ARTICLE

Prenatal exposure to selective serotonin reuptake inhibitors and risk of disorders of gut-brain interaction in children

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Preclinical data suggest that gestational exposure to selective serotonin reuptake inhibitors (SSRI) alter gut innervation, and delays colonic motility. In this study we investigated associations between gestational SSRI exposure and offspring disorders of gut-brain interaction (DGBI). Using population-based registries, we included all single-birth Danish children born 1997–2015 with follow-up until outcome occurrence, age 15 years, death, emigration, or December 2018. Children to mothers who continued SSRIs during pregnancy and children to mothers who discontinued SSRI use before pregnancy were compared using Cox regression. Main outcomes were the first diagnosis of a childhood DGBI (functional nausea and vomiting, functional abdominal pain disorders, functional diarrhea, and functional constipation), or a physician-prescribed laxative. Among 1,158,560 children, 21,969 children (1.9%) were exposed to SSRIs prenatally and 30,174 children (2.6%) were born to mothers who discontinued SSRIs before pregnancy. Overall, the estimated 15-year cumulative incidence of any DGBI was 15.5% (95% CI, 14.9–16.2) in the SSRI-exposed group and 14.7% (14.0–15.3) in the unexposed group. SSRI-exposed children had an overall increased risk of DGBIs (HR 1.08, [1.02–1.14]), which was driven by functional constipation (HR 1.19, [1.10–1.28]) rather than functional nausea and vomiting (HR 0.97, [0.83–1.13]) or functional abdominal pain disorders (HR 0.90, [0.81–1.00]). These data suggest that prenatal SSRI exposure is associated with an increased risk of developing functional constipation. These findings are also consistent with extensive preclinical data supporting key roles for serotonin in gut development and function. Together findings support the need for further investigation of the long-term impact of maternal depression and SSRI exposure on development of common gastrointestinal disorders.

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INTRODUCTION

Serotonin [5-hydroxytryptamine; 5-HT] plays key roles in neurodevelopment, and gestational 5HT perturbations, whether through genetic manipulation or prenatal pharmacological exposures (e.g. selective serotonin reuptake inhibitor [SSRI] antidepressants) are shown to alter neurogenesis and circuit formation in the central nervous system [CNS] [1–4]. The majority of the body's serotonin, however, is synthesized not in the brain but in the gastrointestinal (GI) tract, reaching ~95% by midterm fetal maturation [5]. The serotonin transporter (SERT), critical for serotonin availability, is also abundant in the intestine [5, 6]. Yet the role of serotonin in the development of the enteric nervous system [ENS] is less well understood. Preclinical studies, including by us, have linked gestational serotonergic manipulations to abnormalities in innervation of the ENS, and increased GI symptoms such as dysmotility, visceral pain, abnormal colonic transit, and pelvic outlet dysfunction-induced constipation in the absence of any structural gut abnormalities [7, 8].

Whether these disturbances translate to human populations is less clearly understood, but has wide-raging clinical implications given the bi-directional connectivity between the gut-brain axis, and the high pediatric prevalence of disorders of gut-brain interaction (DGBI), the most common GI diagnoses in children [9]. DGBI, previously known as functional gastrointestinal disorders, encompass a spectrum of diagnoses including functional constipation, irritable bowel syndrome [IBS] and functional dyspepsia [10, 11]. DGBIs are believed to have developmental underpinnings attributable to abnormal gut-brain communication and are characterized by recurrent GI symptoms not attributable to identifiable structural or biochemical abnormalities [10, 11]. They remain challenging to treat owing to incomplete understanding of their pathophysiology and they are associated with increased healthcare utilization and poorer quality of life [9, 10]. Only two human studies to our knowledge have tested GI outcomes of gestational serotonin manipulations. One study identified an

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increased risk of self-reported GI symptoms in preschool children prenatally exposed to SSRIS [12]; the other, a greater likelihood to receive prescriptions for laxatives in infancy [13]. These reports are consistent with the constipation-like phenotypes suggested by the aforementioned preclinical literature; however, they were limited by lack of control for maternal depression (for which SSRIs are primarily prescribed, and thus a critical potential confounder), small and unrepresentative samples, self- or parent- reported outcomes rather than clinician diagnoses, and lack of follow up beyond early childhood.

In this study, we used Danish population data to address these key issues and investigate the associations between SSRI exposure in pregnancy and risk for clinician-diagnosed DGBI. To reduce potential confounding from maternal depression and meaningfully extend the time of follow-up, we used multiple analytic approaches, and we followed offspring from birth through mid-adolescence (age 15)

METHODS

Study design and data sources

The study was a population-based cohort study leveraging individual-level data from Danish nationwide health and administrative registries. From the Danish Medical Birth Registry [14], we identified all liveborn children during 1997–2015 and linked each child to parental information on diagnoses, drug prescriptions and sociodemographic information by use of the unique personal identification number assigned to all Danish residents. Non-singleton births and children with missing or likely errors in gestational age (<154 or >315 days) were excluded. The study was approved by the institutional board at the University of Southern Denmark. According to Danish law, informed consent or approval from an ethics board are not required for register-based research.

Exposure to SSRIs

Maternal use of SSRIs was determined from the Danish National Prescription Registry which covers all prescriptions dispensed in Denmark since 1995 [15]. The main exposure was prenatal exposure to SSRIs, which was defined as mothers who had at least one prescription fill for any SSRI drug (Anatomical Therapeutic Chemical (ATC) code N06AB) from 30 days before start of pregnancy to the day of delivery. Start of pregnancy was defined using the gestational age registered in the Danish Medical Birth Register, which is based on first- or second-trimester ultrasound scans, or, if unavailable, on the date of the first day of the mother's last menstrual period. The main comparison group consisted of children born to mothers who had used SSRIs but discontinued use before pregnancy (discontinuation group). This comparison group was chosen to mitigate confounding by indication, as women who discontinued SSRIs might be more comparable to women who continued SSRIs during pregnancy than women never treated. Discontinuation of SSRI use was defined as having filled a prescription for an SSRI in the window from two years to 91 days before start of pregnancy but not during pregnancy.

Outcomes

All pediatric DGBI outcomes were based on International Classification of Diseases, 10th revision (ICD-10) codes recorded during inpatient or outpatient hospital visits in the Danish National Patient Registry [16] as well as prescription fills for laxatives from the Danish National Prescription Registry [15]. In clinical practice, DGBI are diagnosed and classified using the current version of the Rome criteria [11, 17]. In accordance with main diagnosis groups in the Rome IV guidelines, we categorized childhood DGBI into four main outcome groups: functional nausea and vomiting disorders, functional abdominal pain disorders, and functional defecation disorders (split into functional constipation and functional diarrhea). Not all diagnosis groups in the Rome guidelines have a 1:1 translation into the ICD-10 adaptation used in Denmark for diagnostic coding. Some DGBI (e.g., infant colic, functional dyspepsia, and irritable bowel syndrome) have specific ICD-10 codes. Others, however, (e.g., functional vomiting and functional abdominal pain) are coded using symptom-based diagnosis codes not specific to DGBI. To reflect clinical coding practices, functional nausea and vomiting disorders constituted a composite outcome defined by hospital contacts with diagnosis codes for infant regurgitation, nausea, vomiting, rumination, and flatulence; functional abdominal pain disorders by hospital contacts for infant colic, functional dyspepsia, irritable bowel syndrome, and abdominal pain not otherwise specified. Functional constipation was defined by hospital contacts with constipation and prescription fills for a laxative. Although laxatives are also available over-the-counter, a subsidy is available for chronic constipation in children if dispensed on prescription. Individual disorders were evaluated as secondary outcomes. For symptom-based diagnosis codes (e.g., vomiting), we limited our definitions to diagnoses given in outpatient clinics to leave out symptom-based diagnoses related to acute conditions. Detailed information on codes used to define outcomes are available in the supplementary material (S-Table 1).

Statistical analyses

Follow-up began at birth and ended on the day of the outcome, censoring, migration, death, age 15 years or end of follow-up on December 31, 2018, whichever occurred first. Propensity score-based standardized mortality ratio (SMR) weighting was applied to adjust for potential confounders. Thus, we calculated the conditional probability of belonging to each exposure group using logistic regression given prespecified covariates including demographics, maternal life-style factors, socioeconomic background, parental history of psychiatric disease and DGBIs as well as proxies for the severity of the maternal health disorder, as detailed in Supplementary Table 2. Exposed children were assigned the weight of 1, while unexposed children were weighted according to the propensity score odds, creating a pseudo-population among unexposed children with covariate distribution equal to that observed in the exposed group [18]. Covariate imbalances were assessed using standardized mean differences (SMD) with differences less than 0.1 considered negligible [19]. For covariates with missing values, missing were coded as a separate category. BMI and smoking had a proportion of missing above 5%, but these were assumed missing-at-random because these values were not mandatorily reported into the Danish Medical Birth Registry until the early 2000s.

We estimated cumulative incidences for each primary and secondary outcome in the weighted cohorts using the Kaplan-Meier method. Cox proportional hazard regression was used to estimate hazard ratios (HR) with 95% confidence intervals (CI) after 1, 5, 10 and 15 years of follow-up, using child age as the underlying time scale. To account for dependence between siblings, we used robust estimation of standard errors.

Sensitivity analyses

Additional analyses were performed to test robustness of our findings and to address different sources of potential bias. First, to reduce potential confounding by indication, the definition of SSRI discontinuation was restricted to mothers with a filled prescription for an SSRI from one year until 91 days before the start of pregnancy. Second, analyses were restricted to children born to mothers with a documented psychiatric disorder (ICD-10; F00-F99) within two years prior to pregnancy. Third, to reduce exposure misclassification resulting from mothers redeeming but not taking SSRIs, prenatal SSRI exposure was redefined as children born to mothers who filled at least two prescriptions for SSRIs during pregnancy. This was based on the premise that patients who obtain refills of their prescription, are more likely to also consume. Fourth, to minimize effects of exposure to severe psychopathology and polypharmacy, children were excluded if their mother filled prescriptions for other psychotropic medications (ATC codes N05 and N06 excluding N06AB) during pregnancy. Fifth, to investigate the specificity of intrauterine exposure to SSRI, we repeated analyses using paternal SSRI use during the index pregnancy as a negative control exposure and compared children of fathers who used SSRI during pregnancy to those of fathers who discontinued SSRI use prior to pregnancy. Sixth, to reduce outcome misclassification resulting from use of DGBI diagnoses codes during diagnostic work-up of other GI disorders or likely non-functional etiology of symptoms, children were censored if diagnosed with such a disorder during follow-up or at the time of their DGBI diagnosis if they received such a diagnosis within 12 months of the DGBI diagnosis code. Specific censoring criteria are listed in supplementary S-Table 3. Seventh, to test the specificity of codes used for DGBI, we required at least two contacts with the same diagnosis code or at least two laxative prescription fills within one year, using the day of the second occurrence as the outcome date. Finally, as a post-hoc analysis to mitigate effects of infant feeding, we did not start follow-up for functional constipation until the child's first birthday. Similarly, to increase specificity of the diagnosis codes used for functional abdominal pain disorders, follow-up was not started until age six years.

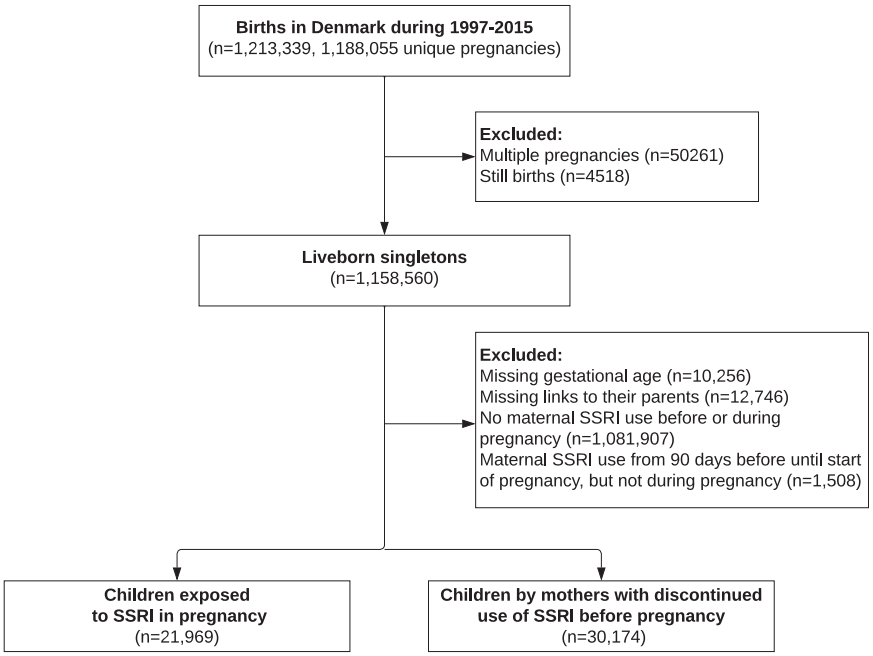

Fig. 1 Flow chart of Cohort. Flow chart showing the cohort construction from all live children in Denmark during 1997-2015.

RESULTS

Among the 1,213,339 children born in Denmark during 1997–2015, we identified 21,969 singleton children (1.8%) born to mothers who used SSRIs during pregnancy. For comparison, we included 30,174 children born to mothers who had discontinued use of SSRIs prior to pregnancy (Fig. 1).

Mothers who used SSRIs during pregnancy and those who discontinued use prior to pregnancy did not differ significantly on demographic, socioeconomic and pregnancy-related characteristics (Table 1). Prior to adjustments, mothers using SSRIs were more likely to have a history of hospital-diagnosed psychiatric disorders, increased numbers of psychiatric contacts during pregnancy and more prescriptions for other psychotropic drugs during pregnancy than the discontinuers. These group differences were eliminated after propensity score weighting [SMD < 0.1 for all covariates, Table 1)].

SSRI exposure and DGBI in children

Overall, 5,669 children (10.8%) had a DGBI outcome during follow-up (mean age at last follow-up, 9.1 years). The estimated 15-year cumulative incidence of DGBIs was 15.5% (95% confidence interval 14.9–16.2) in children exposed to SSRIs and 14.7% (14.0–15.4) in the discontinuation group (Fig. 2) with an overall adjusted hazard ratio (aHR) of 1.08 [1.02–1.14], (Table 2).

When each DGBI class was tested individually, the association was present for functional constipation (aHR 1.19 [1.10–1.28]) but not functional nausea and vomiting (aHR 0.97 [0.83–1.13]), functional abdominal pain (aHR 0.90 [0.81–1.00]) disorders, nor functional diarrhea (aHR 0.72 [0.43–1.19] (Table 2). Results were similar when stratified by child sex (Supplementary Table 4).

Specificity to functional constipation

The incidence of functional constipation was higher for children with prenatal exposure to SSRI than in the discontinuation group throughout childhood (Fig. 2) with statistically increased HRs after 1, 5, 10 and 15 years of follow-up (Supplementary Table 5).

The associations with functional constipation were significant regardless of whether the outcome was characterized by outpatient diagnostic codes (aHR 1.17 [1.08–1.27]) or by laxative prescriptions (aHR 1.25 [1.10–1.43]) (Table 2). Estimates further increased in magnitude when requiring at least two separate outpatient diagnoses or laxative prescriptions within a 12-month period (aHR 1.27 [1.06–1.52] and 1.59 [1.21–2.09], Table 3), supportive of the notion that gestational SSRI exposure increases the risk of developing chronic constipation.

Finally, to rule out the possibility that a constipation diagnosis was secondary to other medical conditions e.g. inflammatory bowel disease, food intolerances or psychiatric disorders, we repeated the main analysis censoring any children diagnosed with a disorder that was likely to cause chronic GIproblems. As shown in Supplementary Table 6, this had no impact on the estimated risk of functional constipation (aHR 1.18 [1.08,1.28]).

Sensitivity analyses

To reduce misclassification resulting from women being prescribed but not taking the medications, we repeated the analyses in the subset of exposures where the mother filled at least two SSRI prescriptions within the pregnancy window (69%, n = 15,188; Supplementary Tables 7, 8). Using this exposure definition increased associations slightly with an aHR of 1.24 [1.14–1.35] for functional constipation, compared with the discontinuation group. The associations between SSRI exposure and functional constipation were also increased when restricting analyses to children born to mothers with a documented psychiatric disorder in pregnancy (aHR: 1.34 [1.18–1.51]) or excluding children of mothers with psychotropic polypharmacy (aHR: 1.23 [1.14–1.33]). Redefining discontinuation to use of SSRIs within one year to 3 months before pregnancy had no impact on results (aHR: 1.19 [1.09–1.30]) (Supplementary Table 8).

Finally, to test specificity to SSRI exposure in utero, we used paternal SSRI exposure during pregnancy as a negative control. Paternal SSRI exposure was not associated with functional constipation (aHR 1.07 [0.98–1.18] (Supplementary Table 8) in the children.

The post-hoc analysis, starting follow-up at age one to mitigate the effects of infant feeding on functional constipation, did not alter study findings (Supplementary Table 9). Similarly, the sensitivity analysis for functional abdominal pain disorders, limited to children followed from six years of age, did not affect the main findings though it was limited by low number of events of

Table 1. Characteristics of the study cohort according to SSRI exposure during pregnancy.

	SSRI exposed (n = 21,969)	Unexposed (n = 30,174)	SMD	Unexposed weighted (n = 22,208)	SMD
Maternal demographic characteristics					
Maternal age, Median (IQR, years)	30 (26–34)	29 (26–33)	0.12	30 (26–34)	0.00
Marital status					
Unmarried	12,417 (57)	17,708 (59)	0.04	12,675 (57)	0.01
Married/registered partnership	9551 (43)	12,466 (41)	0.04	9,533 (43)	0.01
Employment status					
Unemployed	10,302 (47)	13,715 (45)	0.03	10,793 (49)	0.03
Student	1297 (5.9)	1875 (6.2)	0.01	1,293 (5.8)	0.00
Employed	10,022 (46)	14,094 (47)	0.02	9,782 (44)	0.03
Self-employed	347 (1.6)	488 (1.6)	0.00	338 (1.5)	0.00
Highest education					
Short (7-10 years)+Vocational	12,698 (59)	18,356 (62)	0.06	12,991 (60)	0.01
Medium (11–13 years)	3115 (14)	4170 (14)	0.01	3,187 (15)	0.00
Long (13+ years)	5751 (27)	7085 (24)	0.06	5,625 (26)	0.02
Income					
First quartile (Lowest)	8386 (38)	11,528 (38)	0.00	8,688 (39)	0.02
Second quartile	8471 (39)	11,411 (38)	0.02	8,560 (39)	0.00
Third quartile	3674 (17)	5157 (17)	0.01	3,574 (16)	0.02
Forth quartile (Highest)	1422 (6.5)	2055 (6.8)	0.01	1,370 (6.2)	0.01
Pregnancy					
Parity					
First childbirth	9624 (44)	13,846 (46)	0.04	9,724 (44)	0.00
2–3 childbirth	10,662 (49)	14,073 (47)	0.04	10,745 (49)	0.00
4+ childbirth	1610 (7.4)	2145 (7.1)	0.01	1,665 (7.5)	0.01
Pre-pregnancy BMI					
Underweight	796 (4.5)	1148 (5.0)	0.01	816 (4.6)	0.00
Normal weight	9431 (53)	12,462 (54)	0.03	9,486 (53)	0.00
Overweight	4073 (23)	5290 (23)	0.03	4,093 (23)	0.00
Obese, class 1	1983 (11)	2452 (11)	0.03	2,009 (11)	0.00
Obese, class 2 & 3	1409 (8.0)	1759 (7.6)	0.02	1,454 (8.1)	0.01
Smoking in pregnancy					
No smoking	14,859 (71)	20,483 (72)	0.01	14,869 (70)	0.02
Light smoking (1–10 cigarettes per day)	4112 (20)	5603 (20)	0.00	4,205 (20)	0.01
Heavy smoking (11+ cigarettes per day)	2025 (9.6)	2487 (8.7)	0.03	2,149 (10)	0.02
Parental medical history					
Psychiatric disease					
Maternal	8765 (40)	7503 (25)	0.33	9,089 (41)	0.02
Paternal	1265 (5.8)	1565 (5.2)	0.03	1,296 (5.8)	0.00
DGBI					
Maternal	944 (4.3)	1234 (4.1)	0.00	953 (4.3)	0.00
Paternal	302 (1.4)	426 (1.4)	0.01	298 (1.3)	0.00
Maternal health utilization in pregnancy					
Number of psychiatric contacts	0 (0-0)	0 (0-0)	0.28	0 (0-0)	0.03
Dispensing of other psychotropics drug	4688 (21)	2796 (9.3)	0.34	5,136 (23)	0.04
Number of hospital visits not related to psychiatry	1 (1–2)	1 (1–2)	0.03	2 (1–2)	0.00
Child characteristics					
Birth year					
1997–2003	3573 (16)	6089 (20)	0.10	3,486 (16)	0.02
2004–2009	8807 (40)	10,939 (36)	0.08	9,075 (41)	0.02
2010–2015	9589 (44)	13,146 (44)	0.00	9,647 (43)	0.00

Table 1. continued

	SSRI exposed (n = 21,969)	Unexposed (n = 30,174)	SMD	Unexposed weighted (n = 22,208)	SMD
Sex					
Male	11,343 (52)	15,581 (52)	0.00	11,511 (52)	0.00
Female	10,626 (48)	14,593 (48)	0.00	10,697 (48)	0.00

Baseline characteristics of children prenatally exposed to SSRIs and the unexposed comparator group of children to mothers who discontinued SSRI use before pregnancy.
Data are n(%) unless stated otherwise.
Maternal pre-pregnancy BMI, smoking in pregnancy and education had missing of 21.8%, 5.0% and 1.9%. Parity, marital status, and income all had missing values of less than 0.5%.
SMD standardized mean difference, *IQR* interquartile range, *BMI* body mass index, *DGBI* disorder of gut–brain interaction.

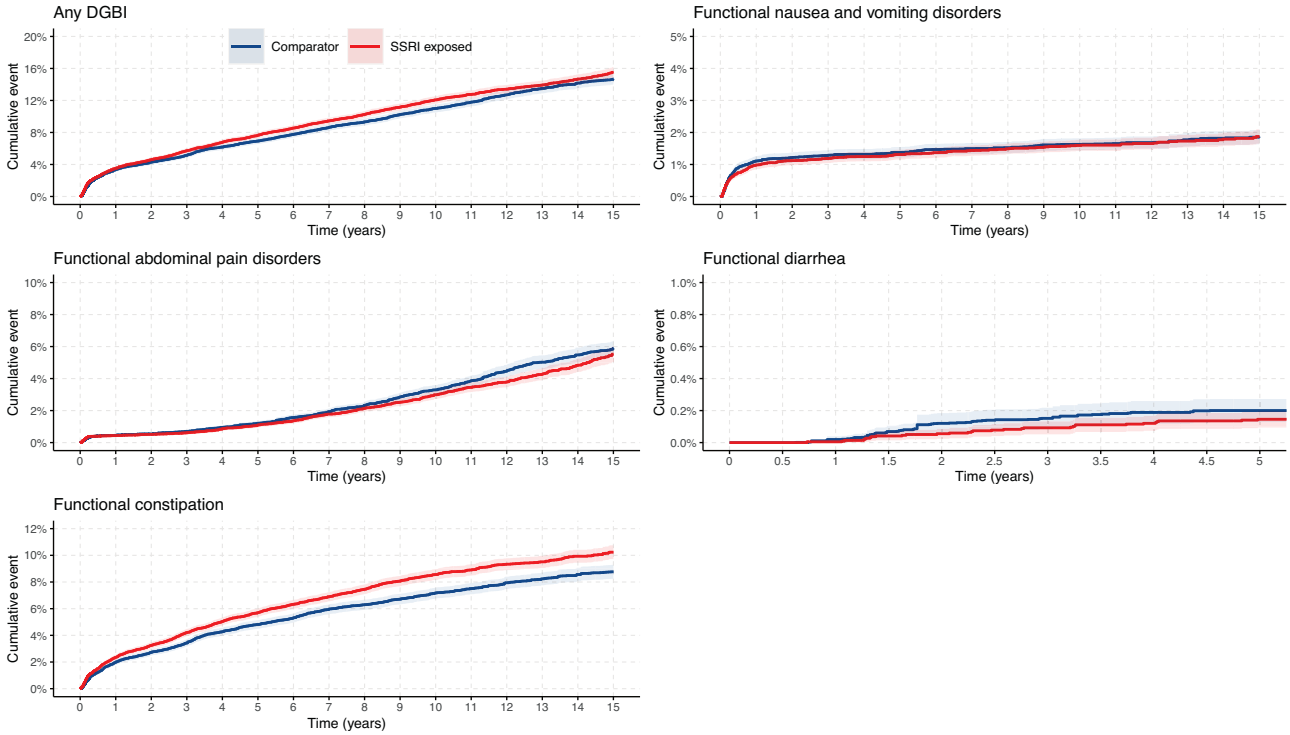

Fig. 2 Cumulative incidence of disorders of gut-brain interaction according to SSRI exposure status. Cumulative incidence of any disorder of gut-brain interaction, functional nausea and vomiting disorders, functional abdominal pain disorders, functional constipation and functional diarrhea as a function of child age in weighted cohorts of children exposed to SSRIs in utero and unexposed children born of mothers who discontinued SSRI use prior the pregnancy. Curves are adjusted for demographics, socioeconomic background, parental history of psychiatric disease and DGBIs as well as proxies for the severity of the maternal health disorder. Shaded areas represent 95% confidence intervals. For risk tables for all cumulative incidence graphs, please see Supplementary S-Fig. 1.

functional dyspepsia and irritable bowel syndrome (Supplementary Table 10)

DISCUSSION

In this study, we tested prenatal exposure to SSRIs as a risk factor for childhood DGBI based on the following premises: maternal perinatal depression is associated with an increased risk of DGBI in the children [20]; SSRIs are the most commonly prescribed antidepressants during pregnancy [21, 22] and early exposure to SSRIs or other serotonin modulators (e.g., genetic) can impact both brain and gut development to induce long-term changes in predisposition to constipation and visceral pain [8, 13, 23, 24]. Prior clinical studies that sought to link prenatal SSRI exposure to GI outcomes had extensive limitations including lack of control for maternal depression, they key factor for which SSRIs are prescribed.

Using a longitudinal cohort constructed from Danish nationwide register data, we showed that children prenatally exposed to SSRIs had an increased risk for DGBI, which was almost exclusively accounted for by functional constipation. Further analyses demonstrated that the associations with constipation: (i) were significant after accounting for measured underlying differences in maternal depression, other psychopathology and family characteristics; (ii) were found regardless of whether constipation was indexed using diagnostic codes or laxative prescriptions (which has implications for future research where only specific types of data may be available); (iii) began in the first year of life and persisted through early adolescence; (iv) increased in magnitude when requiring two or more codes or laxative prescriptions within a year (consistent with a chronic phenotype); and (v) were not attributable to organic medical conditions that could affect gut structure or function. Finally, associations were not observed for other DGBIs or when paternal SSRI use in

Table 2. Absolute numbers and propensity score weighted hazard ratios of DGBI outcomes in children exposed to SSRI in utero and children of mothers who discontinued use of SSRIs prior to pregnancy.

Outcome	Exposure	Events	Person Yrs	Incidence rate	Crude HR (95% CI)	Adjusted HR[a] (95% CI)z
Any DGBI						
	No	3,167	275,977	11.5 (11.1–11.9)	1.00 (ref)	1.00 (ref)
	Yes	2,532	197,670	12.8 (12.3–13.3)	1.11 (1.05–1.17)	1.08 (1.02–1.14)
Functional nausea and vomiting disorders						
	No	477	290,345	1.6 (1.5–1.8)	1.00 (ref)	1.00 (ref)
	Yes	343	209,898	1.6 (1.5–1.8)	0.99 (0.86–1.14)	0.97 (0.83–1.13)
Infant regurgitation						
	No	249	29,848	8.3 (7.4–9.4)	1.00 (ref)	1.00 (ref)
	Yes	164	21,752	7.5 (6.5–8.8)	0.90 (0.74–1.10)	0.89 (0.72–1.10)
Functional nausea, vomiting or rumination						
	No	235	292,133	0.8 (0.7–0.9)	1.00 (ref)	1.00 (ref)
	Yes	183	211,132	0.9 (0.7–1.0)	1.07 (0.89–1.30)	1.05 (0.84–1.32)
Functional abdominal pain disorders						
	No	1,025	288,875	3.5 (3.3–3.8)	1.00 (ref)	1.00 (ref)
	Yes	661	209,195	3.2 (2.9–3.4)	0.90 (0.81–0.99)	0.90 (0.81–1.00)
Infant colic						
	No	79	15,002	5.3 (4.2–6.6)	1.00 (ref)	1.00 (ref)
	Yes	67	10,922	6.1 (4.8–7.8)	1.16 (0.84–1.61)	1.29 (0.91–1.82)
Functional dyspepsia						
	No	17	293,112	0.1 (0.0–0.1)	1.00 (ref)	1.00 (ref)
	Yes	16	211,943	0.1 (0.0–0.1)	1.32 (0.66–2.64)	1.48 (0.73–3.01)
Irritable bowel syndrome						
	No	9	293,210	0.0 (0.0–0.1)	1.00 (ref)	1.00 (ref)
	Yes	n < 5[b]	211,986	–	–	–
Functional abdominal pain not specified otherwise						
	No	933	289,587	3.2 (3.0–3.4)	1.00 (ref)	1.00 (ref)
	Yes	591	209,732	2.8 (2.6–3.1)	0.88 (0.80–0.98)	0.88 (0.78–0.98)
Functional constipation						
	No	1,970	282,194	7.0 (6.7–7.3)	1.00 (ref)	1.00 (ref)
	Yes	1,768	201,651	8.8 (8.4–9.2)	1.24 (1.17–1.33)	1.19 (1.10–1.28)
Diagnosis of constipation						
	No	1,544	284,971	5.4 (5.2–5.7)	1.00 (ref)	1.00 (ref)
	Yes	1,388	204,199	6.8 (6.4–7.2)	1.24 (1.16–1.34)	1.17 (1.08–1.27)
Prescription laxative use						
	No	598	289,671	2.1 (1.9–2.2)	1.00 (ref)	1.00 (ref)
	Yes	558	208,583	2.7 (2.5–2.9)	1.29 (1.15–1.45)	1.25 (1.10–1.43)
Functional diarrhea						
	No	56	145,074	0.2 (0.1–0.2)	1.00 (ref)	1.00 (ref)
	Yes	31	105,712	0.1 (0.1–0.2)	0.76 (0.49–1.18)	0.72 (0.43–1.19)

DGBI disorders of gut-brain interaction, *SSRI* selective serotonin reuptake inhibitors, *HR* hazard ratio.
[a]HRs in propensity-score weighted cohorts. The propensity score included covariates on demographics, maternal life-style factors, socioeconomic background, parental medical history, and proxies for the severity of the maternal mental health disorder. The full list of covariates is available in Supplementary Table 2.
[b]Due to Danish data privacy regulations counts less than five cannot be reported.

pregnancy was used as a negative control, suggesting specificity of both exposure and outcome.

Importantly, our results support the comprehensive findings of preclinical studies, demonstrating that antenatal SSRI exposure, and other early-life manipulations of serotonin homeostasis, result in distal colon abnormalities most indicative of a pelvic outlet-associated constipation (the most common type of functional constipation in humans), that persists long-term [6–8, 25]. While this could be secondary to ENS developmental abnormalities seen in murine models, these findings cannot be easily confirmed in human studies because of the inability to remove full thickness colon, which includes the ENS, in healthy humans with constipation. Nonetheless, because the studies in mice have now been found to align in important functional ways with human data

Table 3. Absolute numbers and propensity score weighted hazard ratios of DGBI outcomes in children exposed to SSRI in utero and children of mothers who discontinued use of SSRIs prior to pregnancy when requiring at least two diagnoses of a DGBI or two prescriptions for a laxative within 12 months.

Outcome	Exposure	Events	Person Yrs	Incidence rate	Crude HR	Adjusted HR
Any DGBI						
	No	670	289,705	2.3 (2.1–2.5)	1.00 (ref)	1.00 (ref)
	Yes	601	208,876	2.9 (2.7–3.1)	1.24 (1.11–1.38)	1.20 (1.06–1.36)
Functional nausea and vomiting disorders						
	No	117	292,438	0.4 (0.3–0.5)	1.00 (ref)	1.00 (ref)
	Yes	81	211,483	0.4 (0.3–0.5)	0.95 (0.72–1.26)	0.97 (0.72–1.31)
Infant regurgitation						
	No	91	29,963	3.0 (2.5–3.7)	1.00 (ref)	1.00 (ref)
	Yes	59	21,826	2.7 (2.1–3.5)	0.89 (0.64–1.23)	0.96 (0.68–1.34)
Functional nausea, vomiting or rumination						
	No	26	293,111	0.1 (0.1–0.1)	1.00 (ref)	1.00 (ref)
	Yes	22	211,897	0.1 (0.1–0.2)	1.18 (0.67–2.08)	1.00 (0.52–1.89)
Functional abdominal pain disorders						
	No	155	292,676	0.5 (0.5–0.6)	1.00 (ref)	1.00 (ref)
	Yes	98	211,618	0.5 (0.4–0.6)	0.89 (0.69–1.14)	0.95 (0.73–1.25)
Infant colic						
	No	18	15,024	1.2 (0.8–1.9)	1.00 (ref)	1.00 (ref)
	Yes	12	10,942	1.1 (0.6–1.9)	0.92 (0.44–1.90)	1.17 (0.55–2.47)
Functional dyspepsia						
	No	n < 5[a]	293,227	–	–	–
	Yes	n < 5[a]	211,980	–	–	–
Irritable bowel syndrome						
	No	n < 5[a]	293,238	–	–	–
	Yes	n < 5[a]	211,993	–	–	–
Function abdominal pain not specified otherwise						
	No	134	292,788	0.5 (0.4–0.5)	1.00 (ref)	1.00 (ref)
	Yes	85	211,702	0.4 (0.3–0.5)	0.89 (0.68–1.18)	0.94 (0.70–1.25)
Functional constipation						
	No	428	290,985	1.5 (1.3–1.6)	1.00 (ref)	1.00 (ref)
	Yes	441	209,701	2.1 (1.9–2.3)	1.42 (1.24–1.62)	1.32 (1.13–1.54)
Diagnosis of constipation						
	No	336	291,481	1.2 (1.0–1.3)	1.00 (ref)	1.00 (ref)
	Yes	327	210,282	1.6 (1.4–1.7)	1.34 (1.15–1.56)	1.27 (1.06–1.52)
Prescription laxative use						
	No	114	292,676	0.4 (0.3–0.5)	1.00 (ref)	1.00 (ref)
	Yes	143	211,299	0.7 (0.6–0.8)	1.72 (1.34–2.20)	1.59 (1.21–2.09)
Functional diarrhea						
	No	n < 5	145,218	–	–	–
	Yes	6	105,776	0.1 (0.0–0.1)	–	–

Cumulative incidence curves and risk tables for each secondary outcome in available in Supplementary Fig. 2.
DGBI disorders of gut-brain interaction, *SSRI* selective serotonin reuptake inhibitors, *HR* hazard ratio.
[a]HRs in propensity-score weighted cohorts. The propensity score included covariates on demographics, maternal life-style factors, socioeconomic background, parental medial history and proxies for the severity of the maternal mental health disorder. The full list of covariates is available in Supplementary Table 2.
[b]Due to Danish data privacy regulations counts less than five cannot be reported.

through this study, these findings together build a stronger scientific premise for studying murine models as a way to potentially identify underlying mechanisms linking in utero SSRI exposure to DGBIs. When considering the translation of preclinical data published thus far, however, it is also important to consider the multiple mechanisms by which SSRIs may impact DGBI development in humans. Although we suggest abnormalities in ENS development as a potential etiology underlying the observed effects demonstrated in this study, serotonin has also been shown to play important roles in gut sensation, which is key for both homeostatic GI function and DGBI pathophysiology, including for pelvic outlet dysfunction-induced constipation. This may involve mechanisms outside of the intrinsic ENS, including gut enterochromaffin cells and/or extrinsic primary afferent neurons

[26–28]. Such mechanisms may explain why only functional constipation was affected by in utero SSRI exposure in this study and now warrant further investigation in translational research settings.

The finding that in utero SSRI exposure is associated with an increased risk of developing functional constipation also has potentially important clinical implications. Functional constipation accounts for ~95% of constipation diagnoses [29] and is the most commonly diagnosed pediatric DGBI, with a prevalence rate of ~10–15% [30, 31]. Functional constipation has been associated with decreased health-related quality of life measures as well as progressively increasing healthcare costs [32, 33]. Understanding novel risk factors involved in the development of functional constipation, and associated underlying mechanisms, are thus important foundational steps to providing evidence-based clinical guidance and defining novel targets for treatment.

There are several strengths of this study. The scientific premise based on extensive preclinical data is a unique strength and exemplifies the power in studying preclinical model systems in regard to SSRIs and intestinal function. Furthermore, use of the Danish nationwide registers allowed creation of discontinued SSRI use as a more balanced comparator group, the longest follow-up period to date, and minimized the risk of selection bias. Finally, the study relied on physician diagnoses and filled prescriptions rather than either maternal or child recall, converging outcomes (e.g., constipation diagnosis and laxative use) and the use of propensity scores to minimize group differences between exposed and unexposed children.

The study also has some limitations. While the use of propensity scores minimized group differences, unobserved confounding cannot be fully eliminated. For example, mothers in treatment with SSRIs during pregnancy may have more severe underlying psychiatric illness than mothers discontinuing SSRI treatment before pregnancy. Second, diagnoses are drawn from hospital visits and likely underrepresent milder cases that do not warrant specialized medical attention. Also, while a subsidy is available for laxatives filled by prescription, laxatives are also sold over the counter and number of laxative users in childhood and adolescence is likely underestimated. Such misclassifications are, however, likely non-differential. Third, overall prevalence for some DGBIs was low. The largest cross-sectional study utilizing Rome-IV criteria showed that DGBIs affect approximately 25% of children and adolescents in the U.S.; however, the data was acquired solely utilizing screens, rather than physician-diagnosed DGBIs [34]. The observed specificity for functional constipation could also reflect limited power to observe associations for other DGBI. For example, we did not detect associations with IBS which was underreported due to national coding practices; in Denmark, the diagnosis code for IBS was not routinely administered in pediatric departments until the mid-2010s. Thus, children meeting criteria for IBS would likely be registered with diagnosis codes for defecation disorders or abdominal pain. Also, we were not able to estimate valid dose-response associations for prenatal SSRI exposure and childhood DGBI. Large interindividual variations in the effective dose for SSRI treatment complicates the estimation of dose-response associations during pregnancy as the available registry data only includes package size and dose per tablet, leaving the actual dose used unknown. We did, however, observe an enhancement of the association between SSRI exposure and functional constipation when requiring at least two prescription fills for an SSRI suggestive of a dose-response effect. It is also important to note that the risk of DGBIs in childhood is influenced by a number of factors during childhood including nutrition, anxiety and other gastrointestinal disorders. As such factors are potential mediators in the relationship between SSRI exposure and risk of DGBIs, these were not included in the main analysis [35, 36]. We did, however, conduct sensitivity analyses censoring on such conditions as well as factors that contribute to DGBI outcomes during childhood (e.g. abuse, gastroenteritis) which had no impact on results. Finally, while the study population was unselected and should generalize to the Danish population, it is yet to be determined whether the findings generalize to other populations or countries with different healthcare systems or prescription practices.

This study provides a foundation for more comprehensive investigation into how developmental exposure to SSRIs and other serotonin-modulating drugs affect predisposition to gastrointestinal disorders in exposed individuals. There are multiple serotonin-altering medications prescribed to pregnant women and children during times at which intestinal neurodevelopment and/or plasticity are continuing to be impacted. Serotonin modulation is not only an important feature of antidepressants, but also multiple other medications used to treat conditions such as migraine headaches, and body dysmorphic disorders [37, 38]. A greater understanding of the underlying pathophysiology linking in utero SSRI exposure to DGBI outcomes is thus an important, expansive research direction. There are many additional important factors that should be considered in future studies. For example, DGBI diagnoses frequently co-aggregate in families with anxiety and depression. A better understanding of their co-development in the earliest years, and the role of serotonin therein, may help lead to better prevention or development of novel therapies for the treatment of DGBI that could have concurrent benefits for mental health. Although usually much smaller in scope, a prospective, longitudinal birth cohort study would be relevant to confirm our findings as well as enable the investigation of differences in disease severity of DGBIs and the role of many potential confounding factors, such as maternal smoking, other exposures, and maternal/infant nutrition, to provide a broader understanding of how serotonin impacts intestinal neurodevelopment and DGBI outcomes.

Our finding that functional constipation is increased following prenatal SSRI exposure should not be taken as a directive to change clinical practice or current recommendations for antidepressant treatment in pregnancy. Treating depression in pregnancy is a high priority, as untreated depression can have significant adverse consequences on both the mother and the fetus. Although our study shows a specific and consistent association between prenatal SSRI exposure and functional constipation across multiple analyses, the study cannot confirm causality. The study, however, supports preclinical research implicating serotonin in the pathogenesis of DGBI symptoms and highlights the importance of studying the long-term impact of maternal depression and fetal SSRI exposure on the development of common gastrointestinal disorders. This study should thus serve as a foundation on which to base further research but should not guide clinical decisions until more extensive data can be obtained.

DATA AVAILABILITY

Because of Danish data privacy regulations, individual level data cannot be shared directly by the authors. De-identified data from Danish healthcare registries can be made available for authorized researchers upon application to the Danish Health Data Authority. The underlying code used to produce study results is available upon request to the corresponding author.

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