Building a career in observational clinical research

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Prevalence of diabetes in adults (20-79 years) 2013

2013 382 million

Source: IDF Diabetes Atlas 2013
Public Health

Masters in Community Medicine, London School of Hygiene and Tropical Medicine

Specialist training in Public Health

Harkness Fellowship, Harvard
Epidemiology

Prevalence (%)

Men

Women

Mapuche Indian
Bantu-Tanzania
Chinese-China
Poland
Polynesian-Wallis
W. Samoa-rural
W. Samoa-urban
Cook Islands
Chinese-Singapore
US White
US Black
US Hispanic
Arab-Oman
Chinese-Mauritius
Indian-Mauritius
Nauru
Pima Indian

20
40
60
Map of North America showing Paloeindian (Clovis and Folsom) sites. Camps near big game kills occur in lower elevations from Wyoming to Arizona, New Mexico, and west Texas.

Lands of the Pima

Arizona Pima USA

Piméria Mexico Pima

Mexico
Prevalence of Type 2 Diabetes in Pima Indians in Mexico and Arizona
Prevalence of Obesity (BMI >30) in Pima Indians in Mexico and Arizona

Percent

Mexican Pima

Arizona Pima
Amount of Physical Activity in Pima Indians in Mexico and Arizona

- **Mexican Pima**: Approximately 30 hours per week
- **Arizona Pima**: Approximately 5 hours per week

- **Occupational**
- **Leisure**
Possible explanations for between-population differences in prevalence

Diabetes Mellitus: A “Thrifty” Genotype Rendered Detrimental by “Progress”?

JAMES V. NEEL
Department of Human Genetics,
University of Michigan Medical School,
Ann Arbor, Mich.

Source: Neel, Am J Human Genetics 1962
Possible explanations for between-population differences in prevalence

Review

Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis*

C. N. Hales¹ and D. J. P. Barker²

¹ Department of Clinical Biochemistry, Addenbrooke’s Hospital, Cambridge, and
² MRC Environmental Epidemiology Unit, University of Southampton, Southampton General Hospital, UK

Source: Hales and Barker, Diabetologia 1992
University of Cambridge

PhD in Epidemiology

Institute of Public Health
Population Distribution of 2-Hour Glucose in a Previously Unscreened Population: Ely Study

Estimation of the independent relationship between physical activity energy expenditure and diabetes risk

- 1 SD difference in PAEE ~ 0.97 mmol/l difference in 2h PG
- 20-30 mins walking per day ~ 0.29 mmol/l difference in 2h PG
- ~ 0.86 relative risk of DM since RR for diabetes for each 1 mmol/l 2 hr glucose = 0.6

The EPIC-InterAct Study

- EPIC-Europe - 455,680 individuals at baseline

- EPIC-Norfolk

- Stored blood
- Data on diet/physical activity
- Exposure heterogeneity

- Long follow-up
  - 4 million person years
  - 12,403 incident cases of T2D

- Nested case-cohort study within EPIC Europe

Source: Langenberg C et al, Diabetologia 2011
Estimation of relationship between physical activity and diabetes risk

Physical activity reduces the risk of incident type 2 diabetes in general and in abdominally lean and obese men and women: the EPIC–InterAct Study

The InterAct Consortium

One category difference in physical activity index associated with a 13% reduction in risk of T2DM in men and 7% in women

Source: Ekelund et al Diabetologia 2012
## Diet and type 2 diabetes risk - contributions from InterAct

<table>
<thead>
<tr>
<th>Decreased risk</th>
<th>Null association</th>
<th>Increased risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fruit and vegetable intake</td>
<td>• Milk intake; total dairy intake</td>
<td>• Red meat, processed meat intake</td>
</tr>
<tr>
<td>• Fermented dairy products</td>
<td>• Total fish intake</td>
<td>• Sweetened beverages</td>
</tr>
<tr>
<td>• Oily fish intake</td>
<td>• Dietary energy density</td>
<td></td>
</tr>
<tr>
<td>• Tea intake</td>
<td>• Carbohydrate intake, &amp; glycaemic properties</td>
<td></td>
</tr>
<tr>
<td>• Mediterranean diet pattern; other ‘prudent’ dietary patterns</td>
<td>(glycaemic index &amp; glycaemic load)</td>
<td></td>
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<tr>
<td>• Flavonoids</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Individual saturated fatty acids</td>
<td>• Individual SFA</td>
<td>• Individual SFA</td>
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<tr>
<td><strong>Nutritional biomarkers</strong></td>
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</tr>
</tbody>
</table>
Progress in identifying susceptibility loci for type 2 diabetes

Source: Voight et al, Nature Genetics 2010
Genetics currently plays only a limited role in improving prediction of type 2 diabetes

Genetic associations with intermediate pathways can identify new pathways to type 2 diabetes
Discovery of genetic loci may aid in testing the causal inference of associations

Association between circulating 25-hydroxyvitamin D and incident type 2 diabetes: a mendelian randomisation study

Zheng Ye, Stephen J Sharp, Stephen Burgess, Robert A Scott, Fumiaki Imamura, InterAct Consortium, Claudia Langenberg, Nicholas J Wareham, Nita G Forouhi

Source: Ye et al, Lancet Diabetes Endo 2014
Discovery of genetic loci may aid in pharmaceutical target validation

**CARDIOVASCULAR GENOMICS**

A genomic approach to therapeutic target validation identifies a glucose-lowering *GLP1R* variant protective for coronary heart disease

<table>
<thead>
<tr>
<th>Disease outcome</th>
<th>n_cases</th>
<th>n_controls</th>
<th>OR (95% CI)</th>
<th>P value</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 diabetes</td>
<td>25,868</td>
<td>122,393</td>
<td>0.83 (0.76 – 0.91)</td>
<td>9.4 x 10⁻⁵</td>
<td>0</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>61,846</td>
<td>163,728</td>
<td>0.93 (0.87 – 0.98)</td>
<td>9.2 x 10⁻³</td>
<td>0</td>
</tr>
</tbody>
</table>

Early growth and development and type 2 diabetes risk

Source: Hochberg et al. Endocrine Reviews 2011
Age at menarche and risk of type 2 diabetes in later life

Hazard ratio for type 2 diabetes (95% CI)

8 to 11 | 12 | 13 | 14 | 15 to 18

Unadjusted for BMI

Adjusted for BMI

Source: Elks et al, Diabetes Care 2013
Using a gene score for age at menarche with 123 loci

HR for T2D is 1.20 (95%CI 0.99-1.44)
InterAct findings: Main genetic effect of known variants

49 variants previously demonstrated to be associated with T2DM

Genetic risk score strongly associated with incident T2DM – HR per allele 1.08 (1.07-1.10) p = 10^{-41}

Per SD of GRS HR = 1.41 (1.34-1.49) p = 10^{-41}

No evidence of interaction for individual gene variants with age, sex, family history, BMI or physical activity

# InterAct findings: Main genetic effect by country

<table>
<thead>
<tr>
<th>Country</th>
<th>Cases/Subcohort</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>159/334</td>
<td>1.57 (1.29, 1.90)</td>
</tr>
<tr>
<td>Spain</td>
<td>1134/1536</td>
<td>1.51 (1.39, 1.64)</td>
</tr>
<tr>
<td>Italy</td>
<td>1820/2595</td>
<td>1.35 (1.26, 1.44)</td>
</tr>
<tr>
<td>UK</td>
<td>856/1115</td>
<td>1.41 (1.29, 1.56)</td>
</tr>
<tr>
<td>Netherlands</td>
<td>644/1211</td>
<td>1.58 (1.41, 1.77)</td>
</tr>
<tr>
<td>Germany</td>
<td>1400/1806</td>
<td>1.36 (1.26, 1.47)</td>
</tr>
<tr>
<td>Sweden</td>
<td>2232/2536</td>
<td>1.32 (1.24, 1.40)</td>
</tr>
<tr>
<td>Overall</td>
<td>2232/2536</td>
<td>1.41 (1.34, 1.49)</td>
</tr>
</tbody>
</table>

**Source:** Langenberg et al, PLoS Med 2014
Incidence of diabetes by BMI and GRS

Prevalence of diabetes in adults (20-79 years) 2013

2013  382 million
2035  592 million

Source: IDF Diabetes Atlas 2013
4.5% Prevalent but undiagnosed diabetes

Screening for diabetes

Should we screen for type 2 diabetes? Evaluation against National Screening Committee criteria

Nicholas J Wareham, Simon J Griffin

- Disease is serious
- Natural history is understood
- Disease in detectable in preclinical stage
- Screening test is cheap, safe, acceptable, reliable, sensitive, and specific
- Facilities are adequate for diagnosis and treatment
- Treatment is safe and acceptable
- Screening programs improve outcomes
- Early treatment is more effective than late treatment

Source: Wareham BMJ 2001
Individually focused lifestyle change programmes are effective in reducing progression to diabetes.

Source: The DPP Research Group, *NEJM* 346:393-403, 2002
Global prevalence of IGT (20-79 years) 2013

Source: IDF Diabetes Atlas 2013
Population Distribution of 2-Hour Glucose in a Previously Unscreened Population

## Comparison of risk groups

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Number</th>
<th>Cases</th>
<th>Inc/1000pyrs</th>
<th>PAF (%)</th>
<th>NNT (58%)</th>
<th>NNT (20%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedentary</td>
<td>14227</td>
<td>284</td>
<td>4.21</td>
<td>27</td>
<td>410</td>
<td>1188</td>
</tr>
<tr>
<td>Sedentary, family history, &gt;55yrs</td>
<td>818</td>
<td>31</td>
<td>8.03</td>
<td>4</td>
<td>215</td>
<td>623</td>
</tr>
<tr>
<td>Obese (BMI), family history, &gt;55yrs</td>
<td>246</td>
<td>25</td>
<td>21.6</td>
<td>5</td>
<td>80</td>
<td>233</td>
</tr>
<tr>
<td>Sedentary, obese (BMI + WC), family history, &gt;55yrs</td>
<td>86</td>
<td>12</td>
<td>32.6</td>
<td>3</td>
<td>53</td>
<td>153</td>
</tr>
</tbody>
</table>

- transport policy
- foot/cycle paths
- school characteristics
- workplace layout
- family activity levels
- attitudes
- preference
Non-home takeaway food exposure

Participants exposed to:
• 32 takeaway outlets on average
• up to as many as 165 outlets
• majority of outlets at work.
Evidence for environmental effects

<table>
<thead>
<tr>
<th>Environmental exposure</th>
<th>Difference in takeaway food consumption (g/day) relative to Q1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td></td>
</tr>
<tr>
<td>Q2</td>
<td></td>
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<tr>
<td>Q3</td>
<td></td>
</tr>
<tr>
<td>Q4</td>
<td></td>
</tr>
</tbody>
</table>

+5.7 grams

<table>
<thead>
<tr>
<th>Environmental exposure</th>
<th>Difference in body mass index relative to Q1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td></td>
</tr>
<tr>
<td>Q2</td>
<td></td>
</tr>
<tr>
<td>Q3</td>
<td></td>
</tr>
<tr>
<td>Q4</td>
<td></td>
</tr>
</tbody>
</table>

+1.2 units

Source: Burgoine et al BMJ 2014
A natural experimental study of investment in cycling infrastructure

CDT = ‘Cycling Demonstration Towns’, funded 2005-2011
CCT = ‘Cycling Cities and Towns’, funded 2008-2011

Contributions of observational clinical research

• Identifying risk factors and quantifying the magnitude of association and public health importance

• Investigating the causal significance of observed associations

• Informing the prediction of disease

• Investigating alternative preventive strategies

• Understanding the population level determinants of disease

• Evaluating the impact of interventions