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Association of HDL-Cholesterol, hypertension and left ventricular hypertrophy in youths with overweight or obesity

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Abstract *Background and aim:* To evaluate the relationship between HDL-Cholesterol (HDL-C), hypertension, and left ventricular hypertrophy (LVH) in a large sample of Caucasian youths with overweight/obesity (OW/OB).
Methods and results: A cross-sectional multicenter study was performed in 1469 youths (age 6−16 years) with OW/OB observed in the period 2016−2020. An additional independent sample of 244 youths with an echocardiographic evaluation, observed in a single center was analyzed. The sample was divided in six quantiles (Q) of HDL-C: Q1: >56, Q2: ≤56 > 51, Q3: ≤51 > 45, Q4: ≤45 > 41, Q5: ≤41 > 39, Q6: <39 mg/dL. The nadir of the relationship was identified in youths in the first quantile. Among HDL-Cholesterol quantiles the distribution of hypertension was non-linear with a percentage of 25.0%, 40.1%, 33.6%, 31.3%, 35.2% and 39.7% in the six quantiles, respectively. The percentage of LVH was 21.8%, 43.6%, 48.8%, 35.5%, 38.5% and 52.0% in the six quantiles, respectively. The highest odds [95%CI] of hypertension were 2.05 (1.33−3.16) ($P < 0.01$) in Q2, 1.67 (1.10−2.55) ($P < 0.05$) in Q3 and 1.59 (1.05−2.41) ($P < 0.05$) in Q6 vs Q1. The odds of LVH were 3.86 (1.15−10.24) ($P < 0.05$) in Q2, 4.16 (1.58−10.91) ($P < 0.05$) in Q3 and 3.60 (1.44−9.02) ($P < 0.05$) in Q6 vs Q1, independently by centers, age, sex, prepubertal stage, and body mass index.

Abbreviations: BMI, body mass index; BP, blood pressure; CETP, cholesteryl ester transfer protein; CV, cardiovascular; HDL-C, HDL-Cholesterol; HTN, hypertension; HOMA-IR, homeostasis model assessment of insulin resistance; IVST, interventricular septum thickness; LVDD, left ventricular diastolic diameter; LVH, left ventricular hypertrophy; LVMi, left ventricular mass index; PWT, posterior wall thickness; RWT, relative wall thickness; OB, obesity; OW, overweight; SDS, standard deviation score.

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Conclusion: Contrary to the common belief, the present study shows that high levels of HDL-C may be not considered a negative predictor of hypertension and LVH, two risk factors for future CV disease.

1. Introduction

The inverse relationship between HDL-Cholesterol (HDL-C) and CV (CV) events has long been considered a determinant to identify individuals at risk of CV disease. Low HDL-C levels have been considered a risk factor for CV events, while high levels have been considered "protective" [1,2]. However, doubts have been raised about the real strength of this paradigm from the analysis of intervention studies aimed at increasing HDL-C levels. In fact, a study demonstrated that the addition of the HDL-increasing molecule niacin with a prostaglandin receptor antagonist (to reduce niacin-induced facial flushing) to statin-based LDL cholesterol-lowering therapy increased marginally HDL-C levels respect to the placebo group but did not reduce the risk of CV events [3]. Other approaches which have been tried to raise HDL-C, including cholesteryl ester transfer protein (CETP) inhibition, lecithin–cholesterol acyltransferase activation, and infusing nascent HDL particles to regress atheroma volume, have also failed to reduce the CV events and in some cases have produced an increase of systemic inflammation [4–11]. Furthermore, in patients treated with statins, the residual risk of CV events was not related to HDL-C levels [12]. Consequently, these and other studies have contributed to open the debate concerning the protective role of high levels of HDL-C respect to incident CV disease [13,14]. Interestingly, the relationship between HDL-C levels and CV morbidity or mortality might be not linear. In fact, a recent analysis of 37 prospective cohort studies showed that the all-cause and CV mortality followed a J pattern in relation to HDL-C, because it was highest in people with either low or high HDL-C concentration [15]. Based on recent evidence in adult populations, HDL-C may have a nonlinear relationship with blood pressure (BP) and with the risk to develop hypertension, a major driver of CV morbidity [13–16]. This suggests that the nonlinear relationship between HDL-C and hypertension may underpin the nonlinear relationship between HDL-C and CV mortality. In childhood, low levels of HDL-C (<40 mg/dL) are considered an established element in defining dyslipidemia [17] and are invariably considered a building block of the metabolic syndrome. However, whether in childhood the relationship between HDL-C and BP is linear or not it still unexplored. This has an important clinical relevance considering that CV risk begins already in childhood [18].

Therefore, the aim of our study is to verify the hypothesis that HDL-C has a nonlinear relationship with both the prevalence of hypertensive levels of BP, and the prevalence of left ventricular hypertrophy, a recognized marker of long-standing high BP, in Caucasian children and adolescents with overweight/obesity (OW/OB).

2. Methods

2.1. Study population

The "CARdiometabolic risk factors in overweight and obese children in ITALY" (CARITALY 2.0) Study is a retrospective survey endorsed by the Childhood Obesity Group of the Italian Society of Pediatric Endocrinology and Diabetology, and it is designed to investigate the prevalence of the major cardiometabolic risk factors in Italian outpatient children on behalf of the pediatric obesity study group of Italian Society for Pediatric Endocrinology and Diabetology (ISPED). Nine tertiary Italian centers for the diagnosis and care of pediatric obesity distributed throughout the country participated and provided anthropometric, clinical and biochemical data of 1562 children and adolescents aged 5–18 years consecutively evaluated at the first referral in the period June 2016–June 2020. Thirteen youths who showed glycemic data within the category of T2DM were excluded [19]. One hundred youths were excluded for age <6 or >16 years, therefore data from 1469 records of young people aged 6–16 years were analyzed. All the young people were referred by their family doctor to each center for the evaluation of the degree of OW/OB. None of them had genetic obesity or endocrine disorders, congenital malformations, chronic use of medications potentially affecting blood pressure, lipid or glucose profiles. No patient had a previous diagnosis of hypertension (HTN) that had led to lifestyle modifications and/or drug therapy instituted before the first referral at our centre.

Additional data of a sample of 244 youths with OW/OB (age 6–16 years) consecutively referred to the outpatient unit of the Pediatric Department of Pozzuoli Hospital between 2004 and 2013 with availability of an echocardiographic examination [20], was separately analyzed.

The protocol was in accordance with the 1975 Declaration of Helsinki as revised in 1983, and informed consent was obtained from all children and their parents. The study was conformed to the guidelines of the European Convention of Human Rights and Biomedicine for Research in Children.

2.2. Measurements

Anthropometric variables were measured in each center by an expert examinator with standard methods. Height

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was measured to the nearest 0.1 cm with a wall-mounted stadiometer; weight was determined to the nearest 0.1 kg on a medical scale. Body mass index (BMI) was calculated as weight (Kg)/height (m^2). BMI values were transformed into standard deviation scores (SDS), based upon the established Italian BMI normative curves [21]. BP was measured in a seated position after 5 min of resting, using aneroid sphygmomanometers with cuffs of appropriate size, according to standard procedures as elsewhere described [19,20]. Three readings were taken 2 min apart and the average of the two last values was used in the analyses [20].

Glucose, insulin, total cholesterol, HDL-C, triglycerides were analyzed in fasting state. Insulin-resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR) as: glucose (mg/dL) x insulin (mU/mL)/405. Biochemical analyses were performed in the centralized laboratory of each center. All laboratories belong to the Italian National Health System and are certified according to International Standards ISO 9000 (www.iso9000.it/), undergoing to semi-annual quality controls and inter-lab comparisons.

2.3. Echocardiography

The echocardiographic evaluation based of an internal protocol was available in 244 youths observed in the center of Pozzuoli as previously reported [20]. Left ventricular mass was normalized for height in meters$^{2.7}$ (LVMi). Relative wall thickness (RWT) was calculated from posterior wall thickness (PWT), interventricular septum thickness (IVST) and LV diastolic diameter (LVDD) using the formula: (PWT + IVST)/LVDD. RWT was normalized for age using the formula RWT-0.05 × age (years)-10 (RWTa) [22].

2.4. Definitions

Overweight (OW) and obesity (OB) were defined based on the Italian BMI standards (respectively the 75th and 95th percentiles) [21]. Prepubertal stage was defined by Tanner Stage I of breast development in girls and testicular volume in boys [23]. HTN was defined as follows: BP values ≥ 95th percentile for age, gender and height in young people aged 6–16 years as suggested by European Society of Cardiology task-force on arterial HTN in children and adolescents [24]. Definition of left ventricular hypertrophy (LVH) vas based on 95th percentile of LVMi using age- and gender-specific quantiles as proposed by Khoury et al. [25].

2.5. Statistical analyses

The continuous variables are expressed as mean ± standard deviation, and categorical data are presented as number (%). The skewed variables (triglycerides, HOMA-IR) are presented as median and interquartile range and their use in parametric tests was preceded by ln-transformation. Means were compared by Student's *t* test or ANOVA. Distribution of categories was compared by χ^2 test and, when needed, exact tests were performed using the Monte Carlo method. The shape of the relationship between HDL-C and BP was firstly assessed graphically. Subsequently, the absence of a linear relationship between HDL-C and BP was confirmed by Pearson correlation analysis between HDL-C and mean BP adjusted for age, sex, height, BMI-SDS, centre and pre-pubertal stage (standardized residuals) ($r = -0.025$, $p = 0.34$). Similarly, the absence of linear relationship between HDL-C and the logit-risk to present HTN or LVMi, was confirmed by logistic regression between HTN/LVMi and HDL-C, adjusted for age, sex, SDS-BMI, center and pre-pubertal stage [OR = 0.99 (0.98–1.002), p = 0.10], and [OR: 0.98 (0.95–1.00), p = 0.106] respectively. We divided the studied sample into six HDL-C quantiles, to assess how the prevalence of HTN or LVH varied across the quantiles. Six was the highest number of quantiles providing a large enough average quantile sample size (244 individuals) to have ≥90% power to detect a significant difference of at least 0.15 between the HTN prevalence of the reference quantile and the HTN prevalence of the other quantiles, with a 0.05 α error. The at least 0.15 difference arises from a ≥20% decrease of prevalence compared to the average population prevalence, in case of "protective" quantile, and a ≥20% increase of prevalence compared to the average population prevalence, in case of "unfavourable" quantile (considering a 0.34 overall prevalence, this means comparing a ≤0.27 prevalence to a ≥0.41 prevalence). The at least 20% change from the overall prevalence was arbitrarily considered clinically meaningful. To assess how the prevalence of HTN and LVH varied across the HDL-C quantiles, the odds ratio of HTN, or LVH was calculated by logistic regression analysis for each of the 2–6 quantiles, compared to the first quantile, corresponding to the highest HDL-C concentration, and used as the reference. We used age, sex, prepubertal stage, BMI-SDS, and the recruitment center as covariates. The statistical analysis was performed using the IBM SPSS Statistics, Version 20.0. Armonk, NY.

3. Results

The sample was constituted by 1469 youths, 742 boys and 727 girls, with age 11.5 ± 2.4 years mean ± standard deviation (range 6–16 years). The characteristics of the main sample are reported in the supplemental table.

The six quantiles differed for all variables analyzed, but no difference was observed for sex distribution. The distribution of both systolic and diastolic BP among HDL-C quantiles was non-linear and the nadir of the relationship was identified in subjects with HDL >56 mg/dL (first quantile) (Table 1 and supplemental figure). Similarly, the proportion of youths with HTN was not linear among HDL-C quantiles (Fig. 1, upper panel).

The characteristics of the additional sample in which an echocardiographic evaluation was available are shown in Table 2. Interestingly, although this sample showed lower age 10.3 ± 2.7 years, as compared to the main sample, the

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Table 1 Characteristics of the sample across quantiles of HDL-Cholesterol.

	Quantile 1	Quantile 2	Quantile 3	Quantile 4	Quantile 5	Quantile 6	*P* value
HDL-C (mg/dL)	>56	≤56 > 51	≤51 > 45	≤45 > 41	≤41 > 39	<39	
n = 1469	232	222	271	259	213	272	
Age, years	11.2 ± 2.6	11.6 ± 2.2	11.2 ± 2.3	11.3 ± 2.3	11.5 ± 2.4	12.0 ± 2.4	0.002
Boys, n (%)	116 (50.0)	115 (51.8)	138 (50.9)	143 (55.2)	101 (47.4)	129 (47.7)	0.506
Prepubertal, n (%)	40 (17.2)	18 (8.1)	33 (12.2)	30 (11.6)	21 (9.9)	26 (9.6)	0.038
BMI, kg/m^2	30.0 ± 5.3	30.5 ± 5.1	29.9 ± 4.9	31.0 ± 5.5	31.2 ± 5.3	32.1 ± 5.9	<0.0001
BMI-SDS	2.3 ± 0.6	2.3 ± 0.5	2.2 ± 0.6	2.3 ± 0.6	2.4 ± 0.6	2.4 ± 0.6	<0.0001
FG (mg/dL)	87.2 ± 9.4	87.0 ± 9.0	88.3 ± 10.1	87.8 ± 9.7	88.4 ± 9.8	89.3 ± 9.3	0.089
HOMA-IR	3.3 (2.3–4.7)	3.5 (2.4–5.0)	3.5 (2.4–5.1)	3.8 (2.4–5.7)	3.9 (2.6–5.8)	4.4 (3.1–6.6)	<0.0001
TC (mg/dL)	158.7 ± 28.4	158.2 ± 29.1	154.7 ± 30.3	153.6 ± 27.8	153.4 ± 27.4	147.0 ± 27.1	<0.0001
TG (mg/dL)	68.0 (51.0–93.8)	75.0 (61.8–98.0)	78.0 (61.0–99.0)	86.0 (63.0–112.0)	88.0 (66.0–112.5)	87.0 (66.0–113.8)	<0.0001
SBP (mmHg)	110.8 ± 12.3	113.8 ± 14.2	113.7 ± 14.6	113.7 ± 13.6	112.7 ± 13.6	114.6 ± 13.7	0.050
DBP (mmHg)	66.4 ± 8.9	67.7 ± 10.1	67.5 ± 9.4	67.6 ± 9.7	67.5 ± 8.8	68.7 ± 9.4	0.177

Data are expressed as mean ± standard deviation, median (IQ range), n (%).
HDL-C: HDL-Cholesterol. BMI, body mass index (calculated as weight in kilograms divided by height in meters squared). SDS: standard deviation score. FG: fasting glucose. HOMA-IR: homeostasis model assessment of insulin resistance. TC: total cholesterol. TG: triglycerides. SBP: systolic blood pressure. DBP: diastolic blood pressure.

relationship between systolic and diastolic BP among HDL-C quantiles showed a similar trend as observed in the main sample. Also, the prevalence of HTN (Table 2) and LVH (Figure, bottom panel) showed a similar tendency among quantiles of HDL-C.

The highest odds of HTN were observed in the second, third and lowest quantile of HDL-C of the sample of 1,469 children/adolescents, compared to the first one (Table 3). A similar result was obtained in the sample of 244 young people with echocardiographic evaluation where the odds of HTN and LVH were 3–5 times higher in the second, third and lowest quantile compared to the first one (Table 3).

4. Discussion

The results of the present study performed in more than 1500 children/adolescents with OW/OB highlight that HDL-C was not linearly associated either with BP as continuous variable or with the probability to have HTN. While the participants in the first quantile (quantile 1) had the lowest prevalence of high BP/HTN, those in the medium–high and the last quantiles (quantiles 2, 3 and 6) had a significantly higher prevalence, and those in the low-medium range (quantiles 4 and 5) had a not significantly different prevalence compared to the first quantile. This depicts a sort of horizontal sigmoidal relationship (∼). Very interestingly, in a different cohort of 244 children/adolescents with OW/OB, a relation with a similar shape was found between the HDL-C concentration and the prevalence of LVH, a well-recognized marker of high BP levels [26]. These findings challenge the dogma “the higher the better” that has for long characterized the state of the art about HDL-C, because of its presumed inverse linear relationship with the CV risk and are somehow in line with some evidence in adults. In particular, HDL-C was found to be positively associated with HTN among more than 60000 adults, after adjusting for BMI and other confounders [16] or to be U-shaped-associated with the incidence of HTN among more than 14000 adult males [27]. Both these observations are consistent with the hypothesis that a high HDL-C concentration may be related with an increased risk of HTN, which agrees with our findings if the top-quantile of HDL-C is not considered. The “protected” top quantile could represent a category of children with a very different profile from that of all the other categories, for example because of a very active lifestyle or because of a high insulin sensitivity, both of which are negative predictors of HTN and are also associated with high HDL-C [28]. Unfortunately, while we can confirm that youths the first quantile of HDL-C had the lowest insulin resistance (HOMA-IR) (Table 1), we cannot confirm that they were also the most active, because we did not assess their physical activity. From the second quantile upwards, following the nadir of the first quantile, the relationship between HDL-C and HTN is U-shaped, with HTN peaking at the middle–high and at the low quantiles of HDL-C. In contrast with our findings and with the above-mentioned studies, an inverse relationship between HDL-C levels and incident HTN was described among the almost 4000 adults of the “Prevention of Renal and Vascular End Stage Disease – PREVEND” Cohort [29]. However, the subgroup analysis highlighted that this relationship was present only in females and from 50 years of age and was significant only in the subgroup with a baseline systolic blood pressure lower than the median (119 mmHg). This suggests that the relationship between HDL-C and HTN is complex and may be modulated by several interacting factors. The fact that not only a low HDL-C concentration, a well-known risk factor for atherosclerosis and endothelial dysfunction, but also a medium–high HDL concentration, can be a risk factor for HTN and LVH, may have several potential explanations.

First, among children/adolescents with OB the HDL-C particles may be dysfunctional because of systemic inflammation, contributing to the oxidative stress and the endothelial dysfunction. In presence of diabetes, it is

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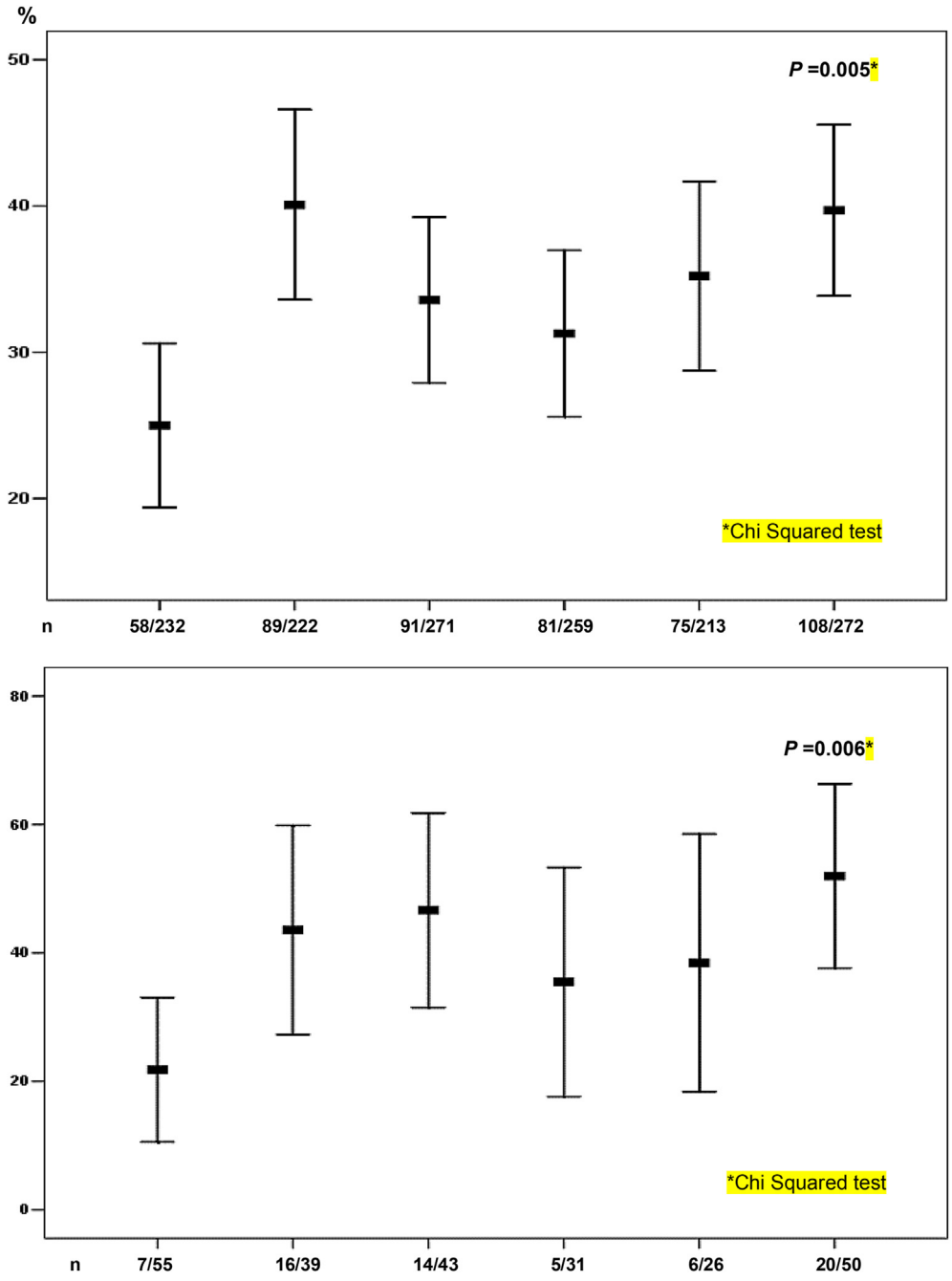

Figure 1 Proportion (95%CI) of youths with hypertension (upper panel) in the main sample (n = 1469) and left ventricular hypertrophy (bottom panel) in the independent sample (n = 244) among quantiles of HDL-Cholesterol.

known that reactive oxygen species together with inflammation induce the myeloperoxidase and decrease the paraoxonase-1, leading to oxidative modification of the main protein component of HDL-C, apoA-I. The resulting dysfunctional and pro-inflammatory HDL-C impacts immune response in macrophages increasing the toll-like receptors 2/4 signaling and impairs the cholesterol efflux leading to cholesterol accumulation and oxidation within macrophages entrapped in the subendothelial space [30,31]. Additionally, oxidative environment induces the acute phase protein haptoglobin. Haptoglobin-hemoglobin complexes tend to bind to the HDL-C particles through the ApoA1 protein, oxidating them and making them dysfunctional and oxidative in their turn [31]. As OB is characterized by inflammation and oxidative stress, it is very plausible that HDL-C particles of patients with obesity may be both oxidized and oxidative.

Second, we cannot exclude that the group corresponding to the medium–high range of HDL-C level may be enriched of individuals with the unfavorable haptoglobin genotype Hp2-2, which is known to be overrepresented among people with high HDL-C levels [32]. Compared to the haptoglobin phenotype 1-1 (Hp1-1) and Hp1-2, the Hp2-2 isoform, which is carried by almost 40%

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Table 2 Characteristics of the sample with echocardiographic evaluation among quantiles of HDL-Cholesterol.

	Quantile 1	Quantile 2	Quantile 3	Quantile 4	Quantile 5	Quantile 6	*P* value
HDL-C (mg/dL)	>56	≤56 > 51	≤51 > 45	≤45 > 41	≤41 > 39	<39	
n = 244	55	39	43	31	26	50	
Age, years	10.4 ± 2.4)	9.7 ± 2.4	9.9 ± 2.4	11.5 ± 2.8	10.0 ± 2.8	10.4 ± 2.9	0.084
Boys, n (%)	25 (45.5)	17 (43.6)	20 (46.5)	19 (61.3)	17 (65.4)	24 (48.0)	0.366
BMI, kg/m^2	27.6 ± 3.6	26.4 ± 4.5	27.5 ± 4.3	30.7 ± 5.3	29.2 ± 5.7	29.6 ± 4.7	<0.0001
BMI-SDS	2.0 ± 0.4	1.9 ± 0.5	2.0 ± 0.6	2.3 ± 0.5	2.3 ± 0.5	2.3 ± 0.5	<0.0001
HOMA-IR	3.0 (1.8–4.3)	2.5 (1.7–3.9)	2.9 (2.4–4.0)	2.7 (2.2–5.9)	2.7 (2.1–6.4)	3.0 (1.8–4.4)	0.353
SBP, mmHg	105.0 ± 8.3	107.9 ± 12.0	107.0 ± 11.9	108.4 ± 10.5	106.7 ± 13.6	109.1 ± 12.0	0.531
DBP, mmHg	63.5 ± 7.8	67.6 ± 10.8	66.3 ± 11.0	64.5 ± 8.6	63.8 ± 9.2	64.9 ± 9.5	0.341
LVMi/h$^{2.7}$	34.9 ± 11.9	36.2 ± 9.2	40.0 ± 11.8	38.5 ± 7.2	39.6 ± 11.4	39.9 ± 10.0	0.082
RWT$_a$	0.340 ± 0.06	0.359 ± 0.05	0.353 ± 0.06	0.359 ± 0.05	0.379 ± 0.07	0.370 ± 0.06	0.058
HTN, n (%)	7 (12.7)	16 (41.0)	14 (32.6)	5 (16.1)	6 (23.1)	20 (40.0)	0.006

Data are expressed as mean ± SD, median (IQ range), n (%).
HDL-C: HDL-Cholesterol. BMI, body mass index. SDS: standard deviation score. HOMA-IR: homeostasis model assessment of insulin resistance. SBP: systolic blood pressure. DBP: diastolic blood pressure, LVMi: left ventricular mass index, RWT$_a$: relative wall thickness. HTN: hypertension.

Table 3 Odds ratio [95%Cl] of hypertension or left ventricular hypertrophy among quantiles of HDL-Cholesterol.

	Quantile 1	Quantile 2	Quantile 3	Quantile 4	Quantile 5	Quantile 6
HDL-C (mg/dL)	>56	≤56 > 51	≤51 > 45	≤45 > 41	≤41 > 39	<39
n = 1469	**232**	**222**	**271**	**259**	**213**	**272**
Hypertension	1.00	2.05 (1.33–3.16)*	1.67 (1.10–2.55)**	1.22 (0.79–1.87)	1.53 (0.98–2.39)	1.59 (1.05–2.41)**
n = 244	**55**	**39**	**43**	**31**	**26**	**50**
Hypertension	1.00	5.6 (1.96–16.0)*	3.27 (1.15–9.29)**	0.91 (0.25–3.28)	1.45 (0.42–5.03)	3.89 (1.43–10.63)*
LVH	1.00	3.86 (1.15–10.24)**	4.16 (1.58–10.91)**	1.47 (0.51–4.23)	1.53 (0.52–4.51)	3.60 (1.44–9.02)**

P value adjusted for centers, sex, age, prepubertal stage, BMI-SDS.
*$P < 0.01$ vs Q1, **$P < 0.05$ vs Q1.
HDL-C: HDL-Cholesterol. LVH: left ventricular hypertrophy.

of people in the general population, is less likely to be cleared by the endothelial macrophages, and consequently it is much more likely to bind to the HDL-C particles, oxidizing them [33,34]. The clinical significance of the Hp2-2 isoform is well known in diabetes because the antioxidant therapy with vitamin E decreases the CV mortality by 30–50% only in patients with this genotype [33,34]. Provided that children/adolescents with obesity and HDL-C concentration in the medium–high range are at higher risk to carry the Hp-2-2 genotype, they should be genetically screened and possibly treated with vitamin E, once appropriate trials will demonstrate the efficacy of a pharmacological treatment. Third, the HDL-C concentration tends to be higher also when the CETP activity is decreased or dysfunctional because of unfavorable genetic polymorphism or systemic inflammation/oxidation [35]. In normal conditions, the CETP decreases the HDL-C concentration favoring the transport of cholesteryl esters to peripheral tissues and to ApoB-containing lipoproteins. In addition, it increases the antioxidant and anti-atherogenic function of the HDL-C, favoring the clearance of oxidized lipids and of LDL-C particles [36,37]. Thus, in children/adolescents with obesity and HDL-C concentration at the high-medium range, the HDL-C particles might exert decreased protective effects because of a decreased CETP function. Unfortunately, the above-mentioned hypotheses cannot be verified in our study sample, because we did not perform any functional test of the HDL-C particles, nor we measured our patients' systemic oxidative stress to put it into relation with the HDL-C concentration and function, nor we genotyped our patients at the *Hp* and *CETP* loci.

The principal limitation of the study is the cross-sectional design, which does not allow to draw causal inferences. In fact, the study just provides epidemiological evidence that HDL-C may not have a linear relationship with BP/hypertension, challenging the idea that a high HDL-C concentration is always favorable. The definition of HTN was not confirmed in a subsequent day; therefore, the real prevalence of HTN may be overestimated. However, it should be considered that high BP levels are associated with LVH as previously demonstrated [20,38].

The study has also some strengths, like the analysis of a large cohort of children/adolescents with OW/OB and the confirmation of the nonlinear HDL-BP relation in an independent cohort where a similar relation has been observed between HDL-C and LVH, making the hypothesis of nonlinear chronic effects of HDL-C on BP particularly convincing.

Contrary to the common belief, the present study shows that while frankly high HDL-C may be a negative risk factor for HTN, medium–high levels of HDL-C may be considered a positive risk factor. The reason is

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unexplained, but a complex interplay between genetic and environmental factors can be hypothesized in the regulation of HDL-C levels or their functions. Our findings highlight that considering only low HDL-C as a risk factor may be misleading, and significantly contribute to fuel the debate about the complex role of HDL-C on the CV risk, particularly on the BP levels of youths with OW/OB. Future epidemiological and interventional research should shift the focus from HDL-C concentrations to HDL-C subclasses or functions. This would improve, for each patient, the risk assessment and clinical approach associated to HDL-C, in optics of precision medicine.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2023.09.005.

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