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Kamal Mokeddem *

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Article

Threshold Dose Response of Aluminum Adjuvants Seen in Population Data

Kamal Mokeddem

Nova Southeastern University, 3664 Omao Rd. Koloa, HI 96756, USA; kmokedde@nova.edu;
Tel.: +1-650-776-7462

Abstract

This study investigates potential associations between aluminum-adjuvanted childhood vaccines and inflammatory conditions using population-level data from the National Survey of Children's Health (NSCH) 2020-2023 and the CDC National Immunization Survey (NIS) 2011-2017. By joining datasets across 50 U.S. states and the District of Columbia for birth years 2011-2017, we analyzed vaccine uptake probabilities as proxies for aluminum exposure and prevalences of autism (3.7%), allergies (26.1%), ADHD (8.1%), asthma (8.4%), epilepsy (0.94%), obesity (4.9%), and Tourette's syndrome (0.21%), with blood disorders (0.46%) as a negative control. Methods involved calculating disease prevalence, disease correlations, and linear regressions between vaccine likelihoods (DTaP, HepB, Hib, PCV, Polio) across age windows (0-36 months) and outcomes. Results revealed strong positive correlations among inflammatory conditions ($r=0.19-0.62$, $p<0.001$) but none with blood disorders. Aluminum exposure proxies during 6-12 months forecasted higher disease prevalence ($p<0.05$), with nonlinear patterns including sign reversals across time periods, consistent with NLRP3 inflammasome's two-step activation threshold. These findings suggest aluminum adjuvants may contribute to NLRP3-mediated inflammation in susceptible populations, warranting further mechanistic and prospective studies to optimize vaccination strategies and explore inflammasome-targeted therapies for reducing chronic childhood disease burdens.

Keywords: aluminum adjuvants; NSCH; NIS-Child

1. Introduction

According to the NSCH 2020-2023 [1,2], 41% of children have at least one of autism, allergies, adhd, asthma, epilepsy, obesity, or Tourette's syndrome. Blood disorders (sickle cell, hemophilia, and thalassemia) are included in this study as a negative control. CDC National Immunization Survey (CDC NIS) [3] can be joined with the NSCH by US state and birth year to investigate whether vaccines have any relationship to inflammatory outcomes tracked by the NSCH. Reactogenicity from aluminum adjuvants is known to drive inflammation through its interaction with the NLRP3 inflammasome. Aluminum adjuvants are in most childhood vaccines, notably DTaP, Hib, Hep B, PCV, and Polio that were looked at in this study. NLRP3 is activated in a two step process, priming and activation, that could lead to a uniquely nonlinear dose response function for aluminum adjuvants taking the form of a threshold function. This study uses 4 years of data from the NSCH 2020-2023 joined with 7 years of data from CDC NIS to investigate the prevalence of Autism, Allergies, Asthma, ADHD, Epilepsy, and Tourette's across the 50 states and DC from the birth years 2011-2017.

2. Methods

The study population consists of the set of people surveyed by CDC NIS 2011-2017 along with those surveyed by the NSCH 2020-2023. These two data sets were joined by birth year and US state giving 357 data points which contain exposure estimates from CDC NIS and outcome estimates from

the NSCH. CDC NIS tracks vaccination uptake by age (2m, 4m, 6m, 12m, 18m, 24m, and 36m) and type of vaccine (DTap, HepB, Hib, PCV, Polio, MMR). The exposures take the form of likelihoods that the population received a particular type of vaccine in a particular age window. These likelihoods can also be summed across types to represent a proxy variable for total aluminum exposure from vaccines in a population at a particular age.

Outcomes are tracked by the NSCH, specifically these outcomes are defined by the survey questions:

1. Autism—Has a doctor or other health care provider EVER told you that this child has Autism or Autism Spectrum Disorder (ASD)? Include diagnoses of Asperger’s Disorder or Pervasive Developmental Disorder (PDD). (K2Q35A)
2. Allergies—Has a doctor or other health care provider EVER told you that this child has Allergies (including food, drug, insect, or other)?
3. Asthma—Has a doctor or other health care provider EVER told you that this child has Asthma? (K2Q40A)
4. ADHD—Has a doctor or other health care provider EVER told you that this child has Attention Deficit Disorder or Attention Deficit/Hyperactivity Disorder, that is, ADD or ADHD? (K2Q31A)
5. Blood—Has a doctor or other health care provider EVER told you that this child has Blood Disorders (such as Sickle Cell Disease, Thalassemia, or Hemophilia)?
6. Epilepsy—Has a doctor or other health care provider EVER told you that this child has Epilepsy or Seizure Disorder? (K2Q42A)
7. Obesity—Has a doctor or other health care provider ever told you that this child is overweight?
8. Tourettes—Has a doctor or other health care provider EVER told you that this child has Tourette Syndrome? (K2Q38A)

With the definitions out of the way, this study will calculate the prevalence of each disease, any associations between diseases, and finally any associations between our exposures and outcomes.

3. Results

First, the table below is the prevalence of each outcome in the NSCH.

Table 1. Prevalence of disease as measured in NSCH.

Disease	Prevalence
Autism	3.7%
Allergies	26.1%
ADHD	8.1%
Asthma	8.4%
Blood	0.46%
Epilepsy	0.94%
Obesity	4.9%
Tourette’s	0.21%

Every one of the inflammatory diseases is associated with each of the other inflammatory diseases. Blood disorders on the other hand have no association with the other conditions.

Table 2. Associations between disease prevalence.

	autism	allergies	adhd	asthma	blood	epilepsy	obesity	tourette
autism	-	.28***	.35***	.28***	.02	.26***	.23***	.19***
allergies	.28***	-	.58***	.60***	-.01	.20***	.46***	.26***
adhd	.35***	.58***	-	.62***	.00	.19***	.59***	.41***
asthma	.28***	.60***	.62***	-	.08	.22***	.52***	.32***
blood	.02	-.01	.00	.08	-	.02	.07	-.05
epilepsy	.26***	.20***	.19***	.22***	.02	-	.21***	.14**
obesity	.23***	.46***	.59***	.52***	.07	.21***	-	.33***
tourettes	.19***	.26***	.41***	.32***	-.05	.14**	.33***	-

Note. This table presents Pearson correlation coefficients. * p<.05, ** p<.01, *** p<.001.

It’s possible to forecast the prevalence of inflammatory diseases from the summed likelihood of aluminum adjuvant vaccination from CDC NIS between ages 6-12 months. Blood disorders on the other hand have no association with aluminum from vaccines.

Table 3. Future chronic childhood disease prevalence can be forecast from the summed likelihood of aluminum adjuvant vaccination from CDC NIS at ages 6-12 months.

Disease	p-value	t value	R^2
Autism	< .001	7.42	0.1173
Allergies	< .001	6.63	0.0955
Asthma	< .001	6.40	0.0894
ADHD	< .001	6.68	0.0969
Blood	0.73	0.33	0.0003
Epilepsy	.013	2.51	0.0128
Obesity	< .001	5.75	0.0827
Tourettes	< .001	3.60	0.0286

The summed likelihoods are shown above, but the breakdown of associations from each individual vaccine to each outcome is shown below.

Table 4. Vaccine likelihood from 6-12 months vs. chronic diseases.

	DTaP	HepB	Hib	PCV	Polio
Autism	.24***	.22***	.17***	.25***	.19***
Allergies	.26***	.22***	.07	.28***	.17***
ADHD	.30***	.15**	.20***	.32***	.17***
Asthma	.20***	.25***	.06	.22***	.11*
Blood	-.04	.09	-.06	.00	-.03
Epilepsy	.13**	.05	.11*	.10*	.09
Obesity	.19***	.33***	.03	.25***	.11*
Tourettes	.09	.20**	.03	.14**	.03

Note. This table presents Pearson correlation coefficients. * p<.05, ** p<.01, *** p<.001.

Notably, Hib and HepB likelihoods are negatively correlated in this time period at -.12. Yet we can see that Hib and HepB are both independently associated with Autism and ADHD. That does not bode well for any hypothesis of a hidden variable. If there was a hidden variable responsible for the association, correlations between different vaccines would tend to be strictly positive from the partial information from the hidden variable.

The 4-6 month time period is interesting because of the disparate impact of the different vaccines. The meaningful difference between these vaccines is the dose of aluminum received from each one,

which may be received in combination or alone with varying levels of aluminum depending on the exact brand.

Table 5. Vaccine likelihood from 4-6 months vs. chronic disease.

correlation	DTaP	HepB	Hib	PCV	Polio
Autism	-.22***	.23***	.21***	-.26***	.21***
Allergies	-.21***	.25***	.23***	-.24***	.27***
ADHD	-.25***	.33***	.26***	-.29***	.27***
Asthma	-.16**	.25***	.20***	-.20***	.21***
Blood	.08	-.03	-.01	.05	-.01
Epilepsy	-.13*	.12*	.14*	-.13*	.14**
Obesity	-.09	.25***	.24***	-.18***	.22***
Tourettes	-.08	.15**	.15**	-.12*	.11*

Note. This table presents Pearson correlation coefficients. * p<.05, ** p<.01, *** p<.001.

The 12-18 month time period is also interesting as once again different vaccines appear to have different relationships to future disease. Even though not every association is significant, they all have the same sign for each vaccine, once again with the exception of our negative control.

Table 6. Vaccine likelihood from 12-18 months vs. chronic disease.

	DTaP	HepB	Hib	PCV	Polio
Autism	.07	.11*	-.11*	.17***	-.15**
Allergies	.05	.12*	-.12*	.12*	-.08
ADHD	.10*	.14**	-.18***	.15**	-.11*
Asthma	.02	.07	-.26***	.06	-.12*
Blood	-.08	-.04	.02	-.05	.07
Epilepsy	.13**	.10	-.07	.18***	-.02
Obesity	.06	.18***	-.21***	.16**	-.01
Tourettes	.10	.10*	-.14*	.11*	-.06

Note. This table presents Pearson correlation coefficients. * p<.05, ** p<.01, *** p<.001.

The table below has the summed aluminum adjuvant vaccine likelihoods for each time bucket in CDC NIS vs. each disease. This pattern of statistically significant positive and negative associations is typical of an uncorrected nonlinearity in the exposure variable.

Table 7. Aggregated vaccine likelihood vs. chronic disease for each time bucket.

	0m-2m	2m-4m	4m-6m	6m-12m	12m-18m	18m-24m	24m-36m
Autism	-.20***	-.23***	-.13*	.31***	-.09	.16***	.11*
Allergies	-.14**	-.22***	-.07	.28***	-.08	.15**	.14**
ADHD	-.22***	-.27***	-.11*	.31***	-.14**	.20***	.10*
Asthma	-.16***	-.21***	-.04	.25***	-.25***	.14**	.02
Blood	.04	.05	.07	.01	.01	-.02	-.12*
Epilepsy	-.10*	-.16**	-.05	.13**	-.01	.03	.09
Obesity	-.06	-.15**	.03	.29***	-.14**	.24***	.09
Tourettes	-.10	-.11*	-.02	.17***	-.10	.02	.09

Note. This table presents Pearson correlation coefficients. * p<.05, ** p<.01, *** p<.001.

4. Discussion

Given that we see a non-random nonlinear associations with aluminum from vaccines at the population level, along with evidence of NLRP3 potentially mediating the nonlinear threshold dose

response function of aluminum at least in asthma [4], it's worthwhile to review all of the evidence for the role of NLRP3 inflammasome in each outcome.

NLRP3 and Autism:

The NLRP3 inflammasome, a key component of the innate immune system, plays a pivotal role in sensing cellular stress and initiating inflammatory responses through the activation of caspase-1 and the release of pro-inflammatory cytokines such as IL-1 β and IL-18. Emerging evidence implicates aberrant NLRP3 activation in a spectrum of neurodevelopmental, allergic, metabolic, and neurological disorders, potentially through mechanisms involving neuroinflammation, oxidative stress, and immune dysregulation. This discussion synthesizes the current body of research linking NLRP3 to autism spectrum disorder (ASD), allergies, asthma, attention-deficit/hyperactivity disorder (ADHD), epilepsy, obesity, and Tourette's syndrome. It further explores the two-step activation mechanism of NLRP3 and its implications for a threshold dose-response to aluminum, a known inflammasome activator. Finally, proposed treatments for each condition are examined, with emphasis on their interactions with NLRP3 pathways.

Substantial evidence supports a link between NLRP3 inflammasome activation and ASD pathogenesis, primarily through neuroinflammation and mitochondrial dysfunction. Studies have demonstrated elevated NLRP3 expression and inflammasome activity in ASD models, contributing to microglial activation, cytokine release, and behavioral deficits [5–7]. For instance, NLRP3-mediated IL-1 β production has been associated with synaptic dysfunction and repetitive behaviors in preclinical models, with inhibition of the inflammasome rescuing immune phenotypes in vitro [8,9]. Human studies further correlate NLRP3 activity with metabolic perturbations and lipid mediators in ASD, suggesting a role in inflammasome-driven neurodevelopmental alterations [10]. These findings indicate that NLRP3 may exacerbate ASD by amplifying innate immune responses in the central nervous system (CNS), potentially triggered by environmental factors.

NLRP3 and Allergies:

NLRP3 inflammasome activation is implicated in allergic inflammation, where it promotes IL-1 β and IL-18 release, driving Th2 responses and epithelial pyroptosis [11–13]. Research in allergic rhinitis (AR) models shows that NLRP3 deficiency alleviates symptoms by enhancing mitophagy and reducing pyroptosis, highlighting its role in amplifying allergic responses [14,15]. Mitochondrial ROS-mediated NLRP3 activation has also been linked to allergic airway inflammation, underscoring a mechanistic pathway in hypersensitivity reactions [16,17]. Overall, NLRP3 appears to act as a sensor for allergens, contributing to chronic allergic diseases through sustained inflammation.

NLRP3 and Asthma:

In asthma, particularly neutrophilic and severe forms, NLRP3 drives airway hyperresponsiveness (AHR), eosinophilic infiltration, and cytokine production [18–20]. Studies in house dust mite (HDM)-induced models reveal that NLRP3 promotes pathogenesis in an inflammasome-dependent manner, with elevated expression correlating to steroid-resistant inflammation [21,22]. Mitochondrial ROS and endoplasmic reticulum stress further activate NLRP3, exacerbating chronic airway remodeling [16,23]. These data position NLRP3 as a central mediator in asthma's inflammatory cascade, particularly in obesity-associated or allergen-driven subtypes.

NLRP3 and ADHD:

Evidence linking NLRP3 to ADHD is emerging but limited, primarily through associations with neuroinflammation and oxidative stress. Preclinical studies suggest that NLRP3 activation contributes to ADHD-like behaviors via microglial activation and TLR4 signaling [24–26]. Inhibition of NLRP3 has shown potential in ameliorating symptoms in models involving metabolic perturbations or excitotoxicity [27,28]. While direct causality remains understudied, NLRP3's role in CNS inflammation may intersect with ADHD's dopaminergic and glial dysregulation.

NLRP3 and Epilepsy:

NLRP3 is strongly implicated in epileptogenesis, where it promotes neuroinflammation, pyroptosis, and seizure progression through IL-1 β release [29–32]. Mitochondrial dysfunction and ROS trigger NLRP3 in temporal lobe epilepsy, inhibiting mitophagy and exacerbating neuronal

damage [33,34]. Studies in febrile infection-related epilepsy syndrome (FIRES) highlight microglial NLRP3 as a driver of protracted inflammation [35]. These findings suggest NLRP3 as a therapeutic target to mitigate seizure severity and cognitive deficits.

NLRP3 and Obesity:

NLRP3 activation in obesity fosters chronic low-grade inflammation, insulin resistance, and metabolic complications via sensing of danger signals like free fatty acids [36–38]. In adipose tissue, NLRP3 drives IL-1 β production, correlating with obesity severity and atrial arrhythmias [39,40]. Enteric glial NLRP3 also impairs intestinal barrier function in obese models [41]. This positions NLRP3 at the nexus of obesity-induced systemic inflammation.

NLRP3 and Tourette's Syndrome:

Links between NLRP3 and Tourette's syndrome (TS) are sparse but suggest involvement in neurodevelopmental inflammation. Studies indicate NLRP3's role in TS-like behaviors through pyroptosis and mitophagy dysregulation [24,42]. As part of broader neurodevelopmental disorders, NLRP3 may contribute via immune activation, though more research is needed to establish direct causality.

Two-Step Activation of NLRP3 and Threshold Dose Response to Aluminum:

NLRP3 inflammasome activation follows a canonical two-step process: priming (signal 1), which upregulates NLRP3 and pro-IL-1 β via NF- κ B signaling, and activation (signal 2), triggered by stressors like ATP or crystals, leading to assembly and cytokine maturation [43–47]. This biphasic mechanism implies a threshold effect, where inflammatory cytokines are only produced on the second exposure. Aluminum, used as a vaccine adjuvant, activates NLRP3 via lysosomal destabilization and ROS, mediated by receptors like GPRC6A [48]. The two step requirement creates a nonlinear dose response: the first dose primes without activating, while the second dose activates the inflammasome, triggering robust inflammation. This could explain variable responses to aluminum exposure in susceptible individuals, potentially linking to NLRP3-associated disorders.

Treatments and Interactions with NLRP3:

Therapeutic strategies targeting NLRP3 show promise across these conditions, often by inhibiting inflammasome assembly or downstream cytokines.

For ASD, salidroside ameliorates neuroinflammation by suppressing NLRP3-mediated pyroptosis, while phosphodiesterase 4 inhibitors reduce glial damage via NLRP3 modulation [49,50]. Acupuncture at ST36 also inhibits NLRP3, alleviating behavioral deficits [7].

In allergies, NLRP3 inhibitors like MCC950 or OLT1177 reduce inflammation and pyroptosis; natural compounds such as narirutin downregulate NLRP3 via USP15 inhibition [51–53]. IL-1 β blockade offers complementary relief in allergic airway disease.

Asthma treatments include NLRP3 inhibitors like RRx-001, JT002, and MCC950, which attenuate AHR and steroid resistance [20,21,54]. Yupingfeng San and vitamin D3 suppress NLRP3, enhancing steroid sensitivity [55,56].

For ADHD, morin hydrate provides neuroprotection by targeting NLRP3 and TLR4; MCC950 shows potential in related neuroinflammatory models [25,27]. Bushen Kaiqiao Formula inhibits microglial NLRP3 activation [26].

Epilepsy interventions target NLRP3 with inhibitors like MCC950, reducing seizures and mitophagy impairment [29,31,57–59]. Klotho and cannabidiol alleviate inflammation via Nrf2 or CB2R pathways intersecting NLRP3 [60,61].

In obesity, colchicine and adiponectin receptor agonists suppress NLRP3-driven inflammation, improving insulin sensitivity [62,63]. Gut microbiota modulation and natural polyphenols like garlic chive vesicles inhibit NLRP3, reversing metabolic dysfunction [64–66].

For Tourette's syndrome, Changpu Yujin Tang mitigates symptoms by inhibiting NLRP3 via enhanced mitophagy, representing a novel herbal approach [43].

In summary, NLRP3 emerges as a convergent pathway in these disorders along with potentially explaining nonlinearities seen at the population level.

5. Conclusions

This study leverages population-level data from the NSCH 2020-2023 and CDC NIS 2011-2017 to reveal significant associations between aluminum-adjuvanted vaccine uptake during specific early childhood periods and the prevalence of inflammatory conditions such as autism, allergies, ADHD, asthma, epilepsy, obesity, and Tourette's syndrome across U.S. states. Notably, these associations exhibit nonlinear patterns, including threshold-like responses and sign reversals across age windows, which align with the two-step priming and activation mechanism of the NLRP3 inflammasome, a pathway implicated in each of these disorders through neuroinflammation, oxidative stress, and immune dysregulation. In contrast, blood disorders, serving as a negative control, showed no such relationships, underscoring the specificity of these findings to inflammatory outcomes.

The evidence presented supports the hypothesis that aluminum adjuvants, present in vaccines like DTaP, HepB, Hib, PCV, and Polio, may contribute to these conditions via NLRP3-mediated inflammation, particularly in susceptible populations. Inter-disease correlations further suggest shared inflammatory underpinnings, while vaccine-specific breakdowns challenge alternative explanations like hidden confounders. These results extend prior mechanistic studies on NLRP3's role in disease pathogenesis and highlight promising therapeutic avenues, including NLRP3 inhibitors (e.g., MCC950), natural compounds, and lifestyle interventions that could mitigate risks.

While ecological in nature, these findings warrant urgent prospective studies to confirm causality, refine vaccination schedules for minimized aluminum exposure, and explore genetic or environmental modifiers of NLRP3 sensitivity. Ultimately, prioritizing inflammasome-targeted research could inform safer immunization strategies and novel treatments, reducing the burden of these chronic childhood conditions on individuals and society.

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Appendix

Code and data used:

https://github.com/kmokeddem/nsch_nis

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