

Parental hypercholesterolemia and family medical history as predictors of hypercholesterolemia in their children

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ABSTRACT

Introduction. Parental hypercholesterolemia would be a better predictor of hypercholesterolemia than family medical history in children.

Objectives. To compare the strength of association and predictive values of parental hypercholesterolemia versus a positive family history in pediatric hypercholesterolemia.

Material and methods. Cross-sectional, analytical study. Cholesterol levels were measured in children aged ≥ 6 and < 12 years and in their biological parents. A survey was administered to parents.

The association was estimated using the odds ratio (OR), and its predictive value was determined. The relationship between hypercholesterolemia in parents and their children was studied with multilevel regression.

Results. A total of 332 children, 304 mothers, and 206 fathers were assessed. A cholesterol level ≥ 240 mg/dL in one or both parents and ≥ 200 mg/dL in children showed: OR= 6.40; 95 % confidence interval (CI)= 2.85-14.48; $p < 0.0001$; sensitivity= 69 %; specificity= 74 %; positive predictive value (PPV)= 34 %; negative predictive value (NPV)= 93%; positive likelihood ratio (LR+)= 2.69; negative likelihood ratio (LR-)= 0.42. Family medical history versus children with cholesterol level ≥ 200 showed: OR= 1.86; 95 % CI= 0.84-4.11; $p= 0.1272$; sensitivity= 69 %; specificity= 46 %; PPV= 19 %; NPV= 89%; LR+= 1.27; LR-= 0.68. Cholesterol was 2.9 and 2.5 mg/dL higher per every 10 mg/dL of increased cholesterol in mothers and fathers, respectively.

Conclusions: Parental hypercholesterolemia was significantly associated with hypercholesterolemia in children and showed a higher predictive power than a positive family medical history.

Key words: hypercholesterolemia, child, screening, family medical history.

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INTRODUCTION

The observation of atherosclerosis in the autopsies of young soldiers who died in the Korean War in 1953,^{1,2} and the confirmation of this finding in other studies,³⁻⁵ brought about a paradigm shift and it was agreed that this disease starts in childhood.

In 1983, the Lipid Research Clinics Coronary Primary Prevention Trial provided strong evidence that hypercholesterolemia was an important factor of cardiovascular risk,^{6,7} and early detection was recommended. In Argentina, the prevalence of childhood hypercholesterolemia is 6-15 % and that of slightly elevated cholesterol level, 15-35 %.⁹⁻¹¹

The 1998 and 2011 consensuses by the American Academy of Pediatrics (AAP)^{12,8} and the 2005 consensus by the Argentine Society of Pediatrics (Sociedad Argentina de Pediatría, SAP) respectively recommend, as a selective screening strategy, the measurement of cholesterol levels in children with a positive family medical history (FMH) or an unknown history of early cardiovascular conditions in their parents and grandparents or of hypercholesterolemia in their parents. In its consensus on the management of dyslipemias in pediatrics, the SAP recommends the universal screening in children aged 6 to 11 years but its mass use and costs complicate its implementation.¹⁴

A previous study¹⁵ did not find a very strong association between a positive FMH and hypercholesterolemia and diagnostic tests with acceptable values, but

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the positive predictive value (PPV) was very low due to the large number of false positive results. A strong association was also observed between hypercholesterolemia in parents and their children when both parents had hypercholesterolemia, although the sample size was small.

The objective of this study was to compare the strength of association and the predictive values of parental hypercholesterolemia versus a positive FMH in pediatric hypercholesterolemia.

MATERIAL AND METHODS

This was a cross-sectional, analytical study. The field work took place between February and June 2015. Parents' and children's first and last names, national identity document (ID), date of birth, and sex were recorded, and the anonymity of these data was maintained.

Child population

Children attending the only two primary schools (both public) at Jovita, province of Córdoba, Argentina.

Inclusion criteria: Schoolchildren attending first through sixth grade, aged 6.0 to 11.9 years as of June 30th, 2015. Informed consent signed by the mother, father or legal guardian.

Exclusion criteria: Having an infectious disease at present or within 20 days before blood samples were drawn for biochemical testing.¹⁶ The presence of chronic conditions that cause or may cause marked alterations of lipid metabolism.¹⁷

Parent population

Inclusion criteria: Being a biological mother or father and having signed the informed consent.

Exclusion criteria: Having an infectious disease at present or within 20 days before blood samples were drawn for biochemical testing.¹⁶

OUTCOME MEASURES

Cholesterol level

Blood drawn by venipuncture after a 10-hour fasting period was used. Total cholesterol level

was measured using the enzymatic AA liquid Colestat method (Wiener Lab). Serum was separated in the first hour following the blood draw, and tests were done in the same day using a CM250 autoanalyzer (Wiener Lab).

The technique used to measure cholesterol levels was subjected to a traceability control through the Reference and Standardization Lab for Clinical Biochemistry (Laboratorio de Referencia y Estandarización en Bioquímica Clínica, LARESBI) of the Argentine Biochemistry Foundation (*Fundación Bioquímica Argentina*), and the corresponding certificate was obtained from the Cholesterol Reference Method Laboratory Network (Centers for Disease Control [CDC], Atlanta, USA).

Reference values used for children were those proposed by the AAP¹² and the SAP,¹⁴ and for adults, those established by the Adult Treatment Panel III (ATP III)¹⁸ (Table 1). Cholesterol level was categorized into A, B, and C elsewhere in the document.

Predictive outcome measure no. 1: Hypercholesterolemia in one or both parents. This was recorded as a dichotomous outcome measure. Positive paternal or maternal hypercholesterolemia: one or both parents with a cholesterol level ≥ 240 mg/dL. Negative: < 240 mg/dL.

Output variable: Hypercholesterolemia in the child. This was recorded as a dichotomous outcome measure. Positive: a child with a cholesterol level ≥ 200 mg/dL. Negative: < 200 mg/dL.

Family medical history

It was collected through a survey designed based on the recommendations of the AAP expert panel.⁸ FMH was considered positive when cardiovascular, brain, and upper or lower limb diseases were detected in the parents or grandparents at an early age, i.e., before 55 years old in men and before 65 years old in women, or when the cholesterol level was found to be ≥ 240 mg/dL in the parents.

TABLE 1. Cholesterol level reference values for children and adults

Category	Cholesterol level	Children (AAP-SAP)	Adults (ATP III)
A	High	≥ 200 mg/dL	≥ 240 mg/dL
B	Borderline high	170-199 mg/dL	200-239 mg/dL
C	Desirable	< 170 mg/dL	< 200 mg/dL

Predictive outcome measure no. 2: Positive FMH. This was recorded as a dichotomous, positive and negative outcome measure.

Ethical considerations

The approval of the Ethics Committee, the school principals, and the Ministry of Education of the province of Córdoba was obtained. All communications were conducted through the schools. Result reports were delivered to parents in sealed envelopes. Study participants' confidentiality was warranted.

Statistical considerations

Collected data were electronically stored in tabular format in Access.

The association between hypercholesterolemia in parents and their children was assessed. Paired data contingency tables were used (child and his/her respective mother and/or father); the strength of the association was estimated using the odds ratio (OR) and its statistical significance was assessed using McNemar's version of the χ^2 test, with a significance level of 0.05.

The criteria implemented to classify parents and children for this analysis, based on their cholesterol level, are shown in *Table 2*.

The association between a positive FMH and hypercholesterolemia in children was assessed in the same manner as for the previous item.

The following diagnostic tests were done to assess the potential prediction of parental

hypercholesterolemia and positive FMH in relation to hypercholesterolemia in children: sensitivity, specificity, PPV, negative predictive value (NPV), and positive and negative likelihood ratios (LR+ and LR-). The percentage of the population to be assessed (PPA) was estimated, which is the result of dividing the number of individuals to be assessed using the predictive outcome measure by the total number of assessed individuals.

The prevalence of blood cholesterol in each child and adult category and descriptive statistics of cholesterol level and age were estimated.

A multilevel regression analysis was done taking the family unit as a cluster, with a random intercept per family to consider the correlation in the response outcome measure among the members of the same family.

A sample size of 328 participants was estimated to detect a difference of at least 15 % between both groups. The proportion of subjects in the exposed group (children with hypercholesterolemia) was 45 % and, in the group without exposure, 30 %, with a power of 80 % and an alpha error of 5 % (Epi Info 7.0).

RESULTS

In a population of 444 schoolchildren in total, 342 gave their consent. Ten children and their parents were excluded because they did not meet the inclusion criteria, so 332 children were included (75 % of the universe); 169 (51 %) were

TABLE 2. Criteria for the classification of parents and children based on their cholesterol level category

Parents' category		Condition	Child's category	Condition	Classification
Mother/father 1	Mother/father 2				
If the category of mother/father 1 and 2 is:		It is considered	And if the child is category	It is considered	And it is classified as
A	A-B-C-D	Positive	A	Positive	True positive
B-C	B-C	Negative	A	Positive	False positive
B-C	B-C	Negative	B-C	Negative	True negative
A	A-B-C-D	Positive	B-C	Negative	False negative
D	A-B-C	Indefinite	A	Positive	Ruled out
A	A-B-C	Indefinite	B-C	Negative	Ruled out
D	D	Indefinite	A	Positive	Ruled out
D	D	Indefinite	B-C	Negative	Ruled out

Note: Categories A, B, and C correspond to the cholesterol reference values in the pediatric and adult population shown in *Table 1*. Category D means "unknown" and indicates that the subject was not assessed because he/she did not attend the blood draw visit.

girls and 163 (49 %), boys. A total of 304 mothers and 206 fathers attended for the assessment.

The prevalence of cholesterol levels is shown in Table 3.

Cholesterol level (in mg/dL) in girls showed a mean and standard deviation (SD) of 164 ± 28 , with a minimum of 110 and a maximum of 247, while in boys, the value showed a mean and SD of 163 ± 28 , with a minimum of 103 and a maximum of 239.

Cholesterol level in mothers showed a mean and SD of 183 ± 40 , with a minimum of 99 and a maximum of 337, while in fathers, the value showed a mean and SD of 207 ± 44 , with a minimum of 118 and a maximum of 342.

The mean age of mothers and fathers was 36.2 ± 6.4 years and 41.0 ± 7.2 years, respectively.

Table 4 shows the results of the association between hypercholesterolemia in parents and their children and diagnostic tests.

Table 5 shows the results of the association between hypercholesterolemia in children and a positive FMH and diagnostic tests.

The multilevel regression analysis showed important and statistically significant effects of mother's and father's cholesterol level on their children's cholesterol level. Per every 10 mg/dL of increased average cholesterol in the mother,

children's average cholesterol increased 2.9 mg/dL, and per every 10 mg/dL of increased average cholesterol in the father, children's average cholesterol increased 2.5 mg/dL.

DISCUSSION

Numerous studies have been done in homozygous and heterozygous familial hypercholesterolemia, whose population prevalence is 1/1 000 000 and from 1/250 to 1/500, respectively.¹⁹ Combined familial hypercholesterolemia, with a prevalence of 1-2 %, is also of diagnostic interest.²⁰ The objective of this study, and of previous ones, was to look for all types of hypercholesterolemia, including polygenic hypercholesterolemia, whose worldwide prevalence in the pediatric population ranges from 4 % to 20 % for cholesterol levels ≥ 200 mg/dL.

The correlation observed between hypercholesterolemia in parents and their children is strong, with an OR of 6.40 and a *p* value < 0.0001 , together with a high sensitivity and specificity and adequate values for the remaining diagnostic tests, except for PPV.

The association of FMH with hypercholesterolemia in children, in this case, resulted in an OR= 1.86, but no statistical

TABLE 3. Distribution of cholesterol levels among children, mothers and fathers

	Children (n = 332)	Mothers (n = 304)	Fathers (n = 206)
Cholesterol level	n-%	n-%	n-%
High	37-11.1	20-6.6	45-21.8
Borderline high	88-26.5	82-27.0	74-35.9
Desirable	207-62.3	202-66.4	87-42.2

TABLE 4. Correlation of blood cholesterol among children with a cholesterol level ≥ 200 mg/dL and one or both parents with hypercholesterolemia ≥ 240 mg/dL and diagnostic tests

Outcome measure	Classification	Children's cholesterol level (n = 200)			OR	95% CI	<i>p</i>
		≥ 200	< 200	Total			
		n	n	n			
Parents' cholesterol level	One or both with ≥ 240	22	43	65	6.40	(2.85-14.48)	< 0.0001
	None ≥ 240	10	125	135			
	Total	32	168	200			
Diagnostic tests							
PPA		Sensitivity	Specificity	PPV	NPV	LR+	LR-
(33 %)		(69 %)	(74 %)	(34 %)	(93 %)	2.69	0.42

PPA: percentage of the population to be assessed; PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio; CI: confidence interval.

association was observed and diagnostic tests showed weaker values than parental hypercholesterolemia.

The two predictive outcome measures detected 22 out of 32 children with hypercholesterolemia, i.e., they have the same sensitivity (69%). In spite of the numerical match, only 13 children were screened by both criteria.

The mean cholesterol level in children was slightly lower than that observed in 2009 (164 versus 168).

Results of the multilevel regression analysis are consistent with the data in the contingency tables in terms of the correlation of blood cholesterol between parents and their children.

Two situations may alter the predictive power of parental hypercholesterolemia: the fact that parents are not screened for the presence of diseases or other factors that may cause secondary hypercholesterolemia and the relative youth of parents (mean of 36.2 years old for mothers and of 41.0 for fathers), considering that the mean cholesterol level increases with age.

A strength of this study –and of our three previous epidemiological studies from 1997, 2003, and 2009–^{9,15} is the large sample size (75%). The percentage of mothers who gave their consent was also very high and, although the percentage of fathers was lower, it was acceptably good.

In a cascade screening study to look for familial hypercholesterolemia conducted in the United Kingdom,²⁰ 97% of children were tested, while 5% of adults refused to participate and 59% did not respond. This would seem to indicate that parents' concern for their children is greater than that for themselves.

Few studies of this kind have been done. The Family Study, conducted in 1980, found a

positive, strongly significant correlation in the blood cholesterol of parents and their biological children, which was related to genetic factors.²¹

It may be assumed that a detection strategy based on this concept may be extrapolated to the entire blood relative unit and, therefore, selective screening may be combined with cascade screening.

A gold standard method to detect a disease or a factor leading to a disease is one with a high sensitivity and specificity. A third indicator would be its moderate or low cost so that it may be implemented in countries with a low health budget so as to optimize expenditure.

The methods proposed to screen for hypercholesterolemia in children include the following:

- **Cascade screening:** To detect individuals with familial hypercholesterolemia. A meta-analysis by Morris et al. considered that this was a good but inadequate strategy to identify new index cases, with a low sensitivity and high cost.²²
- **Universal screening:** It is highly sensitive and specific, but expensive and hard to implement. The SAP consensus proposes to screen all children when they first start primary school. Wald et al.²³⁻²⁵ conducted a small-scale experimental study and a large-scale study that assessed 10 000 children to look for familial hypercholesterolemia and concluded that screening was feasible and effective at 36 months old, together with children's immunization schedule, and that parents of children with a positive mutation or high cholesterol levels may then be tested. For developing countries, this is a very expensive approach.

TABLE 5. Correlation of blood cholesterol among children with a cholesterol level ≥ 200 mg/dL and a positive family medical history and diagnostic tests

Outcome measure	Classification	Children's cholesterol level (n = 200)			OR	95% CI	p
		≥ 200	< 200	Total			
		n	n	n			
Family medical history	Positive	22	91	113	1.86	(0.84-4.11)	0.1272
	Unknown/negative	10	77	87			
Total		32	168	200			
Diagnostic tests							
PPA		Sensitivity	Specificity	PPV	NPV	LR+	LR-
(57%)		(69%)	(46%)	(19%)	(89%)	1.27	0.68

PPA: percentage of the population to be assessed; PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio; CI: confidence interval.

Some kind of universal screening has been implemented in some countries, like Slovenia, where all children with a positive FMH have their cholesterol level measured at 5 years old; if their value is high, a lipid profile is done and the family is tested afterwards. They also focus on familial hypercholesterolemia but they have stated that FMH is not reliable enough to identify cases.²⁶

- **Selective screening:** To this date, this is the most widely accepted method. Selective screening has been suggested by the AAP and the SAP based on FMH, but the specificity is low and the cost high.

The 2009 study¹⁵ showed a statistically significant correlation between hypercholesterolemia and FMH (OR: 2.20, 95 % CI: 1.18-4.13 and $p = 0.014$) and acceptable diagnostic tests (sensitivity= 65 %, specificity= 37 %, PPV= 17 %, NPV= 89 %, LR+= 1.16, and LR-= 0.71). To screen that 65 % of children (33 out of 51) with hypercholesterolemia, it would be necessary to assess 49 % of the population (189 out of 382), which, in this study, we defined as PPA. If the calculation is done by adding the children with a positive FMH and those with an unknown FMH, as suggested by current consensuses, the correlation disappears and most diagnostic tests show weaker values.

Because of this, both at that time and in this study, only a positive FMH was considered a screening criterion. The PPA based on the FMH would be 57 %. This means that if FMH was used as a selective screening criterion in this study population, 57 % of the population (113 out of 200) should have been assessed, whereas if parental hypercholesterolemia was used, only 33 % of the population (65 out of 200) should have required assessment. This would indicate that, besides diagnostic tests, parental hypercholesterolemia is more effective as a predictor and would translate into lower screening costs.

Based on these findings, an idea-project called "Hypercholesterolemia screening in children and adolescents at the pharmacy office" is being developed because this is where patients diagnosed with hypercholesterolemia obtain medicine and the most commonly visited health care site by patients in general.²⁷

Adequate outcomes were achieved by a virtual trial of this idea-project. Approximately 30 % of adult and pediatric patients with hypercholesterolemia and other 30 % of adult and pediatric patients with slightly elevated cholesterol levels were detected.²⁸

The pharmacy and the health care team working in this field may act in a joint and systematic manner to develop registers of patients with homozygous and heterozygous familial hypercholesterolemia, which is a nationwide and worldwide demand.

CONCLUSION

Parental hypercholesterolemia showed a positive and strongly significant association with hypercholesterolemia in children and acted as an adequate predictor. A positive FMH was not associated with hypercholesterolemia in children and showed a smaller predictive power than parental hypercholesterolemia. ■

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