IJC Heart & Vasculature 40 (2022) 101039

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

Long-term health outcomes in young adults after Kawasaki disease

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ARTICLE INFO

Keywords:
Kawasaki disease
Coronary artery aneurysms
Migraine
Vasospasm
Microvascular dysfunction

ABSTRACT

Background: We compared the long-term health of adults with prior Kawasaki disease (KD) to controls and determined whether outcomes varied by coronary artery (CA) status.
Methods: We conducted a prospective cohort study of 258 KD subjects (mean 19 ± 9 years since KD) and 148 age-similar controls who completed extensive health questionnaires. KD subjects were divided into 2 groups, Cohort 1: 109 subjects followed since KD diagnosis at our institution; Cohort 2: 149 KD subjects diagnosed elsewhere.
Results: KD subjects and controls were of similar age at the time of questionnaire completion ($p = 0.50$). Overall, 128 subjects (including 60 in Cohort 1) reported normal CAs during and after KD. Compared to controls, KD subjects with normal CAs reported several medical conditions with increased prevalence including migraine headaches, shortness of breath, and leg pain with walking, among others. When limited to Cohort 1, KD subjects were significantly more likely to report chest pain (47% vs 16%, $p < 0.001$) or palpitations (23% vs 10%, $p = 0.01$) compared to controls. Prevalence of depression was similar (7% vs 5%, $p = 0.73$).
Conclusions: Despite always having normal CAs in the acute and subacute phases of KD, young adults with a history of KD with normal coronaries were more likely than controls to experience cardiovascular symptoms. These differences could be influenced by anxiety or depression, but report of depression was similar between groups. Whether these health differences reflect a heightened awareness of symptoms among KD subjects, or underlying vascular pathology (i.e. vasospasm, microvascular dysfunction, other) merits further study.

1. Introduction

Kawasaki disease (KD) is an acute, self-limited vasculitis that occurs in children. It often goes unrecognized since the presenting symptoms, including fever and rash, are shared by many other pediatric conditions and there is currently no diagnostic test. Approximately 25% of untreated children go on to develop coronary artery aneurysms, compared to about 5% of those treated with intravenous immunoglobulin within the first ten days of illness [1]. Children who develop aneurysms are at risk of future coronary artery stenosis, myocardial infarction, arrhythmias, heart failure, and death. Few studies have assessed the long-term outcomes of children whose coronary arteries either maintain a normal internal diameter as assessed by transthoracic echocardiogram or return to normal shortly after the cessation of fever [2]. Both genetic and environmental factors contribute to KD susceptibility, and these factors may also influence subsequent health. There are no systematic studies of long-term health after KD; existing studies have been limited to subsets of patients with abnormal coronary arteries [3–5], or have addressed only limited cardiovascular or peripheral vascular outcomes [2,6] .

The purpose of this study was to compare the long-term health of adults with a childhood history of KD to age-similar controls with no prior history of KD and to determine whether long-term health outcomes after KD vary by whether there was coronary artery involvement (transient dilation or aneurysms) during the acute and subacute KD. We divided our analysis into two cohorts derived from either patients who were diagnosed initially and followed at our center (Cohort 1), or those diagnosed elsewhere and enrolled remotely (Cohort 2). We did this to avoid the potential bias of remote patients being more likely to seek out our study and enroll due to health concerns after KD. Our local Cohort 1 enrolled consecutive KD patients and therefore is less likely to have selection bias. This study is the first longitudinal assessment of health outcomes in a population of patients encompassing the full spectrum of

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https://doi.org/10.1016/j.ijcha.2022.101039
Received 23 December 2021; Received in revised form 20 April 2022; Accepted 21 April 2022

KD.

2. Methods

2.1. Subjects

Subjects were eligible for enrollment if they were at least 15 years old and had a history of KD based on standard diagnostic criteria. Between 2008 and 2019 adolescents and young adults were enrolled into one of two cohorts. Cohort 1 was comprised of consecutive individuals who were followed since KD diagnosis at Rady Children's Hospital/University of California San Diego (UCSD) in San Diego, California until age 18. Cohort 2 was comprised of subjects with a remote history of KD who were recruited through outreach efforts and/or self-referred, and who were diagnosed and/or followed initially at outside institutions. A subset of subjects were diagnosed at the time of an acute cardiovascular event due to coronary artery aneurysms and the history of a KD-compatible illness was obtained at that time. Subjects were also encouraged to refer a same-sex "best friend control" of similar age who never had KD. Healthy medical students without prior KD were also recruited as controls. All subjects provided written, informed consent or assent with parent or guardian consent, as appropriate. The study was approved by the Institutional Review Board (IRB) at UCSD and all procedures were in accordance with the "Declaration of Helsinki" and the ethical standards of the responsible IRB.

2.2. Data collection and testing

All subjects filled out a detailed questionnaire regarding demographics, medical history, cardiovascular risk factors, family medical history, and lifestyle (including dietary patterns, exercise, and habits). KD subjects also completed a questionnaire regarding their KD history, and medical records relating to their KD diagnosis, treatment and follow-up were obtained whenever available.

For Cohort 1 subjects, coronary artery status was determined based on initial echocardiograms performed during the acute and subacute phases of KD, according to American Heart Association (AHA) guidelines, as previously described [7,8]. For Cohort 2 subjects, coronary artery status was determined based upon review of medical records from their initial illness, when available, and according to the same AHA guidelines. When medical records were unavailable, coronary status was determined by patient report of their initial illness; or by cardiac catheterization results for those presenting acutely years after their KD. Coronary artery calcium scores were performed to verify the absence of coronary artery pathology in a subset of Cohort 2 patients who reported always normal coronaries [7]. Coronary artery z scores were calculated as the standard deviation (SD) from the mean for the internal diameter of the coronary artery, normalized for body surface area, and were based upon measurements of the proximal left anterior descending or proximal right coronary artery. Subjects with a coronary artery z score < 2.0 on serial echocardiograms in the acute and subacute KD phases were designated as "normal". Those with a coronary artery z score between 2.0 and 3.0 (whose arteries generally returned to normal within 6 weeks of fever onset) were designated as "transiently dilated". Subjects with a z score $\geq$3.0 but $<$10.0 were designated as having aneurysms. Giant aneurysms were defined as a z score $\geq$10.0 or an absolute internal diameter $>$8.0 mm. For Cohort 2 subjects, coronary artery status was based upon review of medical records when available, otherwise by subject self-report.

2.3. Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviation; laboratory variables that were not normally distributed are presented as medians (quartile 1- quartile 3). Dichotomous variables are presented as percentages. Differences in baseline levels of risk factors and clinical characteristics between groups were analyzed with t-tests, Mann Whitney U and chi-square tests as appropriate. Fisher's exact tests were used for rare events. 2-sided p values < 0.05 were considered statistically significant. All testing was performed using SPSS, version 28.0 (Chicago, IL).

3. Results

3.1. Baseline characteristics

A total of 258 KD subjects (109 in Cohort 1 and 149 in Cohort 2) and 148 controls completed questionnaires and were included in these analyses. KD subjects and controls were of similar age at the time of questionnaire completion (25 ± 10 years for KD subjects vs 26 ± 8 years for controls, $p = 0.50$). Subjects in Cohort 1 were younger than those in Cohort 2 and had a slightly younger average age at KD diagnosis (Table 1). Just over half of each KD cohort was male. Subjects were on average 19 ± 9 years from their KD diagnosis. Of the 216 subjects with known coronary artery status during their acute and subacute KD, 59% had normal coronary arteries, 11% had transiently dilated coronary arteries, and 30% had coronary aneurysms. Coronary artery status by Cohort is shown in Table 1. Subjects in Cohort 2 were over 2.5 times as likely to have giant aneurysms as those in Cohort 1. Females were more likely to have normal coronary arteries than males. The majority of subjects in both cohorts, as well as controls, reported excellent or very good overall health, though this was more commonly reported in Cohort 1 compared to Cohort 2 subjects. In both cohorts, as well as controls, approximately half of the participants reported engaging in regular strenuous exercise.

In both cohorts, KD subjects were much more likely to report a history of chest pain compared to controls (41% of Cohort 1, 59% of Cohort 2, vs 16% of controls; $p < 0.001$ for both comparisons). They were also more likely to report palpitations (19% in Cohort 1, 40% in Cohort 2, vs 10% in controls; $p = 0.04$ and < 0.001, respectively.) Eczema was more common in Cohort 1 compared to controls, while migraine headaches were more common among Cohort 2 subjects compared to controls (Table 1); these patterns were consistent but non-significant in the other cohort.

3.2. KD subjects with normal coronary arteries

Among the KD subjects, 128 had normal coronary arteries during the acute and subacute phases of KD, including 60 in Cohort 1 and 68 in Cohort 2. Compared to controls, KD subjects with a history of always normal coronary arteries reported a variety of medical conditions with increased prevalence compared to controls, despite being slightly younger (23 ± 6 years vs 26 ± 8 years, $p = 0.01$; **Fig. 1** and **Supplement** Table 1). Regardless of Cohort, KD subjects were almost three times more likely to report symptoms of chest pain and were two to three times as likely to report palpitations or migraine headaches (Table 2). They were significantly more likely to report shortness of breath. They were also significantly more likely to report a history of hypertension or leg pain with walking, though this was predominantly driven by Cohort 2. In Cohort 2 only, they were less likely to categorize their health as either excellent or very good compared to controls (52% vs 77%, $p = 0.002$), and were three times as likely to report a diagnosis of depression (15% vs 5%, $p = 0.01$) or attention deficit hyperactivity disorder (10% vs 3%, $p = 0.04$). Despite the absence of coronary artery abnormalities after KD in these Cohort 2 subjects, the controls were nonetheless more likely than them to have "none of the above" queried medical conditions.

Despite more frequent symptoms in KD subjects with normal coronaries than in the controls, a similar proportion in each group reported engaging in regular strenuous exercise. However, when stratified by the presence or absence of any of the above symptoms, both KD subjects and controls were more likely to exercise regularly if they reported none of the above symptoms compared to those with symptoms. Results were

Table 1
Characteristics of the study population by cohort.

	Controls (n = 148)	Cohort 1 (n = 109)	p (1 vs Controls)	Cohort 2 (n = 149)	p (2 vs Controls)	p (Both Cohorts vs Controls)
Demographics						
Age (yrs)	26 ± 8	19 ± 4	<0.001	30 ± 10	<0.001	0.50
Age at KD diagnosis (yrs)	N/A	4 ± 4	N/A	5 ± 5	N/A	N/A
Years since KD diagnosis	N/A	15 ± 4	N/A	23 ± 10	N/A	N/A
Sex (% male)	47	59	0.07	53	0.31	0.11
Worst Coronary Artery Status, %*			N/A		N/A	N/A
Normal		59		59		
Transiently dilated		18		4		
Aneurysm		15		16		
Giant aneurysm		8		21		
Lifestyle, %						
Cigarettes, ever	16	10	0.23	25	0.07	0.49
Alcohol, any (past year)	91	50	<0.001	78	0.004	<0.001
Regular strenuous exercise	50	46	0.52	51	0.91	0.79
General Health			0.29		<0.001	0.001
Excellent/very good	77	68		52		
Fair/poor	7	9		13		
Symptoms, %						
Palpitations	10	19	0.04	40	<0.001	<0.001
Leg swelling	1	2	1.00	11	<0.001	0.01
SOB <1 block	0	3	0.08	7	<0.001	0.004
SOB uphill	11	15	0.35	27	<0.001	0.006
SOB sitting	0	2	0.18	5	0.007	0.02
SOB lying down	1	4	0.17	9	<0.001	0.004
Leg pain with walking	2	4	0.46	15	<0.001	0.002
Chest pain	16	41	<0.001	59	<0.001	<0.001
Cardiovascular Diagnoses, %						
Hypertension	3	7	0.15	13	0.002	0.008
Hyperlipidemia	7	6	0.92	22	<0.001	0.01
SVT	0	1	0.42	4	0.03	0.05
Atrial fibrillation	0	1	0.42	6	0.003	0.02
CAD/blockages	0	3	0.08	13	<0.001	<0.001
Non-cardiac Diagnoses, %						
Migraine headaches	5	8	0.36	18	<0.001	0.008
Raynaud's phenomenon	1	1	1.00	5	0.07	0.16
Asthma	14	19	0.28	14	0.98	0.58
Eczema	8	17	0.02	11	0.44	0.10
Psoriasis	1	1	1.00	3	0.37	0.42
No inflammatory disease	85	83	0.72	72	0.005	0.04
Food allergies	9	8	0.88	16	0.06	0.22
Medication allergies	13	17	0.31	32	<0.001	0.002
ADHD	3	12	0.004	11	0.006	0.002
Depression	5	7	0.38	22	<0.001	<0.001
NONE OF ABOVE	54	44	0.11	30	<0.001	<0.001

*Worst coronary artery status refers to the coronary dimensions on echocardiography, in the acute and subacute phases of Kawasaki disease.
P values are for Cohort 1 or Cohort 2 versus Controls.
Data are reported as column %, except where otherwise specified.
ADHD, attention deficit hypersensitivity disorder; CAD, coronary artery disease; GERD, gastroesophageal reflux disease; KD, Kawasaki disease; SOB, shortness of breath; SVT, supraventricular tachycardia.

not materially changed when limiting the control subjects to those under 21 years of age (n = 25).

3.3. KD subjects with coronary aneurysms

As expected, the 65 KD subjects with coronary aneurysms were more likely than KD subjects with normal coronary arteries to report chest pain – however this was the only symptom they reported with greater frequency (**Supplement** Table 2). Compared to subjects with normal coronary arteries, those with aneurysms were no more likely to report palpitations, shortness of breath, or a diagnosis of depression, and were just as likely to engage in regular strenuous exercise, despite the fact that a quarter of those with aneurysms reported known coronary artery stenosis or occlusion. Similar majority proportions of each group reported their overall health as either excellent or very good, and similar small proportions reported either fair or poor health. These findings held true when analysis was stratified by Cohort (Table 3).

Assessment of overall health among those with aneurysms was not as favorable when compared to controls instead of other KD subjects (**Supplement** Table 2). Subjects with coronary aneurysms were more likely than controls to report fair or poor general health, palpitations, shortness of breath, and chest pain. However when analyses were limited to Cohort 1 subjects, those with aneurysms reported similar overall health as controls.

4. Discussion

Data on long term health outcomes after KD from systematic studies are limited. We report that most young adults with a childhood history of KD consider themselves to have excellent or very good health, though some aspects of their health vary based upon the status of their coronary arteries.

Despite always having normal coronary arteries during the acute and subacute phases of KD, young adults with a history of KD with normal coronaries were more likely to experience several cardiovascular symptoms. This subgroup reported an increased prevalence of chest pain and leg pain with walking, as well as an increased prevalence of migraine headaches and hypertension compared to controls. While these

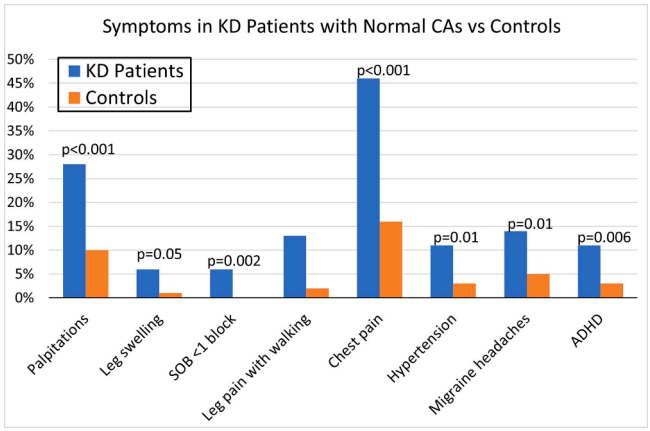

Fig. 1. Prevalence of symptoms in Kawasaki disease patients with normal coronary arteries (n = 128) versus controls (n = 148). ADHD = attention deficit hyperactivity disorder, CA = coronary artery, KD = Kawasaki disease, SOB = shortness of breath.

differences could be influenced by anxiety or depression, report of depression did not vary between this KD subgroup and controls. It is intriguing to speculate that abnormal vascular reactivity could influence both migraines and hypertension. Whether these conditions are consequences of the vascular inflammation suffered during the acute illness or whether these conditions are in some way genetically linked to KD susceptibility remain topics for future study. Selamet-Tierney et al reported that in 136 subjects with always normal coronary artery dimensions, studied a median of 11.6 years after KD, peripheral vascular health indices including endothelial cell function, carotid intima media thickness, and carotid stiffness, were normal and similar to controls [2]. A number of other studies evaluating peripheral vascular health after KD, though, have had conflicting results [9–14].

Our finding that symptoms such as chest pain, shortness of breath, and palpitations were more common in KD subjects with coronary aneurysms than in controls was not surprising. Some of these differences were attenuated when analyses were restricted to Cohort 1, though this may be due in part to the younger age of Cohort 1 subjects.

We found a number of differences based upon Cohort, as well. Cohort 2 (but not Cohort 1) subjects had an increased prevalence of depression compared to controls, and this was most pronounced in those with coronary aneurysms. Cohort 2 subjects were also more likely to report fair or poor overall health, cardiovascular symptoms (chest pain, shortness of breath, palpitations), and a number of other diagnoses. This suggests a probable referral bias in this cohort, whereby individuals with perceived worse sequelae of KD, and/or depression in general, were more likely to seek out and join the present study.

In contrast, the prevalence of ADHD was similarly increased in both Cohort 1 and Cohort 2 compared to controls, and was independent of coronary artery status. The prevalence of ADHD in the United States is approximately 5–10%, depending upon the source and demographics [15]. There are limited studies evaluating the association between ADHD and KD. A prospective study of 651 Taiwanese children with KD found a cumulative incidence of approximately 3% over 5 years, which was higher compared to age- and sex-matched controls, though the association was not independent of age, sex, and comorbidities [16]. A retrospective study of 612 Taiwanese children with a history of KD reported a prevalence of ADHD of 5%, which was not increased compared to the general Taiwanese or worldwide population [17]. Although we report a similar prevalence of ADHD in our control subjects, the prevalence was more than twice as high within both of our KD cohorts. Another Taiwanese study, involving over 8,000 patients with ADHD, found an association between ADHD and autoimmune/allergic diseases, though they did not look specifically at KD [18].

Previous studies have found an association between KD and allergic

Table 2
Characteristics of subjects with normal coronary arteries vs controls.

	Controls (n = 148)	Cohort 1 Normal CAs (n = 60)	p	Cohort 2 Normal CAs (n = 68)	p
Demographics					
Age (yrs)	26 ± 8	19 ± 3	<0.001	27 ± 7	0.24
Age at KD diagnosis (yrs)	N/A	4 ± 3	N/A	5 ± 4	N/A
Years since KD diagnosis	N/A	15 ± 4	N/A	22 ± 8	N/A
Sex (% male)	47	51	0.61	47	1.00
Lifestyle, %					
Cigarettes, ever	16	12	0.50	20	0.47
Alcohol, any (past year)	91	63	<0.001	75	0.004
Regular strenuous exercise	50	48	0.79	48	0.79
General health			0.62		0.002
Excellent/ very good	77	72		52	
Fair/poor	7	6		15	
Symptoms, %					
Palpitations	10	23	0.01	32	<0.001
Leg swelling	1	0	0.59	12	0.002
SOB <1 block	0	3	0.03	9	<0.001
SOB uphill	11	10	0.86	26	0.003
SOB sitting	0	2	0.29	6	0.009
SOB lying down	1	3	0.20	12	<0.001
Leg pain with walking	2	3	0.63	21	<0.001
Chest pain	16	47	<0.001	46	<0.001
Cardiovascular Diagnoses, %					
Hypertension	3	7	0.45	15	0.007
Hyperlipidemia	7	8	0.77	13	0.12
SVT	0	0	1.00	4	0.03
Atrial fibrillation	0	0	1.00	3	0.10
CAD/blockages	0	2	0.29	0	1.00
Non-cardiac Diagnoses, %					
Migraine headaches	5	12	0.11	16	0.009
Raynaud's phenomenon	1	2	1.00	4	0.09
Asthma	14	18	0.45	15	0.92
Eczema	8	15	0.14	9	0.86
Psoriasis	1	2	1.00	3	0.23
No inflammatory disease	85	85	0.98	69	0.006
Food allergies	9	5	0.41	15	0.19
Medication allergies	13	20	0.19	35	<0.001
ADHD	3	12	0.01	10	0.04
Depression	5	7	0.73	15	0.01
NONE OF ABOVE	54	40	0.07	26	<0.001

Data are reported as column %, except where otherwise specified.
Normal coronary arteries (CAs) refers to during the acute and subacute phases of Kawasaki disease.
P values are for Cohort 1 or Cohort 2 versus Controls.
Abbreviations as in Table 1.

diseases, including asthma and atopic dermatitis, among others [19–22]. We found an increased prevalence of allergies to medications among KD subjects compared to controls, though this was not seen in analyses limited to Cohort 1, and a significant increase in eczema among Cohort 1 subjects compared to controls. Previous studies have linked eczema to KD in both Asian and mixed ethnic U.S. populations [20,22].

Table 3
Characteristics of subjects with aneurysms vs normal coronary arteries, by cohort.

	COHORT 1			COHORT 2		
	Aneurysms (n = 23)	Normal CAs (n = 60)	p	Aneurysms (n = 42)	Normal CAs (n = 68)	p
Demographics						
Age (years)	19 ± 4	19 ± 3	0.83	33 ± 14	27 ± 7	0.005
Age at KD diagnosis	4 ± 5	4 ± 3	0.39	7 ± 6	5 ± 4	0.06
Years since KD diagnosis	15 ± 5	15 ± 4	0.61	25 ± 14	22 ± 8	0.31
Sex (% male)	64	51	0.31	70	47	0.02
Lifestyle, %						
Cigarettes, ever	9	12	1.00	26	20	0.47
Alcohol, any (past year)	32	63	0.01	82	75	0.47
Regular strenuous exercise	52	48	0.75	47	48	0.93
General health			0.43			0.56
Excellent/very good	61	72		53	52	
Fair/poor	13	6		8	15	
Symptoms, %						
Palpitations	17	23	0.77	36	32	0.72
Leg swelling	0	0	1.00	7	12	0.53
SOB <1 block	0	3	1.00	2	9	0.25
SOB uphill	26	10	0.08	19	26	0.37
SOB sitting	4	2	0.48	5	6	1.00
SOB lying down	4	3	1.00	7	12	0.53
Leg pain with walking	0	3	1.00	10	21	0.13
Chest pain	39	47	0.54	81	46	<0.001
Cardiovascular Diagnoses, %						
Hypertension	13	7	0.39	12	15	0.68
Hyperlipidemia	4	8	0.53	36	13	0.006
SVT	0	0	1.00	2	4	1.00
Atrial fibrillation	0	0	1.00	10	3	0.20
CAD/blockages	9	2	0.18	36	0	<0.001
Non-cardiac Diagnoses, %						
Migraine headaches	4	12	0.43	17	16	0.95
Raynaud's phenomenon	0	2	1.00	2	4	1.00
Asthma	22	18	0.76	12	15	0.68
Eczema	17	15	0.75	7	9	1.00
Psoriasis	0	2	1.00	2	3	1.00
No inflammatory disease	87	85	1.00	69	69	0.99
Food allergies	13	5	0.34	12	15	0.68
Medication allergies	13	20	0.54	24	35	0.21
ADHD	9	12	1.00	7	10	0.74
Depression	9	7	0.67	24	15	0.23
NONE OF ABOVE	56	40	0.18	31	26	0.61

Data are reported as column %, except where otherwise specified.
Abbreviations as in Table 1; CAs coronary arteries.
Aneurysms and Normal CAs refers to coronary dimensions during the acute and subacute phases of Kawasaki disease.

5. Strengths and limitations

This study has several limitations. Among subjects with normal coronary arteries, the Cohort 1 subset was younger than the Cohort 2 subset, and both were slightly younger than controls. Although this difference was statistically significant, it is not clear that it was physiologically significant; nonetheless, with older age, certain diagnoses such as hypertension become more prevalent. However, even with this limitation, we found several symptoms and conditions that were more common in the younger KD subgroups. It is possible that some young adults with a history of KD have more exposure to medical visits and thus more opportunities to receive medical diagnoses compared to age-similar young adult control subjects; however the likelihood of this bias is low in analyses restricted to KD subjects with normal coronary arteries. This study did not incorporate standard inventories for depression/anxiety that might have uncovered important psychological differences among the cohorts. We cannot exclude the possibility that some of the differences we identified in symptoms and health perception were related to lifestyle factors, given that cigarette smoking and alcohol use varied between groups; however most of this difference was due to the higher prevalence of smoking and alcohol use in the older, self-referred Cohort 2. Further, we did not account for socio-economic status, marriage status, income, or education level, each of which may be significant contributors to cardiovascular disease and symptoms. Finally, lack of physician records for all subjects in Cohort 2 may have led to misclassification of the coronary artery status in some subjects.

Strengths of this study include the inclusion of a substantial number of Cohort 1 patients who have been followed systematically since their diagnosis of KD at a highly experienced center, limiting the misclassification and referral bias.

6. Conclusion

The subset of young adults with a history of KD who had normal coronary arteries during and after their KD diagnosis, are nonetheless more likely to experience several cardiovascular symptoms compared to controls of similar age and sex. These differences could be influenced by anxiety or depression, but report of depression did not vary between KD subjects and controls. Whether these health differences reflect a heightened awareness of symptoms among subjects with a history of KD, or underlying vascular pathology due to vasospasm, microvascular dysfunction, or some other mechanism, merits further study.

Sources of funding

This work was supported in part by grants from the American Heart Association (Award Number 09SDG2010231), the Gordon and Marilyn Macklin Foundation, and the National Center For Research Resources

(Award Number UL1TR001442).

This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2022.101039.

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