Association of plasma metabolomic compounds with the incidence of cardiovascular endpoints in the Hortega Follow-Up Study

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Introduction: The association of metabolic compounds with the incidence of specific cardiovascular (CV) endpoints including coronary heart disease (CHD), stroke and heart failure (HF) has rarely been studied in general population settings. Therefore, we evaluated the prospective association of metabolic compounds with incidence of CHD, stroke and HF in the Hortega study, a representative sample of a general population from Spain.

Methods: Metabolites were measured by NMR in 1016 adults of the Hortega Follow-up Study (15 years of follow-up) without clinical CV diseases at baseline. We estimated hazard ratios (HR) and 95% confidence intervals (CI) of stroke, CHD and HF incidence by plasma metabolites levels (log-transformed) using Cox proportional hazards regression. Models were adjusted for sex, education, smoking status, cumulative tobacco smoking (pack-year), urine cotinine, glomerular filtration rate, physical activity, HDL cholesterol, total cholesterol, lipid lowering and blood pressure medication, type 2- diabetes mellitus and systolic blood pressure.

Results: The number of newly diagnosed cases were 67 for stroke over 13,184 person-years (incidence of 5.1 per 1,000 person-years); 52 for CHD over 12,908.5 person-years (incidence of 4 per 1,000 person-years) and 75 for HF over 13,336.3 person-years (incidence of 5.6 per 1,000 person-years). We observed statistically significant associations [HR (95% CI), comparing the 80^{th} to the 20^{th} percentiles of metabolites distributions] for creatinine phosphate [1.94 (1.18, 3.20)], tryptophan [3.25 (1.48, 7.15)], tyrosine [1.98 (1.18, 3.32)] and O-phosphoethanolamine [2.09 (1.25, 3.50)], among others, with incident heart stroke; cysteine [2.12 (1.23, 3.68)], isopropanol [2.25 (1.20, 4.21)], citrate [2.20 (1.20, 4.01)] and phenylpropionate [2.45 (1.13, 5.31)], among others, with incident CHD; and some fatty acids subclasses as CH_2CH_2CO [0.56 (0.32, 0.97) and CH_2N [0.44 (0.22, 0.88)], acetone [0.45 (0.22, 0.93)] and lactate [0.53 (0.28, 0.99)] with incident HF.

Conclusions: Metabolic patters reflecting amino acids, fatty acids, microbiota co-metabolism and energy-related compounds were prospectively associated with specific CV endpoints in the general population from Spain, which may be relevant for CV diseases prevention and diagnosis. Additional studies for reproduction of our findings are needed.

Keywords: metabolomics, metabolites, cardiovascular disease