

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

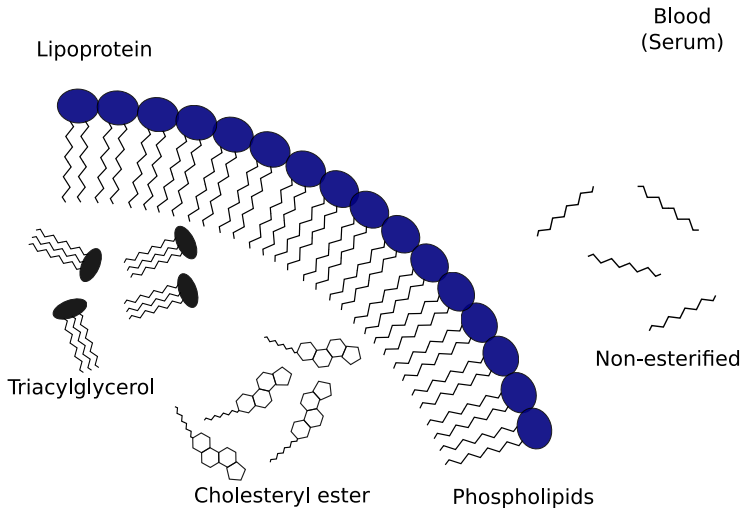
Luke Johnston

Grand Finale
Oct. 27th, 2016

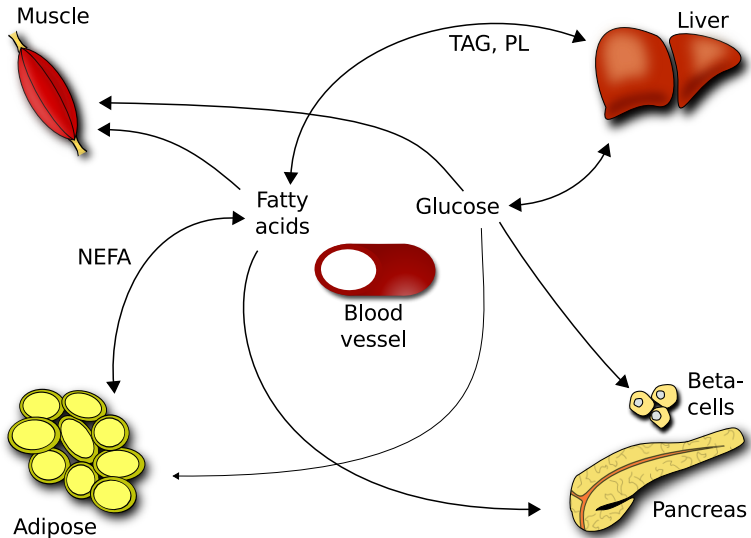
Original title

Serum Composition of Non-Esterified Fatty Acids in the Progression of Metabolic Abnormalities Underlying Type 2 Diabetes

Physiology of serum lipid fractions



Glucose and fatty acid metabolism



Fatty acid length and desaturation

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

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

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

- One study had three fractions: TAG, PL, CE²
 - Multiple flaws
- Mainly cohorts report on PL and CE: CHS, EPIC, ARIC³
 - 16:0 and 18:0 higher risk for DM
 - 18:1n-7, 18:1n-9, 18:3n-3 lower risk for DM

²Lankinen et al. (2015)

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

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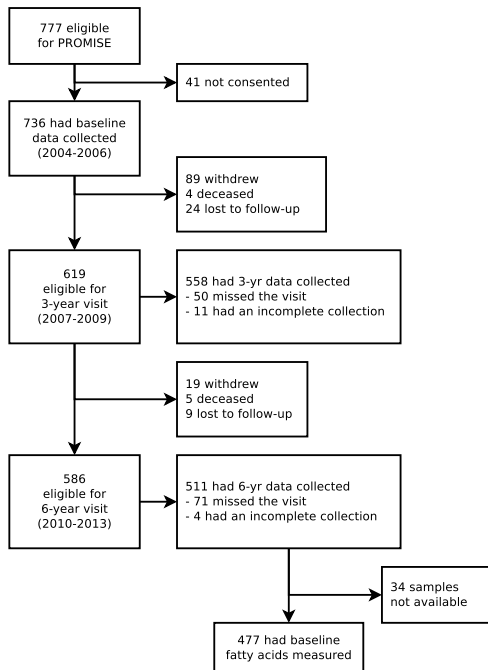
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- TAG: ...

Data source: The PROMISE cohort



PROspective Metabolism and ISlet cell Evaluation cohort.

- Recruited from London and Toronto centers
- Followed every ~3 years (3 time points completed)
- Demographics, lifestyle, anthropometrics, and blood



Variables of interest

Metabolic outcomes

Calculated from OGTT:

- Insulin sensitivity: $1/\text{HOMA-IR}$, ISI
- Beta-cell function: $\text{IGI}/\text{HOMA-IR}$, ISSI-2

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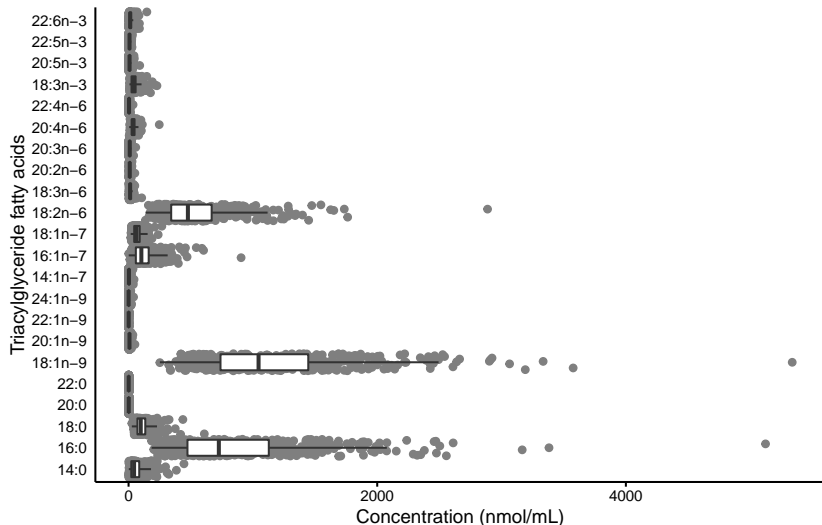
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TAG fatty acids

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 code: <https://github.com/lwjohnst86/seminar2016>

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Why scientists must share their research code

'Reproducibility editor' Victoria Stodden explains the growing movement to make code and data available to others.



Democratic databases: science on GitHub

Scientists are turning to a software-development site to share data and code.

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: TAGFA, NEFA, baseline age, ethnicity, sex

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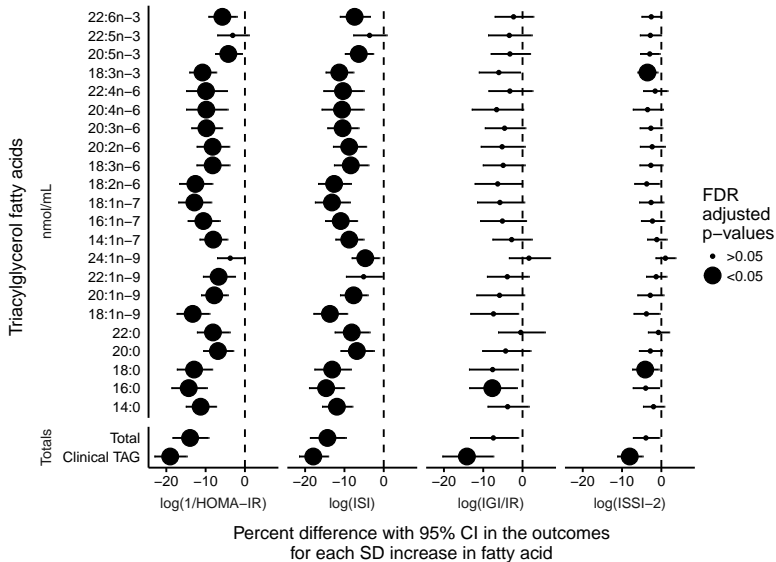
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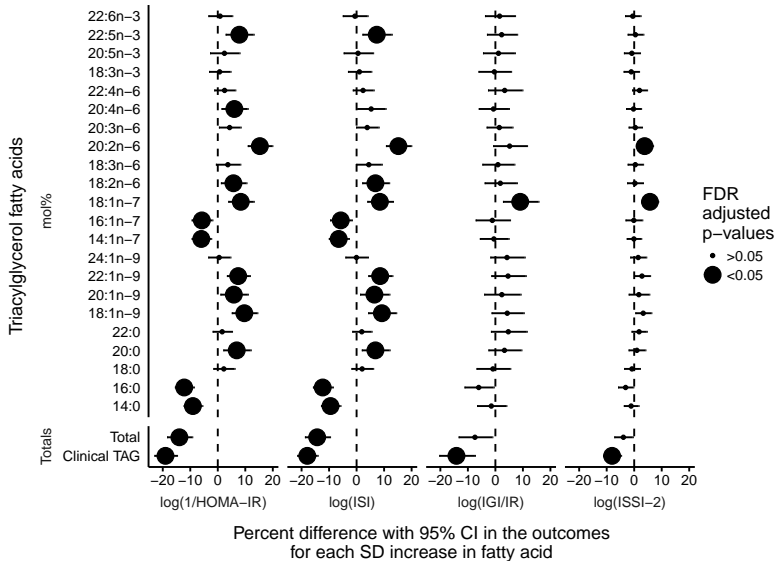
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- Adjust using False Discovery Rate (FDR) correction

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As conc, strong negative association with IS (96 non-FDR vs 77 FDR of 184 models)



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

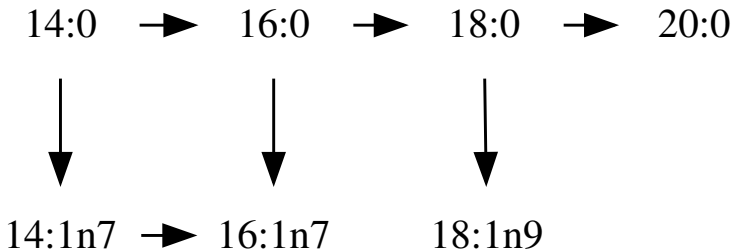


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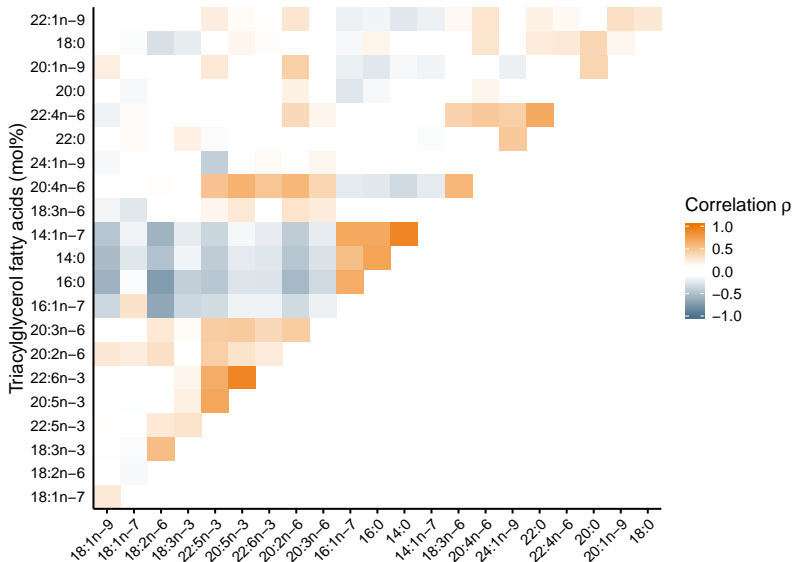
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Correlation between TAG fatty acids



Partial Least Squares (PLS) allows for multivariate data

Takes:

$$ISI = 140 + 141n7 + \dots + 225n3$$

Converts to:

$$ISI = \textit{Comp1} + \textit{Comp2}$$

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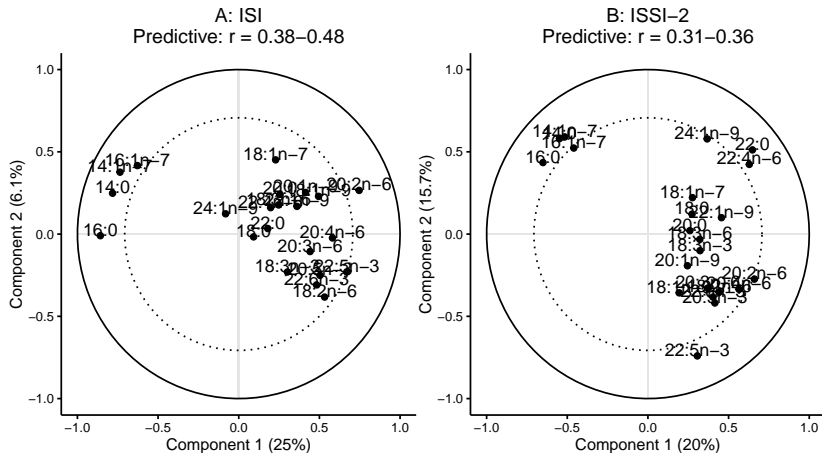
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- PLS: No p-value, no p-value problem
- Cross-validation (CV) determines predictability
- CV splits data into training and test sets
- Flaw: Can only use one time point (cross-sectional)

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 acids⁵
 - 16:1n-7 shown to be highly related to directly measured DNL

⁵Lee et al. (2015); Wilke et al. (2009)

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- Upregulated DNL, increased 14 and 16 chain fatty acids⁵
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- Two other cohort studies⁶ 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

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- Each lipid fraction behaves slightly differently on metabolic functioning
- Fatty acids from DNL may contribute to metabolic dysfunction
- ... Make use of statistical and analytical advances

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