Exposure 3 (childhood hernia surgery) was defined as all individuals having undergone hernia surgery (inguinal, femoral, or umbilical) before age 14 years (n = 35,523) and these were compared to all individuals in the study population unexposed to childhood hernia surgery (n = 1,901,965).

The main exposure was selected to determine whether childhood appendectomy is associated with mental disorders in adulthood. Exposure 2 was selected to explore the potential role of an unknown enteric covariate causing both appendicitis and adult mental disorders. Exposure 3 was selected in an attempt to isolate possible associations between childhood surgical trauma and mental disorders in adulthood that could explain any associations between childhood appendectomy and mental disorders by comparing the effect on mental disorders of two surgical procedures of similar anatomic locale, anesthetic- and recovery-profile. To explore the role of familial confounding on mental disorders in adulthood, we performed within-family analyses where we compared exposed individuals in our study cohorts with unexposed biological siblings.

2.5 | Outcome

Mental disorders that occurred at age 14 or above and before the end of the follow-up period were ascertained through ICD-8, -9, and -10 diagnostic codes registered in the NPR (Table S2). We distinguished between depressive disorder, bipolar affective disorder, anxiety disorder, obsessive–compulsive disorder (OCD), and schizophrenia.

2.6 | Other covariates

Covariates were selected based on known associations with mental disorders and acquired through the same register linkage as previously described. They included: gender, year of birth, disposable income of the parents in the year that the study individual was born, mental disorder diagnoses of biological parents (Bjorkenstam, Burstrom, Vinnerljung, & Kosidou, 2016; Siegenthaler, Munder, & Egger, 2012; Yeung, Linver, & Brooks-Gunn, 2002), and any known asthma diagnosis before age 14. Asthma was used as a proxy for a coexisting chronic low-grade inflammatory condition that if it would increase the risk for both appendicitis and mental disorders, potentially could confound any associations found (Chawes, Stokholm, Bonnelykke, Brix, & Bisgaard, 2015).

2.7 | Statistical analysis

Multivariate analyses were performed with Cox proportional hazards regression models fitted for each exposure against each mental disorder. Fully adjusted hazard ratios (aHRs) of the model on which the presented results are based (Model 6 in Supporting Information Appendices), was used to quantify the changes in relative risk over time of developing any of the mental disorders. Kaplan–Meier incidence plots for the main exposure (childhood appendectomy) were constructed for visual reference. Sensitivity analyses included a gender-adjusted model (Model 2) applied to the main exposure with respect to each mental disorder outcome with birth years stratified into 5-year buckets. Within-family analyses employed fixed-effect (conditional) Cox regression of exposure discordant siblings and adjusted similarly to other analyses, with the exception of parental disposable income and parental mental disorders which did not differ between the siblings. The significance level was set to 95% and all tests of significance were two-sided. Analyses were performed by the IBM SPSS statistics 21 (IBM).

3 | RESULTS

3.1 | Study population

Characteristics of the study population by exposure status are shown in Table 1. Before the age of 14, 44,259 (2.28%) individuals in the study population (N = 1,937,488) had undergone an appendectomy. An additional 1,542 (0.08%) had received an appendicitis diagnosis without removal of the appendix during follow-up, while 35,523 (1.83%) had undergone childhood hernia surgery (Table 1). Slightly more males than females were exposed to childhood appendectomy and appendicitis (53.50% and 52.66%, respectively). Males also accounted for 77.76% of hernia operations as explained by early scrotal hernias (Table 1). Overall, mental disorders were significantly more common among females across the three exposure groups, p < .001: 18.87% (n = 3,884) of the females who had their appendix removed received at least one mental disorder diagnosis after age 14 during follow-up as compared to 11.35% (n = 2,688) of exposed males (Table S3). Similarly, 15.75% (n = 115) of females with conservatively treated appendicitis developed at least one mental disorder as adults during follow-up compared to 11.21% (n = 91) of males with the same exposure (Table S4). Among those exposed to childhood hernia surgery, 17.18% (n = 1,357) of females compared to 10.66% (n = 2,944) of males were diagnosed with a mental disorder as adults (Table S5).
**TABLE 1** Characteristics of the study population by exposure category

| Covariates and outcome | Study population | Childhood (< age 14) appendectomy \(^a\) | Childhood (< age 14) appendicitis without appendectomy \(^b\) | Childhood (< age 14) hernia surgery \(^c\) |
|-----------------------|------------------|----------------------------------------|------------------------------------------------|----------------------------------|
|                       | \(N = 1,937,488\) (100%) | \(n = 44,259\) (2.28%) | \(n = 1,893,229\) (97.72%) | \(n = 1,542\) (0.08%) | \(n = 1,827,909\) (99.92%) | \(n = 35,523\) (1.83%) | \(n = 1,901,965\) (98.17%) |
| Gender                |                  |                                  |                                             |                                   |                                   |                                   |                                   |
| Male                  | 993,530          | 51.28%                           | 23,679                                     | 53.50%                            | 969,851                          | 51.23%                           | 812                               | 52.66%                           | 936,077                          | 51.21%                           | 27,622                           | 77.76%                           | 965,908                          | 50.78%                           |
| Female                | 943,958          | 48.72%                           | 20,580                                     | 46.50%                            | 923,378                          | 48.77%                           | 730                               | 47.34%                           | 891,832                          | 48.79%                           | 7,901                            | 22.24%                           | 936,057                          | 49.22%                           |
| Parental disposable income |              |                                  |                                             |                                   |                                   |                                   |                                   |                                   |                                   |                                   |                                   |                                   |                                   |                                   |
| Lowest quintile       | 381,288          | 19.68%                           | 8,920                                      | 20.15%                           | 372,368                          | 19.67%                           | 294                               | 19.07%                           | 359,233                          | 19.65%                           | 6,695                            | 18.85%                           | 374,593                          | 19.70%                           |
| 4th Quintile          | 389,463          | 20.10%                           | 9,178                                      | 20.74%                           | 380,285                          | 20.09%                           | 346                               | 22.44%                           | 366,681                          | 20.06%                           | 7,124                            | 20.05%                           | 382,339                          | 20.10%                           |
| 3rd Quintile          | 391,116          | 20.19%                           | 8,970                                      | 20.27%                           | 382,146                          | 20.18%                           | 323                               | 20.95%                           | 368,899                          | 20.18%                           | 7,071                            | 19.91%                           | 384,045                          | 20.19%                           |
| 2nd Quintile          | 389,789          | 20.12%                           | 8,701                                      | 19.66%                           | 381,088                          | 20.13%                           | 309                               | 20.04%                           | 368,168                          | 20.14%                           | 7,134                            | 20.08%                           | 382,655                          | 20.12%                           |
| Highest quintile      | 385,832          | 19.91%                           | 8,490                                      | 19.18%                           | 377,342                          | 19.93%                           | 270                               | 17.51%                           | 364,928                          | 19.96%                           | 7,499                            | 21.11%                           | 378,333                          | 19.89%                           |
| Parental mental disorder |                  |                                  |                                             |                                   |                                   |                                   |                                   |                                   |                                   |                                   |                                   |                                   |                                   |                                   |
| Maternal mental disorder | 347,257        | 17.92%                           | 8,723                                      | 19.71%                           | 338,534                          | 17.88%                           | 271                               | 17.57%                           | 326,072                          | 17.84%                           | 6,997                            | 19.70%                           | 340,260                          | 17.89%                           |
| Paternal mental disorder | 327,540        | 16.91%                           | 7,970                                      | 18.01%                           | 319,570                          | 16.88%                           | 250                               | 16.21%                           | 307,758                          | 16.84%                           | 6,375                            | 17.95%                           | 321,165                          | 16.89%                           |
| Asthma                |                  |                                  |                                             |                                   |                                   |                                   |                                   |                                   |                                   |                                   |                                   |                                   |                                   |                                   |
| Asthma diagnosis (< age 14) | 40,081       | 2.07%                            | 1,016                                      | 2.30%                            | 39,065                           | 2.06%                            | 48                                | 3.11%                            | 38,060                           | 2.08%                            | 1,253                            | 35.3%                            | 38,828                           | 20.4%                            |
| Mental disorders during follow-up |          |                                  |                                             |                                   |                                   |                                   |                                   |                                   |                                   |                                   |                                   |                                   |                                   |                                   |
| Depressive disorder (> age 14) | 140,188   | 7.24%                            | 3,771                                      | 8.52%                            | 136,417                          | 7.21%                            | 107                               | 6.94%                            | 130,295                          | 7.13%                            | 2,413                            | 6.79%                            | 137,775                          | 7.24%                            |
| Bipolar affective disorder (> age 14) | 23,698    | 1.22%                            | 688                                       | 1.55%                            | 230,100                          | 1.22%                            | 18                                | 1.17%                            | 21,892                           | 1.20%                            | 401                              | 1.13%                            | 23,297                           | 1.22%                            |
| Anxiety disorder (> age 14) | 182,967    | 9.44%                            | 4,929                                      | 11.14%                           | 178,038                          | 9.40%                            | 153                               | 9.92%                            | 175,698                          | 9.61%                            | 3,141                            | 8.84%                            | 179,826                          | 9.45%                            |
| OCD (> age 14)         | 17,626         | 0.91%                            | 428                                       | 0.97%                            | 17,198                           | 0.91%                            | 13                                | 0.84%                            | 16,566                           | 0.91%                            | 309                              | 0.87%                            | 17,317                           | 0.91%                            |
| Schizophrenia (> age 14) | 4,756        | 0.25%                            | 104                                       | 0.23%                            | 4,652                            | 0.25%                            | 5                                 | 0.32%                            | 4,488                            | 0.25%                            | 123                              | 0.35%                            | 4,633                            | 0.24%                            |

Abbreviation: OCD, obsessive–compulsive disorder.

\(^a\) Childhood (< age 14) appendectomy was compared to all individuals in the study population unexposed to appendectomy before age 14 years \((n = 1,893,229)\).

\(^b\) Childhood (< age 14) appendicitis without appendectomy was compared to all individuals in the study population unexposed to appendicitis before age 14 and appendectomy during the study period \((n = 1,827,909)\).

\(^c\) Childhood (< age 14) hernia surgery was compared to all individuals in the study population unexposed to hernia surgery before age 14 years \((n = 1,901,965)\).

\(^d\) Hazard ratios in the final model were calculated by adjusting for sex, birth year, parental disposable income, parental mental disorder, asthma diagnosis before age 14.
3.2 Risk of mental disorders in adulthood

aHRs for the association between each exposure with each mental disorder is shown in Table 2. Overall, 247,988 (12.80%) individuals in the study population received at least one mental disorder diagnosis during follow-up. Mental illness was most common among individuals exposed to childhood appendectomy (14.85%, n = 6,572), while 13.36% (n = 296) of individuals exposed to childhood appendicitis without appendectomy and 12.11% (n = 4,301) of individuals exposed to childhood hernia surgery were diagnosed with at least one mental disorder at age 14 or later in life (Table 2).

Individuals exposed to appendectomy before age 14 showed increased relative risks during follow-up for depressive disorder (aHR = 1.19; 95% confidence interval [95% CI]: 1.15–1.23), bipolar affective disorder (aHR = 1.27; 95% CI: 1.17–1.37), and anxiety disorder (aHR = 1.20; 95% CI: 1.16–1.23) after adjusting for gender, year of birth, parental disposable income, maternal and/or paternal mental disorder, and childhood asthma compared to those unexposed to childhood appendectomy (Table 2).

There were no associations between childhood appendectomy with relative risk increases of OCD or schizophrenia during follow-up. Further, individuals exposed to childhood appendicitis without appendectomy showed no statistically significant associations with relative risk alterations for any mental disorders in adulthood compared to individuals in the study population unexposed to appendicitis before age 14 and appendectomy during the study period (Table 2). All covariate-adjusted models for the three exposures with mental disorders are shown in Tables S6–S8.

Childhood hernia surgery before age 14 was associated with increased relative risks of schizophrenia (aHR = 1.21; 95% CI: 1.01–1.45) as well as with depressive disorder (aHR = 1.06; 95% CI: 1.02–1.11) and anxiety disorder (aHR = 1.06; 95% CI: 1.03–1.10) compared to those unexposed to childhood hernia surgery (Table 2).

The associations between childhood hernia surgery with depressive disorder and anxiety disorder found in our main analyses disappeared after adjusting for mental disorders in unexposed siblings during follow-up (Table S9).

The associations between childhood appendectomy and adult mental disorders (depressive, bipolar affective, and anxiety) were relatively stable during the 25-year follow-up period as shown by the top-row Kaplan–Meier incidence plot panels in Figure 1. We found no association between exposure to childhood appendectomy and adult OCD and schizophrenia (bottom-row Kaplan–Meier incidence plot panels in Figure 1). Within-family analyses showed attenuated but significant associations between childhood appendectomy with excess relative risks for depressive disorder, bipolar affective disorder, and anxiety disorder in adulthood after conditioning on the family factors resulting from siblingship (Table S9). Similarly, the aHR for the association between childhood hernia surgery with schizophrenia remained greater than one in our within-family analyses (aHR = 1.38; 95% CI: 0.97–1.96) although statistical significance was lacking due to the low prevalence of schizophrenia resulting in low power for this analysis (Table S9). Stratified analysis of excess relative risks for mental disorders in adulthood broken down by birth year in the main exposure group showed stable excess risks for depressive disorder, bipolar affective disorder, and anxiety disorder in adulthood over time independent of the birth year (Table S10).

4 DISCUSSION

Our analysis of data from Swedish nationwide health and administrative registers including nearly two million individuals born between 1973 and 1992 indicates that those exposed to childhood appendectomy have an increased relative risk of depressive disorder, bipolar affective disorder, and anxiety disorder in adulthood compared to individuals who did not have their appendix removed early in life. No such association was found with conservatively treated childhood appendicitis leaving the appendix intact during the follow-up period which corresponded to age between 24 and 43 years among living study subjects. The association between childhood appendectomy and later risk of mental disorders remained, although attenuated, in comparisons between siblings discordant for appendectomy exposure, suggesting that this is unlikely to be entirely explained by shared familial confounding. Our study suggests a possible protective role of the appendix against mental illness in adulthood, an effect that vanishes once the appendix is removed, and is, to the best of our knowledge, the first to investigate an association between childhood appendectomy and adult mental disorders.

Long-term consequences of appendectomy are not well studied, likely due to the longstanding belief that the appendix serves but a vestigial function of redundancy in the human body. However, some earlier studies have shown positive associations between childhood appendectomy and acute myocardial infarction, (Janszky, Mukamal, Dalman, Hammar, & Ahnve, 2011) Crohn’s disease, (Andersson, Olaion, Tysk, & Ekbom, 2003), and chronic kidney disease (Chang et al., 2018). Negative associations between appendectomy and adult ulcerative colitis (Andersson, Olaion, Tysk, & Ekbom, 2001) and Parkinson’s disease (Killinger et al., 2018) have also been shown but, here again, the pathogenesis is not well understood. Although a unifying framework for the physiological function of the appendix is still lacking, recent evidence suggests that it displays ideal anatomical, histological, and molecular properties for inoculation of the colon through regular shedding and regeneration of high concentration secretory IgA microbial biofilm (Girard-Madoux et al., 2018; Kooij et al., 2016; Randal Bollinger et al., 2007). By creating a potential safe-house environment for beneficial gut microbes and protecting against microbial pathogens through processes of immune inclusion and exclusion, the appendix may be important in maintaining colonic microbiota homeostasis and biodiversity, in turn, thought to promote host immune response (Collins et al., 2012; Foster & McVey Neufeld, 2013; Li et al., 2016; Maynard et al., 2012; Naseribafrouei et al., 2014; Raskov et al., 2016; Turnbaugh et al., 2009; Yu et al., 2017).

An alternative explanation of the association between childhood appendectomy with later depressive disorder, bipolar affective
TABLE 2  aHRs and 95% CIs for the association of childhood (< age 14) appendectomy, childhood (< age 14) appendicitis without appendectomy ever, and childhood (< age 14) hernia surgery with mental disorders in adulthood during follow-up

| Outcome                  | Study population | Exposures | Exposures | Exposures |
|-------------------------|------------------|-----------|-----------|-----------|
|                         | N = 1,937,488 (men = 993,530; women = 943,958) | Childhood (< age 14) appendectomy\(^a\) (n = 44,259) | Childhood (< age 14) appendicitis without appendectomy\(^b\) (n = 1,542) | Childhood (< age 14) hernia surgery\(^c\) (n = 35,523) |
|                         | N; % of study population | n; % of main exposure | aHR\(^d\) | 95% CI | n; % of exposure 2 | aHR\(^d\) | 95% CI | n; % of exposure 3 | aHR\(^d\) | 95% CI |
| Depressive disorder after age 14 | n = 140,188; 7.24% | n = 3,771; 8.52% | 1.19 | 1.15–1.23 | n = 107; 6.94% | 1.00 | 0.83–1.21 | n = 2,413; 6.79% | 106 | 1.02–1.11 |
| Bipolar affective disorder after age 14 | n = 23,698; 1.22% | n = 688; 155% | 1.27 | 1.17–1.37 | n = 18; 1.17% | 102 | 0.64–1.62 | n = 401; 1.13% | 109 | 0.99–1.20 |
| Anxiety disorder after age 14 | n = 182,967; 9.44% | n = 4,929; 11.14% | 1.20 | 1.16–1.23 | n = 153; 9.92% | 108 | 0.92–1.27 | n = 3,141; 8.84% | 106 | 1.03–1.10 |
| OCD after age 14 | n = 17,626; 0.91% | n = 428; 0.97% | 1.07 | 0.97–1.18 | n = 13; 0.84% | 0.96 | 0.56–1.65 | n = 309; 0.87% | 106 | 0.94–1.18 |
| Schizophrenia after age 14 | n = 4,756; 0.25% | n = 104; 0.23% | 0.88 | 0.73–1.07 | n = 5; 0.32% | 1.38 | 0.57–3.31 | n = 123; 0.35% | 121 | 1.01–1.45 |
| Any of the above mental disorders | 247,988 (12.80%) | 6,572 (14.85%) | 206 (13.36%) | 4,301 (12.11%) |

Abbreviations: 95% CI, 95% confidence interval; aHR, adjusted hazard ratio; OCD, obsessive–compulsive disorder.

\(^a\)Childhood (< age 14) appendectomy was compared to all individuals in the study population unexposed to appendectomy before age 14 years (n = 1,893,229).

\(^b\)Childhood (< age 14) appendicitis without appendectomy was compared to all individuals in the study population unexposed to appendicitis before age 14 and appendectomy during the study period (n = 1,827,909).

\(^c\)Childhood (< age 14) hernia surgery was compared to all individuals in the study population unexposed to hernia surgery before age 14 years (n = 1,901,965).

\(^d\)aHR are shown after adjusting for sex, birth year, parental disposable income, parental mental disorder, asthma diagnosis before age 14.
disorder, and anxiety disorder found in our study could be that a common unknown predisposing factor, for example, immune dysregulation, increases the risk of both appendicitis and mental disorders. However, analyses of individuals with conservatively treated appendicitis did not reveal any associations with mental disorders in adulthood. This finding supports the notion that removal of the appendix increases the risk of developing mental disorders, rather than appendicitis or its predisposing factors. Yet, the analysis of individuals with appendicitis without appendectomy was somewhat underpowered and we cannot exclude that patients with conservatively treated appendicitis somehow differ systematically from those treated with appendectomy, which may confound the associations with mental disorders (confounding by indication). Another explanation of our findings could be that children with heightened levels of anxiety or other mental health problems are more likely to present to health services with somatization symptoms such as functional abdominal pain and are thus more likely to be treated surgically with appendectomy. Although we controlled for diagnosed childhood mental disorders this may fail to capture all children with mental health problems and, therefore, undiagnosed or milder childhood psychopathology may still be a confounder of the associations found in our study.

A recent study suggested a positive association between childhood hernia surgery under general anesthesia and the risk of behavioral and developmental disorders in young children, possibly as a result of neurotoxic effects of anesthetic agents on the developing brain (DiMaggio, Sun, Kakavouli, Byrne, & Li, 2009). To explore this hypothesis further, we investigated the association of mental disorders in adulthood with exposure to childhood hernia surgery, an operation of similar surgical magnitude, anatomic locale, anesthetic-and recovery-profile to that of appendectomy. Although we did observe significant associations between hernia surgery and adult depressive and anxiety disorders in our main analyses, the sizes of these risk estimates were significantly smaller than those observed for childhood appendectomy. Further, the associations between hernia surgery and adult depressive and anxiety disorders disappeared when comparing to siblings discordant for hernia exposure whilst the effect of childhood appendectomy with adult mental disorders, although attenuated, remained. It is thus unlikely that the associations between childhood appendectomy and adult mood and anxiety disorders could be entirely explained by long-term consequences of surgical stress, neurotoxicity of anesthetic agents, or familial confounding.

The association between exposure to childhood hernia surgery and schizophrenia later in life is in line with an earlier epidemiological study that found early-onset inguinal hernia surgery to be a risk factor for being diagnosed with schizophrenia and psychosis in adulthood (Melkersson & Wernroth, 2017). Dysfunctional collagen synthesis and metabolism expressed in the abdominal wall as well as the brain, has been linked to both predisposition of hernia (Bellon et al., 2001; Friedman et al., 1993) and possibly to schizophrenia, (Fillman et al., 2013; Van Den Bossche, Van Wallendael, Strazisar, Sabbe, & Del-Favero, 2012) and deserves further attention as a possible explanation of this association in future studies. It could be that shared genetic drivers, polygenic and pleiotropic in nature, combined with early-life environmental factors influence phenotype expression of both childhood herniation of the abdominal wall and schizophrenia in adulthood. Other work has linked congenital malformations of the urogenital system like hypospadias and cryptorchidism to autism spectrum disorder, intellectual disability, and other behavioral/emotional disorders but not to schizophrenia (Butwicka et al., 2015; Rotem et al., 2018; Schieve & Shapira, 2018).

In our study, childhood appendectomy appeared to have no impact on the risk of OCD and schizophrenia. It is possible that the
removal of the appendix, leading to reduced microbiotic biodiversity and dysbiosis leading to heightened levels of inflammation, is more relevant to the pathophysiology of mood and anxiety disorders than that of schizophrenia and OCD which may be more genetically driven. Mounting evidence suggests that inflammation, as measured through elevated serum levels of proinflammatory cytokines such as interleukin 1 (IL-1), IL-6, and tumor necrosis factor-α, is important for the development of depression (Bai et al., 2015; Barnes et al., 2017; Dantzer et al., 2008; Leonard & Maes, 2012; Liu et al., 2012; Miller et al., 2009; Moylan et al., 2014; Reichenberg et al., 2001; Stein et al., 2018). Furthermore, some patients with depressive disorder display reduced glucocorticoid sensitivity in the hypothalamic–pituitary–adrenal axis, reduced serotonin levels and elevated neurotoxic serotoninergic metabolites (Dantzer et al., 2008; Leonard & Maes, 2012; Miller et al., 2009; Moylan et al., 2014). Anxiety disorders have been less studied in relation to inflammation and microbiota, but our findings indicate a possible role, calling for further research.

Our findings align with the notion that the appendix plays a role in maintaining and restoring microbiota homeostasis in the gastrointestinal tract and that its surgical removal reduces the body’s capacity for commensal colonic recolonization. However, more research is warranted to understand if and how this is done as well as the potentially modulating effect of the appendix on risks of mental disorders. A possible route is via inflammation or other yet undiscovered mechanisms. Of interest here is the recent finding that nonoperative, antibiotic-only management of appendicitis has an over 50% success rate (Decker et al., 2014). Future cross-disciplinary research linking gut mucosal samples, DNA sequencing and metagenomics in for example patients who undergo appendectomy, to various longer-term clinical outcomes, including mental disorders, could contribute to our knowledge of individual predisposition, pre- and postinflammation levels, and if and how the level of inflammation interacts with psychiatric pathologies.

The large sample size and the use of high-quality population-based register data are major strengths of this study enabling adjustments for a range of possible confounders, including parental characteristics, socioeconomic status, and other inflammatory conditions such as childhood asthma. Yet, an observational cohort study is unable to establish causality and residual confounding can never be excluded. A limitation of our study is the possibility that despite the relatively large sample size of conservatively treated appendicitis (n = 1,542), the group is still underpowered compared to the other two exposure cohorts, which makes claims of a direct effect of appendectomy on adult mental disorders more difficult to make. Furthermore, both exposures and outcomes are based on healthcare registry data of diagnoses that can be confounded by socioeconomic and other factors potentially influencing help-seeking behavior and healthcare access. Although we controlled for a range of socioeconomic variables like gender, disposable income of the parents, and mental disorder diagnoses of biological parents, we cannot exclude that remaining socioeconomic factors that influence help-seeking behavior and access to healthcare, or other residual confounders, may affect our results. Lastly, we cannot rule out intracountry systematic variations in clinical practices leading to a lower or higher proportion of patients with appendicitis being treated with surgery in certain hospitals or over certain time periods although the nationwide and population-based nature of our study in combination with several decades of follow-up likely limits this effect.

5 CONCLUSION

Although causality cannot be confirmed through an epidemiologic study and the effect sizes of the associations between appendectomy and mood and anxiety disorders found in this study were rather modest, these mental disorders make up a significant part of the global burden of disease. Likewise, appendectomy is one of the most common surgical procedures in children. Thus, even modest associations could have a substantial impact on population health at the global level (Vons et al., 2011). By suggesting a novel link between two important health problems, this study opens up for innovation in terms of prevention and clinical management as well as further research into potential causal pathways.

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CONFLICT OF INTERESTS

All authors meet the ICMJE-criteria for authorship and declare no conflict of interests.

DATA AVAILABILITY STATEMENT

Due to Swedish legal restrictions and the current ethical approval for the study, data are not publicly available to share, but the research group can provide descriptive data in table form.

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REFERENCES

Andersson, R. E., Olaison, G., Tysk, C., & Ekbom, A. (2001). Appendectomy and protection against ulcerative colitis. New England Journal of Medicine, 344(11), 808–814. https://doi.org/10.1056/nejm200103153441104
Andersson, R. E., Olaison, G., Tysk, C., & Ekbom, A. (2003). Appendectomy is followed by increased risk of Crohn’s disease. Gastroenterology, 124(1), 40–46. https://doi.org/10.1053/gast.2003.50021
Bai, Y. M., Su, T. P., Li, C. T., Tsai, S. J., Chen, M. H., Tu, P. C., & Chiou, W. F. (2015). Comparison of pro-inflammatory cytokines among patients with bipolar disorder and unipolar depression and normal controls. Bipolar Disorders, 17(3), 269–277. https://doi.org/10.1111/bdi.12259
Barnes, J., Mondelli, V., & Pariante, C. M. (2017). Genetic contributions of inflammation to depression. Neuropsychopharmacology, 42(1), 81–98. https://doi.org/10.1038/npp.2016.169
Bellon, J. M., Bazo, A., Ga-Honduvilla, N., Gimeno, M. J., Pascual, G., Guerrero, A., & Bujan, J. (2001). Fibroblasts from the transversalis
fascia of young patients with direct inguinal hernias show constitutive MMP-2 overexpression. Annals of Surgery, 233(2), 287–291. https://doi.org/10.1097/01.sla.000005658-20102000-00020

Bjorkenstam, E., Burstrom, B., Vinnerljung, B., & Kosidou, K. (2016). Childhood adversity and psychiatric disorder in young adulthood: An analysis of 107,704 Swedes. Journal of Psychiatric Research, 77, 67–75. https://doi.org/10.1016/j.jpsychires.2016.02.018

Butwicka, A., Lichtenstein, P., Landen, M., Nordenval, A. S., Nordenstam, A., Nordsjöld, A., & Frisen, L. (2015). Hypospadias and increased risk for neurodevelopmental disorders. Journal of Child Psychology and Psychiatry and Allied Disciplines, 56(2), 155–161. https://doi.org/10.1111/jcpp.12290

Chang, C. H., Kor, C. T., Wu, C. L., Chiu, P. F., Li, J. R., Tsai, C. C., ... Chang, C. C. (2018). Increased chronic kidney disease development and progression in diabetic patients after appendectomy: A population-based cohort study. PeerJ, 6, e5019. https://doi.org/10.7717/peerj.5019

Chawes, B. L., Stokholm, J., Bonnelykke, K., Brix, S., & Bisgaard, H. (2015). Childhood appendectomy, tonsillectomy, and risk for premature acute myocardial infarction—a nationwide population-based cohort study. European Heart Journal, 32(18), 2290–2296. https://doi.org/10.1093/eurheartj/ehr137

Killinger, B. A., Madaj, Z., Sikora, J. W., Rey, N., Haas, A. J., Vepa, Y., ... Labrie, V. (2018). The veriformum appendix impacts the risk of developing Parkinson’s disease. Science Translational Medicine, 10(465), eaar5280. https://doi.org/10.1126/scitranslmed.aar5280

Kooij, I. A., Sahami, S., Meijer, S. L., Buskens, C. J., & Te Velde, A. A. (2016). The immunology of the veriform appendix: A review of the literature. Clinical and Experimental Immunology, 186(1), 1–9. https://doi.org/10.1111/cei.12821

Leonard, B., & Maes, M. (2012). Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concomitants play a role in the pathophysiology of unipolar depression. Neuroscience and Biobehavioral Reviews, 36(2), 764–785. https://doi.org/10.1016/j.neubiorev.2011.12.005

Li, D., Wang, P., Wang, P., Hu, X., & Chen, F. (2016). The gut microbiota: A treasure for human health. Biotechnology Advances, 34(7), 1210–1224. https://doi.org/10.1016/j.biotechadv.2016.08.003

Liu, Y., Ho, R. C., & Mak, A. (2012). Interleukin (IL)-6, tumour necrosis factor alpha (TNF-alpha) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: A meta-analysis and meta-regression. Journal of Affective Disorders, 139(3), 230–239. https://doi.org/10.1016/j.jad.2011.08.003

Ludvigsson, J. F., Andersson, E., Ekborn, A., Feychting, M., Kim, J. L., Reuterwall, C., ... Olausson, P. O. (2011). External review and validation of the Swedish national inpatient register. BMC Public Health, 11, 450. https://doi.org/10.1186/1471-2458-11-450

Maynard, C. L., Elson, C. O., Hatton, R. D., & Weaver, C. T. (2012). Reciprocal interactions of the intestinal microbiota and immune system. Nature, 489(7415), 231–241. https://doi.org/10.1038/nature11551

Melkersson, K., & Wernroth, M. L. (2017). Early-onset inguinal hernia as risk factor for schizophrenia or related psychosis: A nationwide register-based cohort study. Neuro Endocrinology Letters, 38(5), 333–342.

Miller, A. H., Maletic, V., & Raison, C. L. (2009). Inflammation and its discontents: The role of cytokines in the pathophysiology of major depression. Biological Psychiatry, 65(9), 732–741. https://doi.org/10.1016/j.biopsych.2008.11.029

Moylan, S., Berk, M., Dean, O. M., Samuni, Y., Williams, L. J., O’Neill, A. ... Maes, M. (2014). Oxidative & nitrosative stress in depression: Why so much stress? Neuroscience and Biobehavioral Reviews, 45, 46–62. https://doi.org/10.1016/j.neubiorev.2014.05.007

Naserifardrouei, A., Hestad, K., Avershina, E., Sekelja, M., Linlokkken, A., Wilson, R., & Rudi, K. (2014). Correlation between the human fecal microbiota and depression. Neurogastroenterology and Motility, 26(8), 1155–1162. https://doi.org/10.1111/nmo.12378

Randal Bollinger, R., Barbosa, A. S., Bush, E. L., Lin, S. S., & Parker, W. (2007). Biofilms in the large bowel suggest an apparent function of the human veriform appendix. Journal of Theoretical Biology, 249(4), 826–831. https://doi.org/10.1016/j.jtbi.2007.08.032

Raskov, H., Burchardt, J., Pomergaard, H. C., & Rosenberg, J. (2016). Irritable bowel syndrome, the microbiota and the gut-brain axis. Gut Microbes, 7(5), 365–383. https://doi.org/10.1080/19490976.2016.1218585

Reichenberg, A., Yirmiya, R., Schuld, A., Kraus, T., Haack, M., Morag, A., & Pollmacher, T. (2001). Cytokine-associated emotional and cognitive disturbances in humans. Archives of General Psychiatry, 58(5), 445–452. https://doi.org/10.1001/archpsyc.58.5.445

Rotem, R. S., Chodick, G., Davidovitch, M., Hauser, R., Coull, B. A., & Weisskopf, M. G. (2018). Congenital abnormalities of the male reproductive system and risk of autism spectrum disorders. American Journal of Epidemiology, 187(4), 656–663. https://doi.org/10.1093/aje/kwx367
Schieve, L. A., & Shapira, S. K. (2018). Invited commentary: Male reproductive system congenital malformations and the risk of autism spectrum disorder. American Journal of Epidemiology, 187(4), 664–667. https://doi.org/10.1093/aje/kwx369

Siegenthaler, E., Munder, T., & Egger, M. (2012). Effect of preventive interventions in mentally ill parents on the mental health of the offspring: Systematic review and meta-analysis. Journal of the American Academy of Child and Adolescent Psychiatry, 51(1), 8–17. https://doi.org/10.1016/j.jaac.2011.10.018

Stein, D. J., Naude, P. J., & Berk, M. (2018). Stress, depression, and inflammation: Molecular and microglial mechanisms. Biological Psychiatry, 83(1), 5–6. https://doi.org/10.1016/j.biopsych.2017.10.025

Turnbaugh, P. J., Hamady, M., Yatsunenko, T., Cantarel, B. L., Duncan, A., Ley, R. E., ... Gordon, J. I. (2009). A core gut microbiome in obese and lean twins. Nature, 457(7228), 480–484. https://doi.org/10.1038/nature07540

Van Den Bossche, M. J., Van Wallendael, K. L., Strazisar, M., Sabbe, B., & Del-Favero, J. (2012). Co-occurrence of Marfan syndrome and schizophrenia: What can be learned? European Journal of Medical Genetics, 55(4), 252–255. https://doi.org/10.1016/j.ejmg.2012.02.005

Vons, C., Barry, C., Maitre, S., Pautrat, K., Leconte, M., Costaglioli, B., ... Franco, D. (2011). Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: An open-label, non-inferiority, randomised controlled trial. Lancet, 377(9777), 1573–1579. https://doi.org/10.1016/s0140-6736(11)60410-8

Yeung, W. J., Linver, M. R., & Brooks-Gunn, J. (2002). How money matters for young children’s development: Parental investment and family processes. Child Development, 73(6), 1861–1879. https://doi.org/10.1111/1467-8624.00511

Yu, M., Jia, H., Zhou, C., Yang, Y., Zhao, Y., Yang, M., & Zou, Z. (2017). Variations in gut microbiota and fecal metabolic phenotype associated with depression by 16S rRNA gene sequencing and LC/MS-based metabolomics. Journal of Pharmaceutical and Biomedical Analysis, 138, 231–239. https://doi.org/10.1016/j.jpba.2017.02.008

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