McMaster University

Inspiring Innovation and Discovery

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South Asians and Cardiometabolic Disease: What is the Cause? Does it Begin in-utero?

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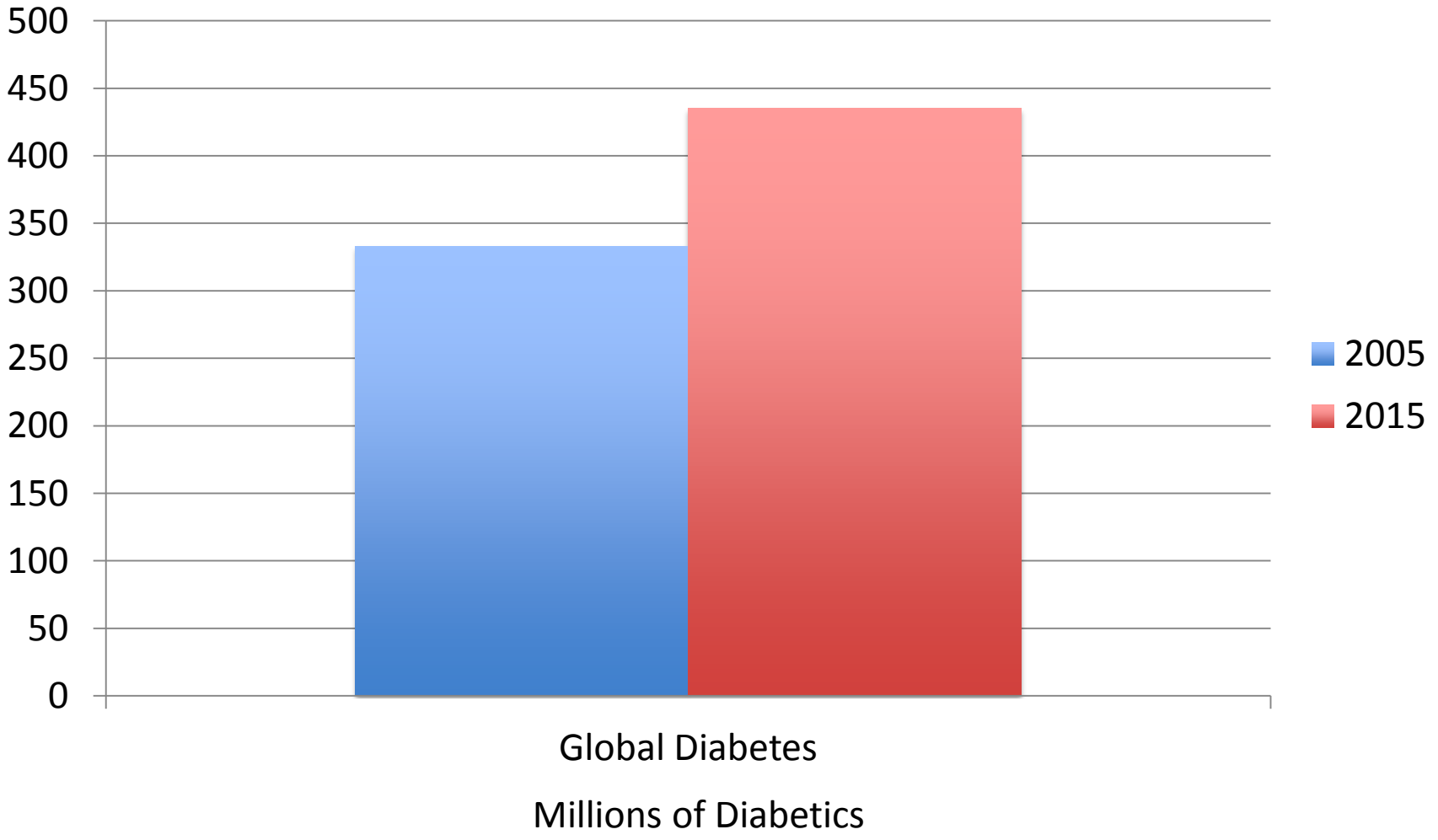
Overview

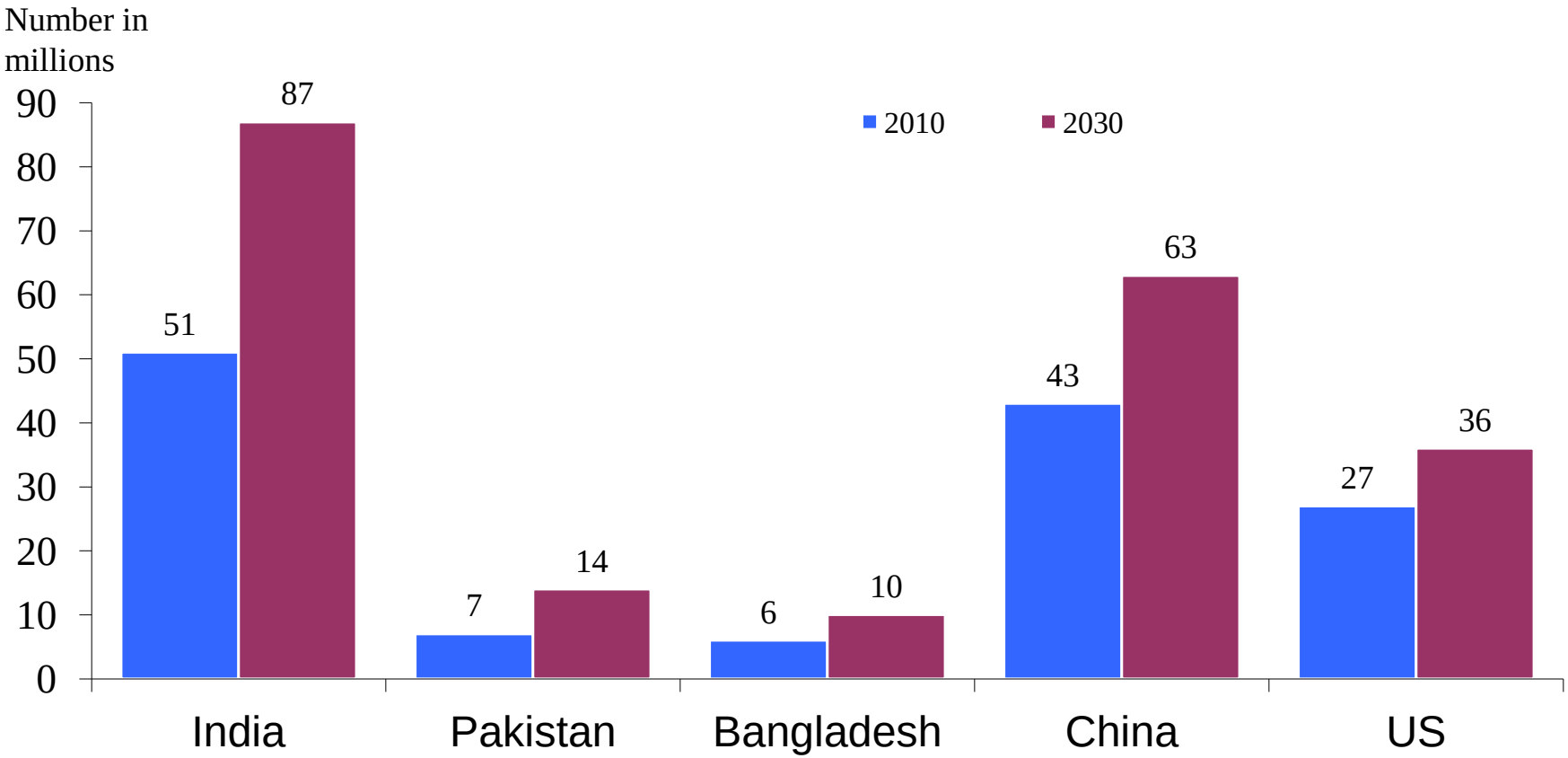
- Global burden of Diabetes in South Asians
- Risk Factors in Adult South Asians
- Etiology of excess type 2 DM in S. Asians – a life-course approach to understanding.

Increase DM Prevalence by 31% in 10 years



GBD 2015

Global Estimates of the burden of Diabetes in Millions for 2010 and 2030: The IDF Diabetes Atlas 2010



Unwin N. Diabetes research and clinical Practice 2010;87:4-14

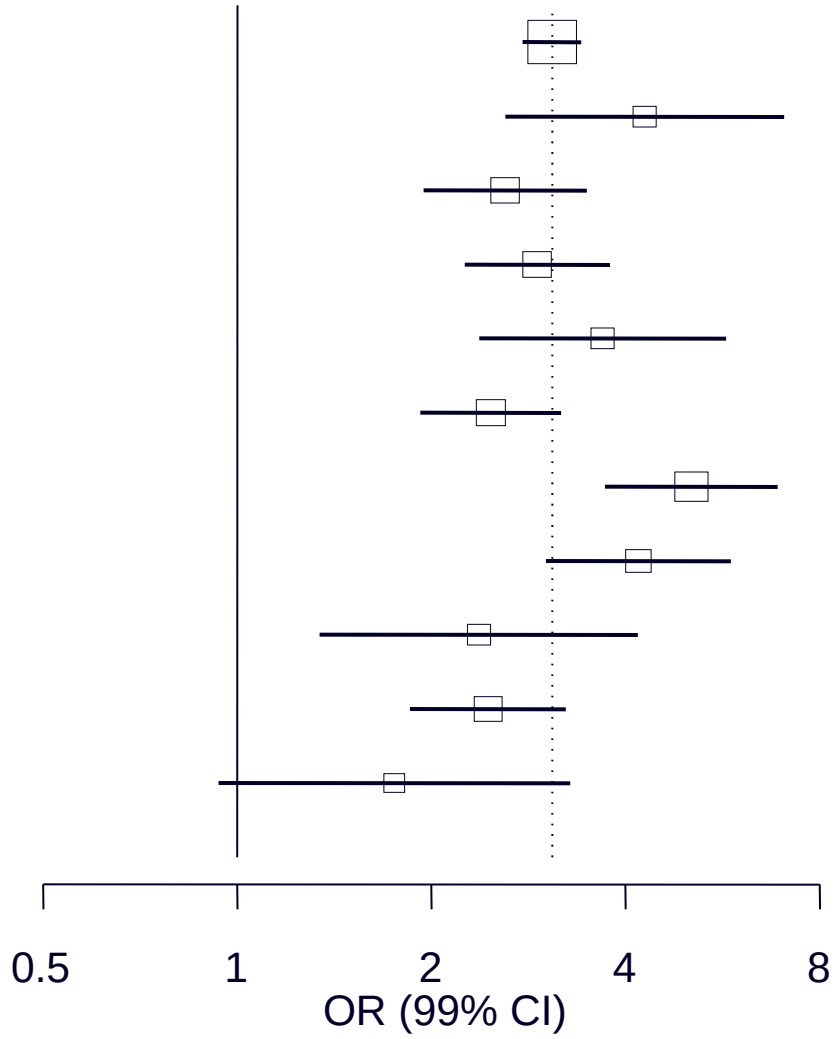
Why do South Asians suffer excess vascular disease?

1) Excess Ectopic fat
2) Adverse Lipid Profile
3) Excess Diabetes
4) Genetic, Epigenetic underpinnings
5) Modified by Diet, Physical activity

A Global Study of Risk Factors in Acute Myocardial Infarction

INTERHEART: Self-reported Diabetes and MI

Region	N	Cont.%
Overall	26903	7.6
W Eur	1422	4.2
CE Eur	3636	6.8
MEC	3401	11.6
Afr	1355	8.0
S Asia	3882	10.6
China/HK	6075	2.9
SE Asia	2140	9.2
ANZ	1269	4.8
S Am	3093	9.0
N Am	630	9.7

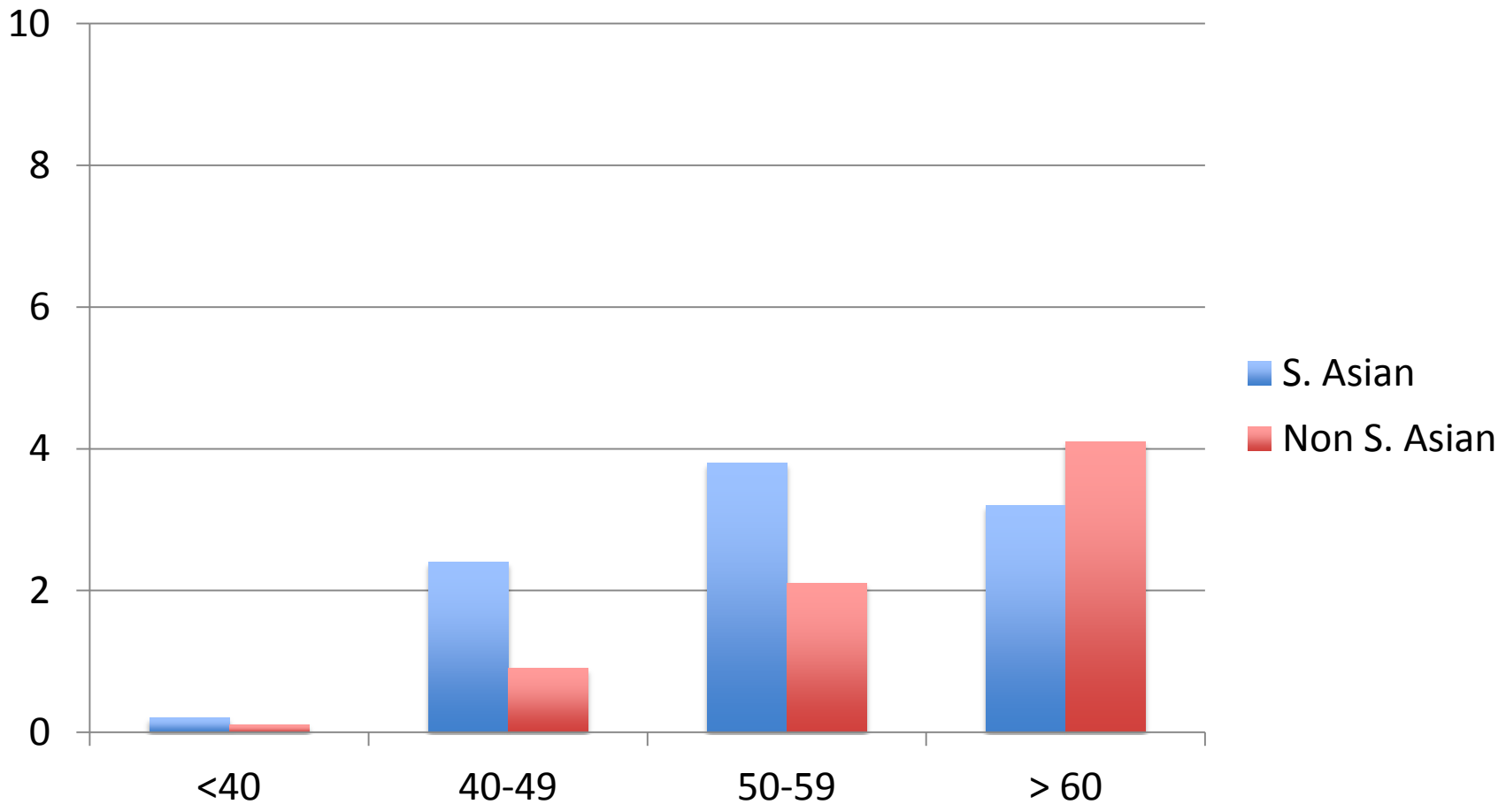


T2DM/Abdominal obesity and MI in South Asians

Risk Factor	Odds Ratio in South Asians	PAR	Odds Ratio in Non-South Asians	PAR
T2DM	2.52 (2.1-3.1)	11.8%	3.20 (2.9-3.5)	7.9%
Abdominal Obesity	2.44 (2.0-2.9)	37.7%	2.21 (2.1-2.4)	33.3%

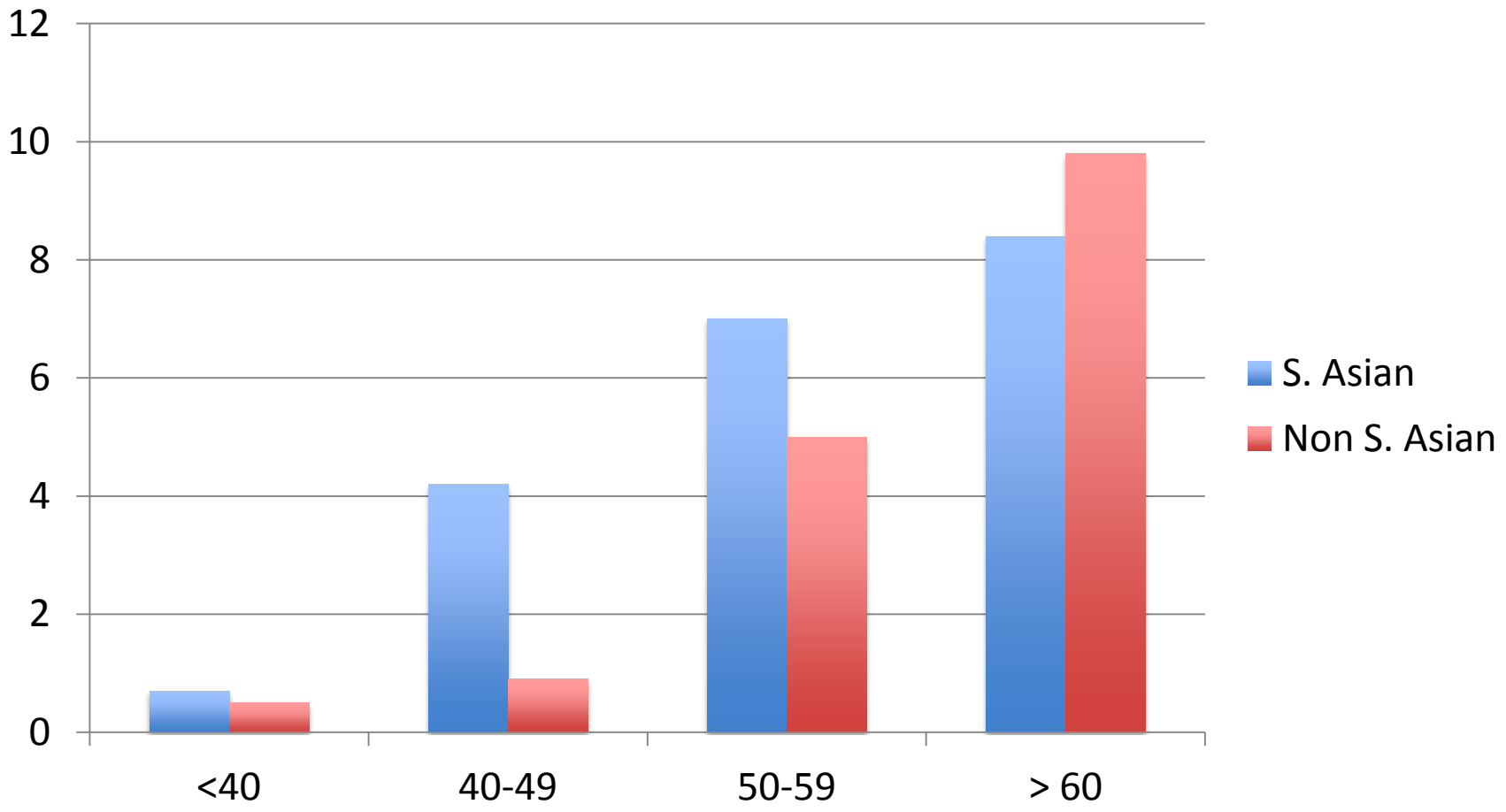
Joshi JAMA 2009

Control DM INTERHEART by Age



Joshi JAMA

Cases DM INTERHEART by Age



Joshi JAMA

Earlier onset of Key CV risk factors

- type 2 Diabetes
- Abdominal obesity
- Adverse lipoprotein profile
- No early difference in hypertension
- Protective Factors are lower across the board in SA's:
  - Moderate or high intensity exercise, fruits and vegetable consumption, alcohol consumption

Joshi et al JAMA

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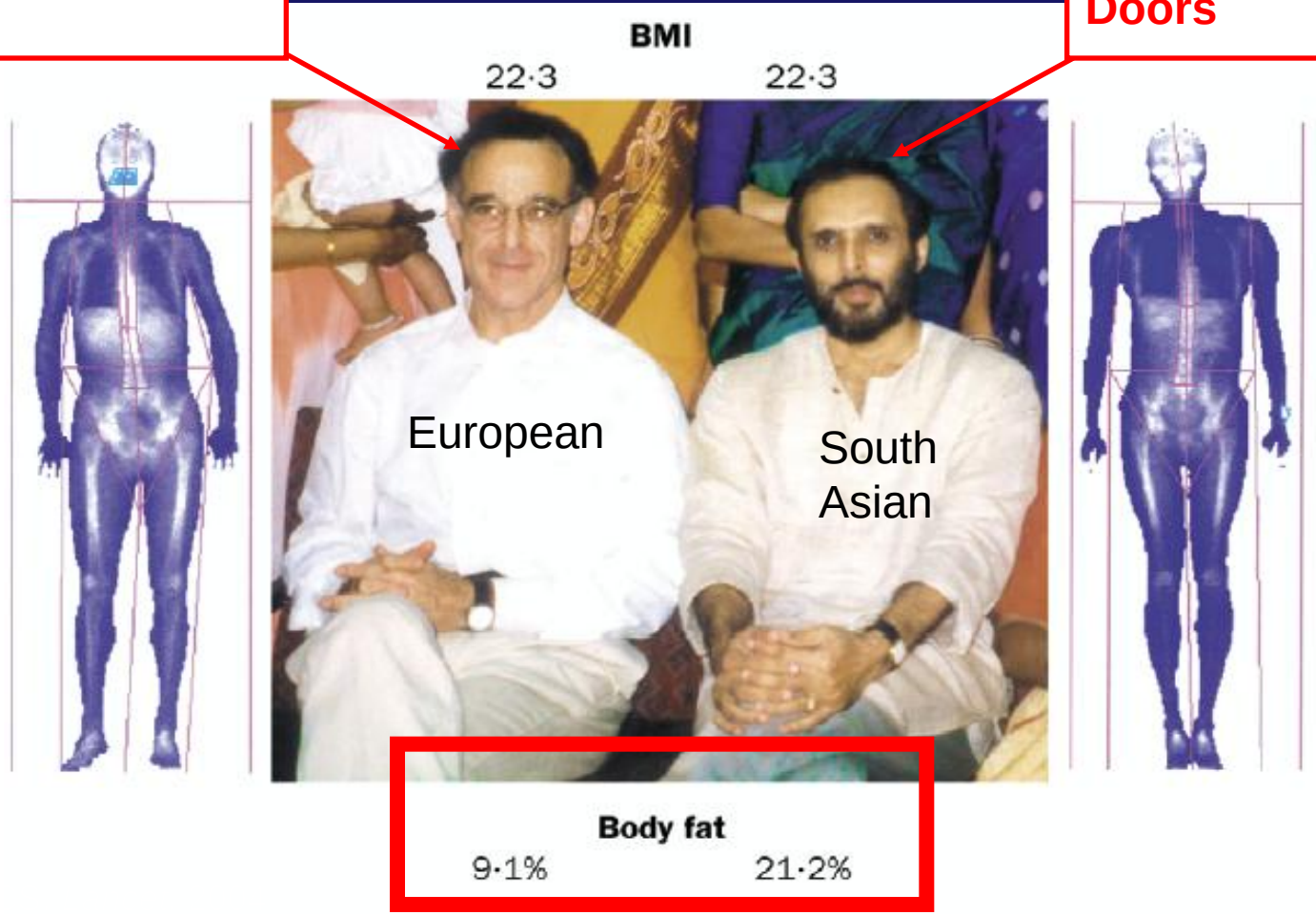
Why Does This Occur?

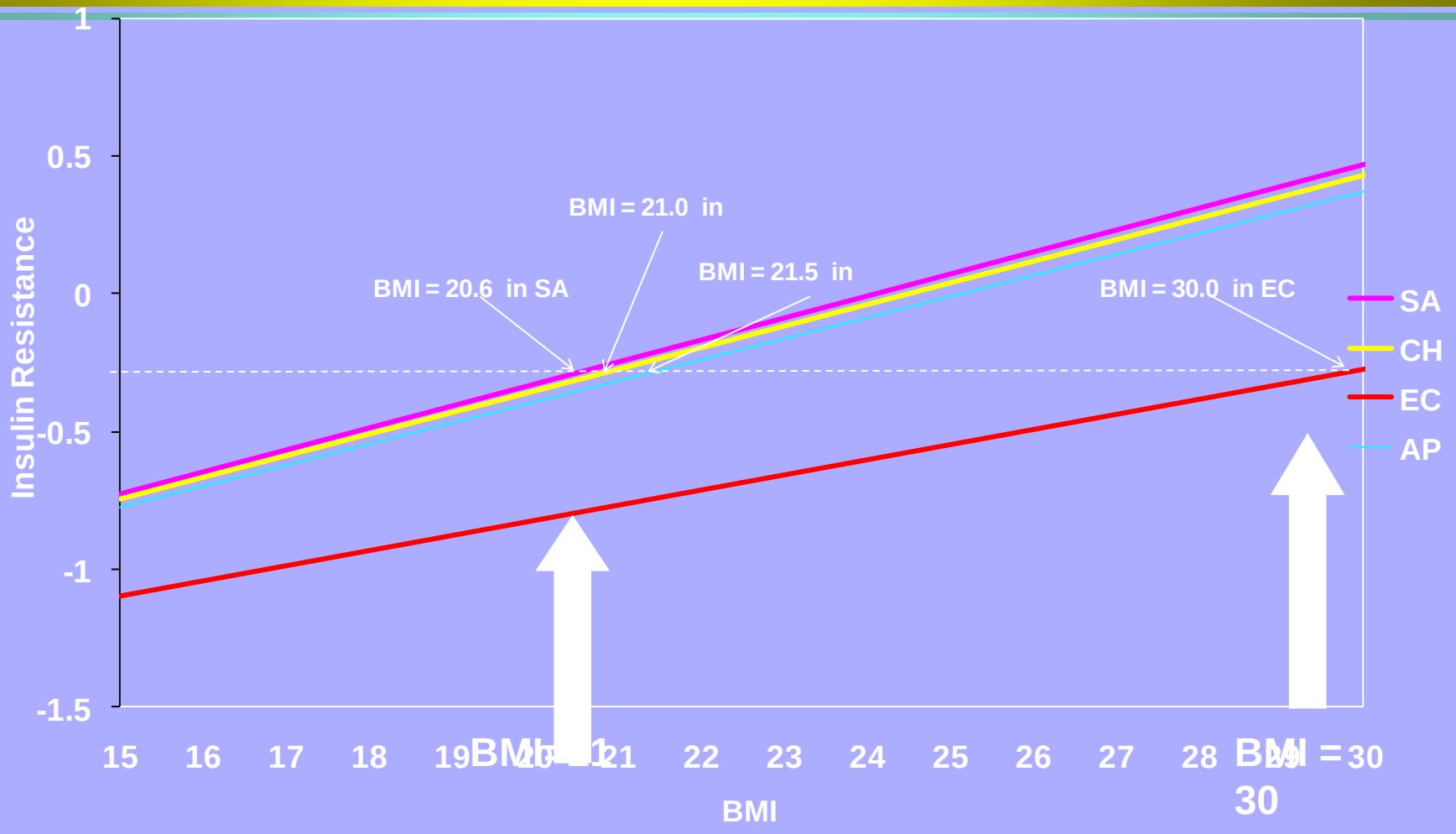
Runs Marathons

Runs to beat the closing Elevator Doors



DXA scan of two individuals with the same BMI but markedly different percent body fat.

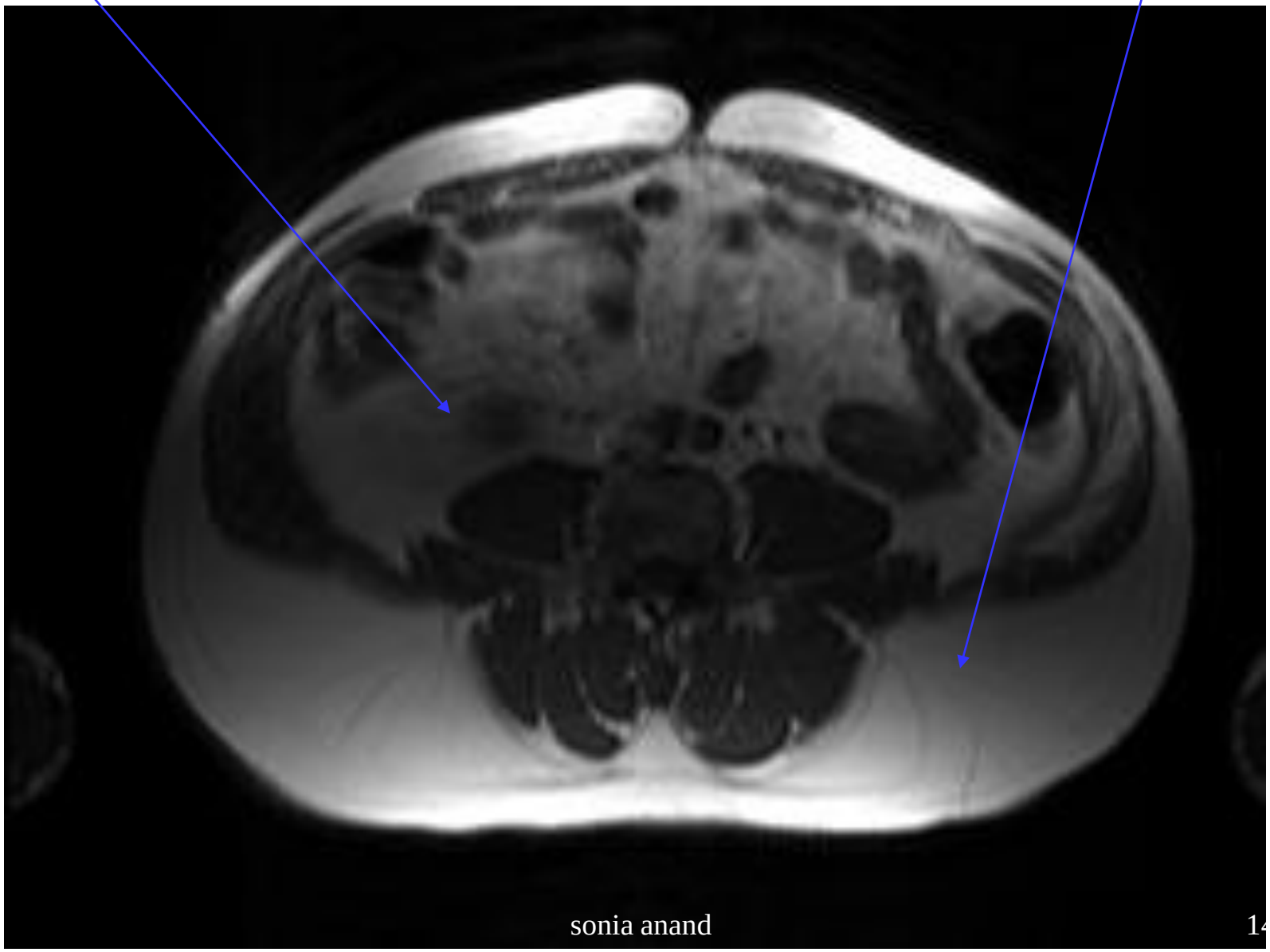
Relationship of Insulin Resistance to Body Mass Index Among South Asians, Chinese, Aboriginals and Europeans



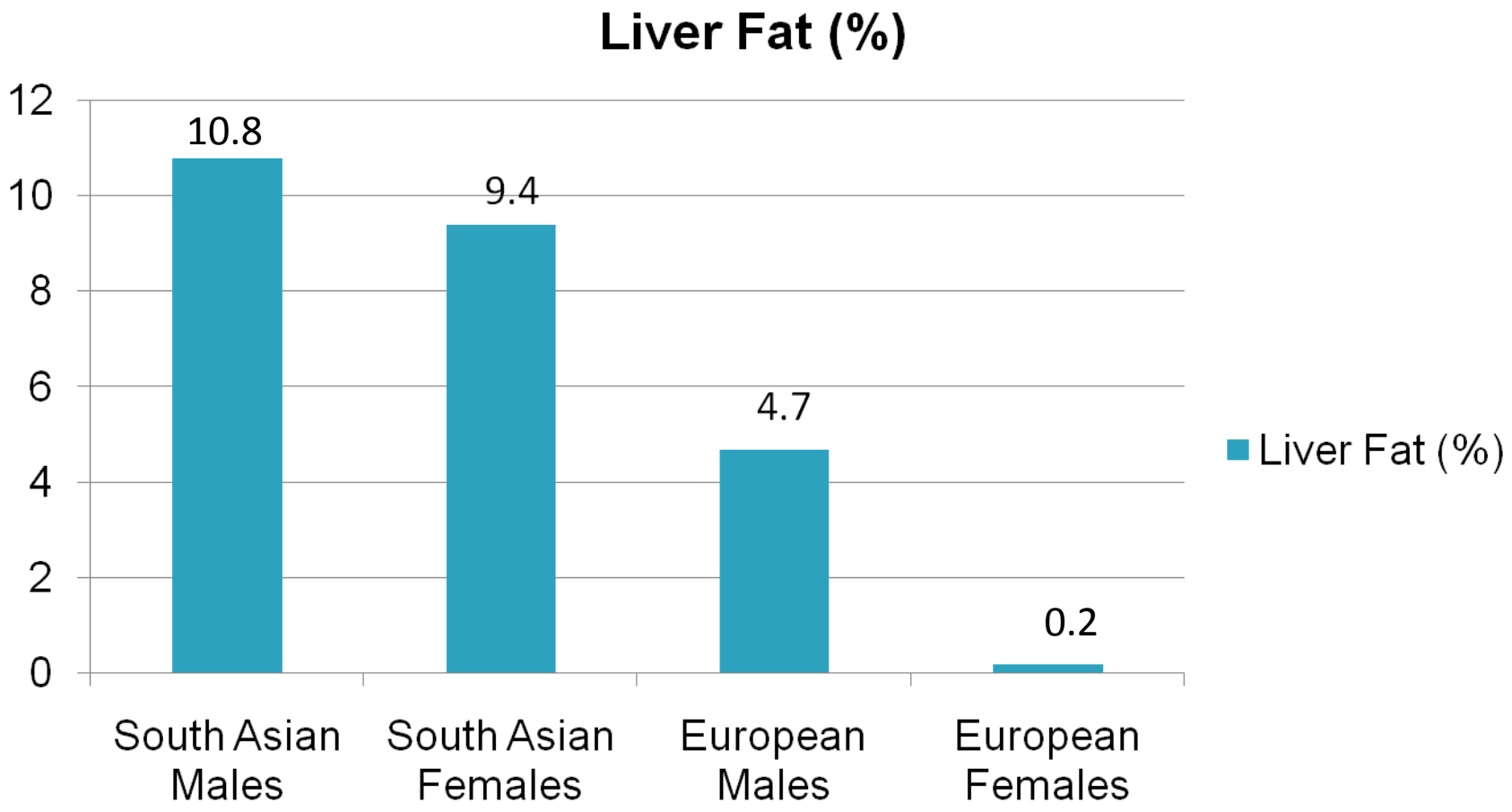
Razak et al Circ 2005

VISCERAL ADIPOSE TISSUE

SUPERFICIAL ADIPOSE TISSUE



Liver Fat (%) by Ethnic and Sex Group

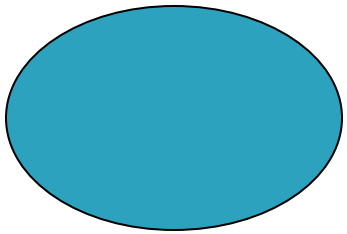


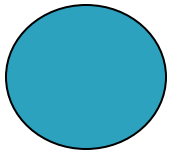
Between ethnicity p=0.005

Anand et al PloS One 2009

Adipocyte Cell Size

- South Asian
  - Max diameter: 259.0
  - Area: 451.8 units^2
- Europeans
  - Max diameter: 238.4
  - Area:387.7 units^2

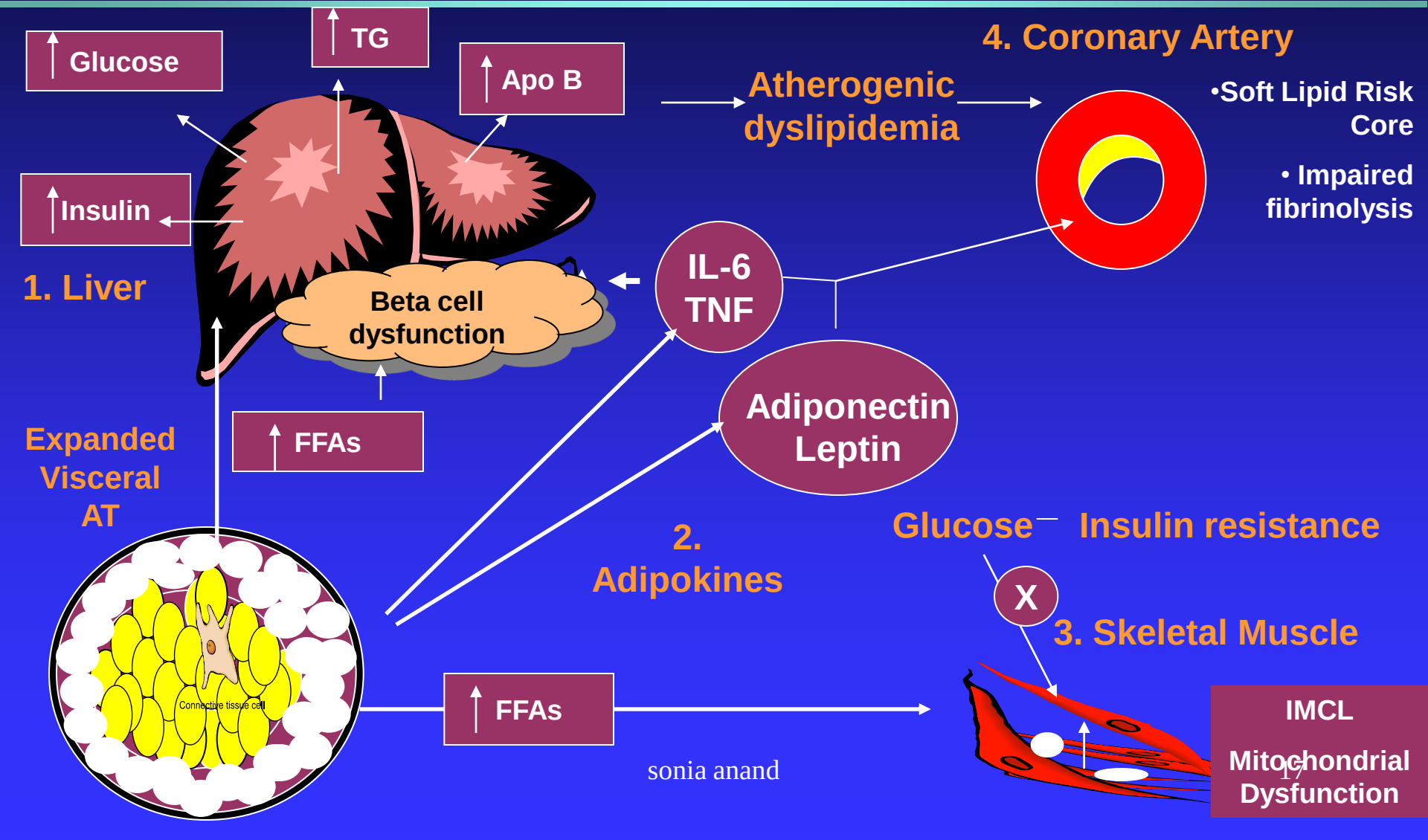




South Asians have larger adipocytes stuffed with triglycerides

Anand et al PloS One 2009

Core Defect: Fat Overflow



Can differences in Ectopic Fat explain the early onset of RF's?

- Abdominal obesity – Yes, Likely
- Diabetes – Partially (insulin resistance) but there are genetic drivers
- Lipoproteins – Partially (Hepatic fat) but there are other drivers (i.e.; + CETP activity by 30%, genetic variants)

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Contribution of Diet as an Environmental Modulator

- Micronutrient deficiency may contribute to low birth weight
- High carbohydrate, Low protein consumption associated with abdominal obesity
- High carbohydrate consumption associated with low HDL cholesterol

Meschant et al J Nutr 2005

SHARE: ↑Carbohydrate, ↓Protein,

	South Asians	Chinese	Euro
N	173	167	185
Age	46.3	45.8	47.7
Calories/Day	1911	1898	2072
% Vegetarian	18.8	2.1	0.6
Carbohydrates g/day	298.8*	240.7	269.5
Protein g/day	70.1*	100.5*	78.0
Sugar g/day	11.2*	6.9	8.9
Saturated Fat g/day	19.6	17.3*	21.6

SHARE: ACJN 2008

Effect of Distinct Lifestyle intervention on Mobilization of Fat storage pools: The CENTRAL MRI randomized controlled trial

Yftach Gepner et. al., *Circulation.* Jan 18, 137 (4).2017

Design (first 6 months)

Study Design:
'CENTRAL' (2012-2014) was a single-centre, open-label, longitudinal RCT comparing the effects of distinct lifestyle strategies on specific body adipose depots

278 subjects with abdominal obesity (WC>102cm for men, WC>88cm for women) or dyslipidemia were included

Randomized split

Low-fat (LF) diet group (n=139)

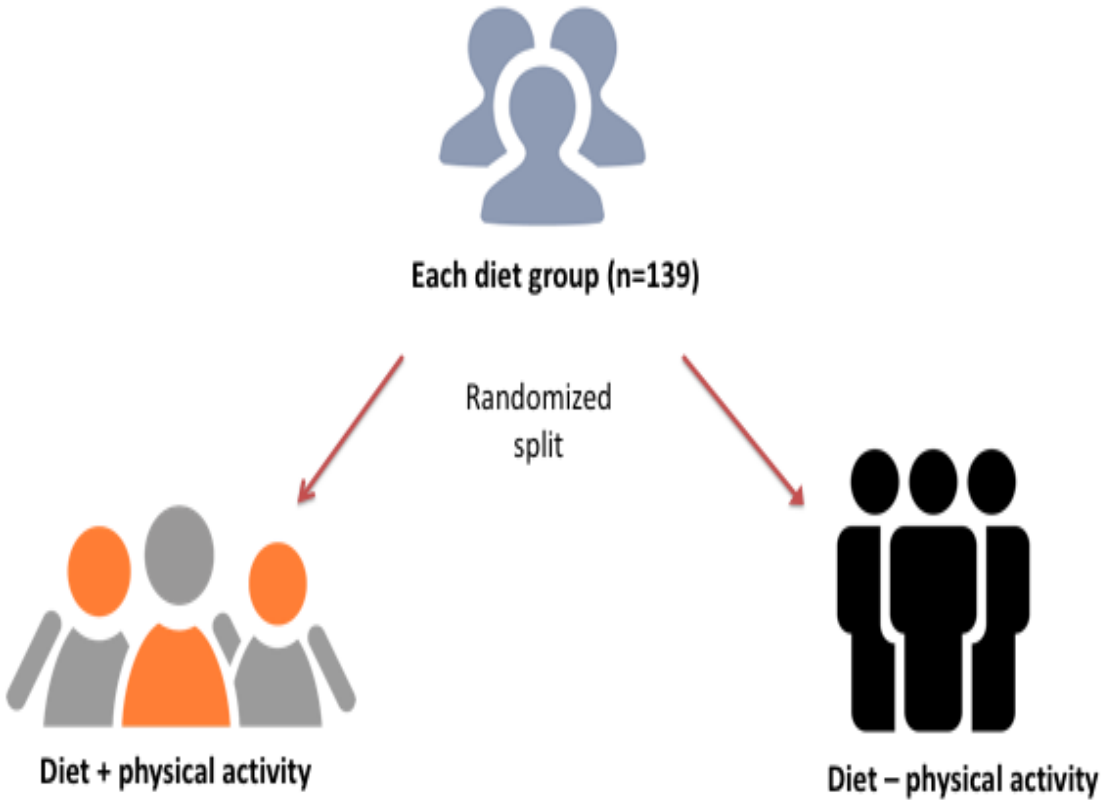
- Limit total fat intake to 30% of calories
- Participants counseled to consume whole grains, vegetables, fruits, and legumes and limit fats, sweets, and high-fat snacks

Mediterranean/low-carb (MED/LC) diet group (n=139)

- Restricted carb intake to less than 40g/day initially, followed by up to 70 g/day
- Increase protein and fat intake with vegetables, legumes and lower red meat
- Given 28g of walnuts/day starting in the 3rd month

Gepner et. al., *Circulation.* Jan 18, 137 (4).2017

Design (after 6 months)



- Received a free supervised gym membership for the following 12 months
- 60 minute educational workshops and aerobic training sessions at the gym (3 sessions/week)

Results (cont'd)

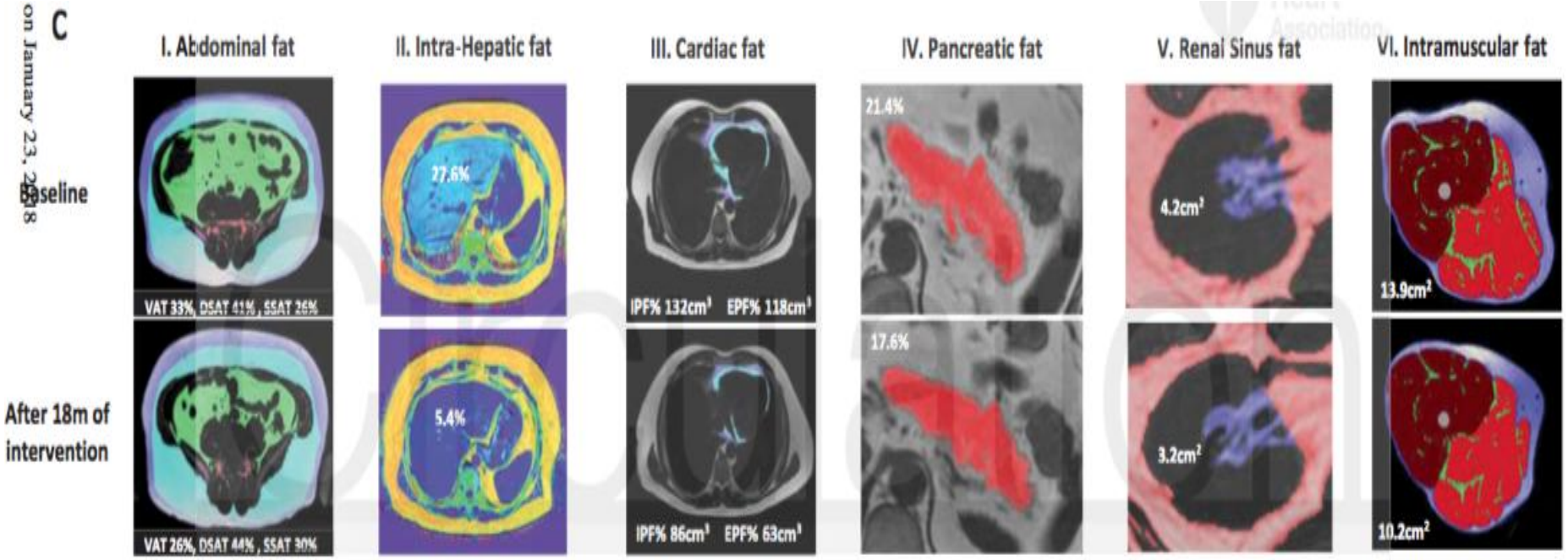


Figure 2 c) MRI illustration of the human fat depots/deposits at baseline and after the 18-month interventions following moderate weight loss (6%):

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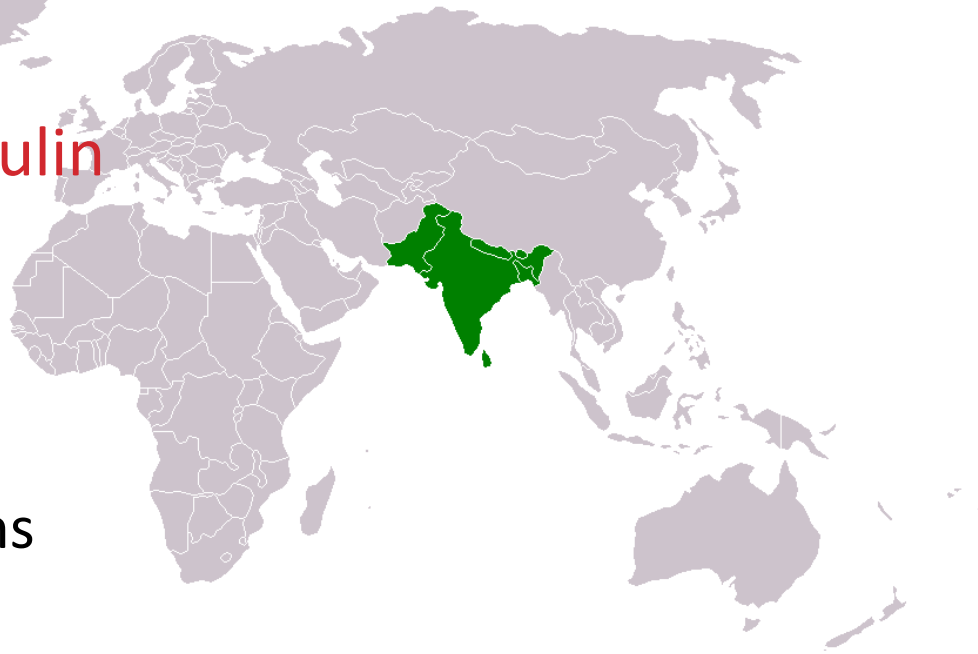
Genetics: South Asians

- 2-5 fold higher risk of diabetes compared to white Caucasians
- Greater propensity for insulin resistance and beta-cell dysfunction
- Anthropometric characteristics also differ
  - Store fat in ectopic regions
- Restricted admixture and consanguineous population



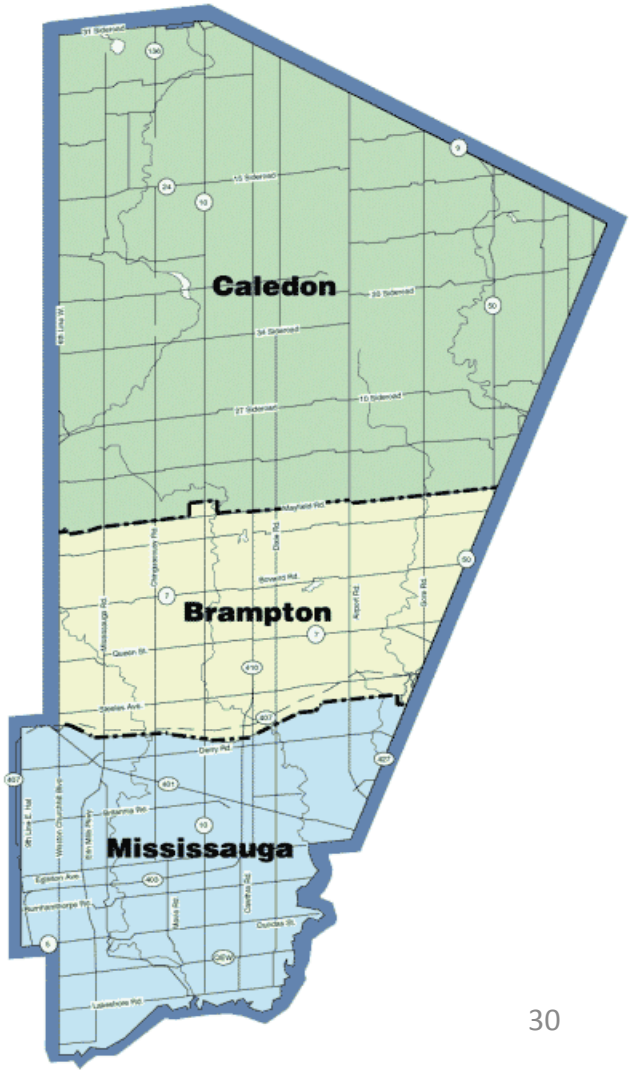
SouTh Asian BiRth Cohort

The causes and consequences of Gestational Diabetes

START: Diverse Environments

Recruitment Area

BRAMPTON CIVIC HOSPITAL
CREDIT VALLEY
TRILLIUM



Methods

START – A Prospective Cohort Study

1000 SA pregnant women with singleton pregnancies during their 2nd trimester

Recruitment

1) OGTT if no pre-existing diabetes
2) Health and diet questionnaire to measure diet quality
3) Blood pressure, body fat, and weight measurements

Maternal Measurements

Type, duration, outcome of labor
Skinfold thickness, newborn weight, length were recorded
Cord blood sample was collected

Newborn Measurements

1) Univariate associations maternal factors and GDM
2) Multivariate logistic regression model
3) Univariate model for anthropometric and maternal GDM using ANCOVA

Statistical Analysis

START versus FAMILY Study Maternal Baseline Characteristics

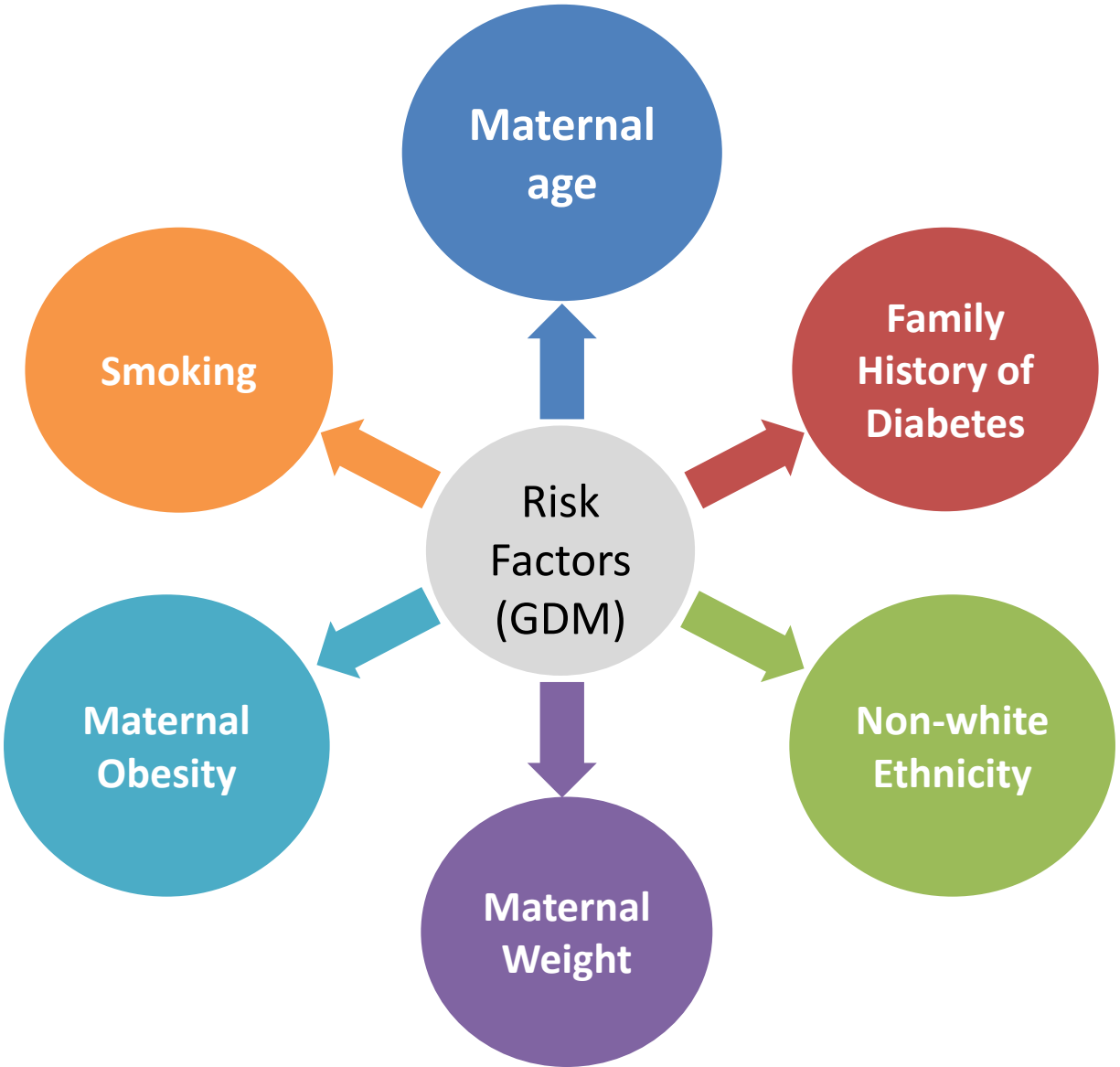
CLINICAL PARAMETERS	South Asian (n=1012)	White Caucasian (n=857)	P Value
Pre-pregnancy weight (kg)	62.6 (12.1)	72.3 (17.9)	<0.0001
Pre-pregnancy BMI (kg/m2)	23.8 (4.5)	26.8 (6.3)	<0.0001
Gestational DM – IADPSG (%)	21.7	13.3	0.005
Birth weight (g)	3217 (491)	3517 (22)	<0.0001
Tricep + subscapular skinfolds (mm)	11.5 (2.6)	10.6 (0.1)	<0.0001

"thin-fat" phenotype in South Asians living in Canada

Means (SE) Adjusted for gestational age and sex Ponderal index defined as: Birthweight in kg/birthlength in meters cubed

Anand et al IJO 2015

Why is Gestational Diabetes so common in South Asians?



Background

CMAJ OPEN

Research

Causes and consequences of gestational diabetes in South Asians living in Canada: results from a prospective cohort study

Sonia S. Anand MD, Milan Gupta MD, Koon K. Teo MBBCh, Karleen M. Schulze MMath, Dipika Desai MSc, Nora Abdalla MBBCh, Michael Zulyniak PhD, Russell de Souza BA, Gita Wahi MD, Mateen Shaikh PhD, Joseph Beyene PhD, Eileen de Villa MD, Katherine Morrison MD, Sarah D. McDonald MD, Hertzel Gerstein MD; for the South Asian Birth Cohort (START) – Canada Investigators

START GDM mothers

Characteristic	GDM* N=359	No GDM N=630	P value
Age	31.2 ± 4.0 0	29.7 ± 3.8	< 0.001
Pre-Preg BMI	24.9 ± 4.6	23.2 ± 4.3	< 0.001
Family hx DM	191 (52.5)	228 (35.7)	< 0.001
Low Quality Diet	121 (33.4)	145 (22.9)	< 0.001

Note: SE – standard error; *Except where noted otherwise, + Adjusted for gestational age, sex and insulin use by mother during pregnancy‡ Determined from gestational age, and sex-specific percentiles from study data; ¶ Non log insulin level used

Newborn characteristics by maternal GDM status

Characteristic	GDM* N=359	No GDM N=630	P
Birth weight, g	3267 (23)	3181 (17)	0.005
Length, cm	51.0 (0.1)	51.1 (0.1)	0.07
Waist circumference, cm	30.8 (0.1)	30.3 (0.1)	0.009
Head circumference, cm	34.1 (0.1)	34.0 (0.1)	0.40
Sum of skinfold measurements, mm	11.7 (0.1)	11.2 (0.1)	0.007

Note: SE – standard error; *Except where noted otherwise + Adjusted for gestational age, sex and insulin use by mother during pregnancy

‡ Determined from gestational age, and sex-specific percentiles from study data

Newborns of GDM mothers has lower insulin sensitivity

Characteristic	GDM* N=359	No GDM N=630	P value
Triceps skinfold thickness, mm	6.1 0.1	5.9 0.1	0.05
Subscapular skinfold thickness, mm	5.5 0.1	5.2 0.1	0.002
Placental weight, g	503.2	474.9	0.007
Cord blood glucose level, mmol/L	4.1 0.1	0.0	0.9
Cord blood insulin (log) level, pmol/L	76.3	2.8	0.002
Glucose/insulin ratio, mmol/pmol	0.092 0.009	0.006	0.001

Note: SE – standard error; *Except where noted otherwise, + Adjusted for gestational age, sex and insulin use by mother during pregnancy‡ Determined from gestational age, and sex-specific percentiles from study data; ¶ Non log insulin level used

Results

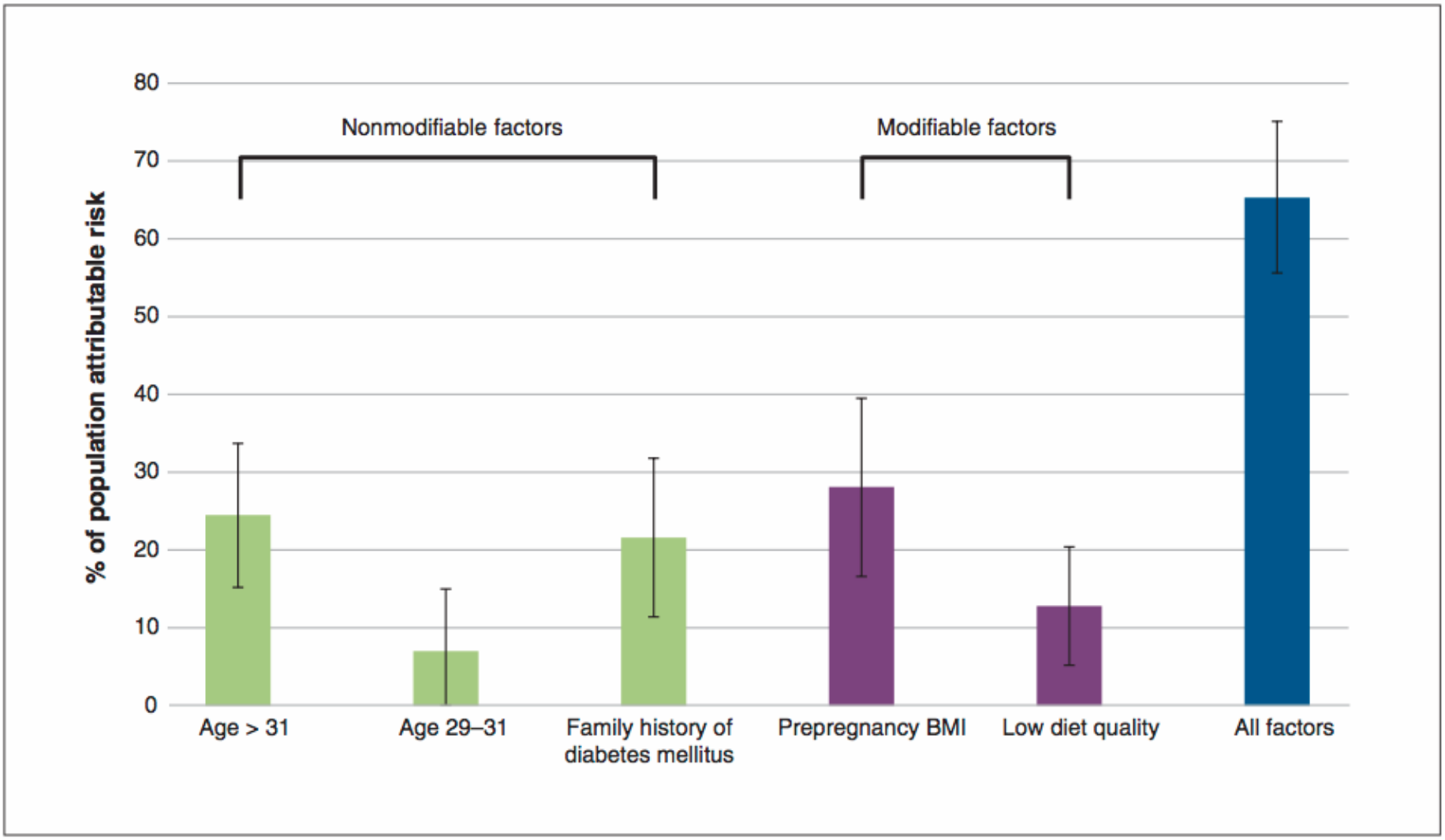
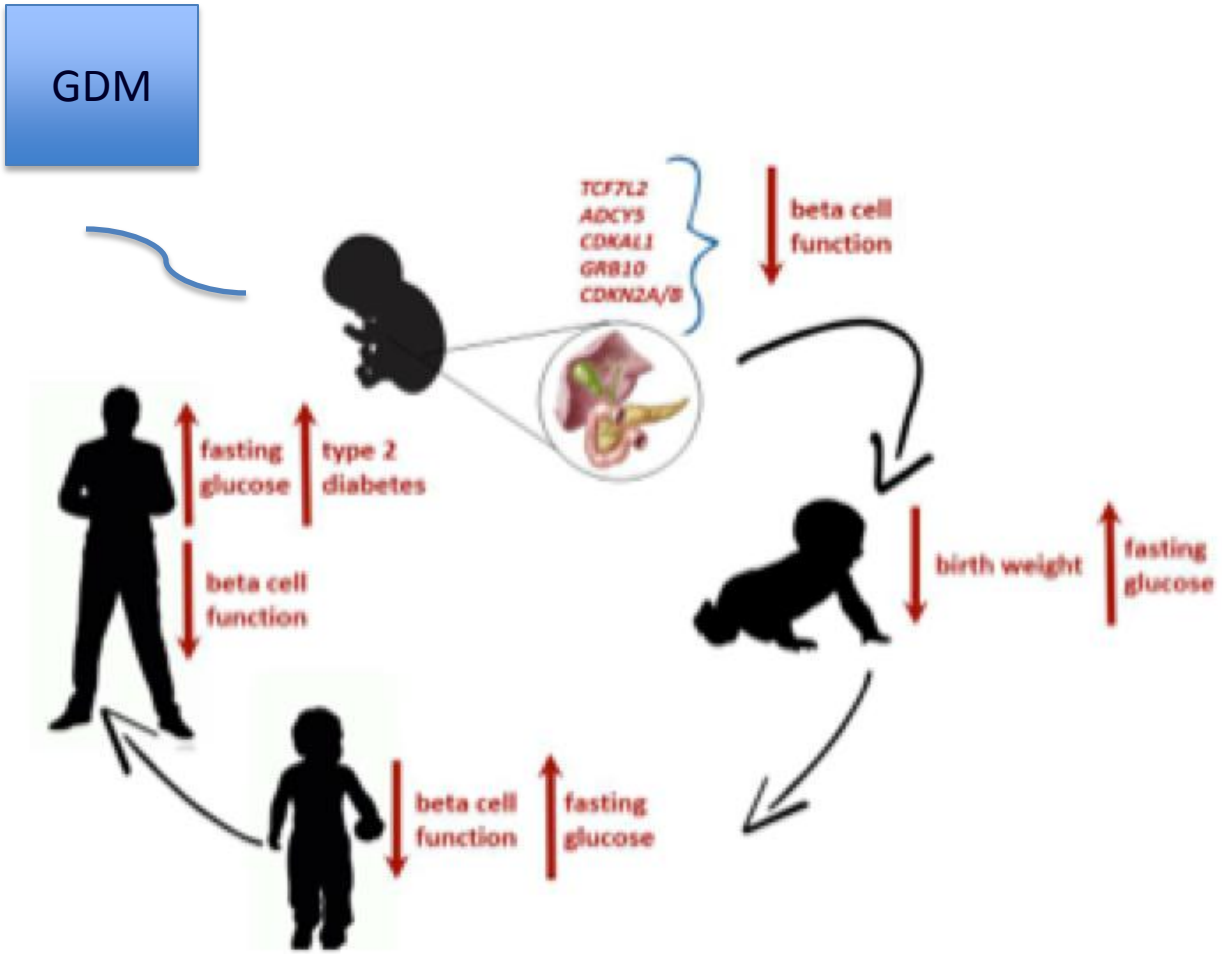


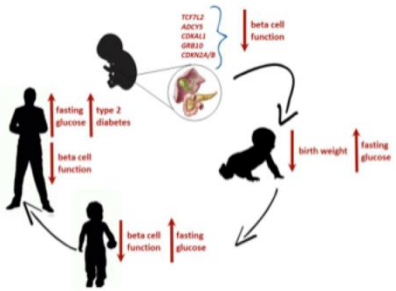
Figure 1: Partial proportional attributable risk for individual risk factors for the development of gestational diabetes mellitus among South Asian women. Error bars represent 95% confidence intervals. Note: BMI = body mass index.

Summary

- GDM affects 1/3rd of South Asian women
- Modifiable factors: 1) High Pre-pregnancy weight, 2) LOW diet quality (37% of PAR) with weight being a dominant predictor of GDM
- Newborns exposed to high maternal glucose levels had higher birth weight, body fat, and lower insulin sensitivity - ? Programming effect

Transgenerational Cycle DM transmission




TCF7L2
ADCY5
CDKAL1
GRB10
CDKN2A/B
beta cell function
fasting glucose
type 2 diabetes
beta cell function
birth weight
fasting glucose
beta cell function
fasting glucose

What about maternal diet?

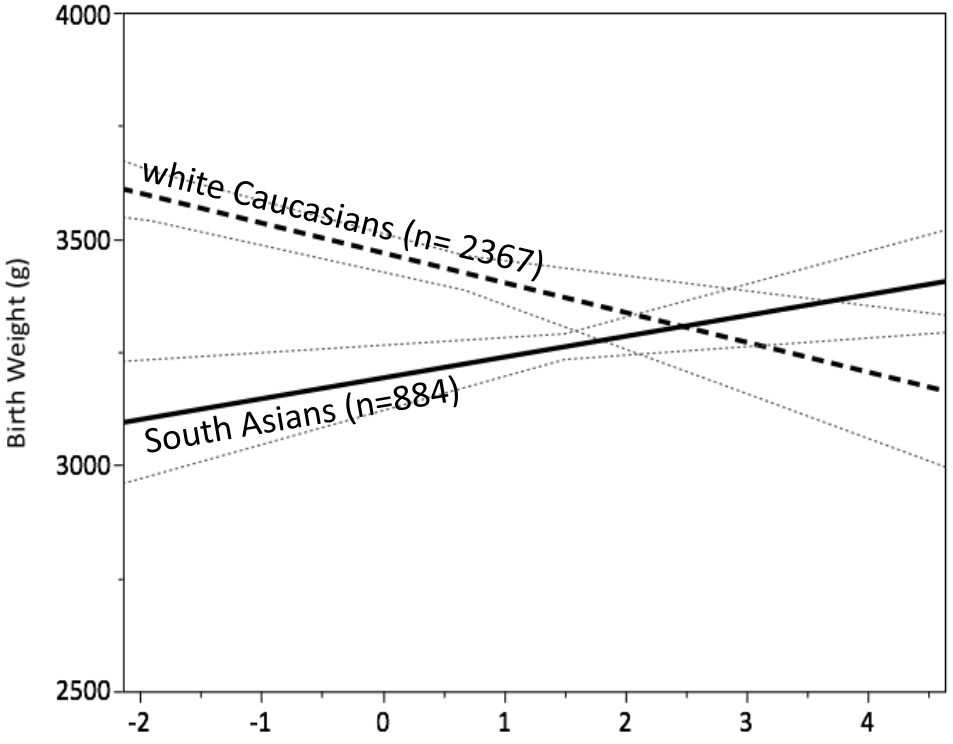
- ? Micronutrient deficiency
of Mothers results in low birthweight babies

Maternal Diet and Birthweight

BMJ Open 2017

Compare white Caucasian to South Asian Mothers and offspring

- Association with plant-based, non-white ethnicity, and interaction term
- In WC, 1-unit change associated with reduced birthweight (-65.9g), increased risk of SGA, and reduced risk of LGA.
- In SA, 1-unit change associated with increased birthweight (+40.5g)
  - 'cooked vegetables' identified as a contributing

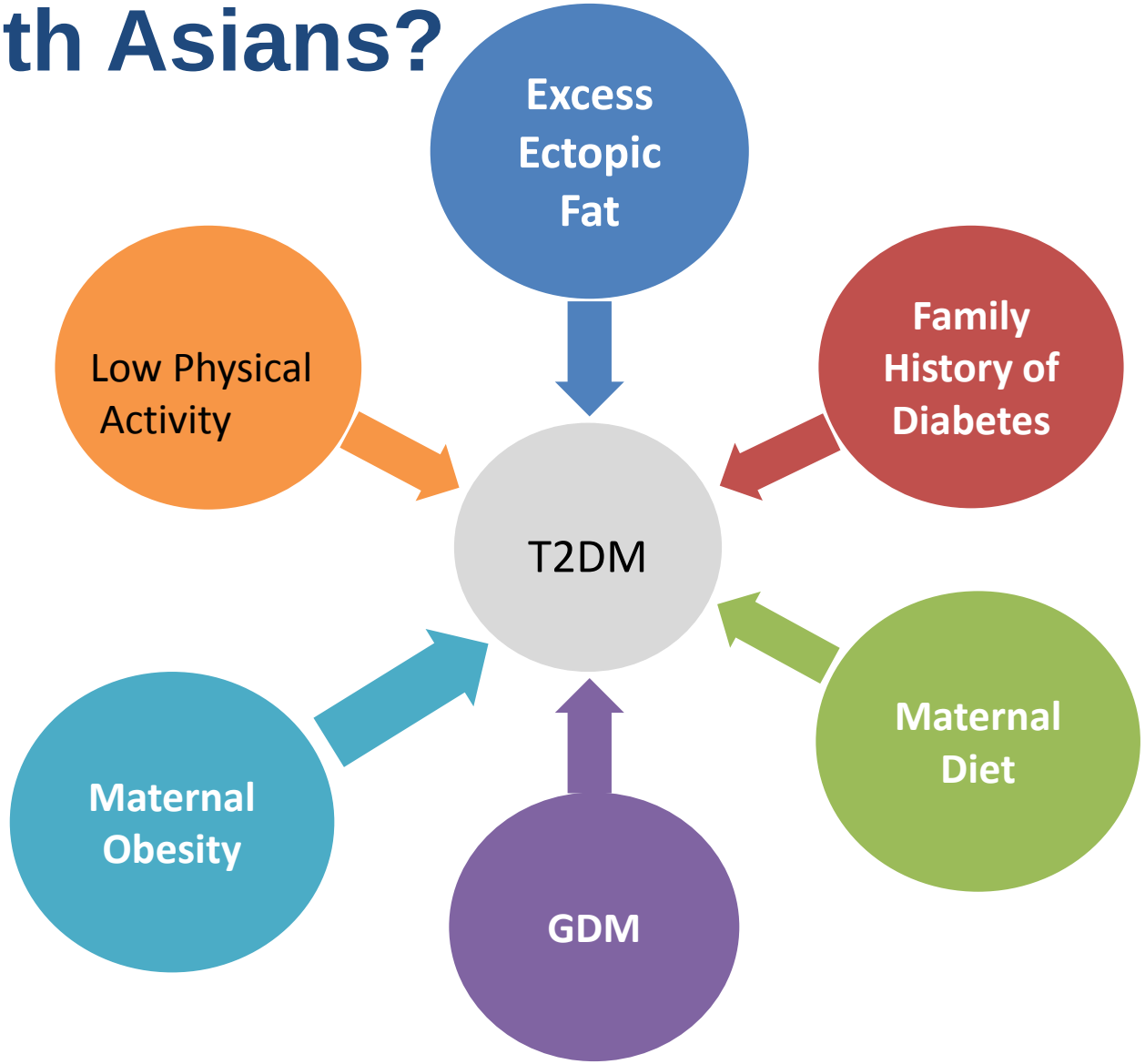


South Asians and white Caucasians well powered (β≥ 80%)

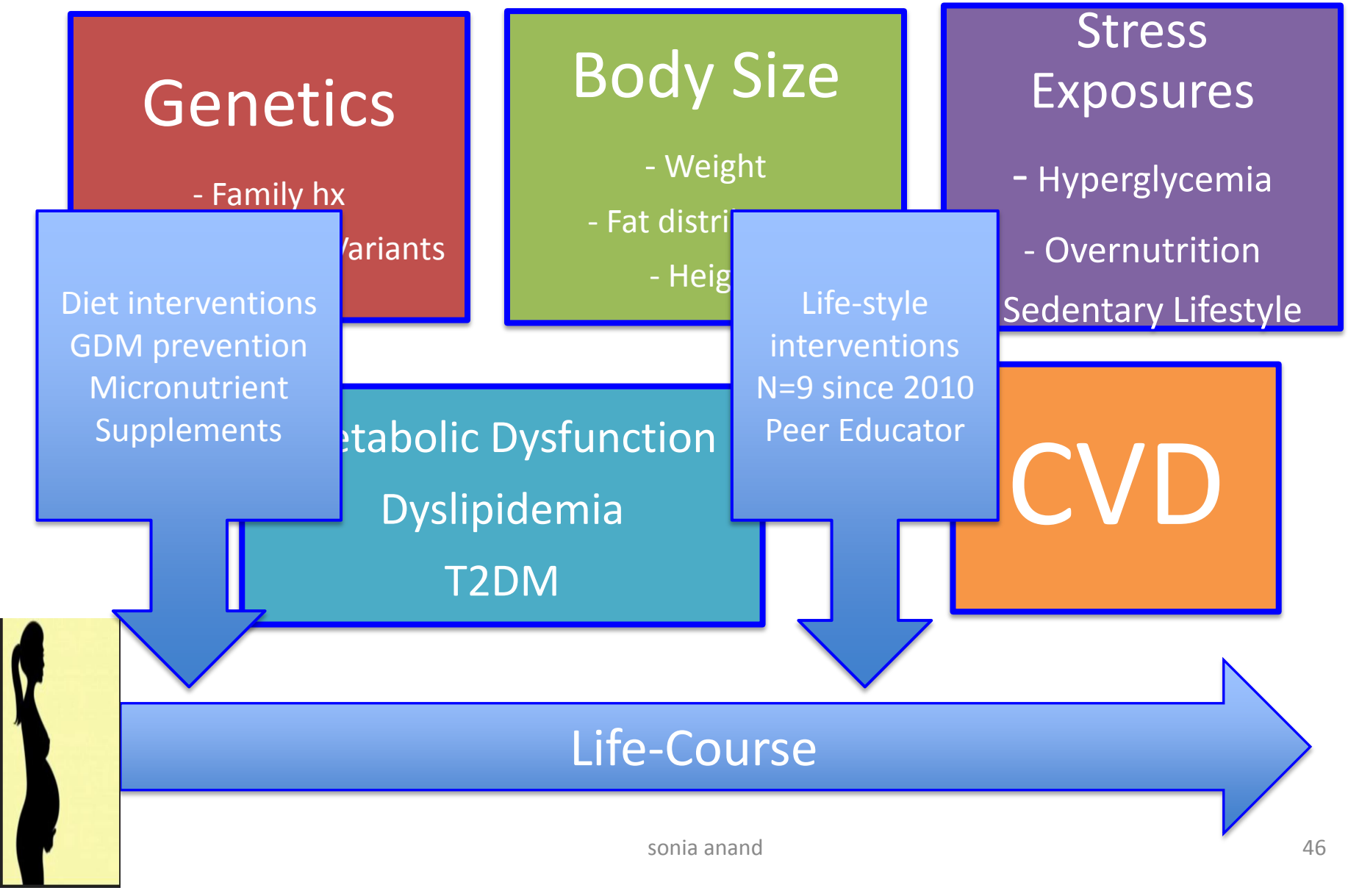
Plant-based diet in North American setting

= Reduces “low birthweight in South Asians

Early life influences associated with excess type 2 Diabetes in South Asians?



We need Intervention studies to break the cycle



Summary

- 1) Early onset of CV risk factors explain early onset MI in South Asians.
- 2) Etiology of early onset of ectopic fat and diabetes have genetic (epigenetic) underpinnings exacerbated by environment (diet, low physical activity)
- 3) High incidence of GDM perpetuates trans-generational transmission of T2DM
- 4) Randomized interventions in pre-conception, pregnancy and early life needed!