

Why do South Asians have a high risk for CVD and diabetes?

D Prabhakaran MD, DM, FRCP, FNASc, FNA, DSc

Executive Director, Centre for Chronic Disease Control, New Delhi

Distinguished Professor, Public Health Foundation of India, Gurgaon, India



Centre for Chronic Disease Control



WHO Collaborating Centre for Surveillance, Capacity building and Translational Research in Cardio-Metabolic Diseases



PUBLIC HEALTH FOUNDATION OF INDIA

65 years ago

Ethnic Group differences in Coronary Heart Disease in Singapore: An Analysis of Necropsy Records

- Danaraj T J et al, AHJ 1959

Ethnic Group By Age	CVD %	CHD %
Indian Males (30-39)	38.8	19.7
Chinese Males (30-39)	25.5	3.5
Indian Males (40- 49)	54.1	28.3
Chinese Males (40-49)	31.3	4.5

Since then
.... many

..... ACROSS THE
WORLD !

Age-specific CHD mortality in age group 40-49 years was 120/100,000/yr. vs.
17.1/100,000/year

80's through 2000.....

- **Conventional risk factors do not explain CVD in SA adequately**
- **Several factors adduced to explain CVD based on migrant South Asian- non migrant comparisons**
- **Wave of migrant studies comparing Indians abroad with Indians in India and local studies suggested the importance of conventional risk factors**

INTERHEART Study

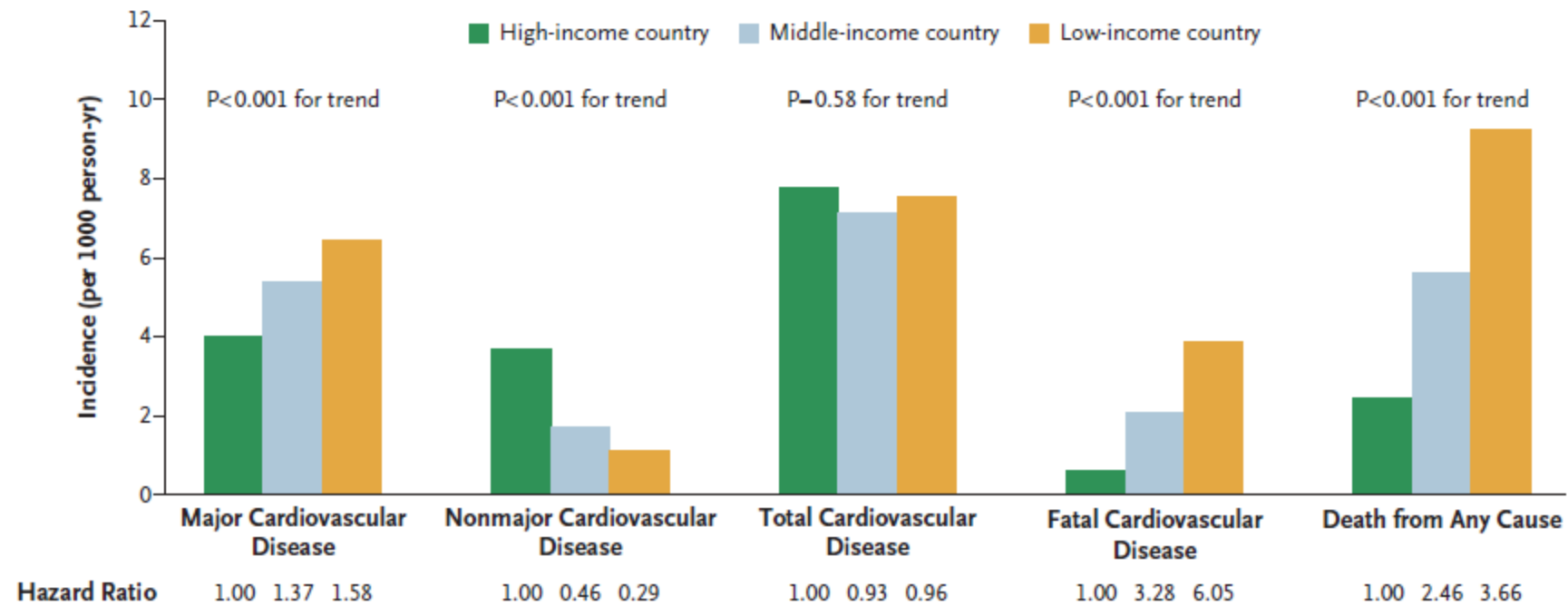
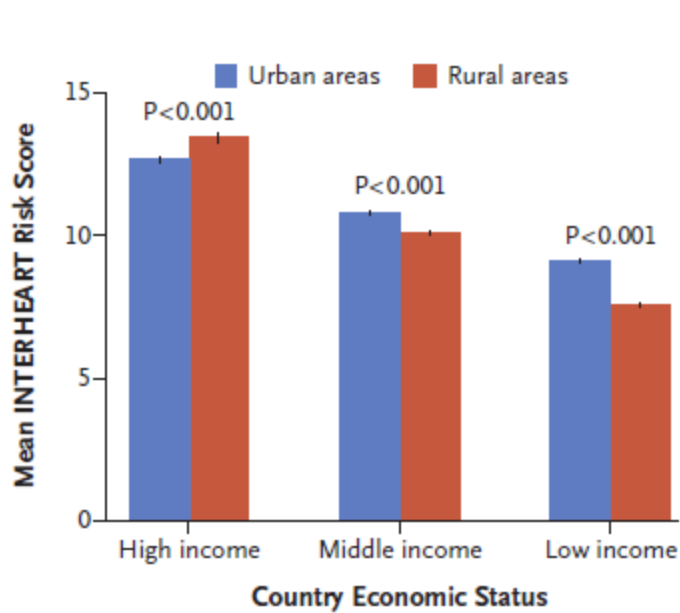
About 90% of CHD Risk (“PAR”) can be explained by 9 Risk Factors:

- Smoking
- Dyslipidemia (↓Apo A/ Apo B Ratio)
- High BP
- Diabetes
- Abdominal Obesity
- Psychosocial Factors
- Fruits & Vegetables
- Exercise
- Alcohol

**INTERHEART India:
Similar results
Joshi et al; JAMA 2007**

**Thresholds at which risk factors
operate appeared to be dependent on
ethnicity**

Risk-Factor Burden and CVD Event Rates in High-, Middle-, and Low-Income Countries



How do we explain this paradox?

- **Epidemiological Transition and SES**
- **Ethnic Variations (High propensity for diabetes among South Asians)**
- **New risk factors such as air pollution**
- **Others such as variations in health systems**

Epidemiologic Transition

Stage I

**Pestilence &
Famine**



Stage II
**Receding
Pandemics**



Stage III
**Degenerative &
Man-Made
Diseases**



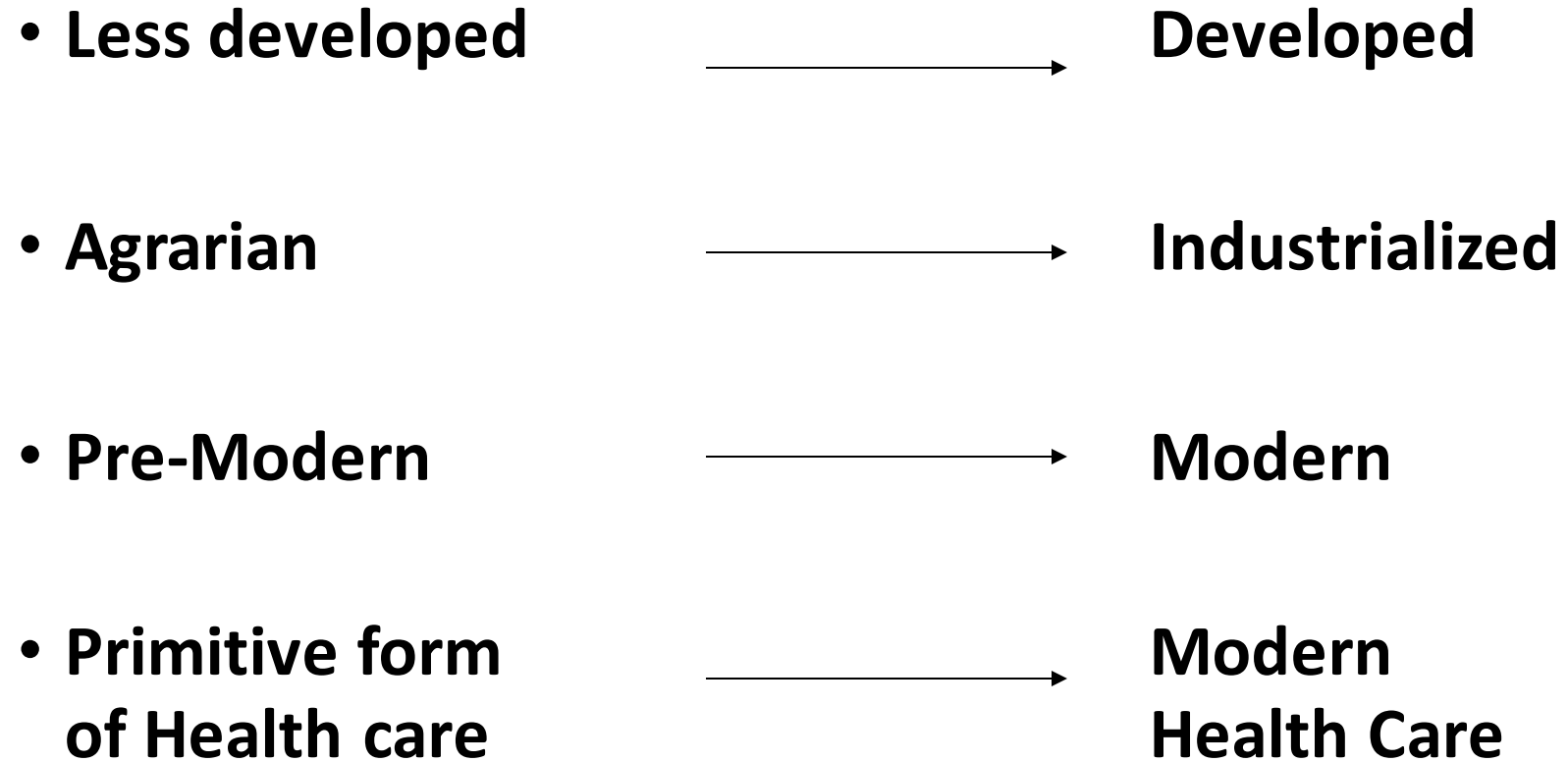
Stage IV
**Delayed Degenerative
Diseases**

Epidemiological transition refers to a change in the pattern of disease in a country away from infectious diseases towards degenerative diseases.

Stage 5 : Reversal of benefits

- **Obesity epidemic in the US**
- **Social upheaval in the former Soviet Union**
- **Wars**

Process



Health Transition: CVD Example

	Stage I	Stage II	Stage III	Stage IV
Life Expectancy	35 yrs	50 yrs	60 yrs	>70 yrs
Dominant Diseases	Infections, Nutritional	Mixed	Chronic (Mid-Life)	Chronic (Elderly)
CVD contribution (to mortality)	5-10%	15-35%	>50%	<50%
CVD Pattern	RHD + Nutritional heart disease	RHD + NHD + Stroke (ICH)	CHD + Stroke (both)	CHD + Stroke (THR)
1° Victims	Higher class	All classes	Lower classes	Lower classes

Health Transition

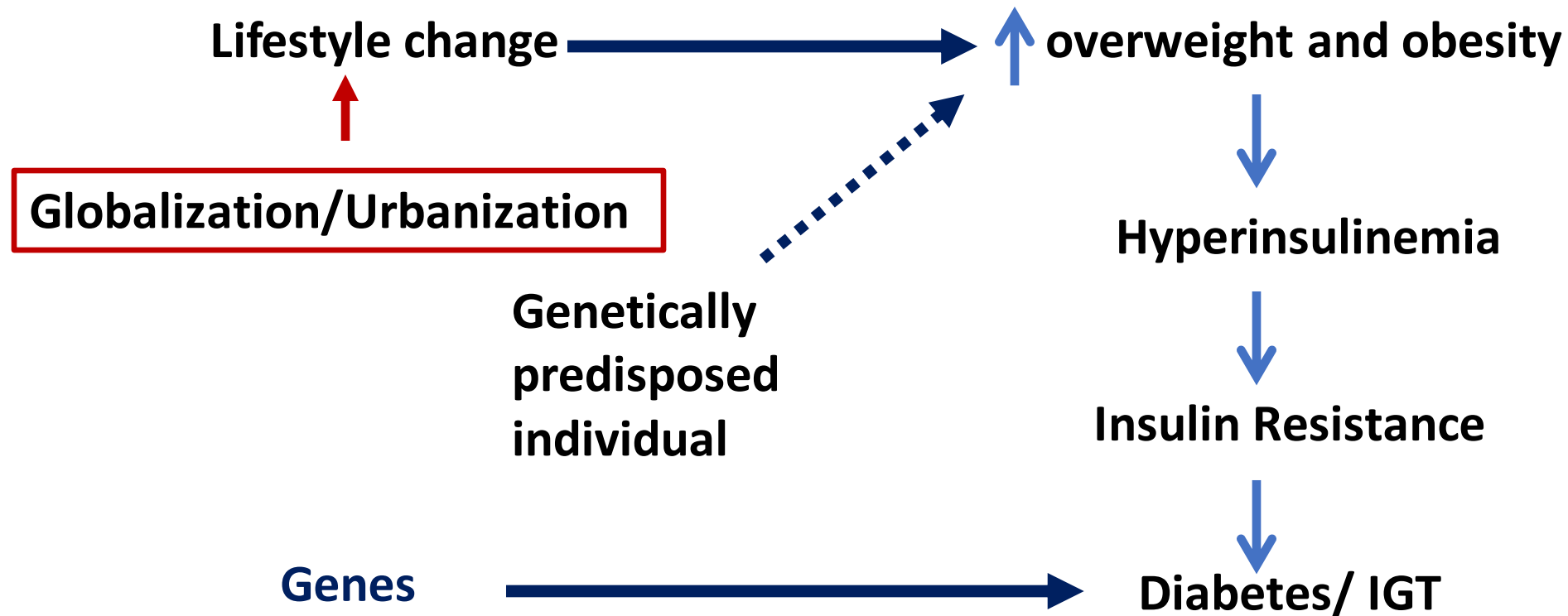
Developed World vs. Developing World

	Industrialized Countries	India
Time Frame of Health Transition	Long	Compressed
Double Burden	Small	Large
Determinants	Urbanization in Prosperous Economies	Urbanization in Dependent Economies
Resources	Ample	Limited

Are there differences in CV risk based on ethnicity ?

The case of lipids and Diabetes

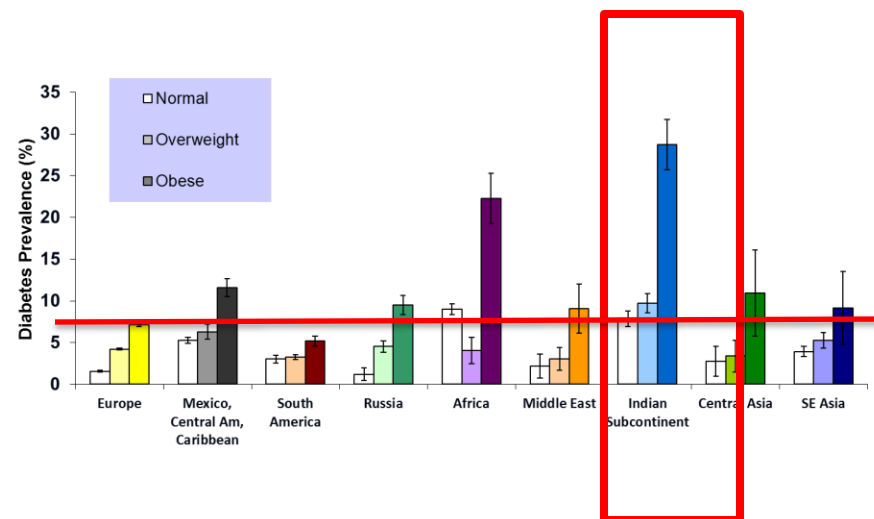
Popular views regarding cause of diabetes



An Ecological Comparison

	Overweight & Obesity (% adults)	Diabetes Prevalence (% adults)
USA	69	9
China	31	9
India	13	9
Japan	29	11

Diabetes prevalence (%) by BMI and region of origin, United States



World Health Organization - NCD Country Profiles 2011, IDF Atlas 2013

Oza-Frank, Reena, and Narayan KM.
American Journal of Public Health 100.4 (2010): 661

**What gout is to the nobility of England,
 diabetes is to the aristocracy of India**

Lancet, 1907 (Editorial)

What are the potential reasons for the heterogeneity in the epidemiology and associations of diabetes among different ethnicities

- **Reduced beta cell mass**
- **Altered body composition**
- **Poor maternal/early child nutrition**
- **High Carb diet**
- **Lipotoxicity**
- **Microbiomes**
- **Endocrine disruption (Air pollution/organic pollutants)**
- **Hepatic infections/NAFLD**
- **Unknown**

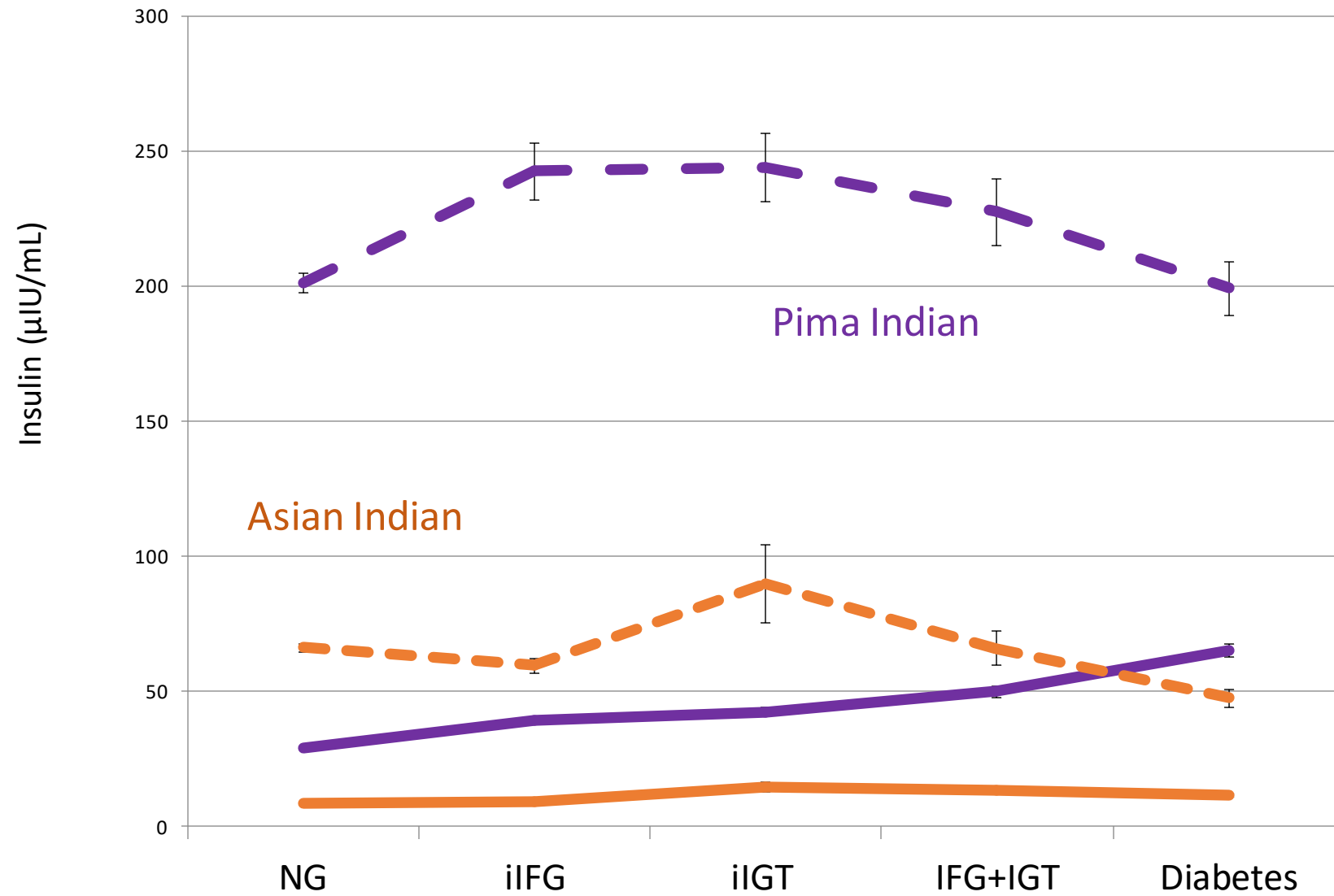
Diabetes and the Tale of the Two Indians

	Pima Indians	Asian Indians (Chennai)
Prevalence of diabetes*	50% by age 55 y	50% by age 55 y
Obesity profile	Very obese (BMI : 33.7 Kg/m ² ; WC 108.6 cms)	Relatively thinner (BMI 25.7 kg/m ² ;WC 83.1cms)
Glucose profile	High 2-hr plasma glucose	High Fasting plasma glucose
Prediabetes distribution	~ 2/3 is iIGT	> 2/3 is iIFG
Insulin resistance Vs secretion (across BMI and glucose strata)	2-4.5 times more insulin resistant than Asian Indian	1/2 to 1/3 insulin secretion than Pima Indians <small>Staimez L et al. Diabetes. June 2014;63 (Supplement 1). Narayan KM. Kelly West Lecture. Diabetes Care May 2016</small>

The course to diabetes in South Asians is rapid once prediabetes sets in

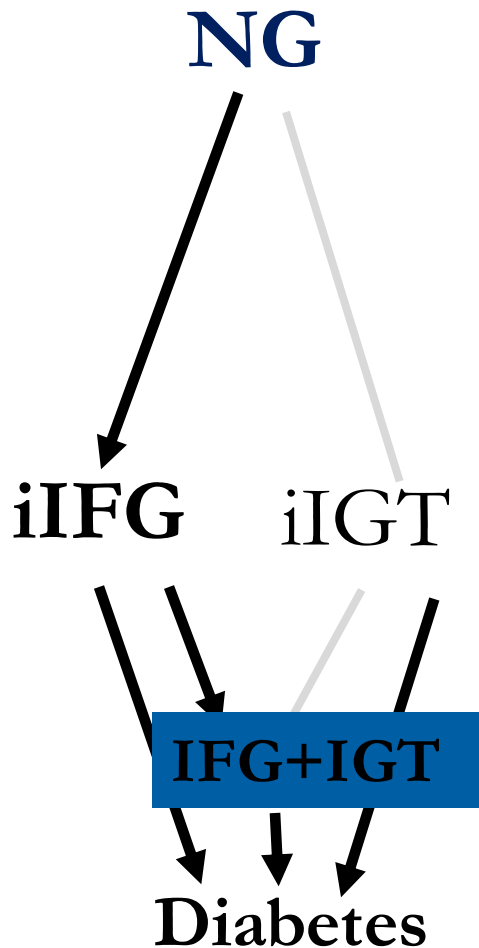
Are we on course for reclassification of diabetes?

WC: waist circumference



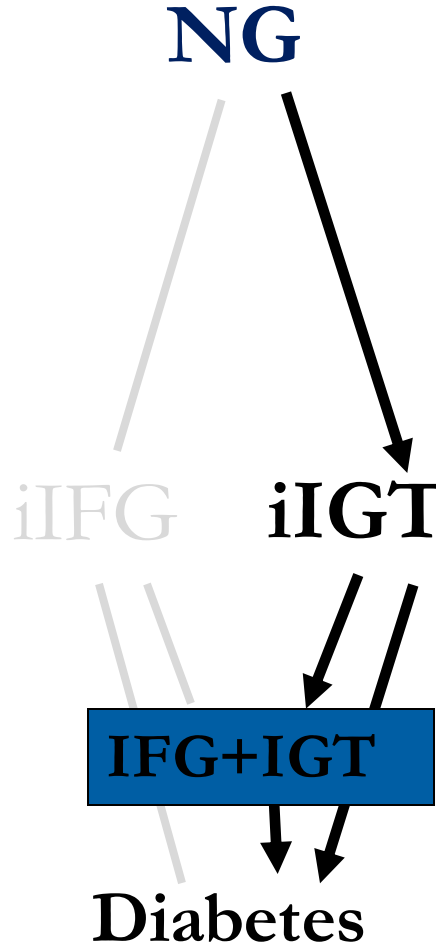
Hypothesis: Phenotypes of Beta-Cell Capacity

Narrow Beta-Cell Capacity



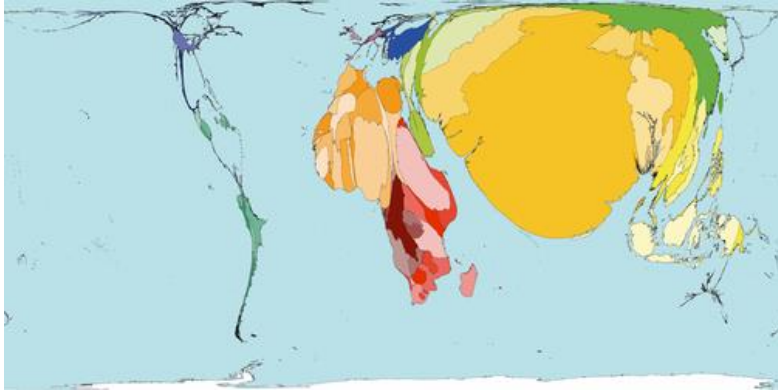
- Basal metabolic state: high fasting glucose
- Slight or moderate demands for insulin lead to strained beta-cells and acceleration of impaired early-phase insulin secretion
- Dominant form of prediabetes: iIFG
- Rapid conversion from prediabetes to diabetes

Wide Beta-Cell Capacity

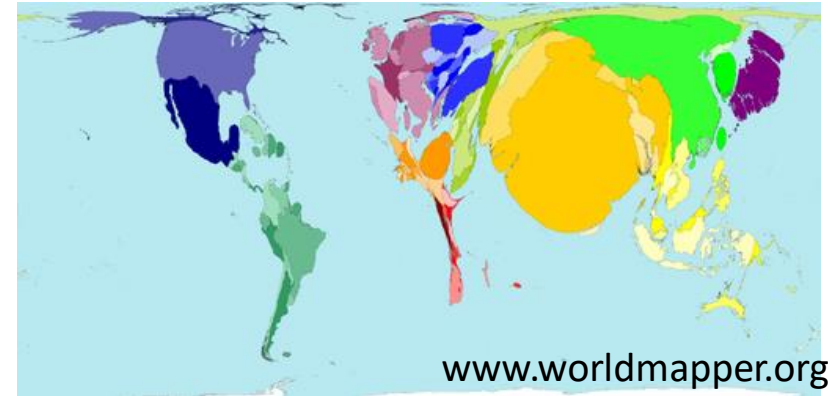


- Basal metabolic state: low fasting glucose
- Slight or moderate demands for insulin are managed efficiently over time through compensatory insulin secretion
- Dominant form of prediabetes: iIGT
- Slower conversion until obesity and insulin resistance are great

LBW, Under 5 undernutrition



Diabetes



“The history of man for nine months preceding his birth would probably be far more interesting and contains events of greater moment than all three score and ten years that follow it”

- Samuel Taylor Coleridge



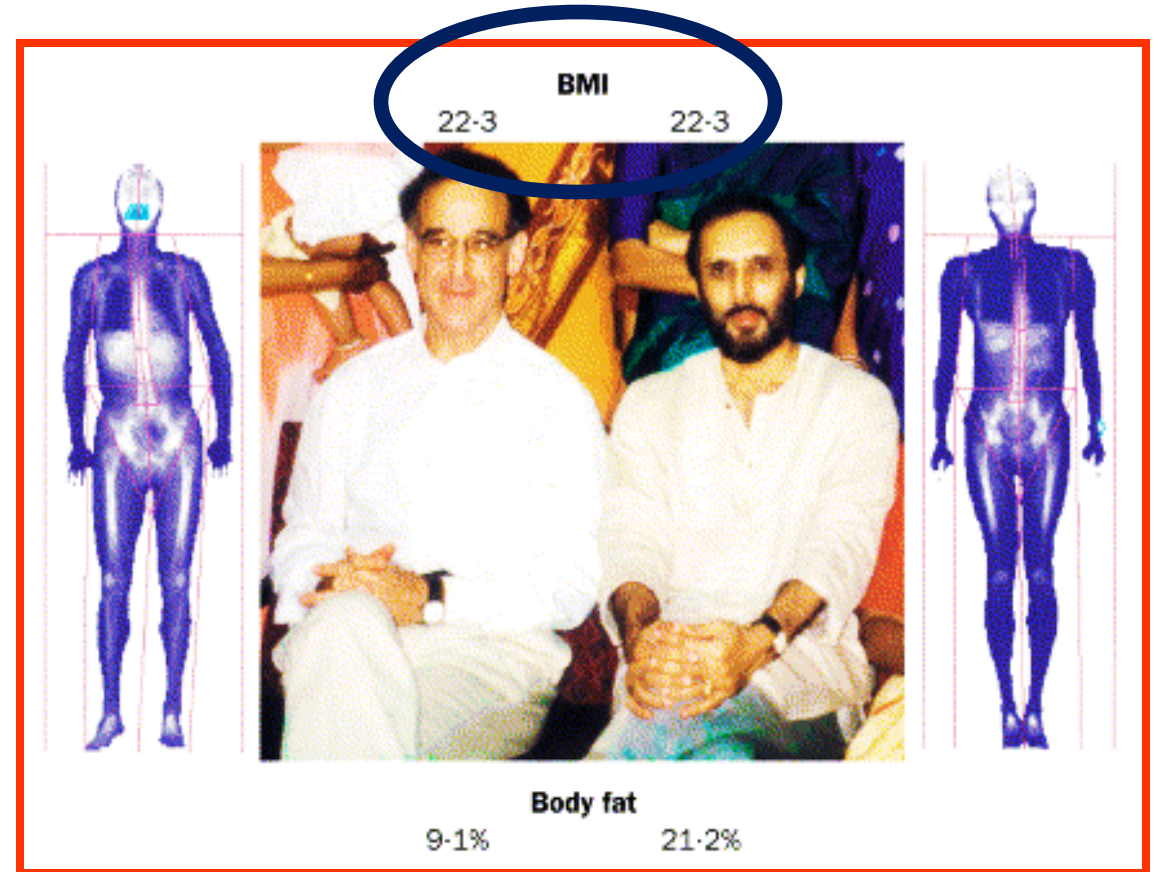
Barker's or Forsdahl-Barker Hypothesis



The 'thin-fat' newborn



Yajnik has 21% Fat, Yudkin 9%



Y – Y Paradox!

Understanding Diabetes in India : Various research Questions

**Association of Persistent
Organic Pollutants with
incident diabetes among
urban Indian adults**

**Air Pollution and
diabetes**

Diabetes and NAFLD

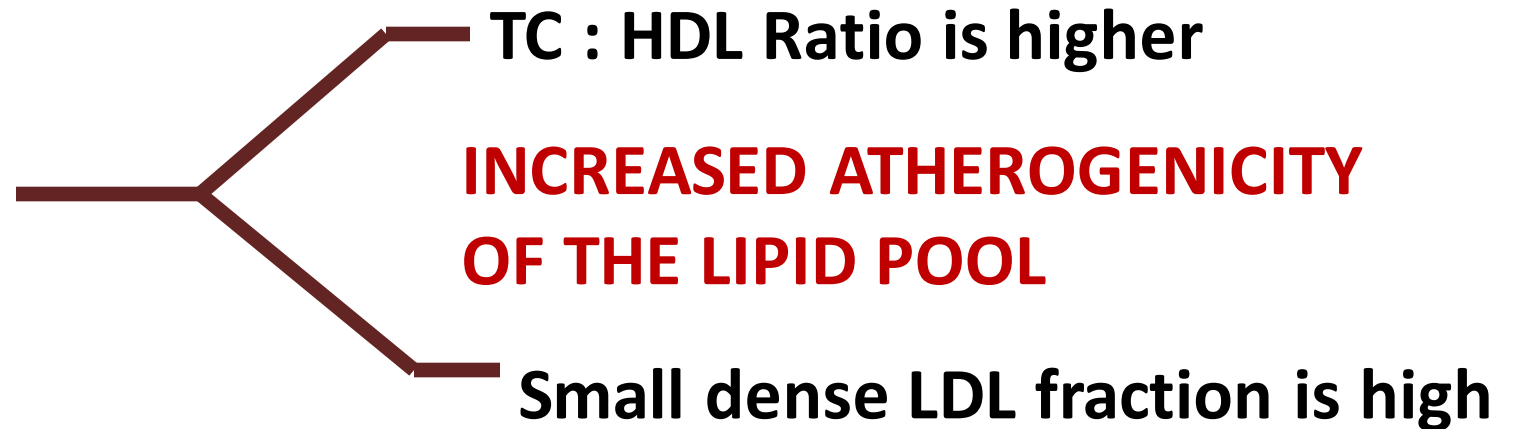
**Beta Cell function and
Capacity**

**Understanding the
mechanisms of diabetes
comorbidity**

Others

Lipids: Indians in Comparison to other Ethnic Groups

For any given level of
Total/LDL cholesterol

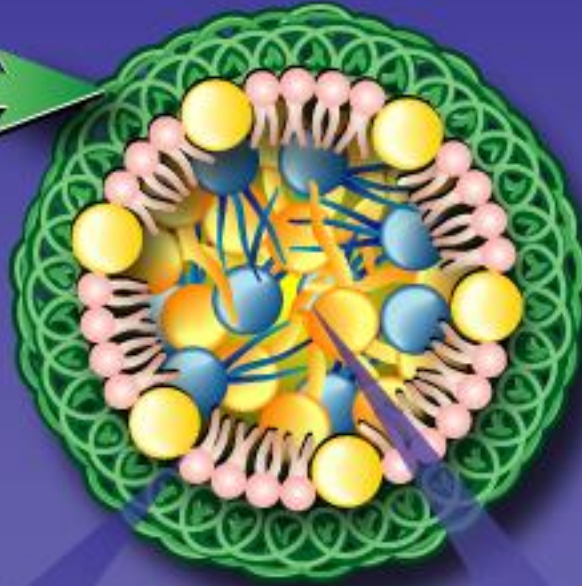


Hyper TG and Hyper apo B

This is an LDL particle

LDL types 1,2, 3

apoB



Polar Surface Coat

Phospholipid



Free Cholesterol



Nonpolar Lipid Core

Cholesterol Ester



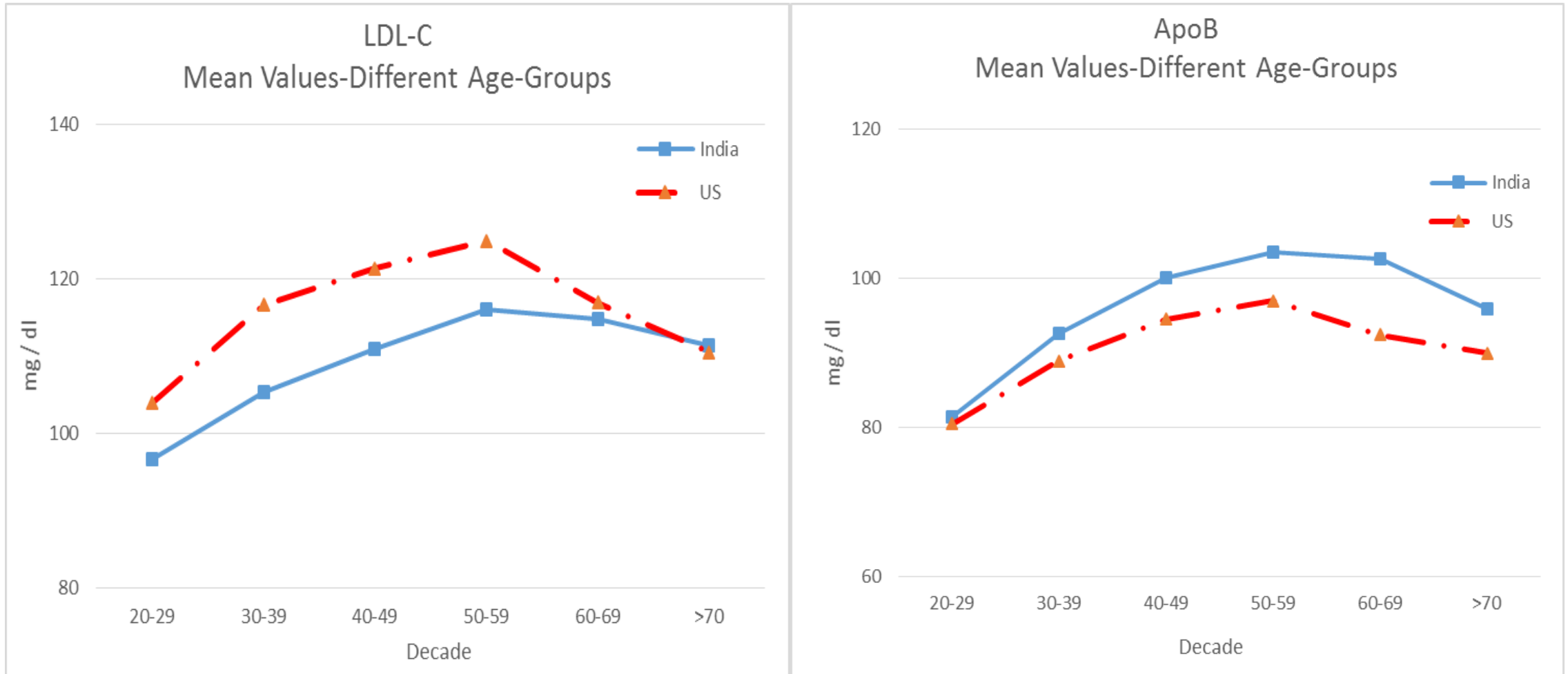
Triglyceride



INTERHEART SA vs OC

Risk Factor	Cases SA	Cases OC
apoB/apoA-I	61.5%	48.3%
Smoking	61.6%	65.7%
Hypertension	29.6%	40.5%
Diabetes	20.2%	18.2%
WHR	44.0%	46.7%

ApoB and LDLc levels in Indians compared to the US



Metabolic risk factors in Indians compared to the US

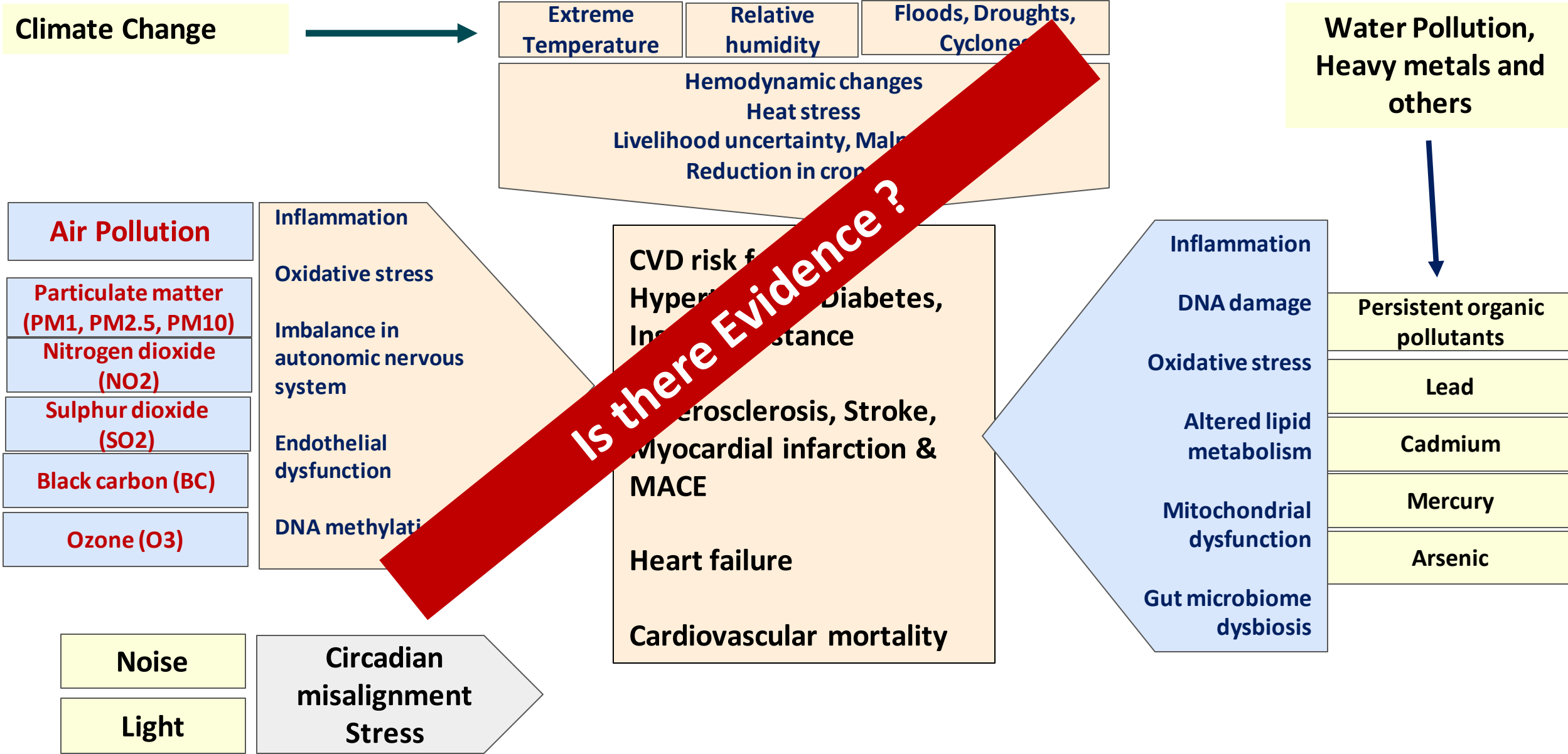
Measure	India		United States		P Value
	Mean (SD)	N	Mean (SD)	N	
Age	41.0 (13.2)	13,717	47.2 (17.2)	10,609	<.0001
TC	179.2 (41.0)	13,717	195.9 (42.2)	10,609	<.0001
TG	145.6 (106.7)	13,716	128.8 (107.0)	4,881	<.0001
LDL-C	107.7 (34.1)	13,389	116.0 (36.9)	4,793	<.0001
HDL-C	44.33 (11.98)	13,713	53.04 (16.29)	10,609	<.0001
ApoB	96.13 (28.91)	4,244	90.52 (25.53)	4,882	<.0001
TC/HDL-C	4.34 (1.34)	13,712	3.98 (1.43)	10,609	<.0001
Non-HDL-C	135.9 (40.1)	13,712	142.8 (42.0)	10,609	<.0001

Lipid distribution very similar to diabetic dyslipidemia

Where are we in terms of Apo B

- **Apo B is a single atherogenic lipid marker present in all lipid sub fractions except HDL-C**
- **Apo B, integrates and extends the information from triglycerides and cholesterol**
- **The conventional lipid panel is complex and can be confusing and sometimes contradictory.**
- **Replacing the conventional lipid panel with apo B for routine follow ups could simultaneously simplify and improve clinical care**
- **Mendelian randomization studies, AI based analysis in the west have shown apo B to be superior**
- **In India, watch the space for the next 1-2 years**

What are the Environmental Determinants of Cardiovascular Health ?



Air Pollution and Hypertension

Summary

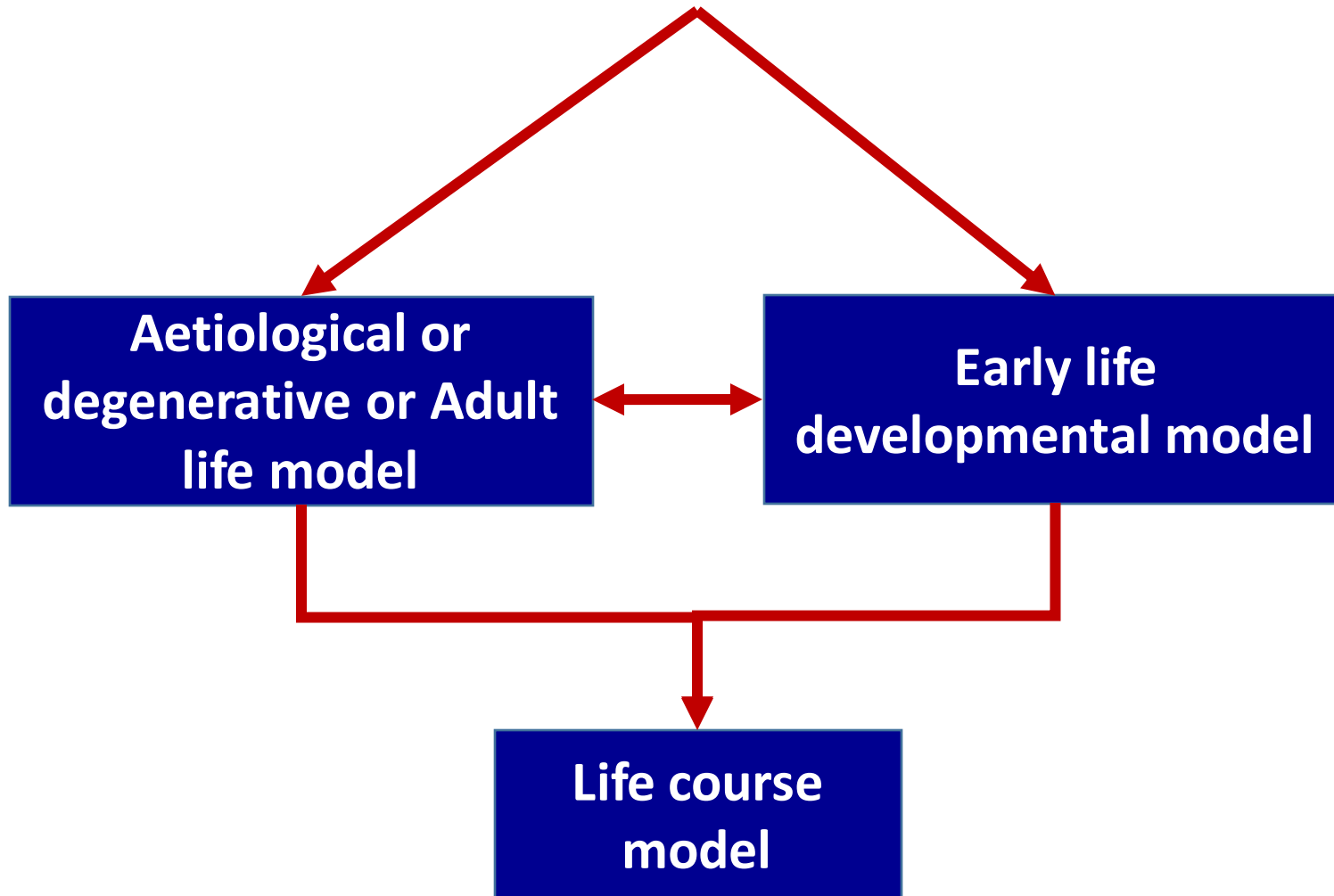
- Long- & short-term exposure to ↑ particulate matter concentrations associated with ↑ BP & risk of developing HTN in urban India
- Every +25 $\mu\text{g}/\text{m}^3$ of $\text{PM}_{2.5}$: ↑ BP by 3.5-5mmHg depending on BMI
- **Achieving national ambient air quality standards can potentially ↓ prevalence of HTN by 15% in urban Delhi**

Even reducing PM 2.5 from current 100 to 75 can reduce prevalence by 5%

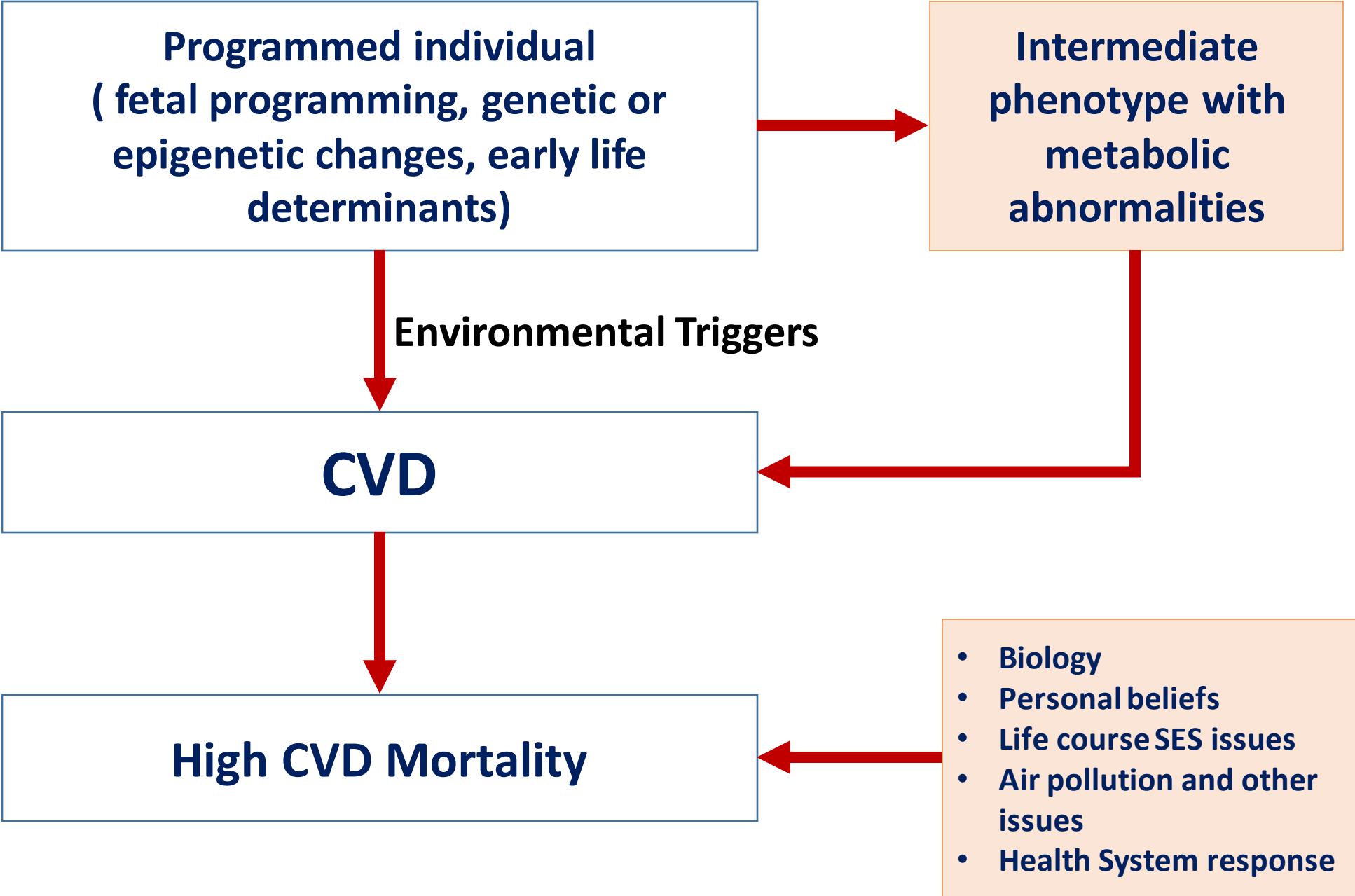
Links with other diseases

- Diabetes
- Heart Failure
- Stroke
- Obesity
- ACS/MI
- Epigenetic changes
- Others

Identifying CVD/NCD risk in Indians: What is needed



- Accumulation of risk
- Longitudinal risk accumulation across the life span from biological and social factors



The South Asian Phenotype appears to be conditioned by fetal programming, genetic/epigenetic/ evolutionary changes and hence like a loaded gun

Keep the loaded gun under lock and key

Or

Unload the gun

Or

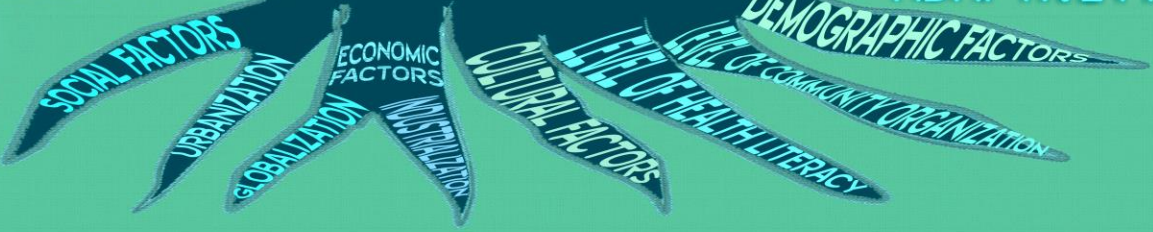
Eliminate the triggers?



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HEREDITY

ADAPTIVE PROGRAM



"
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"Strike, Strike at the Trunk and the Branches will Fall Off by Themselves"
 Old Maratha say