Niklas Worm Andersson, Ingrid Bech Svalgaard, Stine Skovbo Hoffmann, et al. Aluminum-Adsorbed Vaccines and Chronic Diseases in Childhood: A Nationwide Cohort Study. Ann Intern Med. [Epub 15 July 2025]. doi:10.7326/ANNALS-25-00997

Clinical Question: Do aluminum-adsorbed vaccines administered in early childhood increase the risk of chronic diseases?

- **Population:** All children born in Denmark between 1997 and 2018
  - **Exclusions:** Children who had died, emigrated, or were not yet born at the time of the 6-month baseline, or had missing vaccination data.
- **Exposure:** Cumulative exposure to aluminum from vaccines received during the first 18 months of life.
- **Comparison:** Quartiles of aluminum exposure comparing those with the highest vs. the lowest aluminum exposure.
- **Outcome:** Incidence of chronic autoimmune, atopic, allergic, and neurodevelopmental disorders after 6 months of age.
- **Type of Study:** Retrospective population-based longitudinal observational cohort study using linked national registry data.

Authors' Conclusions*: "We found no consistent evidence of increased risk of chronic diseases following early-life exposure to aluminum from vaccines. These findings do not support the hypothesis that aluminum-containing vaccines contribute to the development of chronic disease in childhood."*

Quality Checklist for Observational Studies:

1. Did the study address a clearly focused issue? Yes
2. Did the authors use an appropriate method to answer their question? Yes
3. Was the cohort recruited in an acceptable way? Yes
4. Was the exposure accurately measured to minimize bias? Yes (based on national vaccine registry)
5. Was the outcome accurately measured to minimize bias? Yes (diagnoses from national health registers)
6. Have the authors identified all-important confounding factors? Yes (adjusted for sex, birth year, maternal education, maternal age, income, smoking)
7. Was the follow-up of subjects complete enough? Yes (median follow-up 8.1 years)
8. How precise are the results? Reasonably precise (with 95% CIs provided)
9. Do you believe the results? Yes
10. Can the results be applied to the local population? Yes, for countries with similar vaccination schedules
11. Do the results of this study fit with other available evidence? Yes
12. Who funded the trial? The study was funded by the Swedish Research Council
13. Did the authors declare any conflicts of interest? Yes. Anders Hviid received some grants/contracts from Pharma outside this work.

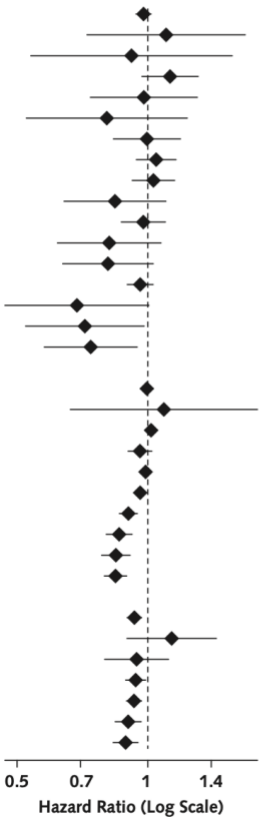
Results: The cohort consisted of 1,224,176 children born in Denmark between 1997 and 2018, who were alive and residing in the country at age two years. 51% were male with a median follow-up of 8.1 years.

Key Result: No observed increased risk in autoimmune disorder, atopic or allergic disorder or any neurodevelopmental disorder.

- **Outcomes:** adjusted Hazard Ratios (aHR) per 1-mg increase in aluminum exposure were
  - aHR 0.98 (95% CI: 0.94 to 1.02) for any autoimmune disorder
  - aHR 0.99 (95% CI: 0.98 to 1.01) for any atopic or allergic disorder
  - aHR 0.93 (95% CI: 0.90 to 0.97) for any neurodevelopmental disorder

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

Outcome	Cases, *n*	Person-Years	Adjusted Hazard Ratio (95% CI) per 1-mg Increase in Aluminum Received Through Vaccines by Age 2 y
Autoimmune outcomes	5174	3 400 369	0.98 (0.94–1.02)
Rheumatoid arthritis	51	3 415 683	1.10 (0.72–1.68)
Hashimoto thyroiditis	26	3 415 737	0.92 (0.54–1.56)
Idiopathic thrombocytopenic purpura	422	3 414 006	1.13 (0.97–1.31)
Hypothyroidism	104	3 414 265	0.98 (0.74–1.30)
Vitiligo	39	3 415 724	0.80 (0.53–1.23)
Kawasaki disease	266	3 414 864	1.00 (0.83–1.19)
Juvenile arthritis	809	3 413 561	1.05 (0.94–1.16)
Type 1 diabetes	669	3 414 203	1.03 (0.92–1.15)
Vasculitis unspecified	97	3 415 308	0.84 (0.64–1.10)
Celiac disease	652	3 414 085	0.98 (0.87–1.10)
Crohn disease	85	3 415 496	0.82 (0.62–1.07)
Psoriasis	114	3 415 456	0.81 (0.64–1.03)
Henoch–Schönlein purpura	1722	3 412 356	0.96 (0.90–1.03)
Myositis	40	3 415 678	0.69 (0.47–1.01)
Ulcerative colitis	68	3 415 469	0.72 (0.52–0.98)
Erythema nodosum	112	3 415 477	0.74 (0.58–0.95)
Atopic and allergic outcomes	39 465	1 562 490	0.99 (0.98–1.01)
Insect sting allergy	33	3 415 745	1.09 (0.66–1.79)
Atopic dermatitis	22 978	2 703 626	1.02 (1.00–1.04)
Drug allergy	2275	3 405 358	0.96 (0.90–1.02)
Allergic rhinoconjunctivitis	22 841	3 174 495	0.99 (0.97–1.01)
Asthma	28 346	2 032 343	0.96 (0.94–0.98)
Angioedema and urticaria	3435	3 399 403	0.90 (0.86–0.95)
Allergy unspecified	1621	3 409 018	0.86 (0.80–0.92)
Anaphylaxis or epinephrine autoinjector	1372	3 411 576	0.84 (0.78–0.91)
Food allergy	2288	3 399 832	0.84 (0.79–0.89)
Neurodevelopmental outcomes	5200	3 409 893	0.93 (0.90–0.97)
Asperger syndrome	175	3 415 664	1.13 (0.89–1.44)
Atypical autism	276	3 415 524	0.94 (0.79–1.12)
Autistic disorder	2686	3 412 494	0.94 (0.89–0.99)
Autism spectrum disorder composite	4806	3 414 259	0.93 (0.89–0.97)
Attention deficit–hyperactivity disorder	1580	3 414 493	0.90 (0.84–0.96)
Other pervasive developmental disorders	1702	3 413 647	0.89 (0.83–0.95)



Five Limitations That Threaten Validity:

1. Residual Confounding: Despite the authors' use of national registry data and statistical adjustment for several potential confounders (including sex, maternal age, education, income, and smoking), there remains the possibility of residual confounding from unmeasured or imperfectly measured variables. Factors such as breastfeeding status, early-life infections, parental health-seeking behaviour, or environmental exposures (air pollution or household allergens) may influence both vaccination timing and disease risk. These were not accounted for in the study. In observational studies, it is not possible to eliminate all confounders, especially when the data sources are administrative. Even advanced modelling cannot adjust for what was not measured. Residual confounding is a common limitation in nonrandomized studies and must temper the strength of any causal inferences.

2. Exposure Misclassification: The exposure variable, cumulative aluminum dose from vaccines, was derived from vaccination records, which are generally reliable in Denmark. However, even small inaccuracies in recording vaccine type, timing, or dosage could result in exposure misclassification. Exposure misclassification is a concern in registry-based studies. If non-differential, it biases toward the null. However, the *Andersson et al* study used reimbursed GP-logged vaccinations, which are strongly

incentivized to be complete (for payment). The authors correctly acknowledge that misclassification would likely bias toward the null.

3. Exclusions: Care must be taken when considering who to exclude in a study to minimize selection bias. The exclusion criteria in this study were clearly defined and methodologically justified. This helps preserve internal validity. Children who died or emigrated before age two could not contribute follow-up data on incident chronic disease outcomes beyond age two. This is a standard epidemiological approach. Those with respiratory or congenital conditions were excluded because such conditions can confound both vaccination schedules and outcome risk. The 2.8% who had extreme vaccination records (n=34,547) likely represented data entry errors, implausible vaccine counts, or outliers with uncertain validity. The final cohort retained over 1.2 million children, and the available evidence doesn't suggest the exclusions systematically biased the results, which would change the conclusions.

4. Potential for Healthy Vaccinee Bias: Healthy user (or healthy subject) bias occurs when individuals who engage in a preventive behaviour (like getting vaccinated) are inherently healthier or have different health-seeking behaviours than those who don't. This is a well-known, potentially confounding aspect of observational study results. However, healthy user bias becomes less relevant in high-coverage, population-wide vaccine settings. In this study, over 98% of children were included, and >98% were vaccinated. The near-universal coverage makes this bias unlikely to meaningfully skew results away from the truth. Truth is defined as the best point estimate of the observed effect size with a confidence interval around the point estimate.

5. Limited Generalizability: While the study's use of Denmark's robust national health registries is a strength, it also raises concerns about external validity. This can indeed be a limitation when comparing different countries' populations, vaccine schedules, and health systems. Denmark has >90% vaccination coverage, and the study used nationwide registries and included over 98% of children alive at age two.

The Danish childhood vaccination schedule, population health system, and social determinants of health may differ substantially from those in other countries, particularly low- and middle-income settings. For instance, differences in vaccine formulations, aluminum content, timing, and coverage rates could alter the exposure-outcome relationship elsewhere. We should consider how applicable study results are to local populations, especially when health systems or exposures differ. Thus, while the findings support safety in the Danish context, caution is warranted in generalizing them globally. This does not automatically invalidate the findings in applying it to a US population, but it does introduce more uncertainty.

Bottom Line: In this large Danish cohort study, there was no consistent evidence that early-life aluminum exposure from vaccines increases the risk of chronic diseases. These findings do not support the claim of increased harm from aluminum-containing vaccines in childhood immunization schedules.