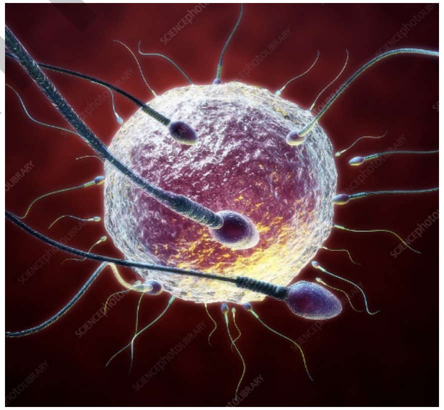
The University of Nottingham

UNITED KINGDOM · CHINA · MALAYSIA

How men’s diet influences the health of the fetus

Dr Adam Watkins

adam.watkins@nottingham.ac.uk



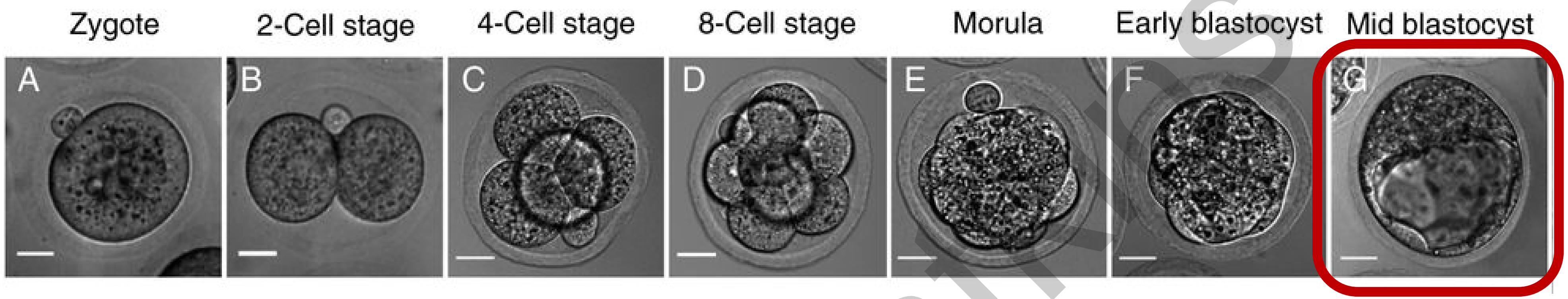
Conflicts of Interest

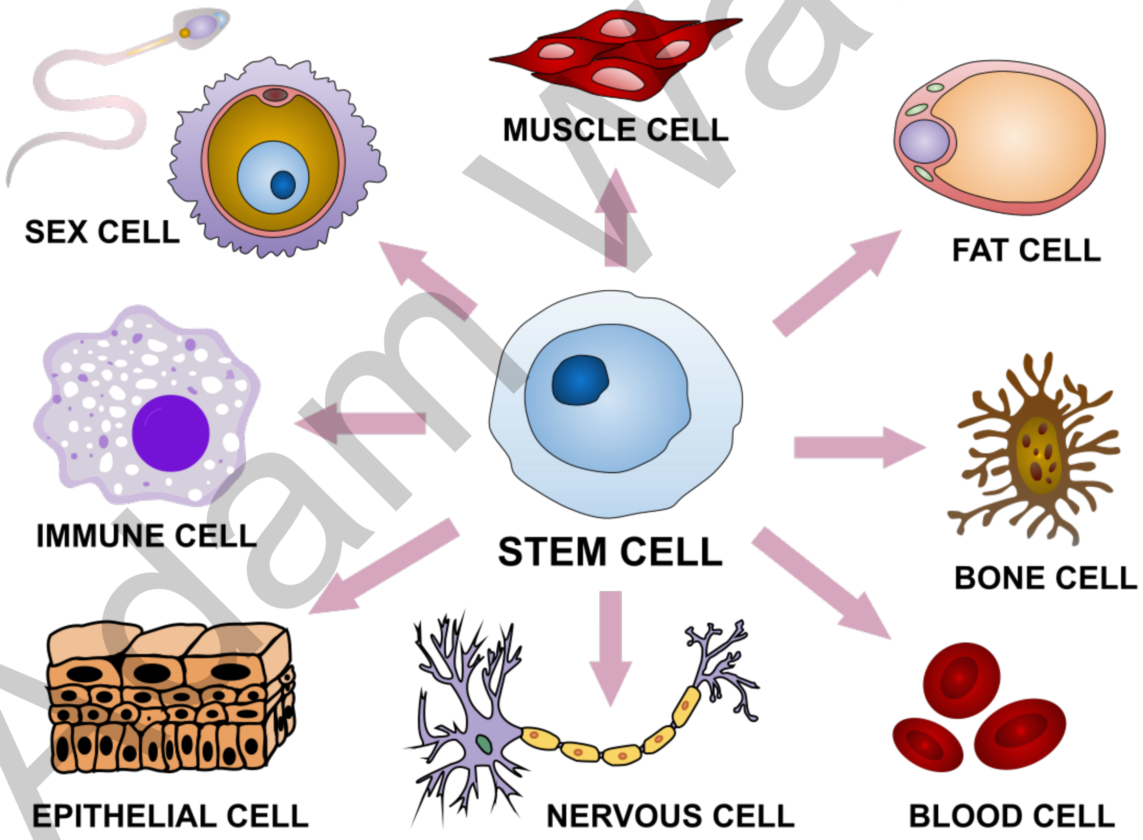
- No conflicts of interest to declare

University of Nottingham

Prof. Tom Fleming

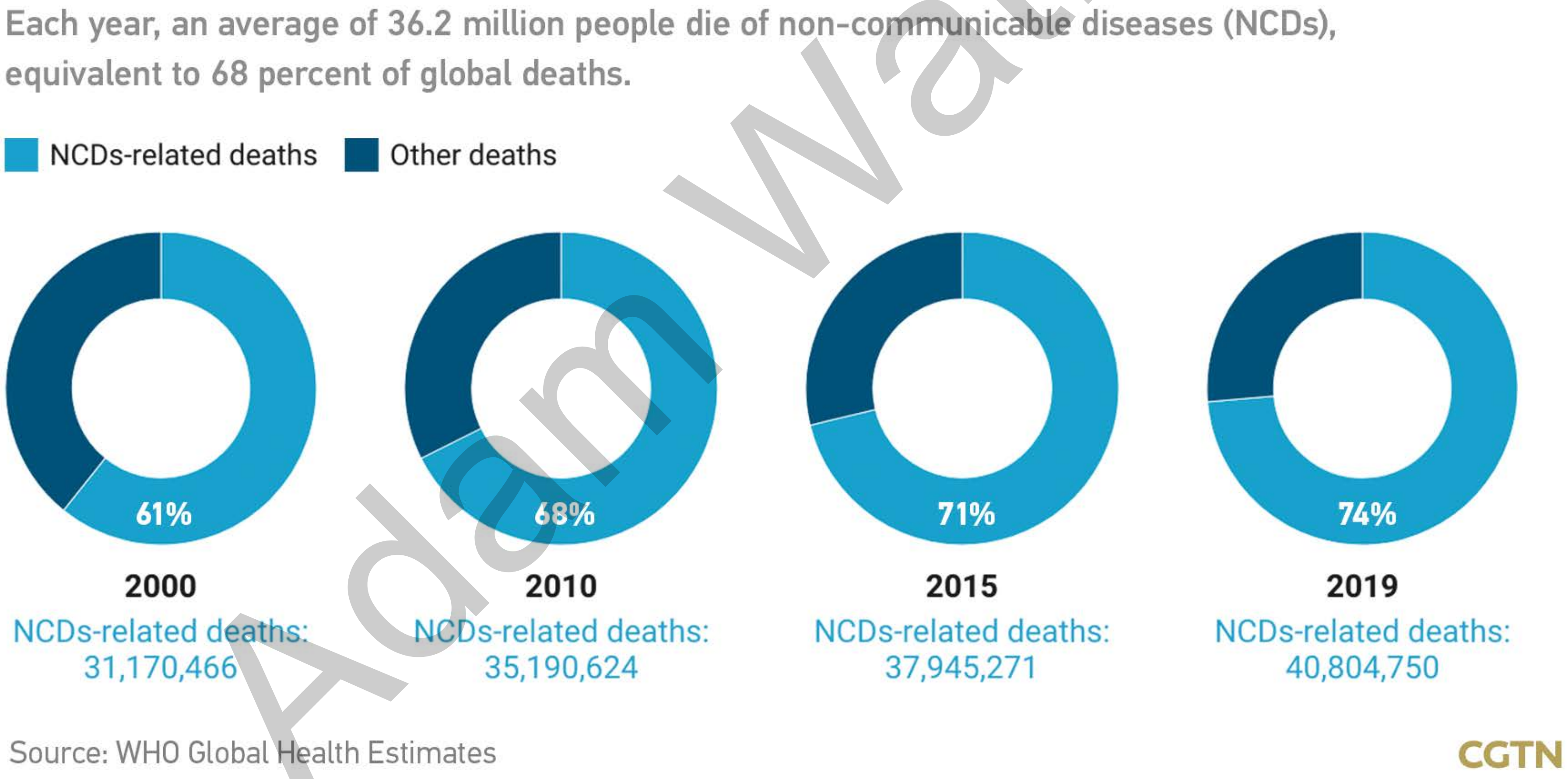
University of Southampton


Zygote
2-Cell stage
4-Cell stage
8-Cell stage
Morula
Early blastocyst
Mid blastocyst
A
B
C
D
E
F
G


SEX CELL
MUSCLE CELL
FAT CELL
IMMUNE CELL
STEM CELL
BONE CELL
EPITHELIAL CELL
NERVOUS CELL
BLOOD CELL

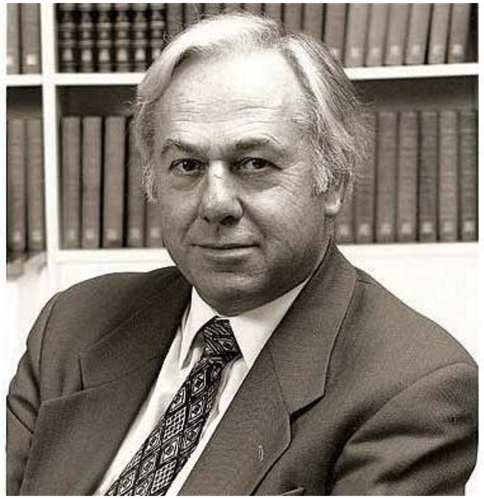
Non-communicable Diseases

Prevalence and deaths from non-communicable diseases (obesity, heart disease and type 2 diabetes) have increased dramatically



Lifestyle and Adult Health

Developmental Origins of Health and Disease (DOHaD)



Professor David Barker:

Patterns of in utero development can be predictive of adult non-communicable disease (obesity, type-2 diabetes, CVD) risk

Smaller / larger babies have :-

- Increased adult hypertension risk
- Raised serum cholesterol and obesity risk
- Impaired glucose tolerance and type 2 diabetes risk

Epidemiological Data Sets

Dutch Hunger Winter: Amsterdam 1944-45.

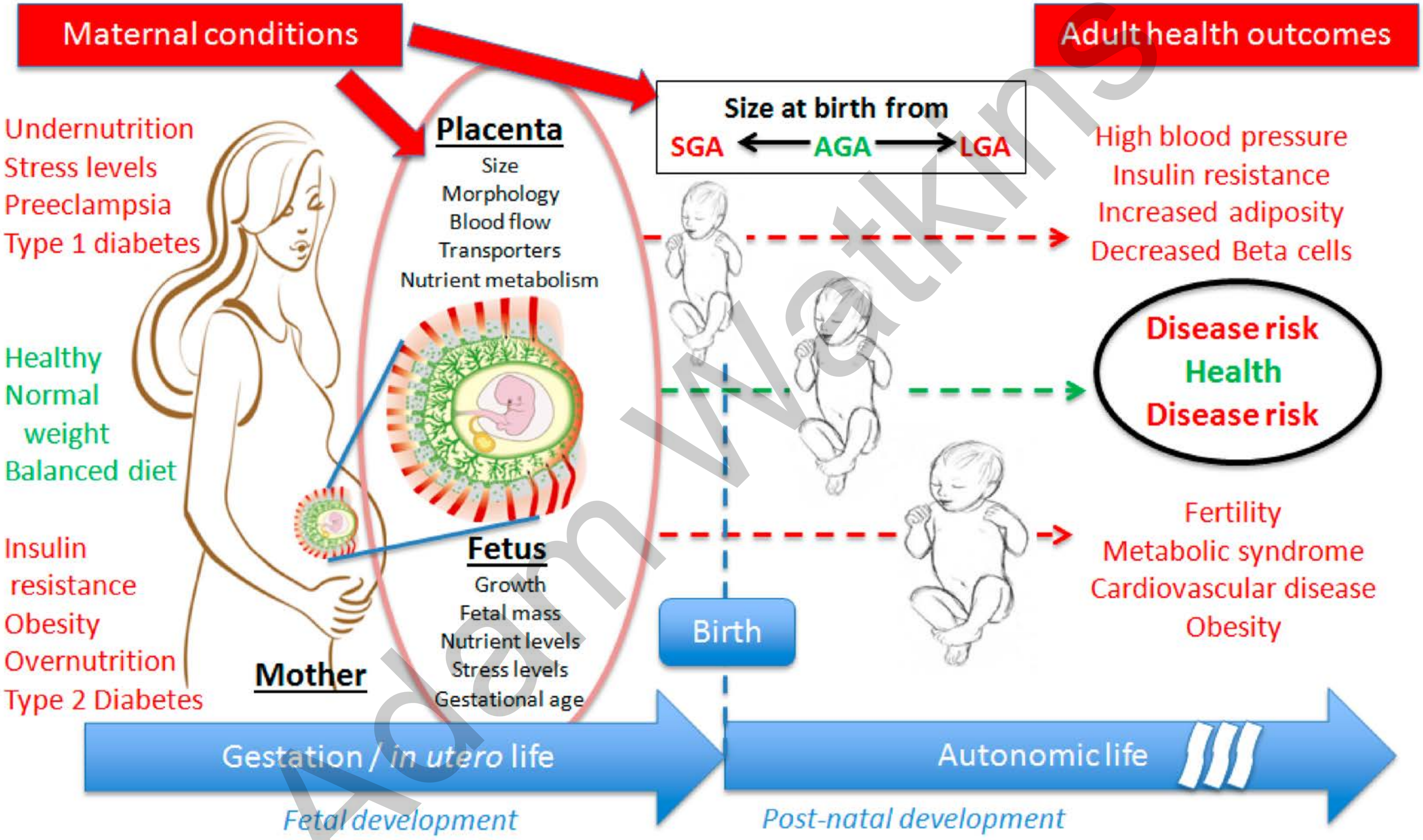
Painter et al, 2006, Am J Clin Nutr 84:322; Painter et al 2006 J Hypertens. 24:1771;
de Rooij et al, 2006, Diabetologia 49:637;
Ravelli et al, 1999, Am. J. Clin. Nutr. 70:811).

Great Leap Forward: (China 1958-1962)

Li, Y. et al. 2010. Diabetes 59, 2400–2406.
Wang, Z et al., 2017. BMC Public Health 17, 488,

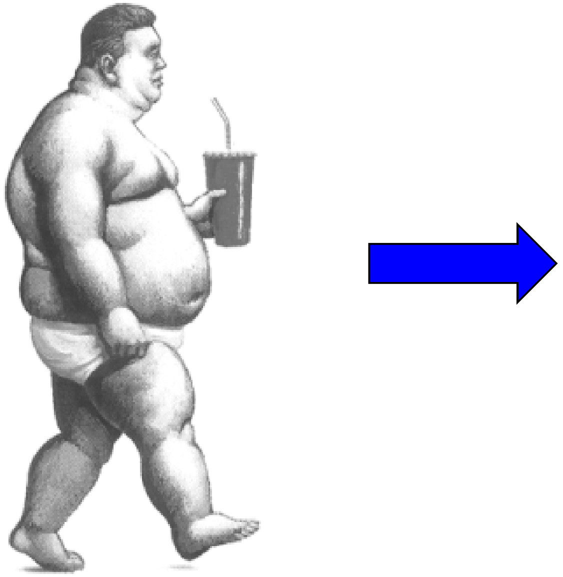
Siege of Leningrad: Russia 1941–1944

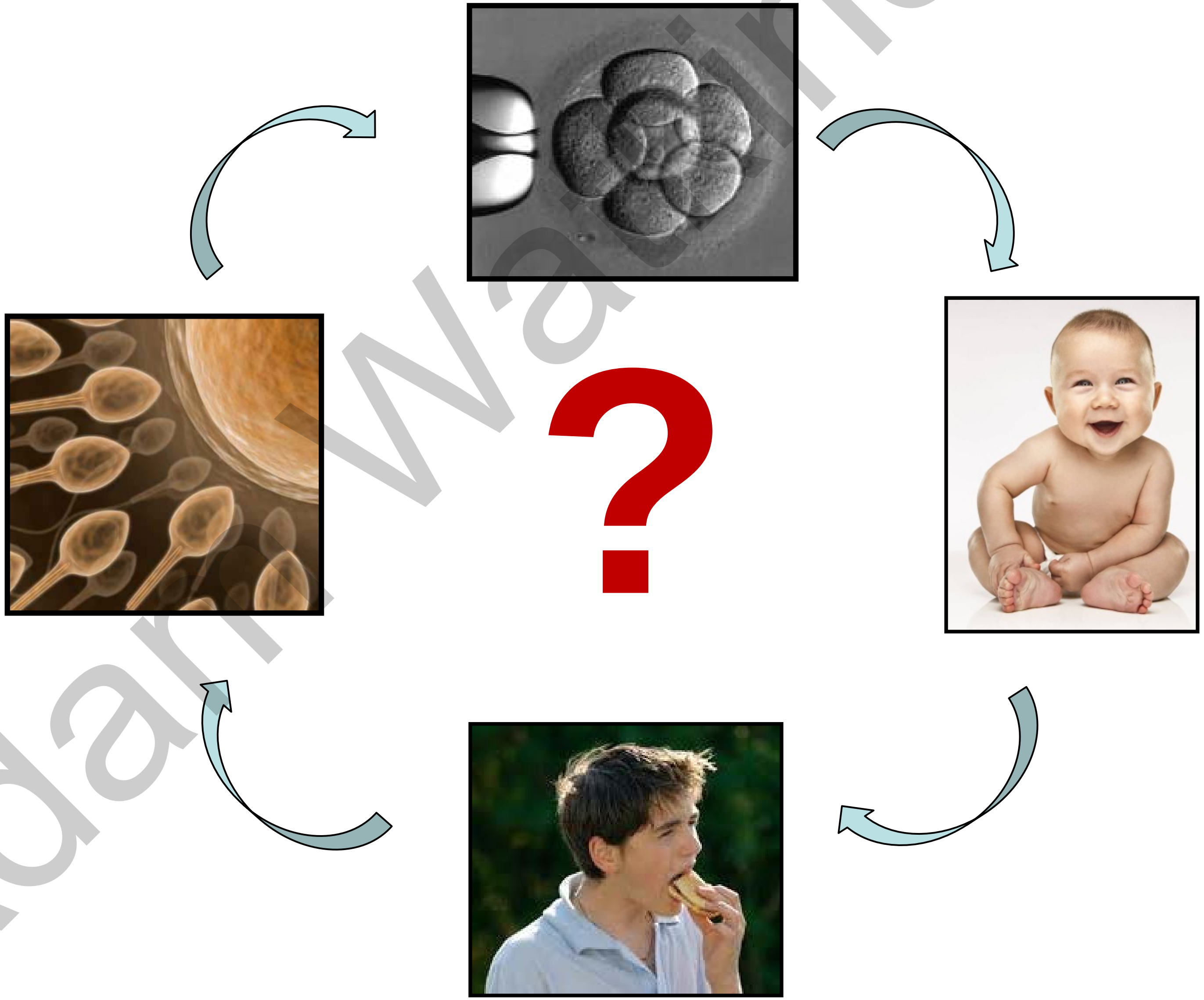
Alexander M. Vaiserman
Nutrients 2017, 9(3), 236;



Int. J. Environ. Res. Public Health 2016, 13(6), 586

Paternal Health and Offspring Development

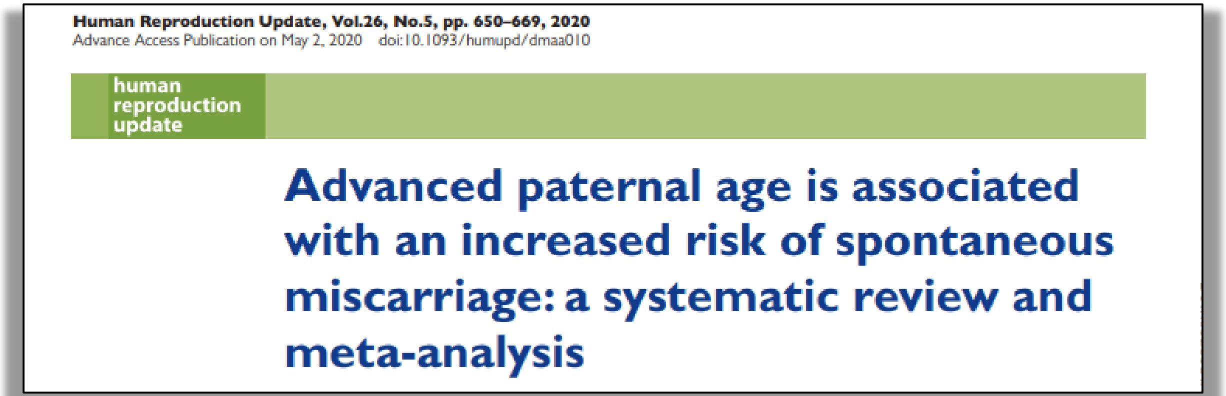




Impact of

- **Poor paternal lifestyle**
- **Increasing male age**
- **Infertility/subfertility**

Paternal Programming Effects



Human Reproduction Update, Vol.26, No.5, pp. 650–669, 2020
Advance Access Publication on May 2, 2020 doi:10.1093/humupd/dmaa010

human reproduction update

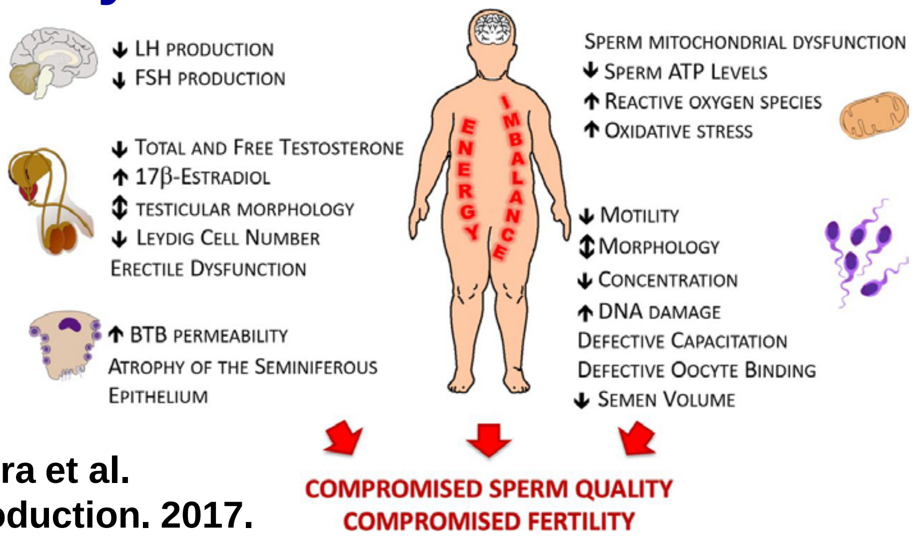
Advanced paternal age is associated with an increased risk of spontaneous miscarriage: a systematic review and meta-analysis

[redacted]

[redacted]

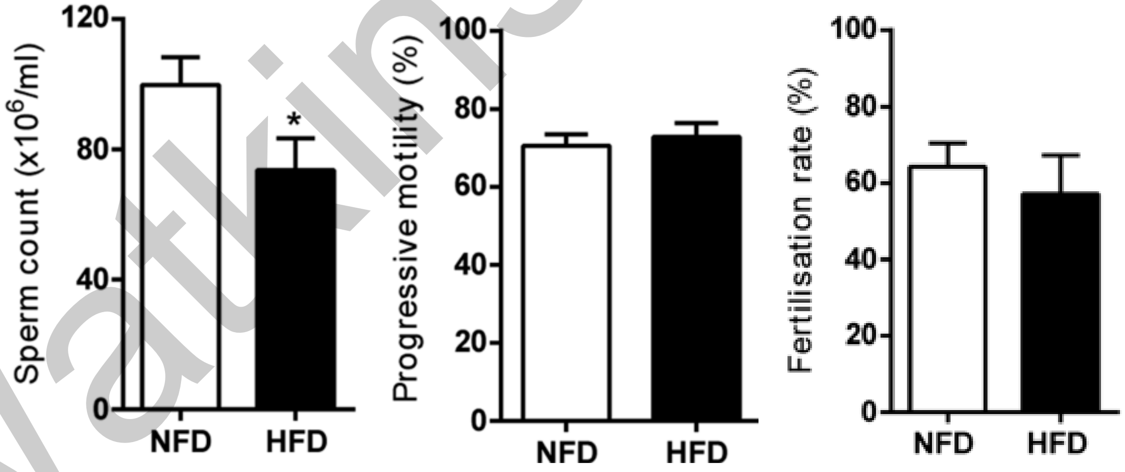
Male Diet and Sperm Quality

Obesity



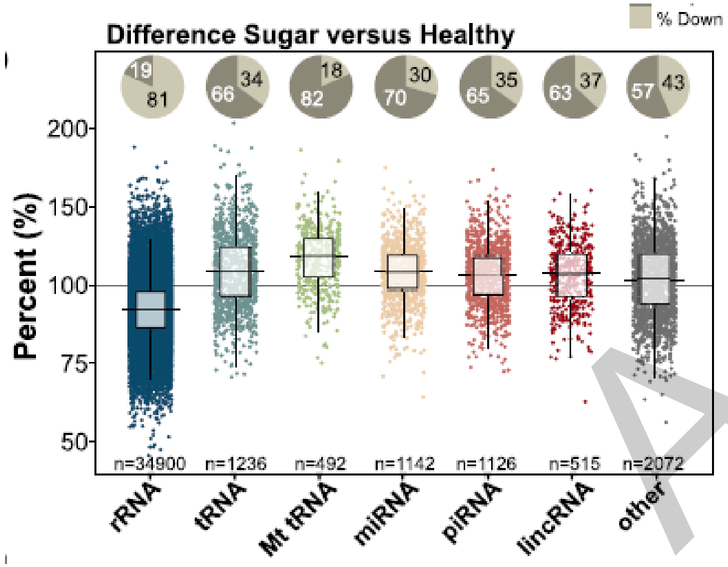
Oliveira et al. Reproduction. 2017. 153(6):R173-R185.

High Fat Diet



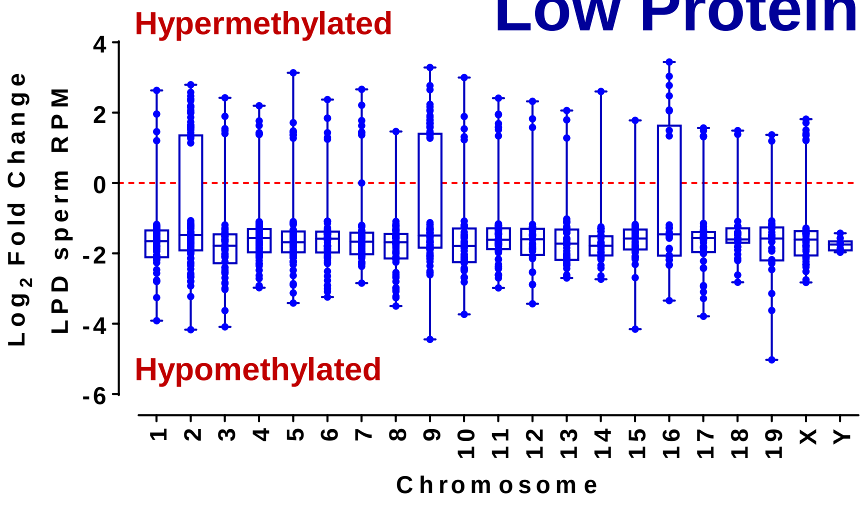
Gómez-Elías et al .Sci Rep. 2019. 6;9(1):18546.

High Sugar



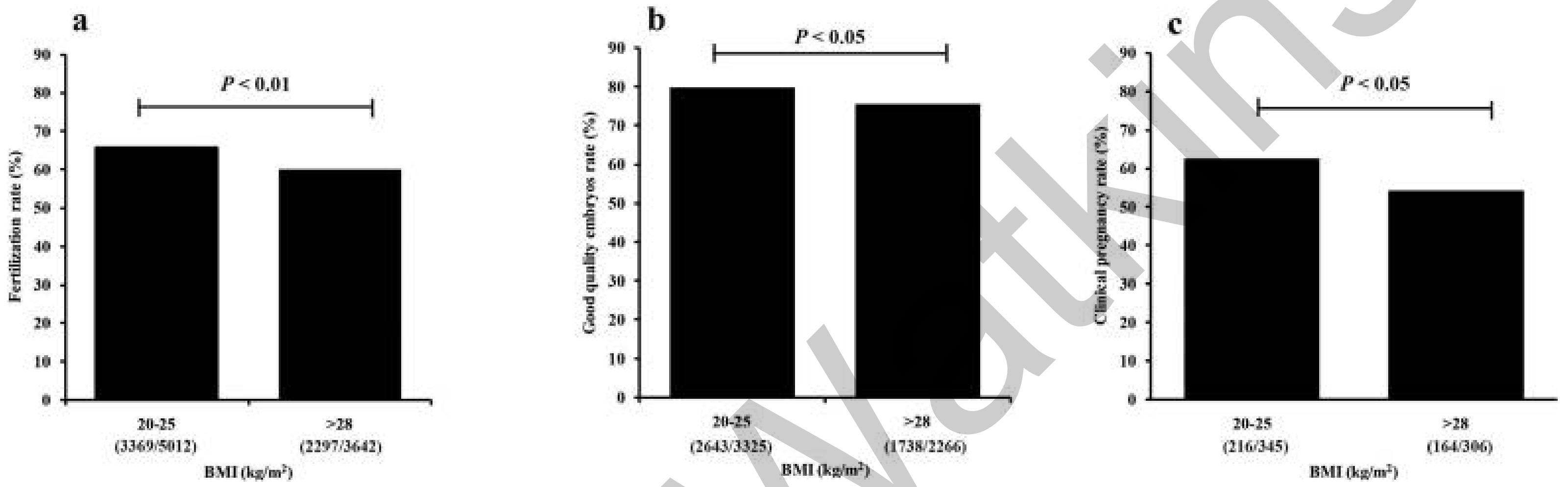
Daniel Nätt et al., PLoS Biol. 2019. 17(12):e3000559.

Low Protein Diet

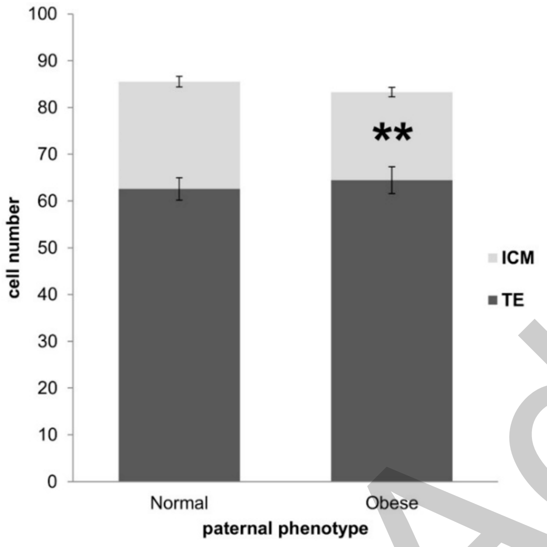


Watkins et al. 2018. P.N.A.S. 115(40):10064-10069

Male Diet and Embryo Development



Yange et al 2016. Scientific Reports. 6: 29787

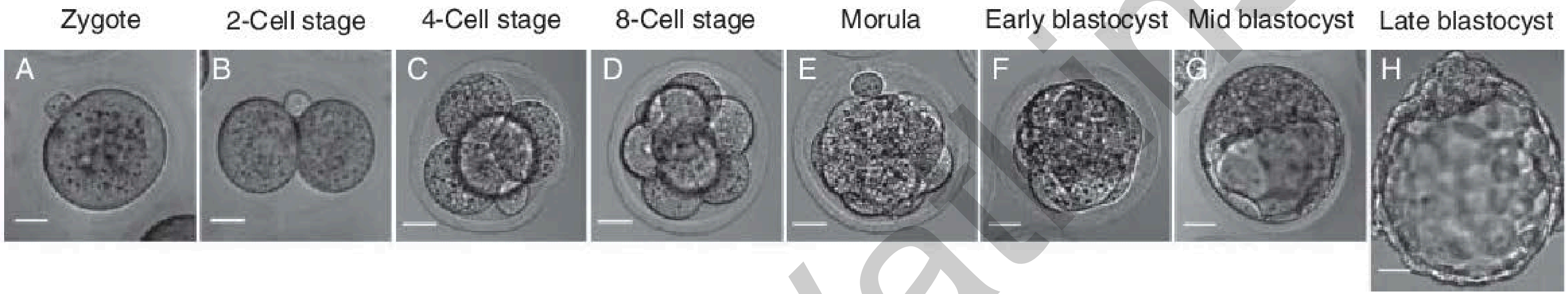


Outcome	Normal (n = 63)	Overweight (n = 148)	Obese (n = 62)	Morbidly obese (n = 32)
β-hCG/OPU (%)	46.03[a]	36.49[b]	35.48[b]	15.15[c]
β-hCG/ET (%)	50.88[a]	41.54[a,b]	38.60[b]	20.83[c]
Sac/OPU (%)	44.44[a]	31.76[b]	32.26[b]	12.12[c]
Sac/ET (%)	49.12[a]	36.15[b]	35.09[b]	16.67[c]
Heart/OPU (%)	42.86[a]	29.73[b]	25.81[b]	12.12[c]
Heart/ET (%)	47.37[a]	33.85[b]	28.07[b]	16.67[c]
Pregnancy loss (%)	10.3[a]	38.5[b]	36.4[b]	20.0[a,b]
Live birth/OPU (%)	41.3[a]	26.4[b]	22.6[b]	12.12[c]

Binder et al 2012. PLoS One 7:e52304
Mitchell et al., 2011. Fert Steril 95 (4):1349-1353.

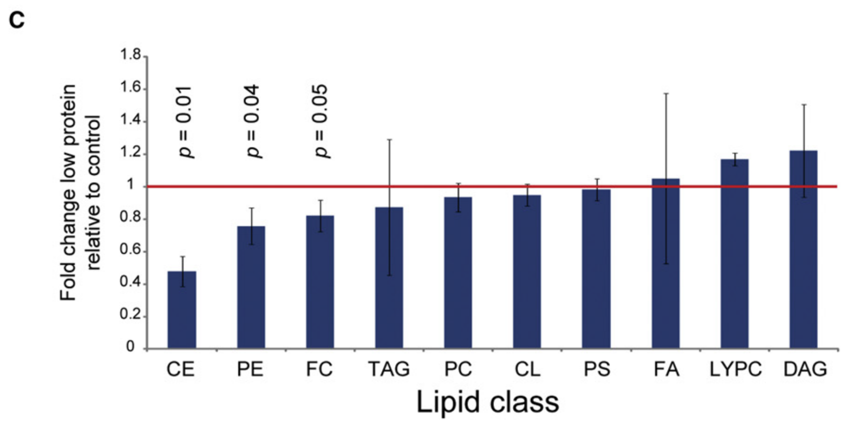
Bakos et al., 2011 Fert Steril. 95; 1700-4

Male Diet and Embryo Development



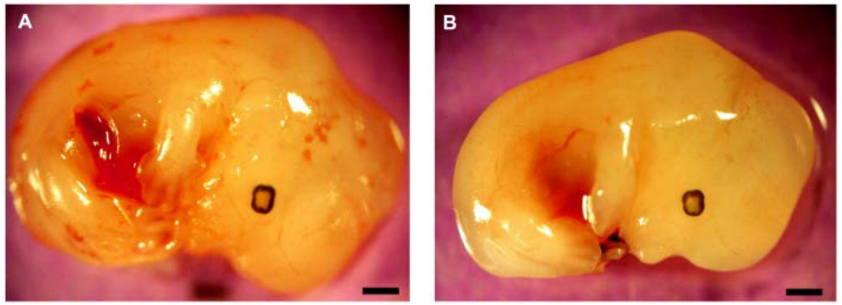
Dr Hannah Morgan, unpublished observations

Paternal Diet and Fetal Development



Paternal low protein diet affects sperm DNA methylation, fetal liver gene expression and lipid levels

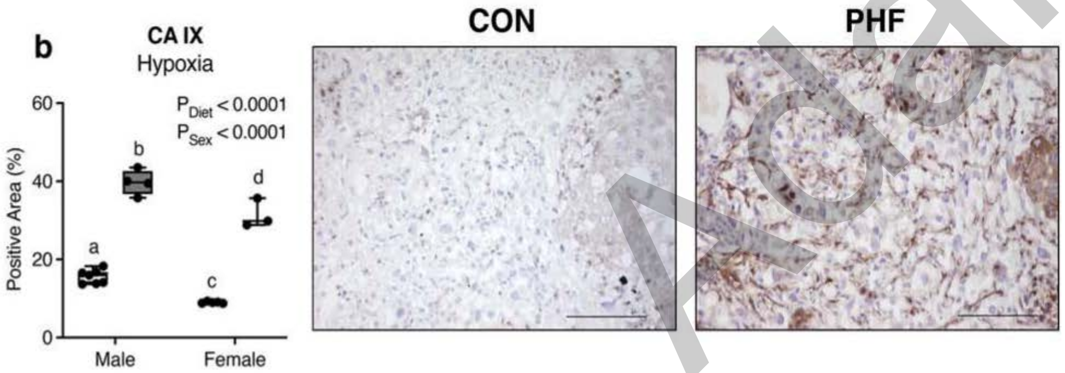
(Carone et al., 2010. Cell. 143: 1084-1096)



Paternal high fat diet fragments sperm DNA, reduces blastocyst development and affects offspring development

(Binder et al., 2012. PloS One 7(12): e52304)

(Ng et al., 2010. Nature. 467: 963-6)



Paternal obesity induced sex-specific placental hypoxia and altered placental angiogenic markers, increased ER stress-related protein levels and altered hepatic expression of gluconeogenic factors at E18.5.

Patrycja et al. Biology of Reproduction, 107(2):574-589 (2022).

Paternal Diet and Fetal Development

Paternal low folate diet in mice:

Lambrot R et al., 2013. Nature Communications. 10; 4: 2889.

Significant changes in sperm DNA methylation, placental gene expression, offspring growth and skeletal formation.

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Paternal Diet and Fetal Development

Paternal obesity is an independent predictor of both SGA and macrosomia

Tests for interaction show the effect of paternal obesity on SGA and macrosomia was significantly affected by maternal obesity

A Forest plot summary of logistic regression analysis for risk of SGA.

Characteristics	B	Standard error	HR (95% CI)	P value
Paternal obesity	1.053	0.161	2.866(2.091-3.930)	<0.001
Maternal obesity	-1.448	0.719	0.235(0.057-0.962)	0.044
Maternal age	-0.052	0.024	0.949(0.907-0.994)	0.027
Paternal age	0.01	0.019	1.010(0.974-1.048)	0.595
Preeclampsia	1.518	0.228	4.561(2.917-7.131)	<0.001
Paternal underweight	2.141	0.197	8.506(5.784-12.509)	<0.001

0.0 2.5 5.0 7.5 10.0

B Forest plot summary of logistic regression analysis for risk of macrosomia.

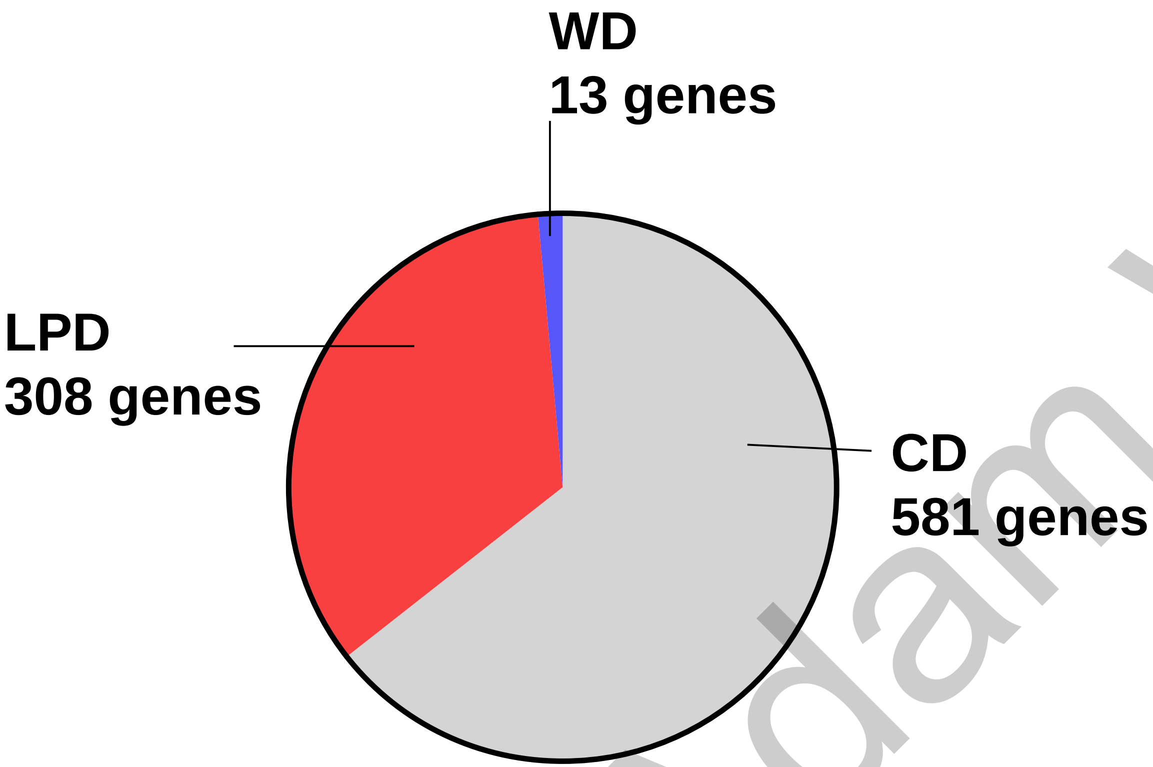
Characteristics	B	Standard error	HR (95% CI)	P value
Paternal obesity	0.525	0.188	1.690(1.168-2.444)	0.005
Maternal obesity	1.577	0.262	4.841(2.894-8.095)	<0.001
Maternal weight gain	0.085	0.013	1.089(1.061-1.117)	<0.001
GDM	0.006	0.194	1.006(0.687-1.471)	0.977

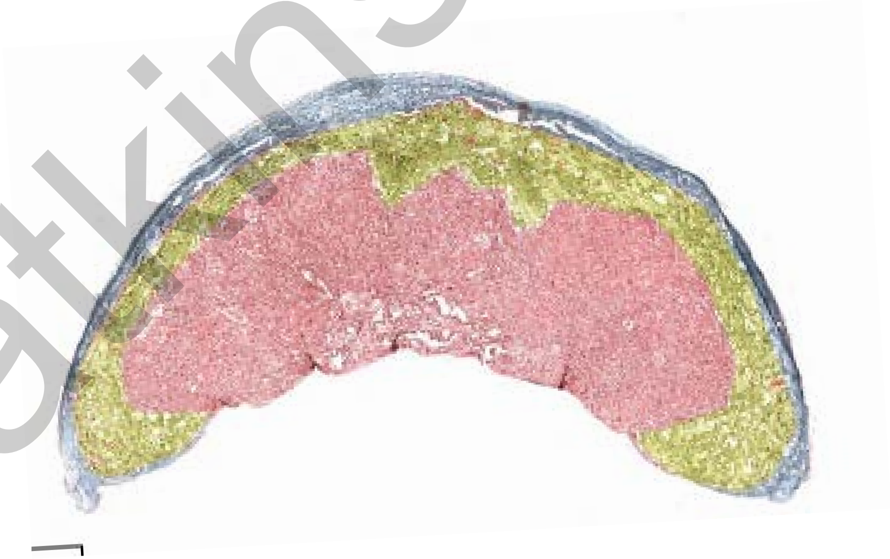
1 2 3 4 5

Lin et al. Front Endocrinol. 2022; 13: 826665.

Paternal Diet and Fetal Development

Sexually Dimorpic Differentially Expressed Genes





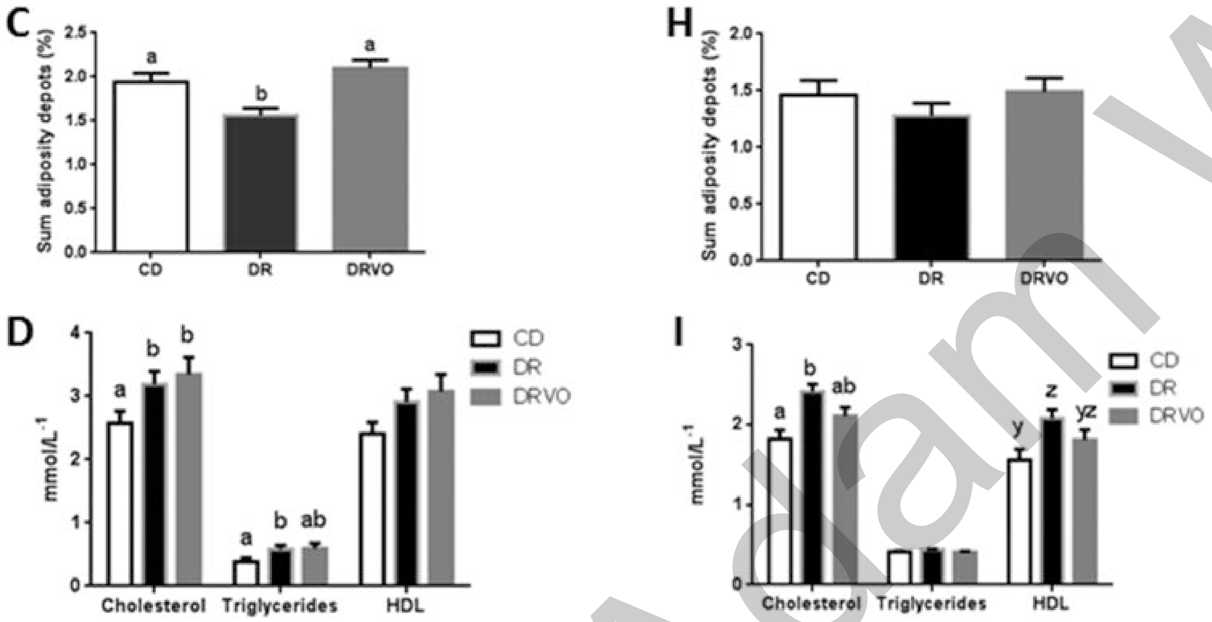
	Number of Diff. Expressed genes		
Diet Groups	**Male**	**Female**	**Overlap**
CD vs LPD	11	212	0
CD vs WD	3	34	0
LPD vs WD	69	155	6

Sex (female vs male) differences

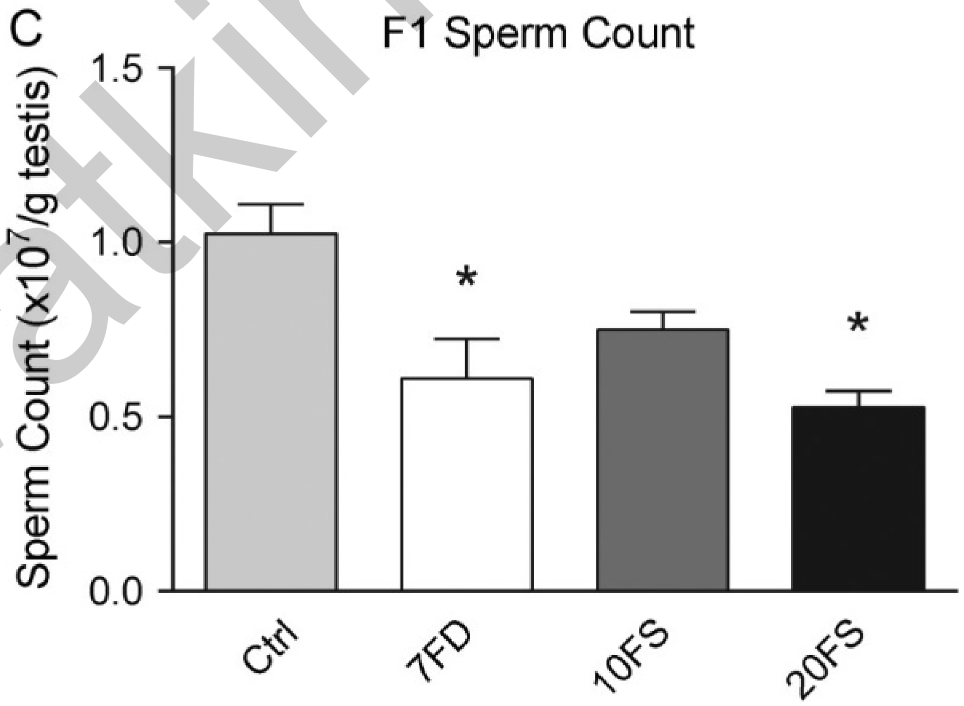
Dr Hannah Morgan, unpublished observations

Paternal Diet and Offspring Development

Paternal dietary restriction (DR) or DR with added vitamins (DRVO) alters offspring metabolism in mice



McPherson et al., Sci. Rep. 2016;6:27010.



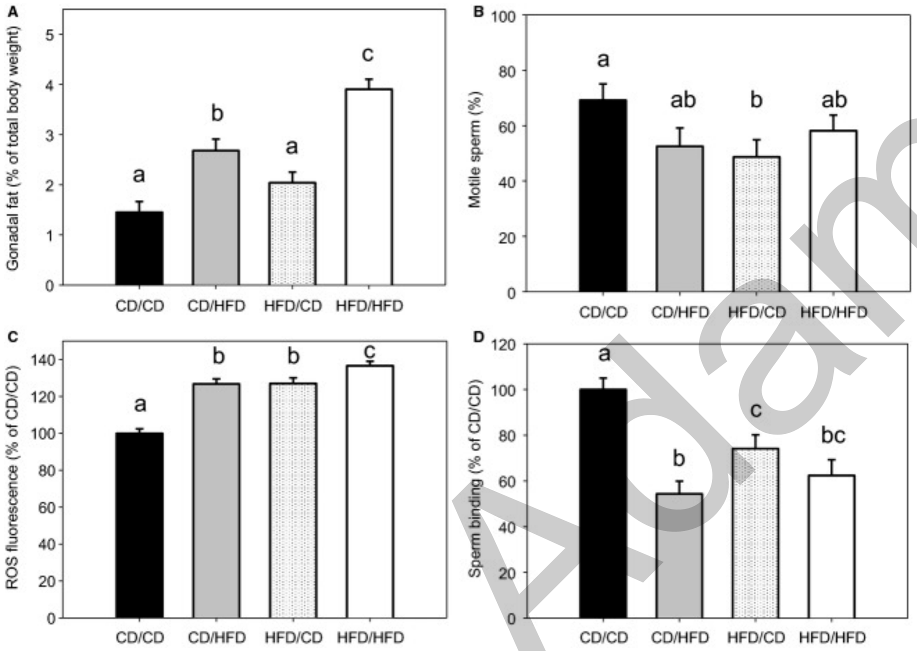
Paternal folate deficiency (FD) or supplementation (FS) decreased offspring sperm production

Ly et al. MHR Basic Sci. Reprod. Med. 2017;23:461–477

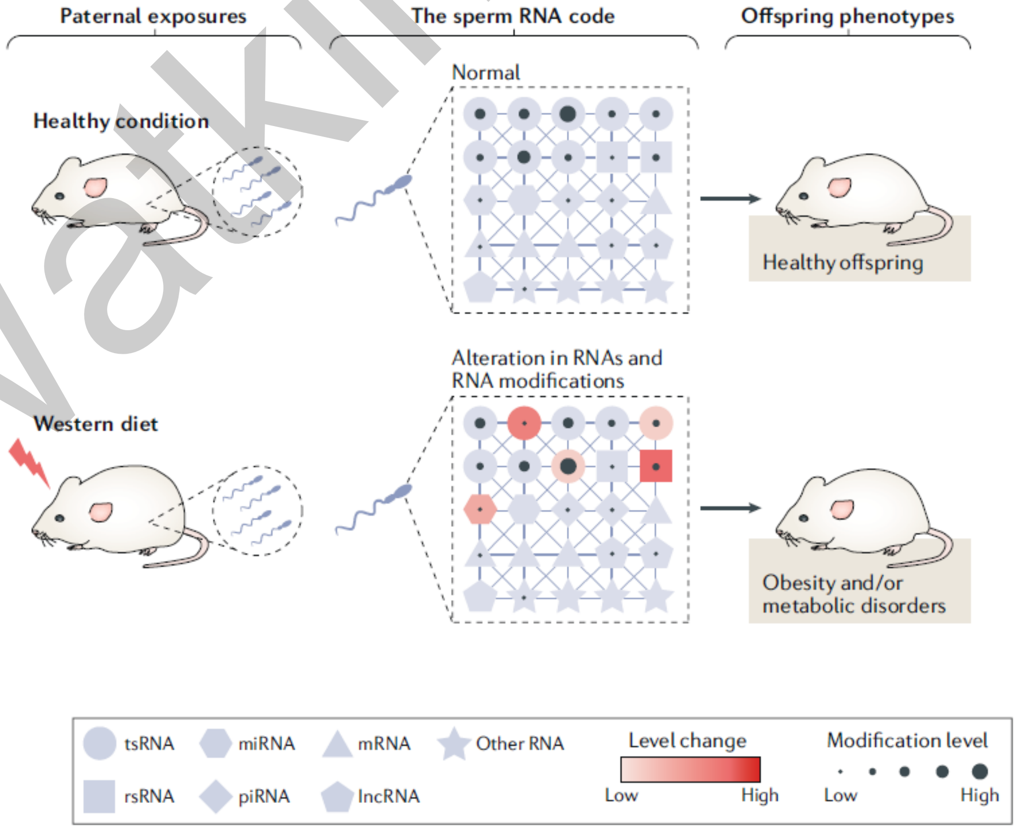
Paternal Diet and Offspring Development

Group	Body Weight, g	HOMA-IR	Triglyceride, mg/dl	Leptin, ng/dl	Adiponectin, µg/dl
HFD-fed male	55.6 ± 4.1*$#	5.21 ± 0.42*#	392 ± 29*$#	8.3 ± 1.0*$#	3.2 ± 0.5*$#
CD-fed male	41.8 ± 3.7*$	4.02 ± 0.33*$	281 ± 36*$	5.3 ± 0.9*$	8.2 ± 1.1*$

Masuyama et al. Am. J. Physiol. Metab. 2016;311:E236–E245.



Fullston et al. Physiol Rep. 2015: e12336.



Zhang et al., Nat Rev Endocrinol 2019. 15(8):489-498.

Paternal Health and Offspring Neurodevelopment

OPEN

Molecular Psychiatry (2018) 23, 1345–1355
www.nature.com/mp

ORIGINAL ARTICLE

A paternal methyl donor-rich diet altered cognitive and neural functions in offspring mice

DP Ryan[1], KS Henzel[1], BL Pearson[1], ME Siwek[2], A Papazoglou[2], L Guo[3], K Paesler[1], M Yu[3], R Müller[4], K Xie[1], S Schröder[1], L Becker[5,6], L Garrett[5,7], SM Hölter[5,7], F Neff[5,8], I Rácz[9], B Rathkolb[5,10,11], J Rozman[5,11], G Ehninger[12], M Klingenspor[13], T Klopstock[6,14,15,16], E Wolf[10], W Wurst[7,15,16,17], A Zimmer[9], H Fuchs[5], V Gailus-Durner[5], M Hrabě de Angelis[5,11,18], K Sidiropoulou[19], M Weiergräber[2], Y Zhou[3] and D Ehninger[1]

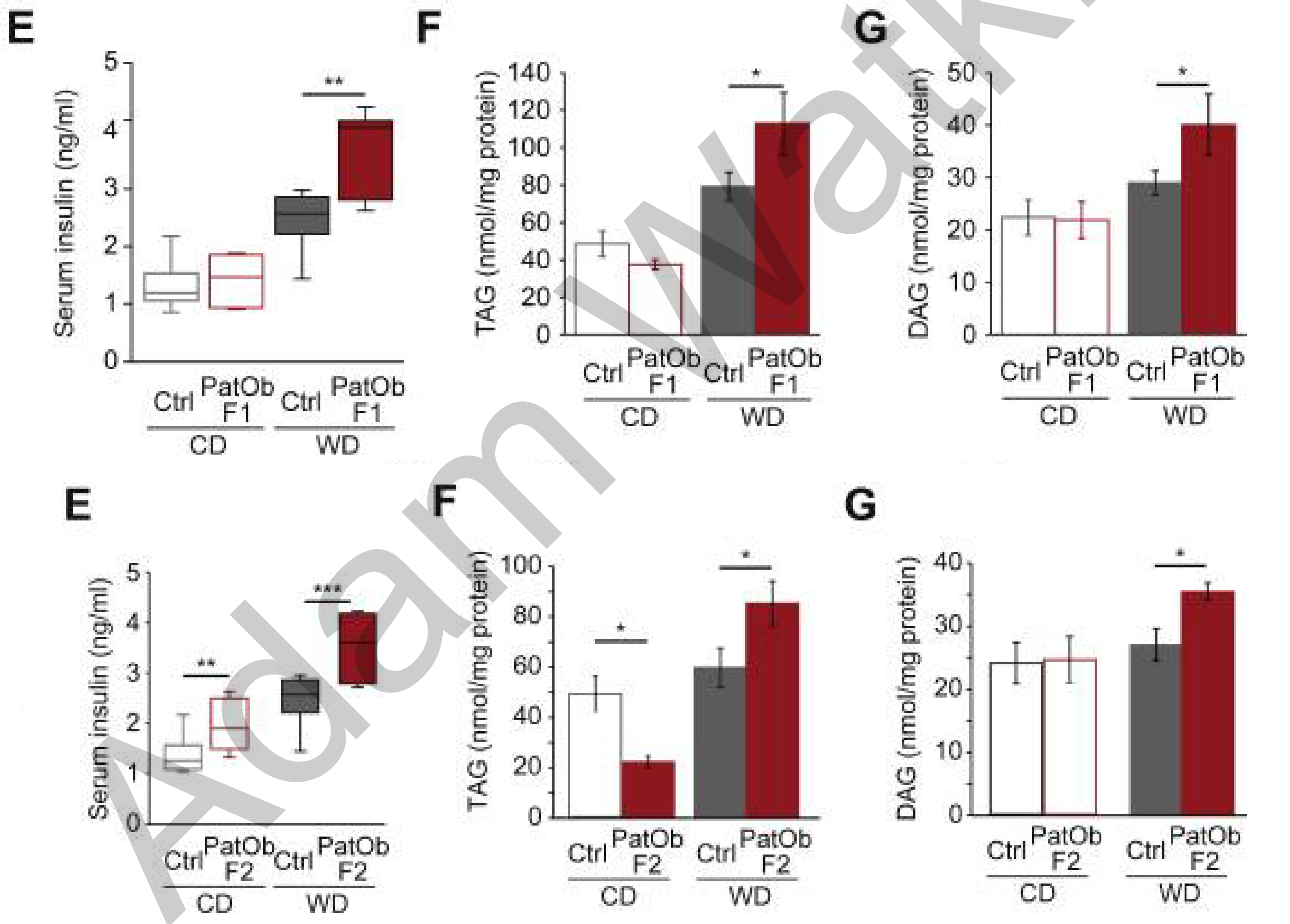
The Journal of Child Psychology and Psychiatry
ACAMH The Association for Child and Adolescent Mental Health
Journal of Child Psychology and Psychiatry 64:2 (2023), pp 277–288
doi:10.1111/jcpp.13695

Paternal perinatal stress is associated with children's emotional problems at 2 years

Fiona L. Challacombe,[1] Johanna T. Pietikäinen,[2,3] Olli Kiviruusu,[2] Outi Saarenpää-Heikkilä,[4,5] Tiina Paunio,[2,6] and E. Juulia Paavonen[2,7]

Paternal Generational Effects

Used a mouse obesity and pre-diabetes model (*A^vy^*) to study transgenerational transmission of metabolic phenotype



Cropley JE et al (2016) Mol Metab. 5(8): 699–708.

Male-lineage transmission of an acquired metabolic phenotype induced by grand-paternal obesity

Jennifer E. Cropley [1,2,∗∗,8], Sally A. Eaton [1,2,8], Alastair Aiken [1], Paul E. Young [1], Eleni Giannoulatou [1], Joshua W.K. Ho [1,2], Michael E. Buckland [3], Simon P. Keam [4], Gyorgy Hutvagner [4], David T. Humphreys [1], Katherine G. Langley [5], Darren C. Henstridge [5], David I.K. Martin [1,6], Mark A. Febbraio [7], Catherine M. Suter [1,2,∗]

European Journal of Human Genetics (2006) 14, 159–166

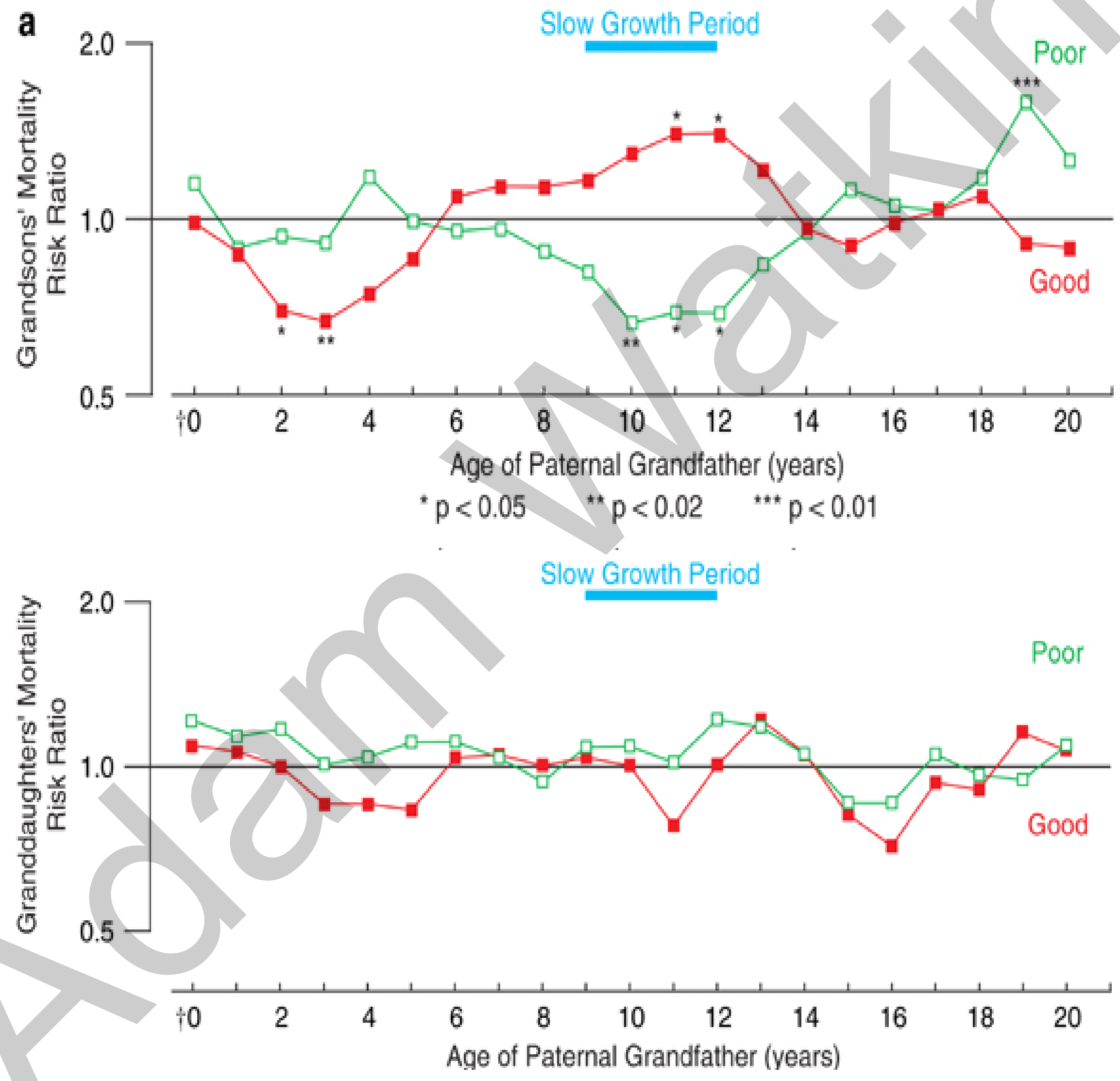
www.nature.com/ejhg

ARTICLE

Sex-specific, male-line transgenerational responses in humans

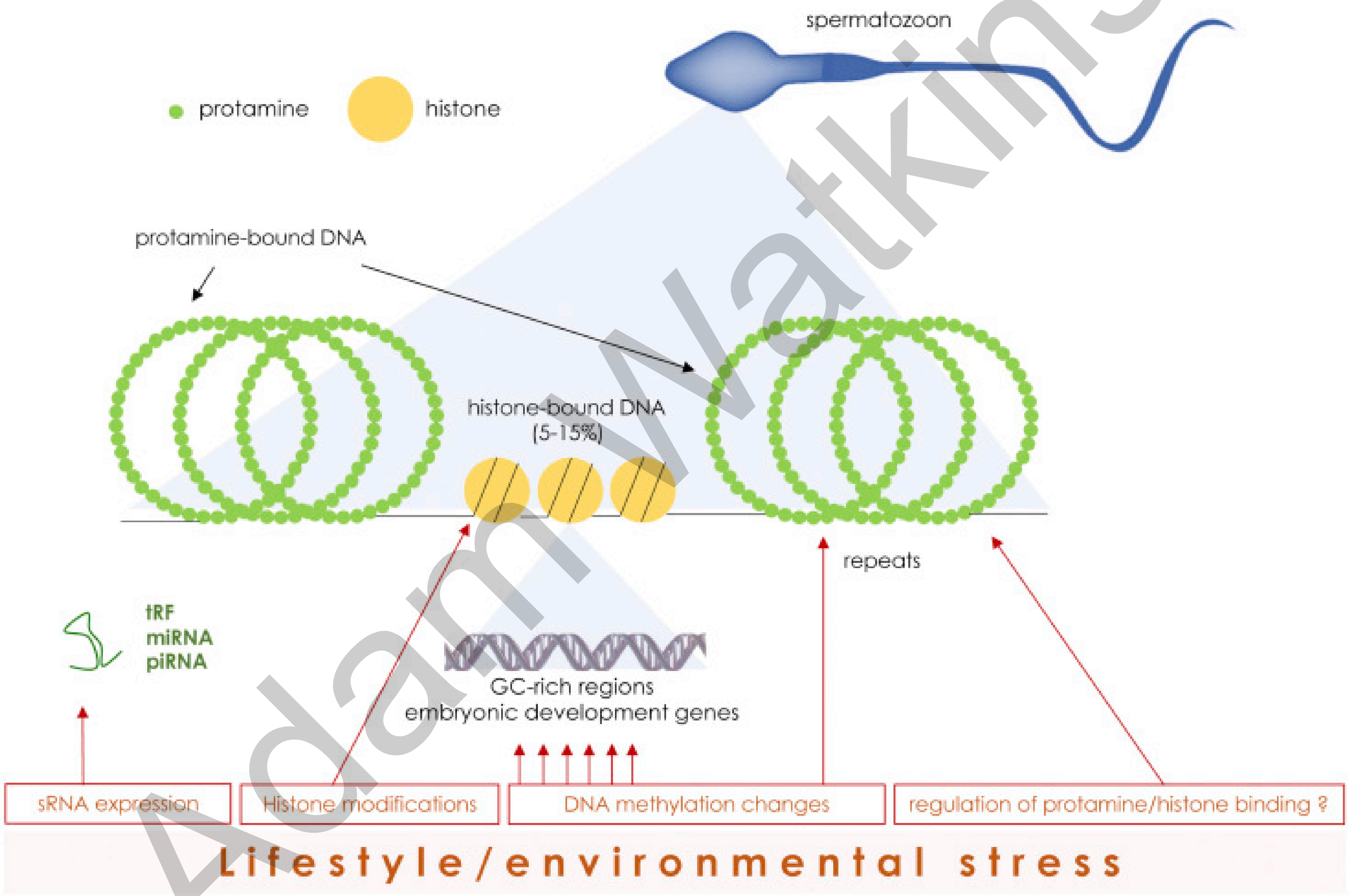
Marcus E Pembrey*[1,2], Lars Olov Bygren[3,6], Gunnar Kaati[4], Sören Edvinsson[5], Kate Northstone[2], Michael Sjöström[6], Jean Golding[2] and The ALSPAC Study Team[2]

Paternal Generational Effects



Pembrey et al., 2006. European Journal of Human Genetics. 14:159–166

Sperm Epigenetic Status



Importance of Seminal Fluid

SVX = seminal vesicle excision

(Bromfield et al., 2014. P.N.A.S 111:2200-5)

Exploring Paternal Programming

Fed male C56BL6 mice either:-

- Normal protein diet (NPD; 18%)
- Low protein diet (LPD; 9%)

○ NN (NPD sperm; NPD seminal fluid)

● LL (LPD sperm; LPD seminal fluid)

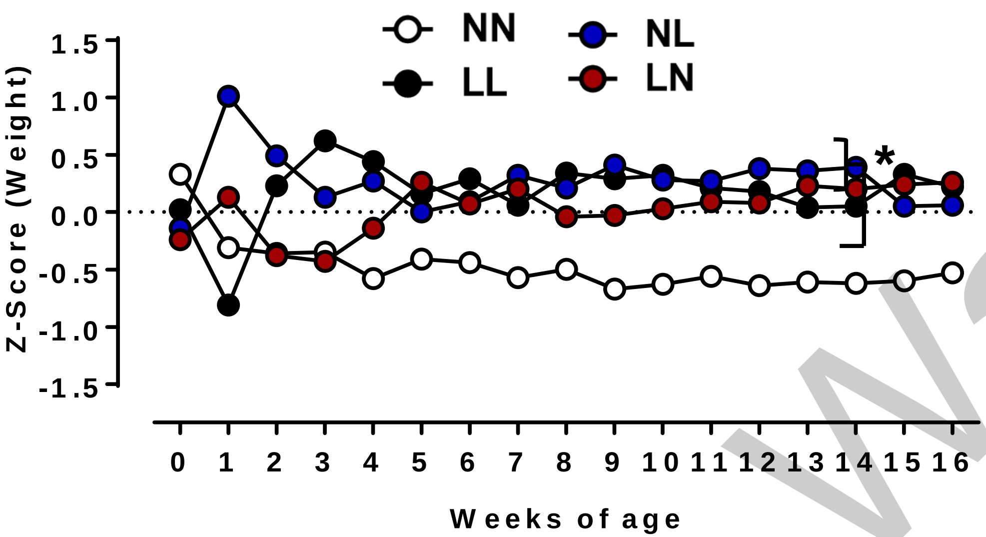
● NL (NPD sperm; LPD seminal fluid)

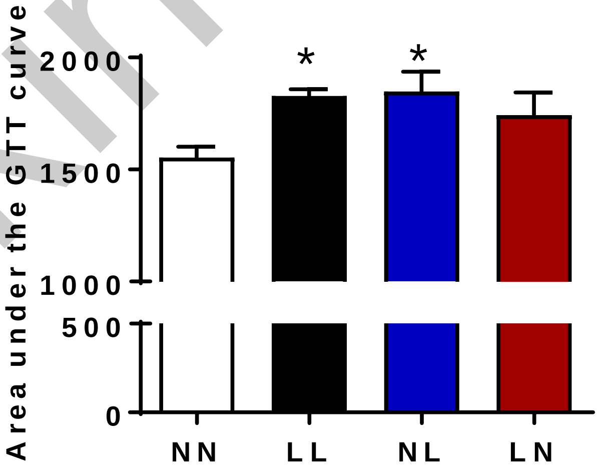
● LN (LPD sperm; NPD seminal fluid)

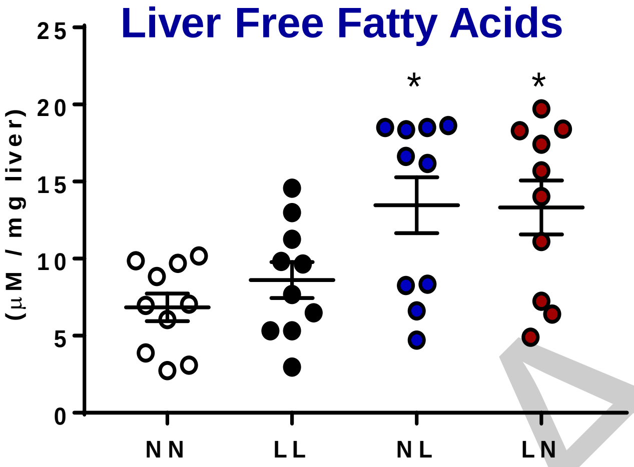
Watkins et al. 2018. P.N.A.S. 115(40):10064-10069

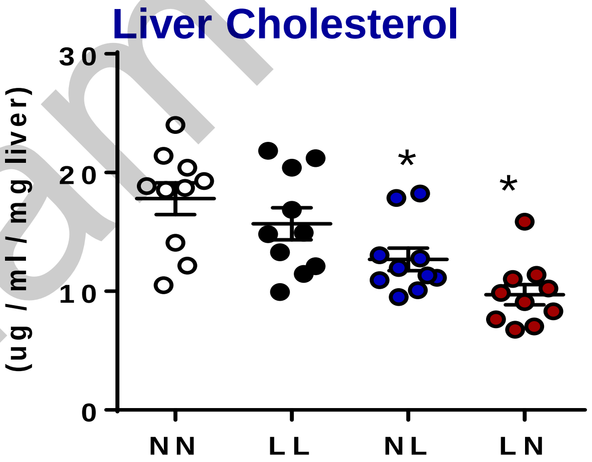
Growth and Glucose Tolerance

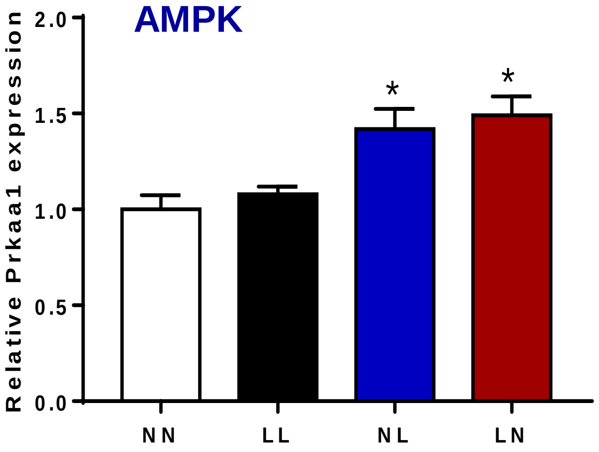
Males











Watkins et al. 2018. P.N.A.S. 115(40):10064-10069

International Journal of *Molecular Sciences*

MDPI

Article

Characterisation of the Paternal Influence on Intergenerational Offspring Cardiac and Brain Lipid Homeostasis in Mice

Samuel Furse [1,2,3], Hannah L. Morgan [4], Albert Koulman [2,3] and Adam J. Watkins [4,*]

J Physiol 598.4 (2020) pp 699–715

Paternal diet impairs F1 and F2 offspring vascular function through sperm and seminal plasma specific mechanisms in mice

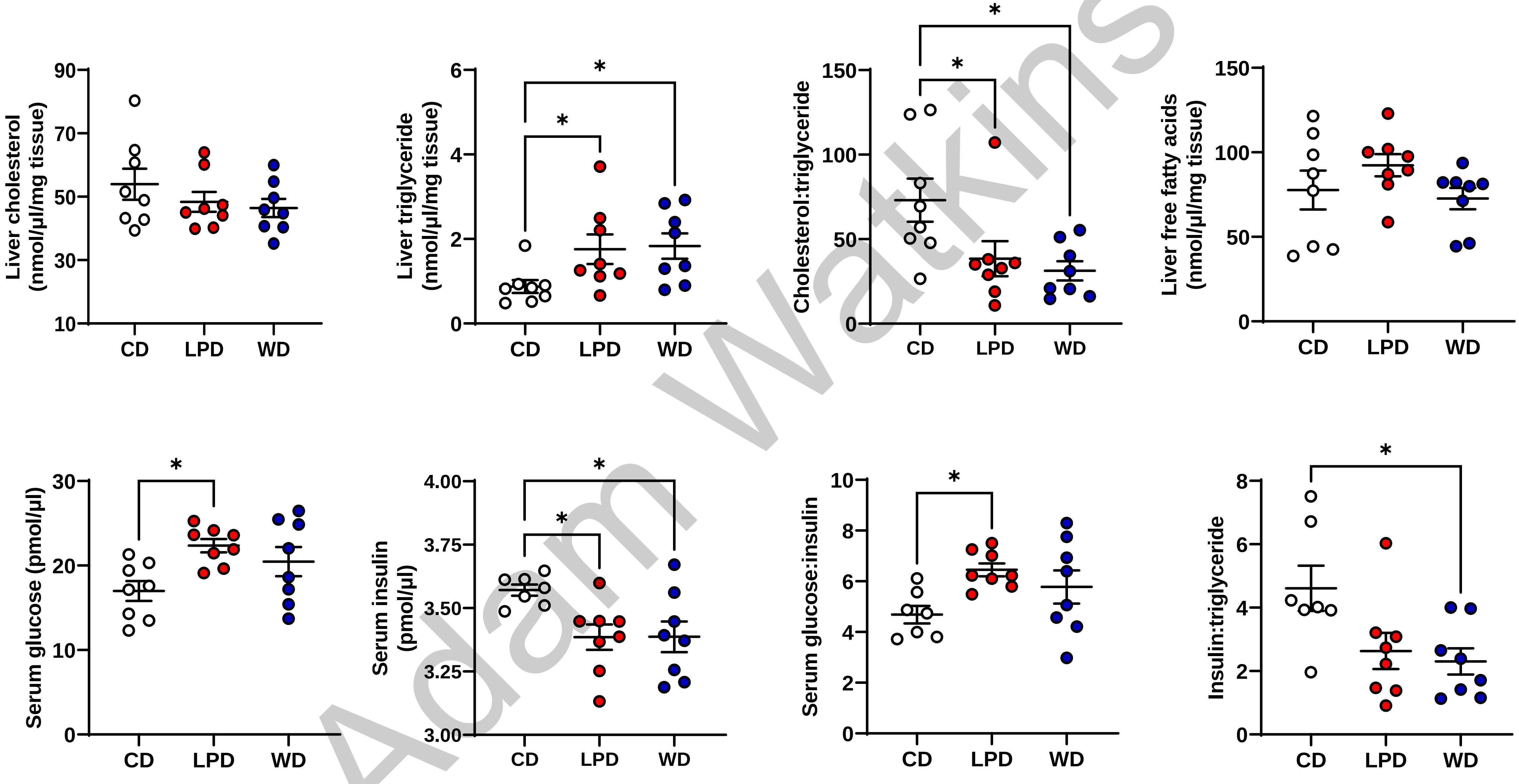
Hannah L. Morgan[1], Panaigota Paganopoulou[1], Sofia Akhtar[2], Natalie Urquhart[2], Ranmini Philomin[2], Yasmin Dickinson[2] and Adam J. Watkins[1,2]

https://doi.org/10.1038/s42003-022-03914-8 OPEN

Paternal low protein diet perturbs inter-generational metabolic homeostasis in a tissue-specific manner in mice

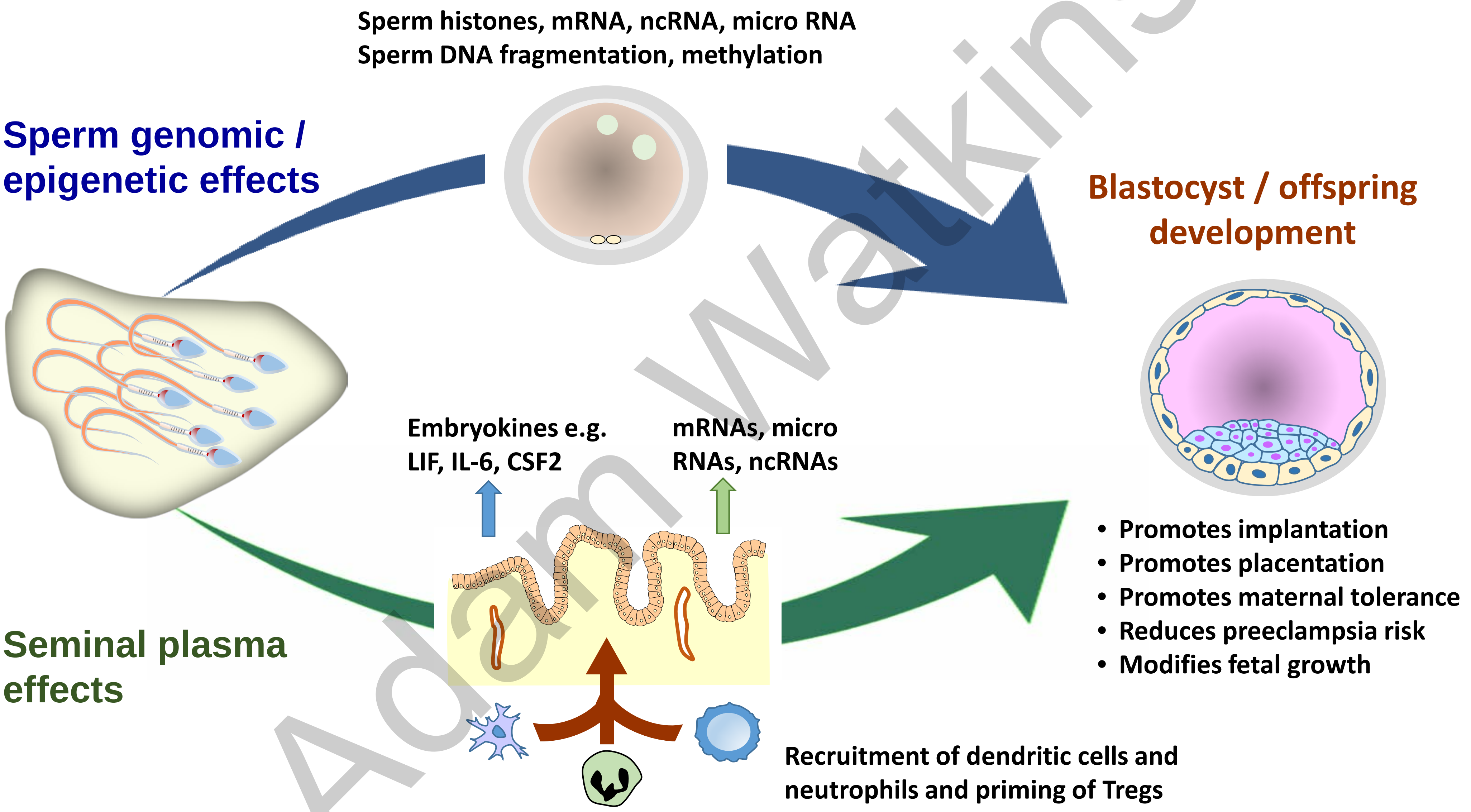
Hannah L. Morgan[1], Samuel Furse[2,3,4], Irundika H. K. Dias[5], Kiran Shabir[5], Marcos Castellanos[6], Iqbal Khan[6], Sean T. May[6], Nadine Holmes[7], Matthew Carlile[7], Fei Sang[7], Victoria Wright[7], Albert Koulman[2,3] & Adam J. Watkins[1✉]

Maternal Metabolic Health



Afsaneh Koshkerdar: Unpublished observations

Paternal Periconceptional Programming



Morgan et al. Semin Cell Dev Biol. 2020. 97:131-137

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Afsaneh Khoshkerdar

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Dr Irundika Dias
Dr Slobodan Sirovica
Dr Alex Morell
Natalie Urquhart
Danielle Allen
Heather Tsuro

Prof Warwick Dunn

Prof Owen Addison