Serum Non-Esterified Fatty Acid (NEFA) Concentrations are Associated with Longitudinal Progression of Beta-Cell Dysfunction: Prospective Metabolism and Islet Cell Evaluation (PROMISE) Cohort

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Disclosures

- Presenter: Luke W. Johnston
- Relationships with commercial interests:
  - None to disclose

Total NEFA: a risk factor for type 2 diabetes

- Higher total NEFA associate with incidence of diabetes[1]
  - Potentially through lipotoxicity and/or inflammation[2]

[1] B. T. Steffen et al. (2015); Djoussé et al. (2012); Il'yasova et al. (2010)
[2] Giacca et al. (2011); Newsholme et al. (2007)

Total NEFA: a risk factor for type 2 diabetes

- Higher total NEFA associate with incidence of diabetes[1]
  - Potentially through lipotoxicity and/or inflammation[2]

- However, NEFA comprised of physiologically diverse species (eg: saturated vs omega-3)
- Limited data in *humans* on:
  - Role in *progression* of underlying disorders
  - Role of individual NEFA species

[1] B. T. Steffen et al. (2015); Djoussé et al. (2012); Il'yasova et al. (2010)
[2] Giacca et al. (2011); Newsholme et al. (2007)

Objective:

- Examine the longitudinal associations of NEFA concentrations and individual NEFA species with 6-yr trends in insulin sensitivity (IS) and beta-cell function.

Prospective Metabolism and Islet Cell Evaluation cohort

- Adults at-risk for diabetes
- Recruited from Toronto and London, Ontario
- Followed every 3-yrs

[3] Matsuda and DeFronzo (1999); Matthews, Hosker, and Rudenski (1985)
[4] Wareham et al. (1995); Retnakaran et al. (2009)

Prospective Metabolism and Islet Cell Evaluation cohort

- Adults at-risk for diabetes
- Recruited from Toronto and London, Ontario
- Followed every 3-yrs

- OGTT at each visit (0, 30, 120 min),
  - *Insulin sensitivity*: 1/HOMA-IR and ISI (Matsuda Index)[3]
  - *Beta-cell function*: Insulinogenic index over HOMA-IR (IGI/IR) and Insulin Secretion-Sensitivity Index-2 (ISSI-2)[4]
- Fasting NEFA at baseline (n=478)
  - Thin layer chromatography (TLC) and gas liquid chromatography (GC) coupled to flame ionization detector (FID)

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- Fasting NEFA at baseline (n=478)
  - Thin layer chromatography (TLC) and gas liquid chromatography (GC) coupled to flame ionization detector (FID)
- Generalized estimating questions (GEE)
  - Adjusted for waist (WC), physical activity (MET), alcohol intake, and sex.

[3] Matsuda and DeFronzo (1999); Matthews, Hosker, and Rudenski (1985)

[4] Wareham et al. (1995); Retnakaran et al. (2009)

Outcomes declined by 14.4% to 27.5% over 6-yrs

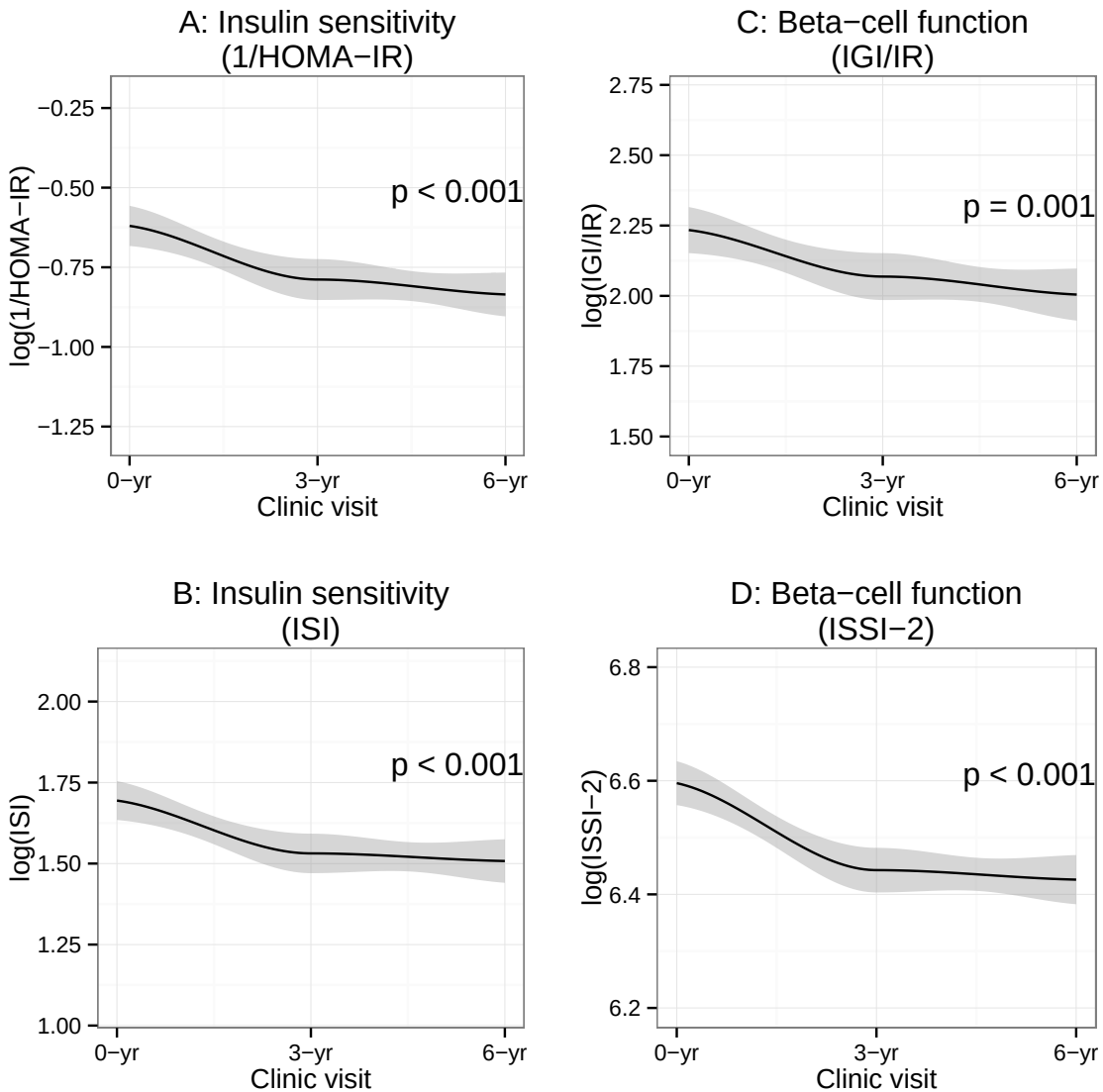

Figure 1:Trends over time, outcomes.

While clinical measures did not change

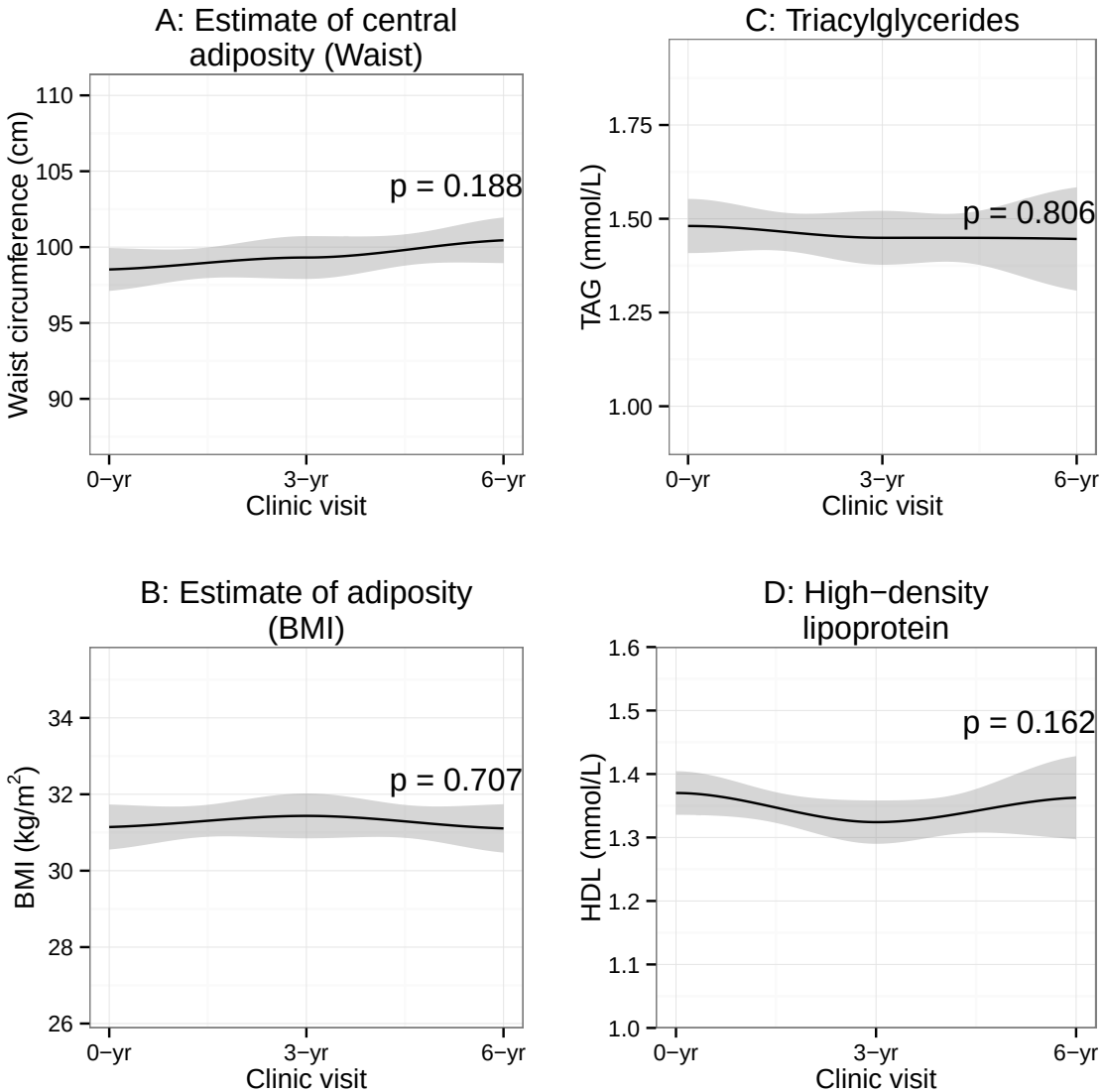

Figure 2:Trends over time, clinical measures.

Higher total NEFA predicts 25%[5] greater risk for dysglycemia

[5] RR = 1.25 (95% CI 1.05 to 1.43) per SD over the 6-yrs

Higher total NEFA predicts 25%[5] greater risk for dysglycemia

. . . and with declines in beta-cell function

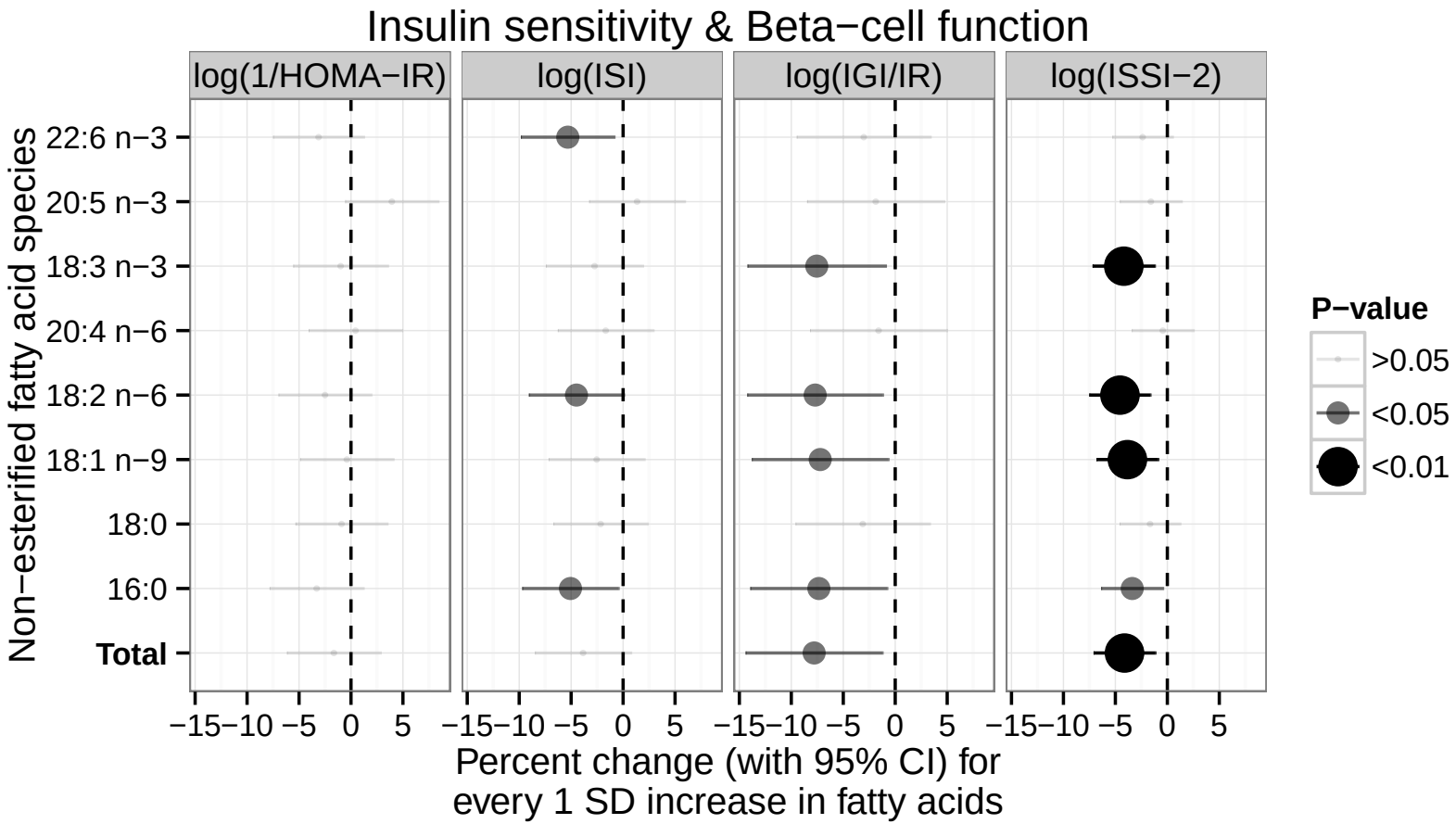

Figure 3:Forest plot of generalized estimating equation results.

[5]RR = 1.25 (95% CI 1.05 to 1.43) per SD over the 6-yrs

Conclusion:

- Total NEFA, rather than any individual species, predicts declines in beta-cell function

[6] Giacca et al. (2011)

Conclusion:

- Total NEFA, rather than any individual species, predicts declines in beta-cell function
- Extends literature by showing strong association with beta-cell function rather than insulin sensitivity
  - Biologically plausible given beta-cells susceptible to lipotoxicity[6]

[6] Giacca et al. (2011)

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Comments or questions? Please contact: **luke.johnston@mail.utoronto.ca**

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