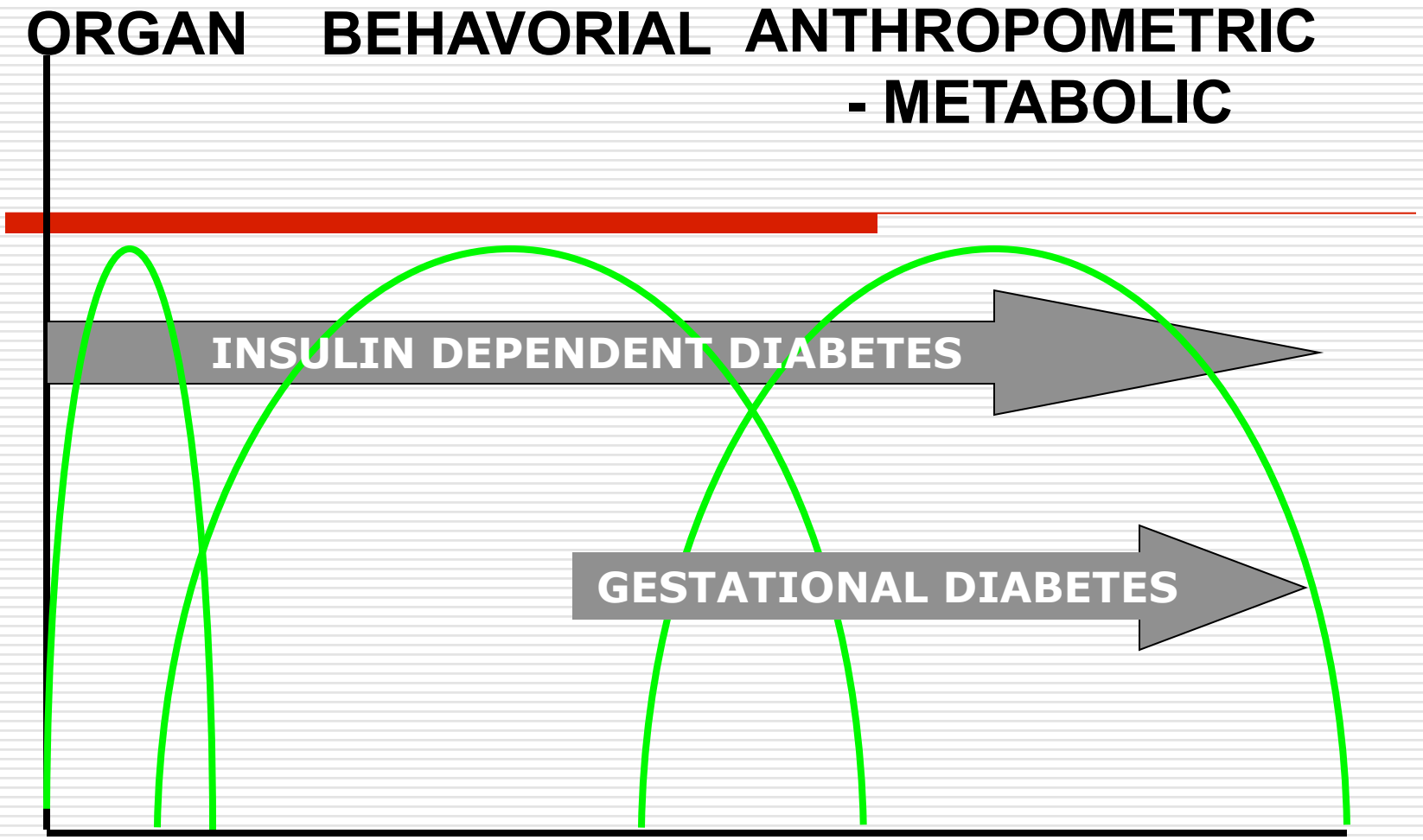
Risiko efter GDM

For barnet

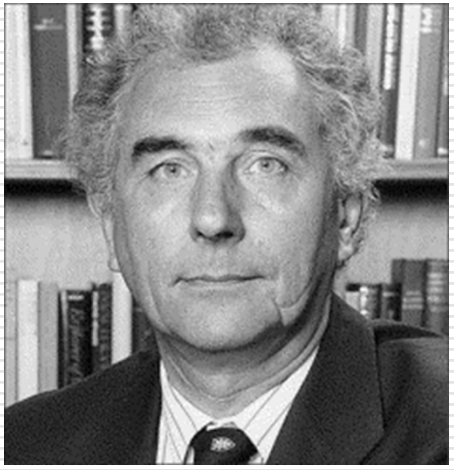
The obstetricians dream

Fuel-mediated teratology



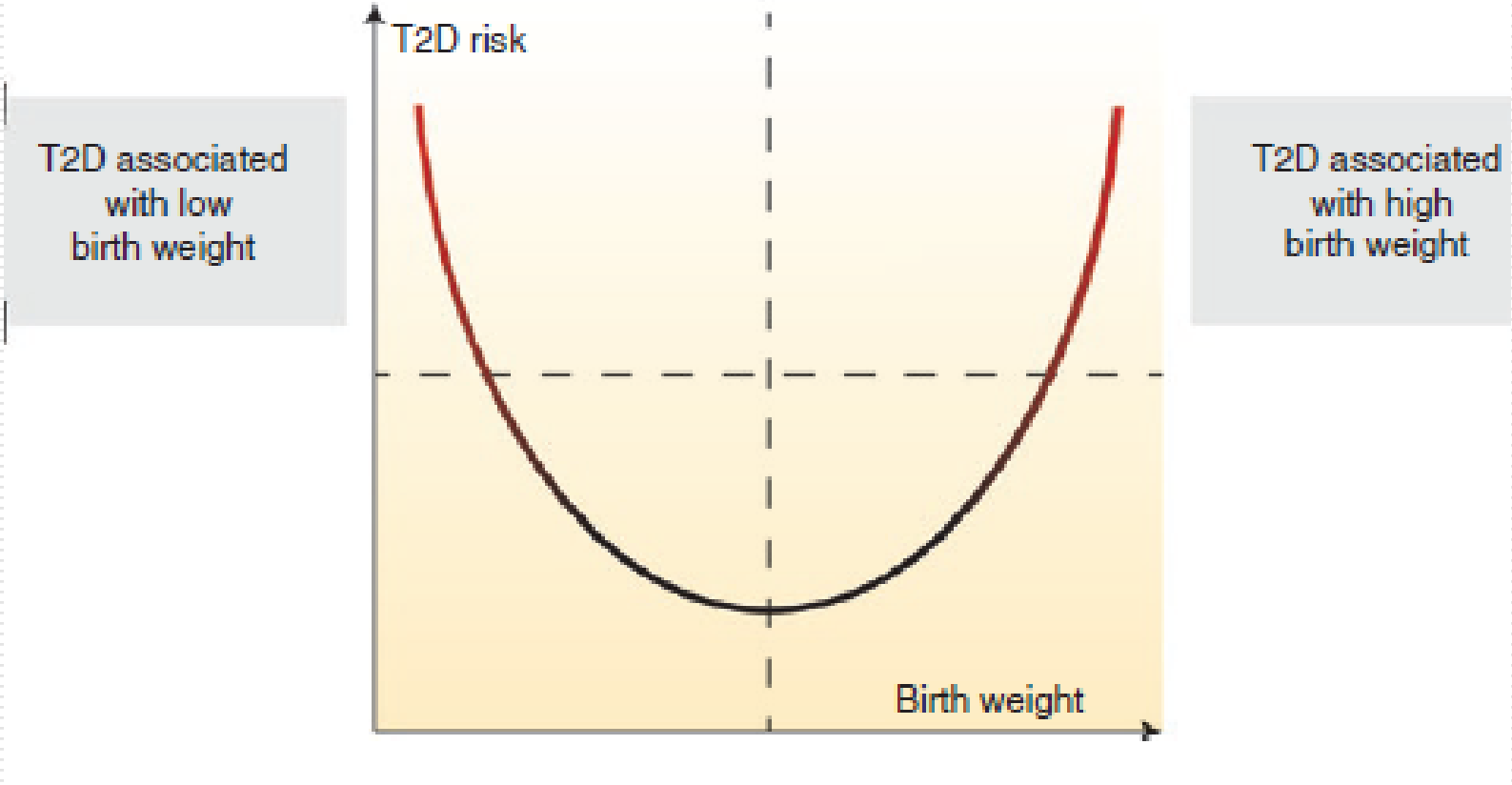
1980 Banting Lecture: "Of Pregnancy and Progeny", Freinkel, Diabetes 1980

Long-lasting consequences of the fetal environment



Hales and Barker, Br Med Bull 2001
Hales and Barker, BMJ 1991

Birthweight and risk of T2D

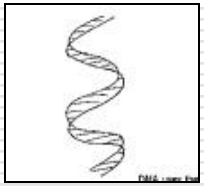


Drong AW et al, Clin Pharmacol Ther, 2015

Agenda

- Follow-up of offspring exposed to maternal diabetes during intrauterine life
- Focus on maternal gestationel diabetes (GDM) and type 1 diabetes
  - Metabolic consequences
  - Cognitive function

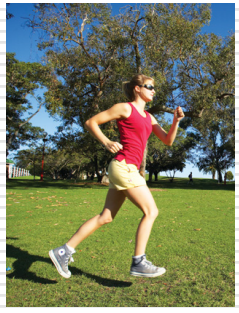
Developmental origin of health and disease



Epigenetics

Genes

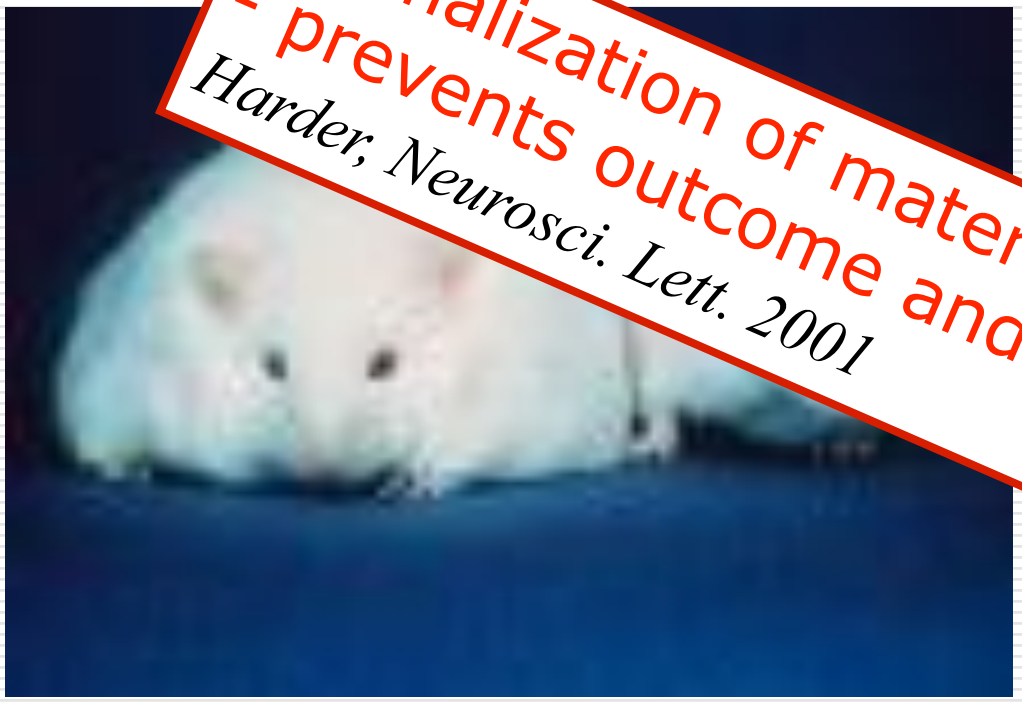
Intrauterine environment



Postnatal environment

Many players
Difficult to control for in clinical studies

Animal studies
(Aerts, Harder, Plagemann)



Harder, Neurosci. Lett. 2001

Normalization of maternal glucose
- prevents outcome and structural changes

Mild maternal diabetes during pregnancy ~ offspring

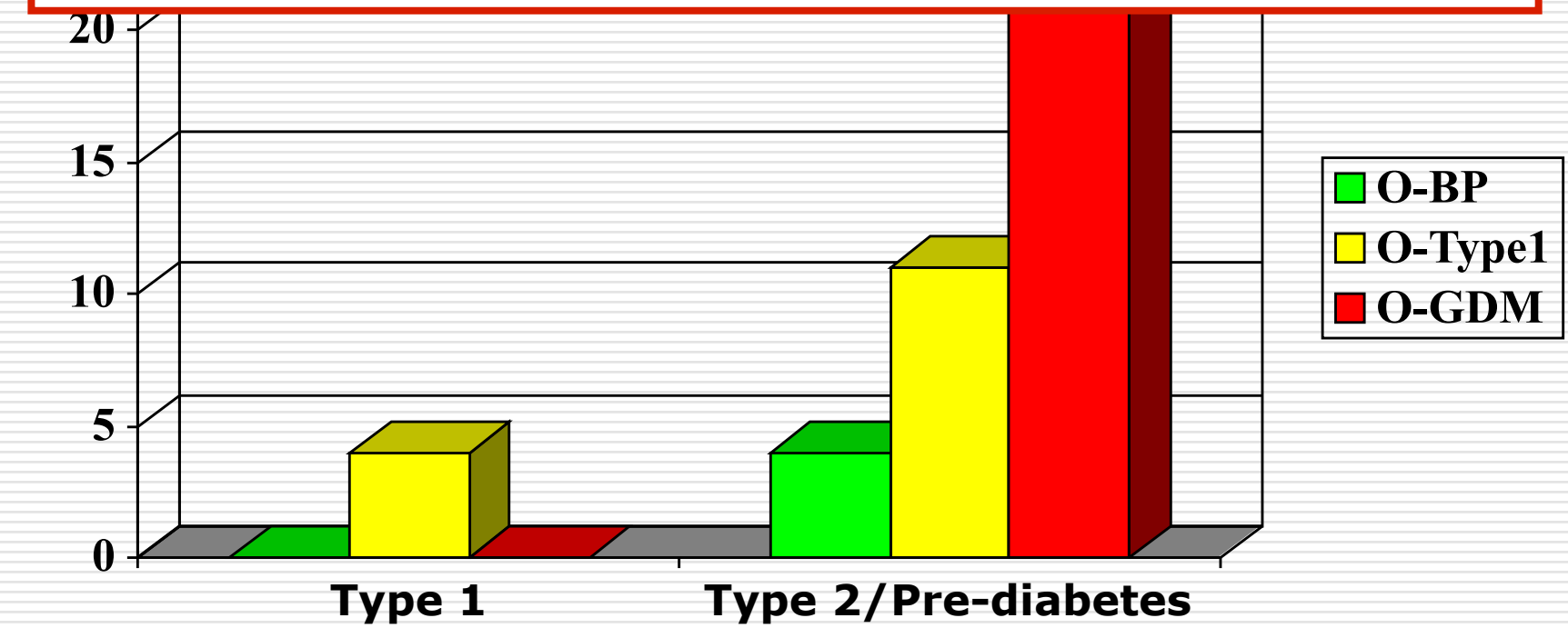
- 2 diabetes
- istance
- ris
- Gestation
- Structural chan
hypothalamus

Diabetes and pre-diabetes

8-fold increased risk in O-GDM vs O-BP
4-fold increased risk in O-Type1 vs O-BP

(Type 1 diabetes)

The higher risk in the offspring

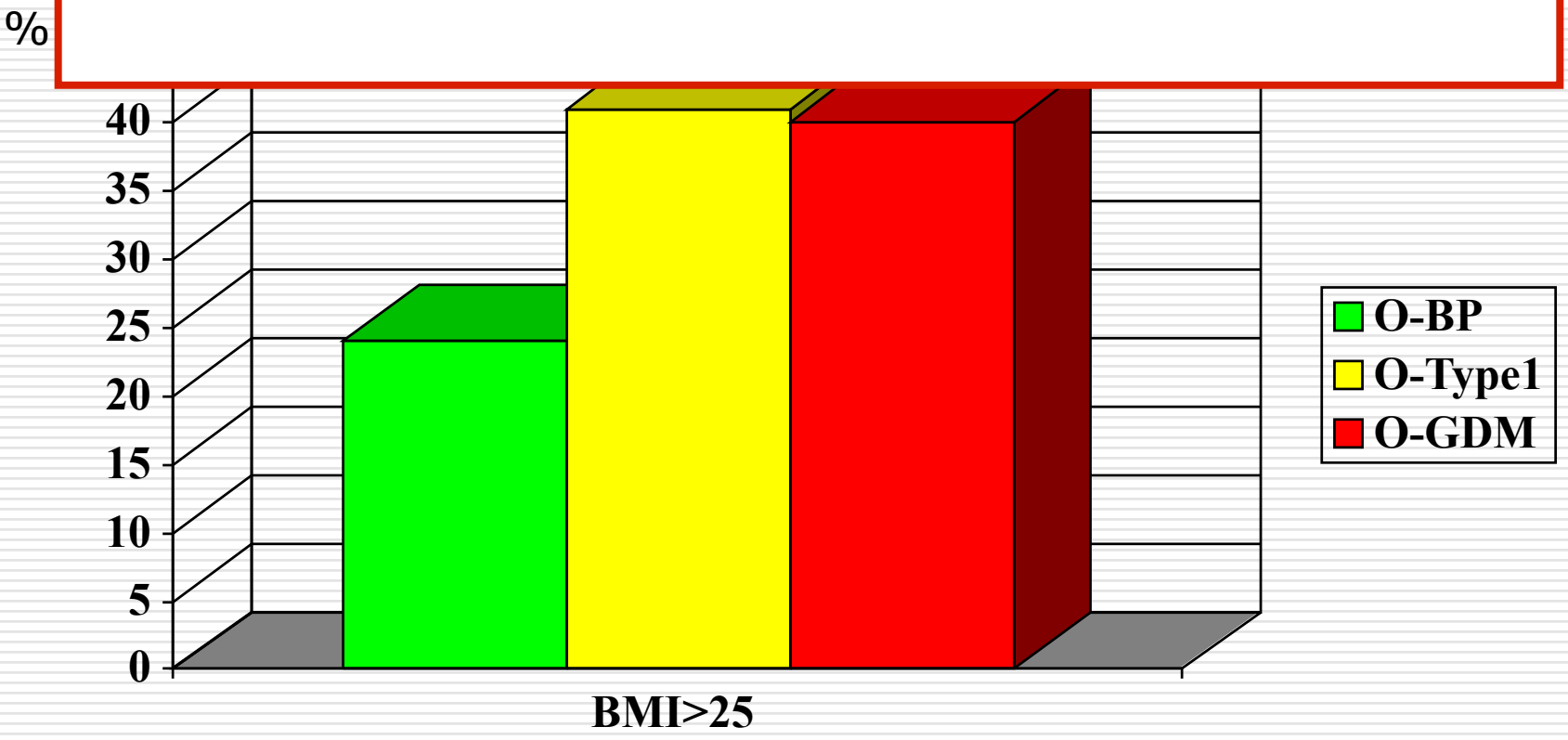


Clausen et al, Diabetes Care 2008

Overweight + the metabolic syndrome

Overweight

2-fold increased risk in both O-GDM and O-Type1 vs O-BP

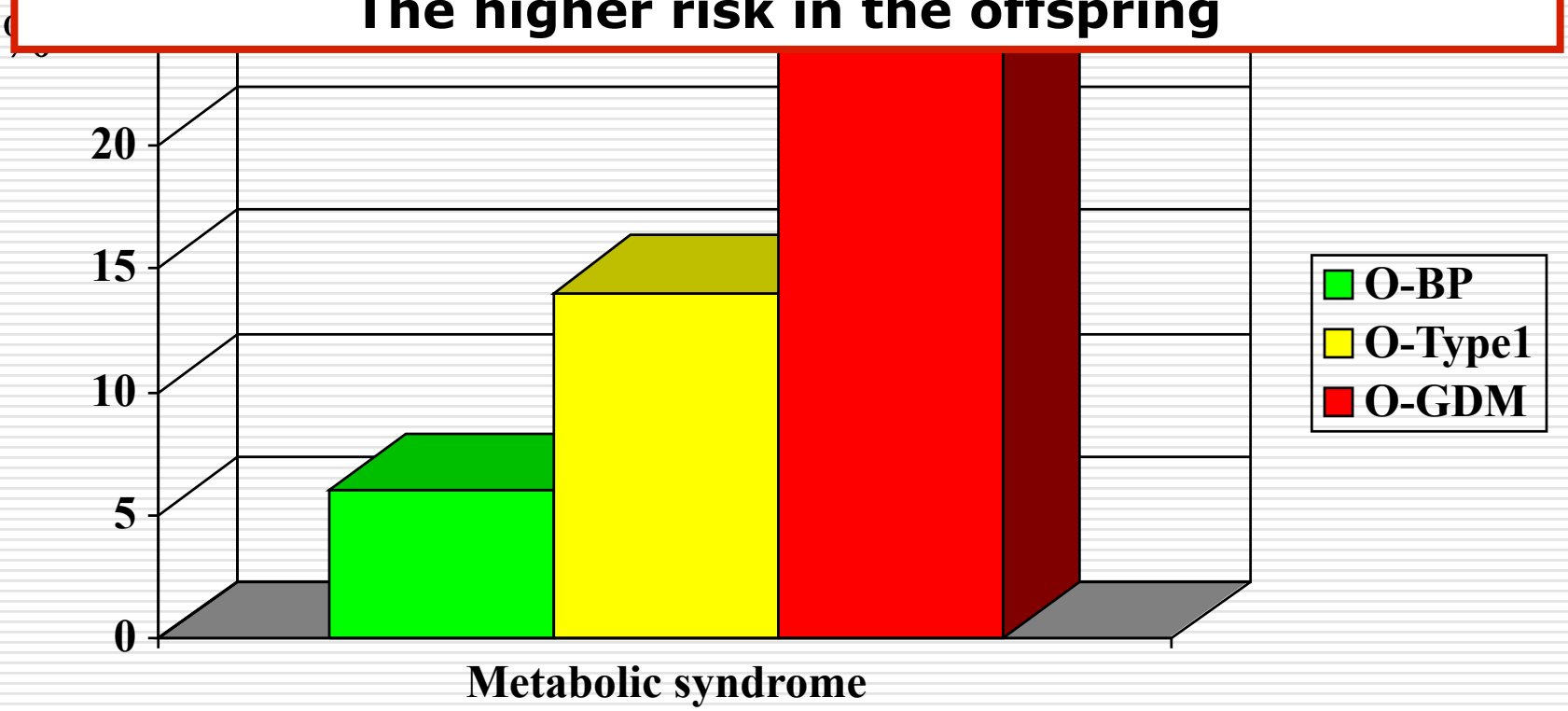


Clausen et al, JCEM 2009

The metabolic syndrome

4-fold increased risk in O-GDM vs O-BP
2-fold increased risk in O-Type1 vs O-BP

The higher risk in the offspring



Clausen et al, JCEM 2009

Another recent Danish study from the Danish National Birth Cohort

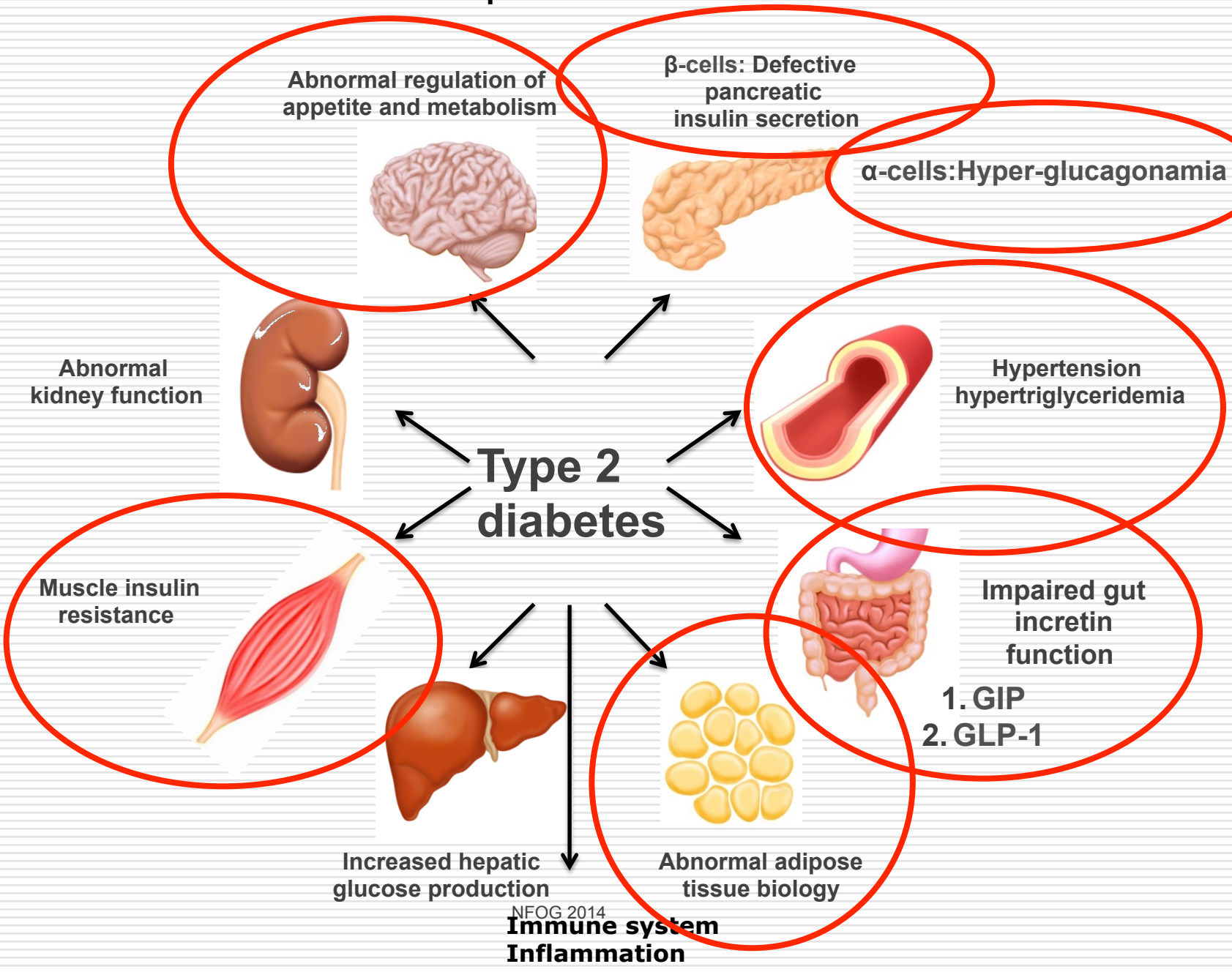
Grunnet et al. Diabetes Care 2017

Danish National Birth Cohort (DNBC) 1996-2002 - N=91748 pregnant women

	GDM offspring	Control offspring	β or ratio (95% CI)	p
	N=546-561	N=590-597		
Age (years)	12.1	12.8	-	
Weight (kg)	48.5	47.2	4.66 (3.48, 5.84)	**<0.001**
Height (cm)	156.8	159.5	1.15 (0.27, 2.03)	**0.01**
BMI (kg/m²)	18.8	17.9	9% (7-11%)	**<0.001**
Waist circumference (cm)	73.3	69.9	4.92 (3.87, 5.98)	**<0.001**
Hip circumference (cm)	83.8	82.7	3.47 (2.55, 4.39)	**<0.001**
Systolic BP (mmHg)	109.7	109.5	1.04 (0.06, 2.01)	**0.04**
Diastolic BP (mmHg)	62.5	62.6	-0.20 (-0.92, 0.51)	0.58

Grunnet et al, Diabetes Care 2017

Perspectives

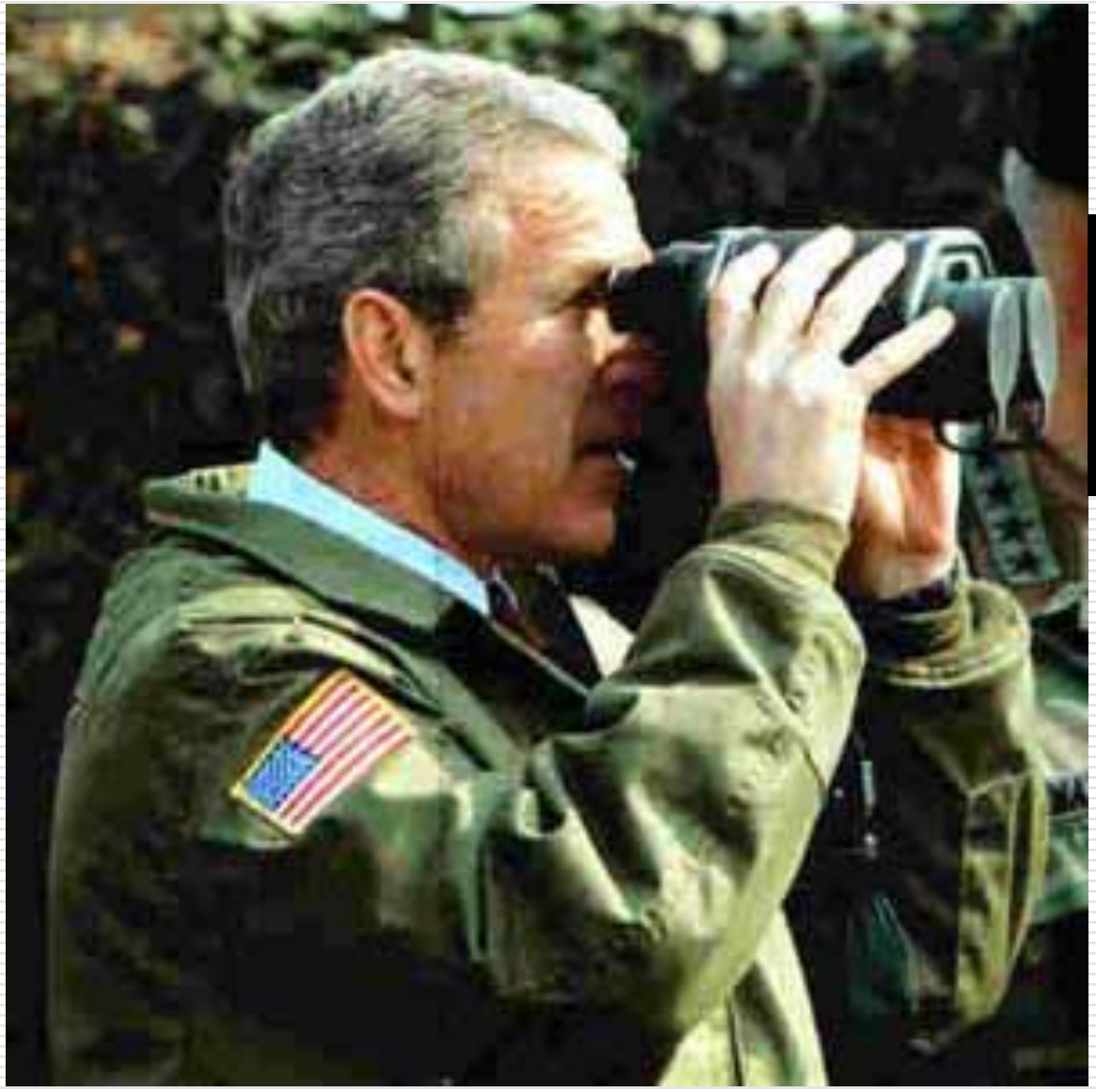


Can treatment of GDM affect the longterm prognosis of the offspring ?

- Follow-up of RCT is needed

Can GDM treatment in pregnancy affect the longterm offspring outcome?

- **No, maybe, yes**



Blinded testing of cognitive function

Clausen et al., PLOSone 2013

Results

GDM vs. background

	O-GDM	O-BP	P
Offspring cognitive score	93.1	100	**<0.001**
M			**001**
			1

No difference in cognitive score when adjusted for socioeconomic status and parental education

Maternal fasting and 2 hour glucose were inversely and significantly associated with offspring cognitive function. However no difference in cognitive score was present when adjusted for socioeconomic status and parental education

Clausen et al., PLOSone 2013

The Journal of Clinical Endocrinology & Metabolism, 2021, Vol. XX, No. XX, 1–11
doi:10.1210/clinem/dgab451
Clinical Research Article

Clinical Research Article

Academic Performance in Adolescents Born to Mothers With Gestational Diabetes—A National Danish Cohort Study

Gerda Ferja Heldarskard,[1,2,3,*] Anne Lærke Spangmose,[1,3,*] Anna-Karina Aaris Henningsen,[1,3] Rikke Wiingreen,[3,4,5] Erik Lykke Mortensen,[6] Tina Wullum Gundersen,[2,3] Rikke Beck Jensen,[3,7] Sine Knorr,[8] Peter Damm,[3,9] Julie Lyng Forman,[10] Anja Pinborg,[1,3] and Tine Dalsgaard Clausen[2,3]

4,286 O-GDM, 501,045 O-BP

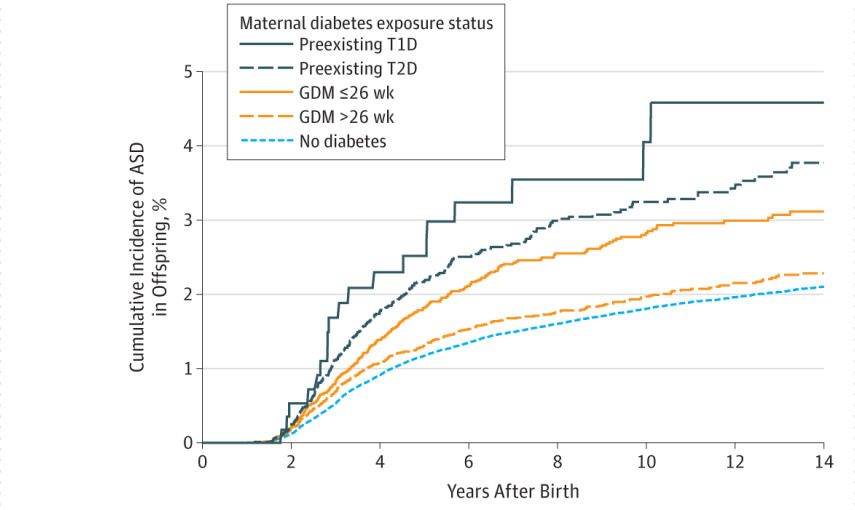
Conclusions

- O-GDM vs. O-BP
  - Gradepoint avarage ↓ (-0.36, Cohen´s D 0.14)
  - Prob. High grade point avarage ↓
  - Finising school ↓

Conclusion: Academic performance in O-GDM was marginally lower than in O-BP. However, this difference is unlikely to be of clinical importance.

From: **Maternal Type 1 Diabetes and Risk of Autism in Offspring**

JAMA. 2018;320(1):89-91. doi:10.1001/jama.2018.7614



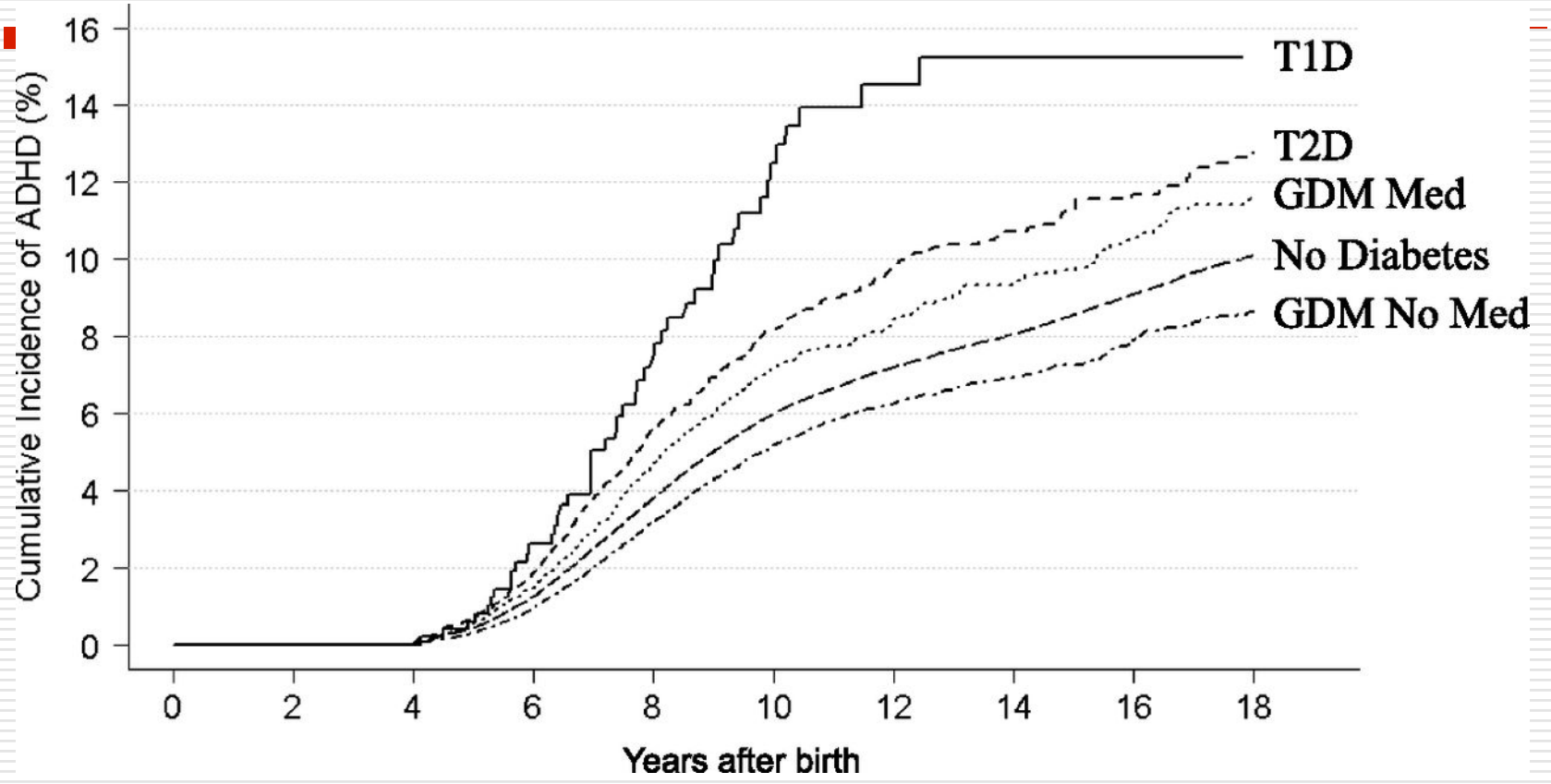
No. at risk

Preexisting T1D	621	553	457	358	272	185	129	91
Preexisting T2D	9453	8532	7090	5370	3758	2592	1864	1318
GDM ≤26 wk	11922	10717	8929	7091	5114	3749	2772	2039
GDM >26 wk	24505	21827	17675	14245	10671	8067	5972	4385
No diabetes	372924	328403	262775	209827	160590	122655	93264	69753

Figure Legend:

Unadjusted Cumulative Incidence of ASD in Offspring by Maternal Diabetes Exposure In UteroASD indicates autism spectrum disorder; GDM, gestational diabetes mellitus; T1D, type 1 diabetes; T2D, type 2 diabetes. ASD includes autistic disorders, Asperger syndrome, or pervasive developmental disorder not otherwise specified.

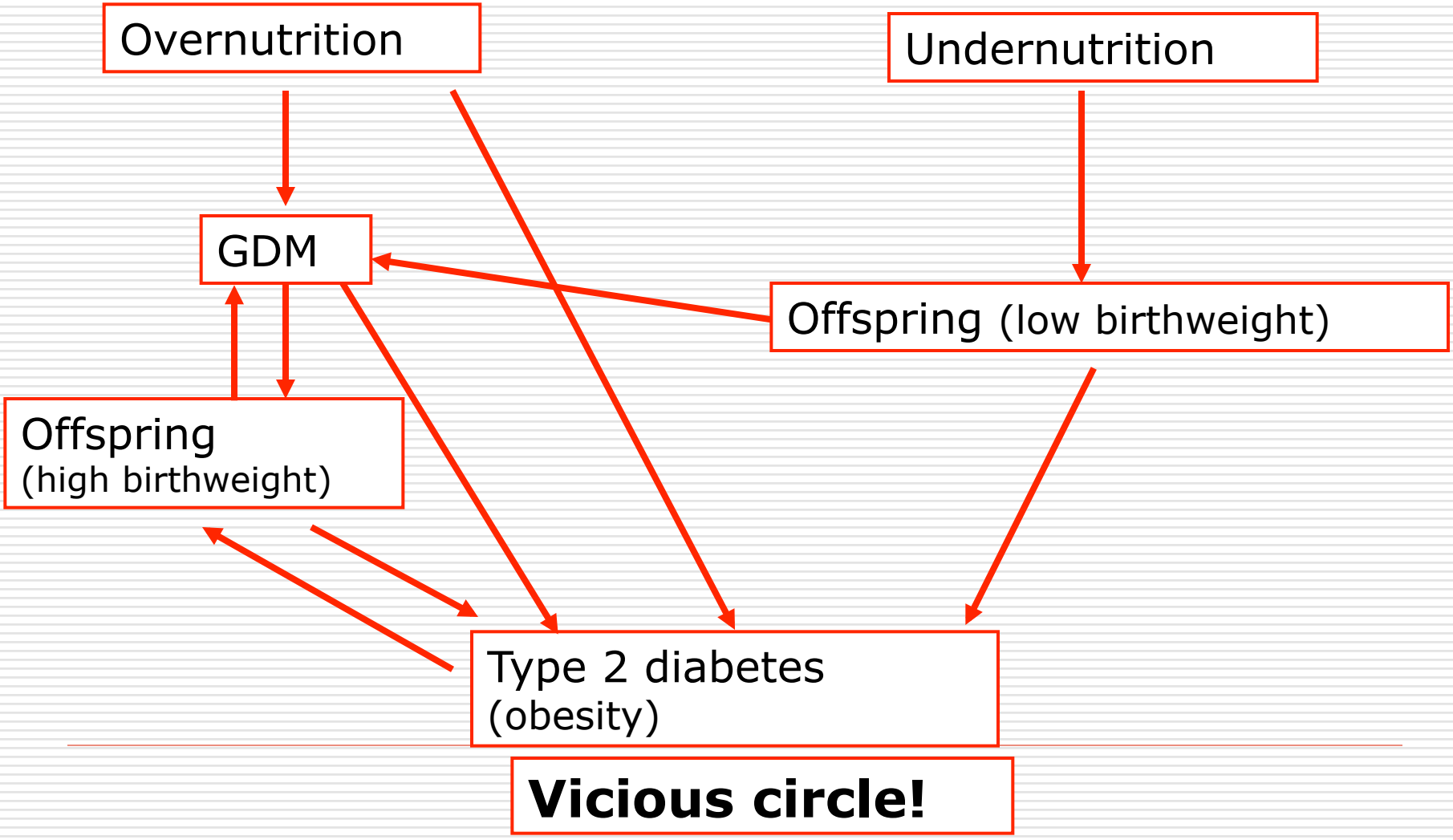
Crude cumulative incidence of ADHD by diabetes exposure in utero: preexisting T1D, preexisting T2D, GDM with dispensed antidiabetes medications during pregnancy (GDM Med), GDM without dispensed antidiabetes medications during pregnancy (GDM No Med), and no diabetes.



Anny H. Xiang et al. Dia Care 2018;41:2502-2508

American Diabetes Association.

Global perspective



Longterm implications intrauterine exposure to hyperglycemia

- Risk groups for **type 2 diabetes/pre-diabetes**, **overweight** and the **metabolic syndrome**
  - A hyperglycemic intrauterine environment seems to play a role
    - in addition to other factors
- Lower cognitive scores
  - But differences seems primarily explained by confounders in offspring of GDM
- Offspring longterm complications might be prevented by optimal treatment of maternal GDM – solid evidence is currently lacking
- GDM most likely plays a significant role in the global diabetes epidemic

The obstetricians dream

Thanks for your attention