GDM: Cause of obesity, diabetes & CVD epidemic?

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MLHD, ICTS-TIFR Bengaluru 24 Jul 2023

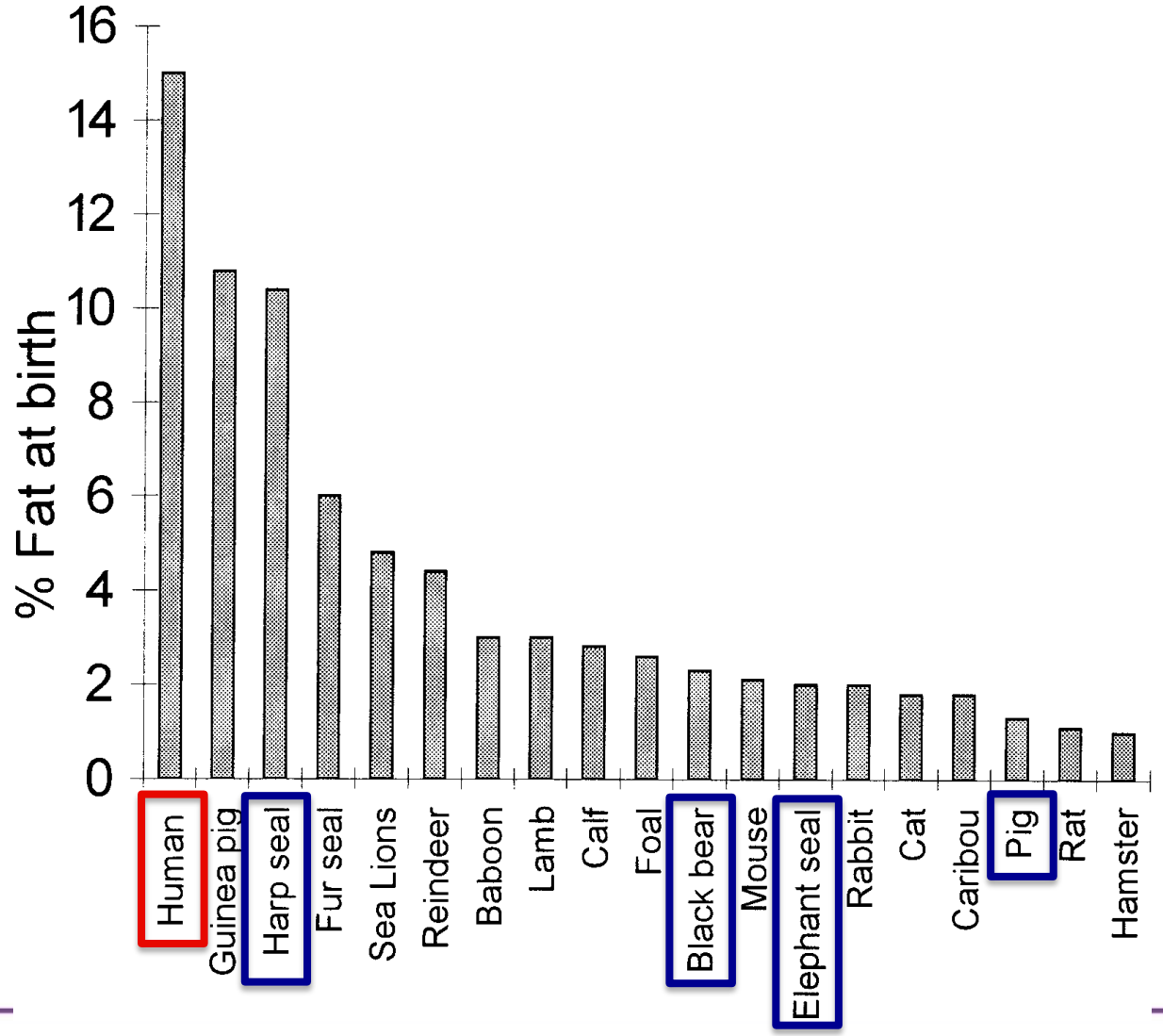
Outline

- Human evolution
- Gestational Diabetes
  - Maternal risk
  - Offspring risk
- Importance of innovative methodologies
  - Learnings from birth weight studies
  - Need for accurate personalized prediction

Rank according to % body fat?

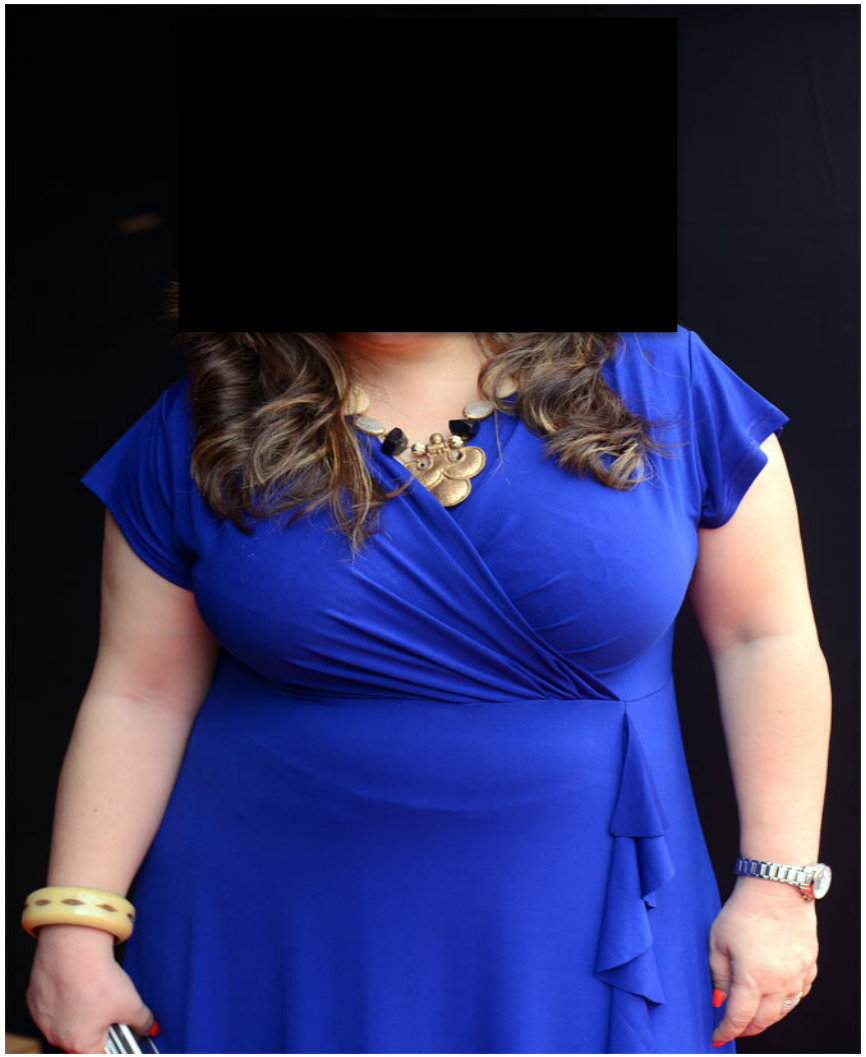
Humans

Humans



Kuzawa CW, Year book Physical Anthropology 1998.41:177-209

Humans



When does the process start?

Outline

- Human evolution
- **Gestational Diabetes**
  - **Maternal risk**
  - **Offspring risk**
- Importance of innovative methodologies
  - Learnings from birth weight studies
  - Need for accurate personalized prediction

What is GDM?

"Glucose intolerance resulting in hyperglycaemia (of varying severity) which *begins or first diagnosed* in pregnancy"

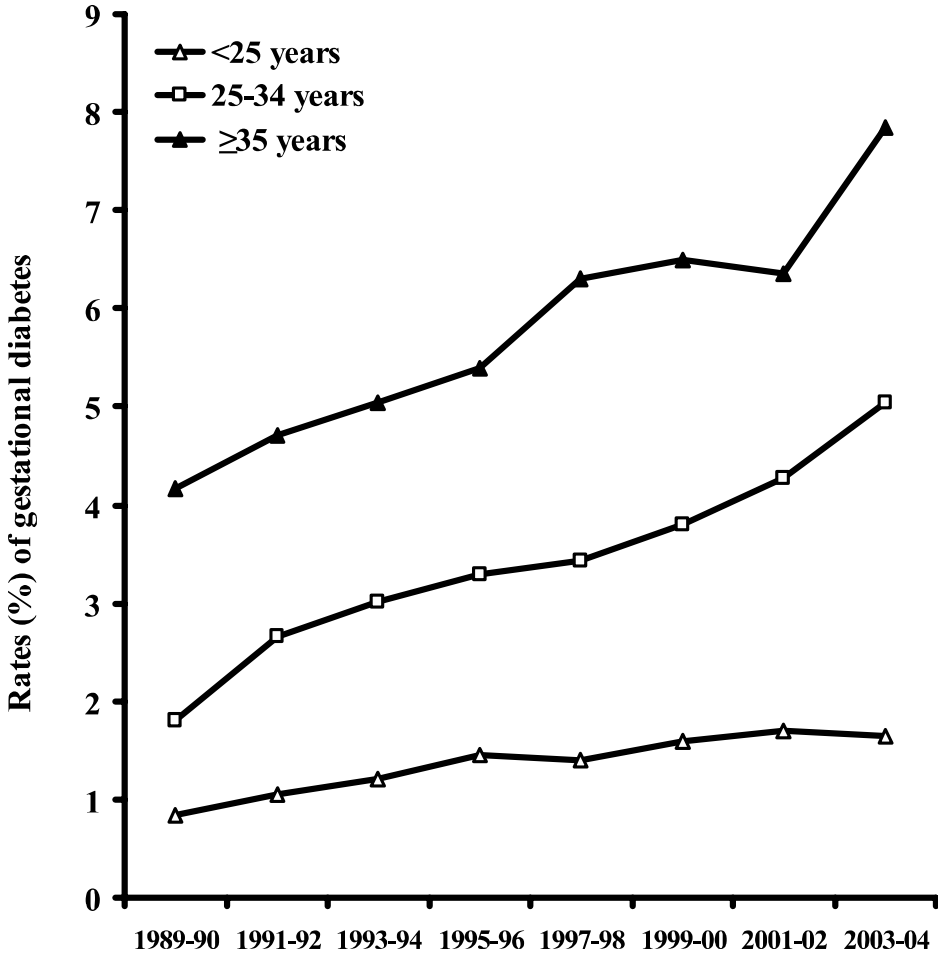
"Hyperglycaemia in pregnancy"

Currently diagnosed by OGTT around 28 weeks of pregnancy

Requires fasting and 2-hr sample

Why worry about GDM?

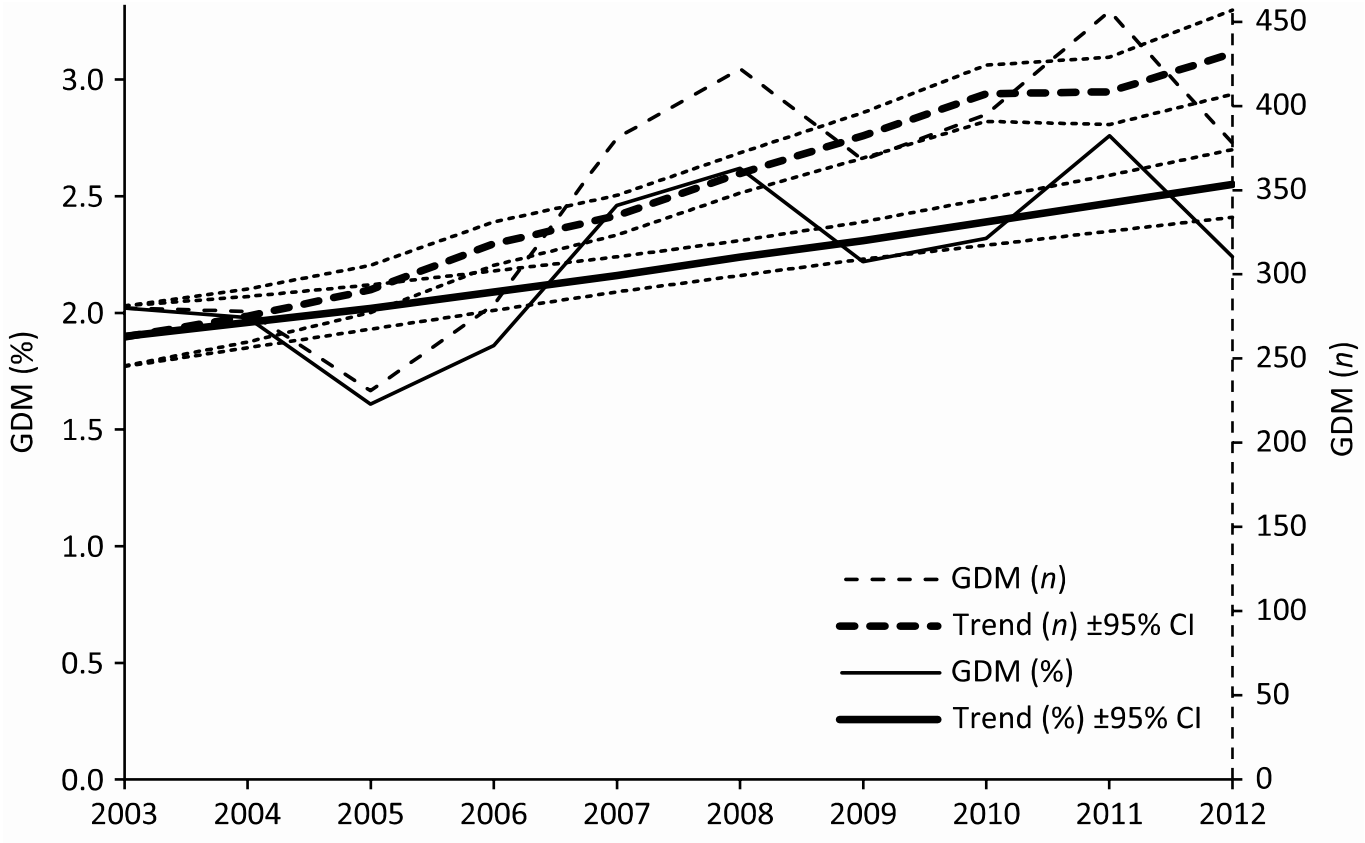
Doubling of GDM



Doubling of GDM in USA in 14 years

Getahun et al, AJOG, 2008

GDM rates in Sweden

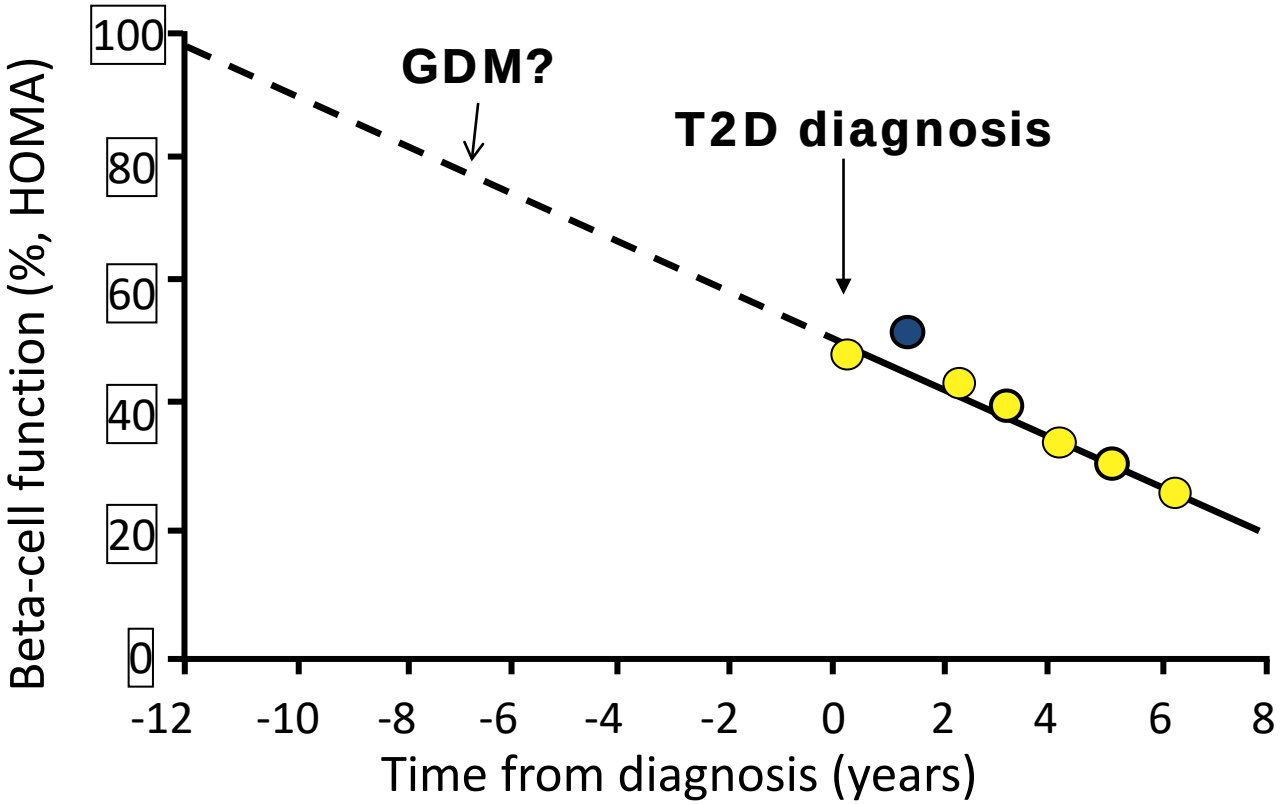


64% higher incidence of GDM in 10 years

Ignell et al, Acta OG Scand, 2014

>90% of GDM happens in developing countries

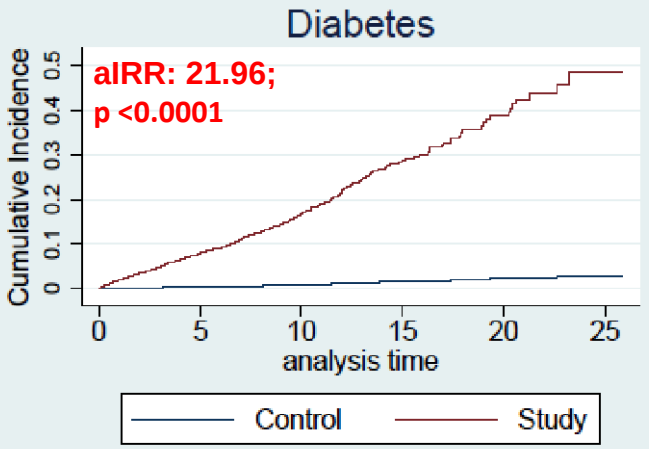
Pre-prediabetes?

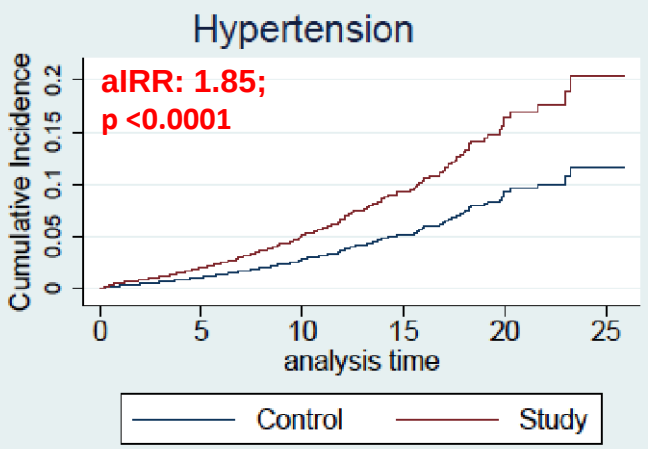


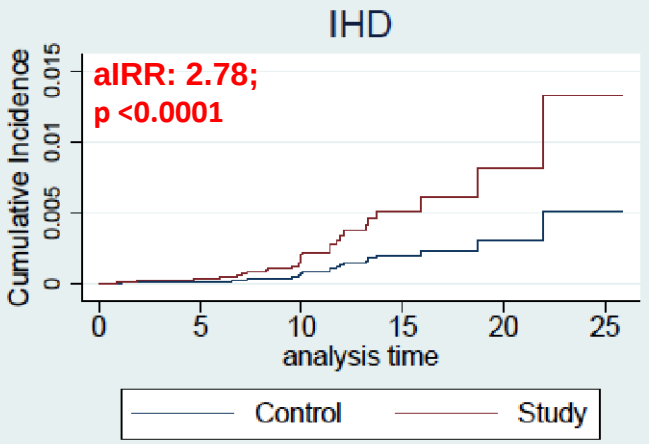
Adapted from Lebovitz H, Diabetes Reviews 1999

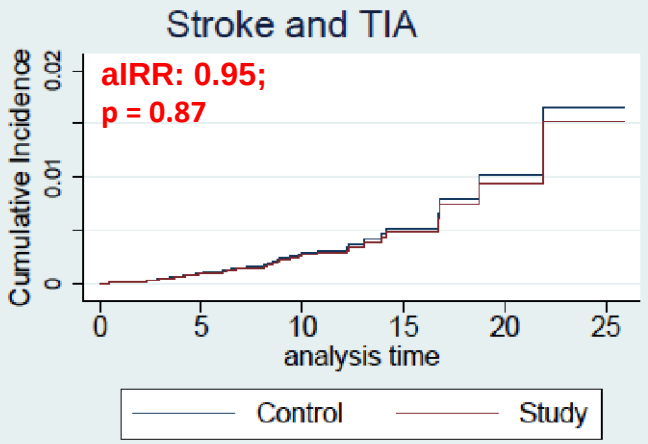
T2D, HTn & CVD post GDM in UK

THIN database:
>9000 GDM
>37000 Controls





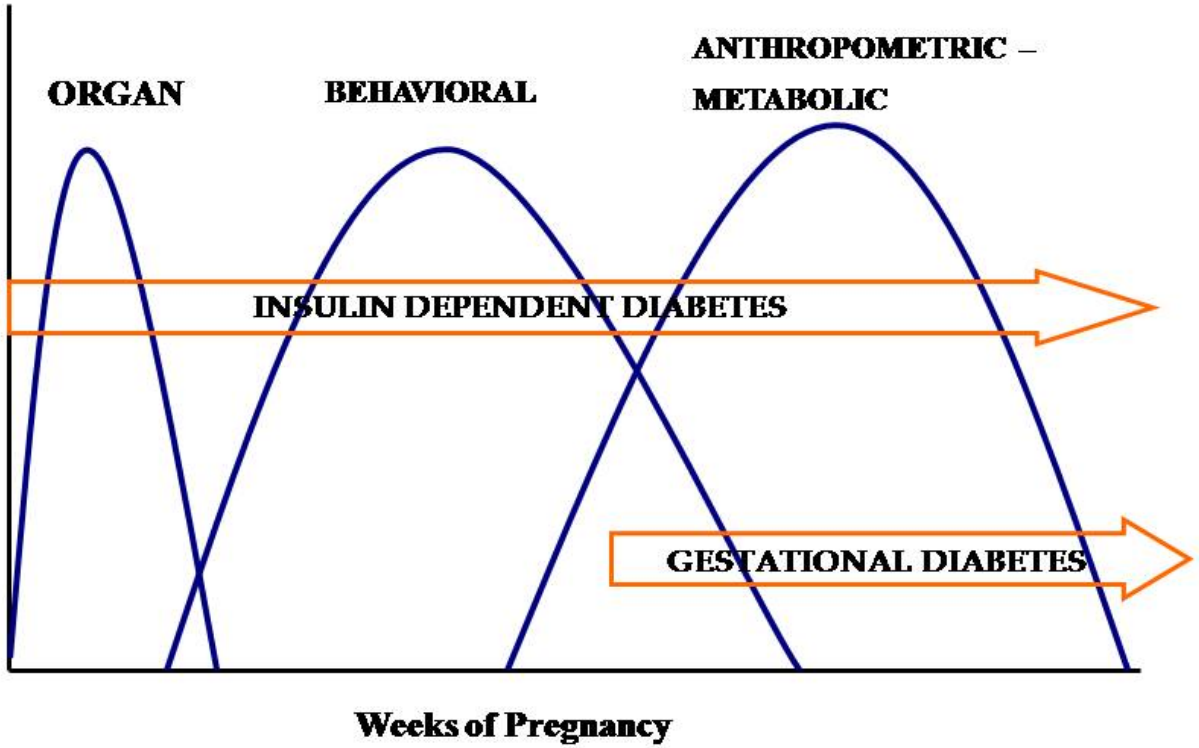




Daly B et al, Plos Med 2018

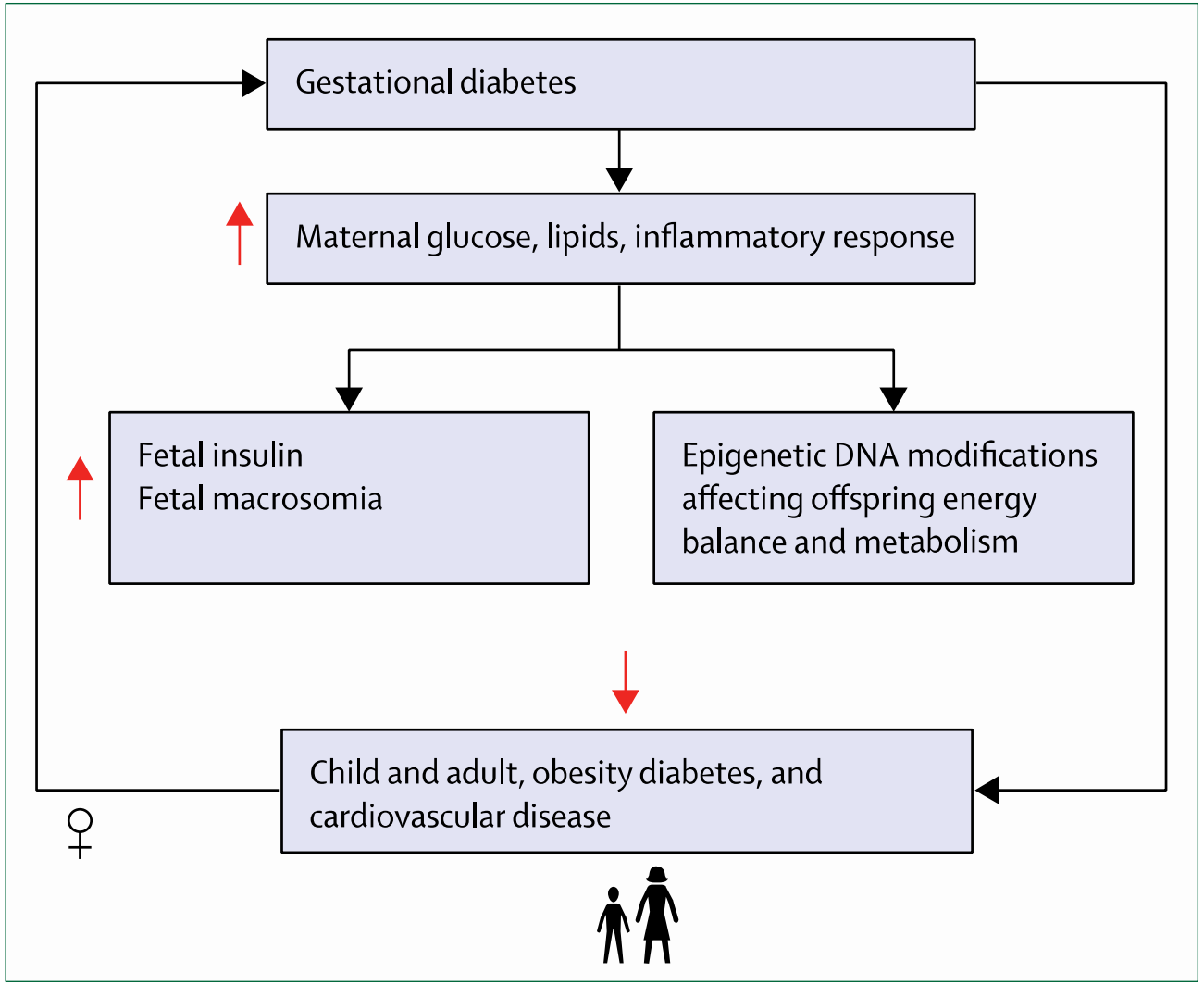
Fuel-mediated Teratogenesis

Permenant change in habitus caused by abnormal concentrations of nutrients during period of intrauterine development



N Frienkel, Diabetes 1980

Offspring effects



Saravanan P et al, Lancet DE, 2020

At birth

Saravanan P et al Diabetic Med 2010

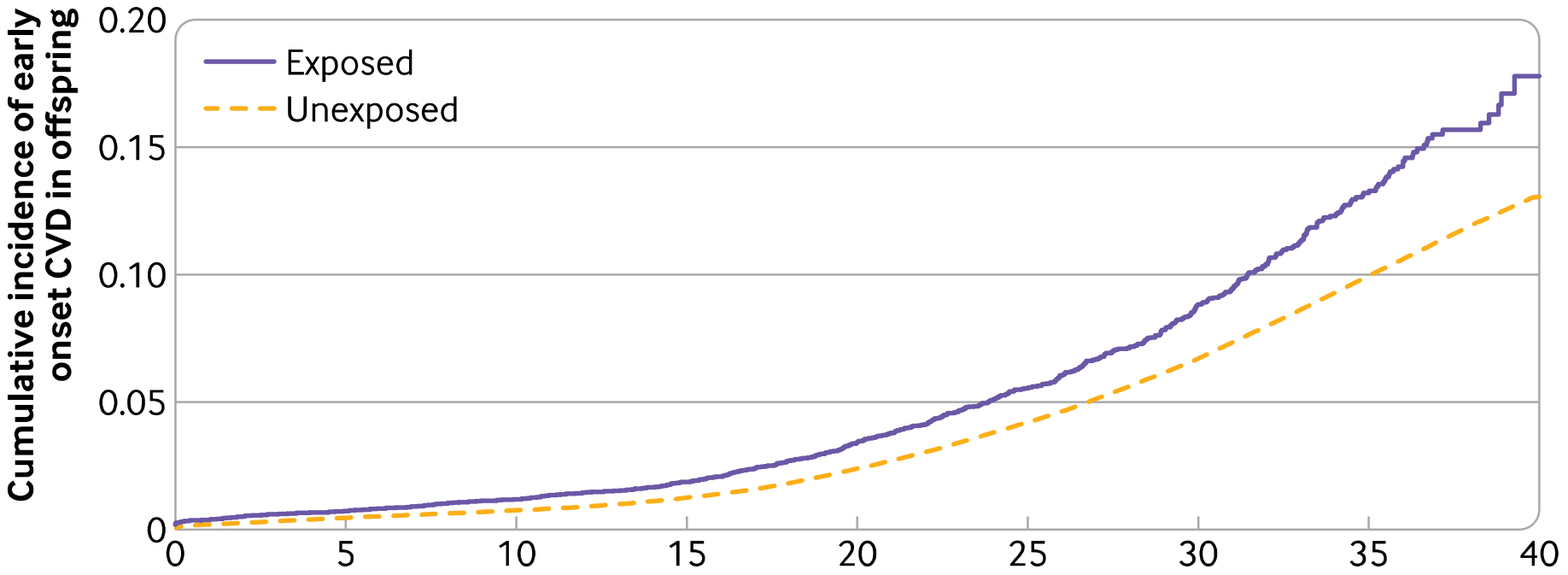
In early adulthood

Variables	O-GDM (n = 168)	O-NoGDM (n = 141)	O-Type1 (n = 160)	O-BP (n = 128)	P[a]
Offspring					
Age (yr)	21.6 (1.8)[b]	21.1 (2.1)[b]	22.5 (2.2)	22.9 (2.2)	**<0.001**
BMI ≥25 kg/m^2	40% (67/168)[b]	30% (42/141)	41% (66/160)[b]	24% (31/128)	**0.005**
BMI ≥30 kg/m^2	13% (21/168)	11% (16/141)	10% (16/160)	5% (6/128)	0.1
Metabolic syndrome[c]	24% (40/168)[b]	15% (21/141)[b]	14% (23/160)	6% (7/128)	**<0.001**
Central obesity (M ≥94 cm; W ≥80 cm)	39% (66/168)	38% (54/141)	43% (68/160)	29% (37/128)	0.1
Triglycerides ≥1.7 mmol/liter	16% (26/167)[b]	14% (20/140)[b]	6% (10/159)	5% (6/128)	**0.002**
Reduced HDL (M <1.03; W <1.29 mmol/liter)	37% (62/167)[b]	31% (43/140)[b]	20% (32/159)	13% (17/128)	**<0.001**
Diastolic blood pressure ≥85 mm Hg	4% (6/167)	2% (3/141)	5% (8/160)	2% (2/128)	0.3
Systolic blood pressure ≥130 mm Hg	37% (62/167)	31% (44/141)	41% (66/160)[b]	24% (31/128)	**0.02**
Fasting plasma glucose ≥5.6 mmol/liter	41% (69/167)[b]	30% (42/138)[b]	25% (39/155)[b]	10% (13/128)	**<0.001**
Physical activity (≥30 min/d)	56% (94/168)	56% (79/141)	48% (77/160)	50% (64/128)	0.4
Smokers	46% (77/168)	42% (59/141)	36% (57/160)	35% (45/128)	0.2
Parents					
Paternal diabetes	8% (13/164)	8% (11/136)	5% (8/157)	9% (11/125)	0.6
Family occupational social class V or VI	27% (45/167)[b]	18% (25/140)	18% (29/160)[b]	8% (10/128)	**<0.001**

Pre-diabetes/T2D (adj. ORs):	**7.76**	**4.46**	**4.02**	**ref**

Clausen et al JCEM 2009

CVD in offspring post GDM



No at risk

Unexposed	2 377 136	2 062 027	1 759 037	1 450 866	1 127 219	787 639	490 892	246 601	0
Exposed	54 864	36 959	22 961	13 816	7591	4369	2394	998	0

Yu Y et al, BMJ 2019

Why worry about GDM?

Panel: **Long-term complications of gestational diabetes**

Complications for the women

- Hypertension[8]
- Type 2 diabetes[8,24,25]
- Vascular dysfunction[41]
- Non-alcoholic fatty liver disease[42,43]
- Dyslipidaemia[8,24,25]
- Chronic inflammation[41,44]
- Chronic kidney disease[45,46]
- Ischaemic heart disease[8,9]

Complications for the offspring

- Childhood obesity[10,25]
- Excess abdominal adiposity[47]
- Metabolic syndrome[48,49]
- Hyperinsulinaemia[50]
- Disordered glucose regulation in adolescents[27]
- Higher blood pressure[51,52]
- Possible early onset of cardiovascular disease[53]
- Possible attention-deficit hyperactivity disorder and autism spectrum disorders[52,54,55]

Outline

- Human evolution
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  - Maternal risk
  - Offspring risk
- **Importance of innovative methodologies**
  - **Learnings from birth weight studies**
  - **Need for accurate personalized prediction**

Why we need innovative methodologies?

Treating GDM may be too late?

Treatment: ~50% risk reduction

2 landmark studies: Crowther et al & Landon et al

Neonatal adiposity in GDM

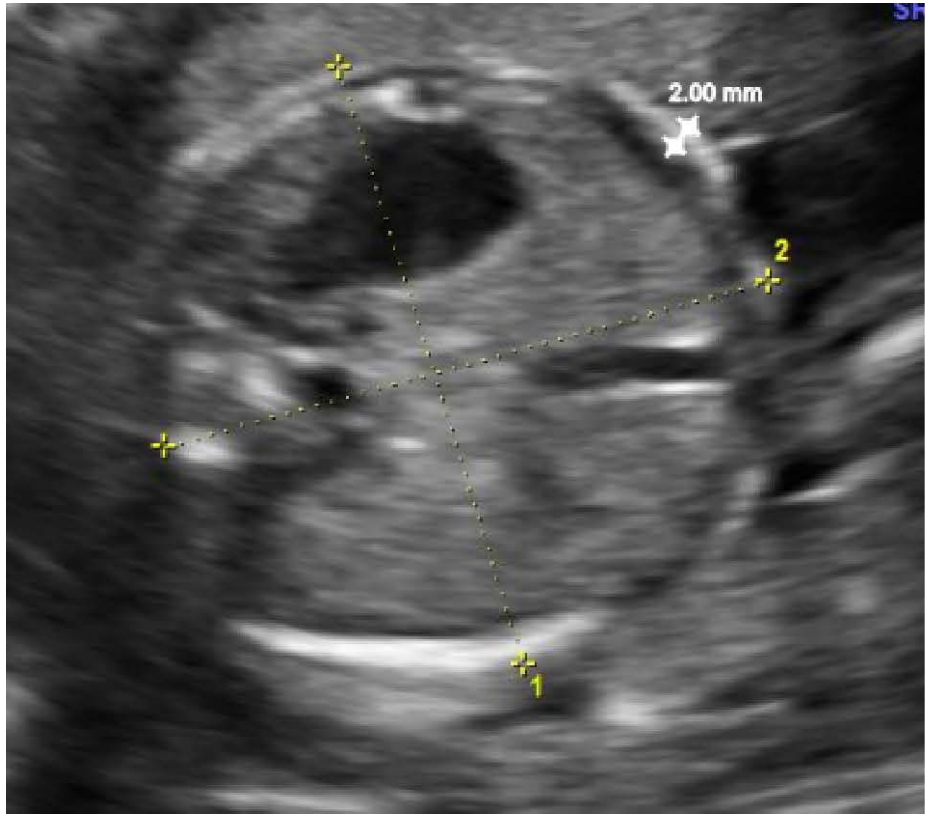
Total adiposity measured by MRI Spectroscopy scan in the first 2 weeks and then at 8-12 weeks; Well controlled GDM; n= 86

	Model 1			Model 2		
Outcomes	Difference (%)	95% CI	*P* value	Difference (%)	95% CI	*P* value
Assessment 1						
Total AT	6.9	−1.4, 15.9	0.11	5.4	−3.6, 15.6	0.24
Internal abdominal AT/nonabdominal superficial subcutaneous AT ratio				1.2	−11.3, 15.6	0.86
IHCL*						
Assessment 2						
Total AT	16.0	6.0, 27.1	0.002	12.5	1.0, 25.0	0.03
Change in total AT	35.8	11.7, 65.2	0.003	32.4	5.2, 66.3	0.02
Internal abdominal AT/nonabdominal superficial subcutaneous AT ratio				−0.2	−15.1, 17.2	0.98
IHCL	5.7	−30.2, 59.6	0.79	3.5	−35.4, 65.6	0.89

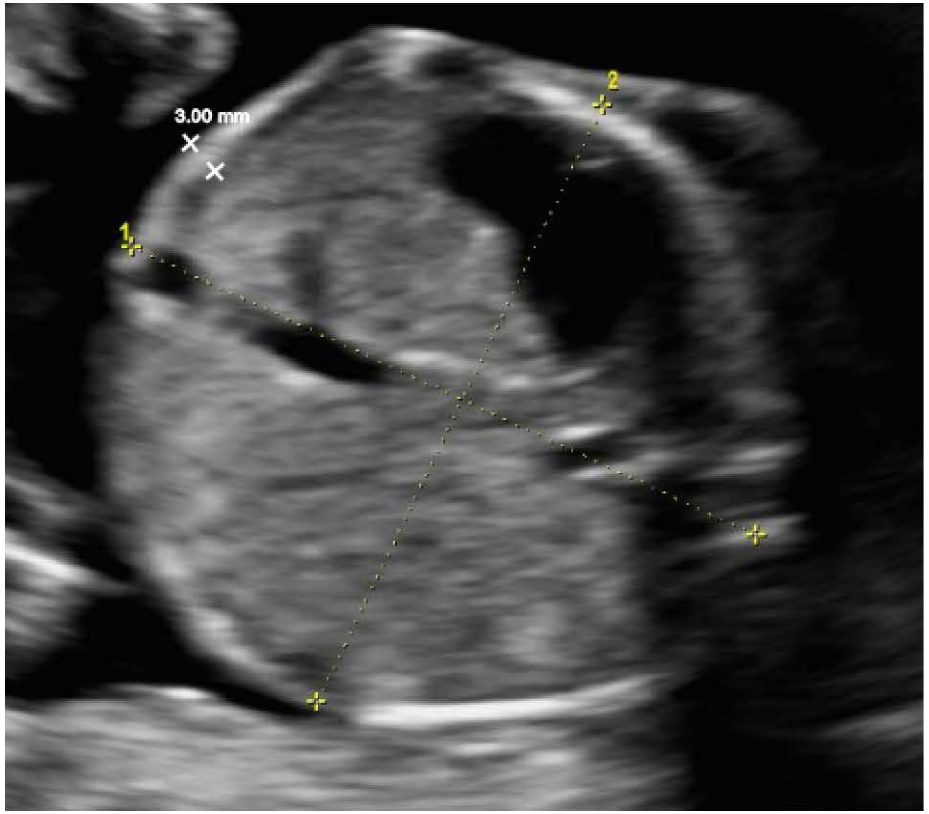
Model 1, adjustment of AT for body size using indices (18) (not applicable for AT ratios) and IHCL for postnatal age; model 2, same as model 1 plus adjustment for infant sex and maternal prepregnancy BMI. *Non-normal distribution, and therefore the percentage difference, was not calculable.

Fetal adiposity precedes onset of GDM

Control



GDM



Venkataraman H et al, Diabetologia 2017

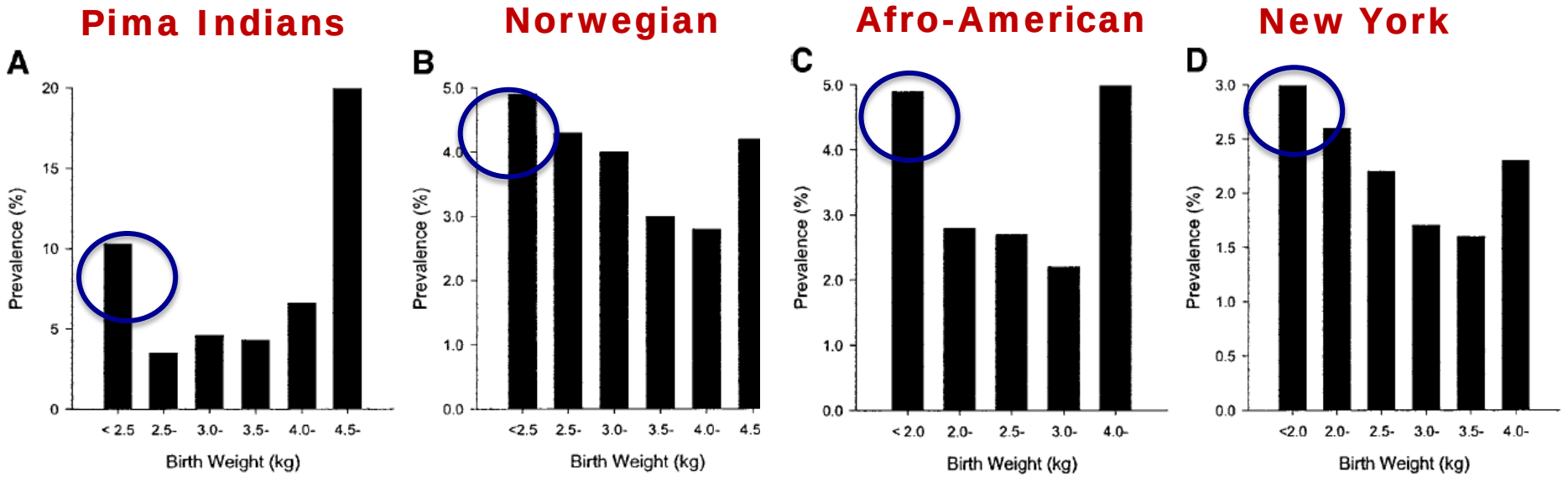
PRiDE
MICRONUTRIENTS IN PREGNANCY STUDY

MRC Medical Research Council

Glucose does not explain everything!

STRIDE
WALK TOGETHER FOR YOUR BABY'S HEALTH

Birth weight & risk of GDM



U shaped relation

Both low and high BW association

Intergenerational risk transmission

Whincup et al, JAMA 2008

Born to GDM

Saravanan P et al Diabetic Med 2010

Ethnic differences

Ethnic specific LGA risk

	All women (N=10 356)		White British women (N=4105)		South Asian women (N=5445)	
	Fasting glucose threshold (mmol/L)	2 h post-load glucose threshold (mmol/L)	Fasting glucose threshold (mmol/L)	2 h post-load glucose threshold (mmol/L)	Fasting glucose threshold (mmol/L)	2 h post-load glucose threshold (mmol/L)
Birthweight >90th percentile	5·3	NP	5·6	NP	5·1	NP
Sum skinfolds >90th percentile	5·2	7·5	5·2	NP	5·2	7·2
Average glucose concentration for both birthweight and sum of skinfolds >90th percentile	5·3	7·5	5·4	NP	5·2	7·2

NP=not possible to work out a threshold because within our study none of the women reached a threshold that gave an odds ratio of 1·75 or greater (the International Association of Diabetes and Pregnancy Study Groups consensus minimal odds ratio deemed to be of clinical importance).

Thresholds of glucose concentrations and OR ~1·75 for birthweight >90th and sum of skinfolds >90th percentiles

GDM were excluded; GDM diagnosed if FPG ≥6.1 and 2-hr ≥7.8 mmol/l (110 and 140mg/dl)

Farrar et al, Lancet DE, 2015

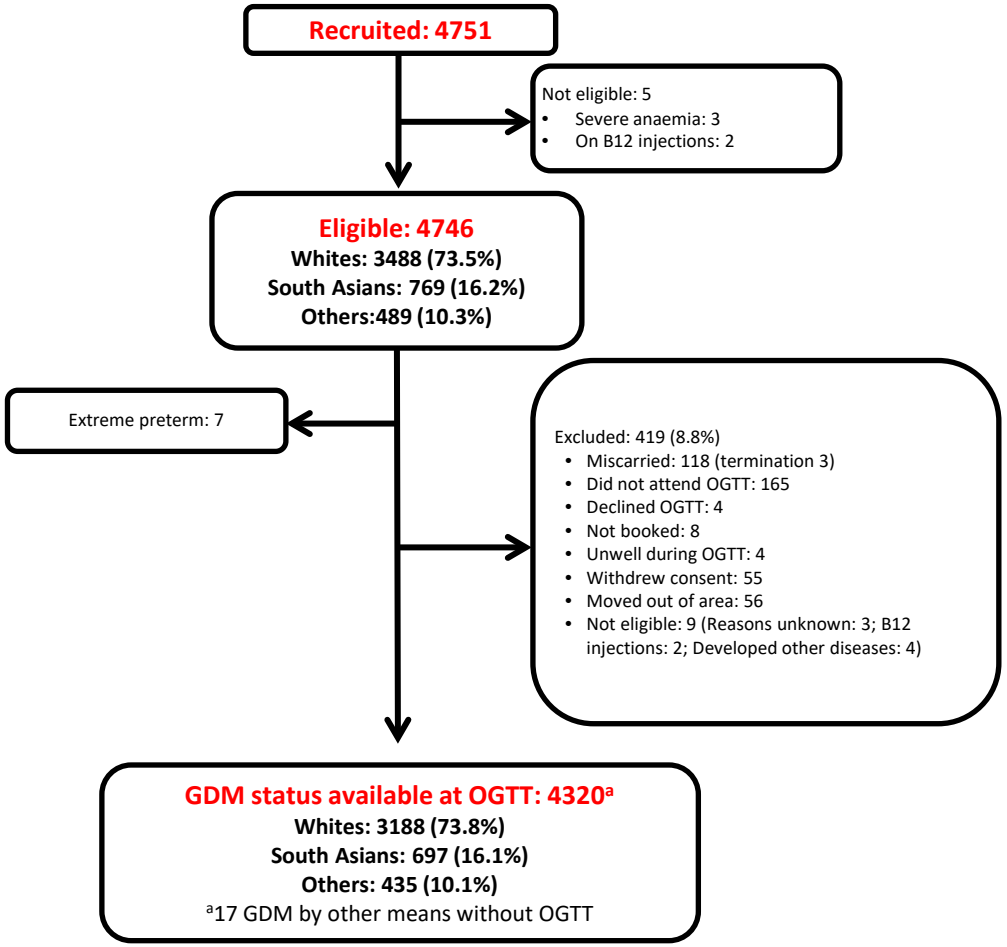
Risk factors for GDM

- Age (lowest <20yrs)
- BMI more than 30
- Previous macrosomic baby (4.5kg)
- Previous GDM
- PCOS
- First degree relative with diabetes
- Polyhydramnios & fetal abdo circumference >97 centile
- Certain ethnic groups:
  - South Asian (India, Pakistan or Bangladesh)
  - Black & Afro-Caribbean
  - Middle Eastern (Saudi Arabia, UAE, Iraq, Jordan, Syria, Oman, Qatar, Kuwait, Lebanon or Egypt)

PRiDE rationale

- **Known risk factors only picks up ~60% of all GDM**
  - **Need for identification of other markers**
  - **n=4500; 10 centres**
- **Damage to the offspring may have already happened**
  - **Accurate early pregnancy prediction can prevent GDM**

Study flow



Saravanan et al, Diabetologia 2021

Baseline characteristics: Early pregnancy

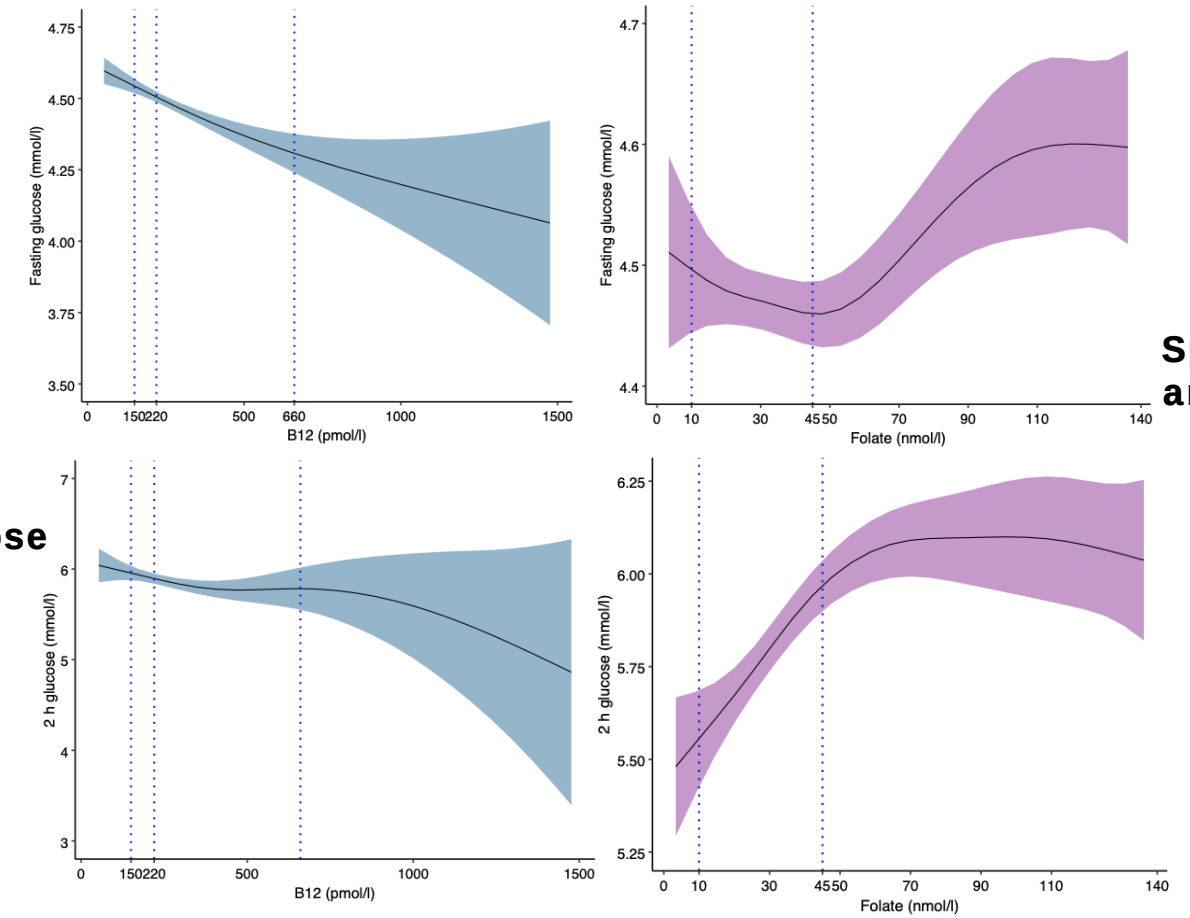
Maternal Characteristics at Booking	All (n=4746) Mean ± SD Median (IQR)§ n (%)^	Whites (n=3488) Mean ± SD Median (IQR)§ n (%)^	South Asians (n=769) Mean ± SD Median (IQR)§ n (%)^	Others (n=489) Mean ± SD Median (IQR)§ n (%)^	p-value
Age (years)	30.51 ± 5.29	30.1 ± 5.35	31.57±4.72	31.4 ± 5.4	<0.0001
Multi parity (≥2) ^	919 (19.4)	698 (20.0)	119 (15.5)	102 (20.9)	0.01
Gestational age (weeks)	12.45 ± 1.44	12.39 ± 1.47	12.51 ± 1.39	12.8 ± 1.21	<0.0001
Height (cm)	164.28 ± 6.83	165.32 ± 6.64	160.69 ± 6.24	162.57 ± 6.84	<0.0001
Weight (kg)	83.33 ± 20.49	88.3 ± 19.6	66.44 ± 13.93	74.44 ± 18.04	<0.0001
BMI (kg/m^2)	30.8 ± 7.06	32.3 ± 6.92	25.7 ± 4.96	28.1 ± 6.27	<0.0001
Waist Circumference (cm)[a]	98.54 ± 16.41	101.9 ± 15.95	87.73 ± 12.78	91.45 ± 15.16	<0.0001
Biochemical characteristics	**n=4630**	**n=3396**	**n=759**	**n=475**	
B12 (pmol/l)§	238.2 (183.3, 311.2)	230.3 (181.1, 298.0)	233.3 (177.9, 319.9)	316.5 (237.3, 429.3)	<0.0001
Folate (nmol/l)§	35.9 (24.8, 52.2)	33.8 (23.2, 51.3)	43.0 (30.4, 54.0)	38.3 (27.0, 51.6)	<0.0001
tHcy (µmol/l)§b	11.3 (8.6, 14.7)	11.4 (8.7, 14.8)	11.1 (8.7, 14.7)	10.9 (8.3, 13.8)	0.12
B12 insufficiency at <150pmol/l^	490 (10.6)	365 (10.7)	101 (13.3)	23 (4.8)	<0.0001
B12 insufficiency at <220pmol/l^	1985 (42.8)	1536 (45.2)	348 (45.8)	98 (20.6)	<0.0001
Folate deficiency (<10nmol/l)^	69 (1.5)	61 (1.8)	1 (0.1)	7 (1.5)	0.003
Folate excess (>45nmol/l)^	1640 (35.4)	1139 (33.5)	342 (45.1)	159 (33.5)	<0.0001
Using Folate supplements^	3424 (78.2)	2569 (79.5)	526 (76.0)	329 (72.3)	<0.0001
Using Multivitamin supplements^	2494 (58.1)	1840 (58.2)	425 (62.7)	229 (50.9)	<0.0001

Saravanan et al, Diabetologia 2021

Relationship between B12-folate with glucose

Fasting glucose

2-hour post glucose

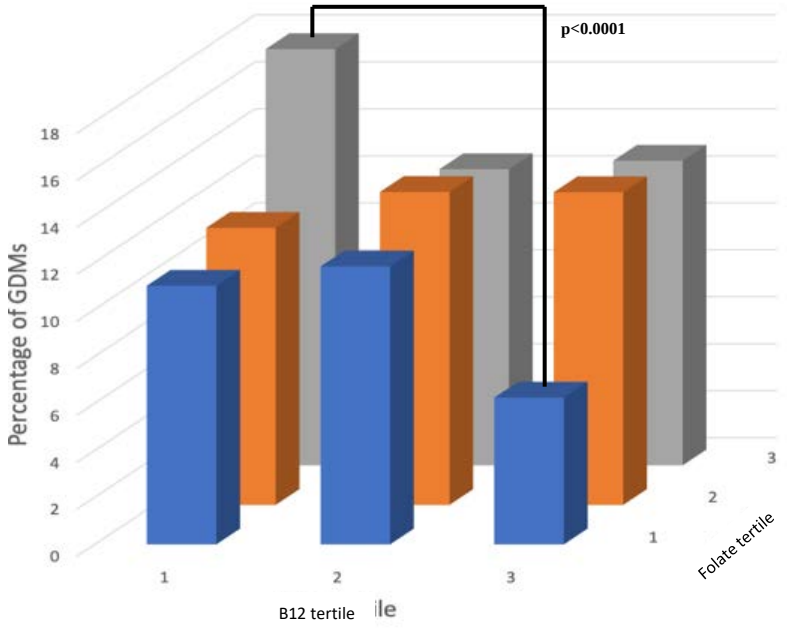


Spline regression analysis

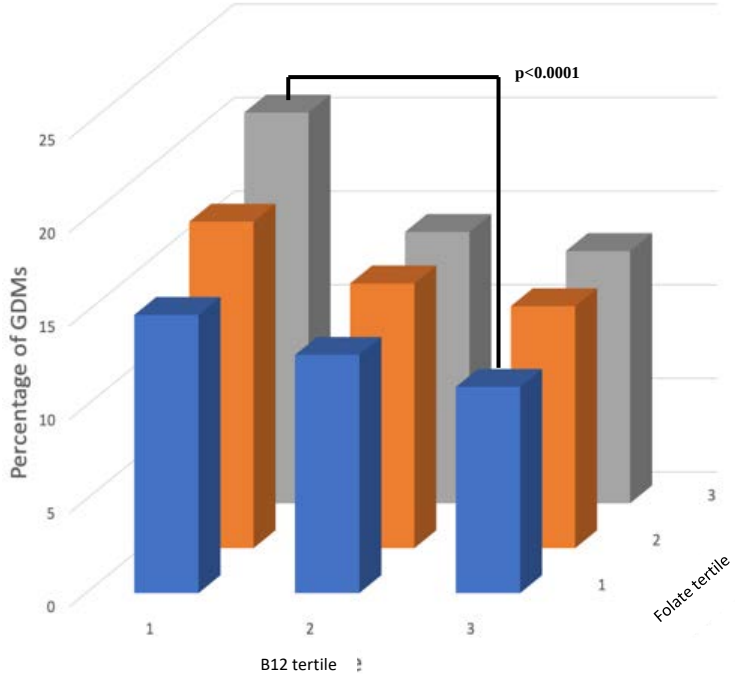
Saravanan et al, Diabetologia 2021

B12-folate imbalance and GDM

‘Low B12 and high folate’ with NICE-GDM

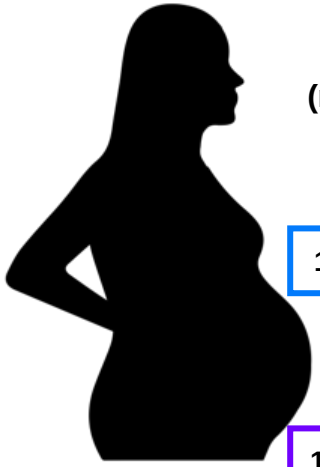


‘Low B12 and high folate’ with IADPSG-GDM



Saravanan et al, Diabetologia 2021

Summary



Early pregnancy
(n=4746; 12.5 weeks)

At 75g oral glucose tolerance test
(n=4320; 26.8 weeks)

1 standard deviation (116 pmol/l) higher B12 levels

- **Relative risk of IADPSG GDM: 14.4% lower**
- **Fasting glucose: 0.06 mmol/l lower**
- **2-hour glucose: 0.07 mmol/l lower**

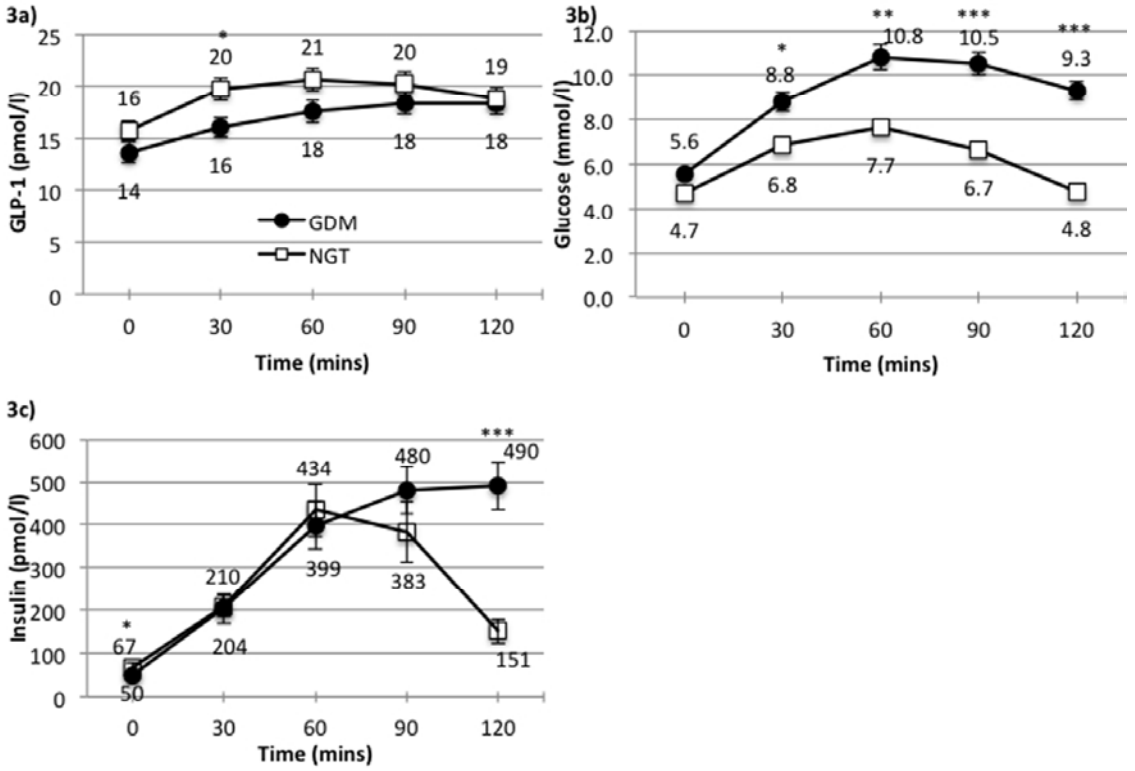
1 standard deviation (12 nmol/l) higher folate levels

- **Relative risk of IADPSG GDM: 11% higher**
- **2-hour glucose: 0.08 mmol/l higher**

42.3% B12 insufficiency (<220 pmol/l)
1.3% Folate deficiency
36.5% Folate excess

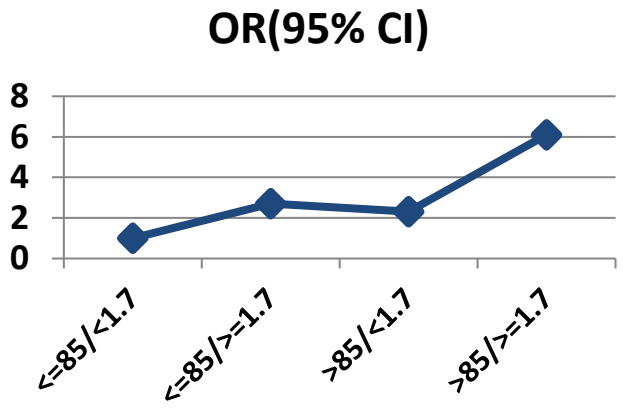
IADPSG: International Association of Diabetes and Pregnancy Study Group
GDM: Gestational Diabetes Mellitus

GLP1 levels in GDM



Sukumar N et al, Diabetes 2018

Hypertriglyceridemic waist and GDM



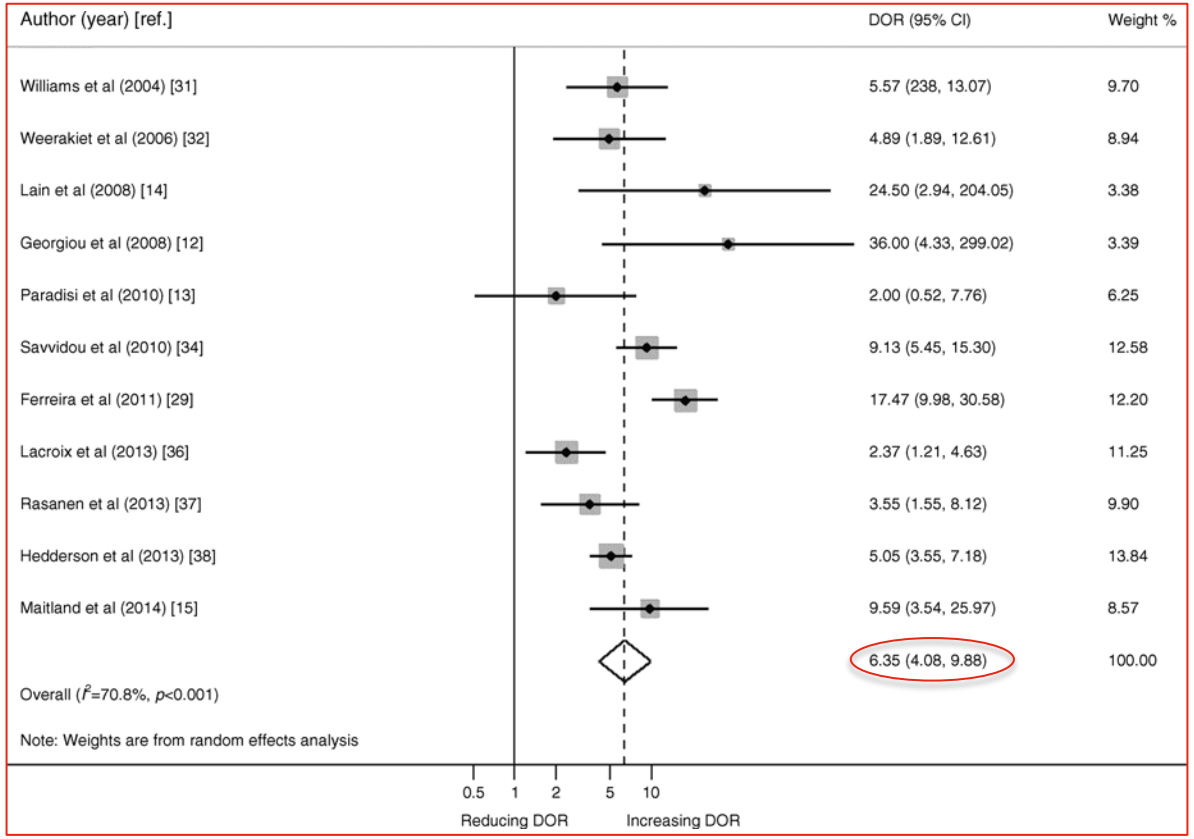
- Measured at 11-14 wks
- 75g OGTT at 24-28 wks
- Waist >85cms, + TG>1.7mM = OR 6.1
- Disturbed metabolism from early pregnancy

Brisson D et.al, CMAJ 2010.

Adiponectin

Accuracy of circulating adiponectin for predicting gestational diabetes: a systematic review and meta-analysis

Stamatina Iliodromiti[1] · Jennifer Sassarini[1] · Thomas W. Kelsey[2] · Robert S. Lindsay[3] · Naveed Sattar[3] · Scott M. Nelson[1]



Iliodromiti S et al, Diabetologia, 2016

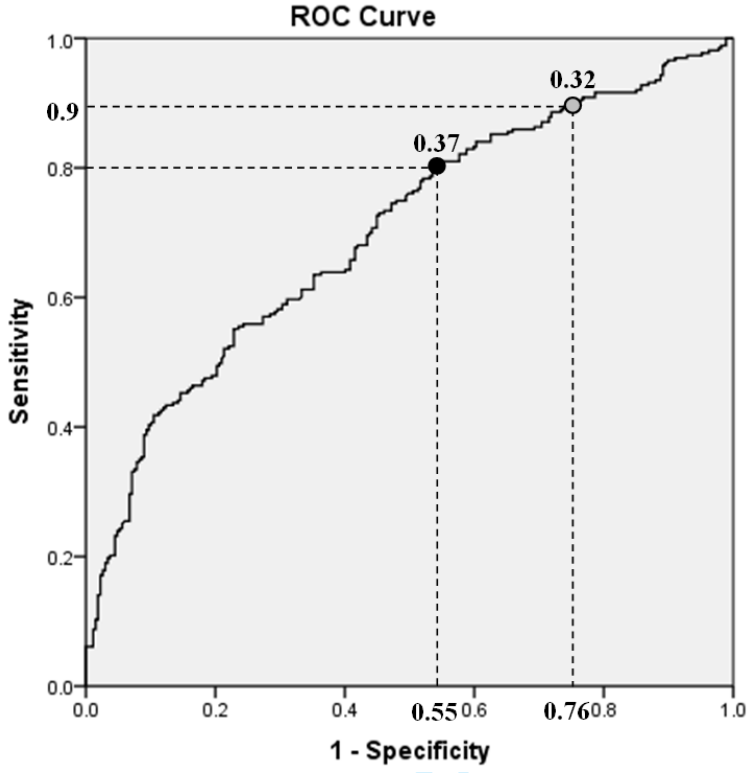
Diastolic BP

Table 2 Multivariable regression analysis result for formulating the composite risk score

	B	Adjusted OR (95% CI)	P Value

Fang Q et al, (submitted)

Composite risk score



Fang Q et al, (submitted)

Need for innovation

- Adverse disease programming is complex
- Identification of novel risk predictors is evolving rapidly
- Ethnic variations
- Factors that affect mothers may not affect offspring and vice versa

Need for innovation

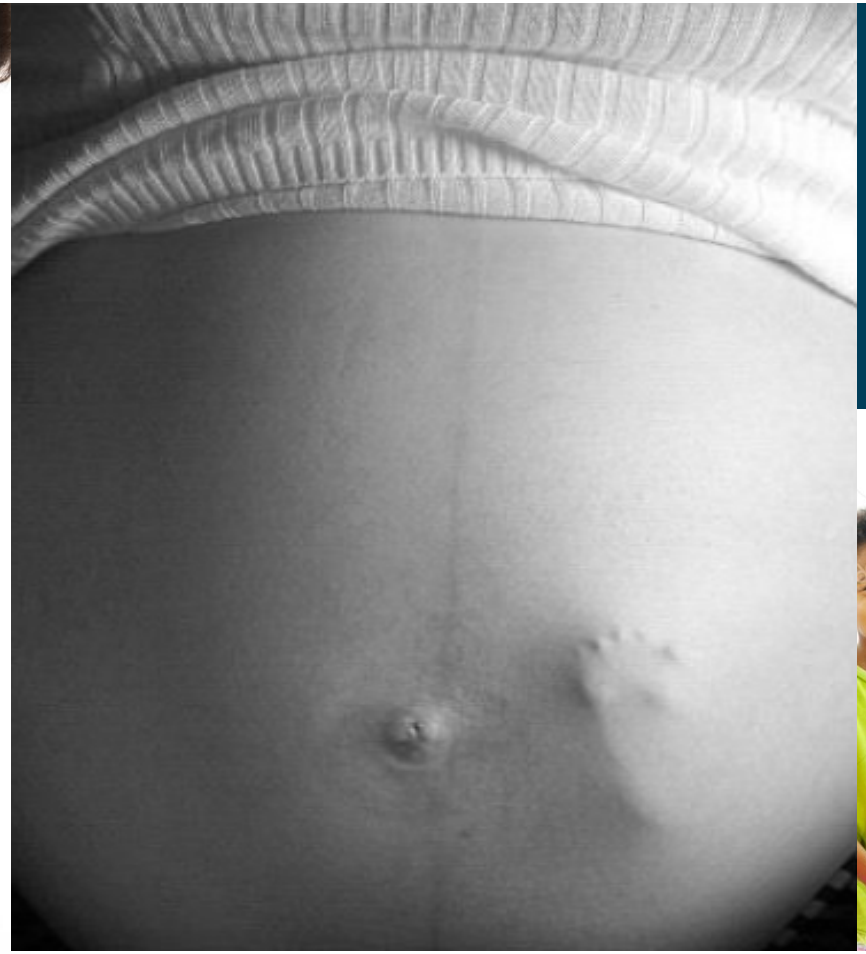
- Composite risk prediction
- Personalization
- Accounting for inter- and intra individual variations
- Availability of better datasets

Summary

- **Human evolution – Still a long way to go…**
- **Gestational Diabetes – Contributes to CVD epidemic; potentially other neurodevelopmental issues**
- **Importance of innovative methodologies – Complex issues & simple analyses cannot solve**

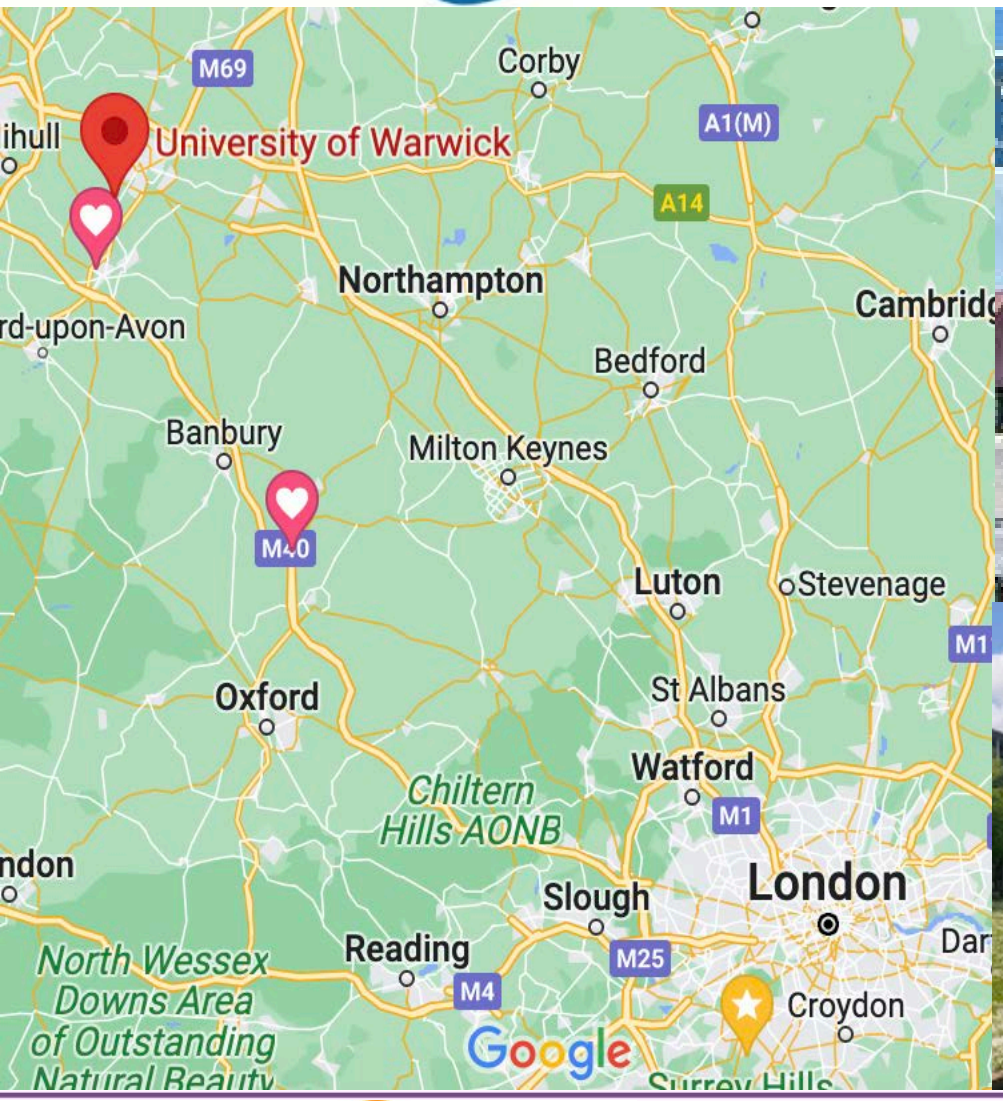
Conclusion - 1

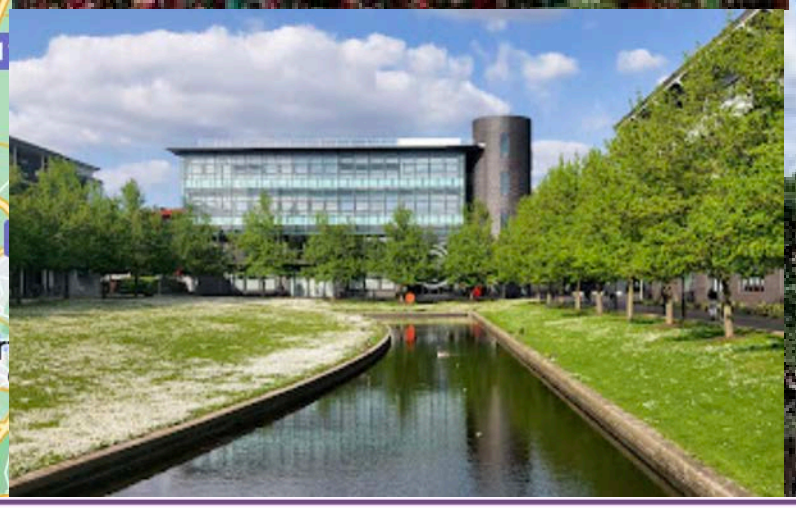
Conclusion - 2



My funders

Thank you





Saravanan; GDM; ICTS-TIFR