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WESTERN SYDNEY UNIVERSITY

Should we diagnose and treat early GDM?

SFOG 5th September 2024

Presenter Disclosure

Speaker’s Bureau-Ascensia, Abbott, Novo-Nordisk

Consultant-Sanofi

Educational grant- Boehringer Ingelheim, Ascensia

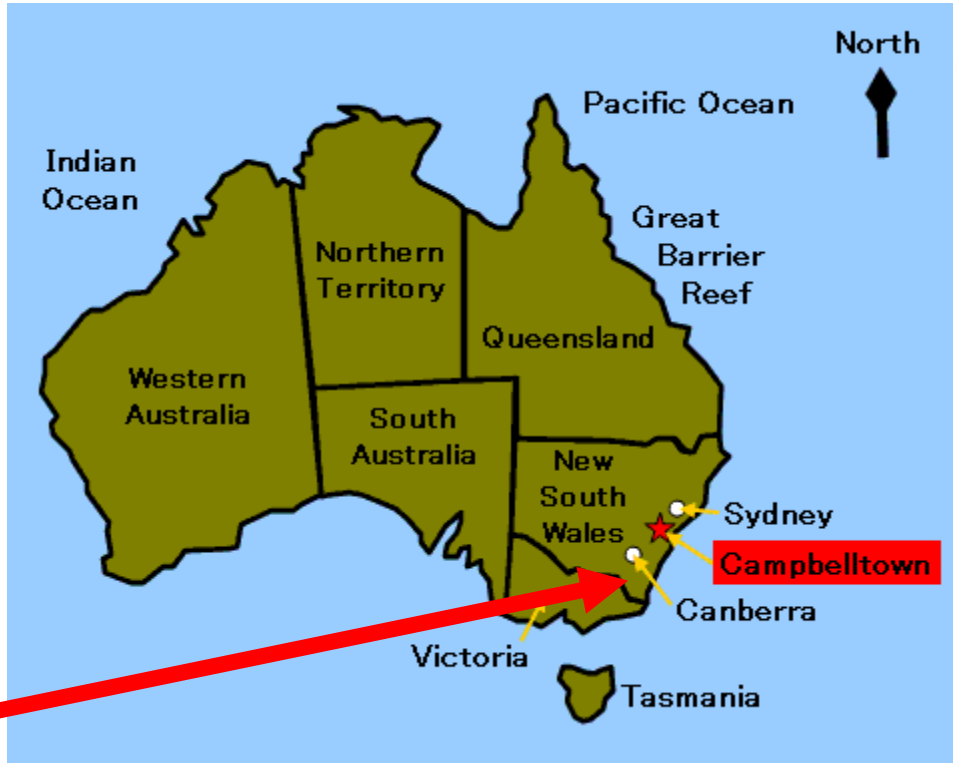
Equipment-Roche

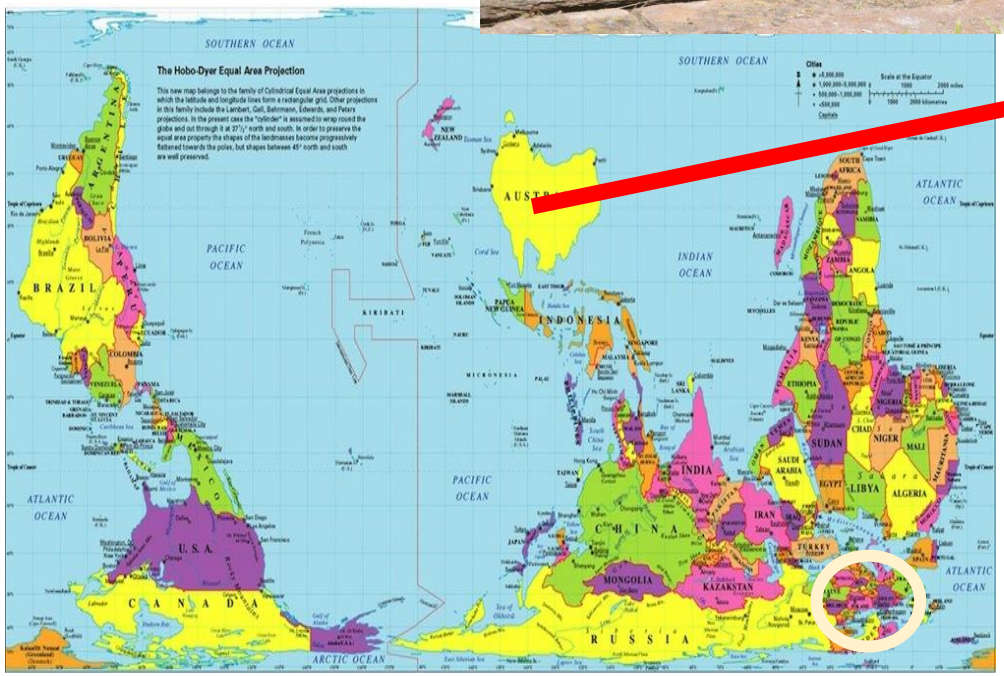
NB-None related to this presentation

Should we diagnose and treat early GDM?

- Where Im from!
- The 24-28 weeks centric view
- GDM as part of a lifecourse condition
- Evidence for early (<20 weeks') GDM
- Evidence for treating GDM
- Conclusion!

Where is Campbelltown?





NSW's most multicultural city is in Sydney's southwest

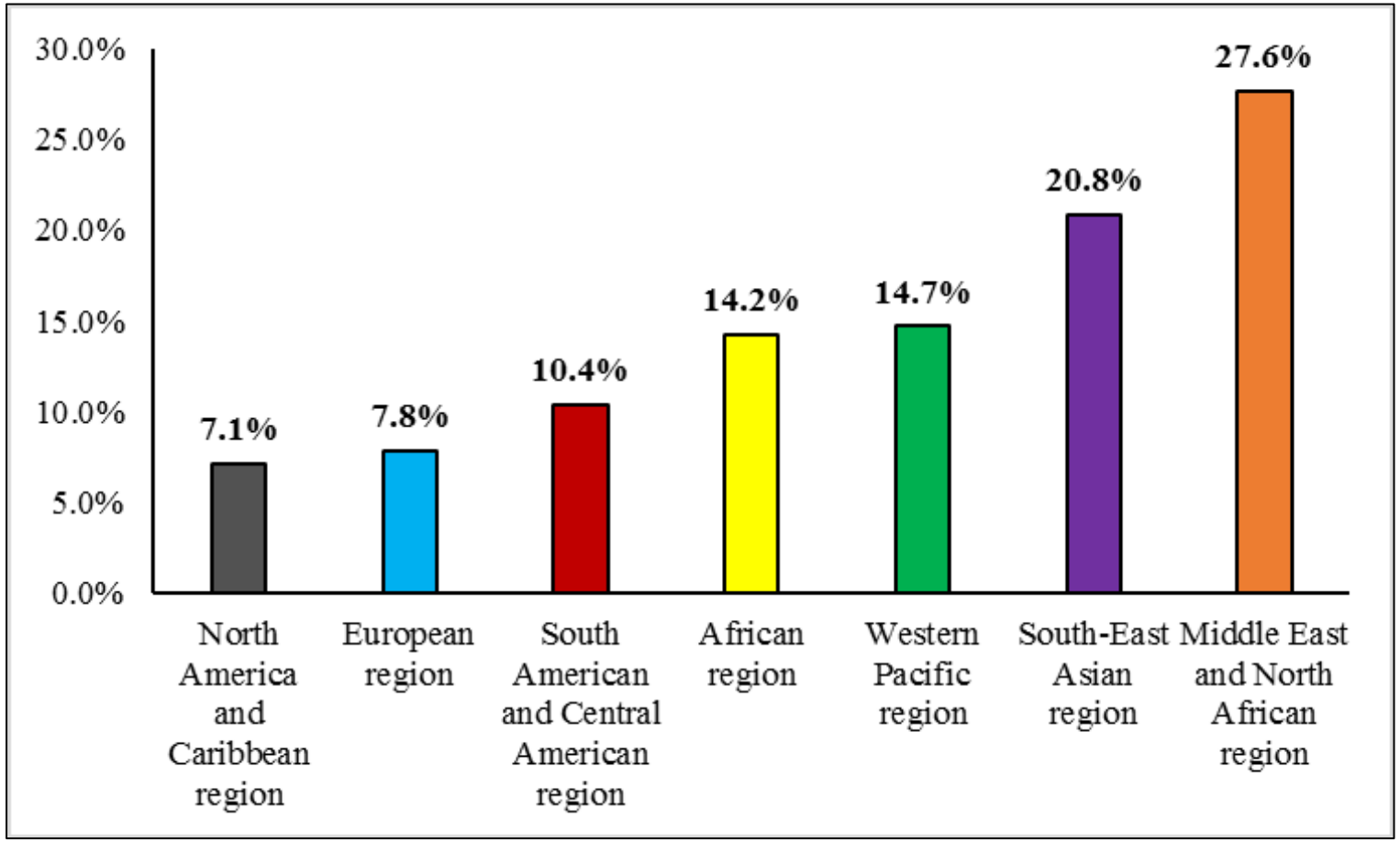
IT'S official: Census figures have uncovered NSW's most multicultural city.

Eliza Barr

less than 2 min read July 4, 2017 - 3:08PM Fairfield Advance 0 comments

Gestational diabetes

Global prevalence: **14%** (standardized to IADPSG criteria)



IDF Atlas

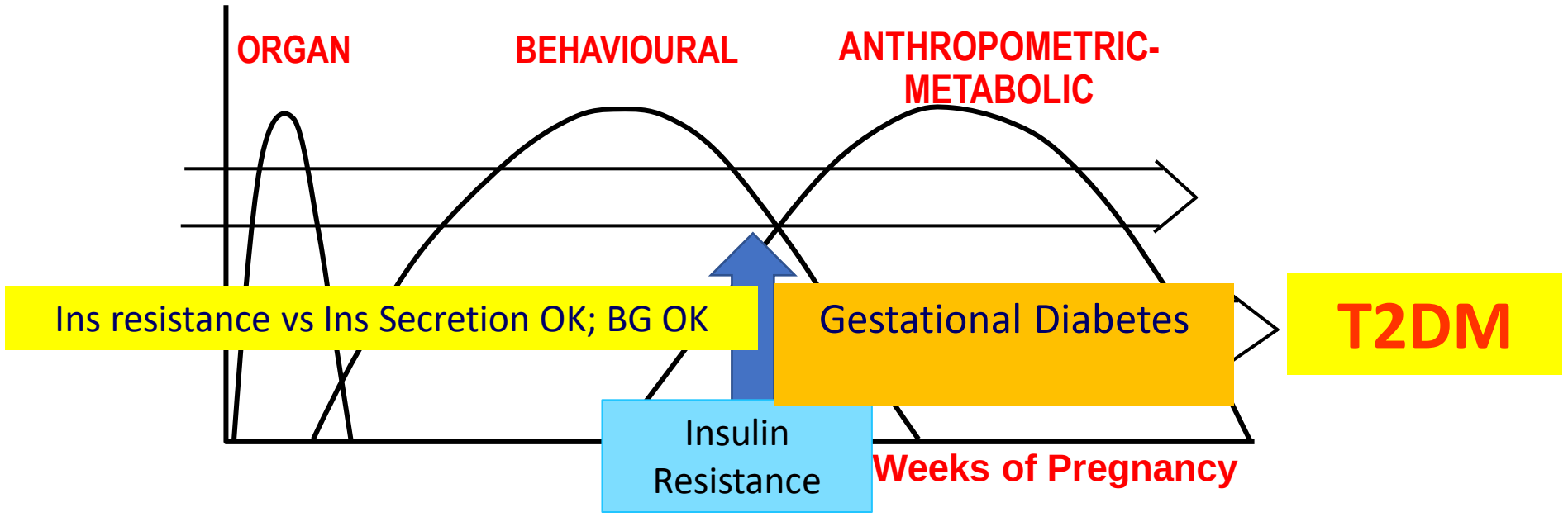
References:
International Diabetes Federation. IDF Diabetes Atlas, 10th edn. Brussels, Belgium: International Diabetes Federation, 2021.

OBOGM Study

Reprinted from DIABETES, VOL. 29, NO. 12, DECEMBER 1980
Copyright 1980 by THE JOURNAL OF THE AMERICAN DIABETES ASSOCIATION.

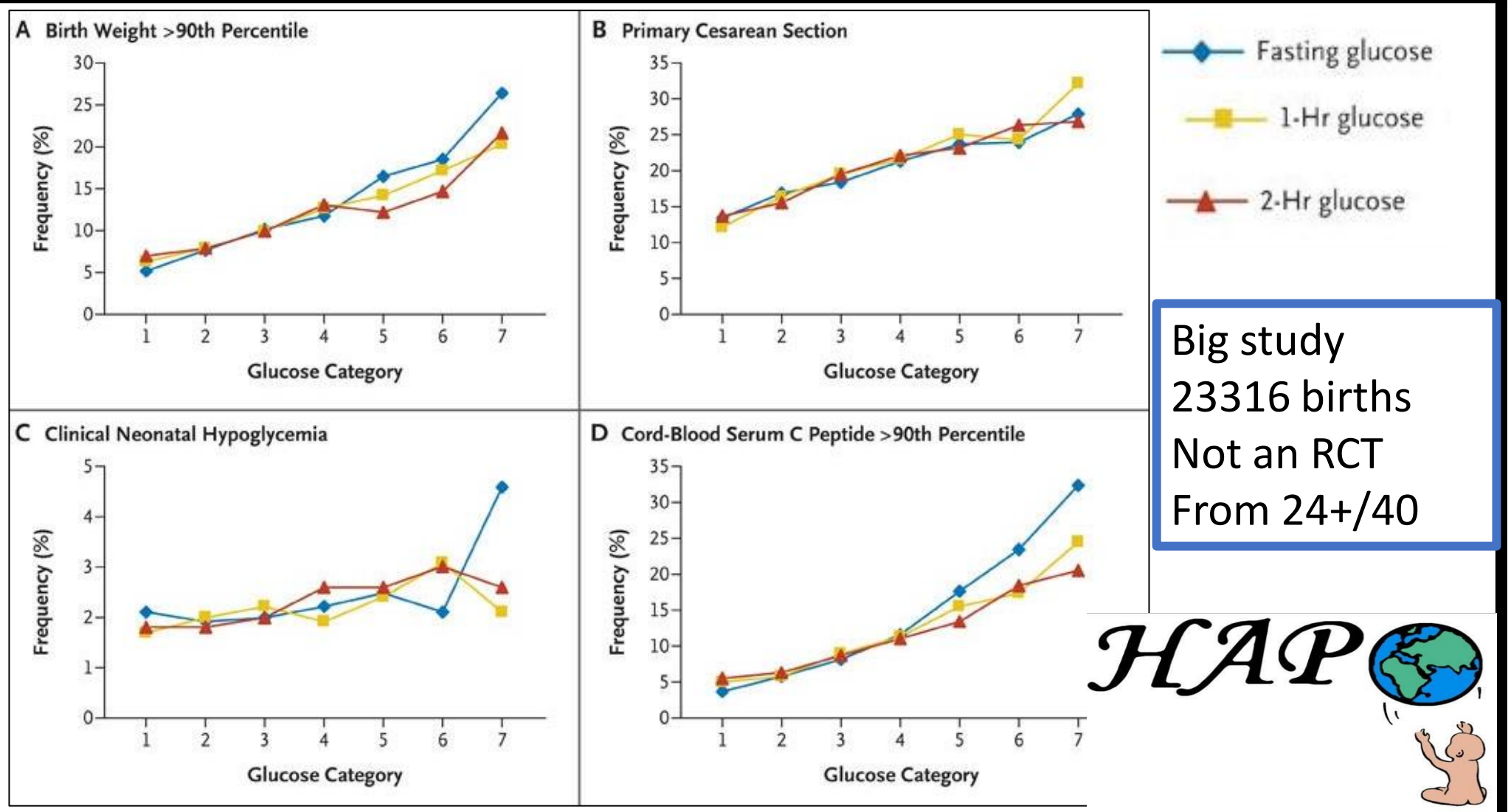
Banting Lecture 1980
Of Pregnancy and Progeny

Potential long-range effects upon the fetus of altered interactions in maternal fuels during pregnancy. Fuel-mediated teratogenesis as the basis for long-range anatomic and functional changes.



Freinkel 1980

Maternal glucose - perinatal outcomes



Big study
23316 births
Not an RCT
From 24+/40

24+/40 RCTs

ACHOIS
Landon
GEMS
CDC4G
->Benefit

HAP

References:
N Engl J Med. 2008 May 8;358(19):1991-2002.

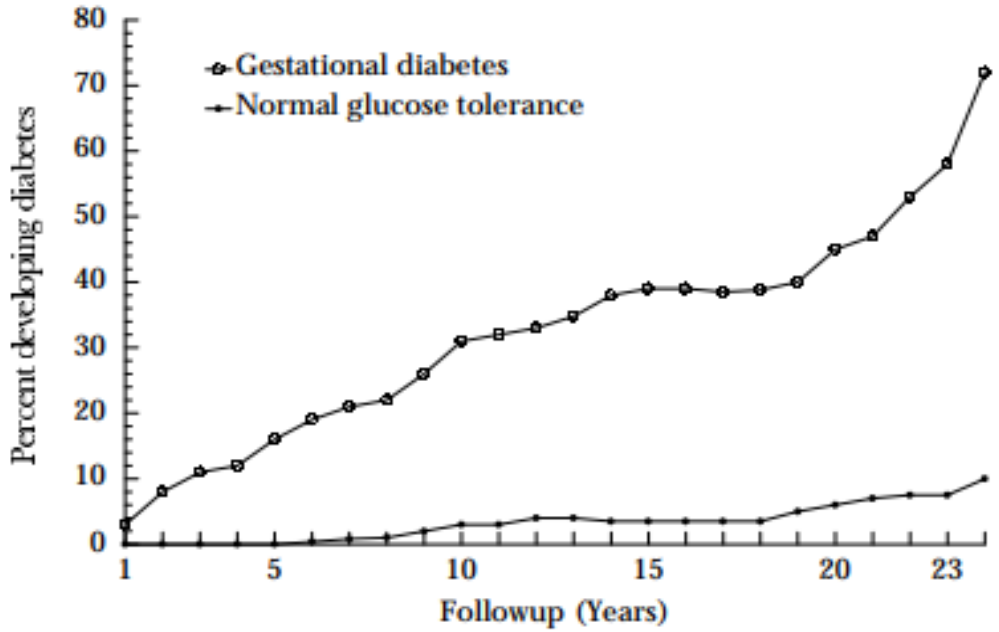
O Sullivan and Mahan From 1964

Cohort of 752 women in 2nd-3rd trimester

- 100g OGTT-3 hours
- 2+/4 tests to avoid reliance on one time point
- Thresholds decided
  - using life tables for mother to develop T2DM in 7-8 years
  - Related to diabetes prevalence (2% at the time)

Figure 35.2

Cumulative Incidence of Diabetes in Women with Normal Glucose Tolerance or Gestational Diabetes During Their Index Pregnancy

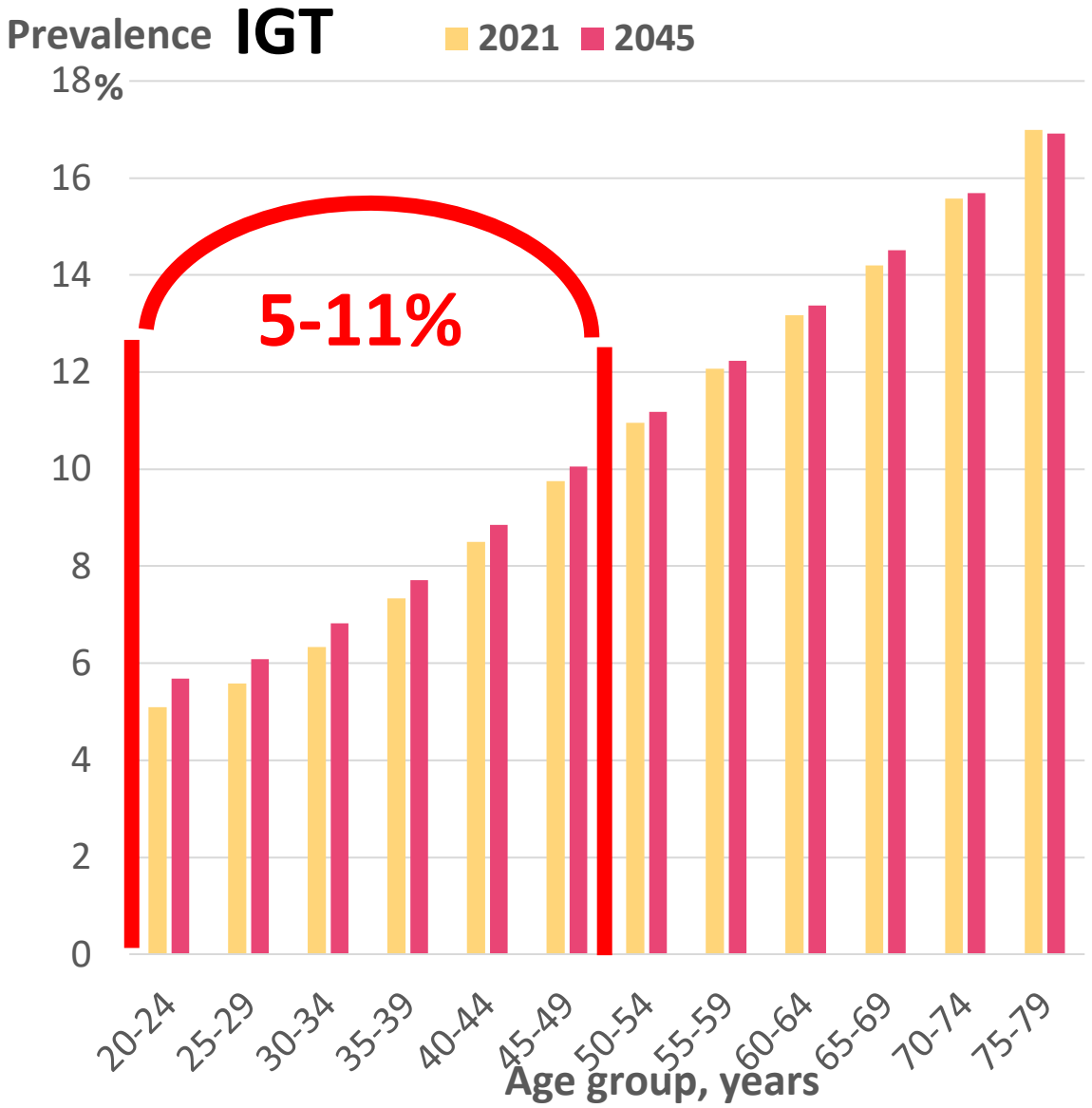


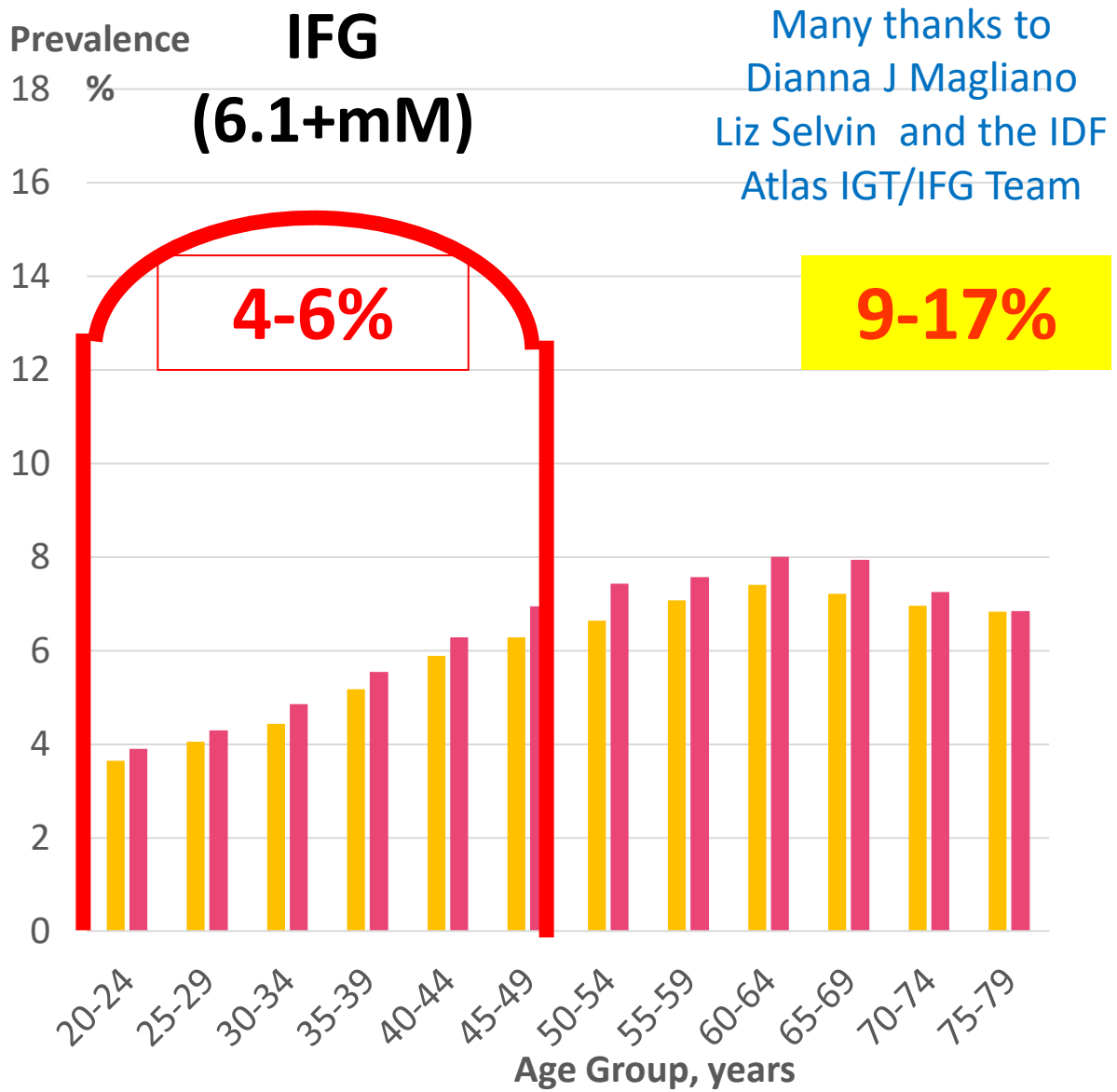
United States Public Health Service criteria were used to diagnose diabetes during the followup.

Source: Reference 81

IDF Diabetes Atlas 10th edition

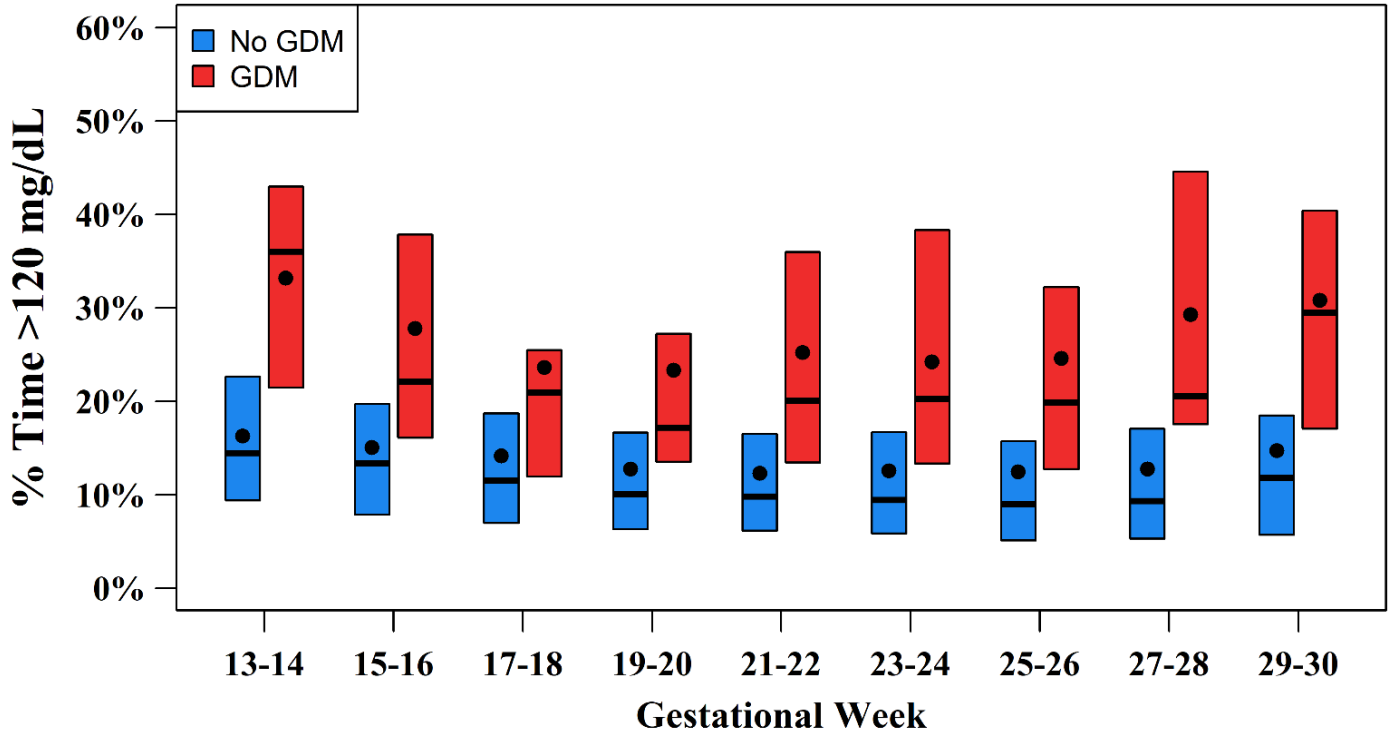
Prevalence of IGT/IFG by age in 2021 & 2045





Many thanks to
Dianna J Magliano
Liz Selvin and the IDF
Atlas IGT/IFG Team

Percent Time >120 mg/dL by Gestational Week and GDM Status



Durnwald; Diabetes Care, 2024

OBOGM Study

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What is actually happening:

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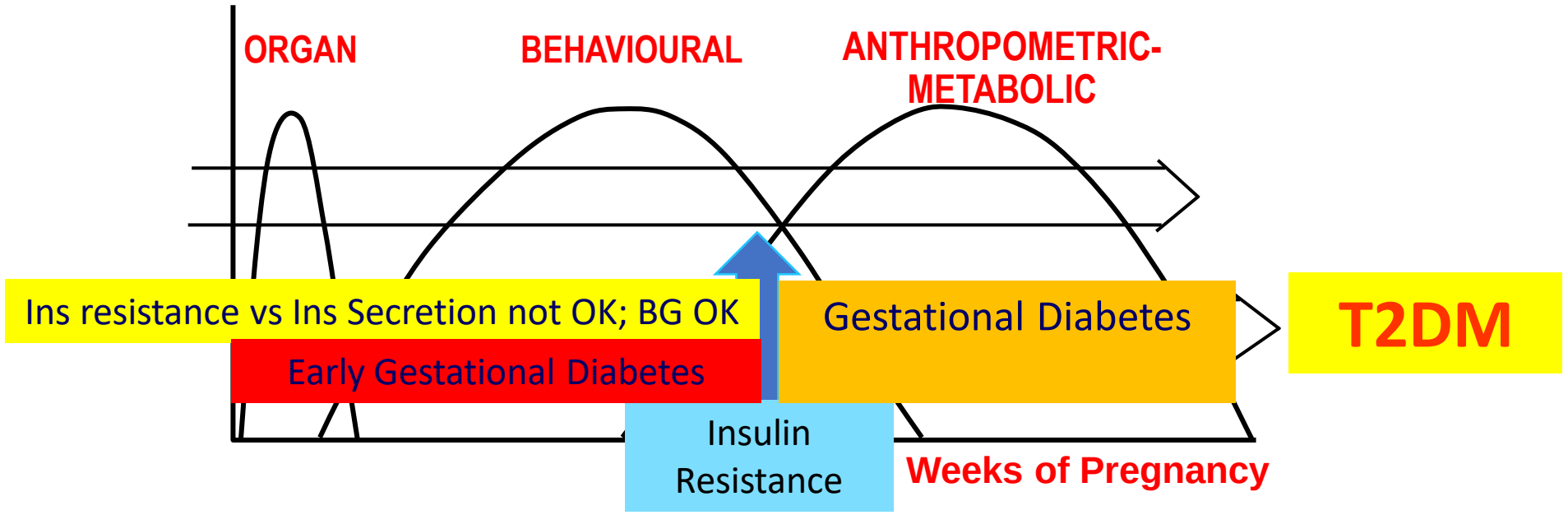
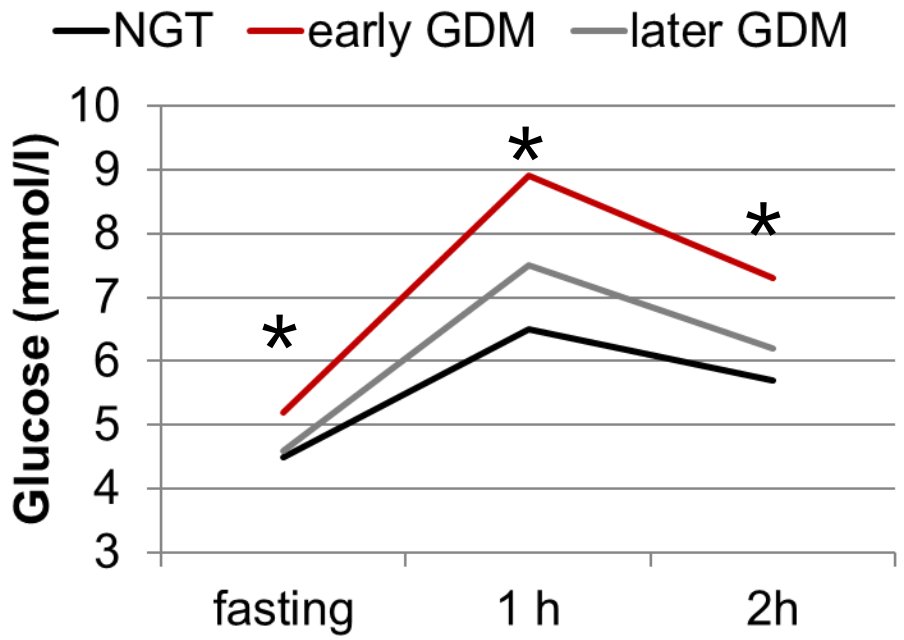
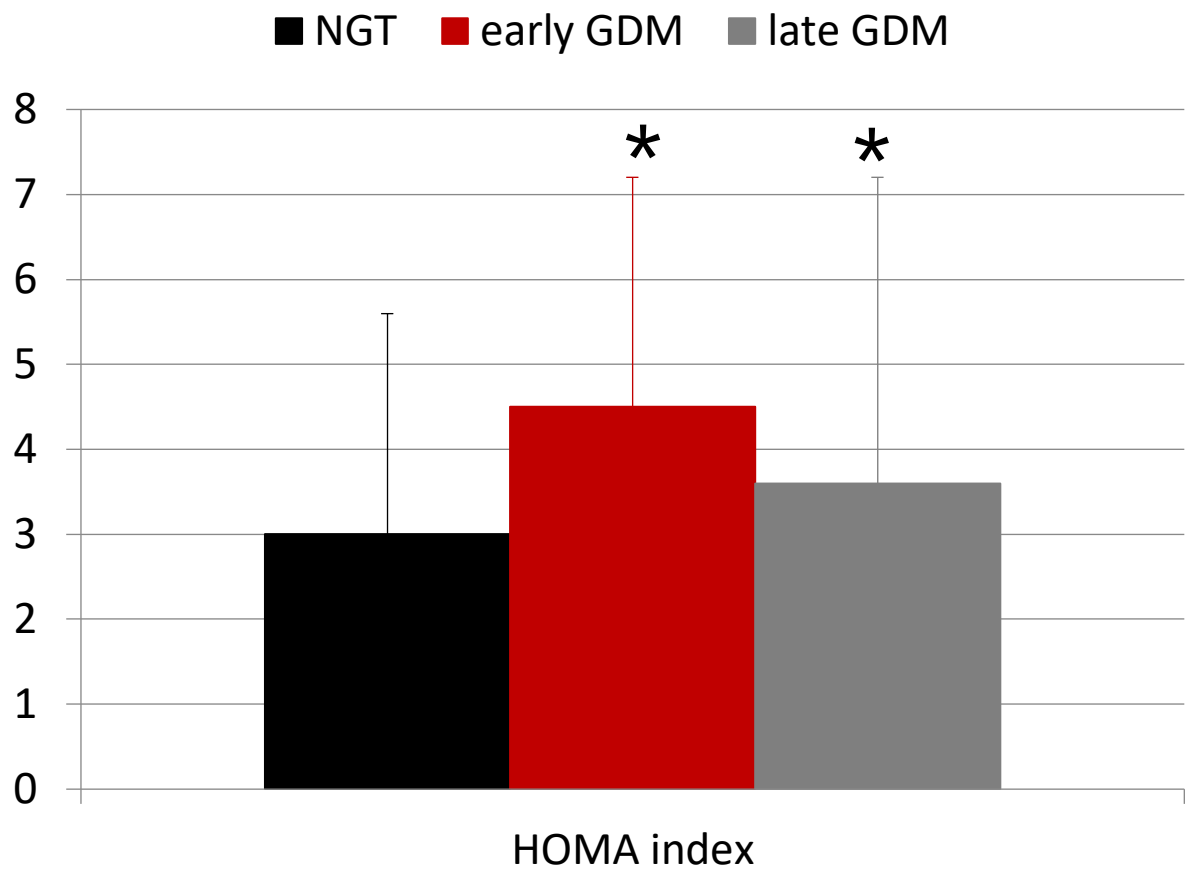


Freinkel 1980

Maternal Metabolic Characteristics





- Women with early GDM:
  - Higher first and second phase insulin response
  - Higher Waist, BP, triglycerides and free fatty acids

Harreiter et al. Diabetes Care 2016; 39: e90-e92; Egan et al. Diabetologia 2017; 60;1913–1921

Prevalent (Early) GDM: Comparison of pregnancy outcomes with late onset GDM women

Outcome Measure	No of studies (participants)	RR (95% CI) Random effect
Large for gestational age	7(9622)	1.07 (0.86 to 1.35)
Perinatal mortality	7 (9130)	3.58 (1.91 to 6.71)
Neonatal hypoglycemia	7(6818)	1.61 (1.02 to 2.55)
Neonatal intensive care unit admission	5(7992)	1.16 (0.90 to 1.49)
Insulin use	11(8103)	1.71 (1.45 to 2.03)
Small for gestational age	5(5900)	1.27 (0.92 to 1.75)
Hypertensive disorders in pregnancy	10(10091)	1.34(0.98 to 1.82)
Preterm delivery	7(7039)	1.16 (0.84 to 1.61)
Cesarean delivery	9(9685)	1.09(0.94 to 1.26)
Shoulder dystocia	2(2936)	1.76(0.96 to 3.24)

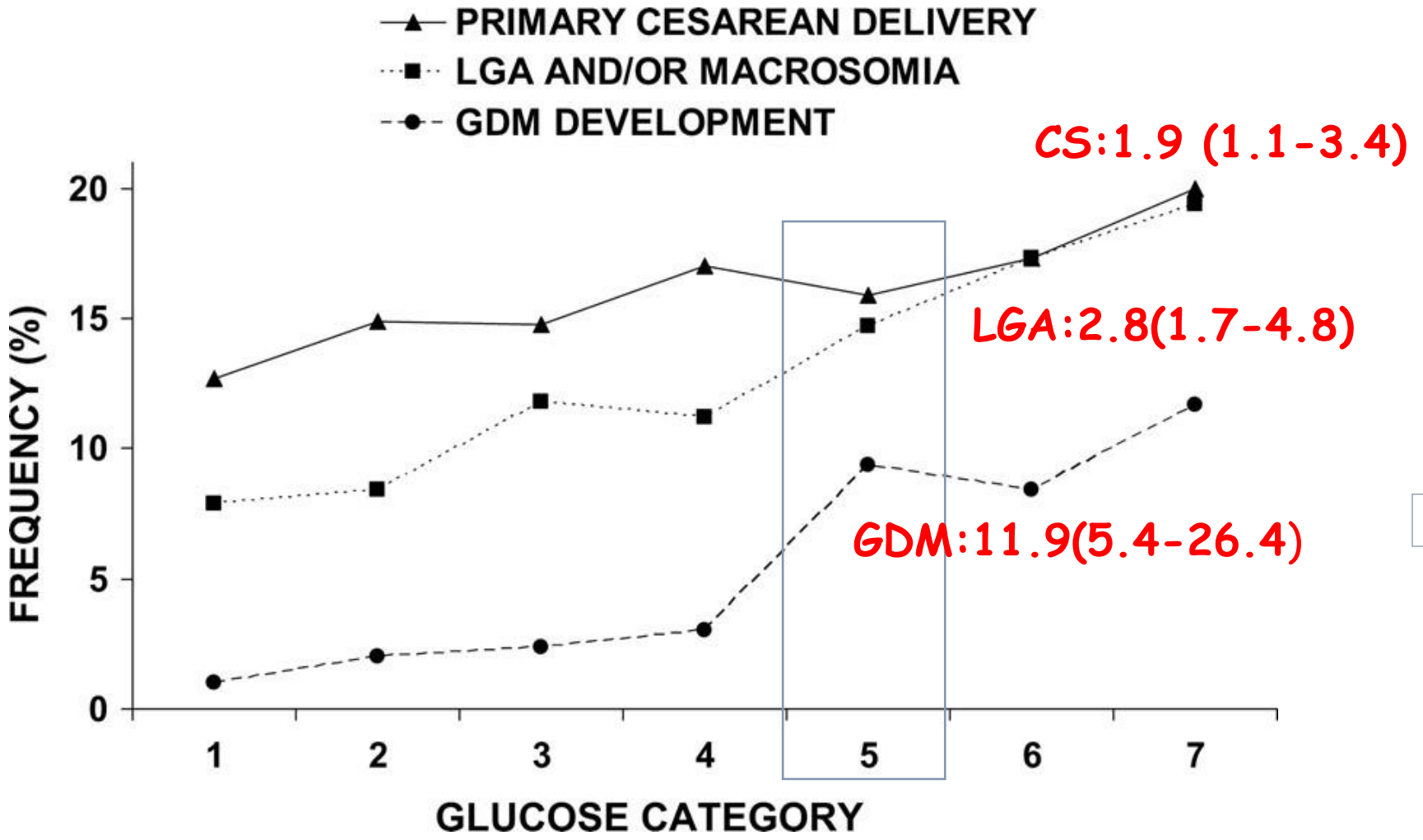
30-70%

All treated, so this is after treatment

Different OGTT criteria (but all used OGTT)

Immanuel, Simmons. Curr Diab Rep. 2017;17:115

The relationship between maternal first trimester glucose and frequency of adverse pregnancy outcomes



GA 9.5 weeks
n=6,129

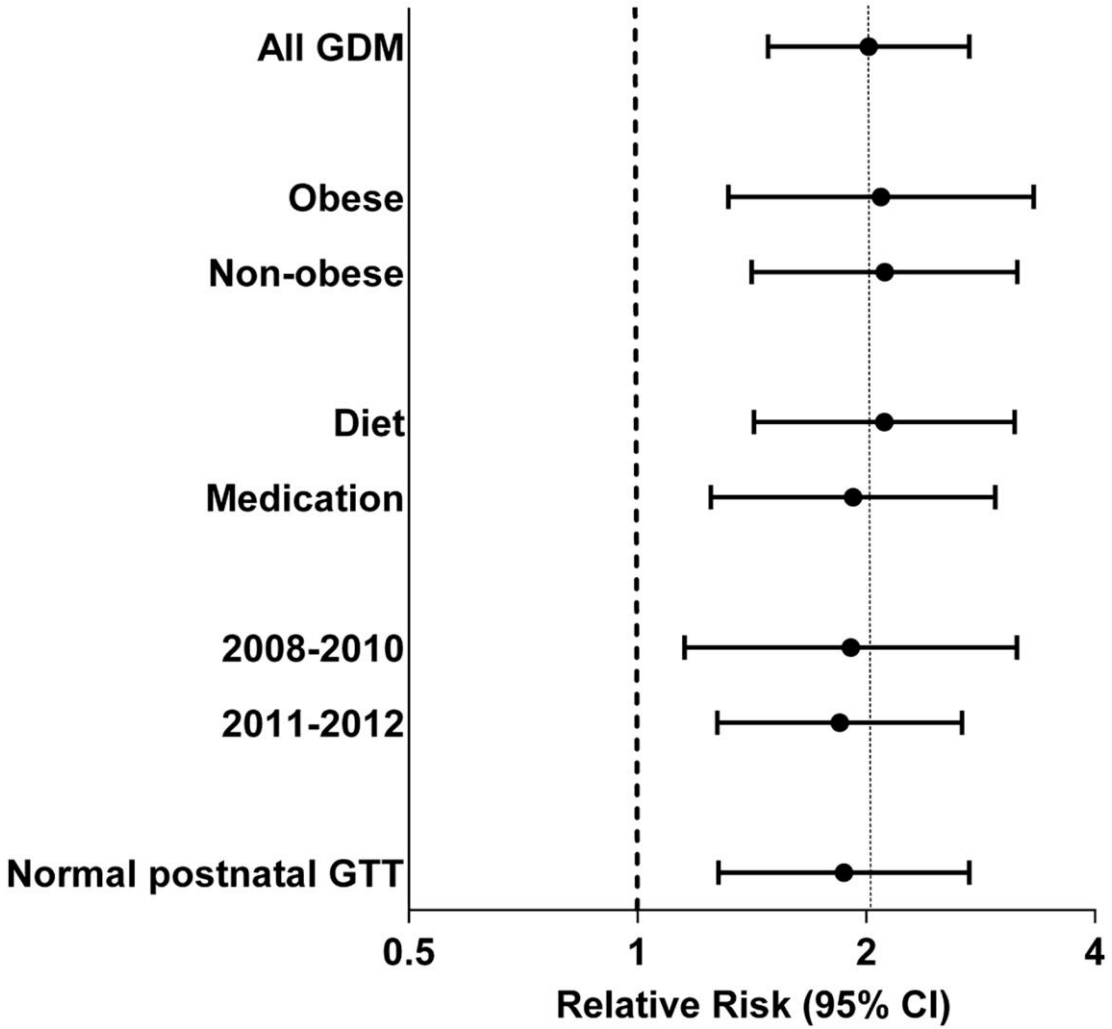
Fasting glucose categories:

1. < 4.2 mmol/L
2. 4.2-4.4 mmol/L
3. 4.4-4.7 mmol/L
4. 4.7-4.9 mmol/L
5. 4.9-5.2 mmol/L
6. 5.2-5.5 mmol/L
7. 5.5-5.8 mmol/L

Riskin-Mashiah et al. Diabetes Care 2010

Slide courtesy of A Sweeting

Stratified analysis of the association between GDM and abdominal circumference (AC) >90th percentile at 28 wkGA: 28/40 too late



But will treatment improve outcomes?

Ulla Sovio et al. Dia Care 2016;39:982-987

American Diabetes Association.

Treatment Of BOoking Gestational diabetes Mellitus Study

TOBOGM Hypothesis

Treatment of ‘booking GDM’

- Reduces the sequelae of maternal ‘hyperglycaemia’

OBOGM Study

Main Trial ACTRN12616000924459

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2023; 388:2132-2144 DOI: 10.1056/NEJMoa2214956

ORIGINAL ARTICLE

Treatment of Gestational Diabetes Mellitus Diagnosed Early in Pregnancy

D. Simmons, J. Immanuel, W.M. Hague, H. Teede, C.J. Nolan, M.J. Peek, J.R. Flack, M. McLean, V. Wong, E. Hibbert, A. Kautzky-Willer, J. Harreiter, H. Backman, E. Gianatti, A. Sweeting, V. Mohan, J. Enticott, and N.W. Cheung, for the TOBOGM Research Group*

This well-conducted trial provides much needed information regarding the benefits and harms of screening for and treating gestational diabetes in early pregnancy.

N Engl J Med 2023; 388:2132-2144
DOI: 10.1056/NEJMoa2214956

International (India, Sweden, Austria, Australia)
Multicentre single blinded RCT of treating early GDM from “booking” or from OGTT results at 24-28 weeks’ gestation

TOBOGM Sites

OBOGM Study

17th May 2017 through 31st March 2022, Last birth October 10th 2022 n=802 in RCT

Participants

Included

- Multicentre study-17 sites-Oz, Swe, India, Austria
- Women aged ≥18 years, Singleton pregnancy
- Risk factor for hyperglycemia in pregnancy
- OGTT between 4 and 19^{+6} weeks' gestation

Excluded from the RCT:

- Women with pre-existing diabetes, No GDM
- FBG 6.1+mM/2HBG 11.1+mM
- Major active medical disorders

ACTRN12616000924459

OBOGM Study

TOBOGM Study Design

Screened (n =43,721)

OGTTs performed before 20 weeks n=3672

DIP, FBG≥110 mg/dl Excluded From RCT

Early GDM Randomised into trial n=802

GDM Treatment

Rx Booking GDM (Intervention) n=406

Clinical team and patient notified of GDM diagnosis, early RX commenced

24-28/40 Rx: Birth outcomes Birth measures

No Treatment

No Rx Booking GDM (Controls) n=396

Clinical team and patient notified that GDM Rx is not required but that they have been selected to continue in the study

Rx if 24-28/40 GDM on OGTT Birth outcomes Birth measures (includes heelprick)

OBOGM Study

Results-Baseline data

Variables	Booking GDM-Intervention (N=400)		Booking GDM-Control (N=393)	
	n/N	%/	n/N	%/
Age (years)	400	32.1 ±4.8	393	32.6 ± 4.9
Ethnicity				
White European	150/399	37.6	166/391	42.5
South Asian	129/399	32.3	106/391	27.1
East Asian/SE Asian	51/399	12.8	60/391	15.3
Middle Eastern	32/399	8.0	17/391	4.3
Māori and Pacific	24/399	6.0	22/391	5.6
Islands Other (Aboriginal/ African/South American)	13/399	3.3	20/391	5.1

OBOGM Study

Results

Variables	Booking GDM-Intervention (N=400)		Booking GDM-Control (N=393)	
	n/N	%/	n/N	%/
BMI at first visit (kg/m^2)	399	32.1 ± 7.7	390	32.9 ± 8.4
OGTT < 14+0 weeks' gestation	104/400	26.0%	80/393	20.4%
HbA1c at 1st OGTT (%) (mmol/mol)	388	5.2 ± 0.3 (33.4 ± 3.7)	384	5.2 ± 0.3 (33.3 ± 3.4)

OBOGM Study

TOBOGM Results

GTT performed before 20 weeks and at 24-28 weeks

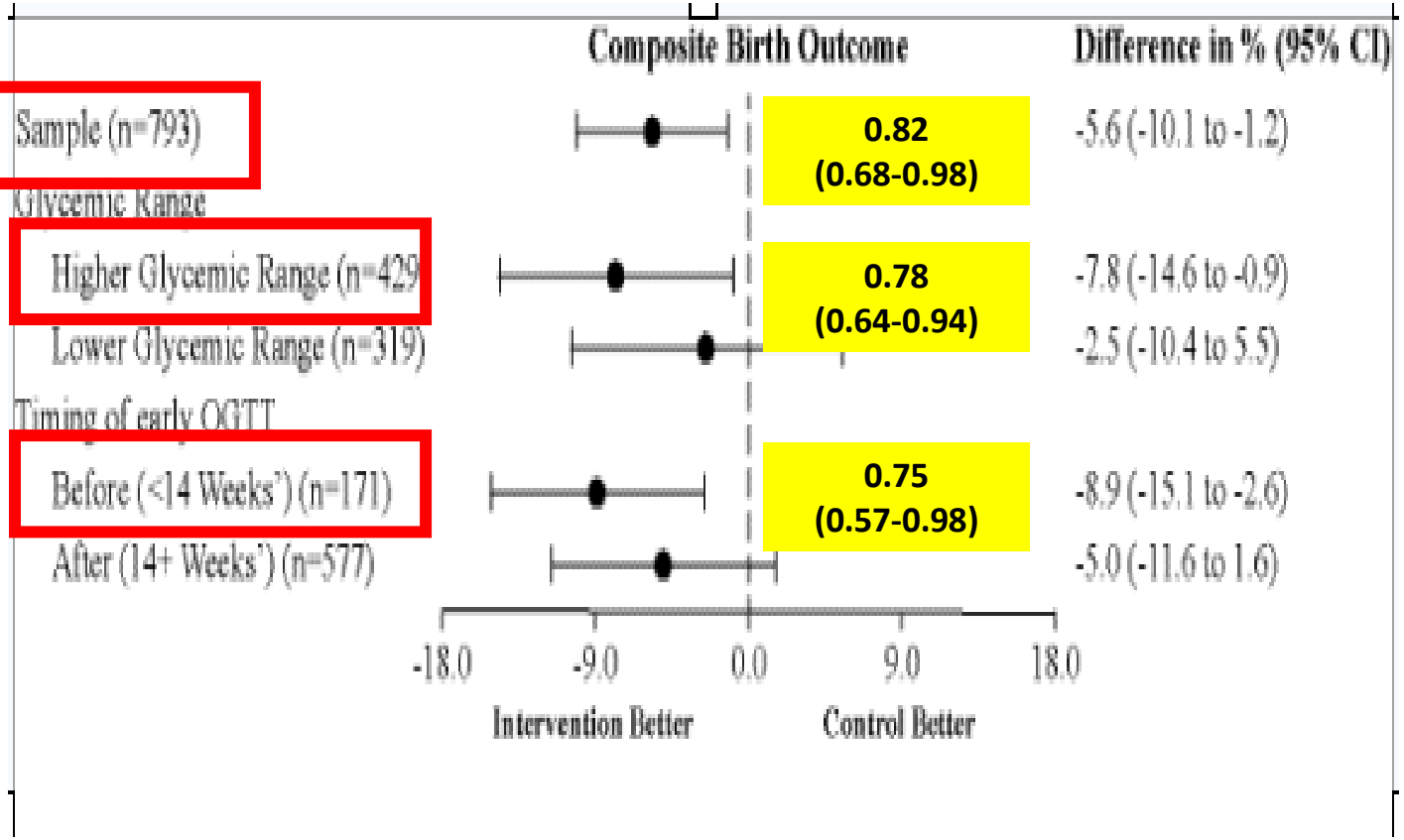
OBOGM Study

PO1: composite of

- Birth <37^{+0} weeks' gestation
- Birthweight ≥4500g
- Birth trauma (IADPSG criteria)
- Neonatal respiratory distress
- Need for phototherapy
- Stillbirth/neonatal death
- Shoulder dystocia

Higher=O.R 2.0
=5.3/10.6/9.0 mmol/L

Lower =O.R 1.75 not 2.0
Fasting BG 5.1–5.2mM
1-Hr glucose 10.0–10.5mM
2-Hr glucose 8.5–8.9 mM



NNT=18

NNT=13

NNT=11

Simmons et al, NEJM 2023

Vs 24-28 weeks gestation Treatment RCTs

GDM at 24+/40	Definition	Treated	Control
MFMUN	Not defined	1.9%	2.9%
ACHOIS	Need for supplemental oxygen in the neonatal nursery beyond four hours after birth	5%	4%
GEMS	Use of respiratory support	5.1%	5.6%
CDC4G	ICD-Respiratory distress (at least 4 hours' respiratory support with supplemental oxygen, continuous positive airway pressure, and/or intermittent positive pressure ventilation in the first 24 h after delivery)	0.83%	0.65%
CLS 02-08	Respiratory distress syndrome [RDS], Transient Tachypnea of newborn [TTN] (not defined)	RDS 4.0%+TTN 5.1%=9.1%	
TOBOGM	warranting ≥4 hrs of respiratory support with supplemental O2	9.8%	17.0%
More severe	Neonatal respiratory distress as above+ Stay in NICU>24 hours	6.3%	9.9%
RDS	Respiratory Distress with admission to neonatal intensive care unit for ≥24 hours with positive pressure ventilatory support for >4 hours.	1.8%	2.0%

Simmons et al. BJOG 2024

NICU Bed days

GDM Treatment	Intervention (n=400)	Control (n=393)
No Neonatal Respiratory distress	52.3% N=363	47.7% N=331
Neonatal Respiratory distress-No or ≤1 day in NICU/SCN	34.3% N=12	65.7% N=23
Neonatal Respiratory distress >1 day in NICU/SCN	39.1% N=25	60.9% N=39

P=0.019

	Adjusted Treatment effect
	Mean (95% CI)
	-0.78 Bed Days (-1.27 to -0.30)

NICU Bed days/Baby

	Adjusted Treatment effect
	%RR (95% CI)
	0.60 (0.41 to 0.89)

Total NICU Bed days

OBOGM Study

No Difference

- Neonatal hypoglycaemia
- LGA
- Lean mass

- PO2: hypertension in pregnancy- composite of:
  - Preeclampsia
  - Eclampsia
  - Gestational hypertension

OBOGM Study

Neonatal anthropometry

Variables	Adjusted Treatment effect
	Mean (95% CI)
Birthweight (g)	-72 (-128 to -17)
Sum of neonatal callipers (mm)	-1.4 (-2.2 to -0.5)

Perineal Injury

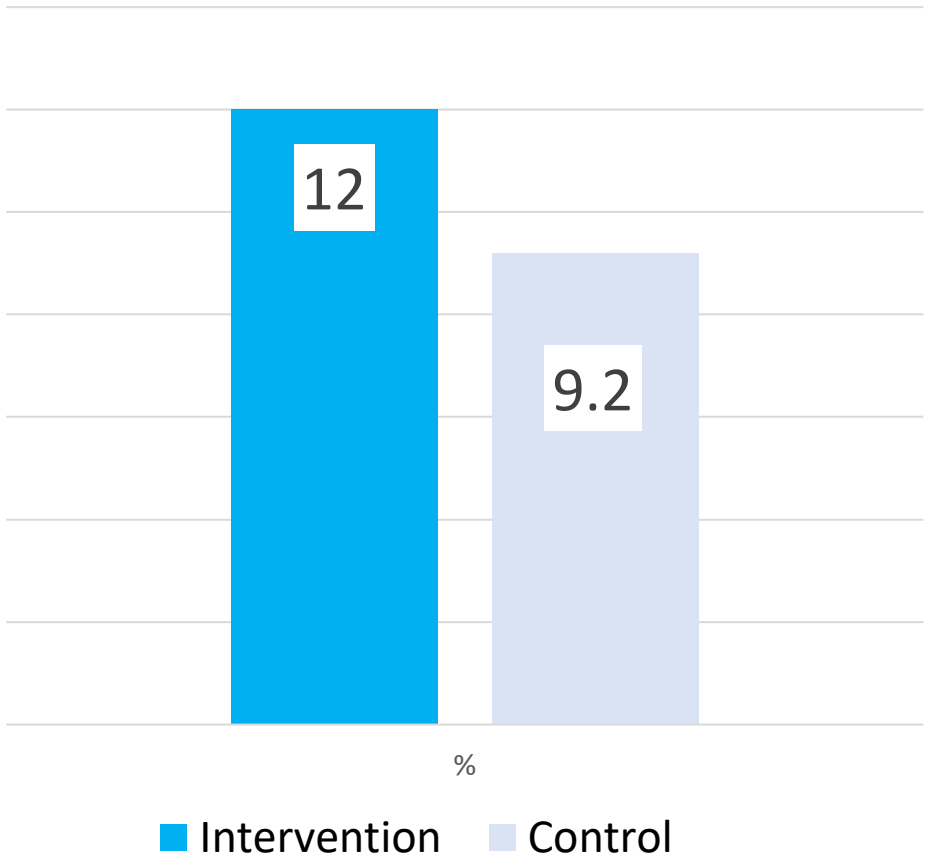
Adjusted treatment effect as difference in % (95% CI)
-2.79 (-4.12 to -1.46)

Adjusted treatment effect (95% CI) RR
0.23 (0.10 to 0.51)

(IADPSG: 3rd or 4th degree tear)

OBOGM Study

SGA



Adjusted treatment effect (95% CI) RR
1.32 (0.93 to 1.85)
1.75 (1.05 to 2.92)

Lower band

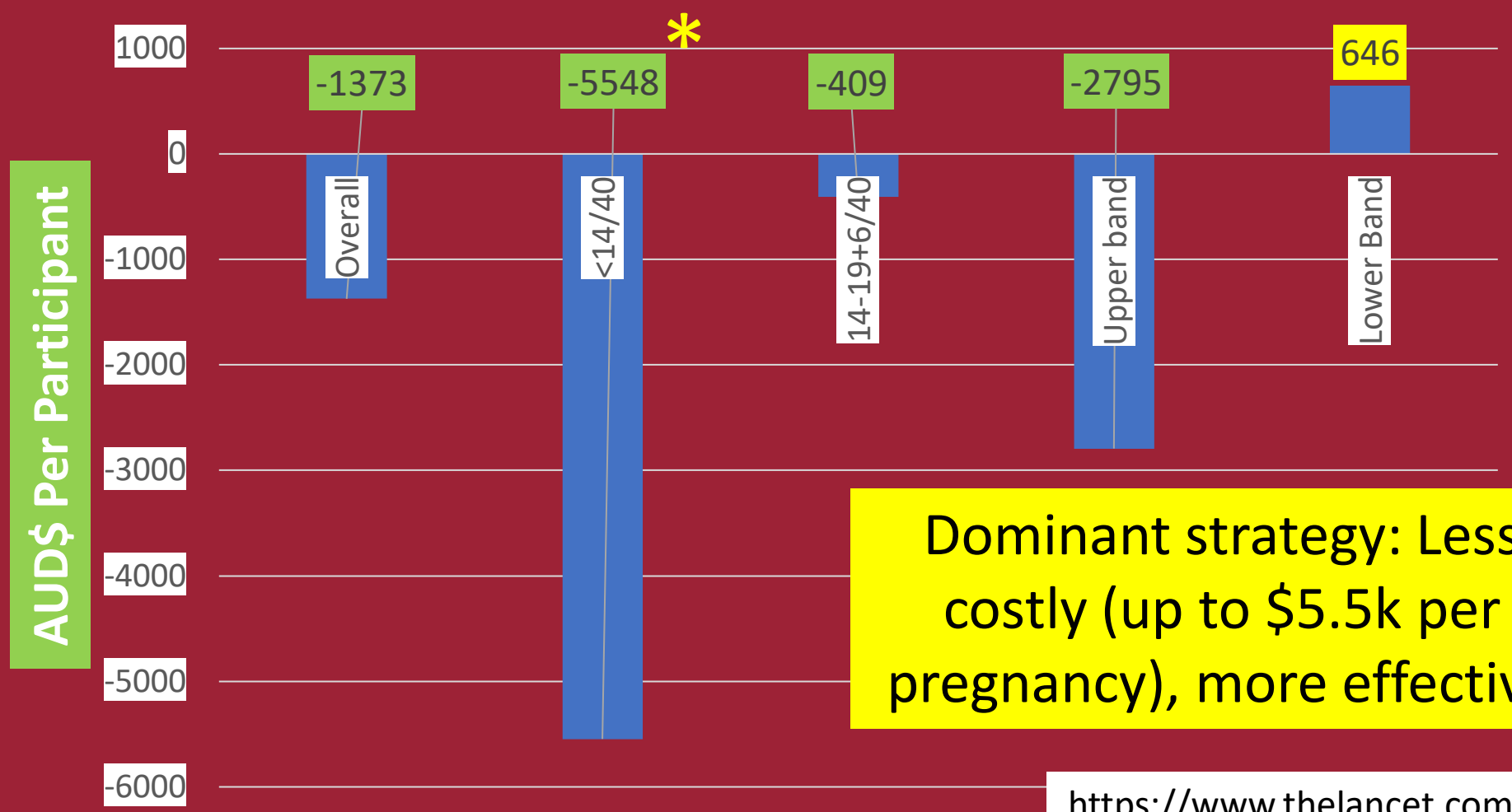
OBOGM Study

Using GROW to adjust for ethnicity, gestation, height, weight, parity

Increase (sig)
Early OGTT
SBGM, Meds
Endo, CDE, dietitian
OBGYN, ED

Decrease (non-sig)
Delivery
NICU/SCN

Cost-effectiveness within the RCT



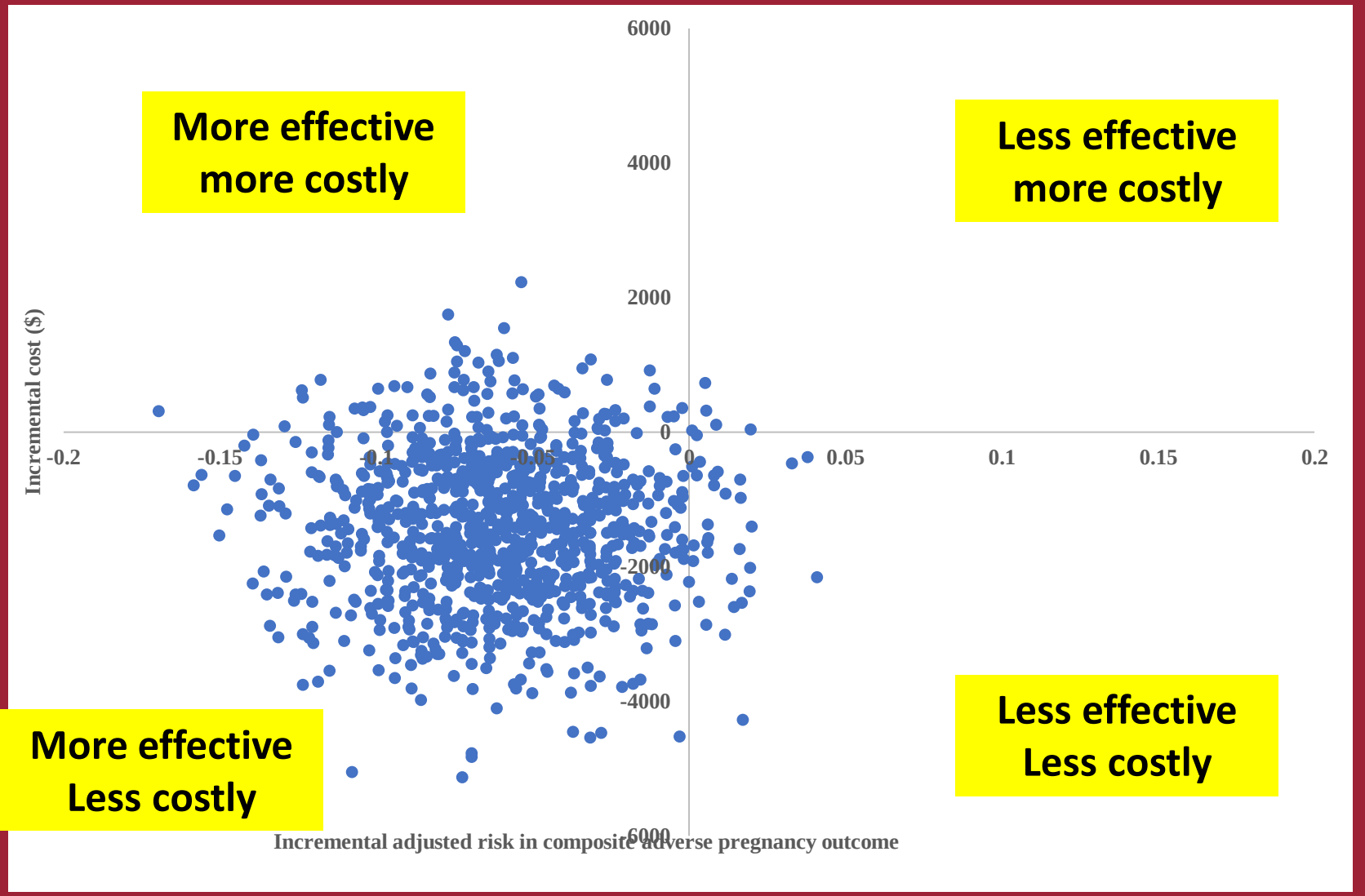
Dominant strategy: Less costly (up to $5.5k per pregnancy), more effective

*P<0.05

https://www.thelancet.com/pdfs/journals/eclinm/PIIS2589-5370(24)00189-5.pdf

OBOGM Study

Cost-effectiveness plane within the RCT



OBOGM Study

https://www.thelancet.com/pdfs/journals/eclinm/PIIS2589-5370(24)00189-5.pdf

Breastfeeding is improved to background with early treatment vs late

- **<u>Adjusted for all confounders including birth/neonatal</u>**
- No GDM 1
- Treated early GDM 0.96(0.66-1.38)
- Treated as late GDM 0.62(0.47-0.83)

OBOGM Study

Seifu et al. Diabetes Care. 2024 Mar 5:dc231635.

Some outcomes can not be reversed with late treatment

Mean (95%CI shown)	GDM on early and late OGTT and Rx late	GDM only on late OGTT and Rx'd	No Late GDM
Composite outcome	**1.59(1.18-2.12)**	1.19(0.94-1.50)	1

No difference in LGA, Ht in pregnancy, LSCS, phototherapy

Adjusting for prespecified factors of site,
age, pre-pregnancy BMI, ethnicity, current smoking, primigravidity, tertiary qualifications;

Simmons D et al, Diabetes Care. 2024 Feb 29:dc231667. doi: 10.2337/dc23-1667. Epub ahead of print. PMID: 38421672.

Summary-Early OGTT and Treatment if GDM

- ↓ 25% Composite (From 10-13+6/40)
  - Birth <37^{+0}/40; Birthweight ≥4500g; Shoulder dystocia;
  - Birth trauma; Neonatal respiratory distress ; Need for phototherapy; death
- ↓77% Perineal Injury (3^{rd}/4^{th} Deg' tears)
- ↓0.8 bed days NICU/SCN
- ↑73% SGA with lower glucose band
- ↑Quality of Life at 24-28/40
- ↑56% Breastfeeding initiation
- A$5548 saved per woman tested if before 14/40

Conclusion

- Treatment of gestational diabetes among women with risk factors before 20 weeks' gestation was effective especially 10-14 weeks' gestation and at
  - Fasting glucose 5.3–6.0 mmol/L
  - 1-hour glucose ≥10.6 mmol/L
  - 2-hour glucose 9.0–11.0 mmol/L

- Harm was suggested in the lower band (5.1mM, 10mM, 8.5mM)
- ADDRESSES neonatal metabolic consequences of early maternal hyperglycaemia not addressed by late treatment
- Follow up study needed-mother and offspring

For the 30-70% of women with early GDM, 24-28 weeks is too late-Yes! We should diagnose and treat!

OBOGM Study

Thanks to
Women participating and their families

TOBOGM project managers and research staff at each site

NHMRC (grants 1104231 and 2009326)
Region Örebro Research Committee, Sweden, Dnr OLL-970566, OLL-942177;
Medical Scientific Fund of the Mayor of Vienna, project 15205
South Western Sydney Local Health District Academic Unit Fund
Western Sydney University (Ainsworth Trust)

Central Team: Claudia Bishop, Lisa Vizza, Jodie Nema, Jincy Immanuel

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Professor Doctor Herbert Kiss
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OBOGM Study

Thank you

OBOGM Study