Interventions during Obese Pregnancy: A Window of Opportunity to Improve the Health of Two Generations

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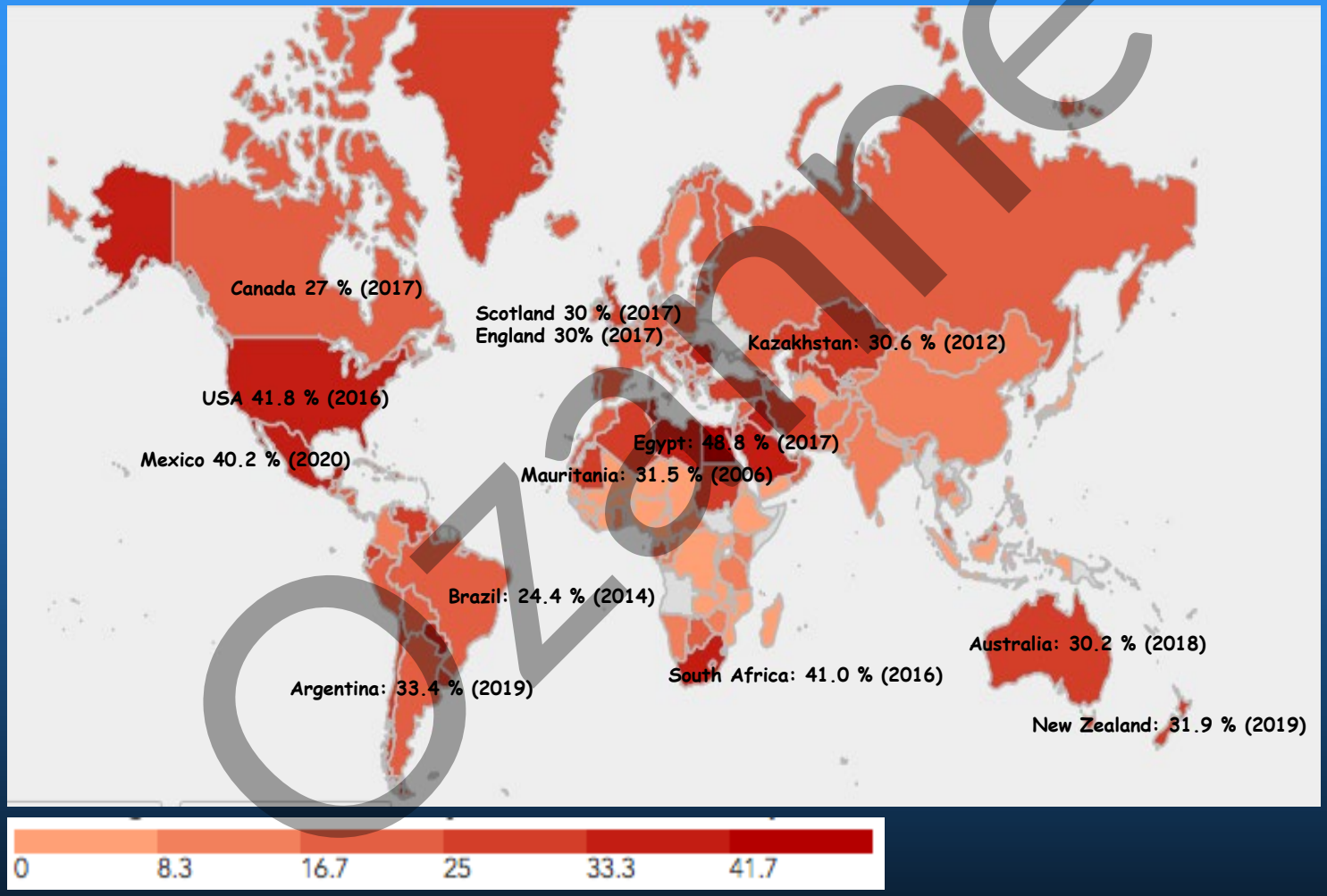
Obesity Prevalence in Women



Developmental Programming

Suboptimal Early Environment

- Under-nutrition
- Over-nutrition
- Stress
- Hypoxia
- Air pollutants
- Smoking

Increased risk of Cardio-metabolic Disease

Evidence for Programming by Maternal Obesity in Humans

Measurement	Born Pre Maternal Bariatric Surgery	Born Post Maternal Bariatric Surgery
% Body Fat	29.9 ± 13.9	21.4 ± 10.3***
Insulin (µU/ml log10)	18.8 ± 12.2	11.3 ± 7.4*
Glucose (mM)	4.9 ± 0.43	4.7 ± 0.43
Systolic BP (mmHg)	111.3 ± 14.7	97.4 ± 12.8*

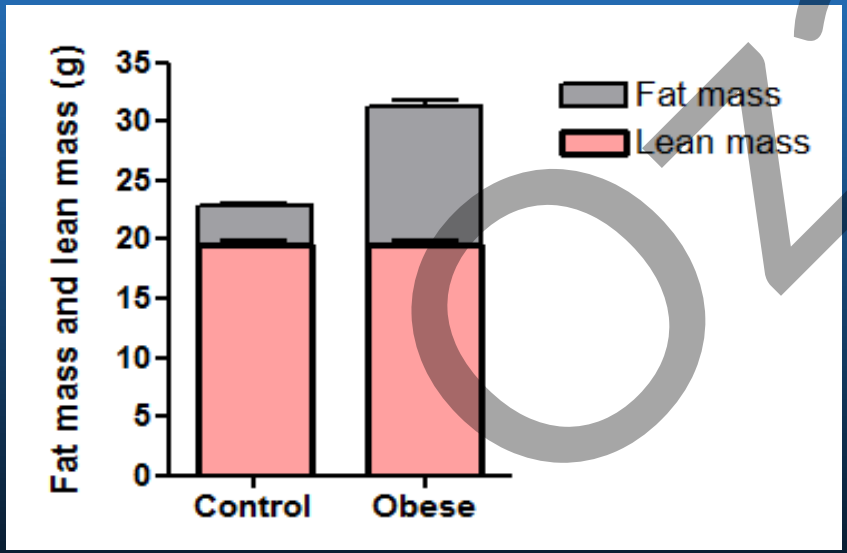
Guenard *et al* PNAS (2013) 110: 11439-44

Using Animal Models to Demonstrate Causality and Understand Underlying Mechanisms

Maternal Diet-Induced Obesity Model

	Pre-mating	Gestation	Lactation	Weaning
Control	10 WEEKS	3 WEEKS	3 WEEKS	
Obese	10 WEEKS	3 WEEKS	3 WEEKS	

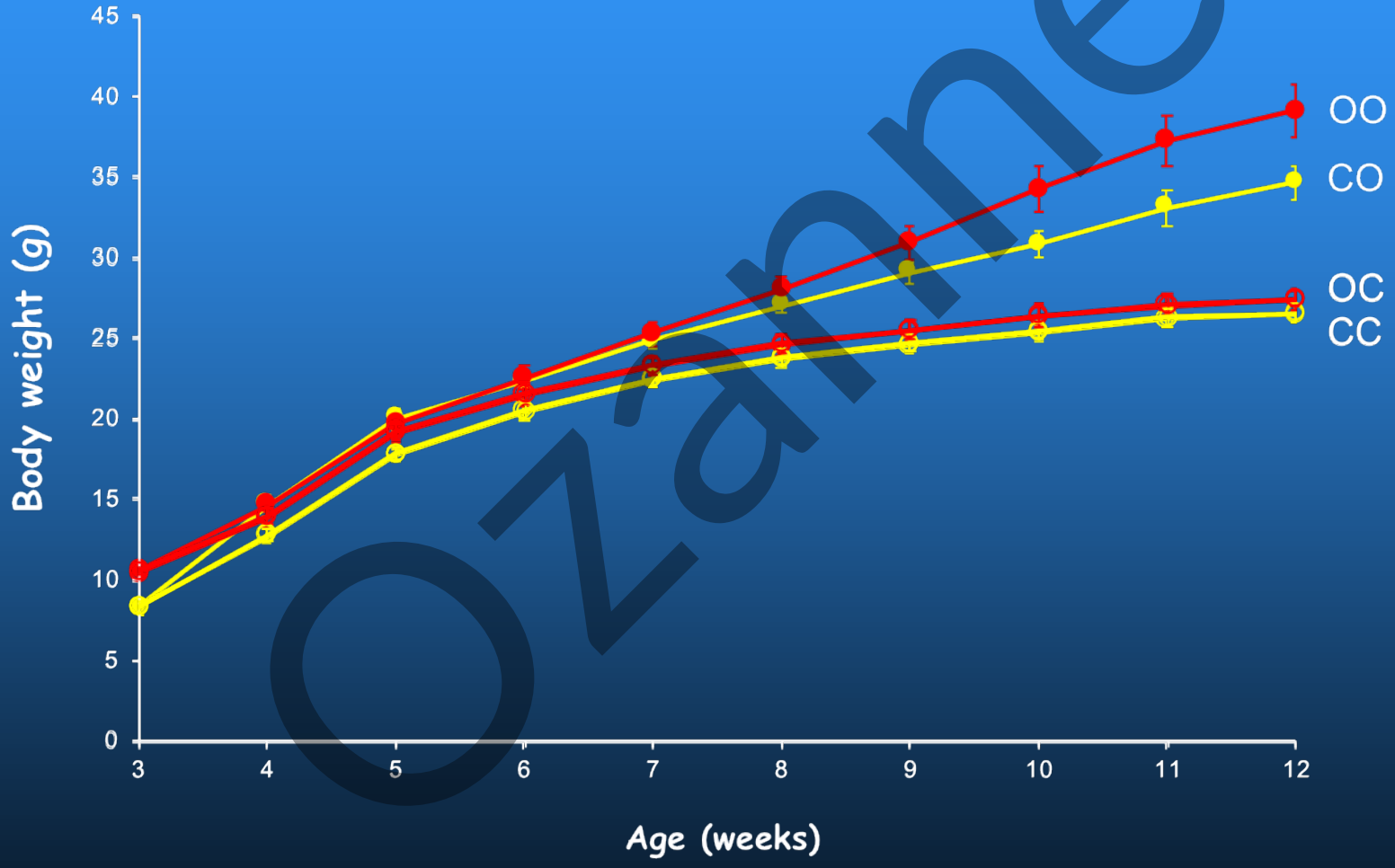
Body Composition at Mating



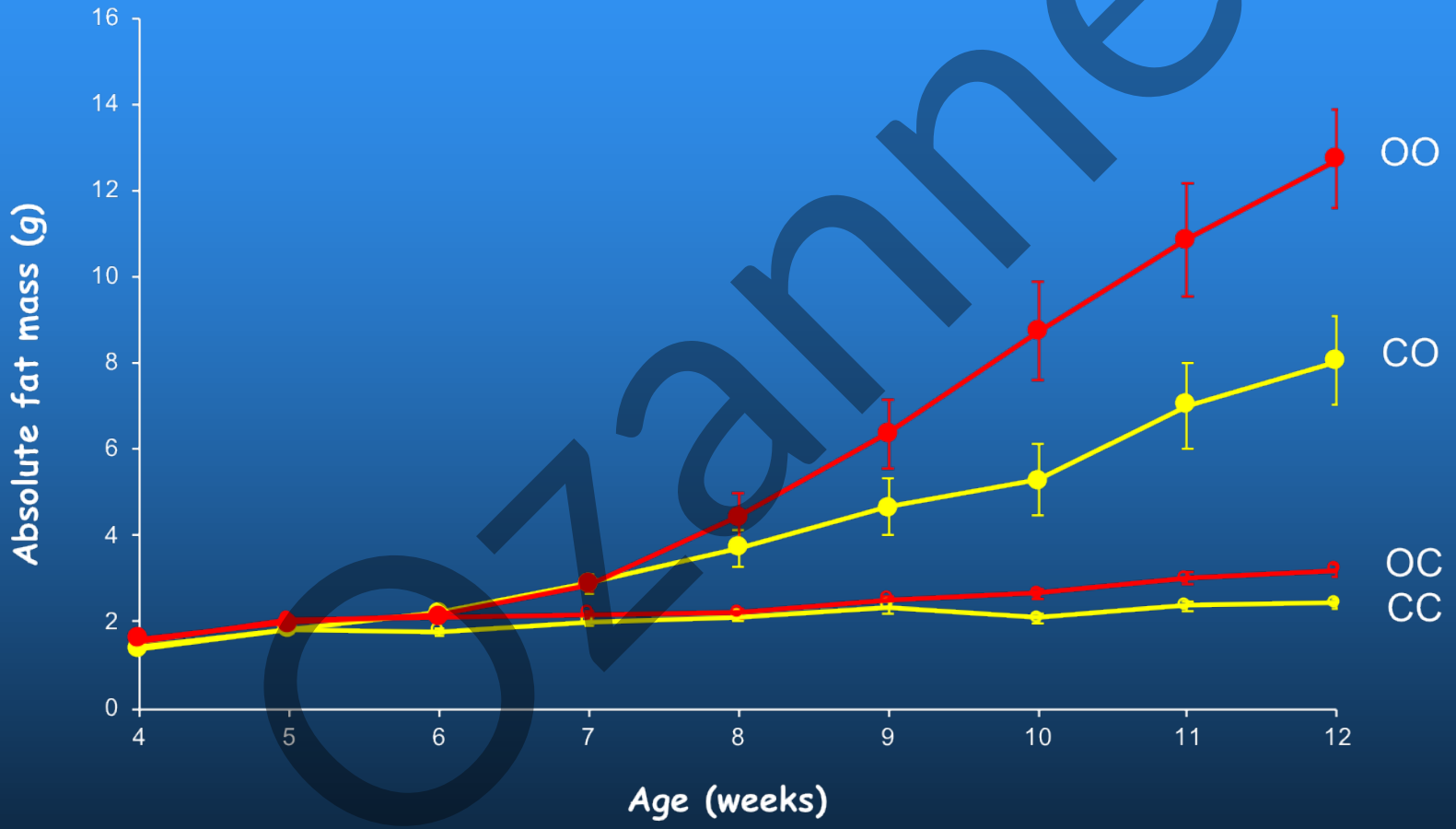
Plasma Parameters during Pregnancy

	CONTROL	OBESE
Insulin (pmol/l)	96 ± 8	224 ± 11**
Triglycerides (mmol/l)	0.77 ± 0.13	0.83 ± 0.15
Free Fatty Acids (µmol/l)	410 ± 46	796 ± 130*
Cholesterol (mmol/l)	2.1 ± 0.2	3.8 ± 0.2***

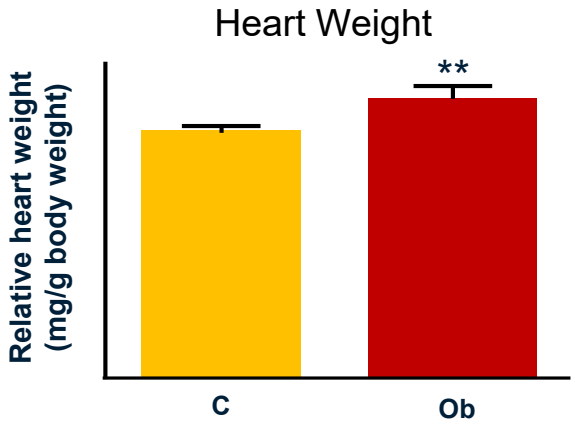
Offspring Body Weight

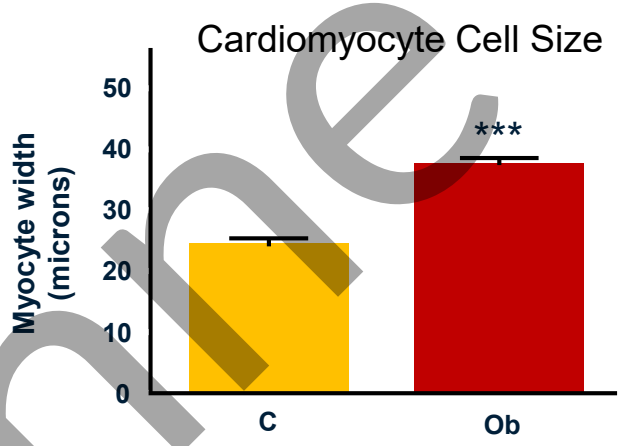


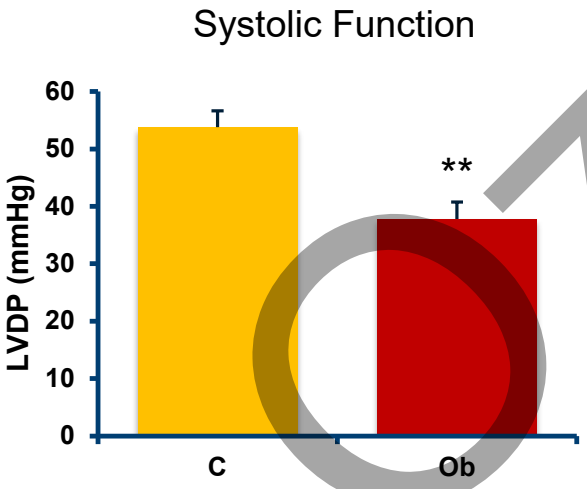
Offspring Adiposity

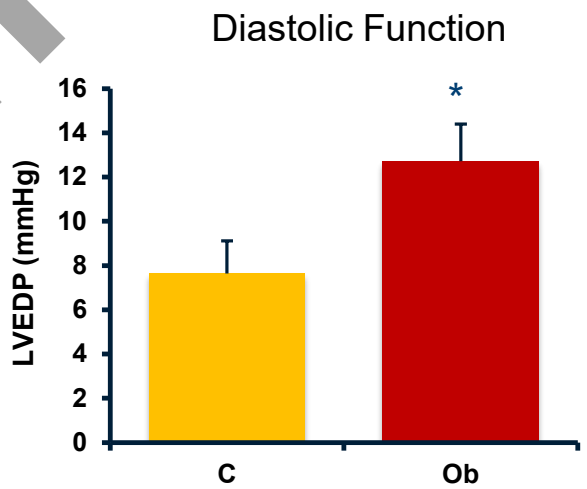


Cardiac Effects





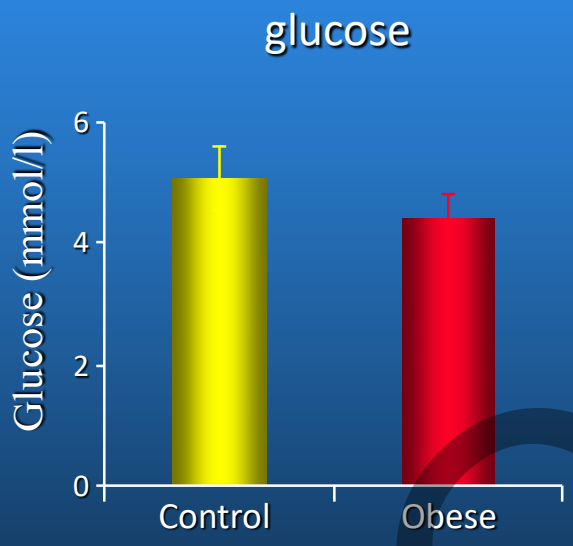


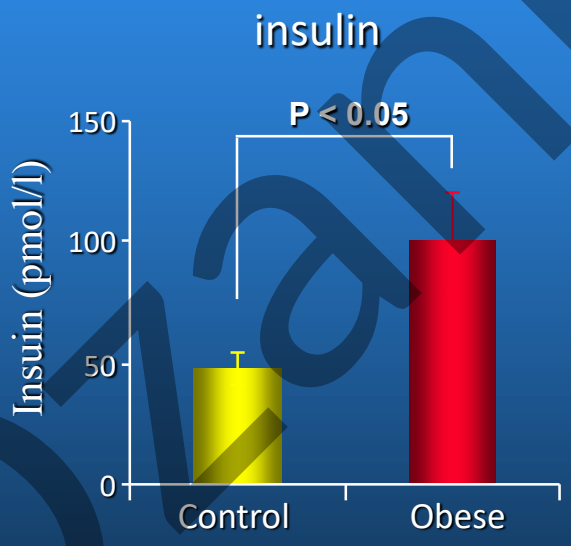


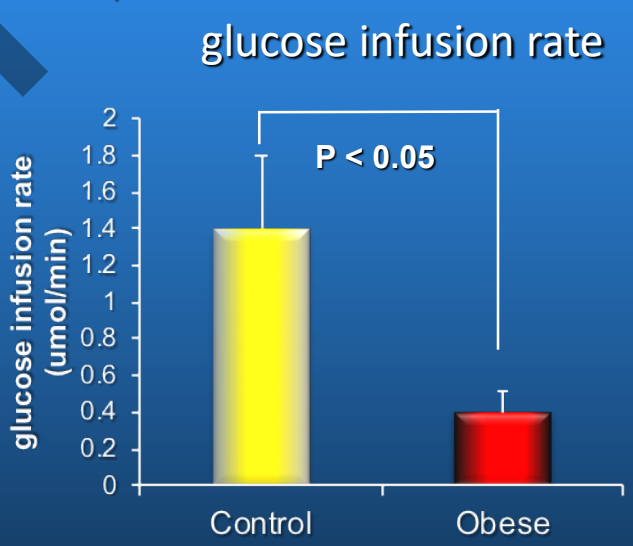
Fernandez-Twinn et al. 2012

Blackmore et al. 2014

Plasma Parameters



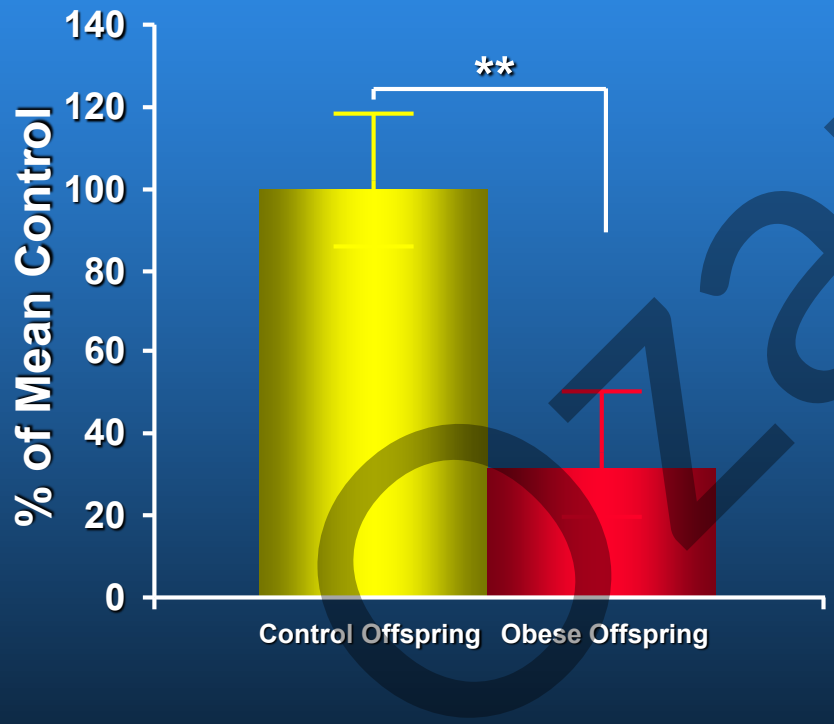


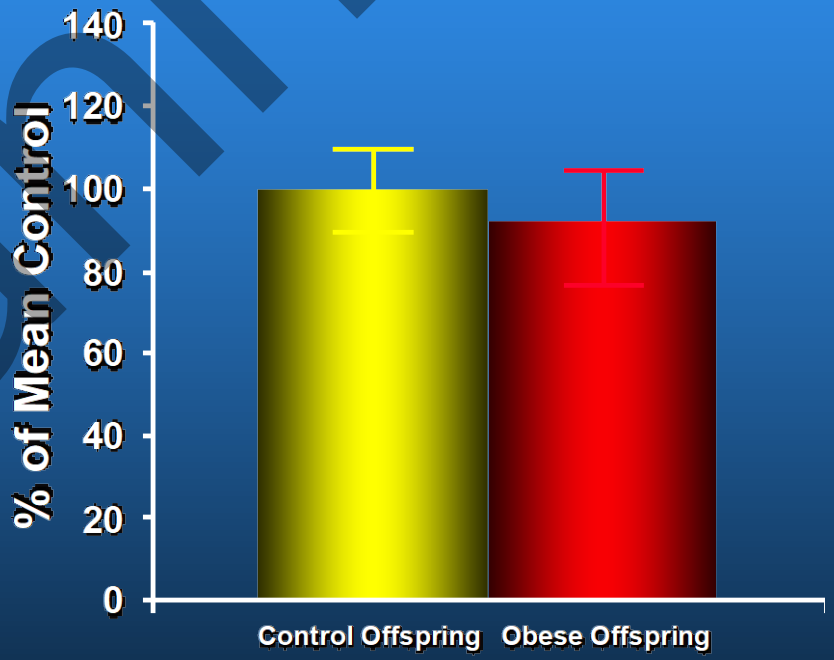


Fernandez-Twinn, et al., 2014

De Almeida-Faria, et al., 2021

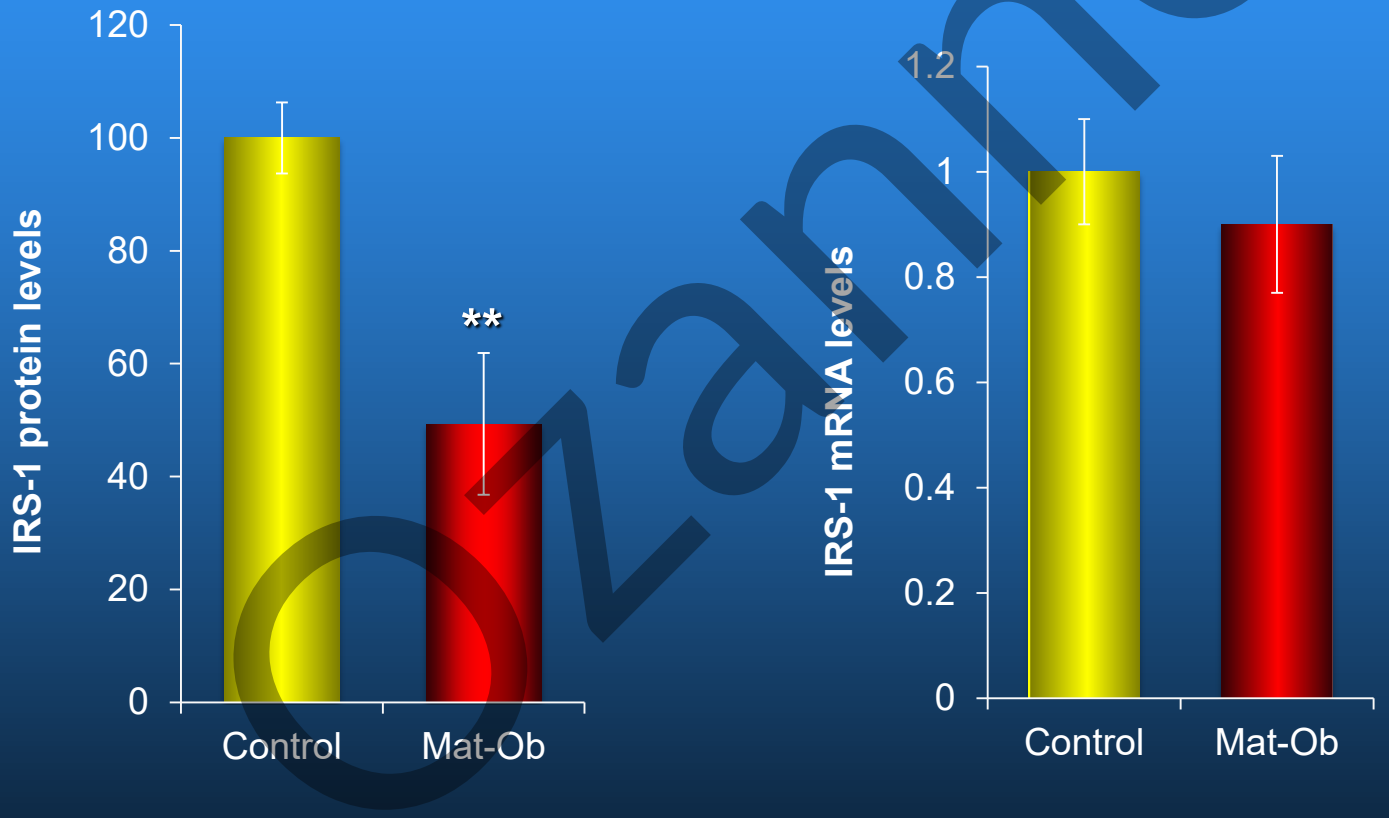
Post-Transcriptional Programming of Adipose Tissue IRS-1 by Maternal Diet-Induced Obesity





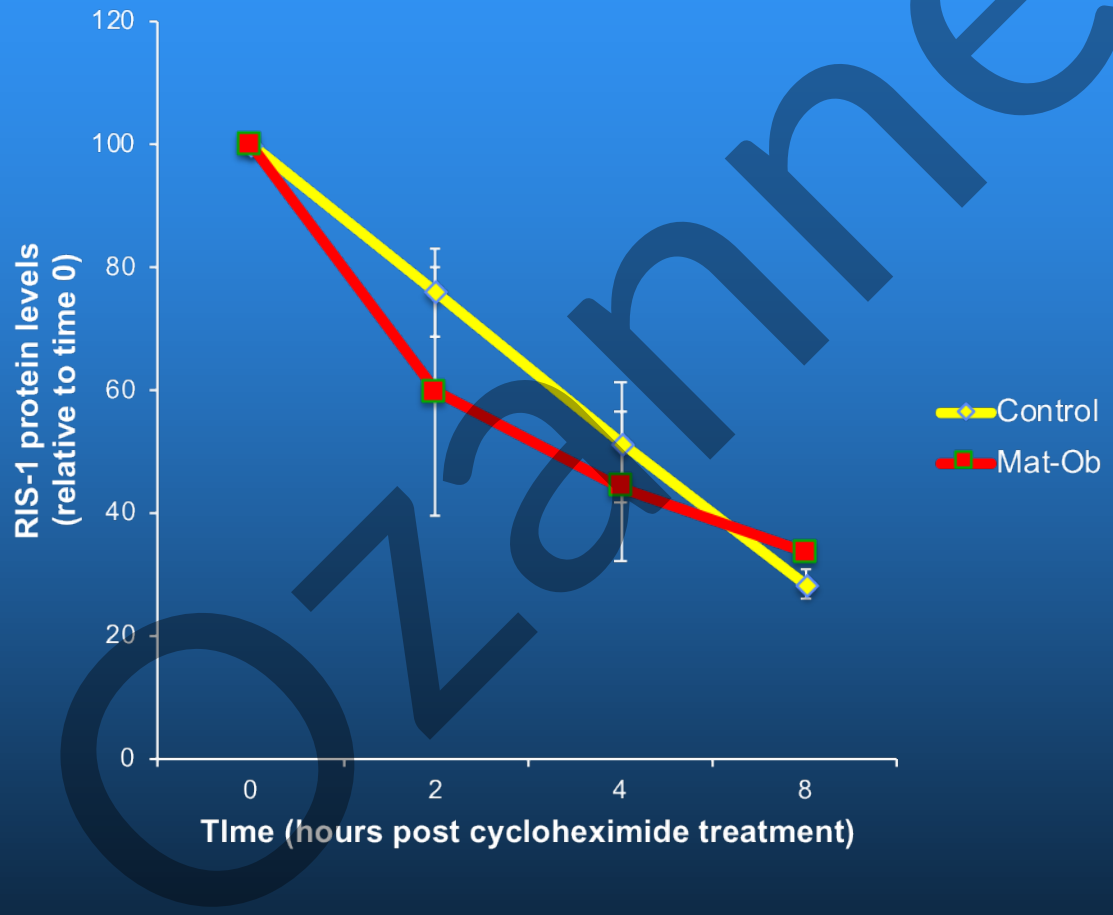
Is this effect maintained following *in vitro* culture?

Cell Autonomous Programming of IRS-1 by Maternal Diet-Induced Obesity



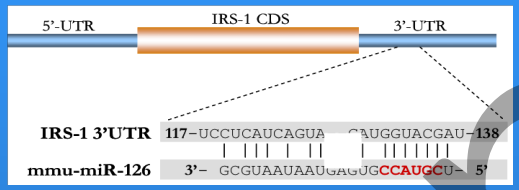
Fernandez-Twinn, et al., 2014

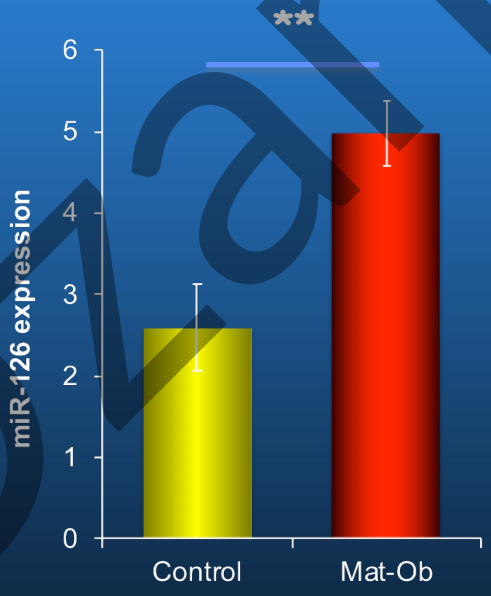
Mechanisms of IRS-1 Programming



Fernandez-Twinn, et al., 2014

miR-126 is Programmed

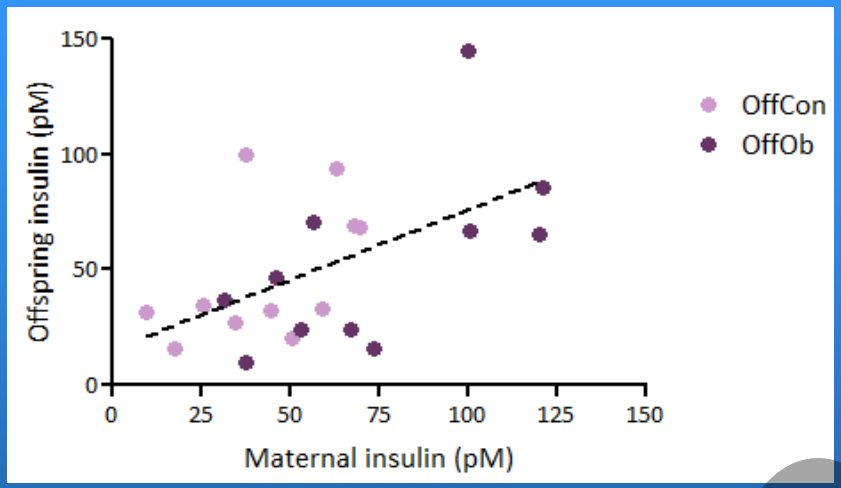




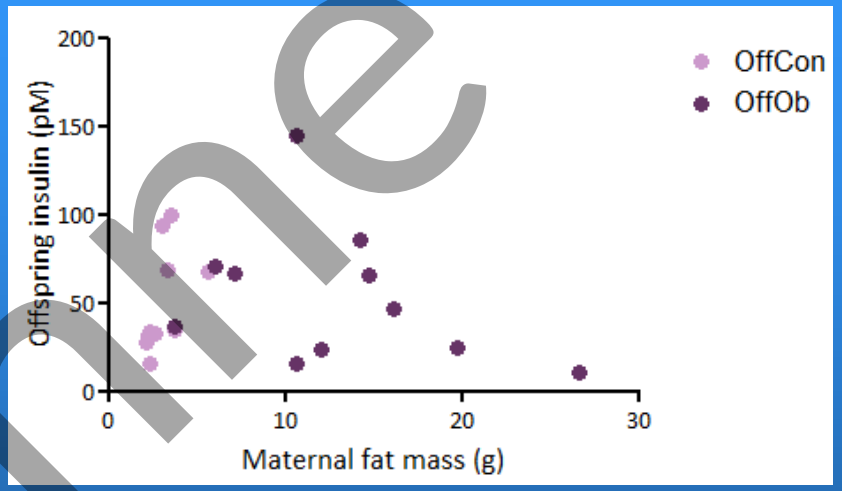
De Almeida-Faria, et al., 2021

Intervention in the Mother: What do we target?

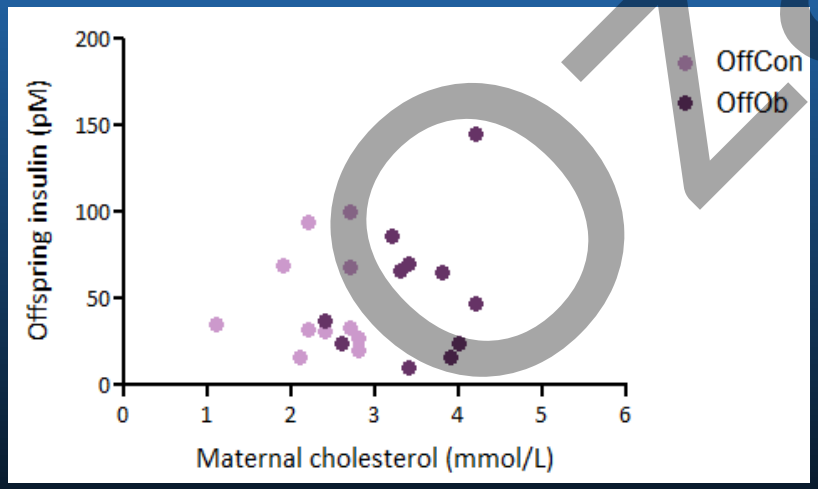
Maternal Predictors of Offspring Insulin



P < 0.01 Pearson's r = 0.54



Pearson's r = - 0.12



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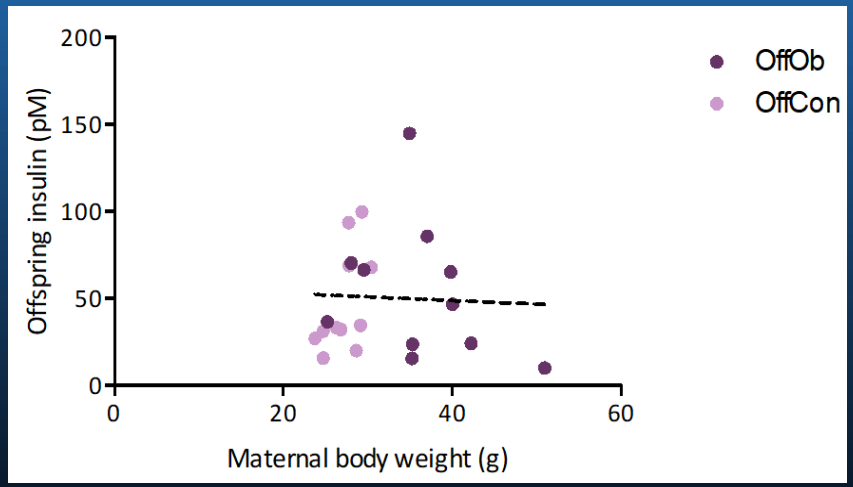


Pearson's r = - 0.042

Can we improve the metabolic milieu in the mother by exercise intervention?

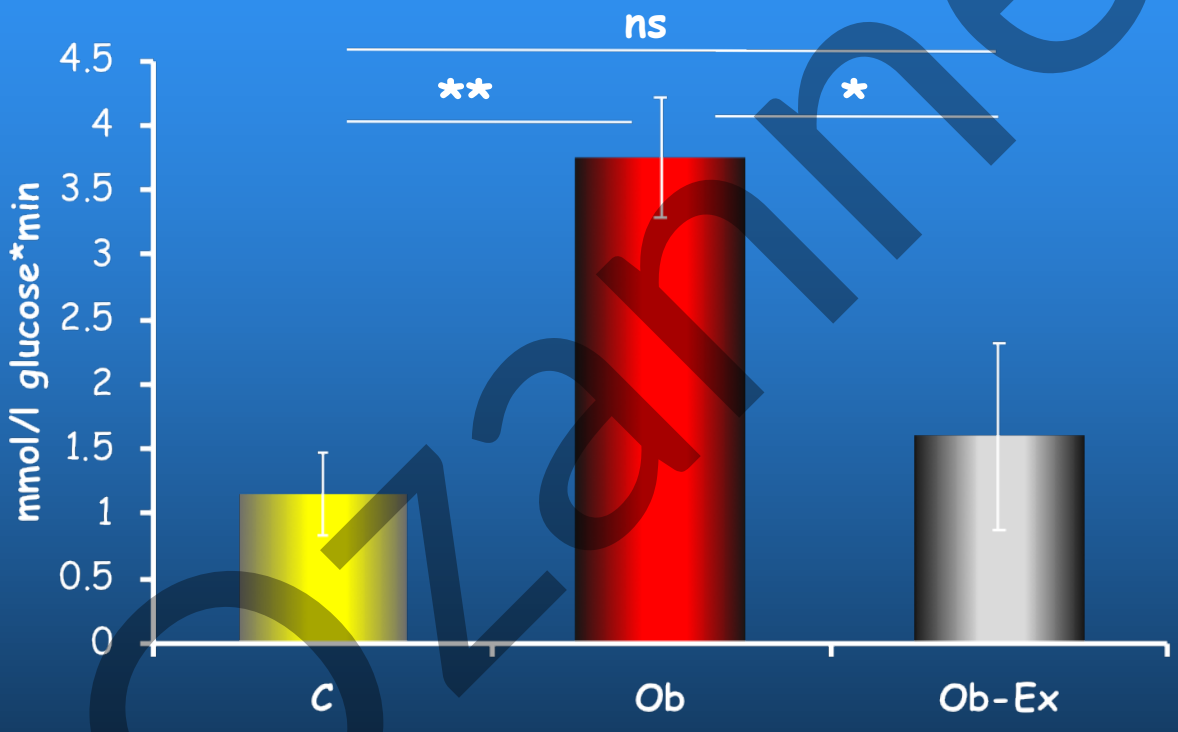
Maternal Exercise Intervention

	Pre-mating	Gestation
Control	10 WEEKS	3 WEEKS
Obese	10 WEEKS	3 WEEKS
Obese-Ex	10 WEEKS	3 WEEKS

1 week training

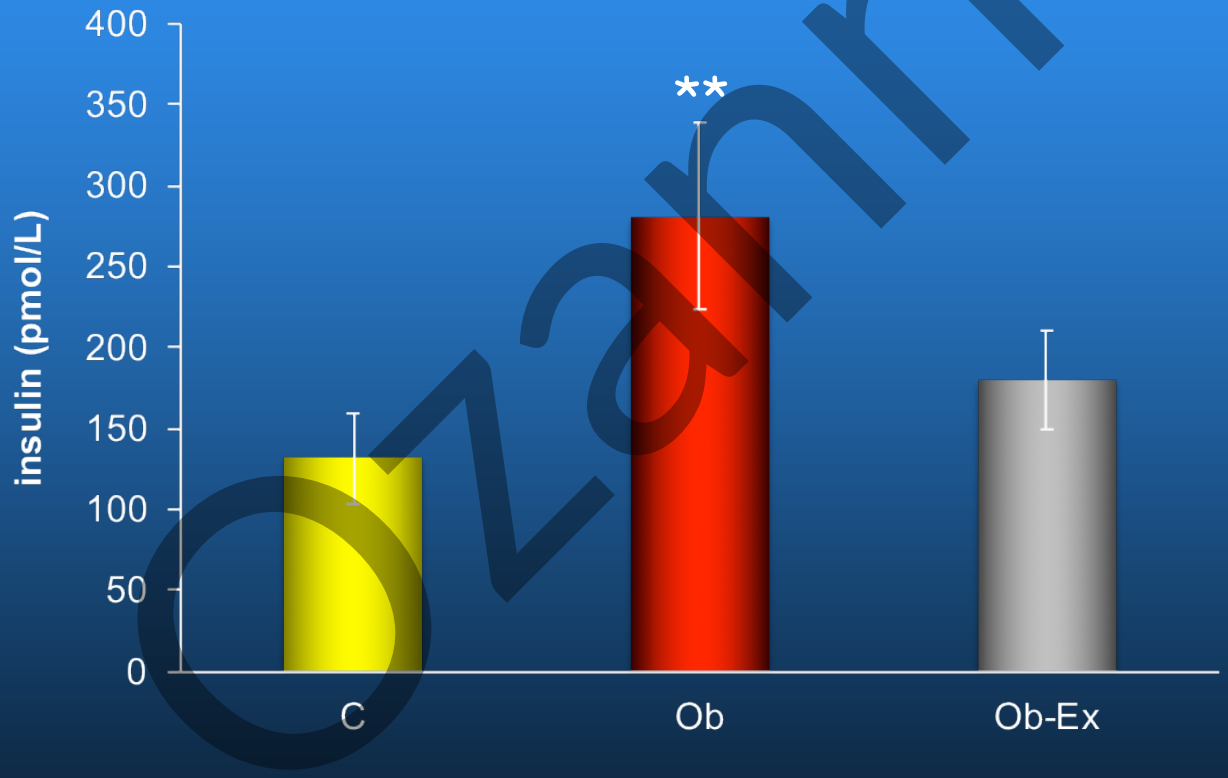
20 min/day
5 days/week

Maternal Glucose Tolerance



Fernandez-Twinn et al. 2017

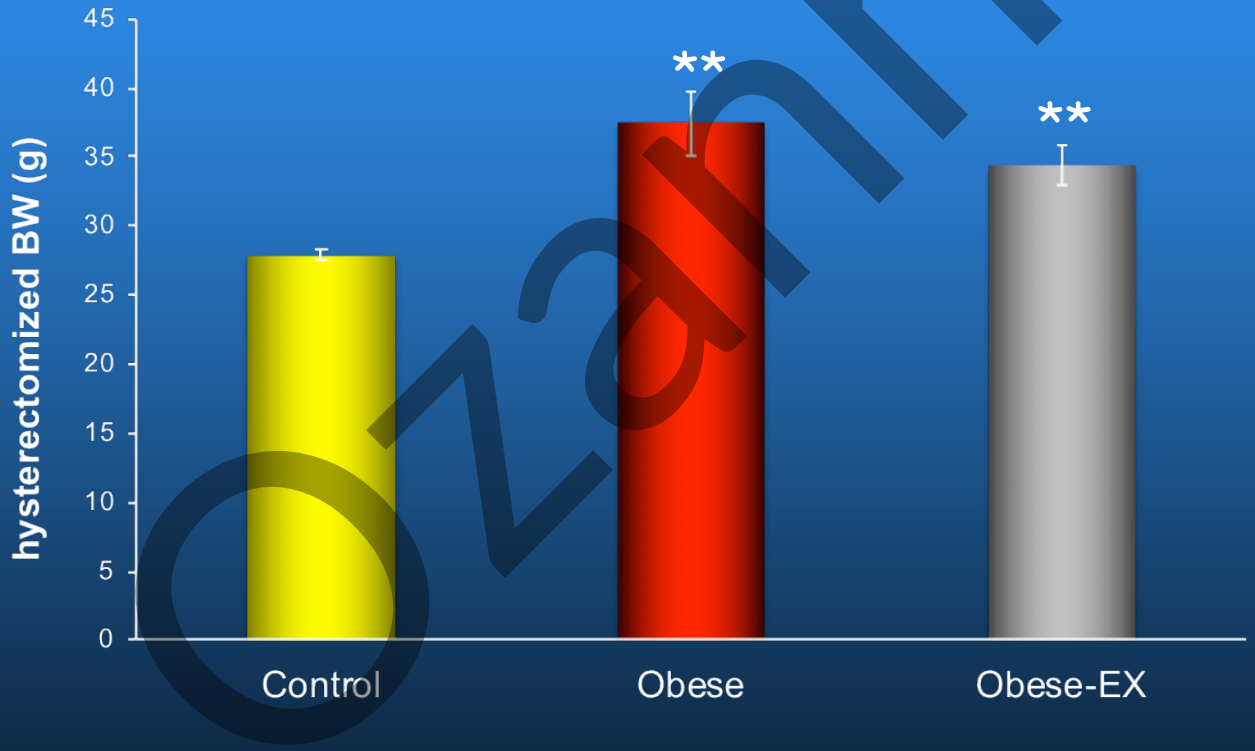
Maternal Insulin



** p < 0.01 compared to controls

Fernandez-Twinn et al. 2017

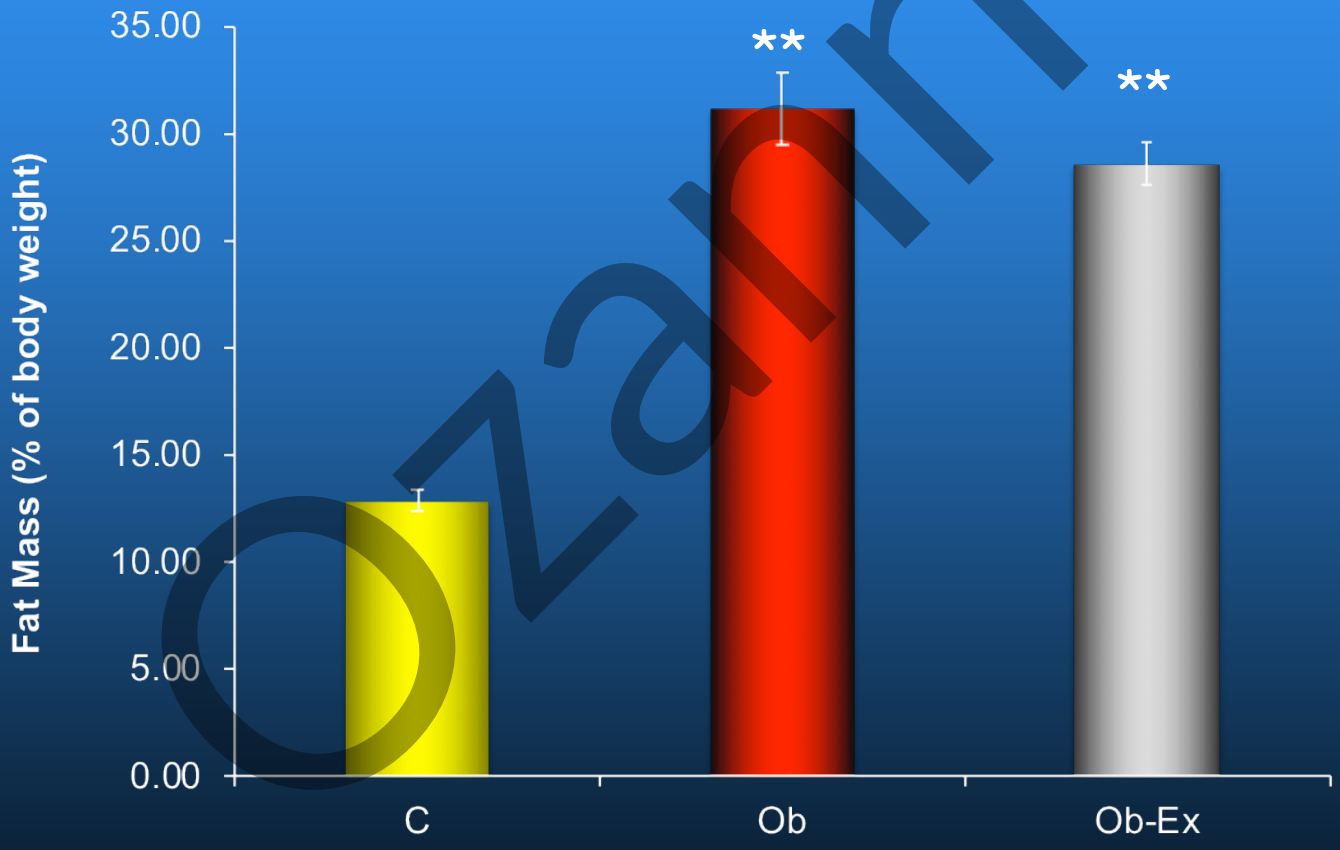
Maternal Weight



** p < 0.01 compared to controls

Fernandez-Twinn et al. 2017

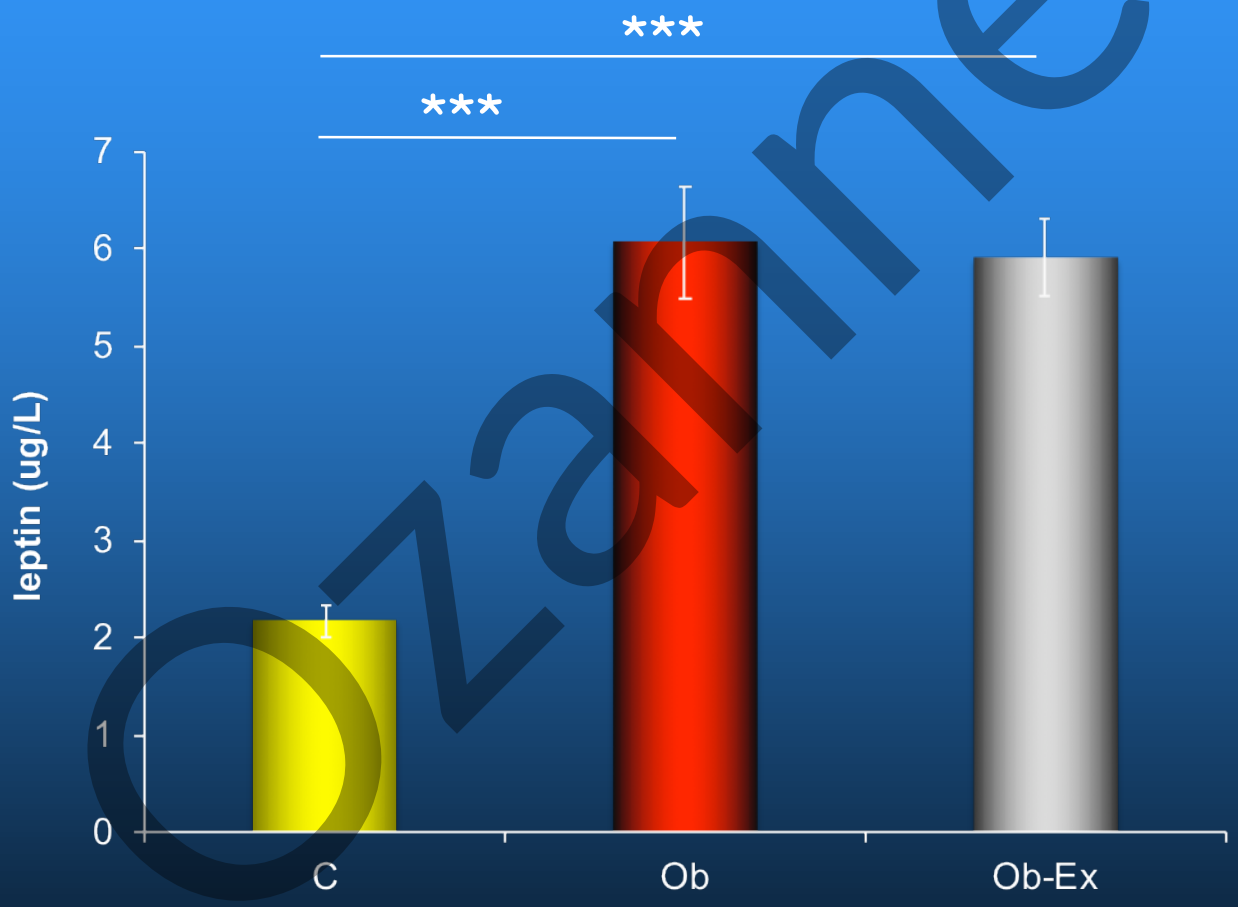
Maternal Fat Mass



*** p < 0.001 compared to controls

Fernandez-Twinn et al. 2017

Maternal Leptin

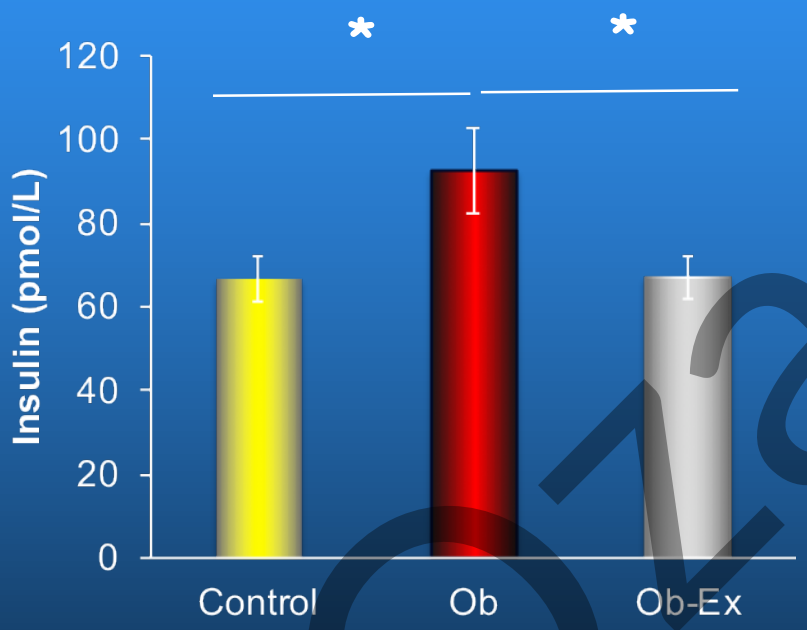


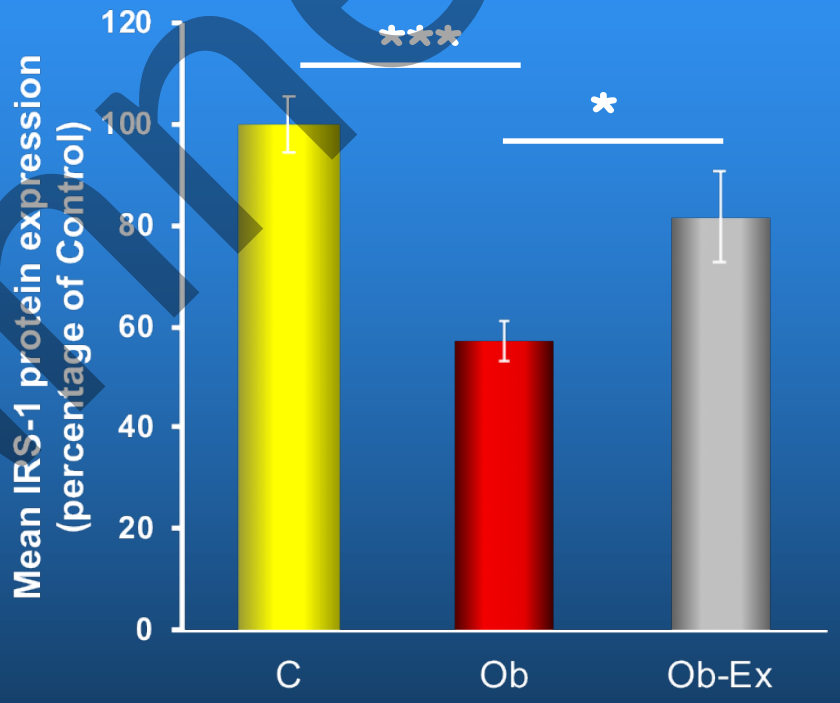
*** p < 0.001 compared to controls

Fernandez-Twinn et al. 2017

Does maternal exercise intervention prevent detrimental effects in the offspring?

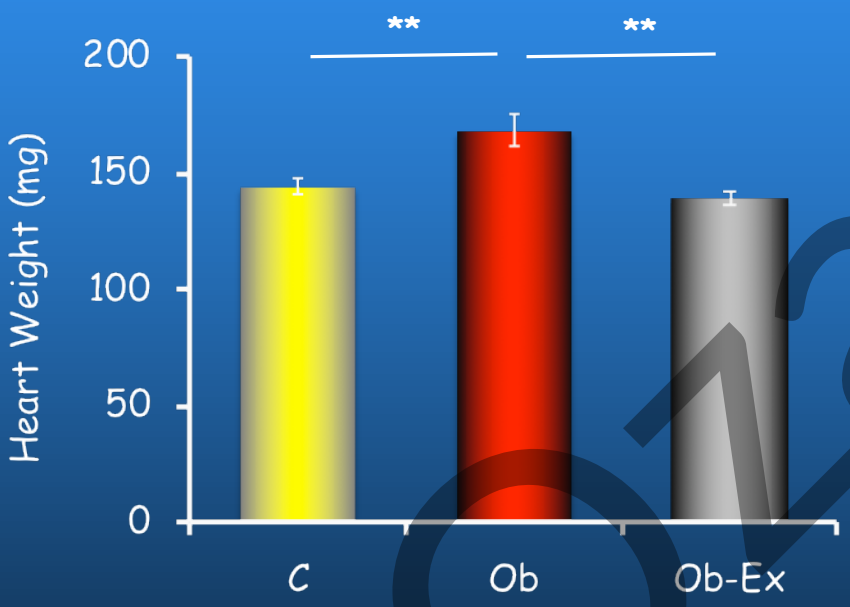
Offspring Insulin and IRS-1

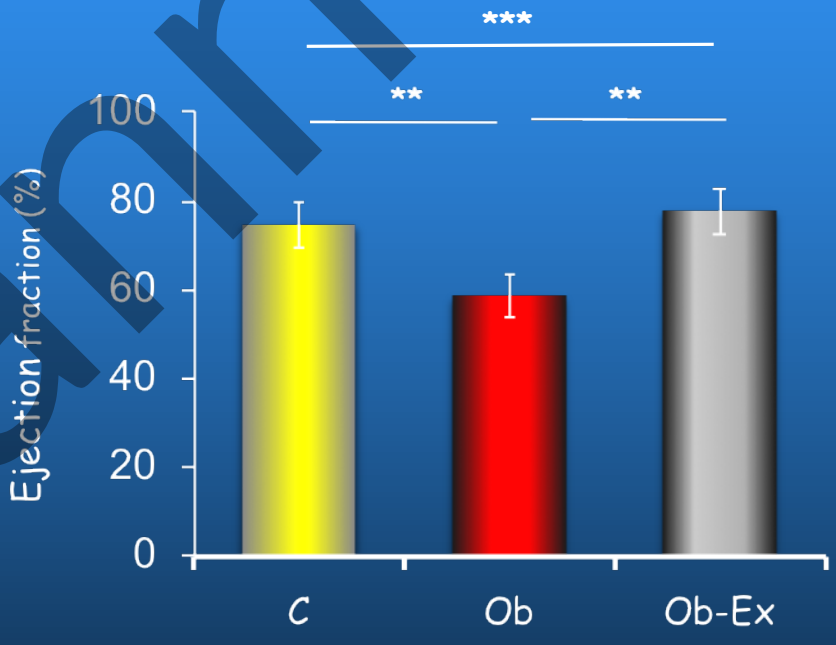




Fernandez-Twinn et al. 2017

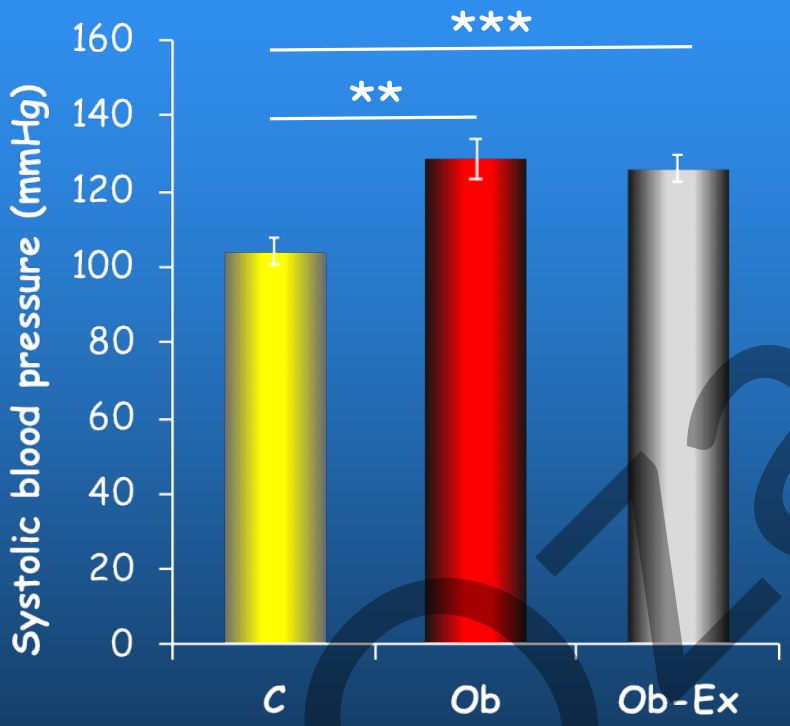
Offspring Heart Weight and Function





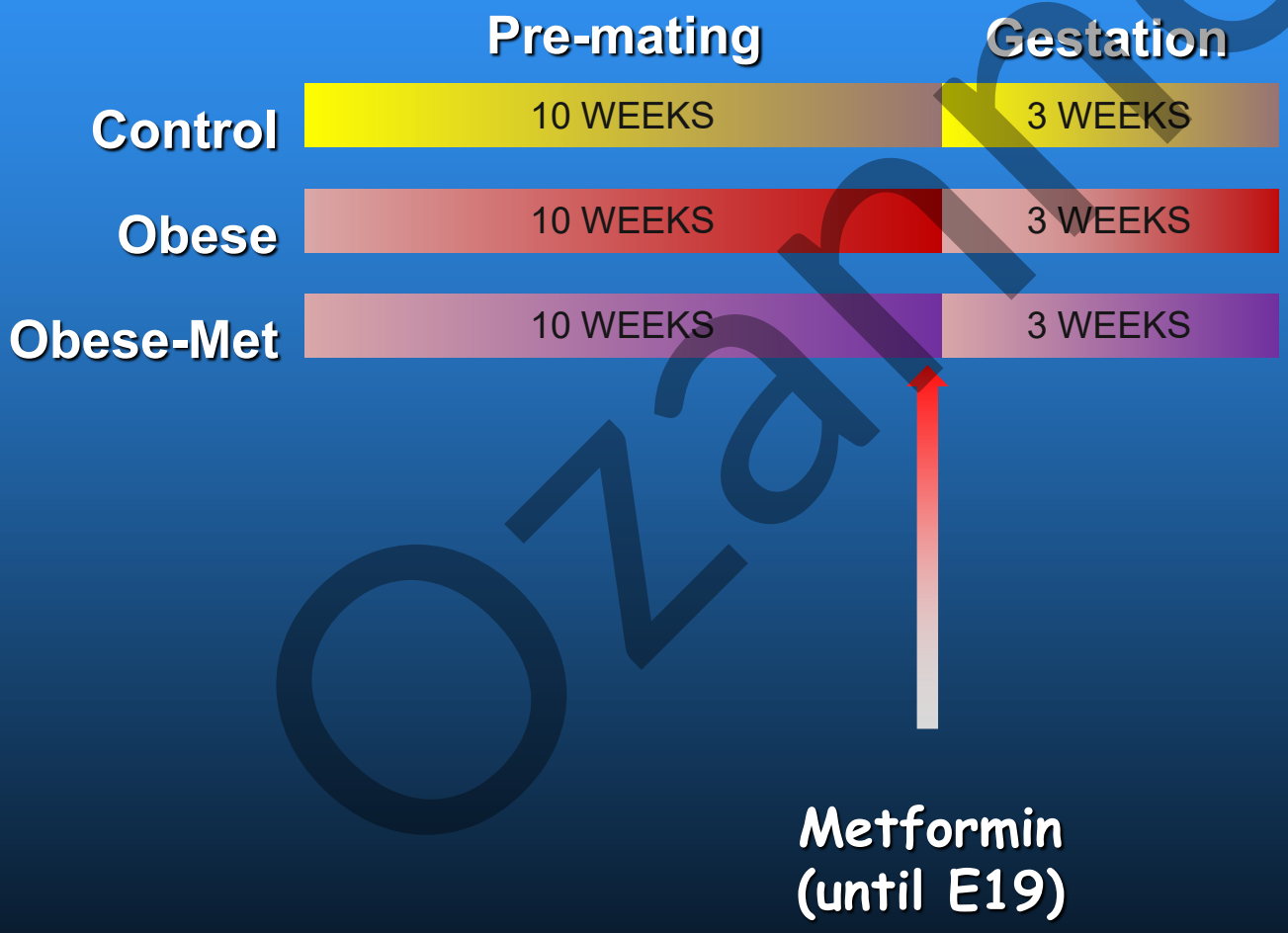
Beeson et al 2018

Offspring Blood Pressure



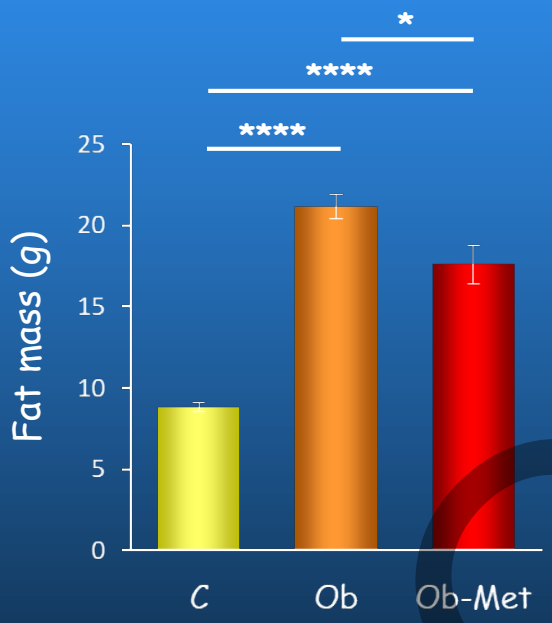
Beeson et al 2018

Maternal Metformin Intervention

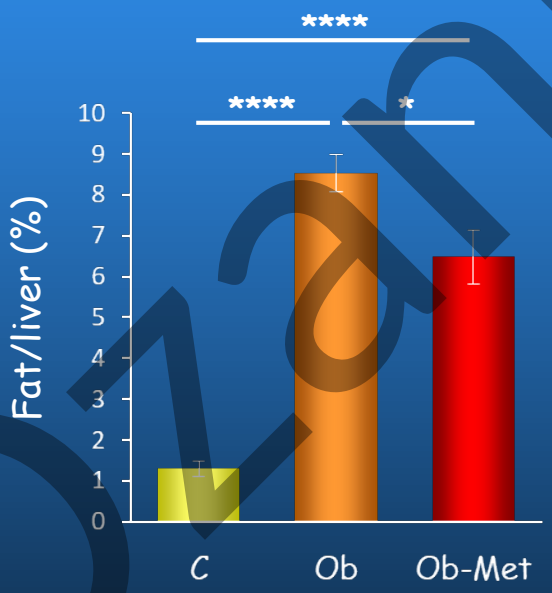


Maternal Physiology

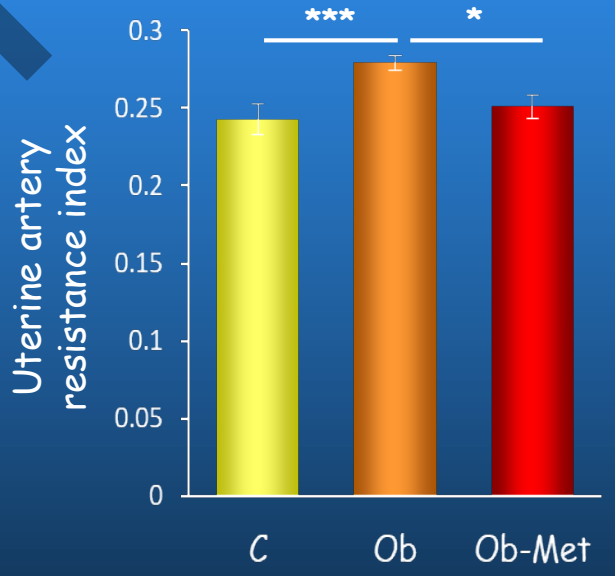
Body Fat



Liver Fat

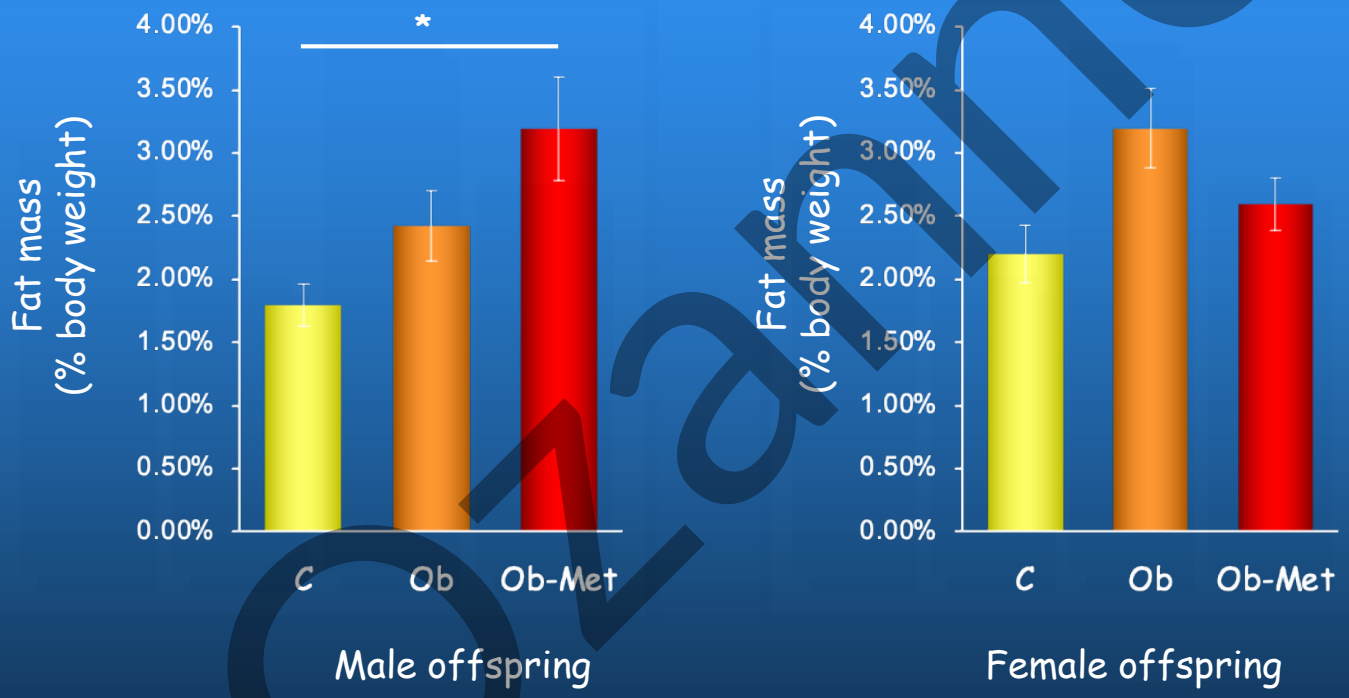


Uterine Artery RI



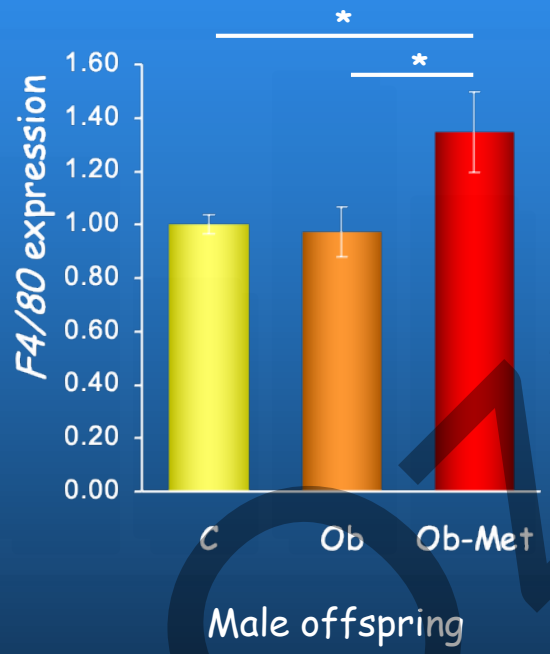
Hufnagel et al 2022

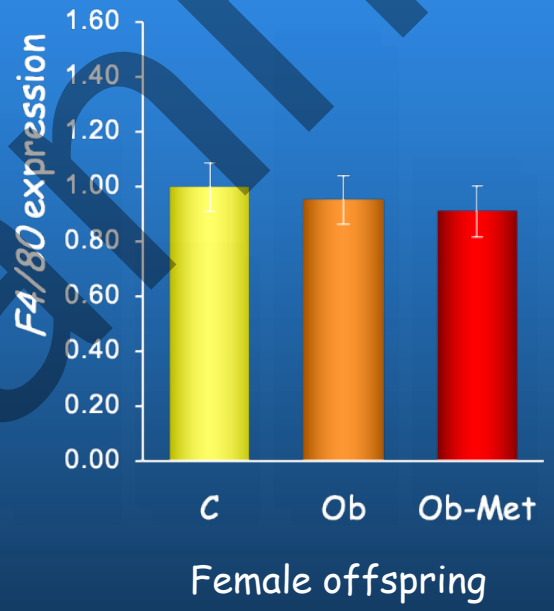
Young Adult Offspring Fat Mass



Schoonejans et al 2021

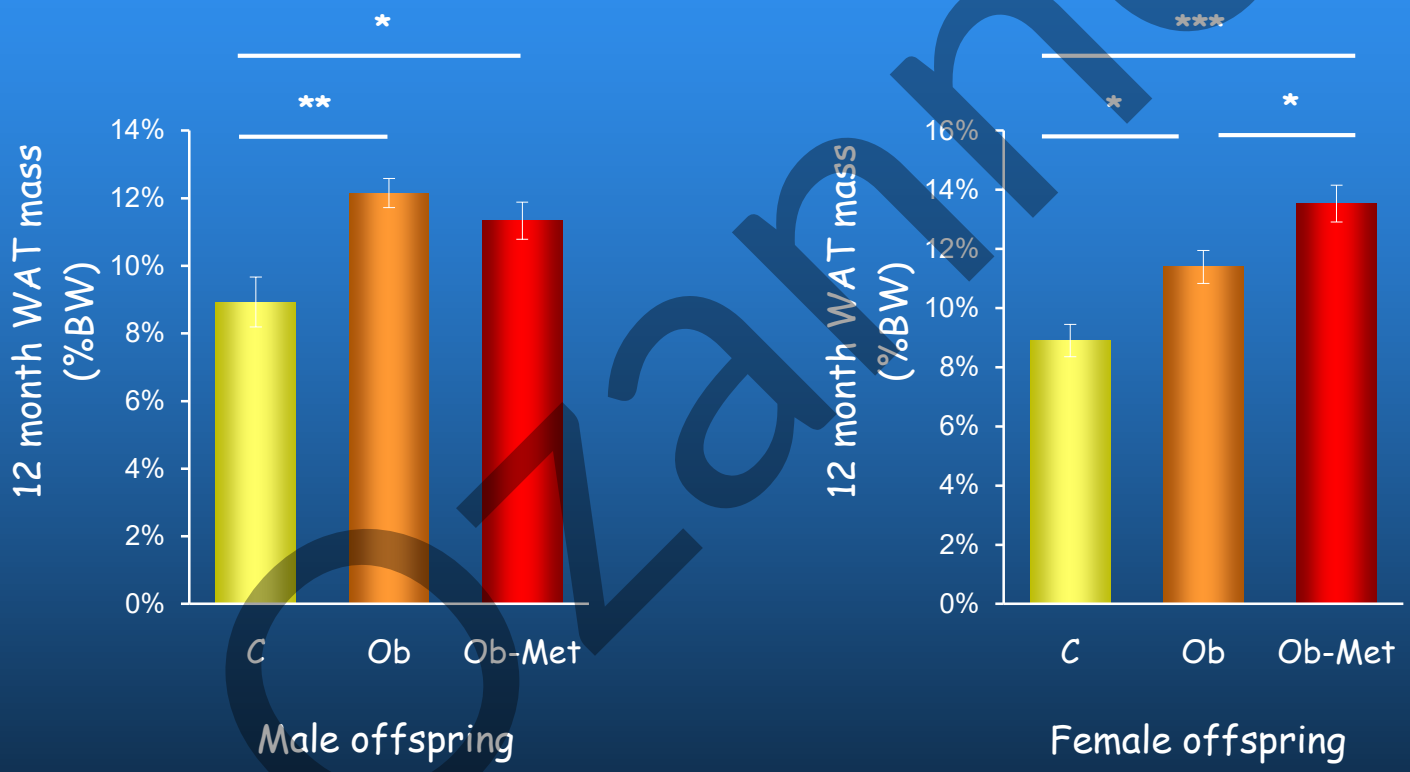
Young Adult Offspring Fat Inflammation





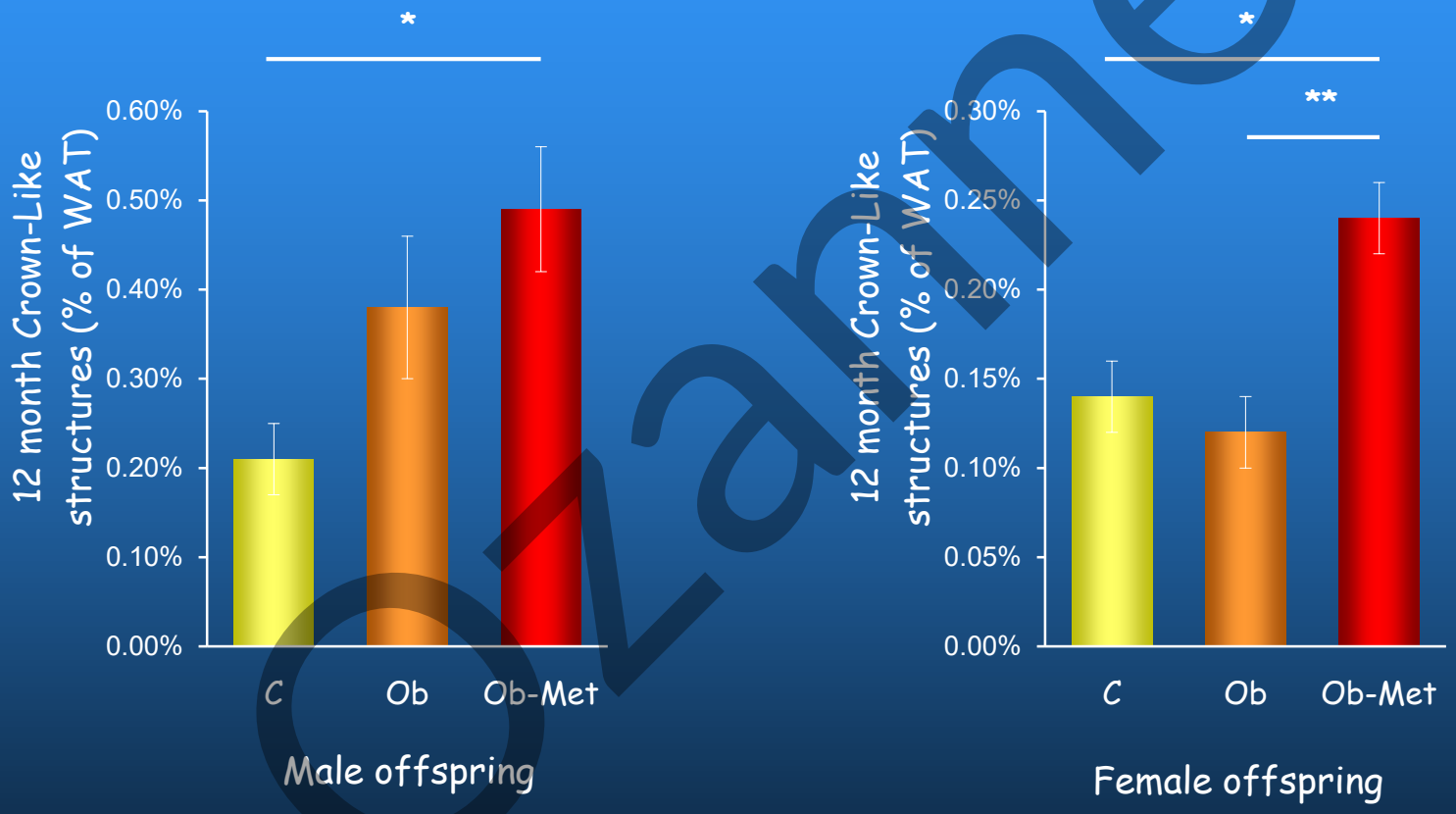
Schoonejans et al 2021

Old Adult Offspring Fat Mass



Schoonejans et al 2022

Old Adult Offspring Fat Inflammation



Schoonejans et al 2022

Meta-Analysis of Randomised to Metformin versus Insulin for GDM

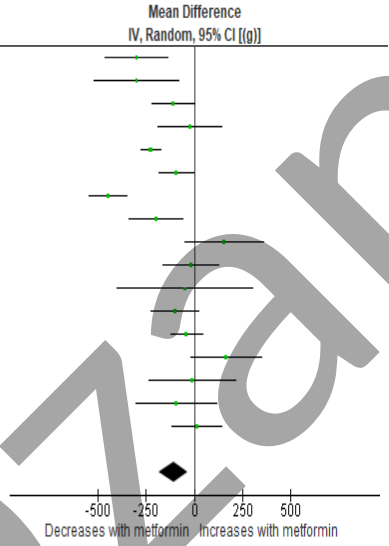
Meta-analysis of studies that randomised to metformin v insulin for GDM

28 studies (n=3976 participants)

Study or Subgroup	Metformin Mean [(g)]	Metformin SD [(g)]	Metformin Total	Insulin Mean [(g)]	Insulin SD [(g)]	Insulin Total	Weight	Mean Difference IV, Random, 95% CI [(g)]
Ainuddin J.A, 2015	3,400	400	43	3,700	500	75	5.7%	-300.00 [-464.62, -135.38]
Arshad R, 2017	3,140	320	25	3,440	460	25	4.7%	-300.00 [-519.66, -80.34]
Ashoush S, 2016	3,431	286	47	3,541	271	48	6.7%	-110.00 [-222.08, 2.08]
Borg et al, 2016	3,338	395	50	3,362	459	50	5.7%	-24.00 [-191.85, 143.85]
Eid S.R, 2018	3,037	204	113	3,264	202	116	7.6%	-227.00 [-279.59, -174.41]
Ghomian N, 2018	3,450	548	143	3,544	57	143	7.1%	-94.00 [-184.30, -3.70]
Hamandi A, 2017	3,220	200	30	3,670	190	30	7.0%	-450.00 [-548.71, -351.29]
Hassan J.A, 2012	3,400	400	75	3,600	460	75	6.3%	-200.00 [-337.96, -62.04]
Ijas H, 2011	3,712	432	47	3,558	593	50	5.0%	154.00 [-51.60, 359.60]
Mesadaghinia E, 2013	3,512	484	100	3,528	563	100	6.1%	-16.00 [-161.52, 129.52]
Moore L.E, 2007	3,451	727	32	3,500	700	31	2.9%	-49.00 [-401.37, 303.37]
Niromanesh S, 2012	3,300	400	80	3,400	400	80	6.5%	-100.00 [-223.96, 23.96]
Rowan J.A, 2008	3,372	572	363	3,413	569	370	7.2%	-41.00 [-123.61, 41.61]
Ruholamin S, 2014	3,342	506	50	3,176	438	50	5.3%	166.00 [-19.50, 351.50]
Somani P.S, 2016	2,840	320	32	2,850	570	33	4.7%	-10.00 [-233.86, 213.86]
Spaulonci C.P, 2013	3,143	444	47	3,237	586	47	4.9%	-94.00 [-304.19, 116.19]
Tertti K, 2013	3,604	488	109	3,589	488	107	6.4%	15.00 [-115.16, 145.16]
Total (95% CI)			1386			1430	100.0%	-107.69 [-182.70, -32.68]

Heterogeneity: Tau² = 18430.52; Chi² = 91.71, df = 16 (P < 0.00001); I² = 83%

Test for overall effect: Z = 2.81 (P = 0.005)



Children exposed to metformin compared to insulin are:

- Are born lighter (108g, p<0.01)

Meta-Analysis of Randomised to Metformin versus Insulin for GDM

Meta-analysis of studies that randomised to metformin v insulin for GDM

28 studies (n=3976 participants)

Study or Subgroup	Metformin Mean [(g)]	Metformin SD [(g)]	Metformin Total	Insulin Mean [(g)]	Insulin SD [(g)]	Insulin Total	Weight	Mean Difference IV, Random, 95% CI [(g)]
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Ruholamin S, 2014	3,342	506	50	3,176	438	50	5.3%	166.00 [-19.50, 351.50]
Somani P.S, 2016	2,840	320	32	2,850	570	33	4.7%	-10.00 [-233.86, 213.86]
Spaulonci C.P, 2013	3,143	444	47	3,237	586	47	4.9%	-94.00 [-304.19, 116.19]
Tertti K, 2013	3,604	488	109	3,589	488	107	6.4%	15.00 [-115.16, 145.16]
Total (95% CI)			**1386**			**1430**	**100.0%**	**-107.69 [-182.70, -32.68]**

Heterogeneity: Tau² = 18430.52; Chi² = 91.71, df = 16 (P < 0.00001); I² = 83%
Test for overall effect: Z = 2.81 (P = 0.005)

Mean Difference IV, Random, 95% CI [(g)]

-500 -250 0 250 500
Decreases with metformin Increases with metformin

Study or Subgroup	Metformin Mean	Metformin SD	Metformin Total	Insulin Mean	Insulin SD	Insulin Total	Weight	Mean Difference IV, Fixed, 95% CI
Rowan J.A - Adelaide 7yrs, 2018	17.2	2.5	98	16.9	2.5	51	33.9%	0.30 [-0.64, 1.24]
Rowan J.A - Auckland 9yrs, 2018	19.3	4.6	45	17.7	3	54	12.3%	1.60 [0.04, 3.16]
Tertti K 5yr, 2016	16.4	2.1	45	15.5	1.5	48	53.9%	0.90 [0.15, 1.65]
Total (95% CI)			**148**			**153**	**100.0%**	**0.78 [0.23, 1.33]**

Heterogeneity: Chi² = 2.16, df = 2 (P = 0.34); I² = 7%
Test for overall effect: Z = 2.80 (P = 0.005)

Mean Difference IV, Fixed, 95% CI

-10 -5 0 5 10
Decreases with metformin Increases with metformin

Children exposed to metformin compared to insulin are:

- Are born lighter (108g, p<0.01)
- Are 0.44kg heavier in infancy (18-24 months, p<0.01)
- Have higher BMI (by 0.8 units, p<0.01) and increased adiposity by mid-childhood (5-9 years)

Conclusions and Perspectives

- Obesity during pregnancy impacts on maternal and offspring cardio-metabolic health
- Mechanistic insight from animal models suggest insulin is a key programming factor
- Improvements in maternal and offspring health can occur without weight loss
- Intervention strategies need to consider short- and long- term effects for both mother and child as well as interaction with fetal sex
- Pregnancy is a window of opportunity to improve health of at least two generations