ESC European Society of Cardiology

European Journal of Heart Failure (2024) **26**, 1655–1658
doi:10.1002/ejhf.3281

INVITED EDITORIAL

Metabolomics to predict heart failure development: A new frontier?

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This article refers to 'Serum metabolomics improves risk stratification for incident heart failure' by R.R. Oexner *et al.*, published in *Eur J Heart Fail* 2024;26:829–840.

Heart failure (HF) is a condition associated with high morbidity, mortality, and healthcare costs, therefore early detection and intervention in the pre-clinical stages hold significant potential to halt progression to symptomatic disease. However, current HF guidelines highlight a gap in evidence with respect to HF screening in asymptomatic individuals, and call for studies searching for biomarkers or prediction models able to reliably identify individuals at risk for HF development.[1] Several clinical risk scores have been developed for HF prediction (*Table 1*).[1–10] An example is the Pooled Cohort equations to Prevent Heart Failure (PCP-HF) risk score, which was derived from pooled individual-level data from five large, racially and geographically diverse populations free of cardiovascular disease at baseline and included clinical (age, blood pressure, smoking status, body mass index), laboratory (cholesterol, fasting glucose) and electrocardiographic variables (QRS duration).[6] The combination of these variables allowed for the generation of sex- and race-specific 10-year estimates of the HF risk. Despite some promising results, HF prediction scores often suffer from limitations such as derivation from small, non-representative cohorts and the integration of inconsistent data sources, making data collection through interviews, physical exams, and tests not only time-consuming, but also expensive and difficult to standardize. These possible issues with traditional scores have prompted the investigation of other approaches to HF prediction.

Recently, Oexner and colleagues investigated the role of serum metabolomics in predicting incident HF in a healthy population.[10] The study was conducted on 68 311 UK Biobank participants from 2006 to 2010 across 22 centres. Participants underwent extensive phenotypic assessments, including the collection of non-fasting serum samples for metabolomic analysis of 168 metabolites detected by proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy. Subjects with missing metabolomic data, incomplete baseline clinical HF risk characterization, those at known risk for HF or with pre-existing HF were excluded. The median age of this cohort was 57 years, with more than half being female. The metabolomic analysis revealed associations between various metabolites and incident HF. Specifically, higher levels of very low-density lipoprotein particles and their lipid contents were positively linked to HF development, while high-density lipoprotein and low-density lipoprotein, albumin, and some amino acids (alanine, glutamine, glycine, and histidine) showed negative associations. Positive correlations were observed with ketone bodies, glycolytic metabolites, and other amino acids (phenylalanine and tyrosine), whereas most unsaturated fatty acids were inversely related to HF development. Importantly, the study also aimed to understand how serum metabolomics could enhance the predictive power of the PCP-HF clinical risk score. Incorporating serum metabolomics into the predictive models significantly improved risk discrimination beyond the baseline PCP-HF score. Moreover, the study showed that models integrating metabolomics with the PCP-HF score not only offered superior predictive accuracy but also improved risk differentiation and model calibration.[10]

Circulating levels of metabolites reflect the interplay of genetic factors, environmental factors, and lifestyle habits, as metabolites are the final outputs of cellular activities. Metabolomic research offers an efficient, standardized, and scalable option compared to clinical algorithms, enhancing our physiological insight into HF. The positive associations between ketone bodies and some glycoproteins and incident HF may derive from a shift in energy substrate utilization within the failing heart (from fatty acids to more ketone bodies and glycolytic metabolites).[10,11] Additionally, the positive association between tyrosine and its precursor phenylalanine is in line with a previous metabolomic study.[7] Conversely, reduced albumin levels are associated with a higher risk of HF development due to their roles in malnutrition, chronic inflammation, and impaired liver and kidney function.

The opinions expressed in this article are not necessarily those of the Editors of the *European Journal of Heart Failure* or of the European Society of Cardiology. doi: 10.1002/ejhf.3226.

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Table 1 Risk prediction models for heart failure development

Algorithm	Population	Follow-up	Variables	C-statistics (95% CI)	Refs.
HF risk prediction algorithms					
Framingham HF risk score	–	38 years	Age, gender, CHD, diabetes, ECG-based LVH, valve disease, HR, and systolic BP	–	Kannel *et al.*[2]
Health ABC score (5-year HF risk predictor)	$n = 2935$ (74 ± 3 years) 52% women 59% Caucasians	6.5 ± 1.8 years	Age, gender, CHD, fasting glucose, ECG-based LVH, HR, systolic BP, serum albumin, serum creatinine, and smoking status	0.73	Butler *et al.*[3]
ARIC basic HF risk score (10-year HF risk predictor)	$n = 13\,555$ (45–64 years) 46–56% women 25–34% Black	15.5 years (210 102 person-years)	Age, race, gender, CHD, diabetes, systolic BP, blood pressure medication use, HR, smoking status, BMI	0.773 (0.753–0.787) ARIC + NT-proBNP: 0.805 (0.792–0.820)	Agarwal *et al.*[4]
MESA (5-year HF risk predictor)	$n = 6814$ (62 ± 10 years) 53% women 38% Caucasians	4.7 (0.1–7.0) years	Age, gender, BMI, smoking status, systolic BP, HR, diabetes, and NT-proBNP	0.87 (0.82–0.88)	Chahal *et al.*[5]
PCP-HF (10-year HF risk predictor)	$n = 33\,010$ (52 ± 12 years) 52% women 22% Black From five population-based cohorts	10 years	Age, BP, fasting glucose, BMI, cholesterol, smoking status, QRS duration	White men: 0.79 White women: 0.85 Black men: 0.71 Black women: 0.78	Khan *et al.*[6]

Cohort	Population	Follow-up	Metabolites	Results	Refs.
HF prediction metabolomic profiles					
PROSPER	$n = 5341$ with high-risk or evidence of vascular disease[a] (70–82 years) 41–52% women	2.7 years	80 metabolite, lipid and lipoprotein by ^{1}H-NMR spectroscopy	• 13 metabolites and lipoproteins were associated with HF • Only phenylalanine (positively) and acetate (inversely) were independently associated with HF after adjustment for classical risk factors and NT-proBNP	Delles *et al.*[7]
Framingham Heart Study	$n = 2336$ (55 ± 10 years) 53% women	15.8 years	Metabolites measured by LC-MS	Phosphatidylcholine (HR 0.63, $p < 0.001$) and ornithine (HR 1.44, $p < 0.001$) were associated with HFrEF incidence	Andersson *et al.*[8]
JHS	$n = 2199$ Black 62% women	9.6 years	Metabolites measured by LC-MS	• Metabolites associated with incident HF included RNA posttranscriptional products, polyamines and nitric oxide metabolism. • The addition of metabolites to a model including risk factors and BNP better predicted HF ($\Delta C = 0.02$)	Tahir *et al.*[9]
UK Biobank	$n = 68\,311$	12.3 years	168 metabolites measured by ^{1}H-NMR spectroscopy	• Adding metabolomics to PCP-HF improved predictive performance ($\Delta C = 0.013$) • Models including age, sex and metabolomics performed almost as well as PCP-HF (0.745 vs. 0.755)	Oexner *et al.*[10]

^{1}H-NMR, proton nuclear magnetic resonance; ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; ECG, electrocardiogram; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, heart rate/hazard ratio; JHS, Jackson Heart Study; LC-MS, liquid chromatography-tandem mass spectrometry; LVH, left ventricular hypertrophy; MESA, Multi-Ethnic Study of Atherosclerosis; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCP-HF, Pooled Cohort equations to Prevent Heart Failure; PROSPER, PROspective Study of Pravastatin in the Elderly at Risk.
[a]Stable angina, stroke, transient ischaemic attack, or myocardial infarction.

The comprehensive nature of metabolomic profiling offers a holistic view of metabolic dysregulation preceding HF onset. Clear strengths of this study are the large cohort, extended follow-up period, and the search for HF predictors among a wide array of variables, without prior assumptions. The proposed metabolomic panel aligns with the call for innovative screening tools, and could be easily applied even in clinical practice. However, the study is not without limitations. The lack of external validation, especially in cohorts with established risk factors like hypertension, diabetes and chronic kidney disease (all disorders for which therapeutic options to prevent HF are available), and differentiation between HF phenotypes, such as HF with preserved and reduced ejection fraction, might limit the generalizability and specificity of the findings. The study evaluates serum metabolomics' predictive power in a general population cohort, regardless of traditional HF risk factors. Additionally, the proposed approach somewhat blurs the lines between prediction of HF development (stage A) and early identification of pre-clinical HF (stage B). Hypothetically, the use

of non-fasting samples that were stored for about 15 years could potentially influence the metabolite profiles and their predictive accuracy. Finally, traditional cardiac biomarkers like N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin (hs-cTn) were not included. These biomarkers remain crucial in the screening setting, particularly with the advent of point-of-care technologies in clinical settings, and have a demonstrated prognostic value for HF development in the general population. For example, a meta-analysis involving 10 studies and 61 467 subjects from the general population demonstrated that hs-cTn values are strong predictors of HF hospitalization.[12] Alternative approaches to screening include imaging-based screening[13] or the combined use of biomarkers and imaging findings.[14] Indeed, various imaging findings have been linked to HF development in the general population, particularly left ventricular (LV) systolic dysfunction and dilatation, as well as diastolic dysfunction and LV hypertrophy.[14] Several studies have underscored the prognostic significance of abnormal LV deformation detected through speckle-tracking echocardiography (STE) or cardiac magnetic resonance (CMR) strain analysis. On the other hand, strategies based on cardiac imaging are more effective in detecting latent cardiac dysfunction (stage B) rather than predicting future disease (stage A), and large-scale screening strategies employing STE or CMR are probably unfeasible. Another possible tool for HF screening is represented by genetic and epigenetic analysis, consisting in the search for gene polymorphisms or epigenetic signatures associated with an increased susceptibility to the disease.[15] Nonetheless, genetic association studies in HF have been controversial, often due to the complex interactions or synergisms among multiple genetic variants collectively contributing to the disease phenotype.[16] Finally, although other omics and multi-omics techniques (e.g. genomics, transcriptomics, proteomics) have been investigated for HF diagnosis, phenotyping, risk stratification, and guide to treatment, their role in HF screening remains largely unexplored.

The study by Oexner *et al.*[10] provides a theoretical framework for a biomarker-based screening strategy to identify individuals at risk of HF within the general population, helping clinicians and patients to make informed decisions about prevention and follow-up strategies for those at high risk of HF. Plasma metabolomic profile may reveal new HF mechanisms, possibly leading to the discovery of novel therapeutic targets, or categorizing HF patients into distinct subsets characterized by specific disease mechanisms, rates of progression, and responses to treatment, thereby contributing to precision medicine in HF. Employing metabolomics as the first step to screen the general population and predict their risk of developing HF may be a cost-effective and scalable strategy. We could envisage a sequential multi-step screening process incorporating first metabolomics, then traditional biomarkers (e.g. NT-proBNP, hs-cTn), and then, in selected cases, imaging modalities like standard echocardiography, STE, and possibly also CMR. Another intriguing perspective is the integration of metabolomics with other -omics technologies for a more refined risk prediction, though these avenues remain largely exploratory at this stage. Future research on screening algorithms should include external validation studies, particularly in populations known to be at risk for HF.

In summary, the study by Oexner *et al.*[10] marks a significant advance in the pursuit of effective HF screening strategies. By showcasing the predictive capacity of metabolomics, the study not only enriches our understanding of HF pathophysiology, but also suggests a precision medicine approach to HF prediction. The journey toward a cost-effective screening tool for HF has just begun, and will hopefully lead to a future where multidisciplinary research and validation in diverse populations will pave the way for preventive strategies against this condition.

Conflict of interest: none declared.

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