

Neurodevelopmental Outcomes in COVID-19-Vaccinated Versus Unvaccinated U.S. Children: Analysis of the National Health Interview Survey, 2022–2024

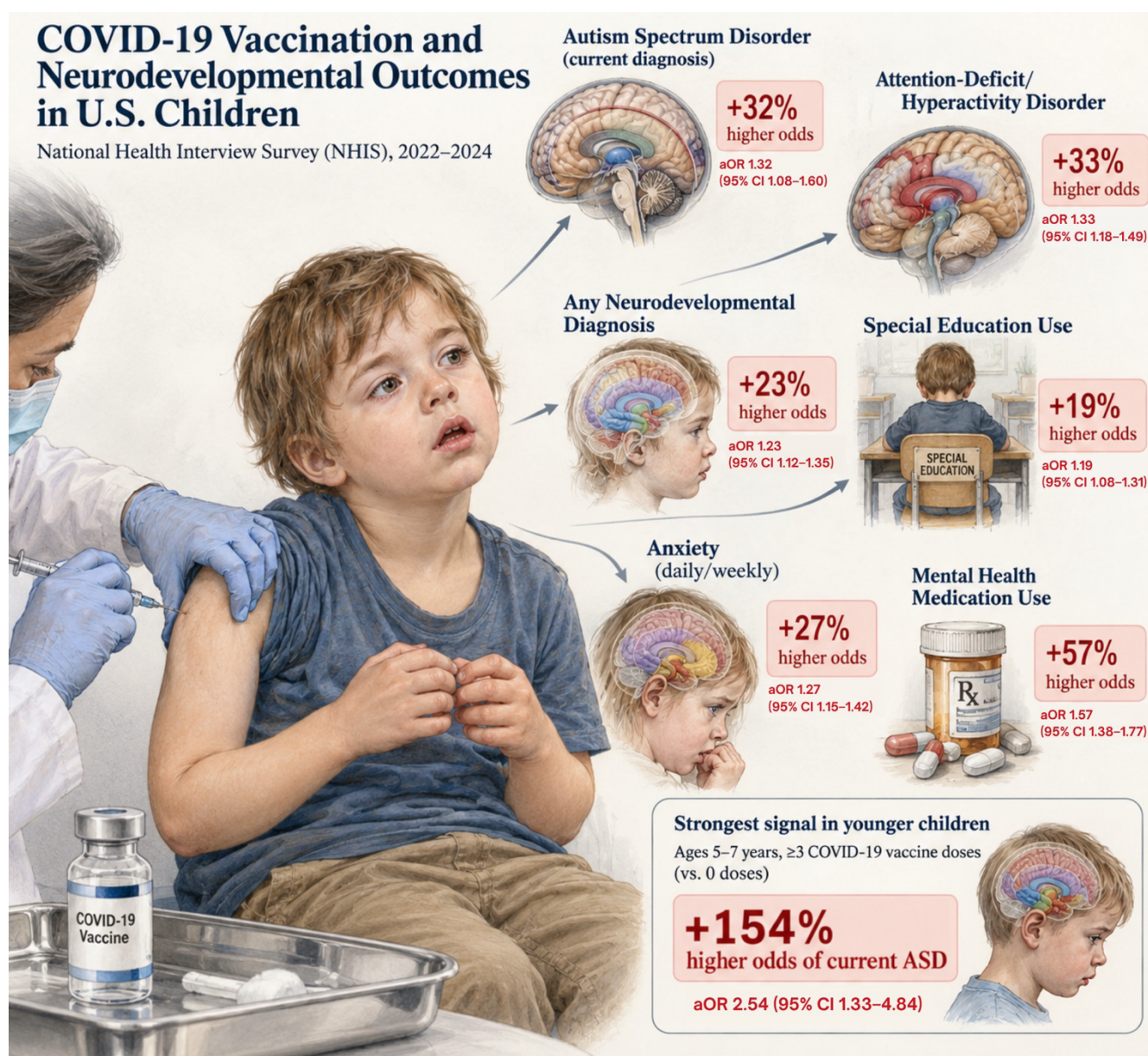
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Abstract

Background. Autism spectrum disorder now affects 1 in 31 U.S. 8-year-olds and continues to rise at an alarming rate. COVID-19 mRNA vaccines were first authorized for U.S. children aged 12–15 in May 2021, 5–11 in October 2021, and 6 months–4 years in June 2022. No pediatric trial or post-marketing surveillance study was designed or powered to detect neurodevelopmental or mental-health outcomes after childhood COVID-19 mRNA vaccination. Vaccine-derived spike protein circulates systemically after vaccination and has been detected in blood, monocytes, cerebral arteries, and peripheral tissue months to years later, the S1 subunit disrupts blood–brain-barrier integrity in vitro, and prenatal spike-protein exposure induces autism-like behavior, neuroinflammation, and reduced BDNF in male rats. A population-level signal-detection analysis is warranted.

Methods. We pooled the 2022–2024 National Health Interview Survey (NHIS) Sample Child files ($n = 21,990$ children aged 0–17 with COVID-19 vaccination status; $n = 19,882$ aged 2–17 for autism, ADHD, and learning-disability items; 844 lifetime and 779 current ASD cases), with the 2021 (ages 12–17) and 2025 (current-season dose) files as supplementary samples. The primary comparison was COVID-19-vaccinated versus COVID-19-unvaccinated children (parental report of ever receiving a COVID-19 vaccine; "unvaccinated" denotes no COVID-19 vaccine, not absence of routine childhood immunization), with number of doses and years since first dose as secondary exposures. Outcomes were parent-reported lifetime and current autism spectrum disorder (ASD), ADHD, learning disability, intellectual disability, developmental delay, special-education use, asthma, diabetes, anxiety and depression frequency, mental-health treatment, general health, and acute-care use. Influenza and HPV vaccination served as negative-control exposures. Survey-weighted logistic regression with stratum/PSU Taylor-linearized variance estimated odds ratios (ORs) across five adjustment tiers.

Results. Compared with unvaccinated children, COVID-19-vaccinated children had higher adjusted odds of lifetime ASD (aOR 1.26, 95% CI 1.04–1.52), current ASD (1.32, 1.08–1.60), ADHD (1.33, 1.18–1.49), any neurodevelopmental diagnosis (1.23, 1.12–1.35), special-education use (1.19, 1.08–1.31), asthma (1.24, 1.11–1.37), daily/weekly anxiety (1.27, 1.15–1.42), and mental-health medication (1.57, 1.38–1.77) and therapy (1.60, 1.43–1.79); the E-value for current ASD was 1.97, and no measured covariate was associated with both vaccination and autism in the same direction at this magnitude. Adjusted odds rose monotonically with dose count (current ASD 1.03, 1.25, 1.40 for 1, 2, ≥ 3 doses vs 0). The association (current ASD) was largest in the youngest exposed cohort: ≥ 3 doses vs 0 at ages 5–7, aOR 2.54 (1.33–4.84); ages 2–7, 2.37 (1.38–4.10); and among children first vaccinated at age ≤ 5 at least one year before interview, 2.46 (1.08–5.62; 9 exposed cases). Under propensity-score overlap weighting, which eliminated all measured covariate imbalance, the autism association was unchanged and remained

significant (lifetime 1.23, 1.01–1.50; current 1.26, 1.03–1.56), while the negative-control outcomes of emergency-department visits and hospitalization were close to the null (0.95 and 1.02). Estimates were unchanged after restriction to children without asthma, diabetes, or fair/poor health ($n = 16,803$; both vaccines vs neither, 1.51, 1.17–1.95), and persisted after additional adjustment for emergency-department use, hospitalization, and prescription use (1.31, 1.04–1.66). In direct comparison, COVID-19-vaccine-only children ($n = 3,205$) had higher odds of ASD than influenza-vaccine-only children ($n = 3,763$; 1.45, 1.03–2.05) despite lower odds of asthma (0.73) and emergency-department visits (0.77). Anxiety showed partial specificity (COVID-19 vaccine 1.34 vs influenza vaccine 1.07 at ages 5–11). Against the unvaccinated reference; however, influenza-vaccine-only and COVID-19-vaccine-only, point estimates were similar and modest (1.11 and 1.12) for ASD. Likewise, HPV vaccination was modestly associated with ASD 1.17 (0.74–1.85). The ASD association was amplified among children receiving both (influenza and COVID-19) vaccines (1.42–1.51). Associations for current ASD weakened with time since first dose, and the COVID-19 vaccine association was confined to girls (1.60 vs boys 1.08; interaction $p = 0.02$).

Conclusions. In a direct comparison of COVID-19-vaccinated with unvaccinated children in a nationally representative U.S. sample, COVID-19 vaccination was associated with higher adjusted odds of autism, ADHD, anxiety, special-education use, and mental-health treatment. The autism association persisted across every adjustment tier; was unchanged under propensity-score balancing that removed all measured covariate imbalance and nullified the acute-care negative controls; was robust to restriction to physically healthy children; increased monotonically with dose count; was largest in the youngest exposed cohorts, including children vaccinated before the school-entry diagnostic window; and exceeded that of influenza vaccination in direct comparison. These properties satisfy the strength, consistency, biological gradient, plausibility, and coherence considerations for causal inference, and no measured confounder explains them. Because the cross-sectional design cannot order exposure and diagnosis, a global scheduled combination childhood vaccine effect on neurodevelopment cannot be evaluated. A linked birth-cohort study of toddlers before age 3 capturing co-administered vaccines, incident diagnoses, and pre-specified negative controls would be the next step in evaluating this concerning association.

Keywords: COVID-19 vaccine; autism spectrum disorder; ADHD; neurodevelopment; children; NHIS; pharmacovigilance; negative-control exposure.

1. Introduction

Autism spectrum disorder (ASD) now affects 1 in 31 U.S. children aged 8 years (32.2 per 1,000 in 2022), up from 1 in 150 in 2000 [1]; a rise of this magnitude constitutes a public-health emergency, and identifying modifiable determinants that could halt it is an urgent priority. COVID-19 vaccines were recommended for U.S. children aged 12–15 in May 2021, 5–11 in October 2021, and 6 months–4 years in June 2022 [2,3,4]; in the National Health Interview Survey, 36–39% of children aged 5–11 and 54–61% of adolescents had received at least one dose by 2023–2024 (Section 3.1). Pediatric authorization proceeded on the basis of immunobridging trials enrolling a few thousand children with follow-up often measured in weeks; none was powered for, or collected, neurodevelopmental or psychiatric endpoints [5,6]. An interim analysis of post-marketing surveillance (Vaccine Safety Datalink rapid cycle analysis) targeted pre-specified acute events—myocarditis, anaphylaxis, seizures (no neurodevelopmental or psychiatric events)—over 21- to 42-day risk windows [7]. The Vaccine Adverse Event Reporting System (VAERS) is an open-ended, passive (spontaneous) reporting system with no pre-specified list of adverse events [8]; V-safe targets some early pre-specified events, but no neurodevelopmental endpoints [9]. With the Food and Drug Administration (FDA)’s Biologics Effectiveness and Safety (BEST) Initiative for COVID-19 vaccine safety monitoring starting in December 2020, they have “monitored about 15 adverse events,” none of a neurodevelopmental or psychiatric nature. The FDA “will use the BEST system to conduct more in-depth analyses should a safety concern be identified from sources such as VAERS” [10]. Outcomes that emerge over months or years, or that are recognized only through later clinical contact, were not within scope. Apart from prospective cohorts of in utero exposure to maternal vaccination, which found no neurodevelopmental differences at timepoints from 12–30 months

of age [11,12], the pediatric COVID-19 vaccine literature contains no test of a neurodevelopmental hypothesis, positive or negative.

A biological rationale for such a test exists. Circulating vaccine-derived spike protein persists for months to years after mRNA vaccination. It is detectable in plasma in the first weeks after injection [13] and by mass spectrometry up to 187 days later [14]; the S1 subunit has been identified in CD16+ monocytes up to 245 days after vaccination in SARS-CoV-2-negative individuals with post-COVID-19 vaccine syndrome [15]; and in a longitudinally characterized case, spike protein remained detectable in plasma and circulating exosomes 1,173 days after the final dose and in skin tissue by immunohistochemistry at 1,364 days, with persistent nucleocapsid negativity excluding prior infection as the source [16]. Vaccine mRNA has been detected in breast milk [17], vaccine-derived spike protein has been identified in brain vascular endothelium at autopsy in a case report [18], and in a series of 19 hemorrhagic-stroke patients, spike protein was detected in the intima of cerebral arteries in 7 of 16 vaccinated patients up to 17 months after vaccination, with in situ hybridization demonstrating evidence of both vaccine- and viral-derived mRNA (nucleocapsid protein negative) in 3 select patients [19]. The S1 subunit disrupts blood–brain-barrier integrity and elicits pro-inflammatory responses in brain microvascular endothelium in vitro [20], and exogenous S1 induces neuronal death and microglial proliferation in neuronal–glial co-culture, although mRNA vaccines themselves did not reduce neuronal viability in the same system [21]. The European Medicines Agency’s assessment report for Spikevax describes a rat biodistribution study performed with the same lipid nanoparticle formulation carrying a different mRNA (mRNA-1647), in which mRNA was detected in brain tissue, indicating that the mRNA/LNP platform crossed the blood–brain barrier [22]; the Comirnaty assessment report similarly noted that LNP-formulated RNAs distribute

non-specifically to several organs including brain [23]. In a rat model, prenatal spike-protein exposure produced autism-like social and repetitive behaviors in male offspring, hippocampal and cerebellar gliosis and neuronal loss, elevated TNF- α , IL-17, and NF- κ B, and reduced brain-derived neurotrophic factor (BDNF)—pathways implicated in human autism [24]. A subsequent study from the same group reported analogous behavioral, histological, cytokine, and WNT/BDNF findings after prenatal BNT162b2 exposure [25] (subsequently retracted [26]; treated here as unreplicated). Neuroinflammation and microglial activation during sensitive developmental windows are established mechanisms in neurodevelopmental disorders [27,28]. We have previously published a comprehensive review of ASD determinants characterizing the disorder as a multifactorial, post-encephalitic state [28]. After childhood vaccination, immune dysregulation, mitochondrial dysfunction, and neuroinflammation converge on a susceptible child with genetic, environmental, perinatal, and iatrogenic exposures resulting in an increased risk for neurodevelopmental disorders [28]. For some children, the COVID-19 vaccines have added to this burden of cumulative early-childhood vaccination. Additionally, the cumulative pediatric vaccine schedule has never been evaluated for neurodevelopmental outcomes with high-quality, prospective, parallel group, comparative studies with clinical adjudication of childhood outcomes [28].

The National Health Interview Survey (NHIS) is one of the few nationally representative U.S. datasets that capture, in the same child, parental report of COVID-19 vaccination (from 2021), number of doses, year of first dose, influenza and human papillomavirus (HPV) vaccination, and a broad panel of neurodevelopmental, mental-health, and physical-health diagnoses [29]. It is cross-sectional and lacks diagnosis dates, so it cannot establish causation as temporality cannot be established. It can, however, detect whether an association exists, whether

it exhibits a dose-response gradient, whether it is specific to COVID-19 vaccination relative to other vaccines, and whether its structure across age and time since exposure is consistent with a causal or non-causal explanation. That is the purpose of a signal-detection analysis, and it is the purpose of this study.

We report a comprehensive exploratory analysis of NHIS 2021–2025 with negative-control exposures and outcomes built into the design [30], so that the strength and the limits of any observed signal are established in the same paper.

2. Methods

2.1 Data source and study population

This cross-sectional analysis is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline. NHIS is a continuous, nationally representative household survey of the civilian non-institutionalized U.S. population conducted by the National Center for Health Statistics (NCHS). One sample child per household is randomly selected and a parent or guardian is interviewed. We used the public-use Sample Child files for survey years 2021 through 2025 [29].

COVID-19 vaccination items differ by year and were harmonized as follows: 2021 (SHTCVD19_C; asked only for ages 12–17 in quarters 3–4; $n = 1,666$), 2022–2024 (SHTCVD191_C; ever received; ages 5–17 in 2022 through mid-quarter 3, and all ages from the second half of quarter 3 onward, following authorization for children under 5 years in June 2022), and 2025 (SHTCVD192_C; receipt of the current-season vaccine only, with year of first dose restricted to 2024–2025). Of 23,516 sample children in the 2022–2024 files, 1,174 were outside the vaccination item’s universe (children aged 0–4 years interviewed in 2022 before the

item was extended to all ages) and 352 had refused, don't-know, or not-ascertained responses (1.6% of those asked), leaving 21,990 children in the primary analytic sample. The 2021 file (ages 12–17) and the 2025 file (season-dose exposure) were analyzed separately as supplementary samples. Public-use NHIS data are de-identified and exempt from institutional review.

2.2 Exposures

The primary comparison was between COVID-19-vaccinated and COVID-19-unvaccinated children, defined by parental report that the child had ever received a COVID-19 vaccine. Throughout, "unvaccinated" refers only to COVID-19 vaccination status and does not imply absence of routine childhood vaccination. Secondary exposures were number of doses (0, 1, 2, ≥ 3 ; SHTCVD19NM_C, SHTCVD19NM1_C, SHTCVD19NM2_C), approximate age at first dose (child age minus [survey year minus year of first dose]), and years since first dose (< 2 vs ≥ 2). Negative-control exposures were influenza vaccination in the past 12 months (SHTFLU12M_C; one vs two shots, SHTFLUNUM_C) and, in the 2022 file only, HPV vaccination (SHTHPV_C; ages 9–17). A four-level combined exposure was constructed: neither vaccine, influenza only, COVID-19 vaccine only, both.

2.3 Outcomes

Lifetime parent-reported diagnoses were autism spectrum disorder (ASDEV_C; ages 2–17), ADHD (ADHDEV_C; 2–17), learning disability (LDEV_C; 2–17), intellectual disability (IDEV_C/IDEV1_C), developmental delay (DDEV_C), any of these five, special education or early-intervention services (SCHSPEDEV_C), asthma (ASEV_C), and diabetes (DIBEV_C). Current ASD and ADHD were reconstructed from the lifetime item and the current-status item

(ASDNW_C, ADHDNW_C), which are asked only of children with a lifetime diagnosis. Functional and mental-health outcomes were anxiety and depression daily or weekly (ANXFREQ_C, DEPFREQ_C; ages 5–17), a lot of difficulty or inability learning (LEARNDF_C), mental-health medication and therapy in the past 12 months (MHRX_C, MHTHRPY_C), and fair/poor general health (PHSTAT_C). Negative-control outcomes were any emergency-department visit and any overnight hospitalization in the past 12 months. Responses coded refused, not ascertained, or don't know were set to missing (fewer than 2% of responses for any exposure or outcome item). Complete-case analysis was used; covariate missingness was minimal (parental education 13 records; wellness visit 134; usual source of care 15 in the 2022–2024 sample).

2.4 Covariates

Covariates were age (continuous and squared), sex, survey year, race/ethnicity (HISPALLP_C), family income as a ratio of the federal poverty level (<100%, 100–199%, 200–399%, ≥400%; POVRATTC_C), highest parental education (≤high school, some college, bachelor's or higher; MAXEDUCP_C), insurance type (private, public, other, uninsured; COVER_C), census region, wellness visit in the past 12 months (WELLNESS_C), and usual source of care (USUALPL_C). Utilization sensitivity covariates were emergency-department use, overnight hospitalization, and prescription-medication use in the past 12 months (RX12M_C). Parent-reported prior COVID-19 infection (EVERCOVID_C), asked from the 2023 file onward and therefore available for the 2023–2024 portion of the primary sample, was used in a sensitivity analysis restricted to those years.

2.5 Statistical analysis

All analyses applied the sample-child final annual weight (WTFA_C), which adjusts for selection probability, non-response, and post-stratification to Census population controls; weights were divided by the number of pooled years for prevalence estimation, which does not affect ratio measures. Dose counts were harmonized across the year-specific items (SHTCVD19NM_C in 2021–2022, SHTCVD19NM1_C in 2023, SHTCVD19NM2_C in 2024) and top-coded at three or more; children reporting no vaccination were assigned zero doses. Variance was estimated by Taylor-series linearization using the public-use strata (PSTRAT) and primary sampling units (PPSU), with a with-replacement approximation for PSUs [31]. Subgroup and restricted analyses were fitted within the relevant subsample, and strata containing a single PSU within a subsample contributed no variance. Weighted prevalence was computed by exposure group. Survey-weighted logistic regression estimated odds ratios in five tiers: M0, crude; M1, age, age², sex, survey year; M2, M1 plus race/ethnicity, poverty ratio, parental education, insurance, region; M3, M2 plus wellness visit and usual source of care; M4, M3 plus emergency-department use, hospitalization, and prescription use (an over-adjustment sensitivity model, because medication use partly reflects treatment of the outcomes). Dose–response was assessed with dose category and, for comparison, influenza-shot count, mutually adjusted.

Subgroups were age at interview (3–4, 5–7, 8–11, 12–14, 15–17), age at first dose, time since first dose, influenza-vaccination stratum, and sex. Effect modification by sex was tested with a product term (vaccination $\times$ sex) in the fully adjusted model. Dose–response was additionally evaluated within narrow age bands by fitting the four-level dose variable as an ordinal term, yielding an odds ratio per dose category. To address the absence of diagnosis dates, we constructed early-exposure cohorts restricted to children whose first COVID-19 vaccine dose preceded the school-entry diagnostic window, defined by an age at first dose at or below a

specified threshold and a minimum interval between first dose and interview, compared with never-vaccinated children of the same ages. We also estimated the reverse association, modeling COVID-19 vaccination as the outcome and each diagnosis as the exposure, to quantify whether an existing diagnosis predicted vaccination. Three analyses addressed confounding by clinical engagement directly: (i) restriction of the sample to children with no lifetime asthma or diabetes and not in fair or poor general health, which removes the pathway by which physical high-risk status drives both vaccination and clinical contact; (ii) a direct comparison of the two single-vaccine groups (COVID-19 vaccine only versus influenza only), in which both groups have demonstrated recent vaccine-seeking behavior and healthcare access, so that any difference between them cannot be attributed to vaccination-seeking per se; and (iii) a sensitivity model adding past-year emergency-department use, hospitalization, and prescription-medication use. Because the head-to-head groups differ in age composition, the same contrast was also evaluated within age strata and as the ratio of coefficients in the full four-level model. As a fourth approach, we estimated propensity scores for COVID-19 vaccination by survey-weighted logistic regression on all covariates (age, age², sex, survey year, race/ethnicity, poverty ratio, parental education, insurance, region, wellness visit, usual source of care, influenza vaccination) and re-estimated the exposure–outcome associations under overlap weights (survey weight multiplied by 1 – propensity score for vaccinated and by the propensity score for unvaccinated children), stabilized inverse-probability-of-treatment weights, and inverse-probability weights trimmed at the 99th percentile; balance was assessed by standardized mean differences, and a doubly robust model added the covariates to the overlap-weighted outcome model. E-values were computed for primary estimates as the minimum risk-ratio association an unmeasured confounder would require with both exposure and outcome to fully explain the observed estimate

[32]. The 2021 and 2025 supplementary samples were analyzed with the fully adjusted (M3) covariate set plus influenza vaccination. Two-sided $p < 0.05$ was considered statistically significant, without correction for multiple comparisons, consistent with an exploratory signal-detection design. Here, a signal denotes an adjusted association that is statistically significant and stable across adjustment tiers; it does not imply a demonstrated effect. Analyses were performed in Python 3.12 (pandas 2.x, statsmodels 0.15).

3. Results

3.1 Sample and vaccination patterns

The 2022–2024 pooled sample comprised 21,990 children (unweighted 9,427 vaccinated, 12,563 unvaccinated; weighted 40.0% ever vaccinated). Coverage increased with age: 11–16% at 0–4 years, 36–39% at 5–11, and 54–61% at 12–17. Vaccination was strongly socially patterned (**Table 1**): 56.7% at $\geq 400\%$ of the poverty level vs 26.2% at $< 100\%$; 51.6% with a bachelor's-educated parent vs 26.8% with high school or less; 48.8% with private vs 28.6% with public insurance; 66.1% among non-Hispanic Asian children; and 58.8% among influenza-vaccinated vs 24.8% among non-influenza-vaccinated children. Parent-reported ASD ran in the opposite direction (5.7% at $< 100\%$ poverty vs 2.8% at $\geq 400\%$; 5.6% public vs 3.4% private insurance), producing negative confounding of the crude vaccine–ASD association.

Characteristic	Unvaccinated (n=12,563)	Vaccinated (n=9,427)
Age group, years		
0-4	30.6	7.8
5-11	43.1	37.8
12-17	26.2	54.5
Sex		
Male	51.4	50.7
Female	48.6	49.3
Race/ethnicity		

Characteristic	Unvaccinated (n=12,563)	Vaccinated (n=9,427)
Non-Hispanic White	51.6	48.5
Non-Hispanic Black	13.3	11.1
Hispanic	26.2	26.2
Non-Hispanic Asian	2.7	7.8
Other/multiple	6.2	6.5
Family income, % FPL		
<100%	18.7	10.0
100-199%	25.7	16.3
200-399%	31.4	26.2
400%+	24.1	47.5
Highest parental education		
High school or less	28.7	15.7
Some college	31.2	20.0
Bachelor's or higher	40.1	64.3
Insurance		
Private	46.8	66.8
Public	44.3	26.7
Other	3.6	3.0
Uninsured	5.1	3.3
Region		
Northeast	13.4	19.5
Midwest	21.6	19.9
South	44.2	32.5
West	20.8	28.1
Wellness visit, past 12 mo (% yes)	88.6	89.0
Usual source of care (% yes)	97.0	97.8
Influenza vaccine, past 12 mo (% yes)	30.8	65.8
Survey year		
2022	28.5	32.4
2023	34.9	35.1
2024	36.6	32.4

Table 1. Weighted characteristics of the 2022–2024 NHIS Sample Child analytic sample by COVID-19 vaccination status (column %).

FPL, federal poverty level. Unweighted n shown in column headers; percentages are weighted column percentages (the composition of each vaccination group), whereas percentages given in the text are the proportion vaccinated within each stratum. Vaccination status from SHTCVD191_C.

3.2 COVID-19 vaccination and outcomes

Crude ASD prevalence did not differ by vaccination status (4.19% vs 4.28%; OR 0.98, 95% CI 0.83–1.16; **Table 2, Figure 1B**). Crude prevalence did differ for ADHD (13.23% vs

9.57%; OR 1.44, 1.30–1.59), any neurodevelopmental diagnosis (20.72% vs 16.45%; 1.33, 1.22–1.44), special-education use (17.92% vs 14.62%; 1.27, 1.17–1.39), asthma (12.73% vs 8.72%; 1.53, 1.40–1.67), diabetes (0.61% vs 0.32%; 1.92, 1.19–3.10), daily/weekly anxiety (19.41% vs 15.26%; 1.34, 1.22–1.47), and mental-health medication (11.59% vs 6.69%; 1.83, 1.64–2.04) and therapy (16.22% vs 9.05%; 1.95, 1.76–2.15), all higher in vaccinated children; and in the opposite direction for a lot of difficulty learning (1.64% vs 2.16%; 0.76, 0.60–0.96), emergency-department visits (13.92% vs 18.44%; 0.72, 0.66–0.78), and hospitalization (2.27% vs 2.77%; 0.81, 0.67–0.99), all lower in vaccinated children. After adjustment for demographics and socioeconomic position (M2), vaccinated children had higher odds of lifetime ASD (aOR 1.28, 1.06–1.54) and current ASD (1.34, 1.10–1.63); these were essentially unchanged with further adjustment for wellness visit and usual source of care (M3: 1.26, 1.04–1.52; 1.32, 1.08–1.60; **Figure 1A**). ADHD (lifetime 1.33, 1.18–1.49; current 1.33, 1.18–1.50), any neurodevelopmental diagnosis (1.23, 1.12–1.35), special-education use (1.19, 1.08–1.31), asthma (1.24, 1.11–1.37), daily/weekly anxiety (1.27, 1.15–1.42), and mental-health medication (1.57, 1.38–1.77) and therapy (1.60, 1.43–1.79) were also elevated. Learning disability (1.10, 0.96–1.26), intellectual disability (1.18, 0.91–1.54), developmental delay (1.12, 0.95–1.31), diabetes (1.43, 0.88–2.33), depression (1.14, 0.95–1.37), a lot of difficulty learning (0.95, 0.72–1.24), fair/poor health (1.14, 0.89–1.46), emergency-department visits (1.02, 0.92–1.12), and hospitalization (1.16, 0.93–1.44) were not.

The E-value for current ASD (aOR 1.32) is 1.97 (lower confidence bound 1.37): an unmeasured confounder would need to be associated with both vaccination and ASD at a risk ratio of at least 1.97 to fully explain the estimate (**Supplementary Table S1**). For reference, the strongest measured predictor of vaccination in this sample, family income $\geq 400\%$ vs $<100\%$ of

the poverty level, carried a prevalence ratio of 2.2 for vaccination but an inverse association with ASD, and the strongest measured predictor of ASD, public insurance, carried a prevalence ratio of 1.7 for ASD but an inverse association with vaccination; no measured covariate was positively associated with both at the required magnitude.

Outcome	n	Cases	% unvacc.	% vacc.	Crude OR (95% CI)	M2 aOR (95% CI)	M3 aOR (95% CI)
Autism, ever	19,882	844	4.28	4.19	0.98 (0.83–1.16)	1.28 (1.06–1.54)	1.26 (1.04–1.52)
Autism, current	19,871	779	3.88	3.93	1.01 (0.85–1.21)	1.34 (1.10–1.63)	1.32 (1.08–1.60)
ADHD, ever	19,874	2,321	9.57	13.23	1.44 (1.30–1.59)	1.34 (1.19–1.50)	1.33 (1.18–1.49)
ADHD, current	19,856	2,143	8.91	12.26	1.43 (1.29–1.58)	1.34 (1.19–1.51)	1.33 (1.18–1.50)
Learning disability	19,877	1,707	8.24	8.79	1.07 (0.95–1.21)	1.11 (0.97–1.26)	1.10 (0.96–1.26)
Intellectual disability	21,973	383	1.67	1.94	1.16 (0.92–1.46)	1.19 (0.91–1.54)	1.18 (0.91–1.54)
Developmental delay	21,978	1,244	6.12	5.57	0.91 (0.79–1.04)	1.12 (0.96–1.31)	1.12 (0.95–1.31)
Any NDD diagnosis	21,985	4,042	16.45	20.72	1.33 (1.22–1.44)	1.24 (1.13–1.36)	1.23 (1.12–1.35)
Special education, ever	21,937	3,486	14.62	17.92	1.27 (1.17–1.39)	1.19 (1.08–1.31)	1.19 (1.08–1.31)
Asthma, ever	21,976	2,320	8.72	12.73	1.53 (1.40–1.67)	1.24 (1.12–1.38)	1.24 (1.11–1.37)
Diabetes, ever	21,984	96	0.32	0.61	1.92 (1.19–3.10)	1.44 (0.89–2.34)	1.43 (0.88–2.33)
Anxiety daily/weekly	17,106	2,955	15.26	19.41	1.34 (1.22–1.47)	1.27 (1.15–1.42)	1.27 (1.15–1.42)
Depression daily/weekly	17,100	976	5.44	6.18	1.14 (0.97–1.34)	1.13 (0.94–1.36)	1.14 (0.95–1.37)
A lot of difficulty learning	19,897	373	2.16	1.64	0.76 (0.60–0.96)	0.94 (0.72–1.23)	0.95 (0.72–1.24)
MH medication, 12 m	19,885	1,865	6.69	11.59	1.83 (1.64–2.04)	1.58 (1.40–1.79)	1.57 (1.38–1.77)
MH therapy, 12 m	19,880	2,571	9.05	16.22	1.95 (1.76–2.15)	1.60 (1.43–1.79)	1.60 (1.43–1.79)
Fair/poor health	21,987	520	2.35	2.50	1.07 (0.86–1.32)	1.13 (0.88–1.44)	1.14 (0.89–1.46)
ER visit, 12 m	21,957	3,723	18.44	13.92	0.72 (0.66–0.78)	1.02 (0.92–1.12)	1.02 (0.92–1.12)
Hospitalized, 12 m	20,977	530	2.77	2.27	0.81 (0.67–0.99)	1.16 (0.94–1.45)	1.16 (0.93–1.44)

Table 2. COVID-19 vaccination (ever vs never) and parent-reported outcomes, NHIS 2022–2024: weighted prevalence and odds ratios across adjustment tiers.

M2: age, age², sex, survey year, race/ethnicity, poverty ratio, parental education, insurance, region. M3: M2 + wellness visit + usual source of care. Variance by Taylor linearization on PSTRAT/PPSU. ASD, ADHD, and learning-disability items asked for ages 2–17; anxiety/depression for 5–17; other items for 0–17. MH, mental health; NDD, neurodevelopmental disorder.

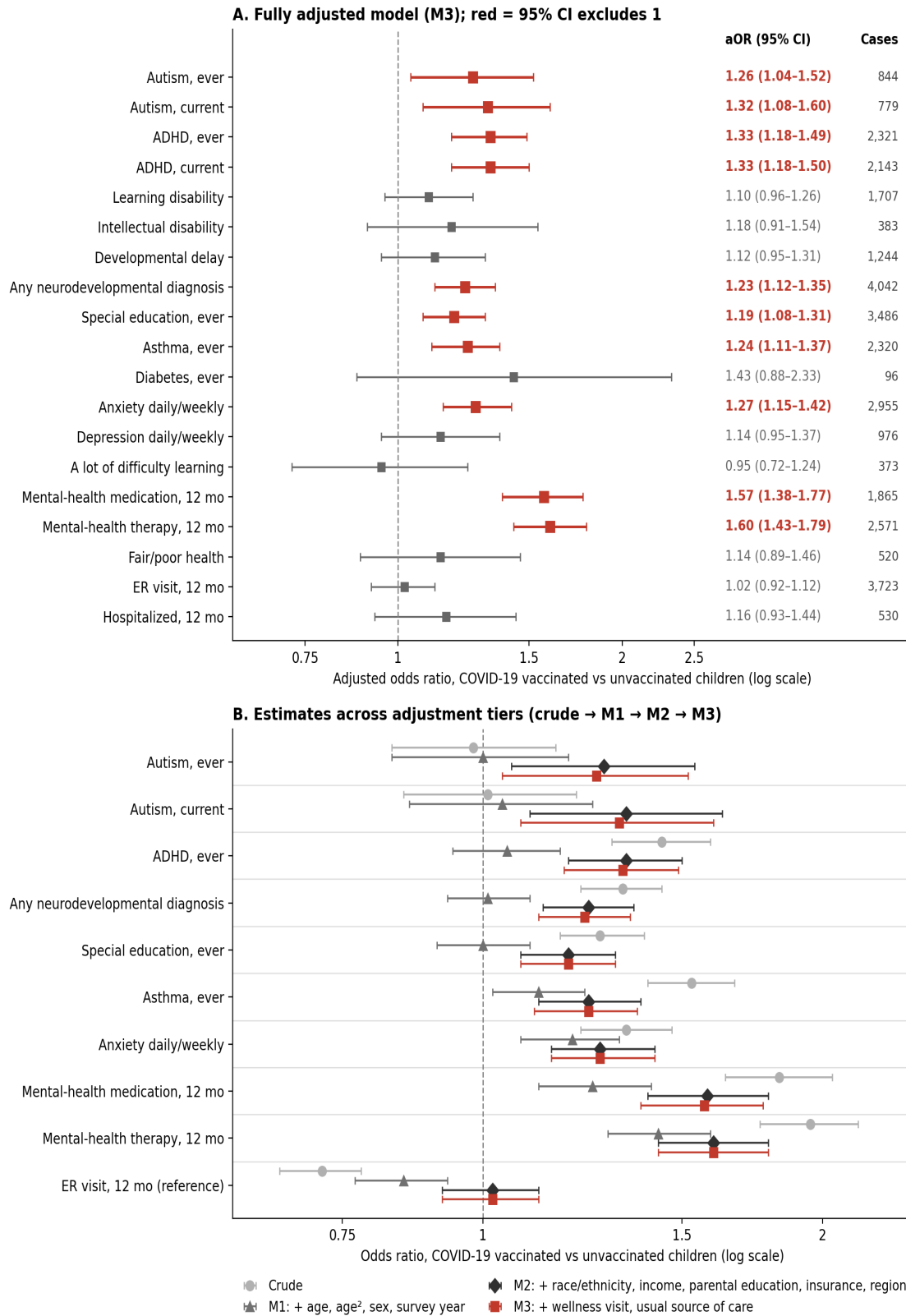


Figure 1. Primary findings, COVID-19-vaccinated versus unvaccinated children, NHIS 2022–2024 (n = 21,990). (A) Adjusted odds ratios for all outcomes in the fully adjusted model M3 (age, age², sex, survey

year, race/ethnicity, poverty ratio, parental education, insurance, region, wellness visit, usual source of care); red, 95% CI excludes 1; case counts at right. (B) Odds ratios for the nine outcomes significant in M3, plus emergency-department visits as a reference outcome, across the four adjustment tiers: crude, M1 (age, age², sex, year), M2 (M1 plus race/ethnicity, income, parental education, insurance, region), and M3. Autism estimates are null in crude and M1 and emerge at M2, when socioeconomic position enters the model; the reference outcome moves from 0.72 to 1.02 under the same adjustment. Variance by Taylor linearization on strata and PSUs.

3.3 Dose-response

Dose count was reported for 9,328 of 9,427 vaccinated children (98.9%): 1,107 with one dose, 5,235 with two, and 2,986 with three or more (analytic n = 21,891; for lifetime ASD, n = 19,788 with 470, 44, 214, and 115 cases across 0, 1, 2, and ≥ 3 doses). Adjusted odds rose monotonically with dose count (**Table 3, Figure 2**). Current ASD: 1.03 (0.67–1.57), 1.25 (0.99–1.58), and 1.40 (1.05–1.86) for 1, 2, and ≥ 3 doses vs 0. Lifetime ASD: 0.97, 1.24, 1.34 (1.02–1.75). ADHD: 1.11, 1.13, 1.46 (1.23–1.74). Anxiety: 1.12, 1.19, 1.44 (1.24–1.67). Mental-health therapy: 1.28, 1.32, 1.82 (1.56–2.13). Crude weighted ASD prevalence; however, was flat across dose groups (4.28%, 4.27%, 4.22%, 4.18%); the gradient emerges after adjustment because dose count rises with socioeconomic position. For comparison, one influenza shot (adjusted for COVID-19 vaccination) gave lifetime ASD aOR 1.19 (1.00–1.41) and two shots 0.94 (0.56–1.58).

Outcome	COVID-19 vaccine: 1 dose	2 doses	≥ 3 doses	Influenza vaccine: 1 shot	2 shots
Autism, ever	0.97 (0.64–1.47)	1.24 (1.00–1.54)	1.34 (1.02–1.75)	1.19 (1.00–1.41)	0.94 (0.56–1.58)
Autism, current	1.03 (0.67–1.57)	1.25 (0.99–1.58)	1.40 (1.05–1.86)	1.22 (1.02–1.47)	0.99 (0.57–1.70)
ADHD, ever	1.11 (0.87–1.42)	1.13 (0.98–1.32)	1.46 (1.23–1.74)	1.31 (1.15–1.48)	1.74 (1.22–2.50)
Any NDD diagnosis	1.09 (0.89–1.33)	1.11 (0.98–1.25)	1.27 (1.11–1.45)	1.26 (1.14–1.39)	1.35 (1.03–1.77)
Asthma	0.93 (0.74–1.17)	1.08 (0.95–1.23)	1.27 (1.09–1.49)	1.42 (1.27–1.58)	1.87 (1.38–2.52)
Anxiety daily/weekly	1.12 (0.88–1.43)	1.19 (1.05–1.35)	1.44 (1.24–1.67)	1.07 (0.96–1.19)	1.26 (0.91–1.75)
MH therapy, 12 mo	1.28 (0.99–1.66)	1.32 (1.15–1.51)	1.82 (1.56–2.13)	1.32 (1.17–1.48)	1.55 (1.13–2.12)

Table 3. Dose-response: adjusted odds ratios by COVID-19 vaccine dose category and by influenza-shot count, mutually adjusted (M3), NHIS 2022–2024.

Reference: 0 doses / no influenza vaccine in past 12 months. Crude weighted ASD prevalence by COVID-19 vaccine dose: 4.28%, 4.27%, 4.22%, 4.18%.

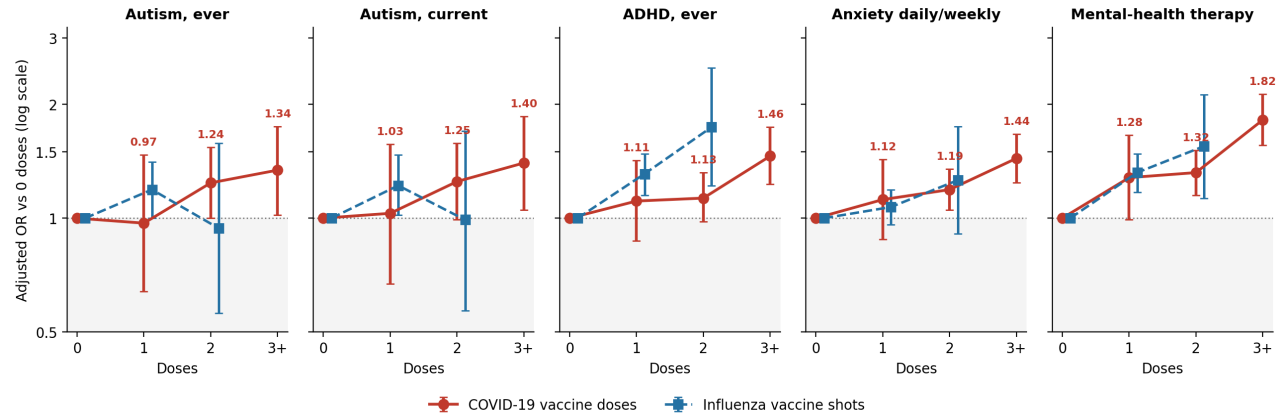


Figure 2. Dose–response: adjusted odds ratios by COVID-19 vaccine dose category (0, 1, 2, ≥ 3) and influenza-shot count (0, 1, 2), mutually adjusted (M3).

3.4 Age at interview

The ≥ 3 -dose vs 0-dose association for current ASD was largest in the youngest exposed cohorts (**Table 4, Figure 3**): ages 3–4, 2.74 (0.85–8.89; 5 exposed cases); ages 5–7, 2.54 (1.33–4.84; 18 exposed cases); ages 2–7 combined, 2.37 (1.38–4.10). At ages 5–7, weighted current-ASD prevalence was 4.02%, 4.45%, 4.46%, and 6.19% across 0, 1, 2, and ≥ 3 doses, and a test for trend across the four dose categories within this age band (adjusted additionally for influenza vaccination; $n = 3,455$, 151 cases) gave an aOR of 1.30 per category (1.05–1.60; $p = 0.015$); the crude ≥ 3 vs 0 estimate was 1.50 (0.82–2.74), 1–2 doses vs 0 was 1.43 (0.87–2.37), and ≥ 3 vs 1–2 doses was 1.63 (0.74–3.62). The ≥ 3 -dose group at ages 5–7 was also elevated for asthma (1.65, 1.06–2.56), current ADHD (1.90, 1.01–3.56), and mental-health therapy (1.69, 1.03–2.76). Estimates at 8–11 (0.85, 0.47–1.55), 12–14 (1.97, 1.18–3.30), and 15–17 (1.62, 0.99–2.64) were non-monotonic across age.

Age at interview	n	Exposed cases	Crude/yr-adj. OR	Adjusted OR (95% CI)
3–4 y	1,818	5	—	2.74 (0.85–8.89)
5–7 y	3,537	18	1.50 (0.82–2.74)	2.54 (1.33–4.84)
8–11 y	4,812	15	—	0.85 (0.47–1.55)
12–14 y	4,773	29	—	1.97 (1.18–3.30)
15–17 y	5,515	42	—	1.62 (0.99–2.64)
2–7 y (combined)	6,288	23	—	2.37 (1.38–4.10)

Age at interview	n	Exposed cases	Crude/yr-adj. OR	Adjusted OR (95% CI)
5–11 y (combined)	8,349	33	—	1.27 (0.82–1.97)
5–7 y, 1–2 doses vs 0	3,258	34	—	1.43 (0.87–2.37)
5–7 y, ≥ 3 vs 1–2 doses	1,126	18	—	1.63 (0.74–3.62)
5–7 y, trend per dose category (0/1/2/ ≥ 3 ; + influenza)	3,455	18	—	1.30 (1.05–1.60), p = 0.015
5–7 y, ≥ 3 vs 0: asthma	—	—	—	1.65 (1.06–2.56)
5–7 y, ≥ 3 vs 0: current ADHD	—	—	—	1.90 (1.01–3.56)
5–7 y, ≥ 3 vs 0: MH therapy	—	—	—	1.69 (1.03–2.76)
5–7 y, influenza → current ASD	3,475	—	—	1.08 (0.69–1.68)

Table 4. ≥ 3 COVID-19 vaccine doses vs 0 doses and current autism, by age at interview, NHIS 2021–2024 (M2 covariates).

Weighted current-ASD prevalence at ages 5–7 by dose: 0, 4.02%; 1, 4.45%; 2, 4.46%; ≥ 3 , 6.19%. Exposed cases at 5–7 by file: 2022, 1/43; 2023, 10/117; 2024, 7/119.

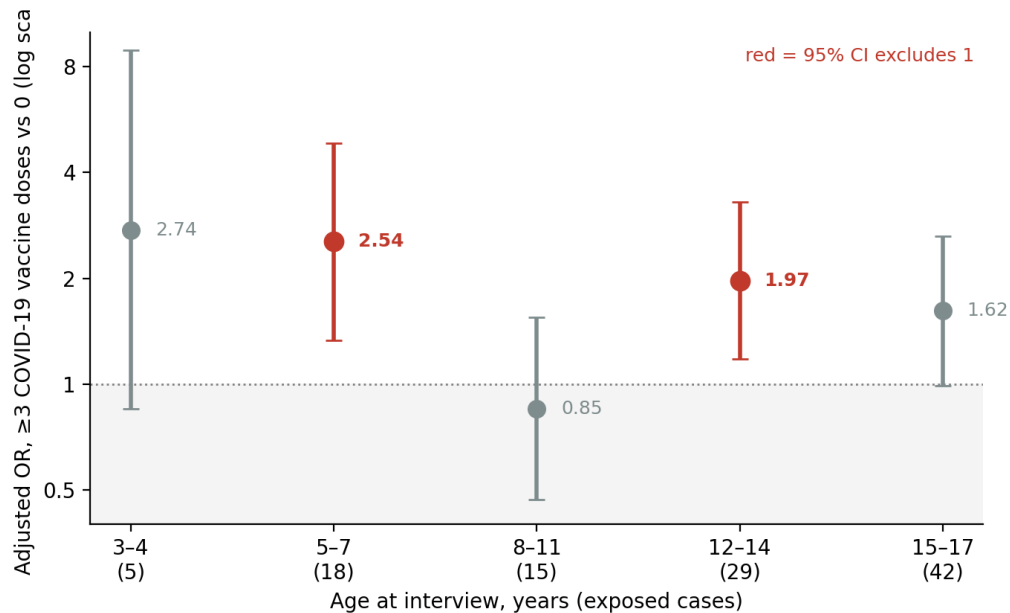


Figure 3. Current autism, ≥ 3 COVID-19 vaccine doses vs 0 doses, by age at interview, NHIS 2021–2024 (M2 covariates). Exposed case counts in parentheses.

3.5 Temporality

NHIS records lifetime diagnoses without dates, so the ordering of exposure and diagnosis must be inferred from age at first dose relative to the age distribution of ASD diagnosis. Median age at earliest documented ASD diagnosis in U.S. surveillance is approximately 4 years [33], but the distribution is wide: a substantial share of diagnoses occur at school entry and in the early

primary grades (ages 5–7), and later still in girls and in children without intellectual disability [33,34]. The diagnostically relevant window is therefore approximately 3–7 years rather than a single age.

Year of first dose was reported for 8,961 of 9,427 vaccinated children (95.1%). Among vaccinated children with lifetime ASD in 2022–2024 ($n = 366$), median age at first COVID-19 vaccine dose was 11 years; 84% received the first dose at age ≥ 6 , 8.7% at ≤ 4 , and 3.0% at ≤ 2 . This distribution reflects the age structure of vaccine eligibility (12–15 in May 2021, 5–11 from October 2021, under 5 from June 2022) as much as any diagnostic sequence, and for adolescents it establishes that vaccination followed diagnosis in nearly all cases.

For the youngest cohorts the ordering is undetermined rather than established. Among the 18 current-ASD cases with ≥ 3 doses at ages 5–7, first-dose age was 3 ($n = 1$), 4 ($n = 4$), and 5–7 ($n = 13$): every first dose fell within the 3–7-year diagnostic window, and 14 of 18 received the first dose at least one year before interview (one at least two years before). Among all 279 children aged 5–7 with ≥ 3 doses, 188 (67%) had received the first dose at least one year before interview. Diagnosis after vaccination is therefore plausible for the majority of exposed cases in this cohort.

We tested this directly in cohorts constructed so that exposure preceded the school-entry diagnostic window (**Table 5**). Among children aged 5–8 at interview who were first vaccinated at age ≤ 5 at least one year before interview ($n = 577$ exposed) versus never vaccinated, current ASD was 1.54 (0.91–2.63; 29 exposed cases) and lifetime ASD 1.32 (0.79–2.22). Within this cohort, ≥ 3 doses versus none gave current ASD aOR 2.46 (1.08–5.62; 121 exposed, 9 cases) and lifetime ASD 2.05 (0.91–4.61). Among children aged 4–8 first vaccinated at age ≤ 4 at least one year before interview ($n = 401$ exposed), current ASD was 1.41 (0.78–2.54; 20 exposed cases).

In the narrowest pre-window cohort (first dose at ≤ 3 years, interviewed at ages 3–6 in 2023–2024; 333 exposed vs 2,351 never vaccinated), lifetime ASD was 4.7% vs 4.9% (aOR 1.11, 0.57–2.20; 18 exposed cases) and developmental delay 8.0% vs 8.5% (0.90, 0.55–1.45).

Requiring a lag of at least two years (first dose ≤ 5 , ages 5–8; 229 exposed) gave current ASD 1.02 (0.43–2.40; 9 exposed cases). Developmental delay was not elevated in any pre-window cohort (0.68–0.92).

Among adolescents aged 12–17 ($n = 8,358$), current ASD was associated with first dose < 2 years before interview (1.49, 1.07–2.06) more strongly than ≥ 2 years (1.33, 0.86–2.05; weighted prevalence 3.6% vs 3.6% never vaccinated); anxiety showed the same pattern (1.31, 1.11–1.55 vs 0.94, 0.78–1.14).

Analysis	Comparison	Weighted prevalence	Adjusted OR (95% CI)
Age at first COVID-19 vaccine dose, vaccinated children with lifetime ASD ($n = 366$)	median 11 y; ≤ 2 y 3.0%; ≤ 4 y 8.7%; ≥ 6 y 84%	—	—
Ages 5–7, ≥ 3 doses, current ASD ($n = 18$): age at first dose	3 y (1); 4 y (4); 5–7 y (13)	—	—
Early exposure: first dose ≤ 3 y vs never; ages 3–6 in 2023–24	Lifetime ASD	4.7% vs 4.9%	1.11 (0.57–2.20)
	Developmental delay	8.0% vs 8.5%	0.90 (0.55–1.45)
Early exposure: first dose ≤ 4 y vs never; ages 3–7	Lifetime ASD	4.6% vs 5.0%	1.10 (0.65–1.86)
Pre-school-entry window: first dose ≤ 4 y, ≥ 1 y before interview vs never; ages 4–8 (401 exposed)	Current ASD (20 exposed cases)	—	1.41 (0.78–2.54)
Pre-school-entry window: first dose ≤ 5 y, ≥ 1 y before interview vs never; ages 5–8 (577 exposed)	Current ASD (29 exposed cases) / lifetime ASD	—	1.54 (0.91–2.63) / 1.32 (0.79–2.22)
same cohort, ≥ 3 doses vs 0 (121 exposed)	Current ASD (9 exposed cases) / lifetime ASD	—	2.46 (1.08–5.62) / 2.05 (0.91–4.61)
same cohort, developmental delay	DD (39 exposed cases)	—	0.80 (0.50–1.27)
Pre-school-entry window, ≥ 2 y lag: first dose ≤ 5 y vs never; ages 5–8 (229 exposed)	Current ASD (9 exposed cases)	—	1.02 (0.43–2.40)
Ages 5–7, ≥ 3 doses: lag from first dose to interview	All exposed ($n = 279$): ≥ 1 y 188 (67%); ≥ 2 y 29. Current-ASD cases ($n = 18$): ≥ 1 y 14; ≥ 2 y 1	—	—
Adolescents 12–17 ($n = 8,358$): first dose < 2 y before interview vs never	Current ASD	4.1% vs 3.6%	1.49 (1.07–2.06)
first dose ≥ 2 y before interview vs never	Current ASD	3.6% vs 3.6%	1.33 (0.86–2.05)

Analysis	Comparison	Weighted prevalence	Adjusted OR (95% CI)
<2 y vs never	Anxiety daily/weekly	23.3% vs 19.6%	1.31 (1.11–1.55)
≥2 y vs never	Anxiety daily/weekly	16.9% vs 19.6%	0.94 (0.78–1.14)
≥2 y vs never, not influenza-vaccinated	Current ASD	—	1.21 (0.66–2.20)
≥2 y vs never, influenza-vaccinated	Current ASD	—	1.82 (0.91–3.62)
≥2 y vs never, + utilization covariates	Current ASD	—	1.23 (0.80–1.90)

Table 5. Temporality: age at first dose, early-exposure sub-cohort, and time since first dose among adolescents.

Adolescent models adjusted for influenza vaccination, age, sex, race/ethnicity, parental education, poverty ratio, insurance, region, usual source of care, wellness visit, and survey year.

3.6 Negative-control exposures

In the four-level combined model (neither, n = 8,600; influenza only, n = 3,763; COVID-19 vaccine only, n = 3,205; both, n = 6,090; analytic n = 19,450 with 832 lifetime ASD cases; **Table 6, Figure 4**), lifetime ASD aORs vs neither vaccine were 1.11 (0.87–1.41) for influenza only, 1.12 (0.84–1.48) for COVID-19 vaccine only, and 1.42 (1.14–1.78) for both; current ASD 1.16, 1.17, and 1.51 (1.19–1.90). ADHD: 1.58, 1.43, 1.59. Asthma: 1.38, 1.04, 1.59. Emergency-department visits: 1.36, 1.04, 1.18. Hospitalization: 1.44, 0.97, 1.49. In the 2022 file (ages 9–17, n = 3,606), with HPV, COVID-19 vaccine, and influenza vaccination in one model, ASD aORs were 1.17 (0.74–1.85), 1.05 (0.67–1.64), and 1.26 (0.80–1.99), respectively.

Anxiety showed partial specificity: at ages 5–11, COVID-19 vaccination aOR 1.34 (1.13–1.59) vs influenza 1.07 (0.91–1.26) in the same model; at 12–17, 1.16 (1.01–1.34) vs 1.06 (0.92–1.22). In the 2023–2024 files, where prior COVID-19 infection was parent-reported (n = 11,355 with anxiety reported), adjusting additionally for prior infection (itself associated with anxiety, 1.42, 1.27–1.59) attenuated the vaccine estimate to 1.11 (0.97–1.28).

Outcome	Influenza only (18.5%)	COVID-19 vaccine only (13.7%)	Both (26.3%)	Any vaccine vs neither
Autism, ever	1.11 (0.87–1.41)	1.12 (0.84–1.48)	1.42 (1.14–1.78)	1.22 (1.01–1.48)
Autism, current	1.16 (0.90–1.50)	1.17 (0.87–1.58)	1.51 (1.19–1.90)	1.29 (1.06–1.57)
ADHD, ever	1.58 (1.35–1.86)	1.43 (1.21–1.68)	1.59 (1.38–1.83)	1.54 (1.37–1.73)
Learning disability	1.12 (0.93–1.36)	1.03 (0.86–1.25)	1.22 (1.03–1.43)	1.14 (0.99–1.30)

Outcome	Influenza only (18.5%)	COVID-19 vaccine only (13.7%)	Both (26.3%)	Any vaccine vs neither
Intellectual disability	1.59 (1.12–2.25)	1.00 (0.66–1.52)	1.62 (1.17–2.25)	1.45 (1.09–1.92)
Developmental delay	1.50 (1.25–1.80)	1.18 (0.92–1.52)	1.37 (1.13–1.65)	1.39 (1.19–1.62)
Any NDD diagnosis	1.40 (1.23–1.59)	1.28 (1.12–1.47)	1.42 (1.27–1.59)	1.38 (1.26–1.51)
Special education	1.30 (1.14–1.47)	1.25 (1.08–1.44)	1.30 (1.16–1.47)	1.29 (1.17–1.42)
Asthma	1.38 (1.18–1.61)	1.04 (0.89–1.23)	1.59 (1.39–1.81)	1.37 (1.22–1.53)
Diabetes	0.86 (0.39–1.90)	1.30 (0.63–2.67)	1.45 (0.81–2.59)	1.24 (0.73–2.10)
Anxiety daily/weekly	1.14 (0.97–1.33)	1.29 (1.12–1.50)	1.32 (1.16–1.50)	1.26 (1.13–1.40)
Depression daily/weekly	1.23 (0.94–1.60)	1.13 (0.88–1.46)	1.24 (1.01–1.53)	1.20 (1.00–1.45)
MH medication, 12 mo	1.88 (1.55–2.28)	1.59 (1.33–1.91)	2.09 (1.80–2.44)	1.88 (1.65–2.15)
MH therapy, 12 mo	1.46 (1.23–1.73)	1.54 (1.32–1.80)	1.91 (1.67–2.18)	1.67 (1.49–1.87)
Fair/poor health	1.25 (0.93–1.67)	1.06 (0.74–1.51)	1.31 (0.97–1.77)	1.22 (0.96–1.55)
ER visit, 12 mo	1.36 (1.22–1.52)	1.04 (0.89–1.20)	1.18 (1.06–1.33)	1.23 (1.13–1.35)
Hospitalized, 12 mo	1.44 (1.08–1.92)	0.97 (0.67–1.40)	1.49 (1.14–1.95)	1.36 (1.09–1.71)
HPV model, 2022, ages 9–17 (n = 3,606): autism, ever	Influenza 1.26 (0.80–1.99)	COVID-19 vaccine 1.05 (0.67–1.64)	HPV 1.17 (0.74–1.85)	—

Table 6. Four-level vaccine-type exposure and all outcomes, NHIS 2022–2024, ages 0–17 (n = 21,658; ages 2–17 for ASD, ADHD, and learning disability): adjusted odds ratios vs neither vaccine (M3).

Weighted share of sample in parentheses in column headers; neither-vaccine group 41.5%. Adolescents 12–17 only, autism ever: influenza only 0.75 (0.40–1.38); COVID-19 vaccine only 1.04 (0.71–1.51); both 1.69 (1.23–2.33).

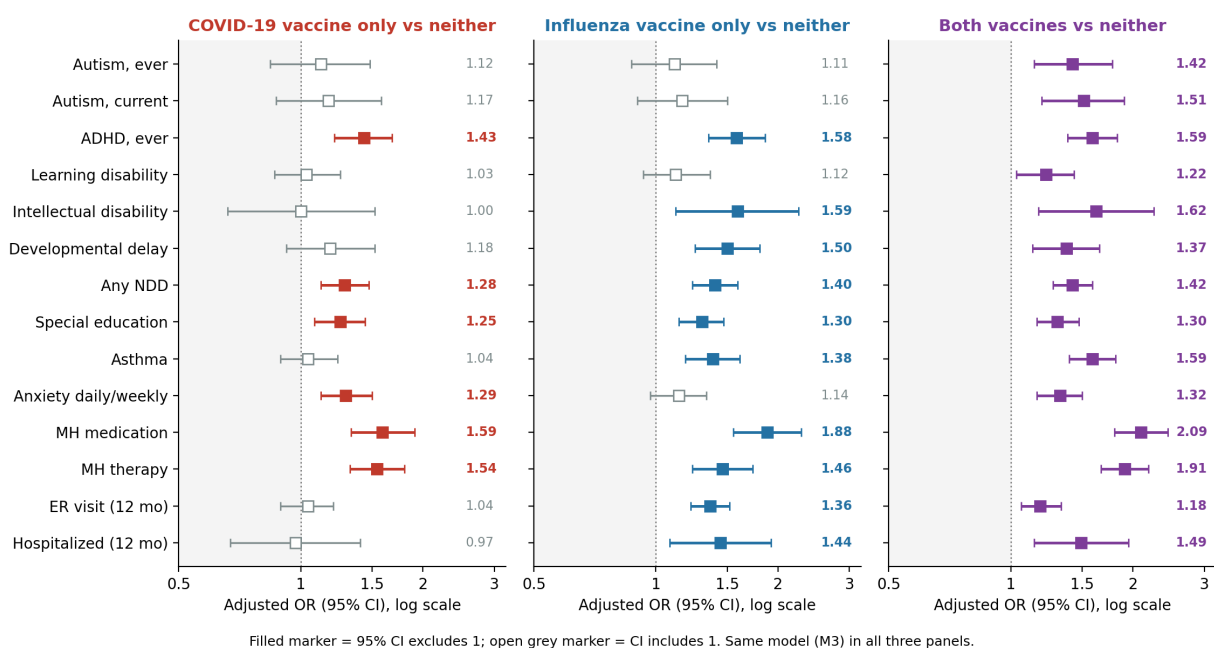


Figure 4. Adjusted odds ratios (M3) for all outcomes by vaccine-type combination vs neither vaccine, NHIS 2022–2024 (ages 2–17 for ASD, ADHD, and learning disability; 5–17 for anxiety; 0–17 otherwise).

COVID-19 vaccine only, influenza only (past 12 months), and both, each compared with children who received neither. Identical models. MH, mental health; NDD, neurodevelopmental disorder.

3.7 Utilization-adjusted sensitivity analysis

In the 2021–2024 sample aged 5–17 ($n = 18,521$), adding emergency-department use, hospitalization, and prescription use (M4) attenuated but did not eliminate the both-vaccines association: current ASD 1.46 (1.16–1.84) to 1.31 (1.04–1.66); current ADHD 1.56 (1.35–1.79) to 1.27 (1.10–1.47). COVID-19-vaccine-only estimates were 1.11 to 1.07 (0.80–1.44) for ASD and 1.28 to 1.21 (1.02–1.43) for ADHD (**Supplementary Table S2**). Prescription use in the past year was reported for 61% of children with current ASD and 76% with current ADHD vs 39% overall.

3.8 Reverse association

Children with an existing diagnosis were more likely to be vaccinated ($n = 19,882$; adjusted odds of vaccination: ASD 1.26, 1.04–1.52; ADHD 1.28, 1.14–1.44; asthma 1.24, 1.12–1.38; special education 1.19, 1.08–1.31). Among vaccinated 5–7-year-olds with current ASD, 31% had received ≥ 3 doses vs 24% of those without.

3.9 Supplementary samples

In 2021 (ages 12–17, quarters 3–4; $n = 1,587$), lifetime ASD was 4.17% among vaccinated vs 2.90% among unvaccinated adolescents (aOR 1.31, 0.65–2.63). In 2025 (current-season dose; 12% uptake; $n = 5,935$), current-season vaccination was associated with lifetime ASD 1.50 (0.97–2.30), any neurodevelopmental diagnosis 1.32 (1.03–1.68), and anxiety 1.67 (1.26–2.22) (**Supplementary Table S3**).

3.10 Additional analyses: restriction, head-to-head comparison, and effect modification by sex

Restricting to children with no lifetime asthma or diabetes and not in fair/poor health ($n = 16,803$ for lifetime ASD, 634 cases; $n = 16,796$ for current ASD, 586 cases; $n = 16,799$ for

ADHD, 1,763 cases) left the estimates unchanged (**Table 7**): lifetime ASD aOR vs neither vaccine 1.12 (0.86–1.47) for influenza only, 1.10 (0.79–1.52) for COVID-19 vaccine only, and 1.51 (1.17–1.95) for both; current ASD 1.16, 1.10, and 1.56 (1.19–2.04). Prioritization for physical high-risk conditions therefore does not account for the association.

In a direct comparison restricted to the two single-vaccine groups (COVID-19 vaccine only, $n = 3,205$; influenza only, $n = 3,763$; analytic $n = 6,313$ for lifetime ASD with 257 cases and 6,310 for current ASD with 239 cases), COVID-19-vaccine-only children had higher adjusted odds of lifetime ASD (1.45, 1.03–2.05; $p = 0.03$) and current ASD (1.47, 1.02–2.12; $p = 0.04$), while having lower odds of asthma (0.73, 0.60–0.89), emergency-department visits (0.77, 0.64–0.93), and hospitalization (0.76, 0.50–1.17), and equivalent odds of ADHD (0.94), any neurodevelopmental diagnosis (1.00), anxiety (1.08), and mental-health therapy (1.06). This contrast is sensitive to model specification: within the full four-level model the ratio of COVID-19-vaccine-only to influenza-only estimates is 1.00, because the two groups differ markedly in age composition (COVID-19 vaccine only predominantly adolescents; influenza only predominantly young children). Within age strata, COVID-19-vaccine-only point estimates exceeded influenza-only estimates for current ASD (ages 5–7, $n = 3,472$, 151 cases: 1.39 vs 1.04; ages 8–11, $n = 4,763$, 198 cases: 1.20 vs 0.82; ages 12–17, $n = 8,511$, 322 cases: 1.10 vs 0.81), but no stratum-specific COVID-19-vaccine-only estimate excluded the null; the COVID-19-vaccine-only group contributed 10, 28, and 70 current-ASD cases in these strata, respectively.

Sex modified the associations. The COVID-19 vaccination–ASD association was present in girls ($n = 9,393$, 209 lifetime cases: 1.60, 1.11–2.32; current 1.71, 1.16–2.53) and absent in boys ($n = 10,057$, 623 lifetime cases: 1.08, 0.86–1.37; current 1.10, 0.86–1.40); sex $\times$ vaccination interaction OR 1.53 (1.06–2.21), $p = 0.02$. The influenza association showed the

reverse pattern (boys 1.27, 1.03–1.56; girls 0.94, 0.69–1.26). The same sex pattern held for ADHD (girls 1.44, boys 1.09; interaction $p = 0.004$) and any neurodevelopmental diagnosis (girls 1.32, boys 1.03; $p < 0.001$). Among children aged 5–7 with ≥ 3 doses, current ASD aORs were 2.78 (1.23–6.29) in boys (12 cases) and 4.93 (1.54–15.75) in girls (6 cases).

Analysis	Outcome	Estimate (95% CI)
Restricted to no asthma, no diabetes, not fair/poor health; aOR vs neither vaccine	Autism, ever (n = 16,803; 634 cases): influenza only / COVID-19 vaccine only / both	1.12 (0.86–1.47) / 1.10 (0.79–1.52) / 1.51 (1.17–1.95)
	Autism, current (n = 16,796; 586 cases)	1.16 (0.87–1.55) / 1.10 (0.79–1.55) / 1.56 (1.19–2.04)
	ADHD, ever (n = 16,799; 1,763 cases)	1.57 (1.31–1.88) / 1.39 (1.15–1.68) / 1.57 (1.34–1.84)
	Anxiety daily/weekly (n = 14,249; 2,273 cases)	1.10 (0.92–1.31) / 1.31 (1.12–1.54) / 1.32 (1.15–1.51)
COVID-19 vaccine only (n = 3,205) vs influenza only (n = 3,763), head to head	Autism, ever (n = 6,313; 257 cases)	1.45 (1.03–2.05), $p = 0.03$
	Autism, current (n = 6,310; 239 cases)	1.47 (1.02–2.12), $p = 0.04$
	ADHD, ever (n = 6,310; 778 cases)	0.94 (0.76–1.17)
	Any NDD diagnosis (n = 6,920; 1,335 cases)	1.00 (0.83–1.20)
	Anxiety daily/weekly (n = 5,327; 932 cases)	1.08 (0.88–1.32)
	Asthma (n = 6,915; 759 cases)	0.73 (0.60–0.89), $p = 0.002$
	ER visit, 12 mo (n = 6,909; 1,246 cases)	0.77 (0.64–0.93), $p = 0.007$
	Hospitalized, 12 mo (n = 6,725; 175 cases)	0.76 (0.50–1.17)
Current autism by age stratum: influenza only / COVID-19 vaccine only / both vs neither	5–7 y (n = 3,472; 151 cases)	1.04 (0.62–1.72) / 1.39 (0.62–3.10) / 1.66 (0.99–2.80)
	8–11 y (n = 4,763; 198 cases)	0.82 (0.47–1.44) / 1.20 (0.68–2.14) / 0.99 (0.63–1.54)
	12–17 y (n = 8,511; 322 cases)	0.81 (0.43–1.55) / 1.10 (0.74–1.64) / 1.79 (1.27–2.51)
Sex-stratified: COVID-19 vaccine ever vs never (adj. influenza) influenza (adj. COVID-19 vaccine)	Autism, ever — boys (n = 10,057; 623 cases)	COVID-19 vaccine 1.08 (0.86–1.37) influenza 1.27 (1.03–1.56)
	Autism, ever — girls (n = 9,393; 209 cases)	COVID-19 vaccine 1.60 (1.11–2.32) influenza 0.94 (0.69–1.26)
	Sex $\times$ COVID-19 vaccine interaction	1.53 (1.06–2.21), $p = 0.02$
	Autism, current — boys / girls	1.10 (0.86–1.40) / 1.71 (1.16–2.53); interaction $p = 0.015$
	ADHD, ever — boys / girls	1.09 (0.92–1.29) / 1.44 (1.19–1.74); interaction $p = 0.004$
	Any NDD — boys / girls	1.03 (0.91–1.17) / 1.32 (1.12–1.55); interaction $p < 0.001$

Analysis	Outcome	Estimate (95% CI)
	Anxiety — boys / girls	1.17 (0.99–1.39) / 1.30 (1.12–1.52); interaction p = 0.007
≥3 doses vs 0, current autism, ages 5–7	Boys (12 exposed cases) / girls (6 exposed cases)	2.78 (1.23–6.29) / 4.93 (1.54–15.75)
≥3 doses vs 0, current autism, ages 5–17	Boys (66) / girls (38)	1.33 (0.93–1.92) / 1.89 (1.17–3.04)

Table 7. Additional analyses: restriction to physically healthy children, direct comparison of single-vaccine groups, and effect modification by sex (NHIS 2022–2024, M3).

Head-to-head model estimated within the two single-vaccine groups only; within the full four-level model the COVID-19-vaccine-only/influenza-only ratio is 1.00 (see text).

3.11 Propensity-score and overlap weighting

The propensity-score model ($n = 21,491$) yielded scores ranging from 0.006 to 0.979, with means of 0.609 in vaccinated and 0.277 in unvaccinated children. Under survey weights alone, vaccinated and unvaccinated children differed substantially on age (standardized mean difference 0.78), influenza vaccination (0.75), family income $\geq 400\%$ of the poverty level (0.51), parental bachelor's degree (0.51), private insurance (0.41), and public insurance (−0.38). Overlap weighting reduced every standardized mean difference to below 0.001, and stabilized inverse-probability weighting to below 0.09 (**Table 8, Figure 5A**).

With covariate balance achieved and no covariates in the outcome model, the association between COVID-19 vaccination and autism was unchanged in magnitude and statistically significant under all three weighting schemes: lifetime autism 1.23 (1.01–1.50) under overlap weights, 1.29 (1.04–1.61) under stabilized inverse-probability weights, and 1.26 (1.04–1.54) under trimmed weights; current autism 1.26 (1.03–1.56), 1.33 (1.06–1.67), and 1.30 (1.05–1.60). The doubly robust model (overlap weights plus covariates) gave 1.24 (1.02–1.52) and 1.28 (1.04–1.58) (**Figure 5B**). Anxiety (1.20, 1.07–1.35) and any neurodevelopmental diagnosis (1.13, 1.02–1.26) remained elevated under overlap weighting; ADHD attenuated to 1.14 (1.00–1.29) and asthma to 1.09 (0.97–1.22).

The negative-control outcomes behaved as balance would predict: emergency-department visits moved from 0.72 (0.66–0.78) crude to 0.95 (0.85–1.05) and overnight hospitalization from 0.82 (0.67–1.00) to 1.02 (0.80–1.29), both null. Weighting that removes measured differences in socioeconomic position and healthcare contact therefore eliminates the acute-care associations while leaving the autism association intact.

Covariate / outcome	Survey weight	Overlap weight	Stabilized IPTW	Trimmed IPTW
Standardized mean differences				
Age	0.780	<0.001	0.081	—
Female	0.014	<0.001	−0.014	—
Income <100% FPL	−0.251	<0.001	0.018	—
Income ≥400% FPL	0.505	<0.001	0.003	—
Parental bachelor's degree	0.505	<0.001	<0.001	—
Private insurance	0.414	<0.001	−0.007	—
Public insurance	−0.381	<0.001	0.002	—
Non-Hispanic White	−0.062	<0.001	−0.039	—
Wellness visit, 12 mo	0.012	<0.001	0.012	—
Usual source of care	0.036	<0.001	0.002	—
Influenza vaccine, 12 mo	0.747	<0.001	0.041	—
Odds ratios (exposure-only outcome model)				
Autism, ever	0.97 (0.82–1.15)	1.23 (1.01–1.50)	1.29 (1.04–1.61)	1.26 (1.04–1.54)
Autism, current	1.01 (0.84–1.20)	1.26 (1.03–1.56)	1.33 (1.06–1.67)	1.30 (1.05–1.60)
ADHD, ever	1.42 (1.28–1.57)	1.14 (1.00–1.29)	1.15 (1.00–1.32)	1.20 (1.06–1.37)
Any NDD diagnosis	1.31 (1.21–1.43)	1.13 (1.02–1.26)	1.18 (1.05–1.33)	1.22 (1.10–1.35)
Asthma, ever	1.52 (1.39–1.66)	1.09 (0.97–1.22)	1.15 (1.01–1.30)	1.17 (1.05–1.32)
Anxiety daily/weekly	1.32 (1.19–1.45)	1.20 (1.07–1.35)	1.17 (1.03–1.33)	1.20 (1.07–1.35)
ER visit, 12 mo (negative control)	0.72 (0.66–0.78)	0.95 (0.85–1.05)	0.97 (0.85–1.11)	0.92 (0.83–1.03)
Hospitalized, 12 mo (negative control)	0.82 (0.67–1.00)	1.02 (0.80–1.29)	0.98 (0.76–1.27)	0.95 (0.76–1.20)
Doubly robust (overlap weights + covariates)				
Autism, ever / current	—	1.24 (1.02–1.52) / 1.28 (1.04–1.58)	—	—

Table 8. Propensity-score weighting: covariate balance and odds ratios for COVID-19 vaccination versus no COVID-19 vaccination, NHIS 2022–2024 (n = 21,491).

Propensity score estimated by survey-weighted logistic regression on age, age², sex, survey year, race/ethnicity, poverty ratio, parental education, insurance, region, wellness visit, usual source of care, and influenza vaccination. Overlap weight = survey weight × (1 − propensity score) for vaccinated and × propensity score for unvaccinated children. Trimmed IPTW: stabilized weights truncated at the 99th percentile. Outcome models contain the exposure only except in the doubly robust row. FPL, federal poverty level; IPTW, inverse probability of treatment weighting; NDD, neurodevelopmental disorder.

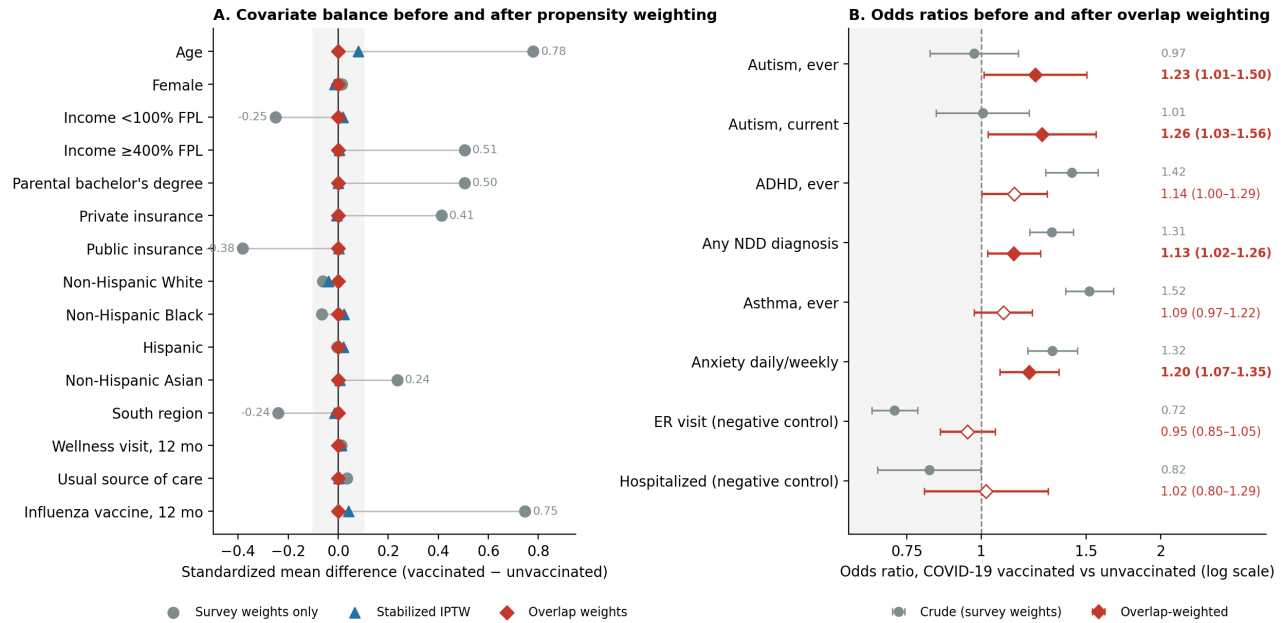


Figure 5. Propensity-score weighting. (A) Standardized mean differences between COVID-19-vaccinated and unvaccinated children for each covariate under survey weights alone, stabilized inverse-probability-of-treatment weights, and overlap weights; the shaded band marks $|0.1|$. (B) Odds ratios for COVID-19 vaccination under survey weights (crude) and under overlap weights with no covariates in the outcome model; filled markers and bold labels, 95% CI excludes 1. Balancing leaves the autism association intact while moving the negative-control outcomes to the null.

3.12 Summary of evidence

Figure 6 summarizes the evidence for the COVID-19 vaccination–autism association in three parts: the opposing social gradients of vaccination and reported autism that mask the association in crude analysis; the crude weighted prevalence of current autism by dose count, which rises from 4.02% to 6.19% across 0 to ≥ 3 doses at ages 5–7; and the adjusted current-autism estimate across all 27 specifications in this study. Twenty-six of 27 point estimates exceed 1 and 13 exclude the null. The estimates that do not reach 1 or that include the null—ages 8–11 with ≥ 3 doses, the two-year-lag cohort, boys, and the single-dose group—are shown alongside the others.

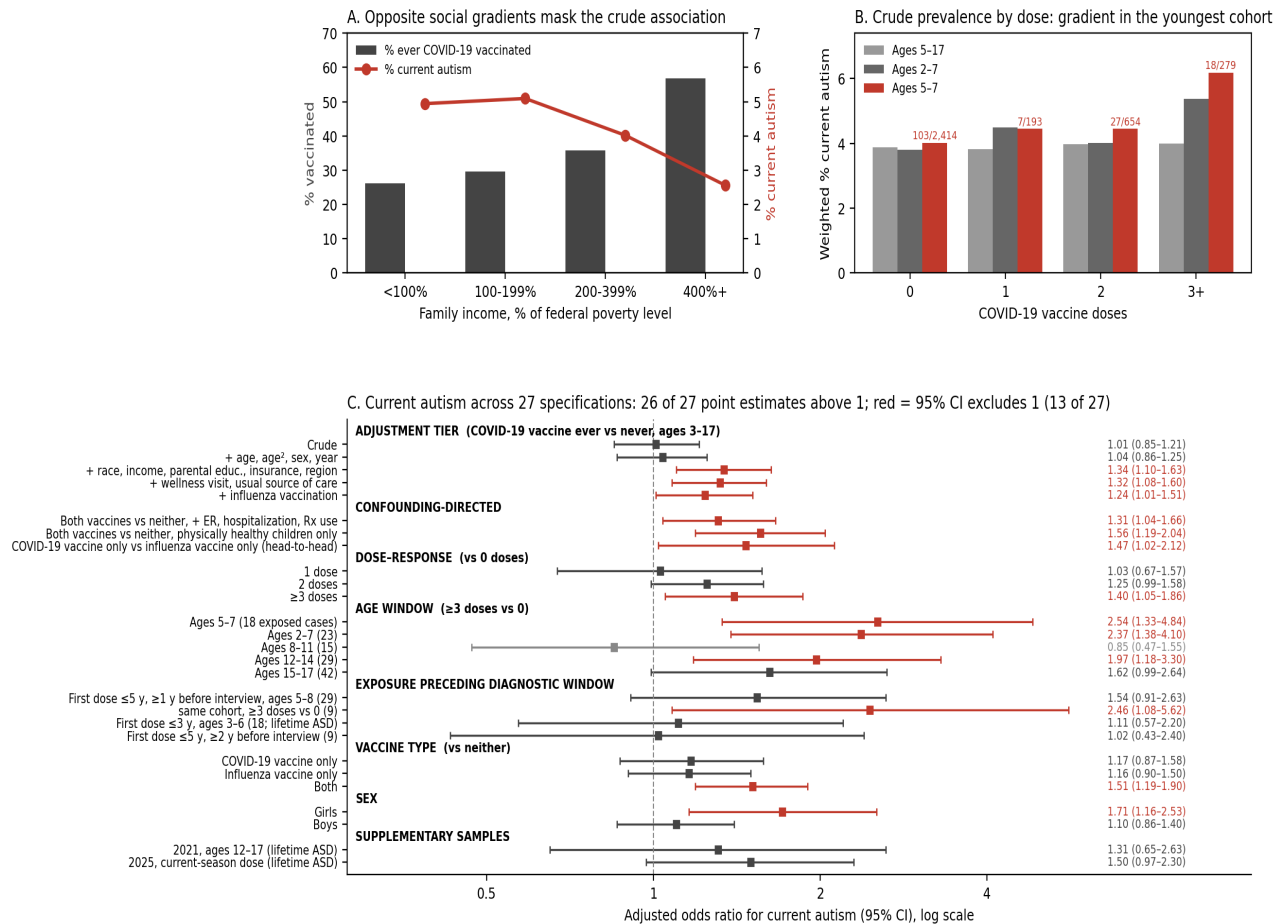


Figure 6. Summary of evidence for the COVID-19 vaccination–autism association. (A) Vaccination coverage rises and reported current-autism prevalence falls across family income, producing negative confounding that masks the association in crude analysis. (B) Weighted prevalence of current autism by COVID-19 vaccine dose count at ages 5–17, 2–7, and 5–7 (cases/n shown for ages 5–7). (C) Adjusted odds ratios for current autism across 27 specifications: 26 of 27 point estimates exceed 1 and 13 exclude the null (red). Grey estimates: point estimate ≥ 1 with CI including 1; light grey: point estimate below 1. Exposed case counts in parentheses.

4. Discussion

4.1 Principal findings

In a nationally representative U.S. dataset capturing both pediatric COVID-19 vaccination and neurodevelopmental diagnoses, and in a direct comparison of COVID-19-vaccinated with contemporaneous unvaccinated children, COVID-19-vaccinated children had 26–34% higher adjusted odds of autism, 33% higher odds of ADHD, and higher odds of anxiety, special-education use, and mental-health treatment than unvaccinated children. Influenza vaccination was associated with the same outcomes at similar magnitude, and the strongest estimates were among children who received both vaccines. Influenza vaccination was ascertained as receipt in the past 12 months rather than lifetime history. The associations were consistent across models, exhibited a monotonic dose gradient after adjustment, and were largest in the youngest exposed cohort, where ≥ 3 COVID-19 vaccine doses carried a 2.4- to 2.5-fold increase in adjusted odds of current autism. Anxiety in school-age children showed a degree of specificity to COVID-19 vaccine relative to influenza vaccination. The associations persisted across every adjustment tier, were unchanged after restriction to physically healthy children, and were larger in COVID-19-vaccine-only than in influenza-only children in direct comparison despite the former's lower acute-care use. After extensive measured adjustment, propensity-score balancing, restriction to physically healthier children, and comparison with influenza vaccination, a residual association with parent-reported ASD and ADHD remains. That residual

is most plausibly consistent with a vaccine-related effect on neurodevelopment. Although unmeasured healthcare-seeking and diagnostic intensity cannot be ruled out as potential contributors, the cross-sectional design cannot fully prioritize or distinguish these explanations. **Figure 7** summarizes the principal associations and the largest subgroup estimate, in children aged 5–7 years who received three or more doses.

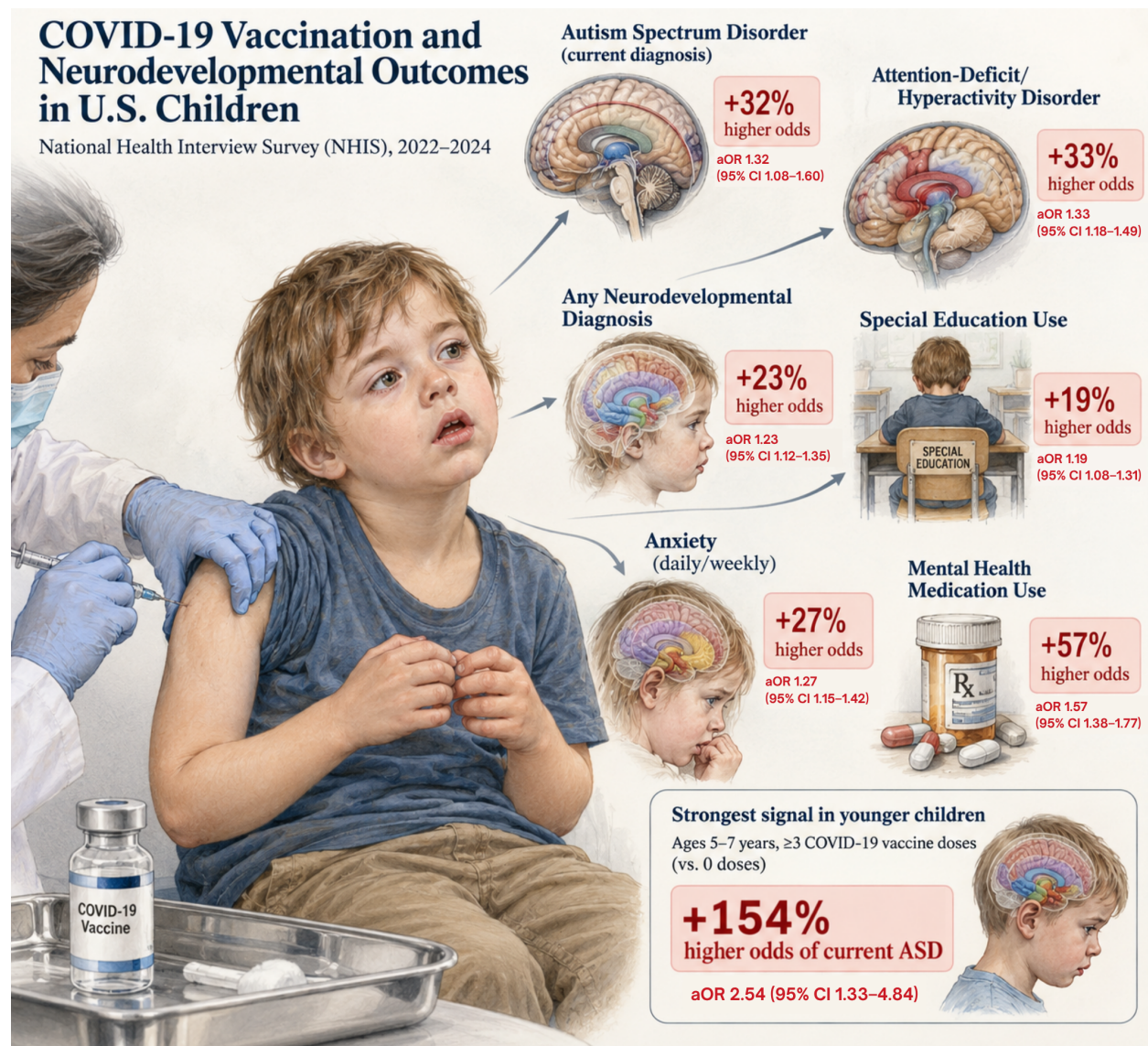


Figure 7. Graphical summary of principal findings. Adjusted odds ratios (aOR) with 95% confidence intervals for current autism spectrum disorder, ADHD, any neurodevelopmental diagnosis, special-education use, daily or weekly anxiety, and mental-health medication use in COVID-19-vaccinated versus unvaccinated U.S. children, NHIS 2022–2024, from the fully adjusted model (age, age², sex, survey year,

race/ethnicity, poverty ratio, parental education, insurance, region, wellness visit, usual source of care; Table 2). Percentages denote the relative increase in odds. Lower panel: current autism in children aged 5–7 years who had received three or more COVID-19 vaccine doses versus none (Table 4). Variance by Taylor linearization on survey strata and primary sampling units. Illustration is schematic.

4.2 Interpretation in light of the negative controls

Two explanations compete for these findings: a biological effect of vaccination on neurodevelopment and confounding by the clinical engagement that produces both vaccination and diagnosis. The analyses in Sections 3.5–3.11 were designed to discriminate between them, and their results should be weighed on both sides.

Several results resist the confounding explanation. Restricting the sample to children without asthma, diabetes, or fair/poor general health (hereafter "physically healthy")—attenuating the principal measurable pathway by which chronic physical illness drives vaccination—left every estimate unchanged, so whatever produces the association is not prioritization for these conditions. In the direct comparison of single-vaccine groups, COVID-19-vaccine-only children had 45–47% higher adjusted odds of autism than influenza-only children while being healthier on every acute-care and physical-health measure; a confounder that raises autism reporting through clinical contact would be expected to raise asthma, emergency visits, and hospitalization in the same group, and it did not. This comparison is limited by the influenza measure, which captures receipt in the past 12 months only; some children classified as COVID-19-vaccine-only will have received influenza vaccine in earlier seasons. Within age strata, COVID-19-vaccine-only point estimates consistently exceeded influenza-only estimates for current autism, and the utilization-adjusted model retained a 31% elevation in the doubly vaccinated group. Among children first vaccinated at or before age 5 and at least one year before the school-entry diagnostic window, ≥ 3 doses carried a 2.5-fold elevation in current autism—the same magnitude as the age 5–7 estimate—in the one cohort where

exposure preceding diagnosis is plausible for most cases. Propensity-score methods provide the most direct test: overlap weighting removed every measured difference between vaccinated and unvaccinated children, including the large imbalances in age, income, parental education, insurance, and influenza vaccination; the autism association was undiminished (1.23–1.33 across weighting schemes, significant in each), while the negative-control outcomes of emergency-department use and hospitalization moved to the null. A confounder acting through socioeconomic position or healthcare contact should have been removed by that balancing, and the acute-care outcomes show that it largely was. The E-value analysis states the remaining requirement explicitly: to nullify the primary estimate, an unmeasured confounder would need associations of risk ratio ≥ 2.0 with both vaccination and autism, and the strongest measured predictor of each is inversely related to the other—high income doubles vaccination but halves reported autism; public insurance raises reported autism but lowers vaccination.

Two patterns are consistent with a causal effect: a monotonic dose gradient in the full sample—including a 30% increase in odds per dose category among children aged 5–7—and the concentration of the largest estimates among the youngest exposed children. The strength criterion is modestly met given the ORs of 1.2–1.3. Similarly, coherence is partially met: influenza and HPV produce similar ASD point estimates; and the sex pattern is opposite the cited rat model (we address this below). Reports of vaccine-derived spike protein persisting in the circulation for months to years [13,14,15,16], including detection in cerebral arteries [19], together with evidence of blood–brain-barrier disruption [20] and autism-like phenotypes after prenatal spike-protein exposure in rats [24], provide a mechanistic rationale for the hypotheses tested here. In addition to biological plausibility, consistency across models and weighting schemes are among the other classical causal considerations satisfied by these findings.

Specificity and temporality are not clearly satisfied by the present study, and the experimental criterion cannot be met by an observational design. First, in terms of specificity, COVID-19 vaccination alone and influenza vaccination alone produced similar ASD estimates (1.11 and 1.12), the ASD association was concentrated among children receiving both vaccines, and HPV vaccination showed an equivalent estimate. Both comparisons are less complete than the COVID-19 vaccination measure: influenza vaccination reflects receipt in the past 12 months only, and HPV vaccination was ascertained in a single survey year (2022) for children aged 9–17. Influenza vaccination was equally or more strongly associated with ADHD, intellectual disability, developmental delay, and asthma, and with emergency-department visits and hospitalization. This pattern may be a signature of confounding by healthcare engagement and high-risk prioritization: children with chronic conditions are both more likely to be diagnosed and, per clinical guidance, more likely to be vaccinated [35]. The reverse association we observed directly (higher vaccination odds given an existing diagnosis) shows that the pathway operates in this population. An alternative reading, consistent with the multifactorial and cumulative-exposure model advanced in a comprehensive review of ASD determinants [28], is that the shared association reflects total vaccine exposure rather than any single product, so that equivalent single-vaccine estimates and the largest estimates in doubly vaccinated children are what a cumulative effect would also produce. The two interpretations diverge on the negative-control outcomes: a cumulative-vaccination effect on neurodevelopment does not predict the parallel elevations in emergency-department visits and hospitalization observed in the same groups, whereas healthcare-engagement confounding predicts exactly that pattern.

Second, consider temporality: the cross-sectional design is by definition a snapshot in time. Thus, it cannot establish that vaccination preceded diagnosis, and for the adolescent

cohorts—where the strongest ≥ 3 -dose estimates at 12–14 (1.97) and 15–17 (1.62) arise from children first vaccinated at 12 or older—it establishes the reverse, so those estimates cannot be causal and must be understood as selection of already-diagnosed children into higher dose counts. For the youngest cohorts the ordering is genuinely undetermined. The conventional assumption that ASD is diagnosed by age 4 would place many of the 18 cases in the 5–7-year ≥ 3 -dose group after diagnosis; but the diagnostic window in practice extends through school entry age, every first dose in that group fell within it, and 14 of 18 preceded the interview by at least a year. In cohorts constructed so that first vaccination preceded the school-entry window by at least one year, the ≥ 3 -dose estimate for current ASD was 2.46 (1.08–5.62), consistent with the age 5–7 finding, although based on 9 exposed cases; the single-exposure estimates in the same cohorts (1.32–1.54) did not exclude the null, and requiring a two-year lag returned a null on 9 cases.

Developmental delay—which is diagnosed earlier and would be expected to move with any true early neurodevelopmental insult—was not elevated in any pre-window cohort, i.e., in any cohort constructed so that vaccination preceded the school-entry diagnostic window. Adjusted odds ratios for this outcome ranged from 0.68 to 0.92. That pattern contrasts with several ASD estimates in the same pre-window samples and is compatible with the autism findings not reflecting a general excess of neurodevelopmental diagnoses. A further consideration is that the timing of clinical presentation after a novel exposure is itself unknown: if vaccine-related neurodevelopmental effects manifest or are recognized later than idiopathic ASD, the age-at-first-dose argument loses force. This hypothesis has never been examined and NHIS cannot test it; it does, however, mean that later age at exposure is not by itself a refutation.

Latency is a related issue. If vaccination contributed to emerging or late-recognized neurodevelopmental conditions in adolescents, associations should strengthen with time since exposure. Instead, they weakened for adolescents: current-ASD odds were higher for first doses within 2 years of interview than for earlier doses, and the anxiety association disappeared beyond 2 years. Associations in adolescence that peak with recent vaccination are more readily explained by recent clinical contact than by delayed pathology.

The utilization-adjusted models attenuated the both-vaccines ASD association from 1.46 to 1.31, indicating that measured healthcare use accounts for part but not all of it. Past-year emergency, hospital, and prescription use are, however, weak proxies for the years of clinical engagement that produce a developmental diagnosis, and prescription use in this population is largely treatment of the outcome. The residual association should not be read as robust to healthcare-engagement confounding; it is robust to three crude measures of it.

The sex-specific pattern warrants particular attention. The prenatal spike-protein rat model shows a male-predominant effect; the present data show the COVID-19 vaccine association confined to girls and the influenza association confined to boys. A female-predominant association is the pattern expected from increased diagnostic evaluation, because autism in girls is systematically under-recognized and surfaces when clinical scrutiny increases [34]. This finding does not support the specific mechanism proposed and is more readily explained by detection than by biology, although a sex-differential vaccine effect not captured by the rat model cannot be excluded.

The anxiety finding is the most difficult to dismiss on specificity grounds, and it is also the outcome least dependent on clinical contact for its ascertainment: anxiety frequency is a parent-rated symptom item rather than a clinician-assigned diagnosis, so a detection mechanism

that raises diagnosed conditions through more frequent evaluation does not readily account for it. It attenuates substantially with adjustment for prior COVID-19 infection, which is independently associated with anxiety, and it is compatible with family-level pandemic-related health concern that drives both vaccination and reported child anxiety [36]. It nonetheless merits follow-up in longitudinal data with symptom-onset dates.

4.3 Biological plausibility and the evidentiary gap

The mechanistic prior is not trivial. Vaccine-derived spike protein persists for months to years after vaccination: it circulates systemically, has been detected in plasma to 187 days and in CD16+ monocytes to 245 days, and has been found in brain vasculature to 17 months, in plasma and circulating exosomes to 1,173 days, and in peripheral tissue to 1,364 days [13,14,15,16,18,19]; the S1 subunit compromises the blood–brain barrier and is neurotoxic in culture [20,21]; prenatal spike-protein exposure in rats reproduces the behavioral, histological, cytokine, and BDNF features of autism models [24], with analogous behavioral and WNT/BDNF findings reported after prenatal BNT162b2 exposure [25]. Neuroinflammation may result from COVID-19 vaccination alone or with other childhood vaccines. Neuroinflammation is a recognized mechanistic contributor to neurodevelopmental disorders; the level of vaccine-induced neuroinflammation required to produce such disorders has not been established [27,28]. Our comprehensive review of ASD determinants concluded that early-timed, clustered childhood vaccination is a candidate modifiable risk factor within a multifactorial model in which immune activation during critical developmental windows converges with genetic and environmental susceptibility [28]; the present COVID-19 vaccine findings are consistent with that framework. Post-marketing disproportionality analyses of VAERS are consistent with a neurological signal. Relative to influenza vaccination, reporting after COVID-19 vaccination exceeded CDC/FDA

safety-signal thresholds for 47 adverse events in the cognitive-impairment category (proportional reporting ratio 118, 95% CI 87.2–160), 28 in the general psychiatric category (115, 85.1–156), and 11 in the suicide/homicide category (80.1, 57.3–112) [37]. A parallel analysis of the same system reported disproportionate reporting across several neurological outcome groupings after COVID-19 vaccination relative to influenza vaccination and to all other vaccines combined [38]. The cognitive and psychiatric categories bear directly on the functional domains examined here. Against this, the mRNA-specific prenatal rat findings are unreplicated and the human studies of in utero mRNA exposure—prospective cohorts followed to 18 and 30 months—found no neurodevelopmental differences [11,12]. Plausibility motivates a test; it does not substitute for one. The salient fact is that no study capable of performing that test has been done: no pediatric trial collected neurodevelopmental endpoints, no known active surveillance system monitored them after childhood vaccination, and the representative survey data that contain both variables cannot resolve timing. The same gap exists for the routine childhood schedule as a whole [28], and the present findings—an association shared by COVID-19 vaccination and influenza vaccination—bear on that broader question as much as on COVID-19 vaccination specifically.

Central nervous system inflammation has been described after COVID-19 vaccination in various age groups [39,40]; proposed etiologies include immune, endothelial, or direct spike protein–related mechanisms [18,20,21,39]. Still, genomic and mitochondrial factors may act as susceptibility modifiers. The associations reported above—a monotonic dose response, the largest current-ASD estimates at ages 5–7 and among children first vaccinated before the school-entry window, and amplification among children who received both COVID-19 and influenza vaccines—may also, in part, reflect a gene–environment model in which an immune or spike-protein insult lands on a metabolically constrained developing brain [28,41,42,43,44]. Of

interest, a mitochondrion under immune or febrile stress releases mitochondrial reactive oxygen species that activate NLRP3, IL-1 β /IL-18, and NF- κ B—the same innate axis implicated in maternal-immune-activation models of ASD [27,28,45]. The S1 subunit reproduces this injury in a human cardiomyocyte line: after a transient ACE2-dependent rise in membrane potential and ATP, prolonged exposure collapses the mitochondrial membrane potential, overloads mitochondrial calcium, fragments the network, down-regulates TOM20, and sustains reactive oxygen species [46].

The same exposure may interrupt the protein–protein interaction networks that couple endothelium, glia, and synapse—the communication layer that converts a systemic inflammatory pulse into a circuit-level phenotype [28]. Vaccine-derived spike protein persists for months to years after injection: it circulates systemically and in CD16⁺ monocytes for months, and has been localized to cerebral arterial intima to 17 months and to peripheral tissue to 1,364 days [13,14,15,16,19]; S1 alone opens the blood–brain barrier in two- and three-dimensional microvascular models and elicits endothelial NF- κ B activation and cytokine release [20]. Within the parenchyma, spike protein drives astroglial activation, TNF- α and IL-17 elevation, hippocampal and cerebellar gliosis, and a fall in BDNF—the tetrad produced by prenatal spike-protein exposure in male rats [24]. BDNF–TrkB and WNT are principal hubs that stabilize excitatory synapses and restrain complement-mediated over-pruning; their interruption yields the excitation–inhibition imbalance that characterizes ASD circuitry [24,27,28]. Concurrent S1 effects on mitochondrial quality-control proteins and innate-immune scaffolds describe a multi-node perturbation rather than a single ligand–receptor event: endothelial ACE2–tight-junction failure, innate-immune amplification, mitochondrial–ROS coupling, and BDNF/WNT synaptic-maintenance failure [20,24,45,46].

4.4 Strengths and limitations

Strengths include a direct comparison of COVID-19-vaccinated with contemporaneous unvaccinated children—a comparison unavailable to self-controlled and historical-rate surveillance designs, which have no unvaccinated group; national representativeness; a pooled sample of approximately 20,000 children with approximately 840 ASD cases; harmonized exposure across four survey years; a transparent, fully reported set of model tiers, subgroups, and negative-control exposures and outcomes; and full survey-design variance estimation.

Limitations include the cross-sectional design with parent-reported exposures and lifetime outcomes; absence of diagnosis dates, with first-dose timing resolved only to year; one sample child per household, precluding sibling designs; residual confounding by unmeasured healthcare engagement, parental health attitudes, and prior infection; small case counts in the youngest subgroups; multiple subgroup comparisons without correction in an exploratory analysis whose secondary analyses were developed sequentially rather than registered in advance; NHIS vaccination items that change across years, with the 2025 item capturing current-season receipt only; and an influenza measure limited to receipt in the past 12 months, so that lifetime influenza exposure, dose history, and time since dose could not be examined and the negative-control comparison rests on a weaker exposure measure than the lifetime COVID-19 vaccination item. Importantly, we did not have data on all concurrently administered childhood vaccines; thus, we cannot discern whether a neurodevelopmental outcome was associated with an individual mRNA product or with the combined effect of multiple childhood vaccines, including COVID-19, at the same clinic visit.

4.5 Concurrent vaccine administration

COVID-19 vaccines are administered under the ACIP child and adolescent immunization schedule and may be co-administered with any other age-indicated vaccine at the same visit [2,3,4,47]. A child receiving a first COVID-19 vaccine dose at a routine well-child or school-entry visit may therefore receive it alongside DTaP or Tdap, inactivated poliovirus vaccine, measles–mumps–rubella and varicella vaccine (or MMRV), *Haemophilus influenzae* type b, hepatitis A and hepatitis B, pneumococcal conjugate, rotavirus, meningococcal ACWY or B, human papillomavirus, respiratory syncytial virus products, or seasonal influenza vaccine, depending on age and catch-up status [47]. The 4–6-year visit in particular combines the DTaP, IPV, and MMR/varicella boosters, and the 11–12-year visit combines Tdap, MenACWY, and HPV [47]. In this sample, 58.8% of influenza-vaccinated children had also received a COVID-19 vaccine compared with 24.8% of those not influenza-vaccinated, and the largest exposure group was children who received both products ($n = 6,090$), consistent with substantial same-visit or same-season co-administration.

NHIS does not record which vaccines were given at the same encounter, and this has three consequences for interpretation. First, an association attributed here to COVID-19 vaccination may reflect the cumulative antigenic, adjuvant, and immune-activating burden of several vaccines delivered together rather than any property of the mRNA product itself; the elevated estimates in the doubly vaccinated group and the dose gradient are both compatible with a cumulative-exposure model [28]. Second, declining the COVID-19 vaccine may have been for many families an active and specific choice made against a background of otherwise routine vaccination, reflecting a product-specific decision by a parent or clinician rather than a general stance toward immunization; such children remain exposed to the rest of the schedule, and the comparison is therefore between children receiving the full schedule plus COVID-19 vaccines

and children receiving the full schedule without them. Third, and in the opposite direction, absence of COVID-19 vaccination may serve in a subset of families as a proxy for broader vaccine refusal, so that some of the reference group received few or no childhood vaccines at all. These two mechanisms are not mutually exclusive and act in opposite directions on the estimate: the first attenuates any COVID-19-specific effect toward the null by placing schedule-vaccinated children on both sides of the comparison, while the second, if vaccination in general contributes to the outcome, would inflate it away from the null. Neither can be quantified in NHIS, which carries no items on the routine schedule. Distinguishing a product-specific effect from a cumulative-schedule effect (as compared to an association), requires immunization-registry data recording every vaccine and every administration date, as well as date of outcome.

4.6 Implications

The associations reported here are of concerning magnitude, reproducible, robust to restrictive sampling and to propensity-score balancing. We adjusted for every known confounder NHIS measures and the associations remained statistically significant. We are concerned the associations may implicate causality because the COVID-19-vaccine-only group carried more autism than the influenza-only group, the relationships were dose-dependent, and the youngest-cohort were more greatly affected. We believe a large, linked birth cohort study (state immunization registry linked to Medicaid or electronic health records, or active surveillance system such as the Vaccine Safety Datalink) enrolling children vaccinated before age 3, accounting for all vaccines administered, with incident ASD and ADHD validated by clinical examination, with influenza (not COVID-19) vaccination as a negative control, and completely unvaccinated children as a second negative control would be an ideal way to further explore this hypothesis.

5. Conclusion

In this nationally representative comparison of COVID-19-vaccinated with contemporaneous unvaccinated U.S. children, COVID-19 vaccination was associated with higher odds of autism, ADHD, anxiety, special-education use, and mental-health treatment. The association with autism was not present in the unadjusted analysis and appeared after adjustment for socioeconomic position. It remained after further covariate adjustment, restriction to children without recorded physical illness, propensity-score weighting that reduced measured covariate imbalance, and sensitivity analyses accounting for healthcare utilization. Notably, the association strengthened with the number of doses received, was strongest in the youngest children exposed to multiple doses (including those vaccinated before the school-entry diagnostic window) and exceeded the association seen with influenza vaccination in direct comparison of the two single-vaccine groups—a group with less asthma, fewer emergency visits, and fewer hospitalizations. Under the same weighting that left the autism association intact, the acute-care negative controls fell to the null. An unmeasured confounder would need to be associated with both vaccination and autism, in the same direction, about twice as strongly as anything we measured, and the strongest measured predictors of the two run in opposite directions. These properties indicate a real effect, and they cohere with what is known of vaccine-derived spike protein: systemic circulation, detection in cerebral arteries long after injection, blood–brain-barrier disruption, and autism-like neurobehavioral and molecular change after prenatal exposure in animals.

Three findings constrain a causal interpretation: (1) influenza vaccination carried a comparable autism association despite containing no spike protein, mRNA, or lipid nanoparticle; (2) the cross-sectional design cannot establish that vaccination preceded diagnosis; and (3) because the NHIS does not record vaccines given with the COVID-19 dose, the observed

association may reflect mRNA vaccination, co-administered vaccines, or the combined burden of both. Autism now affects 1 in 31 American children and continues to rise. To our knowledge, pediatric trial and routine surveillance have not systematically assessed neurodevelopmental outcomes after childhood COVID-19 vaccination. This analysis offers a population-level signal that such an assessment is needed. A linked birth-cohort study should therefore examine COVID-19 vaccination before age 3, incident diagnoses ascertained after exposure, and pre-specified negative-control vaccines.

Declarations

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Conflicts of interest: Nothing to declare.

Ethics: NHIS public-use files are de-identified; institutional review was not required.

Data availability: NHIS public-use files are available at <https://www.cdc.gov/nchs/nhis/>.

Generative AI statement: Artificial intelligence (AI) tools (ChatGPT) were used to assist in the generation of Figure 7.

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Supplementary Material

Outcome	aOR (95% CI)	E-value (point)	E-value (CI bound)
Autism, ever	1.26 (1.04–1.52)	1.83	1.24
Autism, current	1.32 (1.08–1.60)	1.97	1.37
ADHD, ever	1.33 (1.18–1.49)	1.99	1.64
Anxiety daily/weekly	1.27 (1.15–1.42)	1.86	1.57
Current autism, ≥3 doses vs 0, ages 5–7	2.54 (1.33–4.84)	4.52	1.99

Supplementary Table S1. E-values for primary estimates (M3, COVID-19 vaccine ever vs never).

E-value = $OR + \sqrt{[OR \times (OR - 1)]}$; the minimum strength of association, on the risk-ratio scale, that an unmeasured confounder would need with both exposure and outcome to fully explain the observed estimate.

Outcome	Model	Influenza only	COVID-19 vaccine only	Both
Current autism	M3	0.98 (0.73–1.32)	1.11 (0.83–1.49)	1.46 (1.16–1.84)
	M4 (+ER, hosp., Rx)	0.86 (0.64–1.16)	1.07 (0.80–1.44)	1.31 (1.04–1.66)
Autism, ever	M3	0.94 (0.71–1.25)	1.07 (0.81–1.41)	1.39 (1.11–1.73)
	M4	0.83 (0.63–1.10)	1.03 (0.78–1.36)	1.25 (0.99–1.57)
Current ADHD	M3	1.54 (1.31–1.82)	1.28 (1.09–1.50)	1.56 (1.35–1.79)
	M4	1.30 (1.10–1.53)	1.21 (1.02–1.43)	1.27 (1.10–1.47)
Any NDD	M3	1.31 (1.14–1.50)	1.25 (1.09–1.43)	1.38 (1.24–1.55)
	M4	1.16 (1.01–1.33)	1.20 (1.05–1.38)	1.21 (1.08–1.35)
Asthma	M3	1.38 (1.17–1.63)	1.00 (0.86–1.16)	1.58 (1.39–1.79)
	M4	1.21 (1.02–1.43)	0.95 (0.81–1.11)	1.36 (1.20–1.55)
Anxiety daily/weekly	M3	1.14 (0.98–1.33)	1.33 (1.16–1.52)	1.34 (1.19–1.51)
	M4	1.05 (0.90–1.22)	1.30 (1.13–1.49)	1.22 (1.08–1.38)
Prescription use, 12 mo (as outcome)	M3	1.48 (1.31–1.67)	1.17 (1.05–1.31)	1.63 (1.48–1.79)

Supplementary Table S2. Utilization-adjusted sensitivity analysis (M4), NHIS 2021–2024, ages 5–17 (n = 18,521): adjusted OR vs neither vaccine.

Prescription use in past 12 months: 61% among children with current ASD, 76% with current ADHD, 39% overall.

Sample	Outcome	Weighted prevalence (vacc. vs unvacc.)	Adjusted OR (95% CI)
2021, ages 12–17, Q3–Q4 (n = 1,587)	Autism, ever	4.17% vs 2.90%	1.31 (0.65–2.63)
2025, current-season dose (n = 5,935; uptake 12%)	Autism, ever	6.54% vs 4.68%	1.50 (0.97–2.30)
	ADHD, ever	14.39% vs 11.13%	1.28 (0.95–1.72)
	Any NDD diagnosis	22.82% vs 17.70%	1.32 (1.03–1.68)
	Asthma	9.47% vs 9.35%	0.90 (0.64–1.27)
	Anxiety daily/weekly	23.09% vs 14.45%	1.67 (1.26–2.22)
	MH medication, 12 mo	14.08% vs 8.11%	1.38 (1.01–1.88)

Supplementary Table S3. Supplementary samples.