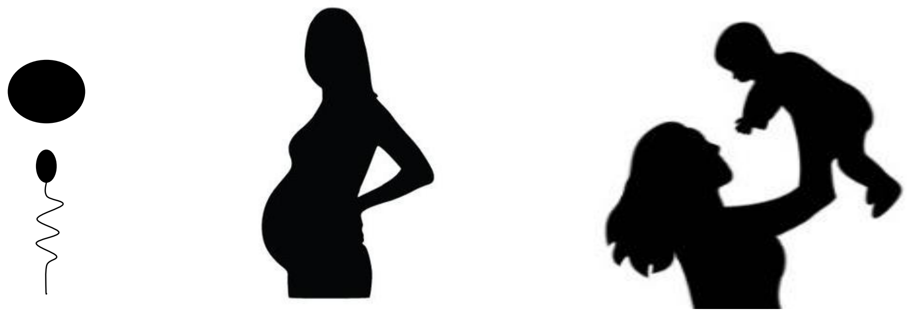
Gestational Diabetes – a nutritional disorder?



Dr Claire Meek

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Diabetes UK Harry Keen Intermediate Clinical Fellow

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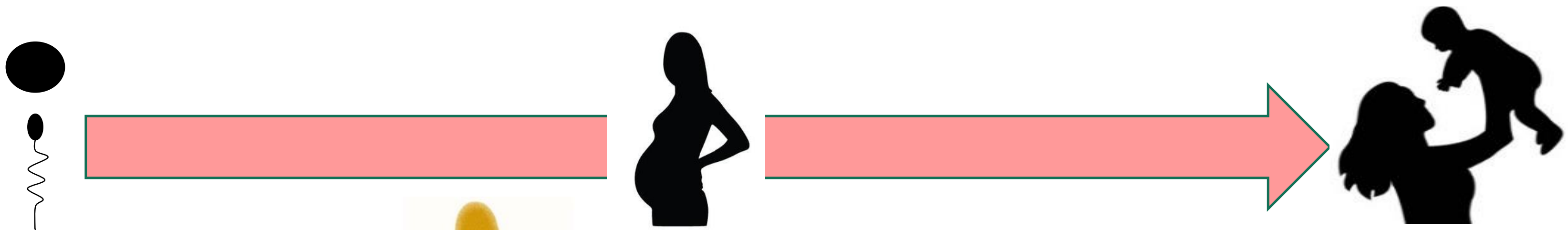
Maternal Metabolism: Studies in Pregnancy Diabetes



Gift

Ophelia

DiGest

DAiSIeS

CONCEPTT

Overall Aims:

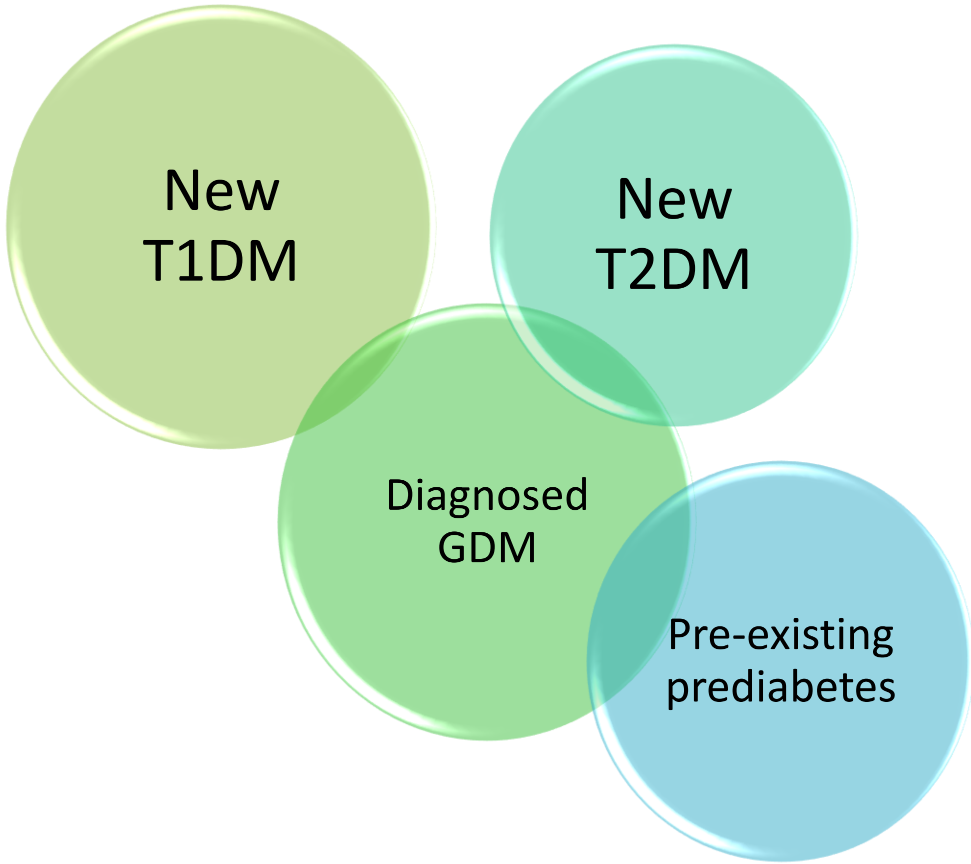
To identify causes and consequences of diabetes in pregnancy

To improve the diagnosis and management of diabetes in pregnancy

Gestational Diabetes – a nutritional disorder?

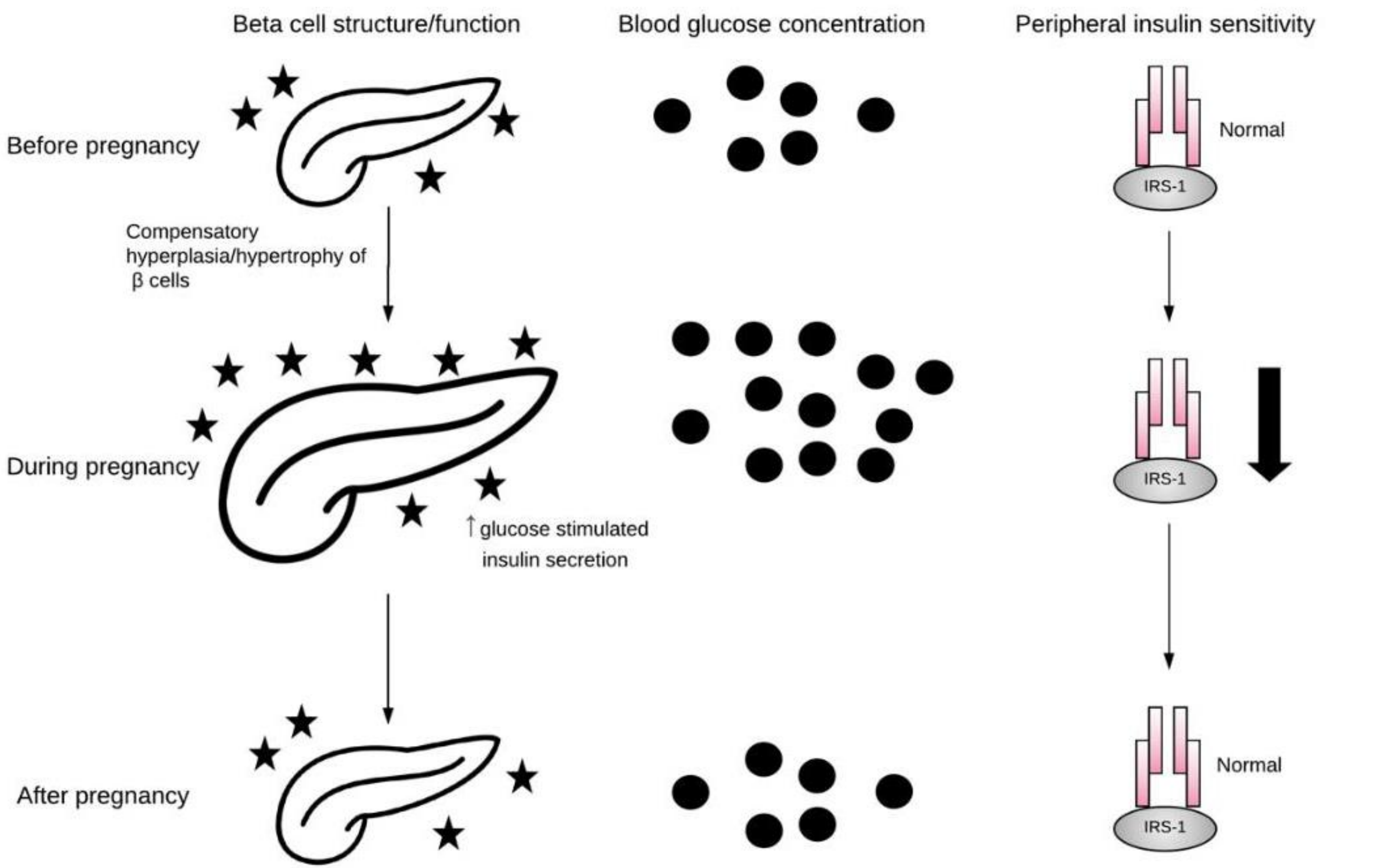
- Gestational diabetes (GDM)
  - Definition
  - Nutrition – a cause of GDM?
  - Nutrition – a tool in GDM management?
  - Nutrition – a tool to improve offspring outcomes?
  - Nutrition – a tool to reduce maternal T2DM risk long-term?
  - Conclusions

GDM = Hyperglycaemia with first onset or recognition in pregnancy



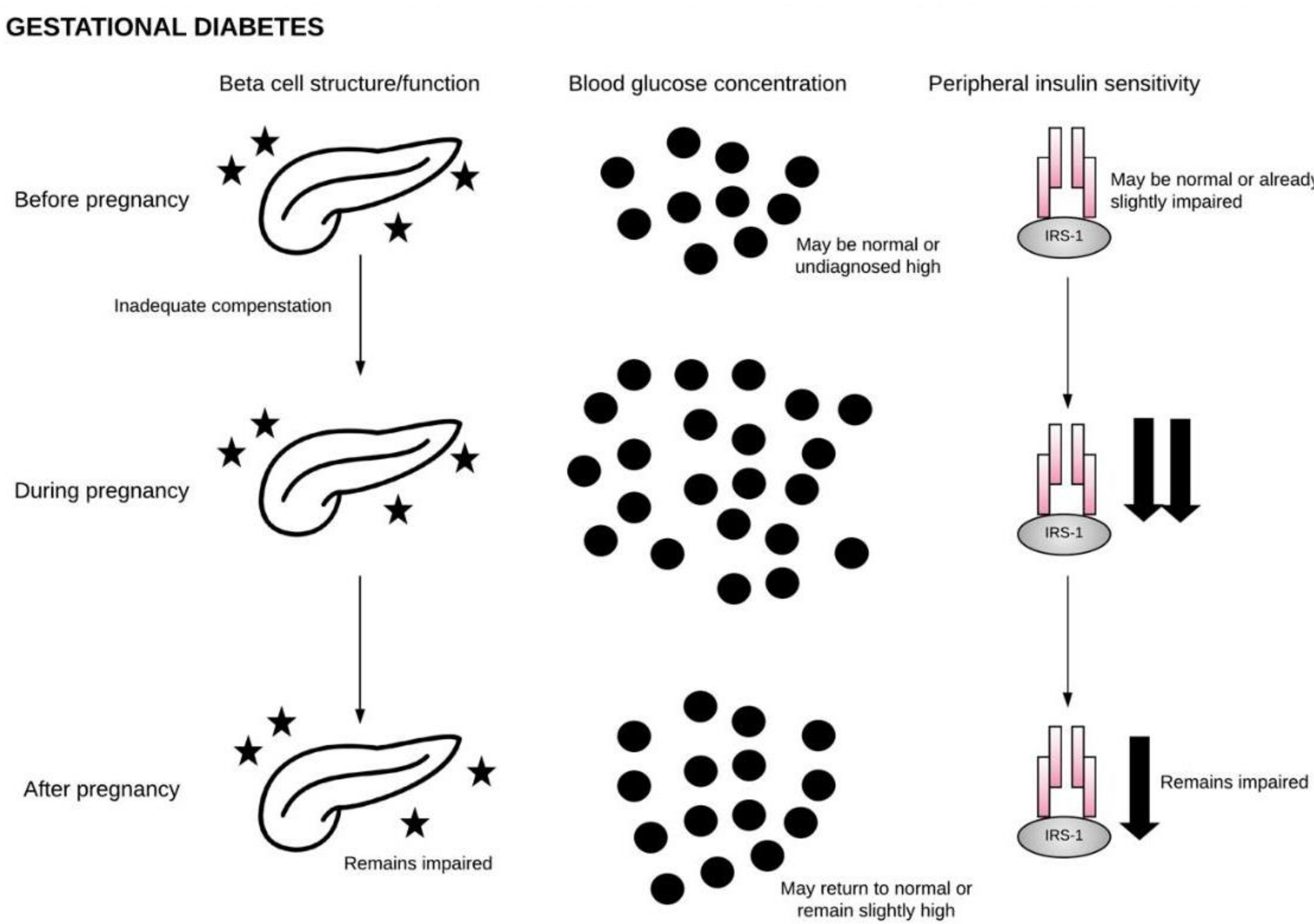
'True' GDM = Inability to increase insulin secretion sufficiently to maintain normoglycaemia during insulin resistance in pregnancy.
Background of subtle abnormal glucose homeostasis before pregnancy but less marked than diabetes or pre-diabetes.

Healthy pregnancy



Plows et al., The Pathophysiology of Gestational Diabetes Mellitus Int J Mol Sci 2018

Gestational diabetes



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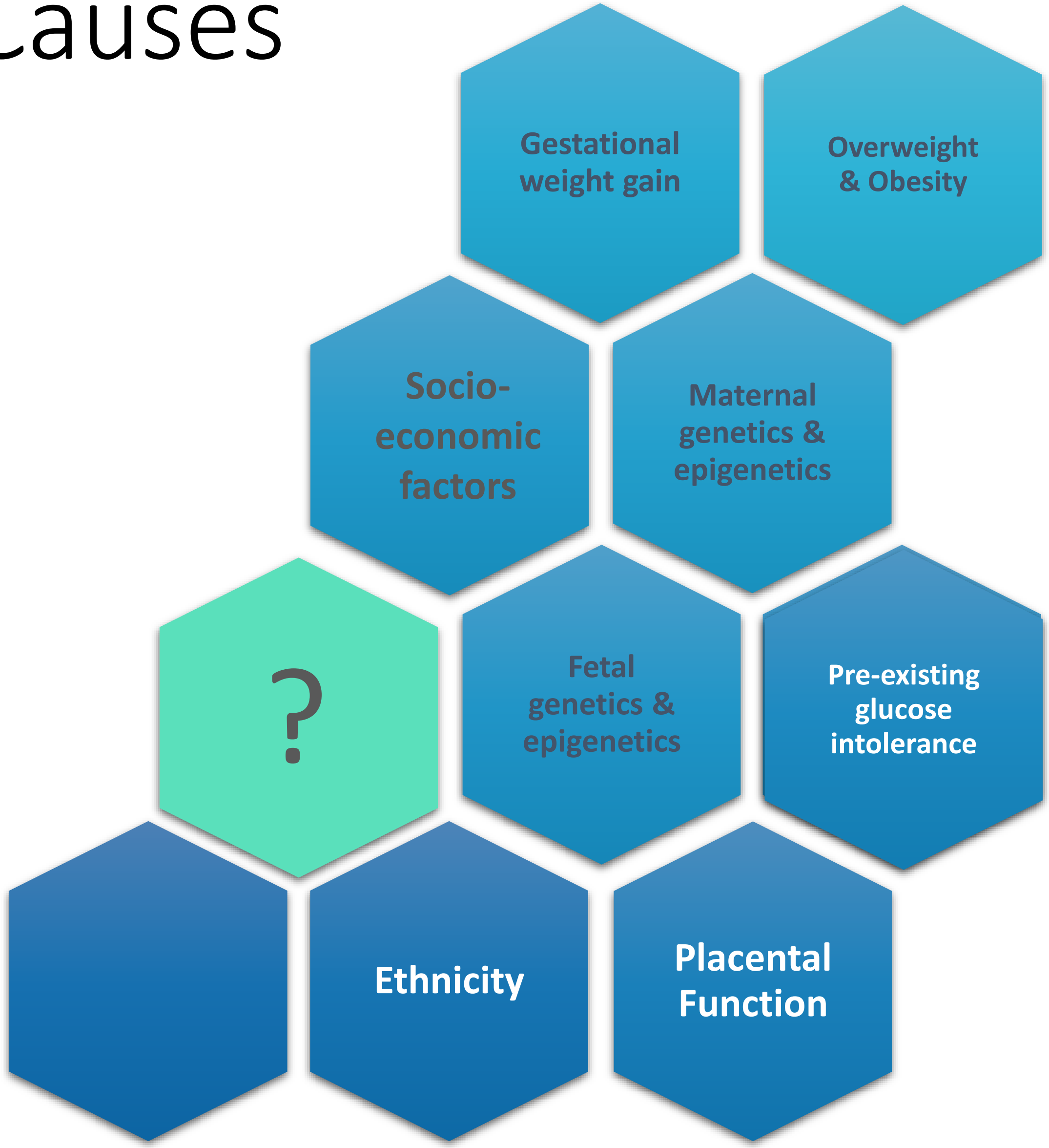
Causes



We have a very incomplete understanding of gestational diabetes

Does nutrition play a role?

Can nutrition cause GDM?

Radiel study – Finland; n=269

Nutritional intervention pregnancy T1/2/3

Advice to increase intake of:

- Fruit & vegetables
- High-fiber grains
- Fish
- Replace animal fat with vegetable oil
- Replace high-fat with low-fat dairy/ meat
- Limiting intake of high-energy products
- Physical activity >150 minutes of moderate intensity activity per week.

- Results:
- 21.6% GDM in control group; 13.9% intervention; p=0.044
- Intervention 0.58kg lower gestational weight; p=0.037

Can nutrition cause GDM?

UPBEAT
Uk Pregnancies Better Eating and Activity Trial

Briley et al., BMC Pregnancy Childbirth. 2014; 14: 74. doi: 10.1186/1471-2393-14-74
Poston et al., Lancet 2015; 3(10):767-777. doi: 10.1016/S2213-8587(15)00227-2

UPBEAT study – UK, Kings College; n=1555 obese women

Nutritional intervention ~17-28wks, 8 sessions/ 8-12hrs

- Individualised dietary/ lifestyle coaching using SMART goals
- Theory of behavioural change

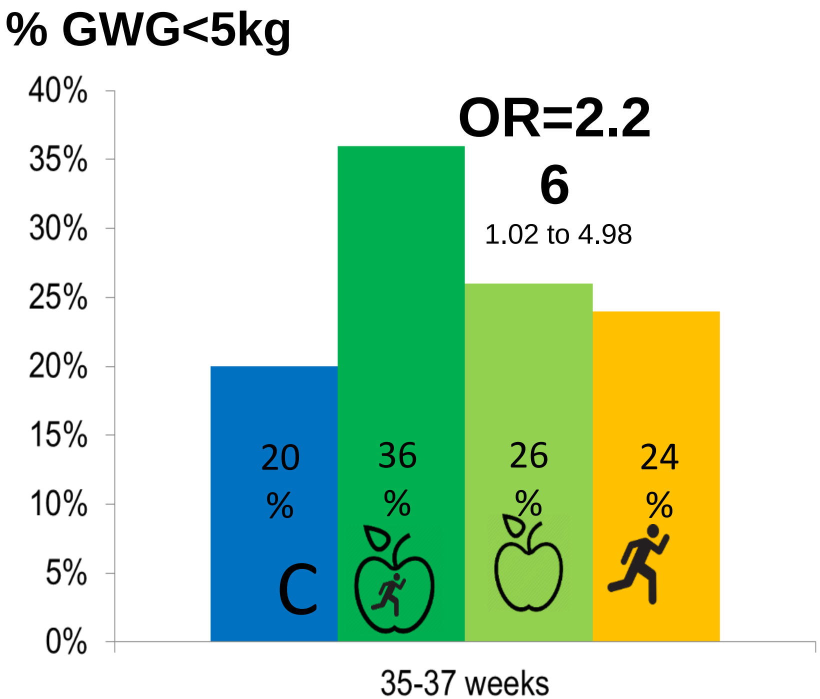
Advice to follow a healthy diet/lifestyle pattern:

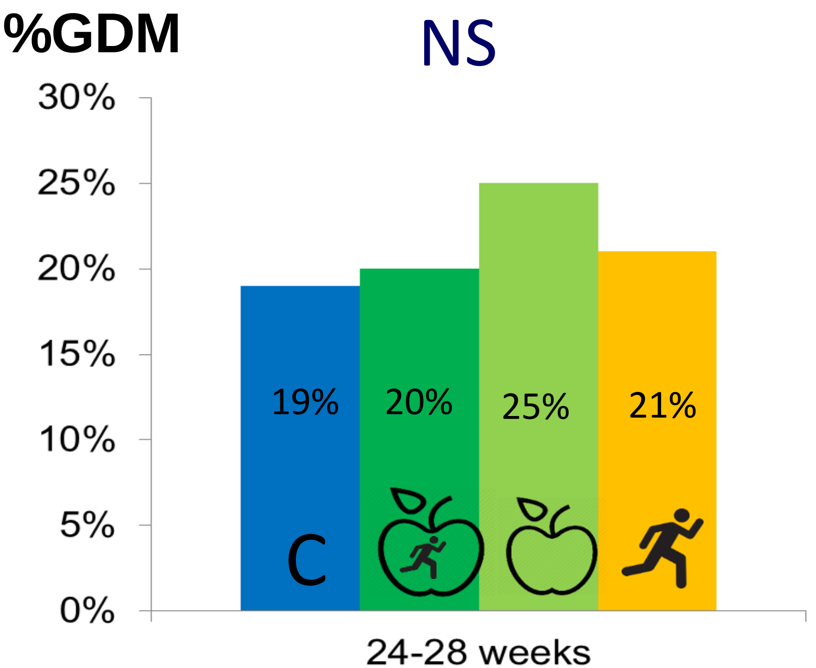
- Fruit & vegetables
- Change from high/medium to low glycaemic index foods
- Reduced saturated fat intake
- Limiting intake of high-energy or high-sugar products
- Physical activity – aimed for incremental increases each week using pedometer

Results:

- 26% GDM in control group; 25% intervention; $p=0.68$
- Intervention 0.51kg lower gestational weight; $p=0.04$
- Intervention group 120 min extra walking/wk $p<0.001$

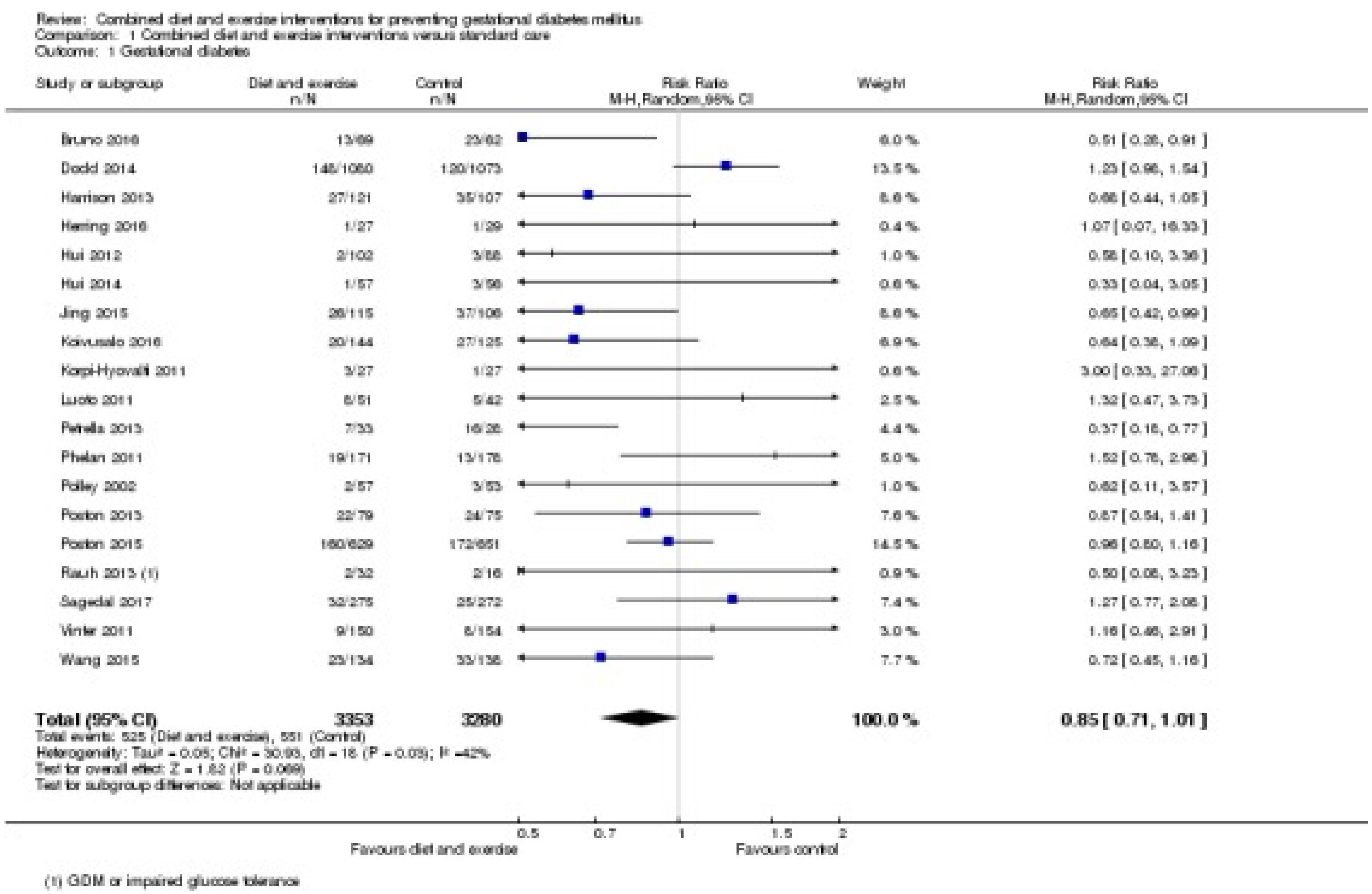
DALI Lifestyle Study-Gestational Weight Gain vs % GDM





Simmons et al. JCEM 2017; 102:903-913

Cochrane – diet and exercise to prevent GDM



Shepherd E et al., Cochrane Database Syst Rev. 2017 Nov; 2017(11): CD010443.

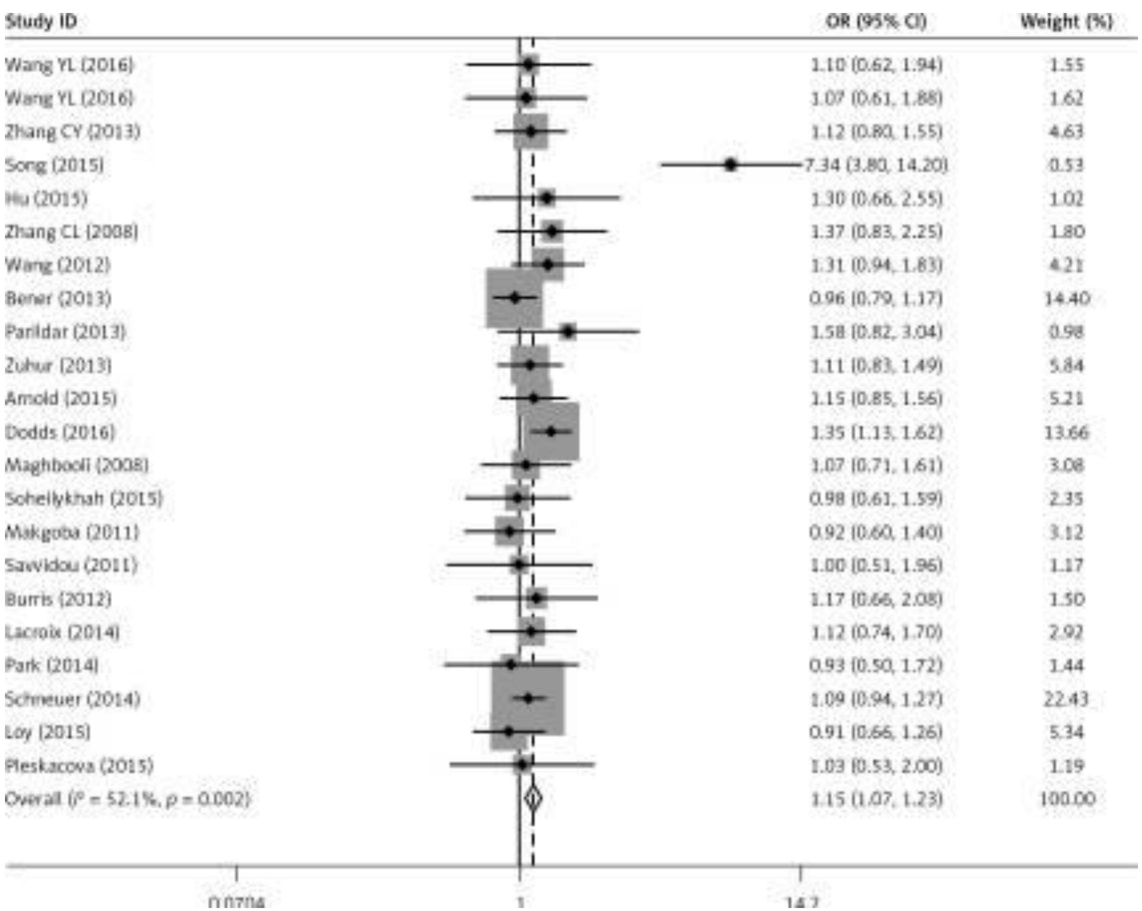
What about longer-term nutrition?

↑ GDM risk has been associated with:

- High blood folate
- Low vitamin B12
- Vitamin D
- High protein; low carb – Chinese study
- High animal protein/fat; low carb – US study

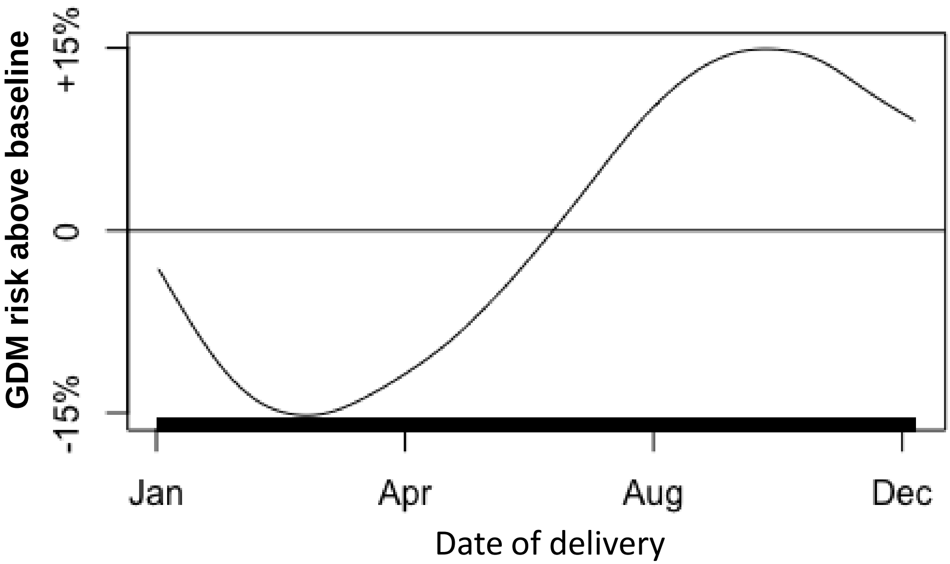
Zhou et al., Br J Nutr. 2018 Nov;120(9):1045-1055.
Bao et al., Am J Clin Nutr 2014 Jun;99(6):1378-84.
Sukumar et al., Nutrients 2016 Dec 1;8(12):768.
Wang et al., Arch Med Sci 2020;16(4): 742-751

Vitamin D



Wang et al., Arch Med Sci 2020;16(4): 742-751

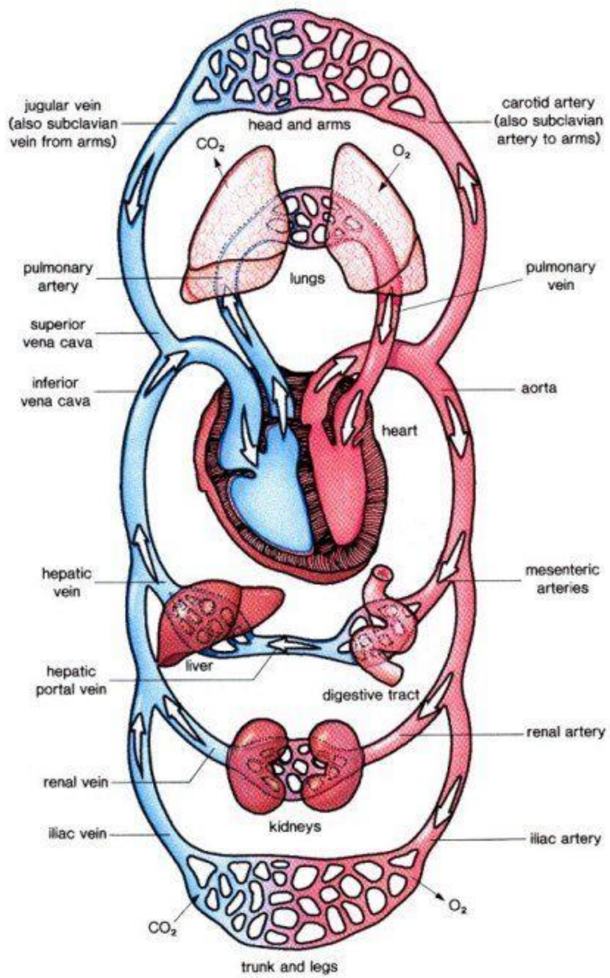
Effect of season on GDM diagnosis



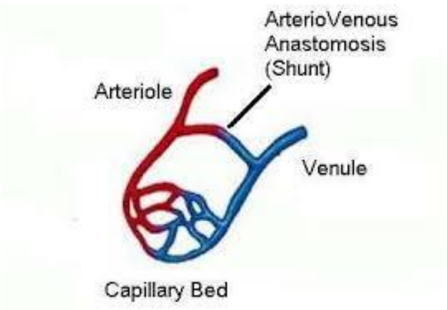
- Summer testing increases the risk – October births
- Winter testing reduces risk – March births
- Winter testing – higher risk population; 9 centile increase in average birthweight
- 50% increase in risk of emergency Caesarean section

Meek CL et al., Diabet Med. 2020 Apr;37(4):674-680.

Temperature regulation



- 75g glucose load absorbed into portal vein to liver
- Transported on to inferior vena cava, heart, lungs and through arterial circulation
- Venous sample from venous circulation
- Arteriovenous shunts open in skin in high temperature



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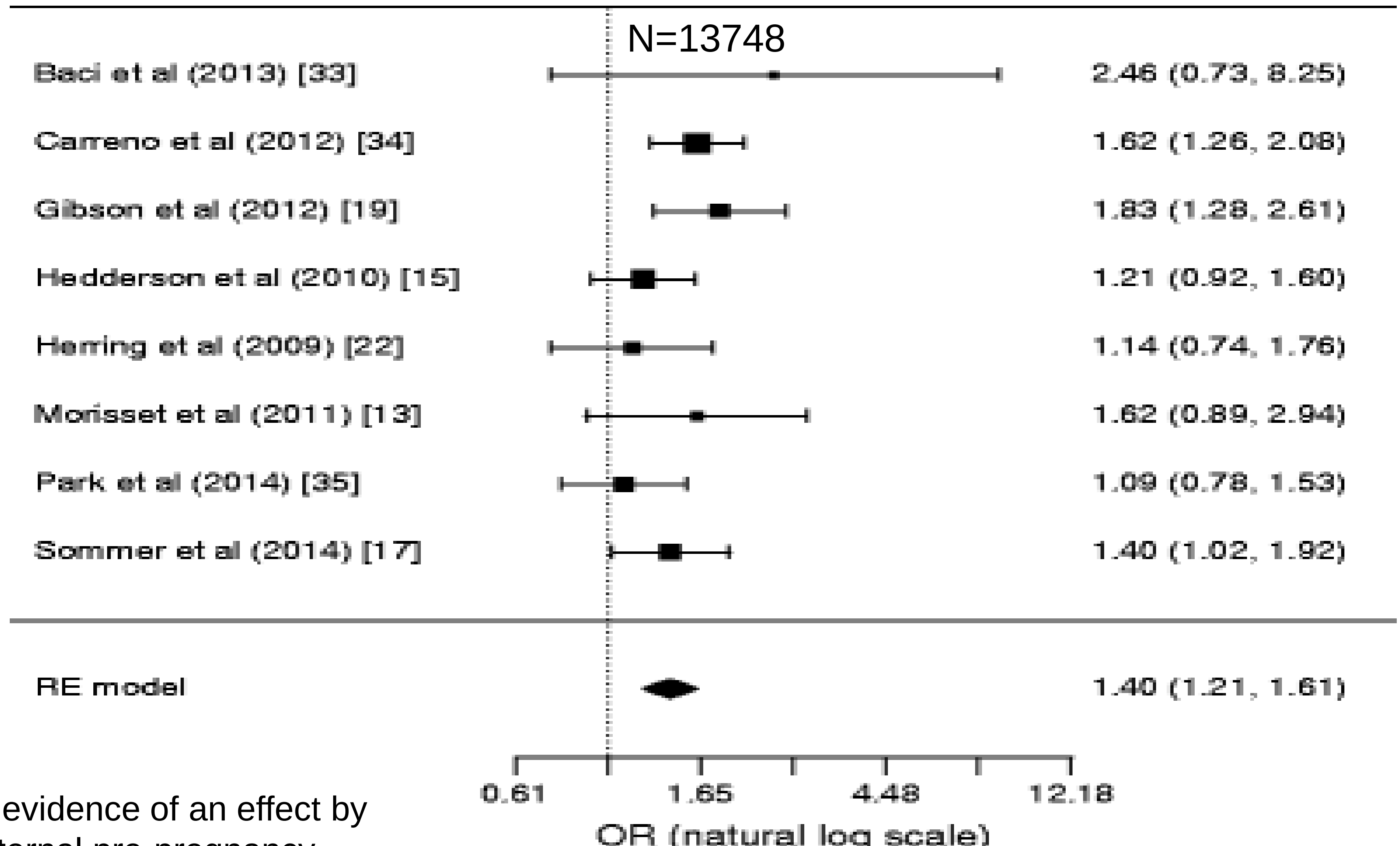
Bao et al., Am J Clin Nutr 2014 Jun;99(6):1378-84.
Sukumar et al., Nutrients 2016 Dec 1;8(12):768.

Excessive vs non-excessive weight gain and GDM



No evidence of an effect by maternal pre-pregnancy BMI category.

Brunner et al. Diabetologia 2015;10:2229–2237

Ophelia

Observational study in Pregnancy Hyperglycaemia: Endocrine causes, Lipids, Insulin and Autoimmunity

OPHELIA Study

Risk Factors or Clinical Concerns

75g OGTT

0 4 8 12 16 20 24 28 32 36 40

Invite to study, extra blood taken at OGTT

Follow up electronically & outcome data collection

Extra blood taken for batch analysis of:
-hormones & insulin
-lipids
-antibodies
-genetic & epigenetic tests

Intake-24 – nutritional info

Information collected about:
-GDM diagnosis & treatment
-Delivery timing & method
-Perinatal complications
-Birth-weight

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Gestational diabetes management

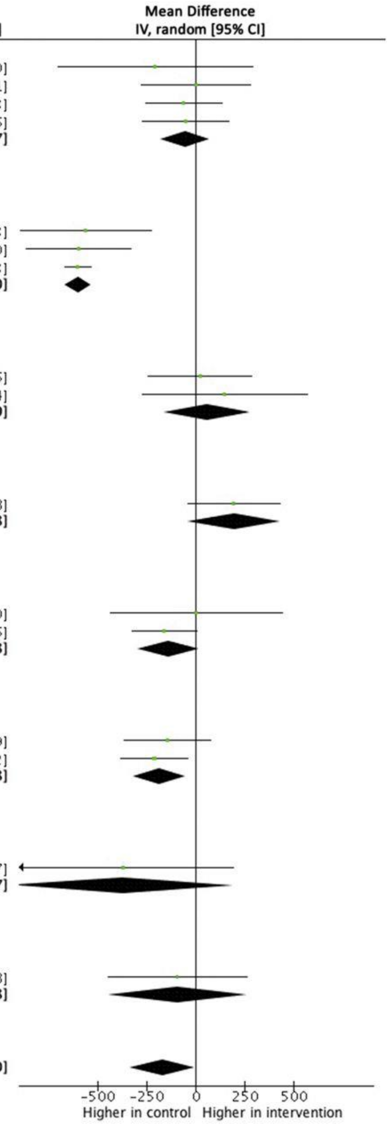
- POCT glucose tests qds
- Low glycaemic index diet
- Restricted carb intake
- Exercise, especially post meals
- Avoid excessive weight gain
- Metformin
- Insulin (insulatard & novorapid)

Targets for all diabetes in pregnancy:
Fasting plasma glucose <5.3 mmol/l
1-hour postprandial plasma glucose <7.8 mmol/l
2-hour postprandial plasma glucose <6.4 mmol/l.

Benefits of Diet in GDM

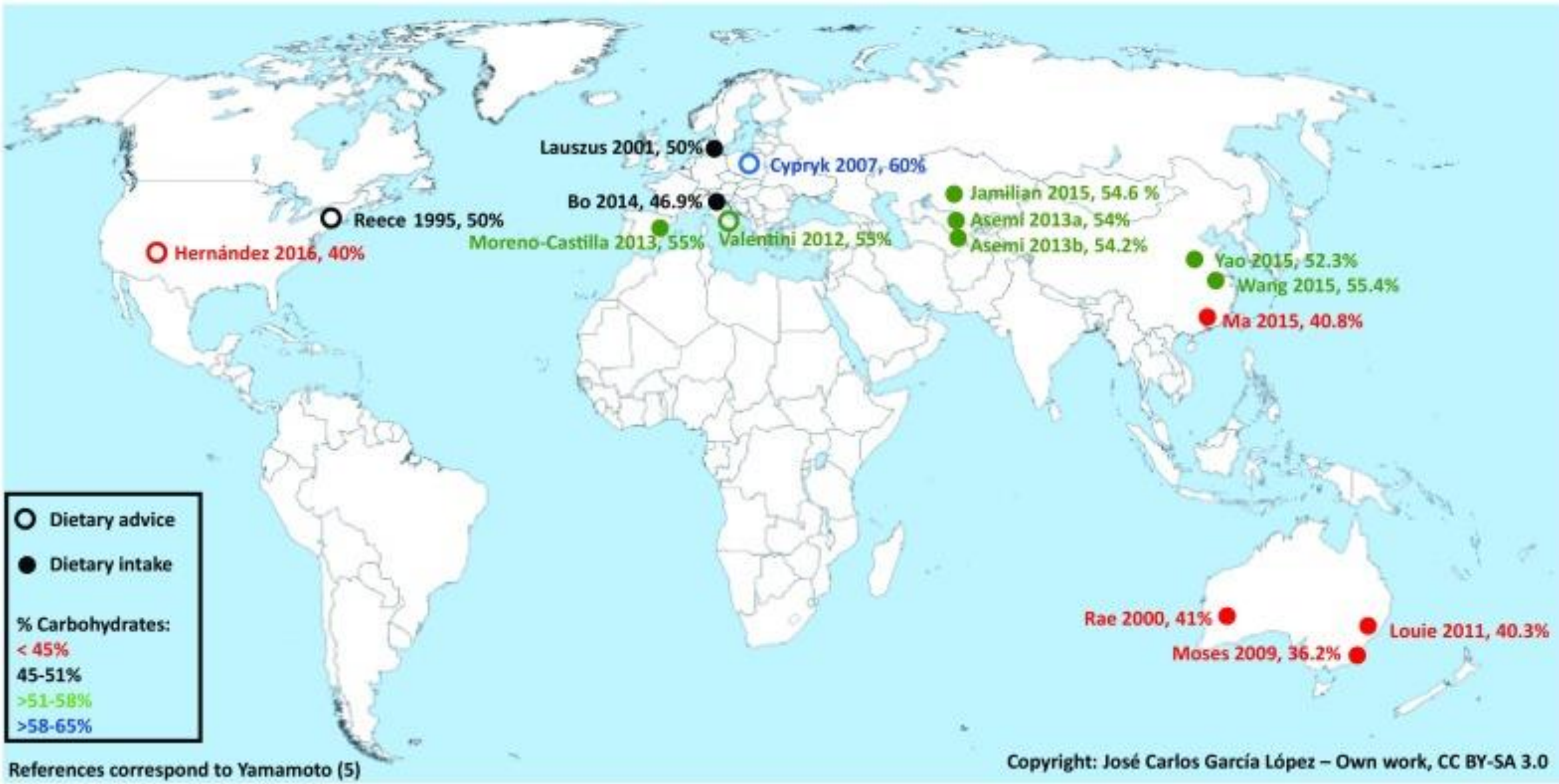
Birth weight after modified dietary interventions vs control diets in women with GDM.

Study or Subgroup	Intervention Mean	Intervention SD	Intervention Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, random [95% CI]
1.35.1 Low GI								
Grant 2011	3,124	526	18	3,330	984	20	4.6%	−206.00 [−701.00, 289.00]
Louie 2011	3,300	686	47	3,300	671	45	6.4%	0.00 [−277.31, 277.31]
Ma 2015	3,240	460	41	3,300	440	42	7.1%	−60.00 [−253.73, 133.73]
Moses 2009	3,278	462	31	3,329	430	32	6.9%	−51.00 [−271.56, 169.56]
Subtotal (95% CI)			**137**			**139**	**25.0%**	**−54.25 [−178.98, 70.47]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.51$, df = 3 (P = 0.92); $I^2 = 0\%$								
Test for overall effect: Z = 0.85 (P = 0.39)								
1.35.2 DASH								
Asemi 2013	3,083	402	17	3,641	579	17	5.9%	−558.00 [−893.07, −222.93]
Asemi 2014	3,222.7	492.1	26	3,818.8	492.1	26	6.5%	−596.10 [−863.60, −328.60]
Yao 2015	3,200	100	17	3,800	100	16	7.8%	−600.00 [−668.27, −531.73]
Subtotal (95% CI)			**60**			**59**	**20.2%**	**−598.19 [−663.09, −533.30]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.06$, df = 2 (P = 0.97); $I^2 = 0\%$								
Test for overall effect: Z = 18.07 (P < 0.00001)								
1.35.3 Low CHO								
Cypryk 2007	3,407	309	15	3,385	418	15	6.5%	22.00 [−241.06, 285.06]
Hernandez 2016	3,421	456.3	6	3,273	254.7	6	5.2%	148.00 [−270.14, 566.14]
Subtotal (95% CI)			**21**			**21**	**11.7%**	**57.73 [−164.93, 280.39]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.25$, df = 1 (P = 0.62); $I^2 = 0\%$								
Test for overall effect: Z = 0.51 (P = 0.61)								
1.35.4 Low calories								
Rae 2000	3,461	595	66	3,267	718	56	6.8%	194.00 [−42.58, 430.58]
Subtotal (95% CI)			**66**			**56**	**6.8%**	**194.00 [−42.58, 430.58]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.61 (P = 0.11)								
1.35.5 Fat modification								
Lauszus 2001	3,743	602	12	3,742	501	13	5.0%	1.00 [−435.10, 437.10]
Wang 2015	3,342	335	41	3,502	437	43	7.3%	−160.00 [−326.06, 6.06]
Subtotal (95% CI)			**53**			**56**	**12.3%**	**−139.61 [−294.80, 15.58]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.46$, df = 1 (P = 0.50); $I^2 = 0\%$								
Test for overall effect: Z = 1.76 (P = 0.08)								
1.35.6 Soy protein								
Jamilian 2015	3,252.7	508.9	34	3,395.3	410.1	34	6.9%	−142.60 [−362.29, 77.09]
Sarathi 2016	2,860	287	33	3,070	390	30	7.3%	−210.00 [−380.48, −39.52]
Subtotal (95% CI)			**67**			**64**	**14.2%**	**−184.67 [−319.35, −49.98]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.23$, df = 1 (P = 0.63); $I^2 = 0\%$								
Test for overall effect: Z = 2.69 (P = 0.007)								
1.35.8 Ethnic diet								
Valentini 2012	3,064	626	10	3,434	649	10	4.1%	−370.00 [−928.87, 188.87]
Subtotal (95% CI)			**10**			**10**	**4.1%**	**−370.00 [−928.87, 188.87]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.30 (P = 0.19)								
1.35.9 Fiber								
Reece 1995	3,519	476	11	3,613	360	11	5.8%	−94.00 [−446.68, 258.68]
Subtotal (95% CI)			**11**			**11**	**5.8%**	**−94.00 [−446.68, 258.68]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.52 (P = 0.60)								
Total (95% CI)			**425**			**416**	**100.0%**	**−170.62 [−333.64, −7.60]**
Heterogeneity: $Tau^2 = 87,744.63$; $Chi^2 = 127.32$, df = 15 (P < 0.00001); $I^2 = 88\%$								
Test for overall effect: Z = 2.05 (P = 0.04)								
Test for subgroup differences: $Chi^2 = 125.82$, df = 7 (P < 0.00001), $I^2 = 94.4\%$								

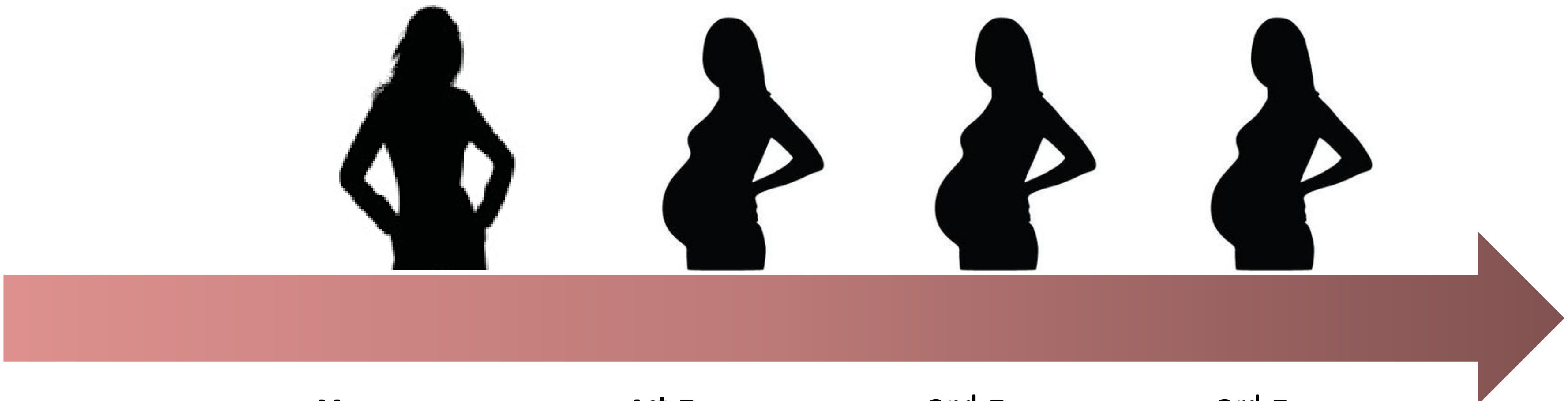


Jennifer M. Yamamoto et al. Diab Care 2018;41:1346-1361

Worldwide variation in CHO intake



Weight Gain & Pregnancy



	Young women	1st Pregnancy	2nd Pregnancy	3rd Pregnancy
All women, BMI kg/m^2	**24.2**	**24.5**	**24.9**	**25.8**
GDM kg/m^2	**27.8**	**28.8**	**30.4**	**33.2**

Gunderson EP. Obstet Gynecol Clin North Am 2009. Meek CL et al. Diabetologia 2014. GWG: gestational weight gain. GDM: gestational diabetes mellitus BMI: body mass index

Controlling weight gain in pregnancy

Outcomes	Weight stable n=47	Weight gain n=50
Late weight gain	0.97kg	5.98 kg
Large-for-gestational-age	4.3%	16.7%
Small-for-gestational-age	8.5%	8.3%
Vaginal delivery	53.2%	36.0%
Caesarean delivery	38.3%	40.8%
Instrumental delivery	8.5%	22.0%
Total insulin (/day, 36wks)	23.6 units	41.1 units
Postnatal 2-hr glucose	4.8 mmol/l	6.1 mmol/l

Neonatal metabolic effects

Maternal metabolic effects

Means, or proportions %

Aiken et al., Diabet Med 2019; 36(2): 167-176

DiGest

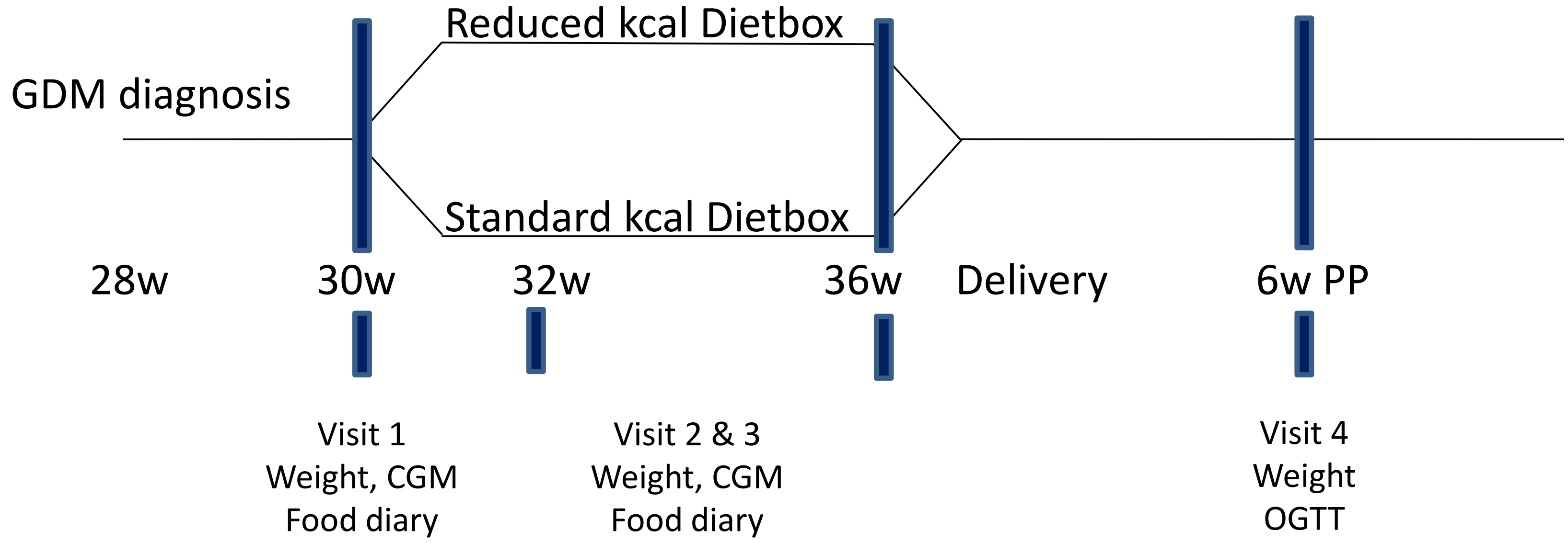
Dietary intervention in Gestational diabetes

500 pregnant women; 100,000 meals

A randomised controlled trial of standard vs reduced calorie diet in women with gestational diabetes

A randomised, controlled, double blind intervention study

DiGest



DiGest Dietbox
Delivered weekly to participant's home

- Appealing, tasty food
- Mediterranean diet, low GI
- Nutritionally balanced for GDM & pregnancy
- 40% carb, 25% protein, 35% fat

DiGest – meal planning

- Weekly deliveries, frozen food
- Dietboxes -3 meals & snacks /day
- Low glycaemic index food
- Nutritionally balanced for pregnancy
- ~7-14 choices for each meal
- Easy to cook at home
- Vegetable/ salad pack per week

Sample DiGest Menu

Weekday	Breakfast	Lunch	Dinner	Snack Pack
Monday	Porridge with nuts and jam	Chilli bean wrap	Turkey roast	Boiled egg, satsuma, small cheese
Tuesday	Cheese and ham omelette with Rosti	Mushroom stroganoff with rice	Macaroni cheese with kale	Apple, Belgian Chocolate covered rice cake, spiced seeds
Wednesday	Breakfast roll	Chicken Schnitzel, wedges and green beans	Venison sausage in red wine sauce with sprouts	Cottage cheese, Ryvita, satsuma
Thursday	Spiced Omelette with Sag Aloo	Seafood lasagne	Beef Madras with rice	Peparami (mini), orange, Belgian chocolate rice cake
Friday	Blueberry yogurt	Edamame and feta wrap	Salmon with lemon Puy lentils	Peperami (mini), pear, spiced seeds, popcorn
Saturday	Granola	Spiced Moroccan Chicken wrap	Fish Goujon, wedges and minted peas	Small cheese, apple, Philadelphia snack light herbs and breadsticks
Sunday	Cheese and mushroom omelette	Thai red chicken curry with rice	Vegetarian bean stew, rice and halloumi	Satsuma, Belgian chocolate covered rice cake, spiced seeds.
Weekly Veg/Salad Pack	Contains a range of vegetables and salad options including carrots, broccoli, cauliflower, baby tomatoes, cucumber, lettuce, celery, red pepper.			

Progress so far

DiGest

- Open at 3 sites Nov 2019-Feb 2020
- New recruitment paused Covid19
- Restarting recruitment shortly
- 9 participants all delivered, nearly finished protocol.
- Very positive feedback from patients about food
- No logistics/delivery problems

nutrients

MDPI

Article

Dietary Intervention in Pregnant Women with Gestational Diabetes; Protocol for the DiGest Randomised Controlled Trial

Laura C. Kusinski [1], Helen R. Murphy [2,3], Emanuella De Lucia Rolfe [4], Kirsten L. Rennie [4], Linda M. Oude Griep [4], Deborah Hughes [1,2], Roy Taylor [5] and Claire L. Meek [1,2,*]

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2 Cambridge Universities NHS Foundation Trust, Cambridge CB2 0QQ, UK; helen.murphy@uea.ac.uk
3 Norwich Medical School, University of East Anglia, Norwich NR4 7UQ, UK
4 NIHR Cambridge Biomedical Research Centre—Diet, Anthropometry and Physical Activity Group, MRC Epidemiology Unit, Institute of Metabolic Science, University of Cambridge, Cambridge CB2 0QQ, UK; emanuella.de-lucia-rolfe@mrc-epid.cam.ac.uk (E.D.L.R.); Kirsten.Rennie@mrc-epid.cam.ac.uk (K.L.R.); Linda.OudeGriep@mrc-epid.cam.ac.uk (L.M.O.G.)
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check for updates

Received: 31 March 2020; Accepted: 16 April 2020; Published: 22 April 2020

Abstract: Gestational diabetes mellitus (GDM) annually affects 35,000 pregnancies in the United Kingdom, causing suboptimal health outcomes to the mother and child. Obesity and excessive gestational weight gain are risk factors for GDM. The Institute of Medicine recommends weight targets for women that are overweight and obese, however, there are no clear guidelines for women with GDM. Observational data suggest that modest weight loss (0.6–2 kg) after 28 weeks may reduce risk of caesarean section, large-for-gestational-age (LGA), and maternal postnatal glycaemia. This protocol for a multicentre randomised double-blind controlled trial aims to identify if a fully controlled reduced energy diet in GDM pregnancy improves infant birthweight and reduces maternal weight gain (primary outcomes). A total of 500 women with GDM (National Institute of Health and Care Excellence (NICE) 2015 criteria) and body mass index (BMI) ≥ 25 kg/m^2 will be randomised to receive a standard (2000 kcal/day) or reduced energy (1200 kcal/day) diet box containing all meals and snacks from 28 weeks to delivery. Women and caregivers will be blinded to the allocations. Food diaries, continuous glucose monitoring, and anthropometry will measure dietary compliance, glucose levels, and weight changes. Women will receive standard antenatal GDM management (insulin/metformin) according to NICE guidelines. The secondary endpoints include caesarean section rates, LGA, and maternal postnatal glucose concentrations.

Keywords: gestational diabetes; pregnancy; study protocol; randomised controlled trial; large-for-gestational age; diet; dietary intervention; maternal or gestational weight gain; continuous glucose monitoring (CGM); neonatal outcomes; neonatal hypoglycaemia; neonatal growth; maternal obesity

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MOTHER

↑ 25%

INCREASE IN IMMEDIATE HEALTHCARE COSTS

↑ 15%

INCREASE IN HEALTHCARE COSTS FOR 2-5 YEARS

↑ x7

RISK TYPE 2 DIABETES IN LATER LIFE

BABY

MACROSOMIA

(BEING LARGE FOR GESTATIONAL AGE)

£2,392

DIRECT NEO-NATAL COSTS PER INFANT

SHOULDER DYSTOCIA

LIFE THREATENING FOR BABY (CAN CAUSE INJURY, HYPOXIA, CEREBRAL PALSY AND STILLBIRTH)

OFFSPRING

OBESITY

AND OR

METABOLIC DYSFUNCTION

WHICH PERSIST INTO

ADULTHOOD

Nutrition in utero and perinatal complications

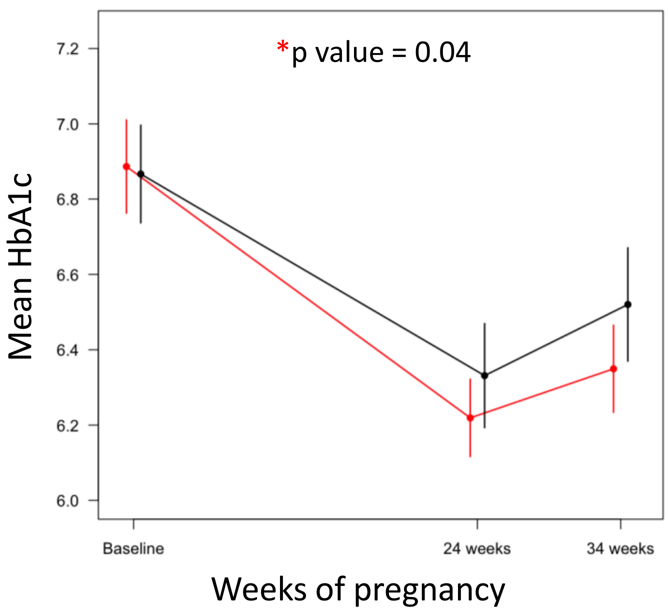
Metanalysis ~2700 cases, ~2700 controls

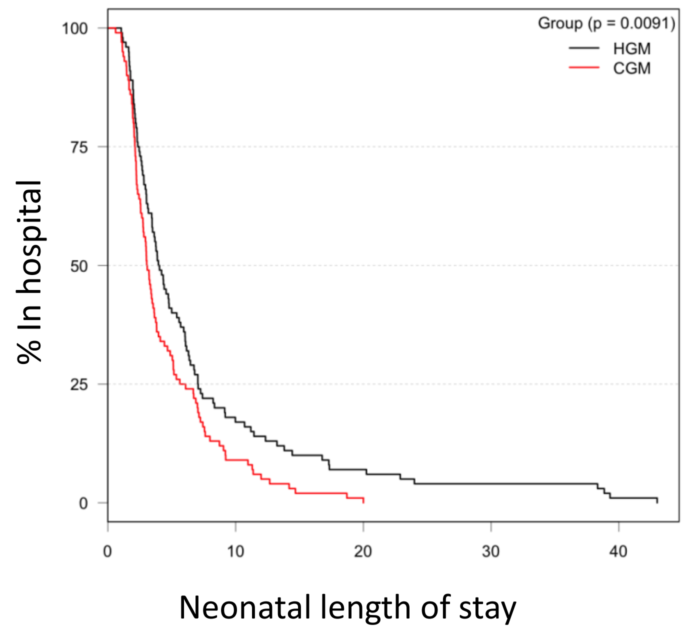
Diet and exercise interventions to prevent:

- GDM RR 0.86 (95% CI 0.72-1.02)
- Pre-eclampsia 0.98 (0.79-1.21)
- Caesarean section 0.95 (0.88-1.02)
- Large for gestational age 0.93 (0.81-1.07)
- Perinatal mortality 0.82 (0.42-1.63)

Shepherd E et al., Cochrane Database Syst Rev. 2017 Nov; 2017(11): CD010443.

CONCEPTT RESULTS

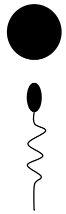




- 249 pregnant women with T1DM
- Continuous Glucose Monitoring vs standard capillary testing
- 225 infants born
  - Mean gestational age 37 weeks
  - Mean birth weight 3564g

CONCEPTT

Lancet. 2017;390: 2347.



ELGA

Trimester 1	Trimester 2	Trimester 3	Cord Blood
No associations	Positive associations: Carnitines	Positive association: Carnitines Free fatty acids & ions	Positive associations: Carnitines Triglycerides Negative associations with: Polyunsaturated triglycerides

CONCEPTT

Lancet. 2017;390: 2347.

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- Gestational diabetes (GDM)
  - Definition
  - Nutrition – a cause of GDM?
  - Nutrition – a tool in GDM management?
  - Nutrition – a tool to improve offspring outcomes?
  - Nutrition – a tool to reduce maternal T2DM risk long-term?
  - Conclusions

What is the risk of T2DM after GDM?

- Incidence of T2DM after GDM is 7x population risk
- Differences in GDM definitions make precision challenging
- 5-16% to year 1
- 28% to year 5

- Early screening (6-12 weeks PP) with:
  - 75g OGTT
  - HbA1c (sensitivity 22-65%)
  - Fasting BG (sensitivity 60-83%)
  - Fasting BG and HbA1c (sensitivity 83-90%)

Protective factors: Breastfeeding

- 1035 women with GDM & singleton delivery >35/40
- OGTT at 6wks PP and follow-up for 2 years (95%)

	Mostly formula	Mixed	Mostly lactation	
Hazard Ratios Comparison to exclusive formula fed babies	0.64	0.54	0.46	P (trend) =0.016

- Increased intensity (adjusted for insulin resistance) associated with
  - Increased HDLc
  - Decreased fasting trigs, leptin, adiponectin

	>2-5 months	>5-10 months	>10 months	
Hazard Ratios Comparison to 0-2 months	0.55	0.50	0.43	P (trend) =0.007

Gunderson et al. Lactation and Progression to Type 2 Diabetes Mellitus After Gestational Diabetes Mellitus: A Prospective Cohort Study. Ann Intern Med. 2015;163(12):889-98. doi: 10.7326/M15-0807.

Diabetes prevention attempts

Diabetes prevention programme, n=1776

- Lifestyle intervention vs metformin vs standard care
- 16-lesson lifestyle curriculum
- High risk group – included 350 GDM women (~12 yrs post GDM)
- GDM - metformin or lifestyle intervention reduced T2DM by 50%
- GDM group were less able to maintain lifestyle changes over time than non-GDM group

Other smaller studies:

- Conflicting results about whether or not lifestyle interventions work
- Troglitazone, metformin and pioglitazone all effective
- Some endpoints included time doing exercise, weight loss, food choices etc – may not translate directly into reduce diabetes incidence.

Barriers to interventions

- Lack of time, finances, childcare, social support, work flexibility
- Psychological wellbeing
- 'Difficulty balancing household expectations and leading a healthy lifestyle'
- Feelings of abandonment after the birth
- Worse baseline health behaviours – too great a change needed
- Concern about T2DM risk not translated into action towards weight loss or healthy eating
- Expectations of exercise – only for weight control
- Further pregnancies, more weight gain.
- Cultural obligations
- Home based interventions/ internet/ telephone

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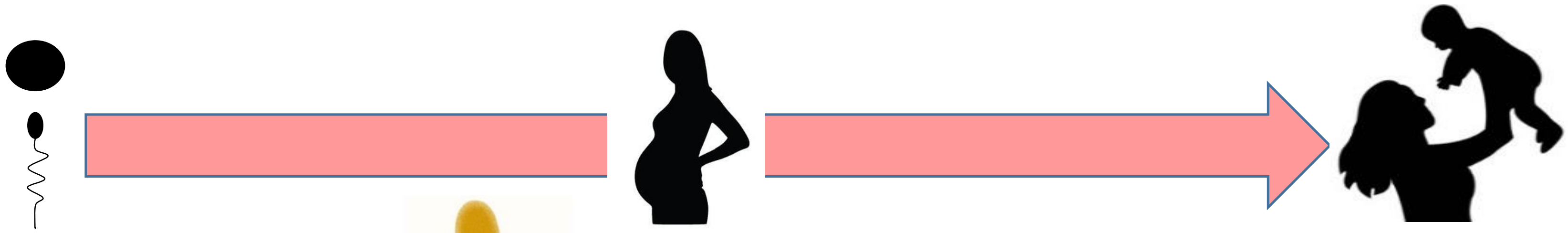
Peacock AS, **Bogossian** F, McIntyre HD, Wilkinson S. A review of interventions to prevent Type 2 Diabetes after Gestational Diabetes. Women Birth. 2014 Dec;27(4):e7-e15. doi: 10.1016/j.wombi.2014.09.002.

Gestational Diabetes – a nutritional disorder?

- Gestational diabetes (GDM)
  - Definition
  - Nutrition – a cause of GDM? MAYBE, OBESITY
  - Nutrition – a tool in GDM management? YES, PROBABLY
  - Nutrition – a tool to improve offspring outcomes? MAYBE
  - Nutrition – a tool to reduce maternal T2DM risk long-term? YES, but challenging
  - Conclusions – need much better studies…

Maternal Metabolism: Studies in Pregnancy Diabetes



Gift

Ophelia

DiGest

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CONCEPTT

Healthy mothers, healthy babies and healthy families in gestational diabetes

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