Trans-generational impact of the double burden of malnutrition
A case study from India

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www.kemdiabetes.org
Life can only be understood backwards
- Soren Kierkegaard
Historic cyclical undernutrition imprinted fat deposition when food was available
Linked to insulin secretion and sensitivity
Multigenerational stunting, low SES and Diabetes in India

[Graph showing data from Cambodia, France, Germany, India, Indonesia, Netherlands, 1810-1980]

Age-standardised percentage change, 1990-2016

[Map of India with states in different colors indicating percentage change of prevalence]

GBD India 1990-2016, Lancet 2018

INDIAB, Lancet 2017
Plasticity & Programming

• Freedom for a developing system to choose the most favourable pathway
• Restriction of the freedom by the prevailing environment
  • Lifelong effects (Programming)
  • Structure and function
• Windows of vulnerability / opportunity
  • Pre- and peri-conceptional period
  • Pregnancy & Lactation
  • Adolescence
• ‘Genetic’ & ‘Epigenetic’ mechanisms
• Environment:
  • Nutrition, Metabolism
  • Stress, Pollutants
  • Early life abuse
  • Microbiome
• Multigenerational, ?? Reversibility
Diabetes

Undernutrition: LBW, under 5y

Capital of two

Micronutrients
Iron, B12, vit D, folate....

Macronutrients
Glucose, FAs, Cholesterol....

www.worldmapper.org
Born small, Big later

4 yrs

Pune Children’s Study (1992-94)
Age 4 years

Bhargav et al. NEJM 2004

Insulin Resistance

8 yrs

Bavdekar et al, Diabetes, 1999

21 yrs

Bhargav et al. NEJM 2004
Pune Maternal Nutrition Study

1993
Preconception
Maternal Size
Hemoglobin 2675

1994-96
Intrauterine
Maternal Size
Nutrition
Metabolism
Paternal size
Metabolic variables
Fetal growth (USG) 244
Size Phenotype 770

1995
Birth
Growth every 6 months 743

1996-98
Preconception
Maternal Size
Hemoglobin 2675

1994-96
Intrauterine
Maternal Size
Nutrition
Metabolism
Paternal size
Metabolic variables
Fetal growth (USG) 244
Size Phenotype 770

1995
Birth
Growth every 6 months 743

2000-03
Postnatal
6 and 12 y
Children & parents
Size, body composition
IR
CVD risk markers
Cognition 698/723 (96%)

2006-08
18 y
Children & parents
Size, body composition
IR
CVD risk markers
Genetics and Epigenetics n=663/690

Bio Bank: DNA, Plasma, Urine, Buccal swabs

Bio Bank: DNA, Plasma, Urine, Buccal swabs, Microbiota
Maternal Nutrition, Fetal Growth & NCD Risk

Mothers: 42 kg, 1.52m, 18.1 kg/m²
Thin-fat babies: (2.7 kg), 70% SGA

Adjusted for gestation, sex, and maternal size

Yajnik CS, APJC,N 2003
Yajnik CS et al, IJ Ob 2003
N Modi, Ped Res 2009
Pune Maternal Nutrition Study
18y follow up of Thin-fat babies

<table>
<thead>
<tr>
<th>356</th>
<th>N</th>
<th>307</th>
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<tbody>
<tr>
<td>2.7</td>
<td>Birthweight kg</td>
<td>2.6</td>
</tr>
<tr>
<td>42</td>
<td>Underweight %</td>
<td>55</td>
</tr>
<tr>
<td>8</td>
<td>Over wt and Obese %</td>
<td>4</td>
</tr>
<tr>
<td>11</td>
<td>Stunted %</td>
<td>10</td>
</tr>
<tr>
<td>27</td>
<td>IFG %</td>
<td>8</td>
</tr>
<tr>
<td>10</td>
<td>IGT %</td>
<td>9</td>
</tr>
<tr>
<td>0</td>
<td>DM (n)</td>
<td>2</td>
</tr>
</tbody>
</table>

Prediabetes (190, 28.7%)
Males: 133, 37%, Females: 57, 18.5%
Pune Rural Intervention in Young Adolescents (PRIYA)

Pre-intervention screening (n=690)
• Exclusion
  - 117 low B12
  - 2 anemic
  - 14 medical

Randomisation (n=557)

Intervention

Vitamin Sep 2012
Milk powder May 2013
Mid-trial sample Apr 2013
Mid-trial analysis Jun 2014

Feb-June 2012

1) B12 (2mcg)
2) B12 (2mcg) + MMN+ milk powder
3) Placebo

Newborn
• Cord blood B12, OMICs etc
• Anthro
• Follow up

1st delivery Jun 2013

Iron and folic acid tablets as per Government of India guidelines to all; Nov 2012
1993-96

2013-18
Predicted mean trajectory
Linear Mixed Effects, random intercept, cubic smoothing spline
Locally weighted scatterplot smoothing

Correlation matrix of fasting glucose

<table>
<thead>
<tr>
<th>Corr Coeff</th>
<th>F0 28 wks</th>
<th>F1 6 Yrs</th>
<th>F1 12 Yrs</th>
<th>F1 18 Yrs</th>
<th>F1 28 Wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1 28 Wks</td>
<td>0.1209</td>
<td>0.2926</td>
<td>0.3742</td>
<td>0.2904</td>
<td>1</td>
</tr>
</tbody>
</table>
Maternal and Offspring Characteristics  
(F0, F1 & F2 PMNS - PRIYA+Non-PRIYA)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>F0 (N=125)</th>
<th>F1 (N=125)</th>
<th>F1-F0 [N=111]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marriage Age (years)</td>
<td>17.0</td>
<td>18.8***</td>
<td>+ 1.6 yrs</td>
</tr>
<tr>
<td>Education (years)</td>
<td>6.0</td>
<td>12.0***</td>
<td>+ 7 yrs</td>
</tr>
<tr>
<td>Primips (%)</td>
<td>32.0</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>152.0</td>
<td>157.5***</td>
<td>+ 6 cm</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>20.2</td>
<td>21.3***</td>
<td>+ 1.1 kg/m2</td>
</tr>
<tr>
<td>GDM (%)</td>
<td>2.4 (2h ≥ 140)</td>
<td>11.2 (IADPSG)</td>
<td></td>
</tr>
<tr>
<td>F Glucose (mg%)</td>
<td>71.0</td>
<td>80.0***</td>
<td>+ 10.0 mg%</td>
</tr>
<tr>
<td>2hr Glucose (mg%)</td>
<td>76.0</td>
<td>112.5***</td>
<td>+ 31.0 mg%</td>
</tr>
<tr>
<td>F Insulin (mU/L)</td>
<td>2.3</td>
<td>6.1***</td>
<td>+ 3.4 mU/L</td>
</tr>
<tr>
<td>2hr Insulin (mU/L)</td>
<td>11.5</td>
<td>52.7***</td>
<td>+ 40.2 mU/L</td>
</tr>
<tr>
<td>Cholesterol (mg%)</td>
<td>184.5</td>
<td>191.0**</td>
<td>+ 7.0 mg%</td>
</tr>
<tr>
<td>HDL (mg%)</td>
<td>42.0</td>
<td>57.0***</td>
<td>+ 16.0 mg%</td>
</tr>
<tr>
<td>Triglycerides (mg%)</td>
<td>133.5</td>
<td>113.5*</td>
<td>- 10.0 mg%</td>
</tr>
<tr>
<td>HOMA IR</td>
<td>0.3</td>
<td>0.7***</td>
<td>+ 0.4</td>
</tr>
<tr>
<td>Disposition index</td>
<td>239.9</td>
<td>130.3***</td>
<td>- 106.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neonate characteristics</th>
<th>F1 (Female) [N=118]</th>
<th>F2 (Female) [N=54]</th>
<th>F2 (Male) [N=64]</th>
<th>(F2-F1) Female [N=51]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (gm)</td>
<td>2575</td>
<td>2760*</td>
<td>2688</td>
<td>200 gm</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>47.4</td>
<td>48.2</td>
<td>48.0</td>
<td>0.7 cm</td>
</tr>
<tr>
<td>Head circ (cm)</td>
<td>32.6</td>
<td>33.0*</td>
<td>33.2</td>
<td>0.2 cm</td>
</tr>
<tr>
<td>Abd circ (cm)</td>
<td>28.9</td>
<td>29.6*</td>
<td>29.6</td>
<td>0.9 cm</td>
</tr>
<tr>
<td>Sum of skinfolds (mm)</td>
<td>8.4</td>
<td>8.1</td>
<td>7.6</td>
<td>-0.6 mm</td>
</tr>
</tbody>
</table>

Median or %, * p<0.05, ** p<0.01, *** p<0.001
Preconception health 1

Before the beginning: nutrition and lifestyle in the preconception period and its importance for future health

Judith Steptoe, Nicola Healy, Joanna Violanti, Jennifer Hull, Yoko Hirose, Marie-Claude A Bouchard, Jean E Cook, Lisa P facet, Carol Beppler, Sarah E. Van Dusen, Mary E. Dyer, Despina Sakrison, Silke E. Goethe, Anne M. Allen, Alan F. Jacobson

A woman who is healthy at the time of conception is more likely to have a successful pregnancy and a healthy child. We reviewed published evidence and present new data from low-income, middle-income, and high-income countries on the timing and importance of preconception health for subsequent maternal and child health. We describe the extent to which pregnancy is planned, and whether planning is linked to preconception health behaviors. Observational studies have shown links between health before pregnancy and maternal and child health outcomes, with consequences that can extend across generations, but awareness of these links is not widespread. Poor nutrition and obesity are the emerging causes of reproductive age, and differences between high-income and low-income countries have become less distinct, with typical diets falling far short of nutritional recommendations in both settings and especially among adolescents. Several studies show that inconsistent supplementation during pregnancy can cause important maternal and fetal outcomes. Poor diet can affect health behaviors that women may not be aware of preconception, and poor health at the time of conception can also affect future outcomes. Other interventions to improve diet during pregnancy have had little effect on maternal and newborn health outcomes. Comparatively few interventions have been made for preconception diet and lifestyle. Improvements in the measurement of preconception planning have quantified the degree of pregnancy planning and suggest that it is more common than previously recognized. Planning for pregnancy is associated with a reduced pattern of health behaviors before conception. We propose several preconception interventions to reduce developmental and lifelong adverse outcomes. Increased focus on intervention before conception is needed to improve maternal and child health and reduce the growing burden of non-communicable disease. Adolescent continued efforts to reduce smoking, alcohol consumption, and obesity in the population, we call for heightened awareness of preconception health, particularly regarding diet and nutrition. Importantly, health professionals should be alerted to ways of identifying women who are planning a pregnancy.

Preconception health 2

Origins of lifetime health around the time of conception: causes and consequences

Torm Fimming, Ada E. Fleten, Miguel A. Khatib, John C. Alton, Andrew W. Perry, Judith Steptoe, Marry G. Lister, Richard Jeffery, Jon-Mark Albon, Bernadette R. Harten, Evangelia Antoniou, Kristin Johannessen, Kasey Jeffery, Michael L. Smith, Jennifer G. Jepson, John C. Alton

Parental environmental factors, including diet, body composition, metabolism, and stress, affect the health and chronic disease risk of people throughout their lives, as captured in the Developmental Origins of Health and Disease concept. Research across the epidemiological, clinical, and basic science fields has identified the period around conception as being crucial for the processes mediating parental influences on the health of the next generation. During this time, from the maturation of gametes through early embryonic development, parental lifestyle can adversely influence long-term risk of offspring cardiometabolic, metabolic, immune, and neurological outcomes, often termed developmental programming. We review preconception induction of disease risk from four broad sources: maternal accumulation and obesity, maternal endocrinology, related paternal factors, and the use of assisted reproductive treatment. Studies in both humans and animal models have demonstrated the multifaceted biological mechanisms, including epigenetic, cellular, biochemical, and metabolic processes. We also present a meta-analysis of mouse paternal and maternal protein and nutriment that suggests distinct parental preconception contributions to paternal outcomes. We propose that the evidence for preconceptional effects on offspring is now compelling, that it calls for new guidance on parental preparation for pregnancy, beginning before conception, to protect the health of offspring.

Preconception health 3

Intervention strategies to improve nutrition and health behaviours before conception


The multidisciplinary nature of both health and sex education before conception has produced implications for the growth, development, and long term health of future offspring. Evidence of the effectiveness of preconception interventions for improving outcomes for mothers and babies is scarce. However, given the huge potential health return and relatively low cost and risk of harms, research into potential interventions is warranted. We identified three preconception strategies for intervention that are likely to be scalable and have positive effects on a range of health outcomes: supplement and fortification, cash transfers and vouchers, and lifestyle change interventions. On the basis of these strategies, we suggest a model specifying pathways to effect. Pathways are incorporated into a lifetime framework using individual motivations and vulnerabilities at different preconception action phases, to guide design and targeting of preconception interventions. Interventions for individuals not planning immediate pregnancy take advantage of settings and implementation platforms outside of the maternal and child health arena, since this group is unlikely to be engaged with maternal health services. Interventions to improve women’s nutritional status and health behaviors at all preconception action phases should consider social and behavioural determinants, to avoid overwhelming health and grade inequalities, and be underpinned by a social movement that reaches the study population. We propose a dual-strategy that targets specific groups already planning a pregnancy, while improving the health of the population more broadly. Modern marketing techniques could be used to present a social movement based on an emotional and symbolic connection between improved preconception maternal health and nutrition, and offspring health. We suggest that novelty and scalable benefits to public health might be achieved through strategic engagement with the private sector. Political theory supports the development of an advocacy coalition of groups interested in preconception health, to harness the political will and leadership necessary to turn high-level policy into effective coordinated action.

Lancet, Preconception Health, 2018
Pregnancy with a Female Child

From two to three!
Dual Teratogenesis

Undernourished (small) mother
Fetal undernutrition
Small baby (Thin-fat)
Insulin resistance

Undernutrition

Fetal adiposity and islet dysfunction
Postnatal undernutrition
Macrosomia

Overnutrition

Altered fuels
Pre gestational and gestational hyperglycemia
Obesity and hyperglycemia

Postnatal over nutrition (Urbanisation)
Fuel-mediated Teratogenesis

Nutrient-mediated Teratogenesis

Type-2 Diabetes
Mean Birth Weight (Kg)

Yajnik CS 2009
Multigenerational Undernutrition Increases Susceptibility to Obesity and Diabetes that Is Not Reversed after Dietary Recuperation

Authors
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Sarang N. Satoor,
Mahesh S. Karandikar, ..., Anthony C. Keech, Alicia J. Jenkins, Chittaranjan S. Yajnik

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In Brief
In a rat model of undernutrition over 50 generations, closely mimicking human populations in developing countries, Hardikar et al. show that undernourished rats display metabolic abnormalities associated with epigenetic changes, which are not reversed following unrestricted access to normal chow in two subsequent generations.
Summary

• We usually think ‘short term’ in transition
• Historical and Long term imprints dictate the response
• Part of it is genetic (distant past), a substantial part is epigenetic
  • not so distant
  • Intergenerational (pre- and gestational)
  • Lifecourse
• Past history is mostly undernutrition, the modern life mostly overnutrition
• Together they contribute to Obesity and NCDs
• There may be some inevitability due to biology
THANK YOU!
Evolving double burden of malnutrition in India, Pune Cohorts

Nutrition Transition

<table>
<thead>
<tr>
<th>F₀ Mothers</th>
<th>F₀ Fathers</th>
<th>F₁ Babies</th>
<th>F₁ Young Adults</th>
<th>F₂ Babies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urban 26yrs 155 cm 25kg/m²</td>
<td>Urban 31yrs 169 cm 26 kg/m²</td>
<td>Thin-fat BW= 2.9 kg SGA 22% LGA 11%</td>
<td>15yrs 30% Overweight/Obese 5% DM 40% pre-diabetes</td>
<td>NA</td>
</tr>
<tr>
<td>Excess Energy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Micronutrients</td>
<td>All</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA -</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate Energy</td>
<td>&lt;5%</td>
<td>Thin-fat BW= 2.8 kg SGA 35% LGA &lt;1%</td>
<td>21yrs 22 kg/m² BMI 22 kg/m² Taller 5 cm</td>
<td>20% Overweight/Obese 5% DM 20% prediabetes 15% GDM</td>
</tr>
<tr>
<td>Low Micronutrient</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA +/-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Energy</td>
<td>&lt;1%</td>
<td>Thin-fat BW= 2.7 kg SGA 54% LGA 0%</td>
<td>20 yrs 19 kg/m² BMI 19 kg/m² Taller (5cm)</td>
<td>28% pre-diabetes 15% GDM</td>
</tr>
<tr>
<td>Low Micronutrients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA ++</td>
<td></td>
<td></td>
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</tr>
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</table>

Multi-gen under nutrition
- Energy scarcity
- Micronutrient deficiencies
- High load of Infections

Lancet-WHO, under review
Height of F0 fathers and F1 boys

- Height distribution
- Difference: +3.9 cm

Height of F0 mothers and F1 girls

- Height distribution
- Difference: +3.7 cm

Birth characteristics of F1 mothers and F2 girls

1. Birth weight
   - Difference: +220 gm

2. Length
   - Difference: +0.6 cm

3. Sum of skinfolds
   - Difference: -0.4 mm
**Newly diagnosed Type 2 DM**
*(Indian vs UK white)*

**Clinical picture**

The Y-Y paradox

O'Hagan S Yajnik, John S Yudkin

The two authors share a near identical body-mass index (BMI), but as dual X-ray absorptiometry imagery shows (right) there is where the similarity ends. The first author (figure, left) has substantially more body fat than the second author (figure, right). Lifestyle may be relevant: the second author runs marathons whereas the first author’s main exercise is running to beat the closing doors of the elevator in the hospital every morning. The contribution of genes to such adiposity is yet to be determined, although the possible relevance of prenatal undernutrition is supported by the first author’s low birthweight. The image is a useful reminder of the limitations of BMI as a measure of adiposity across populations.

Diabetes Unit, KEM Hospital Research Centre, Rastra Path, Pune 411011, India (S Yajnik); International Health and Medical Education Centre, University College London, UK (J S Yudkin)