ORIGINAL ARTICLE

Childhood Obesity, Weight Change, and Pediatric Immune-Mediated Skin Diseases

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Whether childhood obesity or weight gain leads to the development of pediatric immune-mediated skin diseases remains unclear. We aimed to determine the associations between body mass index or body mass index changes and the development of 3 main immune-mediated skin diseases—alopecia areata, atopic dermatitis (AD), and psoriasis—by analyzing a longitudinal cohort of 2,161,900 Korean children from 2009 to 2020. The findings indicated that children who were obese had a higher risk of pediatric immune-mediated skin diseases than those with normal weight (P for trend $< .01$). An increase in body mass index was associated with a higher risk of AD, whereas a decrease in body mass index was correlated with a reduced risk of AD. Children who gained weight, transitioning from normal to overweight, exhibited a higher AD risk than those who maintained a normal weight (adjusted hazard ratio = 1.15, 95% confidence interval = 1.11–1.20). However, those who shifted from being overweight to achieving a normal weight (adjusted hazard ratio = 0.87, 95% confidence interval = 0.81–0.94) had a lower AD risk than children who were overweight who maintained their weight. In summary, early childhood obesity may increase the risk of pediatric immune-mediated skin diseases. Weight gain may increase AD risk, whereas weight loss may lower the risk.

Keywords: Alopecia areata, Atopic dermatitis, Childhood obesity, Psoriasis, Pediatric immune-mediated skin disease

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INTRODUCTION

Immune-mediated skin diseases (IMSDs), such as alopecia areata (AA), atopic dermatitis (AD), and psoriasis, have recently become a major public health concern, particularly among children (Nutten, 2015; Rose, 2016; Svensson et al, 2018). IMSDs have detrimental effects on the QOL, including emotional, physical, social, and functional well-being, in children and their families (Brihan et al, 2020; Manzoni et al, 2013). Furthermore, although some biologics have been proven effective for children with AD or psoriasis (Aslam et al, 2020; Paller et al, 2022), limited treatment options and a lack of clinical trials for systemic therapy present considerable challenges in treating children with IMSDs (Branisteanu et al, 2021; Huang et al, 2017; Kanwar and Kumaran, 2012).

Childhood obesity rates have surged significantly in the past years, transforming it into an undeniable public health crisis compounded by the effects of the pandemic and national lockdowns (The Lancet Diabetes, 2022). Children who are overweight or obese are at a higher risk of developing obesity as adults as well as experiencing noncommunicable diseases, such as diabetes and cardiovascular disease, at an earlier age than those with a healthy weight (The Lancet Diabetes, 2022). Particularly, the involvement of obesity in the development of chronic inflammatory skin diseases, including psoriasis, hidradenitis suppurativa, AD, and skin malignancies, has been investigated. The precise mechanisms responsible for this connection remain uncertain; however, excessive adipose tissue has been hypothesized to trigger proinflammatory mechanisms that influence the development of skin diseases (Darlenski et al, 2022).

On the basis of these biological mechanisms, several studies have investigated the association between childhood obesity and IMSDs, particularly focusing on AD and psoriasis (Boccardi et al, 2009; Hunjan et al, 2018; Iturriaga et al, 2023; Manjunath and Silverberg, 2022; Nicholas et al, 2022; Silverberg et al, 2011). However, most of these studies had cross-sectional or case-control designs with relatively small sample sizes, and very few longitudinal cohort studies have examined the association of body mass index (BMI) with IMSDs among children. Therefore, uncertainty persists regarding whether obesity leads to AD and psoriasis or vice versa. Furthermore, no studies have

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Abbreviations: AA, alopecia areata; AD, atopic dermatitis; aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval; ICD-10, International Classification of Diseases, Tenth Revision; IMSD, immune-mediated skin disease; NHIS, National Health Insurance Service

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investigated the effect of BMI changes on IMSDs and the direct effects of BMI on AA.

Therefore, we aimed to conduct a large population-based longitudinal study using the nationwide database of infants and children from the Korean National Health Insurance Service (NHIS) to examine the association between BMI or BMI changes and the development of 3 main IMSDs—AA, AD, and psoriasis—among children.

RESULTS

Of the total 2,161,900 children in South Korea who underwent the fourth (30−36 months) and fifth (42−48 months) health screenings between 2009 and 2020, the cohorts for AA, AD, and psoriasis comprised 2,012,465; 1,426,241; and 2,012,067 children without a history of each IMSD before the age 48 months, respectively (Figure 1). Throughout the observation period (AA cohort: 10,524,561 person-years; AD cohort: 6,910,806 person-years; psoriasis cohort: 10,530,018 person-years), 4,878 AA; 41,386 AD; and 2,191 psoriasis cases were identified. The median follow-up periods of children who developed IMSD and those who did not were 3.7 and 5.2 years, respectively, for AA; 1.9 and 4.9 years, respectively, for AD; and 3.5 and 5.2 years, respectively, for psoriasis.

Table 1 presents descriptive details regarding the participants. The mean birth weight for all cohorts was 3.22 kg. At the fourth health examination, the mean BMI percentile was 48.8 (BMI z-score: −0.030); however, it slightly increased to 53.1 (BMI z-score: 0.078) at the fifth health examination. Regarding AD, children excluded from the final population because of a prior diagnosis of AD before age 4 years tended to have a higher mean BMI percentile and z-score at the fifth health screening and a higher prevalence of allergic comorbidities than the included participants without AD before age 4 years (Supplementary Table S1).

Before conducting the primary analyses, we examined the risk of a negative control outcome to validate our cohort and identify any observational bias (Supplementary Tables S2 and S3). Our data indicated no significant association between BMI, BMI changes, and melanocytic nevus, thereby confirming the absence of observational bias.

Higher BMI percentile showed a significant association with increased risks of AA, AD, and psoriasis in children, whereas lower BMI percentile was associated with a reduced risk of pediatric AA, AD, and psoriasis (Figure 2). Compared with children with normal weight, those who were overweight had an increased risk of AD (adjusted hazard ratio [aHR] = 1.13, 95% confidence interval [CI] = 1.10−1.17), and those who were obese had an increased risk of all evaluated IMSDs (AA: aHR = 1.15, 95% CI = 1.02−1.29; AD: aHR = 1.12, 95% CI = 1.08−1.17; psoriasis: aHR = 1.24, 95% CI = 1.05−1.47) (Table 2). The elevated IMSD risks for children who were overweight and obese remained mostly consistent even after stratifying the study population on the basis of sex, breastfeeding status, household income, and birth weight (Supplementary Tables S4−S6). The results of sensitivity analyses that utilized data from the third (18−24 months) and fourth (30−36 months) screenings with index dates set at 2 and 3 years, respectively, were consistent with the main results (Supplementary Tables S7 and S8), although there was an attenuation in statistical significance for AA.

An increase in BMI percentile was associated with a higher AD risk, whereas a decrease in BMI percentile was associated with a reduced AD risk (Figure 3). Compared with children who maintained normal weight, those who experienced weight gain and transitioned to overweight had an increased AD risk (aHR = 1.15, 95% CI = 1.11−1.20; *P* for trend < .001) (Table 3). In addition, compared with children with overweight who maintained their weight, those who decreased their weight to a normal level had a reduced AD risk (aHR = 0.87, 95% CI = 0.81−0.94; *P* for trend < .001). Sensitivity analyses that investigated not only the association of BMI changes between the fourth (30−36 months) and sixth (54−60 months) screenings (Supplementary Table S9 and Supplementary Figure S1) but also the association of BMI changes between the fourth (30−36 months) and seventh

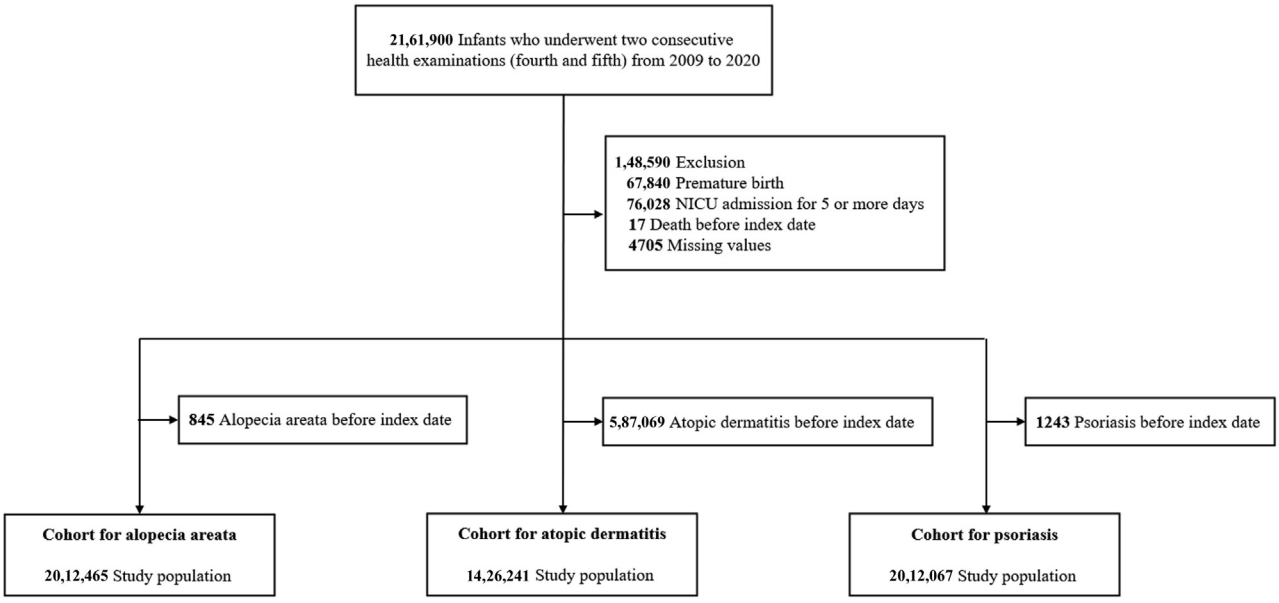

Figure 1. Flow diagram of the selection of study participants. NICU, neonatal intensive care unit.

Table 1. Characteristics of the Study Participants

Characteristics	Cohort for Alopecia Areata			Cohort for Atopic Dermatitis			Cohort for Psoriasis		
	Total	Normal (BMI < 84th Percentile)	Overweight or Obesity (BMI ≥ 85th Percentile)	Total	Normal (BMI < 84th Percentile)	Overweight or Obesity (BMI ≥ 85th Percentile)	Total	Normal (BMI < 84th Percentile)	Overweight or Obesity (BMI ≥ 85th Percentile)
Participants, n (%)	2,012,465	1,656,717 (82.3)	355,748 (17.7)	1,426,241	1,178,833 (82.7)	247,408 (17.3)	2,012,067	1,656,448 (82.3)	355,619 (17.7)
Overweight (BMI 85th–94th percentile)	225,548 (11.2)	—	225,548 (11.2)	155,633 (10.9)	—	155,633 (10.9)	225,462 (11.2)	—	225,462 (11.2)
Obese (BMI ≥ 95th percentile)	130,200 (6.5)	—	130,200 (6.5)	91,775 (6.4)	—	91,775 (6.4)	130,157 (6.5)	—	130,157 (6.5)
Birth weight, kg, mean (SD)	3.22 (0.45)	3.19 (0.44)	3.33 (0.45)	3.21 (0.45)	3.19 (0.44)	3.33 (0.45)	3.22 (0.45)	3.19 (0.44)	3.33 (0.45)
4th health screening examination (30–36 months)									
BMI percentile, mean (SD)	48.8 (28.0)	42.2 (23.9)	92.0 (4.4)	48.8 (28.0)	42.1 (23.9)	92.0 (4.4)	48.8 (28.0)	42.2 (23.9)	92.0 (4.4)
BMI z-score, mean	−0.030	−0.197	1.405	−0.030	−0.199	1.405	−0.030	−0.197	1.405
5th health screening examination (42–48 months)									
BMI percentile, mean (SD)	53.1 (28.5)	44.7 (24.1)	92.3 (4.5)	52.6 (28.6)	44.2 (24.2)	92.4 (4.6)	53.1 (28.5)	44.7 (24.1)	92.3 (4.5)
BMI z-score, mean	0.078	−0.133	1.426	0.065	−0.146	1.433	0.078	−0.133	1.426
Follow-up (years), median	5.2	5.2	5.2	4.8	4.9	4.8	5.2	5.2	5.2
Sex, n (%)									
Male	1,027,557 (51.1)	850,692 (51.4)	176,865 (49.7)	718,515 (50.4)	597,254 (50.7)	121,261 (49.0)	1,027,302 (51.1)	850,515 (51.4)	176,787 (49.7)
Female	984,908 (48.9)	806,025 (48.6)	178,883 (50.3)	707,726 (49.6)	581,579 (49.3)	126,147 (51.0)	984,765 (48.9)	805,933 (48.6)	178,832 (50.3)
Breastfeeding status, n (%)									
Only breast milk	745,858 (37.9)	619,630 (38.2)	126,228 (36.3)	511,532 (36.6)	426,580 (36.9)	84,952 (35.1)	745,663 (37.9)	619,485 (38.2)	126,178 (36.3)
Only formula milk	874,922 (44.4)	717,754 (44.2)	157,168 (45.2)	639,249 (45.8)	526,661 (45.6)	112,588 (46.5)	874,786 (44.4)	717,678 (44.2)	157,108 (45.2)
Both	339,434 (17.2)	276,770 (17.1)	62,664 (18.0)	240,734 (17.2)	197,199 (17.1)	43,535 (18.0)	339,386 (17.2)	276,735 (17.1)	62,651 (18.0)
Special formula milk	10,245 (0.5)	8518 (0.5)	1727 (0.5)	6206 (0.4)	5165 (0.4)	1041 (0.4)	10,236 (0.5)	8512 (0.5)	1724 (0.5)
Household income, quartile, n (%)									
1st (highest)	519,676 (25.8)	435,637 (26.3)	84,039 (23.6)	372,872 (26.1)	313,518 (26.6)	59,354 (24.0)	519,527 (25.8)	435,533 (26.3)	83,994 (23.6)
2nd	807,927 (40.2)	665,982 (40.2)	141,945 (39.9)	575,134 (40.3)	475,886 (40.4)	99,248 (40.1)	807,819 (40.2)	665,911 (40.2)	141,908 (39.9)
3rd	417,220 (20.7)	338,435 (20.4)	78,785 (22.2)	290,753 (20.4)	236,738 (20.1)	54,015 (21.8)	417,116 (20.7)	338,368 (20.4)	78,748 (22.2)
4th (lowest)	267,642 (13.3)	216,663 (13.1)	50,979 (14.3)	187,482 (13.2)	152,691 (12.9)	34,791 (14.1)	267,605 (13.3)	216,636 (13.1)	50,969 (14.3)
Personal history, n (%)									
Food allergy									
Yes	11,738 (0.6)	9930 (0.6)	1808 (0.5)	4414 (0.3)	3750 (0.3)	664 (0.3)	11,733 (0.6)	9927 (0.6)	1806 (0.5)
No	2,000,727 (99.4)	1,646,787 (99.4)	353,940 (99.5)	1,421,827 (99.7)	1,175,083 (99.7)	246,744 (99.7)	2,000,334 (99.4)	1,646,521 (99.4)	353,813 (99.5)
Allergic rhinitis									
Yes	372,648 (18.5)	304,152 (18.4)	68,496 (19.3)	261,026 (18.3)	213,912 (18.2)	47,114 (19.0)	372,528 (18.5)	304,076 (18.4)	68,452 (19.3)
No	1,639,817 (81.5)	1,352,565 (81.6)	287,252 (80.7)	1,165,215 (81.7)	964,921 (81.8)	200,294 (81.0)	1,639,539 (81.5)	1,352,372 (81.6)	287,167 (80.7)

(*continued*)

Table 1. Continued

Characteristics	Cohort for Alopecia Areata			Cohort for Atopic Dermatitis			Cohort for Psoriasis		
	Total	Normal (BMI < 84th Percentile)	Overweight or Obesity (BMI ≥ 85th Percentile)	Total	Normal (BMI < 84th Percentile)	Overweight or Obesity (BMI ≥ 85th Percentile)	Total	Normal (BMI < 84th Percentile)	Overweight or Obesity (BMI ≥ 85th Percentile)
Asthma									
Yes	737,449 (36.6)	595,295 (35.9)	142,154 (39.9)	491,748 (34.5)	398,875 (33.8)	92,873 (37.5)	737,193 (36.6)	595,097 (35.9)	142,096 (39.9)
No	1,275,016 (63.4)	1,061,422 (64.1)	213,594 (60.1)	934,493 (65.5)	779,958 (66.2)	154,535 (62.5)	1,274,874 (63.4)	1,061,351 (64.1)	213,523 (60.1)
Allergic conjunctivitis									
Yes	356,245 (17.7)	294,567 (17.8)	61,678 (17.3)	233,574 (16.4)	193,918 (16.5)	39,656 (16.0)	356,182 (17.7)	294,528 (17.8)	61,654 (17.3)
No	1,656,220 (82.3)	1,362,150 (82.2)	294,070 (82.7)	1,192,667 (83.6)	984,915 (83.5)	207,752 (84.0)	1,655,885 (82.3)	1,361,920 (82.2)	293,965 (82.7)

Abbreviation: BMI, body mass index.

(66–71 months) screenings (Supplementary Table S10 and Supplementary Figure S2) with IMSDs demonstrated results and trends consistent with the main findings.

An additional sensitivity analysis was performed using body weight instead of BMI (Supplementary Tables S11 and S12). The results and trends in most sensitivity analyses were similar with the main findings.

DISCUSSION

This large-scale national cohort study of children provided evidence that higher BMI was linked to an increased risk of developing AA, AD, and psoriasis among children. Moreover, we observed that an increase in BMI was associated with an elevated risk of AD, whereas a decrease in BMI was associated with a reduced risk of AD among children. This is the noteworthy longitudinal investigation that has revealed the association between BMI changes and subsequent occurrences of 3 main pediatric IMSDs—AA, AD, and psoriasis—as well as the direct influence of BMI on AA.

Previous studies have not explored the relationship between BMI changes and IMSDs; however, several have demonstrated the associations between BMI and AD or psoriasis risk (Ali et al, 2018; Armstrong et al, 2012; Boccardi et al, 2009; Iturriaga et al, 2023; Zhang and Silverberg, 2015). Childhood obesity has been linked to a higher risk of AD or psoriasis on the basis of reported findings (Ali et al, 2018; Zhang and Silverberg, 2015); however, research reports on this topic have been controversial. A recent systematic review of observational studies in children discovered a significant positive association between obesity or overweight and AD (Ali et al, 2018); however, the available studies showed some inconsistencies, with some indicating either no association (D'Auria et al, 2017; Mai et al, 2007; Saadeh et al, 2014; Tai et al, 2009; Tanaka et al, 2011; von Kries et al, 2001) or even negative association (Sidoroff et al, 2012). Furthermore, a meta-analysis revealed that patients who were overweight or obese had significantly increased odds of developing AD compared with those with normal weight (Zhang and Silverberg, 2015). However, when stratified by geographical region, this association was significant in North America and Asia but not in Europe and Latin America (Iturriaga et al, 2023; Zhang and Silverberg, 2015). The association between psoriasis and obesity shows relatively consistent directionality. A systematic review and meta-analysis observed that patients with psoriasis had higher odds of obesity than those without psoriasis (Armstrong et al, 2012). Some case-control studies in children have revealed that children with psoriasis were more prone to being obese at the time of diagnosis than those without (Boccardi et al, 2009; Hunjan et al, 2018). The exact mechanisms through which overweight and obesity affect the onset of psoriasis and its severity in children and adolescents are still not fully understood. However, the collective data provide evidence supporting a positive association between psoriasis and obesity in children and adolescents (Gutmark-Little and Shah, 2015). Nonetheless, no correlation has been observed between obesity in early life and psoriasis (Herron et al, 2005). The inconsistency among the studies could be attributed to differences in ethnicity and socioeconomic factors within the study population, variations in study

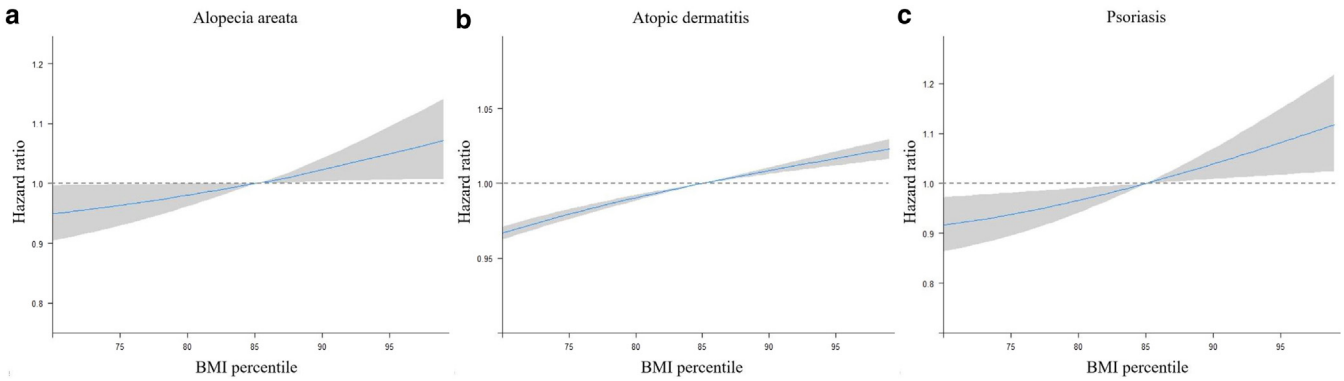

Figure 2. Association of BMI percentile with pediatric immune-mediated skin diseases among children. (**a**) Alopecia areata. (**b**) Atopic dermatitis. (**c**) Psoriasis. Solid lines represent the HR, whereas the shaded areas depict the 95% CIs obtained through restricted cubic spline regression. The reference point is the BMI 85th percentile. Four knots were used to construct the restricted cubic splines, positioned at the 5th, 35th, 65th, and 95th percentiles of the BMI. HRs (95% CI) were calculated using a Cox proportional hazards regression analysis after adjusting for sex, birth weight, breastfeeding status, household income, allergic comorbidities, and infectious diseases. Age- and sex-specific BMI percentiles were measured during the fifth health examination (ages 42–48 months). BMI, body mass index; CI, confidence interval; HR, hazard ratio.

design, small sample sizes, or differing definitions of overweight or obesity. Furthermore, among the previous studies, only a limited number were conducted longitudinally. Therefore, whether obesity leads to AD and psoriasis or whether the opposite holds true remains uncertain.

Our longitudinal study established a defined temporal sequence, indicating that children at young age with higher BMI had an elevated risk of developing pediatric IMSDs, including AA, AD, and psoriasis, which are supported by the previous studies mentioned earlier. The evidence suggests that higher body weight may play a role in the pathogenesis of pediatric IMSDs, including AA, AD, and psoriasis, and may contribute to an elevated risk of their development. Particularly, clinical research on the association between childhood obesity and AA is scarcer than that on AD or psoriasis. Our findings present the real-world evidence suggesting that childhood obesity may play an important role in AA development in children and adolescents.

The physiologic mechanisms underlying the effect of obesity on IMSDs have been suggested in prior studies. Being overweight or obese may lead to an increased release of adipokines from adipose tissue, resulting in proinflammatory effects (Silverberg et al, 2011). Adipose tissue contributes to the recruitment of macrophages and cytotoxic T cells and produces adipokines that lead to the production of inflammatory mediators, such as TNF-α and IL-6, which are associated with the pathogenesis of AA, AD, and psoriasis (Armstrong et al, 2012; Iturriaga et al, 2023; Silverberg et al, 2011; Stochmal et al, 2021). In addition, obesity could disrupt the skin barrier function, influence leptin activity,

Table 2. Hazard Ratios for Immune-Mediated Skin Diseases according to the Weight Status of Children

	Weight status				
Outcome	Underweight (BMI < 5th Percentile)	Normal (BMI = 5th–84th Percentile)	Overweight (BMI 85th–94th Percentile)	Obesity (BMI ≥ 95th Percentile)	*P* for Trend
Alopecia areata					
Events, n	142	3846	562	328	
Person-year	378,848	8,300,280	1,231,712	613,721	
aHR (95% CI)	0.79 (0.67–0.94)[1]	1.00 (reference)	0.99 (0.90–1.08)	1.15 (1.02–1.29)[2]	<.01
Atopic dermatitis					
Events, n	1441	32,149	5073	2723	
Person-year	258,858	5,472,891	784,140	394,917	
aHR (95% CI)	0.94 (0.89–0.99)[2]	1.00 (reference)	1.13 (1.10–1.17)[3]	1.12 (1.08–1.17)[3]	<.001
Psoriasis					
Events, n	64	1691	278	158	
Person-year	379,084	8,304,976	1,232,031	613,927	
aHR (95% CI)	0.87 (0.67–1.12)	1.00 (reference)	1.09 (0.96–1.24)	1.24 (1.05–1.47)[2]	<.01

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval.

aHR (95% CI) was calculated using Cox proportional hazards regression analysis after adjusting for sex, birth weight, breastfeeding status, household income, allergic comorbidity (food allergy, allergic rhinitis, asthma, and allergic conjunctivitis), and infectious diseases (respiratory diseases; urinary tract infections; intra-abdominal infections; infections involving the skin, soft tissue, bone, or joint; and other infections).

[1] $P < .01$.

[2] $P < .05$.

[3] $P < .001$.

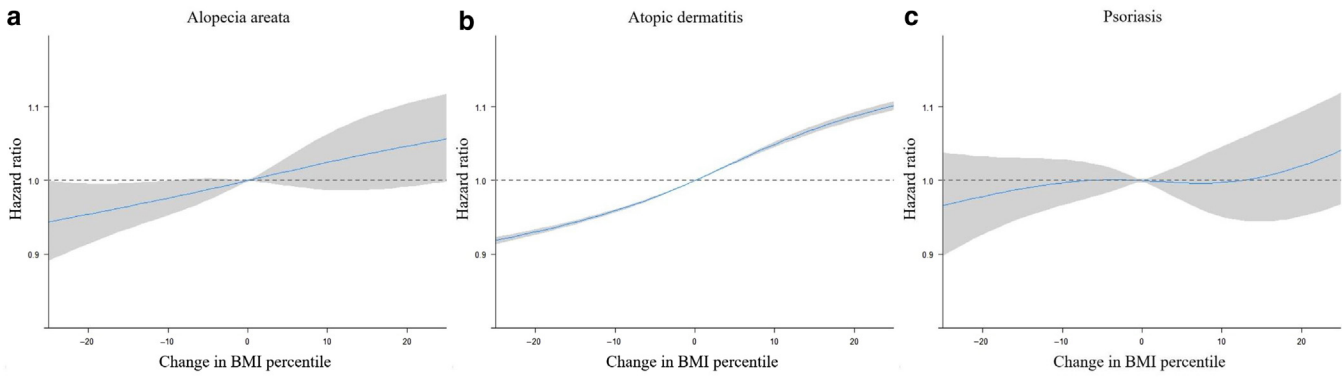

Figure 3. Association of the change in BMI percentile with pediatric immune-mediated skin diseases among children. (**a**) Alopecia areata. (**b**) Atopic dermatitis. (**c**) Psoriasis. Solid lines represent the HR, whereas the shaded areas depict the 95% CIs obtained through restricted cubic spline regression. Four knots were used to construct the restricted cubic splines, positioned at the 5th, 35th, 65th, and 95th percentiles of the change in BMI percentile. HRs (95% CI) were calculated as indicated in the legend to Figure 2 with additional adjustment for baseline BMI percentile, measured during the fourth health examination (ages 30–36 months). BMI, body mass index; CI, confidence interval; HR, hazard ratio.

result in immune imbalances, and contribute to chronic low-grade inflammation (Langan et al, 2020; Nino et al, 2012; Wu and Ballantyne, 2020). Leptin, which is one of the most extensively studied hormones derived from adipocytes, regulates appetite and body weight and plays a crucial role in the inflammatory response by promoting T-cell proliferation and differentiation toward a T helper 1 phenotype (Davidovici et al, 2010), which is associated with psoriasis. In addition, leptin leads to the production of TNF-α, IL-6, IFN-γ, and IL-2, which are also associated with AD (Danso et al, 2014; Toshitani et al, 1993). Furthermore, adipose tissue releases other adipokines into the bloodstream, including adiponectin, which exhibits an anti-inflammatory effect, reduces T-cell activity, and inhibits TNF-α synthesis. Indeed, patients with AA, AD, and psoriasis have revealed a correlation with abnormally low adiponectin levels (Armstrong et al, 2012; Silverberg et al, 2011; Stochmal et al, 2021). Until now, the precise role of leptin, adiponectin, and other adipokines as well as the underlying mechanisms behind the association of childhood obesity with pediatric AA, AD, and psoriasis are yet to be fully understood and require further investigation. Nevertheless, on the basis of the evidence from these studies, obesity or weight gain could be a risk factor for pediatric IMSDs by triggering proinflammatory activation and upregulating various inflammatory cytokines, partially corroborating our findings.

Therefore, ascertaining optimal approaches for managing body weight during childhood is of great clinical importance. Interestingly, our findings revealed a significant correlation between BMI increases from 30–36 months to 42–48 months, 54–60 months, and 66–71 months and an elevated risk of AD. However, a decrease in BMI was associated with reduced risks of AD. This implies that managing weight changes and regulating body weight during childhood may influence the development of subsequent AD. Therefore, our findings support the importance of promoting weight maintenance among children who are already within the normal weight range because it may help reduce the AD risk. In addition, prevention of excessive weight gain and purposeful weight loss, including adopting healthy diet strategies in children with obesity to prevent AD, particularly before school age, should be promoted.

We detected no significant correlation between changes in BMI and pediatric AA or psoriasis, probably because of the much lower incidences of AA and psoriasis than of AD. Furthermore, given that AA and psoriasis are more prevalent at later ages than AD, these 2 diseases may have been less influenced by changes in BMI within the relatively short follow-up period of this study. In-depth research is necessary to explore how potential pathophysiologic mechanisms of childhood obesity differ across various IMSDs in children.

One notable strength of this study is that it is the nationwide cohort study conducted on a large-scale population of children and adolescents, offering valuable real-world evidence about the effects of BMI and BMI changes on pediatric IMSDs, including AA, AD, and psoriasis. In addition, we conducted thorough analyses to address factors that might influence the development of pediatric IMSDs, such as breastfeeding status or allergic comorbidities. This ensured that our study was comprehensively adjusted and accounted for these important variables. In addition, we conducted subgroup and sensitivity analyses, which strengthened the validity and robustness of our findings, increasing the credibility of the study results.

This study had some limitations. First, its retrospective nature hindered us from fully addressing all potential confounding factors, such as maternal health statuses or birth delivery. Further study is warranted to investigate the association between childhood obesity and pediatric IMSDs on the basis of data that integrate information from parents and children. Second, the definition of obesity in this study relied solely on BMI, which might not fully account for specific elements of body composition, such as fat distribution. Future studies should utilize different measures of adiposity, such as dual-energy X-ray absorptiometry, hip and waist measurements, or arm fat measurements. Third, the definition of diseases based on the international diagnostic codes may have resulted in potential disease misclassifications. Finally, the participants in this study were children who voluntarily underwent health examinations, potentially leading to a

Table 3. Hazard Ratios for Immune-Mediated Skin Diseases by Changes in Weight Status among Children

Outcome	Baseline BMI Percentile at the 4th Health Screening (30–36 mo)	Follow-Up BMI Percentile at the 5th Health Screening (42–48 mo): Normal (BMI < 84th Percentile)	Overweight (BMI = 85th–94th Percentile)	Obesity (BMI ≥ 95th Percentile)	*P* for Trend
Alopecia areata	Normal (BMI < 84th percentile)				
	Events, n	3781	357	105	
	Person-year	8,268,276	799,800	194,560	
	aHR (95% CI)	1.00 (reference)	0.98 (0.88–1.09)	1.19 (0.98–1.45)	.35
	Overweight (BMI = 85th–94th percentile)				
	Events, n	171	147	106	
	Person-year	345,234	325,322	188,490	
	aHR (95% CI)	1.08 (0.86–1.35)	1.00 (reference)	1.21 (0.94–1.56)	.48
	Obesity (BMI ≥ 95th percentile)				
	Events, n	36	58	117	
	Person-year	64,156	106,382	230,548	
	aHR (95% CI)	1.16 (0.79–1.70)	1.10 (0.80–1.52)	1.00 (reference)	.40
Atopic dermatitis	Normal (BMI < 84th percentile)				
	Events, n	31,979	3280	784	
	Person-year	5,460,664	506,061	124,495	
	aHR (95% CI)	1.00 (reference)	1.15 (1.11–1.20)[1]	1.06 (0.99–1.14)	<.001
	Overweight (BMI = 85th–94th percentile)				
	Events, n	1338	1340	856	
	Person-year	227,900	209,145	121,212	
	aHR (95% CI)	0.87 (0.81–0.94)[1]	1.00 (reference)	1.06 (0.97–1.15)	<.001
	Obesity (BMI ≥ 95th percentile)				
	Events, n	268	453	1083	
	Person-year	42,148	68,776	149,144	
	aHR (95% CI)	0.88 (0.77–1.01)	0.95 (0.85–1.06)	1.00 (reference)	.07
Psoriasis	Normal (BMI < 84th percentile)				
	Events, n	1663	177	50	
	Person-year	8,273,040	799,973	194,633	
	aHR (95% CI)	1.00 (reference)	1.07 (0.91–1.26)	1.31 (0.99–1.73)	0.04
	Overweight (BMI = 85th–94th percentile)				
	Events, n	81	76	48	
	Person-year	345,303	325,393	188,597	
	aHR (95% CI)	1.00 (0.72–1.38)	1.00 (reference)	1.06 (0.73–1.54)	0.76
	Obesity (BMI ≥ 95th percentile)				
	Events, n	11	25	60	
	Person-year	64,254	106,457	230,574	
	aHR (95% CI)	0.64 (0.32–1.25)	0.96 (0.60–1.54)	1.00 (reference)	0.24

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval.

aHR (95% CI) was calculated using Cox proportional hazards regression analysis after adjusting for sex, birth weight, breastfeeding status, household income, allergic comorbidity (food allergy, allergic rhinitis, asthma, and allergic conjunctivitis), and infectious diseases (respiratory diseases; urinary tract infections; intra-abdominal infections; infections involving the skin, soft tissue, bone, or joint; and other infections).

[1] $P < .001$.

study population with specific sociodemographic characteristics, such as higher income and health consciousness. Despite our efforts to consider this by adjusting for various covariates, further research with a more diverse study population is necessary to confirm the results of our study.

In conclusion, childhood obesity was associated with an increased risk of pediatric IMSDs, including AA, AD, and psoriasis. In addition, weight gain was correlated with an increased AD risk, whereas weight loss was correlated with a decreased AD risk. Implementing purposeful interventions, including nutritional strategies, to decrease body weight may aid in reducing the risk of developing IMSDs in children.

MATERIALS AND METHODS

Study population

The NHIS provides mandatory health insurance coverage for almost the entire Korean population, creating a comprehensive database of clinical data on various healthcare services, including outpatient visits, hospital admissions, and pharmacy prescriptions (CheolSeong et al, 2017; Seong et al, 2017). It has implemented the National

Health Screening Program for Infants and Children as a population monitoring system to promote the health and well-being of children. The National Health Screening Program for Infants and Children conducts screening at 7 stages between the ages of 4 and 71 months: at 4−6 (first), 9−12 (second), 18−24 (third), 30−36 (fourth), 42−48 (fifth), 54−60 (sixth), and 66−71 (seventh) months. During the examination, physicians measure the child's physical characteristics, gather basic perinatal history, and conduct physical examinations (Suh et al, 2016). The NHIS database has been extensively utilized in epidemiological studies, and its reliability and accuracy have been discussed in previous publications (Cheol Seong et al, 2017).

Of the entire population of children in South Korea, 2,161,900 children who underwent the fourth (30−36 months) and fifth (42−48 months) health screenings between 2009 and 2020 were enrolled. To ensure the accuracy and relevancy of the results, we excluded infants who were born prematurely (before 37 weeks of gestation) and those with neonatal intensive care unit stays lasting at least 5 days. Moreover, we excluded individuals who died; those with a history of AA, AD, or psoriasis; and those with missing covariate values before the index date, which was set at 4 years after the birth date (the last possible point for the fifth health screening). Finally, the cohort sizes for AA, AD, and psoriasis were 2,012,465; 1,426,241; and 2,012,067 children, respectively (Figure 1). These individuals were followed from the index date (4 years after the date of birth) until December 31, 2021.

The Institutional Review Board of Seoul Metropolitan Government-Seoul National University Boramae Medical Center approved this study (institutional review board number 07-2022-23). Owing to the rigorous confidentiality regulations in the NHIS cohort database, the necessity for informed consent was waived.

BMI assessment

BMI was assessed during each health checkup. BMI measurements from the fifth health screening (42−48 months) were used to analyze the association between BMI and IMSDs. Childhood overweight and obesity were determined using BMI z-scores at the 85^{th} and 95^{th} percentiles specific to age and sex, as established by the general Korean pediatric population. These percentile values were provided in 2017 by the Korea Centers for Disease Control and Prevention (Lee, 2019). BMI change was computed by estimating the difference in BMI values measured during the fifth and fourth health examination. On the basis of the resulting change, individuals were categorized as normal (BMI $< 85^{th}$ percentile), overweight (BMI $= 85^{th}$−94^{th} percentile), or obese (BMI $\geq 95^{th}$ percentile).

Follow-up for IMSD events

Information regarding hospital or clinic utilization was collected from the NHIS. In addition, IMSD events were identified using the International Classification of Diseases, Tenth Revision (ICD-10) codes. To establish a rigorous definition of IMSDs, children who had at least 3 documented physician visits between the index date (4 years after the date of birth) and December 31, 2021 were defined as patients with the following conditions: AA (ICD-10 code: L63), including alopecia totalis (ICD-10 code: L63.0), alopecia universalis (ICD-10 code: L63.1), and patch-type AA (ICD-10 code: L63.9); AD (ICD-10 codes: L20) (Jung and Lee, 2023; Oh et al, 2023); and psoriasis (ICD-10 codes: L40), including psoriasis vulgaris (ICD-10 codes: L40.0, L40.8, and L40.9). According to previous studies, the positive predictive values of the algorithms selected for use in this study for AA and psoriasis were 93.7 and 96.9%, respectively (Ham et al, 2020; Shin et al, 2020).

To check for potential observation bias and confirm the reliability of our cohort and analyses, we established and examined a negative outcome control, melanocytic nevus (ICD-10 code: D22), which is less likely to be linked to childhood obesity.

Statistical analysis

All children were followed up from 4 years after birth until the occurrence of each IMSD event; death; or December 31, 2021, whichever came first. Cox proportional hazard regression analysis was performed to evaluate the hazard ratios and 95% CIs of IMSDs on the basis of the BMI and BMI change. Restricted cubic splines were used for the graphical evaluation of the associations between BMI, BMI changes, and IMSD (Durrleman and Simon, 1989). In restricted cubic splines, 4 knots were positioned at specific percentiles (5th, 35th, 65th, and 95th) of the BMI or BMI change for analysis (Kim et al, 2022). Furthermore, we performed subgroup analyses on the basis of sex, birth weight, breastfeeding status, and household income.

We adjusted for potential confounding factors, including sex, breastfeeding status, household income, birth weight, allergic comorbidities, and infectious diseases, in the Cox proportional regression model. The National Health Screening Program for Infants and Children surveillance questionnaire was used to assess the breastfeeding status at infancy and was administered to mothers at 2 time points: 4−6 months and 9−12 months after childbirth. The insurance premiums of their parents were considered in evaluating the household income for each infant. The National Health Screening Program for Infants and Children examination was used to gather data concerning the birth weight and preterm birth status of each infant. Furthermore, the medical history of allergic comorbidities and infectious diseases was considered a possible covariate. These allergic comorbidities encompassed food allergy, allergic rhinitis, asthma, and allergic conjunctivitis. The infectious diseases encompassed respiratory diseases; urinary tract infections; intra-abdominal infections; infections involving the skin, soft tissue, bone, or joint; and other infections, as defined by the ICD-10 codes (Supplementary Table S13) (Faillie, 2015; Morens et al, 2008, 2004).

Furthermore, we performed 3 different types of sensitivity analyses. First, to consider the characteristics of IMSDs with early onset, such as AD, and investigate the impact of obesity at a younger age, we conducted sensitivity analyses using data from the third (18−24 months) and fourth (30−36 months) screenings. The index date was set at ages of 2 and 3 years for these analyses. Second, to explore clinically meaningful intervention timing, sensitivity analyses of not only the impact of BMI changes between the fourth (30−36 months) and sixth (54−60 months) screenings on pediatric IMSDs but also the effects of BMI changes between the fourth (30−36 months) and seventh (66−71 months) screenings were conducted. Third, sensitivity analyses based on body weight instead of BMI were conducted.

Statistical significance was determined by a 2-sided $P < .05$. Data mining and statistical analyses were performed using SAS, version 9.4 (SAS Institute).

DATA AVAILABILITY STATEMENT

The study's supporting data can be obtained by reaching out to the corresponding author upon request. As a result of privacy and ethical considerations concerning the study participants, the data supporting this article cannot be made publicly available.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: SRK, HP; Data Curation: SRK; Formal Analysis: SRK; Funding Acquisition: S-JK, HP; Investigation: SRK, S-JK, HP; Methodology: SRK, HP; Project Administration: S-JK, HP; Resources: S-JK, HP; Software: SRK; Supervision: S-JK, HP; Validation: SRK, S-JK, HP; Visualization: SRK; Writing − Original Draft Preparation: SRK; Writing − Review and Editing: SRK, S-JK, HP

Disclaimer

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2024.01.037.

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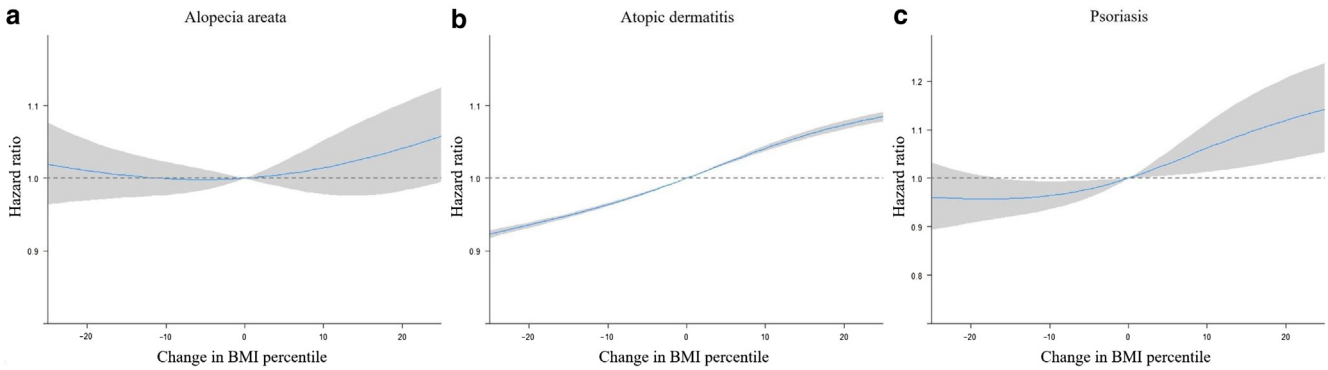
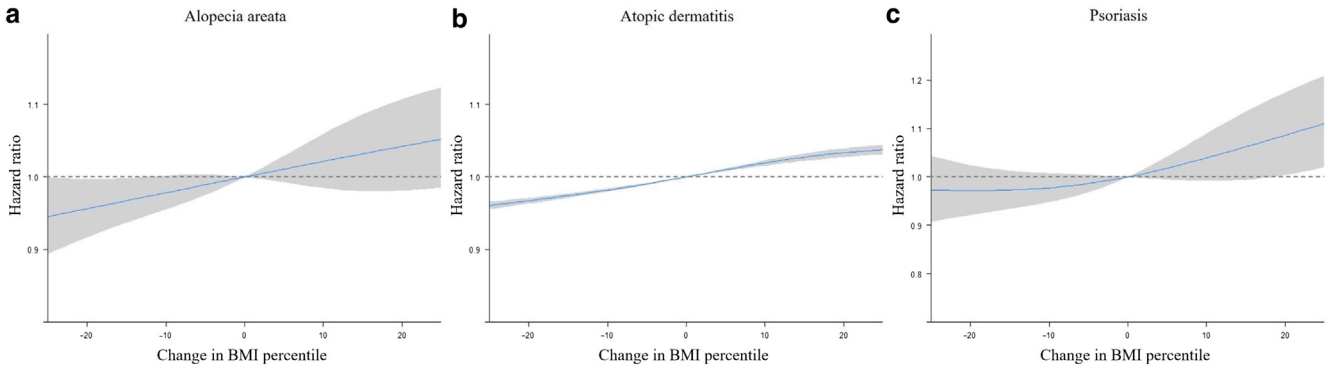


Supplementary Figure S1. Association of the change in BMI percentile between the fourth (30–36 months) and sixth (54–60 months) screenings with pediatric immune-mediated skin diseases among children. (**a**) Alopecia areata. (**b**) Atopic dermatitis. (**c**) Psoriasis. Solid lines represent the HR, whereas the shaded areas depict the 95% CIs obtained through restricted cubic spline regression. Four knots were used to construct the restricted cubic splines, positioned at the 5th, 35th, 65th, and 95th percentiles of the change in BMI percentile. HRs (95% CI) were calculated using Cox proportional hazards regression analysis after adjusting for baseline BMI percentile, sex, birth weight, breastfeeding status, household income, allergic comorbidities, and infectious diseases. BMI, body mass index; CI, confidence interval; HR, hazard ratio.



Supplementary Figure S2. Association of the change in BMI percentile between the fourth (30–36 months) and seventh (66–71 months) screenings with pediatric immune-mediated skin diseases among children. (**a**) Alopecia areata. (**b**) Atopic dermatitis. (**c**) Psoriasis. Solid lines represent the HR, whereas the shaded areas depict the 95% CIs obtained through restricted cubic spline regression. Four knots were used to construct the restricted cubic splines, positioned at the 5th, 35th, 65th, and 95th percentiles of the change in BMI percentile. HRs (95% CI) were calculated using Cox proportional hazards regression analysis after adjusting for baseline BMI percentile, sex, birth weight, breastfeeding status, household income, allergic comorbidities, and infectious diseases. BMI, body mass index; CI, confidence interval; HR, hazard ratio.

Supplementary Table S1. Characteristics of the Included Study Participants and Excluded Study Participants with History of AD

Characteristics	Total	Excluded Study Participants	Included Study Participants (AD Cohort)
Participants, n (%)	2,013,310	587,069	1,426,241
Birth weight, kg, mean (SD)	3.22 (0.45)	3.23 (0.44)	3.21 (0.45)
4th health screening examination (30–36 months)			
BMI percentile, mean (SD)	48.8 (28.0)	48.9 (27.9)	48.8 (28.0)
BMI z-score, mean	−0.030	−0.028	−0.030
Normal weight (BMI < 85th percentile), n (%)	1,744,986 (86.7)	509,537 (86.8)	1,235,449 (86.6)
Overweight (BMI = 85th–94th percentile), n (%)	178,442 (8.9)	51,810 (8.8)	126,632 (8.9)
Obese (BMI ≥ 95th percentile), n (%)	89,882 (4.4)	25,722 (4.4)	64,160 (4.5)
5th health screening examination (42–48 months)			
BMI percentile, mean (SD)	53.1 (28.5)	54.4 (28.3)	52.6 (28.6)
BMI z-score, mean	0.078	0.111	0.065
Normal weight (BMI < 85th percentile), n (%)	1,657,292 (82.3)	478,534 (81.5)	1,178,758 (82.7)
Overweight (BMI = 85th–94th percentile), n (%)	225,635 (11.2)	70,002 (11.9)	155,633 (10.9)
Obese (BMI ≥ 95th percentile), n (%)	130,383 (6.5)	38,533 (6.6)	91,850 (6.4)
Sex, n (%)			
Male	1,027,934 (51.1)	309,419 (52.7)	718,515 (50.4)
Female	985,376 (48.9)	277,650 (47.3)	707726 (49.6)
Breastfeeding status, n (%)			
Only breast milk	746,151 (37.9)	234,619 (40.9)	511,532 (36.6)
Only formula milk	875,292 (44.4)	236,043 (41.2)	639249 (45.8)
Both	339,599 (17.2)	98,865 (17.2)	240734 (17.2)
Special formula milk	10,248 (0.5)	4,042 (0.7)	6206 (0.4)
Household income, quartile, n (%)			
1st (highest)	519,894 (25.8)	147,022 (25.0)	372,872 (26.1)
2nd	808,275 (40.2)	233,141 (39.7)	575134 (40.3)
3rd	417,371 (20.7)	126,618 (21.6)	290753 (20.4)
4th (lowest)	267,770 (13.3)	80,288 (13.7)	187482 (13.2)
Personal history, n (%)			
Food allergy			
Yes	11,747 (0.6)	7333 (1.2)	4414 (0.3)
No	2,001,563 (99.4)	579,736 (98.8)	1,421,827 (99.7)
Allergic rhinitis			
Yes	372,821 (18.5)	111,795 (19.0)	111,795 (18.3)
No	1,640,489 (81.5)	4,752,741 (81.0)	1,165,215 (81.7)
Asthma			
Yes	737,729 (36.6)	245,981 (41.9)	491,748 (34.5)
No	1,275,581 (63.4)	341,088 (58.1)	934,493 (65.5)
Allergic conjunctivitis			
Yes	356,434 (17.7)	122,860 (20.9)	233,574 (16.4)
No	1,656,876 (82.3)	464,209 (79.1)	1,192,667 (83.6)

Abbreviations: AD, atopic dermatitis; BMI, body mass index.

Supplementary Table S2. Hazard Ratios for Melanocytic Nevus according to the Weight Status of Children

Outcome	Weight Status: Normal (BMI < 84th Percentile)	Weight Status: Overweight (BMI 85th–94th Percentile)	Weight Status: Obesity (BMI ≥ 95th Percentile)	*P* for Trend
Melanocytic nevus				
Events, n	3,591	516	227	
Person-year	8,670,544	1,230,581	613,348	
aHR (95% CI)	1.00 (reference)	1.02 (0.93–1.13)	0.91 (0.79–1.04)	.37

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval.
aHR (95% CI) was calculated using Cox proportional hazards regression analysis after adjusting for sex, birth weight, breastfeeding status, household income, allergic comorbidity (food allergy, allergic rhinitis, asthma, and allergic conjunctivitis), and infectious diseases (respiratory diseases; urinary tract infections; intra-abdominal infections; infections involving the skin, soft tissue, bone, or joint; and other infections).

Supplementary Table S3. Hazard Ratios for Melanocytic Nevus by Changes in Weight Status among Children

Outcome	Baseline BMI Percentile At the 4th Health Screening (30–36 mo)	Follow-Up BMI Percentile at the 5th Health Screening (42–48 mo)			*P* for Trend
		Normal (BMI < 84th Percentile)	Overweight (BMI = 85th–94th Percentile)	Obesity (BMI ≥ 95th Percentile)	
Melanocytic nevus	Normal (BMI < 84th percentile)				
	Events, n	3436	337	71	
	Person-year	8,260,002	798,864	194,464	
	aHR (95% CI)	1.00 (reference)	1.02 (0.91–1.14)	0.90 (0.71–1.14)	.69
	Overweight (BMI = 85th–94th percentile)				
	Events, n	135	146	80	
	Person-year	344,947	325,113	188,396	
	aHR (95% CI)	0.87 (0.68–1.10)	1.00 (reference)	0.92 (0.70–1.22)	.53
	Obesity (BMI ≥ 95th percentile)				
	Events, n	19	32	76	
	Person-year	64,137	106,397	230,365	
	aHR (95% CI)	0.93 (0.56–1.55)	0.92 (0.60–1.40)	1.00 (reference)	.72

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval.

aHR (95% CI) was calculated using Cox proportional hazards regression analysis after adjusting for sex, birth weight, breastfeeding status, household income, allergic comorbidity (food allergy, allergic rhinitis, asthma, and allergic conjunctivitis), and infectious diseases (respiratory diseases; urinary tract infections; intra-abdominal infections; infections involving the skin, soft tissue, bone, or joint; and other infections).

Supplementary Table S4. Subgroup Analyses of the Association of BMI with Alopecia Areata among Children

Subgroup	Events, n	Person-y	Weight Status				*P* for Trend
			Underweight (BMI < 5th Percentile)	Normal (BMI = 5th–84th Percentile)	Overweight (BMI = 85th–94th Percentile)	Obesity (BMI ≥ 95th Percentile)	
Sex							
Male	1951	5,382,293	0.79 (0.60–1.04)	1.00 (reference)	0.93 (0.81–1.08)	1.16 (0.97–1.40)	.16
Female	2927	5,143,755	0.79 (0.63–0.99)[1]	1.00 (reference)	1.03 (0.92–1.15)	1.15 (0.99–1.32)	.01
Birth weight							
Low (<2.4 kg)	142	299,736	0.67 (0.33–1.37)	1.00 (reference)	1.11 (0.60–2.06)	0.92 (0.34–2.50)	.47
Normal (2.5–3.9 kg)	4547	9,803,089	0.79 (0.66–0.94)[2]	1.00 (reference)	1.01 (0.92–1.10)	1.10 (0.98–1.25)	.02
High (≥4.0 kg)	168	381,436	1.92 (0.61–6.05)	1.00 (reference)	0.84 (0.53–1.33)	2.14 (1.47–3.11)[3]	<.01
Breastfeeding status							
Only breast milk	1924	4,187,699	0.88 (0.68–1.15)	1.00 (reference)	0.94 (0.81–1.08)	1.17 (0.97–1.41)	.27
Only formula milk	2002	4,270,728	0.76 (0.59–0.99)[1]	1.00 (reference)	1.05 (0.92–1.21)	1.10 (0.92–1.31)	.04
Both	774	1,711,790	0.62 (0.37–1.03)	1.00 (reference)	0.93 (0.74–1.16)	1.25 (0.96–1.63)	.09
Special formula milk	39	57,790	1.32 (0.31–5.59)	1.00 (reference)	1.66 (0.72–3.81)	0.47 (0.06–3.45)	.92
Household income							
Upper half	3190	6,794,269	0.75 (0.61–0.94)[2]	1.00 (reference)	1.07 (0.96–1.19)	1.19 (1.03–1.38)[1]	<.001
Lower half	1688	3,731,779	0.83 (0.63–1.11)	1.00 (reference)	0.90 (0.77–1.05)	1.14 (0.95–1.38)	.37

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval.

aHR (95% CI) was calculated using Cox proportional hazards regression analysis after adjusting for sex, birth weight, breastfeeding status, household income, allergic comorbidity (food allergy, allergic rhinitis, asthma, and allergic conjunctivitis), and infectious diseases (respiratory diseases; urinary tract infections; intra-abdominal infections; infections involving the skin, soft tissue, bone, or joint; and other infections).

[1] $P < .05$.

[2] $P < .01$.

[3] $P < .001$.

Supplementary Table S5. Subgroup Analyses of the Association of BMI with Atopic Dermatitis among Children

Subgroup	Events, n	Person-y	Weight Status				*P* for Trend
			Underweight (BMI < 5th Percentile)	Normal (BMI = 5th–84th Percentile)	Overweight (BMI = 85th–94th Percentile)	Obesity (BMI ≥ 95th Percentile)	
Sex							
Male	19,878	3,488,269	0.97 (0.90–1.04)	1.00 (reference)	1.16 (1.11–1.21)[3]	1.14 (1.08–1.21)[3]	<.001
Female	21,513	3,423,281	0.91 (0.85–0.99)[1]	1.00 (reference)	1.10 (1.06–1.15)[3]	1.11 (1.05–1.17)[3]	<.001
Birth weight							
Low (<2.4 kg)	1310	205,450	0.92 (0.75–1.12)	1.00 (reference)	1.26 (1.03–1.54)[1]	0.93 (0.67–1.29)	.19
Normal (2.5–3.9 kg)	38,531	6,437,118	0.95 (0.90–1.00)[1]	1.00 (reference)	1.12 (1.09–1.16)[3]	1.13 (1.08–1.17)[3]	<.001
High (≥4.0 kg)	1410	243,215	0.89 (0.53–1.51)	1.00 (reference)	1.15 (1.00–1.31)[1]	1.07 (0.91–1.25)	.13
Breastfeeding status							
Only breast milk	16,253	2,665,380	0.94 (0.86–1.02)	1.00 (reference)	1.13 (1.08–1.19)[3]	1.13 (1.06–1.21)[3]	<.001
Only formula milk	16,938	2,893,328	0.94 (0.87–1.01)	1.00 (reference)	1.14 (1.09–1.20)[3]	1.13 (1.06–1.20)[3]	<.001
Both	6973	1,131,278	0.96 (0.84–1.10)	1.00 (reference)	1.09 (1.02–1.18)[1]	1.08 (0.99–1.19)	<.01
Special formula milk	204	32,522	0.76 (0.35–1.62)	1.00 (reference)	0.89 (0.56–1.43)	1.64 (0.99–2.72)	.12
Household income							
Upper half	27,110	4,501,978	0.94 (0.88–1.00)[1]	1.00 (reference)	1.12 (1.07–1.16)[3]	1.15 (1.10–1.21)[3]	<.001
Lower half	14,281	2,409,572	0.92 (0.84–1.01)	1.00 (reference)	1.16 (1.11–1.22)[3]	1.09 (1.02–1.16)[2]	<.001

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval.

aHR (95% CI) was calculated using Cox proportional hazards regression analysis after adjusting for sex, birth weight, breastfeeding status, household income, allergic comorbidity (food allergy, allergic rhinitis, asthma, and allergic conjunctivitis), and infectious diseases (respiratory diseases; urinary tract infections; intra-abdominal infections; infections involving the skin, soft tissue, bone, or joint; and other infections).

[1] $P < .05$.

[2] $P < .01$.

[3] $P < .001$.

Supplementary Table S6. Subgroup Analyses of the Association of BMI with Psoriasis among Children

Subgroup	Events, n	Person-y	Weight Status				*P* for Trend
			Underweight (BMI < 5th Percentile)	Normal (BMI = 5th–84th Percentile)	Overweight (BMI = 85th–94th Percentile)	Obesity (BMI ≥ 95th Percentile)	
Sex							
Male	1114	5,382,518	0.74 (0.51–1.09)	1.00 (reference)	1.13 (0.94–1.36)	1.31 (1.04–1.65)[1]	<.01
Female	1077	5,148,986	1.00 (0.71–1.41)	1.00 (reference)	1.05 (0.87–1.27)	1.18 (0.93–1.50)	.20
Birth weight							
Low (<2.4 kg)	62	299,938	0.58 (0.18–1.88)	1.00 (reference)	1.21 (0.48–3.04)	1.66 (0.52–5.33)	.18
Normal (2.5–3.9 kg)	2018	9,808,345	0.86 (0.67–1.12)	1.00 (reference)	1.10 (0.96–1.26)	1.23 (1.03–1.47)[1]	<.01
High (≥4.0 kg)	99	381,415	2.02 (0.49–8.27)	1.00 (reference)	1.00 (0.59–1.68)	1.22 (0.69–2.15)	.71
Breastfeeding status							
Only breast milk	903	4,189,647	0.64 (0.41–1.02)	1.00 (reference)	1.08 (0.88–1.32)	1.44 (1.12–1.85)[2]	<.001
Only formula milk	875	4,273,134	1.19 (0.86–1.64)	1.00 (reference)	1.06 (0.86–1.30)	1.00 (0.75–1.32)	.85
Both	325	1,712,737	0.51 (0.21–1.24)	1.00 (reference)	1.24 (0.91–1.69)	1.45 (1.00–2.14)[1]	<.01
Special formula milk	13	57,853	N/A	1.00 (reference)	0.59 (0.08–4.62)	1.12 (0.14–8.78)	.90
Household income							
Upper half	1400	6,798,101	0.80 (0.58–1.10)	1.00 (reference)	1.06 (0.90–1.25)	1.12 (0.89–1.40)	.11
Lower half	791	3,733,403	1.01 (0.67–1.50)	1.00 (reference)	1.16 (0.94–1.43)	1.45 (1.12–1.86)[2]	<.01

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval; N/A, not applicable.

aHR (95% CI) was calculated using Cox proportional hazards regression analysis after adjusting for sex, birth weight, breastfeeding status, household income, allergic comorbidity (food allergy, allergic rhinitis, asthma, and allergic conjunctivitis), and infectious diseases (respiratory diseases; urinary tract infections; intra-abdominal infections; infections involving the skin, soft tissue, bone, or joint; and other infections).

[1] $P < .05$.

[2] $P < .01$.

Supplementary Table S7. Hazard Ratios for Immune-Mediated Skin Diseases according to the Weight-For-Length Percentiles of Children Using Data from the Third (18–24 mo) Screening

Outcome	Weight Status			*P* for Trend
	Normal (Weight-For-Length < 84th Percentile)	Preoverweight (Weight-For-Length 85th–94th Percentile)	Overweight (Weight-For-Length ≥ 95th Percentile)	
Alopecia areata				
Events, n	5397	1126	655	
Person-y	14,813,690	3,116,355	1,821,955	
aHR (95% CI)	1.00 (reference)	1.00 (0.94–1.07)	1.02 (0.94–1.11)	.74
Atopic dermatitis				
Events, n	112,364	24,586	14,816	
Person-year	10,132,496	2,110,212	1,221,690	
aHR (95% CI)	1.00 (reference)	1.05 (1.04–1.07)[2]	1.11 (1.09–1.13)[2]	<.001
Psoriasis				
Events, n	2697	627	373	
Person-y	14,818,076	3,117,015	1,822,291	
aHR (95% CI)	1.00 (reference)	1.11 (1.01–1.21)[1]	1.11 (1.00–1.25)[1]	.01

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval.

aHR (95% CI) was calculated using Cox proportional hazards regression analysis after adjusting for sex, birth weight, breastfeeding status, household income, allergic comorbidity (food allergy, allergic rhinitis, asthma, and allergic conjunctivitis), and infectious diseases (respiratory diseases; urinary tract infections; intra-abdominal infections; infections involving the skin, soft tissue, bone, or joint; and other infections).

[1] $P < .05$.

[2] $P < .001$.

Supplementary Table S8. Hazard Ratios for Immune-Mediated Skin Diseases according to the Weight Status of Children Using Data from the Fourth (30–36 mo) Screening

Outcome	Weight Status				*P* for Trend
	Underweight (BMI < 5th Percentile)	Normal (BMI = 5th–84th Percentile)	Overweight (BMI = 85th–94th Percentile)	Obesity (BMI ≥ 95th Percentile)	
Alopecia areata					
Events, n	275	5584	586	296	
Person-y	697,306	13,627,508	1,376,318	670,478	
aHR (95% CI)	0.92 (0.81–1.05)	1.00 (reference)	1.05 (0.96–1.14)	1.10 (0.98–1.24)	.02
Atopic dermatitis					
Events, n	3375	70,599	7,614	4010	
Person-y	471,888	9,114,187	915,928	447,564	
aHR (95% CI)	0.96 (0.93–0.99)[1]	1.00 (reference)	1.04 (1.01–1.06)[2]	1.08 (1.04–1.12)[2]	<.001
Psoriasis					
Events, n	131	2641	309	142	
Person-y	697,668	13,633,048	1,376,565	670,670	
aHR (95% CI)	0.98 (0.82–1.17)	1.00 (reference)	1.17 (1.04–1.32)[1]	1.10 (0.92–1.31)	.03

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval.

aHR (95% CI) was calculated using Cox proportional hazards regression analysis after adjusting for sex, birth weight, breastfeeding status, household income, allergic comorbidity (food allergy, allergic rhinitis, asthma, and allergic conjunctivitis), and infectious diseases (respiratory diseases; urinary tract infections; intra-abdominal infections; infections involving the skin, soft tissue, bone, or joint; and other infections).

[1] $P < .05$.

[2] $P < .01$.

Supplementary Table S9. Hazard Ratios for Immune-Mediated Skin Diseases among Children between the Fourth and Sixth Health Examinations by Changes in Weight Status

Outcome	Baseline BMI Percentile at the 4th Health Screening (30–36 mo)	Follow-Up BMI Percentile at the 6th Health Screening (54–60 mo)			*P* for Trend
		Normal (BMI < 84th Percentile)	Overweight (BMI = 85th–94th Percentile)	Obesity (BMI ≥ 95th Percentile)	
Alopecia areata	Normal (BMI < 84th percentile)				
	Events, n	2848	282	122	
	Person-y	5,903,974	606,576	235,876	
	aHR (95% CI)	1.00 (reference)	0.96 (0.85–1.09)	1.09 (0.91–1.31)	.73
	Overweight (BMI 85th–94th percentile)				
	Events, n	140	94	72	
	Person-y	269,224	200,500	138,037	
	aHR (95% CI)	1.11 (0.85–1.45)	1.00 (reference)	1.16 (0.85–1.58)	.93
	Obesity (BMI ≥ 95th percentile)				
	Events, n	28	46	84	
	Person-y	53,889	75,780	144,174	
	aHR (95% CI)	0.95 (0.61–1.47)	1.11 (0.77–1.60)	1.00 (reference)	.97
Atopic dermatitis	Normal (BMI < 84th percentile)				
	Events, n	17,233	1,885	782	
	Person-y	3,816,278	376,524	149,386	
	aHR (95% CI)	1.00 (reference)	1.15 (1.09–1.20)[1]	1.12 (1.04–1.20)[2]	<.001
	Overweight (BMI = 85th–94th percentile)				
	Events, n	778	611	459	
	Person-y	172,142	124,295	86,958	
	aHR (95% CI)	0.87 (0.78–0.97)[3]	1.00 (reference)	1.02 (0.90–1.15)	<.01
	Obesity (BMI ≥ 95th percentile)				
	Events, n	155	250	487	
	Person-y	34,260	47,040	89,743	
	aHR (95% CI)	0.84 (0.70–1.01)	1.04 (0.89–1.22)	1.00 (reference)	.15
Psoriasis	Normal (BMI < 84th percentile)				
	Events, n	1261	157	68	
	Person-y	5,908,492	606,810	235,960	
	aHR (95% CI)	1.00 (reference)	1.20 (1.01–1.42)[3]	1.38 (1.08–1.77)[2]	<.01
	Overweight (BMI = 85th–94th percentile)				
	Events, n	61	49	32	
	Person-y	269,322	200,530	138,130	
	aHR (95% CI)	0.90 (0.61–1.32)	1.00 (reference)	0.93 (0.59–1.46)	.80
	Obesity (BMI ≥ 95th percentile)				
	Events, n	14	20	41	
	Person-y	53,939	75,855	144,258	
	aHR (95% CI)	0.97 (0.53–1.80)	0.95 (0.55–1.65)	1.00 (reference)	.90

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval.

aHR (95% CI) was calculated using Cox proportional hazards regression analysis after adjusting for sex, birth weight, breastfeeding status, household income, allergic comorbidity (food allergy, allergic rhinitis, asthma, and allergic conjunctivitis), and infectious diseases (respiratory diseases; urinary tract infections; intra-abdominal infections; infections involving the skin, soft tissue, bone, or joint; and other infections).

[1] $P < .001$.

[2] $P < .01$.

[3] $P < .05$.

Supplementary Table S10. Hazard Ratios for Immune-Mediated Skin Diseases among Children between the Fourth and Seventh Health Examinations by Changes in Weight Status

Outcome	Baseline BMI Percentile at the 4th Health Screening (30–36 mo)	Follow-Up BMI Percentile at the 7th Health Screening (66–71 mo): Normal (BMI < 84th Percentile)	Overweight (BMI = 85th–94th Percentile)	Obesity (BMI ≥ 95th Percentile)	*P* for Trend
Alopecia areata	Normal (BMI < 84th percentile)				
	Events, n	2014	202	129	
	Person-y	4,063,938	419,533	251,413	
	aHR (95% CI)	1.00 (reference)	0.97 (0.83–1.12)	1.10 (0.92–1.32)	.52
	Overweight (BMI 85th–94th percentile)				
	Events, n	101	60	46	
	Person-y	206,763	108,454	98,335	
	aHR (95% CI)	0.84 (0.61–1.17)	1.00 (reference)	0.88 (0.60–1.30)	.65
	Obesity (BMI ≥ 95th percentile)				
	Events, n	31	38	48	
	Person-y	45,348	45,982	91,113	
	aHR (95% CI)	1.39 (0.88–2.20)	1.51 (0.97–2.35)	1.00 (reference)	.11
Atopic dermatitis	Normal (BMI < 84th percentile)				
	Events, n	8,930	1,067	608	
	Person-y	2,573,932	258,165	158,032	
	aHR (95% CI)	1.00 (reference)	1.20 (1.12–1.28)[1]	1.07 (0.98–1.16)	<.001
	Overweight (BMI 85th–94th percentile)				
	Events, n	425	281	258	
	Person-y	127,256	66,089	60,296	
	aHR (95% CI)	0.78 (0.67–0.91)[2]	1.00 (reference)	1.18 (1.04–1.35)[3]	<.01
	Obesity (BMI ≥ 95th percentile)				
	Events, n	97	100	219	
	Person-y	27,567	27,266	54,984	
	aHR (95% CI)	0.91 (0.71–1.17)	0.95 (0.75–1.21)	1.00 (reference)	.44
Psoriasis	Normal (BMI < 84th percentile)				
	Events, n	894	106	61	
	Person-y	4,067,904	419,841	251,453	
	aHR (95% CI)	1.00 (reference)	1.17 (0.96–1.44)	1.15 (0.89–1.50)	.10
	Overweight (BMI = 85th–94th percentile)				
	Events, n	59	26	24	
	Person-y	206,765	108,486	98,401	
	aHR (95% CI)	1.16 (0.72–1.86)	1.00 (reference)	1.05 (0.60–1.85)	.63
	Obesity (BMI ≥ 95th percentile)				
	Events, n	14	8	24	
	Person-y	45,416	46,070	91,189	
	aHR (95% CI)	1.21 (0.60–2.42)	0.56 (0.23–1.40)	1.00 (reference)	.75

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval.

aHR (95% CI) was calculated using Cox proportional hazards regression analysis after adjusting for sex, birth weight, breastfeeding status, household income, allergic comorbidity (food allergy, allergic rhinitis, asthma, and allergic conjunctivitis), and infectious diseases (respiratory diseases; urinary tract infections; intra-abdominal infections; infections involving the skin, soft tissue, bone, or joint; and other infections).

[1] $P < .001$.

[2] $P < .01$.

[3] $P < .05$.

Supplementary Table S11. Hazard Ratios for Immune-Mediated Skin Diseases according to the Weight Status Based on the Weight-For-Age Percentiles of Children

Outcome	Weight Status				*P* for Trend
	Weight < 5th Percentile	Weight < 84th Percentile	Weight = 85th–94th Percentile	Weight ≥ 95th Percentile	
Alopecia areata					
Events, n	117	3776	656	327	
Person-y	316,330	8,340,781	1,219,072	649,206	
aHR (95% CI)	0.82 (0.68–0.99)[1]	1.00 (reference)	1.18 (1.08–1.28)[2]	1.12 (1.00–1.24)[1]	<.001
Atopic dermatitis					
Events, n	1182	32,489	4938	2782	
Person-y	219,906	5,493,862	781,151	416,249	
aHR (95% CI)	0.86 (0.81–0.91)[2]	1.00 (reference)	1.09 (1.06–1.13)[2]	1.12 (1.08–1.17)[2]	<.001
Psoriasis					
Events, n	65	1699	277	150	
Person-y	316,447	8,345,085	1,219,828	649,465	
aHR (95% CI)	1.08 (0.85–1.39)	1.00 (reference)	1.10 (0.97–1.26)	1.10 (0.92–1.31)	.19

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval.

aHR (95% CI) was calculated using Cox proportional hazards regression analysis after adjusting for sex, birth weight, breastfeeding status, household income, allergic comorbidity (food allergy, allergic rhinitis, asthma, and allergic conjunctivitis), and infectious diseases (respiratory diseases; urinary tract infections; intra-abdominal infections; infections involving the skin, soft tissue, bone, or joint; and other infections).

[1] $P < .05$.

[2] $P < .001$.

Supplementary Table S12. Hazard Ratios for Immune-Mediated Skin Diseases by Changes in Weight Status Based on the Weight-For-Age Percentiles of Children

Outcome	Baseline Weight Percentile at the 4th Health Screening (30–36 mo)	Follow-Up Weight Percentile at the 5th Health Screening (42–48 mo)			*P* for Trend
		Weight < 84th Percentile	Weight 85th–94th Percentile	Weight ≥ 95th Percentile	
Alopecia areata	Weight < 84th percentile				
	Events, n	3729	284	40	
	Person-y	8,282,405	559,315	81,434	
	aHR (95% CI)	1.00 (reference)	1.09 (0.96–1.23)	1.07 (0.78–1.48)	.18
	Weight = 85th–94th percentile				
	Events, n	155	288	104	
	Person-y	345,297	533,012	216,666	
	aHR (95% CI)	0.86 (0.71–1.05)	1.00 (reference)	0.88 (0.70–1.11)	.69
	Weight ≥ 95th percentile				
	Events, n	9	84	183	
	Person-y	28,614	126,646	351,043	
	aHR (95% CI)	0.66 (0.34–1.29)	1.35 (1.04–1.76)[1]	1.00 (reference)	.52
Atopic dermatitis	Weight < 84th percentile				
	Events, n	32,219	2272	332	
	Person-y	5,468,661	356,036	51,675	
	aHR (95% CI)	1.00 (reference)	1.13 (1.08–1.18)[2]	1.10 (0.98–1.22)	<.001
	Weight = 85th–94th percentile				
	Events, n	1348	2133	888	
	Person-y	226,610	344,783	139,870	
	aHR (95% CI)	0.95 (0.89–1.02)	1.00 (reference)	1.01 (0.93–1.09)	.15
	Weight ≥ 95th percentile				
	Events, n	102	533	1562	
	Person-y	18,010	80,275	224,648	
	aHR (95% CI)	0.88 (0.72–1.08)	0.97 (0.87–1.67)	1.00 (reference)	.20
Psoriasis	Weight < 84th percentile				
	Events, n	1672	137	11	
	Person-y	8,286,750	559,708	81,449	
	aHR (95% CI)	1.00 (reference)	1.19 (0.99–1.42)	0.69 (0.38–1.25)	.47
	Weight = 85th–94th percentile				
	Events, n	86	117	51	
	Person-y	345,391	533,281	216,756	
	aHR (95% CI)	1.13 (0.85–1.51)	1.00 (reference)	1.00 (0.72–1.41)	.46
	Weight ≥ 95th percentile				
	Events, n	6	23	88	
	Person-y	28,596	126,740	351,197	
	aHR (95% CI)	0.90 (0.39–2.07)	0.75 (0.48–1.20)	1.00 (reference)	.35

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval.

aHR (95% CI) was calculated using Cox proportional hazards regression analysis after adjusting for sex, birth weight, breastfeeding status, household income, allergic comorbidity (food allergy, allergic rhinitis, asthma, and allergic conjunctivitis), and infectious diseases (respiratory diseases; urinary tract infections; intra-abdominal infections; infections involving the skin, soft tissue, bone, or joint; and other infections).

[1] $P < .05$.

[2] $P < .001$.

Supplementary Table S13. List of ICD-10 Codes for Identifying Infectious Diseases

Infectious Diseases	ICD-10 Code(s)
Respiratory diseases	
Acute upper respiratory infections	J00, J01, J02, J03, J04, J05, J06
Pneumonia and influenza	J09, J10, J11, J12, J13, J14, J15, J16, J17, J18
Chronic bronchitis	J41, J42
Urinary tract infections	
Cystitis	N30
Acute pyelonephritis	N10
Urethritis	N34, N37
Skin, soft tissue, bone, and joint infections	
Cellulitis	L03
Erysipelas	A46
Impetigo	L01
Folliculitis	L66.2, L66.4
Furuncle and carbuncle	L02
Osteomyelitis	M86
Synovitis	M65, M67, M68, M70
Intra-abdominal infections	
Cholecystitis and cholangitis	K80, K81, K83
Appendicitis	K35, K36, K37
Diverticulitis	K57
Peritonitis	K65
Pancreatitis	K85
Others	
Acute/chronic otitis media	H65, H66
Sepsis	A40, A41
Central nervous system infection	A81, A89

Abbreviation: ICD-10, International Classification of Disease, Tenth Revision.