It begins before the beginning

Early life origins of diabetes in India

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Danish Diabetes Academy

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PERSPECTIVE

Crystal Ball Series

Confessions of a thin-fat Indian

Chittaranjan S. Yajnik[1]

Received: 5 October 2017 / Accepted: 10 October 2017

Clinical picture

The Y-Y paradox

Chittaranjan S Yajnik, John S Yudkin

The two authors share a near identical body-mass index (BMI), but as dual X-ray absorptiometry imagery shows that is where the similarity ends. The first author (figure, right) has substantially more body fat than the second author (figure, left). 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 intrauterine 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, Rasta Peth, Pune 411011, India (C S Yajnik MD); International Health and Medical Education Centre, University College London, UK (J S Yudkin FRCP)

Type 2 Diabetes
The Dogma

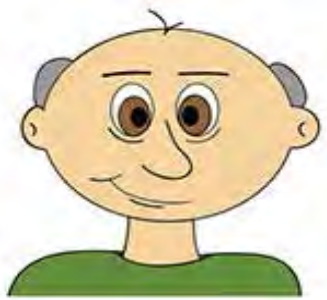
Susceptibility
Genetic
(Polygenic)

Non-Modifiable

+

Precipitating Factors

Age & Obesity
Diet
Physical inactivity
Stress



55y, 34 kg/m2, IGT

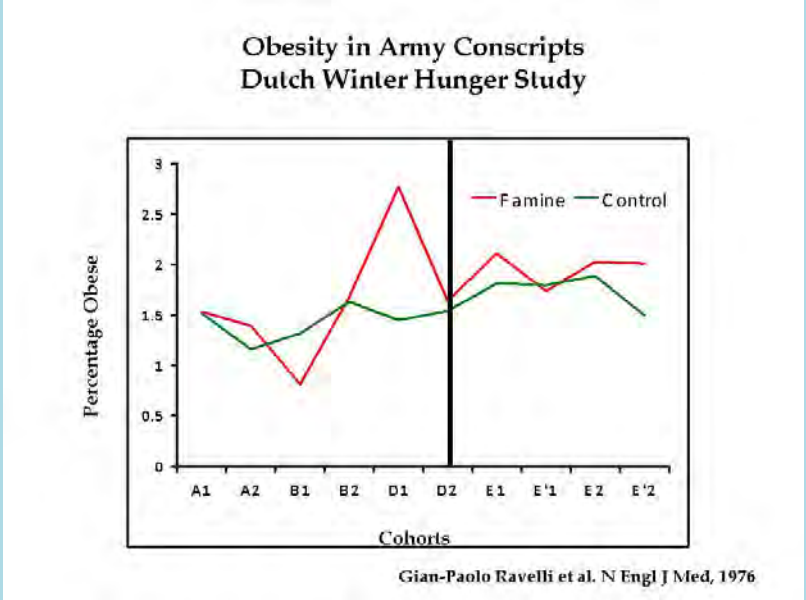
Prevention: Rx precipitating factors

End-stage, Post-reproductive !

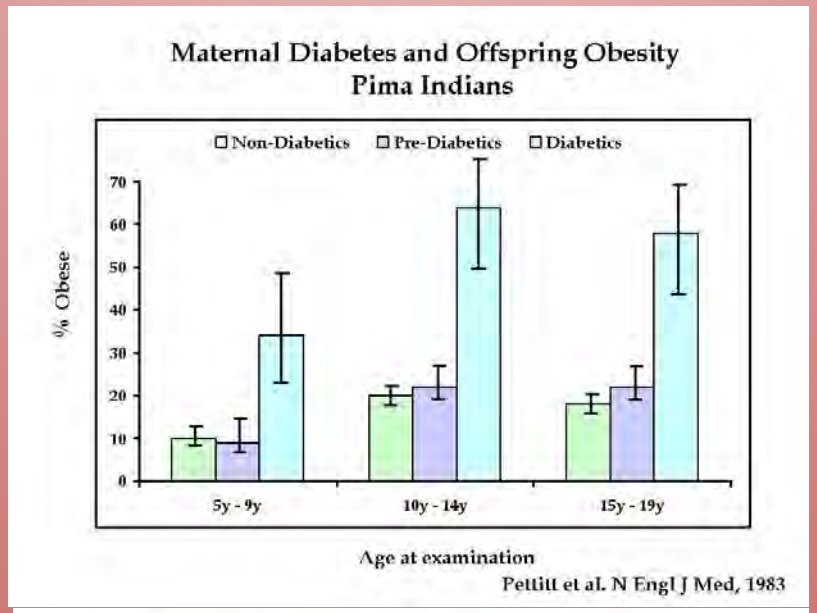
Eat less, walk more

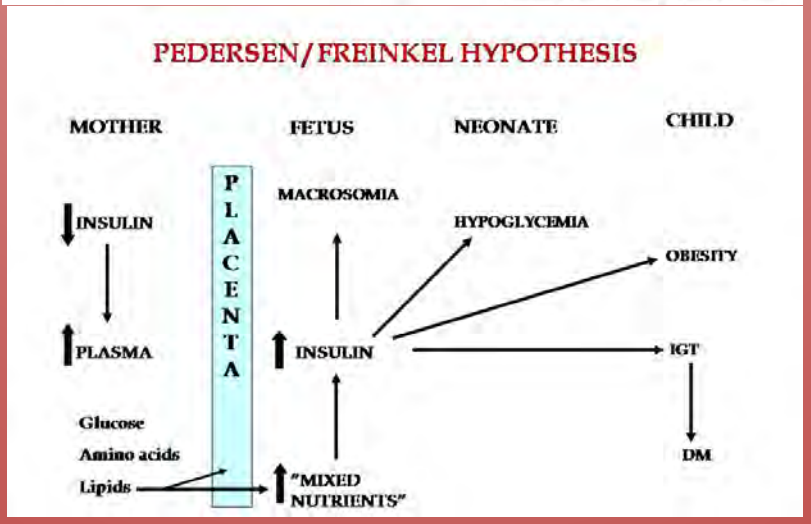
Intrauterine Malnutrition and subsequent Obesity & Diabetes

Gestational undernutrition

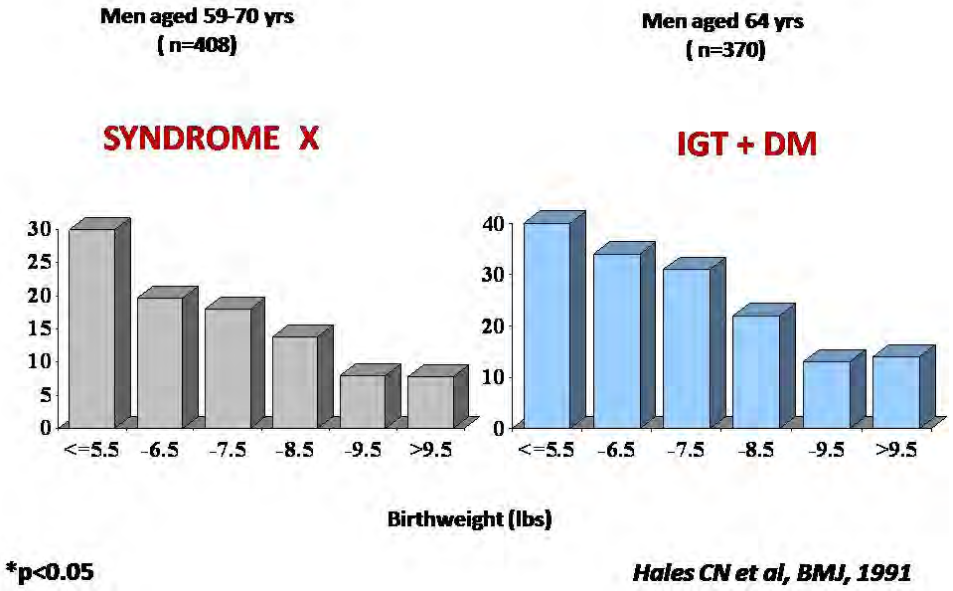


Gestational overnutrition





Thrifty Phenotype



*p<0.05

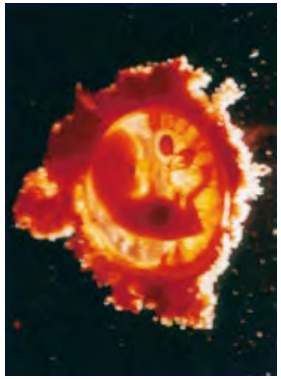
Hales CN et al, BMJ, 1991

Type 2 diabetes is the outcome of the fetus and early infant having to be nutritionally thrifty

Diabetologia 1992

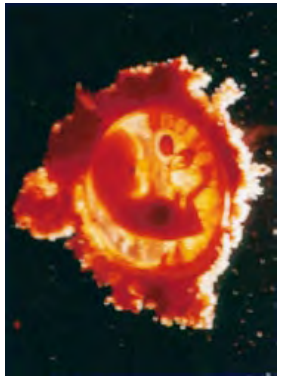
Smaller of the monozygotic twins has higher risk of diabetes

Poulsen P et al, Diabetologia1997



Plasticity & Programming

- Developmental exposure, lifelong effects
- Structure and function
- Adversity related restriction of 'plasticity'
- **Windows of vulnerability / opportunity**
  - **Pre- and peri-conceptional period**
  - **Pregnancy**
  - **Lactation…..**
  - **Adolescence ….**
- 'Genetic' & 'Epigenetic' mechanisms
- Environment:
  - Nutrition
  - Metabolism
  - Stress
  - Pollutants……..
- Multigenerational, **?? Reversibility**



Plasticity & Programming

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  - Stress
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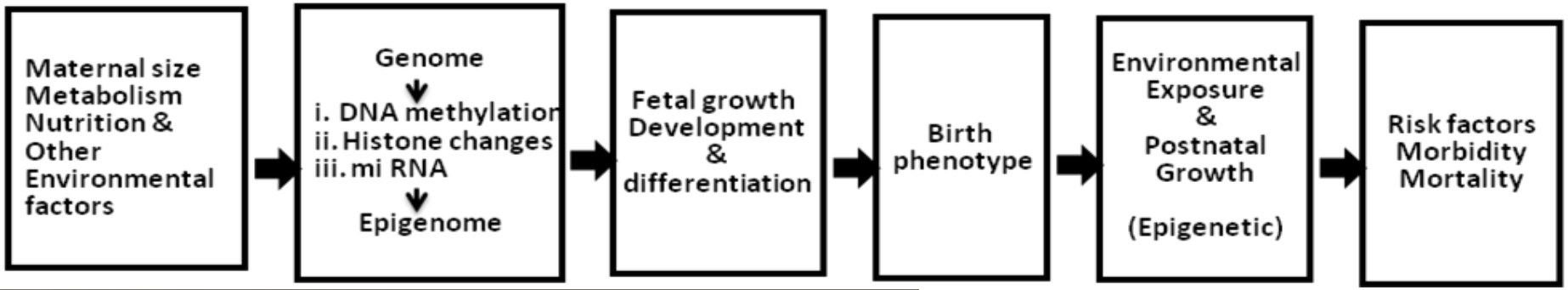
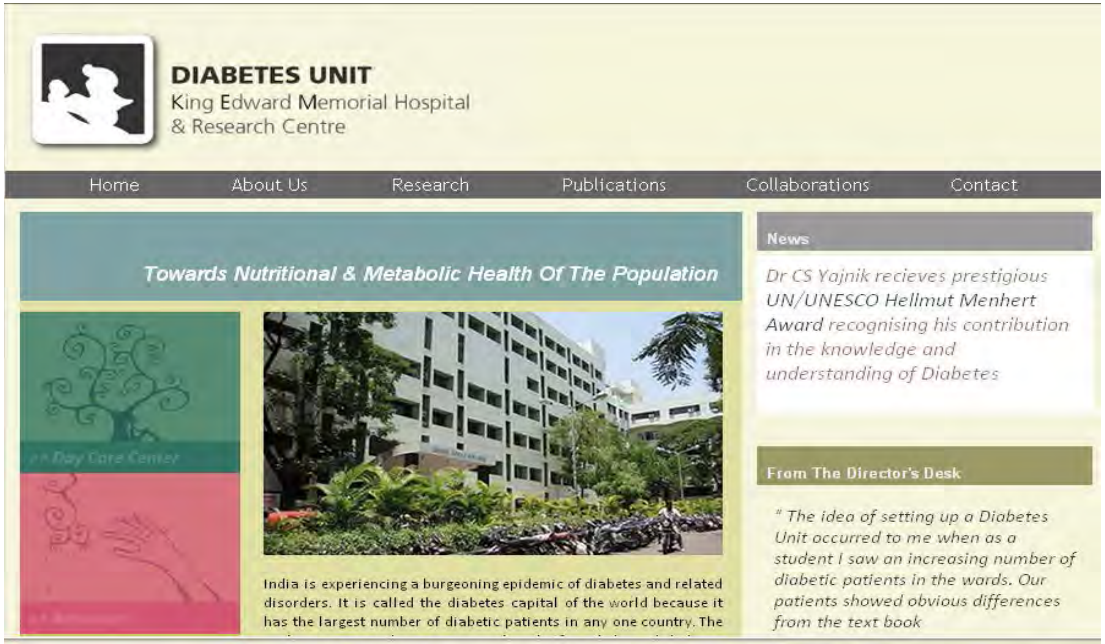
Buddhism and Science
Geshe Ngawang Semten

DOHaD

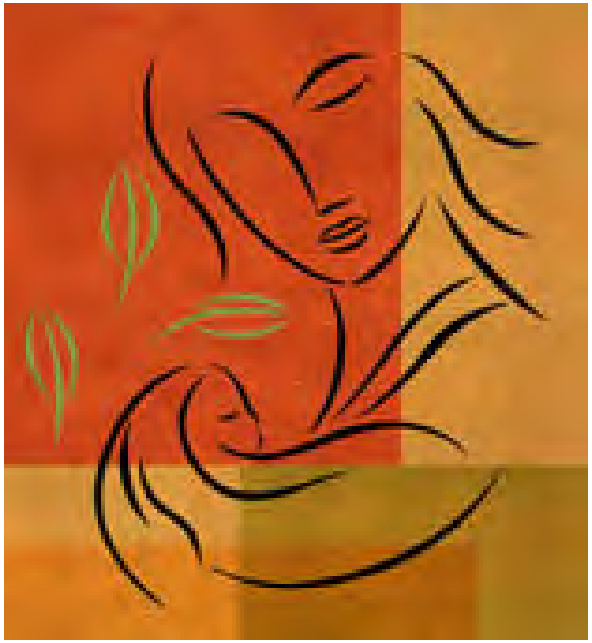


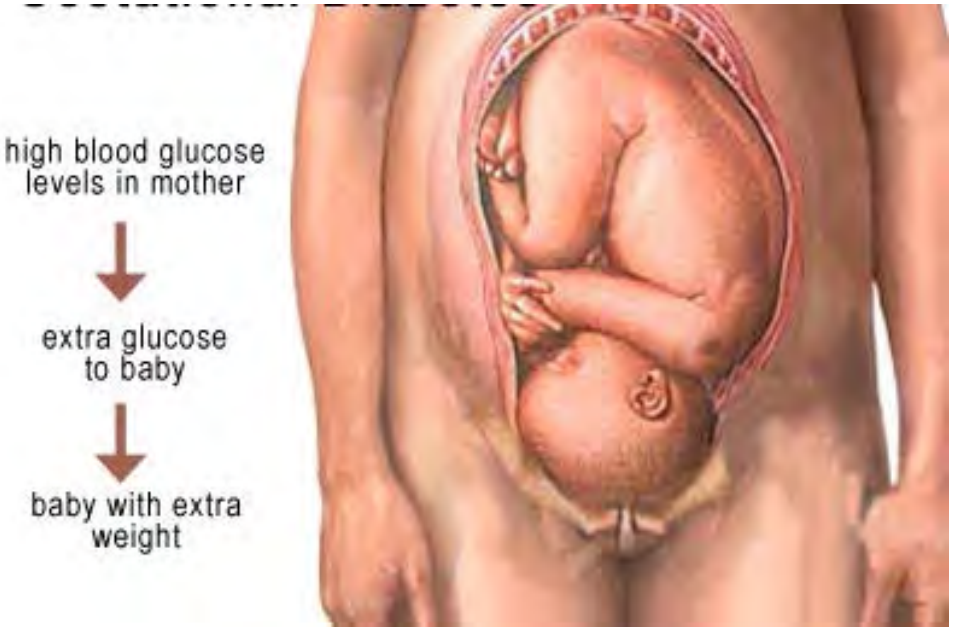


Yajnik CS, Deshmukh U, 2008

Pregnancy

Experience for the two !





Pregnancy with a Female Child

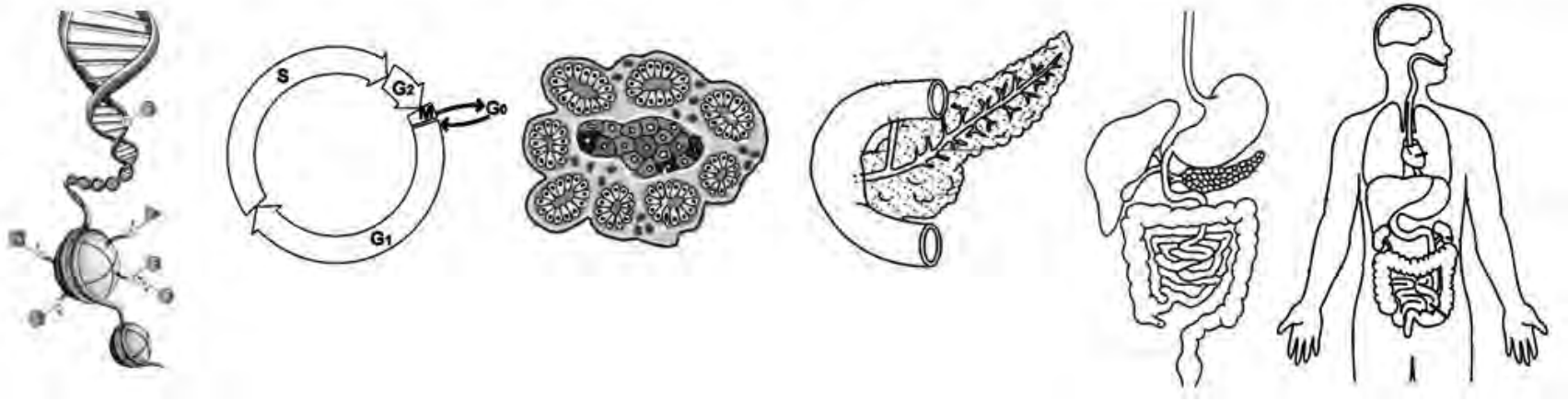
Experience for the three !

Pregnancy with a Female Child

Experience for the three !

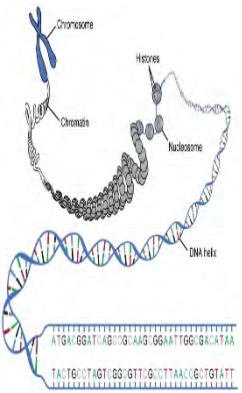
Fetal programming

Molecular → Cellular → Tissues → Organs → Systems → Organism



Epigenetic regulation of growth and development of cells, tissues, organs, systems and the organism

Structure and Function



Epigenetic Mechanisms influencing Gene Expression

1. DNA methylation

Unmethylated

DNA CpG Island Gene Expression

+ SAM

DNMTs

-CH3

Methylated

DNA CpG Island Gene Expression

2. Histone Modifications

K S K T

H2B H2A H2B H2A

Compact DNA-Histone complex

Nucleosome

K

R Different types of modifications on free histone tails:

1. Acetylation
2. Methylation
3. Phosphorylation
4. Ubiquitination
5. Sumoylation

Acetylation

\+ Acetyl group

-Acetyl group

Acetyl group

H2B H2A H2B H2A

DNA accessible for transcription machinery to bind

3. MiRNA activity

mRNA messenger RNA

translation

protein

Inhibition of translation

miRNA microRNA

Blocks translation machinery binding

No protein formation

Type 2 Diabetes
The Changing Dogma

Susceptibility

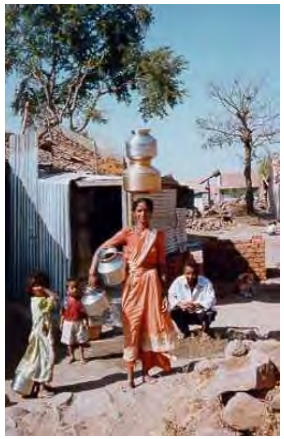
Genetic
(Polygenic)
~~Non-Modifiable~~

Epigenetic
Modifiable

+

Precipitating Factors

Obesity
Diet
Physical inactivity
Stress

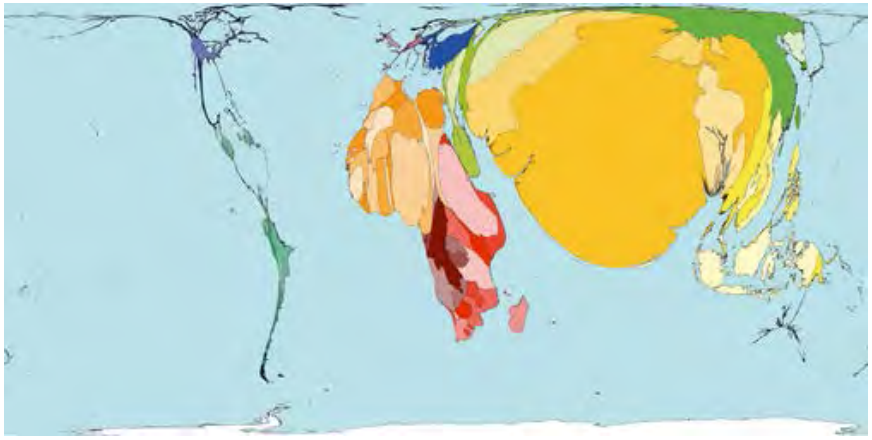


Programming

- Peri-reproductive

Capital of two

Undernutrition: LBW, under 5y



Micronutrients
Iron, B12, vit D, folate….

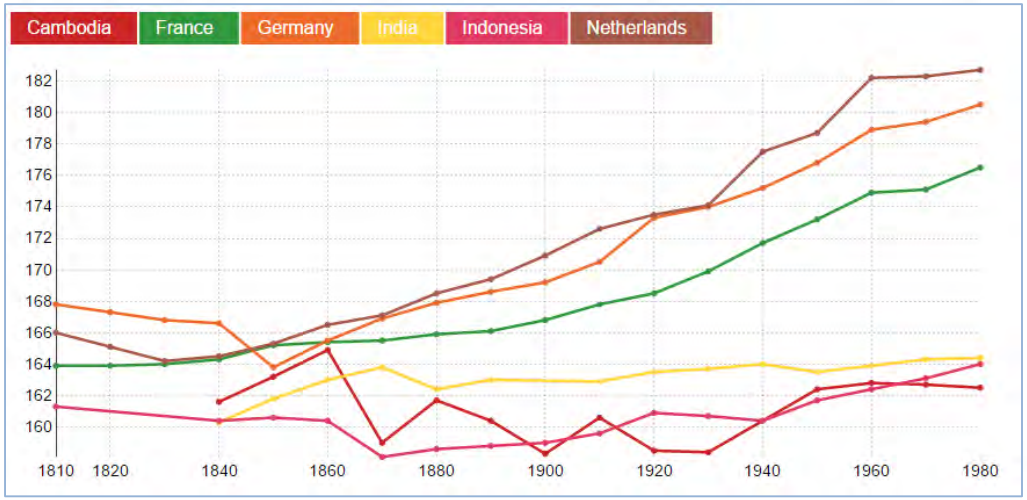
Diabetes

Macronutrients
Glucose, FAs, Cholesterol….

The Elevated Susceptibility to Diabetes in India: An Evolutionary Perspective

Jonathan C. K. Wells[1], Emma Pomeroy[2], Subhash R. Walimbe[3], Barry M. Popkin[4] and Chittaranjan S. Yajnik[5]*

[1] Childhood Nutrition Research Centre, UCL Institute of Child Health, London, UK, [2] McDonald Institute for Archaeological Research, University of Cambridge, Cambridge, UK, [3] Maharashtra Association of Anthropological Sciences, Pune, India, [4] Nutrition Department, Gillings Global School of Public Health, University of North Carolina School of Public Health, Chapel Hill, NC, USA, [5] Diabetes Unit, King Edward Memorial Hospital and Research Centre, Pune, India



REVIEW
published: 07 July 2016
doi: 10.3389/fpubh.2016.00145

Crude prevalence of diabetes in adults aged 20 years or older in the states of India in 1990 and 2016 and change in age-standardized prevalence

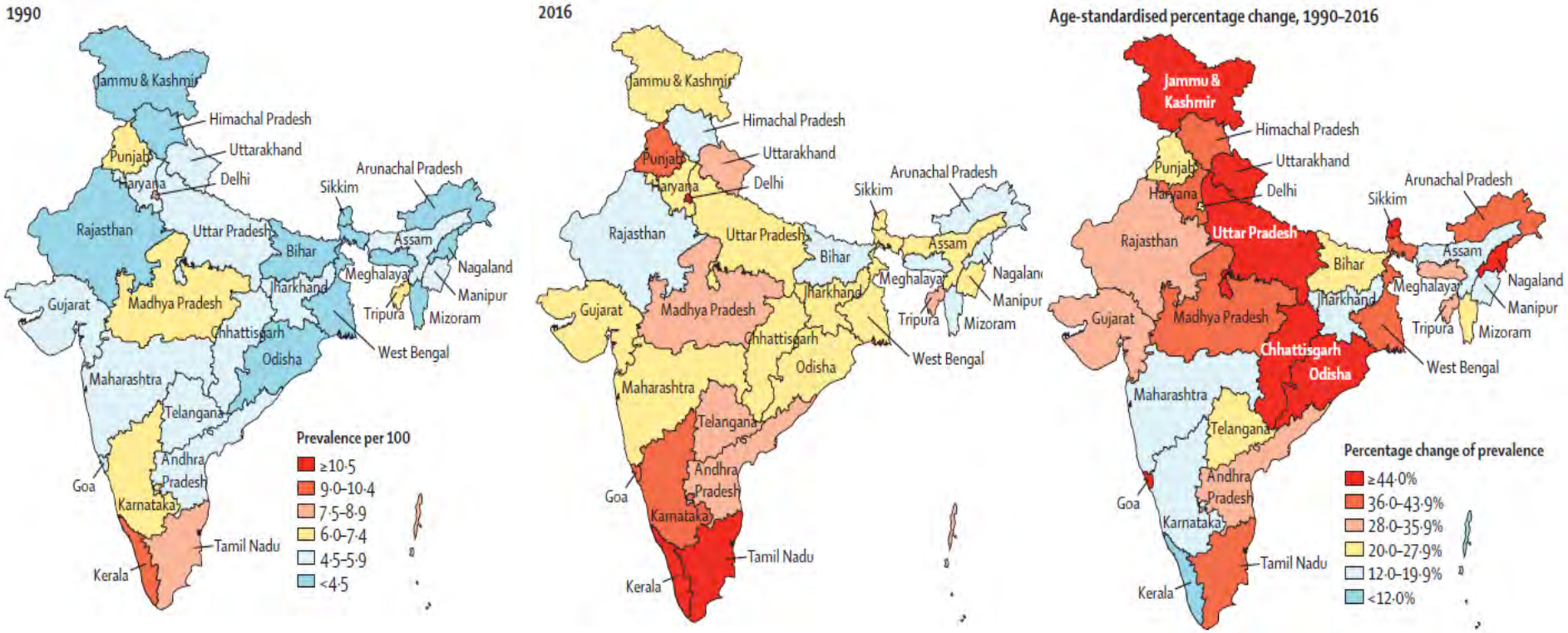


Figure: Crude prevalence of diabetes in adults aged 20 years or older in the states of India in 1990 and 2016 and change in age-standardized prevalence

GBD India 1990-2016, Lancet Sept 2018

Genotype – Phenotype
FTO, Obesity and T2DM

Europeans

BMI

0.10 SDs (0.09-0.12)

FTO

T2D

OR 1.27 (1.26-1.37)

Adj. BMI OR 1.03 (0.96-1.10)

T.Frayling,et.al. Science, 2007

Indians

BMI

0.05 SDs (-0.02-0.12)

FTO

T2D

OR 1.26 (1.13-1.40)

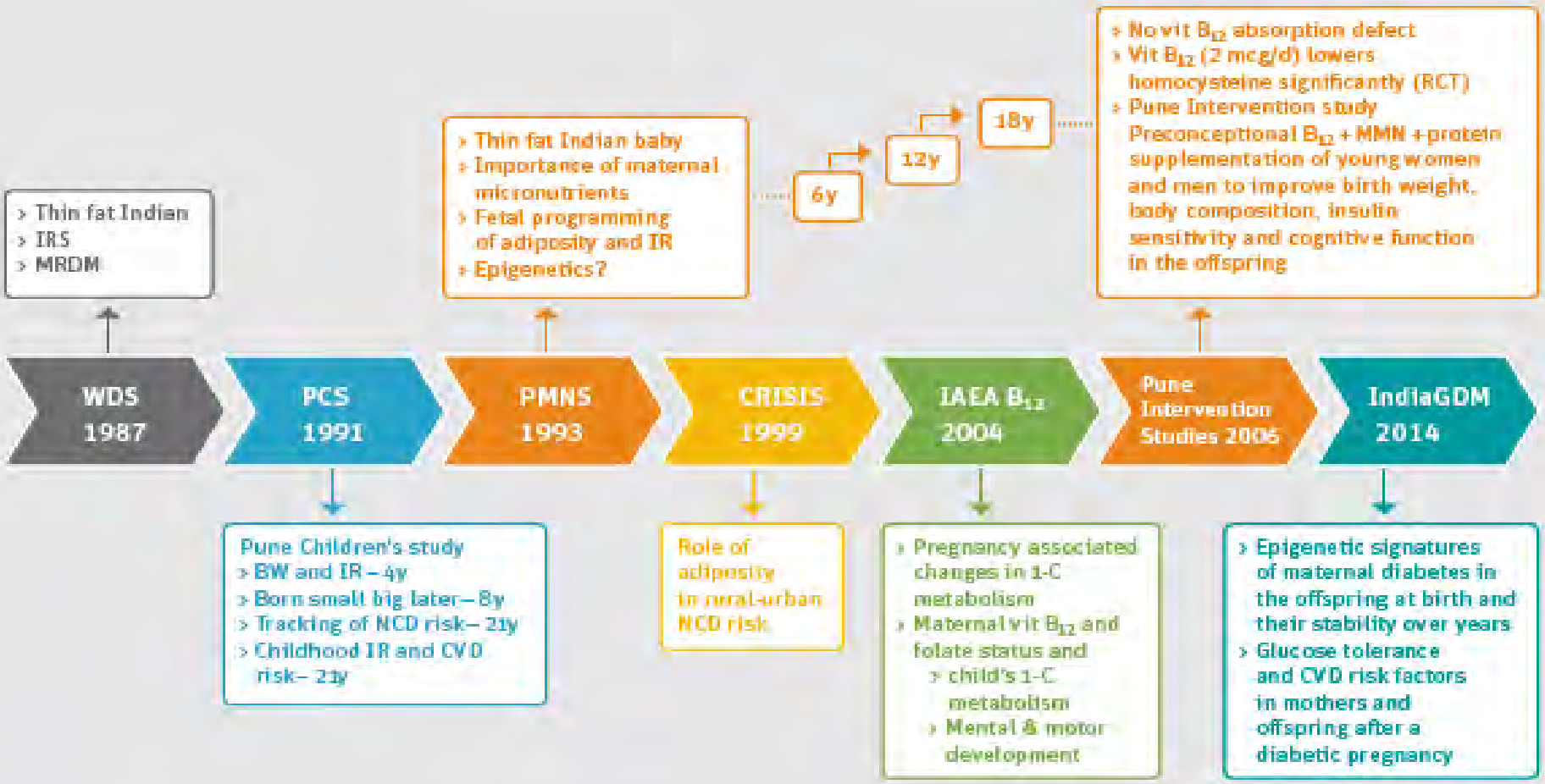
Adj. BMI OR 1.21 (1.06-1.37)

C.S. Yajnik, et.al,Diabetologia, 2008

Life can only be understood backwards

- Soren Kierkegaard

Diab Research, KEM Hospital, Pune 1985 - 2018

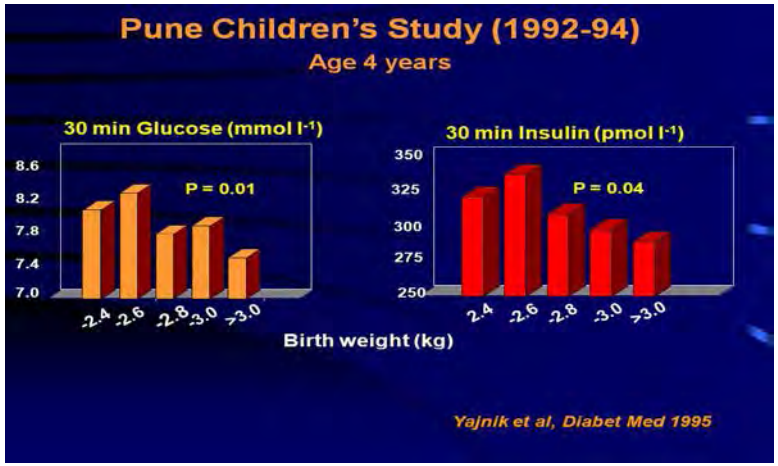


WDS: Wellcome Diabetes Study
PCS: Pune Children's Study
PMNS: Pune Maternal Children Study
CRISIS: Coronary Risk of Insulin Sensitivity in Indian Subjects
IAEA: International Atomic energy agency; Observational study for B12 deficiency in pregnant women
IndiaGDM: Gestational Diabetes study in Indians under Indo Danish-collaboration
IRS: Insulin resistance syndrome
MRDM: Malnutrition Related Diabetes Mellitus
IR: Insulin Resistance

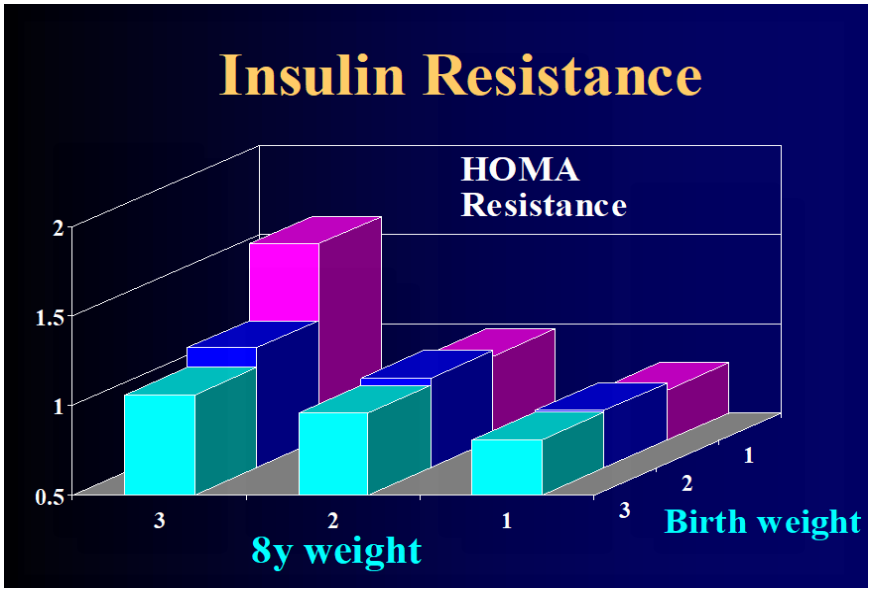
Katre P, Yajnik CS 2015

Pune Children's Study (Born small, Big later)

4 yrs



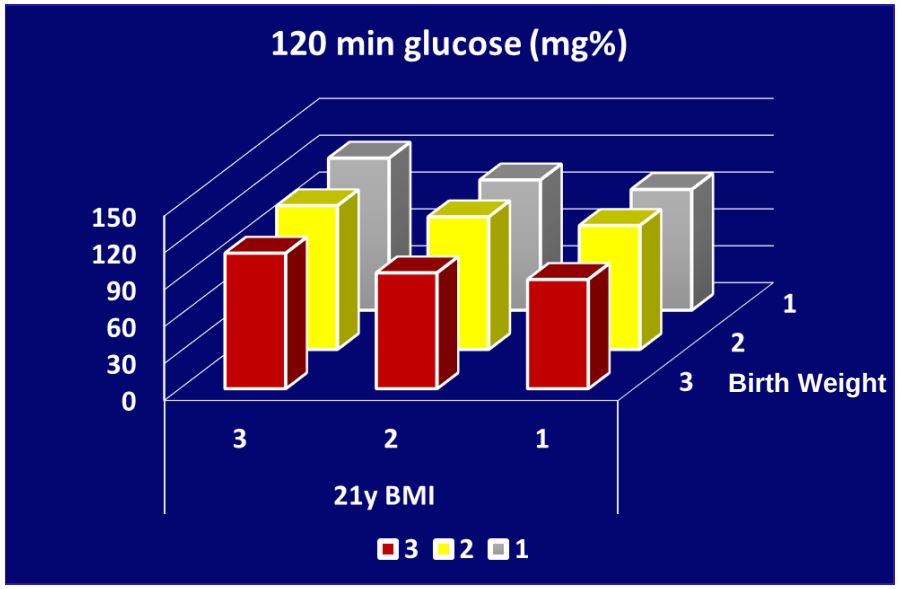
8 yrs



- more adipose, centrally adipose
- higher glucose, BP, lipids
- insulin resistant

Bavdekar et al, Diabetes, 1999

21 yrs



- Matsuda Index
- Disposition Index

Pune Maternal Nutrition Study

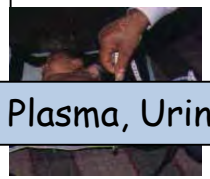
1993 | 1994-96 | 2000-03, 2006-08 | 2013

Preconception | **Intrauterine** | **Birth** | **Postnatal** | **6 and12 y** | **18 y**

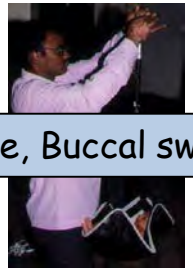
Maternal
Size
Hemo-globin
2675

Maternal
Size
Nutrition
Metabolism
Paternal size
Metabolic variables
Fetal growth (USG)

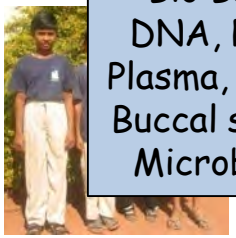
Size
Phenotype
770



Growth
every
6 months
743



Children
& parents
Size, body composition
IR
CVD risk markers
nition
3/723
(96%)

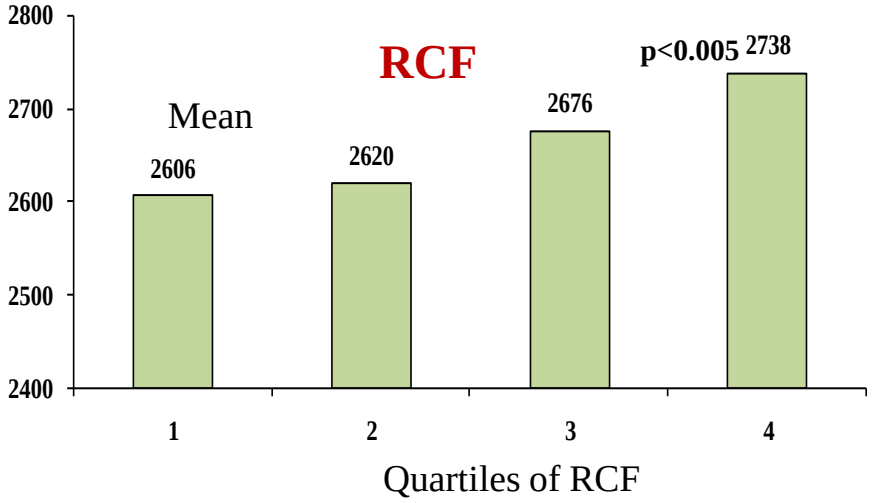


Children
& parents
Size, body composition
IR
CVD risk markers
Genetics and Epigenetics
n=663/690

Bio Bank: DNA, Plasma, Urine, Buccal swabs

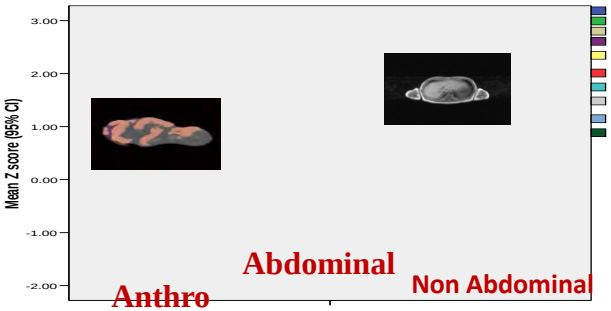
Bio Bank:
DNA, RNA,
Plasma, Urine,
Buccal swabs,
Microbiota

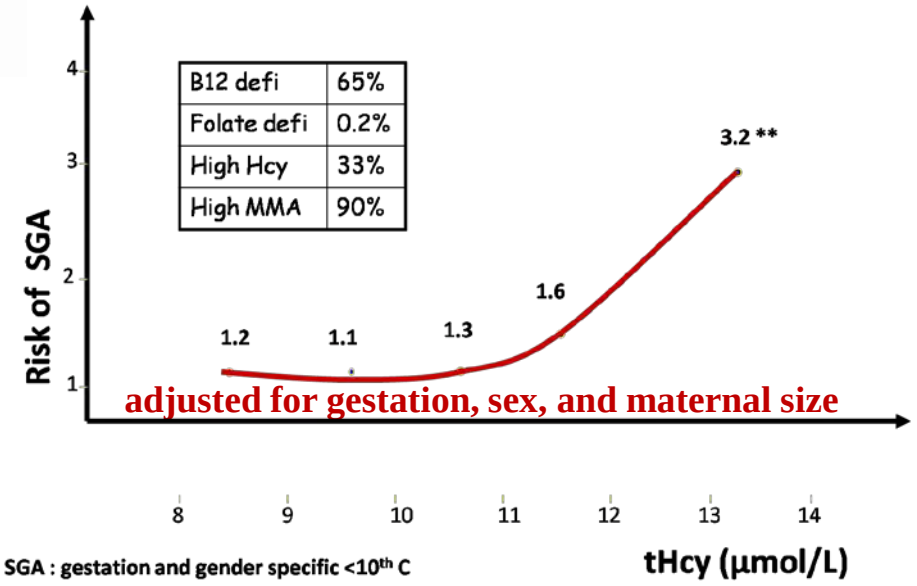
Maternal Nutrition & Fetal Growth



Mothers: 42 kg, 1.52m, 18.1 kg/m²

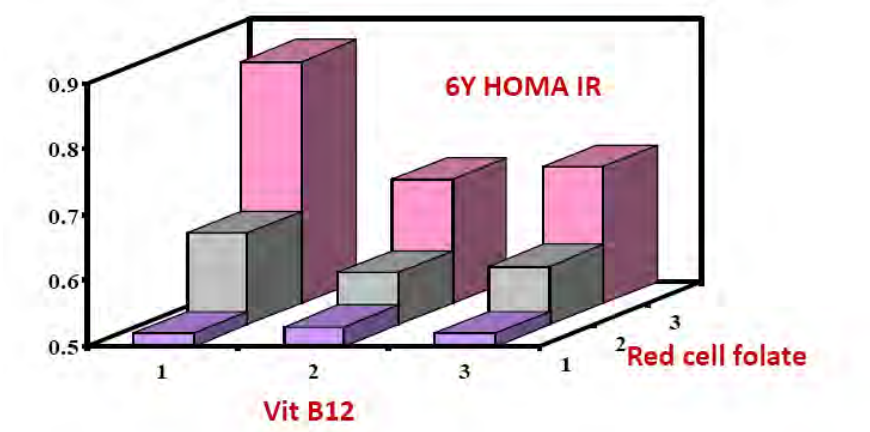
Thin-fat babies: (2.7 kg), 70% SGA





Rao S, et al, J Nutr, 2001
Yajnik CS, APJCN 2003
Yajnik CS et al, IJ Ob 2003
N Modi, Ped Res 2009

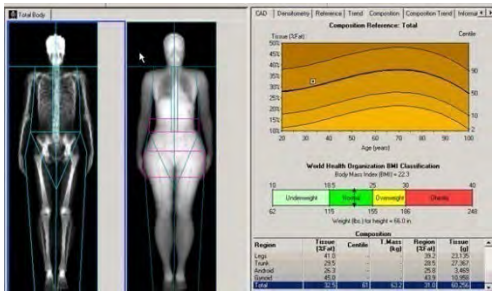
Maternal Nutrition in Pregnancy & Long-term outcomes in the Offspring
(Adiposity,IR,Neurocognition)

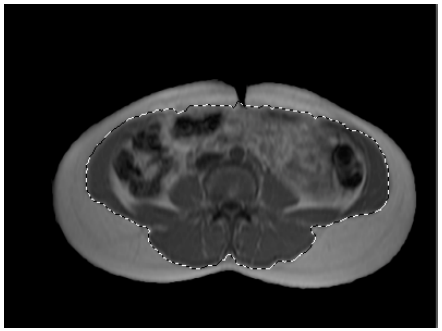


Adjusted for sex, age and fat%; maternal adiposity, protein intake, birth size, vitamin B12

In Nepal, maternal B12 defi
asso with 27% higher IR
Stewart et al, 2011

Adiposity: Total & Regional

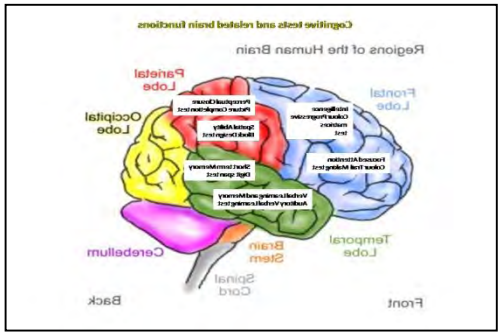




Low Vit D and B12
High Folate

adjusted for gestation, sex, and maternal size

Neurocognition



Yajnik CS, Diabetologia 2008
Bhate V , J DOHaD 2012
Yajnik CS, ADA 2015

Pune Maternal Nutrition Study
18y follow up

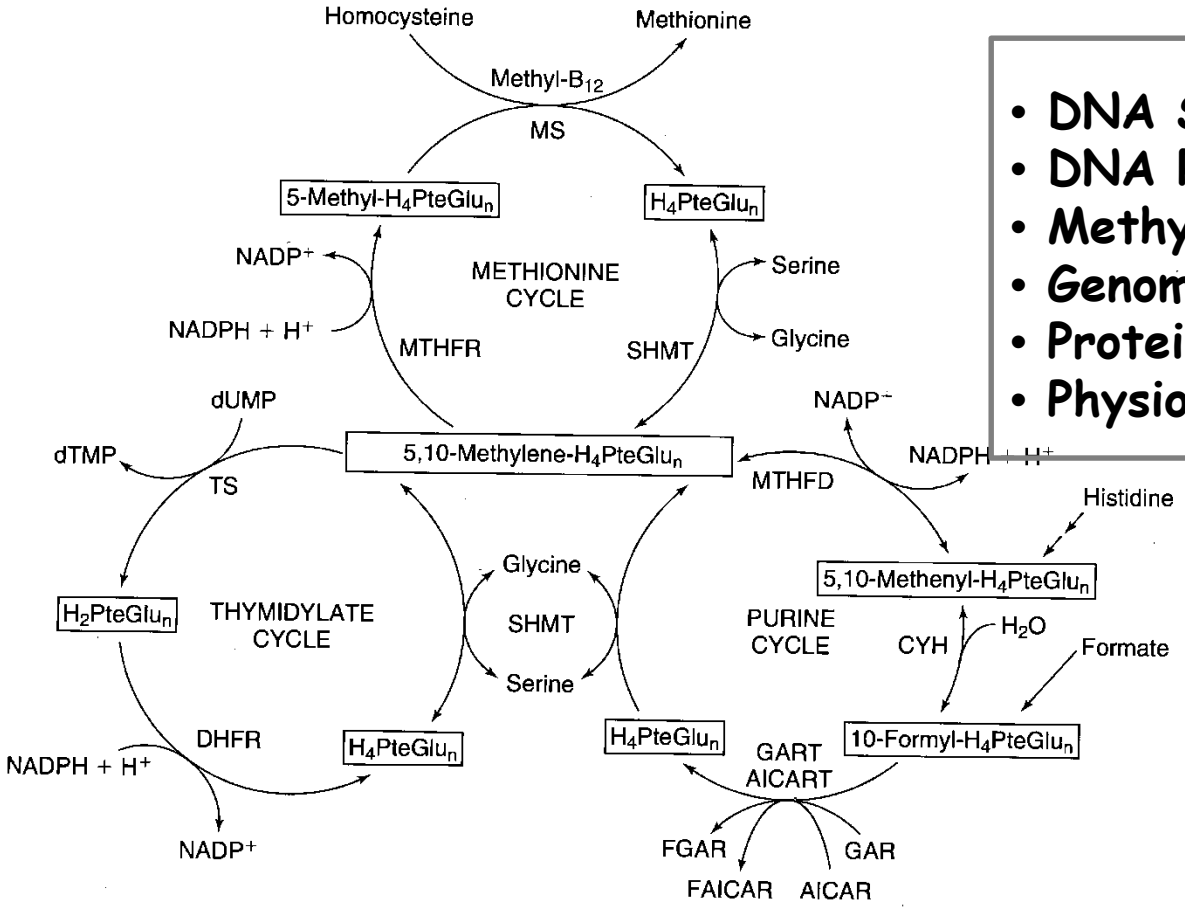
356	N	307
42	Underweight %	55
8	Over wt and Obese %	4
11	Stunted %	10
27	IFG %	8
10	IGT %	9
0	DM (n)	2

Hyperglycemic (190, 28.7%)
Males:133, 37%, Females: 57, 18.5%

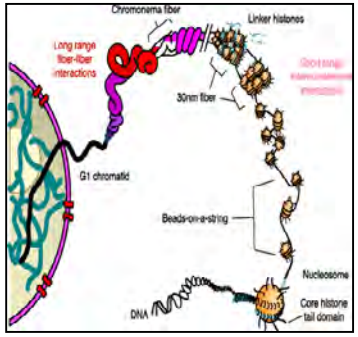
One- Carbon metabolism

"A network of interrelated biochemical reactions that involve the transfer of one carbon group from one site to another."

Folate and B12: co-factors, co-substrates in -CH3 transfer



- DNA Synthesis
- DNA Repair
- Methylation (Epigenetics)
- Genomic Stability
- Protein Synthesis
- Physiological processes



Molecular Characterization and Meta-Analysis of Gut Microbial Communities Illustrate Enrichment Prevotella and Megasphaera in Indian Subjects

Shrikant Bhute[1†], Pranav Pande[2†], Sudarshan A. Shetty[2†], Rahul Shelar[2], Sachin Man Shreyas V. Kumbhare[2], Ashwini Gawali[2], Hemal Makhani[2], Mohit Navandar[2], Dhiraj Dhotre[2], Himangi Lubree[3], Dhiraj Agarwal[4], Rutuja Patil[4], Shantanu Ozarkar[5], Saroj Ghaskadbi[1], Chittaranjan Yajnik[3], Sanjay Juvekar[4], Govind K. Makharia[6] and Yogesh S. Shouche[2]*

[1] Department of Zoology, Savitribai Phule Pune University, Pune, India, [2] Microbial Culture Collection, National Centre fo Sciences, Savitribai Phule Pune University campus, Pune, India, [3] Diabetes Unit, KEM Hospital Research Centre, Pune, [4] Vadu Rural Health Program, KEM Hospital Research Centre, Pune, India, [5] Department of Anthropology, Savitribai Ph Pune University, Pune, India, [6] Department of Gastroenterology and Human Nutrition, All India Institute of Medical Scie New Delh

ORIGINAL RESEARCH
published: 09 May 2016
doi: 10.3389/fmicb.2016.00660

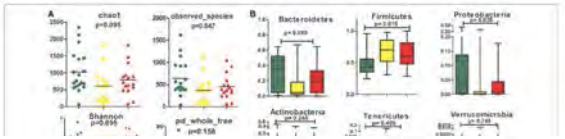
frontiers in Microbiology

ORIGINAL RESEARCH
published: 14 February 2017
doi: 10.3389/fmicb.2017.00214

Gut Microbial Diversity Assessment of Indian Type-2-Diabetics Reveals Alterations in Eubacteria, Archaea, and Eukaryotes

Shrikant S. Bhute[1], Mangesh V. Suryavanshi[2], Suyog M. Joshi[3], Chittaranjan S. Yajnik[3], Yogesh S. Shouche[2*] and Saroj S. Ghaskadbi[1*]*

[1] Department of Zoology, Savitribai Phule Pune University, Pune, India, [2] Microbial Culture Collection-National Centre for Cell Science, Pune, India, [3] Diabetes Unit, KEM Hospital and Research Centre, Pune, India



Human Molecular Genetics, 2017, Vol. 00, No. 0 1–14

doi: 10.1093/hmg/ddx071
Advance Access Publication Date: 27 February 2017
Association Studies Article

Research Article

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Vitamin B_{12} supplementation influences methylation of genes associated with Type 2 diabetes and its intermediate traits

Dilip K Yadav[1], Smeeta Shrestha[1,2], Karen A Lillycrop[3], Charu V Joglekar[4], Hong Pan[5], Joanna D Holbrook[5,6], Caroline HD Fall[7], Chittaranjan S Yajnik[1,4] & Giriraj R Chandak[*,1,1,8]

ASSOCIATION STUDIES ARTICLE

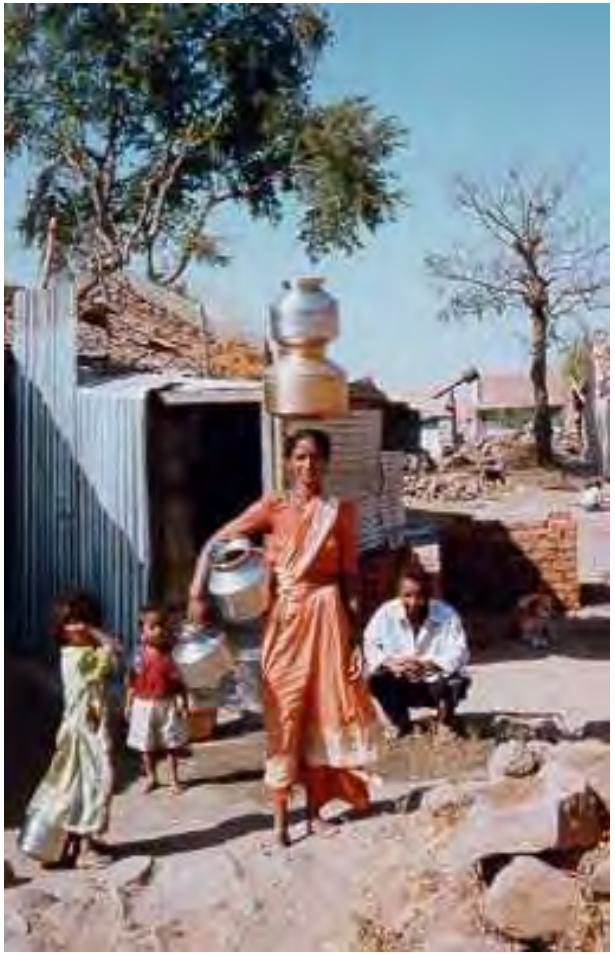
GWAS identifies population-specific new regulatory variants in *FUT6* associated with plasma B12 concentrations in Indians

Suraj S. Nongmaithem[1], Charudatta V. Joglekar[2], Ghattu V. Krishnaveni[3], Sirazul A. Sahariah[4], Meraj Ahmad[1], Swetha Ramachandran[1], Meera Gandhi[4], Harsha Chopra[4], Anand Pandit[5], Ramesh D. Potdar[4], Caroline H.D. Fall[4,6], Chittaranjan S. Yajnik[2] and Giriraj R. Chandak[1,7,*]

FTO, TCF7, KCN…, miR21

FUT 2,6, CUBN, TCN 1,2, MMAA

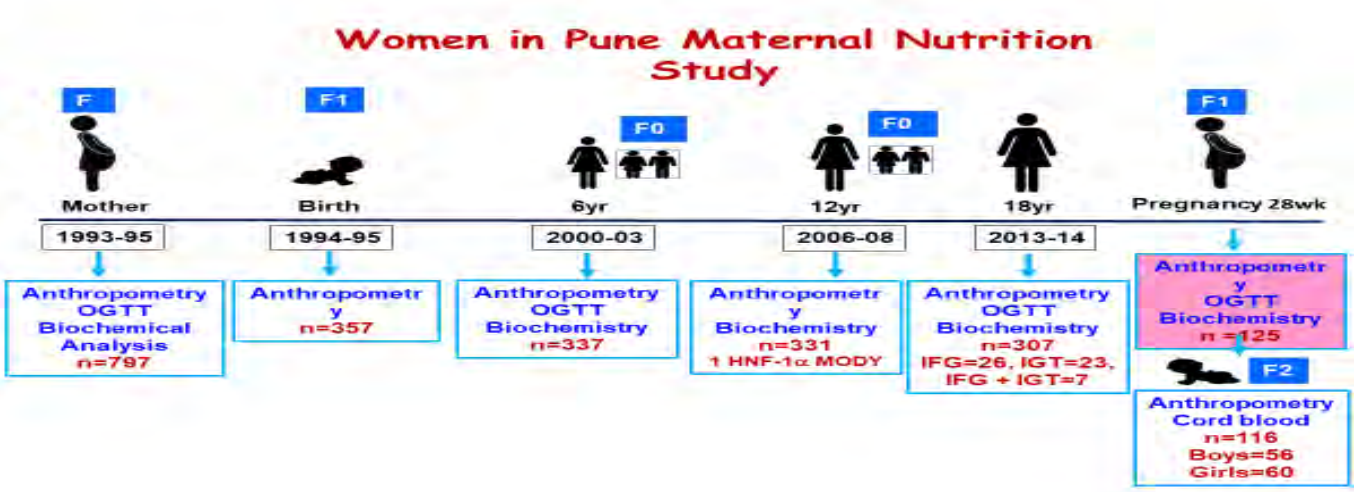
- Glycan metabolism: Gut microbe interaction
- HNF4a differential binding

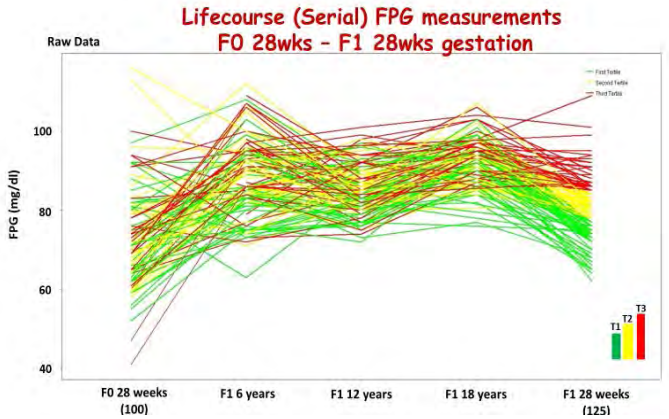


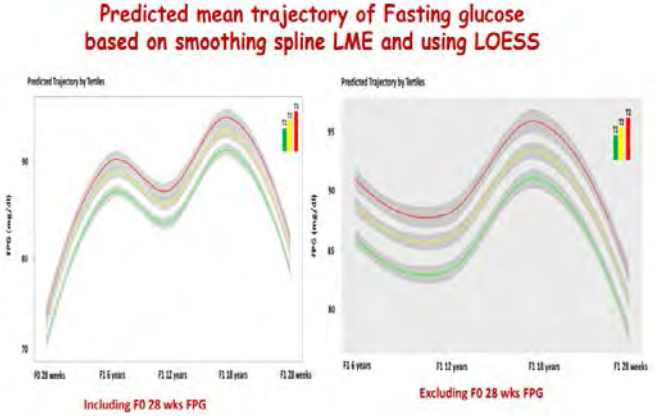
1993-96

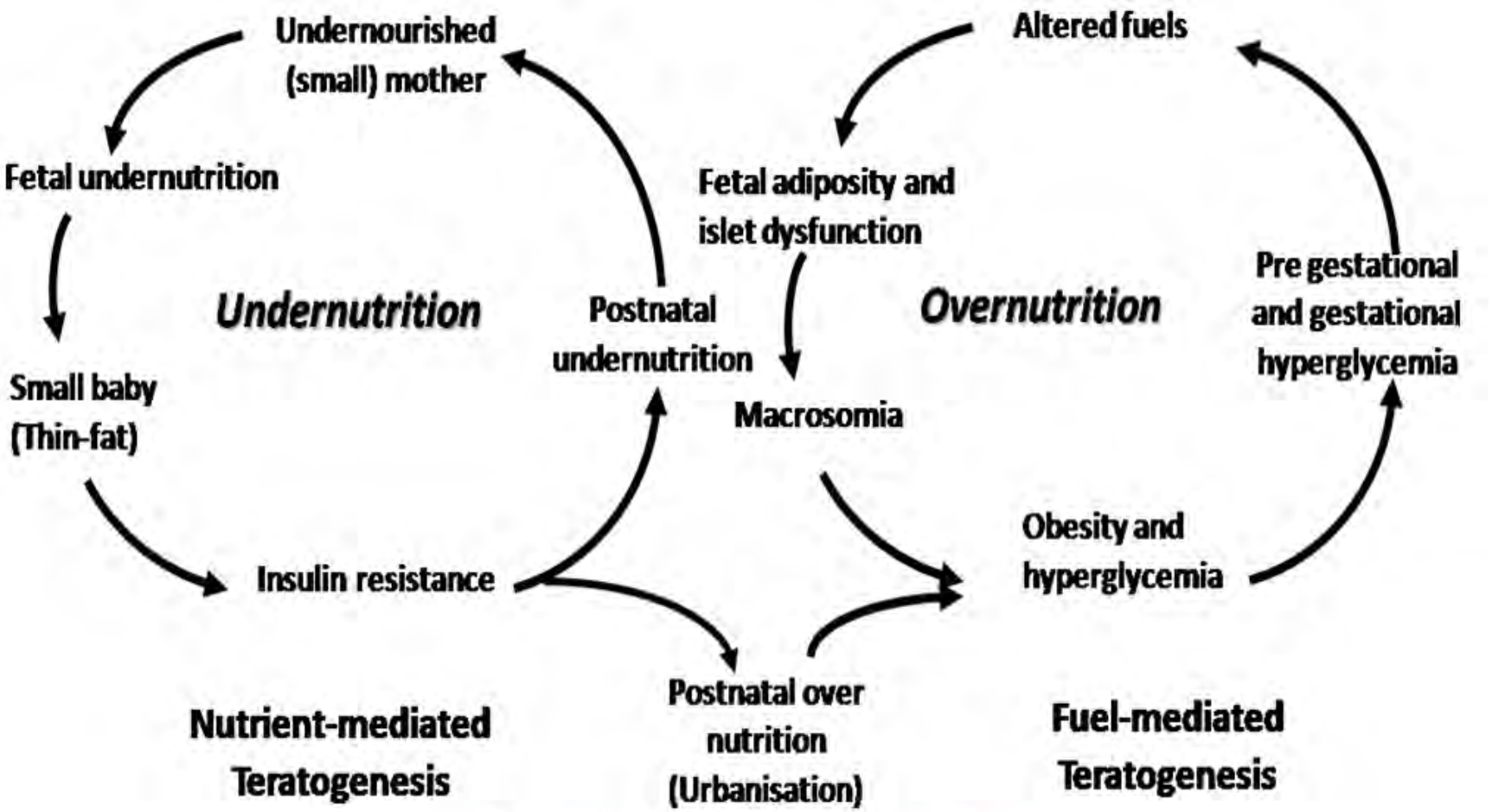
2013-18

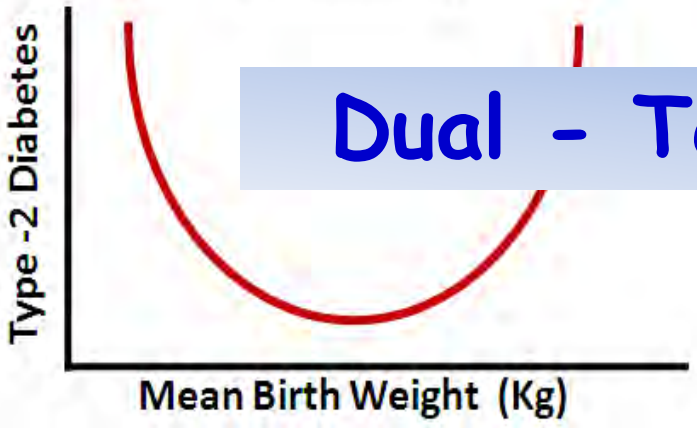
World's first intergenerational glucose curve











Dual - Teratogenesis

Yajnik CS 2009

Summary

- Conventional model of DM: Genetics + adult LSF
- DOHaD: lifecourse evolution, windows
- Periconception & Intrauterine period important
- Modifiable 'epigenetic' susceptibility
- Rapid transition & double burden of malnutrition
- Intergenerational solutions to prevention
- When progress is the problem ……

Thank U

Thank U

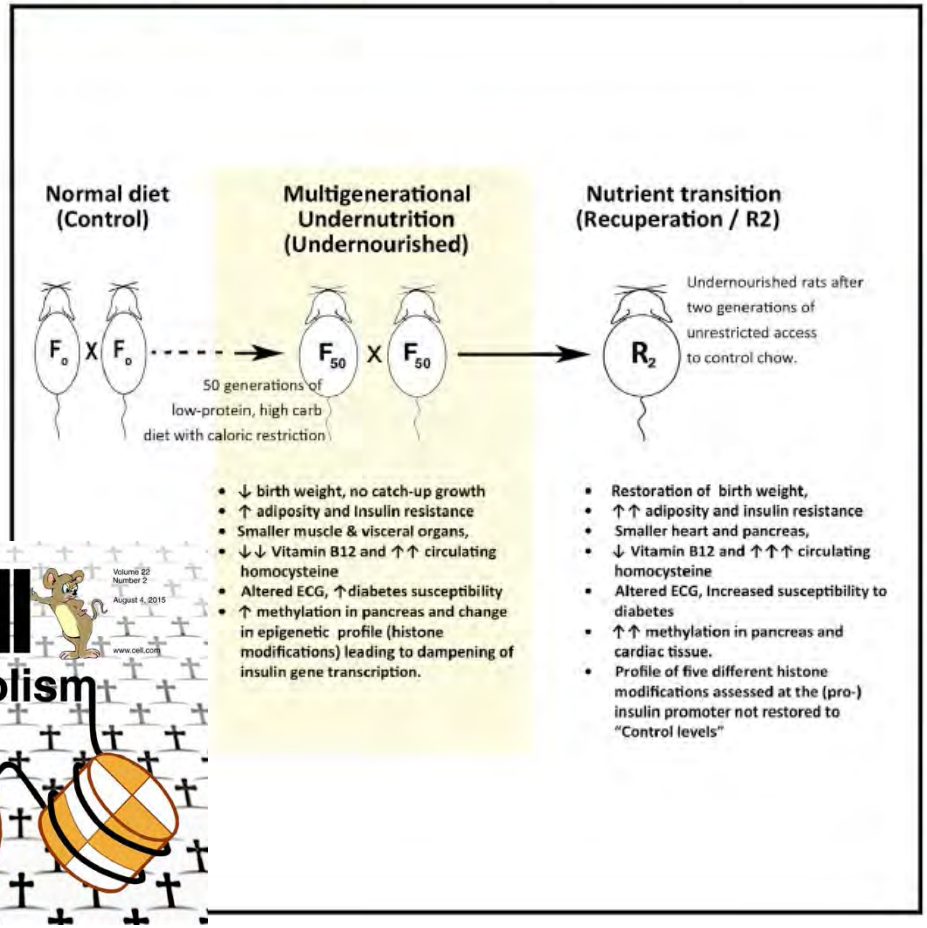
Wellcome Trust, London
MRC, UK
DIFID, UK
DBT, India
ICMR, India,
DST, India,
NIH, USA,
Nestle Foundation

Thrifty Jerry

Cell Metabolism

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

Graphical Abstract



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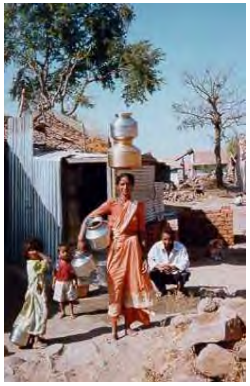
In Brief

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.

Maternal Characteristics at 28wk Gestation and babies at birth
(F0, F1 and F2 PMNS)



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

*Median or %, * p<0.05, ** p<0.01, *** p<0.001*

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

*Median or %, * p<0.05, ** p<0.01, *** p<0.001*

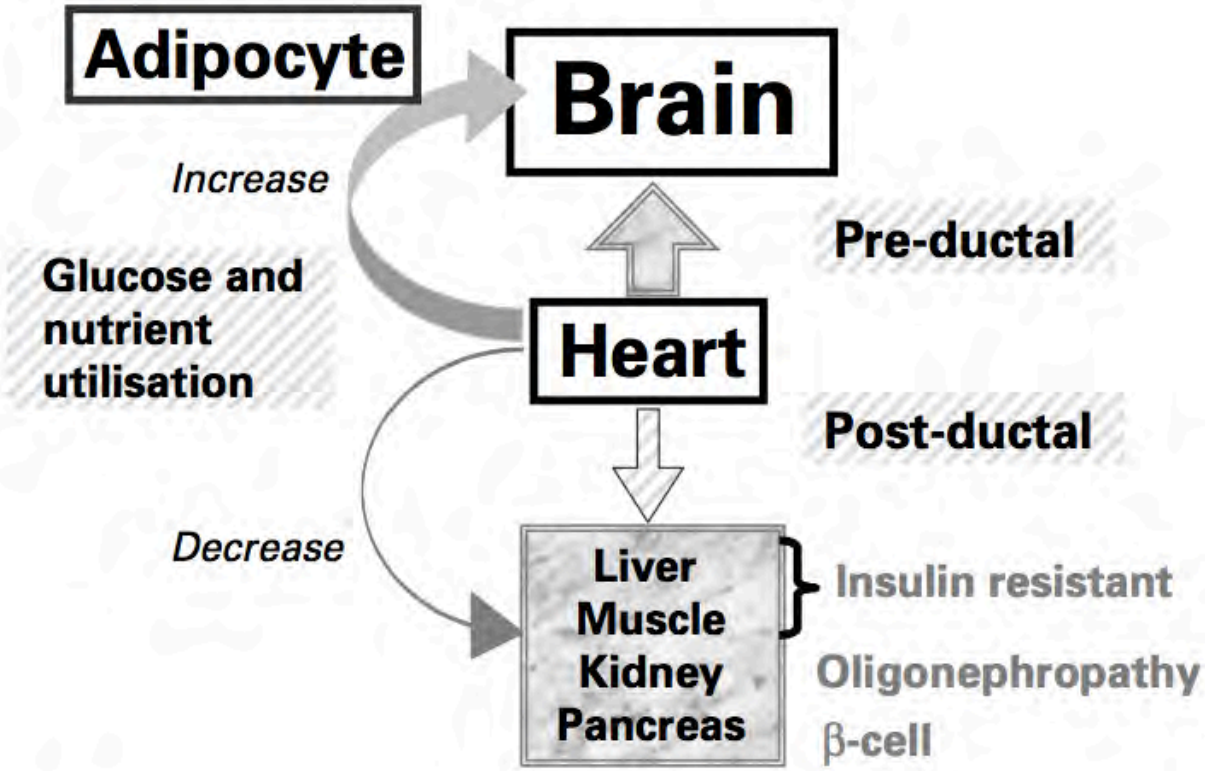


Fig. 7. The concept of 'brain-sparing' during fetal growth. 'Brain-sparing' is achieved by the diversion of blood flow to the pre-ductal circuit and by increased concentrations of nutrients in the blood (glucose, lipids, amino acids). Lipids constitute a large proportion of the brain, and lipid stores in the adipose tissue support rapid growth of the brain in the last trimester of pregnancy and in the postnatal period. The nutrition of the post-ductal structures suffers and their development is affected, which increases their susceptibility to later disease. Intrauterine origins of adiposity may thus be driven by the need for 'brain-sparing'.

Yajnik CS, 2004

Preconception health 1

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

Judith Stephenson, Nicola Heslehurst, Jennifer Hall, Danielle A J M Schoenaker, Jayne Hutchinson, Janet E Cade, Lucilla Poston, Geraldine Barrett, Sarah R Crozier, Mary Barker, Kalyanaraman Kumaran, Chittaranjan S Yajnik, Janis Baird, Gita D Mishra

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 behaviours. Observational studies show strong 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 rife among women 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 micronutrient supplementation starting in pregnancy can correct important maternal nutrient deficiencies, but effects on child health outcomes are disappointing. 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 pregnancy planning have quantified the degree of pregnancy planning and suggest that it is more common than previously recognised. Planning for pregnancy is associated with a mixed pattern of health behaviours before conception. We propose novel definitions of the preconception period relating to embryo development and actions at individual or population level. A sharper focus on intervention before conception is needed to improve maternal and child health and reduce the growing burden of non-communicable diseases. Alongside 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.

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This is the first in a Series of three papers about preconception health

Institute for Women's Health, University College London, London, UK (Prof J Stephenson FFPH, J Hall PhD, G Barrett PhD); Institute of Health and Society, Newcastle University, Newcastle upon Tyne, UK (N Heslehurst PhD); School of Public Health, University of Queensland, Herston, QLD, Australia (D A J M Schoenaker PhD, Prof G D Mishra FAHMS); Nutritional Epidemiology Group, School of Food Science and Nutrition, University of

Preconception health 2

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

Tom P Fleming, Adam J Watkins, Miguel A Velazquez, John C Mathers, Andrew M Prentice, Judith Stephenson, Mary Barker, Richard Saffery, Chittaranjan S Yajnik, Judith J Eckert, Mark A Hanson, Terrence Forrester, Peter D Gluckman, Keith M Godfrey

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 to early embryonic development, parental lifestyle can adversely influence long-term risks of offspring cardiovascular, metabolic, immune, and neurological morbidities, often termed developmental programming. We review periconceptional induction of disease risk from four broad exposures: maternal overnutrition and obesity; maternal undernutrition; related paternal factors; and the use of assisted reproductive treatment. Studies in both humans and animal models have demonstrated the underlying biological mechanisms, including epigenetic, cellular, physiological, and metabolic processes. We also present a meta-analysis of mouse paternal and maternal protein undernutrition that suggests distinct parental periconceptional contributions to postnatal outcomes. We propose that the evidence for periconceptional effects on lifetime health is now so 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

Mary Barker, Stephan U Dombrowski, Tim Colbourn, Caroline H D Fall, Natasha M Krznik, Wendy T Lawrence, Shane A Norris, Gloria Ngaiza, Dilisha Patel, Jolene Skordis-Worrall, Falko F Sniehotta, Régine Steegers-Theunissen, Christina Vogel, Kathryn Woods-Townsend, Judith Stephenson

The nutritional status of both women and men before conception has profound implications for the growth, development, and long-term health of their offspring. Evidence of the effectiveness of preconception interventions for improving outcomes for mothers and babies is scarce. However, given the large potential health return, and relatively low costs and risk of harm, research into potential interventions is warranted. We identified three promising strategies for intervention that are likely to be scalable and have positive effects on a range of health outcomes: supplementation and fortification; cash transfers and incentives; and behaviour change interventions. On the basis of these strategies, we suggest a model specifying pathways to effect. Pathways are incorporated into a life-course framework using individual motivation and receptiveness 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 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 behaviours at all preconception action phases should consider social and environmental determinants, to avoid exacerbating health and gender inequalities, and be underpinned by a social movement that touches the whole population. We propose a dual strategy that targets specific groups actively planning a pregnancy, while improving the health of the population more broadly. Modern marketing techniques could be used to promote a social movement based on an emotional and symbolic connection between improved preconception maternal health and nutrition, and offspring health. We suggest that speedy 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.

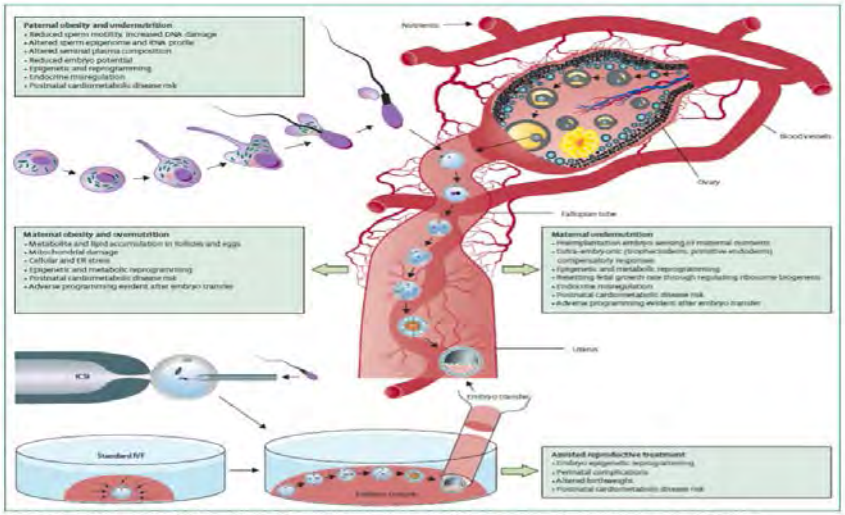

Figure 1: Summary of periconceptional developmental conditioning from the four areas reviewed, with the main mechanisms highlighted in the progression of disease risk
ER=endoplasmic reticulum. ICSI=intracytoplasmic sperm injection. IVF=in vitro fertilisation.

Lancet, Preconception Health, 2018