# Fetal programming of diabetes
# DOHaD Research in Pune


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www.kemdiabetes.org


**Banu Coyaji**

*1917- 2004*

**"Villages are my laboratories, and its residents my precious participants"**

**DJP Barker**

*1938- 2013*

**trust yourself when all men doubt you ….**

# Type 2 Diabetes
## The Dogma

**Susceptibility**

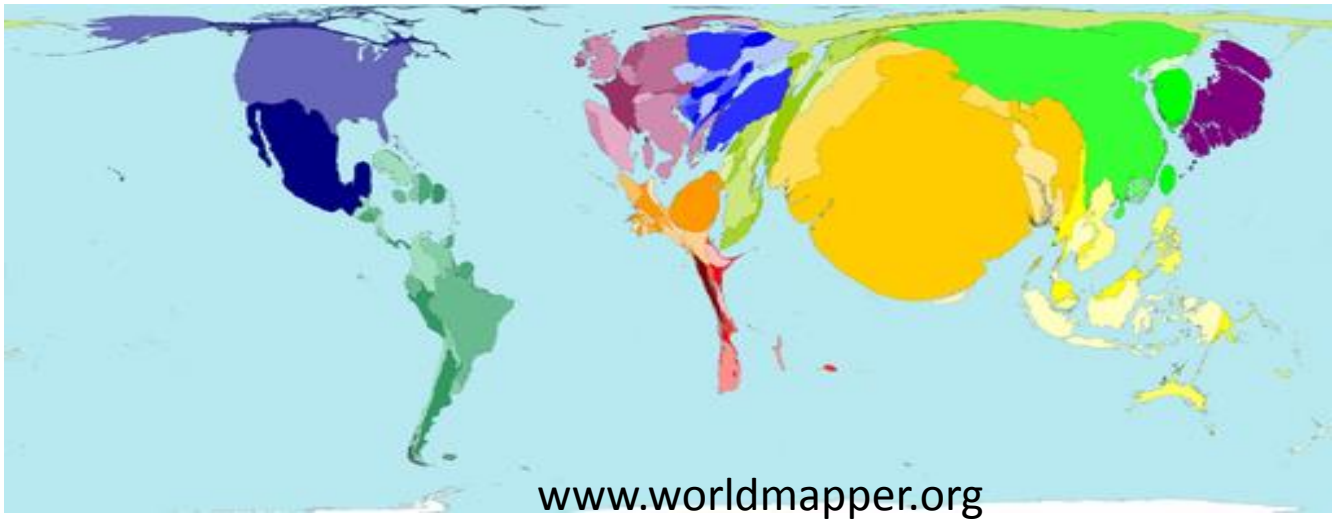
Genetic

+

**Precipitating Factors**

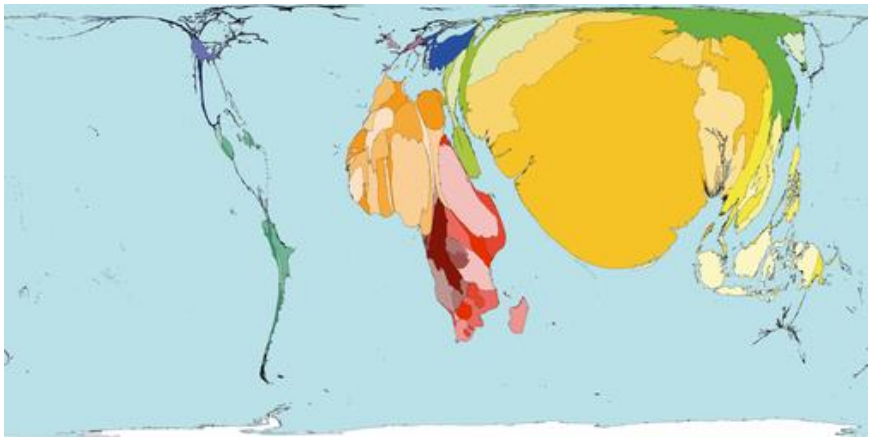
Obesity
Diet
Physical inactivity
Stress

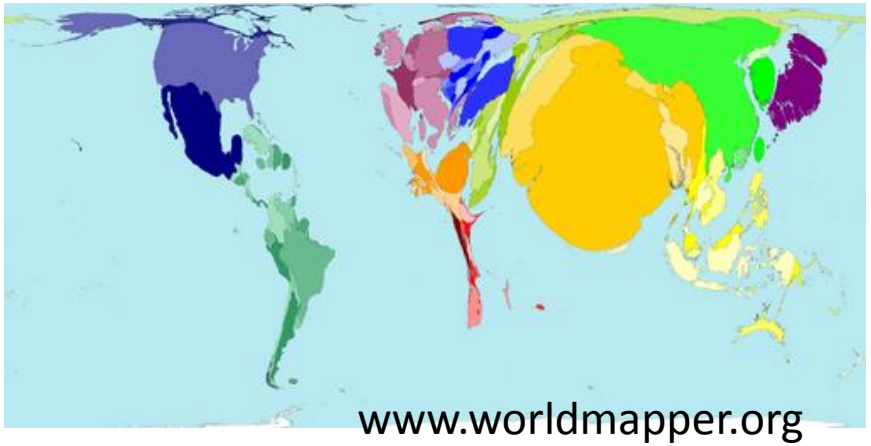
## Diabetes




- 71 million patients with diabetes
- Apparent lack of conventional risk factors
- Young age, low BMI

## Diabetes





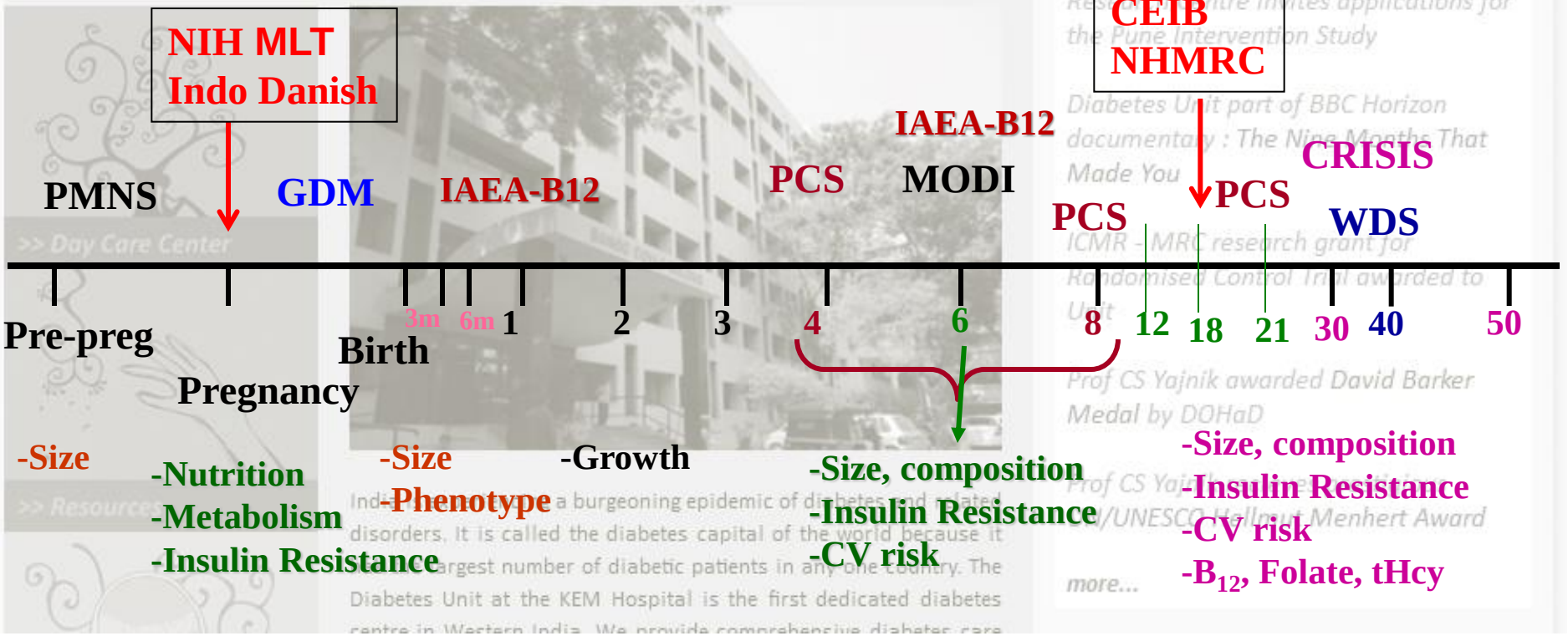

**LBW, Under 5 undernutrition**

Lifecourse history of nutrition important !

DIABETES UNIT
King Edward Memorial Hospital
& Research Centre



*"Towards Metabolic and Nutritional Health of the Population..."*



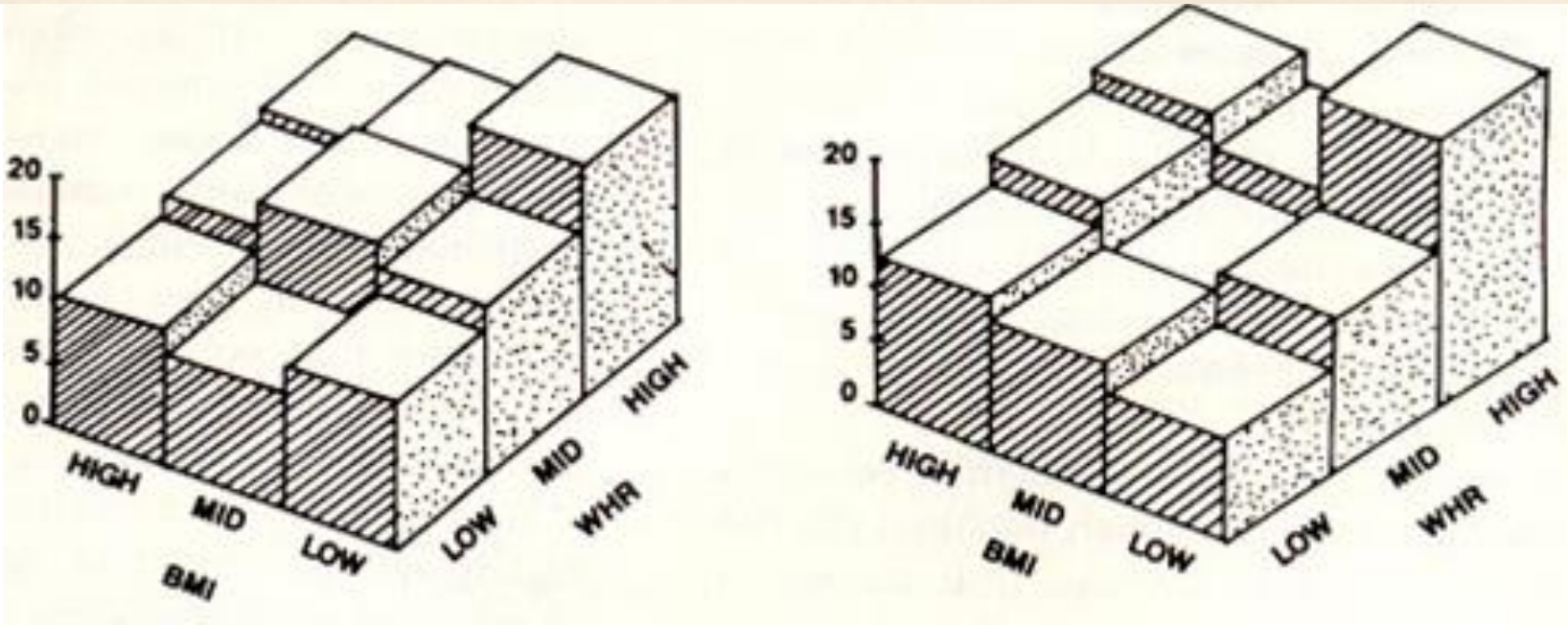

-Characterization of newly diagnosed diabetic Indians

Time scale = age in years

# Central Rather than Generalized Obesity is Related to Hyperglycaemia in Asian Indian Subjects

K.M. Shelgikar[a], T.D.R. Hockaday[b], C.S. Yajnik[a]

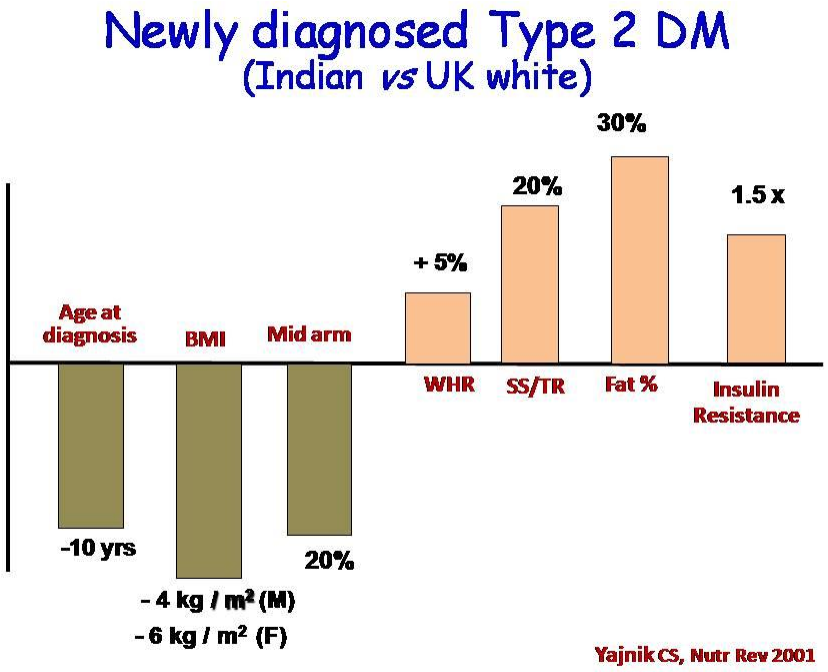
[a]Wellcome Diabetes Study, King Edward Memorial Hospital, Pune, India, and [b]Sheikh Rashid Diabetes Unit, The Radcliffe Infirmary, Oxford, UK




2 hr PG (OGTT), by tertiles of BMI, Waist-hip Ratio

Diabetic Medicine 1991;8:712-717

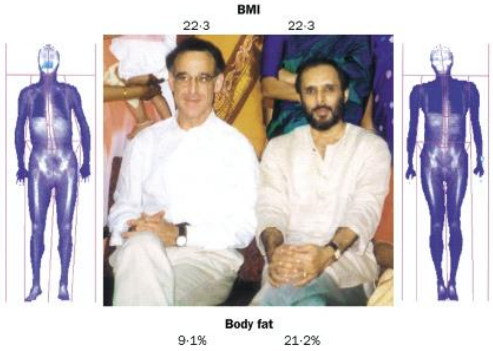
# Thin-fat Indian




## Clinical picture

### The Y-Y paradox

*Chittaranjan S Yajnik, John S Yudkin*

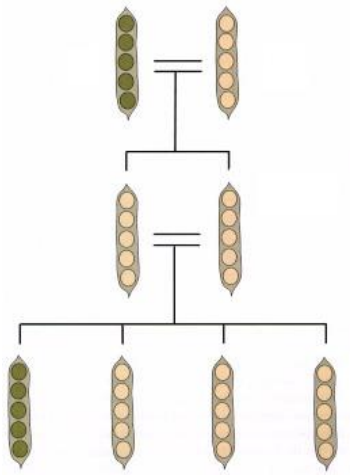


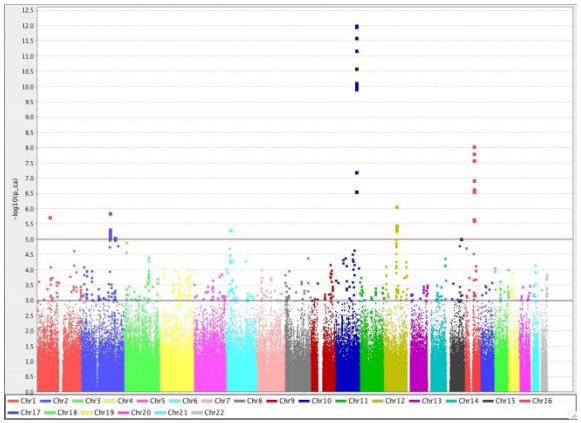

The two authors share a near identical body-mass index (BMI), but as dual X-ray absorptiometry imagery shows that is where the similarity ends. The first author (figure, right) has substantially more body fat than the second author (figure, left). Lifestyle may be relevant: the second author runs marathons 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)

# It must be genetic!

## What Isn't?
## It's the way genes work, that is important

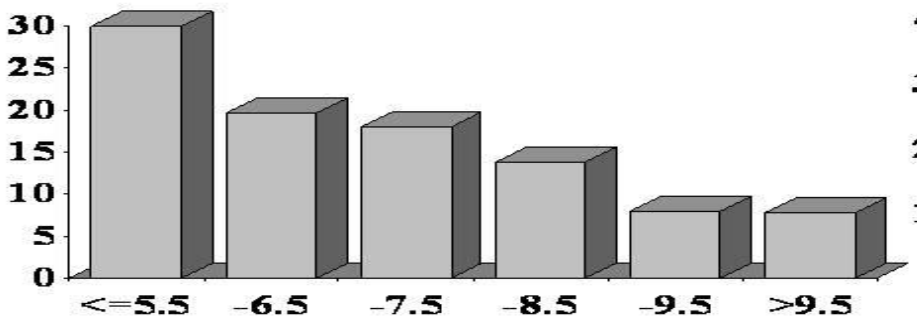




# Hertfordshire, UK

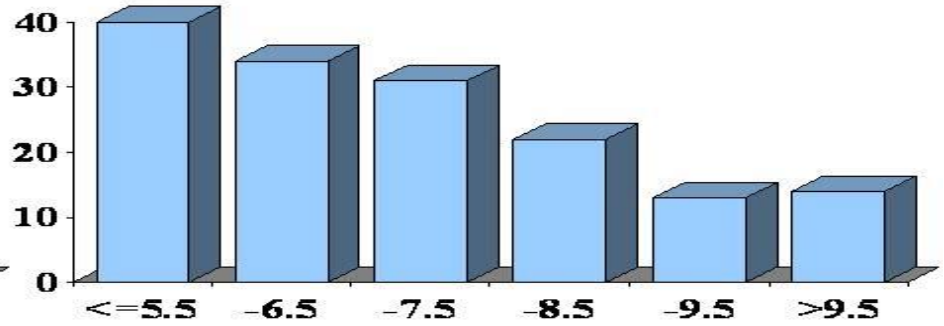
Men aged 59-70 yrs
( n=408)

SYNDROME X




Men aged 64 yrs
( n=370)

IGT + DM




Birthweight (lbs)

*p<0.05

*Hales CN et al, BMJ, 1991*

# Thrifty phenotype hypothesis

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

  - Hales & Barker, Diabetologia,1992

- Thrifty - careful and diligent in the use of resources

# Forsdahl, Norway, 1977

**Growing up in poverty causes 'some sort of permanent damage', perhaps due to a 'nutritional deficit', which left people with a 'lifelong vulnerability' to aspects of an affluent adult lifestyle such as a high fat diet.**

***Br J Prev Soc Med 1977;31:91-95***

# Plasticity & Programming

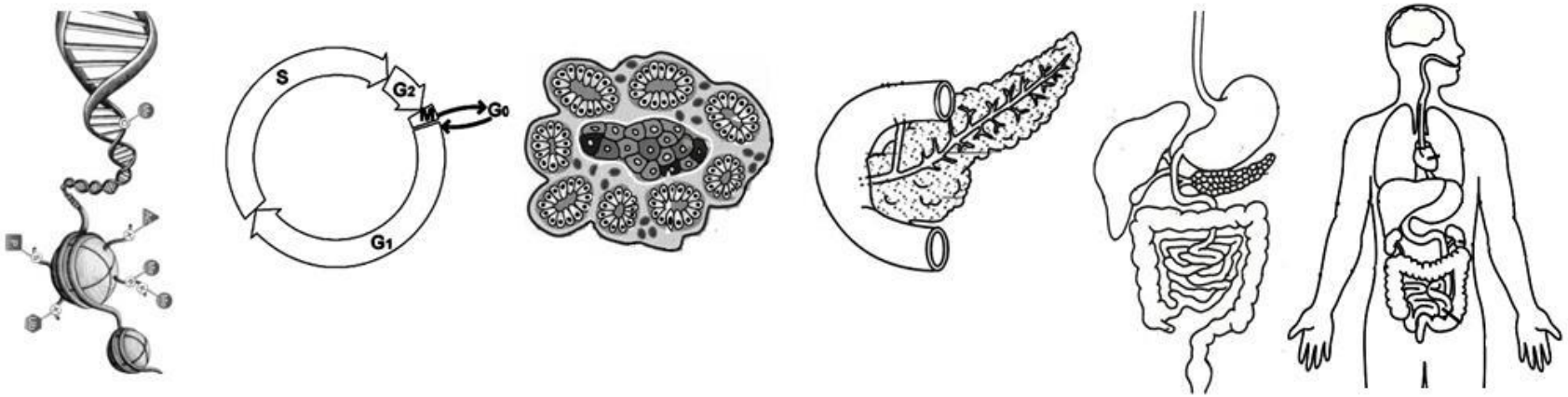
**"..a stimulus applied *in utero* establishes a permanent response in the fetus leading to enhanced susceptibility to later diseases "**

***Alan Lucas***

- *Metabolic, Nutritional, Temperature.*
- Critical periods (*Windows)*
- *Specificity*
- ?Epigenetic
- *'Stable modulation of gene expression'*

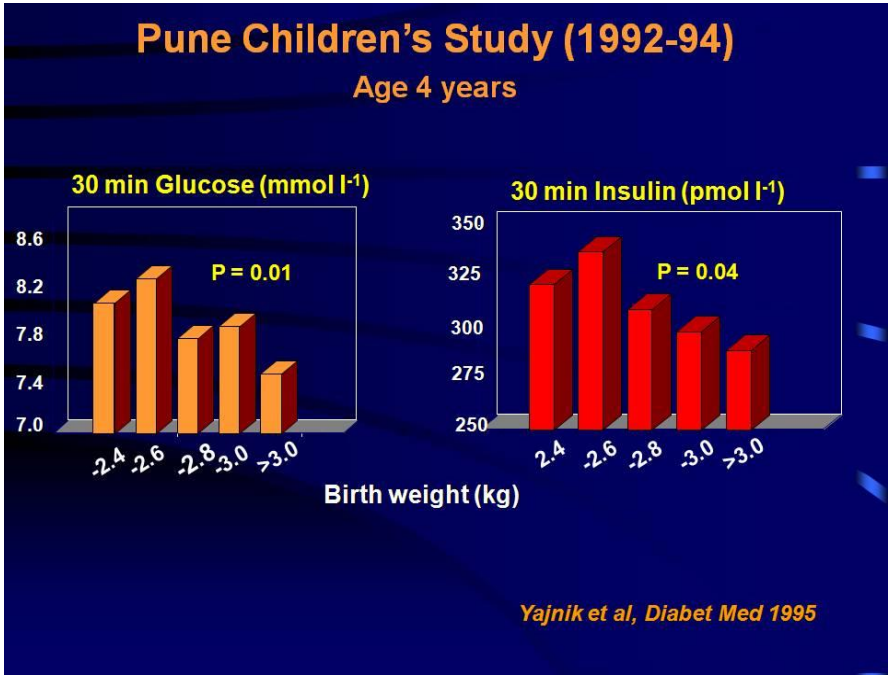
# Fetal programming

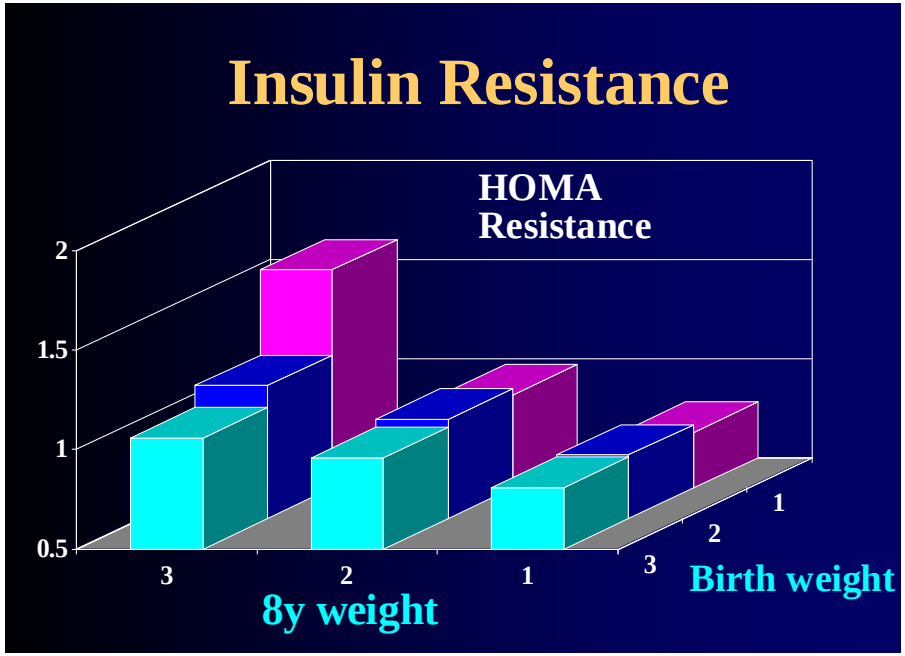
Molecular → Cellular → Tissues → Organs → Systems → Organism




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

# Proof of Concept




Bavdekar Diabetes, 1999


Life can only be understood backwards

Soren Kierkegaard

# 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)
814

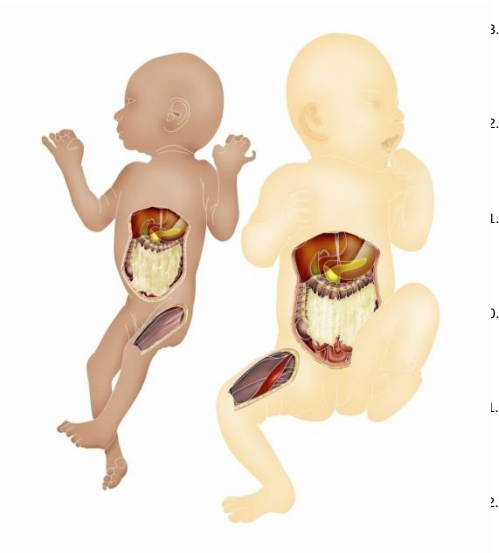
**Size**
Phenotype
770

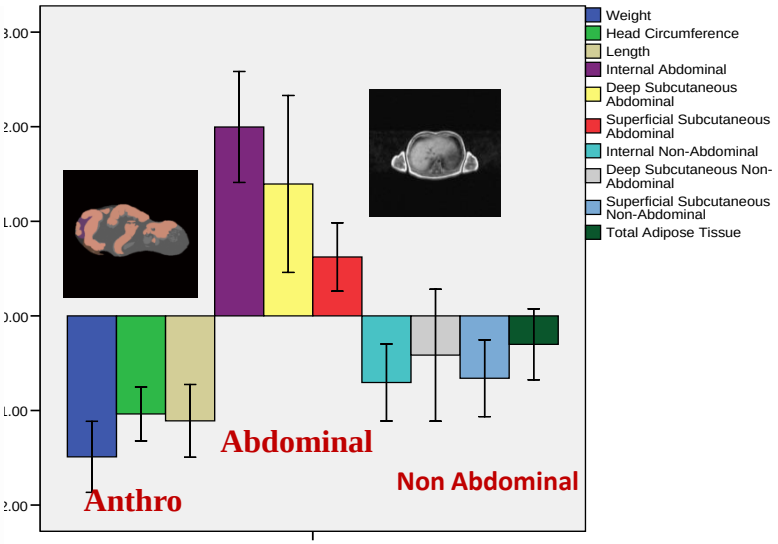
**Growth**
every
6 months
743

**Children & parents**
Size, body composition
IR
CVD risk markers
Cognition
698/723
(96%)

**Children & parents**
Size, body composition
IR
CVD risk markers
Genetics and Epigenetics
N=550
ongoing

# Pune Mothers and Babies

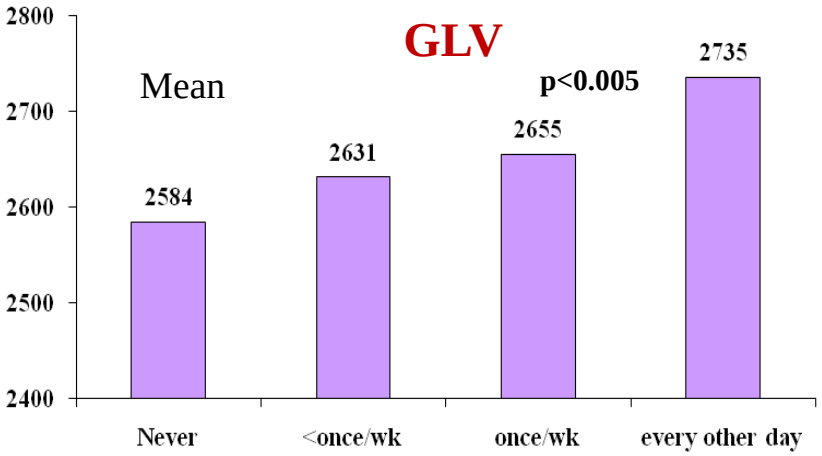


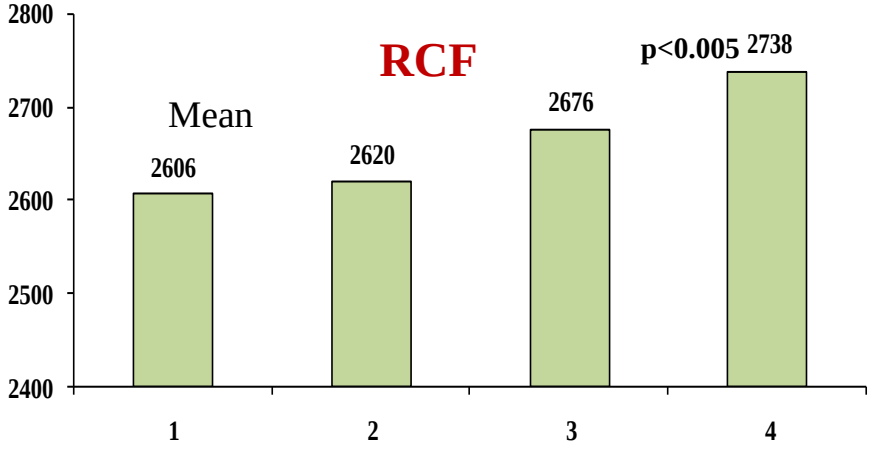


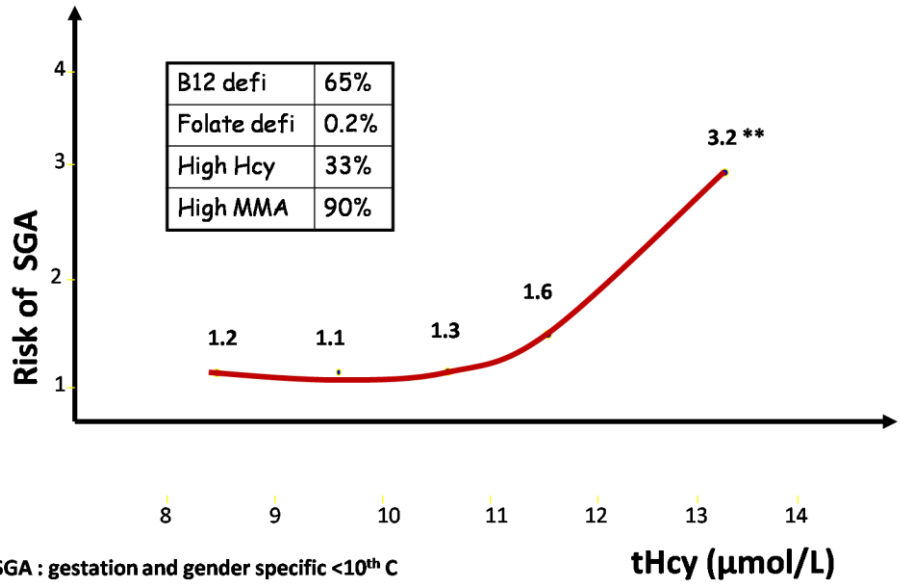

- Small, thin mothers: 42 kg, 1.52m, 18.1 kg/m$^2$
- Thin-fat babies: (2.7 kg), high adiposity
- High cord leptin, insulin, low adiponectin
- No association with macronutrients
- Strong asso GLVs, milk, fruits
- Low B12 , high Hcy predict IUGR

*Fall CHD et al, 1999*
*Rao S et al, J Nutr 2001*
*Yajnik CS et al, IJ Ob 2003*
*N Modi, Ped Res 2009*

# Maternal nutrition, offspring size and IR

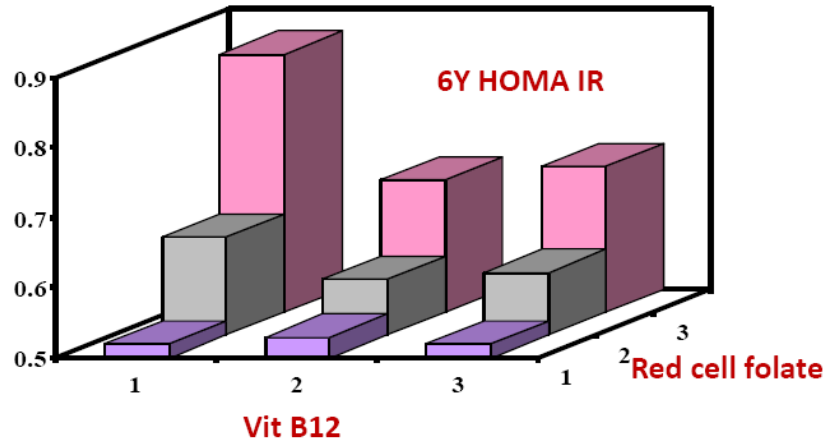



SGA : gestation and gender specific <10th C

**adjusted for gestation, sex, and maternal size**




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

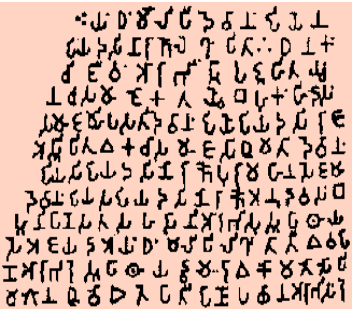
*Rao S, et al, J Nutr, 2001*
*Yajnik CS, APJC,N 2003*
*Yajnik CS, Diabetologia 2008*

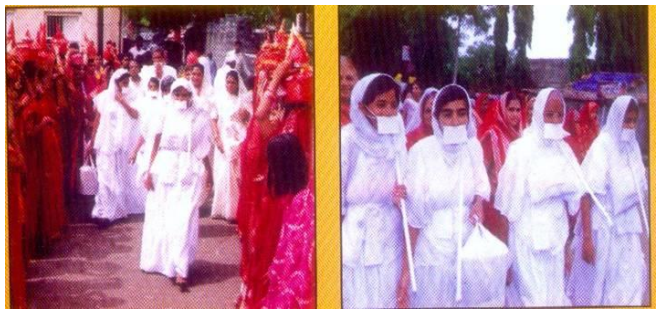
First demonstration that maternal micronutrient nutrition influences risk of diabetes in the offspring

B12 and folate are dietary methyl donors for 1-C metabolism

# Vegetarianism in India (& low vit B12 status)

- **Multigenerational**
  - ✓ **'Ahimsa' (non-killing), Samrat Ashok**
  - ✓ **Religions (Jain, Hindu, Buddha)**
  - ✓ **Education, income & hygiene**
- **Folate 'adequacy' diet + iatrogenic**
  - ✓ **Higher food intake, socio-economic status**
  - ✓ **NAPP (Iron 60mg, folic acid 0.5 mg)**
  - ✓ **Obstetric practice: high dose folate suppl (5mg-15mg)**



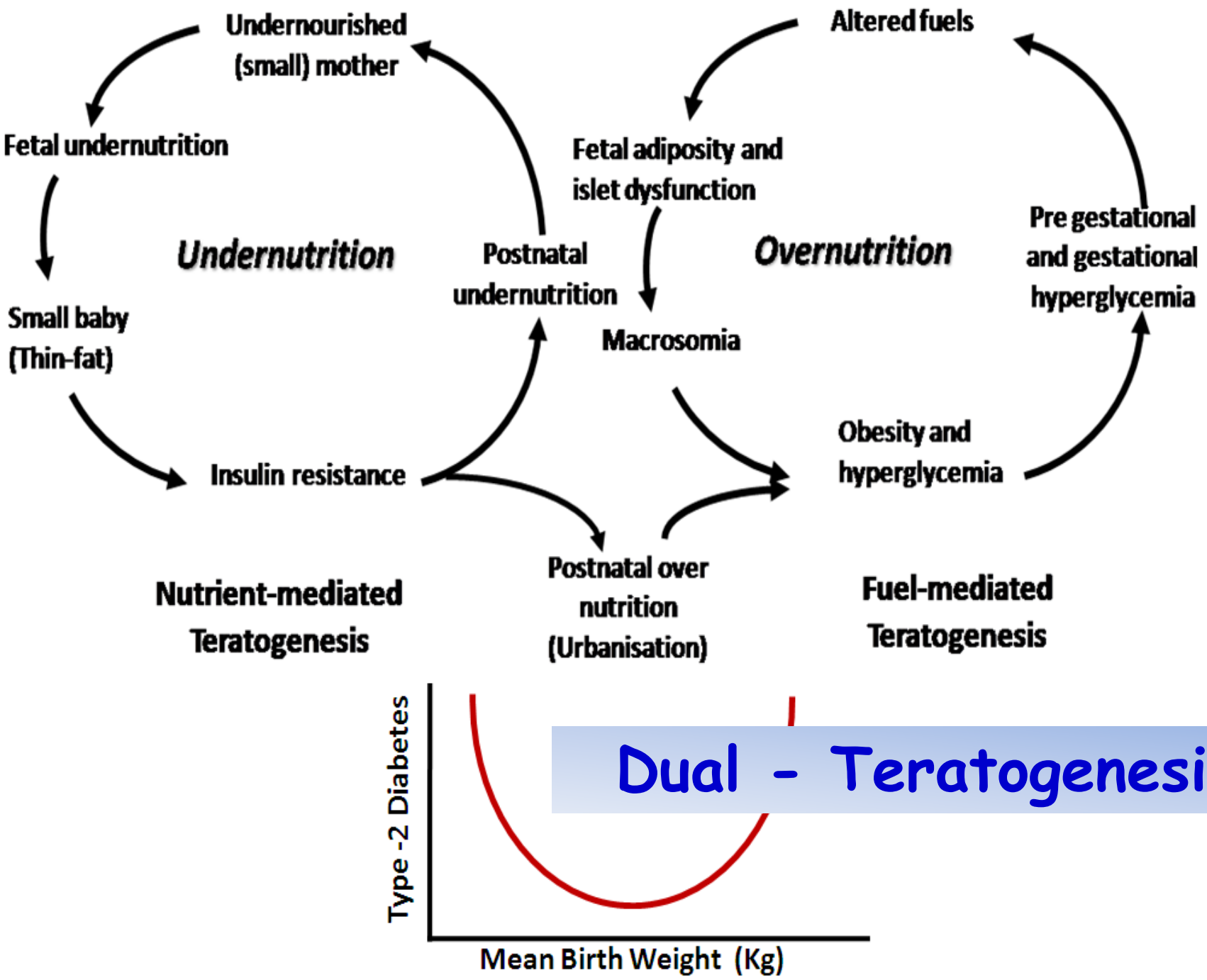


# Prevalence of GDM

| | Centre | N | Prevalence Rate |
|---|---|---|---|
| Dr Balaji et al | North Chennai, Tamil Nadu | 891 | 16.2% |
| Dr Anjalakshi et al | South Chennai, TamilNadu | 1002 | 15% |
| Dr K P Paulose | Trivandrum, Kerala | 750 | 15% |
| Dr Mary John | Ludhiana, Punjab | 220 | 17.5% |
| Dr Prasanna Kumar | Bangalore, Karnataka | 49 | 12% |
| Dr Shyam Mukundan | Alwaye, Kerala | 200 | 21% |
| Dr Aruyerchelvan | Erode, Rural TamilNadu | 562 | 18.8% |
| | TOTAL | 3674 | 16.55% |

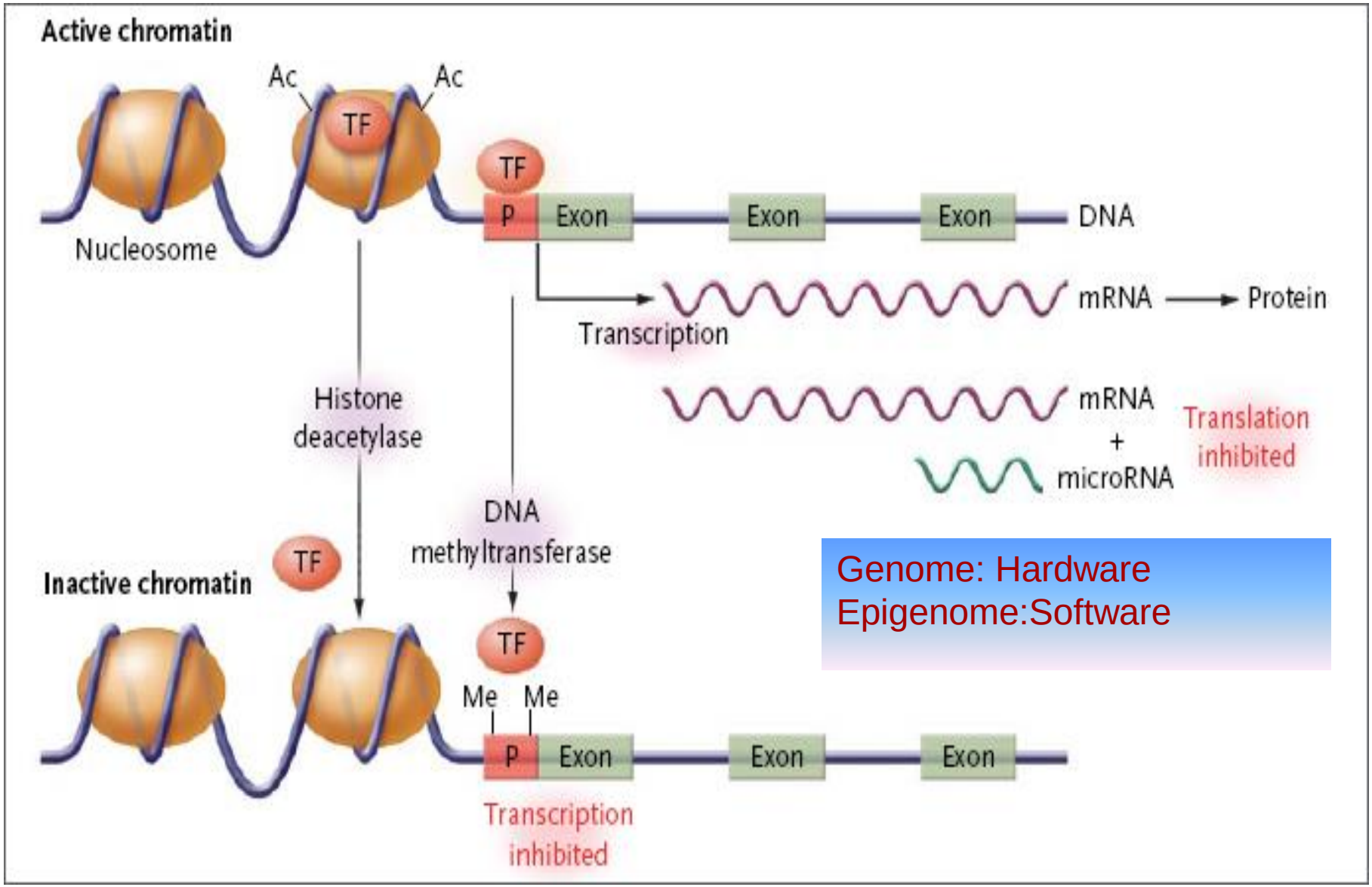
*Criteria used: 75g OGTT: 2hr PG ≥ 140mg/dl*

***Dr V Seshiah Diabetes Care and Research Institute, Chennai***



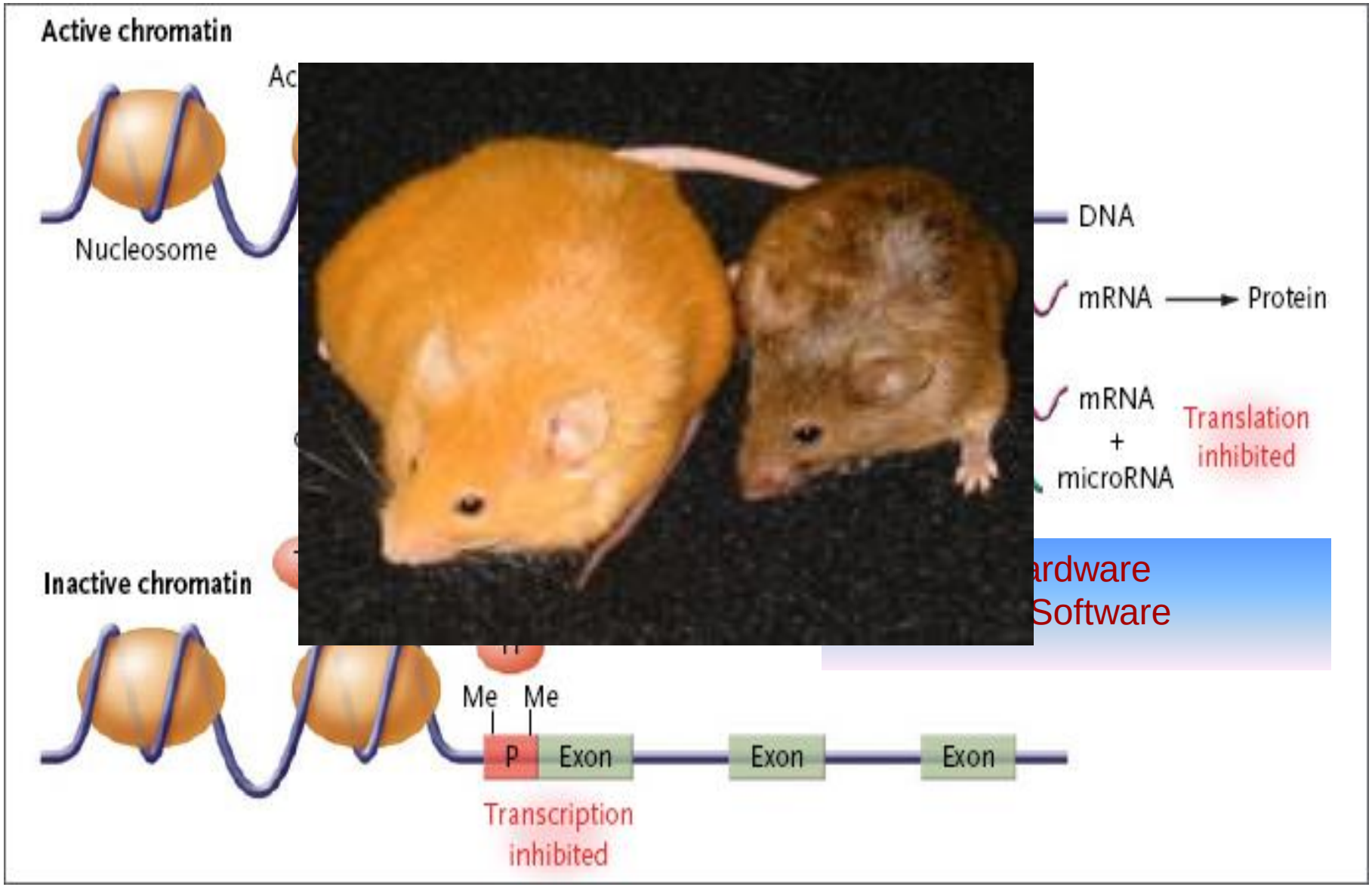

# Dual - Teratogenesis

# *Regulation of Gene Expression through Epigenetic Processes*




Effect of In Utero and Early-Life Conditions on Adult Health and Disease, P Gluckman et al, NEJM 2008

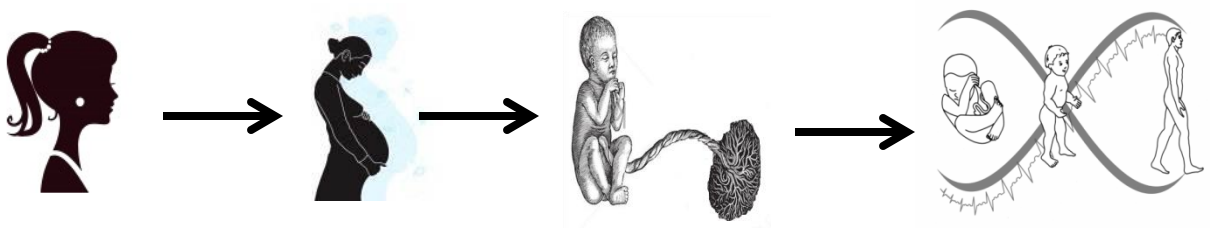
# Agouti Mouse treated with Methyl donor cocktail
# Waterland R & Jirtle J. 2003




Effect of In Utero and Early-Life Conditions on Adult Health and Disease, P Gluckman et al, NEJM 2008


Life can only be understood backwards
But it must be lived forwards.
Soren Kierkegaard

# Pune Intervention Study
# ICMR-MRC 2011- 2015



**Pre-intervention screening**
- **Exclusion**
  - 117 low B12,
  - 2 anemic
  - 14 medical

Feb-June 2012

→ **Randomisation**

July 2012

→ **Intervention**

Vitamin Sep 2012
Protein May 2013
Interim sample Apr 2013
Interim analysis Jun 2014

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

- 557 Adolescents
- Girls (291) and boys (266)
- Physiological doses
- 3y/till first delivery

→ **Newborn**
- Cord blood B12, OMICs etc
- Anthro
- Follow up

1st delivery Jun 2013

July 2014
Married 70
Pregnancies 37
Delivered 22
Currently Preg 11

Iron and folic acid tablets as per Government of India guidelines to all groups

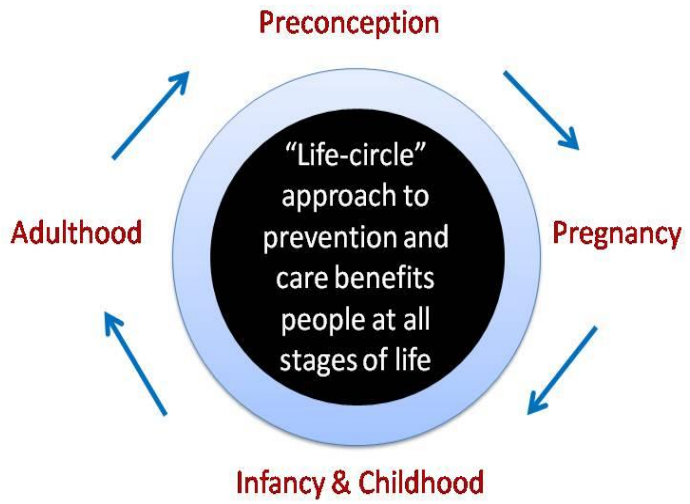
# Summary

- Early life environment important for life-long health and disease susceptibility
- Length of gestation and growth
- Postnatal growth
- First 1000 days
- T2DM phenotype: B-cell, IR

- Trials ongoing
- Primordial Prevention
- Biochemical & molecular mechanisms
- Influence on public health and policy

# KATHMANDU DECLARATION

*Actions following UN Resolution for PREVENTION, TREATMENT and CARE of Diabetes*




# UN DECLARATION

## 'Women's health- Nation's wealth'

Women, Development & Diabetes
UN, April 2008
www.wdf.org

# Acknowledgements


MRC LEU, S'ton, UK
- DJP Barker
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- AT Hattersley
- Tim Frayling
- Tim McDonald
- Jon Mill

Blizard, QMUL, UK
- G Hitman, Sarah Finer
- V Raykan

**CCMB, H'bad**
- Giriraj Chandak

**IISER, Pune**
- Sanjeev Galande

**NIBMG, Kalyani**
- Partha Majumder

**NII, Delhi**
- Satyajeet Rath
- Vineeta Bal

**NCCS, Pune**
- Yogesh Shouche

**IIS, Bangalore**
- Utpal Tatu

**Persistent systems**
- Anand, Abhay, Prachi

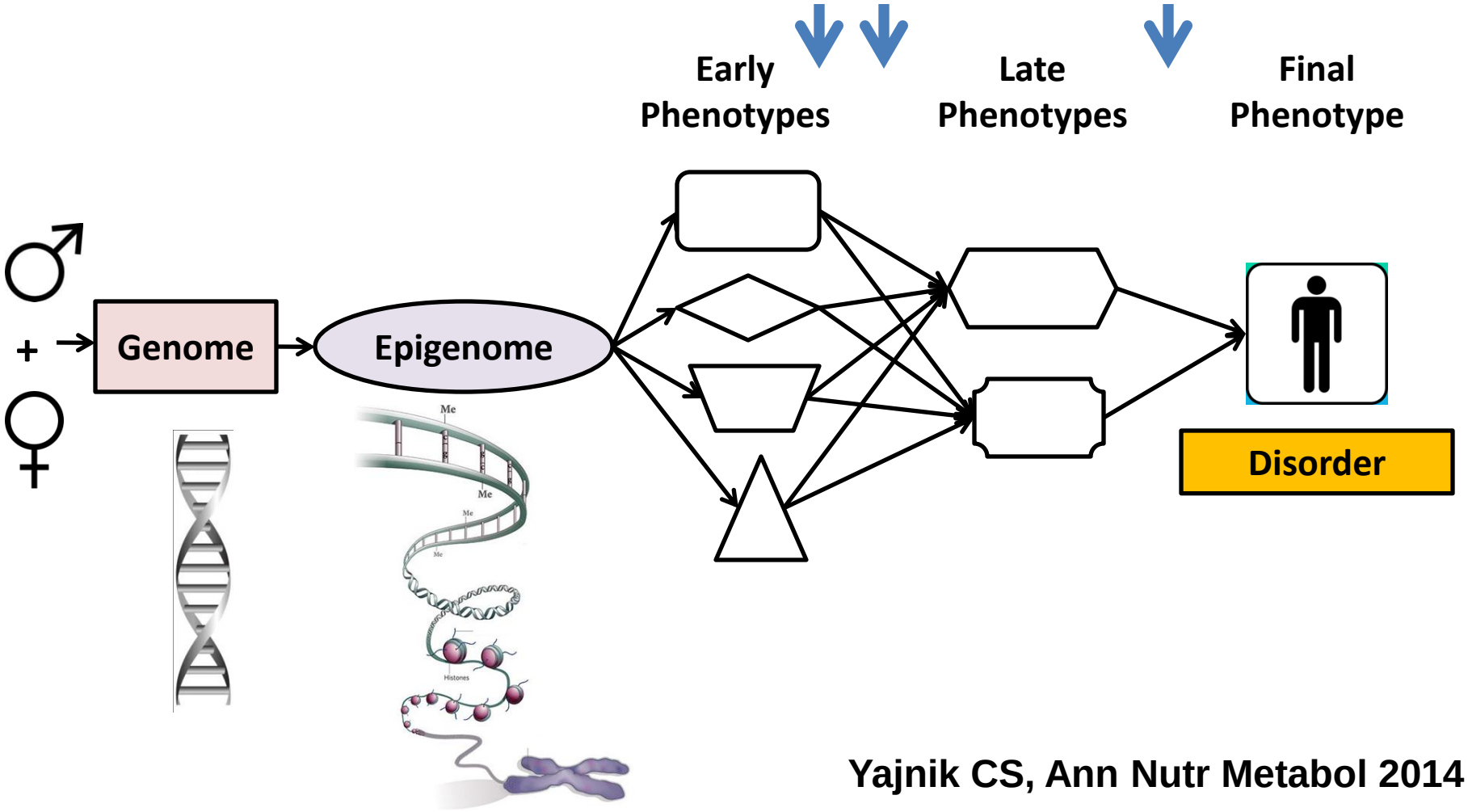
**KEM Hospital Diab Unit**
- Many, many

# PARTICIPANTS

**Funding**

*The Wellcome Trust, London*
*MRC, UK*
*DBT, India*
*EU, IAEA*
*ICMR, India*
*NIH*


# Lifecourse evolution of a phenotype




Yajnik CS, Ann Nutr Metabol 2014

# The periconceptional period, reproduction and long-term health of offspring: the importance of one-carbon metabolism

Regine P.M. Steegers-Theunissen, John Twigt, Valerie Pestinger, and Kevin D. Sinclair, 2013