Obesity and Adiposity-Related CKD Subgroups and Metabolites

Findings from the Chronic Renal Insufficiency Cohort (CRIC) Study

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Presented by

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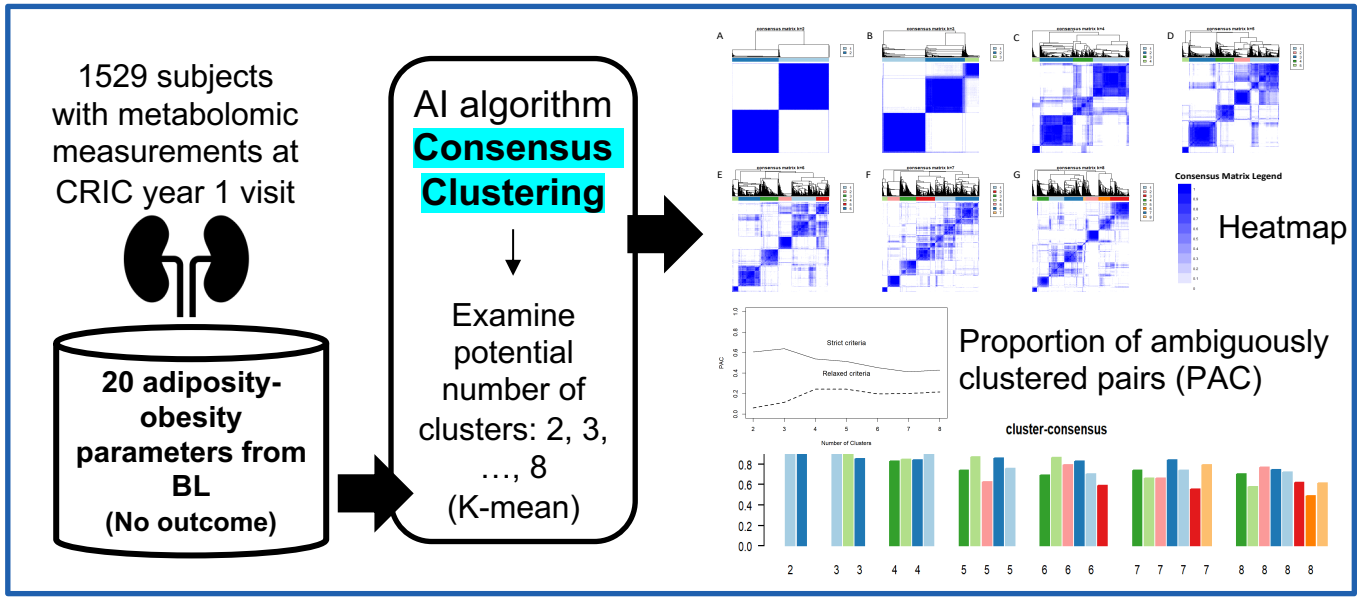
Study Background & Aim

- Chronic kidney disease (CKD) patients are a heterogenous population.
- Obesity and excessive adiposity increases the risks of adverse outcomes of CKD.
- "Obesity-paradox" and CKD survival is not fully understood.

- **Aim: we propose to identify distinct "adiposity-obesity-related" (AOR) CKD subgroups and to perform analysis on high-dimensional metabolomics data with CKD subgroups and clinical endpoints.**

Methods

Study population: 1,529 of 3,939 participants from **Chronic Renal Insufficiency Cohort (CRIC) Study,** an NIDDK-funded, multi-center, longitudinal cohort of well-characterized adults with CKD in the U.S



Metabolomics analysis : Uni/multivariable regression model

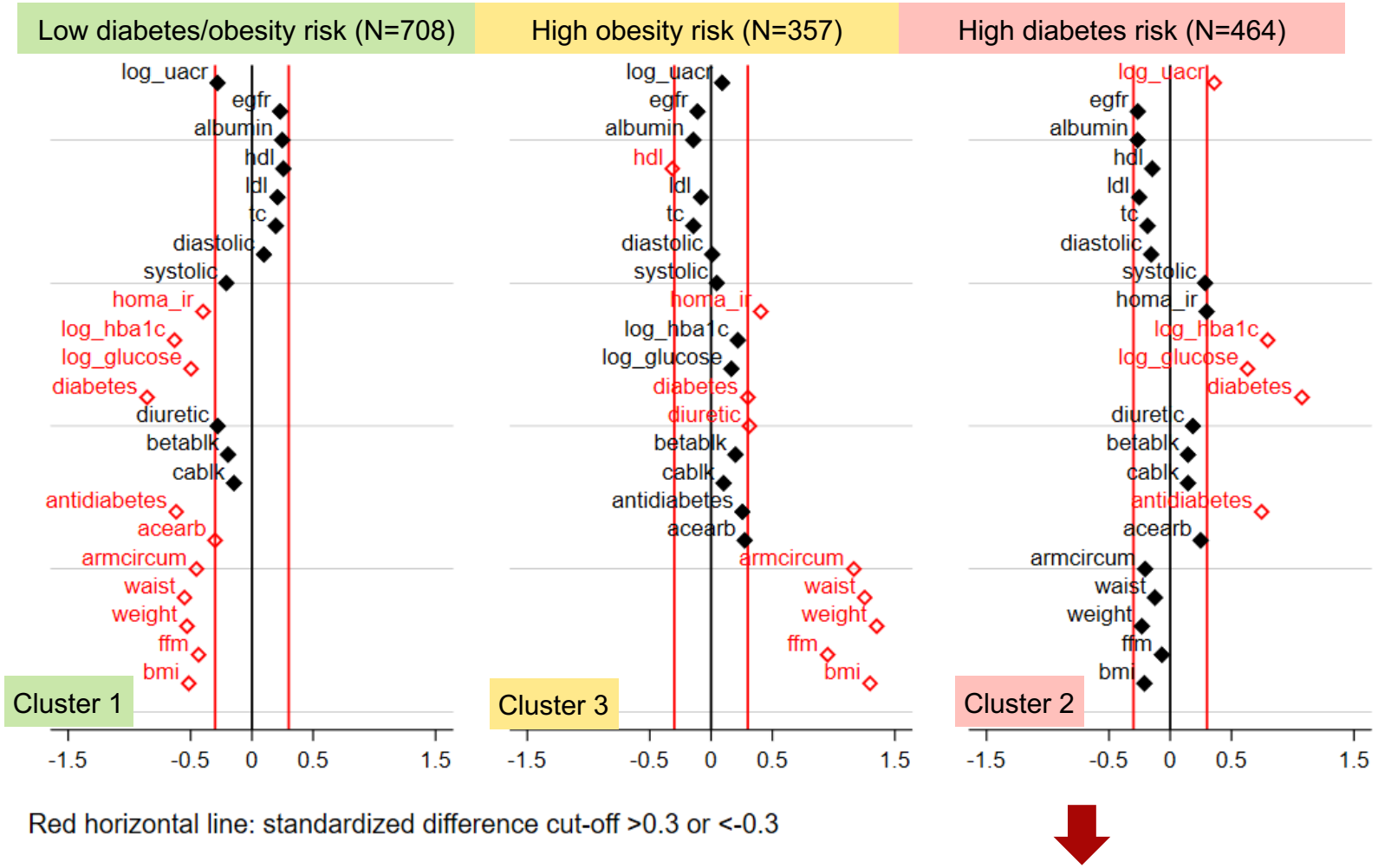
- Bonferroni cut-off: $p < 0.05/634 = 7.9\times10^{-5}$

Survival analysis: Cox regression model

- 6 endpoints: CKD progression (×2), CVD (×3) and death

Model adjustment: age, gender, race, eGFR, Log(UACR), smoking and CVD history

Results



- **Low DM/Ob risk group** has relatively low prevalence of diabetes, preferable diabetic markers and obesity profiles, and uses less medications; the kidney function is the most optimal among all three groups.
- **High Ob risk group** has low HDL, relatively high prevalence of diabetes and high insulin resistance level and non-preferable obesity profiles
- **High DM risk group** has average obesity risks but relatively high prevalence of diabetes WITHOUT adequate glycemic control and uses more diabetes medications; has more proteinuria.

Arise from the adiposity-obesity data pattern of 20 variables, we identified three distinct CKD adiposity-obesity related (AOR) subgroups in a CKD population.

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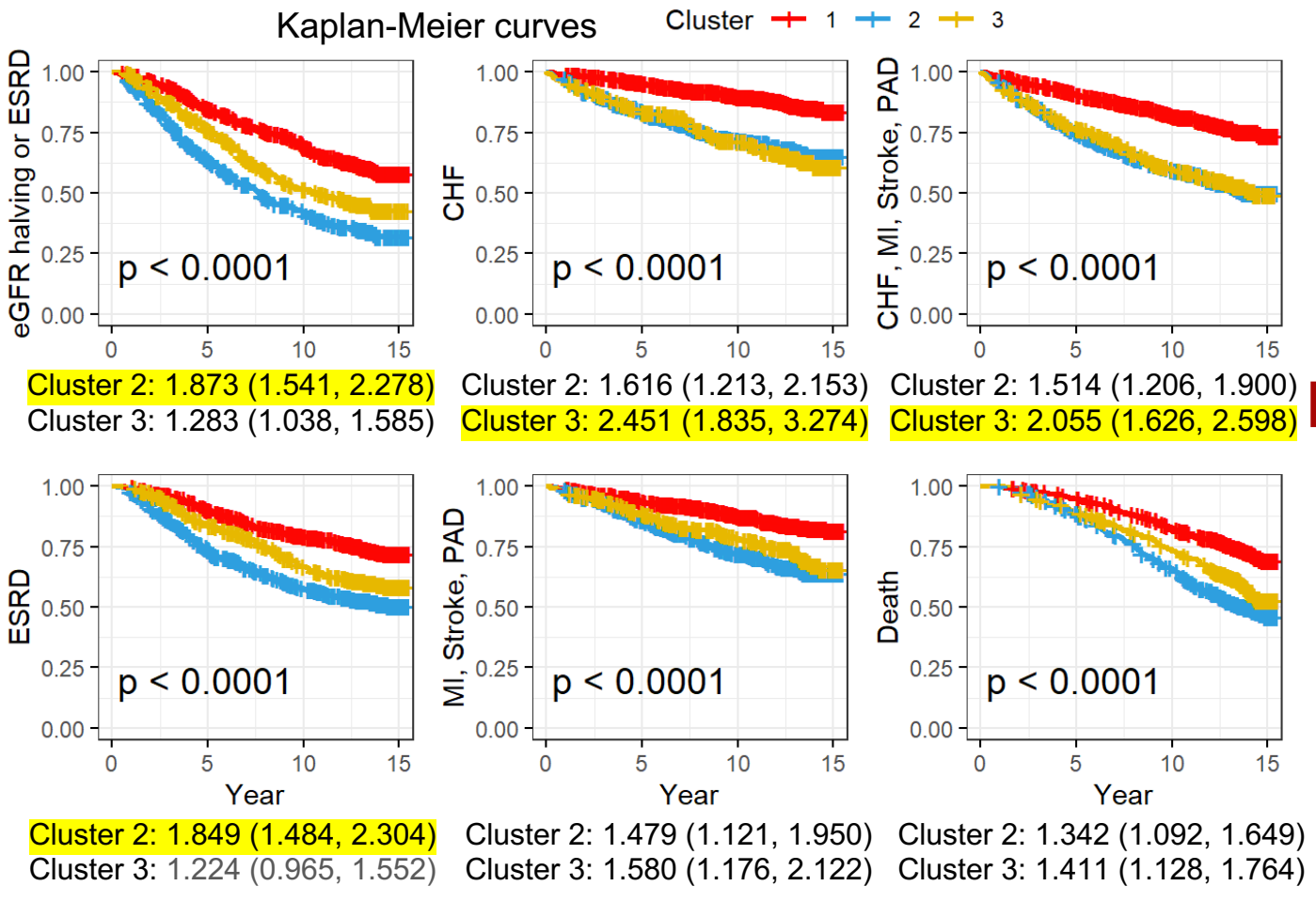
Results

Among 634 known metabolites, 179 metabolites are significantly associated with AOR subgroup.

- 82% lipids metabolites
- 7% amino acid metabolites

Metabolites significantly associated (adjusted) with AOR subgroups ($p<7.9\times10^{-5}$)

Metabolite pathway	N	% Total
Lipid	146	81.56
Amino Acid	12	6.7
Organic acids and derivatives	6	3.35
Cofactors and Vitamins	4	2.23
Nucleotide	4	2.23
Organic oxygen compounds	3	1.68
Organoheterocyclic compounds	2	1.12
Xenobiotics	2	1.12
(missing)	0	0
Total	**179**	**100**



Compared to CKD patients with low DM and obesity risks (ref) with confounder adjustment,

- High DM risk is associated with 87% increased hazard for eGFR halving and ESRD and 85% increased hazard for ESRD.
- High obesity risks is associated with 2.5 times increased hazard for CHF, and 2.1 times increased hazard for composite CVD outcome of CHF, MI, stroke and PAD.

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Conclusions

- With consensus clustering and metabolomics analysis, we discovered three distinct AOR subgroups of CKD patients that were associated with numerous metabolites and different risks of clinical endpoints.
- Novel biomarkers that co-segregate with different patient subgroups could shine a light on the obesity related biology of CKD.