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### Title

1581-P: Circulating Metabolites Are Associated with Glycemic Measures in South Asians

### Permalink

<https://escholarship.org/uc/item/25w2p6jk>

### Journal

Diabetes, 69(Supplement\_1)

### ISSN

0012-1797

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### Publication Date

2020-06-01

### DOI

10.2337/db20-1581-p

Peer reviewed

## **Circulating metabolites are associated with glycemic measures in South Asians**

South Asians are at higher risk for diabetes (DM) than many other racial/ethnic groups. Circulating metabolites are measurable products of metabolic processes that may explain the etiology of elevated risk. We characterized metabolites associated with prevalent DM and incident glycemic measures in South Asians.

We included 717 participants in the Mediators of Atherosclerosis in South Asians Living in America (MASALA) study, aged 40-84 years. We used baseline fasting serum for metabolomics and demographic, behavioral, glycemic data from baseline and at 5 years. We performed LC-MS untargeted metabolomic and lipidomic analysis with targeted integration of known signals. Individual linear and ordinal logistic regression models were adjusted for age, sex, BMI, diet, exercise, alcohol, smoking and family history of DM followed by elastic net regression to identify metabolites most contributory to the outcome.

There were 258 metabolites with detectable signal in >98% of samples. Fifty-nine metabolites were associated with prevalent DM, 32 with fasting glucose and 45 with HbA1c at follow-up [FDR < 0.05]. An elastic net model identified a subset of important metabolites (Table 1). Predominant metabolites associated with glycemic measures in South Asians were sphingomyelins, tri- and di-acylglycerols and carnitines. Future work will externally validate our findings and determine the effects of modifiable risk factors for DM.

Table 1: Association of circulating metabolites with glycemic outcomes in order of coefficient contribution from elastic net model regression			
Prevalent DM at baseline Alpha 0.75 R <sup>2</sup> = 0.21		Incident Fasting glucose Alpha 0.05 R <sup>2</sup> = 0.17	Incident HbA1c Alpha 0.05 R <sup>2</sup> = 0.18
TG(48:1)	TG(54:1)	SM(d18:2/24:1)	SM(d18:1/16:0)
DG(36:2) and DG(18:1/18:1) and DG(18:0/18:2)		LPC(20:0/0:0)	SM(d18:2/14:0)
	Proline	SM(d18:1/16:0)	SM(d18:2/24:1)
TG(52:3)	LPC(20:1/0:0)	LPC(19:0/0:0)	N-acetyl-d-mannosamine
DG(34:2)	SM(d17:1/16:0)	SM(d18:2/14:0)	PC(18:0/18:0)
SM(d18:2/24:0)	CE(18:1)	CER(d18:1/18:0)	laCER(d18:1/16:0)
SM(d18:1/16:0)	CER(d18:1/18:0)	LPC(22:0/0:0)	LPI(20:4/0:0)
SM(d18:2/24:1)	hexCER(d18:1/2 0:0)	DG(18:0/16:0)	Carnitine
DG(18:0/18:1)	PC(18:0/18:0)	SM(d19:1/16:0)	CAR(20:4)
SM(d18:2/22:0)	TG(44:0)	TG(52:1)	PE(16:0/18:2)
PE(18:0/20:4)	FA(16:0)	CAR(26:1)	Bilirubin
hexCER(d18:1/22:0)	CE(18:2)	laCER(d18:1/16:0)	TG(54:6)_2
PE(16:0/20:4)	TG(54:6)_2	SM(d17:1/24:1)	Glutamine
DG(32:1)	PE(16:0/18:2)	PC(18:1/20:3)	LPC(22:0/0:0)
hexCER(d18:1/24:0)	PC(16:0/20:4)_2	hexCER(d18:1/20: 0)	hexCER(d18:1/22:0)
DG(16:0/16:0)	CER(d16:1/20:0)	Cholesterol	LPC(20:1/0:0)
		TG(54:1)	CER(d18:1/18:0)
PE(36:1) and PE(18:0/18:1) and PE(18:1/18:0)	FA(24:4)	SM(d17:1/16:0)	FA(22:4)
DM(d18:2/23:0)	LPC(20:0/0:0)	SM(d18:2/24:0)	Asymmetricdimethylarginine
DG(18:2/18:1)		hexCER(d18:1/22: 0)	PE(36:1) and PE(18:0/18:1) and PE(18:1/18:0)
SM(d19:1/16:0)		PCO(16:0/18:2)	FA(20:3)
SM(d18:1/20:1)		SM(d18:2/22:0)	PCO(16:0/16:0)
SM(d18:1/24:1)		SM(d18:1/24:1)	PE(16:0/20:4)
SM(d18:0/16:0)		PE(16:0/20:4)	CAR(26:1)
SM(d17:1/24:1)		TG(54:6)_2)	LPE(22:4/0:0)
PCO(16:0/18:2)		CER(d16:1/20:0)	CER(d16:1/20:0)
DG(16:0/18:1)		DG(18:0/18:1)	DG(18:0/16:0)
LPE(22:4/0:0)		PE(18:0/20:4)	PCO(16:0/18:2)
Cholesterol		SM(d18:2/16:0)	TG(54:2)
LPI(20:4/0:0)		PC(18:2/18:2)	
laCER(d18:1/16:0)		CE(18:2)	
Betaine			
PC(18:0/18:2)			

TG(52:1)

LPE(20:4/0:0)

FA(22:4)

