Lower Serum Non-Esterified Eicosapentaenoic Acid (EPA) is Associated with Insulin Resistance in the PROMISE Cohort

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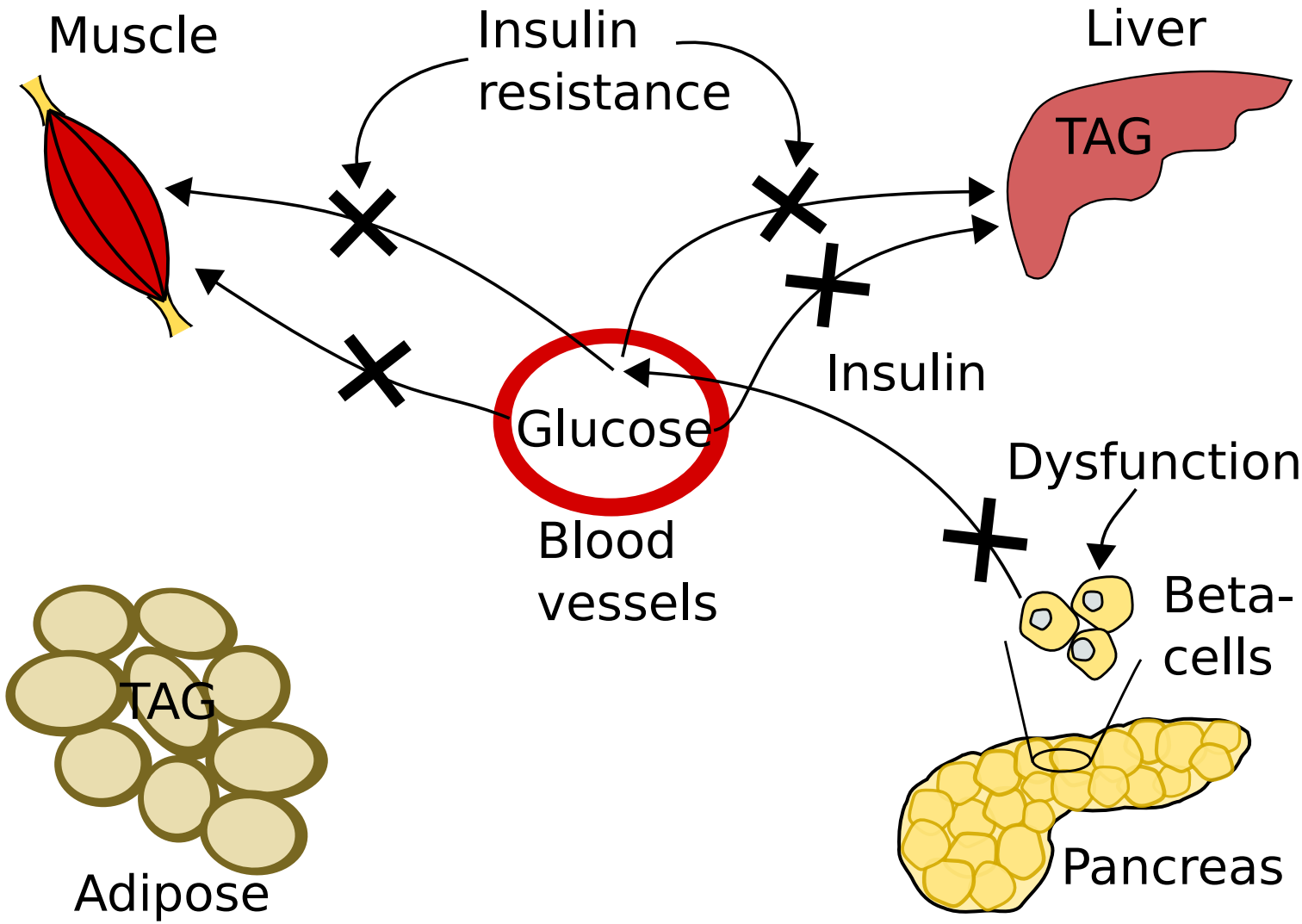
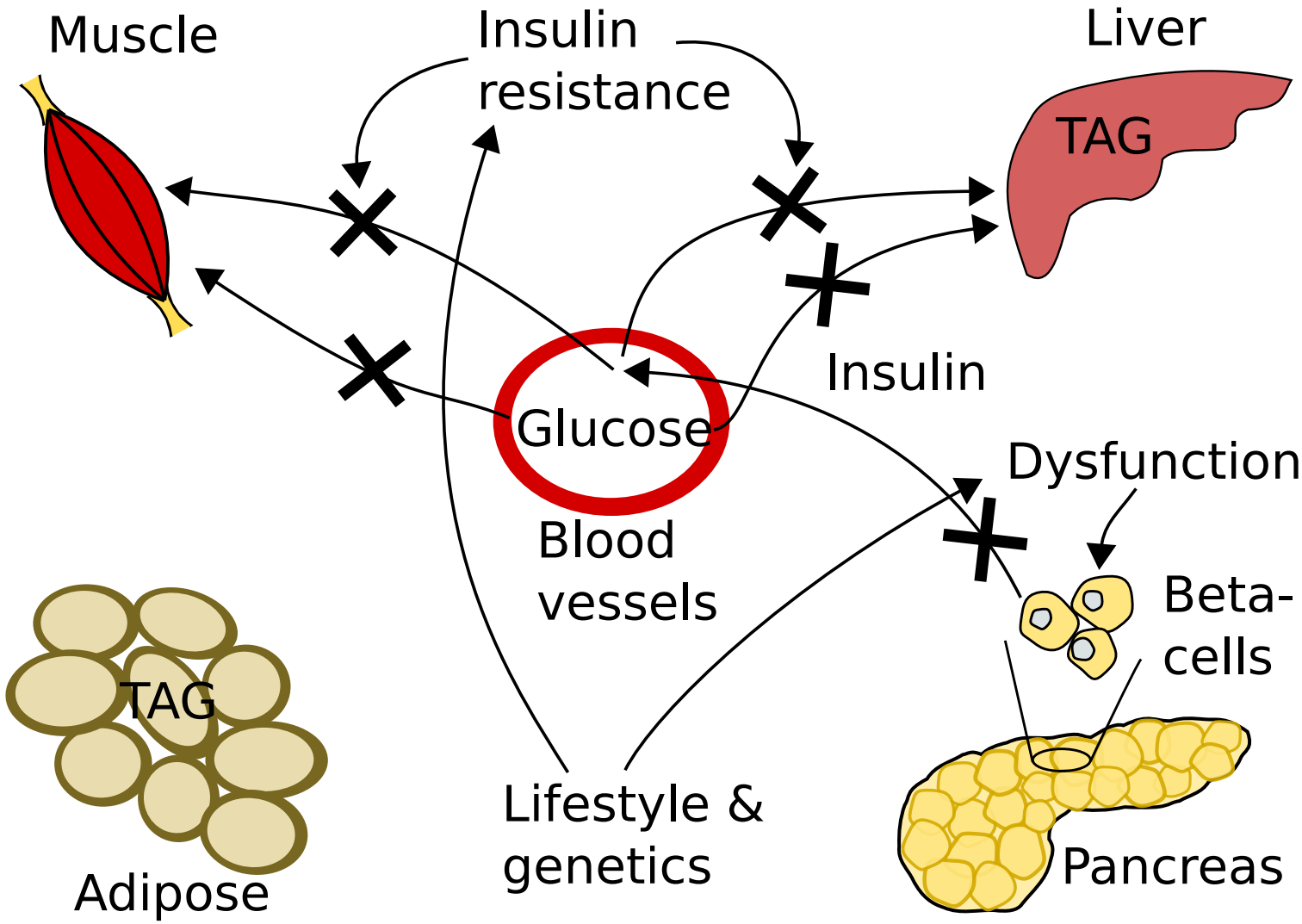
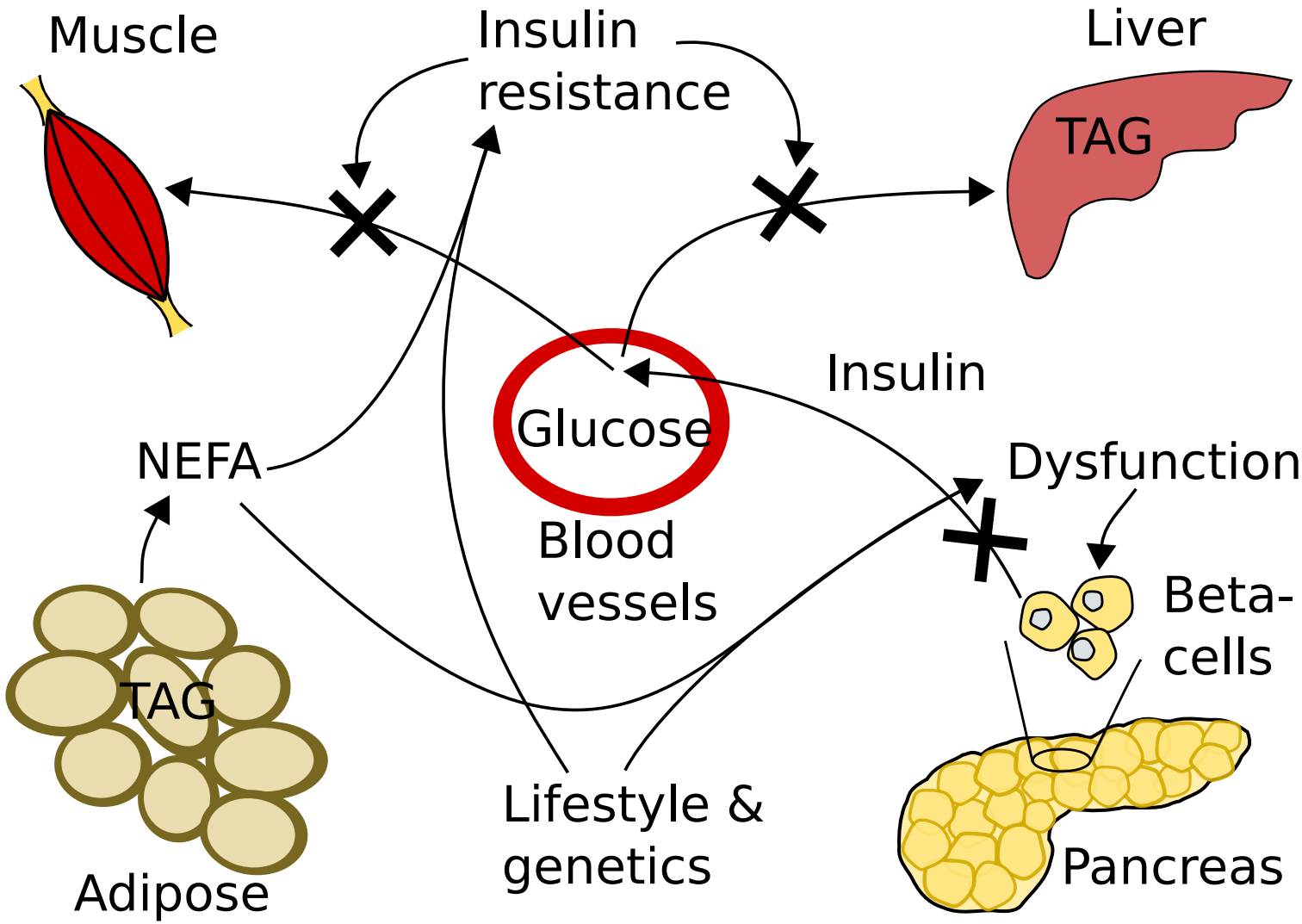
Type 2 diabetes mellitus — Pathophysiology



Risk factors for diabetes include…

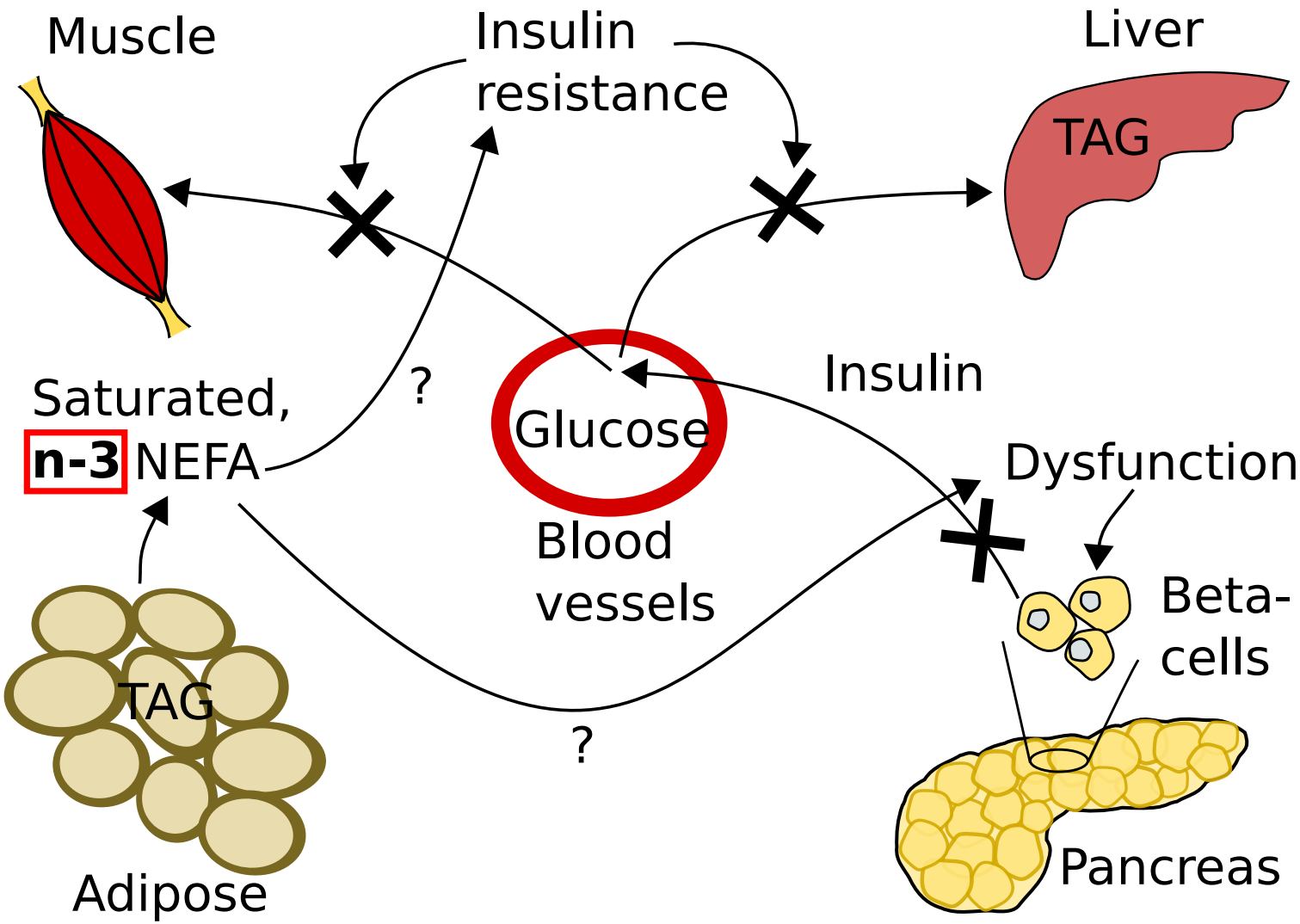


…and total non-esterified FA (NEFA)[1]



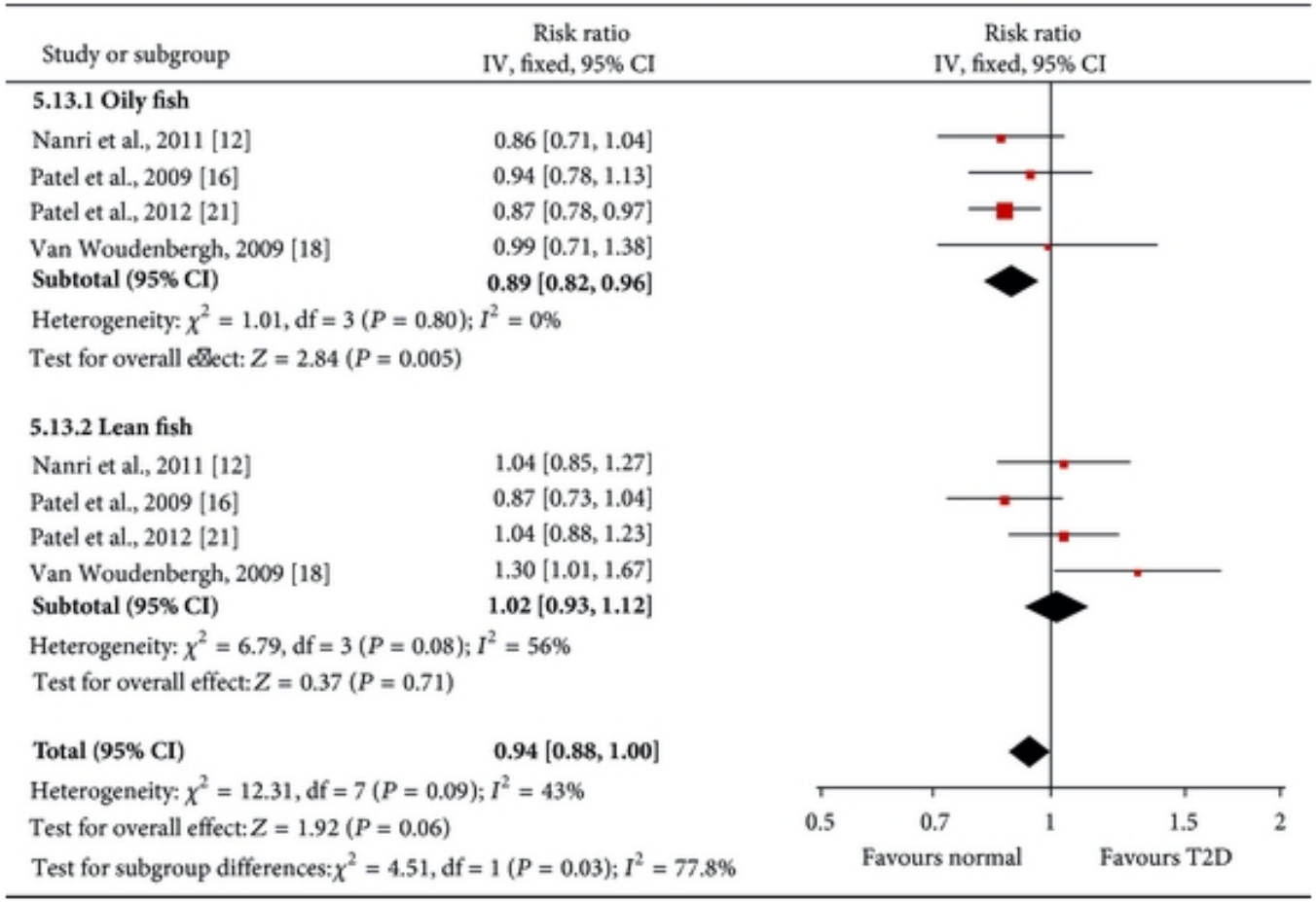
[1] Paolisso and Howard (1998), Cnop (2008), Capurso and Capurso (2012).

However, NEFA are physiologically diverse[2]



[2] Kato et al. (2008), Xiao et al. (2006)

Meta-analysis of cohorts examining association of *consumption* of fish and diabetes[3]



[3] Zhang et al. (2013)

Meta-analysis of cohorts using n-3 highly-unsaturated FA (HUFA) *biomarkers* (i.e. phospholipid / cholesteryl ester)[4]

[4] Wu et al. (2012)

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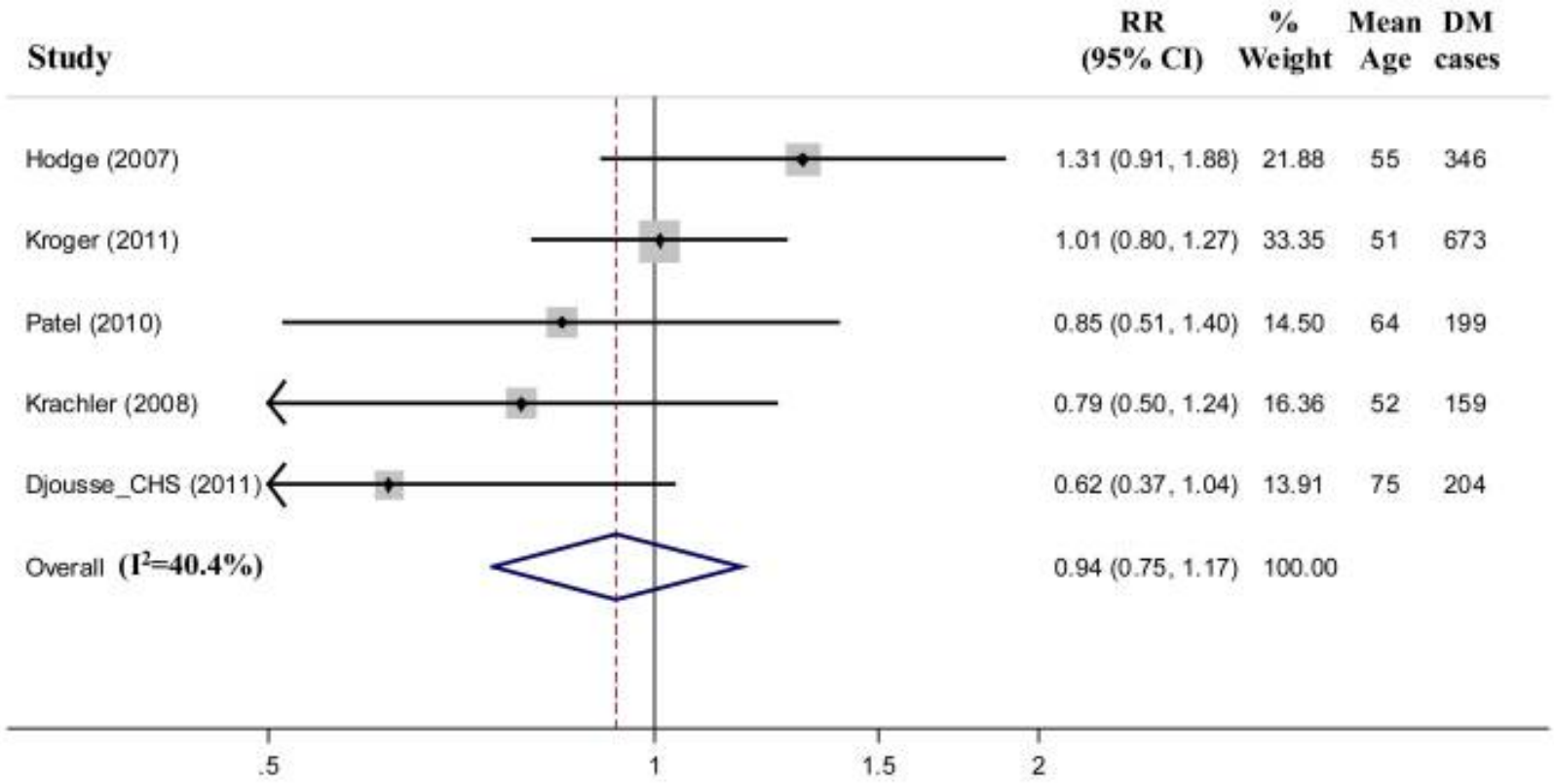

[4] Wu et al. (2012)

Research gaps

- Studies on FA often study diabetes, few on pathophysiology
  - $\rightarrow$ insulin resistance?
  - $\rightarrow$ β-cell function?
- No human studies on non-esterified n-3 HUFA
  - Studies often examine phospholipids or cholesteryl esters[5])

[5] Kim et al. (2013), Wang et al. (2003), Van Woudenbergh et al. (2012)

Objective of study:

To examine the association of individual non-esterified n-3 HUFA with insulin resistance and β-cell dysfunction

Specifically:

- 20:5 n-3, eicosapentaenoic acid (EPA)
- 22:5 n-3, docosapentaenoic acid (DPA)
- 22:6 n-3, docosahexaenoic acid (DHA)
- Total n-3 HUFA

Methods: PROspective Metabolism and ISlet cell Evaluation (PROMISE) Cohort[6]

Longitudinal observational cohort

Participants:

- Toronto and London, Canada
- Older than 30 yrs (mean at baseline: 50.6 yrs)
- **At-risk** for diabetes (e.g. central obesity, family history)
- Clinic vists/3yrs
- Extensively characterized

[6] Hanley et al. (2009), Kayaniyil et al. (2011)

Methods: Metabolic characterization

Metabolic

8–12hr fasting 75g oral glucose tolerance test (OGTT)

- **3 blood samples** collected: 0, 30, and 120 min
- Glucose, insulin measured from OGTT
- Fatty acids (EPA, DHA, etc.) from fasting sample
  - TLC with GC-FID $\rightarrow$ baseline sample only **(n=476)**
  - Current analysis $\rightarrow$ **cross-sectional**

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Anthropometrics

- Anthropometrics (waist, height, weight)
- Sociodemographics using structured questionnaires (73.5% female, 70% Caucasian)

Metabolic measures (outcome variables)

Insulin sensitivity[7]

- Hepatic *resistance* $\rightarrow$ Homeostasis Model of Assessment (HOMA-IR)
- Whole body *sensitivity* $\rightarrow$ Insulin Sensitivity Index using OGTT (ISI)

[7] Matthews et al. (1985), Matsuda and DeFronzo (1999)

[8] Wareham et al. (1995), Retnakaran et al. (2009)

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β-cell function[8]

- 1st phase insulin response $\rightarrow$ Insulinogenic Index over HOMA-IR (IGI/IR)
- Analogous to the disposition index $\rightarrow$ Insulin Secretion Sensitivity Index 2 (ISSI-2)

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Analysis: Linear regression and confounder selection

Outcomes

Insulin sensitivity and β-cell function

Exposures

EPA, DPA, DHA, n-3 HUFA

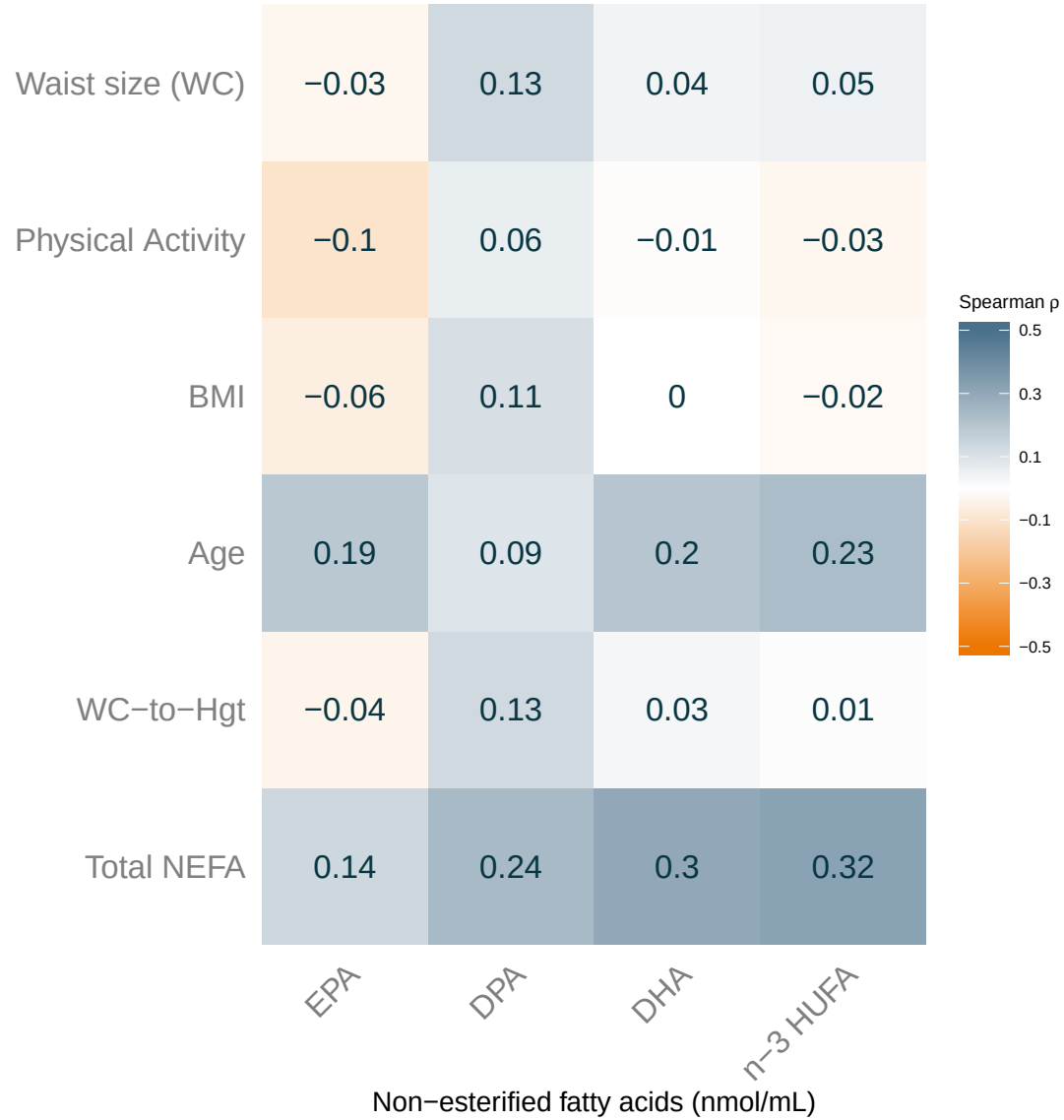
Confounders

Determined using systematic directed acyclic graph[9]

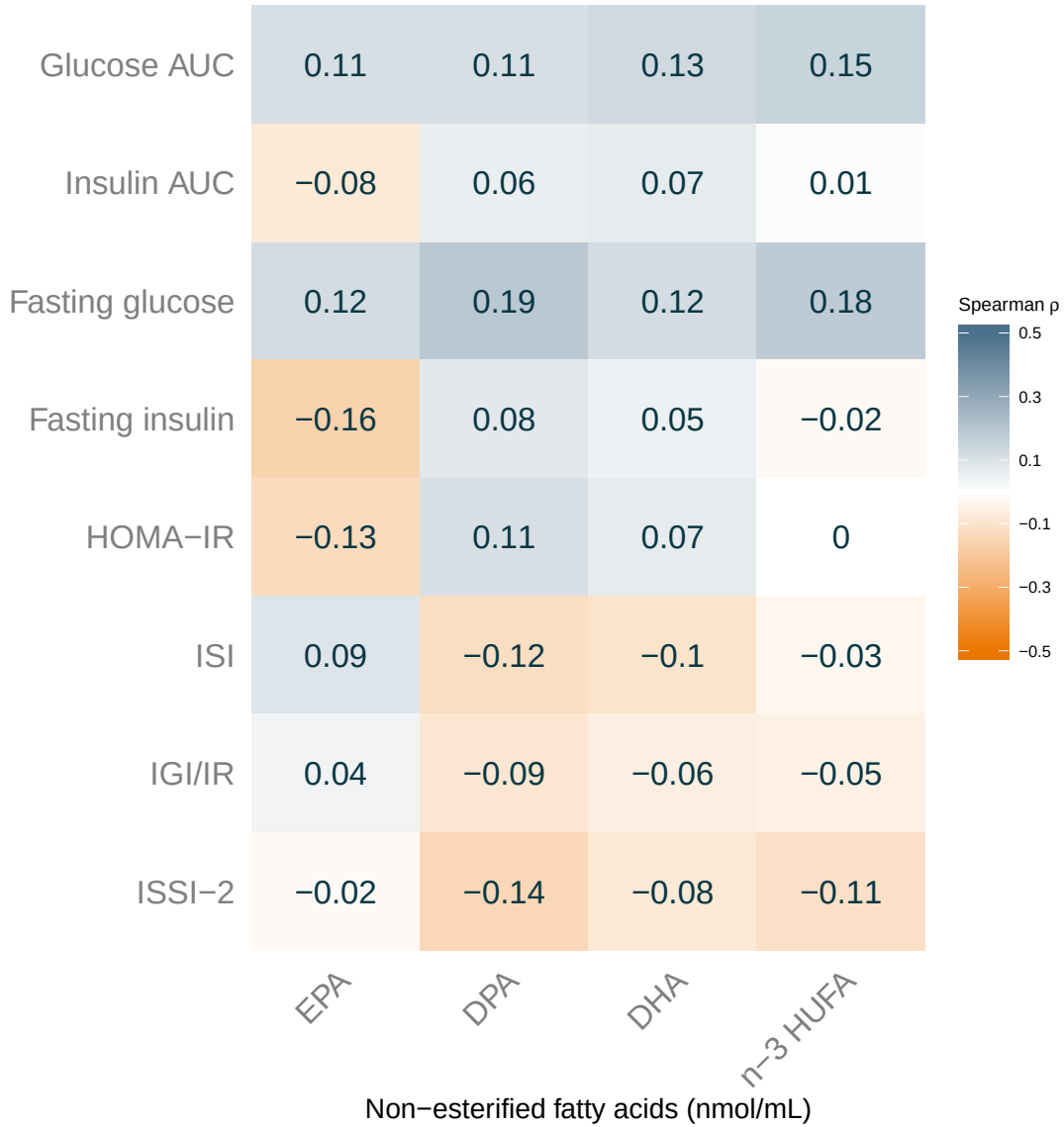
- Sex, age, ethnicity, waist, physical activity, presence of other chronic diseases (e.g. hypertension), and n-6 HUFA.

[9] Shrier and Platt (2008)

Results: Correlation heatmap of key variables with the n-3 HUFA



Results: Correlation heatmap of key variables with the n-3 HUFA

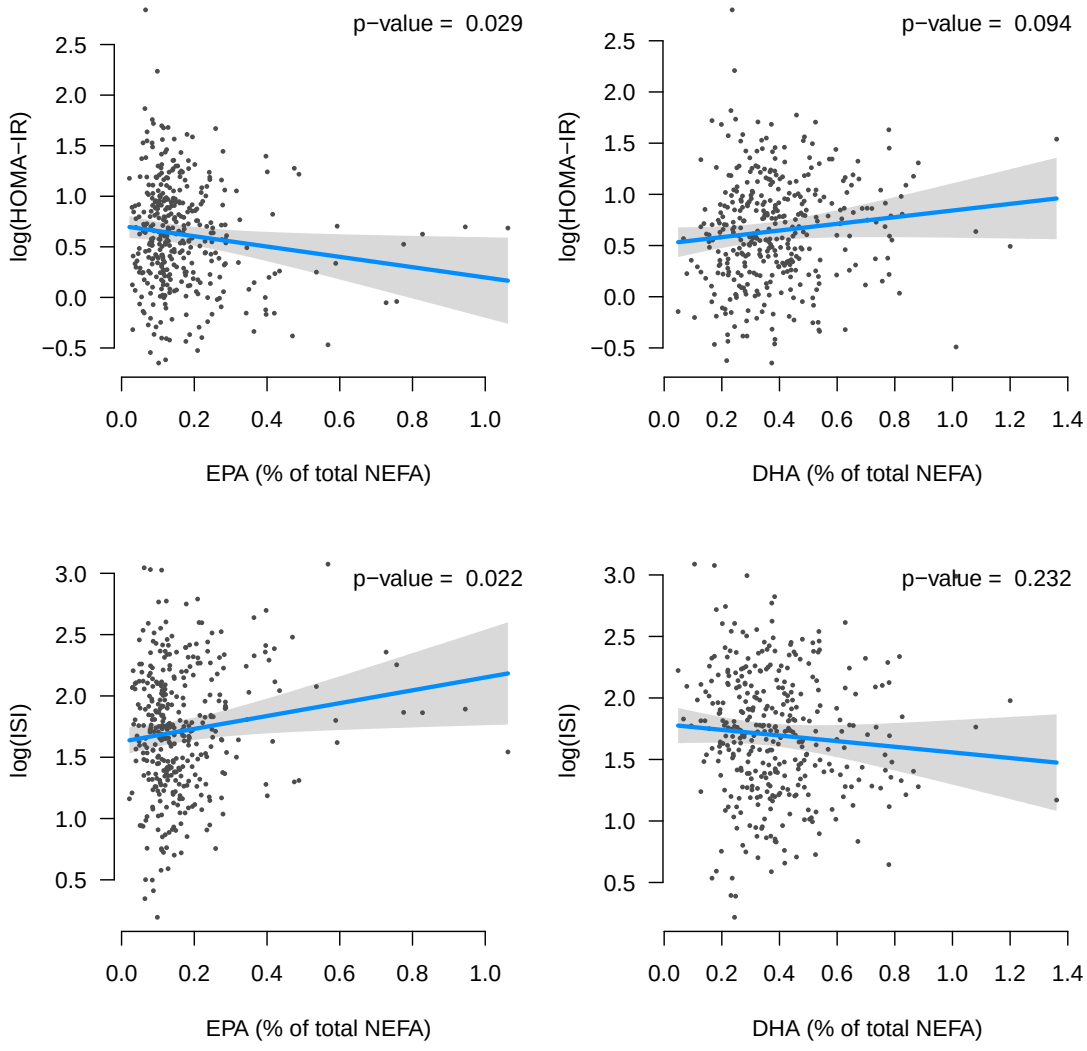


Regression results: EPA is associated with insulin resistance, not with β-cell function

	%EPA		%DHA*	
	β (SE)	*P*	β (SE)	*P*
HOMA-IR				
Model 1	**-0.53 (0.22)**	**0.017**	0.14 (0.16)	0.366
Model 2	**-0.51 (0.23)**	**0.029**	0.33 (0.19)	0.094
ISI				
Model 1	**0.54 (0.22)**	**0.013**	-0.08 (0.16)	0.613
Model 2	**0.52 (0.23)**	**0.022**	-0.23 (0.19)	0.232
IGI/IR				
Model 1	**0.63 (0.3)**	**0.035**	0.31 (0.22)	0.147
Model 2	0.47 (0.32)	0.137	0.15 (0.26)	0.573
ISSI-2				
Model 1	0.24 (0.14)	0.089	0.15 (0.1)	0.141
Model 2	0.18 (0.15)	0.229	0.11 (0.13)	0.390

n=455–466. HOMA-IR, ISI, IGI/IR, and ISSI-2 were log transformed. Model 1: Age, sex, ethnicity, and WC-to-height ratio. Model 2: Model 1 + presence of other chronic diseases (i.e. hypertension, cancer, myocardial infarction, or stroke), physical activity, and % total n-6 HUFA. Note: * %DPA and total n-3 HUFA showed similar non-significance as %DHA.

Results: Fully-adjusted partial residual plots depicting higher EPA with lower insulin sensitivity



Conclusion — Greater EPA is associated with greater insulin sensitivity

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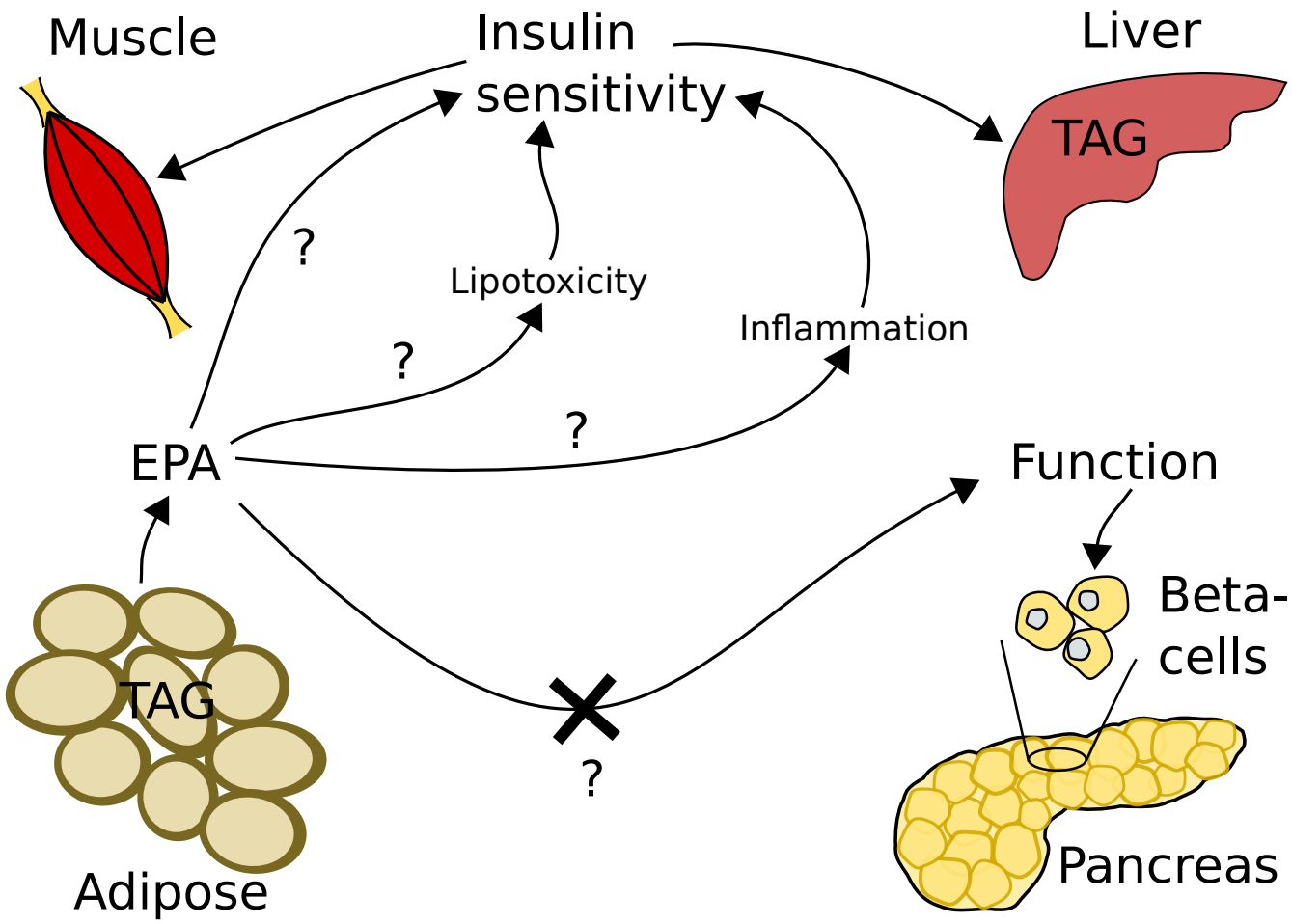
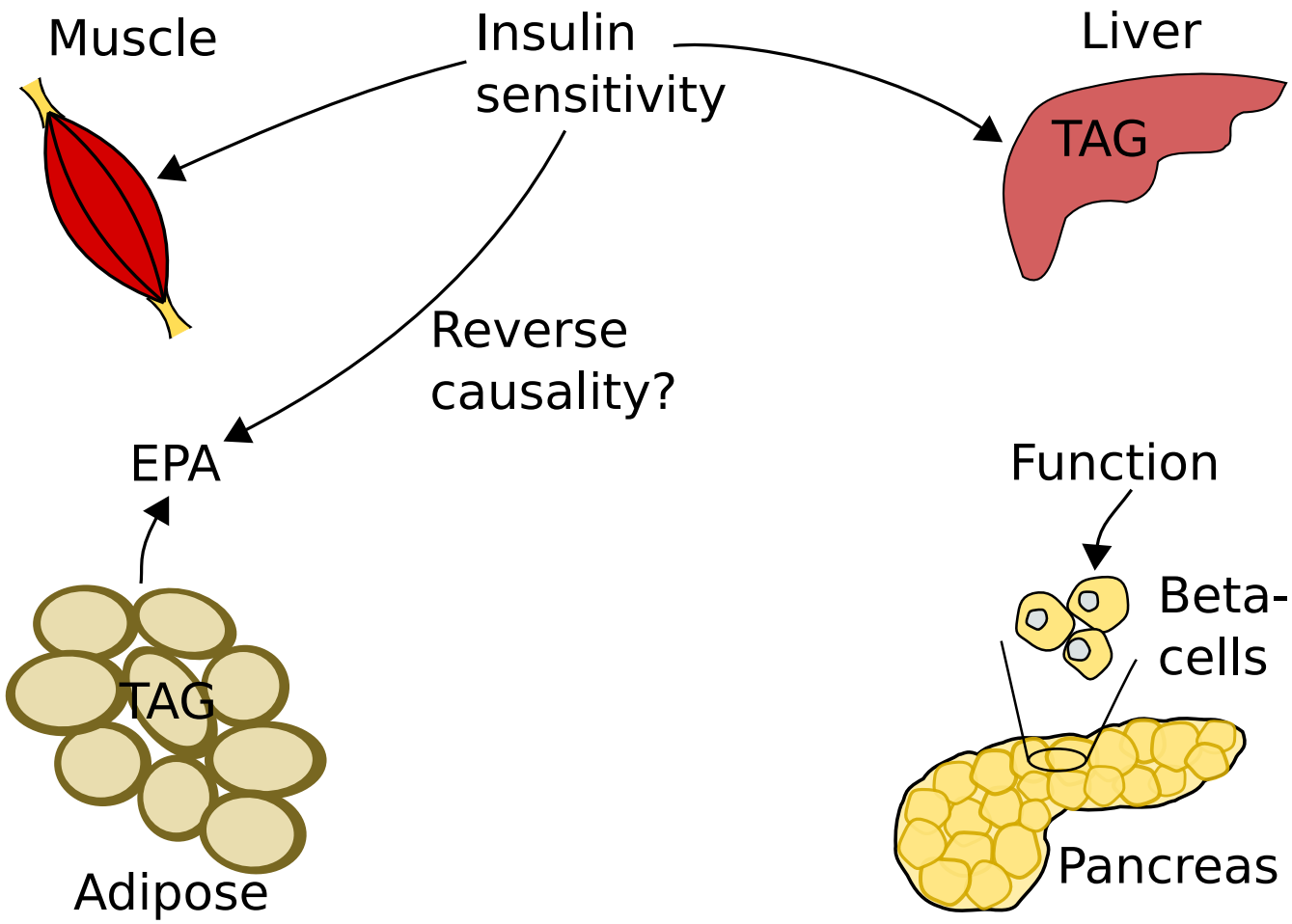


Conclusion — Limitations and caveats



Thank you!

- **Supervisor:** Dr. Anthony Hanley
- **Co-Supervisor:** Dr. Richard Bazinet
- **Hanley Lab:** Sheena Kayaniyil, Ingrid Santaren, Sudaba Mansuri, Christine Lee
- **Bazinet Lab:** Chuck Chen, Katie Hopperton, Marco Trepanier, Anthony Domenichiello, Alex Kitson, Lauren Lin, Lin Lin, Zhen Liu
- **Research Nurses:** Jan Neuman, Paula Van Nostrand, Stella Kink, Annette Barnie, Sheila Porter, Mauricio Marin
- This research was **supported by funds** from: Canadian Institutes of Health Research, Canadian Diabetes Association, Ontario Graduate Scholarship, University of Toronto (School of Graduate Studies, Department of Nutritional Sciences)

Canadian Diabetes Association

CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

Further comments/questions? Contact:
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Equations

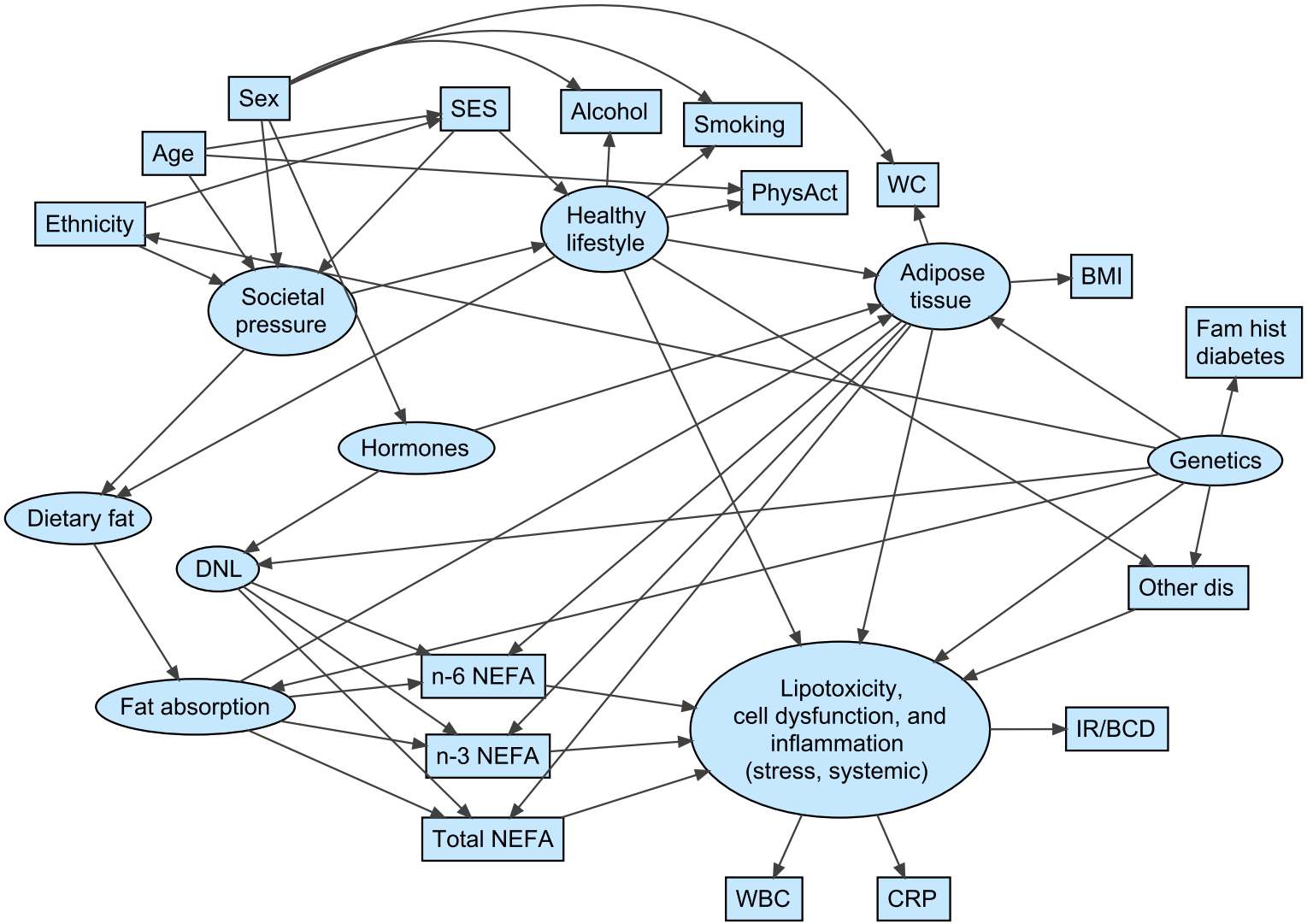
$$\text{HOMA-IR} = \frac{\text{G}_{0\text{min}} \times \text{I}_{0\text{min}}}{22.5}$$

$$\text{ISI} = \frac{10000}{\sqrt{(\text{G}_{0\text{min}} \times \text{I}_{0\text{min}}) \times (\text{G}_{\text{mean}} \times \text{I}_{\text{mean}})}}$$

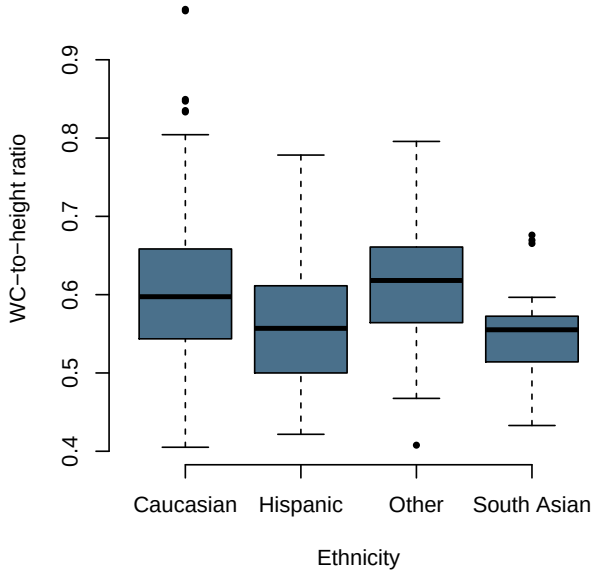
$$\text{IGI/IR} = \frac{\frac{\text{I}_{30\text{min}} - \text{I}_{0\text{min}}}{\text{G}_{30\text{min}} - \text{G}_{0\text{min}}}}{\text{HOMA-IR}}$$

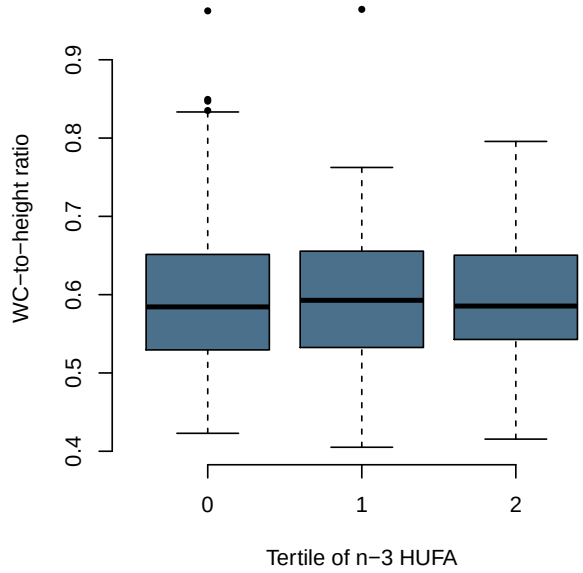
$$\text{ISSI-2} = \left(\frac{\text{Insulin AUC}}{\text{Glucose AUC}} \right) \times \text{ISI}$$

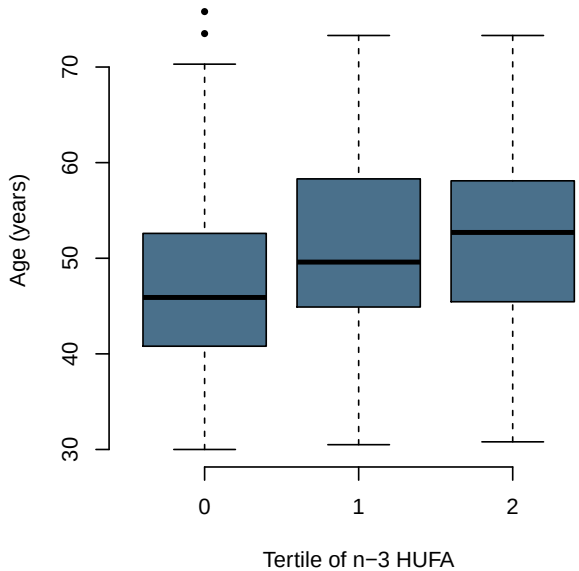
Analysis: Confounder selection (directed acyclic graphs) for linear regression

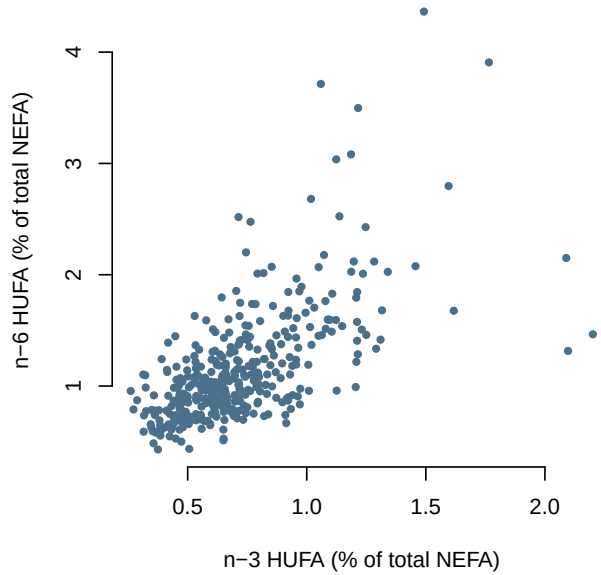


Results: Some basic bivariate characteristics









Results: Density plots of the n-3 neHUFAs