# Meta-analysis of risk factors associated with atherosclerosis in patients with Kawasaki disease

**Han Zhang, Ming-Guo Xu, Li-Jian Xie, Min Huang, Jie Shen, Ting-Ting Xiao**
*Shanghai, China*

***Background:*** **Kawasaki disease (KD) has now become the leading cause of acquired heart disease among children in developed countries. This study investigated whether patients with KD have an increased risk of atherosclerosis.**

***Methods:*** **Electronic databases, including PubMed, Embase and Springer link, were searched through June 1, 2015, for eligible studies. Studies were included when they met the following criteria: 1) an observational study focusing on evaluating the risk factors for atherosclerosis in patients with KD; 2) KD was diagnosed clinically according to the Japan Kawasaki Disease Research Committee or American Heart Association's diagnostic criteria; 3) the study subjects were KD patients without coronary heart disease or related cardiovascular disease (KD group) and non-KD patients as control (control group), and 4) investigation of important atherosclerosis risk factors, total cholesterol (TC), low-density lipoprotein cholesterol (LDL), triglycerides (TG), systolic blood pressure (SBP), and flow-mediated dilatation (FMD). The methodological quality of the included studies was evaluated using the Newcastle-Ottawa Scale. Mean difference (MD) and relative risk (RR) and corresponding 95% confidence intervals (CI) were used to calculate the pooled results.**

***Results:*** **Sixteen studies were included with a total of 870 patients, including 421 KD patients and 449 non-KD controls. Differences in TG and SBP between KD patients and controls were not significant; in contrast, TC and LDL levels were significantly higher in KD patients than the controls, whereas FMD in the KD patients was significantly lower.**

***Conclusion:*** **KD patients may have an increased risk of developing atherosclerosis.**

***World J Pediatr 2016;12(3):308-313***

***Key words:*** **atherosclerosis; flow-mediated dilatation; Kawasaki disease; meta-analysis; total cholesterol**

**Author Affiliations:** Department of Cardiology, Shanghai Children's Hospital, Shanghai Jiaotong University, Shanghai, China (Zhang H, Xie LJ, Huang M, Shen J, Xiao TT); Department of Cardiovascular Center, Shenzhen Children's Hospital, Shenzhen, China (Xu MG)

**Corresponding Author:** Li-Jian Xie, MD, Department of Cardiology, Shanghai Children's Hospital, Shanghai Jiaotong University, 355 Luding Road, Putuo District, Shanghai 200062, China (Tel: +86-21-62474880; Email: naijileix@aliyun.com)

doi: 10.1007/s12519-016-0023-0



## Introduction

First described in Japan by Kawasaki in 1967,[1] Kawasaki disease (KD) has now become the leading cause of acquired heart disease among children in developed countries. KD is an acute, self-limited vasculitis of unknown etiology, predominantly occurring in infants and young children. KD is characterized by a fever lasting more than 5 days, bilateral non-purulent conjunctivitis, rash, erythema of the lips and oropharyngeal mucositis, edema in the extremes, and cervical lymphadenopathy.

In the acute phase of KD, morphological changes occur in coronary arteries, such as the appearance of coronary artery lesions that can result in serious outcome-coronary artery aneurysms (CAA), which have a mortality rate of approximately 15%-25% in untreated children with KD.[1] Recent studies have suggested that KD may cause endothelial dysfunction, even many years after the onset of KD, which may induce atherosclerosis.[2-4] However, tracking individuals diagnosed with KD in infancy in the 1960s has not been sufficient to determine whether there is an increased risk of atherosclerosis, and no direct evidence is available to support this hypothesis. Thus, a meta-analysis approach was undertaken to investigate the relationship between KD patients and atherosclerosis occurrence.

### Search strategy

Electronic databases, including PubMed, Embase and Springer link, were searched from their establishment date to June 1, 2015, without language restrictions. The key search terms were as follows: ("Kawasaki disease" OR "mucocutaneous lymph node syndrome") AND

("atherosclerosis" OR "atherosclerotic" OR "coronary arterial lesions" OR "endothelial"). Written papers were also retrieved by a manual search for additional literature; reviews and reference lists of the included studies were also scanned for additional relevant studies. Studies were included when meeting the following criteria: 1) an observational study focusing on evaluating the risk factors for atherosclerosis in patients with KD; 2) KD was diagnosed clinically according to the Japan Kawasaki Disease Research Committee or American Heart Association's diagnostic criteria; 3) KD patients without coronary heart disease or related cardiovascular disease as the test group and non-KD patients as control (control group), and 4) investigation of important atherosclerosis risk factors or predictive factors between KD patients and non-KD patients, such as total cholesterol (TC), low-density lipoprotein cholesterol (LDL), triglycerides (TG), systolic blood pressure (SBP), and flow-mediated dilatation (FMD). The following exclusion criteria were adopted: 1) studies with incomplete data or data unavailable for statistical analysis; 2) not research papers, such as reviews, letters or comments.

### Data extraction and quality assessment

The databases were searched by two independent investigators using the previously mentioned criteria. Then, data for the necessary information were collected according to a predefined standard form, such as first author's name, publication time, test site, age and gender composition of the participants, type of study, number of subjects in the case and control groups, source of the controls, follow-up time, number lost to follow-up, outcomes and body mass index. Disagreement between the two investigators was resolved by discussion with a third investigator. The methodological quality of the included studies was evaluated using the Newcastle-Ottawa Scale,[5] which has a total score of 9; a score ≥7 is considered high-quality, ≤3 as low-quality, and 3-7 as intermediate.

### Data analysis

Weighted mean difference (WMD) with the corresponding 95% confidence interval (CI) was used to calculate the pooled results for continuous outcomes, and relative risk (RR) with the corresponding 95% CI was used for dichotomous outcomes. Cochran's $Q$ and $I^2$ tests were used to estimate heterogeneity between studies.[6] A random effects model was selected when a significant heterogeneity was indicated ($P<0.05$ and/or $I^2>50\%$), and a fixed effects model was used when heterogeneity was not significant ($P\geq0.05$, $I^2\leq50\%$).[7] Publication bias was also assessed via funnel plot analysis. RevMan5.2 software (Cochrane Collaboration, http://ims.cochrane.org/revman) was used for all statistical analyses.

## Results

### Study inclusion and selection

The study search protocol is shown in Fig. 1. Initially, 2107 studies (473 from PubMed, 810 from Embase, 824 from Springer link) were selected using the key

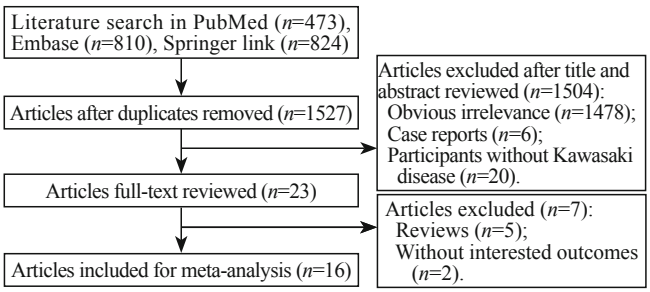


**Fig. 1.** Flow chart of the meta-analysis.

**Table 1.** Characteristics of studies included in the meta-analysis

| Author | Year | Country | Age (y) | | *n*, M/F | | BMI (kg/m²) | |
|---|---|---|---|---|---|---|---|---|
| | | | KD | Control | KD | Control | KD | Control |
| Cho | 2014 | Korea | 7.22±1.49 | 7.65±0.78 | 49, 25/24 | 30, 16/14 | 16.90±0.94 | 16.36±2.66 |
| Laurito | 2014 | Italy | 10.0±3.7 | 10.2±2.4 | 14, 9/5 | 14, 7/7 | 18.5±3.6 | 18.9±3.5 |
| Ishikawa | 2013 | Japan | 6.1±1.3 | 7.9±2.8 | 15, 7/8 | 22, 13/9 | 15.7±1.2 | 16.8±2.2 |
| Ghelani | 2009 | India | 8.4±2.3 | 8.6±2.6 | 20, 13/7 | 20, 13/7 | NR | NR |
| Gupta-Malhotra | 2009 | USA | 20.9±6 | 21.3±7.5 | 28, 19/9 | 27, 16/11 | 22±4 | 22±3 |
| Lee | 2009 | Korea | 12.6±2.0 | 14.5±0.7 | 25, NR | 55, NR | 19.9±4.5 | 20.5±2.40 |
| Liu | 2009 | China | 7.3 (4.9-11.0)* | 8.4 (3.2-14.0) | 20, 12/8 | 22, 13/9 | 17.5±4.1 | 15.8±2.3 |
| Noto | 2009 | Japan | 20.5±9.3 | 19.6±7.2 | 35, 28/7 | 35, 28/7 | 22.0±6.7 | 20.5±5.0 |
| Borzutzky | 2008 | Chile | 10.6±2.0 | 10.4±1.8 | 11, 7/4 | 11, 7/4 | NR | NR |
| Niboshi | 2008 | Japan | 27.0±4.2 | 25.5±3.9 | 35, 16/19 | 36, 19/17 | 20.7±2.3 | 20.8±1.8 |
| Cheung | 2007 | China | 8.6±3.3 | 9.5±2.5 | 24, 16/8 | 22, 14/8 | 15.8±2.0 | 16.9±3.7 |
| McCrindle | 2007 | Canada | 15.5±2.3 | 14.9±2.4 | 52, 35/17 | 60, 30/30 | NR | NR |
| Pozza | 2007 | Germany | 12.1±4.7 | 12.0±3.1 | 20, 12/8 | 28, 10/18 | 17.9±5.5 | 19.8±3.5 |
| Cheung | 2004 | China | 8.9±3.2 | 9.1±2.6 | 29, 20/9 | 36, 24/12 | 16.0±2.7 | 16.9±3.4 |
| Silva | 2001 | Canada | 14.3±1.8 | 14.1±1.5 | 24, 18/6 | 11, 6/5 | 22.9±3.6 | 21.4±3.9 |
| Dhillon | 1996 | UK | 13 (11-19)* | 15 (10-16) | 20, 12/8 | 20, 12/8 | NR | NR |

USA: United States of America; UK: United Kingdom; KD: Kawasaki disease; M: male; F: female; BMI: body mass index; NR: not reported. *: median (range).

**Table 2.** Methodological quality of case-control studies included in the meta-analysis*

| First author | Representativeness of the cases | Case definition adequate | Ascertainment of exposure | Same method of ascertainment for cases and controls | Control for important factor or additional factor† | Selection of controls | Definition of controls | Non-response rate | Total quality scores |
|---|---|---|---|---|---|---|---|---|---|
| Borzutzky | * | * | * | * | - | - | * | * | 6 |
| Cheung | * | * | * | * | * | - | * | * | 7 |
| Cheung | * | * | * | * | * | - | * | * | 7 |
| Cho | * | * | * | * | * | - | * | * | 7 |
| Dhillon | * | * | * | * | - | - | * | * | 6 |
| Ghelani | * | * | * | * | - | * | * | * | 7 |
| Gupta-Malhotra | * | * | * | * | * | * | * | * | 8 |
| Ishikawa | * | * | * | * | * | * | * | * | 8 |
| Laurito | * | * | * | * | * | - | * | * | 7 |
| Lee | * | * | * | * | * | * | * | * | 8 |
| Liu | * | * | * | * | * | * | * | * | 8 |
| McCrindle | * | * | * | * | - | * | * | * | 7 |
| Niboshi | * | * | * | * | * | - | * | * | 7 |
| Noto | * | * | * | * | * | * | * | * | 8 |
| Pozza | * | * | * | * | * | - | * | * | 7 |
| Silva | * | * | * | * | * | - | * | * | 7 |

*: A study could be awarded a maximum of one star for each item except for the item "Control for important factor or additional factor"; †: A maximum of two stars could be awarded for this item.

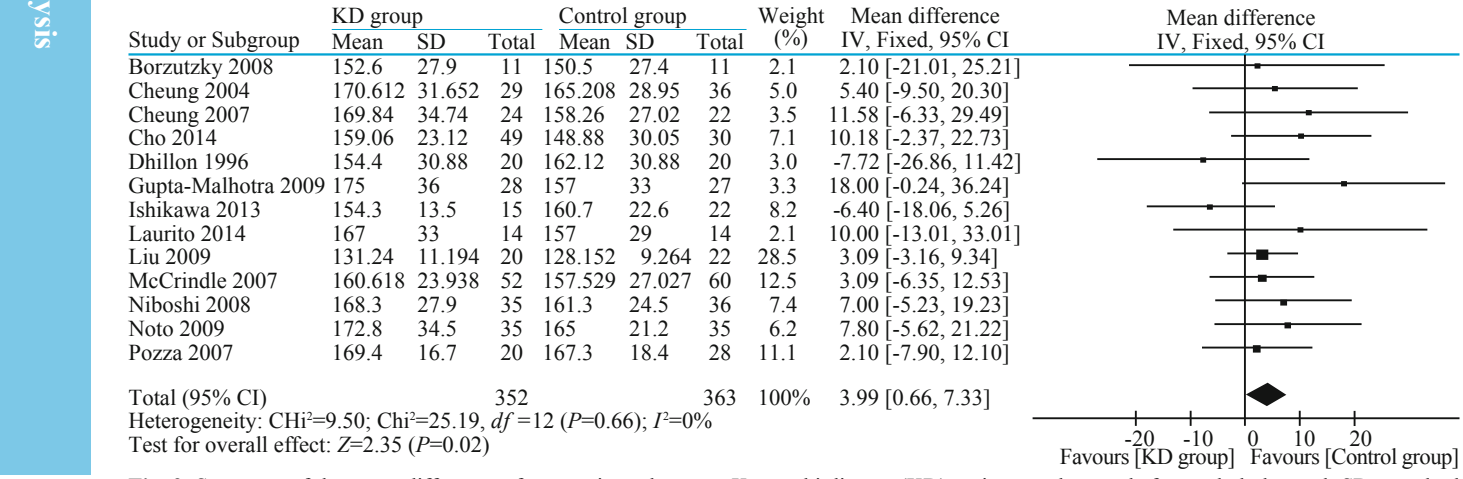


**Fig. 2.** Summary of the mean difference of comparisons between Kawasaki disease (KD) patients and controls for total cholesterol. SD: standard deviation; IV: independent variable; CI: confidence interval.

terms defined above. After excluding repeated results, 1527 studies were retained. Of those, 1504 studies were excluded (1478 not meeting the criteria, 6 case reports and 20 non-KD patients) after title browsing. Finally, after full-text reading, 16 studies were retained and included for later meta-analysis. No studies meeting the inclusion criteria were obtained by manual search.

**Characteristics and quality assessment of eligible studies**

All included studies were case-control studies[8-23] implemented in China, Korea, Japan, America or Canada, etc., during 1996-2014. The included studies involved 870 patients, including 421 KD patients and 449 non-KD controls (Table 1). No significant differences in demographic parameters (e.g., age, gender and BMI) were observed between the KD and control groups. The methodological quality evaluation found that all included studies scored ≥6, indicating intermediate quality or higher (Table 2).

**Factors affecting the risk of atherosclerosis**

A total of 13 studies[8-12,14,16-21,23] reported differences in TC and LDL between the KD and control groups. The heterogeneity test result for TC was as follows: $I^2$=0%, $P$=0.66, indicating no significant heterogeneity; thus, a fixed effects model was applied, and the combined MD (95% CI) was 3.99 (0.66-7.33) mg/dL ($P$=0.02), suggesting a significant difference (Fig. 2). No significant differences in LDL were observed between the KD group and control groups $I^2$=0%, $P$=0.45), indicating no significant heterogeneity. A fixed effects model was used, and the combined MD (95% CI) was 3.42 (0.50-6.33) mg/dL ($P$=0.02), suggesting a significant difference (Fig. 3).

Among the included studies, 9 studies[8-11,14,17-19,21] reported differences in TG (Fig. 4). The heterogeneity test result for TG was as follows: $I^2$=9%, $P$=0.36, indicating no significant difference. A fixed effects model was used, and the combined MD (95% CI) was

| Study or Subgroup | KD group Mean | SD | Total | Control group Mean | SD | Total | Weight (%) | Mean difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Borzutzky 2008 | 77.4 | 20.8 | 11 | 83.6 | 21.1 | 11 | 2.8 | -6.20 [-23.71,11.31] |
| Cheung 2004 | 101.904 | 28.178 | 29 | 91.482 | 25.862 | 36 | 4.8 | 10.42 [-2.87,23.71] |
| Cheung 2007 | 100.36 | 30.88 | 24 | 84.92 | 23.16 | 22 | 3.4 | 15.44 [-0.25,31.13] |
| Cho 2014 | 83.79 | 21.25 | 49 | 80.05 | 8.5 | 30 | 19.0 | 3.74 [-2.94,10.42] |
| Dhillon 1996 | 84.92 | 27.02 | 20 | 100.36 | 27.02 | 20 | 3.0 | -15.44 [-32.19,1.31] |
| Gupta-Malhotra 2009 | 103 | 30 | 28 | 90 | 23 | 27 | 4.3 | 13.00 [-1.10,27.10] |
| Ishikawa 2013 | 87.8 | 19.3 | 15 | 86.5 | 18.6 | 22 | 5.4 | 1.30 [-11.18,13.78] |
| Laurito 2014 | 91 | 23 | 14 | 84 | 21 | 14 | 3.2 | 7.00 [-9.31,23.31] |
| Liu 2009 | 84.534 | 12.352 | 20 | 83.376 | 10.036 | 22 | 18.1 | 1.15 [-5.70,8.00] |
| McCrindle 2007 | 97.3 | 21.62 | 52 | 93.82 | 22.01 | 60 | 12.9 | 3.48 [-4.62,11.58] |
| Niboshi 2008 | 97.3 | 25.3 | 35 | 93.2 | 19.4 | 36 | 7.7 | 4.10 [-6.41,14.61] |
| Noto 2009 | 94.4 | 23.8 | 35 | 90.2 | 17.3 | 35 | 8.9 | 4.20 [-5.55,13.95] |
| Pozza 2007 | 94.3 | 22.4 | 20 | 92.5 | 16.4 | 28 | 6.4 | 1.80 [-9.74,13.34] |
| Total (95% CI) | | | 352 | | | 363 | 100 | 3.42 [0.50,6.33] |

Heterogeneity: CHi$^2$=11.97; Chi$^2$=12, *df* =12 (*P*=0.45); $I^2$=0%
Test for overall effect: *Z*=2.30 (*P*=0.02)

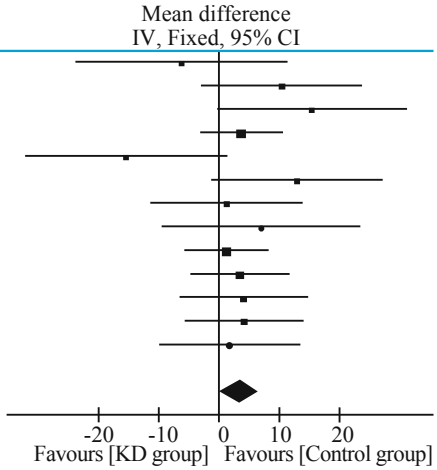


**Fig. 3.** Summary of the mean difference of comparisons between Kawasaki disease (KD) patients and controls for low-density lipoprotein cholesterol. SD: standard deviation; IV: independent variable; CI: confidence interval.

| Study or Subgroup | KD group Mean | SD | Total | Control group Mean | SD | Total | Weight (%) | Mean difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Borzutzky 2008 | 83.2 | 37.8 | 11 | 80.4 | 31.5 | 11 | 6.2 | 2.8 [-26.28, 31.88] |
| Cheung 2004 | 62 | 23.9 | 29 | 77.6 | 32.7 | 36 | 27.7 | -15.6 [-29.38, -1.82] |
| Cho 2014 | 97.29 | 61.34 | 49 | 105.87 | 110.4 | 30 | 2.8 | -8.58 [-51.66, 34.50] |
| Gupta-Malhotra 2009 | 99 | 48 | 28 | 86 | 54 | 27 | 7.2 | 13.00 [-14.04, 40.04] |
| Ishikawa 2013 | 70 | 31.4 | 15 | 79.7 | 44.9 | 22 | 8.7 | -9.70 [-34.29, 14.89] |
| Laurito 2014 | 82 | 38 | 14 | 89 | 79 | 14 | 2.5 | -7.00 [-52.92, 38.92] |
| McCrindle 2007 | 97.4 | 37.3 | 52 | 88.5 | 36.3 | 60 | 28.1 | 8.90 [-4.78, 22.58] |
| Noto 2009 | 91 | 46.1 | 35 | 83.8 | 42.6 | 35 | 12.2 | 7.20 [-13.60, 28.00] |
| Pozza 2007 | 123.6 | 55.6 | 20 | 130.5 | 65.3 | 28 | 4.5 | -6.90 [-41.23, 27.43] |
| Total (95% CI) | | | 253 | | | 263 | 100 | -1.41 [-8.66, 5.85] |

Heterogeneity: Chi$^2$=8.79, *df* =8 (*P*=0.36); $I^2$=9%
Test for overall effect: *Z*=0.38 (*P*=0.70)

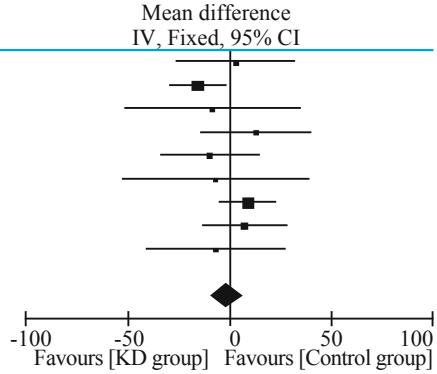


**Fig. 4.** Summary of the mean difference of comparisons between Kawasaki disease (KD) patients and controls for triglycerides. SD: standard deviation; IV: independent variable; CI: confidence interval.

| Study or Subgroup | KD group Mean | SD | Total | Control group Mean | SD | Total | Weight (%) | Mean difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Cheung 2004 | 107 | 8 | 29 | 108 | 11 | 36 | 8.1 | -1.00 [-5.62, 3.62] |
| Cheung 2007 | 107 | 8 | 24 | 107 | 11 | 22 | 6.6 | 0.00 [-5.60, 5.60] |
| Cho 2014 | 106.14 | 9.01 | 49 | 103.25 | 3.24 | 30 | 11.7 | 2.89 [0.11, 5.67] |
| Ghelani 2009 | 92.3 | 5 | 20 | 90.3 | 5.2 | 20 | 10.9 | 2.00 [-1.16, 5.16] |
| Ishikawa 2013 | 95.4 | 4.7 | 15 | 96.1 | 7.5 | 22 | 9.3 | -0.70 [-4.63, 3.23] |
| Laurito 2014 | 105 | 12 | 14 | 101 | 8 | 14 | 4.5 | 4.00 [-3.55, 11.55] |
| Lee 2009 | 113 | 14.1 | 25 | 112.4 | 11.1 | 55 | 5.8 | 0.60 [-5.66, 6.86] |
| Liu 2009 | 99 | 7 | 20 | 95 | 8 | 22 | 8.2 | 4.00 [-0.54, 8.54] |
| McCrindle 2007 | 107 | 12 | 52 | 113 | 10 | 60 | 9.0 | -6.00 [-10.13, -1.87] |
| Niboshi 2008 | 109.2 | 12.3 | 35 | 112.9 | 9.1 | 36 | 7.4 | -3.70 [-8.74, 1.34] |
| Noto 2009 | 113.4 | 11 | 35 | 115.3 | 7.6 | 35 | 8.4 | -1.90 [-6.33, 2.53] |
| Pozza 2007 | 108 | 13.9 | 20 | 110.8 | 8.6 | 28 | 5.1 | -2.80 [-9.67, 4.07] |
| Silva 2001 | 118 | 11 | 24 | 111 | 9 | 11 | 5.1 | 7.00 [0.10, 13.90] |
| Total (95% CI) | | | 362 | | | 391 | 100 | 0.19 [-1.69,2.08] |

Heterogeneity: Tau$^2$=5.86; Chi$^2$=25.19, *df* =12 (*P*=0.01); $I^2$=52%
Test for overall effect: *Z*=0.20 (*P*=0.84)

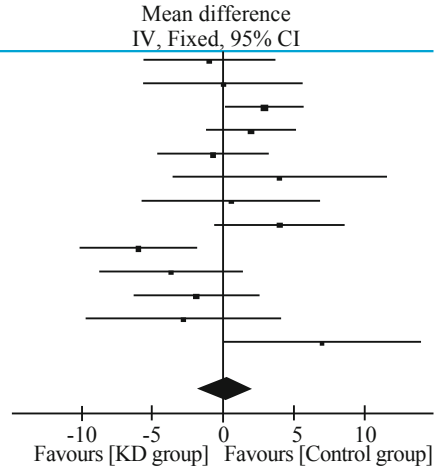


**Fig. 5.** Summary of the mean difference of comparisons between Kawasaki disease (KD) patients and controls for systolic blood pressure. SD: standard deviation; IV: independent variable; CI: confidence interval.

-1.41 (-8.66, 5.85) mg/dL (*P*=0.70), suggesting no significant difference (Fig. 4).

Thirteen studies[8-13,15,16,18-22] reported differences in SBP. The heterogeneity test results for SBP were as follows: $I^2$=52%, *P*=0.01, indicating significant heterogeneity. Thus, a random effects model was used. The combined MD (95% CI) was 0.19 (-1.69-2.08) mmHg, *P*=0.70, indicating no significant difference (Fig. 5).

Five studies reported FMD. The heterogeneity test result for MD was as follows: $I^2$=80%, *P*=0.0004,

| Study or Subgroup | KD group Mean | SD | Total | Control group Mean | SD | Total | Weight (%) | Mean difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Borzutzky 2008 | 11.1 | 5.7 | 11 | 8 | 2.9 | 11 | 13.1 | 3.10 [-0.68, 6.88] |
| Dhillon 1996 | 3.1 | 3.5 | 20 | 9.4 | 3.5 | 20 | 19.8 | -6.30 [-8.47, -4.13] |
| Liu 2009 | 9.5 | 2.8 | 20 | 12.1 | 2.3 | 22 | 22.5 | -2.60 [-4.16, -1.04] |
| Niboshi 2008 | 10.4 | 2.6 | 35 | 14.4 | 3.2 | 36 | 23.3 | -4.00 [-5.35, -2.65] |
| Noto 2009 | 9.1 | 2.7 | 35 | 13.3 | 4.8 | 35 | 21.3 | -4.20 [-6.02, -2.38] |
| Total (95% CI) | | | 121 | | | 124 | 100 | -3.25 [-5.19, -1.31] |

Heterogeneity: Tau²=3.71; Chi²=20.33, *df* =4 (*P*=0.0004); $I^2$=80%
Test for overall effect: *Z*=3.29 (*P*=0.001)

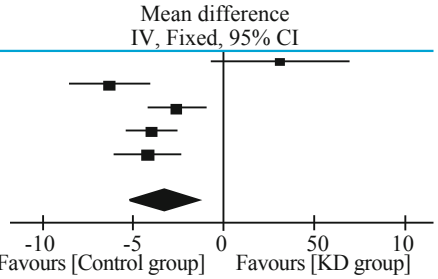


**Fig. 6.** Summary of the mean difference of comparisons between Kawasaki disease (KD) patients and controls for flow-mediated dilatation. SD: standard deviation; IV: independent variable; CI: confidence interval.

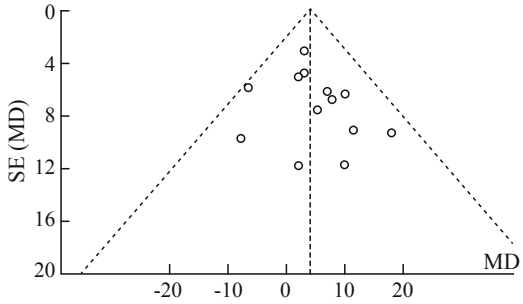


**Fig. 7.** Funnel plot for the publication bias test of the comparisons between Kawasaki disease patients and controls for total cholesterol. MD: mean difference; SE: standard error.

indicating significant heterogeneity. Thus, a random effects model was applied. The combined MD (95% CI) was -3.25 (-5.19, -1.31) mm Hg, *P*=0.001, suggesting a significant difference (Fig. 6).

### Publication bias

Because TC was involved in 13 of the included studies, we estimated the publication bias for TC only. Overall, the plots were distributed symmetrically, suggesting no publication bias in this meta-analysis (Fig. 7).

## Discussion

This study investigated whether KD patients have an increased risk of atherosclerosis development using a meta-analysis approach. Herein, we compared five atherosclerosis risk factors, TC, LDL, TG, SBP and FMD, between the KD patients and controls. TC and LDL levels in the KD patients were significantly higher than those in the controls, and the FMD of KD patients was significantly lower than that of the non-KD patients. Together, these results may indicate an increased risk of atherosclerosis for the KD patients.

TC indicates the total amount of cholesterol in the blood. Because cholesterol is difficult to dissolve in water, it is transported inside lipoproteins, a particle complex consisting of a hydrophilic exterior and lipophilic interior.[24] There are five types of lipoproteins according to the amount of transported fat molecules, chylomicrons, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), LDL, and high-density lipoprotein (HDL).[24] LDL is transported with blood flow across the intact endothelium and becomes trapped in the extracellular matrix of the subendothelial space, where it is oxidized.[25] Oxidized LDLs are cytotoxic to endothelial cells because they stimulate inflammatory signaling by endothelial cells, resulting in the release of chemotactic proteins and growth factors, further leading to the recruitment of monocytes into the arterial wall[26] and promoting the differentiation of monocytes into macrophages. Oxidized LDLs can also inhibit the production of nitric oxide (a key molecule involved in vasodilation) and expression of endothelial leukocyte adhesion molecules.[27] The oxidation of LDL plays an important role in the onset of atherosclerosis.[28,29] Thus, the significantly higher TC and LDL levels in the KD patients may indicate an increased risk of developing atherosclerosis. FMD, an indicator of vasodilation capability, can indicate early atherosclerosis, with very early decreasing values.[30,31] The FMD of the KD patients was significantly lower than that of the non-KD patients, suggesting an increased risk for KD patients to develop atherosclerosis. This meta-analysis of 16 studies investigated whether KD patients are at increased risk for atherosclerosis and found that KD patients may have higher risk for developing atherosclerosis due to the significant differences in TC, LDL and FMD. The studies included in this meta-analysis are of high quality, with low heterogeneity; further, the number of participants included was sufficient, leading to high reliability of the present results. However, significant differences between the KD and non-KD patients were only found for three indicators (TC, LDL and FMD); no significant differences were detected in either TG or SBP between the KD patients and non-KD patients, although higher TG[32] and SBP[33] levels have been reported to increase atherosclerosis risk. Thus, these results should be interpreted cautiously and further validated by prospective studies. Additionally, as greater numbers of adults diagnosed with KD in 1960s or later are entering their fifties, a high-risk age for atherosclerosis, more follow-up studies should be conducted to verify our findings via investigating atherosclerosis incidence.

**Funding:** This study was supported by Shanghai Jiaotong University Medical and Engineer Cross Funding (No. YG2013MS73), Appropriate Technology of Shanghai Municipal Hospital Funding (No. SHDC12012238), National Natural Science Foundation of China (No. 83100124).
**Ethical approval:** None.
**Competing interest:** None.
**Contributors:** Xie LJ conceived and designed the research subject. Zhang H performed the study. Xu MG, Shen J and Huang M analyzed the data. Zhang H and Xiao TT wrote the paper.

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*Received August 4, 2015*
*Accepted after revision November 26, 2015*