Atherosclerosis Plus 62 (2025) 3–7

Contents lists available at ScienceDirect

Atherosclerosis Plus

journal homepage: www.elsevier.com/locate/atherosclerosis

HEART UK 38th Annual Medical & Scientific Conference - Oral Abstracts

Oral 1

POLYGENIC PREDISPOSITION TO INCREASED LDL-CHOLESTEROL CONCENTRATION AND CAROTID ARTERY INTIMA MEDIA THICKNESS IN CHILDHOOD AND EARLY ADULTHOOD

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Background: High polygenic risk score (PRS) for LDL-cholesterol (LDL-C), due to a burden of LDL-C-raising genetic variants, has been associated with increased concentration of LDL-C and risk of coronary heart disease (CHD) in adults. However, the effect of LDL-C PRS on LDL-C in childhood, when the cumulative lifetime effect of genetic risk is lower, remains largely unknown. Using data from the cross-sectional study of the Avon Longitudinal Study of Parents and Children (ALSPAC) we aimed to examine the LDL-C PRS association with LDL-C in children and to assess the genetic predisposition to higher carotid intima media thickness (CIMT), using LDL-C PRS and CIMT PRS.
Methods: Genotyping and cholesterol data were available for seven (n=5424), nine (n=5076), 15 (n=3484), 17 (n=3282) and 24 (n=3248) year olds. CIMT was measured at 17 (n=4633) and 24 (n=2029) years of age. Previously established LDL-C PRS (n=223 SNPs) and CIMT PRS (n=11,600 SNPs) were computed using Plink. Regression analyses were performed in R.
Results: LDL-C PRS was associated with LDL-C concentration across all age groups, with the strongest correlation at the age of seven years ($p<1.3x10^{-57}$). A significant difference in mean (SD) LDL-C between children with LDL-C PRS in 1st vs. 10th decile was observed as early as seven years of age ($p<8x10^{-15}$). CIMT was measured at 17 or 24 years and was not associated with LDL-C or LDL-C PRS. However, the CIMT PRS showed association with CIMT at 17 and 24 years of age, after adjusting for covariates (gender, BMI, blood pressure and body fat). Average right/left CIMT in 17-year-olds with CIMT PRS in 1st decile was significantly lower than in those with CIMT PRS in 10th decile ($p<1.25x10^{-5}$).
Conclusions: LDL-C PRS influences LDL-C concentration as early as seven years of age. CIMT PRS correlates with measures of CIMT at ages 17 and 24 years. Polygenic scores testing in childhood might provide the opportunity to assess future CHD risk before the emergence of clinical risk factors of CHD later in life.

Oral 2

DEVELOPMENT OF A DIAGNOSTIC SCORE TO IDENTIFY CHILDREN WITH FAMILIAL HYPERCHOLESTEROLAEMIA – THE FAMILIAL HYPERCHOLESTEROLEMIA PEDIATRIC DIAGNOSTIC SCORE (FH-PEDS)

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Background: Familial hypercholesterolemia (FH) significantly increases cardiovascular risk from childhood yet remains widely underdiagnosed. Most established FH diagnostic scores were developed and validated in adults, limiting their applicability in pediatrics and contributing to the low diagnosis rates among children. This cross-sectional study aimed firstly to evaluate existing pediatric FH diagnostic criteria in real-world cohorts where limitations due to the unreliability or incompleteness of family history are common, and secondly to develop two novel diagnostic tools: a semi-quantitative scoring system (FH-PeDS) and a machine learning model (ML-FH-PeDS) to enhance early FH detection.
Methods: Five established FH diagnostic criteria were assessed (Dutch Lipid Clinics Network [DLCN], Simon Broome, EAS, Simplified Canadian, and Japanese Atherosclerosis Society) in groups of children and young people (<18 years old previously diagnosed with FH from Slovenia (n=1,360) and Portugal (n=340), using genetically confirmed FH-causing variants as the reference standard. FH-PeDS was developed from the Slovenian cohort, and ML-FH-PeDS was trained and tested using a 60%/40% split before external validation in the Portuguese cohort.
Results: Only 47.4% of genetically confirmed FH cases were identified by all established criteria, while 10.9% were missed entirely. FH-PeDS outperformed DLCN in the combined cohort (AUC 0.897 vs. 0.857; $p<0.01$). ML-FH-PeDS showed superior predictive power (AUC 0.932 in training, 0.904 in testing vs. 0.852 for DLCN; $p<0.01$) and performed best as a confirmatory test in the testing subgroup (39.7% sensitivity, 87.7% PPV at 98% specificity). In the Portuguese cohort, ML-FH-PeDS maintained strong predictive performance (AUC 0.867 vs. 0.815 for DLCN; $p<0.01$) despite population differences. The strongest positive parameter weights for predicting FH were LDL-C and TC, (ie higher concentrations of LDL-C/ TC increased the likelihood of a positive FH diagnosis), while the highest negative weights were with HDL-C, TAG, and Lp(a), (ie higher values corresponded to a lower probability of an FH diagnosis).
Conclusions: Current FH diagnostic criteria perform suboptimally in children. FH-PeDS and ML-FH-PeDS provide tools to improve FH detection and can help guide genetic testing decisions for hypercholesterolemic children. By enabling earlier diagnosis and intervention, these tools may reduce long-term cardiovascular risk and improve outcomes.

Oral 3

APOLIPOPROTEIN B/LDL-C DISCORDANCE AND LIPOPROTEIN(A) AS PREDICTORS OF ASCVD RISK IN GENETICALLY CONFIRMED HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (HEFH): A RETROSPECTIVE COHORT STUDY (2005–2023)

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