Healthy Cardiovascular Ageing: the life course perspective
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Unlike communicable diseases, globally everyone is at risk of non-communicable diseases (NCDs)

- NCDs account for >60% all global deaths (*but tackling them was not part of the Millennium Development Goals!*)
- Risk is partly established during early development
- Risk is passed across generations, by processes which are not simply genetic
- ‘Mismatch’ later amplifies the risk of NCDs established during development
- A life course model suggests that early prevention is needed and indicates periods to intervene
- Addressing this challenge is the greatest public health opportunity since germ theory
A widely believed “fact”

Noncommunicable disease risk = genetic predisposition + bad adult lifestyle

GWAS study of 63 newly discovered and established autosomal loci found that together these genetic variants accounted for only 5.7% of variance in Type 2 diabetes susceptibility in the general population.
Odds ratios for hypertension and diabetes
22,846 US men aged 48-83 years

Hypertension

Diabetes

Birthweight (pounds)

OR

p<0.001*

OR

p<0.001*

<5.5 -7.0 -8.4 -9.9 ≥10.0

<5.5 -7.0 -8.4 -9.9 ≥10.0

*p adjusted for age only
Birthweight and type 2 diabetes

Odds Ratio for Type 2 Diabetes

Birth Weight (kg)

Nurses Health Study USA
Pima Indians

Earlyread collaboration JAMA 2009
Survival (or death from CVD) of population according to maternal BMI categories

From Reynolds RM et al BMJ 2013.
Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants

By 2025 more than 21% of women in the world will be obese
Maternal obesity

"Maternal obesity propagates intergenerational cycles of obesity and diabetes...interruption of these cycles before, during, or after pregnancy might help to stem the rising tide of non-communicable diseases worldwide."
Life course model of NCD risk
Lancet Commission: lifecourse strategy to address the global burden of raised blood pressure

Lancet 2016; 388: 2665–712
Body-Mass Index (BMI) during Adolescence and Subsequent Cardiovascular Mortality.

Cumulative Mortality from Cardiovascular Disease (%)

Yr of Follow-up

BMI Percentile

≥95th
85th–94th
75th–84th
50th–74th
25th–49th
5th–24th
<5th

Adolescence

No. at Risk

Participants at risk 1,712,018 1,042,018 540,636 160,145
Cumulative person-yr 17,201,301 30,718,320 38,472,521 41,926,636
Cumulative cardiovascular deaths 185 609 1,577 2,676

Aortic pulse wave velocity (PWV) as an early marker of cardiovascular risk in 9 year old children

Bryant et al. Circ Res. 2015;116:1202-1205
Maternal oily fish intake in late pregnancy and child’s aortic PWV.

Jennifer Bryant et al. Circ Res. 2015;116:1202-1205
Mismatch concept

Adult Environment

Increasing risk of disease from unpredicted excess

Healthy range

Developmental Environment

Optimal

Impaired

plentiful

sparse

Modified from Gluckman & Hanson (2004) Science 305 (5691):1733-6
Developmental factors amplify effects of later lifestyle on type 2 diabetes risk

Developmental factors amplify effects of later lifestyle on type 2 diabetes risk

Testing the mismatch hypothesis: Adiposity responses to unhealthy childhood diet depend on prenatal growth trajectory

S.R. Crozier, J. Bird, H.M. Inskip, N.C. Harvey, S.M. Robinson, C. Cooper, M. Hanson, K.M. Godfrey (DOHaD 2017)
Underlying mechanisms?

Healthy range

Epigenetic processes tune phenotype

Developmental Environment

Adult Environment

plentiful

sparse

optimal

impaired

Modified from Gluckman & Hanson (2004) Science 305 (5691):1733-6
Mechanisms of epigenetics

Lillicrop K et al. ANRIL promoter DNA methylation: a perinatal marker for later adiposity. EBioMedicine. Apr 26 2017

• inter-individual DNA methylation differences in umbilical cord associated with child's adiposity at age 6 years. Search for DMRs
• level of CpG methylation at birth within the promoter of the long non-coding RNA ANRIL (encoded at CDKN2A gene) significantly related to childhood adiposity at age 6 years. Functionally plausible........

• Association between ANRIL methylation and adiposity also observed in - ethnically diverse neonates in Singapore (skinfolds at 1wk, ponderal index at 18mo
  - peripheral blood from adolescents
  - adipose tissue from obese vs. lean adults
• CpG methylation was associated with ANRIL expression in vivo
• CpG mutagenesis in vitro inhibited ANRIL promoter activity
• CpG methylation enhanced binding to an Estrogen Response Element within the ANRIL promoter.
The Sustainable Development Goals (SDGs)

In September 2015, the Sustainable Development Goals (SDGs) were adopted by the UN General Assembly and the international community, setting goals to achieve by 2030.
Sustainable Development Goal 2.2

By 2030, end all forms of malnutrition, including achieving, by 2025, the internationally agreed targets on stunting and wasting in children under five years of age, and address the nutritional needs of adolescent girls, pregnant and lactating women and older persons.
Sustainable Development Goal 3.4

By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being

Ensure healthy lives and promote well-being for all at all ages
“Implementing the *Global Strategy* ... would yield tremendous returns by 2030: at least a 10-fold return on investments in the health and nutrition of women, children and adolescents through better educational attainments, workforce participation and social contributions”
Why focus on pre-conception interventions?

- Young people often do not know that they may be on a risky health trajectory, even if they appear healthy
- Many young people postpone adopting healthy lifestyles until some future date
- They do not realise that risk of NCDs can be transmitted to their future children by biological as well as environmental processes
- Many young people are not on primary health-care radar, and have poor levels of health literacy so are less likely to access services
- Whether pregnancy is planned or not, many women and their partners do not alter their lifestyles in preparation for it, nor indeed do so during pregnancy
- Women may not access health care until late in the first trimester of pregnancy – too late to prevent some risks for them and their children
Poor educational attainment
Poor diet
Take less exercise
Obese

Ill-prepared for pregnancy.

Minimal changes in diet and health behaviours

Greater fat mass, less lean mass and lower IQ at age 4

Poor infant diet

Poorer educational attainment
Poor educational attainment
Poor diet
Take less exercise
Obese

Greater fat mass, less lean mass and lower IQ at age 4

Poor infant diet

Ill-prepared for pregnancy.
Minimal changes in diet and health behaviours

Poorer educational attainment
Would you be more careful if it was you that got pregnant?
Animal studies showing paternal epigenetic effects on offspring

- Low paternal dietary folate alters the mouse sperm epigenome and is associated with negative pregnancy outcomes - Lambrot R et al *Nature Communications* 10 Dec 2013.
- Male mice fed a low protein diet have offspring with altered expression of cholesterol genes in liver – Carone BR et al (2010) *Cell* 143: 1084-96
- Male mice with pre-diabetes have abnormal sperm methylation and pass increased risk of diabetes to next two generations – Wei Y et al (2014) *PNAS* 111: 1873-78
The Healthy Generation

LifeLab: educating young people through science for their health and that of their future children
First LifeLab RCT. Odds ratio of response to questions 12 months after LifeLab / no visit, relative to baseline response and adjusted for sex and deprivation score.

<table>
<thead>
<tr>
<th>Question</th>
<th>Outcome response</th>
<th>OR</th>
<th>95%CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At what age do you think our nutrition starts to affect our future health?</td>
<td>Before birth</td>
<td>1.87</td>
<td>(1.42,2.45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>The food I eat now may affect my health in the future</td>
<td>Strongly agree or agree</td>
<td>1.19</td>
<td>(1.08,1.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>The food a woman eats when she is pregnant does not affect the health of her child</td>
<td>Strongly disagree or disagree</td>
<td>1.62</td>
<td>(1.20,2.20)</td>
<td>0.002</td>
</tr>
<tr>
<td>The food I eat now may affect the health of any children I have in the future</td>
<td>Strongly agree or agree</td>
<td>1.43</td>
<td>(1.17,1.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>The food a father eats before having a baby will affect the health of his children</td>
<td>Strongly agree or agree</td>
<td>4.05</td>
<td>(2.34,7.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>It is not important for me to eat healthy food now</td>
<td>Strongly disagree or disagree</td>
<td>1.00</td>
<td>(0.88,1.14)</td>
<td>0.9</td>
</tr>
<tr>
<td>At school I feel I have to eat and drink the same things as my friends</td>
<td>Strongly disagree or disagree</td>
<td>1.12</td>
<td>(0.90,1.39)</td>
<td>0.3</td>
</tr>
</tbody>
</table>
Long-Term Persistence of Hormonal Adaptations to Weight Loss

Figure 3. Mean (±SE) Fasting and Postprandial Ratings of Hunger and Desire to Eat at Baseline, 10 Weeks, and 62 Weeks.