Cardiovascular Disease: Scientific Challenges and Opportunities

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Cardiovascular disease

Lawlor et al. BMJ 2001
Cardiovascular disease

- CHD and stroke are rare until middle age
- Adult risk factors: diet, smoking, lack of physical activity, hypertension, adult obesity
Why are birth cohorts important in cardiovascular disease research?
Cardiovascular disease pathology starts early in life
Coronary artery disease in young US war fatalities

Korean war - early 1950s (Enos et al, JAMA 1953)
- 200 autopsied combatants, mean age = 22 years
- 77% evidence of atherosclerosis
- 15% clinically significant narrowing of vessel(s)

Vietnam war - late 1960s (McNamara et al, JAMA 1971)
- 105 autopsied combatants, mean age = 22 years
- 45% evidence of atherosclerosis
- 5% clinically significant narrowing of vessel(s)
Mean BP by age in England

SBP

DBP

HSE 2003
Tracking correlations of BP

Correlation coefficients for tracking and mothers’ average blood pressure with increasing age

1 Year tracking correlation (nn-1)
2 Year tracking correlation (nn-2)

Correlation of child’s blood pressure with mother’s average blood pressure

Age (years)

Correlation coefficient

0.7
0.6
0.5
0.4
0.3
0.2
0.1
0

0 1 2 3 4 5 6 7 8 9 10

de Swiet et al. BMJ 1992
Tracking correlations of lipids from childhood to adulthood

<table>
<thead>
<tr>
<th></th>
<th>Girls</th>
<th>Boys</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Cholesterol</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-8 years</td>
<td>0.48</td>
<td>0.53</td>
</tr>
<tr>
<td>9-14 years</td>
<td>0.42</td>
<td>0.45</td>
</tr>
<tr>
<td><strong>LDLc</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-8 years</td>
<td>0.48</td>
<td>0.51</td>
</tr>
<tr>
<td>9-14 years</td>
<td>0.44</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>HDLc</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-8 years</td>
<td>0.23</td>
<td>0.04</td>
</tr>
<tr>
<td>9-14 years</td>
<td>0.34</td>
<td>0.43</td>
</tr>
<tr>
<td><strong>Triglycerides</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-8 years</td>
<td>0.32</td>
<td>0.18</td>
</tr>
<tr>
<td>9-14 years</td>
<td>0.25</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Webber LS, et al. AJE 1991
Hazard ratio of mortality per 10mmHg SBP mean age 18

Hazard ratio of mortality per 10mmHg DBP mean age 18

Association of childhood (age 12-18) risk factors with CIMT measured 21 years later

<table>
<thead>
<tr>
<th>Risk Variable</th>
<th>Regression Coefficient †</th>
<th>SE</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>0.023</td>
<td>0.006</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age</td>
<td>0.002</td>
<td>0.001</td>
<td>.24</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.010</td>
<td>0.003</td>
<td>.001</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.009</td>
<td>0.003</td>
<td>.007</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.013</td>
<td>0.003</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking (no/yes)</td>
<td>0.016</td>
<td>0.007</td>
<td>.02</td>
</tr>
</tbody>
</table>

Table 4. Multivariable Model of the Relationships Between Risk Variables Measured at Ages 12-18 Years and Common Carotid Artery Intima-Media Thickness Measured 21 Years Later (n = 1170)*

*Mean age at time of first measurement, 14.9 (SD, 2.4) years.
†Expressed in millimeters for a 1-unit change in age (year) and a 1-SD change in other continuous variables and for the presence or absence of smoking.

Raitakari OT, et al. JAMA 2003
### Table 3. Multivariable Model of the Relationships Between Current Risk Variables and Common Carotid Artery Intima-Media Thickness in Adults Aged 29 Through 39 Years (N = 2229)*

<table>
<thead>
<tr>
<th>Risk Variable</th>
<th>Regression Coefficient †</th>
<th>SE</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, sex</td>
<td>0.009</td>
<td>0.004</td>
<td>.02</td>
</tr>
<tr>
<td>Age</td>
<td>0.026</td>
<td>0.002</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.004</td>
<td>0.002</td>
<td>.06</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.011</td>
<td>0.002</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>0.010</td>
<td>0.002</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking (no/yes)</td>
<td>0.011</td>
<td>0.004</td>
<td>.004</td>
</tr>
</tbody>
</table>

Abbreviation: LDL-C, low-density lipoprotein cholesterol.
*Diastolic blood pressure was also a significant correlate of intima-media thickness (P < .001) when entered into the model instead of systolic blood pressure.
†Expressed in millimeters for a 5-unit change in age (year) and a 1-SD change in other continuous variables and for the presence or absence of smoking.

Raitakari OT, et al. JAMA 2003
Number of childhood risk factors and CIMT in adulthood

Raitakari OT, et al. JAMA 2003
Early life influences on CVD

Birth size & CVD

- Low birth weight ~ CVD and risk factors

- Possible interpretations:
  1. Programming of CVD risk by impaired intrauterine nutrition/growth
  2. Genetic variants that affect both foetal growth and insulin resistance
  3. Confounding (e.g. by SEP, shared familial behaviours), statistical artefact or publication bias
Early life influences on CVD

Infant growth & CVD

• Small birth size and rapid growth?

• Sensitive or critical periods of growth?

• Development of adiposity
Child obesity & adult CHD

Behavioural risk factors for CVD

- Established in childhood

- Interventions to reduce risky behaviours in adults tend to have modest success (thus early intervention may be important)
CVD and pregnancy

- Behaviour change in pregnancy
CVD and pregnancy

- Pre-eclampsia, gestational hypertension, gestational diabetes
- Relatively little is known on the causes, full consequences and how to prevent
Gestational weight gain & CVD risk factors in offspring

- Long term risks and benefits to mother and child poorly understood
- Appropriateness of recent guidelines

Fraser et al. Circulation 2010
Challenges in cardiovascular disease research
Cohort effects
Long lag times
Causality

- Causal associations of early life factors and CVD?

Study designs to give clues to causality:
- Mendelian randomisation
- Family-based studies
- Cohort comparisons
The ideal cohort study

• Large
• Siblings, both parents
• Repeat measures during pregnancy
• Repeat measures of behaviours and biomarkers for both parents and children
• Follow-up from pre-conception to into late adulthood
So…

- Collaboration
- Cohort comparisons
- Compare across generations
- Family-based studies
- Mendelian randomisation
Global life course epidemiology

- CVD rates increasing in LMICs
- Little research
- Big differences from HICs
- Need for collaboration, but also investment in cohort studies in LMICs
Thank you

- Debbie Lawlor
- Abigail Fraser