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ORIGINAL RESEARCH

Association of Familial History of Diabetes, Hypertension, Dyslipidemia, Stroke, or Myocardial Infarction With Risk of Kawasaki Disease

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BACKGROUND: There are few studies on the association with Kawasaki disease in children and the family's history of cardiovascular disease (CVD). The aim of this study was to identify the association of increased risks for Kawasaki disease in children with a family history of CVD.

METHODS AND RESULTS: Clinical data of children born in 2008 and 2009 (n=917 707) were obtained from the National Health Insurance Service and the National Health Screening Program for Infants and Children for this study. The cohort consisted of 495 215 participants (53.8%) who completed the family history questionnaire for children 54 to 60 months old. Family history of CVD included 5 medical conditions: hypertension, dyslipidemia, myocardial infarction, stroke, and diabetes. Kawasaki disease was defined using the disease code, intravenous immunoglobulin prescription, and use of antipyretics for more than 25 days. Severe Kawasaki disease was defined as diagnosis of accompanied cardiac/coronary artery complications or intravenous immunoglobulin use ≥2 times. The incidence rate of Kawasaki disease was 124/100 000 person-years (95% CI, 117.5–131.5) for children <2 years old, 95/100 000 person-years (95% CI, 90.5–100.4) in children 2 to 5 years old, and 14/100 000 person-years (95% CI, 12.6–15.6) in children >5 years old. After propensity-score matching, 829 participants with a family history of CVD were diagnosed as having Kawasaki disease (0.68% [95% CI, 0.63–0.72]), and 690 patients with Kawasaki disease (0.56% [95% CI, 0.52–0.61]) had no family history of CVD. The family history of CVD was associated with increased risk for Kawasaki disease (risk ratio, 1.20 [95% CI, 1.08–1.32]) but not for severe Kawasaki disease (risk ratio, 1.23 [95% CI, 0.92–1.65]).

CONCLUSIONS: In this nationwide propensity-score matched study, those with a family history of CVD had a significantly greater risk of Kawasaki disease compared with those who had no family history of CVD.

Key Words: cardiovascular disease ■ family history ■ Kawasaki disease

Kawasaki disease (KD) is an acute febrile disease that causes systemic inflammation of all medium arteries and multiple organs and tissues.[1] This disease is the most common cause of childhood-acquired heart disease in most industrialized countries.[2] The incidence rate of KD is increasing, but despite 40 years of investigation, the cause of KD remains unknown.[3] Environmental toxin exposure, autoimmune causes, and infectious diseases are the most widely proposed theories. Epidemiological clustering (such as seasonal variation) suggests that infection may be the main trigger factor of KD, although unique specific microorganisms have not yet been identified.[4,5]

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CLINICAL PERSPECTIVE

What Is New?

- In this nationwide propensity-score matched study, those who had a family history of cardiovascular disease had a significantly increased risk of Kawasaki disease (KD) compared with those who had no family history of cardiovascular disease.
- However, family history of cardiovascular disease was not associated with severe KD.

What Are the Clinical Implications?

- Although the cause of KD is still unknown, a family history of cardiovascular disease was significantly associated with an increased risk of KD, suggesting that genetic predisposition is important in the pathogenesis of KD.

Nonstandard Abbreviations and Acronyms

KD	Kawasaki disease

Recently, host genetic factors may be involved in the pathophysiology of KD, which results in activation of the innate immune system.[6] The high prevalence of KD in Asian populations, especially Korean and Japanese children, strongly supports the genetic predisposition for the onset of KD. For decades, KD researchers have attempted to identify candidate genes that induce susceptibility to the disease, particularly human leukocyte antigens. However, those approaches could not model the possible causations at the current state of research.[7] Definitive research results are still lacking. Some studies have shown an increase in the incidence of KD history among parents of patients with KD and siblings and extended family members in index cases.[8,9] One study reported that genetic predisposition and family pattern may be related to its occurrence.[10]

Family history of cardiovascular disease (CVD) is important and is considered a risk factor for a patient developing KD.[11] Nevertheless, there are few studies on the association of KD and a family`s CVD history. Some study results revealed higher incidence of ischemic heart disease in fathers of the subjects with severe KD.[12] In this study we identify the risk factors for KD in children with a family history of CVD from a propensity-score matched analysis in a national cohort.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Data Source

Data were obtained from the National Investigation of Birth Cohort in Korea study.[13] This large-scale cohort provided retrospective administrative data of 919 707 participants who were born in 2008 (n=469 248) and 2009 (n=448 459) in the Republic of Korea (hereinafter Korea). This birth cohort included information from the National Health Screening Program for Infants and Children and medical use obtained through the National Health Insurance Service in Korea. The deidentified individual keys can be used for research purposes to secure ethical clearance under the current National Health Insurance Act,[14] and the protocol of this study was reviewed and approved by the institutional review board of the Korea National Institute for Bioethics Policy (P01-201603-21-005). Informed consent in this study was not required.

We analyzed those who participated in the sixth round of the screening program (conducted in children 54–60 months old). The questionnaire includeed items about family history of CVD from the data in the National Health Screening Program for Infants and Children as well as history of hypertension, dyslipidemia, myocardial infarction, stroke, and diabetes.[15]

Using the National Health Insurance Service data, we selected patients who were prescribed intravenous immunoglobulin (IVIG) medication and aspirin with the diagnosis of KD (*International Classification of Diseases, Tenth Revision* [*ICD-10*] code M30.3).[16]

Study Population

The cohort consisted of 495 215 participants (53.8%) who answered the family history questionnaire including 919 707 children in Korea. Patients who did not answer the family history questionnaire (n=411 206) or who did not properly respond to the question on family history (n=11 286) were excluded. Among the participants who answered the family history questionnaire, propensity-score matching (maximum 1:1) was done for participants who had a family history of CVD and participants who did not. Among the 495 215 participants, 269 609 children had a family history of CVD. Propensity-score matching (maximum 1:1) was done to assign 122 669 participants to each group who had a family history of CVD and who did not. We selected the participants diagnosed with KD who fit our definition using National Health Insurance Service data and divided them into 2 groups, KD with and without a family history of CVD. The flowchart of participants through the study is shown in the Figure.

Exposure

There were 5 medical conditions for family history on the CVD questionnaire, which were

hypertension, dyslipidemia, myocardial infarction, stroke, and diabetes. The scope of the relationship with the family history includes not only the parents but also the grandparents. The questionnaire was completed by a guardian.[17] If the guardian answered that there is 1 medical condition in the family history, the family history was positive, and if there was no relationship at all, the family history was classified as negative.

Outcomes Measures

The primary outcome was to evaluate the association between KD development in children with a family history of CVD. A KD diagnosis was defined as someone who received IVIG and antipyretics containing aspirin for >25 days (*ICD-10* code M30.3). It was possible to define KD using the *ICD-10* diagnostic code and IVIG use, but in our study, days of aspirin use were included to apply a more stringent diagnostic criterion.

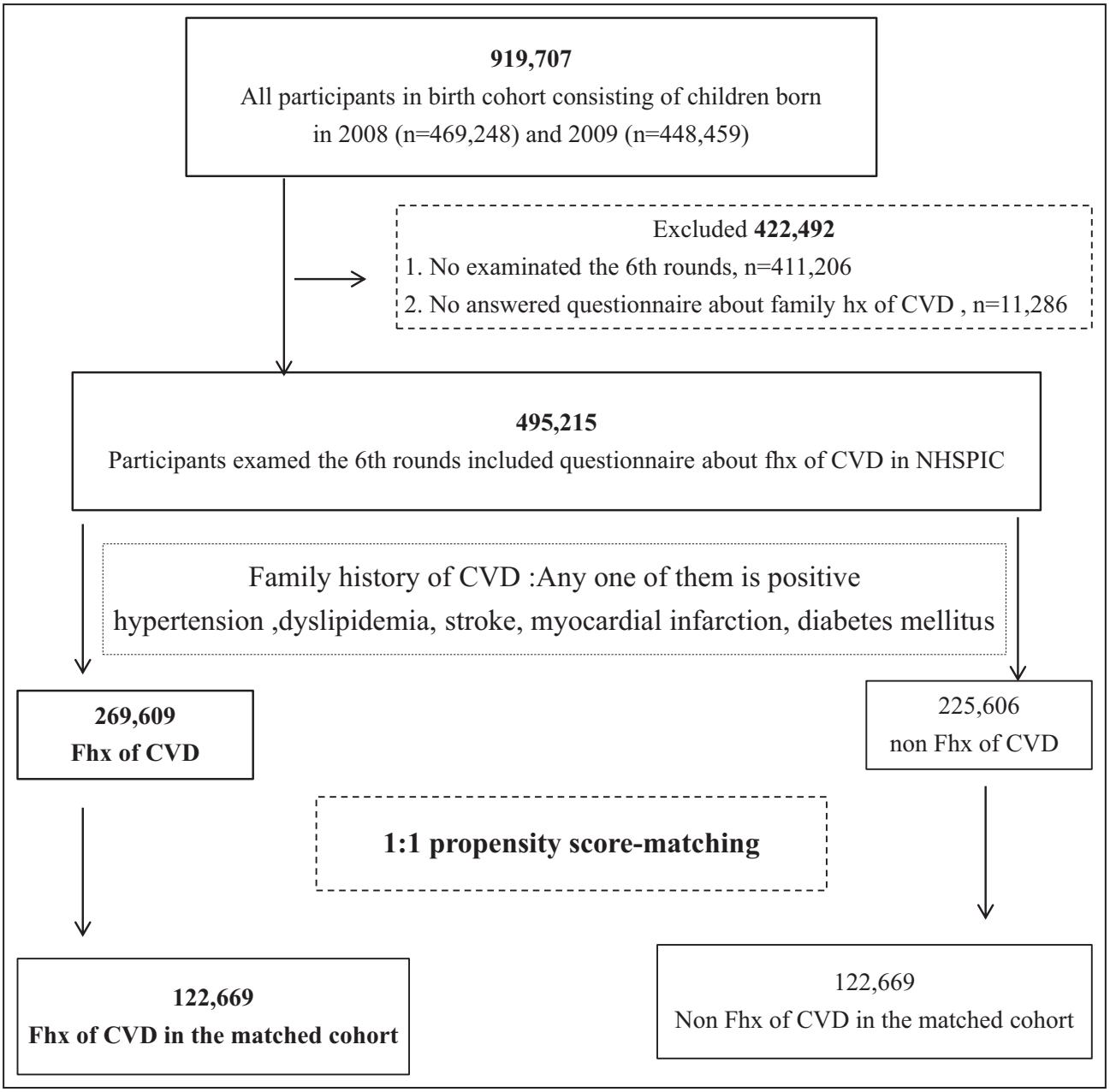

Figure. Disposition of participants in the birth cohort.
The cohort consisted of 495 215 Korean participants (53.8% of the children born during 2008 and 2009) whose parents or guardians answered a family history questionnaire. Individuals who did not answer this questionnaire (n=411 206) or who did not properly respond to questions on family history (n=11 286) were excluded. Propensity-score matching (1:1) was performed for participants who did or did not have family histories of CVD (269 609 children per group). CVD indicates cardiovascular disease; Fhx, family history; hx, history; and NHSPIC, National Health Screening Program for Infants and Children.

The secondary outcome was to evaluate the association between severe KD in children with a family history of CVD. The severe KD definition was ≥1 recorded complication of KD, a coronary angiogram performed (for evaluation of coronary artery complications), or ≥2 IVIG treatments. Complications of KD were identified using *ICD-10* code records of the following diagnoses: coronary artery aneurysm, coronary thrombosis, and acute and chronic ischemic heart disease (Table S1).

Sensitivity analyses were conducted using 4 methods using different ranges of family history of CVD, alternative definitions of KD, number of positive family medical conditions of CVD, and different confounders matched for the primary and secondary outcomes.

First, we performed sensitivity analysis only considering stroke and myocardial infarction as CVD. Then, we performed sensitivity analysis including the risk factors of CVD[18], such as diabetes mellius, dyslipidemia, and hypertension in addition to stroke and myocardial infarction.

Second, we applied these modified criteria for KD diagnosis, and the sensitivity analysis considered diagnostic criteria to be a wide range; therefore, we rechecked the statistical significance. A sensitivity analysis was conducted using 3 alternative diagnostic definitions. Aspirin KD (aKD) was defined with an alternative duration of aspirin prescription (>25 days). The wide-range Kawasaki disease (wKD) was defined as a main KD diagnosis using the *ICD-10* code and IVIG treatment. The widest-range Kawasaki disease (wiKD) was defined as all recorded KD diagnosis *ICD-10* codes.

Third, the sensitivity analysis by number of positive family histories of CVD was conducted for primary and secondary outcomes. Results were analyzed in subgroups divided by the number of CVD family histories, 1 to 2, and 3 family history groups.

Table 1. Baseline Demographic Characteristics of the Participants With or Without a Family History of CVD

Demographic characteristics	Observed data, n=495 215			Propensity-matched data, n=245 216		
	Family history, n (%)*			Family history, n (%)*		
	No	Yes	SMD	No	Yes	SMD
Total, n (%)	225 606	269 609		122 608	122 608	
Boy	115 304 (51.11)	138 848 (51.50)	0.57	63 303 (51.39)	66 008 (53.84)	7.53
Girl	110 302 (48.89)	130 761 (48.50)		59 605 (48.61)	56 600 (46.16)	
Prematurity, n (%)†	12 251 (5.43)	16 876 (6.26)	−0.02	6889 (5.62)	8336 (6.80)	−0.04
Birth weight, kg (SD)‡	3.19 (0.45)	3.19 (0.46)	−0.01			0.00
Birth place, n (%)§						
Seoul	52 003 (23.27)	70 604 (26.44)	−6.05	28 695 (23.40)	28 069 (22.89)	4.74
Metropolis	51 986 (23.26)	60 259 (22.56)		29 867 (24.36)	30 955 (25.25)	
Urban area	89 118 (39.88)	103 458 (38.74)		49 456 (40.34)	49 473 (40.35)	
Rural	30 358 (13.59)	32 754 (12.26)		14 590 (11.90)	14 111 (11.51)	
Economic status, n (%)‖						
1st (low)	18 853 (8.71)	20 568 (7.91)	−6.06	9965 (8.13)	9858 (8.04)	0.88
2nd	34 571 (15.96)	37 958 (14.61)		19 294 (15.74)	19 804 (16.15)	
3rd	60 544 (27.96)	70 577 (27.16)		35 205 (28.71)	34 414 (28.07)	
4th	68 891 (31.81)	86 395 (33.24)		39 908 (32.55)	40 871 (33.33)	
5th	33 685 (15.56)	44 381 (17.08)		18 236 (14.87)	17 661 (14.40)	
Type of lactation, n (%)¶						
Breast milk	56 219 (43.74)	71 883 (45.20)	−1.40	53 592 (43.71)	51 975 (42.39)	5.70
Formula milk	46 866 (36.46)	54 880 (34.51)		44 696 (36.45)	46 376 (37.82)	
Both breast and formula milk	24 911 (19.38)	31 664 (19.91)		23 818 (19.43)	23 709 (19.34)	
Special formula milk	542 (0.42)	619 (0.39)		502 (0.41)	548 (0.45)	

Values are reported as number (percent) unless otherwise indicated. CVD indicates cardiovascular disease; and SMD, standardized mean difference (a value >10% is interpreted as a meaningful difference).

*Family history of CVD included hypertension, dyslipidemia, myocardial infarction, stroke, and diabetes.

†The prematurity status data obtained by the parental-reporting general questionnaire of the National Health Screening Program of Infants and Children. Premature is defined as being born before gestational age 36 weeks.

‡The birth weight data obtained by the parental-reporting questionnaire of the National Health Screening Program of Infants and Children.

§We defined metropolitan areas as 6 metropolitan cities including Busan, Incheon, Gwangju, Daejeon, and Ulsan; urban areas as cities; and rural areas as noncity areas. Number of missing patients in observed data=4675.

‖Economic statuses were divided into quintile based on insurance contribution. Number of missing patients in observed data=18 792.

¶Type of lactation given to patients between the age of 4 to 6 months.

Table 2. Risk of KD in Children Associated With Family History of Cardiovascular Disease

	Observed data, n=495 215				Propensity-matched data, n=245 338				Risk ratio (95% CI)	*P* value
	Family history, n				Family history, n					
	No	%	Yes	%	No	%	Yes	%		
Primary outcome										
Total number of subjects	225 606		269 609		122 669		122 699			
KD*	1264	0.56	1734	0.64	690	0.56	829	0.68	1.20 (1.08–1.32)	<0.001
Secondary outcomes										
Complication of KD†	115	9.10	153	8.82	71	10.29	80	9.65	1.12 (0.81–1.55)	0.464
Radiologic test‡	12	0.95	22	1.27	8	1.16	11	1.33	1.37 (0.55–3.41)	0.493
≥2 IVIG treatments§	11	0.87	25	1.44	6	0.87	15	1.81	2.50 (0.97–6.44)	0.057
Severe KD‖	132	10.44	186	10.73	81	11.74	100	12.06	1.23 (0.92–1.65)	0.158

Family history included hypertension, dyslipidemia, myocardial infarction, stroke, and diabetes. *ICD-10* indicates *International Classification of Diseases, Tenth Revision*; IVIG, intravenous immunoglobulin; and KD, Kawasaki disease.

*KD was defined from *ICD-10* code M30.3, IVIG treatment, and aspirin prescribed.

†Complication of KD refers to complication by *ICD-10* code: coronary artery aneurysm: I25.4, coronary thrombosis: I24.0, acute and chronic ischemic heart disease: I24.8, I24.9, I25.0, I25.9.

‡Radiologic test refers to coronary angiogram by catheterization was performed; treatment code (services received: HA670).

§≥2 IVIG treatments refers to IVIG treated more than once during hospitalization period between 2 and 7 days.

‖Severe KD was defined as ≥1 positive result in the diagnosis complication of KD, or performed coronary angiogram, or treated ≥2 times with IVIG.

Fourth, our findings were consistent when statistical analyses were repeated with more related confounding factors for KD were considered. Additional propensity-score matching, thought to be more strongly associated with KD, was also performed to reduce potential confounding factors that could affect KD diagnosis. Sex and age, which are known to be related to the prevalence of KD, were used, and because environmental factors are known to affect KD, place of birth and economic status were used as variables.[19] We matched previously reported prematurity,[20] birth weight,[21] and type of lactation as variables.[22] Certain conditions originating in the perinatal period were excluded from the matching confounder, because we thought that it was a broad category that some diseases are related to KD and others are not.

Statistical Analysis

Statistical analysis was performed with SAS for Windows (SAS Institute, Cary, NC). We performed propensity-score matching to balance the baseline characteristics of the 2 groups. The propensity score was estimated using multivariable logistic regression with covariates for the following: sex, region of birth (Seoul, metropolitan, city, and rural), income quintile (1–5 classified with insurance fee), type of lactation (breast milk feeding, formula feeding, and mixed feeding at 4–6 months old), prematurity (yes versus no), birth weight (continuous value), and certain conditions originating in the perinatal period (defined in Table 1 and Table S4). The patients in the reference group were matched.[23] Differences between groups in baseline

Table 3. Sensitivity Analysis for Risk of KD in Children Associated With Family History of Stroke and Myocardial Infarction

	Observed data, n=495 215				Propensity-matched data, n=245 338				Risk ratio (95% CI)	*P* value
	Family history, n				Family history, n					
	No	%	Yes	%	No	%	Yes	%		
Primary outcome										
Total no. of subjects	430 228		64 987		215 818		29 520			
KD	2571	0.60	427	0.66	1303	0.60	216	0.73	1.21 (1.05–1.39)	<0.008
Secondary outcome										
Severe KD	277	0.06	41	0.06	157	0.07	24	0.08	1.11 (0.72–1.71)	0.611

KD indicates Kawasaki disease.

Table 4. Sensitivity Analysis for Risk of KD in Children by Definition Category

Diagnostic definition	Propensity-matched data, n=245 338					
	Family history, n					
	n=122 669		n=122 669			
	No	%	Yes	%	Risk ratio (95% CI)	*P* value
aKD*	690	0.56	829	0.67	1.20 (1.08–1.32)	<0.001
wKD†	1222	0.99	1405	1.14	1.14 (1.06–1.24)	<0.001
wiKD‡	1746	1.42	2042	1.66	1.16 (1.09–1.24)	<0.001

KD was defined as *ICD-10* code M30.3, IVIG treatment, and aspirin prescribed. Family history included hypertension, dyslipidemia, myocardial infarction, stroke, and diabetes. aKD indicates aspirin KD; *ICD-10*, *International Classification of Diseases, Tenth Revision*; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; wKD, wide-range KD; and wiKD, widest-range KD.

*aKD depends on *ICD-10* code M30.3, IVIG treatment, and ≥15 days of aspirin prescribed.

†wKD depends on *ICD-10* code M30.3 and IVIG treatment.

‡wiKD depends on only *ICD-10* code M30.3.

characteristics were compared using standardized differences in both the prematched and postmatched samples[24] (differences >10% were considered meaningful). The risk and 95% CIs were obtained using modified Poisson regression[25] and hazard ratio. Two-tailed *P* values <0.05 were interpreted as statistically significant.

RESULTS

Patients

KD occurred in 2998 of the total 495 215 patients (0.61% [95% CI, 0.58%–0.63%]), and the most prevalent age was 1 to 2 years. KD incidence rate was 124.4 cases/100 000 person-years (95% CI, 117.5–131.5) in children <2 years old, 95.5 cases/100 000 person-years (95% CI, 90.5–100.4) in children 2 to 5 years old, 14 cases/100 000 person-years (95% CI, 12.6–15.6) in children >5 years old. Crude KD per 100 000 person-years incidence rate in children <5 years old was 107.0 cases/100 000 person-years. Prevalence of KD among children before propensity matching by alternative definition at timing of diagnosis in the birth cohort are shown in Figure S1.

For each family history of CVD, participants answered diabetes (33.9%), stroke (8.3%), myocardial infarction (6.9%), hypertension (40.5%), and dyslipidemia (2.6%) in propensity-matched data (Table S2). The number of cases with a family history of CVD is shown in Table S3. In the propensity-matched data of 122 669 people who had a family history of CVD, 106 847 (87.1%) people had 1 to 2, and 15 822 (12.9%) had ≥3 relevant CVD histories.

Baseline demographic characteristics of the participants with or without family history of CVD, except sex, did not show meaningful standardized differences before matching as shown in Table 1. Clinical characteristics of the participants with or without a family history of CVD are shown in Table S4. After matching, matched cohorts were balanced.

Table 5. Sensitivity Analysis for Risk of KD With Number of Positive Family Histories of Cardiovascular Disease

	Observed data, n=495 215		Propensity-matched data, n=245 338		MOD Poisson (risk ratio difference)		
	n	%	n	%	Estimate	Wald 95% CI	*P* value
Primary outcome, KD							
Family history, n							
1–2	1508	0.64	713	0.67	1.09	1.03–1.15	<0.001
>3	226	0.81	116	0.73	1.26	1.06–1.49	0.007
0	1264	0.56	690	0.56			
Secondary outcome, severe KD							
Family history, n							
1–2	61	0.05	33	0.06	1.14	0.90–1.44	0.26
>3	11	0.01	5	0.01	1.28	0.57–2.89	0.541
0	51	0.02	29	0.02			

KD was defined as *ICD-10* code M30.3, IVIG treatment, and aspirin prescribed. Severe KD was defined as ≥1 positive result among diagnosis complications of KD or performed coronary angiogram or treated ≥2 times with IVIG. Family history included hypertension, dyslipidemia, myocardial infarction, stroke, and diabetes. *ICD-10* indicates *International Classification of Diseases, Tenth Revision*; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; and MOD, modified.

KD and Family History of CVD

In all observed patients (n=495 215), KD occurred in 1734 children who had a family history of CVD, in comparison to 1264 children without family history of CVD. KD occurred in 829 children (0.68% [95% CI, 0.63–0.72]) with a family history of CVD and 690 children (0.56% [95% CI, 0.52–0.61]) without family history (Table 2) in propensity matched data. Family history of CVD was associated with increased risk of KD (risk ratio [RR], 1.20 [95% CI, 1.08–1.32]).

As a secondary outcome, severe KD occurred in 181 patients (12.0% [95% CI, 10.4%–13.7%) out of 1519 participants with KD. One hundred patients (12.3% [95% CI, 10.0%–14.5%]) were defined as severe KD among 829 patients with KD who had a family history of CVD, whereas 81 patients (12.0% [95% CI, 9.6%–14.4%) were defined as severe KD among 690 patients with KD without a family history of CVD. Unlike the primary outcome, the family history of CVD was not associated with a higher risk of severe KD (RR, 1.23 [95% CI, 0.92–1.65]).

Sensitivity Analyses

The sensitivity analysis results with stroke and myocardial infarction are shown in Table 3. Family history of CVD and KD showed a statistically significant association. Family history of stroke and myocardial infarction were associated with increased risk of KD (RR, 1.21 [95% CI, 1.05–1.39]). However, severe KD also did not show a significant association with family history of stroke and myocardial infarction (RR, 1.11 [95% CI, 0.72–1.71]). Regardless of the difference of family history, the results were statistically significant.

The results of sensitivity analysis for risk of KD in children by definition category are shown in Table 4. The increased association for aspirin KD (RR, 1.20 [95% CI, 1.08–1.32]), wide-range KD (RR, 1.14 [95% CI, 1.06–1.24]), and widest-range KD (RR, 1.16 [95% CI, 1.09–1.24]) were significant (P<0.01). This may be interpreted as family history of CVD was related to increased risks of all of the alternatively defined KD groups (aspirin KD, wide-range KD, widest-range KD).

The results of the sensitivity analyses by number of positive family histories of CVD are shown in Table 5. Results were consistent in the analyses in subgroups divided by the number of CVD family histories, showing increased risk in both 1 to 2 (RR, 1.09 [95% CI, 1.03–1.15]) and 3 family histories groups (RR, 1.26 [95% CI, 1.06–1.49]). Regardless of the number of family histories, the results were statistically significant. KD had a higher association of the number of positive family histories with CVD, and all were statistically significant (P<0.01). However, the number of positive family histories was not associated with a higher risk of severe KD.

In sensitivity analysis, which analyzes the matching confounder differently, the results of risk of KD in children associated with a family history of CVD with a stricter matching variable are shown in Table S5. Family history of CVD was associated with increased risk of KD (RR, 1.17 [95% CI, 1.05–1.29]). Also, unlike the primary outcome, the family history of CVD was not associated with a higher risk of severe KD (RR, 1.25 [95% CI, 0.94–1.68]). It can be concluded that the family history of KD and CVD is related, because the same result is obtained even with different statistical confounding factors.

DISCUSSION

In this nationwide propensity-score matched study, those who had a family history of CVD had a significantly increased 1.2 times risk (95% CI, 1.08–1.32) of KD compared with those who had no family history of CVD. Study results were also supported by several sensitivity analyses performed with various diagnostic definitions of KD; however, the number of positive family histories of CVD and occurrence of severe KD were not associated with the family history of CVD. Our study suggests that the risk of KD was higher in children with a family history of CVD; however, it was not related to complications or a more severe hospital course. This result suggests that the family history of KD and the shared environment of the family may be simultaneously involved in its occurrence epidemiologically. We defined severe KD as children with coronary complications, children who underwent coronary angiography, and children who used IVIG twice or more for intractable KD. Patients with severe KD, as defined by our study, do not necessarily mean those who eventually develop CVD. This discrepancy might be because longer durations of fever increase the likelihood of long-term coronary complications, but refractory KD does not necessarily mean a significantly increased risk of coronary complications.[22,23]

The cause of KD is under discussion, but it is thought to be a complex interplay of genetic factors, infections, environment, and immunity.[26] It appears to be a reciprocal influence of genetic susceptibility and infectious triggers followed by an abnormal immune response. Although poorly understood, even if East Asian and Pacific children migrate to other regions, their incidence of KD is higher in other regions, which means the genetic predisposition is important for the pathogenesis of KD.[27] Several additional studies support genetic factors to KD susceptibility, by showing the risk of coincidence in identical twins up to 13%, a higher occurrence of KD in siblings of affected patients, and increased incidence of KD in children with affected parents.[28] These differences also suggest that

genetic factors play a major role in the pathogenesis of KD. Many investigations are ongoing to detect candidate genes contributing to KD. These studies are being conducted to provide insight into the pathogenesis as well as to confirm the genetic relationship of KD.[29]

Usually, detailed family history provides the first genetic screen for an individual and contains considerable medical information. As genetic testing becomes increasingly available, and clinicians embrace primary prevention and early intervention, family history will become increasingly important in clinical decision making, especially in pediatrics, where universal screening approaches are already engrained in the culture. In this study, the result that family history of CVD is related to KD provides insight in that family history can be derived not only from genetic susceptibility but also from sharing environment and life style within families. Therefore, by taking a careful family history from parents of KD, conducting follow-up studies of children with this disease until adulthood, and investigating children in prospective studies, we can get more valuable information to identify the cause and pathogenesis of KD.

It is known that patients with KD have a high CVD risk when they grow up. Children diagnosed with KD remain at increased risk of cardiovascular events for >10 years after index hospitalization. Patients with KD should be considered as having CVD risk factors, such that necessary assessment and management are given.[19] Among many reports of KD as a CVD risk, patients with KD are associated with an increased risk of atherosclerosis compared with healthy controls.[30] After KD, patients tend to have a more unfavorable cardiovascular risk, indicating an increased tendency to potentially experience premature atherosclerosis changes. A study of the blood pressure of patients with KD using outpatient blood pressure readings reported a decrease in night dipping,[31] whereas another study reported no change in blood pressure control[32]; therefore the relationship to blood pressure is still ambiguous. One study found an increase in glycated hemoglobin when compared with normal controls.[31] It would appear that patients with KD do not differ significantly from the general population with regard to CVD risk factors.

Patients with KD with clear genetic factors are at high risk for CVD. Our study indicated that the incidence of KD was significantly higher in the offspring of those parents who had a history of CVD. The definition of CVD is disorders of the heart and blood vessels, which include coronary heart disease, cerebrovascular disease, peripheral vascular disease, and heart failure, but in our study, CVD criteria included diabetes as well as myocardial infarction, stroke, hypertension, and dyslipidemia. This assumption was because familial aggregation in type 2 diabetes is associated with the presence of cardiac metabolic abnormalities in children.[33] CVD and type 2 diabetes often occur together[34] and share risk factors such as hypertension and obesity. The increased risk with the presence of coronary complication in KD requires careful attention and more active management of lifestyle and CVD risk factors.[19]

There are studies on what types of CVD risk increase after children with KD grow up.[12] However, to our knowledge, there are no studies on whether a family history of CVD is associated with the development of KD in children. In a current study, fathers of children with severe KD had a higher incidence of only ischemic heart disease, which may be associated with KD in childhood.[12]

Strength and Limitations

Our population-based study implies that the family history of CVD plays an important role in the occurrence of KD. Because our study was conducted in the setting of usual clinical care and included a representative sample of children with KD in Korea with universally diagnosed KD, the findings are generalizable. However, some hospitals tend to overdiagnose KD, whereas others underdiagnose it. Therefore, a nationwide survey cannot reflect the true incidence of KD despite its traditional value and merit to provide clues about its pathophysiology and risk factors. Therefore, sensitivity analyses were conducted, and all supported the main findings.

This study has several limitations. Variables on health behaviors are limited, because those data were obtained from parental reporting in nationwide health screenings. In addition, because it is recorded information for the Korean fee-for-service payment and reimbursement system, the disease diagnosis code might not accurately reflect the patient's health status. In addition, unlike adults, there is a paucity of data about the results of blood tests in health screening programs in children and adolescents. The use of parental history and physician reports without independent verification by review of medical records, echocardiographic reports, and other laboratory testing result may have resulted in overreporting KD cases.

Furthermore, family history reflects genetic susceptibility as well as environment and lifestyle shared within families,[37] and this study was not designed to answer the question of whether the potential risk of family history outweighs a developed disease, so the results of this study alone could not accurately reveal the relationship between KD and family history of CVD.

CONCLUSIONS

This study was the first to report that family history of CVD has a significant association in increasing the risk

of KD. If verified, these risks should be balanced against the other risks of KD, considering that KD is an important disease with an unknown pathogenesis.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S6

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