Metabolic signatures and incident diabetes in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL)

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Introduction

- **Previous metabolomic studies have identified many metabolites associated with diabetes.**
- **Despite high prevalence of diabetes among US Hispanics/Latinos, metabolomic studies have scarce among the US Hispanic/Latino population.**

Objectives

- **To identify serum metabolomic signatures associated with risk of diabetes in US Hispanics/Latinos.**
- **To examine the associations between diabetes-associated metabolites and diet/lifestyle factors in US Hispanics/Latinos.**

Study Design

Baseline clinic visit
(2008-2011)
N= 16,415

Metabolomics on V1 serums
(Random selection)
N=3,972

1171 participants excluded
- Died (~5%)
- Ineligible (~5%)
- Did not attend V2 (<20%)

~ 6 years of follow-up

Second clinic visit
(2014-2017)
N=2801

791 participants excluded
- Baseline diabetes (ADA)
- Baseline CVD
- Baseline Cancer

Participants included
N=2010
(224 incident diabetes cases)

- **Sample size:** 224 incident diabetes cases, 1786 non cases
- **Outcome variables:** incident diabetes at SOL visit 2
  - **American Diabetes Association definition**
    - Fasting time > 8hr and Fasting glucose ≥ 126 mg/dL
    - Fasting time ≤ 8hr and Fasting glucose ≥ 200 mg/dL
    - 2h post OGTT ≥ 200 mg/dL
    - Hemoglobin (A1C) ≥ 6.5%
  - Self-report medication use
- **Exposure variables:** 624 known metabolites
- **Statistical model:** Survey Poisson regression
- **Covariates:** age, gender, household income, education, current smoking, alcohol use, field center, family history of diabetes, Hispanic background, general health variables, medication use, alternative healthy eating index 2010 (AHEI-2010), and total physical activity, BMI, waist and hip ratio, HDL, total cholesterol, systolic blood pressure, diastolic blood pressure.

Results

Table 1. Basic characteristics

	Non-diabetes (N=1,786)	Incident diabetes (N=224)
Age, years	45 (34-53)	50 (46-56)
Female	60 %	62 %
Current smoking	20 %	17 %
Current alcohol use	53 %	47 %
Education > high school	41 %	38 %
Income <$30,000	60 %	71 %
Lipid-lowering medicine use	5 %	10 %
Antihypertensive medicine use	9 %	17 %
Family history of diabetes	40 %	53 %
Body mass index, kg/m²	28 (25-32)	31 (28-35)
High density lipoprotein, mg/dL	49 (42-58)	45 (39-52)
Triglycerides, mg/dL	106 (75-153)	142 (101-200)
Systolic blood pressure, mmHg	117 (108-128)	124 (112-134)
Diastolic blood pressure, mmHg	72 (65-79)	77 (70-83)

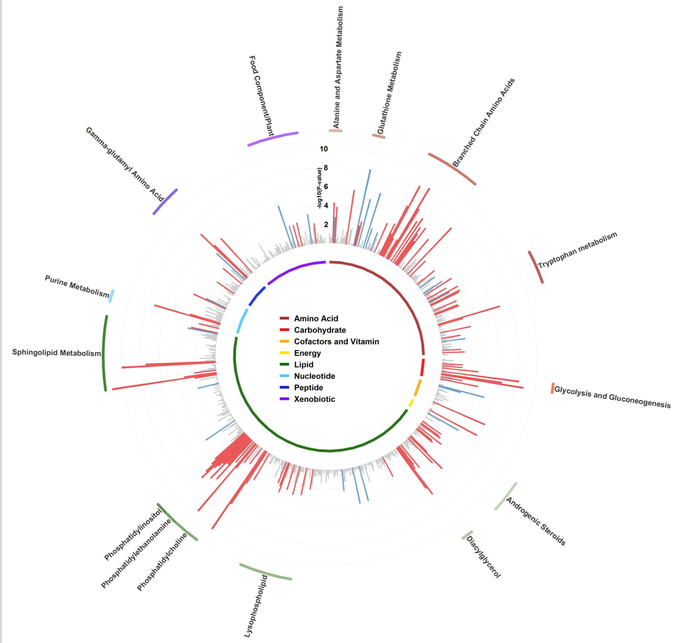

Figure 1. Overall metabolites polar bar plot and metabolites proportion.

Associations between 624 metabolites and incident diabetes (A) . Data were presented according to supper- and sub-pathways of metabolites. The inner-circle indicated the super-pathways of metabolites included in the analyses. The middle bar plot represents –log10 P-value of individual metabolites associated with incident diabetes, and 134 significant metabolites are highlighted in red (positive associations) or in blue (inverse association). Metabolites with FDR-adjusted P values ≥0.05 were shown in gray. The outer circle indicates 15 sub-pathways which have ≥5 significant metabolites, or in which the proportion of significant metabolites ≥50%.

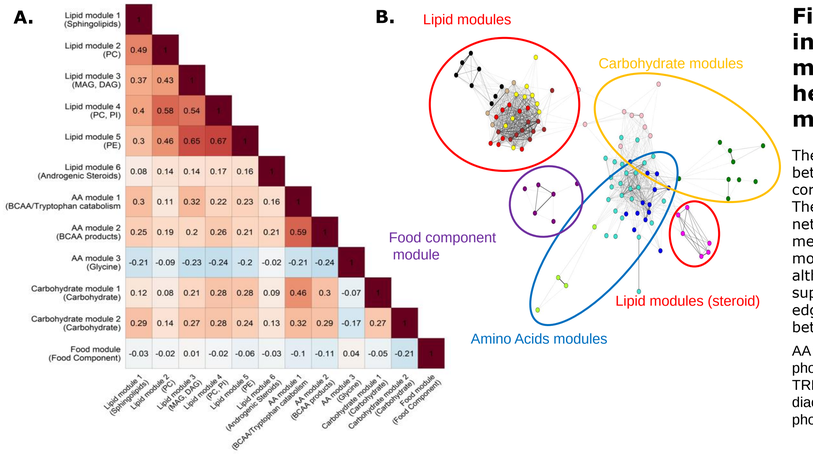

Figure 2. Network of 134 incident diabetes associated metabolites and Correlation heatmap among sub-network modules.

The correlation heatmap showed partial correlation between 12 network sub-modules. Color indicated correlation coefficient between two modules (A). The network represents the overall correlation network among 134 incident diabetes associated metabolites (B). The colors indicate 12 sub-network modules detected by topological overlap measures, although many of the metabolites within the same super-pathway belong to the same module. The edges indicate a weighted correlation coefficient between each metabolite.

AA indicated amino acids; Carb, carbohydrates; PC, phosphatidylcholine; BCAA, branched-chain amino acid; TRP, tryptophan; MAG, monoacylglycerol; DAG, diacylglycerol; PI, phosphatidylinositol; PE, phosphatidylethanolamine.

Table 2. Poisson regression model on incident diabetes related network sub modules.

Metabolites modules	Sub-pathways	No. Of metabolites	Top metabolites	Model 1		Model 2	
				Risk ratio (95% CI)	P-value	Risk ratio (95% CI)	P-value
Lipid module 1	Sphingolipids	8	behenoyl dihydrosphingomyelin (d18:0/22:0)	1.70 (1.42-2.02)	<0.001	1.41 (1.18-1.67)	<0.001
Lipid module 2	PC, PI (20:4)	4	1-stearoyl-2-arachidonoyl-GPI (18:0/20:4)	1.46 (1.19-1.79)	<0.001	1.30 (1.07-1.57)	0.013
Lipid module 3	MAG, DAG	9	1-palmitoleoylglycerol (16:1)	1.56 (1.33-1.82)	<0.001	1.31 (0.87-1.96)	0.198
Lipid module 4	PC, PI	10	1-palmitoyl-2-palmitoleoyl-GPC (16:0/16:1)	1.63 (1.36-1.95)	<0.001	1.40 (1.12-1.74)	0.005
Lipid module 5	PE	10	1-palmitoyl-2-oleoyl-GPE (16:0/18:1)	1.52 (1.27-1.83)	<0.001	1.21 (0.95-1.54)	0.125
Lipid module 6	Androgenic Steroids	6	androstenediol (3beta,17beta) disulfate (1)	1.47 (1.19-1.82)	<0.001	1.30 (1.04-1.62)	0.026
AA module 1	BCAA/TRP catabolism	25	urate	2.03 (1.65-2.50)	<0.001	1.57 (1.26-1.95)	<0.001
AA module 2	BCAA products	13	2-hydroxy-3-methylvalerate	2.04 (1.60-2.58)	<0.001	1.68 (1.29-2.18)	<0.001
AA module 3	Glycine	4	glycine	0.61 (0.51-0.74)	<0.001	0.75 (0.61-0.93)	0.013
Carb Module 1	Hydrocarbon derivative	9	ribitol	1.61 (1.35-1.91)	<0.001	1.33 (1.11-1.60)	0.005
Carb Module 2	Energy related	9	pyruvate	1.93 (1.65-2.24)	<0.001	1.59 (1.35-1.89)	<0.001
Food Module	Food Component	6	oxalate (ethanedioate)	0.66 (0.56-0.77)	<0.001	0.70 (0.59-0.83)	<0.001

Risk ratios (RR) and 95% confidence intervals (CI) of incident diabetes per SD increment of module score, adjusted for age, gender, current smoking, alcohol use, education, income, fasting hour, lipid lowering medication use, antihypertensive medication use, family history of diabetes, Hispanic background, study field center, total physical activity, and AHEI-2010 (Model 1); and further adjusted for BMI, waist to hip ratio, HDL-cholesterol, triglycerides, systolic blood pressure, and diastolic blood pressure (Model 2). BCAA, branched-chain amino acid; DAG, Diacylglycerol; MAG, Monoacylglycerol; PC indicates Phosphatidylcholine; PE, Phosphatidylethanolamine; PI, Phosphatidylinositol; TRP, tryptophan.

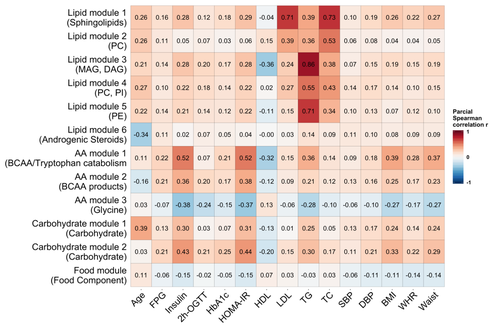

Figure 3. Correlation between 12 modules and diabetes risk factors.

Results were partial Pearson correlation heatmap with adjustment for age, gender and Hispanic background. The y-axis indicated risk factors of diabetes and x-axis indicated metabolomic sub-modules.

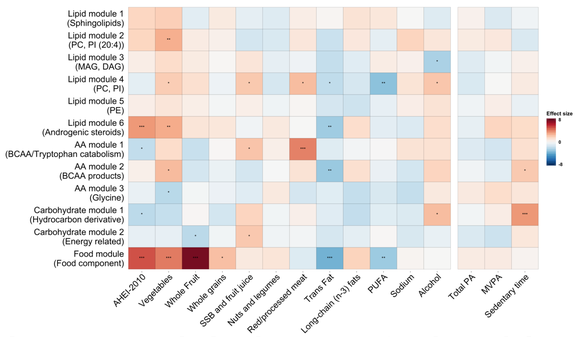

Figure 4. Association between 12 sub-modules and dietary/lifestyle factors.

Results were survey linear regression with adjustment for age, gender, current smoking, alcohol use, education, income, fasting hour, lipid lowering medication use, antihypertensive medication use, family history of diabetes, Hispanic background, study field center, total physical activity, and AHEI-2010. Color indicated effect size.
* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

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Conclusions

- **In a six-year follow-up study, we identified multiple metabolites associated with risk of diabetes in a large cohort of US Hispanics/Latinos.**
- **A large number of metabolites are involved in known metabolic pathways (e.g., BCAA, ceramides, glucose metabolism) which have been associated with insulin resistance and diabetes.**
- **Six metabolites in a food component module were associated with lower risk of diabetes and healthier diet.**
- **Six metabolites in an androgenic steroid module were associated higher risk of diabetes.**

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