Sex differences in arginine- and polyamine-related metabolites in ME/CFS

Cornelia Pipper-Krampl[1], Dalibor Jeremic[1], Bernhard Wagner[1], Markus Hausl[2], Reingard Raml[2], Anita Eberl[2], Christoph Magnes[2], Francisco Westermeier[1]

[1] Institute of Biomedical Science, Department of Health Studies, FH Joanneum University of Applied Sciences, Graz, Austria.
[2] Institute for Biomedical Research and Technologies (HEALTH), Joanneum Research, Graz, Austria.

ME/CFS - associated with cardiometabolic abnormalities and impaired vascular regulation

Complex multisystem disease

ME/CFS is a complex multisystem disease characterized by profound fatigue and post-exertional malaise and increasingly associated with **cardiometabolic abnormalities and impaired vascular regulation**.[1,2]

Cardiometabolic regulation - NO axis

The **Arginine pathway** including methylated Arginines and Polyamines, contribute to **cardiometabolic regulation** through their effects on **NO** bioavailability, **endothelial function** and cellular stress responses.[3]

Metabolites - do they differ?

However, **whether these metabolites differ between male and female patients with ME/CFS** remains poorly understood.

[1] Bateman L, Bested AC, Bonilla HF, Chheda BV, Chu L, Curtin JM, u. a. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Essentials of Diagnosis and Management. Mayo Clin Proc. 1. November 2021;96(11):2861–78. doi:10.1016/j.mayocp.2021.07.004
[2] Sandvik MK, Sørland K, Leirgul E, Rekeland IG, Stavland CS, Mella O, u. a. Endothelial dysfunction in ME/CFS patients. PLOS ONE. 2. Februar 2023;18(2):e0280942. doi:10.1371/journal.pone.0280942
[3] Schibalski RS, Shulha AS, Tsao BP, Palygin O, Ilatovskaya DV. The role of polyamine metabolism in cellular function and physiology. Am J Physiol-Cell Physiol. 1. August 2024;327(2):C341–56. doi:10.1152/ajpcell.00074.2024

Precise analytics is key for success

Cohort: UK ME/CFS Biobank

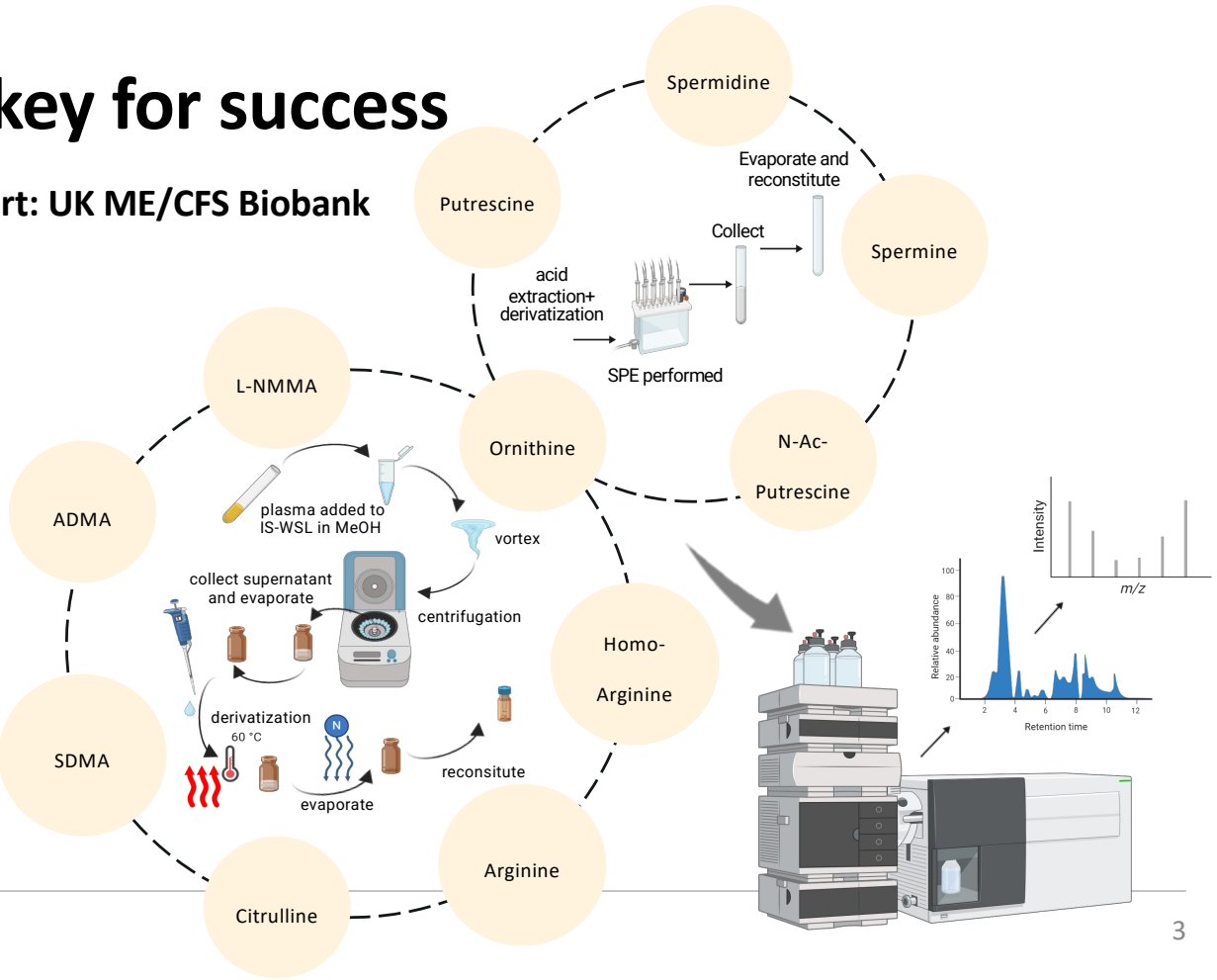
Sample preparation

Arginine metabolites - ADMA, SDMA, L-NMMA, Arginine, Homo-Arginine and Citrulline

- **protein precipitation**
- **derivatization** (butanol solution containing 5% (v/v) acetyl chloride)
- **UHPLC-MS/MS**

Polyamines - Ornithine, N-Ac-Putrescine, Putrescine, Spermidine and Spermine

- **acid extraction**
- **derivatization** (isobutyl chloroformate)
- **SPE** (RP, Strata-X 33)
- **HPLC-MS/MS**



ME/CFS shows sex-specific alterations in Arginine- and Polyamine-related metabolites

female ME/CFS patients (n=70) vs. controls (n=27)
→ **no significant differences** observed

male ME/CFS patients (n=25) vs. controls (n=18)
→ **significant metabolic alterations** observed

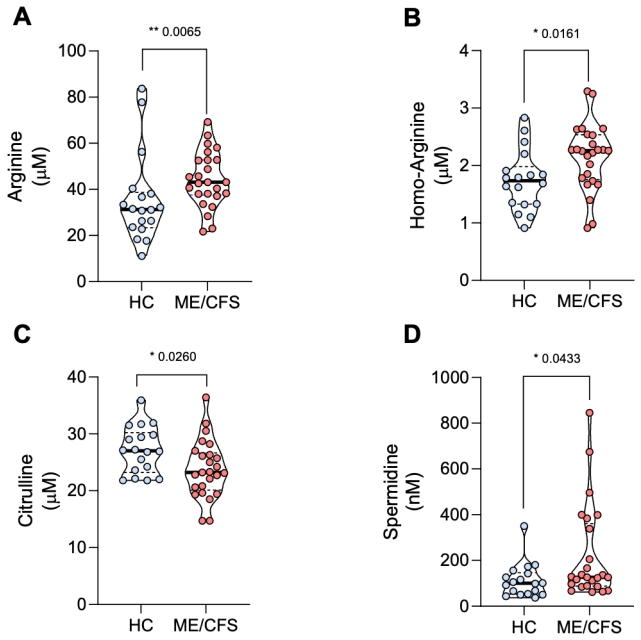
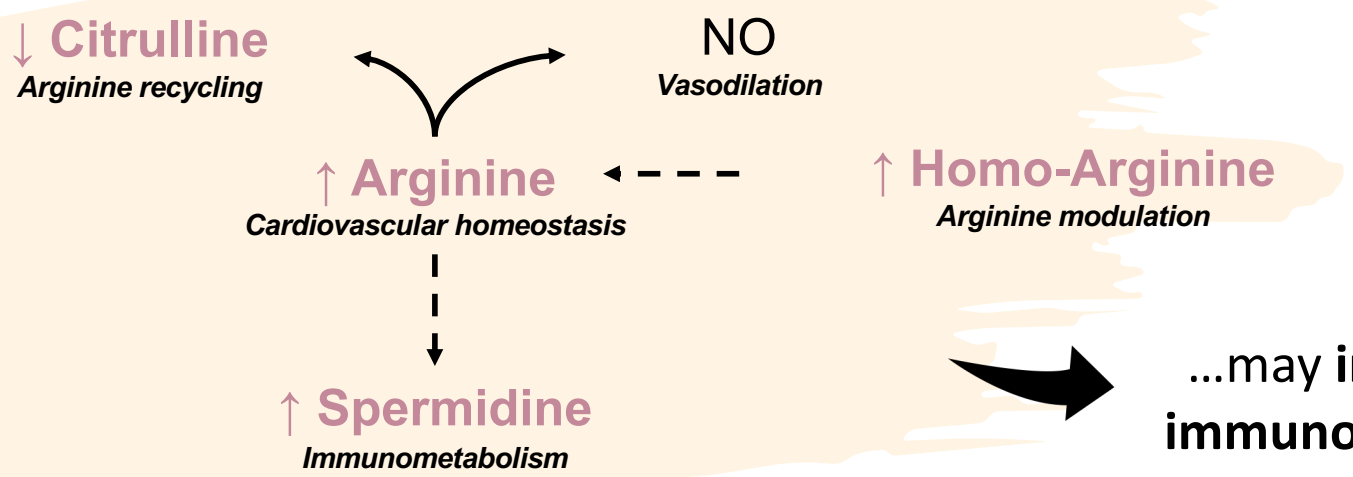


Figure 1: Group comparisons of Arginine (A), Homo-Arginine (B), Citrulline (C) and Spermidine (D) between male healthy controls (HC, blue) and male ME/CFS patients (red). Data are presented as median and interquartile ranges.

Imbalance in Arginine utilization between NO and Polyamine pathways…



…may **impact vascular and immunometabolic function**

These findings support a **sex-dependent role of the arginine-NO axis in ME/CFS**

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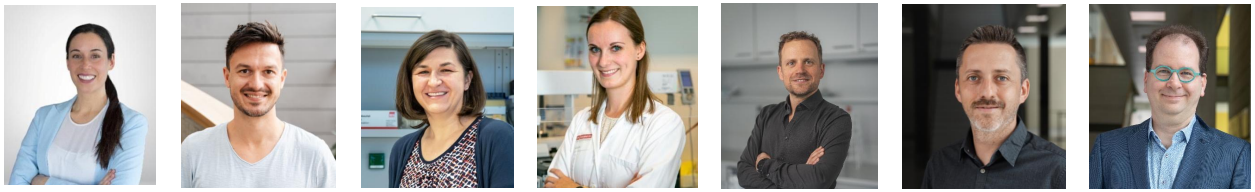
Thank you to the team…



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…thank you for your attention!

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