Impact of gender differences in metabolomics and lipidomics on precision medicine

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Introduction

Precision medicine aims to tailor disease prevention and treatment by taking into account differences in genetics, environment and lifestyle. Ground zero of this approach is understanding and leveraging the differences that exist in the baseline profiles of healthy women and men. At times, these differences can either mask or drive disease profiles and treatment responses.

Modern approaches to this question have developed together with omics technologies. However, stratification of omic data based on gender is still severely underutilized, slowing down the implementation of this most basic level of precision medicine.

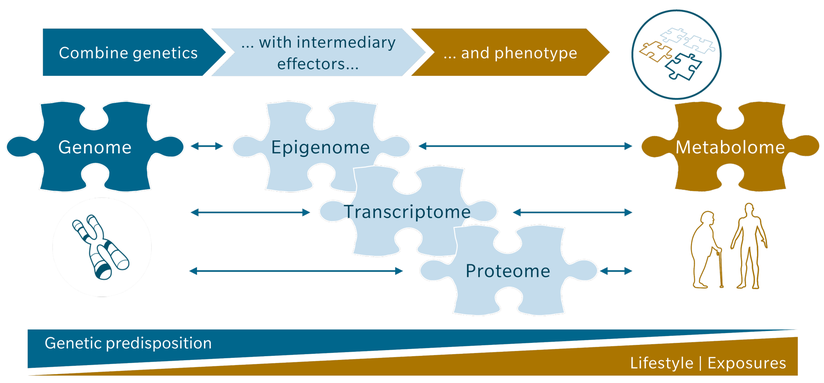

Figure 1 | Metabolomics offers a unique access to a person's phenotype, with distinct profiles for women and men, due to both genetics and lifestyle factors.

Metabolomics is the omic most directly impacted by both genetics and outside factors like environment and lifestyle (Figure 1), and thus a powerful tool for precision medicine.

Methods

Metabolomics

Plasma samples from healthy control individuals were analyzed using the standardized kit MxP® Quant 500 for metabolomics and lipidomics measurements (Figure 2).

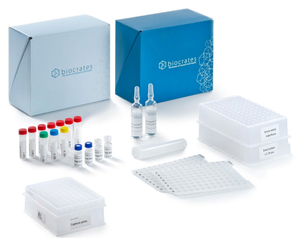

Figure 2 | Example of a standardized metabolomics kit (MxP® Quant 500) containing 96-well plates, internal standards, calibrators and quality control samples to quantify up to 630 metabolites (small molecules and lipids) in 10 µL of human plasma sample.

Database

The quantitative metabolomics database (QMDB) computes blood plasma metabolomic profiles from thousands of healthy individuals to provide reference ranges for up to 630 metabolites (1). Data from several population studies were collected with the approval of each research institution that collected samples, performed studies and shared anonymized data with consent of participants according to local ethics rules.

Sub-groups

Reference ranges can be calculated for any subset of the database. In this study, stratifications based on gender, age, ethnicity and lifestyle factors were applied, and the subsets' average metabolite concentrations were compared to identify differences in baseline biology of healthy individuals.

Data analysis

Transformed data (log2) was downloaded from the QMDB for each group separately. A threshold of 100 measurements was set as an inclusion threshold for all groups except the age groups where the threshold was set to 10 due to small numbers in the extreme groups. Only metabolites with at least 80% of values above the limit of detection in at least one group were subjected to statistical analysis. The p values were calculated with the test for comparison of two means (2, 3) and adjusted for multiple comparisons with the Benjamini-Hochberg method (4).

References

1. Tian & Adam (2023) Human Metabolome Reference Database in a Biracial Cohort across the Adult Lifespan. Metabolites | 2. Altman DG (1991) Practical statistics for medical research. London: Chapman and Hall | 3. Kirkwood BR, Sterne JAC (2003) Essential medical statistics, 2nd ed. Oxford: Blackwell Science | 4. Benjamini & Hochberg (1995) Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. Journal of the Royal Statistical Society: Series B (Methodological).

Results

Stratification by gender (Figure 3) was in line with previously described differences in small molecules (e.g. glycine higher in women, creatinine higher in men) and lipid classes (e.g. sphingomyelins and phosphatidylcholines higher in women, acylcarnitines and lysophosphatidylcholines higher in men). Several microbiome-derived metabolites were differentially impacted, possibly due to differences in diet and lifestyle between genders.

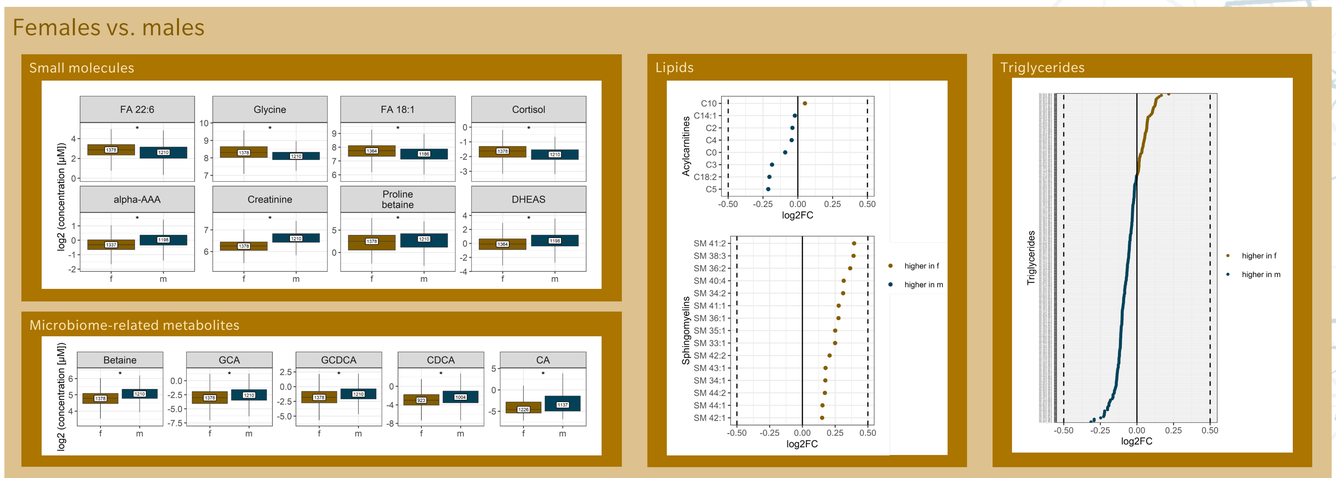

Figure 3 | Gender-based differences in plasma metabolite concentrations in healthy control samples from the QMDB. * : adj. p-value < 0.01.

Double stratification was applied to investigate additional gender differences hidden in the dataset by other factors. Both gender and ethnicity have a strong imprint on the metabolome. Trigonelline only showed significant differences between black men and women and not in the combined dataset. For GDCA and CDCA, double stratification showed that the gender-based differences are driven by one ethnicity group only.

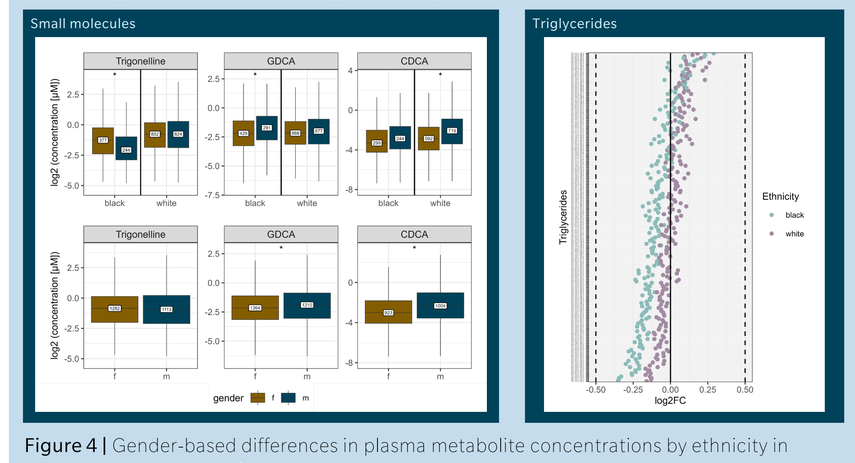

Figure 4 | Gender-based differences in plasma metabolite concentrations by ethnicity in healthy control samples from the QMDB. * : adj. p-value < 0.01; log2FC > 0: higher in women.

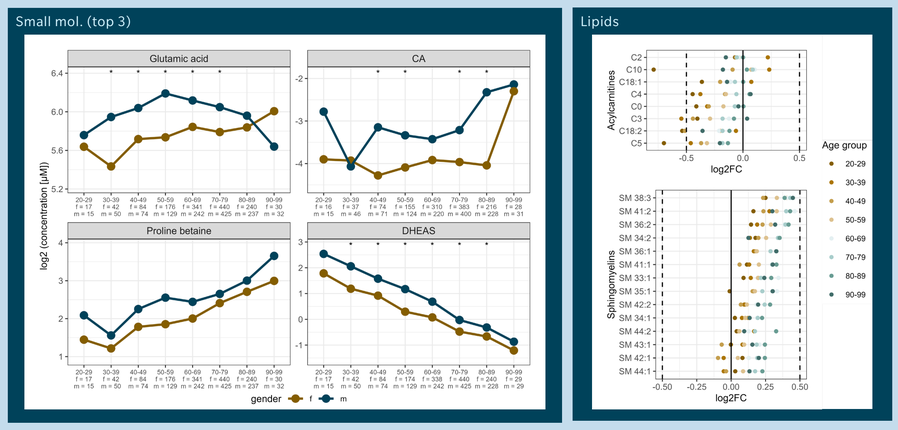

Figure 5 | Gender-based differences in age-related changes in plasma metabolite concentrations in healthy control samples from the QMDB. * : adj. p-value < 0.01; log2FC > 0: higher in women.

Double stratification by gender and age group revealed differences in metabolic ageing (Figure 5). Gender effects on glutamic acid and cholic acid (CA) are age-dependent. Age stratification reduces the gender effect for proline betaine (Figure 1). The gender difference is consistent through all age groups for DHEAS. Gender effects resorb with age for acylcarnitines while increa-sing for sphingomyelins.

Lifestyle factors such as alcohol consumption impacted gender difference for several metabolites (Figure 6), including changes in 3-indole acetic acid (3-IAA), a tryptophan metabolite linked to cardiovascular disease, but also cancer therapy response. Of note, the gender effects for 3-IAA, DCA and proline betaine were driven by one of the subgroups with high or low alcohol consumption, respectively.

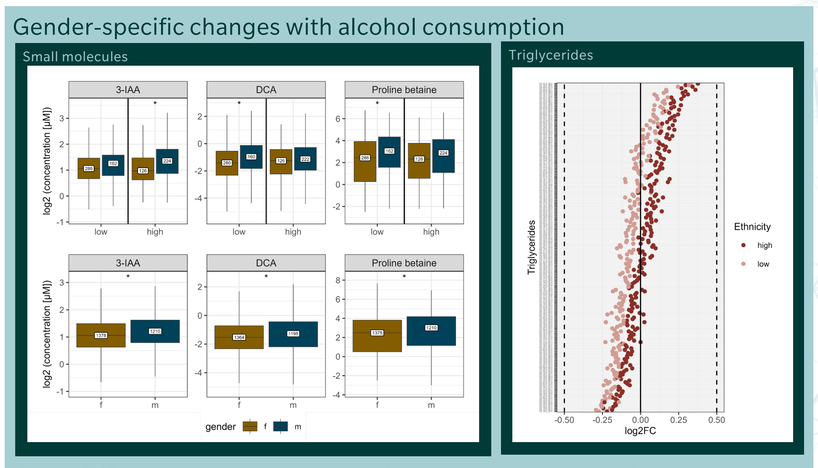

Figure 6 | Gender-based differences stratified by alcohol consumption in plasma metabolite concentrations in healthy control samples from the QMDB. * : adj. p-value < 0.01; log2FC > 0: higher in women.

More Information

For further details, scan the QR code to read the first peer-reviewed paper using QMDB data.

Conclusions

These baseline metabolic differences between women and men warrant the use of different approaches to health monitoring, diagnosis and treatment of disease. Our results demonstrate the importance of establishing healthy reference ranges to enable the application of metabolomics-powered precision medicine in the clinics and in drug development.