

Distinct Metabolic Perturbations Link Liver Steatosis and Incident CVD in Lean but Not Obese PLHIV

Nadira Vadaq^{1*}, Louise E. van Eekeren^{1*}, Marc Blaauw^{1,2}, Albert L. Groenendijk^{1,3}, Willem Vos^{1,4}, Erni J. Nelwan⁵, Annelies Verbon³, Janneke E. Stalenhoef⁴, Marvin A.H. Berrevoets², Jan van Lunzen¹, Mihai G. Netea¹, Gert Weijers¹, Niels P. Riksen¹, Joost H.W. Rutten¹, Quirijn de Mast¹, Eric T.T.L. Tjwa¹, Leo A.B. Joosten¹, André van der Ven¹

¹Radboudumc, Nijmegen, The Netherlands, ²Elizabeth-Tweesteden Ziekenhuis, Tilburg, The Netherlands, ³Erasmus Medical Center, Rotterdam, The Netherlands, ⁴OLVG, Amsterdam, The Netherlands, ⁵Universitas Indonesia, Jakarta, Indonesia. *Shared first authorship



BACKGROUND

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a key risk factor for cardiovascular disease (CVD), potentially driven by shared metabolic mechanisms. However, the metabolic perturbations linking MASLD and CVD remains unexplored in people living with HIV (PLHIV).

METHODS

Cohort: Longitudinal multi-center 2000HIV study (NCT03994835)

- 1895 virally suppressed PLHIV on antiretroviral treatment
- 970 participants underwent liver measurements

Liver Assessment:

- Method: Transient elastography with the controlled attenuation parameter (CAP)
- Steatosis: CAP > 263 dB/m and Fibrosis: LSM ≥ 7.0 kPa

Cardiovascular Disease Assessment:

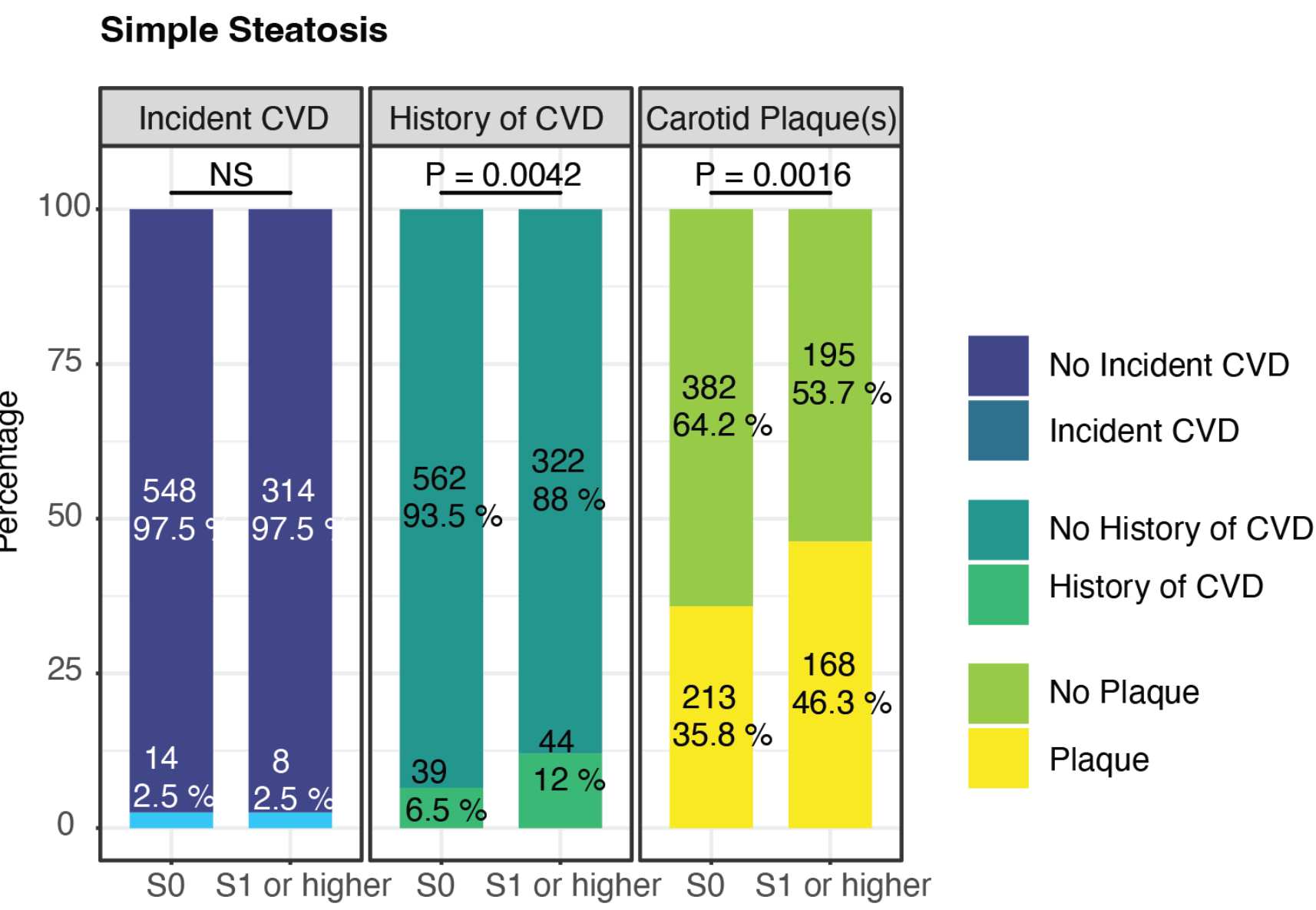
- CVD history and new incidents during 2-year follow-up (myocardial infarction, stroke, peripheral arterial disease, angina) from medical records
- Carotid artery plaques assessed via ultrasonography

Metabolic Measurements:

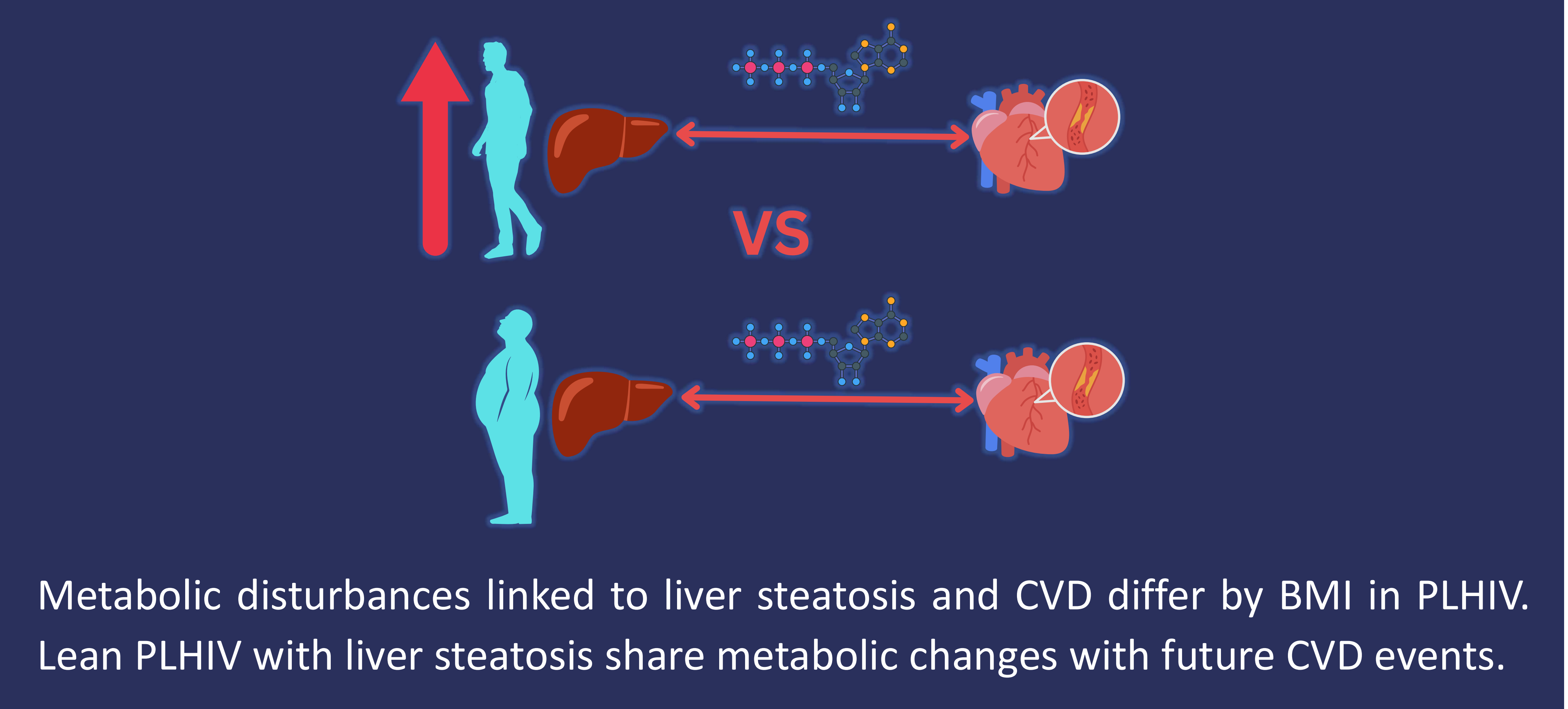
- Untargeted Metabolomics: Mass spectrometry (n=500 metabolites)
- Targeted Lipoproteomics: Nuclear magnetic resonance
- spectroscopy (n=246 metabolites)

RESULTS

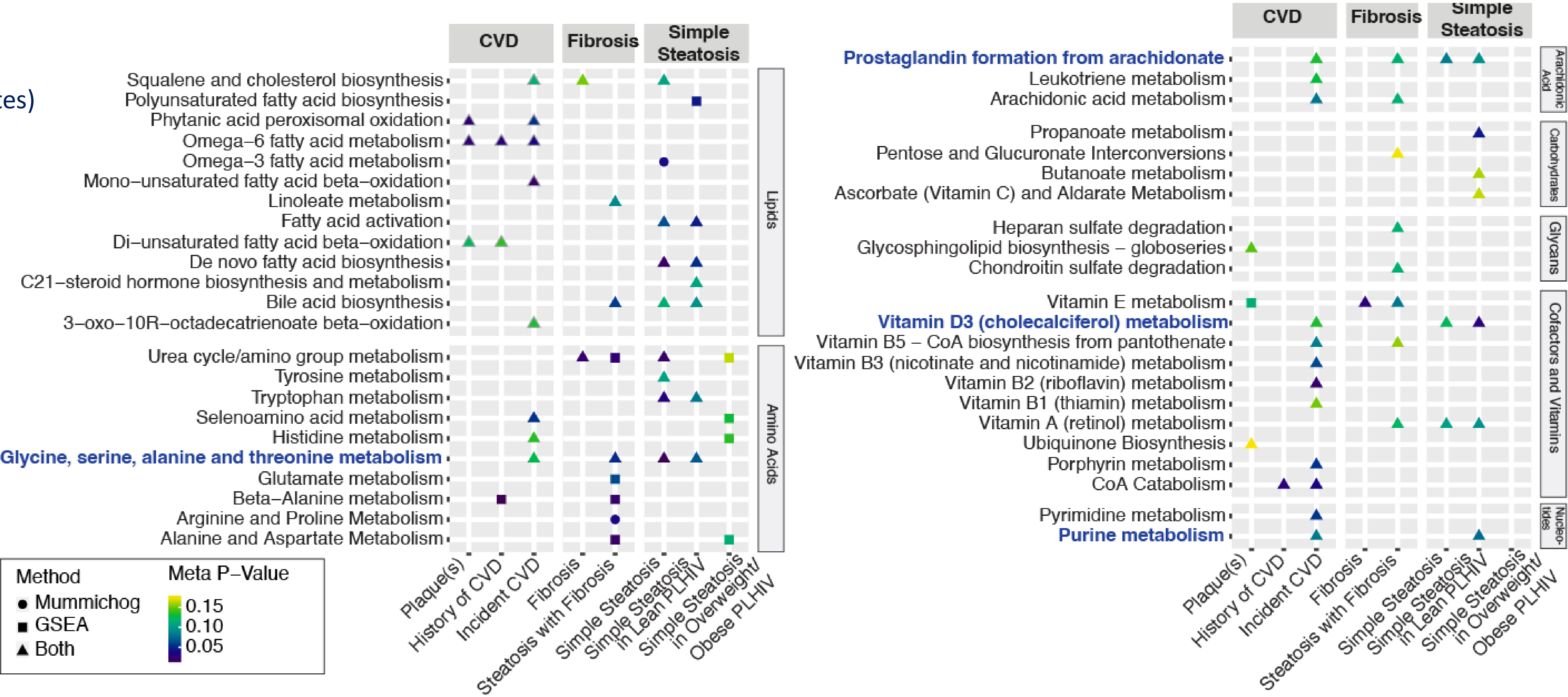
A. Associations between MASLD and CVD



- PLHIV with liver steatosis (S1 or higher) had more arterial plaques (P=0.003) and CVD history (P=0.021), especially in lean individuals.



B. Metabolomic analysis



- Metabolic pathways associated with liver steatosis and fibrosis primarily involved lipid and amino acid metabolism (Figure B), a finding validated by targeted lipoproteomic measurements (Figure C). Notably, metabolomic pathways and lipoproteomic signatures associated with MASLD were mostly distinct from those associated with CVD parameters. However, several pathways were shared, especially in lean PLHIV (Figure B)

CONCLUSIONS

Metabolic disturbances linked to liver steatosis and CVD differ across BMI categories in PLHIV. Lean PLHIV with liver steatosis, unlike their overweight/obese counterparts, show common metabolic perturbation with future CVD events.

This suggests a heightened CVD risk in lean PLHIV with liver steatosis, potentially opening avenues for interventions targeting the arachidonic acid metabolism, such as aspirin therapy, to mitigate this risk.

ADDITIONAL KEY INFORMATION

Correspondence: N.Nadira@radboudumc.nl

C. Lipoproteomic analysis

