A Positive Association Between Dietary Intake of Higher Cow's Milk-Fat Percentage and Non–High-Density Lipoprotein Cholesterol in Young Children

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Objectives To determine the association between cow's milk-fat and non–high-density lipoprotein (non-HDL) cholesterol, a marker of cardiovascular disease (CVD) risk in young children, and whether this association is mediated by the typical volume of cow's milk consumed.

Study design A longitudinal study in 2- to 8-year-old children (n = 2890) was conducted through The Applied Research Group for Kids (TARGet Kids!), a practice-based research network in Toronto, Canada. Generalized estimating equations were used to examine the relationship between parent-reported cow's milk-fat percentage intake and serum non-HDL cholesterol concentrations as well as having high non-HDL cholesterol (≥3.75 mmol/L [145 mg/dL]), adjusting for covariates including age, sex, body mass index z score, breastfeeding duration, mother's ethnicity, and parental history of CVD. Bootstrap resampling (10 000 repetitions) was used to assess whether typical volume consumed mediated the association between cow's milk-fat percentage and non-HDL cholesterol.

Results In total, 156 (5.4%) had high non-HDL cholesterol. Each percent increase in cow's milk-fat was associated with a 0.035 mmol/L (1.35 mg/dL) ($P < .001$) and 0.024 mmol/L (0.92 mg/dL) ($P = .01$) increase in non-HDL cholesterol, unadjusted and adjusted for covariates respectively. Cow's milk-fat percentage was not associated with greater odds of having high non-HDL cholesterol. Volume of cow's milk partially mediated the association between cow's milk-fat percentage and non-HDL cholesterol, accounting for 28% of the relationship ($P < .001$).

Conclusions Consumption of higher-fat cow's milk was associated with a small increase in non-HDL cholesterol but not greater odds of having high non-HDL cholesterol. Further research is needed to assess this relationship with other CVD risk factors in young children. *(J Pediatr 2019;211:105-11)*.

Trial registration ClinicalTrials.gov: NCT01869530.

Serum lipid levels during childhood have been identified as risk factors for cardiovascular disease (CVD). Specifically, non–high-density lipoprotein (non-HDL) cholesterol levels during childhood are associated with premature atherosclerosis and also track into adulthood.[1-3] Dietary patterns and feeding behaviors during childhood have been shown to be associated with both markers of subclinical atherosclerosis and serum cholesterol.[4,5]

Cow's milk is a prominent component of the diet during early childhood.[6] According to the National Health and Nutrition Examination Survey and Canadian Community Health Survey, greater than 70% of young children consume cow's milk in the US and Canada.[7,8] Cow's milk contains nutrients such as protein, calcium, and vitamin D that promote the growth of children, and milk avoidance has been associated with short stature and poor bone health.[9] The energy density and dietary saturated fat content of whole cow's milk may be of concern, as previous research suggests that saturated fat may contribute to CVD and obesity by the elevation of low-density lipoprotein (LDL) cholesterol and increased caloric intake, respectively.[10,11]

The American Academy of Pediatrics endorses dietary recommendations from the American Heart Association that reflect these concerns,[12] advising lower-fat cow's milk over whole milk for children 2 years of age or older. However, we previously found that consuming higher-fat cow's milk was associated with a reduced body mass index (BMI) z score in children aged 1-3 years after we adjusted for potential confounders, with similar findings in other prospective and longitudinal studies on adiposity in children.[13-16] Furthermore, recent

BMI	Body mass index
CVD	Cardiovascular disease
LDL	Low-density lipoprotein
Non-HDL	Non–high-density lipoprotein
TARGet Kids!	The Applied Research Group for Kids

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epidemiologic studies in adults have demonstrated that increased dairy intake was associated with lower CVD risk and saturated fat intake may not be associated with CVD and mortality.[17,18]

The contribution of cow's milk-fat intake to the cardiovascular health, including cholesterol levels, of young children remains unknown; some studies suggest that consuming a greater volume of cow's milk is associated with improved cardiometabolic outcomes in preadolescents and adolescents, but these studies did not consider the milk-fat content.[19,20] Therefore, the primary objective of this study was to determine the association between cow's milk-fat percentage and serum non-HDL cholesterol in young children. The secondary objective was to determine whether the association between cow's milk-fat percentage and non-HDL cholesterol is mediated by the typical volume of cow's milk consumed.

Methods

The present longitudinal study included children enrolled in an on-going cohort study conducted through TARGet Kids! (The Applied Research Group for Kids), a primary care, practice-based research network in Toronto, Canada (www.targetkids.ca). Data were collected annually on children aged 2-8 years when they attended well-child visits at primary care practices participating in TARGet Kids! between December 2008 and July 2016. Children with health conditions affecting growth, severe development delay, and families unable to communicate in English were excluded from the study. Complete details of this cohort have been previously described.[21] Consent was obtained from parents, and ethical approval was granted from the Research Ethics Boards at The Hospital for Sick Children and St. Michael's Hospital.

The primary exposure variable for this study was cow's milk-fat percentage, defined as the fat percentage of cow's milk the parent reported that the child typically consumed. The volume of milk was determined using the parent's response to the following statement for each of the following beverages including skim, 1%, 2%, and whole cow's milk (3.25%) from the TARGet Kids! Nutrition and Health Questionnaire: "Circle how many cups of each drink your child has currently in a typical day, if none then circle 0." If the child consumed more than one type of cow's milk, a weighted average of the different types was calculated.

The primary outcome variable, non-HDL cholesterol, was calculated by subtracting HDL cholesterol from total cholesterol. Nonfasting blood samples were collected by pediatric phlebotomists in the primary care offices at the time of the child's scheduled visit. Specimens were transported on ice and analyzed daily by Mount Sinai Services (Toronto, Canada). HDL and total cholesterol were measured using enzymatic colorimetric on the Roche Modular Platform (www.mountsinaiservices.com). Nonfasting values of non-HDL cholesterol have been shown to be a valid measure of cardiometabolic risk, reliable in children, and recommended by the US National Heart, Lung, and Blood Institute as a lipid-screening tool.[22-24] High-risk cut points used for this study were based on the US National Heart, Lung, and Blood Institute Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents.[24]

Covariates were identified a priori based on a review of the literature and included child's age, sex, BMI z score, daily free play, total breastfeeding duration, mother's ethnicity, self-reported family income, and self-reported parental history of CVD (diabetes, heart disease, hypertension, stroke, and high cholesterol).[25-27] Maternal ethnicity was collected using a geographically based ethnicity question, using questions from the Canadian Census.[28] Daily free play was measured by the question, "On a typical weekday, how much time does your child spend outside in 'unstructured free play'?" Total breastfeeding duration was determined by the response to the question, "For how long has your child been breastfed?"[29] Height and weight were measured by trained research staff using standardized methods.[30] Weight was measured using a digital scale (SECA, Hamburg, Germany); standing height was measured using a stadiometer (SECA). Children's BMI was calculated as the weight in kilograms divided by the height in meters squared. BMI z scores were based on World Health Organization growth standards for children younger than 5 years and World Health Organization growth references for children 5 years or older, which represent optimal growth for children and are recommended for use in these age groups in Canada.[31,32]

Descriptive statistics were performed to describe exposure, outcomes, and covariates for children's initial visit. Continuous variables were expressed as mean ± SD; categorical variables were expressed as frequencies and percent. For the primary analysis, the independent association between cow's milk-fat percentage and non-HDL cholesterol was determined using generalized estimating equations with an exchangeable correlation structure, which takes into account potential correlation within subjects with repeated measures.[33] The generalized estimating equation model was adjusted for potential confounding variables including age, sex, BMI z score, daily free play, total breastfeeding duration, mother's ethnicity, self-reported family income, and self-reported family history of CVD. A sensitivity analysis was performed without BMI z scores in the model and yielded similar results (data available on request). The exposure and outcome measures of cow's milk-fat intake and non-HDL cholesterol, respectively, were analyzed as continuous variables. Non-HDL cholesterol also was dichotomized using a "high" concentration of ≥3.75 mmol/L (145 mg/dL), as published,[24] and analyzed as a categorical variable. Multicollinearity was assessed using variance inflation factor, which remained under 2 for all covariates.[34] Missing data were believed to be unrelated to the respective covariates and assumed to be missing at random.[35] Therefore, multiple imputation using chained equations was performed for covariates. Analyses for 30 datasets were pooled together to give an overall estimate with SEs, CIs, and *P* values.[36]

For the secondary analysis, we explored whether typical volume of cow's milk consumed mediated the relationship between cow's milk-fat percentage and non-HDL cholesterol. Bootstrap resampling (10 000 repetitions) was used to estimate the regression coefficients and 95% CIs for the models used in the mediation analysis.[37] Results were considered statistically significant at $P < 0.05$. All statistical analyses were performed using R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Of the 7788 children whose parents consented to their participation in TARGet Kids!, 2890 children had blood samples collected, visits during 2-8 years of age, and parent-reported milk-fat percentage and volume of cow's milk consumed (**Figure 1**). Baseline characteristics for the study population are summarized in **Table I**. Baseline characteristics of those with and without blood samples (excluded) are summarized in **Table II** (available at www.jpeds.com). Children with blood samples collected visually appeared clinically similar to those without blood samples. In total, 32% (n = 930) of the participants had repeated measures with a total of 4296 observations included for analysis; 586 provided data from 2 visits, 239 from 3 visits, and 105 from 4 or more visits.

In the unadjusted analysis, there was a statistically signification association between higher cow's milk-fat percentage and greater non-HDL cholesterol (**Table III**); each 1% increase in cow's milk-fat was associated with an increase of 0.035 mmol/L (95% CI 0.016-0.054; $P < .001$) (1.35 mg/dL [95% CI 0.62-2.08]) in non-HDL cholesterol. After we adjusted for covariates, each 1% increase in cow's milk-fat percentage was associated with a 0.024 mmol/L (95% CI 0.005-0.044; $P = .01$) (0.93 mg/dL [95% CI 0.19-1.70]) increase in non-HDL cholesterol. When analyzing non-HDL cholesterol as a dichotomized variable (above or below 3.75 mmol/L [145 mg/dL]), we found that cow's milk-fat was not associated with increased odds of having high non-HDL cholesterol (OR 1.04, 95% CI 0.89-1.21; $P = .16$). In a post-hoc analysis, we examined the association between cow's milk-fat percentage and having borderline high non-HDL cholesterol (≥3.10 mmol/L [120 mg/dL]) and found that cow's milk-fat percentage was associated with increased odds (OR 1.12, 95% CI 1.03-1.21; $P = .03$) of having above borderline high non-HDL cholesterol.

In the mediation analysis (**Figure 2**), each 1% increase in cow's milk fat was associated with 0.38 cup/day increase in typical volume of cow's milk consumed (model a). Each one cup/day increase in cow's milk consumption was associated with a 0.026 mmol/L (1.00 mg/dL) increase in non-HDL cholesterol (model b). When adjusted for typical volume of cow's milk consumed, cow's milk-fat remained positively associated with non-HDL cholesterol (model c′; 0.025 mmol/L [0.96 mg/dL] increase per 1% cow's milk-fat; 95% CI 0.003-0.017 mmol/L [0.12-0.66 mg/dL]). Volume of cow's milk consumed partially mediated the association between cow's milk-fat and non-HDL cholesterol, accounting for 28% of the relationship.

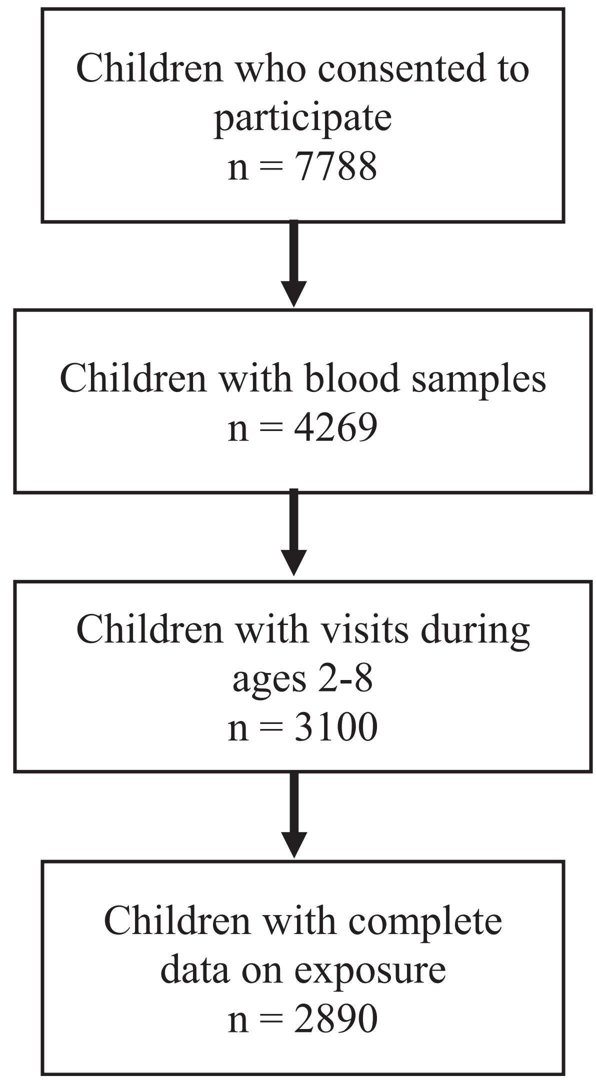

Figure 1. Participant flowchart.

Discussion

Our study identified that consumption of higher-fat cow's milk was associated with a small increase in non-HDL cholesterol levels among 2- to 8-year-old healthy children. The typical volume of cow's milk consumed partially mediated this association. However, higher cow's milk-fat percentage was not associated with greater odds of incident high non-HDL cholesterol, using the published cut-off of 3.75 mmol/L (145 mg/dL).

The positive association between cow's milk-fat percentage and non-HDL cholesterol supports findings from other published studies that have shown modifications in dietary fat intake is associated with changes in serum cholesterol levels in children.[38-40] In the Special Turku Coronary Risk Factor Invention Project (STRIP) trial, non-HDL cholesterol levels were 0.32 mmol/L (12.4 mg/dL) lower in 5-year-old boys

Table I. Baseline characteristics of study participants

Baseline characteristics	Whole-fat cow's milk (3.25%) (n = 754)	Lower-fat cow's milk (2%, 1%, skim) (n = 1856)	Non-cow's milk (n = 280)	All participants (n = 2890)
Age, mo, mean (SD)	39.2 (17.0)	48.8 (18.5)	45.6 (19.9)	46.0 (18.7)
Male, n (%)	413 (54.8)	976 (52.6)	141 (50.4)	1530 (52.9)
Female, n (%)	341 (45.2)	880 (47.4)	139 (49.6)	1360 (47.1)
BMI z score, mean (SD)	0.08 (1.06)	0.37 (1.06)	0.12 (1.17)	0.27 (1.08)
Missing, n (%)	4 (0.5)	39 (2.1)	21 (7.5)	74 (2.6)
Maternal ethnicity, n (%)				
European	380 (50.3)	1180 (63.6)	143 (51.1)	1703 (58.9)
East Asian	56 (7.4)	112 (6.0)	18 (6.4)	186 (6.4)
South Asian	93 (12.3)	100 (5.4)	22 (7.9)	215 (7.4)
Southeast Asian	35 (4.6)	61 (3.3)	6 (2.1)	102 (3.5)
Arab	21(2.8)	24 (1.3)	3 (1.1)	48 (1.7)
African	42 (5.6)	67 (3.6)	18 (6.4)	127 (4.4)
Latin American	24 (3.2)	61 (3.3)	6 (2.1)	91 (3.1)
Mixed ethnicity	36 (4.8)	87 (4.7)	25 (8.9)	148 (5.1)
Other	1 (0.1)	8 (0.4)	0 (0)	9 (0.3)
Missing	66 (8.7)	156 (8.4)	39 (14.0)	261 (9.0)
Family income, n (%)				
Less than $79 999	162 (21.5)	325 (17.5)	68 (24.3)	555 (19.2)
$80 000-$150 000	201 (26.6)	467 (25.2)	66 (23.6)	734 (25.4)
More than $150 000	235 (31.2)	709 (38.2)	109 (38.9)	1053 (36.4)
Missing	156 (20.7)	355 (19.1)	37 (13.2)	584 (20.2)
Parental history of CVD, n (%)				
Yes	116 (15.4)	285 (15.3)	38 (13.6)	439 (15.2)
No	577 (76.5)	1410 (76.0)	208 (74.3)	2195 (76.0)
Missing	61 (8.1)	161 (8.7)	34 (12.1)	256 (8.8)
Daily free-play, min, mean (SD)	61.0 (59.1)	57.1 (53.2)	55.6 (54.3)	58.0 (54.9)
Missing, n (%)	23 (3.1)	87 (4.7)	44 (15.7)	154 (5.3)
Breastfeeding duration, mo, mean (SD)	12.3 (7.8)	11.8 (7.7)	13.4 (9.5)	12.1 (7.9)
Missing, n (%)	22 (2.9)	154 (8.3)	59 (21.1)	235 (8.2)
Non-HDL cholesterol, mmol/L, mean (SD)	2.71 (0.67)	2.64 (0.65)	2.48 (0.63)	2.64 (0.65)
(mg/dL [SD])	(104.6 [25.7])	(101.9 [25.1])	(95.7 [24.3])	(101.9 [25.1])
≥3.75 mmol/L (145 mg/dL), n (%)	54 (7.2)	92 (5.0)	10 (3.6)	156 (5.4)
3.10-3.74 mmol/L (120-144 mg/dL), n (%)	152 (20.2)	346 (18.6)	34 (12.1)	532 (18.4)
<3.10 mmol/L (120 mg/dL), n (%)	548 (72.6)	1418 (76.4)	236 (84.3)	2202 (76.2)
Volume of cow's milk (cups/d), mean (SD)	2.1 (1.1)	2.0 (1.0)	0 (0)	1.8 (1.1)

whose families received repeated dietary advice, including reducing dietary fat during childhood, compared with the control group, with no effect in girls.[39] In the Dietary Intervention Study in Children (DISC),[38] LDL cholesterol levels were 0.08 mmol/L (3.1 mg/dL) lower in 8- to 10-year-old children with high cholesterol who received a behavioral intervention to lower dietary fat, saturated fat, and cholesterol, compared with controls. In a study in school-aged children in Mexico, Villalpando et al showed that LDL cholesterol levels decreased by 0.28 mmol/L (10.8 mg/dL) in children receiving 400 mL of 0.5% fat cow's milk for 4 months compared with those receiving whole cow's milk.[40]

It is difficult to attribute the cholesterol reductions in these studies solely to changes in cow's milk-fat. For example, recommendations to consume lower-fat cow's milk after 12 months of age was only part of the intervention in the STRIP study protocol.[39] In the study by Villalpando et al, cow's milk-fat was the only dietary intervention and intake of energy, dietary carbohydrates, fat, and protein did not differ between the groups.[40] The lower-fat cow's milk groups may have compensated dietary fat intake through other fatty acids with less LDL cholesterol-raising potential compared with dairy fat, such as polyunsaturated fatty acids.[41,42] In our study, we were able to look specifically at cow's milk-fat percentage within a large cohort of children with a proportion of participants with longitudinal data and in an age group that corresponds with pediatric nutrition guidelines. However, although consuming higher-fat cow's milk was associated with statistically significant greater levels of non-HDL cholesterol in our study, this also may reflect other dietary factors that were not measured; comprehensive

Table III. Generalized estimating equations models determining the association between cow's milk-fat percentage and non-HDL cholesterol

Characteristics	Non-HDL cholesterol mmol/L (mg/dL)	95% CI mmol/L (mg/dL)	*P* Value
Univariate analysis			
Cow's milk-fat (%)	0.035 (1.35)	0.016, 0.054 (0.62, 2.08)	<.001
Multivariate analysis*			
Cow's milk-fat (%)	0.024 (0.93)	0.005, 0.044 (0.19, 1.70)	.01

*Multivariate model was adjusted for age, sex, BMI z-score, daily free play, total breastfeeding duration, mother's ethnicity, self-reported family income, and self-reported parental history of cardiovascular disease.

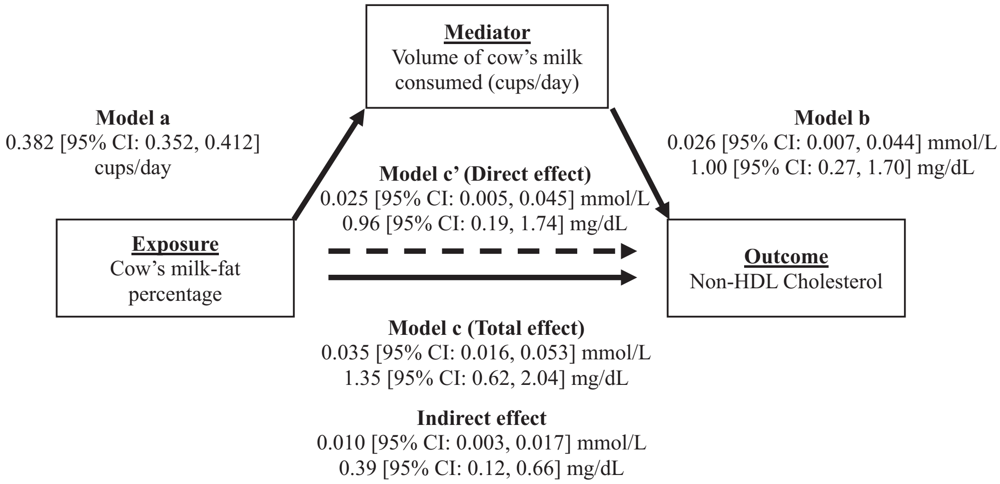

Figure 2. Conceptual model. Volume of cow's milk consumed mediating the association between cow's milk-fat percentage and non-HDL cholesterol. 0.010 mmol/L (0.39 mg/dL) (indirect effect) of the 0.035 mmol/L (1.35 mg/dL) increase (total effect) in non-HDL cholesterol associated with cow's milk-fat was mediated by volume of cow's milk consumed. To determine the percent of total efffect mediated by volume of cow's milk, the beta coefficient from the indirect effect was divided by the total effect and multiplied by 100.

dietary information on fat intake is an important limitation of our study.

Previous studies have found a relationship between volume of cow's milk consumed and cardiometabolic health in children. However, these studies did not account for milk-fat.[19,20] In our study, we found that typical volume of cow's milk only partially mediated the increase in non-HDL cholesterol associated with higher cow's milk-fat percentage. Our findings illustrate the importance of considering both volume and fat content of cow's milk when analyzing the contribution of cow's milk to cardiovascular outcomes.

We did not find an association between higher cow's milk-fat percentage and greater odds of having high non-HDL cholesterol. Several mechanisms have been proposed regarding the association between dairy fat and cardiovascular health. Calcium found in dairy may attenuate intestinal fat absorption and increase fat excretion in feces, resulting in smaller increases in serum cholesterol levels compared with other dietary sources of fat.[43] Dairy fat contains fatty acids, such as conjugated linoleic acid, butyric acid, and phytanic acid, that may have health benefits that counter detrimental cardiovascular effects from other fatty acids.[44] In addition, statistical modeling has demonstrated that isocaloric substitution of saturated fat from meat with dairy saturated fat is associated with lower risk of cardiovascular events in adults.[18]

Assessing the clinical impact of our results requires further inquiry. We demonstrated an association between cow's milk-percentage and non-HDL cholesterol, although the effect size in our study is considerably smaller than those found in intervention studies.[38-40] Although we report that cow's milk-fat percentage was not associated with greater odds of incident high non-HDL cholesterol, less than 5% of our study population had high non-HDL cholesterol. Thus, our study may have been underpowered for this analysis. In a post-hoc analysis, we found that higher cow's milk-fat percentage was associated with increased odds having above borderline high non-HDL cholesterol (≥3.10 mmol/L [120 mg/dL]). Further information on how consumption of cow's milk-fat and other dietary factors contributes to non-HDL cholesterol levels over time as well as the development of subclinical atherosclerosis (as measured by carotid intima media thickness via ultrasound scan) will help us better understand the clinical implications of our results.

Limitations of this study include the potential for residual confounding; we were unable to account for other dietary factors that may contribute to serum non-HDL cholesterol. Questionnaire data collected from the parents may be recalled incorrectly. The children in our study are primarily of European ethnicity, from families that make greater than the average median household income and reside in an urban environment. Thus, the results in this population may not be generalizable to all children in North America.

Further research is needed to determine how other dietary intake factors, in addition to cow's milk, may contribute to cardiovascular outcomes in young children over time. The clinical impact of small increases in non-HDL cholesterol during childhood requires further investigation to guide interventions for meaningful outcomes in the prevention of CVD. ■

We thank all of the participating families for their time and involvement in TARGet Kids! and are grateful to all collaborators and practitioners who are currently involved in the TARGet Kids! practice-based research network.

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References

1. Srinivasan SR, Frontini MG, Xu J, Berenson GS. Utility of childhood non−high-density lipoprotein cholesterol levels in predicting adult dyslipidemia and other cardiovascular risks: the Bogalusa Heart Study. Pediatrics 2006;118:201-6.
2. McMahan CA, Gidding SS, Malcom GT, Tracy RE, Strong JP, McGill HC Jr, et al. Pathobiological determinants of atherosclerosis in youth risk scores are associated with early and advanced atherosclerosis. Pediatrics 2006;118:1447-55.
3. Juhola J, Magnussen CG, Viikari JS, Kahonen M, Hutri-Kahonen N, Jula A, et al. Tracking of serum lipid levels, blood pressure, and body mass index from childhood to adulthood: the Cardiovascular Risk in Young Finns Study. J Pediatr 2011;159:584-90.
4. Kaikkonen JE, Mikkila V, Magnussen CG, Juonala M, Viikari JS, Raitakari OT. Does childhood nutrition influence adult cardiovascular disease risk? Insights from the Young Finns Study. Ann Med 2013;45:120-8.
5. Persaud N, Maguire JL, Lebovic G, Carsley S, Khovratovich M, Randall Simpson JA, et al. Association between serum cholesterol and eating behaviours during early childhood: a cross-sectional study. CMAJ 2013;185:E531-6.
6. Briefel RR, Reidy K, Karwe V, Jankowski L, Hendricks K. Toddlers' transition to table foods: Impact on nutrient intakes and food patterns. J Am Diet Assoc 2004;104(1 suppl 1):s38-44.
7. Garriguet D. Beverage consumption of children and teens. Health Rep 2008;19:17-22.
8. O'Connor TM, Yang SJ, Nicklas TA. Beverage intake among preschool children and its effect on weight status. Pediatrics 2006;118:e1010-8.
9. Black RE, Williams SM, Jones IE, Goulding A. Children who avoid drinking cow milk have low dietary calcium intakes and poor bone health. Am J Clin Nutr 2002;76:675-80.
10. Hu FB, Stampfer MJ, Rimm E, Ascherio A, Rosner BA, Spiegelman D, et al. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. Am J Epidemiol 1999;149:531-40.
11. McGee DL, Reed DM, Yano K, Kagan A, Tillotson J. Ten-year incidence of coronary heart disease in the Honolulu Heart Program. Relationship to nutrient intake. Am J Epidemiol 1984;119:667-76.
12. Gidding SS, Dennison BA, Birch LL, Daniels SR, Gillman MW, Lichtenstein AH, et al. Dietary recommendations for children and adolescents: a guide for practitioners. Pediatrics 2006;117:544-59.
13. Vanderhout SM, Birken CS, Parkin PC, Lebovic G, Chen Y, O'Connor DL, et al. Relation between milk-fat percentage, vitamin D, and BMI z score in early childhood. Am J Clin Nutr 2016;104:1657-64.
14. Barba G, Troiano E, Russo P, Venezia A, Siani A. Inverse association between body mass and frequency of milk consumption in children. Br J Nutr 2005;93:15-9.
15. Scharf RJ, Demmer RT, DeBoer MD. Longitudinal evaluation of milk type consumed and weight status in preschoolers. Arch Dis Child 2013;98:335-40.
16. Berkey CS, Rockett HR, Willett WC, Colditz GA. Milk, dairy fat, dietary calcium, and weight gain: a longitudinal study of adolescents. Arch Pediatr Adolesc Med 2005;159:543-50.
17. de Souza RJ, Mente A, Maroleanu A, Cozma AI, Ha V, Kishibe T, et al. Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. BMJ 2015;351:h3978.
18. de Oliveira Otto MC, Mozaffarian D, Kromhout D, Bertoni AG, Sibley CT, Jacobs DR Jr, et al. Dietary intake of saturated fat by food source and incident cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis. Am J Clin Nutr 2012;96:397-404.
19. Moschonis G, van den Heuvel EG, Mavrogianni C, Singh-Povel CM, Leotsinidis M, Manios Y. Associations of milk consumption and vitamin B(2) and Beta12 derived from Milk with fitness, anthropometric and biochemical indices in children. The Healthy Growth Study. Nutrients 2016;8.
20. Abreu S, Moreira P, Moreira C, Mota J, Moreira-Silva I, Santos PC, et al. Intake of milk, but not total dairy, yogurt, or cheese, is negatively associated with the clustering of cardiometabolic risk factors in adolescents. Nutr Res 2014;34:48-57.
21. Carsley S, Borkhoff CM, Maguire JL, Birken CS, Khovratovich M, McCrindle B, et al. Cohort Profile: the Applied Research Group for Kids (TARGet Kids!). Int J Epidemiol 2015;44:776-88.
22. Anderson LN, Maguire JL, Lebovic G, Hanley AJ, Hamilton J, Adeli K, et al. Duration of fasting, serum lipids, and metabolic profile in early childhood. J Pediatr 2017;180:47-52 e1.
23. Steiner MJ, Skinner AC, Perrin EM. Fasting might not be necessary before lipid screening: a nationally representative cross-sectional study. Pediatrics 2011;128:463-70.
24. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and AdolescenTS. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics 2011;128(suppl 5): S213-56.
25. Anand SS, Yusuf S, Vuksan V, Devanesen S, Teo KK, Montague PA, et al. Differences in risk factors, atherosclerosis, and cardiovascular disease between ethnic groups in Canada: the Study of Health Assessment and Risk in Ethnic groups (SHARE). Lancet 2000;356:279-84.
26. Dennison BA, Kikuchi DA, Srinivasan SR, Webber LS, Berenson GS. Parental history of cardiovascular disease as an indication for screening for lipoprotein abnormalities in children. J Pediatr 1989;115:186-94.
27. Srinivasan SR, Myers L, Berenson GS. Distribution and correlates of non-high-density lipoprotein cholesterol in children: the Bogalusa Heart Study. Pediatrics 2002;110:e29.
28. Omand JA, Carsley S, Darling PB, Parkin PC, Birken CS, Urquia ML, et al. Evaluating the accuracy of a geographic closed-ended approach to ethnicity measurement, a practical alternative. Ann Epidemiol 2014;24:246-53.
29. Li R, Scanlon KS, Serdula MK. The validity and reliability of maternal recall of breastfeeding practice. Nutr Rev 2005;63:103-10.
30. Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey (NHANES) Anthropometry Procedures Manual. Atlanta (GA): Centers for Disease Control and Prevention; 2007.
31. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ 2007;85:660-7.
32. Onis M. WHO Child Growth Standards based on length/height, weight and age. Acta Paediatr 2006;95:76-85.
33. Ziegler A, Vens M. Generalized estimating equations. Methods Inf Med 2010;49:421-5.
34. O'Brien RM. A caution regarding rules of thumb for variance inflation factors. Quality Quantity 2007;41:673-90.
35. Royston P. Multiple imputation of missing values: update. Stata J 2005;5:188.
36. Buuren S, Groothuis-Oudshoorn K. mice: Multivariate imputation by chained equations in R. J Statistical Software 2011;45(3).
37. MacKinnon DP. Introduction to statistical mediation analysis. New York: Routledge; 2008.
38. Lauer RM, Obarzanek E, Hunsberger SA, Van Horn L, Hartmuller VW, Barton BA, et al. Efficacy and safety of lowering dietary intake of total fat, saturated fat, and cholesterol in children with elevated LDL cholesterol: the Dietary Intervention Study in Children. Am J Clin Nutr 2000;72(5 suppl):1332S-42S.
39. Rask-Nissila L, Jokinen E, Ronnemaa T, Viikari J, Tammi A, Niinikoski H, et al. Prospective, randomized, infancy-onset trial of the effects of a low-saturated-fat, low-cholesterol diet on serum lipids and lipoproteins before school age: the Special Turku Coronary Risk Factor Intervention Project (STRIP). Circulation 2000;102:1477-83.

40. Villalpando S, Lara Zamudio Y, Shamah-Levy T, Mundo-Rosas V, Manzano AC, Lamadrid-Figueroa H. Substitution of whole cows' milk with defatted milk for 4 months reduced serum total cholesterol, HDL-cholesterol and total apoB in a sample of Mexican school-age children (6-16 years of age). Br J Nutr 2015;114:788-95.
41. Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. PLoS Med 2010;7:e1000252.
42. Hodson L, Skeaff CM, Chisholm WA. The effect of replacing dietary saturated fat with polyunsaturated or monounsaturated fat on plasma lipids in free-living young adults. Eur J Clin Nutr 2001;55:908-15.
43. Soerensen KV, Thorning TK, Astrup A, Kristensen M, Lorenzen JK. Effect of dairy calcium from cheese and milk on fecal fat excretion, blood lipids, and appetite in young men. Am J Clin Nutr 2014;99:984-91.
44. Kratz M, Baars T, Guyenet S. The relationship between high-fat dairy consumption and obesity, cardiovascular, and metabolic disease. Eur J Nutr 2013;52:1-24.

50 Years Ago in *The Journal of Pediatrics*

Anaphylactoid Purpura: Streptococcal Antibody Titers and β_{1c}-Globulin Levels

Ayoub EM, Hoyer J. J Pediatr 1969;75:193-201.

The authors investigated the association between 33 patients with Henoch-Schönlein purpura (now called IgA vasculitis) and antecedent streptococcal infection. They found a positive throat culture for β-hemolytic streptococcus in 11 of 23 patients (48%) in whom a culture was obtained and serologic evidence for prior streptococcal infection among 39% of the entire cohort. However, the rate of serologic evidence of prior streptococcal disease did not differ significantly from 33 healthy controls. They concluded that, although streptococcal infection may have an (unknown) role in the pathogenesis of IgA vasculitis, streptococcal infection is not an etiologic cause, unlike rheumatic fever.

Indeed, these findings have been corroborated in other studies, showing evidence of prior β-hemolytic streptococcus infection in about 25%-40% cases of IgA vasculitis. However, more evidence has since been uncovered to (partially) explain the role of streptococcus in the pathogenesis of this disease.

Nephritis-associated plasmin receptor, a group A streptococcal antigen, was found in the glomeruli of 30% of patients with IgA vasculitis-related nephritis vs 3% with other renal diseases. Patients with IgA vasculitis were found to develop antibodies to these receptors. The IgA-binding M proteins of group A streptococci of 3 strains (M4, M22, and M60) have been detected in the majority of skin and kidney biopsies of these patients and were able to form immune complexes with the Fc portion of IgA.[1] Furthermore, in patients with IgA vasculitis-related nephritis, the hinge region between the CH1 and CH2 domains of the heavy chain of IgA1 was found to be deficient in sialic acid and galactose glycosylation.[2] Glycosylation deficient IgA1 exposes *N*-acetylgalactosamine-containing neoepitopes that are recognized by naturally occurring IgG or IgA1 antibodies. This was shown to lead to the formation of immune complexes which stimulate proliferation of human mesangial cells.

Thus, the combined effects of infection with certain strains of group A streptococcal with the formation of abnormal IgA may lead to immune complexes that stimulate inflammatory processes and endothelial activation that may result in clinical features of IgA vasculitis.

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References

1. Schmitt R, Carlsson F, Mörgelin M, Tati R, Lindahl G, Karpman D. Tissue deposits of IgA-binding streptococcal M proteins in IgA nephropathy and Henoch-Schönlein purpura. Am J Pathol 2010;176:608-18.
2. Saulsbury FT. Alterations in the O-linked glycosylation of IgA1 in children with Henoch-Schönlein purpura. J Rheumatol 1997;24:2246-9.

Appendix

TARGet Kids! Collaborators

Co-leads: Catherine S. Birken, Jonathon L. Maguire; advisory committee: Ronald Cohn, Eddy Lau, Andreas Laupacis, Patricia C. Parkin, Michael Salter, Peter Szatmari, Shannon Weir; science review and management committees: Laura N. Anderson, Cornelia M. Borkhoff, Charles Keown-Stoneman, Christine Kowal, Dalah Mason; site investigators: Murtala Abdurrahman, Kelly Anderson, Gordon Arbess, Jillian Baker, Tony Barozzino, Sylvie Bergeron, Dimple Bhagat, Gary Bloch, Joey Bonifacio, Ashna Bowry, Caroline Calpin, Douglas Campbell, Sohail Cheema, Elaine Cheng, Brian Chisamore, Evelyn Constantin, Karoon Danayan, Paul Das, Mary Beth Derocher, Anh Do, Kathleen Doukas, Anne Egger, Allison Farber, Amy Freedman, Sloane Freeman, Sharon Gazeley, Charlie Guiang, Dan Ha, Curtis Handford, Laura Hanson, Leah Harrington, Sheila Jacobson, Lukasz Jagiello, Gwen Jansz, Paul Kadar, Florence Kim, Tara Kiran, Holly Knowles, Bruce Kwok, Sheila Lakhoo, Margarita Lam-Antoniades, Eddy Lau, Denis Leduc, Fok-Han Leung, Alan Li, Patricia Li, Jessica Malach, Roy Male, Vashti Mascoll, Aleks Meret, Elise Mok, Rosemary Moodie, Maya Nader, Katherine Nash, Sharon Naymark, James Owen, Michael Peer, Kifi Pena, Marty Perlmutar, Navindra Persaud, Andrew Pinto, Michelle Porepa, Vikky Qi, Nasreen Ramji, Noor Ramji, Danyaal Raza, Alana Rosenthal, Katherine Rouleau, Caroline Ruderman, Janet Saunderson, Vanna Schiralli, Michael Sgro, Hafiz Shuja, Susan Shepherd, Barbara Smiltnieks, Cinntha Srikanthan, Carolyn Taylor, Stephen Treherne, Suzanne Turner, Fatima Uddin, Meta van den Heuvel, Joanne Vaughan, Thea Weisdorf, Sheila Wijayasinghe, Peter Wong, John Yaremko, Ethel Ying, Elizabeth Young, Michael Zajdman; research team: Farnaz Bazeghi, Vincent Bouchard, Marivic Bustos, Charmaine Camacho, Dharma Dalwadi, Christine Koroshegyi, Tarandeep Malhi, Sharon Thadani, Julia Thompson, Laurie Thompson; project team: Mary Aglipay, Imaan Bayoumi, Sarah Carsley, Katherine Cost, Karen Eny, Theresa Kim, Laura Kinlin, Jessica Omand, Shelley Vanderhout, Leigh Vanderloo; Applied Health Research Centre: Christopher Allen, Bryan Boodhoo, Olivia Chan, David W.H. Dai, Judith Hall, Peter Juni, Gerald Lebovic, Karen Pope, Kevin Thorpe; Mount Sinai Services Laboratory: Rita Kandel, Michelle Rodrigues, Hilde Vandenberghe.

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The other authors declare no conflicts of interest.

Table II. Baseline characteristics of participants

Baseline characteristics (n = 2890)	Children with blood samples (n = 2890)	Children without blood samples (n = 4308)
Age, mo (SD)	46.0 (18.7)	44.2 (19.1)
Male, n (%)	1530 (52.9)	2240 (52.0)
Female, n (%)	1360 (47.1)	2068 (48.0)
BMI z score, mean (SD)	0.27 (1.08)	0.24 (1.04)
Missing, n (%)	74 (2.6)	96 (2.2)
Maternal ethnicity, n (%)		
European	1703 (58.9)	2763 (64.1)
East Asian	186 (6.4)	286 (6.6)
South Asian	215 (7.4)	253 (5.9)
Southeast Asian	102 (3.5)	125 (2.9)
Arab	48 (1.7)	62 (1.4)
African	127 (4.4)	162 (3.8)
Latin American	91 (3.1)	118 (2.7)
Mixed ethnicity	148 (5.1)	183 (4.2)
Other	9 (0.3)	11 (0.2)
Missing	261 (9.0)	345 (8.0)
Family income, n (%)		
Less than $79 999	555 (19.2)	680 (15.8)
$80 000-$150 000	734 (25.4)	1037 (24.1)
More than $150 000	1053 (36.4)	1599 (37.1)
Missing	584 (20.2)	992 (23.0)
Parental history of CVD, n (%)		
Yes	439 (15.2)	602 (14.0)
No	2195 (76.0)	3134 (72.7)
Missing	256 (8.8)	572 (13.3)
Daily free-play, min, mean (SD)	58.0 (54.9)	55.8 (51.0)
Missing, n (%)	155 (5.4)	536 (12.4)
Breastfeeding duration, mo, mean (SD)	12.1 (7.9)	11.7 (7.5)
Missing, n (%)	235 (8.2)	341 (7.9)
Non-HDL cholesterol, mmol/L, mean (SD) (mg/dL [SD])	2.64 (0.65) (101.9 [25.1])	N/A
≥3.75 mmol/L (145 mg/dL), n (%)	156 (4.7)	
3.10-3.74 mmol/L (120-144 mg/dL), n (%)	532 (18.4)	
<3.10 mmol/L (120 mg/dL), n (%)	2202 (76.2)	
Volume of cow's milk (cups/d), mean (SD)	1.8 (1.1)	1.8 (1.1)
Cow's milk-fat percentage, mean (SD)	1.9 (1.0)	2.0 (1.1)

N/A, not available.