

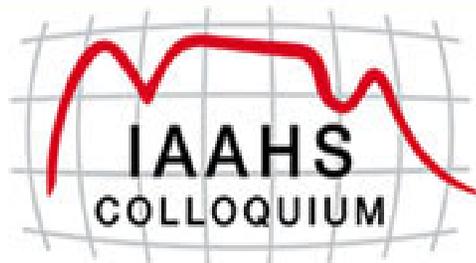
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2007 Colloquium

13th - 16th May 2007 Cape Town, South Africa

GENETICS AND HEALTH INSURANCE

Angus Macdonald

Department of Actuarial Mathematics and Statistics
and the Maxwell Institute for Mathematical Sciences
Heriot-Watt University, Edinburgh
www.maxwell.ac.uk

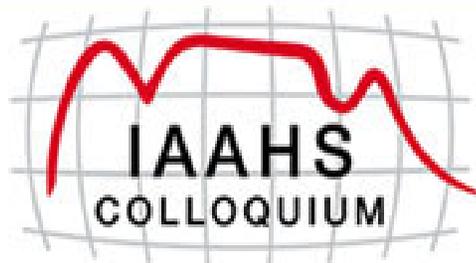


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“I am not opposed to people knowing their predisposition to an illness. ... I do oppose insurance companies and others taking this into account when they are assessing premiums, the prospects of getting a mortgage and employment.”

(Dr Ian Gibson MP, Daily Mail, 12 October 2000)

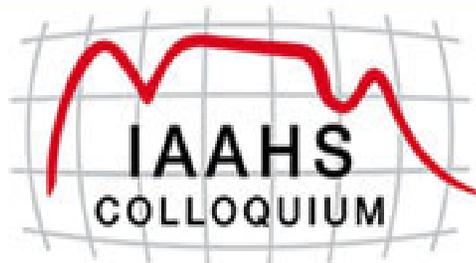


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Outline

- Review of genetics and insurance
- Genetics yesterday and tomorrow
- Actuarial modelling (1)
 - Epidemiology of multifactorial disorders
 - UK Biobank
 - A simulation study
- Actuarial modelling (2)
 - Breast cancer as a single-gene disorder
 - Breast cancer as a polymorphic disorder



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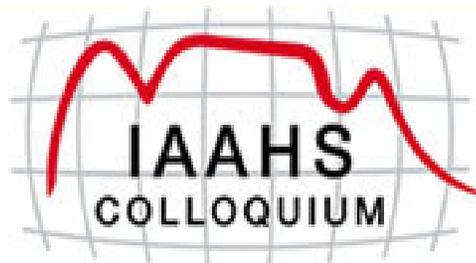
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Genetics (and Insurance) of Yesterday

- Family history of Mendelian disorders – clear genetics
- Family history of common diseases – unclear genetics
- DNA-based genetic tests – mid-1990s to now
- The “genetics and insurance debate”
 - unfair discrimination *versus* adverse selection
 - genetics = precise prediction?
 - argument from a few models e.g. Huntington’s disease
 - strong media focus

Single-Gene Disorders

Gene → Disease

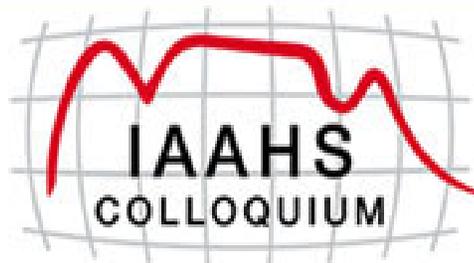


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Outcomes – the UK as an Example

- Participants
 - Government (HoC, DoH, DTI)
 - Industry (Association of British Insurers)
 - Commissions (HGAC, HGC)
 - Academia (GIRC)
- Outcomes
 - List of “significant” disorders
 - Moratoria (1996, 2001, 2005 ...)
 - Genetics and Insurance Committee (GAIC)

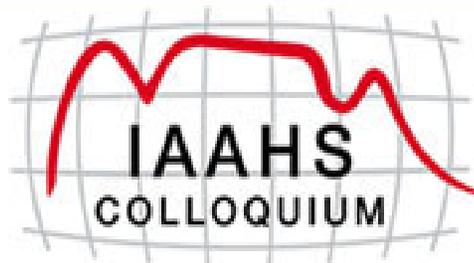


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Moratoria

- Insurers will not ask someone to take a genetic test
- Insurers will not ask about results from research trials
- Insurers will not ask about existing predictive tests
 - Up to £500,000 of life insurance
 - Up to £300,000 of critical illness insurance
 - But only for approved genetic tests
- Use of family history not restricted (compare Sweden)

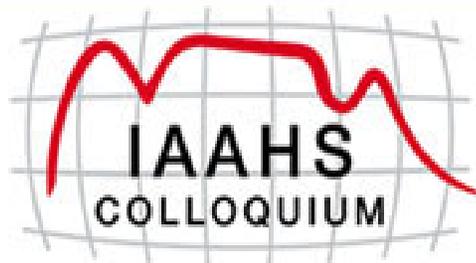


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The Genetics and Insurance Committee (GAIC)

- Insurers may apply to GAIC to be allowed to use *specific* test results, above the limits in the moratorium
- GAIC will assess:
 - The technical relevance of the test
 - The clinical relevance of the test – does it predict outcomes?
 - The actuarial relevance of the test – is it material?
- So far, one application (Huntington's, life insurance)
- Evidence of impact precedes use in underwriting – a precedent for insurance or a one-off?



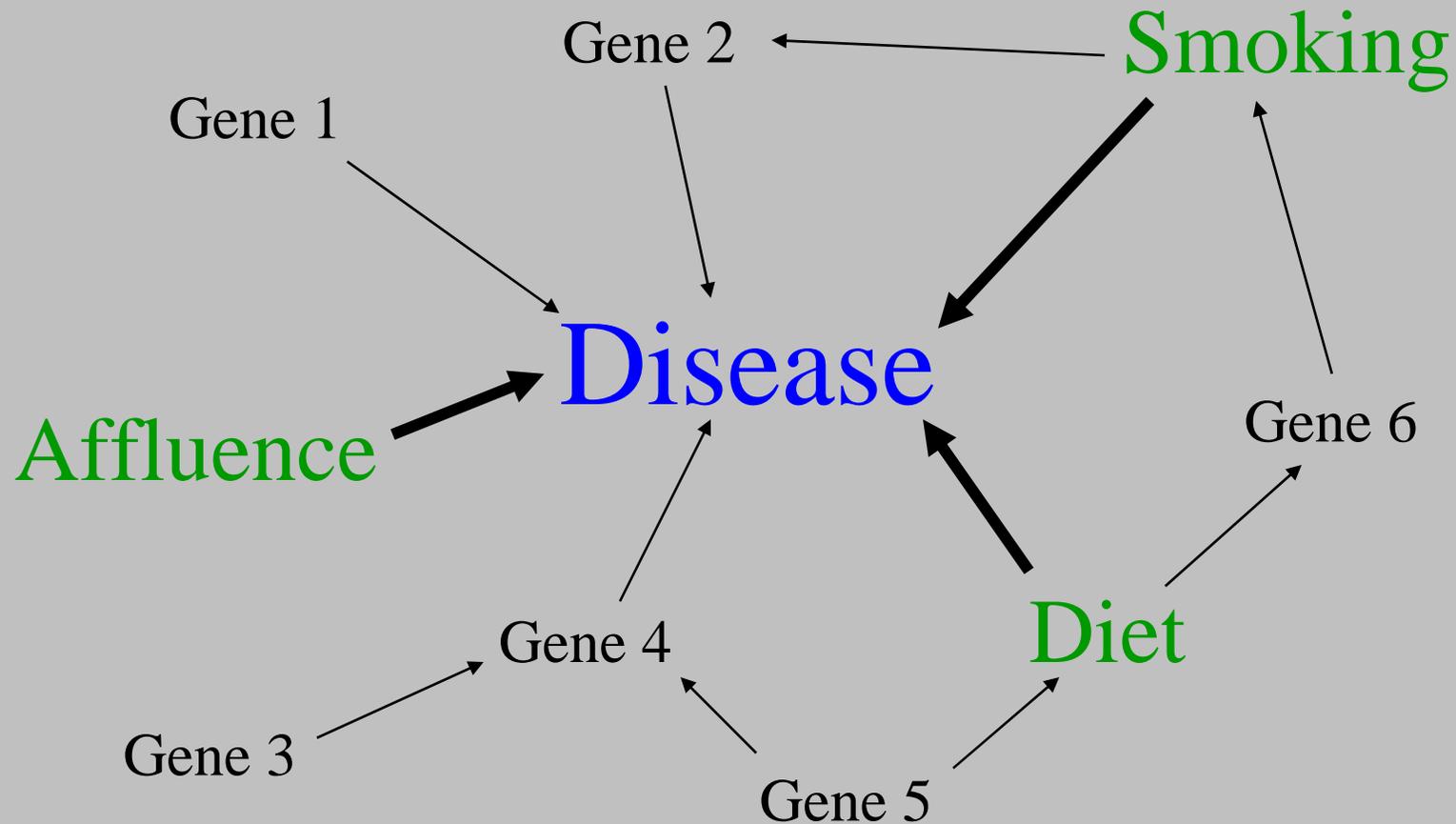
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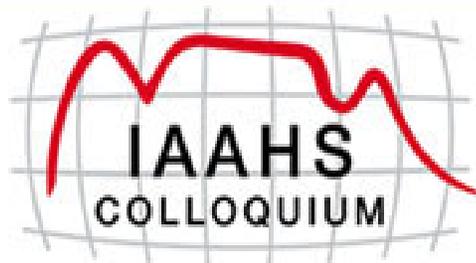
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Genetics of Tomorrow

- Genetics of common diseases
- Gene-gene, gene-environment interactions
- Whole-genome scans
- Genetic arrays
- Large-scale population studies
- Novel mechanisms (epigenetics, RNA interference)
- Genetic therapy

Multifactorial Disorders



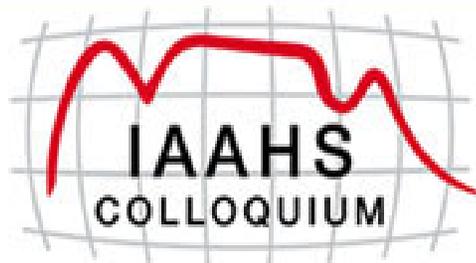


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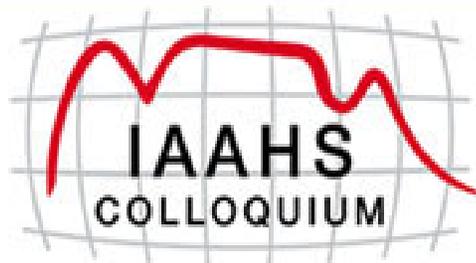


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UK Biobank

- Recruit 500,000 subjects age 40-69
- DNA samples from all subjects
- Lifestyle/medical details collected
- Follow up for 10 years
- Linkage to health records through personal doctor
- Linkage to cancer registries
- Linkage to death registries

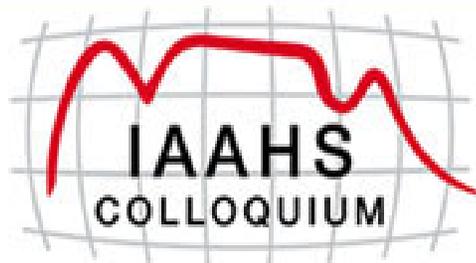


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UK Biobank

- UK Biobank only collects data
- Analysis is separate (not yet funded)
- Investigators apply to obtain UK Biobank data
- Most analyses will be case-control studies

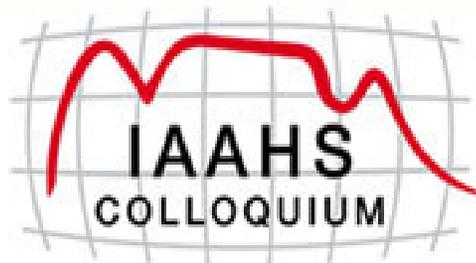


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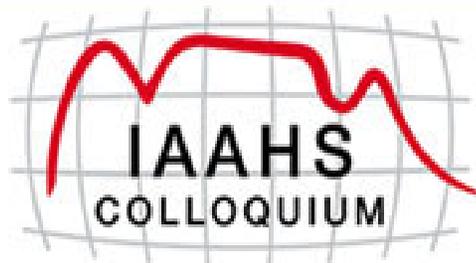
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- Most analyses will be case-control studies
- “Data from the project will not be accessible to the insurance industry or any other similar body” (UK Biobank draft protocol).



Case-Control Studies

- Method of analysing data retrospectively
- Hypothesis: some factor (e.g. genotype) is associated with some outcome (e.g. disease)
- Step 1: collect cases, $a+c$ in total:
 - a have genotype G
 - c have genotype g
- Step 2: collect undiseased controls, $b+d$ in total:
 - b have genotype G
 - d have genotype g

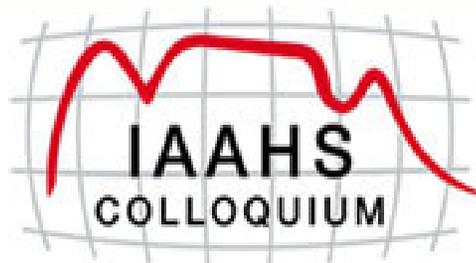


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Odds Ratios

- Actuaries will only have access to published case-control studies which will report **odds ratios**
- The odds of an event with probability P are $P/(1-P)$
- The odds ratio of an event with probability Q with respect to an event with probability P is $P(1-Q)/Q(1-P)$
- In the case-control study, ad/bc is an unbiased estimate of the odds ratio of disease, of genotype G compared with genotype g

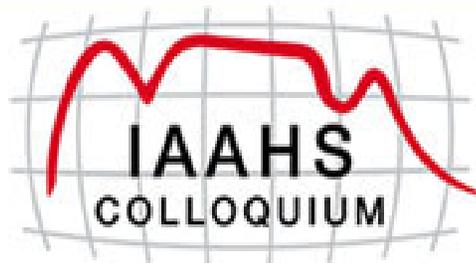


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Actuarial Use of Odds Ratios

- Actuarial models are based on intensities or forces (or probabilities obtained from them)
- Given a baseline force or intensity (e.g. risk in general population) all we need are relative risks (e.g. for each genotype)
- If P and Q are small then the odds ratio approximates the relative risk

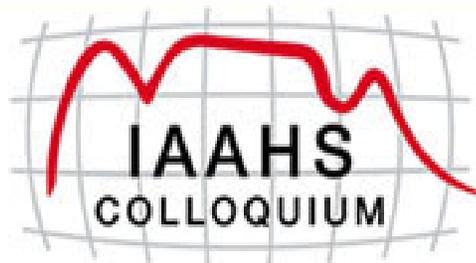


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Simulating UK Biobank

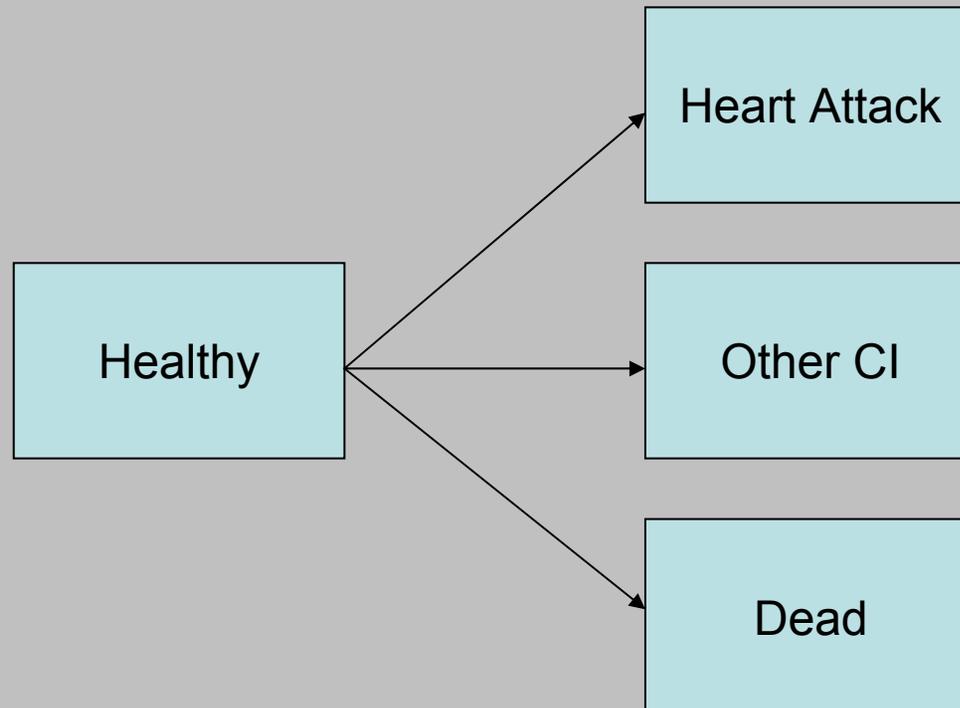
- Model of health insurance contract (critical illness)
- Sub-model of common disease risk (heart attack)
- Model of gene-environment interaction
 - Population frequencies and relative risks
- Simulate UK Biobank recruitment phase
 - Allocate 500,000 persons to age, genotype and environment
- Simulate 500,000 lifetimes over 10 years
- We have UK Biobank!

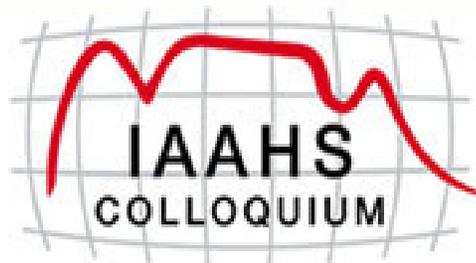


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A Simple Critical Illness Insurance Model

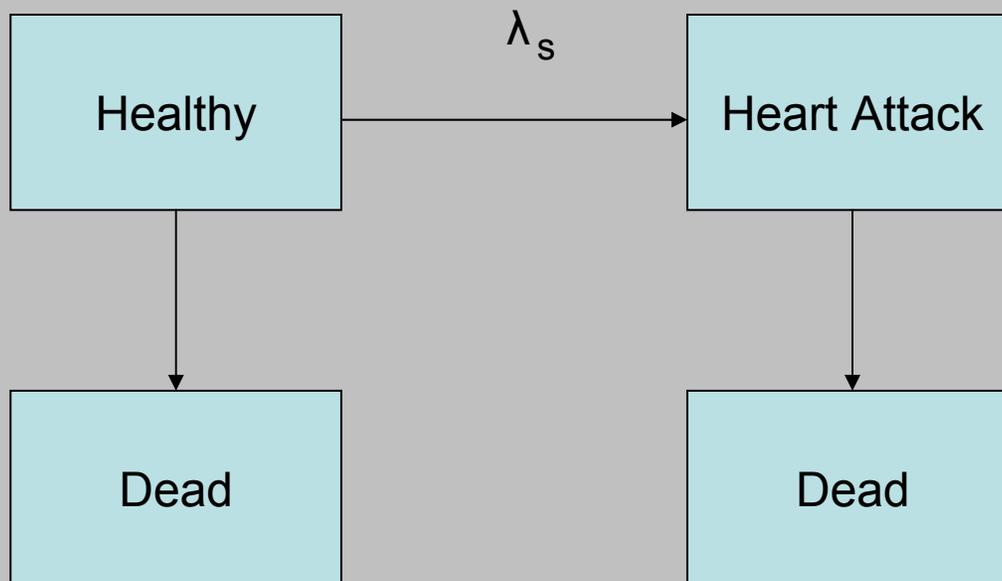


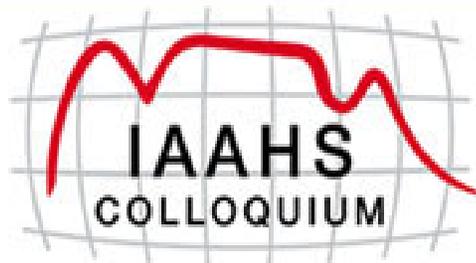


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A Simple Heart Attack Model





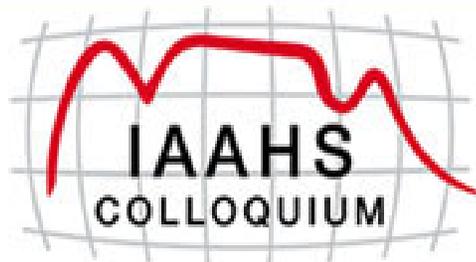
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Gene-Environment Interaction Model

- Beneficial genotype g and adverse genotype G
- Beneficial environment e and adverse environment E
- Four **strata** ge , Ge , gE , GE , for each sex
- 10% of population in each of G and E (independently)
- Table shows relative risks in each stratum, with respect to population heart attack risk

| | G | g |
|-----|-----|-----|
| E | 1.3 | 0.9 |
| e | 1.1 | 0.7 |

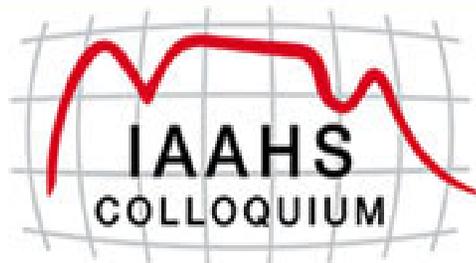


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Five UK Biobank Life Histories

| ID | Stratum | Sex | Age | Age at HA | Age at Death |
|----|---------|-----|-------|-----------|--------------|
| 1 | ge | M | 41.10 | | |
| 2 | Ge | M | 58.74 | 63.89 | 63.94 |
| 3 | ge | M | 52.27 | | |
| 4 | ge | M | 68.39 | | |
| 5 | Ge | F | 60.94 | 62.81 | |

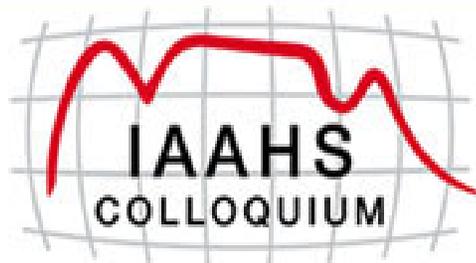


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Model Epidemiologist and Model Actuary

- Our model epidemiologist obtains funding to do a case control study, and publishes odds ratios:
 - Each sex
 - Each stratum, with respect to stratum ge
 - 5-year age bands
- Our model actuary “extracts” relative risks from odds ratios and parameterises critical illness model

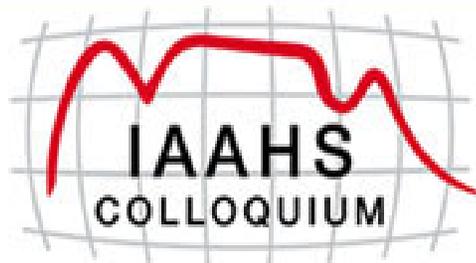


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Results – Extra Premiums w.r.t. Stratum *ge*

| Stratum | Age | Males | | Females | |
|-----------|-----|---------|---------|---------|---------|
| | | Term 15 | Term 25 | Term 15 | Term 25 |
| <i>gE</i> | 45 | 11% | 9% | 3% | 4% |
| | 55 | 8% | 7% | 5% | 5% |
| <i>Ge</i> | 45 | 21% | 17% | 7% | 8% |
| | 55 | 16% | 14% | 10% | 10% |
| <i>GE</i> | 45 | 31% | 26% | 10% | 12% |
| | 55 | 24% | 21% | 15% | 15% |

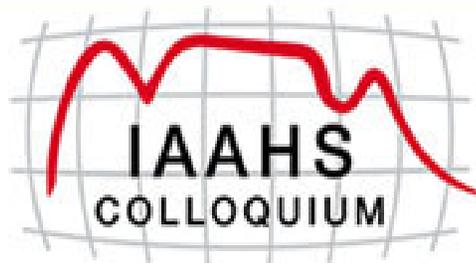


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Reliability – GAIC's Questions

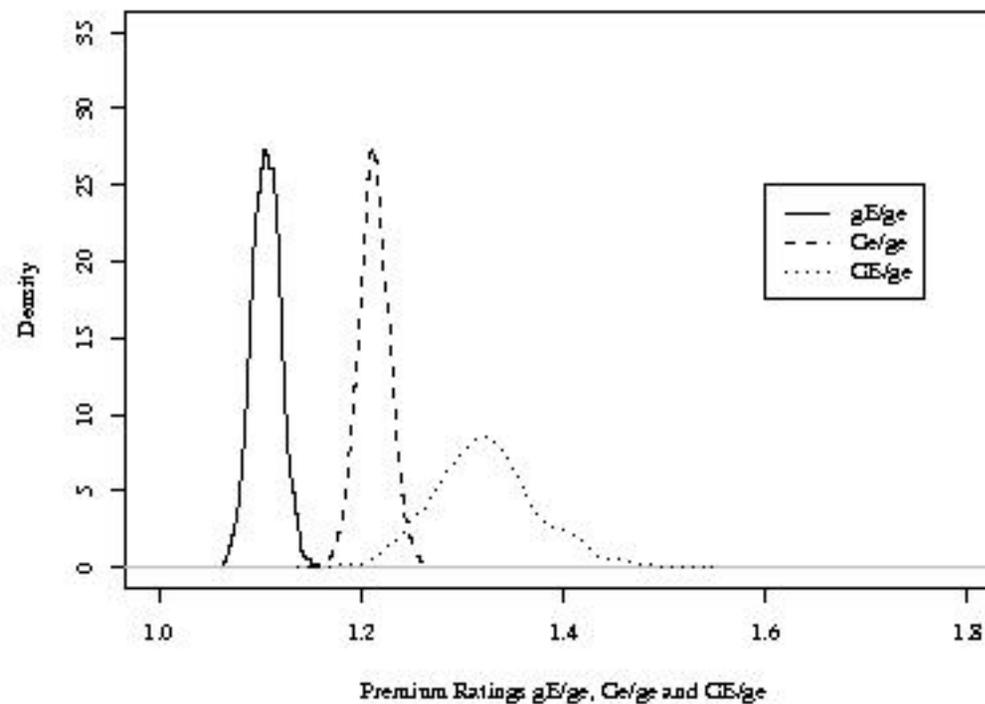
- What would GAIC want to know?
- Does genotype + environment constitute an effective, predictive risk factor?
- Approach:
 - Fix environmental and genetic risk model
 - Simulate 500,000 life histories
 - Do case-control studies and calculate premiums
 - Repeat 1,000 times

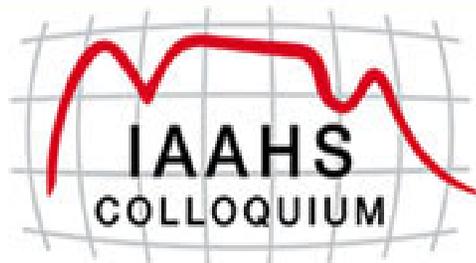


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Premium Ratings as a Proportion of Premium in Stratum ge

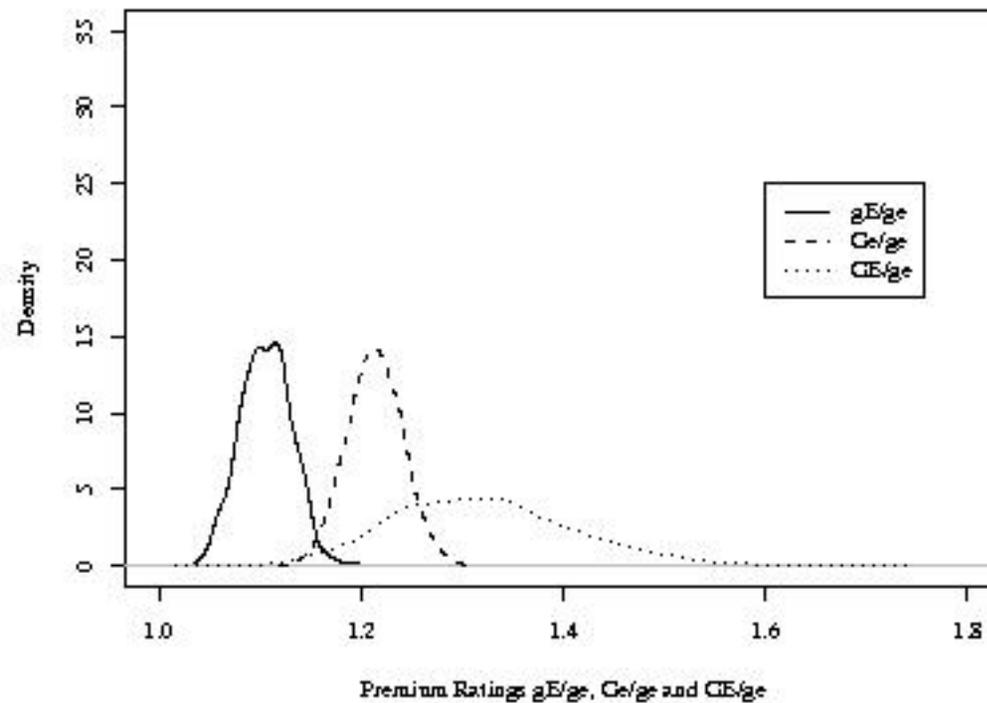


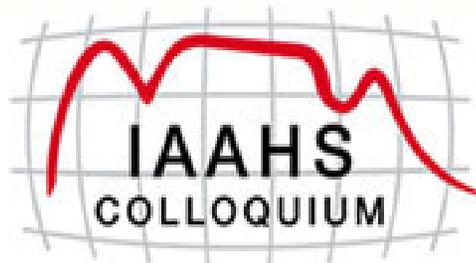


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Case Control Study With 10,000 Cases



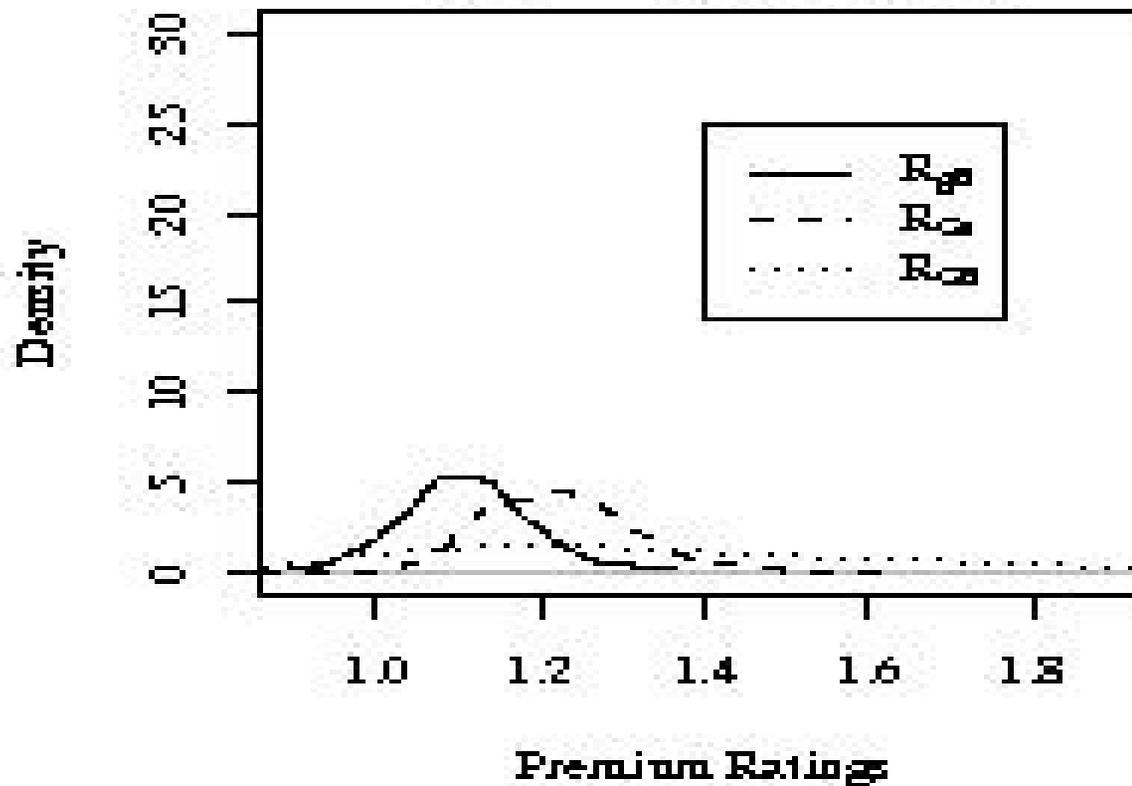


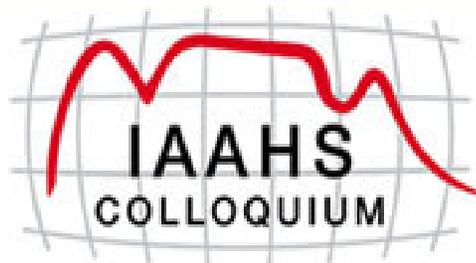
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Case-Control Study With 1,000 Cases

Base - 1,000 Cases.



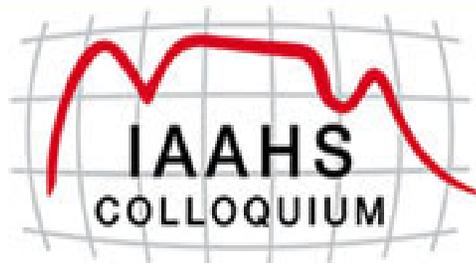


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Is Our Model Realistic?

- Only 2 genotypes
- Only 2 environmental factors
- Age and sex only other covariates
- Simple multiplicative interaction
- Epidemiologist hits on “correct” model
- Study population free of “noise” and dependencies



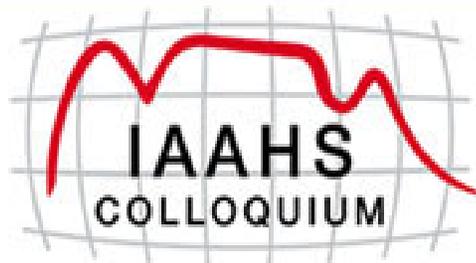
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Conclusion: Will Biobank Be Relevant?

- UK Biobank can distinguish risk differentials of the order of +50% or more (as it was designed to do)
- Point estimates of these differentials can be used to find premium ratings
- But the distributions of these ratings may not be reliably distinct, in GAIC terms, unless very large numbers of cases are used.

Macdonald, Pritchard & Tapadar (2006). ASTIN Bulletin **36** 311-346.

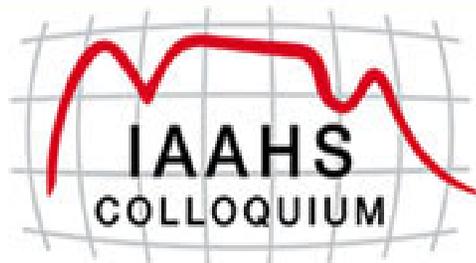


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Insurance in the Multifactorial World

- High-throughput genetic arrays **will** reveal much about complex genetic influences on biological processes – but this is not the same as disease.
- Understanding biological processes better **will** help to understand disease – but this is not the same as epidemiology.
- Epidemiology **will** emerge:
 - But it will not be highly predictive, as for single-gene disorders
 - And if subjected to GAIC-like criteria it might fail “reliability”.



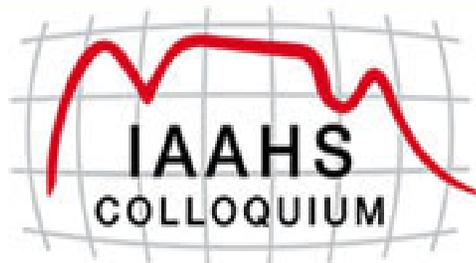
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Personalised Medicine – Here At Last?

- Oncotype DX: 21 gene screen test
 - Algorithm profiles breast cancer recurrence risk
 - Identifies value of chemotherapy
 - Cost \$3,400
- Will be paid for by insurers covering 40% of US market
- Insurers' costs will increase? (cost of tests)
- Insurers' costs will decrease? (fewer ineffective treatments)

Gewin (2007). Nature **445** 354-355



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What Will the Press Think?

- The chain from genetic discovery to reliable underwriting is very long and getting longer:
 - Association of genes with disease
 - Understanding complex mechanisms
 - Gene-environment and other interactions
 - Epidemiological studies
 - Moratoria and GAIC-type approval processes
- But the press will not understand this.
- **THIS** is the actuarial research message.