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Protecting Health, Saving Lives—*Millions at a Time*

Methods Development for Measurement of Environmental Exposures of Diabetes and Diabetes-related Outcomes

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Diabetes

- Group of metabolic diseases characterized by hyperglycemia due to β-cell dysfunction, insulin resistance, or both that results in long-term complications
  - Type 1 Diabetes
  - Type 2 Diabetes (90-95% of all cases, in particular in adult populations)
  - Gestational Diabetes
- Pre-diabetes: impaired fasting glucose (fasting plasma glucose levels 100 to 125 mg/dl), or impaired glucose tolerance (2-h values in the oral glucose tolerance test of 140 to 199 mg/dl), or hemoglobin A1C levels of 5.7 to 6.4% are defined as having pre-diabetes (ADA guidelines)

Outcome ascertainment

- Based on established clinical guidelines (e.g. American Diabetes Association)
  1. Hemoglobin A1C ≥ 6.5% using a method certified and standardized to the Diabetes Control and Complication Trial (DCCT) assay OR
  2. Fasting plasma glucose ≥ 126 mg/dl. No caloric intake for at least 8 h OR
  3. 2-hour plasma glucose ≥ 200 mg/dl during an oral glucose tolerance test (OGTT) OR
  4. In a patient with classic symptoms of hyperglucerima or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dl (11.1 mmol/l)

For clinical purposes, in the absence of unequivocal hyperglycemia, criteria 1-3 should be confirmed by repeat testing.

Reference: American Diabetes Association (2010)

Diabetes outcome definition

- Very good:
  - ADA definition without repeated measures
  - Self-reported physician diagnosis
- Good / Adequate:
  - ADA definition without repeated measures and no other information provided on fasting and assays
  - Use of medical records with details on criteria used
- Limited:
  - Use of medical records without details on criteria used
- Deficient:
  - Unclear questions or information used
  - Glucosuria
  - Diabetes mortality

Diabetes related outcomes

- Measures of glycemia: fasting plasma glucose or hemoglobin A1c (no fasting required)
  - Persons without diabetes: inform on future risk
  - Persons with diabetes: informs on diabetes control
  - Analyses need to be stratified by diabetes status
- Insulin and its related measures based on the homeostatic model assessment (HOMA) of insulin resistance (HOMA-IR) and β-cell function (HOMA-β)
  - HOMA measures, especially HOMA-IR, are preferred versus insulin for epidemiological research
  - Analyses need to be restricted to participants without diabetes

Diabetes related outcomes

- Metabolic syndrome
  - Clustering of biochemical and physiological abnormalities in triglycerides, waist circumference, blood pressure, cholesterol and fasting glucose
  - ATP III definition: 3 of 5 components need to be present

Waist circumference	
Men	> 102 cm
Women	> 88 cm
Triglycerides	≥150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥ 130 / ≥ 85 mmHg
Fasting blood glucose	≥110 mg/dL

National Cholesterol Education Program's Adult Treatment Panel III (ATP III)

Methodological considerations

- Prospective cohort design
- Participants at risk of developing the disease (diabetes-free of appropriate age range)
- Sensitivity analyses excluding participants with pre-diabetes, especially for biomarkers of environmental exposures, as pre-diabetes could affect the biomarker toxicokinetics
- Adequate follow-up:
    - Long-latency (early life exposures)
    - Short-latency (similar to BMI)

Confounding

- Biological consideration
  - Age, sex, SES, lifestyle factors
  - Body mass index (careful thinking regarding its possible role as mediator) and other measures of adiposity
- Unadjusted / minimally adjusted and progressively adjusted results
- Discussion about residual and unmeasured confounding

Analysis (beyond confounding)

- Description information by disease status and exposure levels
- Report participants with missing data and strategy to deal with it
- Evaluation of model assumptions
- Evaluation of non-linear exposure-responses
- Evaluation of effect modification conducted with an a-priori rationale or a senstivity analysis to evaluate the consistency of the findings by participants characteristics
- Analysis of insulin and HOMA restricted to participants without diabetes
- Analysis of glycemia should be stratified by diabetes-status
- Sensitivity analysis excluding participants with pre-diabetes

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