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Metabolomics in cardiovascular medicine – not personalised, not diagnostic

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Dona and colleagues recently published a review on metabolomics in cardiovascular research in this journal. They discussed the current status of metabolomics applications in cardiovascular medicine. I agree with many of the authors’ standpoints. However, they gave a rather optimistic view on personalised medicine and presented a multivariate statistical example on metabolomics-based diagnostics. These are concepts that are often unrealistically interpreted. I would like to reflect on related challenges and caveats.

Polygenic traits, such as common cardiovascular outcomes, are quantitative traits and as a result of that, continuous by nature. The distributions of metabolic phenotypes are also continuous. This is a background that poses a fundamental limitation for both risk assessment and diagnostics. At the population level, we may identify several biomarkers that relate to the outcome. However, the substantial phenotypic overlap between those with the disease (cases) and those without the disease (controls) precludes such cut-off values for diagnostic models that would provide both high sensitivity and high specificity.

While these fundamentals are well recognised in the cardiovascular research arena, they are continually ignored in many metabolomics applications. In the core of the problem is the lack of quantitative molecular data and the generally accepted convention to express the biological motivation as the black-and-white classification of individuals to those with and without a disease. The common solution to apply “multivariate chemometrics” (e.g., orthogonal partial least squares discriminant analysis, OPLS-DA, as illustrated by Dona and colleagues) typically misguides the analyses and interpretations, particularly when the often (almost) perfect (i.e., highly implausible) classification results are not critically evaluated in the light of the analysis method used and with respect to the underlying biology of the application. The key hurdles of this type of multivariate metabolomics applications are currently well identified: overtraining of the classification models with a high number of variables (typically spectral data points), very small numbers of individuals and the lack of independent biological replications.

It would be beneficial for the increasing numbers of medical scientists using metabolomics that the caveats of multivariate analyses would be critically communicated. Yet, quantitative metabolomics data, as also called for by Dona and colleagues, are directly amenable to
standard statistical methods, e.g., linear regression models, with appropriate variable adjustments and replications. To appraise the true value of metabolomics in cardiometabolic research, we should, firstly, to tenaciously reject implausible diagnostic applications of metabolomics, and, secondly, to abandon the current logic of “one common risk model for all individuals”. I would anticipate that moving towards specific molecular characterisation of people as well as disease subgroups would give us means to improve cardiovascular risk assessments via metabolomics. Nevertheless, the abovementioned fundamental limitations would restrict the applicable results to population subgroups, thereby meeting the challenges of personalised medicine only halfway.

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MAK is a shareholder of Brainshake Ltd. (www.brainshake.fi), a company offering NMR-based metabolic profiling.
References:


