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Sterol pathway disruption in pregnancy: a link to autism

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Cholesterol is a vital molecule, especially during embryonic development. Disruption of the cholesterol biosynthetic pathway can arise from pathogenic genetic variants or exposure to prescription medications. We investigated the relationship between fifteen sterol biosynthesis inhibiting medications (SBIM) prescribed during pregnancy and the incidence of autism spectrum disorders (ASD) in the resulting offspring. Our study of the Epic Cosmos database queried linked child and maternal health records for births between 2014 and 2023 with follow-up to December 2025. The study included 6,135,213 children with linked maternal health records. We evaluated the incidence of ASD associated with maternal prescription of aripiprazole, atorvastatin, bupropion, buspirone, fluoxetine, haloperidol, metoprolol, nebivolol, pravastatin, propranolol, rosuvastatin, sertraline, simvastatin, and/or trazodone during pregnancy using Cox proportional hazard modeling. We found that exposure to at least one SBIM during pregnancy was associated with a 1.47-fold (95% CI 1.45–1.49) increased risk of an ASD after adjusting for potential confounders. For each additional SBIM co-prescribed, there was a 1.33 (95% CI 1.32–1.34) times increased risk of ASD, reaching 2.33-fold risk when 4 or more SBIMs were prescribed simultaneously. In the ten years of our cohort, we identified 234,971 (3.8%) children with an ASD diagnosis. Of the children with an ASD diagnosis, 35,152 (15.0%) of the mothers were prescribed at least one SBIM during pregnancy. Notably, in our dataset, utilization of SBIM medications by pregnant women increased from 4.6% in 2014 to16.8% in 2023. In conclusion, SBIMs may be potentially harmful to the developing fetus. Given that these drugs account for over 400 million prescriptions annually in the U.S. we recommend these findings be considered before prescribing SBIM medications during pregnancy.

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INTRODUCTION

Cholesterol is essential for life, serving as a critical structural component of all cells. The sterol biosynthesis pathway provides precursors for numerous vital molecular processes [1–3]. Cholesterol biosynthesis is particularly critical during intrauterine development in all vertebrates [4, 5]. Initially, maternal circulation supplies sterols, but around 19–20 weeks of gestation the fetal brain – the most cholesterol-rich organ in the body – begins its own sterol biosynthesis [6]. Disruptions to this process can arise from both genetic factors and external influences [7–10]. For example, pathogenic variants in sterol biosynthesis genes lead to developmental and intellectual disabilities such as Smith-Lemli-Opitz syndrome (SLOS), lathosterolosis, and desmosterolosis [8].

Among these, SLOS is the most studied and well-understood. It is characterized by intellectual disability and complex dysmorphologies [11–13]. SLOS arises from two pathogenic variants in the *DHCR7* gene which produces 7-dehydrocholesterol reductase, an enzyme that catalyzes the final step in cholesterol biosynthesis: conversion of 7-dehydrocholesterol (7-DHC) to cholesterol [14, 15]. The pathology of SLOS is produced by two synergistic mechanisms: a reduction in cholesterol levels, coupled with an accumulation of intermediates such as 7-DHC [16]. Notably, 7-DHC is the most oxidizable lipid [17–20] and gives rise to the formation of reactive autoxidation sterols which disrupt cell viability, differentiation, growth [21–25], and potentially vitamin D metabolism [26].

Approximately 75% of individuals with SLOS are diagnosed with an autism spectrum disorder (ASD) [27]. In addition, recent publications highlight abnormalities in cholesterol metabolism in children with ASDs [28, 29]. The incidence of ASDs has risen sharply over the past few decades [30, 31]. While better diagnostic practices, broader Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, and increased reach and testing have contributed to this increase, there is growing belief that environmental factors also play a role [32, 33]. One example is the considerable literature and debate around the impact of maternal antidepressant use in pregnancy on ASD risk [34–38], which is especially notable given the emerging data on the relationship between cholesterol homeostasis and the risk of developing depression [39].

The sterol biosynthesis pathway can also be disrupted by commonly prescribed medications [40–43]. In 2013, several individuals - nearly all of which had developmental delays and/or behavioral abnormalities - were noted to have SLOS-like elevation of 7-DHC levels [44]. However, genetic testing revealed

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no pathogenic variants in the DHCR7 gene. Instead, all patients were receiving aripiprazole or trazodone. The ability of these medications to inhibit DHCR7 and block the conversion of 7-DHC to cholesterol was later confirmed in vitro and in vivo in mouse models [45–47], human dermal fibroblasts [9], and postmortem brain analyses [48]. Follow-up studies identified several other commonly prescribed sterol biosynthesis inhibiting medications (SBIM), including haloperidol, sertraline, aripiprazole, cariprazine, trazodone, bupropion, buspirone, fluoxetine, propranolol, nebivolol and metoprolol [40–43, 49]. Most of these findings have been consistently validated across various in vitro and in vivo models, including in human biomaterials [50, 51]. Despite a 2016 study by Bolland and Tatonetti [9] concluding that first-trimester exposure to pharmaceuticals with DHCR7-inhibitory effects resulted in outcomes similar to those of known teratogens, there has been no comprehensive investigations into the outcomes of prenatal sterol biosynthesis inhibition.

Using the Epic Cosmos electronic medical record database with over 10 million paired maternal and child records, we hypothesized that exposure to SBIMs - regardless of their primary therapeutic indication - would increase the risk of ASD [52]. We queried four statins, which inhibit HMGCR, the first enzyme in the cholesterol biosynthesis pathway [53]. We also assessed eleven medications with post-lanosterol inhibitory side effects, which inhibit the final steps of cholesterol biosynthesis.

MATERIALS AND METHODS

Study setting

Data used in this cohort study came from Epic Cosmos [52, 54, 55], a de-identified, de-duplicated dataset created in collaboration with a community of Epic health systems representing more than 300 million patient records from over 1880 hospitals and 42,400 clinics. The database was accessed for this study between March 1, 2025 and January 26, 2026. This study was determined exempt by the University of Nebraska Medical Center's Institutional Review Board.

Cohort construction and inclusion criteria

This study included all paired maternal-child dyads with a birth between January 1, 2014, and December 31, 2023, with follow-up to January 14, 2026. To ensure sufficient follow-up for ASD ascertainment, children were required to have at least one healthcare encounter documented in Cosmos ≥ 18 months after birth [56]. We excluded children delivered at non-U.S. health systems, those with missing sex, and those whose mothers were also prescribed the known teratogen valproic acid during the included pregnancy. Due to low missingness for the primary covariates of interest, we performed complete case analysis.

Outcome definition

The primary outcome was ASD, defined as any of 51 diagnostic codes relating to ASD (Supplemental Material 1). The outcome was treated as a time-to-event variable, measured from birth date to the first qualifying ASD diagnosis, censored at the last follow up of the children (minimum of 18 months after birth).

Exposure variables

The primary exposure variables were medications with preclinical and/or translational data suggesting post-lanosterol biosynthesis inhibition (i.e. aripiprazole, cariprazine, haloperidol, trazodone, bupropion, sertraline, buspirone, fluoxetine, metoprolol, propranolol, and nebivolol) [40–43, 49] or hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitory effects (i.e. atorvastatin, simvastatin, rosuvastatin, pravastatin) [57, 58]. The individual prescription names are listed in Supplemental Material 2, and their mechanism of action and indications are described in Supplemental Material 3. Notably, this is not an exhaustive list of medications with potential sterol biosynthesis side effects. Other CNS-specific and somatic medications may also be SBIMs, and this should be investigated in further follow-up studies.

Medication exposures were identified using Cosmos's pregnancy linkage logic, which flags prescriptions, dispensations, administrations, and orders as overlapping with pregnancy if any part of the medication duration intersects with the gestational period (Supplemental Material 4). Prescribed and dispensed medications were considered exposures if documented during pregnancy. For medication orders, exposures were included if the start or stop date occurred within the pregnancy window. This approach captures both medications initiated during pregnancy and those initiated before conception but still active during gestation.

Composite exposure variables were constructed to classify patients by the number of unique SBIMs received during pregnancy (≥ 1, ≥2, ≥3, and ≥4 SBIMs). Comparator medications included commonly prescribed prenatal medications without known sterol biosynthesis inhibition and served as a reference to evaluate the specificity of observed associations. These included diphenhydramine, docusate sodium, famotidine, ferrous sulfate, ondansetron, and polyethylene glycol 3350. These medications were chosen from an analysis of the most commonly prescribed medications in the pregnancy cohort within Cosmos. Indications for these medications include seasonal allergies, constipation, gastroesophageal reflux, iron deficiency, and nausea.

Covariates

Sex and preterm birth (<37 weeks' gestation) were considered as covariates based on the higher incidence of ASD in males [59–61] and increased risk for ASD after preterm birth. These variables were not included in the models, however, as fetal/neonatal sex is associated with the outcome but not the exposure, and preterm birth is likely within the causal pathway rather than being a true confounder. Maternal age at delivery [62, 63], maternal diabetes mellitus (DM) [64–67], maternal pre-eclampsia or eclampsia, race, ethnicity, year of birth (given the increase in SBIM use over time), rural residency (Rural Urban Commuting Areas Codes 1–3 defined as urban and 4–10 as rural) [68], Social Vulnerability Index [69], tobacco use during pregnancy, alcohol use during pregnancy, and maternal pre-pregnancy BMI were chosen as potentially confounding covariates during pregnancy. Notably, our model accounted for missing values, which had different proportions for the covariates. Diagnoses used to define DM and other diagnoses are listed in Supplemental Material 1.

Statistical analyses

Descriptive statistics were generated to compare demographic and clinical characteristics between individuals with and without SBIM exposure during pregnancy. Cumulative incidence plots were constructed to visualize the timing and magnitude of ASD diagnoses over the follow-up period, stratified by SBIM exposure status.

We assessed the proportional hazards assumption for all models using Schoenfeld residuals, with no meaningful violations detected for the primary exposures. Cox proportional hazards models [70] were then used to estimate hazard ratios and 95% confidence intervals (CIs) for two analytic approaches: (1) separate models for each SBIM medication compared with no SBIM exposure and (2) modeling SBIM exposure as an ordinal polypharmacy variable (≥ 1, ≥2, ≥3, and ≥4 SBIMs versus no SBIM). Each approach was evaluated using both unadjusted and adjusted models, with adjustment for the covariates described above. BMI was not included as a covariate in the model due to its high rate (> 35%) of missing values. We performed a sensitivity analysis by including BMI as a covariate (reference: normal weight) using complete case analysis excluding those with missing BMI). Comparator medications were individually analyzed in both unadjusted and adjusted models to allow for direct comparison with the SBIM results.

Although not all SBIMs are psychiatric medications, we conducted extensive sensitivity analyses to understand the potential confounding effects and interaction effects of maternal psychiatric diagnoses. We examined potential effect modification by including both the main effect terms and interaction terms between SBIM exposure and each psychiatric diagnosis (bipolar disorder, schizophrenia, schizoaffective disorder, anxiety, and major depression). In these sensitivity analyses, the main effect terms of the psychiatric conditions characterize the association between these conditions and ASD; the interaction terms assess whether the SBIM–ASD association differs across psychiatric subgroups. However, conditioning on these diagnoses might induce potential power loss in the association identification, given the small sample sizes of the psychiatric condition diagnosed groups. Another notable consideration is that our data may also encompass proxy markers for past psychotropic use. Biological effects might not cease with discontinuing medications before pregnancy (e.g. long-term epigenetic programming).

Table 1. Descriptive Statistics for Patients with and Without Sterol Biosynthesis-Inhibiting Medication During Pregnancy with at Least One Visit 18 Months After Birth, 2014–2023.

Characteristic[1]	Overall N = 6,135,213	No SBIM N = 5,435,521	Any SBIM N = 699,692
Gestational Age (Weeks)	39.1 (38.1,39.9)	39.1 (38.1,39.9)	39.0 (37.4,39.4)
Preterm	681,652 (11%)	576,804 (11%)	104,848 (15%)
Child Male Sex	3,184,486 (52%)	2,822,610 (52%)	361,876 (52%)
Maternal Age (Years)	30 (25, 34)	30 (25, 34)	30 (26, 34)
Race			
White	3,291,423 (54%)	2,830,279 (52%)	461,144 (66%)
Black or African American	913,154 (15%)	839,948 (15%)	73,206 (10%)
Asian	202,666 (3%)	196,504 (4%)	6162 (1%)
Other	1,388,770 (23%)	1,264,278 (23%)	124,492 (18%)
Missing/Unknown	*339,200 (5%)*	*304,512 (6%)*	*34,688 (5%)*
Ethnicity			
Not Hispanic or Latino	4,611,043 (75%)	4,022,447 (74%)	588,596 (84%)
Hispanic or Latino	1,121,526 (18%)	1,053,972 (19%)	67,554 (10%)
Missing/Unknown	*402,644 (7%)*	*359,102 (7%)*	*43,542 (6%)*
Social Vulnerability Index (SVI)			
Q1: Lowest SVI	1,141,335 (19%)	996,537 (18%)	144,798 (21%)
Q2: Lower-middle SVI	1,282,183 (21%)	1,121,759 (21%)	160,424 (23%)
Q3: Upper-middle SVI	1,443,383 (24%)	1,262,652 (23%)	180,731 (26%)
Q4: Highest SVI	2,236,053 (36%)	2,024,875 (37%)	211,178 (30%)
Unknown	*32,259 (<1%)*	*29,698 (<1%)*	*2561 (<1%)*
Rurality			
Urban	5,327,919 (87%)	4,749,973 (88%)	577,946 (83%)
Rural	779,839 (13%)	660,070 (12%)	119,769 (17%)
Unknown	*27,455 (<1%)*	*25,478 (<1%)*	*1977 (<1%)*
Multiple Birth	212,251 (3.5%)	184,616 (3.4%)	27,635 (3.9%)
Year of Birth	2019 (2017, 2021)	2019 (2017, 2021)	2021 (2018, 2022)
Autism Spectrum Disorder	234,971 (3.8%)	199,819 (3.7%)	35,152 (5.0%)
Body Mass Index (BMI)	27 (23, 33)	27 (23, 32)	29 (24, 35)
Unknown	*2,218,340 (36%)*	*2,083,025 (38%)*	*135,315 (19%)*
BMI Category			
Normal weight (18.5–24.9)	1,403,794 (23%)	1,241,128 (23%)	162,666 (23%)
Underweight (<18.5)	91,870 (2%)	81,491 (1%)	10,379 (2%)
Overweight (25.0–29.9)	1,047,308 (17%)	904,075 (17%)	143,233 (21%)
Obese (>=30.0)	1,373,901 (22%)	1,125,802 (21%)	248,099 (35%)
Missing/Unknown	*2,218,340 (36%)*	*2,083,025 (38%)*	*135,315 (19%)*
Comorbidities			
Diabetes	940,558 (15%)	804,985 (15%)	135,573 (19%)
Pre-Eclampsia/Eclampsia	654,320 (11%)	554,209 (10%)	100,111 (14%)
Tobacco Use During Pregnancy	25,897 (<1%)	20,138 (<1%)	5759 (<1%)
Alcohol Use During Pregnancy	35,851 (<1%)	29,433 (<1%)	6418 (<1%)
Bipolar Disorder	175,841 (3%)	106,877 (2%)	68,964 (10%)
Schizophrenia	15,325 (<1%)	8751 (<1%)	6574 (<1%)
Schizoaffective Disorder	10,403 (<1%)	5269 (<1%)	5134 (<1%)
Anxiety	1,452,841 (24%)	975,248 (18%)	477,593 (68%)
Depression	884,468 (14%)	534,255 (9.8%)	350,213 (50%)

[1]Median (Q1, Q3); n (%).

Statistical analyses were conducted in R within the Cosmos Data Science Virtual Machine and can be replicated by any Epic Cosmos customer. All statistical code and clinical concept sets used in this study are available in a public GitHub repository [71].

RESULTS

11,991,115 linked maternal and child records were available, of which 8,547,221 of the children were born between 2014 and 2023 (Supplemental Material 5). When restricted to US-born

children with at least 18 months of follow-up after birth that did not meet any exclusion criteria, there were 6,135,213 remaining maternal-child dyads for inclusion. This cohort includes births from all 50 states (Supplemental Material 6) and represents nearly one-third of all pregnancies occurring during the time frame. Overall, 699,692 (11%) pregnant mothers were prescribed at least one SBIM. The proportion of pregnant women prescribed SBIMs rapidly increased during the study period (Supplemental Material 7). Table 1 describes the demographics of the population, stratified by maternal prescription of at least one SBIM. The cumulative incidence of ASD was significantly increased in those children whose mothers received any SBIM (Fig. 1) during pregnancy versus those that received none. The cumulative incidence further increased when pregnant women were prescribed more than one SBIM during pregnancy (Fig. 2).

There were 234,971 (3.8%) children in this cohort who were diagnosed with ASD. Of the children with an ASD diagnosis, 35,152 (15.0%) of the mothers were prescribed at least one SBIM during pregnancy. Figure 3 demonstrates the adjusted hazard ratios (aHRs) of ASDs in medication-positive compared to pregnancies that were not exposed to any of the SBIMs as the reference group. Cariprazine showed the highest ASD aHR of 2.59 (2.23–3.00, $p < 0.001$) relative to pregnancies not exposed to cariprazine after adjusting for all the tested primary confounders. aHRs for ASD showed a strong correlation ($R^2 = 0.7801$, $p = 0.008$) with previously published magnitude of 7-DHC elevation in pregnancy when receiving SBIMs (Fig. 4) [51]. Being prescribed multiple concurrent SBIMs (polypharmacy) resulted in further increased hazard ratios for ASD (Fig. 5 and (Supplemental Material 8). While the aHR for having a child diagnosed with ASD if mothers were prescribed at least 1 SBIM during pregnancy was 1.47 (1.45–1.49), the risk increased by 1.33 times (1.32–1.34) for each additional SBIM during pregnancy (trend test assigning linear score for ordinal dose levels using robust standard errors for Wald type statistics $p < 0.001$). The risk reached as high as 2.33-fold (2.09–2.60) with 4 SBIMs in adjusted analyses. Specific examples of polypharmacy are also demonstrated in Fig. 5.

We performed two sensitivity analyses. The first included pre-pregnancy BMI as a covariate in the model, excluding those who did not have a documented BMI (Supplemental Material 9). This analysis demonstrated minimal change in the HR of ASD if the mother was prescribed at least one SBIM, from 1.47 (1.45–1.49) without including BMI in the model to 1.43 (1.41–1.45) when BMI was included in the model. The second sensitivity analysis, which included mental health diagnoses and their interactions with each SBIM, r resulted in slightly attenuated adjusted hazard across most SBIMs (Supplemental Material 10 and 11). As would be expected, the magnitude of the change in aHR was related to the class of medication, with medications used for psychoses and/or depression, like aripiprazole, decreasing from 2.18 (2.08–2.30)–1.31 (1.24–1.38), while SBIMs in other classes were minimally impacted, such as simvastatin (from 1.64 [1.37–1.96]–1.57 [1.31–1.87]) and pravastatin (from 1.95 [1.64–2.32]–1.73 [1.46–2.06]). Across all the sensitivity analyses, the psychiatric conditions demonstrate consistent positive associations with ASD risks, but these maternal conditions do not explain the strength of our findings. Also, it should be noted that these also could be proxy markers of longer-term psychiatric medication use [72].

Supplemental Material 12 and 13 show the aHRs for several medications commonly prescribed during pregnancy that have no known sterol biosynthesis effects, demonstrating that the degree of elevated HRs of the SBIMs are not seen with non-SBIMs. The aHRs ranged from 1.02 (1.01–1.03) for docusate sodium to 1.17 (1.15–1.18) for famotidine. These were further attenuated by the sensitivity analysis (Supplemental Material 14), resulting in an aHR of 1.02 (1.01–1.02) for docusate sodium and 1.13 (1.12–1.15) for famotidine.

DISCUSSION

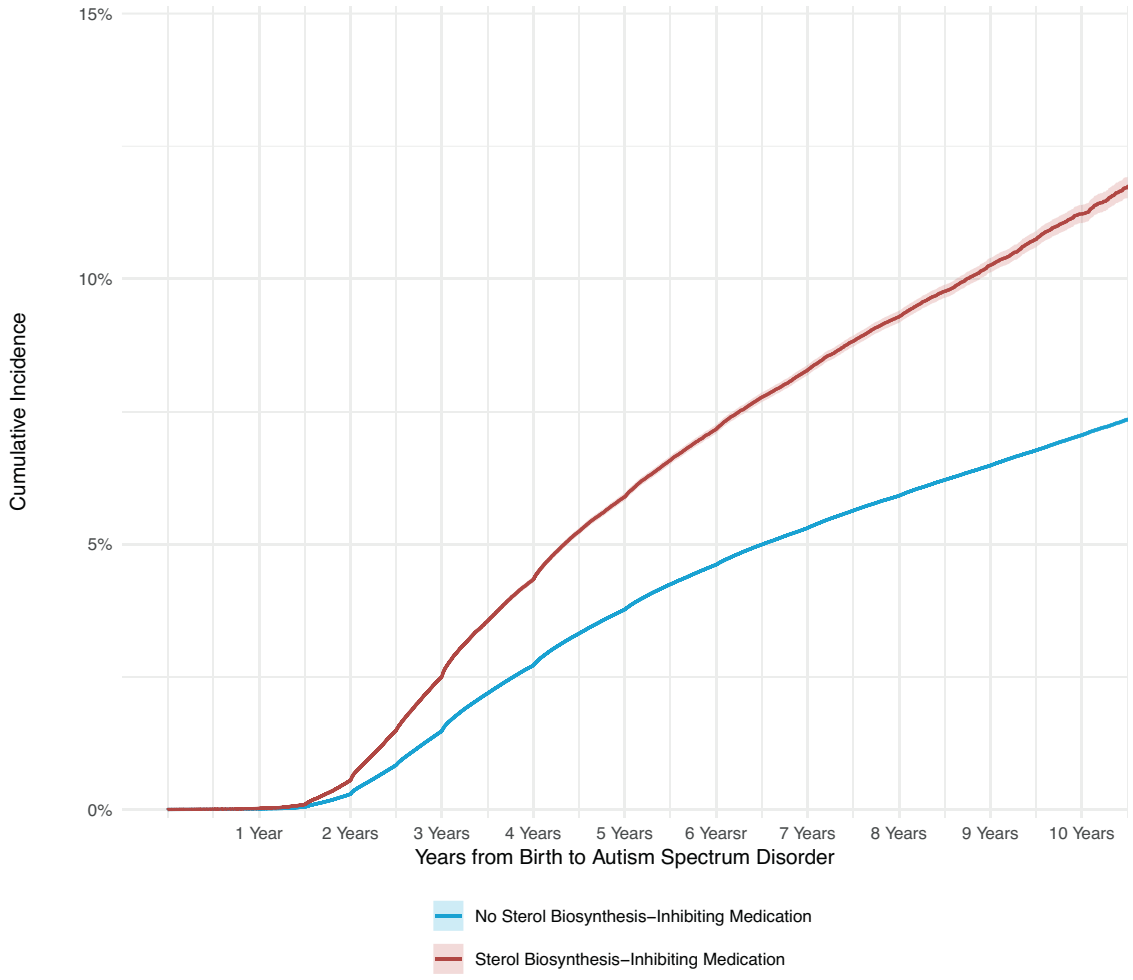
The births in this study represent nearly one-third of all births in the United States over this 10-year period. The increased utilization of SBIMs over time in our cohort suggests increased provider comfort with prescribing these medications during pregnancy. If this comfort comes with higher doses and/or longer duration, this could result in disproportionate elevations of ASD diagnosis in the SBIM-treated group. Also, it is notable that the average age at which ASD is diagnosed in the USA is about 4 years of age [73], thus, a significant number of our 18–72-month-old offspring might not have an established diagnosis yet (being censored). Furthermore, ASD diagnosis is often documented in medical records outside the EPIC database. As a result, our data might underestimate the potential impact of maternal SBIM use on developing ASD in the offspring.

There have been previous concerns of long-term neurodevelopmental outcomes for children exposed *in utero* to antipsychotics and antidepressants [74]. A national birth cohort study assessed the association of antipsychotic drug exposure during the second half of pregnancy with risk of neurodevelopmental disorders [75]. The unadjusted results were consistent with an approximate 2-fold increased risk. After adjusting for over 30 covariates, the risks were no longer significant, with the potential exception of aripiprazole (which is a strong sterol biosynthesis inhibitor) [41, 50]. The authors concluded that a potential signal for aripiprazole required replication in other data before causality can be assumed. We believe that our study provides this replication specifically for ASDs.

Not all SBIMs reported the same hazard ratios for ASD in our study. We believe that this is the function of their mechanism of action, half-life, metabolism differences, drug interactions, blood-brain barrier penetration and magnitude of sterol inhibition. For example, while statins all target HMGCo-A reductase, they differ in their degradation pathways [58]. In addition, the post-lanosterol inhibitors also vary in their mechanisms: fluoxetine is an emopamil binding protein (EBP) and dehydrocholesterol reductase 24 (DHCR24) inhibitor [40], while cariprazine is a primary DHCR7 inhibitor [50]. These findings suggest that disruption at any point along the sterol biosynthesis pathway may pose developmental risks to the fetus.

Another concerning observation from our studies involves polypharmacy, which has become increasingly common [76, 77]. This is also true for pregnant women [78–83]. A recent review found that two or more medications were prescribed up to62.4% of pregnant women [84]. In addition, our recent analysis of 1312 de-identified serum samples in pregnant women revealed that 302 samples had elevated 7-DHC levels, and 43 of these samples contained measurable amounts of at least one SBIM [51]. Taking multiple medications further elevated 7-DHC levels, indicating a potential additive or synergistic effect. We believe that this is likely the biological underpinning of the increased hazard ratios for offspring ASD when pregnant women are prescribed two or more SBIMs concurrently.

The public health implications of our findings are substantial [85]. The medications we examined had approximately 400 million prescriptions in 2022, and 9 of the 15 medications we studied were in the top 25 most prescribed medications in the US [86]. Furthermore, our current study shows that SBIM utilization during pregnancy is sharply rising in the US. Statins had long been contraindicated for use during pregnancy, but this warning was removed by FDA in 2021 [87]. The percentage of pregnant mothers receiving at least one SBIM had already more than tripled between 2014 and the removal of the warning in 2021 (Supplemental Material 7), so the change in the FDA warning labeling may be considered more a symptom of increasing comfort with these medications rather than a policy response to updated safety information, which does not appear to be available. Most of the SBIM package labels we evaluated come

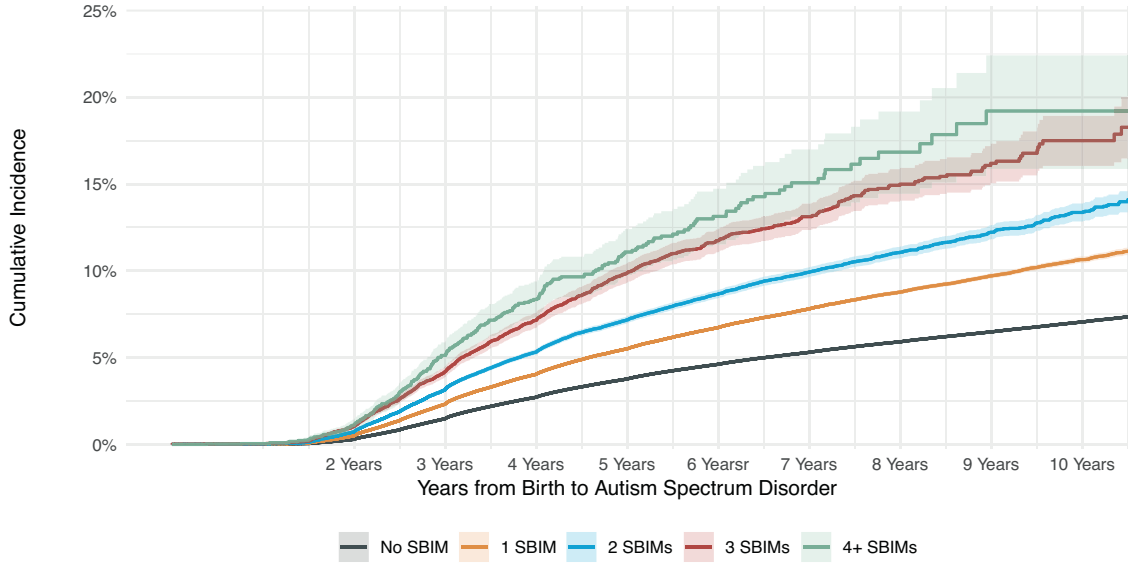


No Sterol Biosynthesis–Inhibiting Medication										
At Risk	5434911	5127782	4144791	3334888	2626318	1993402	1449836	990632	617779	324256
Censored	0	294518	1222483	1984674	2660826	3273307	3804245	4255308	4623114	4913617
Events	615	15671	70600	117523	149878	170314	182763	190566	195396	198216
Sterol Biosynthesis–Inhibiting Medication										
At Risk	699546	656665	490922	362863	261881	182423	120604	74678	42532	20552
Censored	0	39645	194155	314051	409857	486317	546275	591087	622580	644201
Events	148	3806	15013	23029	28130	31153	32959	34029	34642	34972

Fig. 1 Cumulative Incidence of Autism Spectrum Disorders by Any Sterol Biosynthesis-Inhibiting Medication Exposure During Pregnancy. Exposure groups were defined using medication exposure overlapping pregnancy from linked maternal-child health records in Cosmos. Follow-up began at birth and continued through the last available clinical encounter. Those with <18 months of follow-up were excluded due to inability to establish a reliable ASD diagnosis. Cumulative incidence accounts for censoring so the perceived incidences in this figure are higher than the raw incidence (3.8%) in our cohort. The censoring rate is similar between the groups, however, so the divergence in the lines is due to the rate of events and not censoring. Shaded area denotes 95% confidence range.

with significant warnings regarding pregnancy [88], although these warnings are deeply buried within the documents, and the prescribing physicians and patients are rarely aware of them. Thus, it appears that several widely used medications could have unintentionally contributed to a rise of ASD, without prior awareness of this risk.

Both confounders and overadjustment were major concerns in our study, complicating the interpretation of our findings. Namely, statins are typically not prescribed to those who don't have hyperlipidemia, and psychotropic medications are rarely utilized when a patient does not have a mental disorder. As a result, the genetic factors (e.g. familial predisposition to ASD and/or mental



At Risk									
No SBIM	5127782	4144791	3334888	2626318	1993402	1449836	990632	617779	324256
1 SBIM	534718	404117	301665	219629	154054	102522	63905	36598	17752
2 SBIMs	99692	71696	51047	35539	24006	15387	9254	5121	2439
3 SBIMs	18366	12609	8575	5749	3758	2340	1320	703	309
4+ SBIMs	3889	2500	1576	964	605	355	199	110	52
Censored									
No SBIM	294518	1222483	1984674	2660826	3273307	3804245	4255308	4623114	4913617
1 SBIM	31945	153995	250107	328087	391252	441267	478974	505746	524288
2 SBIMs	6164	32088	51326	65963	77031	85363	91341	95373	98009
3 SBIMs	1280	6556	10248	12863	14750	16123	17100	17704	18089
4+ SBIMs	256	1516	2370	2944	3284	3522	3672	3757	3815
Events									
No SBIM	15671	70600	117523	149878	170314	182763	190566	195396	198216
1 SBIM	2795	11318	17544	21542	23972	25446	26316	26822	27097
2 SBIMs	764	2830	4219	5074	5550	5823	5977	6067	6114
3 SBIMs	202	692	1022	1232	1331	1379	1419	1432	1440
4+ SBIMs	45	173	244	282	300	311	317	321	321

Fig. 2 Cumulative Incidence of Autism Spectrum Disorders by Multiple Sterol Biosynthesis-Inhibiting Medication Exposure During Pregnancy. Exposure groups were defined using medication exposure overlapping pregnancy from linked maternal-child health records in Cosmos. Follow-up began at birth and continued through the last available clinical encounter. Those with <18 months of follow-up were excluded due to inability to establish a reliable ASD diagnosis. Cumulative incidence accounts for censoring so the perceived incidences in this figure are higher than the raw incidence (3.8%) in our cohort. The censoring rate is similar between the groups, however, so the divergence in the lines is due to the rate of events and not censoring. The risk increased by 1.33 times (1.32–1.34) for each additional SBIM during pregnancy (trend test assigning linear score for ordinal dose levels using robust standard errors for Wald type statistics $p < 0.001$). Shaded area denotes 95% confidence range.

disorders) and maternal medication use are challenging to separate. However, increased risks for ASD were comparable across multiple classes of medications studied - including antipsychotics, antidepressants, anxiolytics, and medications for cardiac and metabolic conditions. Despite differences in clinical indication, chemical structure, metabolism and pharmacological class, however, they share a common effect: inhibition of the sterol biosynthesis pathway [89]. Together with the increased

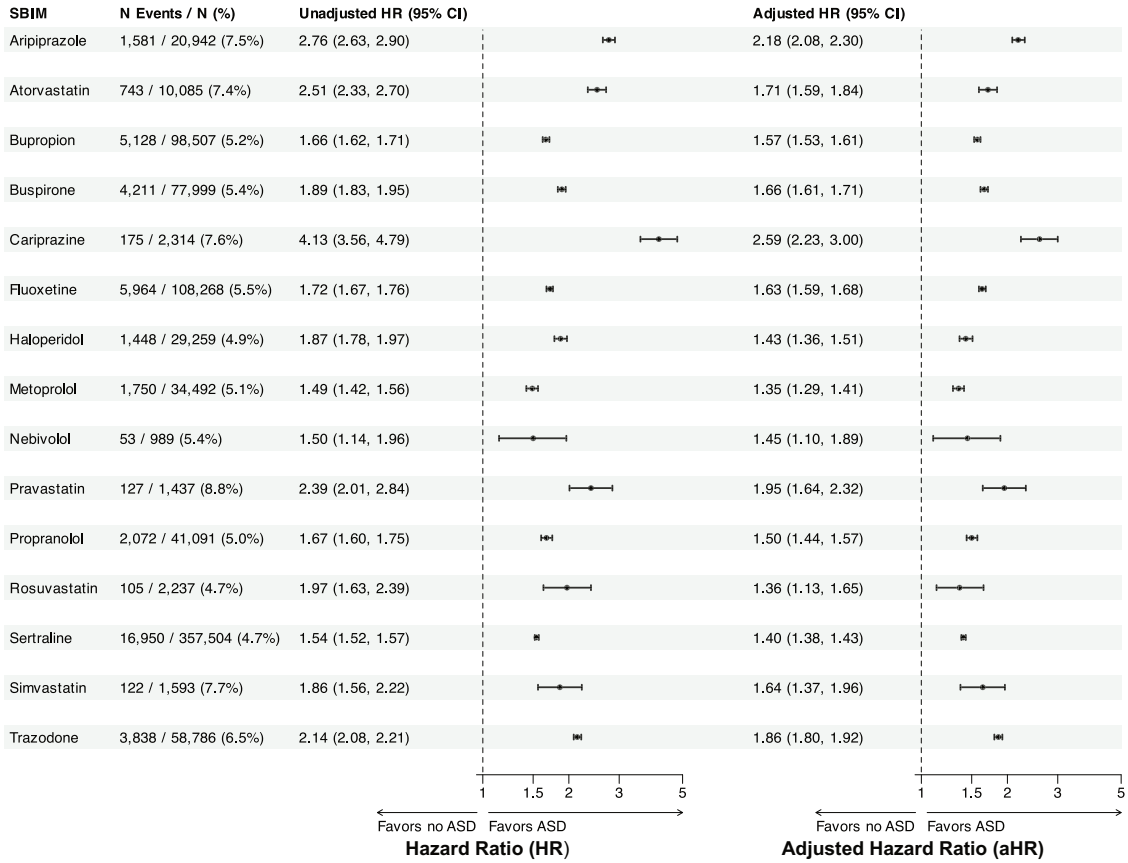


Fig. 3 Hazard Ratios for Autism Spectrum Disorders by Individual Sterol Biosynthesis-Inhibiting Medication (SBIM) Exposure During Pregnancy. Unadjusted and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between maternal exposure to individual SBIM during pregnancy and autism spectrum disorder (ASD) in offspring. Each SBIM was modeled separately using Cox proportional hazards regression, with pregnancies that were not exposed to any of the SBIMs as the reference group. All adjusted models included the covariates specified in the Methods. Full model output is available in Supplemental Material 8.

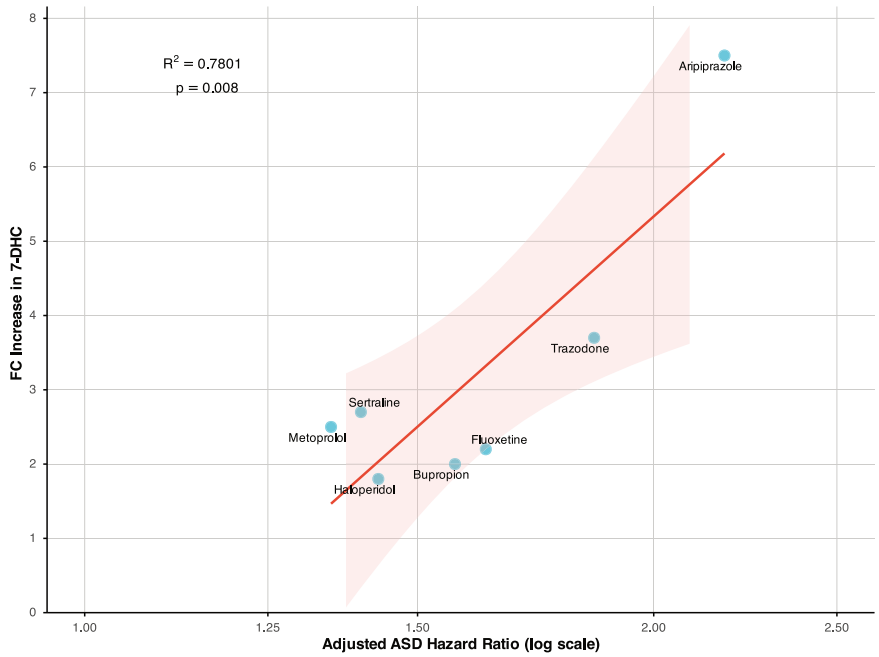


Fig. 4 Correlation between adjusted hazard ratios (HR) for the development of autism spectrum disorders (ASD) and the 7-dehydrocholesterol (7-DHC) fold change (FC) in pregnancies. Data represents maternally prescribed aripiprazole, bupropion, fluoxetine, haloperidol, metoprolol, sertraline, and trazodone relative to non-exposed pregnancies. Adjusted HR data (x-axis) shown are from our current dataset while 7-DHC level FC (y-axis) are from previously published data (PMCID: PMC8033759).

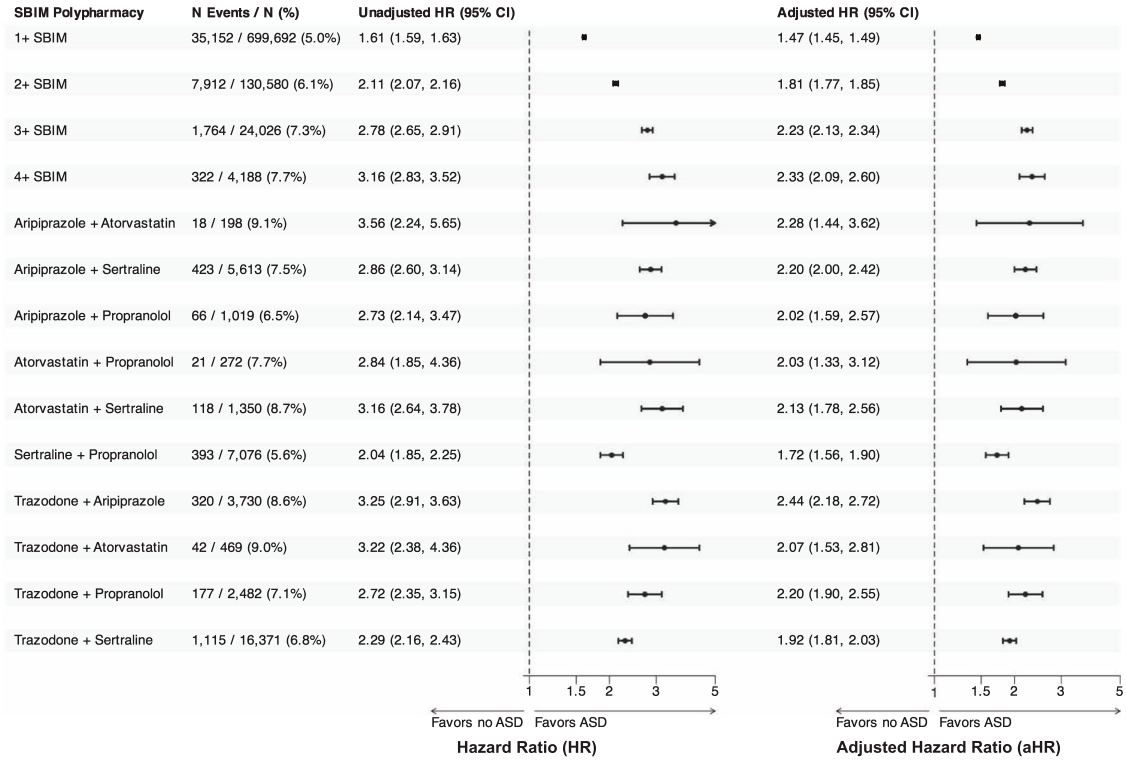


Fig. 5 Hazard Ratios for Autism Spectrum Disorders by Polypharmacy Sterol Biosynthesis-Inhibiting Medications (SBIM) Exposure During Pregnancy. Unadjusted and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between maternal exposure to at least one SBIM or SBIM polypharmacy during pregnancy and autism spectrum disorder (ASD) in offspring. SBIM exposure was modeled as an ordinal variable (≥ 1, ≥2, ≥3, and ≥4 distinct SBIMs) compared with no SBIM exposure, with selected SBIM combinations evaluated in separate models. All adjusted models included the covariates specified in the Methods. Full model output is available in Supplemental Material 8.

signal in polypharmacy, this is a strong argument that the medications with sterol inhibiting effects or side effects that we studied are significant contributors to the increased risk of ASD seen in the current study.

We acknowledge several important limitations to our studies. Not all pregnancies prescribed SBIMs result in ASD, and our research does not yet provide insight into all factors that may exacerbate the sterol-inhibiting side effects of these medications. Potential contributors include pharmacogenetic interactions between the medications and single allele pathogenic variants (of mother or child) in sterol biosynthesis genes, found in approximately 3% of the population [90]. Additionally, the role of all possible comorbidities could not be adequately addressed in this dataset. Environmental (e.g. insecticides, air pollution, heavy metals, pesticides) and socioeconomic factors might further interact with all the above-listed factors [91–93]. Nutritional factors such as vitamin deficiencies (especially low vitamin D levels) might also increase vulnerability [94]. Furthermore, while we did not have detailed information on the dosage or duration of medication use, previous studies suggest that vulnerability is highest during the first trimester [9]. We acknowledge that our study is not able to define what would be a “safe” dose of these medications for the developing fetal brain. We do not have reliable data on this in our current dataset, and we acknowledge that we have no independent confirmation of ASD diagnosis or potential misclassifications, either. Finally, future studies will have to determine the ASD risk of a child when the mother stopped SBIM use before pregnancy, as SBIMs might lead to epigenetic modifications that can exert an effect even after discontinuation of medication.

We strongly caution against overinterpreting our findings, especially by attempting to extrapolate the developmental findings to adult patients. The medications we evaluated are lifesaving and critically important treatments for adults. While developmental processes (including growth, cell division, and differentiation) have the highest demand for sterols and are therefore most likely to be impacted by sterol inhibition, cholesterol turnover in the adult brain occurs over a period of years [4, 5]. As a result, while sterol inhibition may pose significant risks to developing brains and bodies, these effects are likely negligible for already-formed structures in adults.

In summary, we propose that the use of SBIMs during pregnancy may increase the risk of ASD in offspring through a multistep biochemical cascade. Maternal exposure to SBIMs inhibits DHCR7 (or other sterol biosynthetic enzyme) activity, leading to accumulation of highly reactive oxysterols and reduced availability of cholesterol. These oxysterols can enter the fetal circulation and exert toxic effects on developing neurons and glial cells. As intrinsic sterol biosynthesis becomes established in the fetal brain, pharmacologic inhibition of biosynthetic enzymes similarly disrupts fetal sterol metabolism, further increasing local sterol precursor levels and oxysterol formation. The combined maternal and fetal burden of high sterol precursors and low cholesterol availability is expected to impair cellular homeostasis, perturbing progenitor proliferation, neurite outgrowth, and circuit formation, ultimately contributing to ASD-related (or other) phenotypes later in life. Clearly, the outcome of these processes will depend on the magnitude of sterol biosynthesis inhibition in the fetal brain, which will be dependent on SBIM type, dose, timing, duration of exposure, genetic makeup of the child and mother and many other factors. Notably, our data suggests that the stronger DHCR7 inhibitors are likely to be associated with greater predisposition to ASD (see Fig. 4, $R^2 = 0.78$). Alternatively, or in addition, SBIMs might lead to epigenetic changes that could

interfere with normal fetal development. Based on the overall data, we believe it is time to rethink our clinical practices and drug development strategies, including an evaluation of SBIM use to detect potential long-term effects. We recommend 1) creating a comprehensive catalog of all currently used medications known to have sterol-inhibiting side effects; 2) systematically testing all new drugs for their potential to unintentionally inhibit sterol biosynthesis; 3) educating providers and advising women about the effects of any SBIM shown to have potential effects on the pregnancy and/or resulting offspring, as well as examining the biological effects after medication discontinuation (e.g. long-lasting epigenetic effects); 4) discussing the use of safer alternatives whenever discontinuing treatment is not feasible; 5) further studies to determine the effect of these medications when the mother and/or child carries a single-allele pathogenic variant in sterol biosynthesis genes; 6) limiting SBIM polypharmacy during pregnancy; and 7) investing in research focused on this critically overlooked area of drug safety and development.

DATA AVAILABILITY

All statistical code and clinical concept definitions used in this study, including ICD-10-CM diagnosis codes and RxNorm and National Drug Code (NDC) medication identifiers, are publicly available in a GitHub repository (https://github.com/Anzalone-Lab/Sterol-Pathway-Disruption-in-Pregnancy). Statistical code is provided for all analyses conducted in R. Extract code (SQL) for the Epic Cosmos database is available to qualified investigators (those with affiliation to an organization with Epic that participates in Cosmos) with active Cosmos portal access and can be shared internally via the Cosmos GitLab instance. This restriction is necessary because the Epic Cosmos data model is proprietary and owned by Epic Systems Corporation and therefore cannot be shared publicly.

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AUTHOR CONTRIBUTIONS

ESP and KM had full access to all data in the present study population and takes responsibility for the integrity of the data and the accuracy of the data analysis. ESP, ZK, AJA, and RD designed and conceptualized the study; ESP and KM obtained funding for the study; ESP, AJA and ER acquired the data; AJA and RD performed the statistical analyses; KM and ESP supervised the study; ESP, KM, RD, AJA, RD and ZK interpretated the data; KM, ZK and ESP drafted the manuscript. All authors revised the manuscript for important intellectual content.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL

All methods were performed in accordance with the relevant guidelines and regulations. This study was determined "exempt" by the University of Nebraska Medical Center's Institutional Review Board.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41380-026-03610-7.

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