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Childhood vaccination as a protective factor for developmental psychopathology

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ABSTRACT

Backgrounds: Despite multiple studies demonstrating no relationship between childhood vaccination and increasing Autism Spectrum Disorder (ASD) prevalence, parental fear for vaccination and subsequent refusal to vaccinate their children continue, resulting in recent outbreaks of childhood infections such as measles in the US. We examine the relationship between the completion of 6 recommended vaccinations in childhood and the likelihood for having developmental psychopathology.

Methods: Two large-scale South Korean epidemiologic samples were used to examine whether completion of childhood vaccinations decrease likelihood of having ASD as assessed by Autism Spectrum Screening Questionnaire (ASSQ) and behavioral problems scores. Parental reports on vaccination completion were categorized in groups: <3, 4−5, & 6. The primary outcome is the likelihood of having ASD and/or, internalizing, and externalizing behavioral symptoms. Likelihood of having ASD was categorized as: low (ASSQ < 10), intermediate (ASSQ = 10–14), and high (ASSQ ≥ 15). The risk for externalizing/internalizing symptoms was assessed with the Behavior Assessment System for Children-Parent Rating Scale. We examined the hypothesis in a Discovery Sample (DS) (N = 10,006) and verified findings in a Replication Sample (RS) (N = 29,381).

Results: 84.3 % of DS and 80.1 % of RS participants were fully vaccinated. In the DS, after adjusting for demographics and confounders, children with incomplete-vaccinations were at greater risk for ASD when compared to those fully vaccinated (adjusted odds ratio [aOR] = 1.42, 95 % Confidence Interval [CI] 1.17−1.73 with 4−5 vaccinations; aOR = 2.33, CI 1.53−3.56 with vaccination <3). The DS finding was confirmed in the RS (aOR = 1.44, CI 1.32−1.58 with 4−5

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vaccinations and aOR = 2.19, CI 1.80−2.67 with < 3 vaccinations). In the DS, those with incomplete-vaccinations were at a greater risk for internalizing and externalizing symptoms.
Conclusions: We replicate our own and prior findings that vaccination does not increase ASD risk. Further, completing recommended vaccinations may offer protection against the risk of having ASD and other developmental psychopathology.

Key points and relevance

What's Known on This Subject: Despite multiple studies demonstrating no relationship between childhood vaccination and increasing ASD prevalence, parental fear for vaccination and subsequent refusal to vaccinate their children continue, resulting in recent outbreaks of measles in the US.

What This Study Adds and what's relevant: Not only does vaccination prevent common childhood infections, but the present study also suggests that completion of childhood vaccination is associated with decreased likelihood of having ASD and/or emotional and behavioral problems.

1. Introduction

Vaccination is a major achievement of modern medicine. By preventing common childhood infection, mortality and morbidity have decreased significantly (Andre et al., 2008). For example, MMR vaccinations have played a significant role by reducing US measles infections by 99 % when compared with the pre-vaccine era (Centers for Disease Control & Prevention, 2016). Measles is no longer endemic in the US ("Measles elimination by the year 2000, 1994Measles elimination by the year 2000, 1994); in 2006, it was eliminated in South Korea (World Health Organization, 2007). Similarly, the influenza vaccine significantly decreased influenza-associated death among children (Flannery et al., 2017). While recommended vaccinations vary by country, depending on endemic diseases, the US Centers for Disease Control and Prevention (CDC) recommends the following vaccines: Hepatitis B (HepB), Rotavirus (RV), Diphtheria, tetanus, & acellular pertussis (DTaP), *Haemophilus* influenza type b (Hib), Pneumococcal conjugates (PCV13), Inactivated Polio Vaccine (IPV), Measles-Mump-Rubella (MMR), Varicella (VAR), and Influenza. In addition to CDC-recommended vaccines, Bacilli Calmette-Guerin (BCG) and Inactivated Vero cell culture-derived Japanese Encephalitis Vaccine (IJEV)/Live attenuated Japanese Encephalitis Vaccine (LJEV) have been added to the standard schedule of recommended vaccinations for Korean children (Jo et al., 2013; Korea Centers for Disease Control & Prevention, 2017). Current vaccination schedules protect children and adolescents against 12 common diseases. Current vaccination uptake is 92 % for measles, and 95 % for DTaP in the US with similar rates of 98 % and 98 %, respectively, in South Korea (The World Bank Group, 2016).

Claims that vaccination increases the risk for Autism Spectrum Disorder (ASD) have garnered substantial attention in both the lay and scientific communities, especially after publication of the now retracted Wakefield 1998 paper that falsely linked MMR vaccination with the onset of ASD (reporting that 8 of 12 children with "regressive" ASD referred to a pediatric gastroenterology department had MMR vaccination prior to the onset of their "regression") (Birmingham & Cimons, 1998; Wakefield et al., 1998; Retraction–Ileal-lymphoid-nodular hyperplasia, 2010; Retraction–Ileal-lymphoid-nodular hyperplasia, 2010). In many instances, this vaccine-related risk has been erroneously tied to the rapid increase in ASD prevalence over the last 4 decades. In part, this may be the result of increasing frustration associated with the current lack of disorder-specific treatments/cure for ASD. Despite scientific evidence that childhood vaccinations are not associated with increased ASD prevalence, vaccine hesitancy continues due to parental fear. The temporal relationship between the onset of a so-called "regressive form of ASD" (average onset age 24–36 months) and childhood vaccination administration have furthered parental confusion about "the truth," resulting in declining vaccination rates in some parts of the world. For example, MMR vaccination uptake has significantly declined in the UK (Digital, 2017). In the US, the rate of vaccination among younger siblings of children with ASD is also lower compared to children without siblings who have ASD (Glickman, Harrison, & Dobkins, 2017). In South Korea, parents' intention to vaccinate their children was negatively correlated with the false perceptions about vaccination, such as the increased ASD risk from vaccination preservatives (Cha, Ryoo, & Park, 2012). Vaccination refusal is directly related to the recent re-emergence of measles in the United States, with current, ongoing outbreaks in 22 states (Centers for Disease Control & Prevention, 2019). The annual numbers of measles patients ranged from 37 to 667 each year during 2004–2018; in 2019, the number of cases was 1164 by 25 July 2019 (Centers for Disease Control and Prevention, 2019), the highest number since measles was "eliminated" in 2000.

Genetic and epidemiological studies suggest that infections and immunological dysfunction may play a significant role in the etiology of ASD (Atladottir et al., 2007; Atladottir, Henriksen, Schendel, & Parner, 2012; Patterson, 2012; Zerbo et al., 2013), and other behavioral disorders (Instanes et al., 2017; Jolving et al., 2017; Jones et al., 2017). Childhood vaccination modulates host immune function via "trained immunity," providing heterologous, protective, ***non-specific effects (NSE)*** for children (direct mechanism of protection), in addition to preventing childhood infections and related symptoms (indirect mechanism of protection) (Uthayakumar et al., 2018). We hypothesize that via the direct and/or indirect mechanisms, completion of a significant number of recommended vaccinations in childhood serves as a protective factor (decreasing risks) for later developmental psychopathology, including ASD, as well as internalizing and externalizing behavioral symptoms. We test this hypothesis using two independent, large-scale epidemiological samples in which we: 1) Examine the relationship between parental report of completing recommended vaccinations and the likelihood of having ASD, based on the Autism Spectrum Screening Questionnaire scores (hereafter: likelihood of having ASD) and

internalizing/externalizing behavior symptoms in children, using the Discovery Sample (DS) of 10,002 children; and, 2) Verify the initial findings for the likelihood of having ASD in an independent Replication Sample (RS) with a sample size of 29,381.

2. Methods

2.1. Participants

The study population consists of two independently-ascertained, community samples of school-aged children: DS and RS. The DS includes 7−13-year-old children from 13 cities, who participated in a Simons Foundation Autism Research Initiative (SFARI) project, forming a cohort representative of the South Korean population. These children were recruited in Korea for a project examining impacts of environmental factors on children's health outcomes. Among 15,981 target subjects, 10,503 parents (66 % of the target population) agreed to participate in the survey. In order to replicate initial DS findings in an independent study population, we used an additional cohort with non-overlapping samples (RS). The RS was ascertained from the entire population in one city, Cheonan, South Korea. Among the targeted 49,570 children in 65 elementary schools, 42,746 questionnaires were distributed; 30,552 (62 % of the target population) were completed and retrieved from parents.

The Yale and Dankook University Institutional Review Boards approved the study; informed consent was obtained from all parents participating in the survey.

2.2. Predictor measurement

A table outlining the Korean Pediatric Association guidelines for recommended immunizations was provided in a parent survey. It included the six vaccinations recommended for administration at different developmental stages in early childhood: BCG, HepB, MMR, IJEV/LJEV, DPT and IPV. Parents were asked to respond to the following question: "How many vaccinations from this chart has your child completed?" The completion of immunizations was categorized into three groups: $\leq$ 3, 4−5 and all 6 vaccinations.

2.3. Behavioral outcome measures

2.3.1. Autism Spectrum Screening Questionnaire (ASSQ)

The likelihood of having ASD was assessed in both the DS and RS using the ASSQ, a 27- item screening questionnaire measuring social interaction, communication problems, restricted and repetitive behaviors, and other associated ASD features. Each item in the ASSQ is rated from 0 to 2; the total score ranges from 0 to 54 points. The ASSQ was translated, back-translated, and standardized for Korean elementary school-aged children (Yim, 2012). An ASSQ score in the upper 5th percentile (score $\geq$ 15) was defined as "Screen positive." This cut-off score demonstrated optimal agreement with clinical best estimate diagnoses of ASD (75 % positive predictive value) in a previous validation study (Kim et al., 2011; Yim, 2012). The likelihood of having ASD was divided into three groups, based on ASSQ scores: 1) "High Likelihood:" score $\geq$15 (<5th percentile); 2) "Intermediate Likelihood:" score = 10–14 (6−10th percentile); and, 3) "Low Likelihood:" score <10 ($\geq$10th percentile).

2.3.2. Behavior Assessment System for Children 2 – Parent Rating Scale-Child (BASC2-PRS-C)

Externalizing and internalizing behavior symptoms were measured in the DS using the BASC2-PRS-C, a behavioral rating of psychopathology in 6–12 years-old children, completed by parents (Gladman & L. S., 2003). The BASC2-PRS-C yields T-scores for 9 clinical scales (hyperactivity, aggression, conduct problem, anxiety, depression, somatization, atypicality, withdrawal, and attention problems), 5 adaptive scales (adaptability, social skills, leadership, activities of daily living and functional communication), and 4 composite scales (internalizing problems, externalizing problems, adaptive skills, and behavioral symptoms index) (Reynolds & K. R., 2004). The BASC2-PRS-C is standardized and validated in Korean children (Song et al., 2017).

2.4. Covariates

Children's age and gender, along with parental demographics associated with the completion of vaccination in Korean children (parental age, educational level, and marital status) were included in our final analyses (Lee & Jeon, 2015). Because they qualified as confounders, we added birth order, prematurity at birth and family history of psychiatric disorder in the analyses: they are associated with the completion of vaccinations (predictors) and the likelihood of having ASD and/or behavioral symptoms (outcomes) (Davis et al., 1999; Gavrielov-Yusim, Battat, Neumann, Friger, & Balicer, 2012; Lu et al., 2015; Sandin et al., 2014).

2.5. Statistical analyses

Those with missing responses in child's age, gender, ASSQ, and vaccination histories (501 in DS; 1171 in RS) were excluded from the analyses. Missing values for parental demographics were considered "no response" in the analyses. A total of 10,002 children from the DS and 29,381 children from the RS were included in final analyses.

Multivariable ordinal logistic regression was performed to examine the relationship between parental reports of vaccination completion and likelihood of having ASD ("low," "intermediate," and "high"). A proportional odds assumption test was also performed. There were two models: Model 1 controlled for demographic factors; and, Model 2 controlled for demographic covariates and

Table 1
Demographics and Characteristics of Study Sample in Discovery and Replication Sample by vaccination status.

Characteristics	Discovery sample				Replication Sample			
	Total (N = 10002)	< 3 (N = 198)	4-5 vaccines (N = 1371)	6 vaccines (N = 8433)	Total (N = 29381)	< 3 (N = 681)	4-5 vaccines (N = 5179)	6 vaccines (N = 23521)
Children Characteristics								
Age, mean(SD), y	9.61(1.68)	9.78 (1.67)	9.64(1.68)	9.60(1.69)	9.19(1.74)	9.51 (1.68)	9.16(1.72)	9.18(1.75)***
Male sex, N(%)	5148 (51.47)	105 (53.03)	714(52.08)	4329(51.33)	14664 (49.91)	331 (48.60)	2599(50.18)	11734(49.89)
Prematurity								
Yes	451(4.51)	10(5.05)	70(5.11)	371(4.40)***	1479(5.03)	46(6.75)	261(5.04)	1172(4.98)***
No	8484 (84.82)	133 (67.17)	1128(82.28)	7223(85.65)	27382 (93.20)	607 (89.13)	4813(92.93)	21962(93.37)
Unknown	1067 (10.67)	55(27.78)	173(12.62)	839(9.95)	520(1.77)	28(4.11)	105(2.03)	387(1.65)
Birth order								
First	4543 (45.42)	52(26.26)	497(36.25)	3994(47.36) ***	14628 (49.79)	255 (37.44)	2444(47.19)	11929(50.72) ***
Second	4045 (40.44)	77(38.89)	611(44.57)	3357(39.81)	12293 (41.84)	321 (47.14)	2209(42.65)	9763(41.51)
Third	983(9.83)	36(18.18)	174(12.69)	773(9.17)	2219(7.55)	92(13.51)	475(9.17)	1652(7.02)
>_fourth	126(1.26)	11(5.56)	34(2.48)	81(0.96)	206(0.70)	12(1.76)	48(0.93)	146(0.62)
unknown	305(3.05)	22(11.11)	55(4.01)	228(2.70)	35(0.12)	1(0.15)	3(0.06)	31(0.13)
Parents Characteristics								
Parental marriage status								
Unmarried	356(3.56)	11(5.56)	49(3.57)	296(3.51)***	2137(7.27)	41(6.02)	372(7.18)	1724(7.33)***
Married/ cohabitation	8497 (84.95)	126 (63.64)	1086(79.21)	7285(86.39)	24330 (82.81)	480 (70.48)	4145(80.03)	19705(83.78)
Separation/ divorce/widowed	612(6.12)	41(20.71)	147(10.72)	424(5.03)	1401(4.77)	100 (14.68)	362(6.99)	939(3.99)
unknown	537(5.37)	20(10.10)	89(6.49)	428(5.08)	1513(5.15)	60(8.81)	300(5.79)	1153(4.90)
Fa[a] age at pregnancy, yr	30.89(4.46)	31.74 (6.22)	31.36(4.71)	30.80(4.37) ***	32.11(3.96)	32.02 (5.04)	31.89(4.10)	32.16(3.90) ***
Mo[b] age at pregnancy, yr	27.95(4.19)	28.26 (6.02)	28.29(4.31)	27.89(4.13)**	29.27(3.70)	29.10 (4.89)	28.99(3.79)	29.34(3.64) ***
Fa education level, yr								
<12	223(2.23)	15(7.58)	49(3.57)	159(1.89) ***	584(1.99)	58(8.52)	136(2.63)	390(1.66) ***
12	3341 (33.40)	76(38.38)	527(38.44)	2738(32.47)	10937 (37.22)	344 (50.51)	2224(42.94)	8369(35.58)
>12	5643 (56.42)	60(30.30)	657(47.92)	4926(58.41)	16972 (57.77)	242 (35.54)	2636(50.90)	14094(59.92)
unknown	795(7.95)	47(23.74)	138(10.07)	610(7.23)	888(3.02)	37(5.43)	183(3.53)	668(2.84)
Mo education level, yr								
<12	212(2.12)	13(6.57)	42(3.06)	157(1.86) ***	591(2.01)	53(7.78)	131(2.53)	407(1.73) ***
12	4216 (42.15)	89(44.95)	619(45.15)	3508(41.60)	15434 (52.53)	407 (59.77)	3003(57.98)	12024(51.12)
>12	4737 (47.36)	45(22.73)	562(40.99)	4130(48.97)	12411 (42.24)	170 (24.96)	1851(35.74)	10390(44.17)
unknown	837(8.37)	51(25.76)	148(10.80)	638(7.57)	945(3.22)	51(7.49)	194(3.75)	700(2.98)
Fhx of Psychiatric dis[c]								
Yes	577(5.77)	19(9.60)	89(6.49)	469(5.56) ***	1479(5.03)	52(7.64)	322(6.22)	1105(4.70) ***
Likelihood of having ASD								
Low	8897 (88.95)	149 (75.25)	1167(85.12)	7581(89.90) ***	25760 (87.68)	505 (74.16)	4343(83.86)	20912(88.91) ***
Intermediate	677(6.77)	23(11.62)	115(8.39)	539(6.39)	2099(7.14)	76(11.16)	466(9.00)	1557(6.62)
High	428(4.28)	26(13.13)	89(6.49)	313(3.71)	1522(5.18)	100 (14.68)	370(7.14)	1052(4.47)
Behavioral Symptoms								
Externalizing								
Mean t-score(SD)	50.19(9.78)	54.27 (13.87)	51.42(10.22)	49.90(9.55) ***				
Internalizing								
Mean t-score(SD)	49.50(9.10)	52.01 (12.86)	50.70(9.59)	49.25(8.89) ***				

*p < 0.05, **p < 0.01, *** p < 0.001; [a]Father, [b]Mother.
[c]Family history of Psychiatric disorder, included father, mother and siblings with NDD, schizophrenia, depressive disorder, bipolar disorder, anxiety disorder, substance use and addictive disorder, neurocognitive disorders, trauma related disorder, and other neuropsychiatric disorder by DSM-V.

confounders. The relationships between vaccination and the externalizing and internalizing symptoms were analyzed using linear regression. Bonferroni corrections for multiple comparisons were applied for the three analyses using the three outcomes; significance for the p-value was set at a corrected level of 0.0167. All analyses were conducted using STATA (version 14.0) and R (version 3.0.3; https://cran.r-project.org).

3. Results

Table 1 summarizes the characteristics of the DS and RS by vaccination status. Children with a high likelihood of having ASD were 4.28 % and 5.18 % in the DS and RS, respectively; this is compatible to prior studies (Kim et al., 2011). Parents of 84.3 % (n = 8433) of DS and 80.1 % (n = 23,521) of RS reported that their children were fully vaccinated with the 6 recommended childhood vaccines. There were significantly more prematurely born children and fewer first-born children in the DS and RS incomplete vaccination groups. Similarly, in the incomplete vaccination groups, significantly more parents were less educated, older, and/or not living with their partners. Additionally, a family history of psychiatric disorder was noted to be more frequent in the incomplete vaccination groups when compared to the fully vaccinated group. Finally, children who were not fully vaccinated had a significantly higher risk for having ASD and significantly higher BASC T-scores for externalizing and internalizing behavioral symptoms.

Compared to fully vaccinated children, for children in the less vaccinated groups, the unadjusted odds ratios (ORs) for likelihood of having ASD were significantly increased; a vaccination dose-response was also noted in the DS. ORs were 1.57 and 3.03 for completion of 4−5 vaccination and ≤ 3 vaccinations, respectively. When the statistical models included demographic variables (Model 1) and confounders (Model 2), the magnitude of the adjusted ORs (aORs) decreased slightly, however, they remained statistically significant with a dose-response noted. In our final Model 2, aORs were 1.42 (95 % confidence intervals [CI] 1.17−1.73, p < .001) in the group with 4−5 vaccinations and 2.33 (CI 1.53−3.56, p < .001) in the group with ≤ 3 vaccinations. This initial finding was replicated in the RS. The final RS Model 2 aORs were 1.44 (CI 1.32−1.58, p < .001) in the group with 4−5 vaccinations and 2.19 (CI 1.80−2.67, p < .001) in the group with ≤ 3 vaccinations, respectively (Table 2).

Incomplete vaccination is also significantly associated with higher externalizing and internalizing symptom scores, again with a dose-response relationship in the DS. Adjusted *beta* coefficients were 1.20 (standard error (SE) 0.31) and 3.64 (SE 0.84) for completion of 4−5 vaccination and ≤ 3 vaccinations for externalizing symptoms, respectively, and 1.37 (SE 0.29) and 2.86 (SE 0.79) for 4−5 vaccination and ≤ 3 vaccinations in internalizing symptoms, respectively in DS. (Table 3).

4. Discussion

Unlike prior studies that focused on vaccination-associated, increased risk for ASD, our study examines whether completion of recommended vaccinations protects children against the risk of having ASD, as well as internalizing and externalizing behavioral symptoms. Our study hypothesis is based on cumulative research findings from genetic, environmental and epidemiological studies indicating that infections and subsequent immunological dysfunction may play a significant role in the etiology of ASD (Atladottir et al., 2007, 2012; Patterson, 2012; Zerbo et al., 2013), and other behavioral disorders (Instanes et al., 2017; Jolving et al., 2017; Jones et al., 2017). Our study hypothesis was supported by the initial findings in our DS and verified by findings from our RS. Compared to children whose parents reported receiving incomplete immunizations, those receiving the full schedule of recommended vaccinations had a decreased risk for ASD on the ASSQ. Additionally, we were able to test the hypothesis that the beneficial effects of vaccination are not limited to ASD, but likely also extend to other developmental psychopathology, specifically those associated with externalizing and internalizing symptoms. Not only does vaccination prevent common childhood infections, but the present study also suggests that completion of childhood vaccination may decrease likelihood of having ASD and/or emotional and behavioral problems. Two potential mechanisms can be proposed for the observed, beneficial effects of childhood vaccination on ASD and externalizing and/or internalizing behavioral problems: Direct effects of immune modulation; and, Indirect effects of prevention of childhood infections and related symptoms.

Direct effects of disease-specific immune modulation by vaccination are based on the induction of specific immunological memory that enhances adaptive immune responses in lymphocytes upon subsequent infection with a similar pathogen. In addition to these diseases-specific eff ;ects, live-attenuated vaccines, such as BCG, OPV, small pox and measles vaccine (MV), could also induce heterologous, protective, NSE, aff ;ecting overall mortality (Blok, Arts, van Crevel, Benn, & Netea, 2015; Higgins et al., 2016; Jensen, Benn, & van Crevel, 2016). Trained immunity in which immunological memory is developed by the innate immune system is considered as an underlaying mechanism of NSE (Uthayakumar et al., 2018). Although some molecular mechanisms of trained immunity (for example, epigenetic changes in immune cells) have been understood, trained immunity by cell types and tissue levels are yet to be discovered (de Bree et al., 2018). Protective impacts of vaccination-related NSE in decreasing overall risks for childhood leukemia have been demonstrated in multiple studies (Morra et al., 2017). It is plausible that brain tissue-specific NSE may play a role in decreasing ASD and other developmental psychopathology.

Indirect beneficial impacts of vaccination on the risks for ASD and developmental psychopathology come from prevention of childhood infections. Childhood infections can exert adverse effects on developing brains via exposures to toxic infectious agents and/or infection-related symptoms and damage such as hyperthermia. Postnatal infections in children, including ear infection, respiratory

Table 2
Multivariable Ordinal Logistic Regression to Examine Relationships between Vaccination Completion Status and Likelihood of having ASD.

	Discovery Sample (n = 10002)						Replication Sample (n = 29381)					
	Unadjusted Model		Model 1		Model 2		Unadjusted Model		Model 1		Model 2	
	OR[c] (95% CI[d])	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Vaccination												
6 vaccines	[reference]	NA	[reference]	NA	[reference]	NA	[reference]	NA	[reference]	NA	[reference]	NA
< 3 vaccines	3.03(2.19-4.22)	<.001	2.36(1.56-3.58)	<.001	2.33(1.53-3.56)	<.001	2.91(2.44-3.46)	<.001	2.19(1.80-2.67)	<.001	2.19(1.80-2.67)	<.001
4-5 vaccines	1.57(1.33-1.85)	<.001	1.42(1.17-1.71)	<.001	1.42(1.17-1.73)	<.001	1.55(1.42-1.69)	<.001	1.45(1.33-1.59)	<.001	1.44(1.32-1.58)	<.001
Age			0.99(0.95-1.04)	0.761	1.00(0.96-1.05)	0.949			1.36(1.01-1.06)	0.001	1.04(1.02-1.06)	0.001
Sex												
Female			[reference]	NA	[reference]	NA			[reference]	NA	[reference]	NA
Male			1.75(1.51-2.02)	<.001	1.74(1.51-2.02)	<.001			1.40(1.30-1.51)	<.001	1.40(1.30-1.51)	<.001
Fa age			1.03(1.01-1.06)	0.006	1.04(1.01-1.06)	0.003			1.00(0.98-1.01)	0.481	0.99(0.98-1.01)	0.434
Mo age			0.97(0.94-0.99)	0.012	0.97(0.95-1.00)	0.029			1.01(1.00-1.02)	0.188	1.01(1.00-1.02)	0.188
Fa education, yrs												
12			[reference]	NA	[reference]	NA			[reference]	NA	[reference]	NA
<12			1.61(1.03-2.52)	0.038	1.56(0.99-2.45)	0.053			2.05(1.64-2.45)	<.001	1.94(1.55-2.43)	<.001
>12			0.83(0.70-1.00)	0.047	0.83(0.69-0.99)	0.037			0.76(0.69-0.83)	<.001	0.76(0.69-0.84)	<.001
unknown			0.65(0.26-1.62)	0.360	0.69(0.28-1.70)	0.414			0.88(0.60-1.30)	0.527	0.90(0.61-1.33)	0.584
Mo education, yrs												
12			[reference]	NA	[reference]	NA			[reference]	NA	[reference]	NA
<12			1.67(1.06-2.64)	0.028	1.67(1.06-2.65)	0.028			1.55(1.23-1.95)	<.001	1.49(1.18-1.88)	0.001
>12			0.98(0.92-1.16)	0.792	0.96(0.80-1.14)	0.624			0.87(0.79-0.96)	0.004	0.87(0.79-0.95)	0.003
unknown			2.07(0.90-4.75)	0.086	1.95(0.85-4.47)	0.117			1.11(0.76-1.62)	0.575	1.11(0.76-1.61)	0.603
Marital status												
Married/cohabitation			[reference]	NA	[reference]	NA			[reference]	NA	[reference]	NA
Unmarried			0.93(0.63-1.37)	0.697	0.91(0.61-1.34)	0.626			1.06(0.93-1.22)	0.370	1.06(0.93-1.22)	0.375
Separation/divorce/ widowed			1.88(1.40-2.51)	<.001	1.86(1.39-2.48)	<.001			1.79(1.52-2.11)	<.001	1.72(1.46-2.02)	<.001
unknown			2.07(0.90-4.75)	0.510	0.87(0.55-1.38)	0.552			1.04(0.87-1.25)	0.664	1.03(0.86-1.24)	0.725
Family history												
Yes					1.46(1.12-1.91)	0.006					1.68(1.46-1.94)	<.001
Prematurity												
No					[reference]	NA					[reference]	NA
Yes					1.15(0.85-1.57)	0.367					1.14(0.97-1.33)	0.117
Unknown					1.13(0.84-1.53)	0.420					1.10(0.83-1.44)	0.507
Birth order												
1st					[reference]	NA					[reference]	NA
2nd					0.80(0.68-0.94)	0.006					0.93(0.85-1.00)	0.066
3rd					0.78(0.60-1.02)	0.072					0.98(0.84-1.13)	0.758
>_4th					1.24(0.72-2.12)	0.436					1.49(1.04-2.15)	0.031
unknown					1.47(0.29-7.41)	0.638					0.98(0.34-2.86)	0.976

Model 1: controlled for demographic covariates (Children's age and gender, parental age, parental educational level and marital status), Model 2: controlled for demographic covariates and confounders (prematurity at birth, birth order, and family history of psychiatric disorders). [a]Father, [b]Mother; [c]odds ratio, [d]confidence interval.

Table 3
Multivariable Linear Regression Analysis Demonstrating Coefficient of Risk of Behavioral Symptoms (Externalizing and Internalizing Symptoms).

	Externalizing Symptom (t-score)						Internalizing Symptom (t-score)					
	Unadjusted Model		Model 1		Model 2		Unadjusted Model		Model 1		Model 2	
	Coef[c].(SE[d])	P value	Coef.(SE)	P value	Coef. (SE)	P value	Coef.(SE)	P value	Coef.(SE)	P value	Coef.(SE)	P value[1]
Vaccination												
6 vaccines	1[Reference]		1[Reference]		1[Reference]		1[Reference]		1[Reference]		1[Reference]	
< 3 vaccines	4.37 (0.74)	<.001	3.41(0.84)	<.001	3.64(0.84)	<.001*	2.75(0.69)	<.001	2.51(0.79)	0.001	2.86(0.79)	<.001*
4–5 vaccines	1.52(0.30)	<.001	1.13(0.31)	<.001	1.20(0.31)	<.001*	1.45(0.28)	<.001	1.23(0.29)	<.001	1.37(0.29)	<.001*
Age			−0.278(0.07)	<.001	−0.23(0.07)	0.001			−0.17(006)	0.008	−0.10(0.06)	0.101
Sex												
Male			1[Reference]		1[Reference]				1[Reference]		1[Reference]	
Female			2.94(0.21)	<.001	2.96(0.21)	<.001			−0.83(0.19)	<.001	−0.83(0.19)	<.001
Fa[a] age			0.01(0.04)	0.758	0.04(0.04)	0.264			0.04(0.04)	0.268	0.08(0.04)	0.023
Mo[b] age			−0.05(0.04)	0.198	−0.02(0.04)	0.612			−0.13(0.04)	<.001	−0.09(0.04)	0.024
Fa education, yrs												
12			1[Reference]		1[Reference]				1[Reference]		1[Reference]	
<12			2.57(0.90)	0.004	2.52(0.90)	0.005			3.10(0.84)	<.001	3.05(0.84)	<.001
>12			−0.57(0.27)	0.033	−0.63(0.27)	0.017			−0.43(0.25)	0.082	−0.55(0.25)	0.028
Unknown			−1.91(1.72)	0.268	−1.94(1.72)	0.260			−3.28(1.63)	0.044	−3.08(1.63)	0.058
Mo education, yrs												
12			1[Reference]		1[Reference]				1[Reference]		1[Reference]	
<12			1.01(0.88)	0.249	1.10(0.88)	0.210			1.02(0.82)	0.212	1.04(0.82)	0.205
>12			0.37(0.256)	0.147	0.21(0.26)	0.418			0.41(0.24)	0.087	0.22(0.24)	0.358
Unknown			3.19(1.64)	0.052	3.16(1.64)	0.055			4.15(1.56)	0.008	3.86(1.56)	0.013
Marital status												
Married/cohabitation			1[Reference]		1[Reference]				1[Reference]		1[Reference]	
Unmarried			−0.12(0.56)	0.836	−0.21(0.56)	0.710			−0.14(0.53)	0.790	−0.25(0.53)	0.634
Separation/divorce/ widowed			1.18(0.56)	0.037	1.14(0.56)	0.044			1.57(0.53)	0.003	1.52(0.53)	0.004
Unknown			−1.65(0.69)	0.016	−1.53(0.69)	0.026			−0.71(0.64)	0.268	−0.58(0.64)	0.364
Family history												
No					1[Reference]						1[Reference]	
Yes					1.96(0.44)	<.001					1.10(0.41)	0.007
Prematurity												
No					1[Reference]						1[Reference]	
Yes					0.39(0.49)	0.428					0.92(0.46)	0.047
Unknown					−0.44(0.46)	0.332					−0.27(0.43)	0.523
Birth order												
1st					1[Reference]						1[Reference]	
2nd					−0.53(0.23)	0.022					−1.46(0.22)	<.001
3rd					−1.76(0.40)	<.001					−2.00(0.37)	<.001
>_4th					−1.99(1.01)	0.048					−2.88(0.94)	0.002
Unknown					−2.83(3.59)	0.430					0.38(3.35)	0.911

Model 1: controlled for demographic covariates (Children's age and gender, parental age, parental educational level and marital status), Model 2: controlled for demographic covariates and confounders (prematurity at birth, birth order, and family history of psychiatric disorders). [a]Father, [b]Mother ; [c]beta coefficient, [d]standard error; [1]Bonferroni-corrected significance threshold = 0.0167; *p < 0.01.

infection and cytomegalovirus and enterovirus infections, are reported to be associated with the increased risk for ASD, delayed neurodevelopment and behavioral problems in children (Atladottir et al., 2010; Bittker & Bell, 2018; Chang et al., 2007; Hadjkacem et al., 2016; Lee et al., 2015; Saigal, Lunyk, Larke, & Chernesky, 1982; Zerbo et al., 2015). Additionally, the cerebellum, an anatomical site that has been implicated in ASD pathophysiology, is particularly intolerant to fever/hyperthermia (Walter & Carraretto, 2016). Infection also can exert impacts on remote body organs, such as the brain, via the altered immunological function (Atladottir et al., 2007, 2012; Patterson, 2012; Zerbo et al., 2013). These disruptions in immunologic function have been suggested to contribute to ASD risk. For example, some children with ASD have been reported to have a shift in the $CD4^{+}$- cell population from Th_1 cells toward Th_2 cells (Ashwood et al., 2011b; Gupta, Aggarwal, & Heads, 1996; Gupta, Aggarwal, Rashanravan, & Lee, 1998), which increases susceptibility to chronic viral infections (Croonenberghs et al., 2002). Abnormal T helper cell cytokine profiles (Ashwood & Wakefield, 2006) (in a chronic state of cytokine induction), increase susceptibility to chronic viral infections (Croonenberghs et al., 2002). Abnormal T helper cell cytokine profiles have been reported in children with ASD (Ashwood et al., 2011a, 2011c). These changes can lead to altered T cell responses to mitogens and recall responses (Molloy et al., 2006), an imbalance of serum immunoglobulin levels (Enstrom, Krakowiak et al., 2009), NK cell activation (Enstrom, Lit et al., 2009), increased monocyte response (Enstrom, Onore, Van de Water, & Ashwood, 2010), and increased level of complement components (Corbett et al., 2007). Evidence of dysregulation of inflammatory response via pro-inflammatory cytokines, induced by immune response to recruit cells of immune systems to the site of infection (Fassbender et al., 1997), has been reported in ASD, including increasing levels of Interferon-gamma (IFN-r) or Interferon-12 (IL-12), increased monocyte response (Enstrom et al., 2010), and increased levels of complement components (Corbett et al., 2007). For other children with ASD, there is evidence of inflammatory response dysregulation via pro-inflammatory cytokines, which is induced by an immune response to recruit immune cells to the site of infection (Fassbender et al., 1997); these changes include increased levels of IFN-r or IL-12 (Singh, 1996; Sweeten, Posey, Shankar, & McDougle, 2004) and decreased production of Transforming Growth Factor Beta 1(TGFβ-1) (Okada et al., 2007). Hypotheses for the immunological effect of infection on risks for ASD are particularly interesting when combined with transcriptomic analyses of postmortem brains from individuals with autism (Voineagu et al., 2011) in which increased neuroinflammation has been reported in brains of individuals with ASD (Cabanlit, Wills, Goines, Ashwood, & Van de Water, 2007; Connolly et al., 2006; Wills et al., 2009). Furthermore, when compared to individuals without ASD, brains of individuals with ASD demonstrate downregulation of 209 genes, enriched for gene categories related to synaptic function along with upregulation of 235 genes implicated in immune and inflammatory responses (Kim & Leventhal, 2015). The former group was significantly enriched for association signals in Genome-Wide Association Study (GWAS), whereas the latter group was not. These studies suggest that relevant immunologic changes are likely caused by environmental factors, such as childhood infections.

Our study differs from prior work and has several strengths. 1) We studied the completion of all 6 recommended vaccinations rather than any one vaccine. This approach enabled us to evaluate the cumulative effect of vaccination on the increased risk for ASD on the ASSQ and emotional or behavioral problems; 2) The study subjects were assessed with dimensional phenotyping instruments, the BASC II PRS-C, along with three incremental vaccination and likelihood for having ASD categories. This method likely reduced phenotype heterogeneity (Abrahams & Geschwind, 2008; Losh, Sullivan, Trembath, & Piven, 2008) and sampling bias because it is less likely to miss cases (Berkson, 2014); 3) We used a two-step, internal replication which provides greater confidence in the observed associations between parental reports of completed vaccination in childhood and decreased risk for ASD on the ASSQ; 4) Study subjects were drawn from epidemiologically-ascertained, representative samples; and, 5) We used Bonferroni corrections to adjust for multiple comparisons in statistical analyses.

Limitations of our study include: 1) Vaccination history was obtained retrospectively. Recall error can occur in retrospective collection of information in case-control studies or cross-sectional studies. In case-control studies, subjects with disease may remember past exposures differently than those who do not have the disease. This systematic error occurs because study subjects are aware of their disease status (Grimes & Schulz, 2002). On the other hand, study subjects in cross-sectional studies, such as ours, are not recruited based on disease or exposure status, and they are blind to the study hypothesis. When surveys are conducted based on symptoms (via ASSQ and BASC) and exposures (vaccination), disease or exposure status is not assigned as part of study recruitment. Therefore, recall errors of past events (such as vaccination) in study subjects are not systematically affected by their disease or exposure status, but only by their ability to remember. For these reasons, recall error in our study is not a systematic error, but a random error. This type of non-systematic recall error tends to lead to a bias toward null, a conservative bias (Osborne & Blanchard, 2010). Retrospective recall of vaccination in this study might have decreased observed associations between incomplete vaccinations and the risk for ASD on the ASSQand other emotional and behavioral problems; 2) The general medical condition, other infection histories, family stress, and history of ASD in older siblings were not assessed and were not controlled in this study; 3) The risk for ASD on the ASSQ, externalizing and internalizing behavioral phenotypes were measured with parent-reports, not by direct clinical examination; 4) Differences in the South Korean vaccination schedules, relative to other countries, limit the generalizability of the current findings. These findings will be aided by replication studies in other countries, with different vaccination schedules; 5) Data for non-participants (34∼38 % of target populations) are not available, limiting our capacity to examine a potential non-response bias;and, 6) Our data do not allow for examination of which mechanisms (direct and/or indirect) of childhood vaccinations have played protective roles to decrease risk for ASD on the ASSQ, as we have observed in this study.

5. Conclusion

Children with a history of completing all recommended vaccinations have a lower likelihood of having ASD, as well as externalizing and internalizing symptoms when compared to children with histories of incomplete vaccination. Vaccination has proven to be a successful and effective public health strategy to prevent life-threatening infectious disease in childhood and to improve their well-

being and health. While replications in other populations are warranted, added to this benefit is that vaccination might extend protective effects to common childhood neurodevelopmental disorders, such as ASD as well as internalizing and externalizing disorders.

Author contributions

Drs YS Kim, M Ha and B Leventhal conceptualized and designed the study, analyzed and interpreted data, drafted the initial manuscript, and reviewed the manuscript.Dr B Kim analyzed and interpreted data, drafted the initial manuscript and reviewed the manuscript. Drs YJ Koh, MH Lim, KC Paik and HJ Kwon and Ms P Hong acquired data, carried out the initial analyses, and reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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CRediT authorship contribution statement

Bora Kim: Formal analysis, Writing - original draft, Writing - review & editing. **Mina Ha:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Project administration, Writing - original draft, Writing - review & editing. **Young Shin Kim:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Project administration, Writing - original draft, Writing - review & editing. **Yun-Joo Koh:** Data curation, Project administration, Writing - review & editing. **Ho-Jang Kwon:** Data curation, Writing - review & editing. **Myung-Ho Lim:** Data curation, Writing - review & editing. **Ki-Chung Paik:** Data curation, Writing - review & editing. **Hosanna Kim:** Data curation, Writing - review & editing. **Patricia Hong:** Data curation, Writing - review & editing. **Bennett L. Leventhal:** Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors have no conflicts of interest to report in relation to the research presented in this manuscript.

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