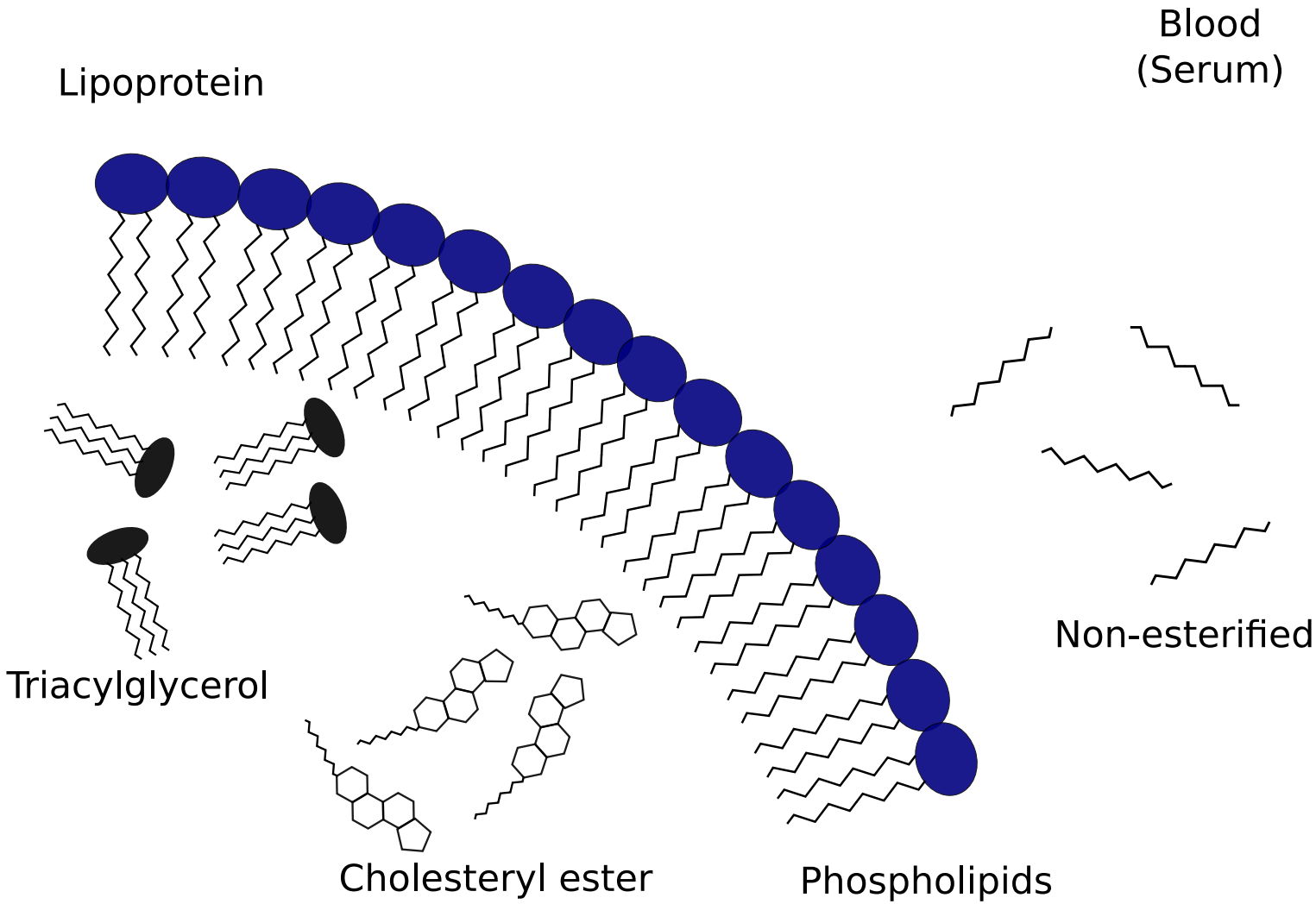
Fatty acid composition in four serum lipid fractions and the pathogenesis of diabetes

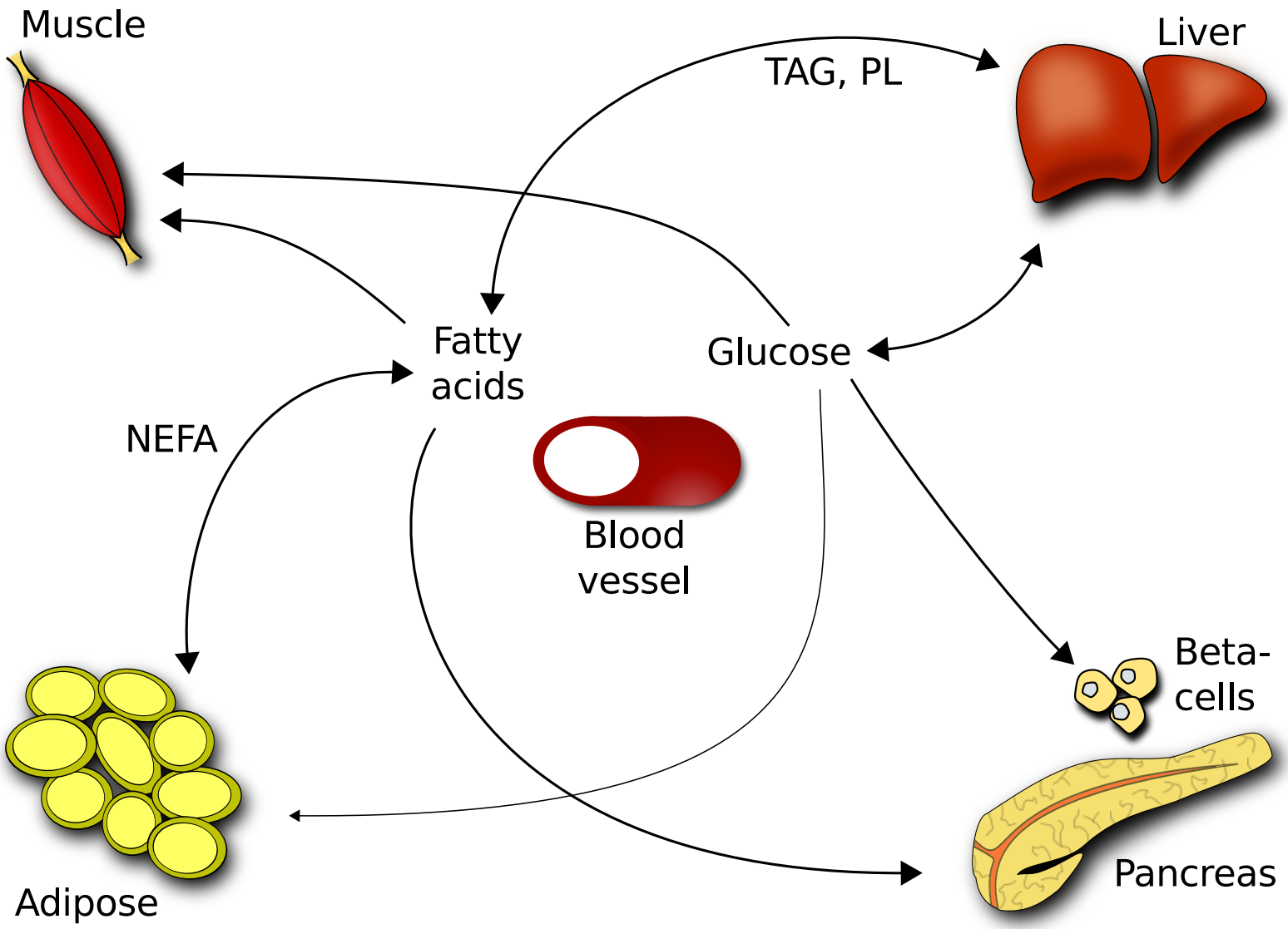
Luke Johnston

Grand Finale (4th)
Oct. 27th, 2016

Physiology of serum lipid fractions



Glucose and fatty acid metabolism



Various fatty acid length and desaturation

- Range in length and number of double bonds
- Fatty acids either from diet or *de novo* lipogenesis (DNL)
- Physiological role dependent on molecule
- Eg: higher palmitic acid (16:0) lipotoxic to beta-cells *in vivo* and *in vitro*[1]

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

Few large cohorts on fatty acid composition, fraction, and diabetes

- One study (METSIM) had three fractions: TAG, PL, CE[2]
  - Multiple flaws
- Mainly cohorts report on PL and CE: CHS, EPIC, ARIC[3]
  - 16:0 and 18:0 higher risk for DM
  - 18:1n-7, 18:1n-9, 18:3n-3 lower risk for DM

[2] Lankinen et al. (2015)

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

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- CE: *No strong associates with diabetes pathogenesis*
- TAG: ...

Data source: The PROMISE cohort

PROspective Metabolism and ISlet cell Evaluation cohort.

- Recruited from London and Toronto centers
- At-risk for diabetes
- Followed every ~3 years (3 time points completed)
- Demographics, lifestyle, anthropometrics, and blood
- n=**477** participants with fatty acids measured

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Metabolic outcomes

Calculated from OGTT:

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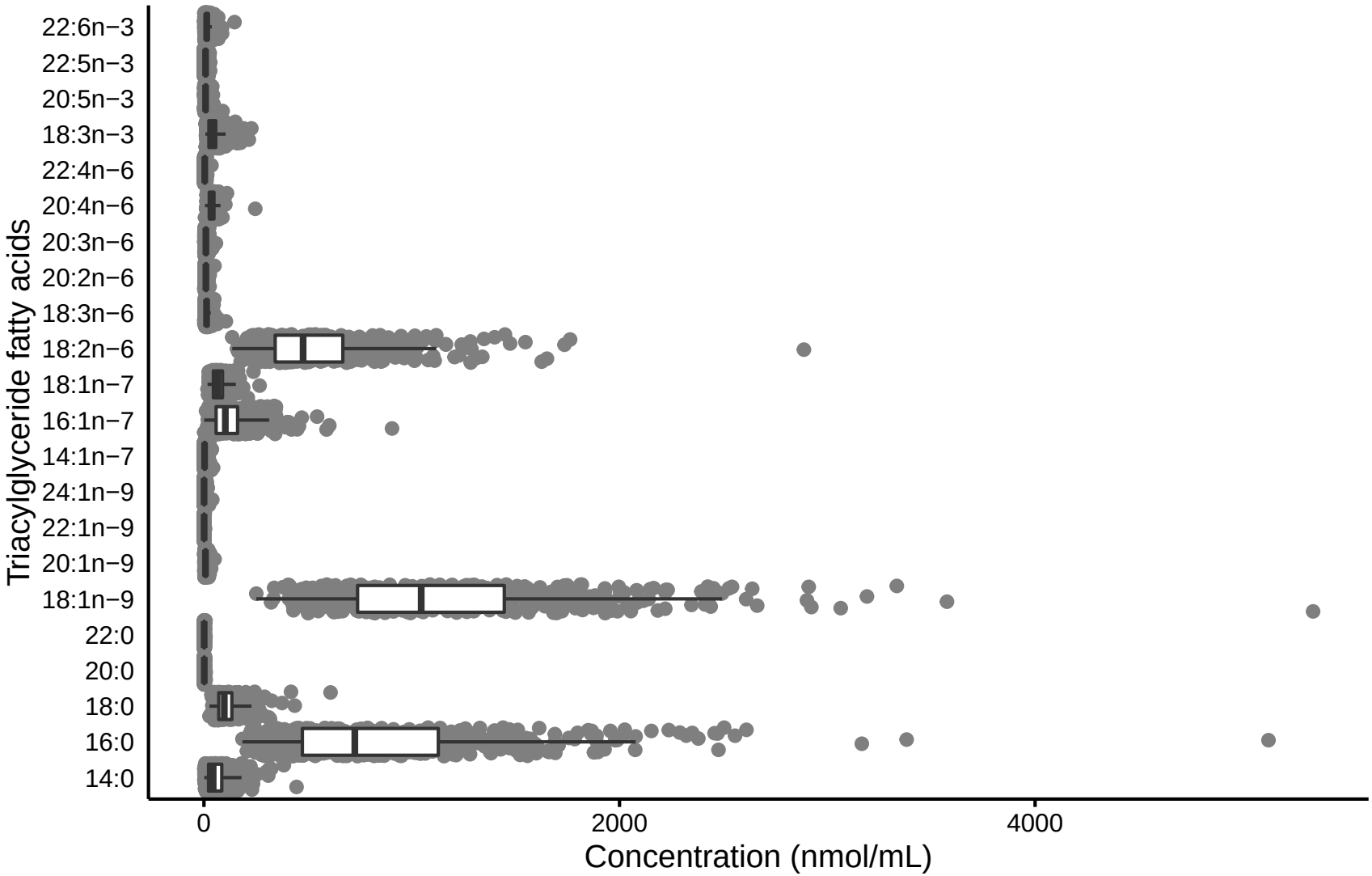
TAG fatty acids

Thin layer chromatography to split the lipid fractions, gas chromatography for the fatty acids:

- 22 TAG fatty acids, as concentration (nmol/mL) and percent of total (mol%)

TAG fatty acid composition within PROMISE



Statistical analysis

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R code for these results:

`https://github.com/lwjohnst86/seminar2016`

Statistical analysis: Generalized estimating equations (GEE)

Variables GEE model:

> *Visit number, waist size, baseline age, ethnicity, sex, ALT (marker of liver fat), physical activity (MET), and total NEFA.*

Time-*independent*: TAG, NEFA, baseline age, ethnicity, sex

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- Adjust using BH False Discovery Rate (FDR) correction

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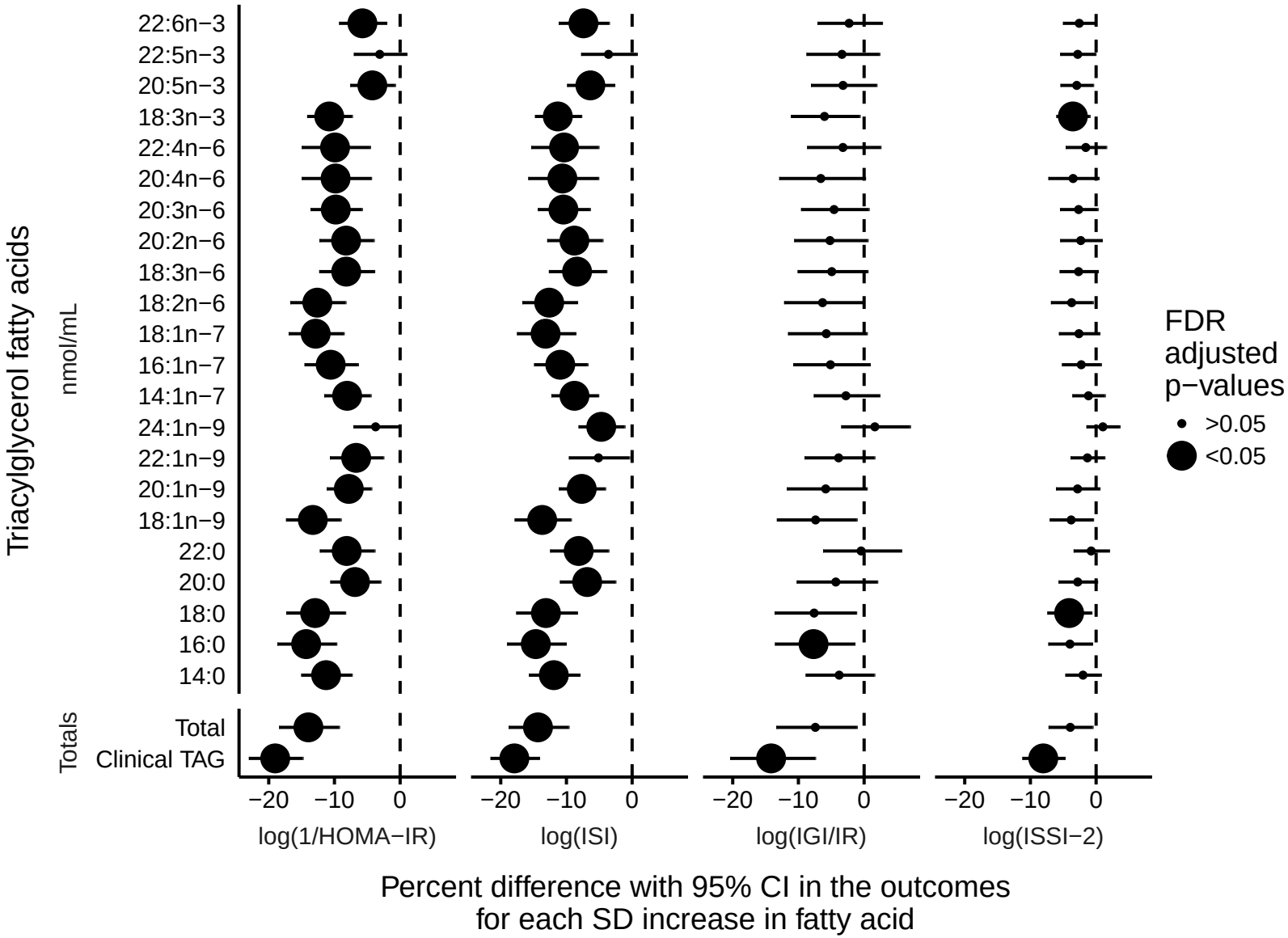
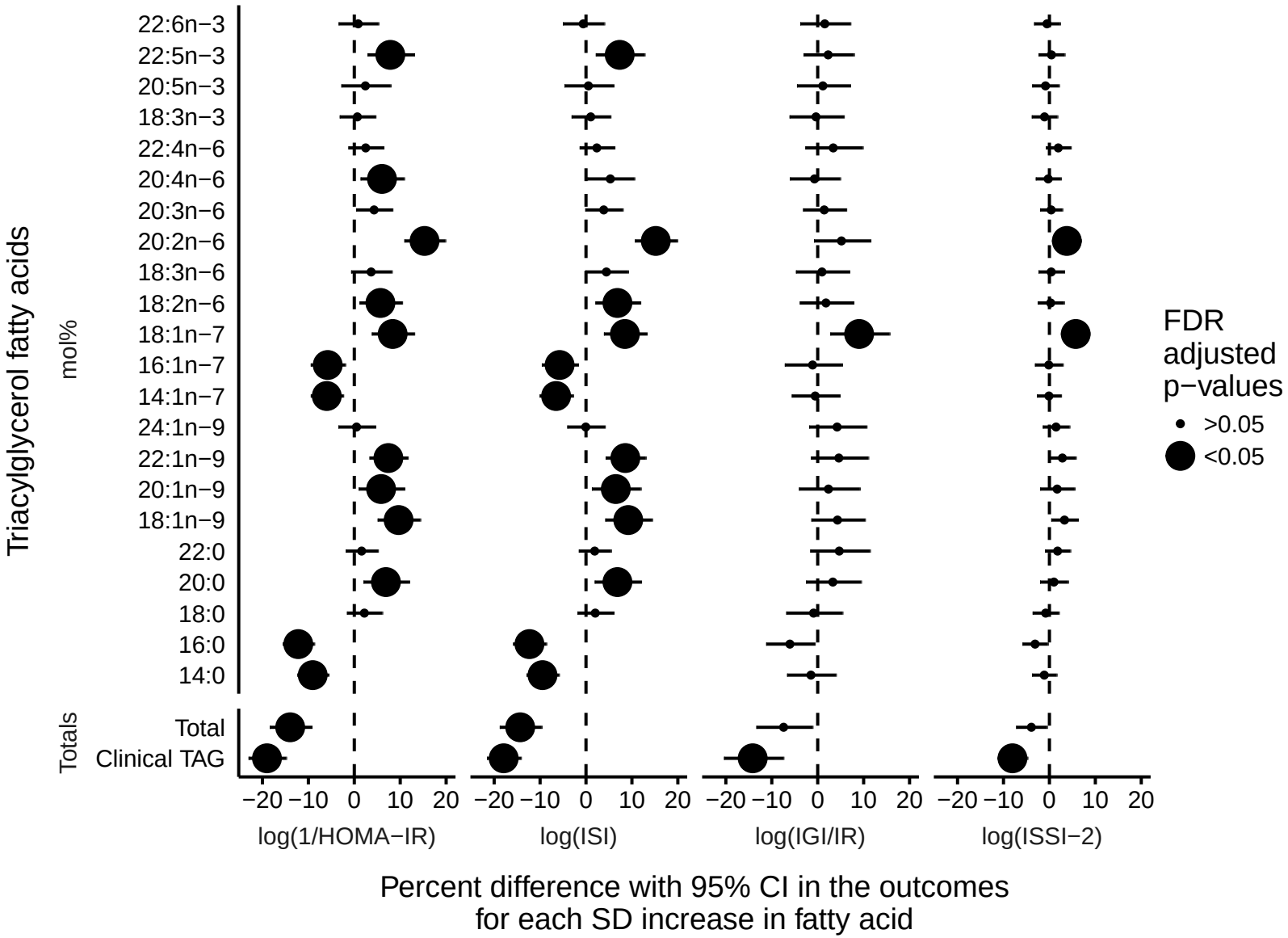


As mol%, very different story — different FA have positive or negative roles



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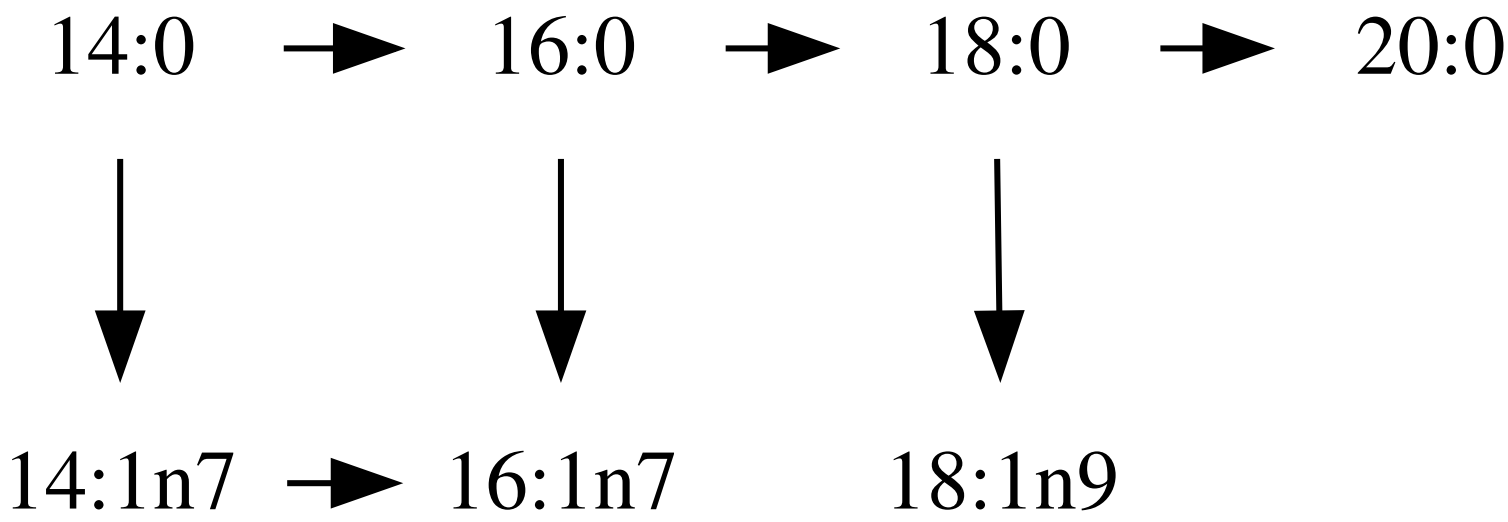
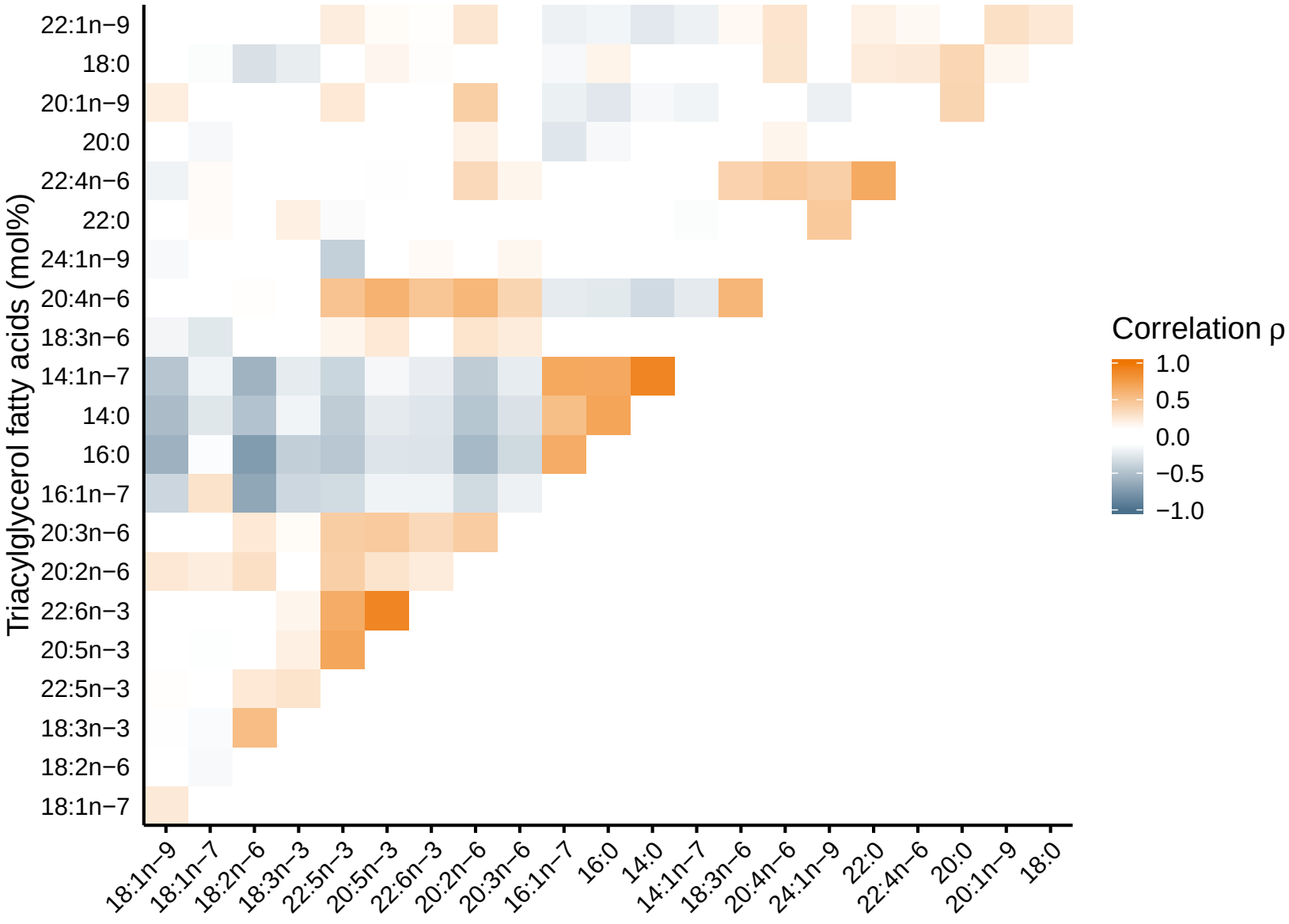


Correlation between TAG fatty acids



Partial Least Squares (PLS) allows for multivariate data

Takes:

$$ISI = 140 + 141n7 + ... + 225n3$$

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$$ISI = Comp1 + Comp2$$

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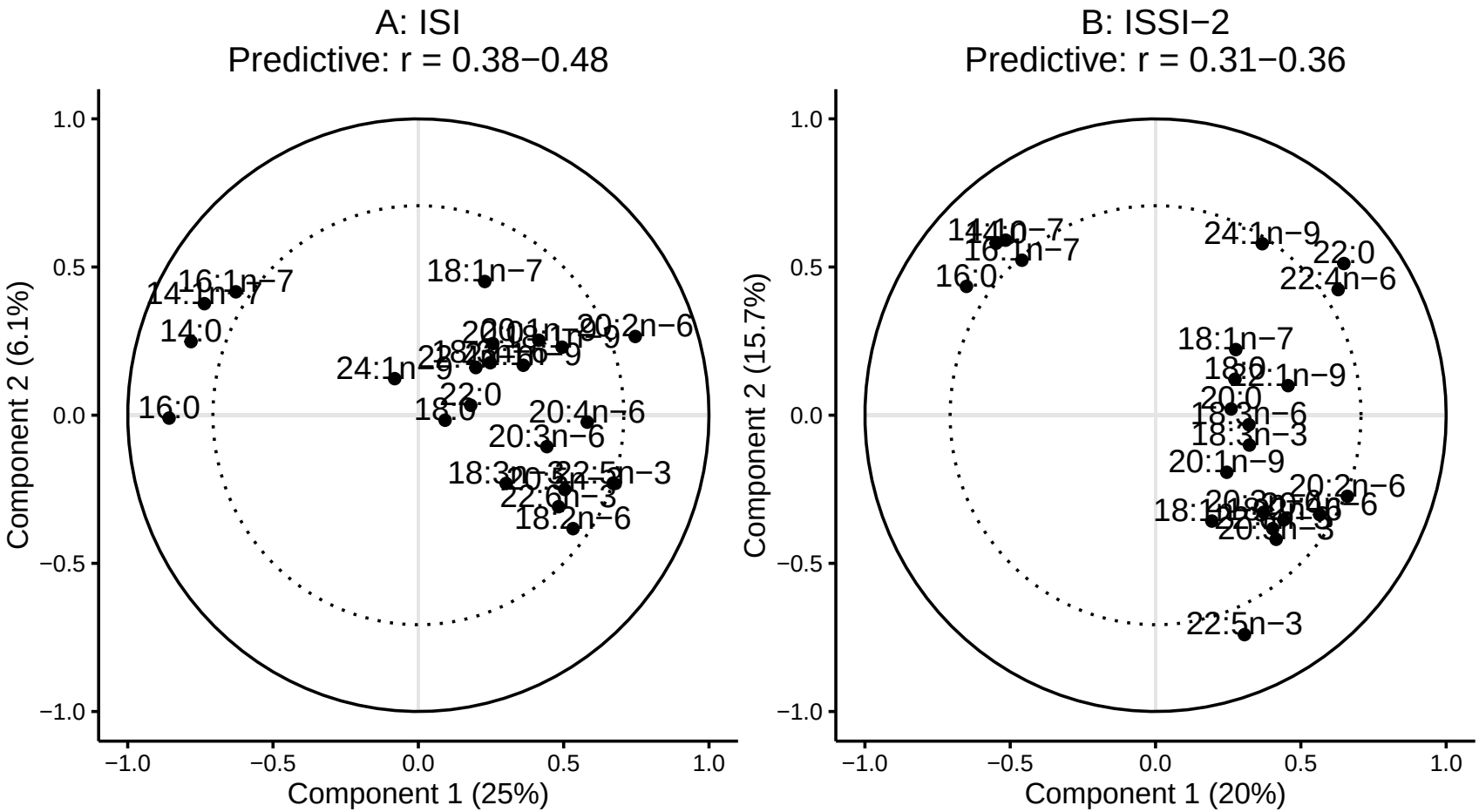
- Cross-validation (CV) determines predictability
- CV randomly splits data into training and test sets
- Limitation: Can only use one time point (cross-sectional) and no covariates

Four long chain fatty acids (14:0, 14:1n-7, 16:0, 16:1n-7) cluster and strongly explain the variance in metabolic function



FA involved in DNL from higher carb intake associate with lower metabolic functioning

- Upregulated DNL, increased 14 and 16 chain fatty acids[5]
  - 16:1n-7 shown to be highly related to directly measured DNL
  - Shown to be lipotoxic

[5]Lee et al. (2015); Wilke et al. (2009)
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- Upregulated DNL, increased 14 and 16 chain fatty acids[5]
  - 16:1n-7 shown to be highly related to directly measured DNL
  - Shown to be lipotoxic
- Two other cohort studies[6] had similar findings for diabetes and HOMA-IR.

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Overall conclusions of PhD research

- Each lipid fraction behaves slightly differently on metabolic functioning
- Fatty acids from DNL may contribute to metabolic dysfunction
- DNL fatty acids may be useful biomarker for clinical use

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- . . . Make use of statistical and analytical advances

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Code: `https://github.com/lwjohnst86/seminar2016`

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