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## Integrative exploration of metabolic syndrome in older men

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**Background:** Metabolic syndrome (MetS), a cluster of factors associated with risks of developing cardiovascular diseases, is a public health concern because of its growing prevalence. Considering the combination of concomitant components, their development and severity, MetS phenotypes are largely heterogeneous, inducing disparity in diagnosis.

**Objective:** The objective of the present work was to better characterize metabolic perturbations in MetS and define a comprehensive MetS signature stable over time in older men.

**Design:** A case/control study was designed within the Quebec NuAge longitudinal cohort on aging. From a 3-year follow-up of 123 stable individuals, we present a deep phenotyping approach based on a multiplatform metabolomics and lipidomics untargeted approach. A full feature selection strategy was developed to build a comprehensive molecular MetS signature, stable over time.

**Results:** We characterize significant changes associated with MetS, involving modulations of 476 metabolites and lipids, and representing 16% of the detected serum metabolome/lipidome. These results revealed a systemic alteration of metabolism, involving various metabolic pathways (urea cycle, amino-acid, sphingo- and glycerophospholipid, and sugar metabolisms...) not only intrinsically interrelated, but also reflecting environmental factors (nutrition, microbiota, physical activity...). These findings allowed identifying a comprehensive MetS signature, reduced to 26 metabolites for future translation into clinical applications for better diagnosing MetS.

**Conclusions** The refinement of the comprehensive signature, performed both in terms of measurement reliability, but also by showing the consistent association between the modulated metabolites/lipids and the underlying biological mechanisms, is increasing the value of the proposed biomarker combination within the reduced signature for further investigation and possible clinical application.

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