

Original Contribution

Allergy and Risk of Childhood Acute Lymphoblastic Leukemia: A Population-based and Record-based Study

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Initially submitted July 5, 2011; accepted for publication November 9, 2011.

A deficit of normal immune stimulation in early childhood is a suspected risk factor for both childhood acute lymphoblastic leukemia (ALL) and allergies. The present study utilized a population-based case-control design using medical claims data from the National Health Insurance Research Database of Taiwan to evaluate the association between allergy and childhood leukemia. Eight hundred forty-six childhood ALL patients who were newly diagnosed during 2000 to 2008 and were older than 1 but less than 10 years of age were individually matched with 3,374 controls based on sex, birth date, and time of diagnosis (reference date for the controls). Conditional logistic regression was performed to assess the association between childhood ALL and allergies. An increased risk of ALL was observed with having an allergy less than 1 year before the case's ALL diagnosis (odds ratio (OR) = 1.7, 95% confidence interval (CI): 1.5, 2.0), more than 1 year before the case's diagnosis (OR = 1.3, 95% CI: 1.1, 1.5), and before the age of 1 year (OR = 1.4, 95% CI: 1.1, 1.7). These results suggest that the pathogenesis of childhood ALL and allergy share a common biologic mechanism.

allergy; immunology; leukemia

Abbreviations: ALL, acute lymphoblastic leukemia; CI, confidence interval; ICD-9-CM, *International Classification of Diseases*, Ninth Revision, Clinical Modification; IL, interleukin; NHI, National Health Insurance; NHIRD, National Health Insurance Research Database; OR, odds ratio.

Editor's note: An invited commentary on this article appears on page 979, and the authors' response appears on page 984.

Childhood leukemia is the leading cancer among children in the world, accounting for approximately one third of all childhood cancers (1). Although the definitive causes of childhood leukemia are largely unknown, it is thought that a lack of "priming" by infections during early childhood may cause a dysregulated immune response to infections later in childhood, leading to the development of childhood leukemia, particularly acute lymphoblastic leukemia (ALL) (Greaves' "delayed infection" hypothesis) (2). The delayed infection hypothesis is supported by a recent meta-analysis of 14 studies in which Urayama et al. reported an inverse association between day care attendance, a proxy measure of childhood infection, and childhood ALL

(3). In contrast, the association between childhood ALL and birth order (another proxy measure for childhood infection) (4–16) or direct measure of childhood infections (6, 8, 9, 11–13, 17–23) has been less consistent. Medical record-based studies have shown that children with ALL may experience more infectious events in the first year of life, suggesting the presence of immune dysregulation (19, 21, 24). This immune dysregulation may have already existed at birth, as suggested by a recent study in which it was shown that children with ALL had reduced levels of neonatal interleukin (IL)-10 (25), a key regulator for modulating the intensity and duration of immune responses (26).

The underlying biologic mechanism in the delayed infection hypothesis is also applicable to the hygiene hypothesis proposed by Strachan to explain the rising prevalence of allergy in the Western population (27). The hygiene hypothesis has been supported by epidemiologic studies in which an inverse association between allergy and higher

birth order (28–32) or early day care attendance (33, 34) was reported, similar to the associations seen with childhood leukemia. However, in recent studies, it has been reported that infections do not protect against allergy (35–37); in fact, they may even be positively associated with risk of allergy among children (36, 37). In addition, investigators in other studies have suggested the presence of immune dysregulation at birth among children who develop allergies (38, 39).

Given the similarities between the delayed infection hypothesis of childhood leukemia and the hygiene hypothesis of allergy, it is counterintuitive that in the majority of the studies, an inverse association between allergy and childhood leukemia (mostly childhood ALL) (9, 17, 20, 23, 40–44) was observed with only one exception (45). In a recent meta-analysis, Linabery et al. showed that the association between allergy and childhood ALL can be influenced by different study characteristics, including the sources of allergy data (parental report vs. medical records), subject response rates, and the inclusion of a latency period (the time between the occurrence of allergy to the diagnosis of childhood leukemia) (46). Those studies in which investigators used parental-report of the child's allergy, the response rate less than 80%, or researchers did not consider a latency period tended to show a stronger inverse association between allergies and childhood ALL (46).

The present study utilized the population-based and record-based control design to evaluate the association between allergy and childhood leukemia using data from the National Health Insurance Research Database (NHIRD) of Taiwan. This is the third record-based study on this topic; the 2 previous medical-record based studies of allergy and childhood leukemia have reported opposite results (44, 45). In addition, only 1 Asian study on this topic, which had a small sample size (63 ALL cases and 126 controls), has been previously published (40). The present large (846 ALL cases and 3,374 matched controls) Asian population-based and record-based study will provide results that are not affected by a low response rate or recall error and bias.

MATERIALS AND METHODS

Data source

Taiwan's National Health Insurance (NHI) program, which is run by the Bureau of the National Health Insurance, is a single-payer program launched on March 1, 1995, that covers approximately 99% of the 23 million Taiwanese citizens. The insurees of the NHI have access to inpatient care, ambulatory care, dental care, and prescription drugs provided by the health care facilities contracted under the NHI. The claims data of the NHI are routinely monitored by the Bureau of the National Health Insurance for accuracy and completeness (47). The National Health Research Institutes was commissioned by the Bureau of the National Health Insurance to create the NHIRD, a population-based database for medical research using the administrative and health claims data generated by the NHI program.

Subject selection

Two data sets from the NHIRD were used for subject selection. The first was the Catastrophic Illness Dataset, which contained health claims data associated with serious illnesses, including cancer. The second was from the 2005 Longitudinal Health Insurance Database. This was a data set created by randomly sampling 1 million enrollees from the 2005 NHIRD enrollment file. This 1 million-person random sample is representative of the entire insured population of Taiwan.

Because of privacy issues, data in the NHIRD could not be linked to those in the cancer registry. Therefore, children newly diagnosed with ALL (*International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD-9-CM) code 204.0) between January 1, 2000, and December 31, 2008, who were older than 1 year of age and younger than 10 years of age were identified from the Catastrophic Illness Dataset. Patients who are diagnosed with malignant tumors are eligible to apply for a certificate of catastrophic illness to be exempted from all copayments. To apply for the certificate of catastrophic illness, one is required to have an official certificate of diagnosis from the hospital with confirmation by the department of pathology. Therefore, cancer cases identified from the Catastrophic Illness Dataset should be highly accurate and complete. The number of childhood ALL cases identified from the NHIRD were very similar to the number of childhood ALL cases reported by the cancer registry of Taiwan (data not shown). In addition, because of the nearly universal coverage of Taiwan's NHI, the number of childhood ALL cases missed is likely very small. The date of diagnosis was based on the date recorded in the Catastrophic Illness Dataset or the first date of inpatient claims for childhood leukemia, whichever came first. Children diagnosed with ALL at 1 year of age or younger were excluded because infant leukemia has a distinct pathogenesis that is different from noninfant childhood leukemia (48). Children diagnosed with ALL at 10 years of age or older (born before January 1, 1999) were also excluded to allow for a complete exposure assessment from birth to the diagnosis of leukemia (the earliest available data in our database are from January 1, 1999). For each ALL case, up to 4 controls with no history of cancer and individually matched to the case on date of birth, sex, and time of case diagnosis (reference date for the control) were identified from the Longitudinal Health Insurance Database 2005. Because all of the data were obtained from the records in the NHIRD, participation of the study subjects was considered to be 100%. This study was approved by the Institutional Review Board of the National Health Research Institutes, Taiwan.

Data collection

Allergies. History of allergy before the date of case's diagnosis (reference date for the matched controls) was identified from 2 NHIRD files: 1) *Ambulatory Care Expenditures by Visits*; and 2) *Inpatients Expenditures by Admission*. The allergic conditions included allergic rhinitis (ICD-9-CM code 477), asthma (ICD-9-CM code 493),

urticaria (ICD-9-CM code 708), atopic dermatitis (ICD-9-CM code 691), dermatitis due to drugs and medicine taken internally (ICD-9-CM code 693.0), dermatitis due to food taken internally (ICD-9-CM code 693.1), anaphylaxis (ICD-9-CM codes 995.0), angioneurotic edema (ICD-9-CM code 995.1), and unspecified allergy (ICD-9-CM code 995.3). Before 2000, diagnoses in the NHIRD were recorded in A-codes or ICD-9-CM codes (only ICD-9-CM codes have been used since 2000). Because the A-code system groups allergy and other nonallergic conditions under the same code (for example, A-code A319 includes not just allergic rhinitis but also peritonsillar abscess, chronic laryngitis, and other diseases of the upper respiratory tract), it was not possible to determine the definite allergy status for some subjects. For those subjects, an unknown status was given to separate them from the no-allergy group to achieve a more pure comparison group.

Covariates. Potential confounders, including monthly income and levels of urbanization, were determined by the following methods. Income-related insurance amount of the parent (either the father or the mother) was used as a proxy for monthly income, with 17,880 New Taiwanese Dollars being the lowest income-related insurance amount (approximately 623 \$US). City of residence was used to determine the level of urbanization according to the categorization scheme developed in a previous study (49).

Statistical analysis

Chi-squared tests were used to compare the distributions of income-related insurance amount with urbanization levels. Conditional logistic regression was performed to generate odds ratios and 95% confidence interval estimating the risk of ALL associated with having any allergy (yes vs. no), the number of allergies (0, 1, 2, or ≥ 3), and specific types of allergies (allergic rhinitis, asthma, urticaria, and atopic dermatitis). Dermatitis due to drugs and medicine taken internally, dermatitis due to food taken internally, anaphylaxis, angioneurotic edema, and unspecified allergy had too few exposed subjects for separate analyses. The interpretation of the odds ratios comparing the unknown allergy status group with the no allergy group may not be meaningful and is not recommended. The association between allergy and childhood ALL was examined by time of allergy occurrence: before 1 year of age, less than 1 year before diagnosis of childhood leukemia, or more than 1 year before diagnosis of childhood leukemia (reference date for the matched controls). Subjects diagnosed at 2 years of age or younger were excluded from analysis of allergy occurring more than 1 year before diagnosis. Allergy occurring before 1 year of age was used as an indicator for immune development during infancy. Allergies occurring more than 1 year before the case's diagnosis of childhood leukemia were considered as a primary risk variable to avoid reverse causality due to the influence of childhood leukemia on immune function.

Additional analyses were performed by age groups (ages 2–5.9 years vs. ages 6–9.9 years) and by urbanization levels (high urbanization vs. low urbanization). Childhood ALL diagnosed at ages 2–5.9 years is particularly thought

to have an immune-related etiology (2). Urban status may affect a child's early immune development because of different levels of exposure to microbial challenges and has been shown to influence the occurrence of allergies (50, 51). The heterogeneity of the associations between allergies and childhood leukemia by age groups or urbanization levels were assessed using the log-likelihood ratio test comparing the conditional logistic regression model with the interaction term (allergy $\times$ age groups or allergy $\times$ urbanization level) to the model without the interaction term. Because adjustment for income-related insurance amount and urbanization levels produced odds ratios that were almost identical as those without adjustment, only the unadjusted results are presented here.

RESULTS

A total of 846 children with ALL and 3,374 matched controls older than 1 but less than 10 years of age were identified. The majority of the children in the present analysis were diagnosed between 2 and 5.9 years of age (63%) (Table 1). There were more males than females (58% males). The distributions of income-related insurance amount and urbanization levels did not differ significantly between cases and controls.

The strongest association with allergy was observed within 1 year before the case's diagnosis (reference date for the controls) (Table 2), with an increased risk of ALL associated with having any allergy (odds ratio (OR) = 1.72, 95% confidence interval (CI): 1.46, 2.03), the number of allergies (OR = 1.39, 95% CI: 1.24, 1.54), allergic rhinitis (OR = 1.65, 95% CI: 1.35, 2.02), asthma (OR = 1.43, 95% CI: 1.10, 1.85), and urticaria (OR = 1.64, 95% CI: 1.25, 2.16). The positive associations between childhood ALL and allergy were attenuated for allergies occurring more than 1 year before the case's diagnosis but were nevertheless statistically significant for having any allergy (OR = 1.29, 95% CI: 1.08, 1.53), the number of allergies (OR = 1.16, 95% CI: 1.05, 1.27), urticaria (OR = 1.28, 95% CI: 1.02, 1.60), and atopic dermatitis (OR = 1.33, 95% CI: 1.08, 1.64). For allergies diagnosed before 1 year of age, a significant positive association was observed for having any allergy (OR = 1.36, 95% CI: 1.11, 1.67), the number of allergies (OR = 1.20, 95% CI: 1.04, 1.40), and atopic dermatitis (OR = 1.33, 95% CI: 1.05, 1.69).

The association between allergy and childhood leukemia did not differ significantly by age groups according to the tests of heterogeneity (Table 3). No significant interaction between urbanization level and having any allergy on the risk of childhood leukemia was noted (Table 4).

DISCUSSION

In the present study, childhood ALL was positively associated with having allergies before 1 year of age, less than 1 year before diagnosis, and more than 1 year before diagnosis (reference date for the controls). This positive association between childhood ALL and allergies is contrary to the results of most previous studies (9, 17, 20, 23, 40–44). The inconsistency may be partly explained by the sources

Table 1. Characteristics of Childhood Acute Lymphoblastic Leukemia Cases and Controls, Taiwan, 2000–2008

Characteristics	Cases (n = 846)		Controls (n = 3,374)		P Value ^a
	No.	%	No.	%	
Age, years ^b					
1 to <2	84	9.9	331	9.8	
2 to <6	532	62.9	2,124	63.0	
6 to <10	230	27.2	919	27.2	
Sex ^b					
Male	487	57.6	1,943	57.6	
Female	359	42.4	1,431	42.4	
Income-related insurance amount, \$NT					0.11
<17,881	201	23.9	810	24.0	
17,881–30,000	383	45.5	1,421	42.1	
30,001–40,000	84	10.0	443	13.1	
40,001–50,000	94	11.1	407	12.1	
50,001–60,000	43	5.1	150	4.5	
60,001–70,000	26	3.1	82	2.4	
>70,000	11	1.3	60	1.8	
Urbanization level					0.70
1 (high)	255	30.1	959	28.4	
2	226	26.7	898	26.6	
3	157	18.6	652	19.3	
4	104	12.3	459	13.6	
5	20	2.4	69	2.1	
6	22	2.6	118	3.5	
7 (low)	34	4.0	127	3.8	
Unknown	28	3.3	92	2.7	

Abbreviation: \$NT, New Taiwanese Dollar.

^a P values were derived using χ^2 tests.^b Matching variable.

of exposure data (medical records vs. parental report), participation rate, and exposure latency. In a meta-analysis of childhood leukemia and allergies, Linabery et al. showed that an inverse association between childhood ALL and allergies is mostly reported by studies that used parental report, had a participation rate less than 80%, and did not account for the exposure latency (46).

A major strength of the present study is the use of medical records, which are not subject to recall errors and recall bias. Parents of cases may be more likely to ruminate about potential factors that may have caused their children to develop leukemia, leading to a false positive association. However, Schüz et al. pointed out that because parents of controls don't have a clear date of reference (date of diagnosis for the corresponding leukemic children), they may tend to over-report exposures occurring after the date of reference (43). This may partially explain the higher prevalence of allergies among controls in studies that relied on parent-reported data. Hughes et al. compared a child's

eczema or asthma recorded in the medical records with that reported by the parents and found only moderate agreement (kappa ranged from 0.45 to 0.69) (44). Thus, results on the association between allergy and childhood leukemia based on parental-reported data may be misleading. In 1 of the 2 previous studies that used data from medical records, having atopy or hives was associated with an increased risk of childhood ALL (45). The other medical record-based study did find an inverse association between allergies and childhood leukemia; however, incomplete participation (70% of the controls with available medical records) may have affected the results of that study (44).

Participation rate is another major issue that may potentially bias the results of a case-control study. This is not an issue with the present study, as the participation rate was 100% for both cases and controls, with the complete ascertainment of medical records. A low participation rate may distort the relation between allergies and childhood ALL when participants and nonparticipants differ in characteristics that may be associated with both allergy status and the risk of childhood ALL.

Our results demonstrated the strongest association between allergy and childhood ALL for allergies that occurred within 1 year before the diagnosis of ALL. The increased allergy/leukemia association proximal to diagnosis of leukemia (irrespective of histologic subtypes) is suggestive of reverse causality and indicates the need for censoring of such data when disease etiology is examined. Alternatively, children with leukemia may be more likely to be diagnosed with other medical conditions while visiting hospitals for symptoms related to the development of leukemia (diagnostic bias). The positive association between allergy and childhood ALL still holds when we only consider the allergies occurring more than 1 year before the case's diagnosis and before 1 year of age, indicating that reverse causality and diagnostic bias are unlikely.

The positive association between allergy and childhood ALL suggest that the 2 diseases may involve a common biologic mechanism. Two paradigms, "missing immune deviation" and "reduced immune suppression," have been proposed to explain the biologic basis of hygiene hypothesis (52). A key cytokine in the missing immune deviation is IL-12, which is produced by the innate immune cells (e.g., dendritic cells) in response to microbial challenges (52). IL-12 is important for the normal immune development that shifts the immune profile from T-helper 2 dominant among newborns to T-helper 1 dominant with increasing age (52–54). The absence of this shift and the presence of a T-helper 2-dominant immune profile are associated with an increased risk of allergy. IL-12 also appears important for childhood ALL. A previous study reported that the variant G allele of the single nucleotide polymorphism rs583911 of the interleukin 12A gene, which codes for a part of IL-12 cytokine, is associated with an increased risk of childhood ALL (55). The increased risk was stronger among children who had less opportunity for microbial challenges (first born children and those with less day care attendance). (55). In the reduced immune suppression hypothesis, the increased risk of allergy occurs when decreased microbial exposures results in reduced stimulation

Table 2. Association Between Childhood Acute Lymphoblastic Leukemia and Allergies Diagnosed During Different Time Periods, Taiwan, 2000–2008

	Before 1 Year of Age				<1 Year Before Diagnosis				>1 Year Before Diagnosis			
	No. of Cases (n = 846)	No. of Controls (n = 3,374)	OR ^a	95% CI ^a	No. of Cases (n = 846)	No. of Controls (n = 3,374)	OR ^a	95% CI ^a	No. of Cases ^b (n = 762)	No. of Controls ^b (n = 3,043)	OR ^a	95% CI ^a
Any allergy ^c												
No	651	2,728	1	Referent	548	2,513	1	Referent	393	1,713	1	Referent
Yes	178	573	1.36	1.11, 1.67	295	812	1.72	1.46, 2.03	339	1,190	1.29	1.08, 1.53
Unknown	17	73	0.97	0.56, 1.71	3	49	0.26	0.08, 0.86	30	140	0.91	0.60, 1.39
Number of allergies												
0	668	2,801	1	Referent	551	2,562	1	Referent	423	1,853	1	Referent
1	147	465	1.39	1.11, 1.73	210	580	1.73	1.44, 2.09	192	691	1.26	1.03, 1.54
2	28	93	1.32	0.85, 2.04	68	191	1.71	1.27, 2.30	93	340	1.26	0.97, 1.63
≥3	3	15	0.85	0.24, 2.97	17	41	2.05	1.15, 3.67	54	159	1.59	1.13, 2.25
Ordinal				1.04, 1.40			1.39	1.24, 1.54			1.16	1.05, 1.27
Allergic rhinitis												
Ao	810	3,228	1	Referent	680	2,917	1	Referent	613	2,449	1	Referent
Yes	32	125	1.02	0.69, 1.52	165	437	1.65	1.35, 2.02	140	536	1.05	0.85, 1.30
Unknown	4	21	0.75	0.25, 2.25	1	20	0.22	0.03, 1.63	9	58	0.61	0.29, 1.24
Asthma												
No	819	3,254	1	Referent	759	3,105	1	Referent	633	2,579	1	Referent
Yes	22	99	0.88	0.55, 1.42	87	252	1.43	1.10, 1.85	123	410	1.24	0.99, 1.55
Unknown	5	21	0.94	0.35, 2.51	0	17	N/A	N/A	6	54	0.45	0.19, 1.04
Urticaria												
No	793	3,220	1	Referent	764	3,157	1	Referent	608	2,524	1	Referent
Yes	35	102	1.40	0.94, 2.08	79	201	1.64	1.25, 2.16	118	387	1.28	1.02, 1.60
Unknown	18	52	1.46	0.82, 1.60	3	16	0.73	0.21, 2.63	36	132	1.13	0.76, 1.67
Atopic dermatitis												
No	717	2,961	1	Referent	788	3,172	1	Referent	570	2,400	1	Referent
Yes	115	366	1.33	1.05, 1.69	55	187	1.20	0.87, 1.66	158	514	1.33	1.08, 1.64
Unknown	14	47	1.25	0.66, 2.37	3	15	0.80	0.23, 2.85	34	129	1.09	0.73, 1.63

Abbreviations: CI, confidence interval; N/A, not applicable; OR, odds ratio.

^a ORs and 95% CIs were calculated using conditional logistic regression with age, sex, and the time of diagnosis (reference date for the controls) as the matching variables.^b Subjects diagnosed with leukemia at 2 years of age or younger and the matched controls were excluded from analysis of allergy occurring more than 1 year before diagnosis.^c Any allergy includes allergic rhinitis, asthma, urticaria, atopic dermatitis, dermatitis due to drugs and medicine taken internally, dermatitis due to food taken internally, anaphylaxis, angioneurotic edema, and unspecified allergy.

Table 3. Association Between Childhood Acute Lymphoblastic Leukemia and Having Any Allergy Diagnosed During Different Time Periods by Age Groups, Taiwan, 2000–2008

Time Period of Allergy Development ^a	2–5.9 Years Old		6–9.9 Years Old		P for Interaction
	OR ^b	95% CI ^b	OR ^b	95% CI ^b	
Before 1 year old	1.40	1.10, 1.78	1.62	0.86, 3.04	0.67
<1 year before diagnosis	1.82	1.48, 2.24	1.29	0.91, 1.82	0.09
>1 year before diagnosis	1.29	1.04, 1.59	1.22	0.89, 1.67	0.77

Abbreviations: CI, confidence interval; OR, odds ratio.

^a Any allergy includes allergic rhinitis, asthma, urticaria, atopic dermatitis, dermatitis due to drugs and medicine taken internally, dermatitis due to food taken internally, anaphylaxis, angioneurotic edema, and unspecified allergy.

^b ORs and 95% CIs were calculated using conditional logistic regression with age, sex, and the time of diagnosis (reference date for the controls) as the matching variables.

of T-regulatory cells, which function to prevent over-reactive immune response (52). A recent study showed that children with ALL had a lower IL-10 level at birth than did healthy children (25). Although IL-10 can be produced by many cell types, it is produced at particularly high levels by a type of T-regulatory cell known as T-regulatory 1 to suppress overactive immune reaction (56). An overactive and dysregulated immune reaction in response to pathogens may lead to the expansion of a preleukemic clone, resulting in the occurrence of additional mutations and the development of childhood leukemia (2).

Allergy occurring before 1 year of age may indicate the presence of dysregulated immune function at birth. The dysregulated immune response may result in more serious infectious symptoms that require medical attention, possibly leading to children who develop eczema or childhood ALL having more infections clinically diagnosed before eczema and ALL onset (36, 44). Cord blood samples of children with allergy have exhibited a lower immune response of a T-helper 1 cytokine, interferon- γ , and the T regulatory 1-related cytokine IL-10 compared with healthy children without allergies (38, 39). As previously mentioned, children

Table 4. Relation of Urbanization Level and Allergy to the Risk of Childhood Acute Lymphoblastic Leukemia, Taiwan, 2000–2008

Urbanization Level by Time Period	Any Allergy ^a	No. of Cases	No. of Controls	OR ^b	95% CI ^b	P for Interaction
Before 1 year of age						0.40
3–7 (low)	No	266	1,146	1	Referent	
3–7 (low)	Yes	66	246	1.24	0.90, 1.70	
1 or 2 (high)	No	363	1,504	1.04	0.87, 1.24	
1 or 2 (high)	Yes	107	315	1.52	1.16, 1.99	
<1 year before diagnosis						0.49
3–7 (low)	No	228	1,070	1	Referent	
3–7 (low)	Yes	108	331	1.61	1.23, 2.10	
1 or 2 (high)	No	301	1,373	1.04	0.86, 1.26	
1 or 2 (high)	Yes	178	459	1.90	1.50, 2.39	
>1 year before diagnosis						0.10
3–7 (low)	No	166	713	1	Referent	
3–7 (low)	Yes	127	516	1.08	0.83, 1.41	
1 or 2 (high)	No	213	951	0.95	0.76, 1.19	
1 or 2 (high)	Yes	205	647	1.37	1.07, 1.74	

Abbreviations: CI, confidence interval; OR, odds ratio.

^a Any allergy includes allergic rhinitis, asthma, urticaria, atopic dermatitis, dermatitis due to drugs and medicine taken internally, dermatitis due to food taken internally, anaphylaxis, angioneurotic edema, and unspecified allergy.

^b ORs and 95% CIs were calculated using conditional logistic regression with age, sex, and the time of diagnosis (reference date for the controls) as the matching variables.

with ALL have a lower IL-10 level at birth than do healthy children (25). The presence of dysregulated immune function at birth also suggests the influence of maternal factors. Children born of mothers with allergies are more likely to have impairment of T-regulatory cells (57) and a decreased ability to respond to microbial challenges (58). Similarly, higher maternal serum immunoglobulin E, an indicator of maternal allergy status, was associated with a higher risk of childhood ALL (59).

Results of the present analysis must be interpreted in the context of several limitations. The NHIRD does not have information on the immunologic subtypes (T cell vs. B cell) or molecular subtypes of childhood ALL (e.g., hyperdiploidy, *TEL-AML1* translocation) to allow for analysis by these subtypes. Because the analyses were based on health claims data, allergies of persons who did not visit health care facilities due to less severe symptoms were not documented; however, this misclassification is likely nondifferential (at least for before 1 year of age and more than 1 year before the case's diagnosis) and would have biased the results toward the null. Finally, we tried to be as inclusive as possible with the allergic conditions; however, the allergic conditions included in the current study may be different from those covered in the previous studies of childhood leukemia and allergies, which may be an additional source of heterogeneity across studies.

In conclusion, the present study suggests that the pathogenesis of childhood ALL and allergies may share a common biologic mechanism.

ACKNOWLEDGMENTS

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Dr. Jeffrey S. Chang was supported by the National Science Council of Taiwan (grant NSC 99-2314-B-400-004) and the Department of Health, Taiwan (DOH101-TD-C-111-004). Dr. Joseph L. Wiemels was supported by the Leukemia and Lymphoma Society of America (grant 6026-10).

This study was based in part on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health, Taiwan, Republic of China, and managed by National Health Research Institutes. The interpretation and conclusions contained herein do not represent those of Bureau of National Health Insurance, Department of Health, Taiwan, Republic of China, or National Health Research Institutes.

Conflict of interest: none declared.

REFERENCES

1. Stiller CA, Parkin DM. Geographic and ethnic variations in the incidence of childhood cancer. *Br Med Bull.* 1996; 52(4):682–703.
2. Greaves M. Infection, immune responses and the aetiology of childhood leukaemia. *Nat Rev Cancer.* 2006;6(3):193–203.
3. Urayama KY, Buffler PA, Gallagher ER, et al. A meta-analysis of the association between day-care attendance and childhood acute lymphoblastic leukaemia. *Int J Epidemiol.* 2010;39(3):718–732.
4. Dockerty JD, Draper G, Vincent T, et al. Case-control study of parental age, parity and socioeconomic level in relation to childhood cancers. *Int J Epidemiol.* 2001;30(6):1428–1437.
5. Hjalgrim LL, Rostgaard K, Hjalgrim H, et al. Birth weight and risk for childhood leukemia in Denmark, Sweden, Norway, and Iceland. *J Natl Cancer Inst.* 2004;96(20):1549–1556.
6. Urayama KY, Ma X, Selvin S, et al. Early life exposure to infections and risk of childhood acute lymphoblastic leukemia. *Int J Cancer.* 2011;128(7):1632–1643.
7. Schuz J, Kaatsch P, Kaletsch U, et al. Association of childhood cancer with factors related to pregnancy and birth. *Int J Epidemiol.* 1999;28(4):631–639.
8. van Steensel-Moll HA, Valkenburg HA, van Zanen GE. Childhood leukemia and infectious diseases in the first year of life: a register-based case-control study. *Am J Epidemiol.* 1986;124(4):590–594.
9. Jourdan-Da Silva N, Perel Y, Mechinaud F, et al. Infectious diseases in the first year of life, perinatal characteristics and childhood acute leukaemia. *Br J Cancer.* 2004;90(1):139–145.
10. Ou SX, Han D, Severson RK, et al. Birth characteristics, maternal reproductive history, hormone use during pregnancy, and risk of childhood acute lymphocytic leukemia by immunophenotype (United States). *Cancer Causes Control.* 2002;13(1):15–25.
11. Perrillat F, Clavel J, Auclerc MF, et al. Day-care, early common infections and childhood acute leukaemia: a multicentre French case-control study. *Br J Cancer.* 2002;86(7):1064–1069.
12. Dockerty JD, Skegg DC, Elwood JM, et al. Infections, vaccinations, and the risk of childhood leukaemia. *Br J Cancer.* 1999;80(9):1483–1489.
13. Neglia JP, Linet MS, Shu XO, et al. Patterns of infection and day care utilization and risk of childhood acute lymphoblastic leukaemia. *Br J Cancer.* 2000;82(1):234–240.
14. Reynolds P, Von Behren J, Elkin EP. Birth characteristics and leukemia in young children. *Am J Epidemiol.* 2002;155(7):603–613.
15. Rosenbaum PF, Buck GM, Brecher ML. Early child-care and preschool experiences and the risk of childhood acute lymphoblastic leukemia. *Am J Epidemiol.* 2000;152(12):1136–1144.
16. Von Behren J, Spector LG, Mueller BA, et al. Birth order and risk of childhood cancer: a pooled analysis from five US States. *Int J Cancer.* 2011;128(11):2709–2716.
17. Schuz J, Kaletsch U, Meinert R, et al. Association of childhood leukaemia with factors related to the immune system. *Br J Cancer.* 1999;80(3–4):585–590.
18. Chan LC, Lam TH, Li CK, et al. Is the timing of exposure to infection a major determinant of acute lymphoblastic leukaemia in Hong Kong? *Paediatr Perinat Epidemiol.* 2002;16(2):154–165.
19. Roman E, Simpson J, Ansell P, et al. Childhood acute lymphoblastic leukemia and infections in the first year of life: a report from the United Kingdom Childhood Cancer Study. *Am J Epidemiol.* 2007;165(5):496–504.

20. Rosenbaum PF, Buck GM, Brecher ML. Allergy and infectious disease histories and the risk of childhood acute lymphoblastic leukaemia. *Paediatr Perinat Epidemiol.* 2005;19(2):152–164.
21. Cardwell CR, McKinney PA, Patterson CC, et al. Infections in early life and childhood leukaemia risk: a UK case-control study of general practitioner records. *Br J Cancer.* 2008; 99(9):1529–1533.
22. MacArthur AC, McBride ML, Spinelli JJ, et al. Risk of childhood leukemia associated with vaccination, infection, and medication use in childhood: the Cross-Canada Childhood Leukemia Study. *Am J Epidemiol.* 2008;167(5):598–606.
23. Rudant J, Orsi L, Menegaux F, et al. Childhood acute leukemia, early common infections, and allergy: The ESCALE Study. *Am J Epidemiol.* 2010;172(9):1015–1027.
24. Simpson J, Smith A, Ansell P, et al. Childhood leukaemia and infectious exposure: a report from the United Kingdom Childhood Cancer Study (UKCCS). *Eur J Cancer.* 2007; 43(16):2396–2403.
25. Chang JS, Zhou M, Buffler PA, et al. Profound deficit of IL10 at birth in children who develop childhood acute lymphoblastic leukemia. *Cancer Epidemiol Biomarkers Prev.* 2011;20(8):1736–1740.
26. Couper KN, Blount DG, Riley EM. IL-10: the master regulator of immunity to infection. *J Immunol.* 2008; 180(9):5771–5777.
27. Strachan DP. Hay fever, hygiene, and household size. *BMJ.* 1989;299(6710):1259–1260.
28. Westergaard T, Rostgaard K, Wohlfahrt J, et al. Sibship characteristics and risk of allergic rhinitis and asthma. *Am J Epidemiol.* 2005;162(2):125–132.
29. Bernsen RM, de Jongste JC, van der Wouden JC. Birth order and sibship size as independent risk factors for asthma, allergy, and eczema. *Pediatr Allergy Immunol.* 2003; 14(6):464–469.
30. Lewis SA, Britton JR. Consistent effects of high socioeconomic status and low birth order, and the modifying effect of maternal smoking on the risk of allergic disease during childhood. *Respir Med.* 1998;92(10):1237–1244.
31. Matricardi PM, Franzinelli F, Franco A, et al. Sibship size, birth order, and atopy in 11,371 Italian young men. *J Allergy Clin Immunol.* 1998;101(4):439–444.
32. Strachan DP, Taylor EM, Carpenter RG. Family structure, neonatal infection, and hay fever in adolescence. *Arch Dis Child.* 1996;74(5):422–426.
33. Haby MM, Marks GB, Peat JK, et al. Daycare attendance before the age of two protects against atopy in preschool age children. *Pediatr Pulmonol.* 2000;30(5):377–384.
34. Kramer U, Heinrich J, Wjst M, et al. Age of entry to day nursery and allergy in later childhood. *Lancet.* 1999; 353(9151):450–454.
35. Bremner SA, Carey IM, DeWilde S, et al. Infections presenting for clinical care in early life and later risk of hay fever in two UK birth cohorts. *Allergy.* 2008;63(3):274–283.
36. Hughes AM, Crouch S, Lightfoot T, et al. Eczema, birth order, and infection. *Am J Epidemiol.* 2008;167(10):1182–1187.
37. Michos A, Terzidis A, Kanariou M, et al. Association of allergic sensitization with infectious diseases burden in Roma and non-Roma children. *Pediatr Allergy Immunol.* 2011; 22(2):243–248.
38. Kondo N, Kobayashi Y, Shinoda S, et al. Reduced interferon gamma production by antigen-stimulated cord blood mononuclear cells is a risk factor of allergic disorders: 6-year follow-up study. *Clin Exp Allergy.* 1998;28(11):1340–1344.
39. Neaville WA, Tisler C, Bhattacharya A, et al. Developmental cytokine response profiles and the clinical and immunologic expression of atopy during the first year of life. *J Allergy Clin Immunol.* 2003;112(4):740–746.
40. Nishi M, Miyake H. A case-control study of non-T cell acute lymphoblastic leukaemia of children in Hokkaido, Japan. *J Epidemiol Community Health.* 1989;43(4): 352–355.
41. Petridou E, Trichopoulos D, Kalapothaki V, et al. The risk profile of childhood leukaemia in Greece: a nationwide case-control study. *Br J Cancer.* 1997;76(9):1241–1247.
42. Wen W, Shu XO, Linet MS, et al. Allergic disorders and the risk of childhood acute lymphoblastic leukemia (United States). *Cancer Causes Control.* 2000;11(4): 303–307.
43. Schuz J, Morgan G, Bohler E, et al. Atopic disease and childhood acute lymphoblastic leukemia. *Int J Cancer.* 2003;105(2):255–260.
44. Hughes AM, Lightfoot T, Simpson J, et al. Allergy and risk of childhood leukaemia: Results from the UKCCS. *Int J Cancer.* 2007;121(4):819–824.
45. Spector L, Groves F, DeStefano F, et al. Medically recorded allergies and the risk of childhood acute lymphoblastic leukaemia. *Eur J Cancer.* 2004;40(4):579–584.
46. Linabery AM, Jurek AM, Duval S, et al. The association between atopy and childhood/adolescent leukemia: a meta-analysis. *Am J Epidemiol.* 2010;171(7):749–764.
47. Bureau of National Health Insurance, Department of Health, Taiwan, Republic of China. *National Health Insurance in Taiwan 2010.* Taipei, Taiwan: Bureau of National Health Insurance; 2010. (http://www.nhi.gov.tw/English/webdata/webdata.aspx?menu=11&menu_id=290&webdata_id=2974&WD_ID=290). (Accessed June 8, 2011).
48. Ries LAG, Smith MA, Gurney JG, et al. eds. *Cancer Incidence and Survival Among Children and Adolescents: United States SEER Program 1975–1995.* NIH Pub. No. 99–4649. Bethesda, MD: National Cancer Institute; 1999.
49. Liu CY, Hung YT, Chuang YL, et al. Incorporating development stratification of Taiwan townships into sampling design of large scale health interview survey. *J Health Manag.* 2006;4(1):1–22.
50. Schram ME, Tedja AM, Spijker R, et al. Is there a rural/urban gradient in the prevalence of eczema? A systematic review. *Br J Dermatol.* 2010;162(5):964–973.
51. Majkowska-Wojciechowska B, Pelka J, Korzon L, et al. Prevalence of allergy, patterns of allergic sensitization and allergy risk factors in rural and urban children. *Allergy.* 2007;62(9):1044–1050.
52. Romagnani S. The increased prevalence of allergy and the hygiene hypothesis: missing immune deviation, reduced immune suppression, or both? *Immunology.* 2004; 112(3):352–363.
53. Prescott SL, Macaubas C, Holt BJ, et al. Transplacental priming of the human immune system to environmental allergens: universal skewing of initial T cell responses toward the Th2 cytokine profile. *J Immunol.* 1998;160(10): 4730–4737.
54. Prescott SL, Macaubas C, Smallacombe T, et al. Reciprocal age-related patterns of allergen-specific T-cell immunity in normal vs. atopic infants. *Clin Exp Allergy.* 1998; 28(suppl 5):39–44.
55. Chang JS, Wiemels JL, Chokkalingam AP, et al. Genetic polymorphisms in adaptive immunity genes and childhood

- acute lymphoblastic leukemia. *Cancer Epidemiol Biomarkers Prev.* 2010;19(9):2152–2163.
56. Allan SE, Broady R, Gregori S, et al. CD4+ T-regulatory cells: toward therapy for human diseases. *Immunol Rev.* 2008;223(1):391–421.
57. Schaub B, Liu J, Hoppler S, et al. Impairment of T-regulatory cells in cord blood of atopic mothers. *J Allergy Clin Immunol.* 2008;121(6):1491–1499.
58. Amoudruz P, Holmlund U, Malmstrom V, et al. Neonatal immune responses to microbial stimuli: is there an influence of maternal allergy? *J Allergy Clin Immunol.* 2005;115(6):1304–1310.
59. Chang JS, Buffler PA, Metayer C, et al. Maternal immunoglobulin E and childhood leukemia. *Cancer Epidemiol Biomarkers Prev.* 2009;18(8):2221–2227.