EBioMedicine 74 (2021) 103702

Contents lists available at ScienceDirect

EBioMedicine

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

Commentary

Predicting long-term cardiometabolic risk: Do childhood metabolomic signatures hold the key?

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ARTICLE INFO

Article History:
Received 2 November 2021
Accepted 4 November 2021
Available online xxx

Cardiovascular disease (CVD) in adults represents a significant health and economic burden worldwide and particularly in Western societies [1]. Atherosclerosis is the main pathology behind CVD involving a chronic inflammation of the medium/large arteries, alongside lipid deposition within the sub-endothelial intimal layer of the vascular wall [2]. Atherosclerosis development can be predicted by several cardiometabolic risk factors including hyperglycaemia, elevated blood pressure, dyslipidaemia, abdominal obesity and autoimmunity, all of which are included in commonly used CVD-risk evaluation scores [2]. However, while CVD is largely considered a disease affecting older adults, the development of atherosclerosis is thought to start in childhood and adolescence [3]. Thus, a case can be made for early identification of children at elevated risk of developing CVD as adults; such screening could reinforce more healthy lifestyle choices and safe existing pharmaceutical interventions for young people at a time when these are likely to be most effective [4,5] (Fig. 1).

A recent study published in eBioMedicine [6], has gone some way to identifying metabolic biomarkers able to predict cardiometabolic risk in young people. Cardiometabolic risk was assessed in children followed longitudinally from pre-puberty to early adulthood using a previously defined cardiometabolic risk score based on standardised continuously distributed variables (including mean arterial pressure, abdominal fat mass, fasting glucose, high-density lipoprotein (HDL)-cholesterol and triglycerides), with a high score indicating elevated cardiometabolic risk. The authors then analysed serum metabolomics using an NMR-based platform and machine learning classification techniques. Three biomarkers were associated with elevated risk in early adulthood: glycoprotein acetyl (a marker of inflammation), large HDL-phospholipids, and the apolipoprotein (Apo)-B:ApoA1 ratio (measures of lipid transport). These associations were confirmed in large longitudinal and cross-sectional validation cohorts in both younger and older adults.

Lipoproteins are essential for cholesterol transport in the body and imbalances in lipoprotein particles are associated with pathogenic processes and complications of atherosclerosis. ApoB and ApoA1 are the major protein components in very-low and low-density lipoproteins (atherogenic), and HDL (atheroprotective) particles, respectively. ApoB:ApoA1 ratio is particularly interesting and represents the balance between atherogenic- and anti-atherogenic particles, the higher the value, the higher the risk of CVD. Notably, ApoB:ApoA1 ratio has been identified by previous studies in relation to prediction of CVD risk in young people; a prospective study identified that ApoB and ApoA1 profiles in children and adolescents reflected the development of subclinical atherosclerosis in adulthood [7] and ApoB:ApoA1 ratio was associated with cardiometabolic risk in a subset of adolescent patients with autoimmune juvenile-onset systemic lupus erythematosus, who are known to be at increased risk of CVD related to chronic inflammation [8]. In addition, the finding that reduced HDL-phospholipid levels are associated with elevated cardiometabolic risk in young people, is corroborated by previous studies linking HDL-phospholipids with CVD, potentially through defects in cholesterol efflux mechanisms [9].

Therefore, this current study adds to the growing body of evidence suggesting that circulating biomarkers in children and adolescents can predict future CVD risk [6]. This is important since while there has been improvement in cardiovascular health among older populations, there is a worrying trend towards younger adults having increasingly unhealthy cardiometabolic risk profiles, potentially suggesting an increasing burden of CVD in the future [4]. However, despite the promise of this and similar studies, some caveats exist; prospective studies are needed to firmly establish the association between cardiometabolic risk factors in children and CVD outcomes in adults; furthermore, although this study did not find differences in biomarker profiles and cardiometabolic risk score between men and women, it is known that sex hormones play an important role in driving lipoprotein profiles and this can be impacted by inflammation [10]. This suggests that sex-specific (including puberty), as well as other health indicators need to be considered when predicting cardiometabolic risk in young people. Finally, consideration needs to be

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2021.103611.
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https://doi.org/10.1016/j.ebiom.2021.103702

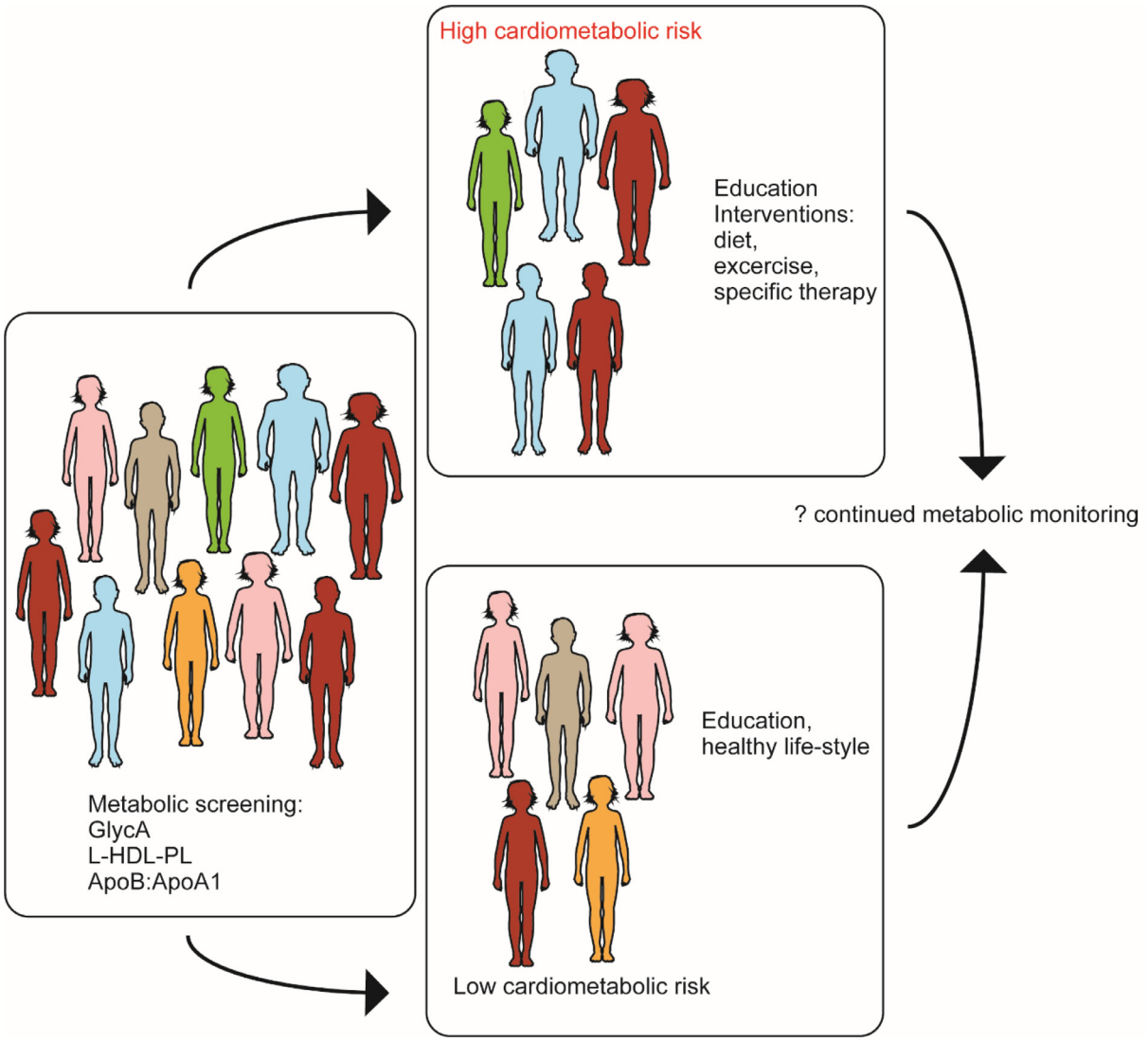

Fig. 1. Potential model for childhood cardiometabolic risk screening: Atherosclerosis can start in childhood/adolescence leading to early elevation in cardiometabolic risk: risk factors include hyperglycaemia, elevated blood pressure, dyslipidaemia, abdominal obesity and autoimmunity (chronic inflammation). Metabolic screening could allow early identification of children at elevated risk of developing cardiovascular disease as adults. Interventions could reinforce more healthy lifestyle choices and use of safe existing pharmaceutical therapies when they are likely to be most effective.

given to how such elevated risk, when identified, should be best managed. Education about life-style choices including the benefits of a healthy diet and exercise, as well as age-tailored strategies for atherosclerosis primary prevention based on individual characteristics, the presence of other comorbidities, and lipid biomarkers, are currently implemented in clinical practice. Further research is required to investigate the biomarkers with the best clinical predictive value for development of atherosclerosis earlier in life [5].

Declaration of Competing Interest

The authors declare no conflict of interest exists

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