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Beliefs in vaccine as causes of autism among SPARK cohort caregivers

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Abstract

Background: Fear of autism has led to a decline in childhood-immunization uptake and to a resurgence of preventable infectious diseases. Identifying characteristics of parents who believe in a causal role of vaccines for autism spectrum disorder (ASD) in their child may help targeting educational activities and improve adherence to the immunization schedule.

Objectives: To compare caregivers of children with ASD who agree or disagree that vaccines play an etiological role in autism for 1) socio-demographics characteristics and 2) developmental and clinical profiles of their children.

Methods: Data from 16,525 participants with ASD under age 18 were obtained from SPARK, a national research cohort started in 2016. Caregivers completed questionnaires at registration that included questions on beliefs about the etiologic role of childhood immunizations and other factors in ASD. Data were available about family socio-demographic characteristics, first symptoms of autism, developmental regression, co-occurring psychiatric disorders, seizures, and current levels of functioning.

Results: Participants with ASD were 80.4% male with a mean age of 8.1 years (SD = 4.1). Overall, 16.5% of caregivers endorsed immunizations as perceived causes of autism.

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CRediT authorship contribution statement

Eric Fombonne: Conceptualization, Data curation, Formal analysis, Methodology, Writing original draft, Writing-review & editing. **Robin P. Goin-Kochel**: Formal analysis, Methodology, Writing-review & editing. **Brian J. O'Roak**: Formal analysis, Methodology, Writing-review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. E. Fombonne was a paid expert witness in ligation involving autism and vaccines between 2004 and 2011 for Glaxo Smeeth & Kline. He was an expert witness for the US Department of Justice in the class action litigation before the Vaccine Compensation Injury Court in Washington DC (2005–2009). Drs B. J. O'Roak and R. P. Goin-Kochel have no conflict of interest to declare.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.12.026.

Compared to caregivers who disagreed with vaccines as a cause for ASD, those who believed in vaccine causation came disproportionately from ethnic minority, less educated, and less wealthy backgrounds. More often their children had experienced developmental regression involving language and other skills, were diagnosed earlier, had lost skills during the second year of life, and had worse language, adaptive, and cognitive outcomes.

Conclusion: One in six caregivers who participate in a national research cohort believe that child immunizations could be a cause of autism in their child. Parent social background (non-White, less educated) and child developmental features (regression in second year, poorer language skills, and worse adaptive outcomes) index caregivers who are more likely to harbor these beliefs and could benefit from targeted educational activities.

Keywords

Autism; Autism spectrum disorder; Immunizations; Vaccines; Psychiatric disorder; Seizure; Disorder; Sex; Language; Language delay; Regression; Intellectual disability; Ethnicity; Social factors

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Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder manifesting in the first years of life with a combination of developmental impairments in communication and reciprocal social interactions and atypical patterns of play, behavior, and sensorimotor responses. Although improvements occur as a function of maturation and early behavioral interventions, ASD is a lifelong disorder with persisting long-term impairments in core-symptom domains of ASD, especially social functioning [26]. Current epidemiological estimates for ASD in the US child population range between 1.7% [2] and 2.5% [24].

In the late 1990s, claims that childhood vaccinations accounted for upward trends in autism prevalence were widely publicized despite weak, if any, supporting empirical evidence. One purported mechanism incriminated the measles component of the triple MMR vaccine, arguing that in children previously normally developing, a regression and loss of skills occurred 5 to 6 days after vaccination, leading to autism associated with gastrointestinal symptoms and inflammatory pathology [45] The second one implicated the cumulative dose of thimerosal (ethylmercury) received through other childhood vaccines up to age 2 that was deemed to be too high and possibly exceeding safety thresholds.

Numerous controlled observational studies (case-control and cohort studies) failed to show that exposure to MMR vaccination [40] or to thimerosal-containing vaccines in various doses raised the risk of autism [21], findings that extended to their high-risk siblings [22,48]. The convergence of negative studies across investigators, study designs, samples and countries has been impressive and the absence of association between MMR and autism confirmed in several meta-analyses [23,42].

Further claims were subsequently made that the risk could be confined to a small, vulnerable, subgroup that epidemiological studies would not be capable to detect. Limited evidence was brought forward to describe this group (defined by regression/loss of skills days following the MMR vaccine, association with gastrointestinal symptoms, and demonstrated abnormal persistence of the measles virus in the gut and other biological

specimens). A systematic search for this hypothetical phenotype failed to validate its existence [10,15]. Regression/loss of skills in the developmental trajectory of autism had been described since the 1940s in up to 30% of children with ASD, and there is no evidence that this regressive phenotype has increased recently or in post-MMR years [10]. Comparative studies showed that children exposed to MMR were not more likely than unexposed children to experience regression, or a combination of regression and GI symptoms [10]. Moreover, studies of peripheral blood mononuclear cells RNA and measles antibodies titers [6] and measles RNA in gut specimen [20] all failed to document the presumed persistence of the measles virus in biological compartments of children with autism exposed to MMR. Of note, the initial research was shown to be fraudulent and the original paper was retracted by the *Lancet* [13].

Despite the strong convergence of negative scientific findings on this issue, fears that vaccines might cause ASD have persisted in the community of individuals with autism and their caregivers, as well as the lay public. In fact, misperception about an ASD-vaccine link has been proposed as a leading explanation behind increases in vaccine delays and refusals [30], the public-health consequences of which are evident in increased outbreaks of vaccine-preventable diseases [32]. These outbreaks and steadily declining immunization rates prompted the World Health Organization to identify vaccine hesitancy as one of the 10 greatest threats to global health in 2019 [47], as well as the publication of The Salzburg Statement on Vaccine Acceptance [35], which appeals to social media, government, healthcare, education, and families to actively promote confidence in vaccines. A public health focus is increasingly centered on parents who are *vaccine hesitant* (VHPs), which refers to a continuum of vaccine concerns that may include delaying/refusing one or more vaccines; however, VHPs are more amenable to vaccination compared to parents who refuse vaccines entirely.

Prevalence of parental vaccine hesitancy varies geographically, but in the general population, estimates range from 9 to 15% [18,31,19]. However, emerging evidence suggests that this rate is much higher among parents of children with ASD. Two recent studies on vaccine hesitancy and beliefs about causes of autism/developmental delays among parents of chi at approximately 28% of parents were vaccine hesitant [28,17]. Not surprisingly, the bulk of these parents endorsed vaccines as a cause for their children's ASD. Considering that (a) children later diagnosed with ASD are well-vaccinated for childhood vaccines recommended during the first two years of life [15,48] and (b) the median age of ASD diagnosis in the U.S. is four years, it is possible that many of these families become vaccine hesitant and endorse vaccines as a cause for ASD only *after* receiving the autism diagnosis. Unfortunately, once these beliefs are founded, they can be difficult to change and easy to disseminate, and little is known about the content and format of vaccine-information delivery that resonates most with parents who have concerns about vaccine safety [29].

As part of the Simons Foundation Autism Research Initiative, the SPARK cohort was recently initiated nationwide to increase genetic discovery and research capacity in ASD (SPARK, 2018). Since April 2016, recruitment from academic sites and the public at large has allowed for rapid accrual of a very large sample of individuals with ASD of all ages and from all US regions. A majority of these individuals and their parents consented to

provide saliva samples for genetic characterization (https://www.sfari.org/resource/spark/). Data were collected on family background, medical and social history, and specific autism symptom patterns. As part of these baseline data, caregivers were asked questions about their beliefs about causes of autism in their child. We dichotomized the group into those participants who either did or did not identify immunizations as a possible cause of autism. We compared the two groups of participants with respects to familial sociodemographics and index child developmental and clinical profiles. Our objectives were to identify: (1) characteristics of caregivers and households associated with belief in immunizations as a potential cause of autism; and (2) features of developmental trajectories and clinical profiles of children with ASD whose parents are most vulnerable to endorsing such beliefs.

1. Material and methods

1.1. SPARK cohort

In April 2016, SPARK began nationwide recruitment with 21 clinical sites, stakeholder partner organizations, and a multipronged social media strategy. Any individual living in the US with a professional diagnosis of ASD (by provider or school), alongside their parents (or legal guardians) and an unaffected sibling, are eligible to participate in SPARK. SPARK collects phenotypic data and biospecimens remotely so that participants can complete the study protocol online at their convenience, usually from home.

As part of participation in SPARK, individuals are also asked to complete a battery of online questionnaires (https://www.sfari.org/resource/spark/). For children under age 18, all questionnaires are completed by parents/caregivers.

Although phenotypic information and ASD diagnoses in SPARK are self- or parent-reported, past research on the first web-based registry for ASD, the Interactive Autism Network [25], as well as recent analyses of the dependent adults SPARK participants [11] suggest that parent-reported diagnosis of ASD is valid. Participants consent to share their de-identified data and to be contacted about future ASD research studies for which they may be eligible. Participants can also consent to contribute a saliva sample for genetic analysis and have the option to receive individual genetic results related to ASD should a primary genetic cause of ASD be identified. Detailed aspects of genetic material collection, genomic analyses, and return of results to participants are described elsewhere [39,11,9]. In SPARK's first 32 months of recruitment, through December 2018, SPARK enrolled 150,064 participants, including 59,218 individuals with ASD.

1.2. Data and instruments

Online registration requires completing a basic set of registration questions about each individual who enrolls, and a series of supplementary questionnaires.

• **Registration Questions—**The registration questions (hereafter referred to as 'Registration Questions') for individual participants with ASD cover: age at registration, sex, ASD diagnosis, professional/s who made the ASD diagnosis, age at first diagnosis, lifetime receipt of any services or therapies specifically for ASD, presence of an individualized education program/plan (IEP), lifetime diagnosis of intellectual disability or cognitive

impairment, and current everyday language level (coded on 4 levels: *No words/does not speak, Uses single words meaningfully (for example, to request), Combines 3 words together into short sentences, Uses longer sentences of his/her own and is able to tell you something that happened*). From this, we generated a dichotomous variable for current language functioning with: 0 = Sentence speech, 1 = Minimally or non- verbal (3 other levels).

• **Medical questionnaire—**Respondents can endorse any of the 5 following medical domains questions for diagnoses made by a professional: Birth or pregnancy complications, Neurological conditions, Growth conditions (e.g., obesity, head size), Vision or Hearing conditions, and Birth defects. A positive answer for any domain leads to more detailed follow-up questions. From these, we selected the following variables for subsequent analyses. We constructed a variable *Any birth defect* that was scored 1 when any of the 25 birth defects was endorsed and 0 otherwise. The five birth/pregnancy complications were similarly summarized in a binary variable *Any birth problem* scored 1 (=Any complications) or 0 (=No complications). Sleep disorder and Seizure disorder or epilepsy were similarly coded 1 for Yes and 0 for No. For psychiatric disorders, we created summary binary variables for *Any disruptive disorder, Any emotional disorder*, and *Any psychiatric disorder*. We also examined specific disorders for their particular relevance–*ADHD* because of its high prevalence and impact on management and caregivers [38], and *Tics* because of prior concerns about an increased risk of tics following vaccine exposure [44,3]. ADHD and Tics were included in *Any psychiatric disorder* but not in *Any disruptive disorder*. Questions on psychiatric disorders apply retrospectively to the lifetime period and no data were collected about date of onset, duration, or treatment.

• **Background history—**This questionnaire covered socio-demographic information about the parents (marital status, race/ethnicity, annual household income, education level, occupation/employment status) and current living arrangements. From the child's developmental history, the following variables were used: *Motor delay* (0 = No; 1 = Sat after 8 months or walked after 18 months), *Delay in 1st words* (0 = No; 1= >= 24 months), *Delay in first phrases* (0 = No; 1= >=33 months), *Age of parental recognition of 1st symptoms, Type of parental concern, Stopped progressing or "plateaued"* (0 = No, 1 = yes), *Stopped talking, lost language* (0 = No, 1 = yes), *Loss of other skills* (0 = No, 1 = yes), *Age at diagnosis, Diagnosed with Asperger/PDDNOS* (0 = No, 1 = yes), *Ever diagnosed with cognitive impairment/intellectual disability* (0 = No, 1 = yes), and *Presence of a sibling with ASD* (0 = No; 1 = Yes). Cut points for delays in milestones were selected to be similar to those of the *Autism Diagnostic Interview–Revised*, a widely used caregiver interview for the diagnosis of autism. In the current functioning questions, parents were asked to rate the level of functioning of their child as compared to same-age peers. Questions covered the level of support required, general understanding of concepts and problem-solving capacity, daily functioning, and current level of spoken language. For each domain, parents indicated if their child was functioning above or at age level, slightly below age, or significantly below age. A composite variable was generated by calculating the *Number of areas* where the child was most behind his peers (significantly below age or very substantial support required), with a range from 0 to 4.

One final question was about the caregiver's perceptions about the causes of ASD: "What is your opinion as to what may have caused X's ASD?". Nine options were listed: Genetic causes, Other medical conditions, Environmental exposures, Problems during pregnancy, Drug or alcohol exposure in pregnancy, Birth or delivery complication, Infection in infancy or early childhood, Immunizations, Don't know/Other. Parents could select as many responses as they liked. A positive response to the 'Immunizations' modality was used to stratify the sample into caregivers who endorsed immunizations (EI) or not (NEI) as a cause of ASD.

• **Other SPARK data—**Other questionnaire data used were:

- The *Social Communication Questionnaire* (SCQ) is a parent-report questionnaire that evaluates 3 major aspects of ASD: communication, social interaction, and repetitive behaviors. The development of the SCQ was modeled after the *Autism Diagnostic Interview* to generate a brief, parent-completed, screening tool (Berument et al., 1999). The questionnaire exists in two forms: lifetime and current. The "lifetime" version (used in this study) evaluates the child's developmental history as well as current behaviors. It comprises 40 questions with "yes" or "no" responses. Each item is scored as 0 or 1, and the sum of 39 items yields a total SCQ score ranging from 0 to 39 (the first item documents whether or not the child has phrase speech and is not scored). Total scores are prorated when there are 3 items or less missing; with 4 or more items missing, total score is set to missing. Cutoffs of 15 and 22 were initially proposed to select children likely to have a broader or narrower form of ASD, with a cut-off of 12 recommended in subsequent epidemiologic studies.

-The *Repetitive Behavior Scale-Revised* (RBS-R) is a caregiver completed rating scale that evaluates 43 restricted, repetitive, self-injurious behaviors rated on a zero (Behavior does not occur) to 3 (Behavior occurs and is a severe problem) scale as observed during the last month. An overall score is derived from the sum of items scores, and scale-specific scores can also be derived for six dimensions (Stereotyped behavior; Self-injurious behavior; Compulsive behavior; Ritualistic behavior; Sameness behavior; Restricted behavior). The RBS-R overall score was dichotomized by using the 75th (47) and 90th (65) centiles of the whole sample distribution.

The SCQ and the RBS-R were examined both as continuous and categorical scores.

1.3. Sample selection

Data for participants registered in the SPARK cohort were downloaded December 20, 2018, from the SFARI website (https://www.sfari.org). There were 59,218 participants with an ASD diagnosis, of whom 50,505 were under age 18 at registration. Of these, 18,480 had Background history data with the vaccine-belief question answered. We further excluded 1,955 subjects who were siblings or half-siblings of an already registered child in order to maintain independence of observations, leaving a sample of 16,525 participants under age 18 with available data. They were comparable to participants without Background history data for sex, age, cognitive and language levels, and history of ASD services.

1.4. Ethical approval

All recruiting sites for SPARK delegated institutional oversight of the study to a central institutional review board (Western IRB). Only de-identified data were used in this study.

1.5. Statistical analyses

Data were analyzed in SPSS v25 and conventional statistical tests for categorical (Fisher exact test; chi-square) and continuous variables (t-tests, Pearson or Spearman correlation coefficients) were used. Binary and multivariate logistic regression was used to evaluate predictors of binary dependent variables. In line with current recommendations [34,37], we did not use Bonferroni's adjustment for multiple tests. Owing to the large sample size, a p-value of <=0.01 was retained throughout as a pre-set level of statistical significance.

2. Results

The SPARK-participant sample was 80.4% male (male:female ratio: 4.1), and the mean age was 8.1 years (SD = 4.1) at registration. Overall, 2,730 caregivers (16.5%) endorsed immunizations as a possible cause of ASD in their child; this was the fourth most frequent potential etiology endorsed by respondents, preceded by genetic causes (N = 9,650, 58.4%), environmental exposures (N = 3,611; 21.9%) and birth or delivery complications (N = 2,796, 16.9%).

2.1. Attributions to immunizations versus other causes

EI and NEI caregivers were compared with respect to other endorsed etiologic beliefs (Table 1). Genetic causes were the most frequently endorsed etiology, with no difference between the EI and NEI groups in likelihood of endorsing that cause. For 6 of the remaining 7 potential causes, the EI group had significantly higher levels of endorsement than the NEI group. When causes were added up, EI caregivers endorsed a higher number of causes than NEI caregivers (2.8 vs 1.3; $p < 0.001$).

2.2. Socio-demographic characteristics by caregiver-belief status

Sociodemographic characteristics are summarized in Table 2. Children did not differ by gender but were significantly older in the EI group compared to the NEI group. There was a marked tendency for children from ethnic minority backgrounds (with the exception of Native Americans) to have parents belonging to the EI group. Compared to NEI caregivers, EI caregivers were significantly less often married, had lower income, were less educated, less often employed, and more likely to be full-time caregivers for their child. Sibling recurrence of ASD had no impact on beliefs.

2.3. Developmental and clinical profiles by caregiver belief status

Children from NEI caregivers had slightly higher rates of birth problems; otherwise, the 2 groups were comparable for the incidence of birth defects, motor delay, and language delay when estimated by first-word onset (Table 3). However, phrase-speech delay was significantly more frequent in the EI group. The EI caregivers also differed from their NEI counterparts in their reports of first ASD symptoms in their child. EI caregivers less

often reported early (<12 months) or late (>36 months) recognition of first symptoms but identified them more frequently during the second year of life. The type of first ASD symptom recognized by parents significantly differed across groups, with EI caregivers reporting a change or loss of skills three times more frequently than NEI parents. Irrespective of age at symptom identification, over half the EI caregivers reported a loss of language in their child and over two fifths reported a loss of another skill, with both reports occurring about twice as frequently in the EI compared to the NEI group. Similarly, reports of plateauing in development was much more frequent in the EI than the NEI group. In addition, when language loss occurred, children from the EI group lost language skills at an earlier age than in the NEI group (21.0 vs 23.1 months; $p < 0.001$). When asked if speech ever came back to the level it was just before the loss, NEI caregivers had more frequent positive answers than EI caregivers (69.5% vs 59.7%; $p < 0.001$) and the reported duration of the loss (<1 year) was significantly different across the two groups and shorter in the NEI group (NEI: 34.3%; EI: 18.8%; $p < 0.001$).

A similar pattern was observed for loss of other skills (i.e., non-language skills), which occurred at a significantly younger age in the EI group compared to the NEI group (27.5 vs 37.5 months; <0.001). The return to pre-loss skill level was endorsed by 51.1% of NEI and 44.0% of EI caregivers ($p < 0.001$) and a duration of loss < 1 year was reported by 29.4% of NEI and 16.4% of EI caregivers ($p < 0.001$).

The mean age at diagnosis in this sample was 4.4 years (SD = 2.7; IQR: 2.5–5.5). The age at diagnosis was significantly lower in the EI group than in the NEI group (3.7 vs 4.5 years; $p < 0.001$), with higher proportion of children diagnosed before age 3 and the opposite pattern after age 6 (Table 3). Severity was more pronounced in children of the EI group, with a higher rate of lifetime diagnosis of intellectual disability, similarly indexed by less reliance on ‘high-functioning’ diagnostic categorization.

With the exception of Tics, lifetime prevalence of psychiatric disorders was slightly higher among NEI compared to EI offspring. By contrast, other indicators of clinical severity were significantly raised in the EI group, including sleep disorders, epilepsy, as well as minimally verbal status (currently, no sentence speech). Likewise, when asked about the level of support currently required by their child, findings were consistent across the 4 areas investigated, with EI children endorsing a higher number of areas with significant needs than NEI children by a factor that ranged from 1.3 (Spoken language) to 1.6 (Support required) (Fig. 1).

Finally, levels of autistic symptomatology, whether measured by the general autism SCQ questionnaire or by the more symptom-domain specific RBS-R scale, showed consistently higher levels of symptoms in the EI compared to the NEI group. This was true when scores were examined both continuously or categorically (Table 3).

Thus, children from parents endorsing immunization as a potential cause of ASD had a developmental course marked on average by an ‘onset’ in the second year of life, a regressive pattern involving language and other skills, an earlier (<3) age at diagnosis, and greater clinical severity as shown by heightened developmental language and cognitive

impairments, as well as more pronounced deficits in current level of functioning across key areas. Moreover, parents in the EI group more frequently tended to come from minority, less educated, and less wealthy backgrounds. The findings on psychiatric disorders ran in the opposite direction; however, previous analyses [11] showed that psychiatric prevalence is decreased among individuals with lower levels of language and cognitive functioning, likely indicating under-detection among those who are more severely impaired.

Because factors associated with vaccine-belief status were intercorrelated, we employed multiple logistic regression analyses to obtain a more parsimonious set of correlates of such beliefs. Using belief in immunization as a dependent variable, three *a priori* defined blocks of variables with a significant ($p < 0.01$) association with belief status were entered as predictors as follows: (a) demographic characteristics (child ethnicity, living arrangements, parent's marital status, annual household income, mother's education, and mother's occupation; see Table 2 variables); (b) developmental trajectory characteristics (sex, age, any birth problems, cognitive impairment, motor delay, phrase-speech delay, age at first ASD symptoms, type of parental concern, plateau, any regression [language or other skill], age at diagnosis, Asperger/PDDNOS diagnosis; see Table 3 variables, Section Early Development); c) current behavioral/adaptive functioning (history of seizures, any lifetime psychiatric disorder, diagnosed sleep problems, minimally verbal status, total SCQ score [continuous], total RBS-R score [continuous], and number [0–4] of areas [support required, understanding concepts/problem solving, daily functioning, spoken language] with significantly below-age functioning; see Table 3 variables, section on Current behavioral/adaptive functioning). Gender was initially forced in the models because of its general developmental and biological significance. Results of the three resulting logistic models are provided in the Supplement alongside rules for recoding variables. In summary, of the 25 variables tested as predictors in the 3 models, 11 no longer significantly contributed to the model (- marital status, living arrangements, household income; - sex, cognitive impairment, motor delay, Asperger/PDDNOS diagnosis; - seizure history, any psychiatric disorder, RBS-R total score) and were not further considered. The remaining 14 variables were entered into a stepwise logistic regression with forward selection procedure and a $p = 0.01$ for inclusion in the model. Results are shown in Table 4. Three variables (total SCQ score, mother's occupation, and delay in phrase speech) were not retained in the final model. The model fit was good (Hosmer-Lemeshow $\chi^2 = 3.7$; $df = 8$; $p = 0.89$). The 11 predictors remaining in the model reflected the role of both sociodemographic (child's race, child age, maternal education), developmental (regression, plateau, age at diagnosis, age and type of symptom for parental recognition, birth problems), and current functioning (language deficits, number of areas with significant below age functioning) factors. Interestingly, levels of autistic symptomatology (other than language deficits) were no longer contributory.

3. Discussion

In this large community sample of caregivers of children with ASD under age 18, one in six participants believed immunizations could be a cause of ASD in their child; this was the fourth most frequently endorsed cause. Caregivers who endorsed vaccinations as a potential cause also more frequently endorsed other external, environmental causes and came from more adverse social backgrounds; their children had developmental trajectories

characterized by skill loss in the second year of life and longterm, persisting impairments in language and overall functioning.

In our sample, beliefs in vaccines as a cause for ASD was not associated with a lessened endorsement of genetic factors as causal, as well; rather, it was paralleled with more frequent endorsement of multiple, additional, putative environmental causes. As the SPARK cohort relies on voluntary research participation in a cohort with strong underpinning of genetic research, our observed proportion of caregivers harboring vaccine beliefs is likely to be an underestimate of the true frequency among the population of caregivers of children with ASD. Data were not available on actual vaccine uptake of the children concerned, thus caution is needed in extrapolating from parental beliefs to actual opting out of the vaccination schedule. However, previous studies have shown that parents of children with ASD are more likely to be vaccine-hesitant [28,36] and parental beliefs in vaccine causation is associated with lower immunization rates of ASD children at later ages [4,48] and lower rates of immunizations in unaffected younger siblings compared to their peers [1,4,12,48]. Taken all together, the results of these studies strongly suggest that parental beliefs in vaccine causation lead to delays or declines in vaccine uptake in both children with ASD and their unaffected siblings.

Interestingly, the proportion of EI believers was higher in caregivers of older children. This might reflect a cohort effect in which parents of children born around 2000 may have been more affected by the vaccine controversy in general, or by earlier concerns arising from the use of thimerosal that have subsided following discontinuation of the preservative in vaccine preparation since 2004. Alternatively, it may reflect an age effect by which the persistence of substantial impairments at older ages may be associated with different patterns of parental beliefs. The cross-sectional and retrospective nature of the data did not permit further investigation of these competing hypotheses.

The sociodemographic factors related to parental beliefs showed that parents from ethnic minority and less-educated backgrounds were more prone to endorse these beliefs, findings that are consistent with previous results [4]. Already, ethnic minority and underserved social groups have well-established decreased access to diagnostic and early intervention services [2,7]. Our findings show that they also are more vulnerable to embracing unproven attributions that may, in turn, result in increased medical risk or morbidity associated with preventable infectious diseases. In multivariate analysis, both ethnicity and lower maternal education increased significantly the odds of erroneous vaccine beliefs beyond the effect of individual clinical characteristics, suggesting that preemptive educational efforts should be specially targeted at caregivers with these social risk characteristics. Moreover, it is worth noting that minority groups have been specifically targeted by anti-vaccine movements [46,8], which makes preventative education within these subgroups even more necessary.

Both early developmental and current clinical characteristics influenced the likelihood of vaccine beliefs. In the early developmental period, both the emergence of specific symptoms and their timing separately increased odds of belief in vaccine causation. A first parental concern about a change or loss of abilities in the child and report of regression or loss of language/other skills were the two developmental features with the strongest association

with vaccine causation beliefs. With respect to timing, parental recognition of first alarming symptoms during the second year of life and a diagnosis before age 3 were predictive of later antivaccine sentiment. In addition, loss of skills occurred earlier in that group and lasted longer. Loss of skills occurs in 20–40% of children with ASD, usually during the second year of life, and is associated in several studies with more severe language, adaptive behavior and cognitive outcomes [10,14,27,33,43]. The origin of the regressive pattern is unknown but has been associated with increased frequency of de novo variants in genes encoding for post-synaptic density proteins [16] or in a few specific genes involved in chromatin remodeling or synapse formation and adhesion [41].

Belief in a vaccine-based etiology was also associated with increased overall current severity of the child at SPARK registration. In particular, risk was increased in parents of children with current language limitations, either being non-verbal or having single words or word combinations, as well as those functioning below chronological age in multiple areas. Interestingly, when past and current delays in milestones or functioning were adjusted for, autism symptomatology scores no longer contributed to the prediction of parental beliefs. Thus, it appears that severity as indexed by non specific delays in development, especially in language and communication, rather than autism specific symptoms is the most predictive characteristic.

It is worth noting that the type, and more so the timing, of first autism symptoms identified in our sample make the measles-mumps-rubella (MMR) immunization a more likely target for parental causal attribution, as MMR is usually given during ages 12–18 months, a period that coincides with the emergence of parental concerns in a high proportion of families [5]. In an earlier study, when parents harboring anti-vaccine beliefs were asked to compare different vaccines, MMR came well ahead of other vaccines or vaccine combinations (49% vs <26%) as the culprit for ASD [4].

Taken together, our results suggest that preemptive educational activities should preferentially target families from ethnic minority and less educated backgrounds and whose children exhibit loss of skills in the second year of life. Professionals involved in multidisciplinary specialist teams who diagnose ASD may not always have enough time to educate parents about what ASD is *not* caused by. Additionally, teams led by nonmedical professionals may feel less competent to talk through medical matters and may refer families to later discussions with their community providers, which may or may not occur. Because of the recent resurgence of measles outbreaks, it is important that professionals tackle this information gap. There is a need to develop evidence-based tools for practitioners and families to facilitate this process.

4. Limitations

This cohort comprises participants who volunteered for research, with special emphasis on genetic research, and the representativeness of the SPARK cohort cannot be fully assessed. Data, including those on diagnosis, are reported by parents online and no independent validation is yet available. However, preliminary phenotypic [11] and genetic [9] data provide indirect evidence for diagnostic validity among affected SPARK participants. Data

on early developmental trajectories of ASD was retrospectively collected. Beliefs in vaccine causation of ASD were investigated globally and no analysis could be done for beliefs relating to specific childhood vaccines. We did not have vaccination records and could not test if parents who hold beliefs that vaccines can cause ASD were also less likely to have their child with ASD up-to-date with the vaccination schedule or whether their younger offspring were under-vaccinated.

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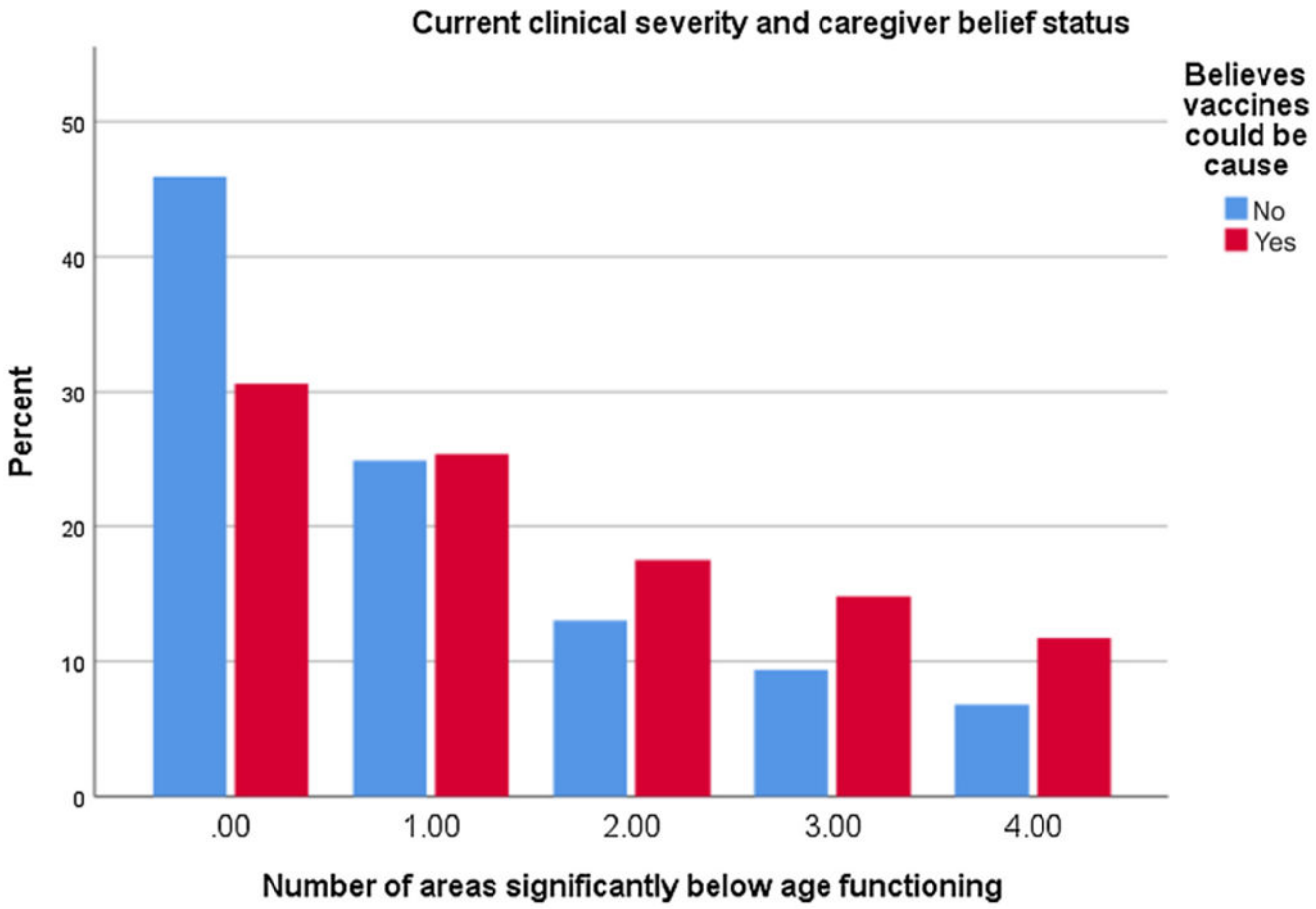

Fig. 1.
Current clinical severity and caregiver belief status.

Table 1

Vaccines versus other etiologic beliefs.

What is your opinion as to what may have caused your child's ASD…	Immunizations				
	No (NEI) N = 13,795		Yes (EI) N = 2,730		p-value
	N	%	N	%	
Genetic causes	8,099	58.7	1,551	56.8	0.066
Other medical conditions	980	7.1	359	13.2	<0.001
Environmental exposures	2,408	17.5	1,203	44.1	<0.001
Problems during pregnancy	2,186	15.8	540	19.8	<0.001
Drug or alcohol exposure in pregnancy	348	2.5	80	2.9	0.22
Birth or delivery complication	2,166	15.7	630	23.1	<0.001
Infection in infancy or early childhood	473	3.4	261	9.6	<0.001
Other causes	1081	7.8	308	11.3	<0.001

Table 2

Sociodemographic characteristics, by belief status.

	Immunizations may have caused my child's ASD…				
	No (NEI)		Yes (EI)		p-value
	N	%	N	%	
Child					
Gender male	11,045	80.1	2,233	81.8	0.038
Age at joining the study					
• Under 3 years	916	6.6	172	6.3	<0.001
• 3–5 years	3,647	26.4	696	25.5	
• 6–11 years	6,118	44.3	1,094	40.1	
• 12–17 years	3,114	22.6	768	28.1	
Ethnicity					
• African-American	617	4.5	219	8.1	<0.001
• White	10,902	79.3	1,921	70.7	
• Native American	83	0.6	10	0.4	
• Asian	258	1.9	87	3.2	
• Other	1,892	13.8	479	17.6	
Living arrangements					
• With both parents	9,697	70.4	1,893	69.5	0.001
• With mother	3,466	25.2	749	27.5	
• With father	155	1.1	28	1.0	
• Adopted/foster home/relatives	424	3.1	50	1.8	
• Residential	26	0.2	2	0.1	
Has a sibling with ASD	1,680	12.2	333	12.2	0.98
Family					
Marital status biological parents					
• Married	8,770	65.4	1,645	62.4	0.003
• Never married	2,369	17.7	544	20.6	
• Divorced and remarried	977	7.3	186	7.1	
• Divorced/separated	1,286	9.6	263	10.0	

	Immunizations may have caused my child's ASD…				
	No (NEI)		Yes (EI)		p-value
	N	%	N	%	
Household income/year					
• <$20,000	1,552	11.5	381	14.4	<0.001
• $20,000 to $50,000	3,729	27.7	760	28.7	
• $51,000 to $80,000	2,834	21.0	607	22.9	
• $80,000 to $130,000	3,209	23.8	579	21.9	
• Over $131,000	2,152	16.0	318	12.0	
	Immunizations may have caused my child's ASD…				
	No (NEI)		**Yes (EI)**		**p-value**
	N	**%**	**N**	**%**	
Mother's education					
• Did not complete high school	728	5.3	192	7.0	<0.001
• High school	1,271	9.2	278	10.2	
• Trade or Associate degree	2,854	20.7	631	23.2	
• Some college	2,370	17.1	530	19.4	
• Bachelor degree	3,697	26.8	652	23.9	
• Professional degree	2,854	20.7	442	16.2	
Mother's occupation					
• Employed	6,360	46.4	1,130	41.5	<0.001
• Home carer	4,801	35.0	1,076	39.6	
• Temporary or Part-time	1,410	10.3	271	10.0	
• Unemployed	1,129	8.2	243	8.9	

Table 3

Developmental and clinical characteristics, by belief status.

	Immunizations may have caused my child's ASD…				
	No (NEI)		Yes (EI)		p-value
	N	%	N	%	
Early development					
Any birth defect	446	*3.2*	65	*2.4*	0.019
Any birth problems	4,230	*30.7*	751	*27.5*	0.001
Motor delay (sitting > 8 or walking > 18 mos)	2,894	*21.2*	519	*19.2*	0.02
Delay in 1st words (>=24 mos)	4,936	*37.0*	977	*36.9*	0.96
Delay in 1st phrases (>=33 mos)	6,722	*50.9*	1,595	*61.7*	<0.001
Age at parental recognition of 1st symptoms					
• =<12 months	4,782	*34.9*	738	*27.2*	<0.001
• 13–24 months	5,304	*38.7*	1,370	*50.4*	
• 25–36 months	2,054	*15.0*	433	*15.9*	
• >36 months	1,571	*11.5*	176	*6.5*	
First parental concern					
• Motor or language delay	5,446	*39.8*	970	*35.7*	<0.001
• Loss or change in abilities	1,029	*7.5*	623	*22.9*	
• Atypical social interaction	2,631	*19.2*	463	*17.0*	
• Unusual speech or habits	1,608	*11.7*	238	*8.8*	
• Other	2,981	*21.8*	423	*15.6*	
Stopped progressing or "plateaued"	6,967	*50.7*	1,972	*72.3*	<0.001
Stopped talking, lost language	3,950	*28.7*	1,561	*57.3*	<0.001
Loss of other skills	3,457	*25.1*	1,194	*43.9*	<0.001
Age diagnosis					
• <3 years	4,781	*34.7*	1,300	*47.6*	<0.001
• 3–5 years	5,739	*41.6*	1,099	*40.3*	
• >= 6 years	3,273	*23.7*	331	*12.1*	
Asperger or PDDNOS diagnosis	2,237	*16.2*	368	*13.5*	<0.001
Cognitive impairment/ID (ever diagnosed with)	2,100	*15.2*	546	*20.0*	<0.001

	Immunizations may have caused my child's ASD…				
	No (NEI)		Yes (EI)		p-value
	N	%	N	%	
Current behavioral/adaptive functioning					
Seizure disorder or epilepsy (lifetime)	683	*5.0*	179	*6.6*	0.001
Psychiatric comorbidity (lifetime)					
• ADHD	5,129	*37.2*	856	*31.4*	<0.001
• Any disruptive disorder	5,319	*38.6*	910	*33.3*	<0.001
• Any emotional disorder	3,881	*28.1*	652	*23.9*	<0.001
• Tics	512	*3.7*	105	*3.8*	0.74
• Any psychiatric disorder	7,670	*55.6*	1,402	*51.4*	<0.001
Sleep Disorder/problem diagnosed by a professional	2,542	*18.4*	606	*22.2*	<0.001
Minimally or non verbal	5,463	*39.6*	1,521	*55.7*	<0.001
Level of support required					
• No or minimal support	1,388	*10.1*	187	*6.9*	<0.001
• Some support	5,677	*41.3*	883	*32.5*	
• Substantial	4,691	*34.1*	1,029	*37.8*	
• Very substantial	1,998	*14.5*	620	*22.8*	
General understanding of concepts/problem-solving					
• At age or above age level	6,352	*47.0*	861	*32.6*	<0.001
• Slightly below age	3,712	*27.5*	779	*29.4*	
• Significantly below age	3,443	*25.5*	1,006	*38.0*	
Daily functioning					
• At age or above age level	3,189	*23.3*	534	*19.7*	<0.001
• Slightly below age	6,634	*48.4*	1,206	*44.4*	
• Significantly below age	3,885	*28.3*	979	*36.0*	
Current level of spoken language					
• Above age level	2,383	*17.4*	261	*9.6*	<0.001
• At age level	2,658	*19.4*	344	*12.7*	
• Slightly below age	3,604	*26.4*	643	*23.7*	
• Significantly below age	5,031	*36.8*	1,461	*53.9*	
Number of areas with lowest functioning					

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	Immunizations may have caused my child's ASD…				
	No (NEI)		Yes (EI)		p-value
	N	%	N	%	
• 0	7,688	*45.9*	1,029	*30.6*	<0.001
• 1	4,168	*24.9*	853	*25.4*	
• 2	2,190	*13.1*	589	*17.5*	
• 3	1,571	*9.4*	499	*14.8*	
• 4	1,141	*6.8*	394	*11.7*	
Autism symptomatology measures					
Categorical scores					
SCQ					
• >=15	11,504	*83.4*	2,379	*87.1*	<0.001
• >=22	7,445	*54.0*	1,696	*62.1*	<0.001
RBS-R					
• >75 h centile	3,265	*23.7*	775	*28.4*	<0.001
• >=90th centile	1,287	*9.3*	310	*11.4*	0.001
Continuous scale scores					
SCQ total score, X (*SD*)	22.2	*6.8*	23.7	*6.7*	<0.001
RBS-R total score, X (*SD*)	34.77	*20.6*	37.30	*21.8*	<0.001

Table 4

Predictors of belief in the role of immunizations: multiple logistic regression model (N = 16,239).

	B	S.E.	Wald	df	Sig.	Odds-ratio	95%CI lower	95%CI upper
Minimally or non verbal	0.322	0.062	26.863	1	0.000	1.379	1.221	1.558
Number of significantly below age areas	0.077	0.021	13.947	1	0.000	1.080	1.037	1.124
Child race	0.420	0.050	70.619	1	0.000	1.522	1.380	1.678
Mother's education: College/Professional	–		20.307	2	0.000	[Ref]	–	–
Some college	0.199	0.049	16.585	1	0.000	1.220	1.109	1.343
High school or less	0.217	0.065	11.231	1	0.001	1.242	1.094	1.411
Any birth problems	−0.163	0.049	10.901	1	0.001	0.849	0.771	0.936
Stopped progressing or "plateaued"	0.374	0.055	45.357	1	0.000	1.453	1.303	1.620
Any regression/loss of skills	0.600	0.055	118.462	1	0.000	1.822	1.635	2.029
Age at diagnosis	0.313	0.050	38.719	1	0.000	1.367	1.239	1.509
Age at parental recognition	0.298	0.046	42.054	1	0.000	1.347	1.231	1.473
First parental concern	0.702	0.062	128.158	1	0.000	2.018	1.787	2.279
Age at registration under 3 years	–		163.513	3	0.000	[Ref]	–	–
3–5 years	0.352	0.099	12.546	1	0.000	1.421	1.170	1.727
6–11 years	0.666	0.101	43.244	1	0.000	1.946	1.596	2.373
12–17 years	1.113	0.107	107.148	1	0.000	3.042	2.465	3.756
Constant	−3.611	0.116	962.297	1	0.000	0.027		

Variables were coded: Minimally or non verbal: 0 = No, 1 = Yes; - Number of significantly below age areas: 0 = Does not require very substantial support *or* is significantly below age in either general understanding of concepts/problem-solving *or* in daily functioning *or* for current level of spoken language, 1 = meets criteria for 1 area, 2 = meets criteria for 2 areas, 3 = meets criteria for 3 areas, 4 = meets criteria for 4 areas; - Child race: 0 = White, 1 = Otherwise; - Mother's education: 0 = Bachelor/professional, 1 = Some college, Trade/Associate degree, 2 = High school or less; - Any birth problems: 0 = No, 1 = Yes; - Stopped progressing or "plateaued": 0 = No, 1 = Yes; - Any regression/loss of skills: 0 = No language regression or loss of other skills, 1 = Language regression or loss of other skill; - Age at diagnosis: 0 = after age 3, 1 = under age 3; - Age at parental recognition: 0 = before 1 or after 2 years, 1 = between 13 and 24 months; - First parental concern: 0 = Other concerns than change or loss in abilities, 1 = Change or loss in abilities; - Age at registration: 0 = Under 3 years, 1 = 3–5 years, 2 = 6–11 years, 3 = 12–17 years.