Columns and Rose: Epidemiology, Risk and Building Evidence for Population Health Interventions

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Epidemiology is:

“The study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of health problems.”

The Tasks of Epidemiology

• illustrate distributions - descriptive task
• investigate causes - inferential task
• inform interventions - applied task

in populations
CHOLERA OUTBREAK, BROAD STREET, GOLDEN SQUARE, 1854

(668 Deaths: Onsets unknown = 127; Deaths unknown = 46)

Rev H Whitehead, 1867
Rate per 100K

Age-adjusted Cardiovascular Disease Mortality, USA, 1900-1998

- All CVD
- "Heart Disease"
- CHD
- All Stroke

Age-standardised death rate (per 100,000)

USA
Finland
France
Ireland
Italy
United Kingdom
Australia

(ICD Codes 410-414, 8th/9th Division and 120-125, 10th Revision WHO 2002)
Death Rates from CHD and Stroke, US, 1950-2002

- **CHD**: 70% rate per 100,000
- **Stroke**: 70% rate per 100,000
Our understanding of “causes” needs to help explain all of these phenomena as parsimoniously as possible.

Columns and Rose

The Importance of Individual and Population Causes of Health
Our job in public health research and practice is to understand what caused this rise and fall in the population and then intervene to improve disease rates.

What are the ‘causes’ of CHD and stroke?

Which are the “important” causes? And how do we decide which are important?

- Cholesterol, hypertension, smoking, diabetes

- homocysteine, CRP, fibrinogen

- stress, social capital, physical activity, depression, income inequality, job strain ....?
## CHD

### 1+ Conventional Risk Factors

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**PPV 0.17**

Only 17% of those with the risk factors get CHD

### Specificity and Sensitivity

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<tbody>
<tr>
<td></td>
<td>0.17</td>
<td>0.95</td>
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False +ve: 0.83, False -ve: 0.05

95% of cases have the risk factors

**KIHD Study (2006)**
Risk Factors and Individual Health

Thinking Across Rows
At least 1 conventional risk factor

<table>
<thead>
<tr>
<th></th>
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<th>Yes</th>
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<tr>
<td>No</td>
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</tr>
<tr>
<td>Yes</td>
<td>80%</td>
<td>20%</td>
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Only ~ 20% of those with the risk factors get CHD?

1. These are not good predictors of individual risk?

2. What makes those individuals susceptible to the risk factors?
Guidelines on preventing cardiovascular disease in clinical practice

Absolute risk rules—but raises the question of population screening

Screening for atherosclerosis: numerous risk factors and disease markers.

Numerous Risk Factors:
- High LDL
- Low HDL
- High BP
- Diabetes
- Smoking
- CRP
- Metabolic Syn
- Lp(a)
- Homocysteine
- Dense LDL
- Lp-PLA2
- ApoB/ApoA
- Family History
- Sedentary Life
- Obesity
- Stress

Over 200 risk factors have been reported.

Examples of Arterial Structure Tests:
- Carotid IMT and Plaque Measured by Ultrasound
- Aortic and Carotid Plaque Detected by MRI
- Coronary Calcium Score Measured by CT
- Ankle Brachial Index
- Vascular Compliance Measured by Radial Tonometer

Examples of Arterial Function Tests:
- Brachial Vasoreactivity Measured by Ultrasound
- Microvascular Reactivity Measured by Fingertip Tonometer

Screening for subjects at risk for cardiovascular complications: blood biomarkers/risk factors and/or markers of subclinical disease. Apo indicates apolipoprotein; BP, blood pressure; CT, computed tomography; HDL, high-density lipoprotein; IMT, intima-media thickness; LDL, low-density lipoprotein; Lp(a), lipoprotein a; Lp-PLA2, lipoprotein-associated phospholipase A2; MRI, magnetic resonance imaging; and Syn, syndrome. Reprinted from Naghavi M et al. Am J Cardiol. 2006;98(suppl):2H–15H, with permission from Elsevier. Copyright 2006.
Association of Carotid Artery Intima-Media Thickness, Plaques, and C-Reactive Protein With Future Cardiovascular Disease and All-Cause Mortality: The Cardiovascular Health Study
Jie J. Cao, Alice M. Arnold, Teri A. Manolio, Joseph F. Polak, Bruce M. Psaty, Calvin H. Hirsch, Lewis H. Kuller and Mary Cushman
Circulation 2007;116;32-38; originally published online Jun 18, 2007;

**Composite CVD**

ROC Curves

Conventional risk factors: 0.694
+ CRP 0.696
+ carotid atherosclerosis 0.709

Conclusions

First, global risk assessment, with traditional risk factors, still represents the rational basis for cardiovascular risk stratification.

Second, addition of a robust systemic marker (CRP) of “disease activity” and a marker of structural changes of the arterial vasculature (carotid atherosclerosis), which is a surrogate of clinical disease, does not appreciably improve risk prediction.
Conclusion

“If our analysis is correct, it follows that for many, if not most, diseases we cannot reasonably expect to ever understand exactly why some people are affected and others are not.

The best we can hope for is to identify causes that account for a substantial number of cases and that are amenable to preventive intervention.”
• Epidemiology has a fetish for relative risk (RR)

• There is a 50% increased risk of heart attack in first hour after your morning coffee

The “relevant risk” is the absolute risk, but relative risk just sounds better

As Geoffrey Rose commented:

“Relative risk is not what decision-taking requires …

relative risk is only for researchers; decisions call for absolute measures.”

p. 19, *Strategy of Preventive Medicine*
Individual Risk and the Search for Individual Susceptibility Factors
Metabolically healthy but obese individuals

A subset of obese individuals seems to be protected against obesity-related metabolic complications. These individuals are described as metabolically healthy but obese, or as having uncomplicated obesity, or metabolically benign obesity. Despite having excessive body fat, people who are metabolically healthy but obese have favourable metabolic profiles, characterised by remarkably high insulin sensitivity, no sign of hypertension, and normal lipid, inflammation, and hormonal profiles (low triglycerides and C-reactive protein concentrations and high HDL cholesterol and adiponectin concentrations).

Figure: Factors that might distinguish metabolically healthy but obese individuals from at-risk obese individuals
“Vision for the Transformation of Medicine in the 21st Century”

I predict that comprehensive, genomics-based health care will become the norm with individualized preventive medicine and early detection of illnesses

(Zerhouni, 2006)
Table. Pertinent Details of Findings of Recent Whole-Genome Association Studies (All From 2007)

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<th>Disease</th>
<th>Source</th>
<th>Gene/Locus</th>
<th>No. of SNPs</th>
<th>Primary Study Cases/Controls</th>
<th>Replication Study Cases/Controls</th>
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Abbreviations: CAD, coronary artery disease; het, heterozygotes; hom, homozygotes; MI, myocardial infarction; NR, not reported; CR, odds ratio; PAR, population-attributable risk; SNPs, single nucleotide polymorphisms.

\textsuperscript{a}For information on genes listed here, see the National Center for Biotechnology Information gene database at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search\&DB=gene

\textsuperscript{b}The PAR in individuals of African ancestry was 24%.
Gene–environment interactions in psychiatry: joining forces with neuroscience

Avshalom Caspi and Terrie E. Moffitt

Individuals with one or two copies of the 5-HTT ‘short’ allele exhibited more depressive symptoms, diagnosable depression, and suicidality following stressful life events than individuals with two copies of the ‘long’ allele. A third study, by investigating the

Figure 1 | Approaches to psychiatric genetics research. a | The gene–to–disorder approach assumes direct linear relations between genes and disorder. b | The endophenotype approach replaces the disorder outcomes with intermediate phenotypes. c | The gene–environment interaction approach assumes that genes moderate the effect of environmental pathogens on disorder. d | Neuroscience complements the latter research by specifying the proximal role of nervous system reactivity in the gene–environment interaction.
Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

The Wellcome Trust Case Control Consortium

There is increasing evidence that genome-wide association (GWA) studies represent a powerful approach to the identification of genes involved in common human diseases. We describe a joint GWA study (using the Affymetrix GeneChip 500K Mapping Array Set) undertaken in the British population, which has examined ~2,000 individuals for each of 7 major diseases and a shared set of ~3,000 controls. Case-control comparisons identified 24 independent association signals at $P < 5 \times 10^{-7}$: 1 in bipolar disorder, 1 in coronary artery disease, 9 in Crohn’s disease, 3 in rheumatoid arthritis, 7 in type 1 diabetes and 3 in type 2 diabetes. On the basis of prior findings and replication studies thus far completed, almost all of these signals reflect genuine susceptibility effects. We observed association at many previously identified loci, and found compelling evidence that some loci confer risk for more than one of the diseases studied. Across all diseases, we identified a large number of further signals (including 58 loci with single-point $P$ values between $10^{-5}$ and $5 \times 10^{-7}$) likely to yield additional susceptibility loci. The importance of appropriately large samples was confirmed by the modest effect sizes observed at most loci identified. This study thus represents a thorough validation of the GWA approach. It has also
'Fat' gene found by scientists

A gene that contributes to obesity has been identified for the first time, promising to explain why some people easily put on weight while others with similar lifestyles stay slim.

People who inherit one version of the gene rather than another are 70 per cent more likely to be obese, British scientists have discovered. One in six people has the most vulnerable genetic make-up and weighs an average 3kg more than those with the lowest risk. They also have 15 per cent more body fat.

The findings provide the first robust link between a common gene and obesity, and could eventually lead to new ways of tackling one of the most significant causes of ill health in the developed world.
Predicting Diabetes from Known Susceptibility Genes vs. Clinical Measurements

ROC for Information Provided by TCF7L2, PPARG, and CNJ11 Variants

ROC for Information Provided by BMI, FBG, Family Hx, BP, HDL

AUC = 0.58

AUC = 0.88
Genetic Determinants of Response to Clopidogrel and Cardiovascular Events

Tabassoma Sirren, M.D., Ph.D., Céline Verstuyf, Pharm.D., Ph.D.,
Murielle Mary-Krauss, Ph.D., Lina Qutabneh, M.D., Eldice Drouet, M.C.,
Nicolas Minereau, M.D., F. Gabriel Seng, M.D., Ph.D., Jean-François B.,
Nicolas Danchin, M.D., Ph.D., and Laurent Bescampoun, M.D., Ph.D.,
for the French Registry of Acute ST-Elevation and Non-ST Elevation
Myocardial Infarction (FAST-MI) investigators

ABSTRACT

Background: Pharmacogenetic determinants of the response of patients to clopidogrel contribute to variability in the biologic antplatelet activity of the drug. The effect of these determinants on clinical outcomes after an acute myocardial infarction is unknown.

Methods: We consecutively enrolled 2,208 patients presenting with an acute myocardial infarction in a nationwide French registry and receiving clopidogrel therapy. We then assessed the relation of genetic variants of genes modulating clopidogrel absorption (ABCC1), metabolic activation (CYP2C9 and CYP2C19), and biologic activity (PR31217 and TP556) to the risk of death from any cause, nonfatal stroke, or myocardial infarction during 1 year of follow-up.

Results: Death occurred in 225 patients, and nonfatal myocardial infarction or stroke in 94 patients, during the follow-up period. None of the selected single-nucleotide polymorphisms (SNPs) in CYP2C19, ABCC1, or TP556 were associated with a risk of an adverse outcome. Patients with two variant alleles of ABCC1 (TT at nucleotide 3435) had a higher rate of cardiovascular events in the 1 year of follow-up than those with the ABBE wild-type genotype (CC at nucleotide 3435) (15.9% vs 10.7%; adjusted hazard ratio, 1.66; 95% confidence interval [CI], 1.20 to 2.24). Patients carrying any two CYP2C19 loss-of-function alleles (rs2235741, rs11577178, and rs35652260) or TP556 allele B had a higher event rate than patients with none (21.5% vs 13.3%; adjusted hazard ratio, 1.99; 95% CI, 1.10 to 3.58). Among the 1535 patients who underwent percutaneous coronary intervention during hospitalization, the rate of cardiovascular events among patients with two CYP2C19 loss-of-function alleles was 1.32 times the rate among those with none (95% CI, 1.71 to 7.51).

Conclusions: Among patients with an acute myocardial infarction who were receiving clopidogrel, those carrying CYP2C19 low-activity alleles had a higher rate of subsequent cardiovascular events than those who were not. This effect was particularly marked among the patients undergoing percutaneous coronary intervention. (ClinicalTrials.gov number, NCT00673036.)

CONCLUSIONS

Among patients with an acute myocardial infarction who were receiving clopidogrel, those carrying CYP2C19 loss-of-function alleles had a higher rate of subsequent cardiovascular events than those who were not. This effect was particularly marked among the patients undergoing percutaneous coronary intervention. (ClinicalTrials.gov number, NCT00673036.)

Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study

Lancet (2009)

Jean-Philippe Collet, Jean-Sébastien Ustret, Anna Bares, Eric Villevieille, Jean-Baptiste Steeve, Johanne Sivain, Laurent Beyer, Sylvie Bouyer, Guillaume Couzin, Ezequiel Boggio, Gilbert Berenson, Christian-Failu Antoni, Gilles Montalescot

Summary

Background: Clopidogrel and low-dose aspirin have become the standard oral antiplatelet regimen to prevent recurrent ischaemic events after acute coronary syndromes or stent placement. The frequent genetic functional variant 671 G→A (rs2836268) of cytochrome P450 2C19 (CYP2C19) is an important contributor to the wide variability between individuals of the antiplatelet effect of clopidogrel. We assessed whether the CYP2C19*2 polymorphism affected long-term prognosis of patients who were chronically treated with clopidogrel.

Methods: Between April 1, 1996, and April 1, 2008, 259 young patients (aged <45 years) who survived a first myocardial infarction and were exposed to clopidogrel treatment for at least a month, were enrolled in a multicentre registry and underwent CYP2C19*2-determination. The primary endpoint was a composite of death, myocardial infarction, and urgent coronary revascularisation occurring during exposure to clopidogrel. Follow-up was every 6 months. The key secondary endpoint was stent thrombosis proven by angiography.

Findings: Median clopidogrel exposure time was 1-07 years (IQR 0.28-3.0). Baseline characteristics were balanced between carriers (heterozygous rs1799963, n=64; homozygous rs1799963, n=42) and non-carriers (n=156) of CYP2C19*2 variant. The primary endpoint occurred more frequently in carriers than in non-carriers (15 vs 11 events; hazard ratio [HR] 3.09 [95% CI 1.28-7.59], p=0.005), as did stent thrombosis (eight vs four events; HR 6.66 [1.81-20.04], p=0.009). The detrimental effect of the CYP2C19*2 genetic variant persisted from 6 months after clopidogrel initiation up to the end of follow-up (HR 3.09 [1.27-7.10], p=0.009). After multivariable analysis, the CYP2C19*2 genetic variant was the only independent predictor of cardiovascular events (HR 4.04 [1.81-9.02], p=0.0006).

Interpretation: The CYP2C19*2 genetic variant is a major determinant of prognosis in young patients who are receiving clopidogrel treatment after myocardial infarction.
"We have long known that the tendency to sit down and eat the whole goddamn bag runs in certain families," said team leader Dr. Edward Alvaro. "However, until we completed our work, we weren't sure whether the disposition to cram chips down your greasy gullet was genetic or whether it was a behavioral trait learned from one or both parents."
Risk Factors and Population Health

Thinking Down Columns Leads to Rose
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<tr>
<td>Yes</td>
<td>90%</td>
<td>100%</td>
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- 90% of the cases have the risk factors
- These are good predictors of population risk
“. . . just five risk factors (smoking, lipids, hypertension, diabetes, and obesity), which a large proportion of individuals had, accounted for about 80% of the PAR.” (p. 942)
81% of the CHD decline in females due to declines in cholesterol, blood pressure and smoking.

74% of the CHD decline in males due to declines in cholesterol, blood pressure and smoking.

“Population-based studies have demonstrated that most of the public burden of disease can be attributed to low-risk individuals with relatively "normal" levels of cholesterol or blood pressure.

According to recent National Health and Nutrition Examination Survey data, among healthy adults aged 20 to 79 years, 85% had low-risk Framingham scores while only 2% had high-risk scores.”

Low Risk—and the “No More Than 50%” Myth/Dogma

_The Myth_

“The established major CHD-CVD risk factors account for no more than 50% of CHD-CVD events; and many people who experience CHD-CVD events have no risk factors.”

“The notion that these risk factors account for no more than 50% of CHD-CVD events is myth/dogma, ie, dead wrong.”

Males

- Framingham Risk Points
  - <0: 4, 9, 12
  - 10%: 13, 17
  - 15% cases

73% cases
Framingham Risk Points

- Females

10-year absolute risk

- Non-cases
- Cases

Frequency

- <1%
- 1%
- 5%
- 10%
- 19
- 25
- 51% cases
Comparing 3 Strategies

- **Population-based**: lower mean population cholesterol by 2% and thus CHD 2.7%

- **Single “High” Risk Factor**: use statins to lower cholesterol in all individuals > 6.2 mmol/L (240mg/dL)

- **Absolute Baseline Risk**: use statins to lower cholesterol in all individuals with 5-year baseline multi-factorial CVD risk > 15%

<table>
<thead>
<tr>
<th>Estimated Population Yield</th>
<th>% Treated</th>
</tr>
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<tbody>
<tr>
<td>5,180</td>
<td>42/100K</td>
</tr>
<tr>
<td>15,500</td>
<td>125/100K</td>
</tr>
<tr>
<td>35,800</td>
<td>290/100K</td>
</tr>
</tbody>
</table>

At least 1 conventional risk factor:
- Smoking, or
- Hypertension, or
- Dyslipidemia, or
- Diabetes

"Individual Case-ness" and "Population Case Load"

CHD

No

Yes

No

~ 90% cases

All individuals with >1 risk factor

PPV ~ 20%

(Most people with the risk factors don’t get CHD)

Yes

All Cases

(Most cases have the risk factors)
Individual and Population Causal Effects

How do we know what’s “important”? 
Fetal Programming of Blood Pressure and CVD

In-utero and postnatal effects
Invited Commentary: Association between Restricted Fetal Growth and Adult Chronic Disease: Is It Causal? Is It Important?

Michael S. Kramer

- 1 kg difference in birthweight $\rightarrow$ 4 mm Hg difference in systolic BP
- Difference in BW between smoking/non-smoking mothers $\sim$ 200 gm
- Protein supplementation among under-nourished women $\rightarrow$ 50 gm increase BW
- More realistic change is 100 gm BW improvement $\rightarrow$ 0.4 mmHg
Conclusions—In the largest twin study on the fetal origins of hypertension, we found that decreased birth weight is associated with increased risk of hypertension independently of genetic factors, shared familial environment, and risk factors for hypertension in adulthood, including body mass index. (Circulation. 2007)
Death Rates from CHD and Stroke, US, 1950-2002

- CHD: Rate Per 100,000
- Stroke: Rate Per 100,000

70% for both CHD and Stroke from 1950 to 2002.
Mean Birthweight and Systolic Blood Pressure (INTERSALT)

Figure 1 Association between SBP at 20–29 years and mean birthweight, for different countries included in the INTERSALT study

Owen et al. IJE (2005)
Individual and Population Causes of CVD

**Principle**: What causes most cases among individuals will also be the main causes at the population level, and so trends in those causes should correspond with trends in the outcome e.g., smoking and lung cancer
Cholesterol as an individual and population cause
Table 3  Reduction in risk (95% confidence intervals) of ischaemic heart disease events* for 1.0 mmol/l decrease in serum LDL cholesterol concentration, according to number of years in trial (58 trials)

<table>
<thead>
<tr>
<th>Year in trial</th>
<th>% Reduction in risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>11 (4 to 18)</td>
</tr>
<tr>
<td>2nd</td>
<td>24 (17 to 30)</td>
</tr>
<tr>
<td>3rd-5th</td>
<td>33 (28 to 37)</td>
</tr>
<tr>
<td>6th and subsequent</td>
<td>36 (26 to 45)</td>
</tr>
</tbody>
</table>

*IHD death and non-fatal myocardial infarction.
Sex-Specific Cholesterol Trends and Income Inequality, 1980-2002, USA

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>14.8</td>
<td>13.7</td>
<td>13.2</td>
<td>11.4</td>
<td>9.9</td>
<td>9.2</td>
</tr>
<tr>
<td>Canada</td>
<td>14.5</td>
<td>10.0</td>
<td>9.2</td>
<td>11.4</td>
<td>8.4</td>
<td>7.1</td>
</tr>
<tr>
<td>Denmark</td>
<td>8.3</td>
<td>4.8</td>
<td>8.6</td>
<td>10.8</td>
<td>10.0</td>
<td>9.1</td>
</tr>
<tr>
<td>Holland</td>
<td>5.6</td>
<td>2.7</td>
<td>3.0</td>
<td>4.7</td>
<td>4.3</td>
<td>3.0</td>
</tr>
<tr>
<td>NZ</td>
<td>19.4</td>
<td>16.9</td>
<td>19.6</td>
<td>19.7</td>
<td>19.5</td>
<td>17.9</td>
</tr>
<tr>
<td>Sweden</td>
<td>10.9</td>
<td>13.6</td>
<td>10.5</td>
<td>11.0</td>
<td>8.7</td>
<td>5.8</td>
</tr>
<tr>
<td>UK</td>
<td>10.9</td>
<td>7.7</td>
<td>6.6</td>
<td>8.2</td>
<td>8.8</td>
<td>8.5</td>
</tr>
<tr>
<td>USA</td>
<td>7.5</td>
<td>4.8</td>
<td>4.1</td>
<td>3.5</td>
<td>2.9</td>
<td>2.4</td>
</tr>
</tbody>
</table>

"New Zealanders who want to avoid a premature heart attack should stop eating butter."
-National Heart Foundation

"Quick! Get some margarine!"

Fig. 1. Cartoonist’s depiction of the likely impact of the diet-heart link on farms around New Zealand.
Serum Cholesterol and CVD
Seven Countries Study by Time Period

A “truly causal” effect at the individual level of the A-variant of the FTO gene on obesity risk.
Obesity in South Australia 1991-2003 projected to 2013

![Graph showing obesity trends in different birth cohorts from 1991 to 2013.](image)

**Figure 3:** Birth cohort crude prevalence of obesity (BMI≥30) among females between 1991 and 2003.

**Note:** Regression equations
- 1965-80 (Gen X): $-23.79 + \text{year} \times 0.01197$
- 1946-64 (Baby Boomers): $-26.987 + \text{year} \times 0.01361$
- 1925-45 (Silent Gen & WWII): $-9.262 + \text{year} \times 0.00474$
- Pre 1925 (GI Gen): 10.252

What causes obesity?

- Twin studies show high heritability of 70-80% thus evidence for a strong genetic component
- FTO gene likely causal
- Population obesity trends are increasing
What causes obesity?

- Twin studies are perfectly matched on birth cohort – and thus on secular trends

- Determinants of individual risk (e.g., FTO) may be of minor importance to population health risk

- However, determinants of individual risk may point to potentially modifiable risk processes that are of population health importance by establishing truly causal effects

Where to for epidemiology?

And how can it make a better contribution to population health
“Epidemiology Wars” – Is epidemiology “a science” and if so what sort of science?
Figure 3: New England Journal of Panic-Inducing Gobbledygook.
Exposure | Outcome
-- | --
No | No
Yes | Yes

**Individual cases**
- High clinical relevance
- Poor individual predictive ability
- Individual susceptibility
- Great complexity
- More ‘basic’ research required

**Population case load**
- High population health relevance
- Good population predictive ability
- Individual susceptibility moot once main risk factors reduced
- Less complexity
- More ‘applied’ research required on how to reduce risk factors in the population
Bridging the gap
The role of monitoring and evaluation in Evidence-based policy making
There is a considerable gap between what is known from research and what is done in practice. Part of the problem is not knowing and part is not doing.

The "not knowing" arises from our information overload, e.g., over 1,500 studies and 55 randomised trials - are added to MEDLINE each day. The "not doing" can be broken down into several steps between valid research publishing and improved outcomes ... At each step there is some "leakage".

Addressing these leakages to navigating and using best (evidence-based) practice needs a multifaceted "solution".

Paul Glasziou
From Research to Programs - Slippage at Each Step

- Research – causal?
  - Efficacy
    - Evidence
      - Evidence(s)
      - Policy
      - Implementation
      - Programs and Services
Developmental Origins of Adult Disease:
A Case Study in Biology, Sociology, Theory, Epidemiology, Intervention and Population Health

**Biological Theory**
- Developmental plasticity
- Environmental “mismatch”
- Animal models
- Maternal attachment
- Genetics
- Huge complexity

**Psychosocial Theory**
- Social transitions
- Developmental stages
- Resilience
- Early life intervention
- Maternal attachment
- Parenting

**Epidemiology**
- Retrospective / Prospective birth cohorts
- IUGR
- Genetics
- Large complex, expensive studies
- Too many questions
- Under powered Confounding

**Intervention**
- Perry pre-school
- “Olds” programs
- Limit maternal weight gain
- Smoking/Alcohol
- Infant/toddler feeding
- Physical activity
Complex biological and social theory

Large, expensive cohort studies

Efficacy trials

Effectiveness interventions

Evaluation of services

Population Health
“... the academic public health community has a great need to develop a methodology of similar impact to that of evidence-based medicine in the clinical arena to provide an evidence base for population as well as individual health problems.”

Three challenges for research-driven prevention

• a new mindset and science agenda, giving priority to preventive measures (over treatment) and intervention (over observation)

• new partnerships for preventive research and innovation that engage relevant players across sectors, institutions and borders

• new platforms must be developed, which allow the sharing of knowledge of the effectiveness of interventions for prevention in practice.

Nordforsk Report p. 6
According to Heller and Page, evidence-based public health needs appropriate “statistical” and “implementation” developments. These include:

“Statistical”

- The development and use of appropriate study designs and methods to assess interventions with and without the RCT – practical trials; science of effectiveness evaluations e.g., FHVS
- Use of routinely collected data for research and monitoring – SA NT data linkage / SA Health
- Extensions of the NNT concepts to the population (e.g., population impact number)
- Decision analysis for populations rather than individuals - population simulation modelling
“Implementation”

• Encouragement of data collection across the health and other sectors – SA NT Data linkage

• Methods of accessing data in order to calculate population measures of risk

• Methods to easily access results of public health interventions – coordinated monitoring

• Ways to present risk data to policy makers and the public so that it is easy to understand – translational tools – Sax Institute evidence finder

• Education of policy makers to use evidence – cross jurisdictional public sector engagement

• Population services audit – evaluate programs and services
1. Local Population Health Monitoring - Data Linkage
   (Health, Welfare, Justice, Child Protection, Education)

2. Local Program Effectiveness --- Efficacy
   2a. Evaluation of existing Programs
   2b. RCTs of existing program components
   2c. Novel efficacy interventions to complement/extend existing programs
   2d. Causal “signals” from observational studies

3. Simulations of Effectiveness of Population Interventions

4. Public Health Evidence Synthesis, Integration and Translation
   National and International Evidence
Thank you