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## Lipoprotein Particle Concentrations in Children and Adults following Kawasaki Disease

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### Abstract

**Objective**—To test the hypothesis that children and adults with history of Kawasaki disease (KD) are more likely to have abnormal lipoprotein particle profiles that could place them at increased risk of atherosclerosis later in life.

**Study design**—Fasting serum samples were obtained from 192 children and 63 adults with history of KD and 90 age-similar healthy controls. Lipoprotein particle (P) concentrations and sizes were measured by Nuclear Magnetic Resonance (NMR) spectroscopy (Liposcience Inc., Raleigh, NC) and serum was assayed for total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL)-C. Low-density lipoprotein cholesterol (LDL)-C was estimated using the Friedewald formula. Data were analyzed in a least-square means model adjusting for age and sex and using Holm correction for multiple comparisons.

**Results**—Compared with respective control groups, both adult and pediatric subjects with KD had significantly lower mean very-low-density lipoprotein-chylomicron particle concentrations (VLDLC-P), intermediate-density lipoproteins (IDL), TG, and TC concentrations. Pediatric subjects with KD had significantly lower LDL-P and LDL-C concentrations and lower mean TC/

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HDL-C ratio ( $p < 0.001$ ). In contrast, the adult subjects with KD had significantly lower HDL-P, small HDL-P, and HDL-C concentrations ( $p < 0.001$ ), but HDL-C was within normal range.

**Conclusions**—NMR lipoprotein particle analysis suggests that pediatric and adult subjects with KD regardless of their aneurysm status are no more likely than age-similar, healthy controls to have lipid patterns associated with increased risk of atherosclerosis.

## Keywords

Kawasaki disease; atherosclerosis; lipids and lipoproteins

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Since the first published report in 1967, Kawasaki disease (KD) has become the leading cause of acquired pediatric heart disease in developed countries.[1, 2] Coronary artery aneurysms develop in 25% of untreated patients, putting them at increased risk for cardiovascular complications including myocardial ischemia and infarction.[3-6] The current American Heart Association (AHA) guidelines recommend lipid profile screening for those who have recovered from KD, due to concerns that these patients may be at increased risk of accelerated atherosclerosis.[7] Determination of lipoprotein profiles is one component of risk stratification for the development of atherosclerosis, a process that may be superimposed upon existing arterial wall damage, termed KD vasculopathy.

The protective role of high-density lipoprotein (HDL) and pathogenic role of low-density lipoprotein (LDL), especially the small-dense LDL, in atherosclerosis and coronary artery disease (CAD) are well-established. However, the traditional lipid panel may not provide the most robust measurement of lipoprotein-attributable risk.[8] Nuclear magnetic resonance (NMR) spectroscopy directly quantifies the number of LDL and HDL particles (LDL-P and HDL-P) and their size distribution, and may yield a more accurate assessment of atherosclerotic risk.[9-13] Results of multivariable analyses from several studies in adults have supported the hypothesis that it is the number of lipoprotein particles, not lipoprotein particle size or concentration of cholesterol that is most strongly associated with atherosclerotic risk.[14-16] Studies of lipid profiles in small cohorts of acute and convalescent patients with KD have yielded conflicting results. [17-21] The goal of our study was to assess whether pediatric and young adults with KD are more likely to have atherogenic lipid profiles compared with healthy controls using NMR lipoprotein particle counts.

## Methods

Pediatric subjects included 192 children and adolescents with a history of KD diagnosed and treated at Rady Children's Hospital San Diego, between November 2005 and June 2011. Inclusion criteria were initial diagnosis of KD according to AHA criteria and phlebotomy performed at least 11 months after KD onset.[7] Serum samples were also obtained from 45 age-similar, healthy control children who were fasting prior to undergoing minor orthopedic surgical procedures. Adults with KD included 63 young adults enrolled in the San Diego Adult KD Collaborative study. Fasting serum samples were obtained at study enrollment. Adult healthy controls included 45 age-similar healthy volunteers with no history of KD or heart disease. One pediatric subject and eleven adult subjects who were on lipid-lowering

medications were excluded. Only two subjects with mild mixed hyperlipidemia were on statin therapy for lipid-lowering effects. The remaining ten subjects were on statin therapy either as standard practice post-myocardial infarction or for the potential anti-inflammatory benefits of statins in the setting of coronary artery abnormalities following acute KD. None of the control subjects were on any lipid-lowering medication. Written informed consent, and assent when appropriate, was obtained from the parents of subjects or the subjects themselves. The protocol was approved by the Institutional Review Board at the University of California San Diego.

Fasting serum samples (stored at  $-80^{\circ}\text{C}$  prior to testing) were assayed for total cholesterol (TC), triglycerides and high-density lipoprotein cholesterol (HDL-C) using standard automated methods on a Vitros 5,1 FS Chemistry System instrument. Low-density lipoprotein cholesterol (LDL-C) was estimated using the Friedewald formula. Lipoprotein particle profiles were measured by NMR spectroscopy with the LipoProfile-3 algorithm at LipoScience Inc. (Raleigh, NC). Very-Low-Density Lipoprotein (VLDL) + Chylomicron particle (VLDL-C), LDL-C and HDL-C subclasses were quantified by the amplitudes of their spectroscopically distinct lipid methyl group NMR signals. Weighted-average VLDL, LDL and HDL particle sizes were derived from the sum of the diameter of each subclass multiplied by its relative mass percentage based on the amplitude of its methyl NMR signal.

Body mass index (BMI) was calculated from hospital records (pediatric subjects) or by measurements obtained for this study at the time of phlebotomy (adult subjects). Coronary artery status was determined by echocardiography for the pediatric subjects with KD. Subjects were classified as dilated if the internal diameter of the coronary artery normalized for body surface area and expressed as standard deviation units from the mean (Z score) exceeded 2.5 for the left anterior descending or right coronary arteries assessed by echocardiography during the first 6 weeks after disease onset. Aneurysms were defined as a segment  $\geq 1.5$  times the diameter of the adjacent segment. Adult subjects with KD were evaluated by a combination of invasive, computed tomography, and magnetic resonance angiography and classified as having normal or aneurysmal coronary arteries.

### Statistical Analyses

Patient characteristics were summarized by group. Medians and interquartile ranges (IQRs) were reported for continuous variables and frequency counts and percentages were reported for categorical variables. For each of the lipoprotein outcomes, linear regression models were used to compare the differences between subjects with KD and controls, as well as between subjects with KD with and without coronary artery abnormalities (CAA,  $Z \geq 2.5$ ), after adjusting for age and sex. Least-square means from the models were reported with 95% confidence intervals (CIs), and two-sided p-values  $<0.05$  were considered statistically significant. Holm's multiple testing adjustment procedure was applied. Statistical analyses were performed in R (<http://cran.r-project.org>), version 2.14.0.

### Results

There were no significant differences in the demographic or clinical features of the pediatric and adult groups with KD and their respective controls except for an excess of females in

the adult healthy control group (Table I). These differences were taken into account in the analysis model adjusting for age and sex.

The analysis of serum using the *NMR LipoProfile*® test provided lipoprotein particle concentrations for all groups (Table II) whereas the lipid panel provided cholesterol and TG concentrations. Table III separates lipoprotein particles and cholesterol concentrations that are known to be atherogenic and atheroprotective. High concentrations of VLDL, IDL, LDL, and TG concentrations are all known to be associated with atherosclerosis. Both pediatric and adult subjects with KD had significantly lower mean VLDLC-P, IDL-P, and TG concentrations compared with their respective control groups. Pediatric subjects with KD also had significantly lower mean total LDL-P and LDL-C concentrations ( $p=0.001$  and  $p<0.001$ , respectively), and a lower mean TC/HDL compared with the pediatric healthy controls ( $p<0.001$ ). For the pediatric cohort with KD, we compared lipoprotein particle counts with the maximum Z score of the right and left anterior descending coronary arteries measured by echocardiography during the first six weeks after illness onset. For the adult cohort, we compared lipoprotein particle counts between subjects with and without CAA. Linear regression analysis found no significant relationship between lipoprotein particle counts and coronary artery status when comparing the pediatric or adult cohorts. Similarly, both pediatric and adult subjects with CAA had similar lipoprotein particle counts that did not differ significantly from the respective healthy control cohort. (data not shown)

Higher concentrations of total and large HDL-P are thought to be atheroprotective, and small HDL-P is known to be associated with coronary artery disease.[22] Pediatric subjects with KD had a significantly higher large HDL-P concentration ( $p<0.001$ ) and small HDL-P ( $p=0.003$ ). The adults with KD had significantly lower mean HDL-P and HDL-C concentrations compared with the adult healthy controls ( $p<0.001$ ) (Table II). In contrast to the pediatric subjects, adults with KD displayed significantly lower small HDL-P.

Neither the pediatric nor the adult cohorts with KD had the combination of higher concentrations of small LDL-P and lower concentrations of large HDL-P, the canonical risk profile for atherosclerosis. Compared with controls, the pediatric cohort with KD had significantly higher levels of both atherogenic and atheroprotective particles, specifically small LDL-P and large HDL-P ( $p=0.002$  and  $p<0.001$ , respectively). In contrast, the adult cohort with KD was similar to controls for these particle concentrations.

When both adults with KD and their control cohorts were compared with subjects in the Framingham and MESA studies, their LDL-C and LDL-P values were below the 30th percentile for both studies. Within the adult cohort with KD, the mean LDL-C and LDL-P values fell below the 20th percentile for both the Framingham and MESA population comparisons (Table IV).

## Discussion

We report NMR lipoprotein particle analysis in subjects with KD. Pediatric and adult subjects with KD displayed a mix of both atherogenic and atheroprotective lipoprotein particle profiles compared with healthy controls, after controlling for age and sex. The most

robust predictors of atherosclerotic risk are thought to be the concentrations of very-low-density lipoprotein/chylomicron particle (VLDLC-P), triglycerides (TG), and LDL-P as well as the ratio of TC to HDL-C.[16, 23, 24] Compared with controls, the pediatric KD group had lower mean concentrations of all of these lipids and lipoprotein particles consistent with a lower atherosclerotic risk profile. In contrast, the adult group with KD presented a mixed profile with lower VLDLC-P and TG but similar LDL-P concentrations and a similar ratio of TC to HDL-C compared with controls.

The acute inflammatory vasculitis of KD produces a spectrum of damage to the coronary arteries and other medium-sized, extra-parenchymal muscular arteries throughout the body. [25] Concerns have been raised over the potential for patients with KD to develop accelerated atherosclerosis in these vascular beds.[21, 26-30] Evidence cited to support this concern includes greater carotid intima-media thickness (IMT), abnormal brachial artery reactivity (BAR), and abnormal ankle-brachial indices (ABI) in some studies. However, a more recent study using finger plethysmography (Endo PAT Index) as a more accurate tool to assess endothelial cell function found no difference between subjects with KD and controls.[19, 31] In addition, autopsy reports of atherosclerotic changes including lipid-laden macrophages and cholesterol clefts in regions of the vascular wall affected by KD vasculopathy are rare and do not suggest an increased risk of focal atherosclerotic changes. [32-39] In fact, autopsy reports of sudden death in young adults with a history of KD in childhood have remarked on the relative absence of atherosclerosis.[33] Similarly, the medial necrosis and calcification of the coronary arteries as documented by intravascular ultrasound may be consequences of KD vasculopathy and may not represent early atherosclerosis, as has been widely assumed.[40]

Whether or not KD vasculopathy alone predisposes individuals to an increased risk of atherosclerosis remains unanswered. Lipid profile screening for patients with KD beyond the acute phase remains prudent and individual patients with KD with documented hyperlipidemia, such as elevated LDL-C, should be managed aggressively. However, based on the data presented here, as a group, neither pediatric nor adult patients with KD have lipoprotein particle counts or lipid profiles associated with increased atherosclerotic risk.

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## References

1. Taubert KA, Rowley AH, Shulman ST. Nationwide survey of Kawasaki disease and acute rheumatic fever. *J Pediatr*. 1991; 119:279–82. [PubMed: 1861216]
2. Kawasaki T, Kosaki F, Okawa S, Shigematsu I, Yanagawa H. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. *Pediatrics*. 1974; 54:271–6. [PubMed: 4153258]

3. Kato H, Sugimura T, Akagi T, Sato N, Hashino K, Maeno Y, et al. Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients. *Circulation*. 1996; 94:1379–85. [PubMed: 8822996]
4. Senzaki H. Long-term outcome of Kawasaki disease. *Circulation*. 2008; 118:2763–72. [PubMed: 19106401]
5. Gordon JB, Kahn AM, Burns JC. When children with Kawasaki disease grow up: Myocardial and vascular complications in adulthood. *J Am Coll Cardiol*. 2009; 54:1911–20. [PubMed: 19909870]
6. Daniels LB, Gordon JB, Burns JC. Kawasaki disease: late cardiovascular sequelae. *Current opinion in cardiology*. 2012; 27:572–7. [PubMed: 23075819]
7. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation*. 2004; 110:2747–71. [PubMed: 15505111]
8. Otvos JD, Jeyarajah EJ, Cromwell WC. Measurement issues related to lipoprotein heterogeneity. *Am J Cardiol*. 2002; 90:22i–9i.
9. Soedamah-Muthu SS, Chang YF, Otvos J, Evans RW, Orchard TJ. Lipoprotein subclass measurements by nuclear magnetic resonance spectroscopy improve the prediction of coronary artery disease in Type 1 diabetes. A prospective report from the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetologia*. 2003; 46:674–82. [PubMed: 12743701]
10. Shea S, Aymong E, Zybert P, Berglund L, Shamooh H, Deckelbaum RJ, et al. Fasting plasma insulin modulates lipid levels and particle sizes in 2- to 3-year-old children. *Obes Res*. 2003; 11:709–21. [PubMed: 12805392]
11. Freedman DS, Bowman BA, Otvos JD, Srinivasan SR, Berenson GS. Levels and correlates of LDL and VLDL particle sizes among children: the Bogalusa heart study. *Atherosclerosis*. 2000; 152:441–9. [PubMed: 10998473]
12. Freedman DS, Bowman BA, Srinivasan SR, Berenson GS, Otvos JD. Distribution and correlates of high-density lipoprotein subclasses among children and adolescents. *Metabolism*. 2001; 50:370–6. [PubMed: 11230794]
13. Ford MA, McConnell JP, Lavi S, Rihal CS, Prasad A, Sandhu GS, et al. Coronary artery endothelial dysfunction is positively correlated with low density lipoprotein and inversely correlated with high density lipoprotein subclass particles measured by nuclear magnetic resonance spectroscopy. *Atherosclerosis*. 2009; 207:111–5. [PubMed: 19515370]
14. Cromwell WC, Otvos JD, Keyes MJ, Pencina MJ, Sullivan L, Vasan RS, et al. LDL Particle Number and Risk of Future Cardiovascular Disease in the Framingham Offspring Study - Implications for LDL Management. *Journal of clinical lipidology*. 2007; 1:583–92. [PubMed: 19657464]
15. Otvos JD, Mora S, Shalurova I, Greenland P, Mackey RH, Goff DC Jr. Clinical implications of discordance between low-density lipoprotein cholesterol and particle number. *Journal of clinical lipidology*. 2011; 5:105–13. [PubMed: 21392724]
16. Ip S, Lichtenstein AH, Chung M, Lau J, Balk EM. Systematic review: association of low-density lipoprotein subfractions with cardiovascular outcomes. *Ann Intern Med*. 2009; 150:474–84. [PubMed: 19349632]
17. Newburger JW, Burns JC, Beiser AS, Loscalzo J. Altered lipid profile after Kawasaki syndrome. *Circulation*. 1991; 84:625–31. [PubMed: 1860206]
18. Chiang AN, Hwang B, Shaw GC, Lee BC, Lu JH, Meng CC, et al. Changes in plasma levels of lipids and lipoprotein composition in patients with Kawasaki disease. *Clin Chim Acta*. 1997; 260:15–26. [PubMed: 9101097]
19. Selamet Tierney ES, Gal D, Gauvreau K, Baker AL, Trevey S, O'Neill SR, et al. Vascular health in Kawasaki disease. *J Am Coll Cardiol*. 2013; 62:1114–21. [PubMed: 23835006]
20. McCrindle BW. Kawasaki disease: a childhood disease with important consequences into adulthood. *Circulation*. 2009; 120:6–8. [PubMed: 19546382]



21. McCrindle BW, McIntyre S, Kim C, Lin T, Adeli K. Are patients after Kawasaki disease at increased risk for accelerated atherosclerosis? *J Pediatr.* 2007; 151:244–8. 8 e1. [PubMed: 17719931]
22. Freedman DS, Otvos JD, Jeyarajah EJ, Barboriak JJ, Anderson AJ, Walker JA. Relation of lipoprotein subclasses as measured by proton nuclear magnetic resonance spectroscopy to coronary artery disease. *Arterioscler Thromb Vac Biol.* 1998; 18:1046–53.
23. Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, et al. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA.* 2009; 302:1993–2000. [PubMed: 19903920]
24. Brunzell JD, Davidson M, Furberg CD, Goldberg RB, Howard BV, Stein JH, et al. Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. *Diabetes Care.* 2008; 31:811–22. [PubMed: 18375431]
25. Orenstein JM, Shulman ST, Fox LM, Baker SC, Takahashi M, Bhatti TR, et al. Three linked vasculopathic processes characterize Kawasaki disease: a light and transmission electron microscopic study. *PLoS ONE.* 2012; 7:e38998. [PubMed: 22723916]
26. Noto N, Okada T, Yamasuge M, Taniguchi K, Karasawa K, Ayusawa M, et al. Noninvasive assessment of the early progression of atherosclerosis in adolescents with Kawasaki disease and coronary artery lesions. *Pediatrics.* 2001; 107:1095–9. [PubMed: 11331692]
27. Dalla Pozza R, Bechtold S, Urschel S, Kozlik-Feldmann R, Netz H. Subclinical atherosclerosis, but normal autonomic function after Kawasaki disease. *J Pediatr.* 2007; 151:239–43. [PubMed: 17719930]
28. Fukazawa R, Ogawa S. Long-term prognosis of patients with Kawasaki disease: at risk for future atherosclerosis? *J Nippon Med Sch.* 2009; 76:124–33. [PubMed: 19602819]
29. Gupta-Malhotra M, Gruber D, Abraham SS, Roman MJ, Zabriskie JB, Hudgins LC, et al. Atherosclerosis in survivors of Kawasaki disease. *J Pediatr.* 2009; 155:572–7. [PubMed: 19595365]
30. Noto N, Okada T, Karasawa K, Ayusawa M, Sumitomo N, Harada K, et al. Age-related acceleration of endothelial dysfunction and subclinical atherosclerosis in subjects with coronary artery lesions after kawasaki disease. *Pediatr Cardiol.* 2009; 30:262–8. [PubMed: 19020792]
31. Burns JC, Daniels LB. Assessing vascular health after Kawasaki disease: a cautionary tale. *J Am Coll Cardiol.* 2013; 62:1122–3. [PubMed: 23850904]
32. Takahashi K, Oharaseki T, Naoe S. Pathological study of postcoronary arteritis in adolescents and young adults: with reference to the relationship between sequelae of Kawasaki disease and atherosclerosis. *Pediatr Cardiol.* 2001; 22:138–42. [PubMed: 11178671]
33. Okura N, Okuda T, Shiotani S, Kohno M, Hayakawa H, Suzuki A, et al. Sudden death as a late sequel of Kawasaki disease: postmortem CT demonstration of coronary artery aneurysm. *Forensic Sci Int.* 2013; 225:85–8. [PubMed: 22673706]
34. Rozin L, Koehler SA, Shakir A, Latham S, Wecht CH. Kawasaki disease: a review of pathologic features of stage IV disease and two cases of sudden death among asymptotic young adults. *Am J Forensic Med Pathol.* 2003; 24:45–50. [PubMed: 12604998]
35. Bartoloni G, Salvatrice DM, Carlo R. Sudden death in a 21-year-old man caused by thrombosed coronary aneurysm: late sequelae or a very late onset of Kawasaki disease? *Cardiovasc Pathol.* 2002; 11:318–21. [PubMed: 12459431]
36. Fineschi V, Paglicci Reattelli L, Baroldi G. Coronary artery aneurysms in a young adult: a case of sudden death. A late sequelae of Kawasaki disease? *Int J Legal Med.* 1999; 112:120–3. [PubMed: 10048670]
37. Smith BA, Grider DJ. Sudden death in a young adult: sequelae of childhood Kawasaki disease. *Am J Emerg Med.* 1993; 11:381–3. [PubMed: 8216521]
38. Subramaniam S, Boo K. Sudden death in a young adult due to coronary artery aneurysm secondary to suspected Kawasaki disease. *Malays J Pathol.* 1992; 14:49–51. [PubMed: 1469919]
39. Burns JC, Shike H, Gordon JB, Malhotra A, Schoenwetter M, Kawasaki T. Sequelae of Kawasaki disease in adolescents and young adults. *J Am Coll Cardiol.* 1996; 28:253–7. [PubMed: 8752822]
40. Mitani Y, Ohashi H, Sawada H, Ikeyama Y, Hayakawa H, Takabayashi S, et al. In vivo plaque composition and morphology in coronary artery lesions in adolescents and young adults long after

Kawasaki disease: a virtual histology-intravascular ultrasound study. *Circulation*. 2009; 119:2829–36. [PubMed: 19451352]

41. Kuller L, Arnold A, Tracy R, Otvos J, Burke G, Psaty B, et al. Nuclear magnetic resonance spectroscopy of lipoproteins and risk of coronary heart disease in the cardiovascular health study. *Arterioscler Thromb Vac Biol*. 2002; 22:1175–80.
42. Carmena R, Duriez P, Fruchart JC. Atherogenic lipoprotein particles in atherosclerosis. *Circulation*. 2004; 109:III2–7. [PubMed: 15198959]
43. Contois JH, McConnell JP, Sethi AA, Csako G, Devaraj S, Hoefner DM, et al. Apolipoprotein B and cardiovascular disease risk: position statement from the AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices. *Clinical chemistry*. 2009; 55:407–19. [PubMed: 19168552]
44. Mackey RH, Greenland P, Goff DC Jr, Lloyd-Jones D, Sibley CT, Mora S. High-density lipoprotein cholesterol and particle concentrations, carotid atherosclerosis, and coronary events: MESA (multi-ethnic study of atherosclerosis). *J Am Coll Cardiol*. 2012; 60:508–16. [PubMed: 22796256]

## List of Abbreviations

<b>HDL-C</b>	High-density lipoprotein cholesterol concentration
<b>HDL-P</b>	High-density lipoprotein particle concentration
<b>KD</b>	Kawasaki Disease
<b>LDL-C</b>	Low-density lipoprotein cholesterol concentration
<b>LDL-P</b>	Low-density lipoprotein particle concentration
<b>NMR</b>	Nuclear Magnetic Resonance
<b>TC</b>	Total cholesterol
<b>TG</b>	Triglycerides
<b>VLDL</b>	Very-low-density lipoprotein
<b>VLDLC-P</b>	Very-low-density lipoprotein-chylomicron particle concentrations



**Table I**

Demographic and clinical characteristics of study cohorts.

Characteristics	Pediatric KD (n=192)	Pediatric HC (n=45)	Adult KD (n=63)	Adult HC (n=45)
Median age, years (IQR; range)	5.4 (3.5-7.9; 1.1-15.3)	4.7 (3.3-6.5; 1.4-15.9)	21.7 (18.4-27.6; 16.0-46.3)	23.3 (22.0-25.8; 16.4-49.0)
Male, n (%)	125 (65)	23 (51)	34 (54)	13 (29)
Interval between KD onset and phlebotomy, years (IQR; range)	1.4 (1.1-4.7; 0.9-12.6) *	N/A	17.6 (14.3-24.3; 1.1-37.4) †	N/A
Coronary artery status of subjects: n (%)				
Normal	134 (70)	N/A	51 (81)	N/A
Dilated	35 (18)		3 (5)	
Aneurysm	23 (12)		9 (14)	
BMI, median (IQR; range)	16.5 (15.2-18.6; 12.9-28.7)	16.4 (15.7-18.0; 14.2-38.2) ‡	22.2 (20.0-24.6; 15.6-36.8) §	22.3 (20.8-23.9; 19.0-32.5)
Ethnicity: n (%)				
Asian	29 (15)	2(5)	13 (21)	21 (47)
Black/African American	8 (4)	4 (9)	2 (3)	0 (0)
Caucasian	47 (25)	29 (64)	32 (51)	20 (44)
Hispanic	62 (32)	8 (18)	8 (13)	3 (7)
More than one race	38 (20)	2 (4)	7 (11)	1 (2)
Native Hawaiian or other Pacific Islander	2 (1)	0 (0)	0 (0)	0 (0)
Unknown	6 (3)	0 (0)	1 (1)	0 (0)

HC= healthy controls; BMI = Body Mass Index calculated, kg/m<sup>2</sup>; IQR = Interquartile range\*  
n=188†  
n=60‡  
n=27§  
n=62

**Table II**

NMR lipoprotein particle concentrations and sizes.

Lipoprotein Subclasses	Pediatric KD (n=192)	Pediatric HC (n=45)	P-value	Adult KD (n=63)	Adult HC (n=45)	P-value
Total VLDL/Chylomicron particles (VLDLC-P) (nmol/L)	43.4 (39.9-46.9)	51.6 (44.4-58.9)	0.046	50.3 (43.2-57.4)	72.1 (63.7-80.6)	<0.001
Large VLDL/Chylomicron particles (VLC-P) (nmol/L)	1.4 (0.9-2.0)	3.1 (1.9-4.2)	0.01	1.9 (1.4-2.5)	2.1 (1.5-2.8)	0.61
Medium VLDL particles (VM-P) (nmol/L)	18.3 (16.0-20.5)	14.2 (9.5-18.9)	0.12	16.5 (12.9-20.1)	23.4 (19.2-27.7)	0.017
Small VLDL particles (VS-P) (nmol/L)	23.7 (21.8-25.6)	34.4 (30.4-38.4)	<0.001	31.9 (26.9-36.8)	46.5 (40.6-52.4)	<0.001
Total LDL particles (LDL-P) (nmol/L)	935 (894-975)	1098 (1014-1182)	0.001	937 (854-1020)	1056 (957-1155)	0.075
IDL particles (IDL-P) (nmol/L)	14 (9-18)	113 (104-123)	<0.001	62 (50-75)	89 (74-104)	0.009
Large LDL particles (LL-P) (nmol/L)	382 (358-406)	610 (560-661)	<0.001	498 (453-544)	533 (478-587)	0.35
Small LDL particles (total) (LS-P) (nmol/L)	539 (494-584)	374 (281-467)	0.002	376 (293-458)	434 (336-533)	0.38
Total HDL particles (HDL-P) (μmol/L)	30.4 (29.8-30.9)	30.5 (29.3-31.8)	0.77	34.0 (32.5-35.4)	40.5 (38.8-42.2)	<0.001
Large HDL particles (HL-P) (μmol/L)	9.0 (8.5-9.4)	4.9 (4.0-5.8)	<0.001	6.8 (6.0-7.7)	7.7 (6.7-8.7)	0.21
Medium HDL particles (HM-P) (μmol/L)	3.2 (2.7-3.7)	9.6 (8.5-10.7)	<0.001	11.7 (10.1-13.3)	12.4 (10.4-14.3)	0.61
Small HDL particles (HS-P) (μmol/L)	18.2 (17.6-18.8)	16.1 (14.8-17.3)	0.003	15.4 (14.1-16.8)	20.5 (18.9-22.1)	<0.001
VLDL particle size (VZ) (nm)	53.5 (52.1-54.8)*	44.2 (41.2-47.3)†	<0.001	47.1 (45.9-48.3)‡	43.5 (42.1-44.9)§	<0.001
LDL particle size (LZ) (nm)	21.2 (21.1-21.3)	21.1 (20.9-21.3)	0.49	21.1 (21.0-21.2)	20.9 (20.8-21.1)	0.10
HDL particle size (HZ) (nm)	9.1 (9.0-9.2)	9.2 (9.1-9.3)	0.05	9.2 (9.1-9.3)	9.2 (9.1-9.4)	0.68
Total Triglyceride (TG) (mg/dL)	82 (75-89)	105 (90-119)	0.008	93 (84-103)	116 (105-127)	0.003
Total VLDL/Chylomicron Triglyceride (NVCTG) (mg/dL)	54 (47-61)	69 (55-84)	0.06	63 (54-72)	81 (70-92)	0.012
Total HDL cholesterol (HDL-C) (mg/dL)	50 (49-52)	48 (45-51)	0.13	54 (51-56)	63 (60-66)	<0.001
Total LDL cholesterol (LDL-C) (mg/dL)	85 (82-88)	106 (100-113)	<0.001	87 (81-94)	95 (88-103)	0.12
Total Cholesterol (TC) (mg/dL)	148 (145-152)	169 (161-176)	<0.001	154 (147-161)	176 (168-185)	<0.001
Ratio of Total cholesterol/HDL cholesterol	3.1 (2.9-3.2)	3.6 (3.4-3.8)	<0.001	3.0 (2.8-3.2)	2.9 (2.7-3.2)	0.83

Values are model-estimated means (95% CI). P values are after Holm's correction for multiple testing. HC=healthy controls; VLDL=very-low-density lipoprotein; LDL=low-density lipoprotein; HDL=intermediate-density lipoprotein; HDL=high-density lipoprotein

\* n=191

† n=39

‡ n=55

§ n=43

**Table III**  
**Atherogenic and atheroprotective lipoprotein subclasses and cholesterol concentrations**  
 adapted from Ref.[41, 42]

Lipoprotein Subclasses		KD Cohorts	
Atherogenic Subclasses	Pediatric KD compared to pediatric HC	Adult KD compared to adult HC	
Small LDL-P	↑	NS	
Small HDL-P	↑	↓	
Total LDL-P	↓	NS	
IDL-P	↓	↓	
Total VLDL/Chylomicrons	↓	↓	
LDL-C	↓	NS	
Total Triglycerides	↓	↓	
Atheroprotective Subclasses	Pediatric KD compared to pediatric HC	Adult KD compared to adult HC	
Large HDL-P	↑	NS	
Total HDL-P	NS	↓	
HDL-C	NS	↓	

HC=healthy controls; LDL-P=low-density lipoprotein particles; HDL-P=high-density lipoprotein particles; IDL-P=intermediate-density lipoprotein particles; VLDL=very-low-density lipoprotein; LDL-C= low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol

**Table IV**  
**Population Comparisons of Lipid and Lipoprotein Particle Concentrations**

Framingham Offspring* n=3367 (1367 men; 1732 women)		MESA† n=6697 (3154 men; 3543 women)		
Percentile	LDL-C (mg/dL)	LDL-P (nmol/L)	LDL-C (mg/dL)	LDL-P (nmol/L)
2	70	720	58	670
5	78	850	69	770
10	88	940	79	870
20	100	1100	91	990
30	111	1220	100	1090
40	120	1330	108	1170
50	130	1440	115	1260
60	139	1540	123	1350
70	149	1670	131	1440
80	160	1820	141	1560
90	176	2020	157	1740
95	191	2210	170	1900

LDL-C=low-density lipoprotein cholesterol; LDL-P=low-density lipoprotein particles

\* Specimens collected in 1988-1991 (exam cycle 4). Analysis restricted to subjects with TG <400 mg/dL. Ethnic make-up 99% Caucasian.[43]

† Specimens collected in 2000-2002. Analysis restricted to subjects with TG <400 mg/dL. Ethnic make-up 27.4% African-American, 38.0% Caucasian, 12.3% Chinese, 22.3% Hispanic.[44]