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Aluminum-Adsorbed Vaccines and Chronic Diseases in Childhood

A Nationwide Cohort Study

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Background: Aluminum is used as an adjuvant in nonlive vaccines administered in early childhood. Concerns persist about potential associations between vaccination with aluminum-adsorbed vaccines and increased risk for chronic autoimmunity, atopy or allergy, and neurodevelopmental disorders. Large-scale safety data remain limited.

Objective: To assess the association between cumulative aluminum exposure from early childhood vaccination and risk for autoimmune, atopic or allergic, and neurodevelopmental disorders.

Design: A cohort study linking nationwide registry data on childhood vaccinations, outcome diagnoses, and potential confounders, leveraging the variations in the aluminum content of childhood vaccines over time.

Setting: Denmark, 1997 to 2020.

Participants: 1 224 176 children born in Denmark between 1997 and 2018 who were alive and residing in the country at age 2 years.

Intervention: Cumulative aluminum amount received (per 1-mg increase) through vaccination during the first 2 years of life.

Measurements: Incident events of 50 chronic disorders, including autoimmune (dermatologic, endocrinologic, hematologic, gastrointestinal, and rheumatic), atopic or allergic (asthma, atopic dermatitis, rhinoconjunctivitis, and allergy), and neurodevelopmental (autism spectrum disorder and attention deficit–hyperactivity disorder).

Results: Cumulative aluminum exposure from vaccination during the first 2 years of life was not associated with increased rates of any of the 50 disorders assessed. For groups of combined outcomes, adjusted hazard ratios per 1-mg increase in aluminum exposure were 0.98 (95% CI, 0.94 to 1.02) for any autoimmune disorder, 0.99 (CI, 0.98 to 1.01) for any atopic or allergic disorder, and 0.93 (CI, 0.90 to 0.97) for any neurodevelopmental disorder. For most individually analyzed outcomes, the upper bounds of the 95% CIs were incompatible with relative increases greater than 10% or 30%.

Limitation: Individual medical records were not reviewed.

Conclusion: This nationwide cohort study did not find evidence supporting an increased risk for autoimmune, atopic or allergic, or neurodevelopmental disorders associated with early childhood exposure to aluminum-adsorbed vaccines. For most outcomes, the findings were inconsistent with moderate to large relative increases in risk, although small relative effects, particularly for some rarer disorders, could not be statistically excluded.

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Aluminum-based adjuvants are commonly used in nonlive vaccines to enhance the immune response by adsorbing vaccine antigens (1, 2). Aluminum-adsorbed vaccines include but are not limited to those offered in early childhood vaccination programs, such as diphtheria, tetanus, and pertussis; *Haemophilus influenzae* type b (Hib); pneumococcal conjugate vaccine (PCV); and hepatitis A and B vaccines (3).

Although immunization with aluminum-adsorbed vaccines in children has been used worldwide for many decades and is generally considered safe, concerns about potential harms continue to resurface. In particular, findings from mainly animal studies have fueled theoretical concerns about potential neurotoxic effects of aluminum-adsorbed vaccines and an increased risk for inducing autoimmunity and atopic disorders (3–10). Human data to inform these concerns are lacking, and the available literature is mainly limited to preclinical, ecological, and smaller observational studies of selected outcomes (9–16). Large-scale population studies may be helpful in investigating such potential associations.

The Danish childhood vaccination program, established in 1943 with the introduction of diphtheria vaccination, is a nationwide initiative offering vaccines recommended by the Danish Health Authority free of

See also:

Summary for Patients

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Supplement

charge to all children residing in Denmark. Vaccination coverage during the first 2 years of life is high (94% to 97% in 2023) (17). Over the past 25 years, the specific vaccines included in the program have changed over time because of policy updates, such as the introduction of pneumococcal vaccination in 2007; periodic substitutions of diphtheria, tetanus, and pertussis vaccines due to supply shortages; and the replacement of older with newer formulations. Because the vaccines have varying aluminum content, these uniformly applied policy changes have led to systematically different cumulative doses of aluminum received through childhood vaccination across birth cohorts (mainly before age 2 years). Therefore, these externally imposed systematic variations in aluminum exposure through early childhood vaccination that are independent of individual characteristics provide a natural quasi-experimental framework for estimating the effect of aluminum exposure from early childhood vaccination on health outcomes.

We leveraged Danish nationwide health care registries and these changes in vaccine use to investigate the association between cumulative aluminum exposure from vaccination with aluminum-adsorbed vaccines in the first 2 years of life and risk for chronic autoimmune, atopic or allergic, and neurodevelopmental disorders in a nationwide cohort of children born from 1 January 1997 to 31 December 2018, with follow-up through 2020.

METHODS

Study Population

We established a cohort of all children born live in Denmark from 1 January 1997 to 31 December 2018 using data from the nationwide Medical Birth Registry (18). This registry contains comprehensive information on all births in Denmark, including personal identification numbers (19) for infants and parents, birth date, vital status (that is, dead or alive), maternal smoking during pregnancy, and other infant characteristics. The personal identification number enabled linkage to vaccination records, hospital-recorded diagnoses, and potential confounders at both the child and maternal level (for example, preterm birth, household income, and maternal medical history) (20).

To be included in our study, children needed to be alive at age 2 years, not have emigrated from Denmark, not have been diagnosed with certain congenital or preexisting conditions (including congenital rubella syndrome, respiratory conditions, primary immune deficiency, and heart or liver failure), and not have received an implausible number of vaccines (**Supplement Table 1**, available at Annals.org). In addition, we excluded children whose mothers had not lived in Denmark for at least 2 years before childbirth.

Register-based research in Denmark is exempt from ethics committee approval under Danish law.

Vaccines and Aluminum Content

Since 1997, the Danish childhood vaccination program has offered (that is, not mandated) an aluminum-adsorbed vaccine for diphtheria, tetanus, acellular pertussis, inactivated poliovirus, and Hib (DTaP-IPV/Hib) in 3 doses in the first year of life (at 3, 5, and 12 months). Aluminum-adsorbed PCV (7-valent) was introduced in 2007 (substituted with the 13-valent vaccine in 2010) and is typically co-administered with DTaP-IPV/Hib. A DTaP-IPV booster (1997 to 2002 against diphtheria and tetanus; 2003 against diphtheria, tetanus, and pertussis; and since 2004 against diphtheria, tetanus, pertussis, and polio) is given again at age 5 years. **Supplement Figure 1** (available at Annals.org) shows the chronological sequence of these national changes in the aluminum-adsorbed vaccines used before age 2 years, and **Supplement Table 2** (available at Annals.org) provides a program overview.

All childhood vaccinations in Denmark are administered by local general practitioners, who receive reimbursement from the Danish government on registration in the National Health Service Register (21). From this register, we obtained information on the timing, number, and types of vaccines administered to each child. The aluminum content per dose of aluminum-adsorbed vaccine ranged from 0.125 to 1.00 mg (**Supplement Figure 1** and **Supplement Table 2**). We calculated the total aluminum exposure from all childhood vaccines received by age 2 years, which was the exposure.

Outcomes

We examined 50 adverse events, including 36 autoimmune, 9 atopic or allergic, and 5 neurodevelopmental disorders, with definitions adapted from previous work (22–28). During follow-up, we identified outcome events as any first hospital contact where an outcome diagnosis was recorded in the National Patient Registry (29) or, for some of the atopic disorders and attention deficit–hyperactivity disorder, by filling of prescriptions at any Danish pharmacy recorded in the National Prescription Registry (30) (see **Supplement Table 1** for International Classification of Diseases, 10th revision, codes; Anatomical Therapeutic Chemical codes; and further details). The date of admission or filled prescription was considered the event date. We analyzed each outcome separately and included only incident events occurring after age 2 years.

Statistical Analysis

We followed children from 2 years of age for study outcome events until 31 December 2020, or until they reached age 5 years, died, or were lost to follow-up,

whichever came first. To evaluate the potential association between cumulative aluminum exposure from vaccinations by age 2 years and the study outcomes, we used Cox proportional hazards regression. Time since age 2 years was used as the underlying time scale to estimate adjusted hazard ratios per 1-mg increase in aluminum exposure, along with 95% CIs. These hazard ratios represent how much the hazard changed when a child received 1 additional milligram of aluminum in their vaccines by age 2 years compared with a child who received 1 mg less. Each outcome model was adjusted for a priori–defined potential confounders, including birth year and season, sex, maternal age at delivery, maternal place of birth, maternal smoking during pregnancy, parity, preterm birth, birthweight, number of visits to a general practitioner before age 2 years, maternal prescription drug use during pregnancy, selected maternal conditions within 5 years before the child's birth date, and parental household income (**Supplement Table 1**). Outcomes with fewer than 20 cases were not analyzed separately. Missing data on smoking during pregnancy were imputed using logistic regression with all other covariates as predictors, and children with missing information on other covariates were excluded because there were few of them (**Supplement Table 1**). We assessed the proportional hazards assumption by visually inspecting scaled Schoenfeld residuals and testing for time scale–varying effects. When a variable violated the assumption, the baseline hazard function was stratified accordingly. Secondary analyses included stratifying by sex and birth cohort (1997 to 2006 and 2007 to 2018), removing children not vaccinated with aluminum-adsorbed vaccines by age 2 years (because these could have more different health care use), extending follow-up to age 8 years, shortening follow-up to age 3 or 4 years (to indirectly evaluate the potential for an interaction between the hazard ratio and time scale of follow-up), restricting to complete cases (to indirectly evaluate for bias introduced by our imputation method), redefining exposure and follow-up to start at age 14 months (to also capture earlier events while allowing some grace period from the 12-month appointment), and considering the total aluminum content received through early childhood vaccination as a categorical variable (separated by the median and in groups of >0 to 1.5 mg, >1.5 to 3 mg, and >3 to 4.5 mg; to examine for potential nonlinear associations not captured by the dose–response parameterization). Latter categorized exposure levels were also compared by risk differences calculated from cumulative incidences at age 5 years, which we obtained from the Kaplan–Meier estimator that we adjusted for all baseline covariates using stabilized inverse probability of treatment weights. Statistical tests were 2-sided, and analyses were done in R, version 4.4.0 (R Foundation); see the Methods section of the **Supplement** (available at Annals.org) for R packages and key code used for analytic modeling.

Role of the Funding Source

No funder had any role in the design, conduct, or reporting of the study.

RESULTS

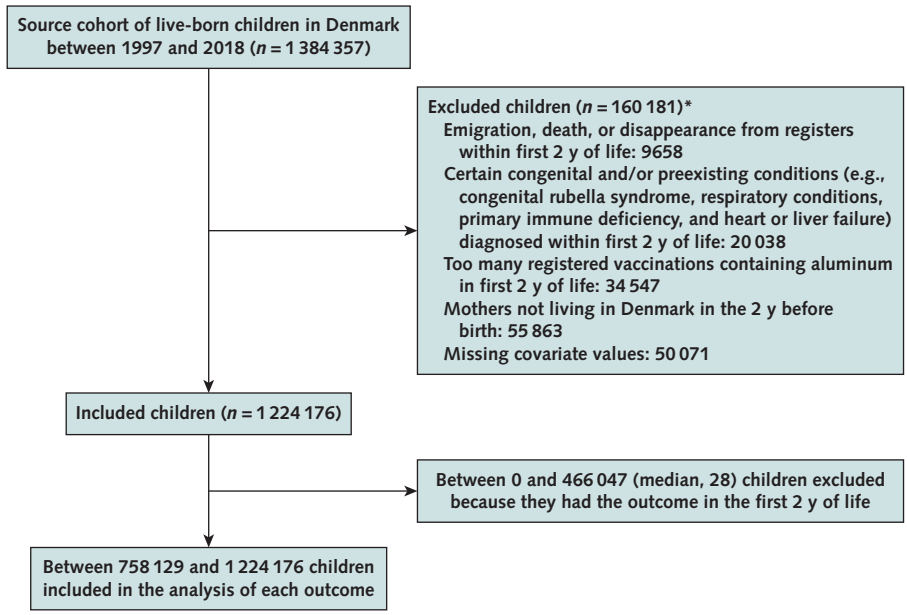
Study Population

Figure 1 shows a flow chart of the construction of the study cohort. A total of 1 224 176 children (48.8% female) born from 1 January 1997 to 31 December 2018 were included. The **Table** shows baseline characteristics by the cumulative amount of aluminum exposure through vaccination. Only 15 237 children (1.2%) did not receive any aluminum-adsorbed vaccines before age 2 years. Among vaccinated children, most baseline characteristics were similar, with absolute standardized mean differences below 0.1 (**Supplement Figure 2**, available at Annals.org); however, those who received more than 0 mg but less than 1.5 mg of aluminum had higher proportions of lower disposable household income and fewer general practitioner encounters. In addition, those who received more than 3 mg of aluminum more often had a maternal history of psychiatric disorders and diabetes. As expected, the total aluminum exposure through vaccination at age 2 years varied by birth year (**Figure 2**); the median was 3 mg (IQR, 2.8 to 3.4 mg), and the total exposure ranged from 0 to 4.5 mg. The median age at the end of follow-up was 5 years (IQR, 5 to 5 years); 6510 participants (0.5%) were censored during follow-up because of emigration or disappearance and 335 (0.03%) because of death.

Risk for Autoimmune, Atopic, and Neurodevelopmental Disorders

Figure 3 shows the number of outcome events between ages 2 and 5 years within the cohort during the 24-year study period (1997 to 2020) and hazard ratios for all of the autoimmune, atopic and allergic, or neurodevelopmental disorders assessed per 1-mg increase in the cumulative aluminum exposure from vaccination during the first 2 years of life. Twenty autoimmune disorders had fewer than 20 cases and were not separately analyzed in the primary analysis (**Supplement Table 3**, available at Annals.org). Most autoimmune disorders were relatively rare (incidence rates ranging from 0.8 to 50.5 per 100 000 person-years), with hazard ratios for specific autoimmune disorders ranging from 0.69 (95% CI, 0.47 to 1.01) to 1.13 (CI, 0.97 to 1.31) and with a hazard ratio for the combined group of outcomes of 0.98 (CI, 0.94 to 1.02) per 1-mg increase in the cumulative aluminum exposure from childhood vaccination. For the 16 autoimmune disorders individually studied, the upper bounds of the 95% CIs were 1.10 or lower for 8 outcomes, 1.30

Figure 1. Study flow diagram.



This flow chart illustrates the construction of the study cohort, including the number of individuals excluded. Details on variable definitions are provided in Supplement Table 1 (available at Annals.org). Each outcome was studied separately for only incident events occurring after age 2 y, which is why the studied sample size varied by different outcome history exclusions.

* The total number of excluded persons by the exclusion criteria is not the sum of those meeting each exclusion criterion because some individuals were excluded for more than 1 of the stated reasons.

or lower for 5 outcomes, and between 1.31 and 1.68 for the remaining 3 outcomes.

Asthma was the most common outcome (28 346 cases), with a hazard ratio per 1-mg increase in the cumulative aluminum exposure from childhood vaccination of 0.96 (CI, 0.94 to 0.98), followed by atopic dermatitis (22 978 cases; hazard ratio, 1.02 [CI, 1.00 to 1.04]) and allergic rhinitis (22 841 cases; hazard ratio, 0.99 [CI, 0.97 to 1.01]). The hazard ratio for the combined group of atopic or allergic disorder outcomes was 0.99 (CI, 0.98 to 1.01). The upper bounds of the 95% CIs were 1.10 or lower for 8 of the 9 individually analyzed outcomes in this group and 1.79 for insect sting allergy.

The hazard ratio for the combined group of neurodevelopmental disorder outcomes was 0.93 (CI, 0.90 to 0.97); 4806 participants had been diagnosed with autism spectrum disorder and 1580 with attention deficit–hyperactivity disorder before age 5 years. The hazard ratios per 1-mg increase in the cumulative aluminum exposure from childhood vaccination before age 2 years were 0.93 (CI, 0.89 to 0.97) and 0.90 (CI, 0.84 to 0.96), respectively. In this primary analysis, except for Asperger syndrome (hazard ratio, 1.13 [CI, 0.89 to 1.44]) and atypical autism (hazard ratio, 0.94 [CI, 0.79 to 1.12]), estimates for the individual outcomes were incompatible with any increased risk, with the upper bounds of the 95% CIs below 1.00.

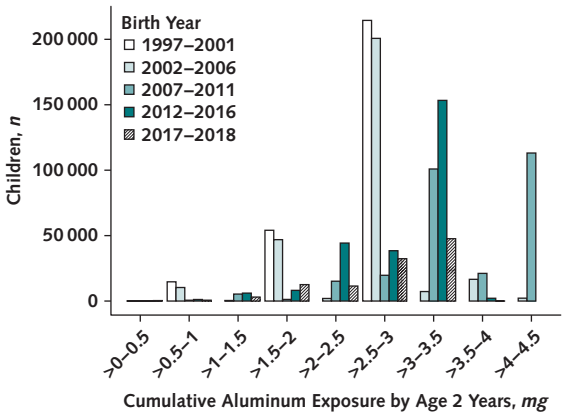
The hazard ratios and corresponding 95% CIs were qualitatively similar in the secondary analyses when we stratified by sex (**Supplement Figure 3**, available at Annals.org) or birth year (**Supplement Figure 4**, available at Annals.org), excluded unvaccinated children (**Supplement Figure 5**, available at Annals.org), redefined exposure and started follow-up at age 14 months instead of 2 years (**Supplement Figure 6**, available at Annals.org), ended follow-up at age 3 or 4 years (**Supplement Figure 7**, available at Annals.org), or restricted to complete cases (**Supplement Figure 8**, available at Annals.org). Categorizing cumulative aluminum exposure from childhood vaccination before age 2 years by the median (**Supplement Figure 9**, available at Annals.org) and levels received (>0 to 1.5 mg, >1.5 to 3 mg, or >3 to 4.5 mg) (**Supplement Figures 10** and **11**, available at Annals.org) did not suggest nonlinear associations. Extending follow-up to age 8 years allowed more outcome events to be analyzed separately (specifically, 20 of all 36 included autoimmune outcomes had ≥20 cases in this analysis) and yielded similar results to our main findings (**Supplement Figure 12**, available at Annals.org). For example, by age 8 years, 12 126 children were diagnosed with autism spectrum disorder (hazard ratio, 0.95 [CI, 0.92 to 0.97] per 1-mg increase in the cumulative aluminum exposure from childhood vaccination) and 12 091 with attention deficit–hyperactivity disorder (hazard ratio, 0.92 [CI, 0.90 to 0.94]). Except for Asperger syndrome (hazard ratio, 1.02 [CI, 0.93 to 1.12]) and atypical autism (hazard ratio, 0.95

Table. Baseline Characteristics of a Nationwide Cohort of Children Born From 1997 to 2018 in Denmark, by Cumulative Aluminum Exposure Through Early Childhood Vaccination*

Characteristic	Cumulative Aluminum Exposure Through Receipt of Aluminum-Adsorbed Vaccines			No Receipt of Aluminum-Adsorbed Vaccines (*n* = 15 237)
	>0–1.5 mg (*n* = 42 990)	>1.5–3 mg (*n* = 701 571)	>3–4.5 mg (*n* = 464 378)	
Female sex	20 826 (48.4)	342 172 (48.8)	227 381 (49.0)	7423 (48.7)
Preterm birth	3327 (7.7)	49 527 (7.1)	31 085 (6.7)	1099 (7.2)
Birthweight				
<1500 g	364 (0.8)	4587 (0.7)	3086 (0.7)	147 (1.0)
1500–<2500 g	1924 (4.5)	28 897 (4.1)	19 339 (4.2)	610 (4.0)
≥2500 g	40 702 (94.7)	668 087 (95.2)	441 953 (95.2)	14 480 (95.0)
Year of birth				
1997–2001	14 697 (34.2)	268 552 (38.3)	0 (0)	5655 (37.1)
2002–2006	10 842 (25.2)	249 620 (35.6)	26 055 (5.6)	3481 (22.8)
2007–2011	6088 (14.2)	36 096 (5.1)	235 177 (50.6)	2264 (14.9)
2012–2016	7319 (17.0)	90 935 (13.0)	155 483 (33.5)	2517 (16.5)
2017–2018	4044 (9.4)	56 368 (8.0)	47 663 (10.3)	1320 (8.7)
Season of birth				
Spring	10 483 (24.4)	180 842 (25.8)	110 499 (23.8)	3833 (25.2)
Summer	10 509 (24.4)	187 602 (26.7)	125 635 (27.1)	3920 (25.7)
Autumn	10 764 (25.0)	172 008 (24.5)	119 472 (25.7)	3789 (24.9)
Winter	11 234 (26.1)	161 119 (23.0)	108 772 (23.4)	3695 (24.3)
Number of contacts with a general practitioner				
Tertile 1 (lowest)	25 859 (60.2)	235 936 (33.6)	147 813 (31.8)	12 452 (81.7)
Tertile 2	9419 (21.9)	219 163 (31.2)	178 316 (38.4)	1539 (10.1)
Tertile 3 (highest)	7712 (17.9)	246 472 (35.1)	138 249 (29.8)	1246 (8.2)
Maternal age at delivery				
<20 y	805 (1.9)	9145 (1.3)	5231 (1.1)	233 (1.5)
20–24 y	5390 (12.5)	79 686 (11.4)	46 893 (10.1)	1770 (11.6)
25–29 y	14 060 (32.7)	243 872 (34.8)	144 807 (31.2)	4550 (29.9)
30–34 y	14 660 (34.1)	248 217 (35.4)	170 392 (36.7)	5089 (33.4)
35–39 y	6764 (15.7)	102 902 (14.7)	81 109 (17.5)	2877 (18.9)
≥40 y	1311 (3.0)	17 749 (2.5)	15 946 (3.4)	718 (4.7)
Maternal place of birth				
Denmark	36 640 (85.2)	616 251 (87.8)	401 666 (86.5)	12 484 (81.9)
Europe	2676 (6.2)	36 431 (5.2)	29 946 (6.4)	1393 (9.1)
Outside Europe	3674 (8.5)	48 889 (7.0)	32 766 (7.1)	1360 (8.9)
Disposable household income				
Quantile 1 (lowest)	13 295 (30.9)	167 683 (23.9)	92 405 (19.9)	5836 (38.3)
Quantile 2	11 302 (26.3)	199 959 (28.5)	95 573 (20.6)	3949 (25.9)
Quantile 3	9623 (22.4)	181 060 (25.8)	123 538 (26.6)	3007 (19.7)
Quantile 4 (highest)	8770 (20.4)	152 869 (21.8)	152 862 (32.9)	2445 (16.0)
Maternal parity				
1	16 509 (38.4)	304 972 (43.5)	216 179 (46.6)	5392 (35.4)
2	16 119 (37.5)	264 238 (37.7)	170 512 (36.7)	5536 (36.3)
≥3	10 362 (24.1)	132 361 (18.9)	77 687 (16.7)	4309 (28.3)
Maternal smoking during pregnancy	8221 (19.1)	112 807 (16.1)	53 621 (11.5)	2545 (16.7)
Maternal medical history during the past 5 y				
Atopic disorder	6571 (15.3)	116 629 (16.6)	65 389 (14.1)	1973 (12.9)
Neurodevelopmental disorder	152 (0.4)	1495 (0.2)	2031 (0.4)	51 (0.3)
Autoimmune disorder	1183 (2.8)	18 849 (2.7)	18 923 (4.1)	454 (3.0)
Psychiatric disorder	2101 (4.9)	25 491 (3.6)	28 591 (6.2)	594 (3.9)
Diabetes	1387 (3.2)	19 892 (2.8)	22 368 (4.8)	391 (2.6)
Maternal prescription drug use during pregnancy				
Antibiotics	14 687 (34.2)	223 078 (31.8)	165 210 (35.6)	4452 (29.2)
Systemic corticosteroids	241 (0.6)	3775 (0.5)	3721 (0.8)	74 (0.5)
Immunosuppressants	34 (0.1)	441 (0.1)	606 (0.1)	≤3 (0.0)
Opioids	511 (1.2)	6198 (0.9)	4907 (1.1)	151 (1.0)
Antiepileptics	204 (0.5)	3328 (0.5)	2655 (0.6)	65 (0.4)

* Values are numbers (percentages). Cells with ≤3 participants (but not 0) cannot be reported to ensure privacy preservation. Details on variable definitions are provided in Supplement Table 1 (available at Annals.org).

Figure 2. Early childhood vaccination with aluminum-adsorbed vaccines in Denmark from 1997 through 2020.



The figure shows the distribution of cumulative aluminum exposure (in milligrams) through vaccination at age 2 y across the study cohort grouped by birth year. The national changes in the aluminum-adsorbed vaccines used in the Danish childhood vaccination program during the study period and their respective aluminum content are shown in Supplement Figure 1 (available at Annals.org).

[CI, 0.88 to 1.03]), estimates for the individual neurodevelopmental outcomes assessed were incompatible with any increases in risk, with the upper bounds of the 95% CIs equal to or below 1.00. With follow-up until age 8 years, the upper bounds were below 1.10 for 17 of 29 individual autoimmune or atopic or allergic outcomes, below 1.30 for 7 outcomes, and between 1.33 and 2.81 for the remaining 5.

DISCUSSION

In this nationwide cohort study of approximately 1.2 million children, estimates of the associations between cumulative aluminum exposure from early childhood vaccination and chronic autoimmune, atopic or allergic, and neurodevelopmental disorders were incompatible with moderate to large relative increases in risk and most consistent with no increased risk, but small relative increases in risk could not be statistically excluded, particularly for some rarer outcomes.

This work was motivated by ongoing concerns about potential harms of aluminum-adsorbed nonlive vaccines. A recent cohort study by Daley and colleagues (16) using data from the U.S. Vaccine Safety Datalink examined the risk for asthma in relation to cumulative aluminum exposure from childhood vaccination in 326 991 children. They identified 7546 children with asthma by age 5 years (2.3%) and reported estimates compatible with small to moderate relative increases in risk per 1-mg aluminum exposure through vaccination before age 2 years: adjusted hazard ratios of 1.26 (CI, 1.07 to 1.49) and 1.19 (CI, 1.14 to 1.25) among children with and without eczema, respectively (16). As the authors also noted, important potential confounders were unavailable, such as maternal smoking, atopic predisposition, and socioeconomic status. In our study, analyzing up to 38 045 asthma cases (5.0% of the studied population for this outcome), the estimated hazard ratio per 1-mg increase in cumulative aluminum exposure from early childhood vaccination was 0.96 (CI, 0.94 to 0.98), with the upper confidence limit incompatible with even small relative increases in risk. Vaccination uptake was lower in the study by Daley and colleagues: 60.6% of participants were fully vaccinated, and effect sizes were attenuated when analyses were restricted to this subpopulation, which could suggest residual confounding (16). We found similar estimates for other atopic disorders and a hazard ratio of 0.99 (CI, 0.98 to 1.01) for the combined group of atopic or allergic disorders.

Neurotoxic effects of aluminum have been observed in animal models (rats) subjected to long-term, high-dose parenteral administration and in humans receiving high-level exposure through dialysis, occupational inhalation, or intravenous parenteral nutrition (6, 31–33). These findings, along with ecological studies, have contributed to the ongoing concerns about aluminum exposure from childhood vaccinations potentially contributing to the development of neurodevelopmental disorders, such as autism spectrum disorder and attention deficit–hyperactivity disorder, as well as autoimmunity (6, 9, 14). However, a previous study suggests that the aluminum levels in infants from vaccinations are well below established minimal risk level thresholds (11). In a cross-sectional study of 85 infants, aluminum concentrations in blood (Spearman $\rho = -0.13$; $P = 0.26$) and hair (Spearman $\rho = 0.06$; $P = 0.56$) did not seem to be positively correlated with receipt of aluminum-adsorbed vaccines, but the precision of these estimates was not reported (12). Similarly, a small study of 15 preterm infants reported no measurable change in serum aluminum concentrations after vaccination with aluminum-adsorbed vaccines, although no specific statistics were provided (13). Despite these preliminary findings, large-scale studies directly evaluating these potential associations between aluminum exposure from vaccines and chronic diseases in childhood have been lacking.

Our study, based on a nationwide cohort of about 1.2 million children with analyses across a 24-year period, offers a large-scale, population-based evaluation of the safety of aluminum-adsorbed vaccines in childhood vaccination programs. The upper bounds of the 95% CIs for the combined outcome groups were incompatible with relative risk increases greater than 2% for autoimmune disorders, 1% for atopic or allergic disorders, and any increase for neurodevelopmental disorders, per 1-mg increase in aluminum exposure through early childhood vaccination. In addition, in the primary analysis of the 30 individually analyzed outcomes, the upper bounds ruled out relative increases greater than 10% for 19 outcomes,

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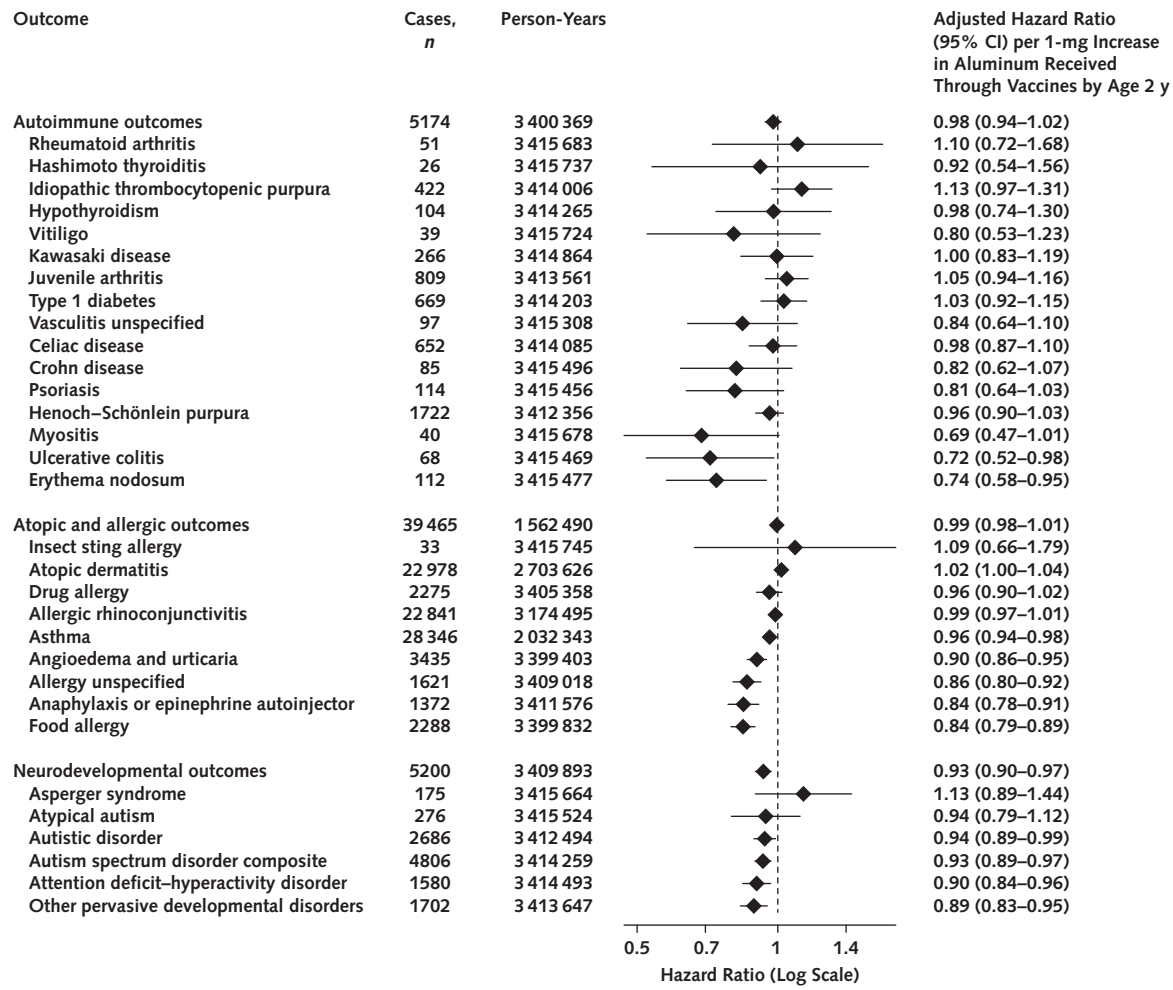
Figure 3. Association between cumulative aluminum exposure through early childhood vaccination and chronic disease in children.



The figure reports adjusted hazard ratios for the association between the cumulative aluminum exposure from vaccination with aluminum-adsorbed vaccines by age 2 y and risk for autoimmune, atopic or allergic, and neurodevelopmental disorders diagnosed between ages 2 and 5 y in children born in Denmark between 1997 and 2018, with follow-up through 2020 (ordered [descending] by the upper bound of the 95% CI). Each outcome was studied separately, which is why there may be differences in the denominators due to different exclusions. Children were followed from age 2 y until age 5 y for respective outcome events. Hazard ratios were adjusted for sex, calendar year and season of birth, preterm birth, birthweight, number of visits to the general practitioner before age 2 y, maternal age at delivery, maternal place of birth, maternal smoking during pregnancy, maternal health conditions, maternal prescription drug use during pregnancy, and parental household income. Outcomes with fewer than 20 cases were not separately analyzed (Supplement Table 3, available at Annals.org).

greater than 30% for 7 outcomes, and between 31% and 79% for the 4 remaining rarer outcomes (the latter 4 outcomes had incidence rates ranging from 7.6 to 14.9 per 1 million person-years).

Our study has limitations. First, because we analyzed data from routine clinical practice, our study lacked true randomization of exposure. Instead, we leveraged the variation in aluminum content of vaccines administered in early childhood over the 24-year study period resulting from systematic national changes in the Danish childhood vaccination program. In addition, we adjusted our analyses for a wide range of potential confounders, including socioeconomic characteristics. Nonetheless, residual confounding cannot be excluded, particularly if unmeasured confounding factors were not adequately indirectly accounted for through the included set of covariates. Second, as expected, children born later in the study period were on average exposed to more aluminum through early childhood vaccination than those born earlier. The prevalence of diagnoses for several analyzed chronic disorders has increased over the past decades (34–38). If no true association exists, these parallel trends in data would tend to skew results toward positive associations, unlike what we observed. Stratifying by birth cohort also did not change the study findings. Third, very early prediagnosis symptoms could potentially either reduce or increase the propensity

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to vaccination, which could bias toward underestimating or overestimating, respectively, the risk in vaccinated children. However, as mentioned above, our analyses are primarily based on the random variation in aluminum exposure through vaccination, in contrast to a vaccinated versus unvaccinated comparison. Fourth, to ascertain our exposure of aluminum-adsorbed vaccination, we used the Danish National Health Service Register wherein registration is required by the general practitioner to receive reimbursement from the Danish government. This implies a high degree of validity. Any exposure misclassification is less likely associated with our outcomes and would bias results toward the null. Of note, although our primary continuous exposure definition most likely mitigates potential biases related to temporal outcome trends, exposure misclassification, and unmeasured confounding from differences in health care use and behaviors, the secondary analyses using categorical exposure comparisons are more susceptible to such biases. Fifth, we studied incident cases of 50 different chronic disorders, some of which were very rare and some of which typically develop or are diagnosed after age 5 years. Consequently, despite our nationwide longitudinal data permitting a large sample size, some outcomes could not be individually analyzed. Cases were defined through hospital diagnoses or as prescription records for disorder-related medications (for atopic or attention deficit–hyperactivity disorder). Of note, the validity of each individual outcome has not been systematically assessed; however, previous evaluations suggest that the National Patient Registry has sufficient data quality overall for recorded diagnoses, including several of the outcomes studied here (or closely defined proxies) (39). Outcome misclassification would tend to be less likely for more severe or rare disorders and is unlikely to be influenced by the extent of aluminum exposure through vaccination in early childhood. However, potential uncaptured disorders in early years (such as through underdiagnosis) relative to later years would tend to skew our estimates toward increased risks. Although associations with the studied disorders when emerging later in life cannot be ruled out, extending follow-up to age 8 years did not indicate such trends. Our results may be generalizable to similar pediatric populations, although their applicability to adult settings is more uncertain. In addition, our findings may not directly generalize to clinical scenarios not studied, such as the use of other vaccines in early childhood (for example, with cumulative aluminum amounts received outside our cohort exposure distribution) or risk for other chronic disorders.

In conclusion, in this nationwide cohort study of approximately 1.2 million children, findings were incompatible with moderate to large relative increases in the risks for autoimmune, atopic or allergic, and neurodevelopmental disorders associated with early childhood exposure to aluminum-adsorbed vaccines for most outcomes, although small relative increases could not be statistically excluded, particularly for some rarer outcomes.

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