Serum Phospholipid (PL) Fatty Acid Composition Predicts Declines in Insulin Sensitivity (IS) and Beta-Cell Function Over 6-years in the Prospective Metabolism and Islet Cell Evaluation (PROMISE) Cohort

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Disclosures

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Fatty acids as risk factor for diabetes and it's pathogenesis

[1] Giacca et al. (2011); Xiao, Giacca, and Lewis (2009)

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- Fatty acids either gotten from diet or *de novo*
- Harm or benefit to metabolism depending on chain length and unsaturation
- Example: higher palmitic acid (16:0) experimentally shown to be lipotoxic to beta-cells *in vivo* and *in vitro*[1]

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[2] Yang, Kang, and Guan (2013); Newsholme et al. (2007); Giacca et al. (2011); Gehrmann, Elsner, and Lenzen (2010); Ebbert and Jensen (2013)

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Potential mechanisms from fatty acid composition[2]

- Fluidity of cell membrane (lipid bilayer)
- Inflammation (eg. via eicosanoids)
- Lipotoxicity (by-product accumulation)

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Key findings from large cohorts on phospholipid (PL) fatty acid composition and incident diabetes:

- CHS (USA)[3]:
  - 16:0 and 18:0 higher risk for DM
  - 18:1n-7 lower risk for DM
  - 18:3n-3 slight lower risk for DM
- EPIC (Europe)[4]:
  - 16:0 higher risk for DM
  - 18:3n-6 higher risk for DM
- ARIC (USA)[5]:
  - 18:1n-9 slight lower risk for DM
  - 18:0 slight higher risk for DM

[3] Ma et al. (2015); Djoussé et al. (2011)
[4] Forouhi et al. (2014); Kröger et al. (2011)
[5] L. Wang et al. (2003)

Limitations: Few longitudinal designs or beta-cell function measures

- Few longitudinal studies
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Objective

To determine whether individual PL fatty acids associate longitudinally with insulin sensitivity (IS) and beta-cell function over a 6 year period.

Methods: Prospective Metabolism and Islet cell Evaluation (PROMISE) Cohort

Longitudinal observational cohort

- At-risk for diabetes:
  - Central obesity
  - Hypertension
  - Family history
- London and Toronto, Canada
- Visits every 3-yrs; 6-yrs of follow-up (3 time points)
- Follow-up rate of 79.6% over 6-yrs
- OGTT (3 samples) at each visit
- 22 PL fatty acids at baseline visit (**n=477**)

Variables of interest

Outcomes

Outcome	Measure	Marker of:
Insulin sensitivity[6]	HOMA-IS[7]	Hepatic IS
	ISI	Whole body IS
Beta-cell function[8]	IGI/IR	1st phase response
	ISSI-2	Disposition index

[6] Matthews, Hosker, and Rudenski (1985); Matsuda and DeFronzo (1999)
[7] Inverted HOMA-IR
[8] N. Wareham et al. (1995); Retnakaran et al. (2009)

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Over the 6-yrs, median declines of **8.7% to 19.5%**.

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Predictors

22 phospholipid (PL) fatty acids quantified using thin-layer chromatography and gas chromatography, using an internal standard.

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Statistical analysis techniques

Generalized estimating equations (GEE)

- Robust longitudinal technique
- Fatty acids: *Time-independent* (only at baseline)
- Outcomes: *Time-dependent*
- P-values adjusted using False Discovery Rate (multiple testing)

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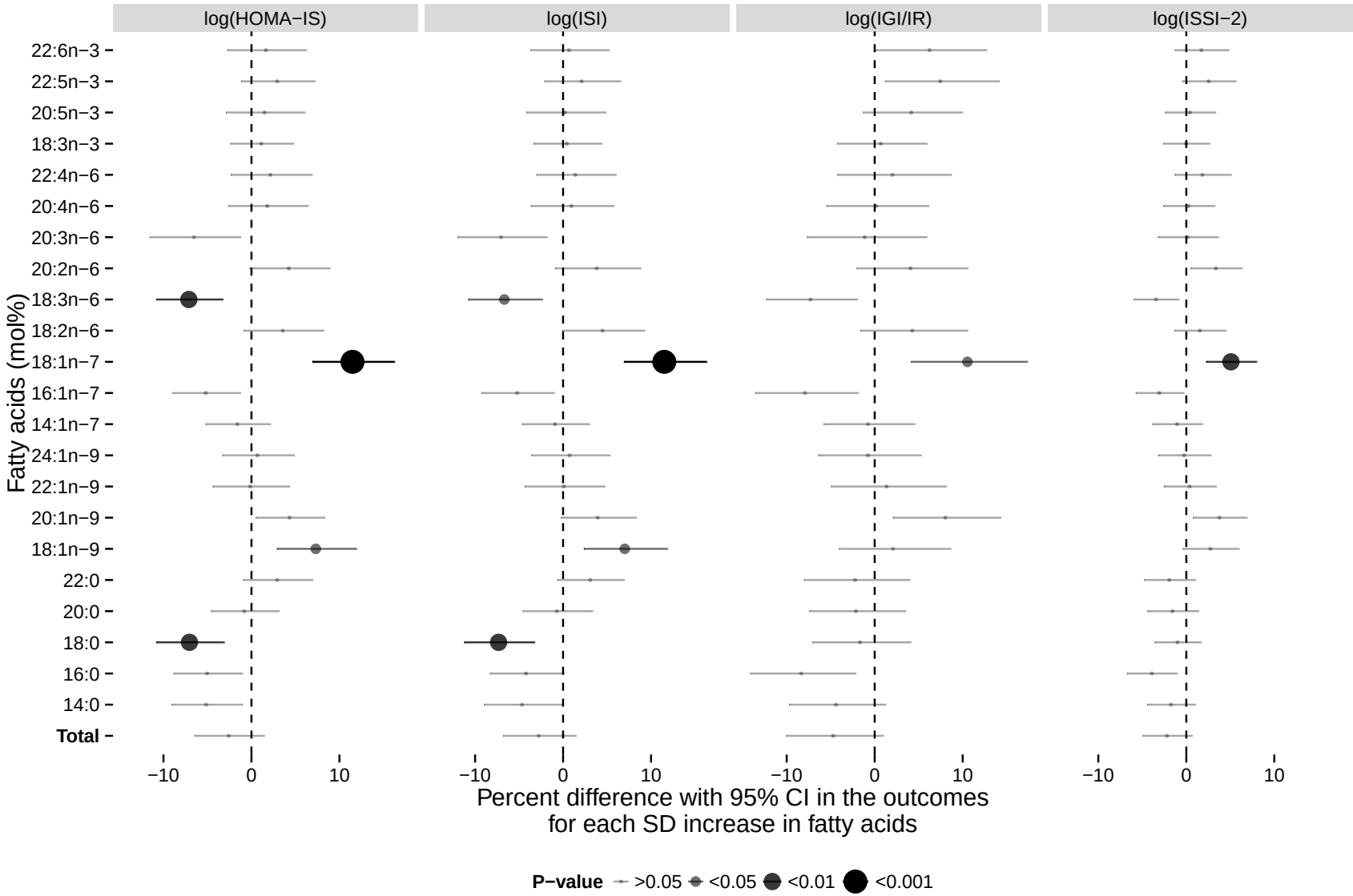
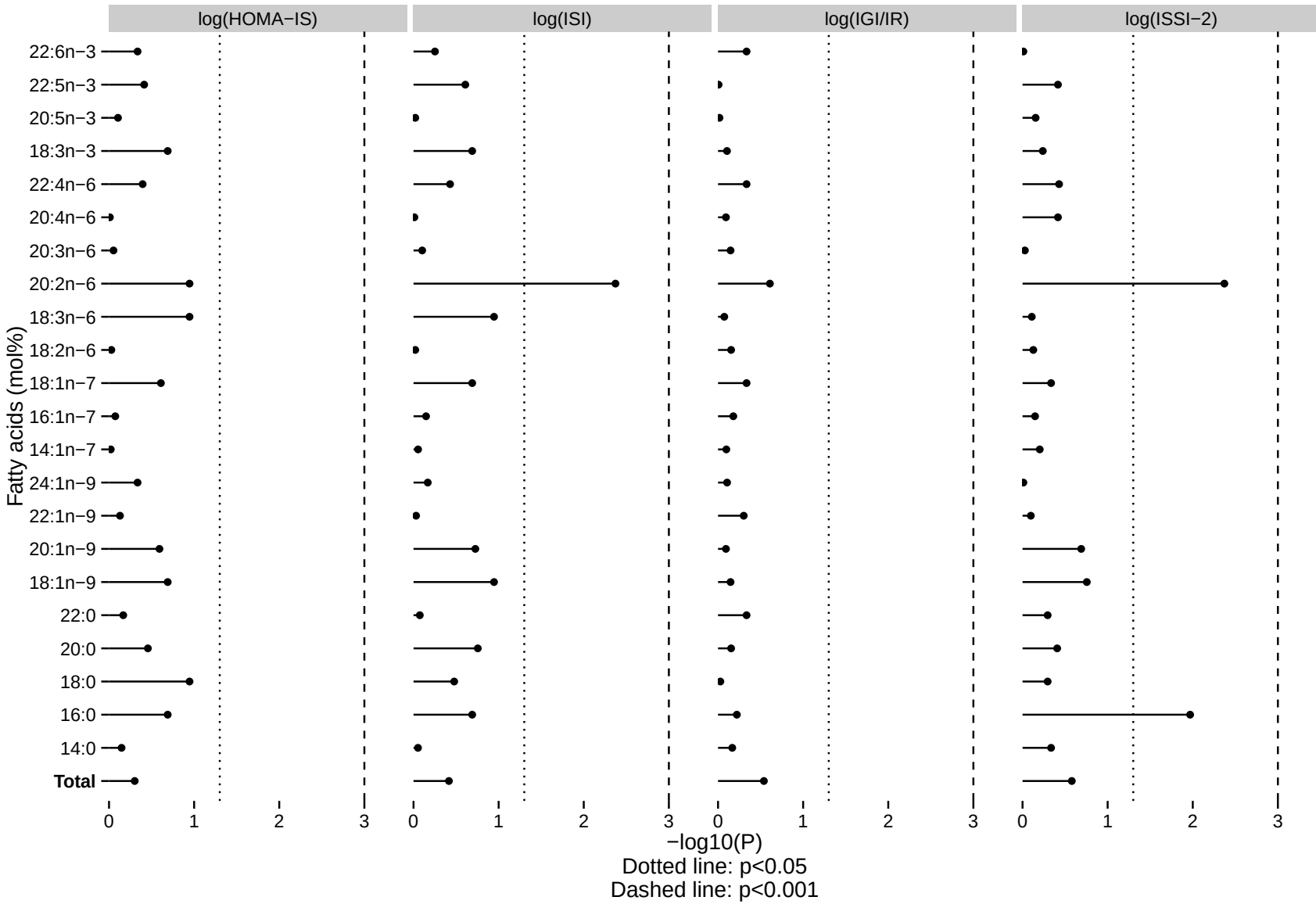
Covariate selection

- Literature + causal directed acyclic graphs + information criteria:
  - Final model: Visit number, sex, ethnicity, baseline age, waist circumference, total free fatty acids, ALT, family history of diabetes

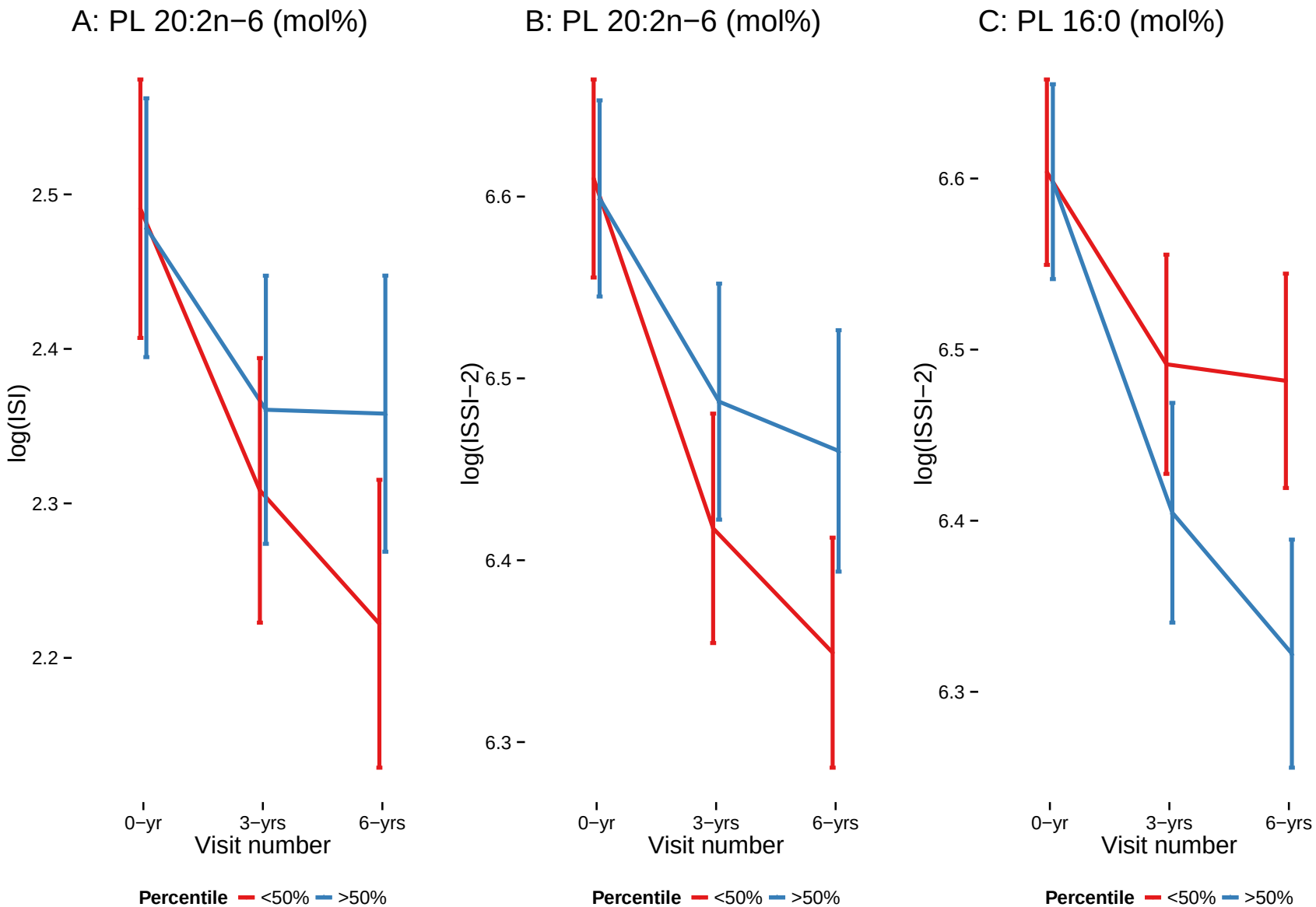
Adjusted GEE results: Several PL fatty acids (mol%) associate with IS and beta-cell function



PL 16:0 and 20:2n-6 (mol%) have significant interactions



Lower PL 20:2n-6 and higher 16:0 associate with steeper declines in beta-cell function



Previous literature is fairly consistent with PL results[9]

- 16:0, 18:0 have consistent harmful associations
- 18:1n-9, 18:1n-7 have consistent positive associations
- Inconsistent for 20:2n-6
- *However, no previous report has been on longitudinal outcomes nor interactions over time*

[9] Forouhi et al. (2014); Kröger et al. (2011); Ma et al. (2015); Mahendran et al. (2014); L. Wang et al. (2003)

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