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Editorial

Linking lifestyle factors to cardiovascular risk through metabolomics: Insights from a large population of diabetic patients followed-up for 11 years

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1. Background

Metabolomics – the systematic study of chemical processes involving metabolites, small molecule substrates, intermediates, and products of cell metabolism [1] – has recently developed as a very powerful tool for risk stratification as well as for investigating the molecular mechanisms underlying cardiovascular disease [2–5].

Precision medicine, which aims to offer "the right treatment to the right patient at the right time", relies heavily on the development of systems biology and omics disciplines, including metabolomics, intended as the assessment of the unique chemical fingerprints that specific cellular processes leave behind [6, 7]. So, the comprehensive analysis of metabolite concentrations provides useful and highly reliable "metabolic snapshots" [8]. A paper published by Lu et al. in this issue of *Atherosclerosis* [9] evidenced that the adherence to multiple healthy lifestyle factors was associated with improved circulating metabolites from 7 different pathways: lipoprotein particles, fatty acids, amino acids, fluid balance, inflammation, ketone bodies, and glycolysis. The study included 5072 participants with diabetes, and 971 events of cardiovascular disease were identified.

Plasma samples from a random subset of ~120,000 UK Biobank participants were profiled for 249 metabolites spanning multiple metabolic pathways. For lipoproteins and fatty acids, a subset of 44 metabolites was assayed. Metabolites were quantified by nuclear magnetic resonance (NMR) spectroscopy and were significantly associated with at least one lifestyle factor. Specifically, NMR metabolites jointly mediated 65.5%, 43.4%, 43.4%, 30.0%, and 16.8% of the association of healthy diet, physically activity, non-central obesity, non-current smoking, and moderate alcohol intake, with a lower cardiovascular risk, respectively [9]. Thus, all forty-four assayed metabolites were associated with at least one lifestyle factor, and three metabolites (PUFA/FA, PUFA/MUFA, and MUFA/FA) were simultaneously associated with all 5 lifestyle factors. The analyses indicated that differences in metabolites could explain, at least in part, the association between healthy lifestyle and lower cardiovascular risk among patients with diabetes (Fig. 1).

2. Lipid metabolites mediate the protective effects of healthy lifestyle

The differences in fatty acids concentrations were a major determinant in the association between the adherence to healthy lifestyle and lower cardiovascular risk. The two major strengths of this study are the long follow-up (median: 11.1 years) and having based the metabolomic profiling on NMR, which enables fast and reproducible measurements of large quantities of biomarkers. The work is not exempt from limitations, which include the missing information on some specific therapies and on diabetes education and psychosocial care and the fact that plasma samples were not taken in fasted conditions [9].

The findings are in agreement with previously published nested case-control studies that had revealed how lipid metabolites could mediate 14% of protective effect of adherence to healthy lifestyle on the risk of coronary heart disease and that 18 principal components of 225 NMR metabolites could potentially explain ~70% of the protective association of physical activity with occlusive cardiovascular risk [10]. Similarly, in the CARDIA (Coronary Artery Risk Development in Young

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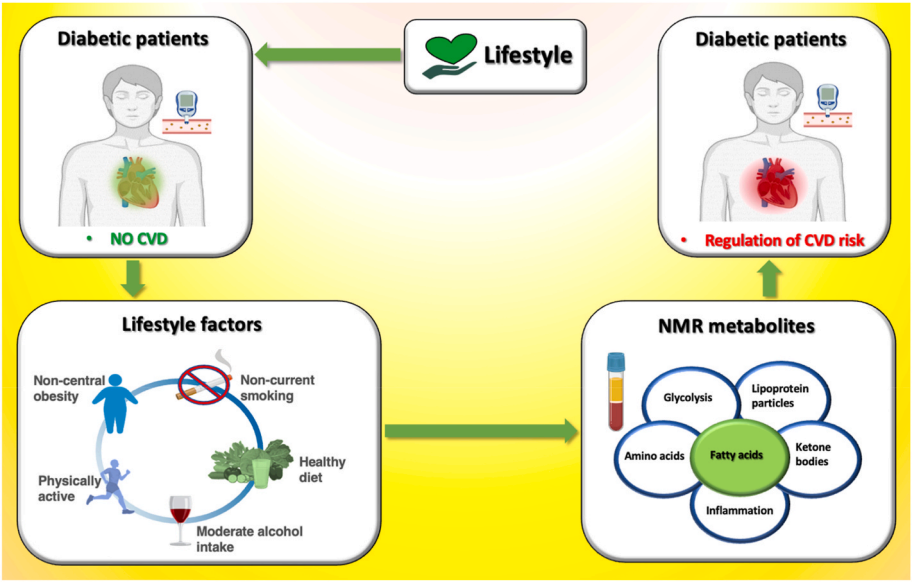

Fig. 1. Schematic representation of the importance of metabolomics in linking lifestyle factors with cardiovascular risk. Some images have been created with Biorender.com. CVD: cardiovascular disease; NMR: nuclear magnetic resonance.

Adults) study, metabolite profiles quantified in early adulthood (2330 subjects; 45% Black; mean age: 32 years) were associated with subclinical development of cardiovascular disease over 20 years [11], suggesting that alterations in metabolism are linked to cardiovascular disease and, more importantly, that early perturbations in metabolism (as reflected by the circulating metabolome) would pinpoint a predisposition to cardiovascular disease early in life. Specifically, the CARDIA study identified two multiparametric, metabolite-based scores linked independently to vascular and myocardial health [11].

A genome-wide association study [12] assessing the genetic influences on circulating metabolic traits quantified by NMR metabolomics from more than 20,000 subjects identified 8 novel loci for amino acids, pyruvate, and fatty acids. In this sense, the association between the LPA locus and cardiovascular risk [13] exemplifies how detailed metabolic profiling might be extremely informative on the underlying etiology via extensive associations with triglyceride and very-low-density lipoprotein metabolism [12].

As shown in the metabolomic evaluation of patients enrolled in the EXAMIN AGE (Exercise, Arterial Crosstalk-Modulation, and Inflammation in an Ageing Population) study, the metabolic fingerprint explained 23% of microvascular and 20% of macrovascular variation [14]. Hence, untargeted metabolic profiling has the potential to greatly improve cardiovascular risk stratification by identifying new underlying metabolic pathways associated with atherosclerosis to vascular end organ damage [15, 16].

Recent reports have shown that metabolomics can be also exploited in other medical fields. Indeed, metabolomic signatures in patients with non-alcoholic fatty liver disease (NAFLD) have identified three subgroups, independent of histological disease severity, that align with cardiovascular and genetic risk factors [17]. Furthermore, metabolomics is uniquely suited to capture essential functional host-microbe interactions, which could be implied in the pathophysiology of cardiovascular disorders [18, 19].

3. Future perspectives

The impact of the above-mentioned results is highly significant inasmuch it might help investigate metabolic mechanisms underlying the protective associations of lifestyle improvement with cardiovascular risk [20], which could offer clinically relevant risk stratification and eventually identify unprecedented targets for disease prevention strategies. These aspects are remarkable when considering that current risk stratification strategies for coronary artery disease have low predictive value in asymptomatic subjects who are generally classified as individuals at intermediate cardiovascular risk.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Tullio Tesorio
Casa di Cura "Montevergine", Mercogliano (Avellino), Italy

Pasquale Mone
Department of Medicine – Wilf Family Cardiovascular Research Center, Institute for Aging Research, Fleischer Institute for Diabetes and Metabolism (FIDAM), Institute for Neuroimmunology and Inflammation (INI), Albert Einstein College of Medicine, New York City, NY, USA
University of Campania "Luigi Vanvitelli", Naples, Italy

Antonio de Donato
University of Campania "Luigi Vanvitelli", Naples, Italy

Valentina Trimarco
"Federico II" University, Naples, Italy

Gaetano Santulli[*]
Department of Medicine – Wilf Family Cardiovascular Research Center, Institute for Aging Research, Fleischer Institute for Diabetes and Metabolism (FIDAM), Institute for Neuroimmunology and Inflammation (INI), Albert Einstein College of Medicine, New York City, NY, USA
"Federico II" University, Naples, Italy
Department of Molecular Pharmacology – Einstein/Sinai Diabetes Research Center (ES-DRC), Albert Einstein College of Medicine, New York City, NY, USA

[*] Corresponding author. 1300 Morris Park Avenue, 10461, New York City, NY, USA.
E-mail address: gsantulli001@gmail.com (G. Santulli).