An American Gene-Environment Study (AGES)?

Alan E. Guttmacher, M.D.

SACGHS

March 1, 2005

Approaches to Discovering and Quantitating Genetic and Environmental Contributions to Disease Risk

- Case-control studies
- Prospective, population-based cohort studies

Case-control studies are great, but there are shortcomings…

- Frequent bias towards more severe end of disease spectrum
- Recall bias for environmental exposures and family history
- Inability to identify predictive biomarkers that signal future onset of disease

Other countries are planning large population studies of genes, environment, and health – but these will not substitute for a major project in the United States

- Other countries do not reflect the population groups of the U.S.
- Other countries do not reflect the environmental factors found in the U.S.
- Access of U.S. researchers to data from other countries' studies will be limited

insight commentary

The case for a US prospective cohort study of genes and environment

Francis S. Collins

National Human Genome Research Institute, National Institutes of Health, Building 31, Room 4B09, MSC 2152, 31 Center Drive, Bethesda, Maryland 20892-2152, USA (e-mail: fc23a@nih.gov)

AGES Working Group

- David Altshuler, MGH
- Joan Bailey-Wilson, NHGRI
- Eric Boerwinkle, UT
- Greg Burke, Wake Forest
- Wylie Burke, U. Wash.
- Chris Hook, Mayo
- Rod Howell, NICHD
- Jean MacCluer, SW Foundation
- Don Mattison, NICHD
- Jeff Murray, Iowa
- Larry Needham, CDC
- Anne Spence, UC-Irvine
- Alec Wilson, NHGRI
- Sam Wilson, NIEHS

Subgroups

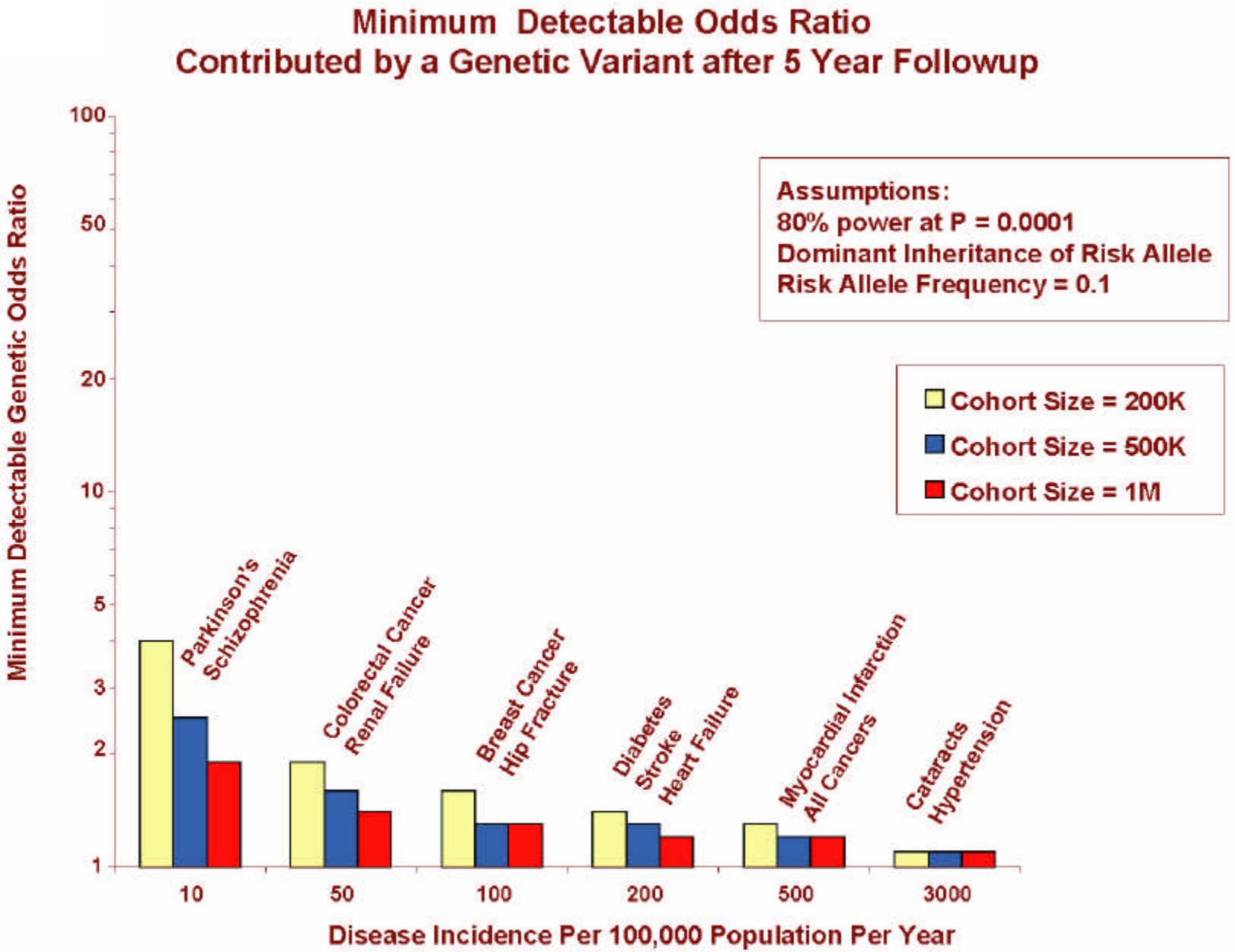
- Sampling
- Data Collection
- Power Analysis
- Community Involvement and Consent
- Phenotyping Technology
- Environmental Technology
- Bioinformatics

Major recommendations of AGES Working Group

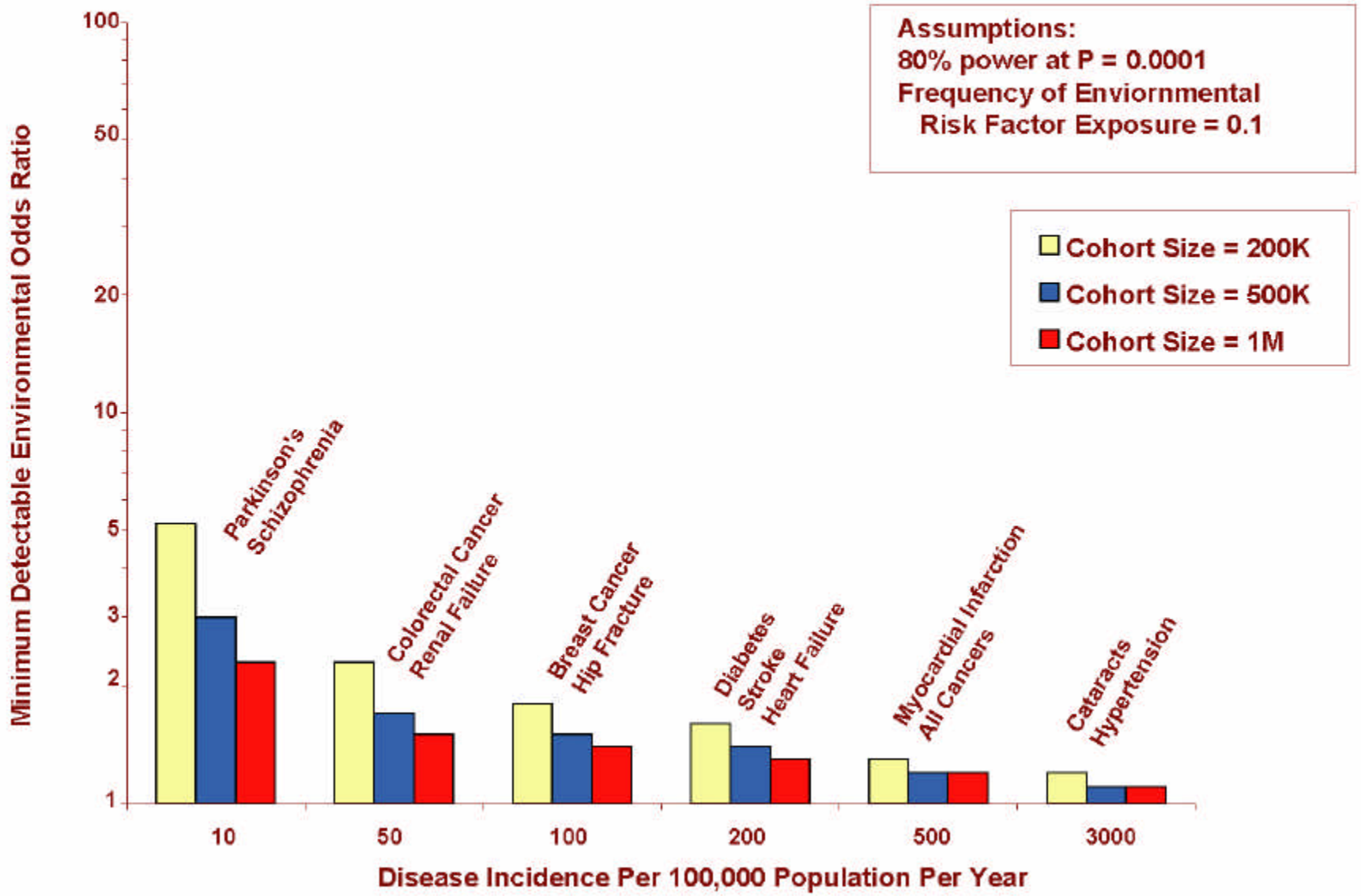
- Cohort should be chosen to match the most recent U.S. census on
  - Age
  - Sex
  - Race/ethnicity
  - Geographic region
  - Education
  - Urban/rural residence

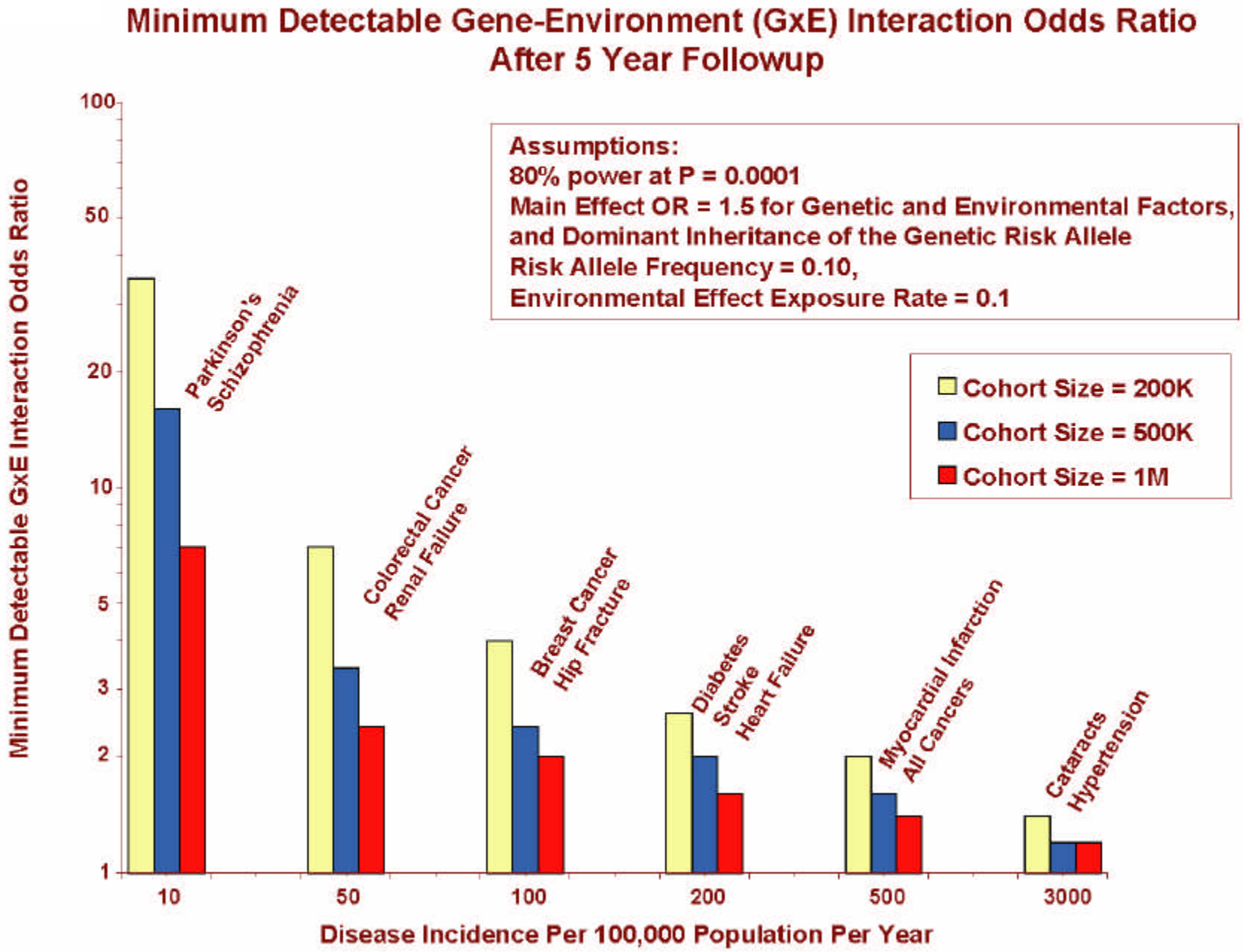
Major recommendations of AGES Working Group (cont.)

- The household should be the primary sampling unit
- Roughly 30% of cases should consist of biologically related individuals
- The cohort should be of significant size to achieve adequate power for most common diseases and quantitative traits


Minimum Detectable Odds Ratio
Contributed by a Genetic Variant after 5 Year Followup
Minimum Detectable Genetic Odds Ratio
100
50
20
10
5
3
2
1
Assumptions:
80% power at P = 0.0001
Dominant Inheritance of Risk Allele
Risk Allele Frequency = 0.1
Cohort Size = 200K
Cohort Size = 500K
Cohort Size = 1M
Parkinson's
Schizophrenia
Colorectal Cancer
Renal Failure
Breast Cancer
Hip Fracture
Diabetes
Stroke
Heart Failure
Myocardial Infarction
All Cancers
Cataracts
Hypertension
10
50
100
200
500
3000
Disease Incidence Per 100,000 Population Per Year

Minimum Detectable Environmental Odds Ratio After 5 Year Followup




Minimum Detectable Gene-Environment (GxE) Interaction Odds Ratio
After 5 Year Followup
Assumptions:
80% power at P = 0.0001
Main Effect OR = 1.5 for Genetic and Environmental Factors,
and Dominant Inheritance of the Genetic Risk Allele
Risk Allele Frequency = 0.10,
Environmental Effect Exposure Rate = 0.1
Cohort Size = 200K
Cohort Size = 500K
Cohort Size = 1M
Minimum Detectable GxE Interaction Odds Ratio
100
50
20
10
5
3
2
1
Parkinson's
Schizophrenia
Colorectal Cancer
Renal Failure
Breast Cancer
Hip Fracture
Diabetes
Stroke
Heart Failure
Myocardial Infarction
All Cancers
Cataracts
Hypertension
10
50
100
200
500
3000
Disease Incidence Per 100,000 Population Per Year

Major recommendations of AGES Working Group (cont.)

- Clinical exam
  - Baseline assessment should be limited to four hours
  - Core group of variables should be collected on all participants, other variables should be age specific
- Biological specimens
  - Core laboratory measurements
  - Stored specimens
  - Genotyping/DNA sequencing
- Follow up
  - Telephone/e-mail contact should occur every six months
  - Re-examination should be carried out every four years

Major recommendations of AGES Working Group (cont.)

- Public consultation should be extensive
  - Town meetings, focus groups
- Open-ended informed consent, with encrypted database to protect privacy and confidentiality
- A Central IRB would be highly advantageous
- Data should be immediately accessible to all investigators who have IRB approval

Reasons to start AGES now

- Urgency of discovering and validating G, E, and GxE causes of common disease
- Opportunity to understand and address causes of health disparities
- A powerful stimulus for technology development
- Potential to reduce skyrocketing health care costs

Can we afford NOT to do something like this?