

# Triacylglyceride Fatty Acid (TAGFA) Composition Longitudinally Associates with Changes in Insulin Sensitivity (IS) and Beta-Cell Function Over 6-yr in the Prospective Metabolism and Islet Cell Evaluation (PROMISE) Cohort

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## Background:

- Hypertriglyceridemia is a known risk factor for type 2 diabetes; however, the role of the specific fatty acid (FA) composition of the triacylglyceride (TAG) serum fraction on the pathogenesis of diabetes has not been well studied.
- Specific fatty acids are known to have harmful or protective associations with diabetes (1), depending on carbon chain length and unsaturation. For instance, palmitic acid has been extensively reported to have negative effects on insulin signaling and production of insulin by the beta-cells (2,3).
- Limited longitudinal studies have examined the role of TAGFA composition on the progression of the underlying metabolic disorders of diabetes.
- Our **objective** was to investigate the contribution of individual TAGFA on declines in insulin sensitivity (IS) and beta-cell function over 6 years in individuals at risk for diabetes.

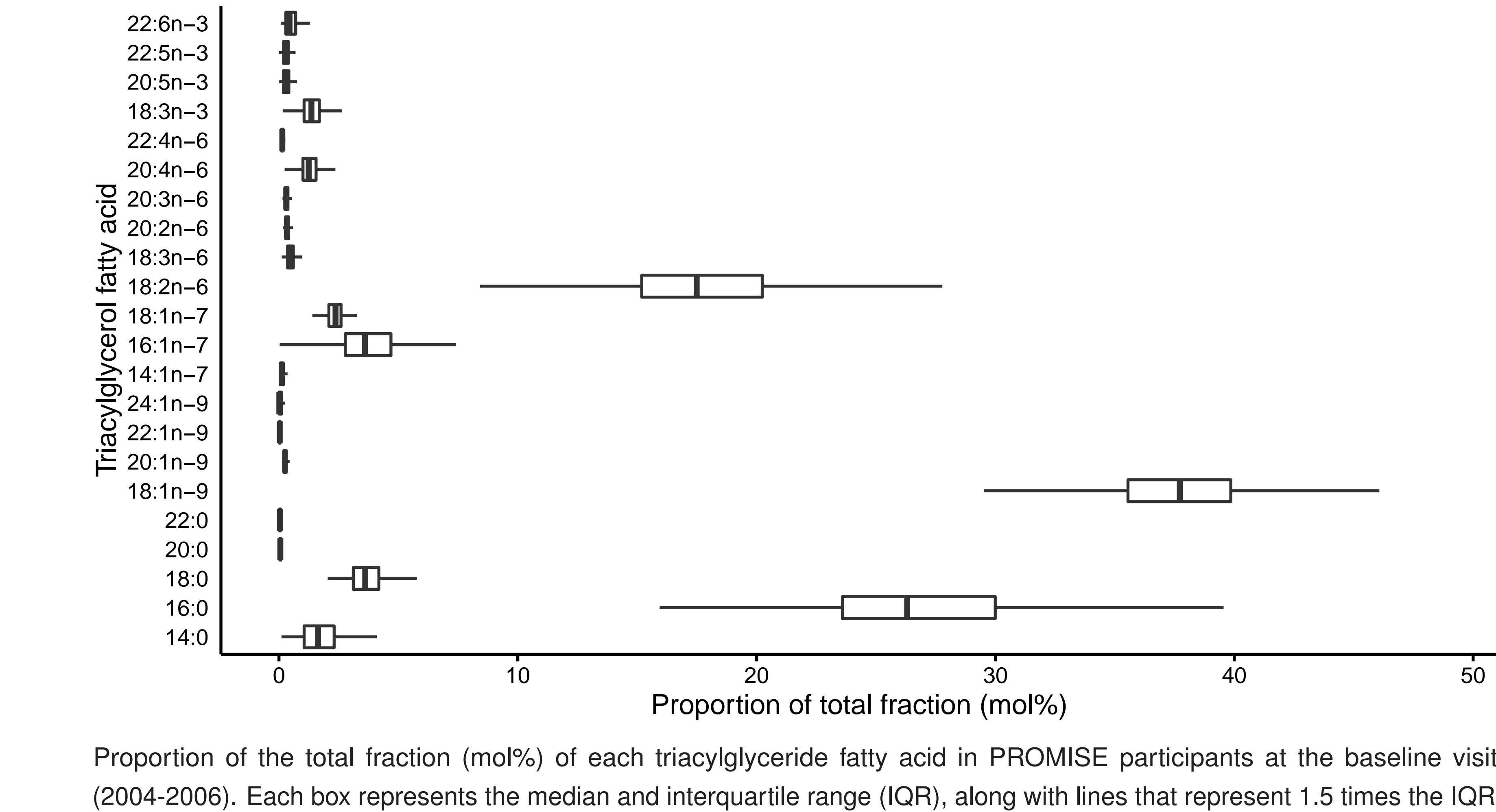
## Methods:

- Adults (n=736) at-risk for diabetes were recruited from Toronto and London, ON and followed every 3-yrs.
- Participants completed an OGTT at each visit with 3 blood samples (0, 30, 120 min), used to measure glucose and insulin, in addition to standard clinical measures.
- Fasting TAGFA were quantified as mol% (proportion of total) using thin layer chromatography and gas liquid chromatography coupled to flame ionization detector using samples from the baseline visit in **477** participants who attended at least one follow-up visit.
- From glucose and insulin values, the following were computed: for IS, 1/HOMA-IR (4) and ISI (Matsuda Index) (5); for beta-cell function: Insulinogenic index (6) over HOMA-IR (IGI/IR) and Insulin Secretion-Sensitivity Index-2 (ISSI-2) (7).
- To analyze the longitudinal data, we used generalized estimating equation (GEE) modeling adjusting for waist circumference, sex, ethnicity, baseline age, and total non-esterified fatty acids. To analyze the multivariate nature of the TAGFA composition on the outcomes, we used partial least squares analysis (PLS), with 1/HOMA-IR and ISI as the response and TAGFA (mol%) as the predictors.

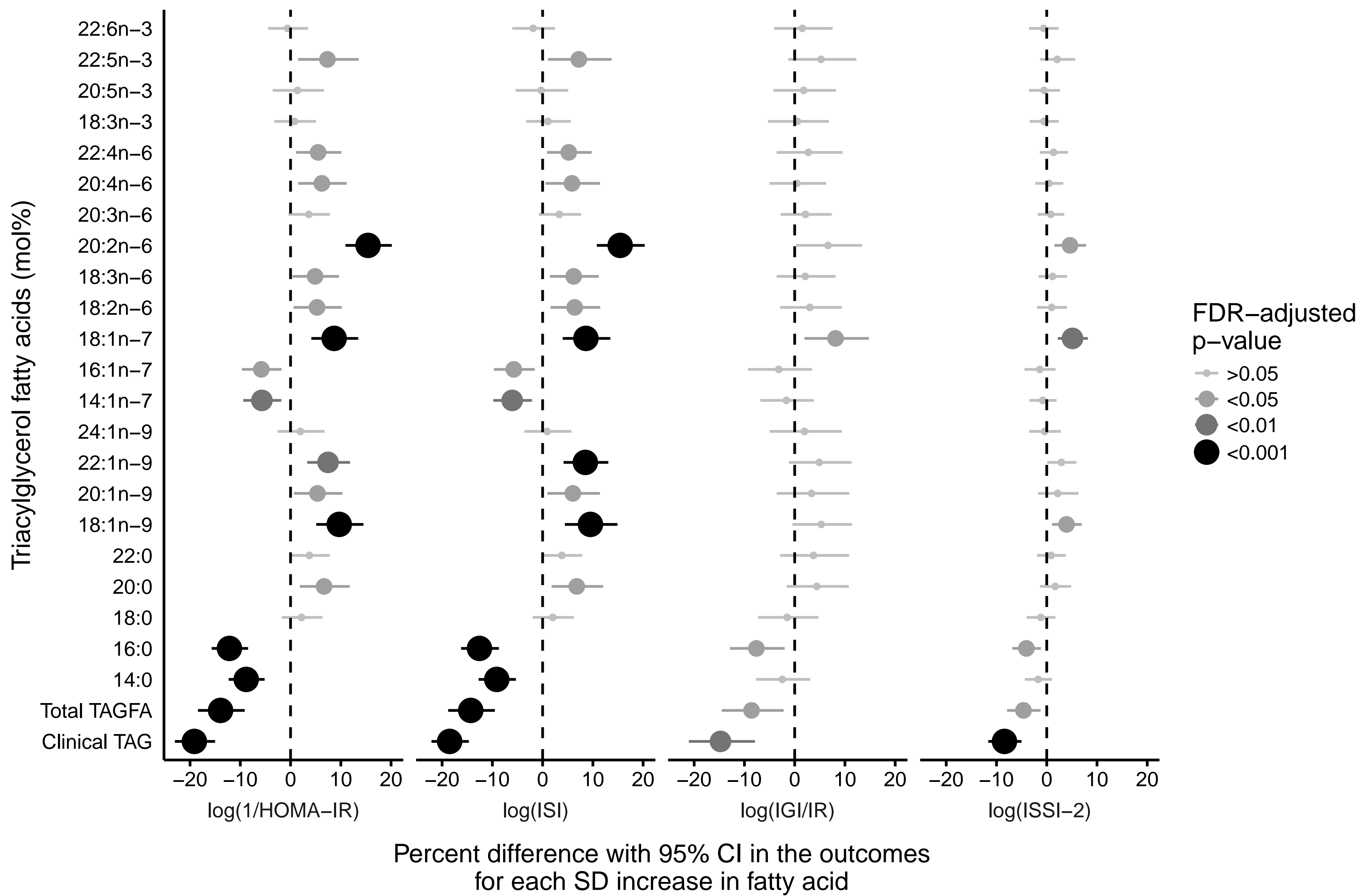
## Results: Basic characteristics over 6 years

Basic characteristics of the PROMISE participants at each of the 3 clinic visits. Values are in mean (SD), median (interquartile range), or n (%).			
Measure	Baseline	3-yr	6-yr
HOMA-IR	13.1 (8.5-22.1)	16.3 (10-27.1)	16.6 (10.9-26.1)
ISI	13.6 (8.7-21.8)	11.6 (6.9-19.1)	11.6 (7.5-17.5)
IGI/IR	7.1 (4.2-10.6)	5.6 (3.6-9.8)	5.6 (3.5-9)
ISSI-2	727.5 (570-922.5)	613.4 (493.9-836.7)	622.5 (472.5-810.3)
WC (cm)	98.5 (15.5)	99.3 (15.7)	100.4 (15.7)
Age (yrs)	50.2 (9.8)	53.2 (9.7)	56.3 (9.5)
HDL (mmol/L)	1.4 (0.4)	1.3 (0.4)	1.4 (0.4)
LDL (mmol/L)	3.1 (0.8)	3.2 (0.9)	3.1 (0.8)
Clinical TAG (mmol/L)	1.5 (0.8)	1.4 (0.8)	1.4 (0.7)
Total NEFA (nmol/mL)	383.4 (116.4)		
Total TAG (nmol/mL)	3136.9 (1684.8)		
Ethnicity			
- European	337 (71%)		
- Latino/a	58 (12%)		
- Other	51 (11%)		
- South Asian	32 (7%)		
Sex			
- Female	349 (73%)		
- Male	129 (27%)		

## Results: Distribution of individual TAGFA

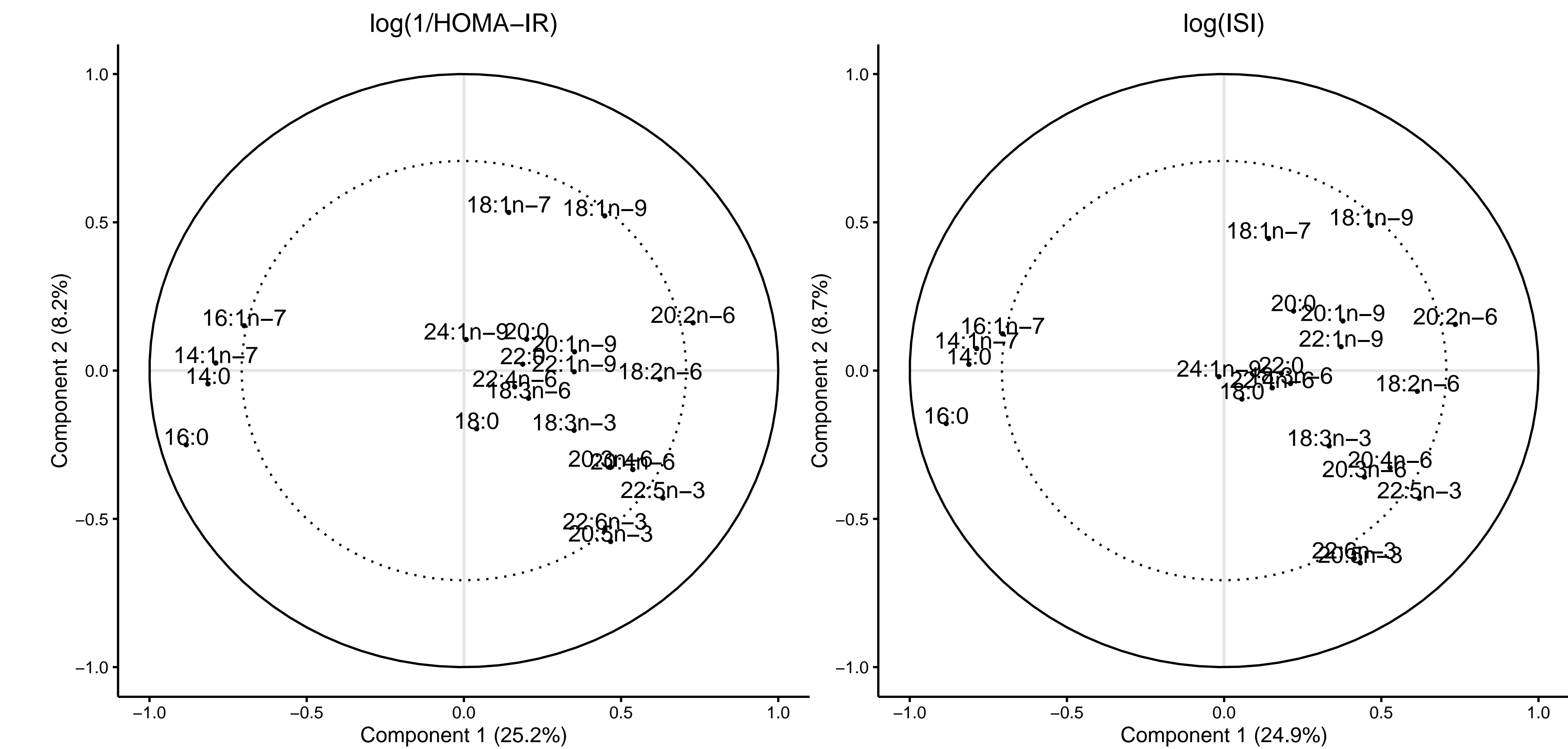


## Results: GEE modeling of TAGFA with IS and beta-cell function



Longitudinal associations of individual triacylglyceride fatty acids (mol%) with insulin sensitivity and beta-cell function using generalized estimating equations (GEE) over the 6 years in the PROMISE cohort. GEE modeling was used as it takes into account the longitudinal nature of the data. Adjustments were made for time, sex, ethnicity, baseline age, waist circumference, and total non-esterified fatty acids. Outcome variables were log-transformed, predictor variables were scaled, and x-axis values were exponentiated to represent a percent difference per SD increase in the fatty acid. P-values were adjusted for the BH false discovery rate (FDR), which is represented as the dot size and darker color.

## Results: Partial Least Squares



## Conclusions:

- Specific fatty acids modeled as a mol% had either negative (14:0, 16:0, 14:1n-7, 16:1n-7) or positive (many other fatty acids) associations with IS over the 6 years.
- Cluster analysis extended the GEE results by emphasizing that 14:0, 16:0, 14:1n-7, and 16:1n-7 cluster together and contribute substantially to the explained variance in IS. All other fatty acids contributed marginally, though positively, to IS. In particular 20:2n-6, 22:5n-3, 20:5n-3 (EPA), and 22:6n-3 (DHA) contributed substantially to the positive explained variance in IS.
- Our findings for specific fatty acids such as palmitic acid confirm previous work, however, findings for fatty acids such as 20:2n-6 or 22:1n-9 are novel. These fatty acids are not well studied, and the mechanism underlying their beneficial association requires further research.

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