Sex-specific relationship between the cardiorespiratory fitness and plasma metabolite patterns in healthy humans – Results of the KarMeN study

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Background: The cardiorespiratory fitness (CRF) represents a strong predictor of all-cause mortality and is influenced by regular physical activity. However, the biological mechanisms involved in the body's adaptation to exercise remain to be fully elucidated. Metabolomics is a powerful tool to assess exercise-induced changes in human metabolism.
Methods: By analyzing data from the cross-sectional Karlsruhe Metabolomics and Nutrition study, we examined the relationship between the CRF and plasma metabolite patterns in 252 healthy women and men. The CRF was assessed by measuring the peak oxygen uptake during incremental exercise. Fasting plasma samples were analyzed by nuclear magnetic resonance spectroscopy and mass spectrometry coupled to one- and two-dimensional gas chromatography or liquid chromatography.
Results: Based on this multi-platform metabolomics approach, 427 plasma analytes were detected. Bi- and multivariate association analyses adjusted for age and menopausal status showed that the CRF in women and men was linked to specific sets of metabolites primarily indicative of lipid metabolism. However, the CRF-related plasma metabolite patterns largely differed between sexes. Several phosphatidylcholine (PC) species were mainly linked to the CRF in females, while single lyso-phosphatidylcholines and sphingomyelins were associated with the CRF in males. When controlling for further clinical and phenotypical parameters, the sex-specific CRF tended to be correlated with a rather small number of metabolites primarily linked to the lipid, amino acid or xenobiotics-related metabolism. Interestingly, explanation models for the sex-specific CRF could be improved when including selected plasma analytes in addition to clinical variables. Particularly acyl-alkyl-PC C40:3 was identified as a possibly relevant metabolite parameter for concluding about the CRF in females.
Conclusions: Our findings demonstrated sex-related differences in CRF-associated plasma metabolite patterns. Future studies examining blood metabolic markers related to the CRF should therefore conduct sex-separated analyses. Besides, more research is needed to clarify mechanisms and metabolic pathways underlying sex-specific differences in CRF-associated metabolite profiles.

Keywords: cardiorespiratory fitness, plasma metabolome, plasma metabolite patterns, plasma metabolite profiles