Metabolic Profiles and Disease Risk
IRAS Studies, March 7, 2015

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Study Goals

IRAS (Classic): Examine the relationship between directly measured insulin sensitivity and carotid atherosclerosis, across the range of glycemic status and ethnicity.

IRAS Family: Examine the genetic and environmental basis of insulin resistance and abdominal adiposity in a minority, family-based cohort


Comparison of IRAS Studies

IRAS (Classic)
- Individuals, age 45-65
- Hispanic/AA/White from 4 regions
- Selected across range of glycemic status
- Primary phenotypes* include FSIGT & carotid IMT
- Metabolomics (baseline non-DMs)
- Baseline 1992-1994, and 5-yr f-up

IRAS Family
- Large families, age 18-81
- Hispanic/AA from 3 regions
- Selected for large families from IRAS
- Primary phenotypes* include FSIGT & adiposity by CT scan
- Metabolomics (all)
- Baseline 1999-2002, and 5-yr f-up

*Full list of phenotypes and baseline characteristics is provided in meeting book.
Emerging Technologies: Metabolomics as an example

• Individual serum metabolites and clusters of metabolites have been shown to predict risk of metabolic diseases (e.g., diabetes) independent of known risk factors

• Well-characterized cohorts can contribute:
  • Genetic and environmental factors
  • Clinical phenotypes (insulin sensitivity, obesity, diabetes, atherosclerosis)
  • Multiple ethnic/race groups, with observed differences in metabolites
Systems Biology Network

Adamski et al., Curr Opinion Biotech 2013; 24:39-47
IRAS Metabolites & Outcomes

• Metabolomics:
  • IRAS: 93 targeted metabolites: fatty acids, sterols, bile acids, amino acids, acylcarnitines (in 750 baseline non-DM)
  • IRAS Family: up to 2300 named compounds, underway at Metabolon, plus targeted panel (in all participants)

• Outcomes:
  • Incident diabetes, hypertension
  • Change in insulin sensitivity, atherosclerosis, weight
  • Cross-sectional measures of BMI, VAT, SAT, liver fat, fat and lean mass
Emerging Technologies: Strengths and Challenges

- Large numbers of metabolites lead to strengths and challenges:
  (+) Identify a variety of biologic pathways
  (-) Increase the type 1 error rate
  (+) Provide opportunity for a variety of analytic approaches (large N and lack of independence among them)
  (+/-) Hypothesis-generating approaches
  (-) Biological role of many metabolites not well-characterized

- Conclusion: there is value in cross-cohort collaboration for replication, analytic strategies
Issues for Cross-Cohort Studies of Emerging Technologies: Metabolites and Outcomes

- Harmonization of metabolite panels
- Harmonization of disease outcomes
- Analytic strategies
- Data sharing/IRB
- Leadership/authorship
- IP/emerging technologies