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Association of early social environment with the onset of pediatric Kawasaki disease

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ABSTRACT

Purpose: The purpose of this study was to investigate the association of early social environment with Kawasaki disease (KD).
Methods: We analyzed the data of children aged up to 10 years derived from the 21st Century Longitudinal Survey in Newborns (n = 41,872) in Japan. Parental education, total household income, and family size were obtained via a questionnaire at 0.5 years after birth. Physician's diagnosis of KD during the past year was surveyed via a questionnaire for caregiver with children aged up to 10 years. We used Cox proportional hazards modeling to examine the risk factors for KD onset.
Results: Children born in households with an annual income of JPY 10 million or more were 1.76 times more likely to have KD onset compared with children born in households with an income of less than JPY 4 million (hazard ratio: 1.76, 95% confidence interval [CI]: 1.15–2.69). Children born in households with three or less persons were 1.62 times more likely to have KD onset compared with those born in households with six or more persons (95% CI: 1.10–2.40). The children who were born in urban municipalities also showed higher risk of KD onset compared with those born in rural municipalities (hazard ratio: 1.55, 95% CI: 1.06–2.26).
Conclusions: Higher household income, smaller family size, and urbanization at birth were associated with increased KD incidence. This study, however, did not find a significant association between lack of exposure to infection in early life and onset of KD.

Introduction

Kawasaki disease (KD) is a form of acute febrile systemic vasculitis [1,2], which is a leading cause of childhood acquired cardiac disease [3]. One of the most serious complications of KD is coronary artery dilatation and/or aneurysm, which can be fatal [4,5]. In Japan, around one in 150 children is diagnosed with KD by the age of 10 years [3], and the most recent estimate of KD incidence in 2012 was one in 75 children by the age of 5 years [6]. Although more than 40 years have passed since the first reported case series of the disease [1,2], the etiology of KD remains obscure. The pathogenesis of KD is characterized by massive immune dysregulation, including hyperinflammatory cytokinemia, marked activation of multilineage T-cell subsets, and systemic vasculitis.

Both genetic and environmental factors are believed to be involved in the etiology of immune dysregulatory disorders. Asia has the highest incidence of KD in the world, and genome-wide association studies have implicated multiple novels and functionally related susceptibility loci for KD [7]. Infectious agents such as bacteria [8–11], fungi [12], and viruses [13–15], as well as microbe-derived factors such as superantigens [16,17], fungi-related components [18], and seasonal variation [19] have attracted major attention as disease-triggering pathogens, as antibodies of these agents were more likely to be isolated from KD patients. A recent epidemiologic report found evidence for rising KD incidence in developed northeast Asian countries such as Japan and South Korea [19], but low levels of risk among indigenous Australians [20],

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although racial difference in susceptibility for KD might explain the difference of KD incidence [21].

Because KD has a peak onset age of around 10–11 months, early life course circumstances are likely to be relevant to its etiology. The hygiene hypothesis states that a lack of early childhood exposure to infectious agents, symbiotic microorganisms (e.g., gut flora), and parasites increases susceptibility to allergic diseases by suppressing the natural development of the immune system [22,23]. According to this theory, factors that lower early life course exposure to infectious agents, such as economic development, urbanization, and higher household income, should cause an increase in the risk of allergic diseases. Conversely, factors that elevate the risk of early exposure to microbes, such as residential overcrowding, should lower the risk of allergic disease.

Previous studies have suggested higher socioeconomic status (SES) [24,25] and urbanization [26] to be associated with KD. To our knowledge, however, few studies [21,27] have focused on early life course circumstances, which can be determined by early social environments such as household income, parental education, family size, and urban/rural difference at infancy as risk factors for KD onset. Thus, the hygiene hypothesis was proposed as an etiology of KD [28,29]. In the present study, we analyzed the data from a nationwide birth cohort of 47,015 children aged up to 10 years, with the specific aim of testing the hygiene hypothesis in the etiology of KD. The data collected in this study allowed to directly test the association between history of infectious disease in early life and the onset of KD.

Methods

Participants

We used data from the 21st Century Longitudinal Survey in Newborns, a birth cohort study conducted by the Ministry of Health, Labour and Welfare in Japan from 2001 to 2010. The objective of this survey was to capture basic data on children born in 2001 and to observe the changes in their status to aid in the planning of policies to overcome declining birthrates. The study sample consisted of all children born in Japan between January 10 and January 17, 2001, and between July 10 and July 17, 2001, and was based on the birth record list of vital statistics for Japan ($N = 53{,}575$). The Ministry of Health, Labour and Welfare sent mail questionnaires to the caregivers of these children when they were aged 6 months. A completed and returned questionnaire was considered consent to participate in the study ($N = 47{,}015$, response rate: 87.8%). Subsequently, questionnaires were sent to the caregivers when the children were aged 1.5, 2.5, 3.5, 4.5, 5.5, 7, 8, 9, and 10 years. For our analyses, we excluded subjects with missing data on the following variables: KD status during the 10-year follow-up period ($n = 3261$), maternal education ($n = 1384$), paternal education ($n = 477$), total household income at 6 months ($n = 7$), and family size ($n = 14$). After these exclusions, we were left with an analytic sample of 41,872 children (89% of all respondents). In the analytic sample, response rates for the follow-up questionnaires at 1.5–10 years of age ranged from 75% to 93%. The study size yielded sufficient power (>0.9) to detect a hazard ratio (HR) of 1.2–1.5, assuming a low- or high-income group ratio of 4:1 and a type I error of 0.05. The study was exempted from approval by the Institutional Review Board because the study was conducted by the Ministry of Health, Labour and Welfare, and the data were stripped of all personally identifiable information.

Measurements

KD diagnosis by physician during the past year was surveyed via caregiver questionnaire at 2.5, 3.5, 4.5, 5.5, 7, 8, 9 and 10 years of age. The survey included the question: "During the previous 1 year, have you ever visited a hospital or clinic to treat the following diseases or injury?" Response items for this question listed various types of diseases and injury, including KD. Respondents marked the item for KD if they had visited a hospital or clinic to treat a child with KD during the previous year. Onset was defined as the year of the first diagnosis of KD by a physician. Caregivers were to check the item for KD in the questionnaire during the 10-year follow-up. Furthermore, existence of each history of the following infectious diseases during 0.5–1.5 years was assessed in the questionnaire: chicken pox, whooping cough, rubella, measles, exanthem subitem, conjunctivitis, otitis, and common cold.

Parental education and total annual household income at 6 months were used as indicators of parental SES. Total household income at 0.5 years was obtained from questionnaires used in the first survey implemented in 2001. We categorized income into five groups: less than JPY 4 million, JPY 4–5.99 million, JPY 6–7.99 million, JPY 8–9.99 million, and JPY 10+ million (JPY 1 million is equivalent to USD 10,000). Information on parental education was obtained from the second survey in 2002. Educational level was categorized into three groups: high school or lower, some college, and college or higher. Furthermore, household income at when the child was aged 4.5 years was queried to check whether social environment at that time has an effect on the onset of KD after 5.5 years.

The baseline survey also inquired about the number of coresident household members at 0.5 years, including parents, siblings, grandparents, and others. Family size was categorized into four groups: two to three persons, four persons, five persons, or six persons or greater.

The urbanization level of the municipality where the child was born was categorized into three levels based on official definitions: urban (cities designated by government ordinance and 23 wards in Tokyo; population of 500,000 or more) or semiurban (other cities) or rural (town and villages; population of <50,000) [30].

Analysis

The association between baseline characteristics and KD status was analyzed by χ^2 test. Furthermore, sensitivity analysis was performed to check whether change of household income between 0.5 and 4.5 years of age affects the potential of having KD after 5.5 years of age, among those who did not have KD at 4.5 years of age.

Furthermore, incidence rate of KD, defined as the newly diagnosed number of children with KD over 100,000 person-years, was calculated for up to 4.5 years of age and up to 10 years of age.

Subsequently, bivariate association between each SES and onset of KD, adjusted child sex and parental age, was analyzed by Cox proportional hazards regression. To confirm hygiene hypothesis, association between any history of infectious disease, each history of infectious disease (i.e., chicken pox, whooping cough, rubella, measles, exanthem subitem, conjunctivitis, otitis, and common cold), and number of these infectious diseases during 0.5–1.5 years old, and KD onset were also investigated. After that, each of the factors of early social environment (i.e., parental education, household income, family size, and urbanization) together with history of infectious disease were included in the multivariate model simultaneously to see the independent effect on the onset of KD in the analysis using Cox proportional hazard regression. After fitting a Cox model, cumulative hazard for KD was described by household income, family size, and urbanization categories. For sensitivity analysis to check the impact of change of income up to 10 years old, a different analysis using household income as time-dependent covariate was performed. Stata MP12 (StataCorp LP, College Station, TX) was used for analysis.

Table 1
Sample characteristics by Kawasaki disease status ($n = 41,872$)

Characteristics	Kawasaki disease (−) ($N = 41,535$, 99.2%), *n* (%)	Kawasaki disease (+) ($N = 337$, 0.8%), *n* (%)	*P*
Child characteristics			
Sex			
Boy	21,540 (51.9)	191 (56.7)	.08
Girl	19,995 (48.1)	146 (43.3)	
Low birth weight			
(+)	3468 (8.4)	29 (8.6)	.87
(−)	38,057 (91.7)	308 (91.4)	
Missing	10	0	
Preterm birth			
(+)	2029 (4.9)	18 (5.3)	.70
(−)	39,482 (95.1)	319 (94.7)	
Missing	30	0	
Feeding			
Breastfeeding only	8972 (21.6)	77 (22.9)	.50
Mixed	29,829 (71.8)	239 (70.9)	
Bottle feeding only	2436 (5.9)	16 (4.5)	
Missing	298	6	
Having infectious disease history during 0.5–1.5 y of age			
(+)	37,592 (90.5)	299 (88.7)	.27
(−)	3943 (9.5)	38 (11.3)	
Chicken pox			
(+)	5650 (13.6)	40 (11.9)	0.36
(−)	35,885 (86.4)	297 (88.1)	
Whooping cough			
(+)	85 (0.2)	0 (0.0)	.41
(−)	41,450 (99.8)	337 (100.0)	
Rubella			
(+)	107 (0.3)	0 (0.0)	.35
(−)	41,428 (99.7)	337 (100.0)	
Measles			
(+)	515 (1.2)	0 (0.0)	**.04**
(−)	41,020 (98.8)	337 (100.0)	
Exanthem subitem			
(+)	17,682 (42.6)	142 (42.1)	.87
(−)	23,853 (57.4)	195 (57.9)	
Conjunctivitis			
(+)	2713 (6.5)	30 (8.9)	.08
(−)	38,822 (93.5)	307 (91.1)	
Otitis			
(+)	5800 (14.0)	39 (11.6)	.21
(−)	35,735 (86.0)	298 (88.4)	
Common cold			
(+)	34,401 (82.8)	271 (80.4)	.24
(−)	7134 (17.2)	66 (19.6)	
Number of infectious diseases			
0	3943 (9.5)	38 (11.3)	.57
1	15,855 (38.2)	135 (40.1)	
2	15,435 (37.2)	112 (33.2)	
3	5122 (12.3)	46 (13.7)	
4	1045 (2.5)	5 (1.5)	
5	128 (0.3)	1 (0.3)	
6	7 (0.02)	0 (0.0)	
Parental characteristics			
Maternal age at birth (y)			
<25	4862 (11.7)	31 (9.2)	.41
25–29	16,043 (38.6)	135 (40.1)	
30–34	15,106 (36.4)	130 (38.6)	
35–39	4944 (11.9)	39 (11.6)	
40+	580 (1.4)	2 (0.6)	
Paternal age at birth (y)			
<25	3105 (7.5)	17 (5.0)	.15
25–29	11,875 (28.6)	89 (26.4)	
30–34	14,999 (36.10)	137 (40.7)	
35–39	8140 (19.6)	72 (21.4)	
40+	3416 (8.2)	22 (6.5)	
Maternal smoking at 6 months of age			
Yes	6378 (15.4)	50 (14.8)	.43
No	34,963 (84.2)	287 (85.2)	
Missing	194 (0.5)	0 (0.0)	
Paternal smoking at 6 months of age			
Yes	25,553 (61.5)	206 (61.1)	.89
No	15,505 (37.3)	128 (38.0)	
Missing	477 (1.2)	3 (0.9)	
Maternal education			
High school or less	18,274 (44.0)	136 (40.4)	.36
Some college	7442 (17.9)	61 (18.1)	
College+	15,819 (38.1)	140 (41.5)	
Paternal education			
High school or less	19,752 (47.6)	148 (43.9)	.39
Some college	5218 (12.6)	47 (14.0)	
College+	16,565 (39.9)	142 (42.1)	
Family characteristics			
Total annual household income			
<4 million yen	11,984 (28.9)	84 (24.9)	**.013**
4–5.99 million yen	14,221 (34.2)	109 (32.3)	
6–7.99 million yen	8690 (20.9)	73 (21.7)	
8–9.99 million yen	3763 (9.1)	32 (9.5)	
10+ million yen	2877 (6.9)	39 (11.6)	
Parents in household			
Both mother and father	41,004 (98.7)	332 (98.5)	.97
Mother only	520 (1.3)	5 (1.5)	
Father only	5 (0.01)	0 (0)	
No parents	6 (0.01)	0 (0)	
Number of elder siblings			
0	20,667 (49.8)	180 (53.4)	.23
1	15,252 (36.7)	121 (35.9)	
2+	5616 (13.5)	36 (10.7)	
Living with grandparents			
Yes	8946 (21.5)	55 (16.3)	**.02**
No	32,589 (78.5)	282 (83.7)	
Number of people in household			
2–3	16,284 (39.2)	156 (46.3)	**.012**
4	12,939 (31.2)	105 (31.2)	
5	6130 (14.8)	43 (12.8)	
6+	6182 (14.9)	33 (9.8)	
Municipality characteristics			
Urbanization			
Urban	8895 (21.4)	86 (25.5)	**.006**
Semiurban	24,670 (59.4)	208 (61.7)	
Rural	7970 (19.2)	43 (12.8)	

Bold signifies $P < .05$.

Results

Sample characteristics stratified by KD status are shown in Table 1. During the 10-year follow-up, 337 cases showed KD onset. In the sample, boys were more likely than girls to have KD onset (56.7%). The number of children who were born with low birth weight and who were preterm infants was 3497 (8%) and 2047 (5%), respectively. Children who were breastfed only, bottle-fed only, and both breastfed and bottle-fed made up 9049 (22%), 2452 (6%), and 30,068 (72%) of the sample, respectively. Maternal and paternal smoking at 6 months was observed in 6428 (15%) and 25,759 (62%) of the sample, respectively. These possible confounders, as well as child gender and parental age, did not significantly vary according to KD status.

Maternal and paternal education were distributed as follows: high school or less, 18,410 (44%) and 19,900 (48%); some college, 7503 (18%) and 5265 (13%); and college or more, 15,959 (38%) and 16,707 (40%), respectively. Twenty-nine percent of households ($n = 12,068$) earned a total income of less than JPY 4 million, whereas 7% ($n = 2916$) earned JPY 10 million or more. More than 98% of the children ($n = 41,446$) were living with both parents, and 22% ($n = 9001$) were also living with grandparents in a multigenerational household. Around half of all participants ($n = 20,847$) were the firstborn of the family. The smallest family size, that is, two to three persons, made up 39% of the sample ($n = 16,440$), whereas the largest family size of six or more members was 15% ($n = 6215$). Most participants (59%; $n = 24,878$) were born in semiurban cities, 21%

Table 2
Incidence of Kawasaki disease by age of onset

Age of onset by year and category	*N*	Percentage of all cases	Incidence rate (per 100,000 person-years)	95% CI
Age of onset (y)				
≤2.5	154	45.7	122.6	104.7–143.6
2.6–3.5	63	18.7	151.0	118.0–193.3
3.6–4.5	48	14.2	115.2	86.8–152.9
4.6–5.5	31	9.2	74.5	52.4–105.9
7	16	4.7	38.5	23.6–62.8
8	11	3.3	26.5	14.7–47.8
9	8	2.4	19.3	9.6–38.5
10	6	1.8	14.4	6.5–32.1
Total				
Up to 4.5 y	265	78.6	126.8	112.4–143.0
Up to 10 y	337	100	80.8	72.7–90.0

($n = 8981$) were born in urban cities, whereas the other 19% ($n = 8013$) were born in rural towns. Children who had no history of infectious disease during 0.5–1.5 years accounted for 9.5% ($n = 3981$). A higher proportion of children who had no history of infectious disease was found in the KD group (11.3%) than in the non-KD group (9.5%). As for each infection, those who infected measles ($n = 515$), rubella ($n = 107$), and whooping cough ($n = 85$) did not have KD (P for χ^2: .04, .35, and .41, respectively). There was no difference in the number of infectious diseases between KD and non-KD groups ($P = .57$).

Table 2 shows the incidence of KD. In early infancy at less than 2.5 years of age, there were 154 cases of KD onset, which accounted for 45.7% of all cases. Furthermore, the number of KD cases up to 4.5 years of age was 265 (78.6% of all KD cases), and incidence of KD was 126.8 (95% confidence interval [CI]: 112.4–143.0) per 100,000 person-years. The incidence of KD onset decreased as the children got older.

HRs of KD incidence were estimated by Cox proportional hazard modeling (Table 3). In the bivariate model, total household income exhibited a statistically significant linear positive association with

Table 3
Hazard ratios of Kawasaki disease diagnosis with socioeconomic status, family size, urbanization, and history of child infectious disease

Characteristics	Bivariate*		Multivariate†	
	HR	95% CI	HR	95% CI
Socioeconomic status				
Maternal education				
High school	Reference	—	Reference	—
Some college	1.10	0.81–1.49	1.01	0.74–1.38
College+	1.18	0.93–1.50	1.05	0.80–1.37
P for trend	.17		.77	
Paternal education				
High school	Reference	—	Reference	—
Some college	1.20	0.87–1.67	1.15	0.82–1.61
College+	1.13	0.89–1.43	0.94	0.72–1.23
P for trend	.29		.71	
Total annual household income				
<JPY 400 million yen	Reference	—	Reference	—
JPY 4–5.9 million	1.10	0.83–1.47	1.0 5	—
JPY 6–7.9 million	1.21	0.88–1.68	1.13	0.81–1.57
JPY 8–9.9 million	1.23	0.81–1.86	1.11	0.72–1.71
JPY 10+ million	1.96	1.31–2.93	1.76	1.15–2.69
P for trend	.004		.036	
Family environment				
Number of people in household				
2–3	1.85	1.27–2.70	1.62	1.10–2.40
4	1.51	1.02–2.24	1.38	0.93–2.06
5	1.29	0.82–2.04	1.23	0.78–1.94
6+	Reference	—	Reference	—
P for trend	<.0005		.009	
Municipality environment				
Urbanization				
Urban	1.78	1.24–2.58	1.55	1.06–2.26
Semiurban	1.56	1.13–2.17	1.45	1.04–2.02
Rural	Reference	—	Reference	—
P for trend	.004		.031	
Childhood disease history				
Having infectious disease history during 0.5–1.5 years of age				
(+)	Reference	—	Reference	—
(−)	1.21	0.87–1.70	1.22	0.92–1.71
P for difference	.26		.25	

* Adjusted child sex and parental age categories.
† Child gender, parental age categories, parental education, family size, urbanization, and child infectious history were included in the model.

the onset of KD (P for trend = .004). Multivariate analysis simultaneously adjusted for parental education, family size, urbanization level, and a history of infectious disease showed that higher annual household income remained linearly associated with the onset of KD (P for trend = .036). More specifically, as shown in Figure 1A, children born in households with an annual income of JPY 10 million or more at birth were 1.76 times more likely to have KD at up to 10 years of age compared with children from households with income less than JPY 4 million (HR: 1.76, 95% CI: 1.15–2.69). However, parental education was not associated with the onset of KD in both bivariate- and multivariable-adjusted models.

Smaller family size showed a significant positive association with the onset of KD (P for trend < .001) in the bivariate model. It remained significant in the model adjusted for parental SES (i.e., parental education and total household income) and urbanization level (P for trend = .009). That is, children born into a small family (i.e., comprising two to three persons) were 62% more likely to develop KD at up to 10 years of age compared with children born into a family of six or more persons (HR: 1.62, 95% CI: 1.10–2.40; Fig. 1B).

The urbanization level of the municipality at birth was also associated with onset of KD. Children born in urban municipalities were more likely to develop KD (P for trend = .004 and .031 for bivariate and multivariate models, respectively). After adjusting for parental SES and family size, children born in urban municipalities were 55% more likely to have KD in comparison with those born in rural municipalities (HR: 1.55, 95% CI: 1.06–2.26). Being born in a semiurban municipality also significantly increases the risk of having KD compared with being born in a rural municipality (HR: 1.45, 95% CI: 1.04–2.02) (Fig. 1C).

Children who had no history of infectious disease 0.5–1.5 years old showed a statistically nonsignificant increase in risk of earlier the onset of KD (HR: 1.21, 95% CI: 0.87–1.70). Adjustment by parental SES, family size, and children born in urban municipalities did not appreciably change the association estimate (HR: 1.22, 95% CI: 0.92–1.71). No specific infectious diseases or number of infectious diseases were significantly associated with the onset of KD (P > .2, data not shown).

In the sensitivity analysis, household income was treated as a time-dependent covariate in a Cox proportional hazards model. As shown in Table 4, the results were similar as in previous analyses: children born in households with an annual income of JPY 10 million or more were significantly more likely to have KD at up to 10 years of age compared with those born in households with income of less than JPY 4 million (HR: 1.21, 95% CI: 1.04–1.39; P for trend = .003).

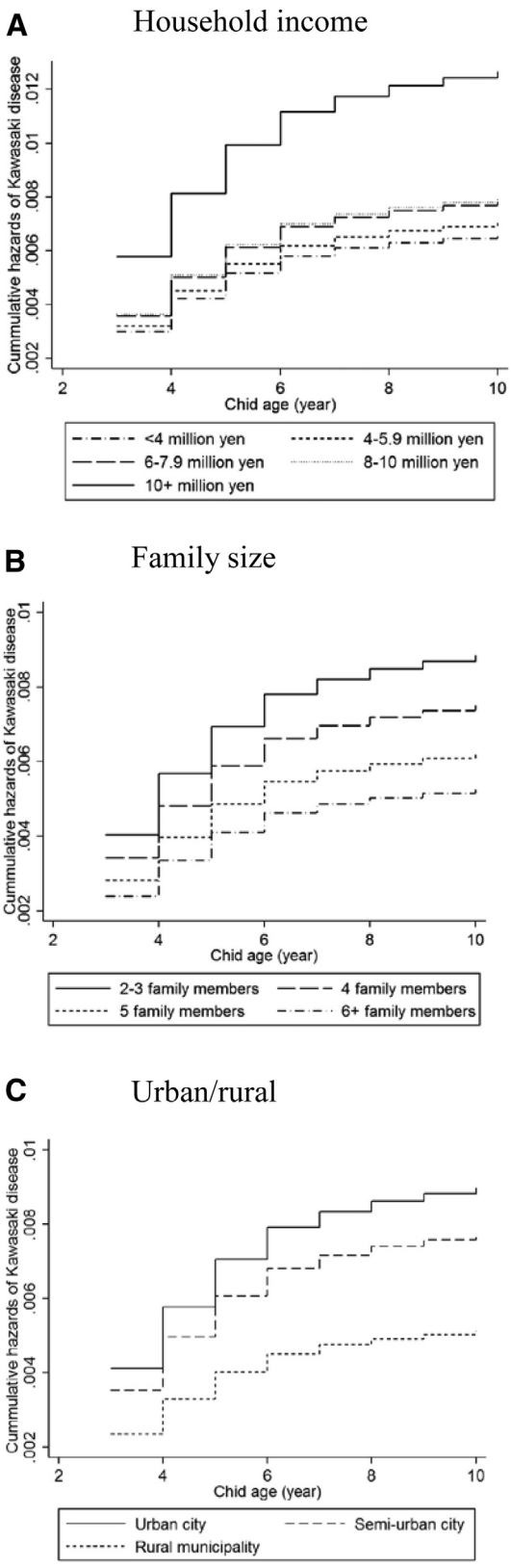

Fig. 1. Cumulative incidence of Kawasaki disease up to 10 years of age by total household income (A), family size (B), and urban/rural municipalities (C).

Discussion

Consistent with the hygiene hypothesis, we found that higher household income, small family size, and urbanization level were associated with increased risk of KD incidence. Absence of a history of infectious disease was weakly and not significantly associated with KD. To our knowledge, this is the first study that reports early social environment as risk factors for KD.

One possibility for the positive association between household income and KD incidence is diagnostic bias, that is, wealthier parents are more likely to seek (and receive) a diagnosis of KD for their sick children, regardless of parental education. However, Japan has maintained universal access to health care since 1961, so that differential access to pediatric care because of financial difficulty is unlikely to account for the epidemiologic pattern we describe.

Smaller family size, which is a proxy for less overcrowding, decreases the risk of early pediatric infection [31], and higher SES families are more likely to live in high-quality housing [32], which decreases the risk of infection [33]. Previous research reported the link between higher SES and KD in San Diego, although SES was measured as health insurance [34]. Furthermore, urban residents

Table 4
Association between household income as time-dependent covariate and incidence of Kawasaki disease

Characteristics	Multivariate*	
	HR	95% CI
Socioeconomic status		
Maternal education		
High school	Reference	—
Some college	0.88	0.52–1.50
College+	0.87	0.56–1.37
P for trend	.55	
Paternal education		
High school	Reference	—
Some college	1.20	0.68–2.14
College+	1.05	0.67–1.63
P for trend	.81	
Total annual household income		
<JPY 400 million yen	Reference	—
JPY 4–5.9 million	1.04	0.93–1.17
JPY 6–7.9 million	1.11	0.98–1.26
JPY 8–9.9 million	1.18	1.02–1.36
JPY 10+ million	1.21	1.04–1.39
P for trend	.003	
Family environment		
Number of people in household		
2–3	2.34	—
4	1.76	1.14–4.80
5	0.91	0.85–3.68
6+	Reference	0.36–2.30
P for trend	.002	
Municipality environment		
Urbanization		
Urban	1.52	0.80–2.89
Semiurban	1.43	0.80–2.55
Rural	Reference	—
P for trend	.25	
Childhood disease history		
Having infectious disease history during 0.5–1.5 years of age		
(+)	Reference	—
(−)	1.13	0.62–2.05
P for difference	.71	

* Adjusted child gender, parental age categories, parental education, family size, urbanization, and child infectious history were included in the model.

are less likely to be exposed to endotoxin compared with rural residents [35]. Thus, a lack of exposure to ubiquitous infectious microbes in early life can be associated with KD onset. Several epidemiologic studies suggested infection as a cause of KD or as a trigger for the development of KD [19] based on, for example, seasonal variation [36] and clustering [37]. Lack of early exposure to ubiquitous infection might increase the risk of adverse reaction to infectious exposure after 6 months of age, which may, in turn, lead to the development of KD because KD has been suggested to be triggered by infection. We found that children without a history of infectious disease showed a slightly higher risk of KD, which was not statistically significant. If the hygiene hypothesis is true, the infection that triggers KD may not have been included in the list of infections assessed in our questionnaire.

Our results are compatible with two observations. First, infection with a specific pathogen may not be a unique etiology for KD although pandemics of the disease have previously been observed in Japan [38]. Second, exposure to common infections early in life may protect children from the onset of KD. This is compatible with the fact that onset of KD peaks at around 10–11 months of age [38] when maternally transferred protective immunoglobulin begins to wane.

Our observations of the early life course risk and protective factors for KD share a number of parallels with the so-called hygiene hypothesis in the etiology of allergic diseases [22]. The hygiene hypothesis predicts that delayed exposure to infectious agents can trigger the onset of allergic disease. The incidence of KD, similar to other allergic diseases such as asthma, is lower among indigenous Australians [20], but with a higher rate of infection [39]. Many of the indigenous people continue to live in rural areas, and even if they move to urban locations, they live in overcrowded conditions with higher bacterial colonization during infancy [40]. In addition, children diagnosed with KD may be more susceptible to allergic diseases [41,42]. According to the hygiene hypothesis, frequent upper respiratory infections or high environmental endotoxin exposure early in life leads to decreased allergic sensitization, which is more likely to occur because of rural environment [35], lower SES [33], and larger family size [31]. This is because of the induction of airborne antigen-specific naive T-cell development toward T-helper cell type 1 (Th1) or regulatory T cells away from T-helper cell type 2 (Th2) through the activation of innate immune responses [22,28,43].

Unlike allergic diseases that are characterized by a Th2-dominant immune predisposition, activated T-helper cell types in KD are not only Th2 but also Th1 and Th17 [44]. Thus, it still remains unclear whether the mechanisms by which the hygiene environment affects the onset of allergic diseases also play a role in KD onset. In addition, the pathogen(s) or antigen(s) that trigger KD are still unknown, and the role of innate immune responses on acquired immune responses in KD requires further investigation.

Our study has several limitations. First, diagnostic misclassification might have occurred as KD status was assessed by a self-reported questionnaire that focused on the history of hospital visits for KD, which was indicated by pediatricians. However, misclassification of KD is unlikely to happen in Japan, even in small pediatric clinics, as pediatricians in Japan are routinely trained in the recognition of KD. Second, some children may not have visited a hospital even if they showed symptoms of KD and may fully recover without medication. It is possible that children from small-sized, high-income families in urbanized areas are more likely to be admitted to hospital with minor symptoms, and therefore, KD cases are more likely to be captured among this population. However, children in almost all municipalities in Japan receive free medical care before they reach elementary school age, so cost is not a barrier to medical access for families with young children in Japan, regardless of household income. Third, because we lacked data on parental KD history, we did not adjust for genetic predisposition. Fourth, our assessment of history of infection in early childhood was not as thorough as it should have been to investigate the hypothesis that a specific infection could trigger KD onset.

Nonetheless, our study found that higher household income, urbanization, and smaller family size at birth were associated with increased KD incidence, which raises the hygiene hypothesis for the etiology of KD. Further study with the hypothesis is needed to replicate the finding and to elucidate the etiology of KD.

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Disclosure

The authors declare that they have no competing interests.

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