A Tale of (More Than ?) Two Cohorts – from Canada

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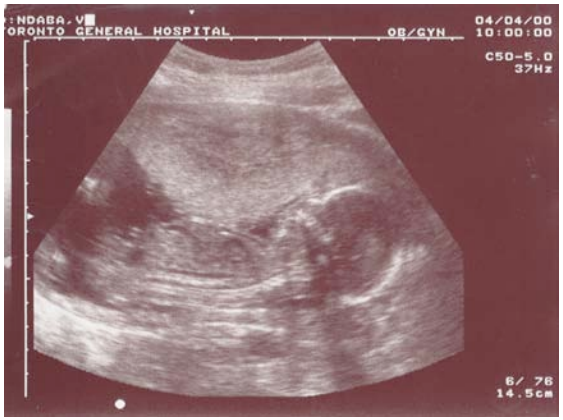
Why study gene-environment interactions?



- Most disease burden is jointly determined by interaction of individual genetic endowments and complex sequence of environmental factors
- These gene-environment interactions require decades to fully manifest over the life course
- Diseases and conditions of later life occur in some and not others because of intense interactions between particular genetic constitutions and particular sequence of social and physical environments

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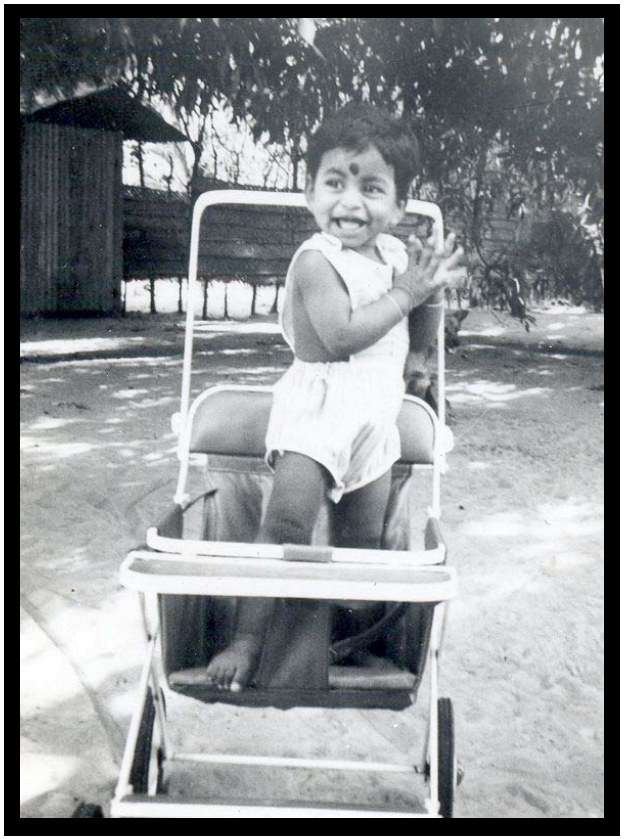
Why study gene-environment interactions? cont'd



- BUT…little is known about underlying causes of these conditions and why they are now increasing in frequency – for e.g. asthma
- Requires study of these sequential events in large numbers of people over time, on whom baseline genetic and repeated environmental exposures are taken, to:
  - understand the causal pathways; and,
  - develop disease prevention strategies

Studying Genetic and Environmental Contributions to Disease Causation: An Uneven Playing Field

Measurement Attribute	Genetic Exposure Measures	Environmental Exposure Measures
Time-varying?	No – one sample per lifetime is enough (unless gene expression arrays are used)	Yes – new samples needed whenever exposure changes
Data Collection Costs	Cheap (on a sample)	Expensive (real-time assays)
Sample Storage (for later analysis)	Easy (buccal swab, buffy coat)	Difficult (e.g. air/water/diet samples)
Data Analysis Costs	Getting cheaper by the day	Getting Costlier (as awareness of chemical/physical/biological complexity increases)
Overall Ease & Cost of Accurate Ascertainment	**Easy / Cheap**	**Difficult / Costly**

Comparison of "Huge, Data-Thin" Cohorts (e.g. U.K. BioBank) And "Small, Data-Thick" Cohorts (e.g. Southampton)

Cohort Attribute	Huge – Thin	Small – Thick
Cost Per Subject due to:	Low (e.g. < $500. / data-wave)	High (if > $1,000. / data-wave)
Sample Size due to choice of:	500,000+	< 30,000
Exposures	Cheap-to-collect/store measures – e.g. genetic	Expensive, balanced mix of environmental and genetic measures
Outcomes	Cheap-to-collect administrative data – e.g. hospitalizations for diagnoses/deaths (dichotomous) → ↑ **SS.**	Expensive, directly measured bi-chemical physiologic, imaging, functional outcomes (often continuous) → ↓ **SS.**
Leading "Exposure-Measure Bias"	Large environmental exposure error >> genetic factor errors	"Better balanced errors" for environmental versus genetic factors
Leading to:	**Biased main effects and interaction results**	**Less biased results**