**Development of an Oral (Poly)Phenol Challenge Test (Opct) to Identify Aggregate Metabotypes for Dietary (Poly)Phenols and Their Drivers: A Study Protocol**

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**Objectives:** Evidence shows that bioactive (poly)phenols are pivotal in the prevention of chronic diseases, in particular in cardiometabolic health. However, the inter-individual variability existing in their bioavailability and physiological response can impact their true efficacy. Individuals showing similar metabolic profiles for specific (poly)phenols can be clustered into phenolic metabotypes, while comprehensive phenolic metabolic profiles derived from main dietary (poly)phenols could be referred to as "aggregate phenolic metabotypes". The main aim of the study is to identify aggregate phenolic metabotypes and the determinants related to their formation.

**Methods:** An intervention study is carried out on 300 healthy volunteers (18–74 y) which are asked to provide information on dietary habits, smoking, physical activity, sleeping, anthropometric measures, health status, and biological samples. Subjects undergo a standardised oral (poly)phenol challenge test consisting in an acute supplementation of several classes of dietary (poly)phenols. Urine samples collected during the following 24h are analysed through UPLC-IMS-HRMS to assess the individual urinary excretion of phenolic metabolites, allowing aggregate metabotype clustering. Blood samples are analysed to determine common cardiometabolic health biomarkers, and buffy coat processed to isolate peripheral blood mononuclear cells (PBMCs) used for whole-genome genotyping. Transcriptomic signatures in PBMCs are also assessed. Gut microbiota composition will be profiled by shallow shotgun metagenomics. Cardiometabolic risk scores are also computed. Predictive models will be used to assess the determinants of inter-individual variation in (poly)phenol metabolism, providing indications in the cardiometabolic health status of each individual.

**Results:** Preliminary results are expected to be available for mid-2023.

**Conclusions:** Metabotyping according to the metabolism of the whole set of dietary (poly)phenols may thus represent a promising attempt for cardiometabolic health promotion through personalised nutrition initiatives.

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