Paternal effects on child health and development: where are we now, where do we need to be?

Ricardo P. Bertolla, PhD, HCLD/ABB
C.S. Mott Center for Human Growth and Development
Department of Obstetrics and Gynecology

Disclosures

- Sperm DNA fragmentation algorithm for clinical use – Royalty payments.
  - Flow Diagnósticos
  - Clínica Huntington

Goals of presentation

- Discuss what and how paternal effects influence obstetric health and development;
- Discuss the main paternal effects and current data;
- Discuss future directions and knowledge gaps.

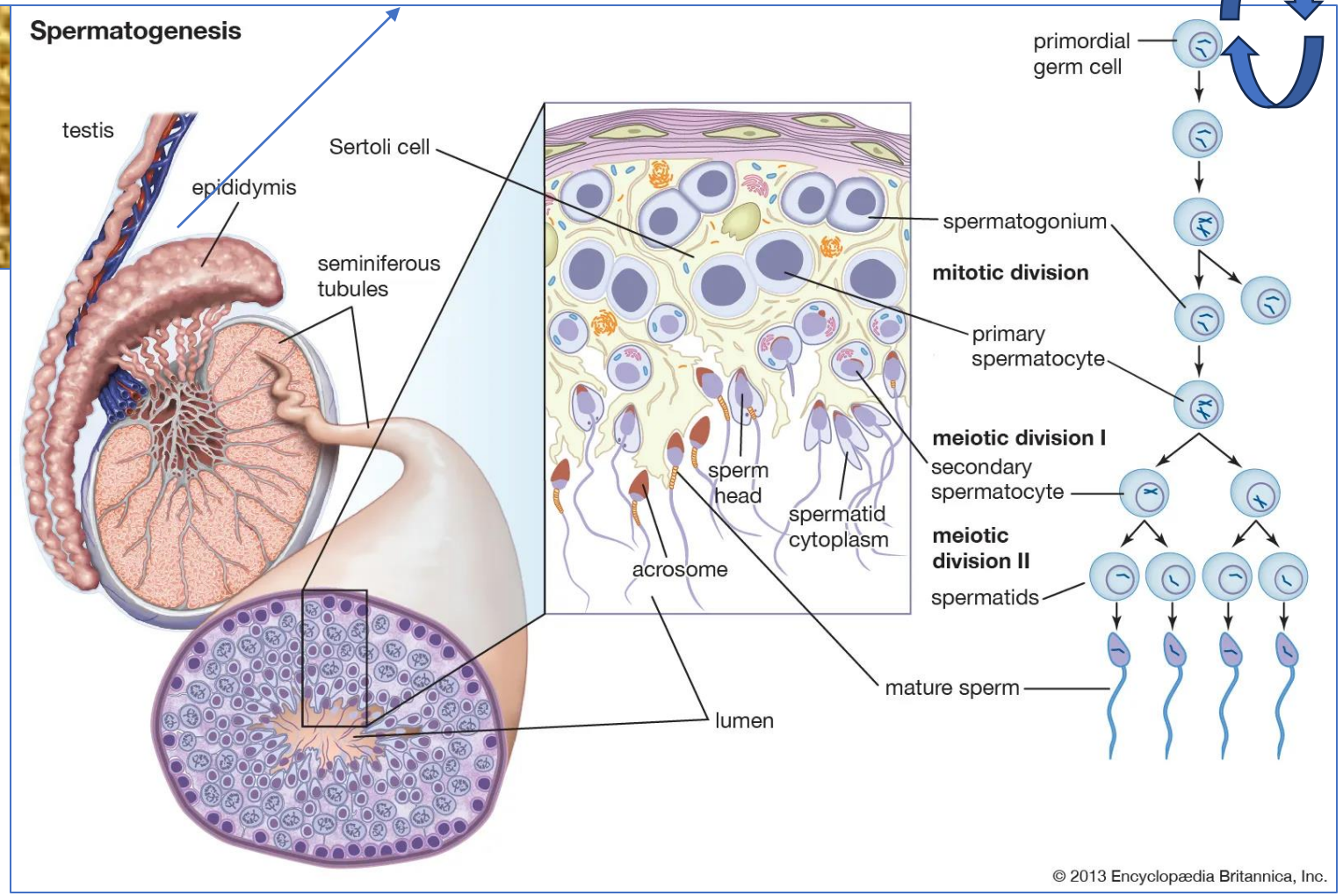
Outline of presentation

- What is the paternal contribution?
- Effects - Paternal Age
- Effects - Paternal Health
- Effects – Altered semen quality
- Effects – Exposure to reproductive toxicants
- Effects – Male factors of infertility
- What don’t we know/where do we need to get?

Paternal contribution

Paternal contribution

2 weeks

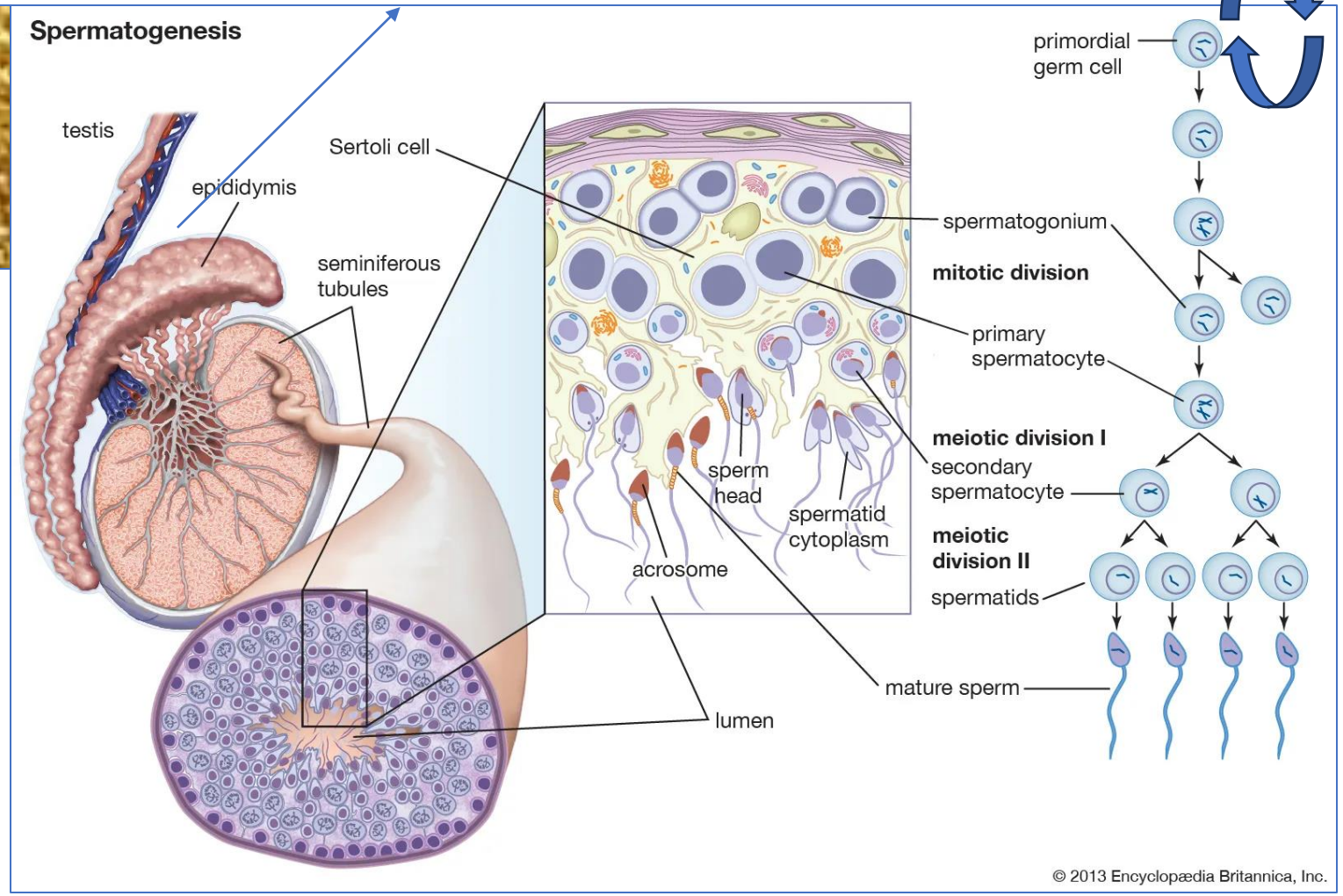


72 days

Paternal contribution

~23 divisions/year
80-97% of *de novo* mutations – paternal origin

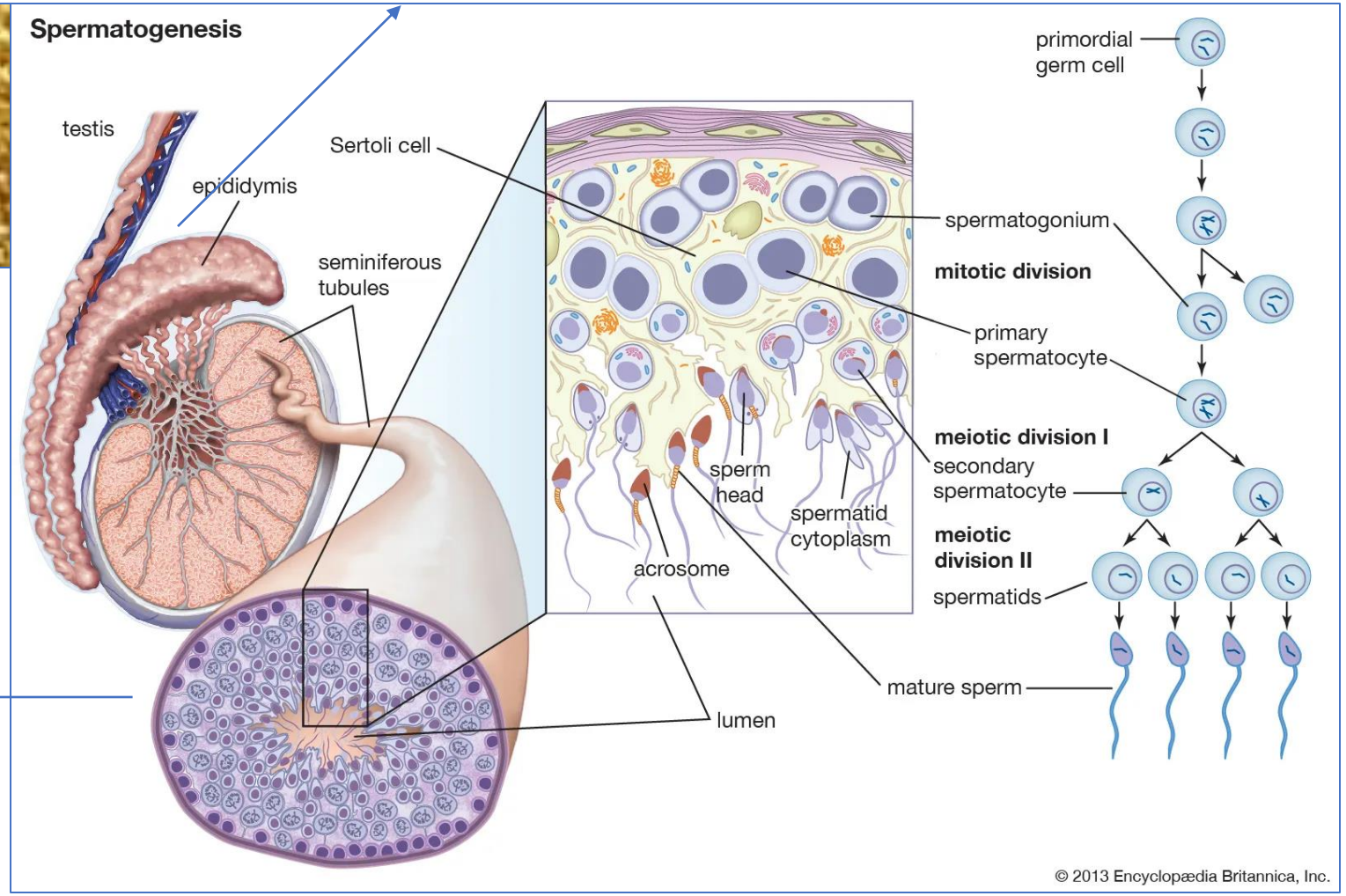
2 weeks



72 days

Paternal contribution

2 weeks

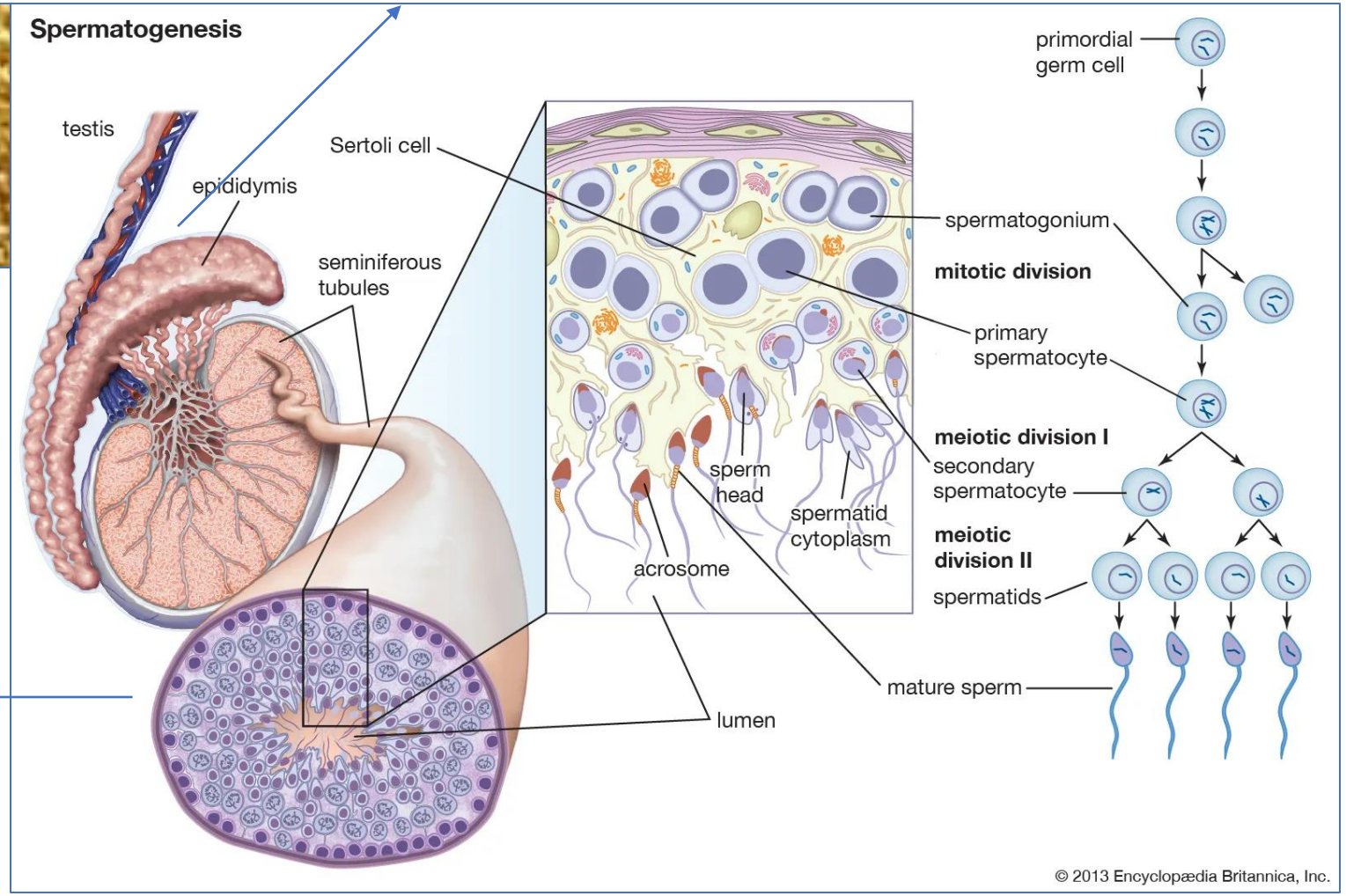


72 days

1,000 sperm per second

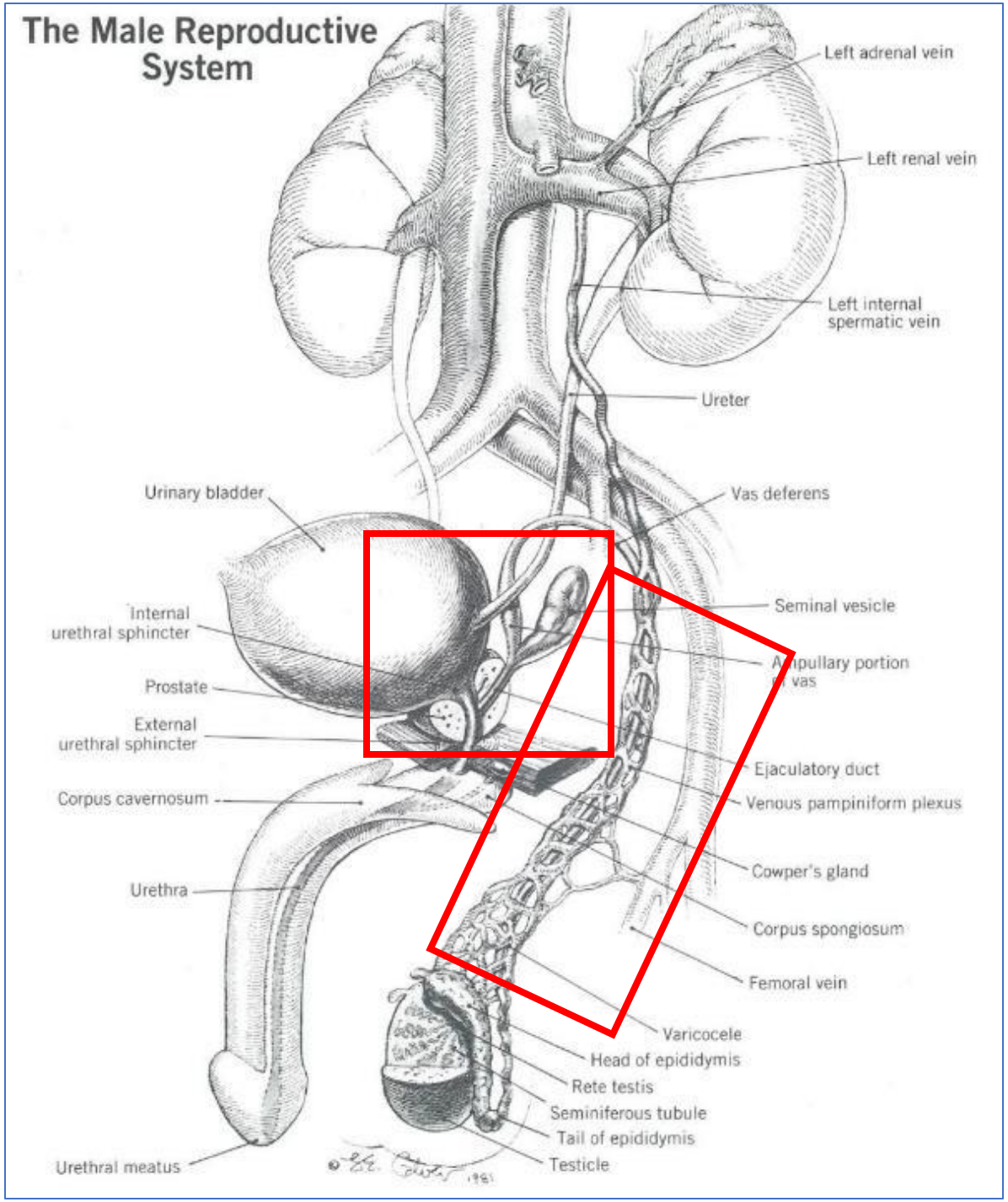
Paternal contribution

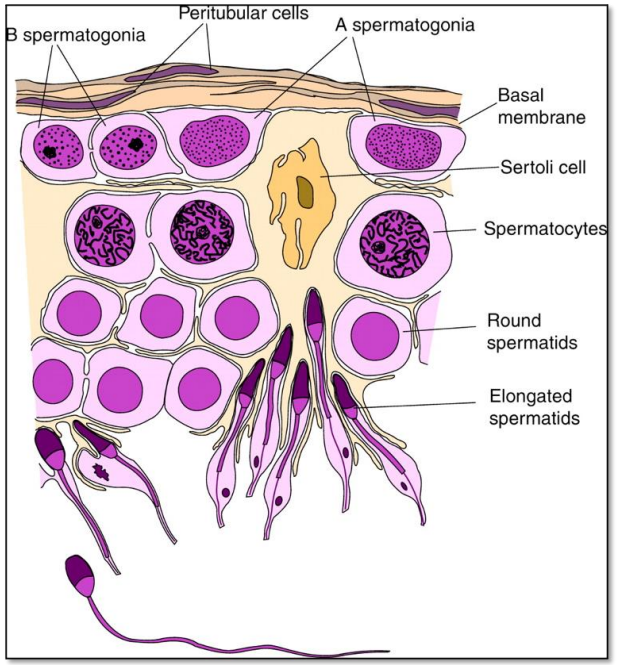
2 weeks

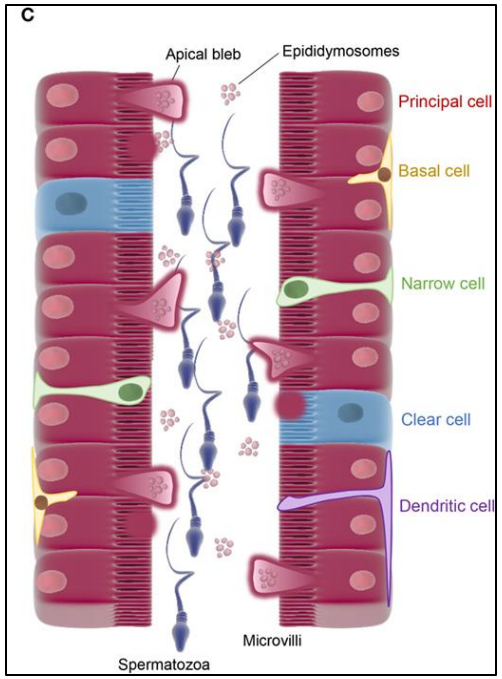


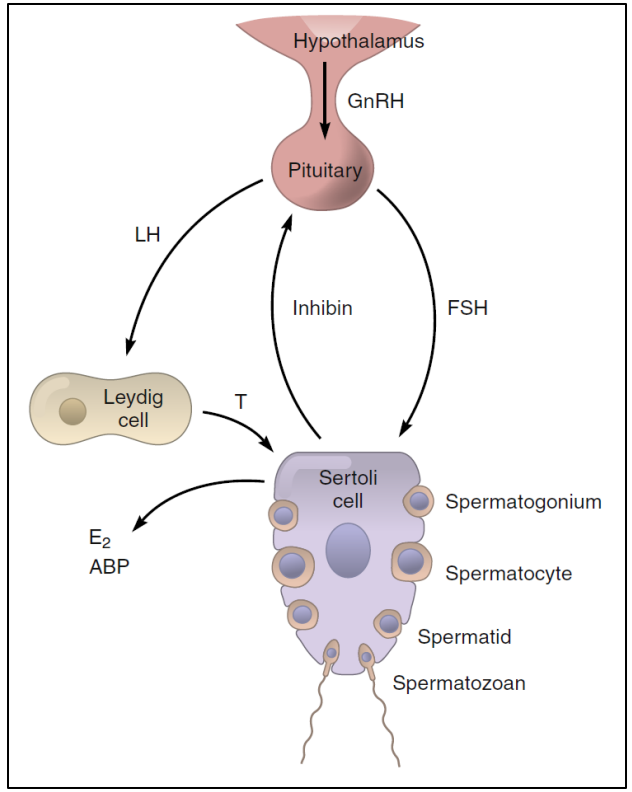
72 days

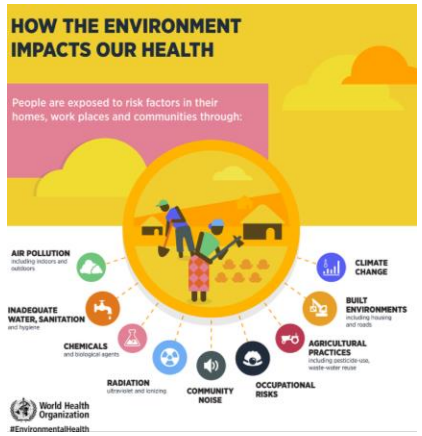
1,000 sperm per second

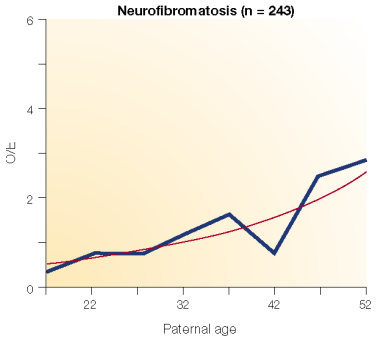

The Male Reproductive System
Left adrenal vein
Left renal vein
Left internal spermatic vein
Ureter
Urinary bladder
Vas deferens
Seminal vesicle
Internal urethral sphincter
Ampullary portion of vas
Prostate
External urethral sphincter
Ejaculatory duct
Corpus cavernosum
Venous pampiniform plexus
Cowper's gland
Urethra
Corpus spongiosum
Femoral vein
Varicocele
Head of epididymis
Rete testis
Seminiferous tubule
Tail of epididymis
Urethral meatus
Testicle

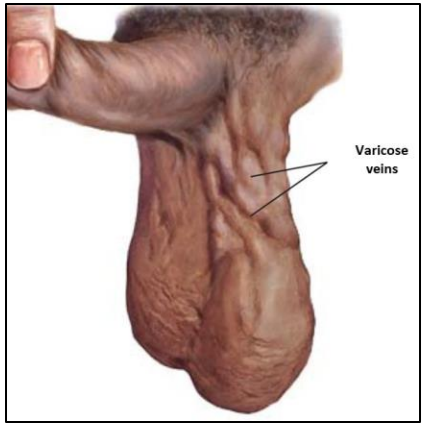

B spermatogonia
Peritubular cells
A spermatogonia
Basal membrane
Sertoli cell
Spermatocytes
Round spermatids
Elongated spermatids

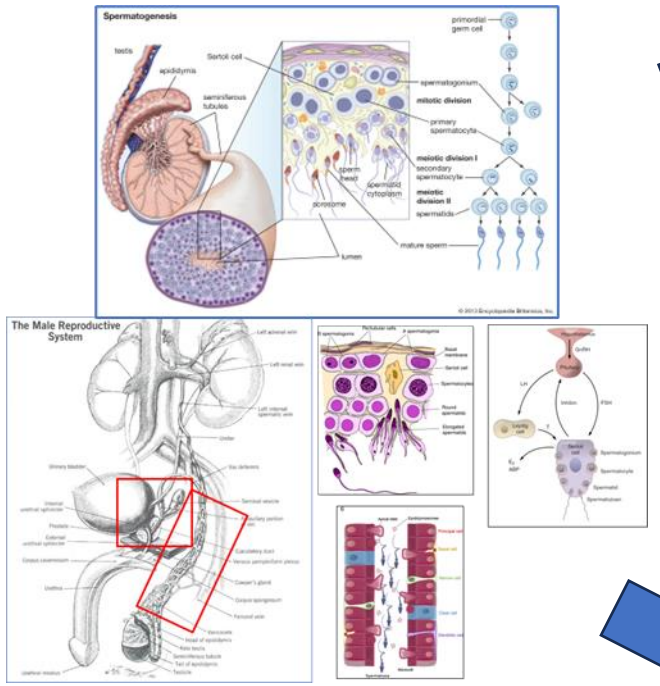

C
Apical bleb
Epididymosomes
Principal cell
Basal cell
Narrow cell
Clear cell
Dendritic cell
Microvilli
Spermatozoa


Hypothalamus
GnRH
Pituitary
LH
Inhibin
FSH
Leydig cell
T
Sertoli cell
Spermatogonium
E_2
ABP
Spermatocyte
Spermatid
Spermatozoan





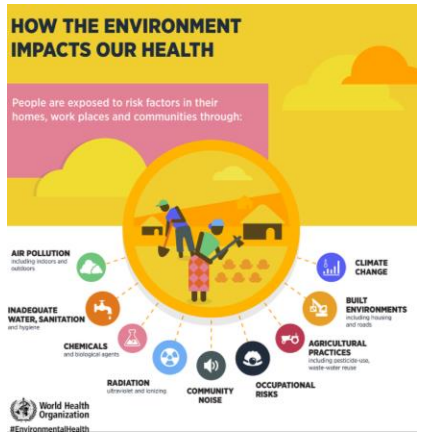


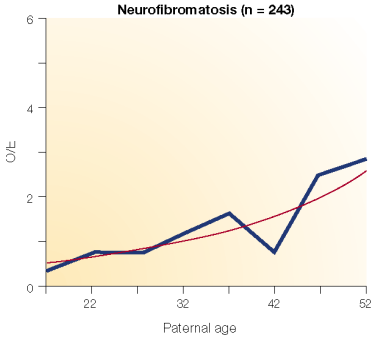


Semen quality
Infertility
Sperm function

Obstetric health and outcomes

Development





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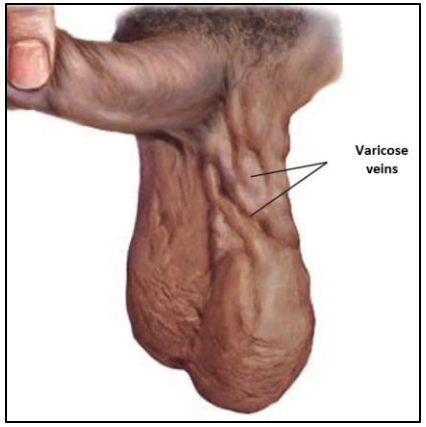

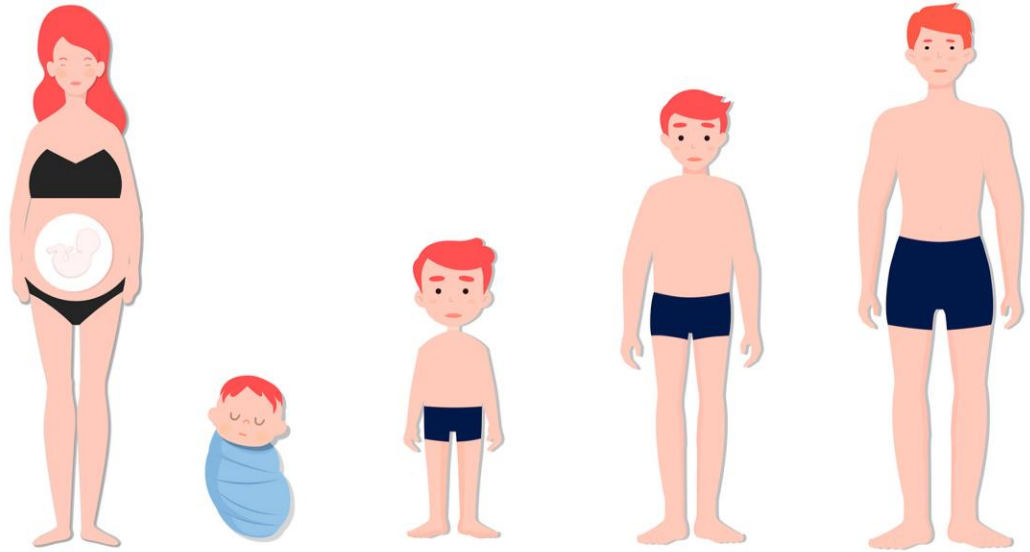

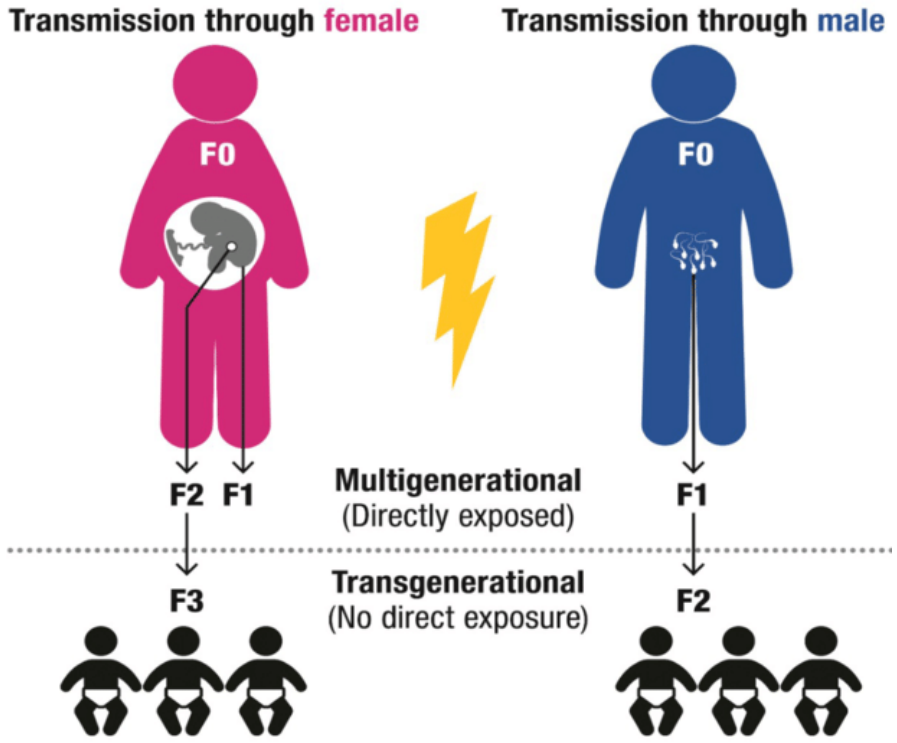

Summary I

- Sperm contribute half of the nuclear genome to the embryo;
- 80% of *de novo* mutations arise from the paternal contribution;
- There are many anatomical, endocrine, cellular and molecular mechanisms to ensure adequate sperm production;
- Alterations may arise from environmental, lifestyle, and individual factors;
- Consequences may be observed in future generations.

Effects - Paternal Age

THE ORIGINS, PATTERNS AND IMPLICATIONS OF HUMAN SPONTANEOUS MUTATION

James F. Crow

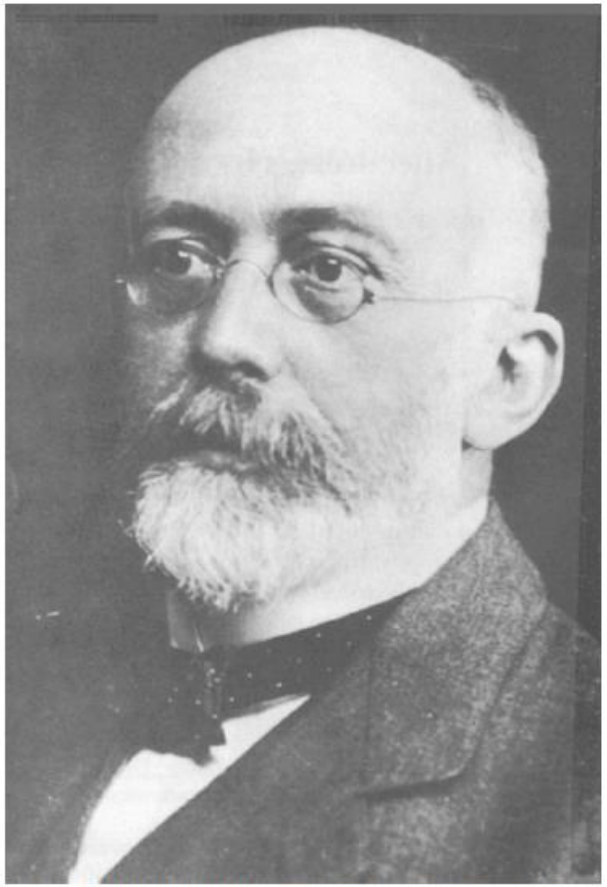

Figure 1 | **Wilhelm Weinberg.** Photograph taken from REF. 56.

"If a more exact analysis of birth order were indeed to confirm a high incidence in last-born children, this would speak for the formation of the initial predisposition for dwarfism by mutation."

Wilhelm Weinberg

THE ORIGINS, PATTERNS AND IMPLICATIONS OF HUMAN SPONTANEOUS MUTATION

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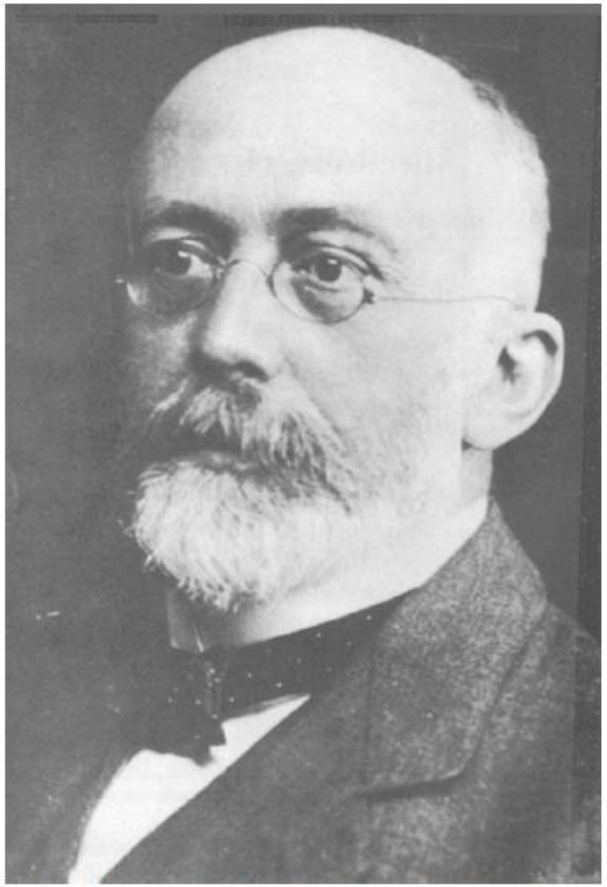

Figure 1 | **Wilhelm Weinberg.** Photograph taken from REF. 56.

"If a more exact analysis of birth order were indeed to confirm a high incidence in last-born children, this would speak for the formation of the initial predisposition for dwarfism by mutation."

Wilhelm Weinberg 1912

Achondroplasia – mainly derived from paternal age (Penrose, 1955)

human reproduction ORIGINAL ARTICLE *Reproductive epidemiology*

The age of fathers in the USA is rising: an analysis of 168 867 480 births from 1972 to 2015

Yash S. Khandwala[1,2], Chiyuan A. Zhang[1], Ying Lu[3], and Michael L. Eisenberg[1,4,*]

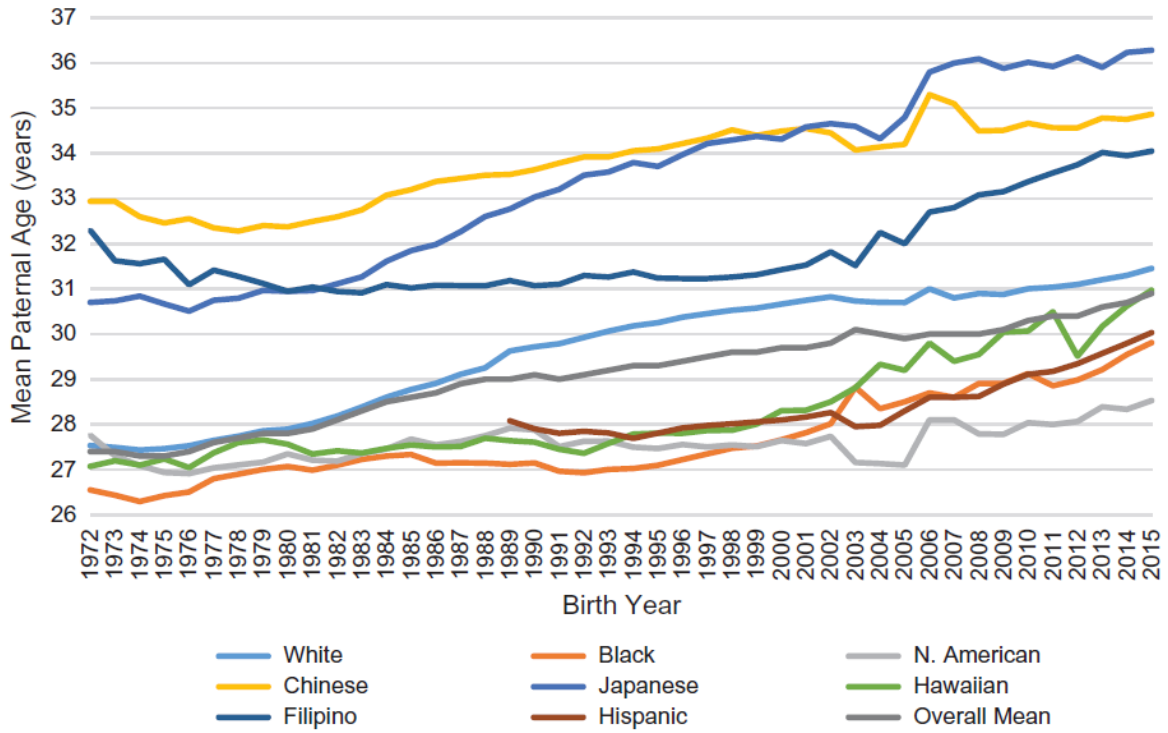

Figure 1 Temporal trend of mean paternal age by race from 1972 to 2015. Asian Indian, Korean, Samoan, and Vietnamese races were not included as they were not collected as distinct races until later in time. The Hispanic trend line begins in 1989, the first year during which this data was collected.

human reproduction ORIGINAL ARTICLE *Reproductive epidemiology*

The age of fathers in the USA is rising: an analysis of 168 867 480 births from 1972 to 2015

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Table I Mean paternal age (in years) by paternal characteristics.

		1972–1975	1976–1980	1981–1985	1986–1990	1991–1995	1996–2000	2001–2005	2006–2010	2011–2015
Advanced paternal age	>40	4.1%	3.6%	3.8%	4.8%	5.8%	6.8%	7.8%	8.2%	8.9%
(% of all annual births)	>45	1.5%	1.3%	1.3%	1.4%	1.7%	2.0%	2.3%	2.6%	2.9%
	>50	0.5%	0.5%	0.5%	0.5%	0.5%	0.6%	0.7%	0.8%	0.9%

*Data was unavailable. Asian Indian, Korean, Samoan, Vietnamese and Hispanic races were not considered specific categories on birth certificates during the earlier years of the study period. Paternal education was not reported nationally between 1994 and 2009 due to unreliability of the data. Regional birth data ceased being publicly available starting in 2004.

Association of paternal age with perinatal outcomes between 2007 and 2016 in the United States: population based cohort study

Yash S Khandwala,[1] Valerie L Baker,[2] Gary M Shaw,[3] David K Stevenson,[3] Ying Lu,[4] Michael L Eisenberg[1,2]

Table 1| Paternal, maternal, and infant characteristics by paternal age group. Values are numbers (percentages) unless stated otherwise

Characteristics	Paternal age (years)					Missing paternal age
	<25	25-34	35-44	45-54	≥55	
Infant characteristics						
Mean (99% CI) birth weight (g)*	3220 (3219.4 to 3220.6)	3306.6 (3306.3 to 3306.9)	3304.6 (3304.1 to 3305.2)	3253.2 (3251.6 to 3254.8)	3202.4 (3197.4 to 3207.4)	3148.4 (3147.7 to 3149.0)
Mean (99% CI) gestational age (weeks)*	38.69 (38.68 to 38.69)	38.72 (38.72 to 38.72)	38.54 (38.54 to 38.54)	38.36 (38.35 to 38.37)	38.26 (38.24 to 38.28)	38.35 (38.35 to 38.36)
Premature birth (<37 weeks)	745 615 (11.8)	1 902 785 (10.4)	993 011 (11.7)	154 819 (14.2)	17 867 (16.1)	959 100 (15.4)
Low birth weight (<2500 g)	518 957 (8.2)	1 273 508 (7.0)	663 742 (7.8)	107 612 (9.9)	13 031 (11.7)	704 080 (11.3)
Low 5 minute Apgar score (<8)	258 283 (4.1)	617 300 (3.4)	281 172 (3.3)	42 269 (3.9)	4928 (4.4)	295 878 (4.7)
Assisted ventilation	200 197 (3.2)	547 699 (3.0)	259 905 (3.7)	37 986 (3.5)	4178 (3.8)	193 697 (3.1)
Admission to NICU	385 777 (6.1)	1 095 543 (6.0)	563 784 (6.7)	89 329 (8.2)	10 648 (9.6)	424 343 (6.8)
Postpartum antibiotics	116 124 (1.8)	302 290 (1.7)	134 836 (1.6)	19 865 (1.8)	2,235 (2.0)	114 295 (1.8)
Seizures	1715 (0.0)	4409 (0.0)	2000 (0.0)	300 (0.0)	33 (0.0)	1986 (0.0)
Adverse event	524 725 (8.3)	1 449 012 (7.9)	720 770 (8.5)	110 645 (10.1)	12 833 (11.6)	543 107 (8.7)

NICU=neonatal intensive care unit

Missing paternal age data are presented as number of birth certificates without paternal age for each category and percentage of total number of missing paternal age data.

Association of paternal age with perinatal outcomes between 2007 and 2016 in the United States: population based cohort study

Yash S Khandwala,[1] Valerie L Baker,[2] Gary M Shaw,[3] David K Stevenson,[3] Ying Lu,[4] Michael L Eisenberg[1,2]

WHAT THIS STUDY ADDS

Men aged 45 years or older had increased odds of fathering infants born premature, of low birth weight, and with a low Apgar score compared with their younger counterparts; the offspring of fathers older than 55 were also more likely to require assisted ventilation and admission to a neonatal intensive care unit

The odds of gestational diabetes was also higher for pregnancies involving fathers older than 45 years

13.2% of premature births and 14.5% of low birth weight infants born to older fathers were estimated to be prevented if all men elected to have children before age 45 years

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Statement on guidance for genetic counseling in advanced paternal age

Helga V. Toriello, PhD[1], and Jeanne M. Meck, PhD[2], for the Professional Practice and Guidelines Committee

Key Words: *paternal age, genetic counseling, mutation, chromosome anomalies*

Type	Specific condition	Age (relative to reference age)	Relative risk (CI, if available)	Population risk (or reference risk)	Adjusted risk	References (first author's name only)
Autosomal dominant	Achondroplasia	>50 (25–29)	7.8	1/15,000	1/1923	Risch[1]
		30–34 (<20)	3.5		1/4285	Tiemann-Boege[21]
		35–39 (<20)	4		1/3750	
		40–44 (<20)	8		1/1875	
		45–49 (<20)	9		1/1666	
		50–54 (<20)	12		1/1250	
	Apert	>50 (25–29)	9.5	1/50,000	1/5263	Risch[1]
	Pfeiffer	>50 (25–29)	6	1/100,000	1/16,666	Glaser[22]
	Crouzon	>50 (25–29)	8	1/50,000	1/6250	
	Progeria	Unknown	Effect seen	"Exceedingly rare"		
	MEN2A	Unknown	Effect seen	1/30,000		
	MEN2B	Unknown	Effect seen	1/30,000		
	Neurofibromatosis I	>50 (25–29)	3.7[a]	1/3000–1/4000	1/810–1/1080	Risch[1]
		>40 (<30)	2.9		1/1034–1/1380	Bunin[23]
	Osteogenesis imperfecta	>35 (<25)	2.5	1/10,000	1/4000	Carothers[24]
		>35 (<35)	1.37 (0.73–6.89)		1/7300	Orioli[25]
	Thanatophoric dysplasia	>35 (<35)	3.18 (1.48–6.89)	1/20,000–1/50,000	1/6290–1/15,723	Orioli[25]
	Retinoblastoma	>45	3[a] (0.21–41.7)	1/15,000–1/20,000	1/5000–1/6667	Dockerty, Yip[26,27]
		>35 (<35)	1.34 (1.04–1.74)		1/11,200–1/14,925	Moll[28]
		>50 (32.5)	5		1/3000–1/4000	DerKinderen[29]

Chromosomal	Down syndrome	40–44 (20–29)	1.37 (0.48–3.86)	1/1200 (mat. age 20–29)	1/876	Zhu[30]
		45–49 (20–29)	2.68 (0.76–9.51)		1/448	
		>49 (20–29)	4.5 (1.0–20.3)		1/267	
		40–44 (25–29)	1.45 (1.26–1.68)	Use maternal age as baseline for counseling purposes[b]		Yang[31]
		45–49 (25–29)	1.28 (1.04–1.57)			
		>49 (25–29)	1.39 (1.04–1.83)			
		None given	"May be increased"			Kuhnert[16]
		None given	"Paternal age effect in association with maternal age (>35) effect"			Fisch[14]
	Klinefelter syndrome	>50 (20's)	1.6[c] (0.69–3.0)	1/500 men	1/312 men	Lowe[32]
Congenital anomalies	VSD	>40 (<40)	1.69[a]	1/200	1/118	Olshan[33]
	ASD	>35	1.95[a]	1/400	1/205	Lian[11]
	Tracheoesophageal fistula	>50 (25–29)	2.55 (1.28–4.6)	1/3600	1/1412	Yang[31]
Other complex disorders	Childhood leukemia	>35	1.5	1/25,000	1/16,667	Murray[34]
		>40 (<25)	1.14 (0.85–1.53)		1/21930	Yip[27]
	Childhood CNS tumor	30–34 (<25)	1.34 (1.04–1.72)	1/36,000	1/26,866	Yip[27]
		35–39 (<25)	1.4 (1.04–1.86)		1/25,714	
		>40 (<25)	1.69 (1.21–2.35)		1/21,302	

Type	Specific condition	Age (relative to reference age)	Relative risk (CI, if available)	Population risk (or reference risk)	Adjusted risk	References (first author's name only)
	Childhood type 1 diabetes	>34 (<25)	1.52 (1.1–2.09)	1/415	1/273	Cardwell[35]
	Epilepsy	35–39	1.18 (1.02–1.26)	1/100	1/85	Vestergaard[36]
		40–45	1.3 (1.08–1.55)		1/770	
	Schizophrenia	>50 (20–24)	4.62 (2.28–9.36)	1/100	1/22	Rasmussen[37]
		35–44 (15–24)	1.6 (1.0–2.6)		1/62.5	Zammit[38]
		45–54 (15–24)	1.6 (0.8–3.1)		1/62.5	
		>54 (15–24)	3.8 (1.3–11.8)		1/26	
		>49 (<25)	3		1/33	Malaspina[12]
		>32 (<28)	3 (1.49–6.04)		1/33	Tsuchiya[39]
	Autism	>40 (<30)	5.75 (2.65–12.46)	1/1000	1/174	Reichenberg[40]
		Unknown	Effect seen			Cantor[9]
	Autism spectrum disorders	35–39 (25–29)	1.38 (1.04–1.84)	1/200	1/145	Croen[41]
		>39 (25–29)	1.52 (1.1–2.1)		1/131	
	Breast cancer	>40 (<30)	1.6 (1.04–2.32)	1/8.5	1/5.3	Choi[42]
	Prostate cancer	>38 (<27)	1.7 (1.0–2.8)	1/5.9	1/3.5	Zhang[43]
	Multiple sclerosis	51–55 (21–25)	2.0 (1.35–2.96)			Montgomery[44]

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ACMG Practice Guidelines

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Other	Spontaneous miscarriages	>35 (<35)	1.26 (1.0–1.6)	1/7	1/5.3	Slama[45]
		>39 (25–29)	1.6 (1.2–2.0)		1/4	Kleinhaus[46]
	Relative infertility	>39 (<39)	2.3 (1.67–3.17)	1/14 couples	1/6.2	De la Rochebrochard[47]
	Low birth weight	>34 (20–34)	1.7 (1.3–2.2)	1/40	1/23	Reichman[48]
	Preeclampsia	35–44 (25–34)	1.24 (1.05–1.46)	1/62	1/50	Harlap[49]
		>44 (25–34)	1.8 (1.04–1.51)	1/62	1/34	
Total risk	For 86 examined congenital anomalies	>40 (<20)	1.2	1/50	1/42	Lian[11]
		>50 (<20)	1.3		1/38	

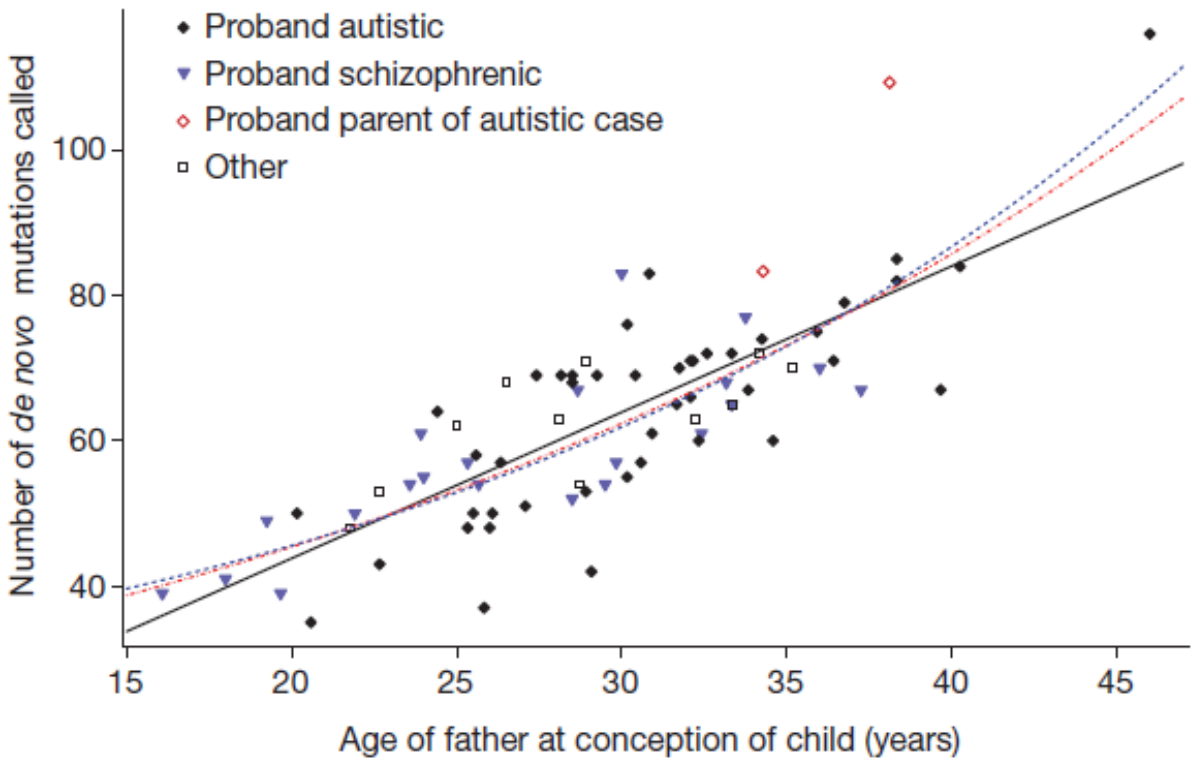


Figure 2 | Father's age and number of *de novo* mutations. The number of *de novo* mutations called is plotted against father's age at conception of child for the 78 trios. The solid black line denotes the linear fit. The dashed red curve is based on an exponential model fitted to the combined mutation counts. The dashed blue curve corresponds to a model in which maternal mutations are assumed to have a constant rate of 14.2 and paternal mutations are assumed to increase exponentially with father's age.

ARTICLE

doi:10.1038/nature11396

Rate of *de novo* mutations and the importance of father's age to disease risk

Augustine Kong[1], Michael L. Frigge[1], Gisli Masson[1], Soren Besenbacher[1,2], Patrick Sulem[1], Gisli Magnusson[1], Sigurjon A. Gudjonsson[1], Asgeir Sigurdsson[1], Aslaug Jonasdottir[1], Adalbjorg Jonasdottir[1], Wendy S. W. Wong[3], Gunnar Sigurdsson[1], G. Bragi Walters[1], Stacy Steinberg[1], Hannes Helgason[1], Gudmar Thorleifsson[1], Daniel F. Gudbjartsson[1], Agnar Helgason[1,4], Olafur Th. Magnusson[1], Unnur Thorsteinsdottir[1,5] & Kari Stefansson[1,5]

Table 1 | *De novo* mutations observed with parental origin assigned

			Number of *de novo* mutations in proband		
	Father's age (yr)	Mother's age (yr)	Paternal chromosome	Maternal chromosome	Combined
Trio 1	21.8	19.3	39	9	48
Trio 2	22.7	19.8	43	10	53
Trio 3	25.0	22.1	51	11	62
Trio 4	36.2	32.2	53	26	79
Trio 5	40.0	39.1	91	15	106
Mean	29.1	26.5	55.4	14.2	69.6
s.d.	8.4	8.8	20.7	7.0	23.5
Variance	70.2	77.0	428.8	48.7	555.3

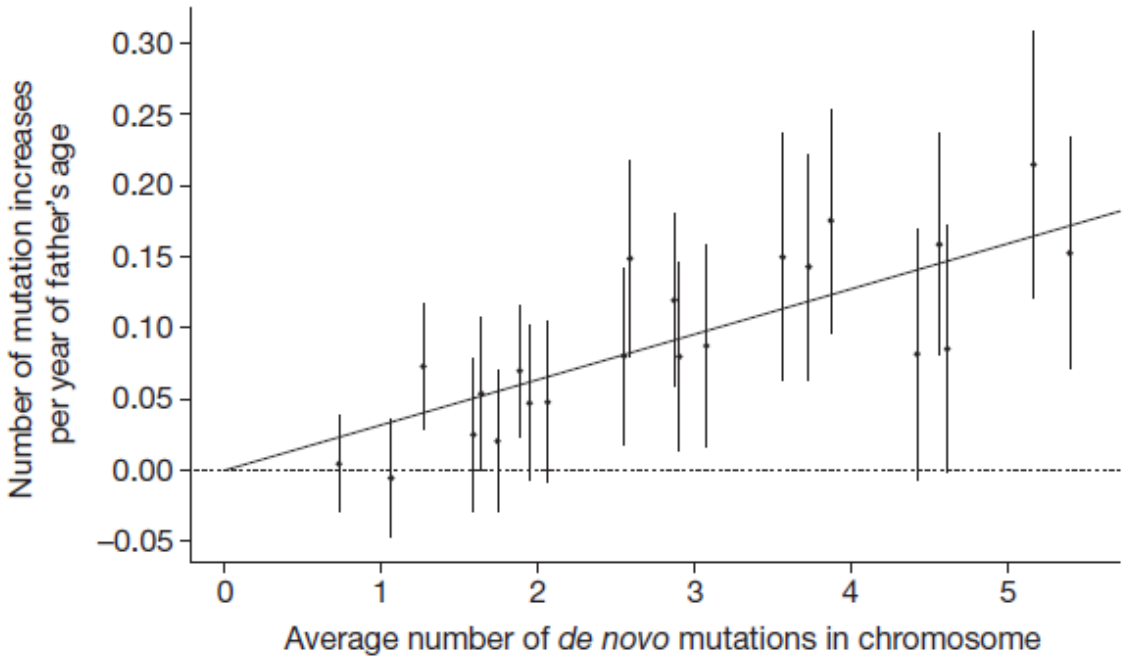


Figure 3 | Effect of father's age by chromosome. By chromosome, the estimated increase in the number of *de novo* mutations per year of father's age is plotted against the average number of mutations observed. The 95% confidence intervals are given. The solid straight line corresponds to the model in which the additive effect of father's age on the number of *de novo* mutations is assumed to be proportional to the mean number of mutations on the chromosome. From left to right, the points correspond to chromosome 21, 22, 19, 20, 15, 17, 18, 14, 16, 13, 12, 9, 10, 11, 8, 7, 6, 3, 5, 4, 2 and 1.

ARTICLE

doi:10.1038/nature11396

Rate of *de novo* mutations and the importance of father's age to disease risk

Augustine Kong[1], Michael L. Frigge[1], Gisli Masson[1], Soren Besenbacher[1,2], Patrick Sulem[1], Gisli Magnusson[1], Sigurjon A. Gudjonsson[1], Asgeir Sigurdsson[1], Aslaug Jonasdottir[1], Adalbjorg Jonasdottir[1], Wendy S. W. Wong[3], Gunnar Sigurdsson[1], G. Bragi Walters[1], Stacy Steinberg[1], Hannes Helgason[1], Gudmar Thorleifsson[1], Daniel F. Gudbjartsson[1], Agnar Helgason[1,4], Olafur Th. Magnusson[1], Unnur Thorsteinsdottir[1,5] & Kari Stefansson[1,5]

Effects - Paternal Health

ORIGINAL ARTICLES: ANDROLOGY

Association of preconception paternal health on perinatal outcomes: analysis of U.S. claims data

Alex M. Kasman, M.D., M.S.,[a] Chiyuan A. Zhang, M.P.H.,[a] Shufeng Li, M.S.,[a] David K. Stevenson, M.D.,[b] Gary M. Shaw, Dr.P.H.,[b] and Michael L. Eisenberg, M.D.[a,c]

[a] Department of Urology, [b] Department of Pediatrics, [c] Department of Obstetrics and Gynecology, School of Medicine, Stanford University, Stanford, California

TABLE 2

Multivariable logistic regression models predicting association of paternal health on birth outcomes after adjustment for year of birth, maternal age, region, and maternal metabolic syndrome or chronic disease components or maternal CCI and paternal and maternal smoking status.

	Preterm birth		Low birth weight		NICU stay	
Parameter	**n (%)**	**OR (95% CI)**	**n (%)**	**OR (95% CI)**	**n (%)**	**OR (95% CI)**
MetS components[a]						
0	38,667 (6.3)	Reference	27,455 (4.5)	Reference	6,319 (1.03)	Reference
1	8,941 (7.4)	1.07 (1.05, 1.10)	6,410 (5.3)	1.08 (1.05, 1.11)	1,457 (1.20)	1.07 (1.01,1.14)
2	3,087 (8.1)	1.11 (1.06, 1.15)	2,197 (5.7)	1.10 (1.05, 1.16)	468 (1.22)	1.02 (0.93,1.13)
3	911 (9.4)	1.18 (1.09, 1.27)	629 (6.5)	1.13 (1.03, 1.23)	154 (1.58)	1.26 (1.06,1.49)
4	153 (9.7)	1.14 (0.95, 1.36)	113 (7.1)	1.21 (0.98, 1.48)	25 (1.58)	1.16 (0.76,1.75)
Hypertension						
No	45,000 (6.4)	Reference	32,026 (4.6)	Reference	7,321 (1.04)	Reference
Yes	6,759 (7.9)	1.11 (1.08,1.14)	4,778 (5.6)	1.09 (1.06,1.13)	1,102 (1.30)	1.12 (1.05,1.20)
DM						
No	49,767 (6.5)	Reference	35,362 (4.6)	Reference	8,085 (1.06)	Reference
Yes	1,992 (8.2)	1.06 (1.01,1.12)	1,442 (5.9)	1.09 (1.02,1.15)	338 (1.39)	1.11 (0.99,1.25)
Obesity						
No	49,009 (6.5)	Reference	34,884 (4.6)	Reference	7,981 (1.06)	Reference
Yes	2,750 (8.4)	1.13 (1.08,1.18)	1,920 (5.8)	1.11 (1.05,1.17)	442 (1.34)	1.14 (1.03,1.26)
Hyperlipidemia						
No	44,800 (6.5)	Reference	31,801 (4.6)	Reference	7,350 (1.06)	Reference
Yes	6,959 (7.6)	1.05 (1.02,1.08)	5,003 (5.5)	1.06 (1.02,1.09)	1,073 (1.17)	0.98 (0.92,1.05)

TABLE 2

Multivariable logistic regression models predicting association of paternal health on birth outcomes after adjustment for year of birth, maternal age, region, and maternal metabolic syndrome or chronic disease components or maternal CCI and paternal and maternal smoking status.

	Preterm birth		Low birth weight		NICU stay	
Parameter	**n (%)**	**OR (95% CI)**	**n (%)**	**OR (95% CI)**	**n (%)**	**OR (95% CI)**
COPD						
No	47,181 (6.5)	Reference	33,588 (4.6)	Reference	7,720 (1.07)	Reference
Yes	4,578 (7.3)	1.08 (1.04,1.11)	3,216 (5.2)	1.06 (1.02,1.11)	703 (1.13)	1.01 (0.93,1.10)
Cancer						
No	51,150 (6.6)	Reference	36,360 (4.7)	Reference	8,324 (1.07)	Reference
Yes	609 (8.1)	1.17 (1.07,1.28)	444 (5.9)	1.20 (1.09,1.33)	99 (1.32)	1.15 (0.94,1.42)
Depression						
No	49,021 (6.5)	Reference	34,853 (4.6)	Reference	7,973 (1.06)	Reference
Yes	2,738 (8.0)	1.19 (1.14,1.24)	1,951 (5.7)	1.18 (1.12,1.24)	450 (1.32)	1.21 (1.09,1.33)
Chronic diseases[b]						
0	34,088 (6.2)	Reference	24,202 (4.4)	Reference	5,600 (1.02)	Reference
1	11,497 (7.2)	1.08 (1.06,1.11)	8,240 (5.1)	1.09 (1.06,1.12)	1,856 (1.16)	1.06 (1.00,1.12)
2	4,200 (7.9)	1.12 (1.08,1.16)	2,978 (5.6)	1.11 (1.06,1.16)	645 (1.21)	1.04 (0.96,1.14)
3	1,497 (9.0)	1.19 (1.13,1.27)	1,049 (6.3)	1.17 (1.09,1.25)	241 (1.46)	1.20 (1.05,1.38)
4+	477 (9.6)	1.19 (1.07,1.32)	335 (6.7)	1.18 (1.05,1.33)	81 (1.63)	1.27 (1.01,1.60)
Paternal CCI						
0	42,782 (6.4)	Reference	30,421 (4.6)	Reference	7,004 (1.05)	Reference
1	6,927 (7.5)	1.09 (1.06,1.12)	4,883 (5.3)	1.11 (1.07,1.15)	1,088 (1.18)	1.08 (1.01,1.15)
2	1,278 (7.9)	1.11 (1.04,1.18)	908 (5.6)	1.15 (1.07,1.23)	203 (1.26)	1.06 (0.92,1.23)
3+	772 (8.7)	1.15 (1.07,1.25)	592 (6.7)	1.31 (1.20,1.44)	128 (1.45)	1.23 (1.03,1.47)

Note: IBM Marketscan Research database reimbursed health care claims data. Percentages may not add to 100% due to rounding. CCI = Charlson Comorbidity Index; CI = confidence interval; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; MetS = metabolic syndrome; OR = odds ratio.

[a] MetS components are hypertension, hyperlipidemia, diabetes mellitus, obesity.

[b] One of seven. Chronic disease included hypertension, diabetes mellitus, obesity, hyperlipidemia, COPD, cancer, and depression.

Kasman. Preconception paternal health birth outcomes. Fertil Steril 2019.

TABLE 3

Multivariable logistic regression models predicting association of paternal health on maternal peripartum outcomes birth outcomes after adjustment for year of birth, maternal age, maternal metabolic syndrome, and region of birth.

	Paternal metabolic syndrome components					
Outcomes	**0**	**1**	**2**	**3**	**4**	**Total**
Total N	614,738	121,418	38,351	9,717	1,585	785,809
Gestational diabetes						
Yes, N (%)	94,859 (15.4)	22,332 (18.4)	8,221 (21.4)	2,438 (25.1)	436 (27.5)	128,286 (16.3)
No, N (%)	519,879 (84.6)	99,086 (81.6)	30,130 (78.6)	7,279 (74.9)	1,149 (72.5)	657,523 (83.7)
OR (95% CI)	Reference	1.07 (1.05,1.09)	1.15 (1.12,1.18)	1.24 (1.18,1.30)	1.16 (1.03,1.31)	—
Preeclampsia						
Yes, N (%)	30,560 (5.0)	7,155 (5.9)	2,618 (6.8)	752 (7.7)	156 (9.8)	41,241 (5.3)
No, N (%)	584,178 (95.0)	114,263 (94.1)	35,733 (93.2)	8,965 (92.3)	1,429 (90.2)	744,568 (94.8)
OR (95% CI)	Reference	1.04 (1.01,1.07)	1.06 (1.02,1.11)	1.04 (0.96,1.13)	1.15 (0.97,1.38)	
Eclampsia						
Yes, N (%)	754 (0.12)	177 (0.15)	71 (0.19)	18 (0.16)	NA[a]	1,020 (0.13)
No, N (%)	613,984 (99.88)	121,241 (99.85)	38,280 (99.81)	11,284 (99.84)	NA[a]	784,789 (99.87)
OR (95% CI)	Reference	0.99 (0.84,1.18)	1.09 (0.84,1.40)	0.78 (0.48,1.26)	NA[a]	—
Maternal hospital stay						
Total N	614,738	121,418	38,351	9,717	1,585	785,809
Average days	2.54 (2.80)	2.67 (3.09)	2.77 (3.44)	2.84 (3.77)	2.99 (3.67)	2.58 (2.89)
Days ≥3	226,918 (36.9)	49,335 (40.6)	16,374 (42.7)	4,355 (44.8)	784 (49.45)	297,766 (37.9)
OR (95% CI)	Reference	1.07 (1.05,1.08)	1.09 (1.07,1.11)	1.11 (1.07,1.16)	1.25 (1.13,1.39)	
Days ≥5	24,404 (4.0)	5,794 (4.8)	2,025 (5.3)	612 (6.3)	112 (7.1)	32,947 (4.2)
OR (95% CI)	Reference	1.06 (1.03,1.10)	1.07 (1.02,1.12)	1.15 (1.05,1.26)	1.13 (0.92,1.39)	
Days ≥7	8,985 (1.5)	2,262 (1.9)	777 (2.0)	246 (2.5)	47 (3.0)	12,317 (1.6)
OR (95% CI)	Reference	1.11 (1.05,1.17)	1.08 (0.99,1.17)	1.19 (1.04,1.37)	1.22 (0.89,1.66)	—

Note: IBM Marketscan Research database reimbursed health care claims data. Percentages may not add to 100% due to rounding. CI = confidence interval; MetS = metabolic syndrome; NA = not available; OR = odds ratio.

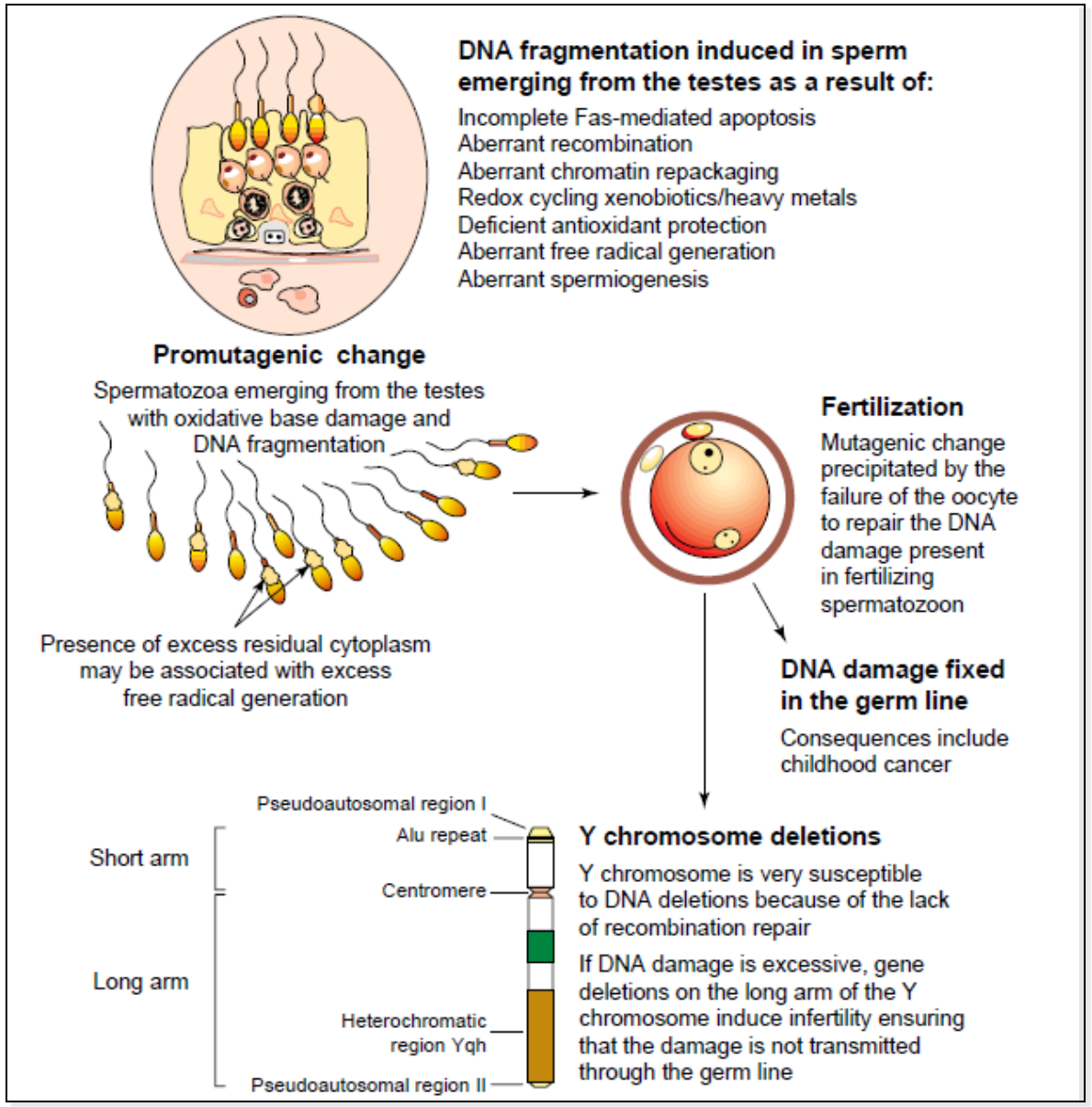
[a] Given the small number of individuals (N) with this condition, stratification was done only for the metabolic syndrome components 0, 1, 2, and 3 only.

Kasman. Preconception paternal health birth outcomes. Fertil Steril 2019.

Effects – Altered semen quality

Sperm DNA fragmentation – Consequences

- Infertility;
- Increased number of low quality embryos;
- Lower pregnancy rates;
- Recurrent Pregnancy Loss;
- Alterations in offspring.



Asian Journal of Andrology (2017) 19, 80–90

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Luke Simon[1,*], Armand Zini[2,*], Alina Dyachenko[2], Antonio Ciampi[2], Douglas T Carrell[1,3,4]

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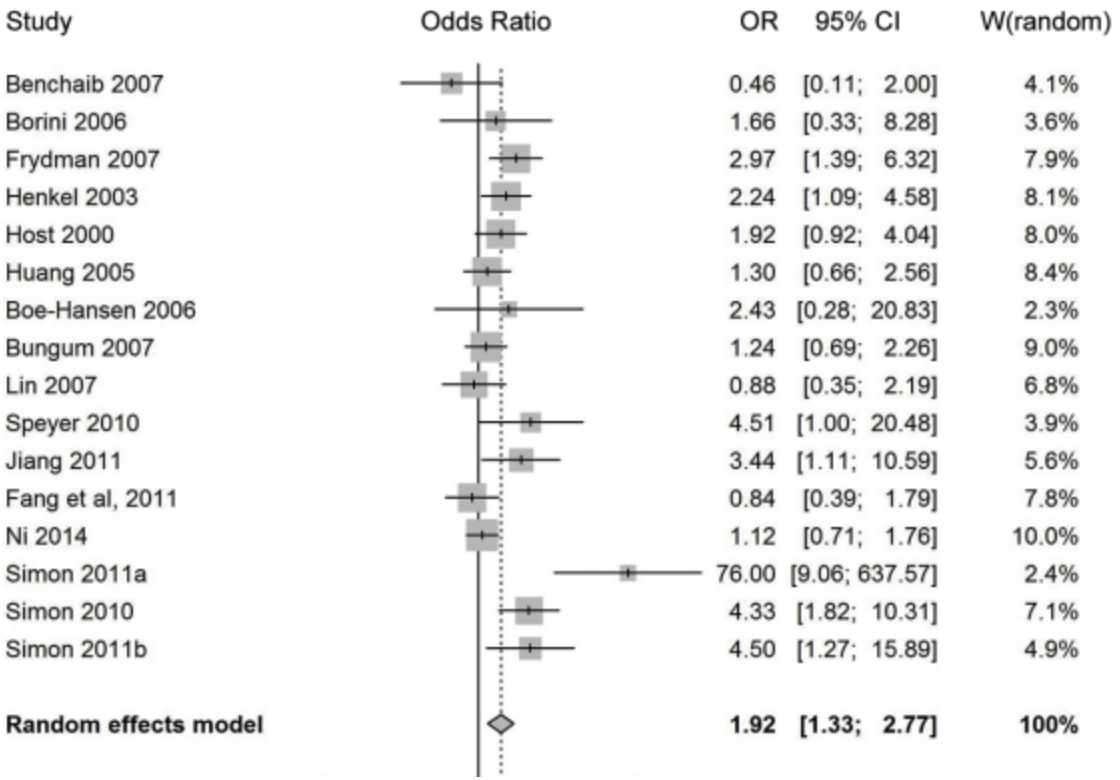
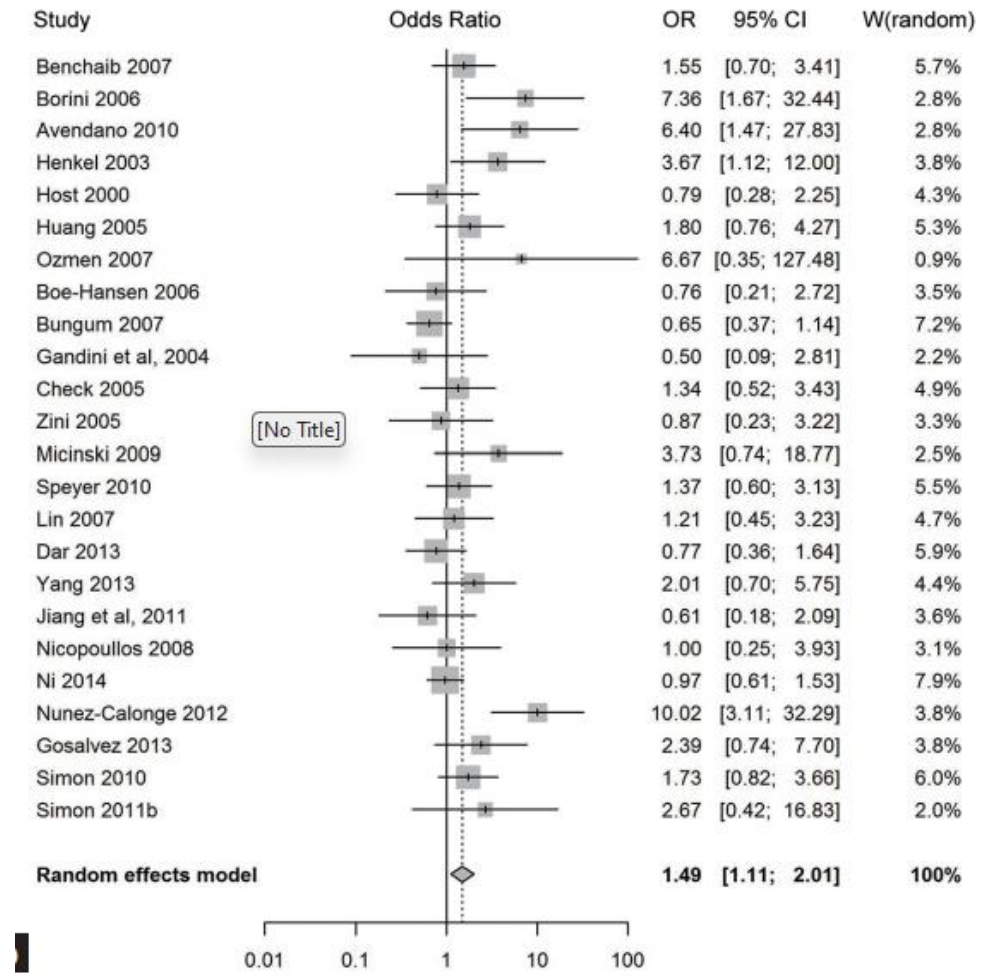
ORIGINAL ARTICLE

Sperm Biology

A systematic review and meta-analysis to determine the effect of sperm DNA damage on *in vitro* fertilization and intracytoplasmic sperm injection outcome





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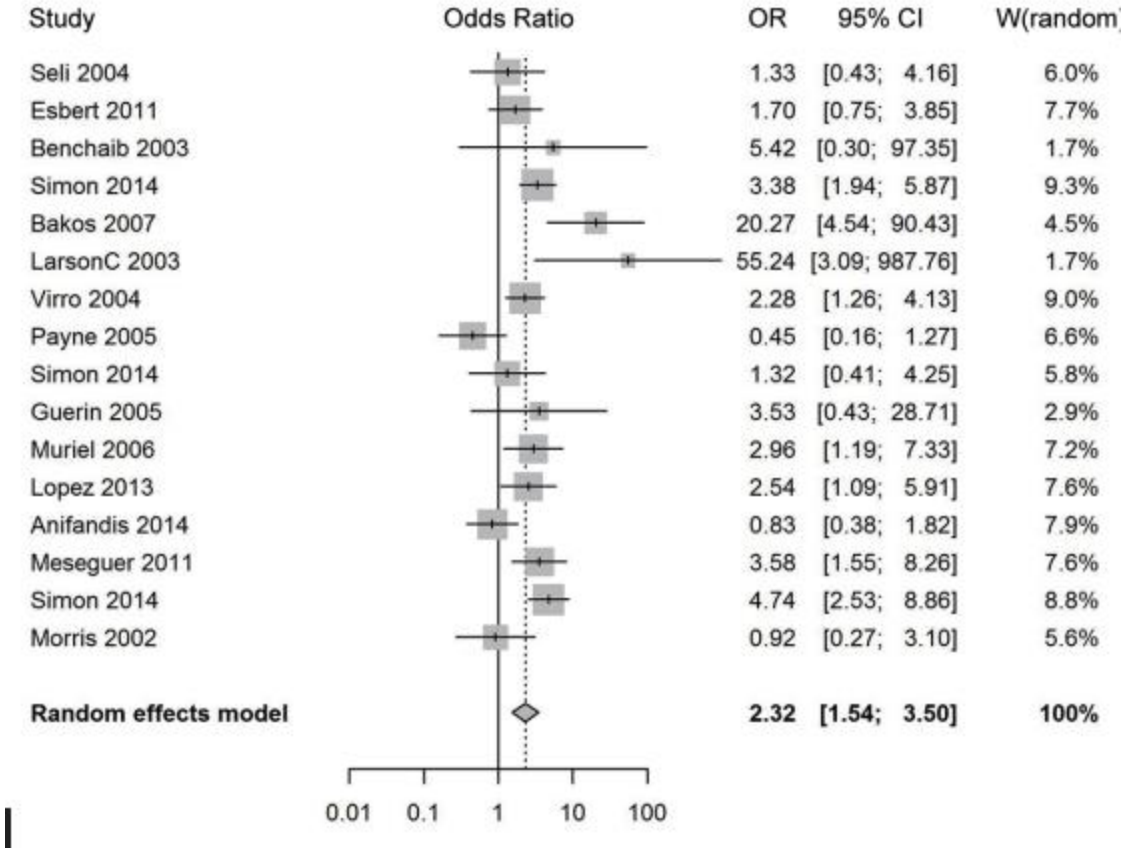


Sperm DNA fragmentation and recurrent pregnancy loss: a systematic review and meta-analysis

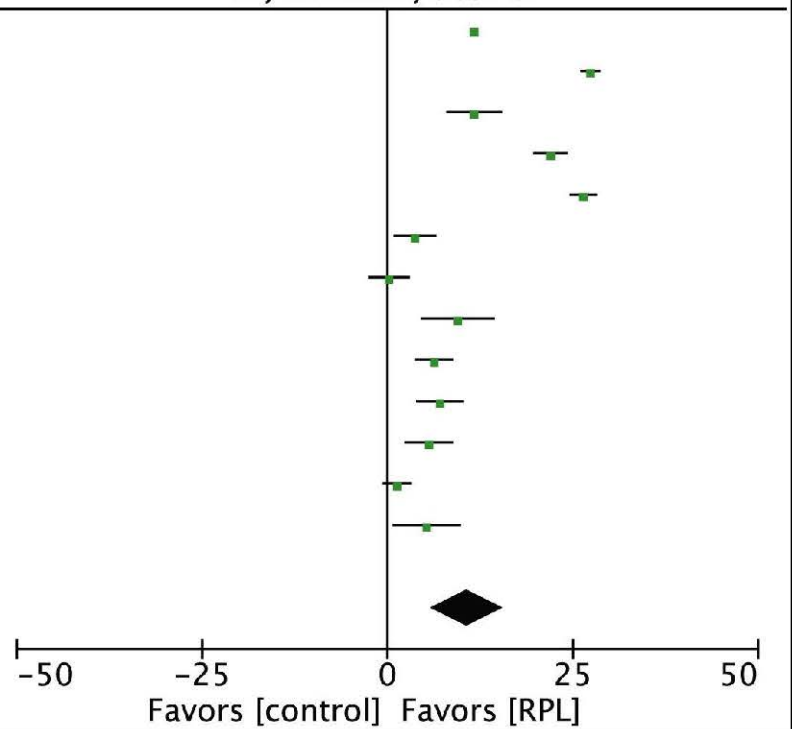
Dana B. McQueen, M.D., M.A.S., John Zhang, Ph.D., and Jared C. Robins, M.D.

Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Northwestern University, Chicago, Illinois

	Recurrent Pregnancy Loss			Fertile Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Absalan 2012	23.3	1.1	30	11.6	0.5	30	7.9%	11.70 [11.27, 12.13]
Bareh 2016	36.8	2.7	26	9.4	2.7	31	7.9%	27.40 [25.99, 28.81]
Bhattachara 2008	18.1	16.1	74	6.4	3.6	65	7.6%	11.70 [7.93, 15.47]
Brahem 2011	32.2	6.1	31	10.2	2.1	20	7.8%	22.00 [19.66, 24.34]
Carrell 2003	38.3	4.2	21	11.9	1	26	7.8%	26.40 [24.56, 28.24]
Coughlan 2014	10.9	1.9	16	7.2	3.7	7	7.7%	3.70 [0.81, 6.59]
Esquerre-Lamare 2018	6.8	5.6	33	6.6	5.5	27	7.7%	0.20 [-2.62, 3.02]
Imam 2011	23.4	9.9	20	13.9	5.4	20	7.3%	9.50 [4.56, 14.44]
Kumar 2012	28.1	5	45	21.8	4.8	20	7.8%	6.30 [3.74, 8.86]
Ribas 2012	19.3	6.1	20	12.2	4.6	25	7.7%	7.10 [3.88, 10.32]
Ruixue 2013	25.6	11.5	68	20	7.7	63	7.6%	5.60 [2.27, 8.93]
Zhang 2012	15.2	6.4	111	13.9	4.4	30	7.8%	1.30 [-0.67, 3.27]
Zidi-Jrah 2016	17.1	9.3	22	11.8	5.7	20	7.4%	5.30 [0.68, 9.92]
Total (95% CI)			**517**			**384**	**100.0%**	**10.70 [5.82, 15.58]**

Heterogeneity: $Tau^2 = 78.10$; $Chi^2 = 1019.62$, df = 12 ($P < 0.00001$); $I^2 = 99\%$

Test for overall effect: $Z = 4.30$ ($P < 0.0001$)



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Sperm DNA fragmentation index affect pregnancy outcomes and offspring safety in assisted reproductive technology

[No Title]

Fei Li[1✉], Xiaoyan Duan[2], Mingming Li[2] & Xing Ma[2]

Group	IVF patients				ICSI patients			
	DFI < 15% (n = 3123)	DFI15-30% (n = 561)	DFI ≥ 30% (n = 46)	*P* value	DFI < 15% (n = 1967)	DFI15-30% (n = 462)	DFI ≥ 30% (n = 171)	*P* value
Miscarriage rates (%)	13.75 (206/1498)	20.15 (53/263)[a]	30.00 (6/20)[a]	0.005	13.62 (131/962)	19.72 (43/218)[a]	33.34 (25/75)[a,b]	< 0.001

Group	IVF patients				ICSI patients			
	DFI < 15% (n = 1292)	DFI15-30% (n = 210)	DFI ≥ 30% (n = 14)	*P* value	DFI < 15% (n = 831)	DFI15-30% (n = 175)	DFI ≥ 30% (n = 50)	*P* value
Birth weight (grams)	2824.9 ± 723.64	2631.2 ± 701.39[a]	2592.7 ± 678.52[a]	< 0.001	2852.3 ± 741.41	2637.2 ± 711.28[a]	2523.2 ± 692.77[a,b]	< 0.001

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Sperm DNA fragmentation index affect pregnancy outcomes and offspring safety in assisted reproductive technology

Fei Li[1✉], Xiaoyan Duan[2], Mingming Li[2] & Xing Ma[2]

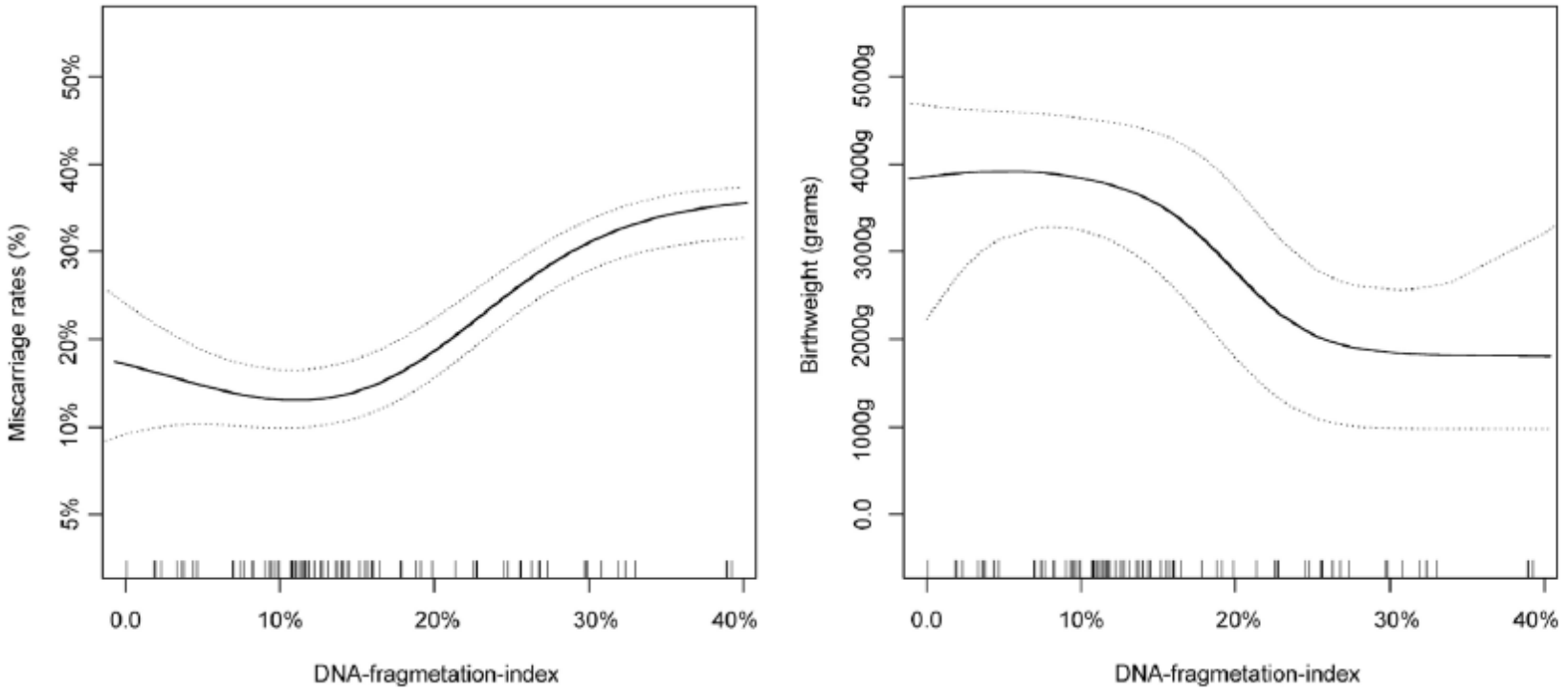


Figure 2. Left graph: association between sperm DFI and miscarriage rates. A nonlinear association between sperm DFI and miscarriage rates was found in a generalized additive model. Right graph: association between sperm DFI and birth weight. Solid line represents the smooth curve fit between variables. Dotted line represent the 95% of confidence interval from the fit.

ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Check for updates

High sperm deoxyribonucleic acid fragmentation index is associated with an increased risk of preeclampsia following assisted reproduction treatment

Amelie Stenqvist, M.D., Ph.D.,[a,b,c] Mona Bungum, Ph.D.,[b] Anja Bisgaard Pinborg, D.M.Sci.,[d] Jeanette Bogstad, M.D.,[d] Anne Lis Englund, D.M.Sci.,[e] Marie Louise Grøndahl, D.M.Sci.,[f] Anne Zedeler, Ph.D.,[g] Stefan R. Hansson, M.D., Ph.D.,[c,h] and Aleksander Giwercman, M.D., Ph.D.[a,b]

TABLE 2

Perinatal outcomes by deoxyribonucleic acid fragmentation index (< 20% vs. ≥20%) and method of fertilization.

Outcome	DFI level of < 20%	DFI level of ≥20%	Adjusted OR (95% CI)	*P* value
Preterm birth				
Total (N = 1,660)	10.8% (137/1,268)	15.1% (59/392)	1.4 (1.0–2.0)	.03
IVF (N = 871)	10.8% (81/748)	15.4% (19/123)	1.5 (0.84–2.5)	.18
ICSI (N = 776)	10.8% (55/509)	15.0% (40/267)	1.5 (0.94–2.3)	.10
Low birth weight				
Total (N = 1,652)	10.0% (126/1,261)	8.7% (34/391)	0.85 (0.57–1.3)	.44
IVF (N = 867)	9.9% (74/744)	8.1% (10/123)	0.75 (0.38–1.5)	.42
ICSI (N = 772)	10.3% (52/506)	9.0% (24/266)	0.88 (0.53–1.5)	.63
Small for gestational age[a]				
Total (N = 1,518)	4.0% (47/1,169)	2.3% (8/349)	0.56 (0.26–1.2)	.13
IVF (N = 806)	4.6% (32/701)	3.8% (4/105)	0.83 (0.29–2.4)	.72
ICSI (N = 701)	3.3% (15/457)	1.6% (4/244)	0.49 (0.16–1.5)	.20
Low Apgar score				
Total (N = 1,652)	1.7% (21/1,262)	2.6% (10/390)	1.6 (0.76–3.5)	.20
IVF (N = 868)	1.6% (12/745)	4.1% (5/123)	2.7 (0.91–7.8)	.07
ICSI (N = 771)	1.6% (8/506)	1.9% (5/265)	1.4 (0.41–4.0)	.67

Note: The odds ratios were adjusted for paternal age. The unit of observation was the child. CI = confidence interval; DFI = deoxyribonucleic acid fragmentation index; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; OR = odds ratio.

[a] Data on small for gestational age were unavailable for multiple birth children.

Stenqvist. Sperm DNA fragmentation and preeclampsia. Fertil Steril 2025.

ORIGINAL ARTICLE: ASSISTED REPRODUCTION

High sperm deoxyribonucleic acid fragmentation index is associated with an increased risk of preeclampsia following assisted reproduction treatment

Amelie Stenqvist, M.D., Ph.D.,[a,b,c] Mona Bungum, Ph.D.,[b] Anja Bisgaard Pinborg, D.M.Sci.,[d] Jeanette Bogstad, M.D.,[d] Anne Lis Englund, D.M.Sci.,[e] Marie Louise Grøndahl, D.M.Sci.,[f] Anne Zedeler, Ph.D.,[g] Stefan R. Hansson, M.D., Ph.D.,[c,h] and Aleksander Giwercman, M.D., Ph.D.[a,b]

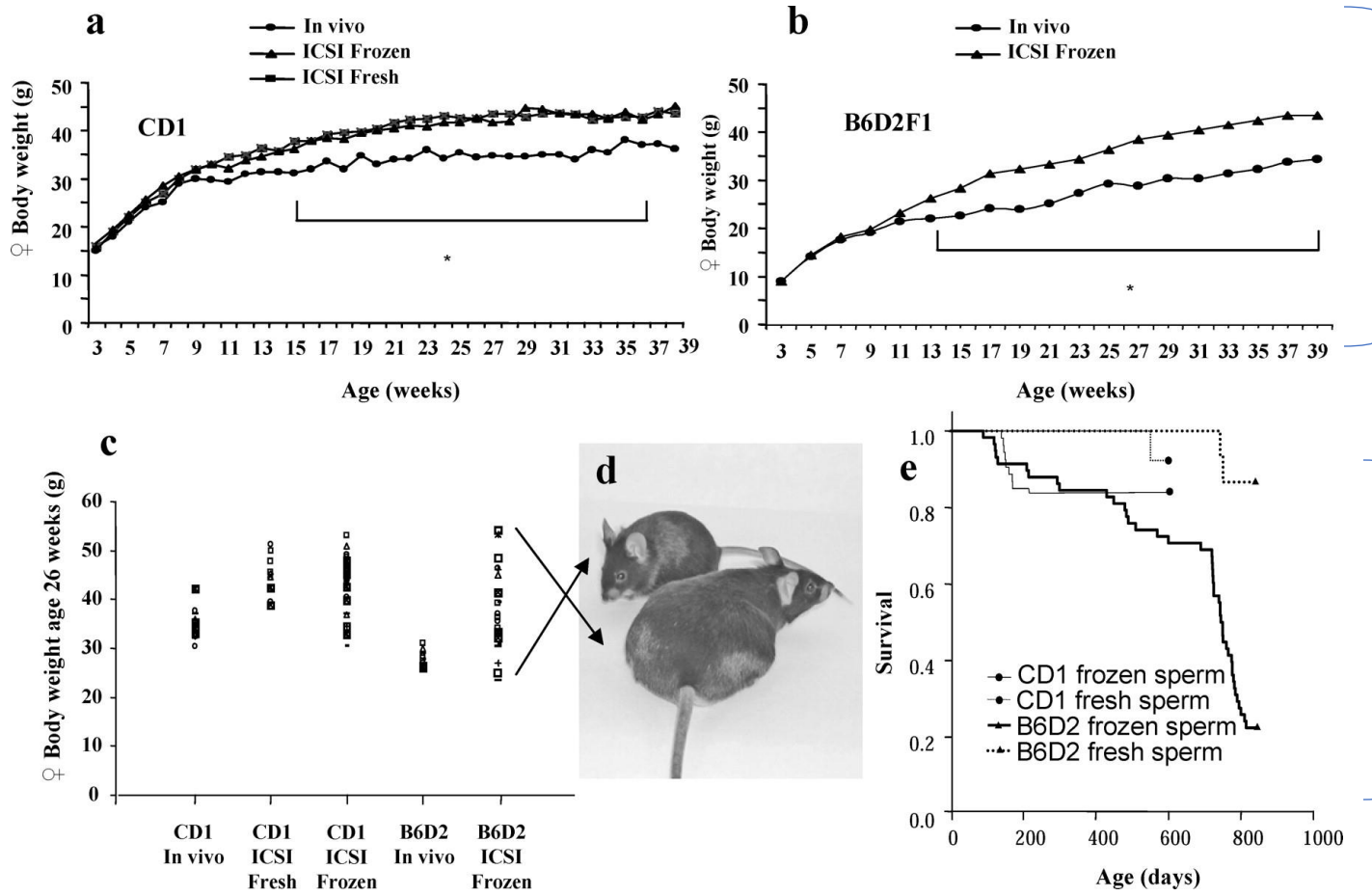
TABLE 3

Odds of preeclampsia by deoxyribonucleic acid fragmentation index groups (< 10% vs. ≥10% and < 20% vs. ≥20%) and method of fertilization.

Outcome	DFI level of < 10%	DFI level of ≥10%	DFI level of < 20%	DFI level of ≥20%
Total (N = 1,594)				
Preeclampsia	3.1% (14/450)	6.5% (74/1,144)	5.1% (62/1,222)	7.0% (26/372)
Adjusted OR (95% CI)	Ref.	2.1 (1.2–3.8)	Ref.	1.4 (0.85–2.2)
IVF (N = 841)				
Preeclampsia	3.1% (10/325)	7.2% (37/516)	4.8% (35/727)	10.5% (12/114)
Adjusted OR (95% CI)	Ref.	2.3 (1.1–4.8)	Ref.	2.2 (1.1–4.4)
ICSI (N = 741)				
Preeclampsia	3.3% (4/122)	5.7% (35/619)	5.4% (26/484)	5.1% (13/257)
Adjusted OR (95% CI)	Ref.	1.8 (0.61–5.1)	Ref.	0.94 (0.47–1.9)

Note: The odds ratios were adjusted for paternal age. The unit of observation was the couple. CI = confidence interval; DFI = deoxyribonucleic acid fragmentation index; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; OR = odds ratio; Ref. = reference category.

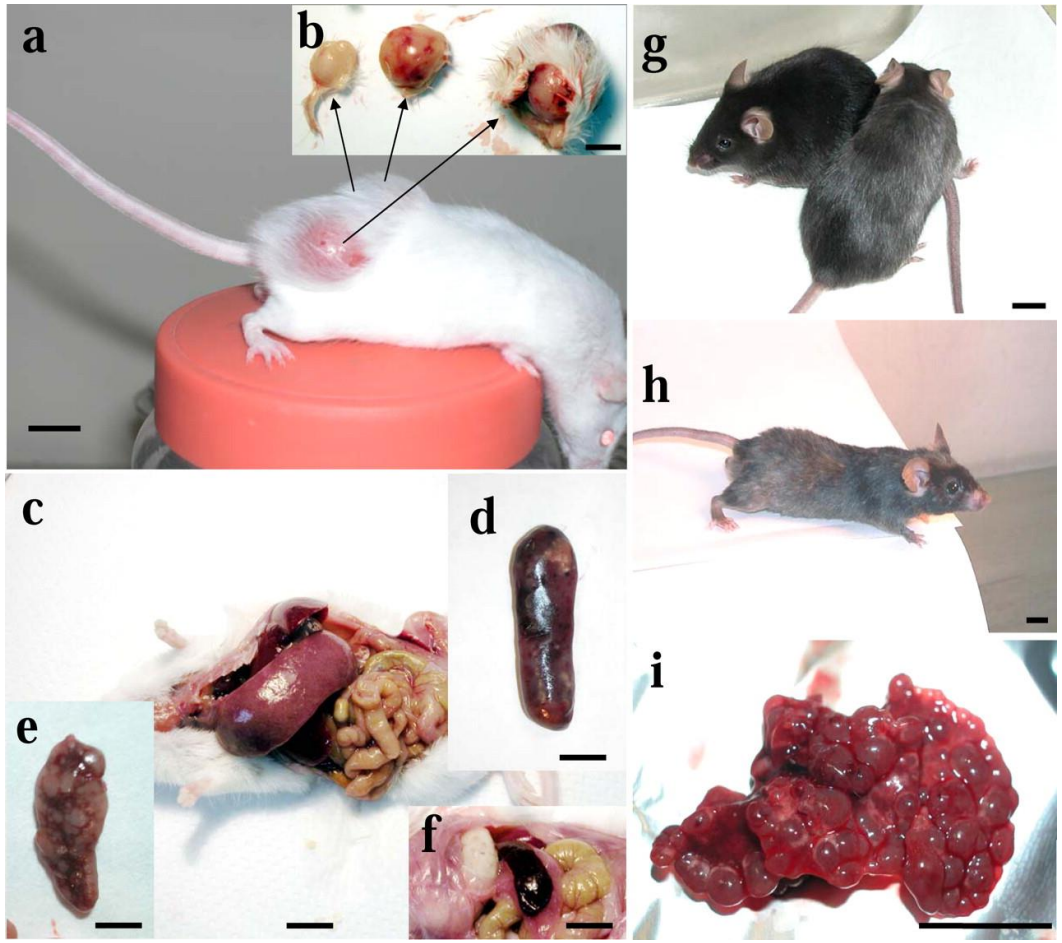
Stenqvist. Sperm DNA fragmentation and preeclampsia. Fertil Steril 2025.



Higher body weight with ICSI

Higher mortality with frozen sperm (for high DFI)

Biol Reprod, Volume 78, Issue 4, 1 April 2008, Pages 761–772, https://doi.org/10.1095/biolreprod.107.065623



"With ICSI using DFS, but not using fresh sperm, **33% of CD1 females developed tumors** (Fig. 3, a–d), and **15% of these females that developed tumors died between 3 and 5 mo of age**.

Biol Reprod, Volume 78, Issue 4, 1 April 2008, Pages 761–772, https://doi.org/10.1095/biolreprod.107.065623

Effects – Exposure to reproductive toxicants

Commentary

A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP5045.

Proposed Key Characteristics of Male Reproductive Toxicants as an Approach for Organizing and Evaluating Mechanistic Evidence in Human Health Hazard Assessments

Xabier Arzuaga,[1] Martyn T. Smith,[2] Catherine F. Gibbons,[1] Niels E. Skakkebæk,[3] Erin E. Yost,[4] Brandiese E. J. Beverly,[5] Andrew K. Hotchkiss,[4] Russ Hauser,[6] Rodrigo L. Pagani,[7] Steven M. Schrader,[8] Lauren Zeise,[9] and Gail S. Prins[7,10]

[1]National Center for Environmental Assessment, U.S. Environmental Protection Agency, Washington, DC, USA
[2]University of California, Berkeley, School of Public Health, Berkeley, California, USA
[3]Department of Growth and Reproduction, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
[4]National Center for Environmental Assessment, U.S. Environmental Protection Agency, Research Triangle Park, NC, USA
[5]Office of Health Assessment and Translation, National Toxicology Program, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC, USA
[6]Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
[7]Department of Urology, University of Illinois at Chicago, Chicago, Illinois, USA
[8]National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Cincinnati, Ohio, USA (retired)
[9]Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, California, USA
[10]School of Public Health, University of Illinois at Chicago, Chicago, Illinois, USA

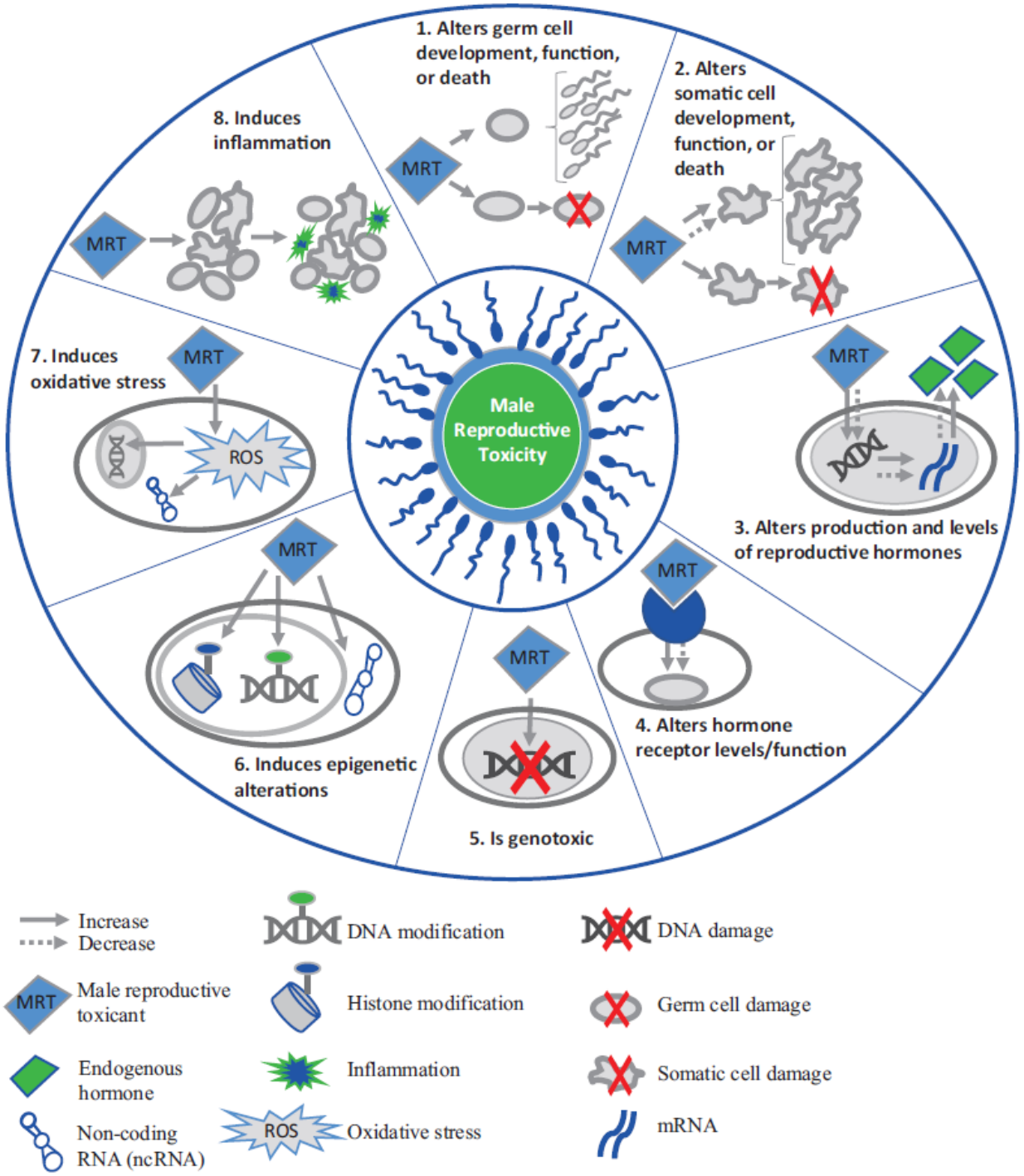


Table 1.

Key characteristics of male reproductive toxicants.

Key characteristic	Examples of relevant evidence
1. Alters germ cell development, function, or death	Increased germ cell apoptosis; alterations in sperm acrosome reaction and motility
2. Alters somatic cell development, functions, or death	Increased Sertoli cell apoptosis; alterations in Sertoli cell functions, cytoskeleton, and interactions with germ cells; alterations in Leydig cell development
3. Alters production and levels of reproductive hormones	Decreased Leydig cell steroidogenic functions; increased hepatic metabolism and excretion of sex hormones
4. Alters hormone receptor levels/functions	Androgen receptor antagonism, estrogen receptor activation, decreased LH receptor expression
5. Is genotoxic	DNA damage, chromosome fragmentation, altered sperm cell chromosome numbers
6. Induces epigenetic alterations	Altered sperm ncRNAs, germ cell DNA methylation patterns, and histone retention sites
7 Induces oxidative stress	Reduced tissue antioxidant levels
8. Induces inflammation	Increased testicular expression of pro-inflammatory markers and prostaglandin levels

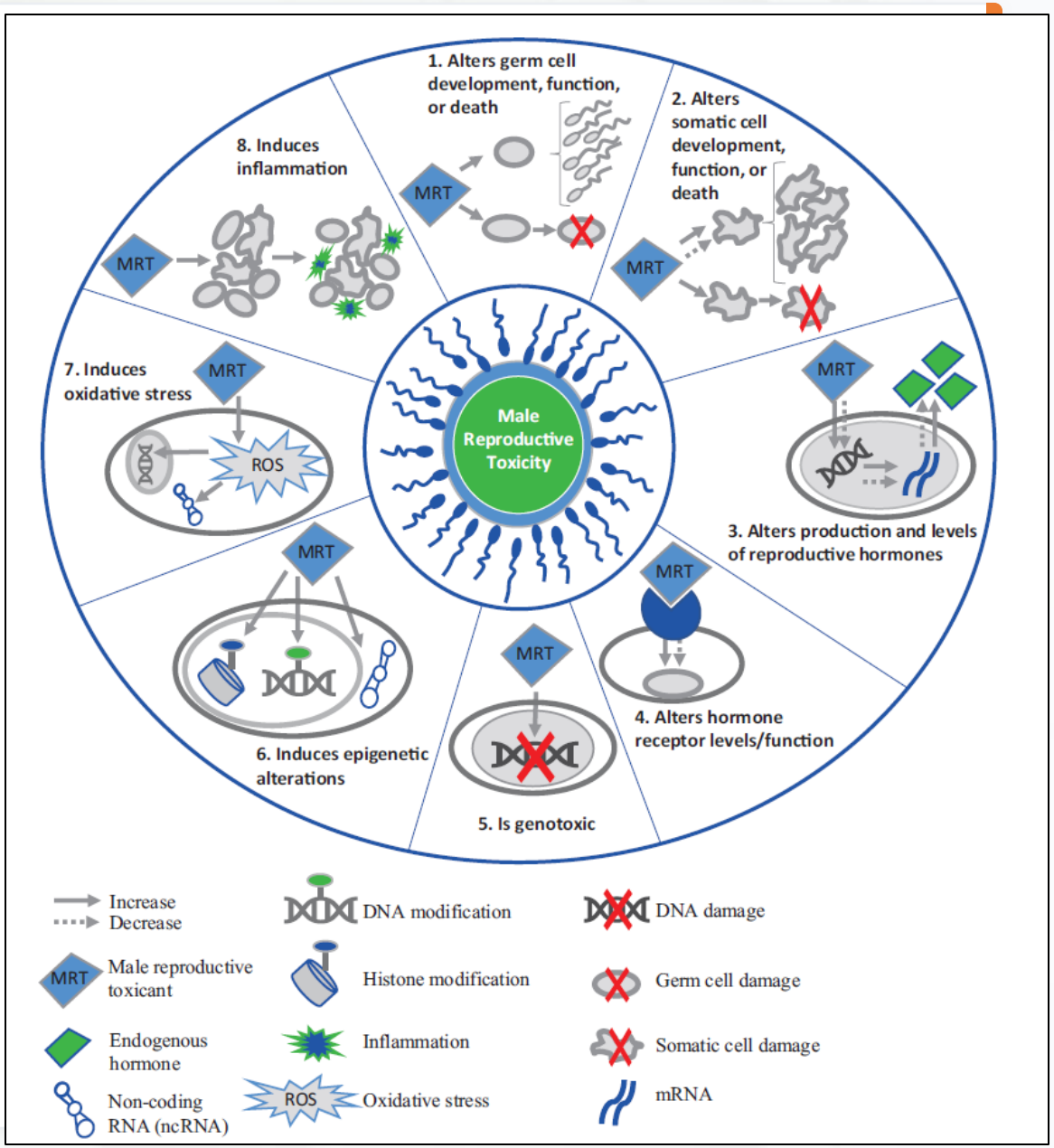


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Table 2. Key characteristics of male reproductive toxicants and examples from chemicals known to affect the male reproductive system.

Key characteristic	Example toxicants	Known mechanism/pathway associated with adverse male reproductive outcomes	References
1. Alters germ cell development, function, or death	B[a]P	Increased spermatogenic cell apoptosis; altered sperm motility and acrosome reaction	Ramesh et al. 2017; U.S. EPA 2017
	Cadmium	Increased spermatogenic cell apoptosis, reduced sperm count, altered sperm motility	ATSDR 2012; Jenardhanan et al. 2016
	Phthalates	Germ cell degeneration and reduced cell number	Howdeshell et al. 2008; Martino-Andrade and Chahoud 2010; Habert et al. 2014
	4-Methylbenzylidenecamphor	Altered sperm motility via disrupted Ca^{2+} channel function	Schiffer et al. 2014
	Cocaine, sirolimus, sulfasalazine, cannabinoids, DES	Decreased sperm count and motility, altered sperm morphology	Li et al. 2003; Semet et al. 2017
2. Alters somatic cell development, functions, or death	B[a]P	Increased Sertoli cell apoptosis	Ramesh et al. 2017
	Phthalates	Altered Sertoli-germ cell interactions; decreased testosterone production in Leydig cells	Boekelheide et al. 2005; Scott et al. 2009
	Cadmium	Disruption of the blood–testis barrier via alterations in Sertoli cell actin filaments, and assembly of tight junctions	Siu et al. 2009; Gao et al. 2015; Li et al. 2016; de Angelis et al. 2017
	PCBs	Decreased Sertoli cell metabolic functions and viability	Jenardhanan et al. 2016
	Alcohol, phthalates	Increased Fas-mediated Sertoli and germ cell apoptosis	Lucas et al. 2009; Pourmasumi et al. 2017; Sansone et al. 2018
3. Alters production and levels of reproductive hormones	DDT	Increased hepatic expression of CYP3A4 and metabolism of sex hormones	Laurenzana et al. 2002; Medina-Díaz et al. 2007
	Linuron	Decreased fetal androgen production/levels	Hotchkiss et al. 2008; Wilson et al. 2008; Scott et al. 2009; Dent et al. 2015
	Phthalates, sirolimus	Decreased expression of steroidogenic enzymes and reduced androgen production	Hotchkiss et al. 2008; Bergman et al. 2013; Semet et al. 2017
	Ketoconazole, prochloraz	Inhibition of the steroidogenic enzyme CYP17A1 activity	Scott et al. 2009; Dent et al. 2015
	PCBs, B[a]P	Decreased serum levels of reproductive hormones; decreased androgen production in Leydig cells	Meeker and Hauser 2010; Jenardhanan et al. 2016; Ramesh et al. 2017; U.S. EPA 2017
	Opiates	Reduced androgen levels and secretion of gonadotropin-releasing hormone; increased aromatase expression	Bawor et al. 2015; Drobnis and Nangia 2017; Semet et al. 2017
	Cadmium	Alterations in LH associated with changes in prolactin secretion; decreased Leydig cell steroidogenic enzyme activity, cAMP levels, and expression of the LH receptor	Siu et al. 2009; Lafuente 2013
4. Alters hormone receptor levels/functions	Prochloraz, linuron, procymidone, vinclozolin, flutamide, cyproterone acetate, DDT	AR antagonism	ATSDR 2002; Hotchkiss et al. 2008; Wilson et al. 2008; Scott et al. 2009; Dent et al. 2015; Semet et al. 2017
	DES	Activation of estrogen receptor	Henley and Korach 2006
	B[a]P	Activation of AHR resulting in increased expression of xenobiotic metabolic enzymes and formation of reactive metabolites and ROS	Ramesh et al. 2017

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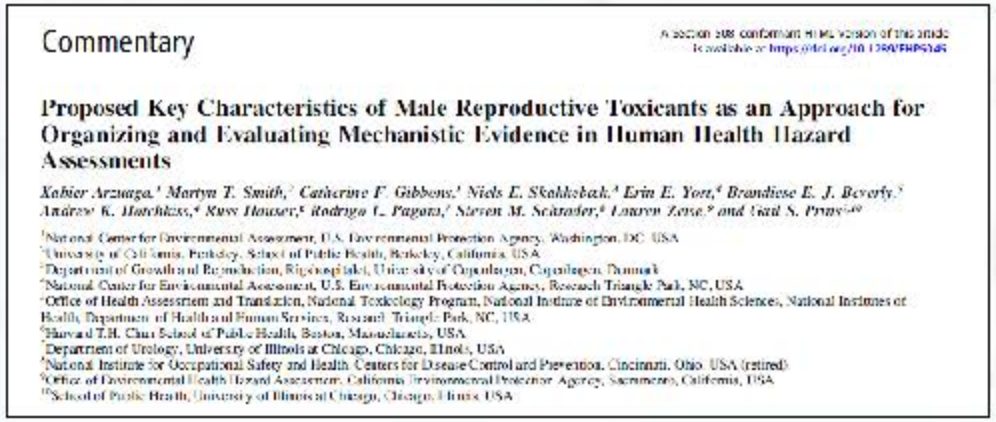
5. Is genotoxic	Acrylamide	Increased germ cell formation of gylcidamide-DNA adducts	Estill and Krawetz 2016
	Cadmium, PCBs	Chromatin fragmentation, and ROS-dependent DNA damage in germ cells	Meeker and Hauser 2010; Tavares et al. 2016; de Angelis et al. 2017
	B[a]P, cisplatin, carboplatin	Increased DNA adducts and DNA fragmentation in spermatozoa and testicular tissue	Vakalopoulos et al. 2015; Tavares et al. 2016; Ramesh et al. 2017; U.S. EPA 2017
	Alcohol	Altered sperm chromosome number (aneuploidy), and increased DNA fragmentation	Kapp 2010; Pourmasumi et al. 2017
	Chlorambucil, cyclophosphamide, procarbazine, melphalan	DNA alkylation, altered DNA structure and function	Vakalopoulos et al. 2015
	Ethane-methane sulfonate	Increased/irreversible spermatogonia DNA damage resulting in necrosis	Woldemeskel 2017
6. Induces epigenetic alterations	TCDD, methoxychlor, alcohol	Altered germ cell DNA methylation patterns	Anway et al. 2005; Paoloni-Giacobino 2014; Skinner 2016; Chastain and Sarkar 2017; Pilsner et al. 2017; Ding et al. 2018
	Vinclozolin	Altered sperm ncRNAs, DNA methylation, histone retention sites	Brieño-Enríquez et al. 2015, 2016; Ben Maamar et al. 2018
	Diethylhexyl phthalate	Altered sperm ncRNAs associated with testicular dysgenesis syndrome in mice	Stenz et al. 2017
7. Induces oxidative stress	Cadmium, B[a]P	Reduction in antioxidant enzyme activity, and antioxidant levels	Kapp 2010; Rezk and Sikka 2011; Lafuente 2013; de Angelis et al. 2017; Ramesh et al. 2017
	TCDD	Decreased tissue antioxidant levels	Lavranos et al. 2012
	Lindane, methoxychlor	Reduction in antioxidant enzyme activity	Jenardhanan et al. 2016
8. Induces inflammation	Cadmium, TCDD, silver nanoparticles	Increased testicular expression/levels of pro-inflammatory markers. Increased testicular edema	Siu et al. 2009; Sengupta 2013; de Angelis et al. 2017; Pilsner et al. 2017
	TCDD	Increased testicular prostaglandin levels	Bruner-Tran et al. 2014

Note: AHR, aryl hydrocarbon receptor; AR, androgen receptor; B[a]P, benzo[a]pyrene; Ca^{2+}, calcium ion; cAMP, cyclic adenosine monophosphate; CYP3A4, cytochrome P450 family 3 subfamily A member 4; CYP17A1, cytochrome P450 family 17 subfamily A member 1; DDT, dichlorodiphenyltrichloroethane; DES, diethylstilbestrol; LH, luteinizing hormone; ncRNA, noncoding RNA; PCBs, polychlorinated biphenyls; ROS, reactive oxygen species; TCDD, tetrachlorodibenzodioxin.

HOW AND WHAT



Commentary

A section 508 conformant HTML version of this article is available at https://doi.org/10.1289/EHP5585

Proposed Key Characteristics of Male Reproductive Toxicants as an Approach for Organizing and Evaluating Mechanistic Evidence in Human Health Hazard Assessments

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[1]National Center for Environmental Assessment, U.S. Environmental Protection Agency, Washington, DC, USA
[2]University of California, Berkeley, School of Public Health, Berkeley, California, USA
[3]Department of Growth and Reproduction, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
[4]National Center for Environmental Assessment, U.S. Environmental Protection Agency, Research Triangle Park, NC, USA
[5]Office of Health Assessment and Translation, National Toxicology Program, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC, USA
[6]Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
[7]Department of Urology, University of Illinois at Chicago, Chicago, Illinois, USA
[8]National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Cincinnati, Ohio, USA (retired)
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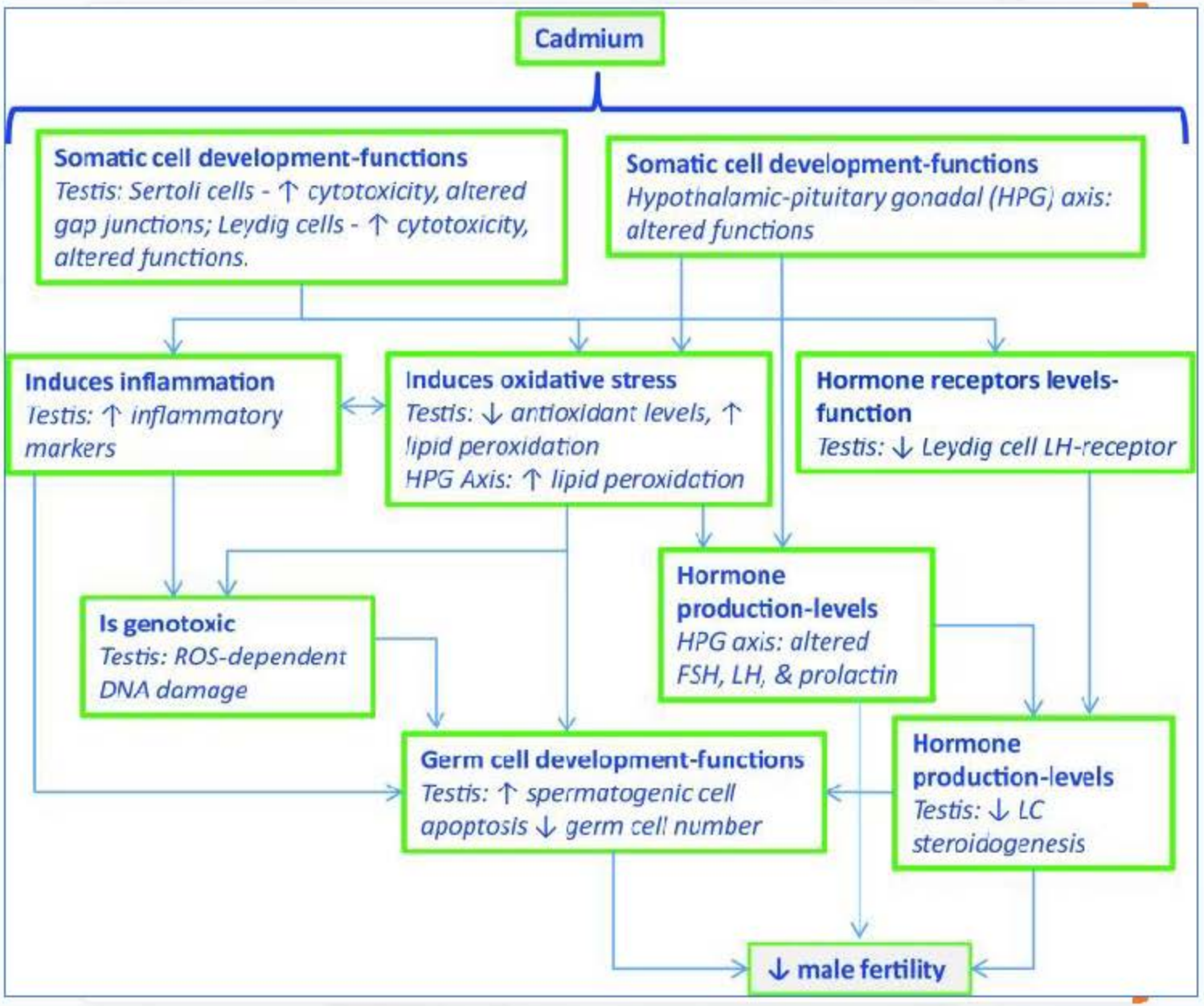

HOW AND WHAT

ORIGINAL ARTICLE: ENVIRONMENT

Check for updates

Environmental exposure to industrial air pollution is associated with decreased male fertility

Joerny M. Ramsay, M.S., Ph.D.,[a] Kiarad Fendereski, M.D.,[a] Joshua J. Horns, Ph.D.,[a] James A. VanDerslice, Ph.D.,[b] Heidi A. Hanson, Ph.D.,[b,c] Benjamin R. Emery, M.S.,[a] Joshua A. Halpern, M.D., M.S.,[d] Kenneth I. Aston, Ph.D.,[a] Elisabeth Perlic, M.D.,[e] and James M. Hotaling, M.D., M.S.[a]

[a] Division of Urology, Department of Surgery, University of Utah, Salt Lake City, Utah; [b] Department of Family and Preventive Medicine, University of Utah, Salt Lake City, Utah; [c] Computational Sciences and Engineering Division, Oakridge National Laboratory, Oak Ridge, Tennessee; [d] Department of Urology, Northwestern University Feinberg School of Medicine, Chicago, Illinois; [e] Intermountain Urological Institute, Salt Lake City, Utah

	Azoospermia	Concentration (M/mL)
Organochlorines		
q1	ref	ref
q2	1.75** (1.34, 2.28)	−4.60** (−7.62, −1.57)
q3	1.98** (1.52, 2.57)	0.21 (−2.93, 3.35)
q4	2.09** (1.62, 2.69)	6.63** (3.48, 9.77)
Trend *P*-value	<.001[a]	<.001
Phthalates		
q1	ref	ref
q2	1.28 (0.95, 1.73)	−11.90** (−15.51, −8.29)
q3	1.33** (1.07, 1.65)	3.81** (0.96, 6.65)
q4	1.44** (1.17, 1.78)	7.23** (4.37, 10.09)
Trend *P*-value	<.001[a]	<.001
Silver particles		
q1	ref	ref
q2	1.37** (1.05, 1.80)	9.29** (5.6, 12.97)
q3	1.59** (1.27, 1.98)	1.66 (−1.2, 4.52)
q4	1.64** (1.32, 2.04)	4.29** (1.36, 7.22)
Trend *P*-value	<.001[a]	.030

HOW AND WHAT

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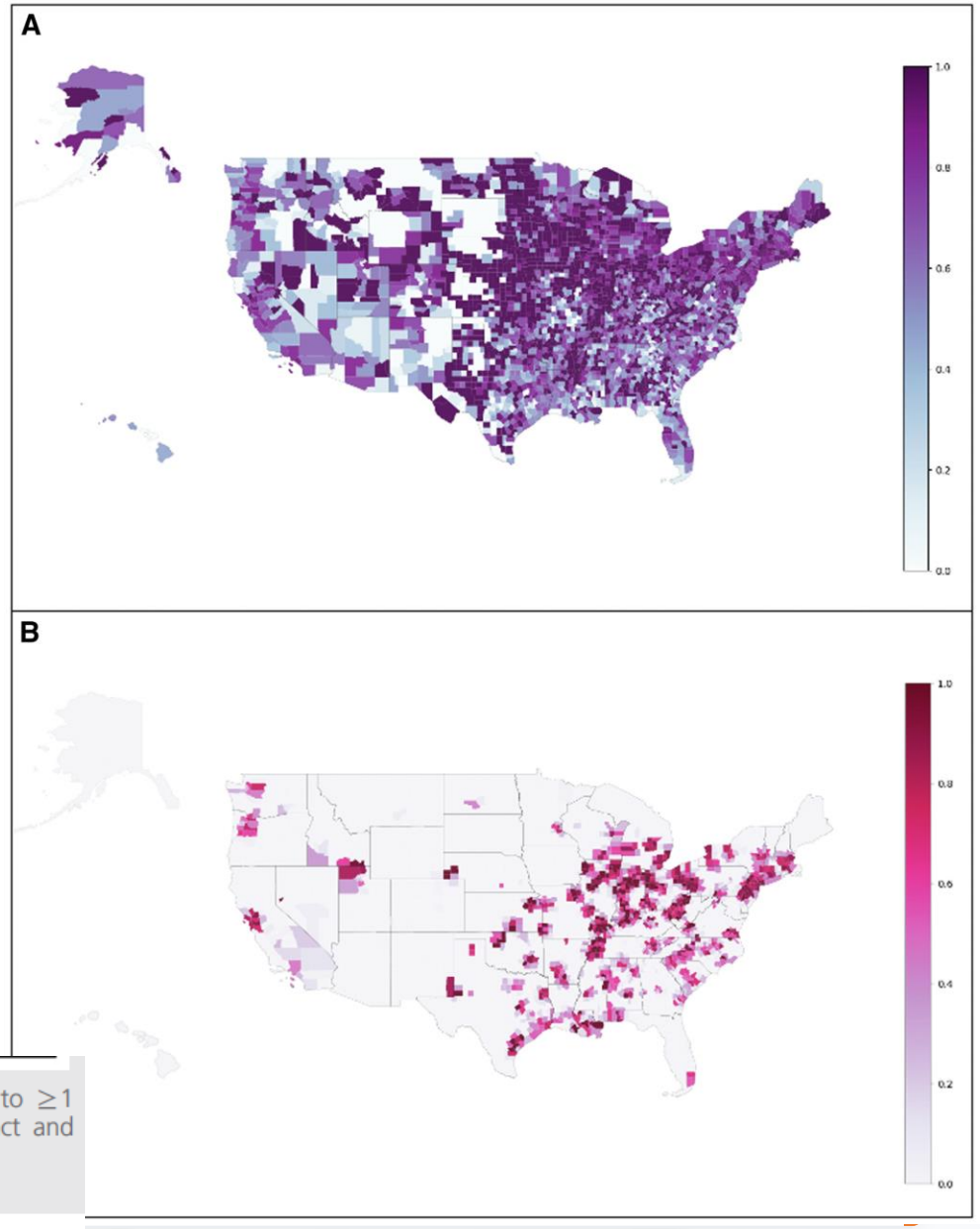


(A) Fraction of reproductive-aged men exposed to ≥1 EDC from industrial sources. (B) Fraction of reproductive-aged men exposed to ≥1 significant EDC above the 75th percentile. Maps were generated using 2020 population and EDC estimates linked by census tract and aggregated to the county level for reporting. EDC = Endocrine-Disrupting Compound.

Ramsay. Industrial air pollution and male fertility. Fertil Steril 2023.

Contents lists available at ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

The impact of air pollution on sperm DNA methylation

Jordan L. Moore [a,1], Seth J. Parks [a,1], Emma R. James [b], Kenneth I. Aston [b], Timothy G. Jenkins [a,*]

[a] Brigham Young University, Department of Cell Biology and Physiology, 4005 Life Sciences Building (LSB), Provo, UT 84602, United States
[b] University of Utah School of Medicine, Department of Surgery, Division of Urology, 30 N Mario Capecchi Drive, Salt Lake City, UT 84112, United States

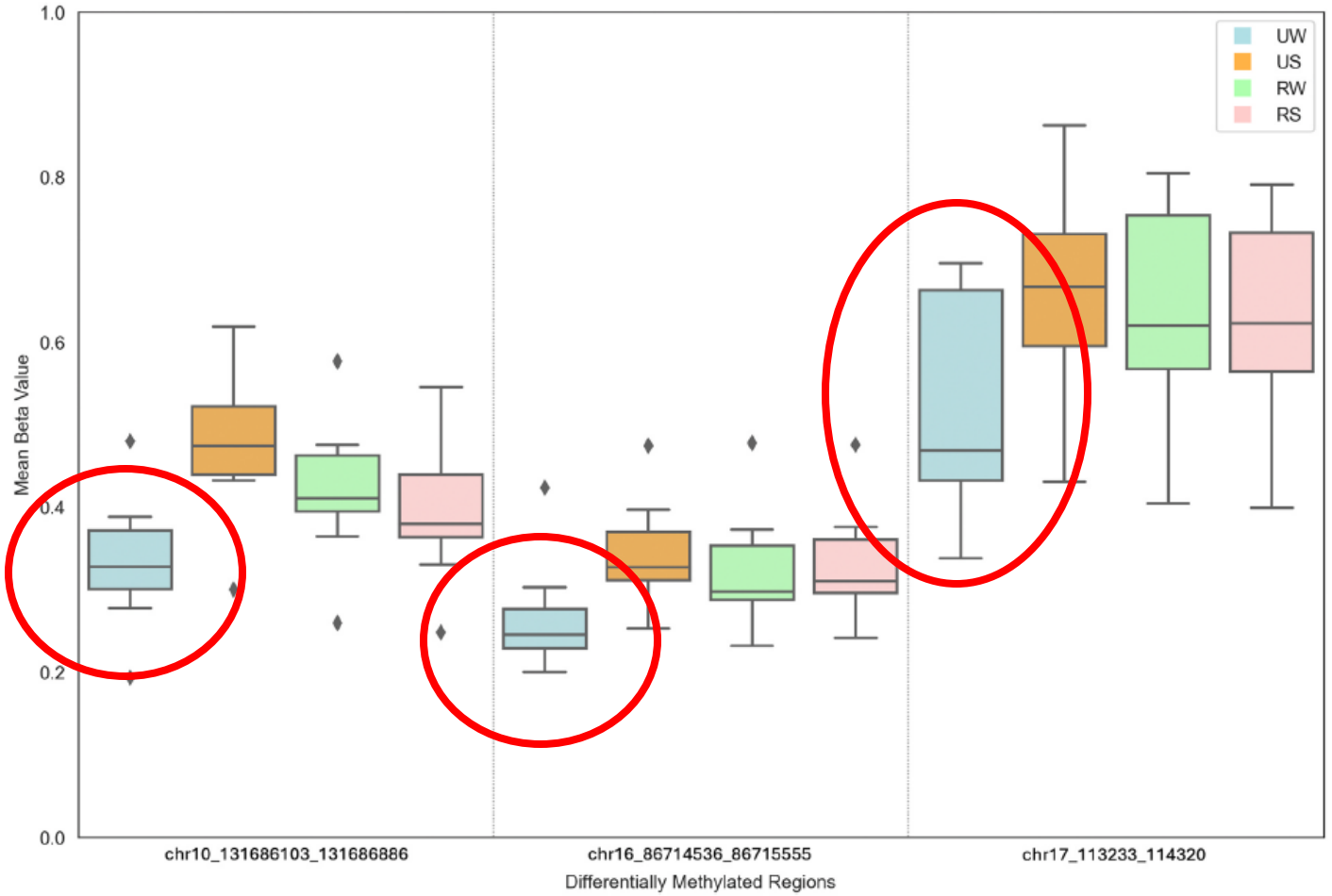
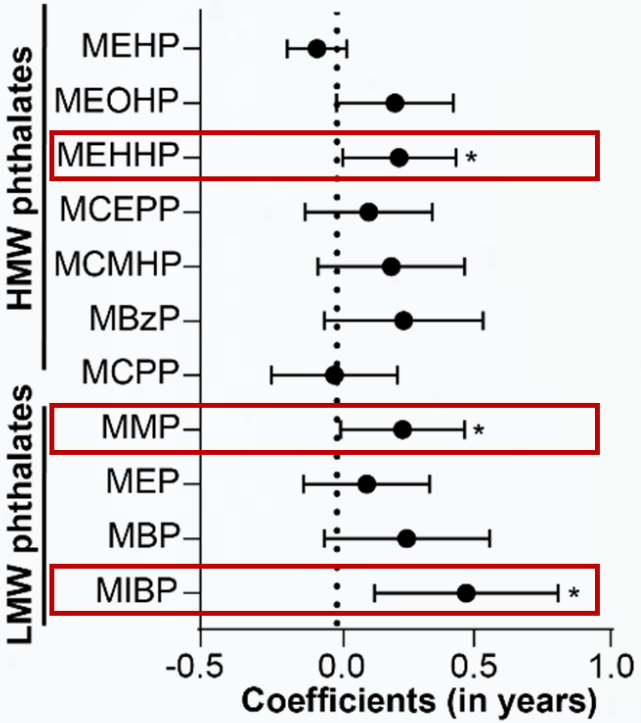


Fig. 1. UW cohort demonstrates significant hypomethylation when compared to additional control groups RS and RW. Mean beta values at three significant DMRs compared between UW, US, RW, and RS (FDR>20, p-value<.01).

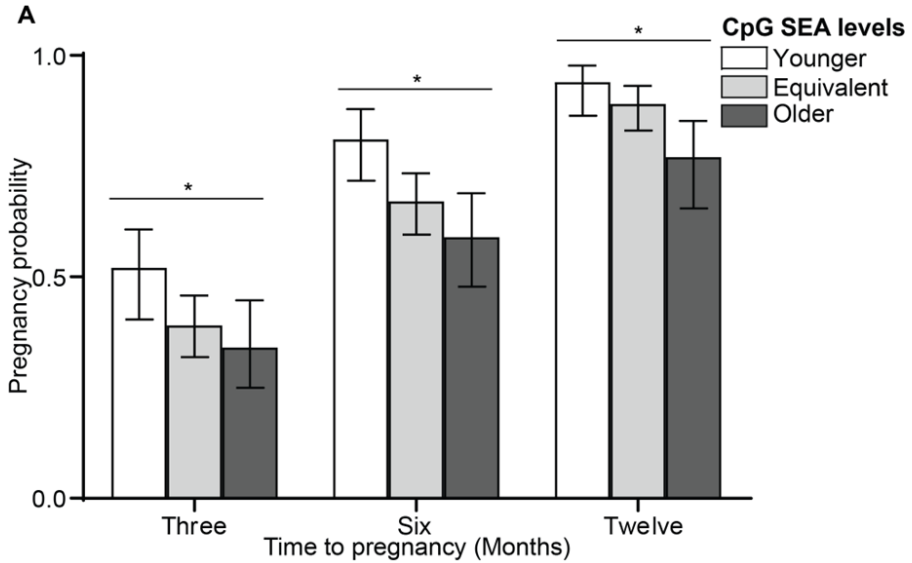
Sperm epigenetic age (SEA) on time-to-pregnancy (TTP) and pregnancy probability (n=379)

Phthalate exposure (n=333)



Oluwayiose et al. Env. Research 2022

17% lower pregnancy probability between old vs. young SEA groups



Sperm epigenetic age (SEA)

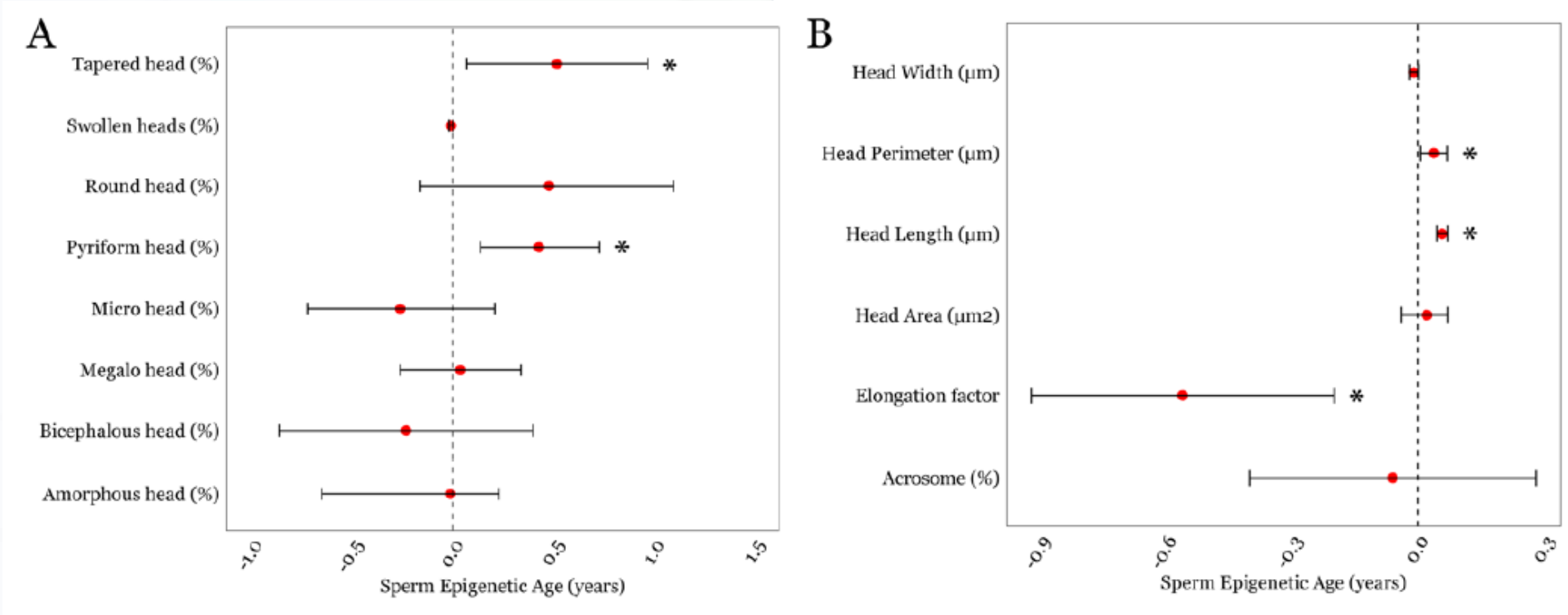
Younger SEA < -1 year difference between chronological and predicted age
Match SEA = within 1 year difference between chronological and predicted age
Older SEA > 1 year difference between chronological and predicted age

Pilsner et al. *Human Repro* 2022

Article

Associations between Sperm Epigenetic Age and Semen Parameters: An Evaluation of Clinical and Non-Clinical Cohorts

Savni Sawant [1,2], Oladele A. Oluwayiose [1], Karolina Nowak [1], DruAnne L. Maxwell [1], Emily Houle [1], Amanda L. Paskavitz [1], Hachem Saddiki [3], Ricardo P. Bertolla [4] and J. Richard Pilsner [1,5,*]



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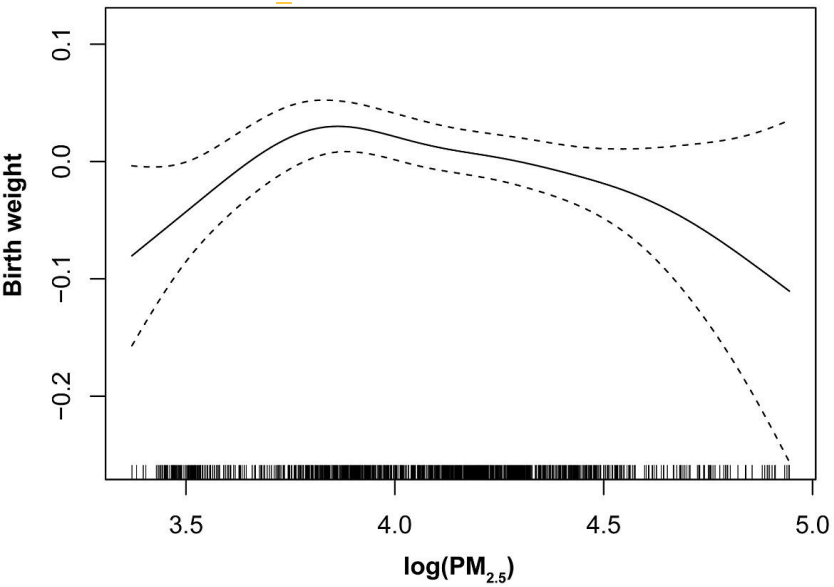
Alterations in sperm DNA methylation may as a mediator of paternal air pollution exposure and offspring birth outcomes: Insight from a birth cohort study

Yuting Cheng [a,b,1], Jialin Feng [a,b,1], Jing Wang [a,b], Yijie Zhou [a,b], Shengjun Bai [a,b], Qiuqin Tang [c], Jinhui Li [d], Feng Pan [e], Qiaoqiao Xu [a,b], Chuncheng Lu [a,b], Wei Wu [a,b,*], Yankai Xia [a,b,**]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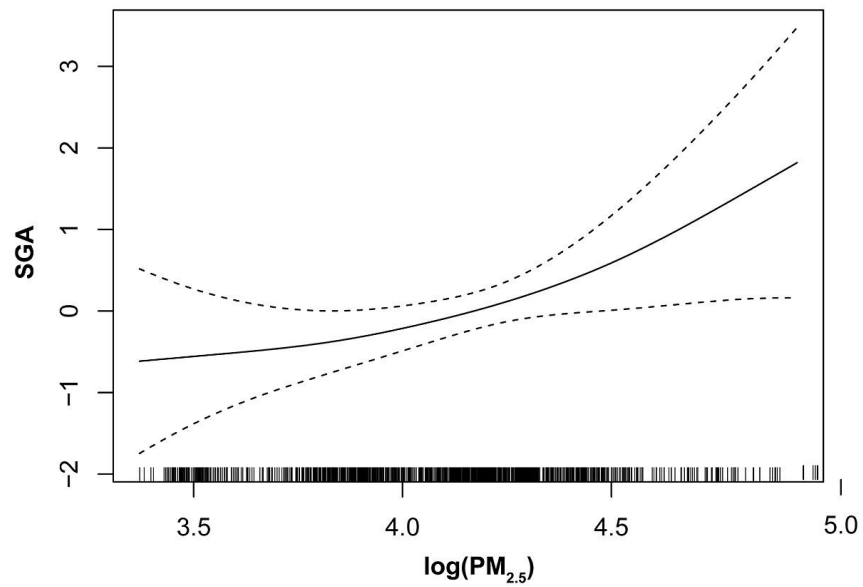
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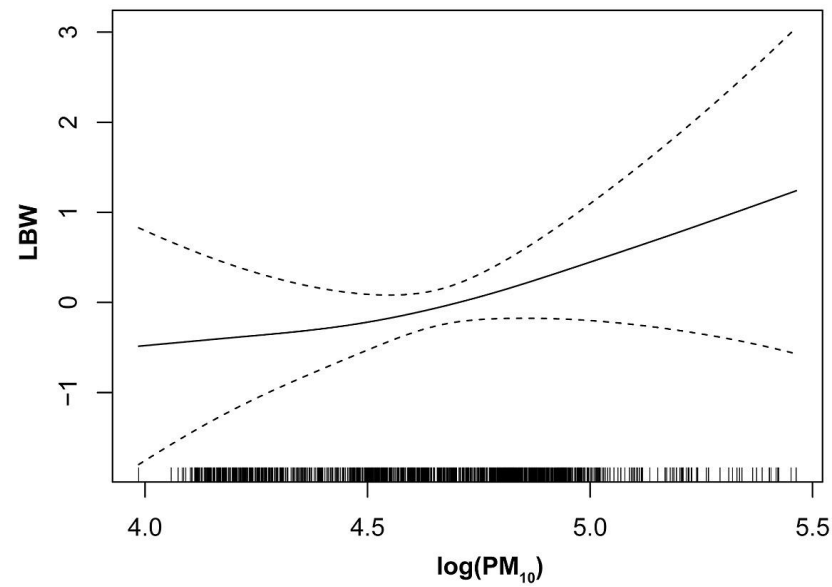
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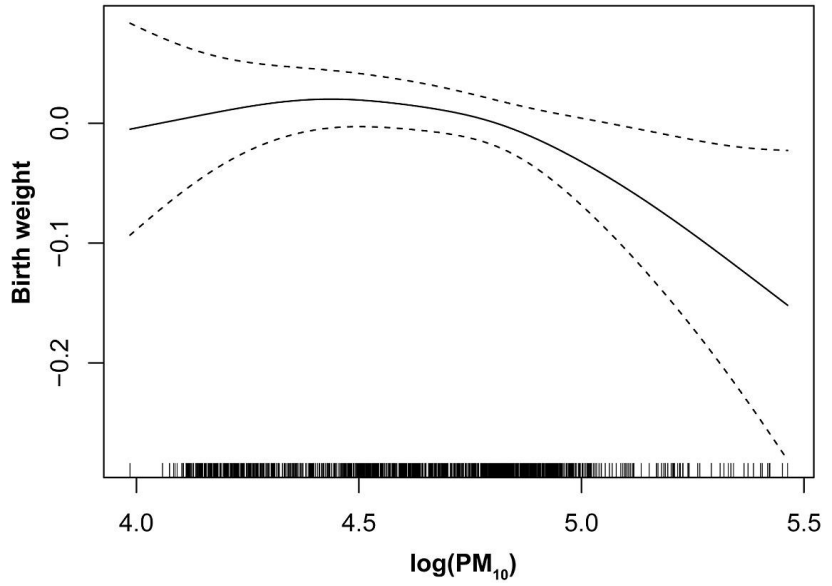
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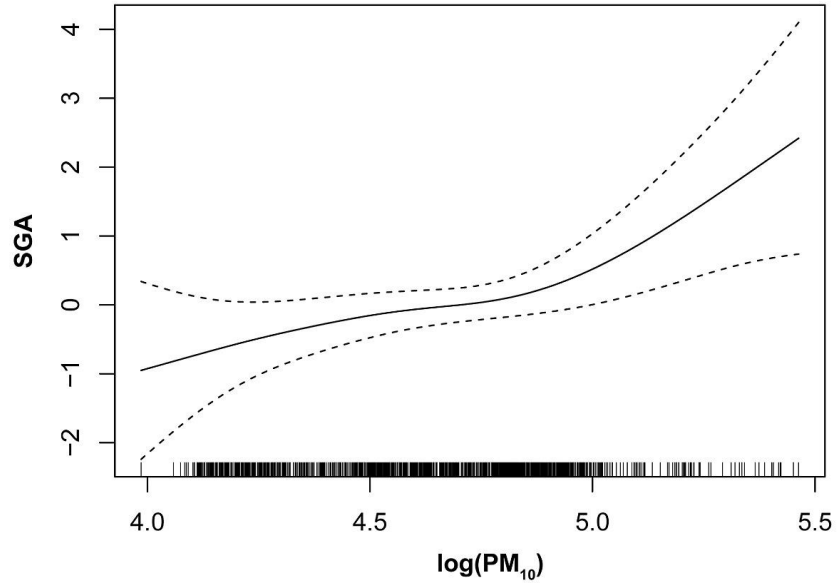
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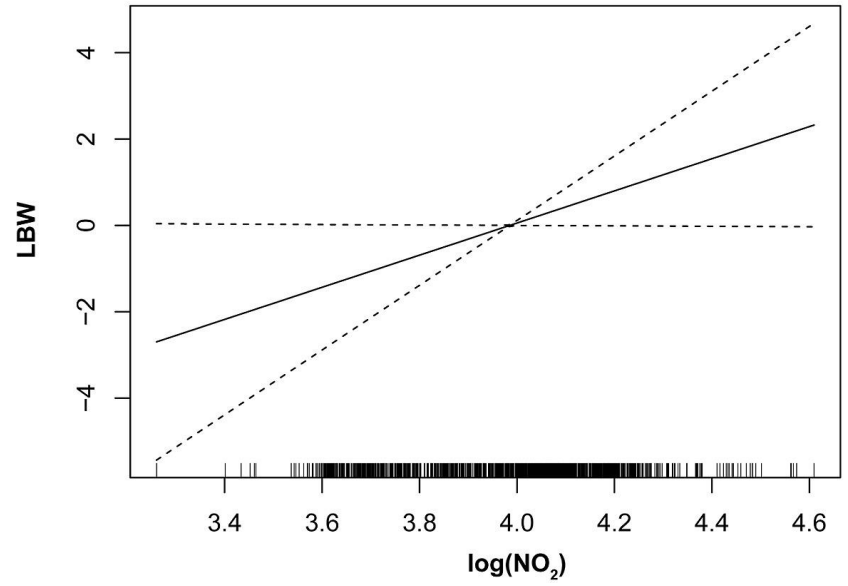
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4.0
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4.4
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log(NO2)

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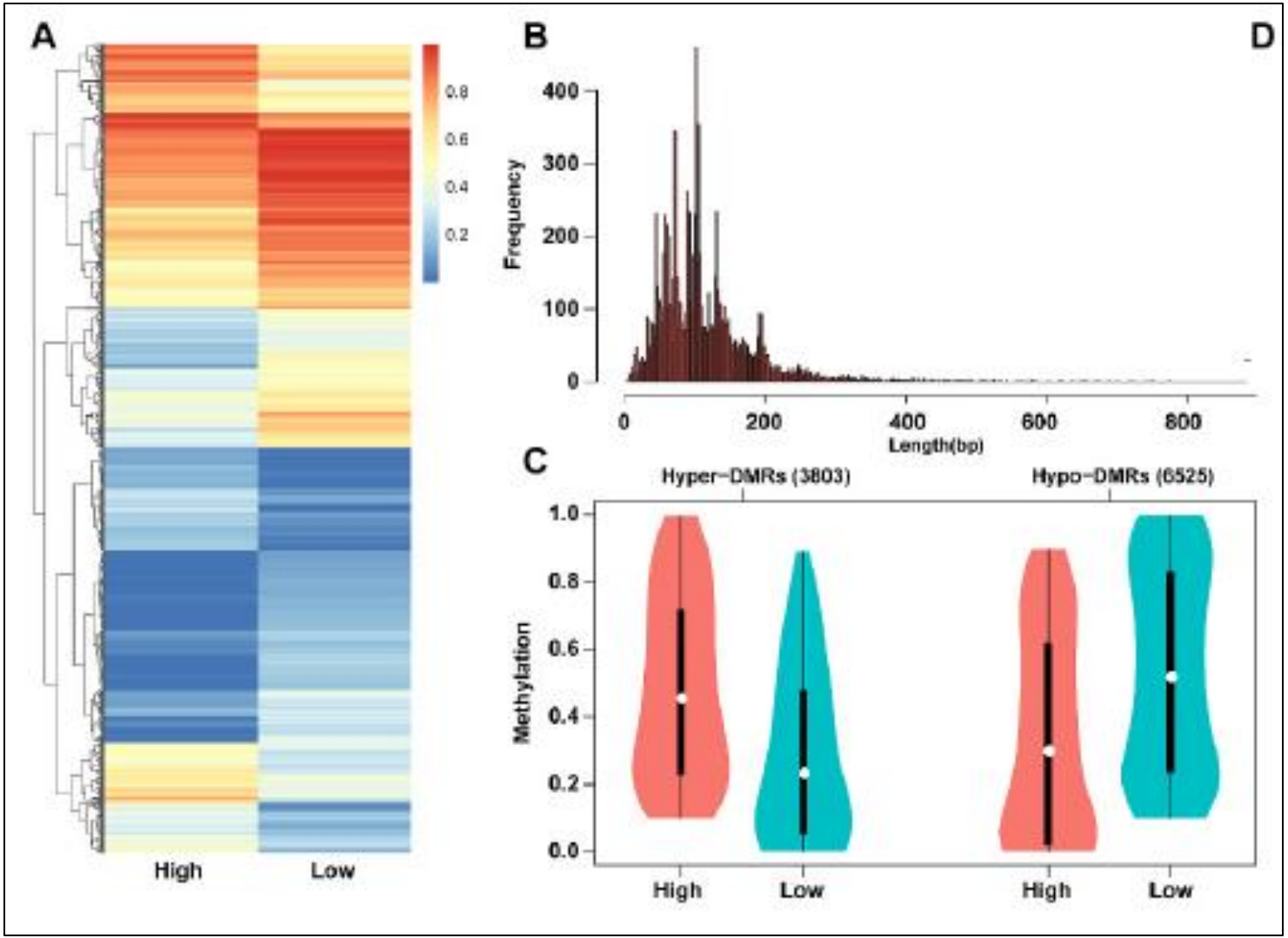
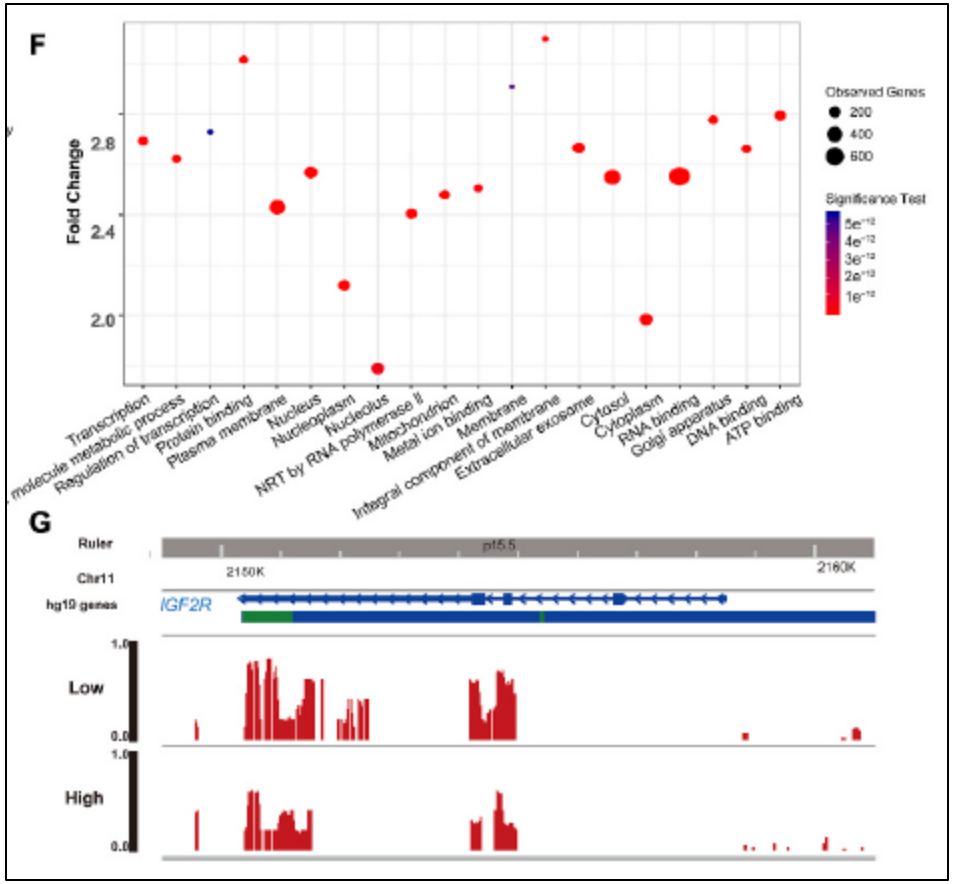




Effects – Male factors of infertility

Sperm nuclear DNA fragmentation in adolescents with varicocele

Ricardo Pimenta Bertolla, D.V.M., Agnaldo Pereira Cedenho, M.D., Ph.D., Pericles Assad Hassun Filho, D.V.M., Ph.D., Samira Barbosa Lima, D.V.M., Ph.D., Valdemar Ortiz, M.D., Ph.D., and Miguel Srougi, M.D., Ph.D.

Department of Surgery, Division of Urology, São Paulo Federal University, São Paulo Hospital, São Paulo, Brazil

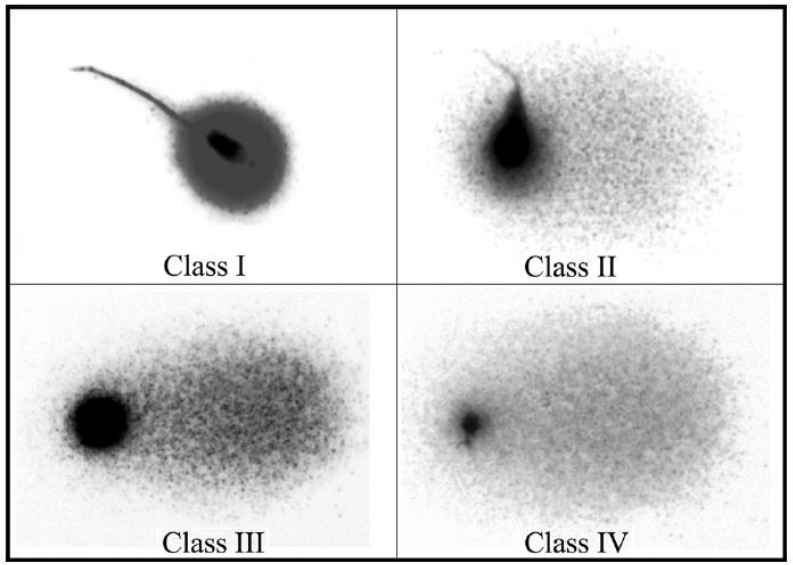


TABLE 1

Comparison of sperm parameters (motility, concentration, and strict-criteria morphology), age, and left and right testicular volumes among varicocele (grades II and III) and control (nonvaricocele) adolescents.

Characteristic	Varicocele group (%) n = 20	Control group (%) n = 20
Motility (a + b)	56.48 ± 8.74	60.31 ± 15.2
Concentration ($\times 10^6$/mL)	78.43 ± 17.43	85.78 ± 24.72
Morphology (%)	9.49 ± 3.97	10.03 ± 4.01
Age	16.1 ± 0.31	16.05 ± 0.69
Left testicular volume (mL)	15.9 ± 3.26[a]	19.2 ± 4.07[a]
Right testicular volume (mL)	18.45 ± 4.01	19.35 ± 3.84

Note: Mean ± standard deviation.
[a] $P=.014$.

Bertolla. Sperm nuclear DNA fragmentation in adolescents with varicocele. Fertil Steril 2006.

TABLE 2

Comparison of sperm nuclear DNA fragmentation results among varicocele (grades II and III) and control (nonvaricocele) adolescents.

Comet assay class	Varicocele group (%) n = 20	Control group (%) n = 20
I	27.52 ± 10.73[a]	47.62 ± 7.69[a]
II	[illegible]	[illegible]
III	20.43 ± 8.97[b]	11.38 ± 5.55[b]
IV	19.57 ± 10.68[c]	5.71 ± 2.35[c]

Note: Mean ± standard deviation.
[a] $P<.0001$.
[b] $P=.0003$.
[c] $P<.0001$.

Bertolla. Sperm nuclear DNA fragmentation in adolescents with varicocele. Fertil Steril 2006.

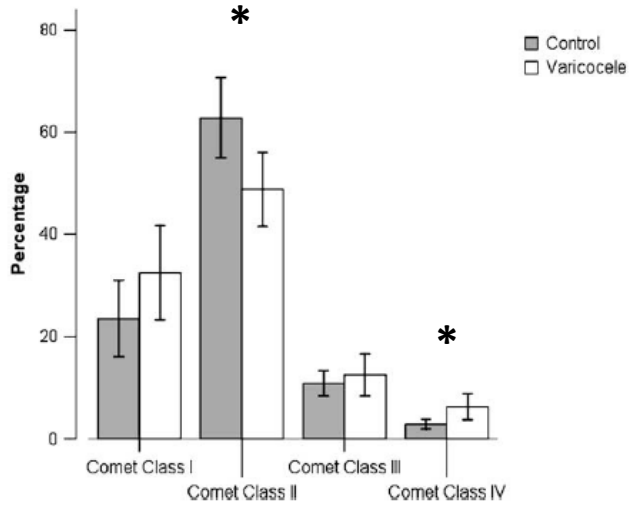
Sperm nuclear DNA fragmentation and mitochondrial activity in men with varicocele

Camile Garcia Blumer, B.S., Roberta Maria Fariello, B.S., Adriana Ester Restelli, M.S., Deborah Montagnini Spaine, M.S., Ricardo Pimenta Bertolla, D.V.M., Ph.D. and Agnaldo Pereira Cedenho, M.D., Ph.D.

Department of Surgery, Division of Urology, São Paulo Federal University, São Paulo, Brazil

FIGURE 1

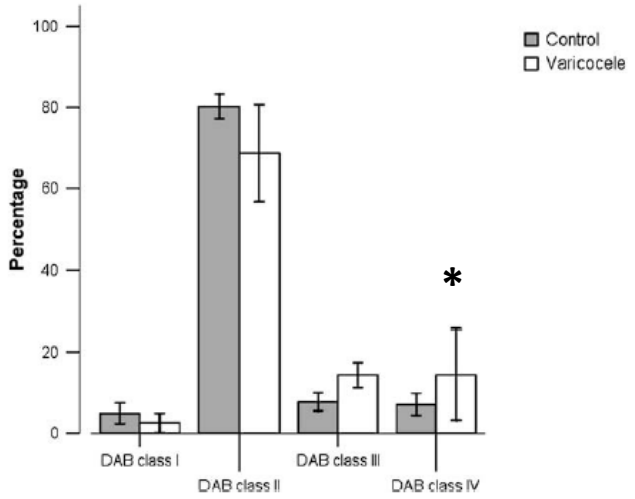
Mean percentages of DNA fragmentation (Comet assay classes I, II, III, and IV) in patients with and without varicocele. Error bars represent the 95% confidence interval of the mean percentage.



Blumer. Sperm function in men with varicocele. Fertil Steril 2008.

FIGURE 2

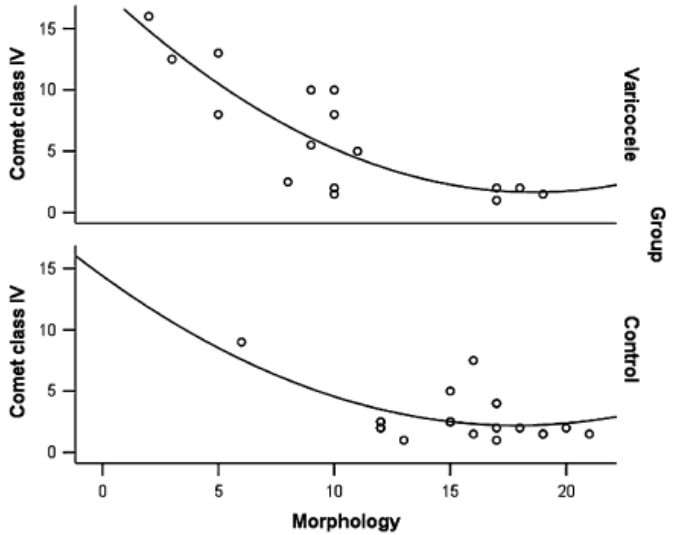
Mean percentages of mitochondrial activity (DAB classes I, II, III, and IV) in patients with and without varicocele. Error bars represent the 95% confidence interval of the mean percentage.



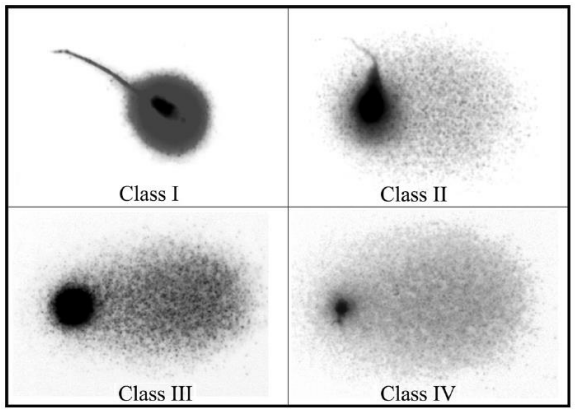
Blumer. Sperm function in men with varicocele. Fertil Steril 2008.

FIGURE 3

Scatter plot of mean percentage of Comet assay class IV and sperm morphology in patients with and without varicocele. Observed R^2 values were 0.701 and 0.330, respectively.



Blumer. Sperm function in men with varicocele. Fertil Steril 2008.



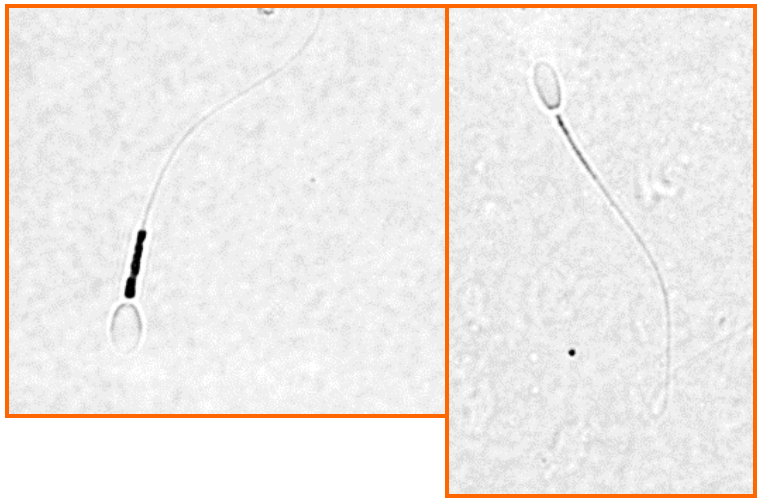
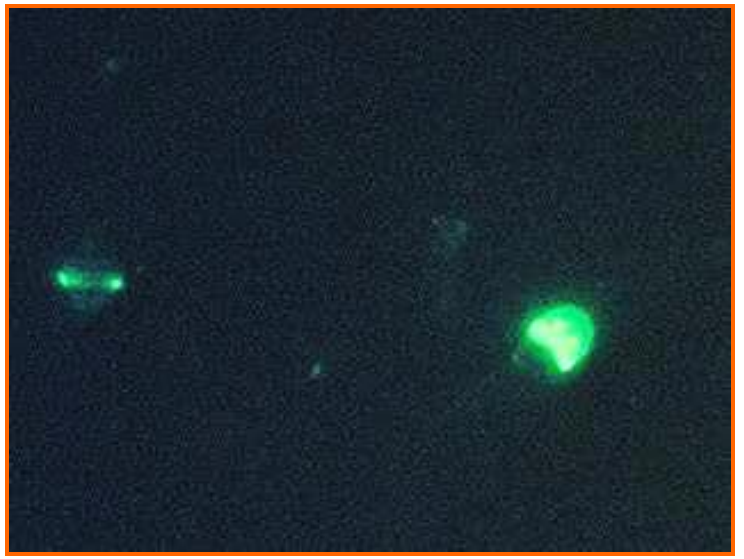


TABLE 2 Comparison of comet assay (sperm nuclear DNA fragmentation), DAB assay (mitochondrial activity), FITC-PNA assay (acrosome integrity) and TBARS (lipid peroxidation) among patients in the varicocele and control (without varicocele) groups

	Without varicocele	With varicocele	*P*
Comet	(*n* = 31)	(*n* = 28)	
Class I	22.5 ± 14.2 (17.3, 27.7)	28.8 ± 15.8 (22.7, 35.0)	0.109
Class II	59.4 ± 14.8 (53.9, 64.8)	51.3 ± 14.7 (45.6, 57.0)	0.040*
Class III	12.7 ± 7.3 (10.0, 15.4)	13.7 ± 6.4 (11.2, 16.2)	0.579
Class IV	5.5 ± 4.6 (3.8, 7.1)	6.1 ± 4.5 (4.4, 7.9)	0.578
DAB	(*n* = 32)	(*n* = 28)	
Class I	15.0 ± 12.5 (10.5, 19.6)	7.2 ± 7.7 (4.2, 10.2)	0.005*
Class II	59.5 ± 17.7 (53.2, 65.9)	61.5 ± 20.6 (53.6, 69.5)	0.685
Class III	11.0 ± 6.1 (8.7, 13.2)	15.3 ± 7.8 (12.2, 18.3)	0.020*
Class IV	14.4 ± 18.1 (7.9, 21.0)	16.0 ± 18.6 (8.8, 23.2)	0.741
FITC-PNA	(*n* = 23)	(*n* = 16)	
(% intact)	68.8 ± 11.2 (64.1, 73.5)	48.1 ± 18.2 (38.4, 57.8)	0.001*
TBARS	(*n* = 19)	(*n* = 12)	
(ng/mL)	301.4 ± 95.9 (258.9, 344.0)	287.1 ± 127.7 (205.9, 368.2)	0.713

**Statistically significant difference ($P < \alpha$). All data are mean ± SD (95% confiden*



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Effect of varicocele on sperm function and semen oxidative stress

Camile Garcia Blumer, Adriana Ester Restelli, Paula Toni Del Giudice, Thiesa Butterby Soler, Renato Fraietta, Marcilio Nichi*, Ricardo Pimenta Bertolla and Agnaldo Pereira Cedenho

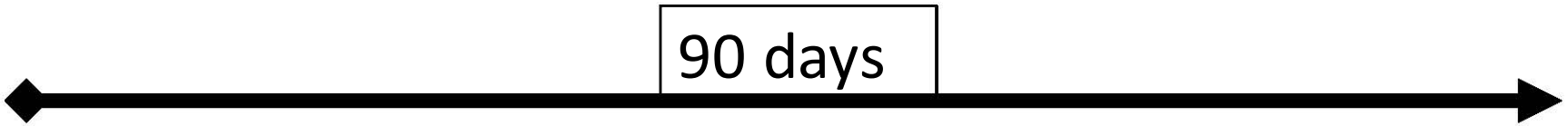
*Department of Surgery, Division of Urology, Human Reproduction Section, Sao Paulo Federal University, and *Department of Animal Reproduction, School of Veterinary Medicine, University of Sao Paulo, Sao Paulo, Brazil*

Accepted for publication 20 January 2011

Adolescent varicocele: improved sperm function after varicocelectomy

Jose Iran Lacerda, Ph.D., M.D.,[a] *Paula Toni Del Giudice, M.Sc.,*[a] *Barbara Ferreira da Silva, B.Sc.,*[a] *Marcilio Nichi, M.Sc., D.V.M.,*[b] *Roberta Maria Fariello, B.Sc.,*[a] *Renato Fraietta, Ph.D., M.D.,*[a] *Adriana Ester Restelli, Ph.D.,*[a] *Camile Garcia Blumer, M.Sc.,*[a] *Ricardo Pimenta Bertolla, Ph.D., D.V.M.,*[a] *and Agnaldo Pereira Cedenho, Ph.D., M.D.*[a]

[a] Department of Surgery, Division of Urology, Human Reproduction Section, Sao Paulo Federal University, and [b] Department of Animal Reproduction, School of Veterinary Medicine, University of Sao Paulo, Sao Paulo, Brazil



Pre-varicocelectomy
- Semen analysis – 2 samples
- DNA fragmentation
- Mitochondrial activity
- TBARS

Post-varicocelectomy
- Semen analysis – 2 samples
- DNA fragmentation
- Mitochondrial activity
- TBARS

TABLE 2

Sperm mitochondrial activity and DNA integrity and seminal plasma TBARS and normalized TBARS levels in adolescents before and after subinguinal microsurgical varicocelectomy.

	Pre-varicocelectomy	Post-varicocelectomy	*P* value
DAB class I (%)			
Mean ± SD	12.44 ± 7.33	13.21 ± 5.43	.599
95% CI	9.01–15.87	10.51–15.91	
DAB class II (%)			
Mean ± SD	63.68 ± 19.79	62.40 ± 7.58	.915
95% CI	54.42–72.93	58.63–66.17	
DAB class III (%)			
Mean ± SD	20.24 ± 4.94	17.06 ± 3.17	.013[a]
95% CI	17.93–22.55	15.48–18.63	
DAB class IV (%)			
Mean ± SD	8.60 ± 4.03	7.44 ± 4.94	.226
95% CI	6.71–10.49	4.99–9.90	
Comet class I (%)			
Mean ± SD	49.61 ± 23.06	64.50 ± 13.59	.011[a]
95% CI	39.11–60.10	58.31–70.69	
Comet class II (%)			
Mean ± SD	35.31 ± 11.90	22.83 ± 9.71	.0002[a]
95% CI	29.89–40.73	18.41–27.26	
Comet class III (%)			
Mean ± SD	13.42 ± 6.65	9.11 ± 5.36	.023[a]
95% CI	10.39–16.44	6.67–11.55	
Comet class IV (%)			
Mean ± SD	6.50 ± 4.03	2.45 ± 1.87	.001[a]
95% CI	4.67–8.33	1.60–3.30	
TBARS (ng/mL)			
Mean ± SD	307.6 ± 123.8	317.6 ± 141.7	
95% CI	251.2–363.9	251.3–383.9	
Normalized TBARS (TBARS/ sperm concentration)			
Mean ± SD	24.98 ± 37.2	20.1 ± 39.2	
95% CI	7.6–42.4	1.8–38.5	

Note: 95% CI = 95% confidence interval of the mean; TBARS = thiobarbituric acid-reactive substance.

[a] Statistically significant difference (paired samples *t*-test).

Lacerda. Importance of varicocelectomy in adolescents. Fertil Steril 2011.

Adolescent varicocele: improved sperm function after varicocelectomy

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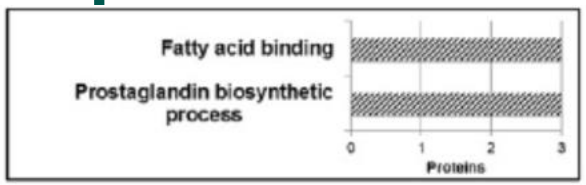
[a] Department of Surgery, Division of Urology, Human Reproduction Section, Sao Paulo Federal University, and [b] Department of Animal Reproduction, School of Veterinary Medicine, University of Sao Paulo, Sao Paulo, Brazil

Seminal plasma – male fertility

Association between the seminal plasma proteome and sperm functional traits

Paula Intasqui, M.Sc.,[a] Mariana Camargo, M.Sc.,[a] Mariana Pereira Antoniassi, M.Sc.,[a] Agnaldo Pereira Cedenho, M.D., Ph.D.,[a] Valdemir Melechco Carvalho, Ph.D.,[b] Karina Helena Morais Cardozo, Ph.D.,[b] Daniel Suslik Zylbersztejn, M.D., Ph.D.,[a,c] and Ricardo Pimenta Bertolla, Ph.D.[a,c]

[a] Department of Surgery, Division of Urology, Human Reproduction Section, São Paulo Federal University; [b] Fleury Group; and [c] São Paulo Hospital, São Paulo, Brazil



Sperm DNA

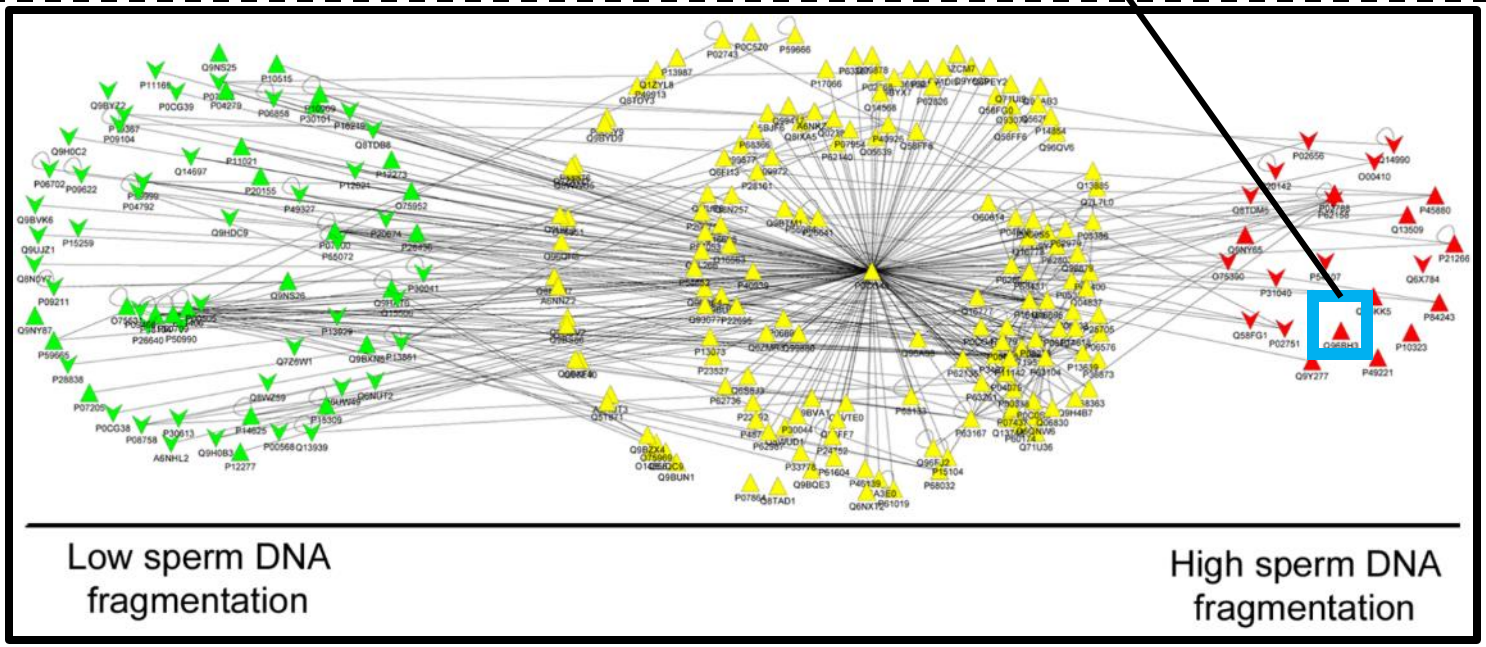
- Inflammation

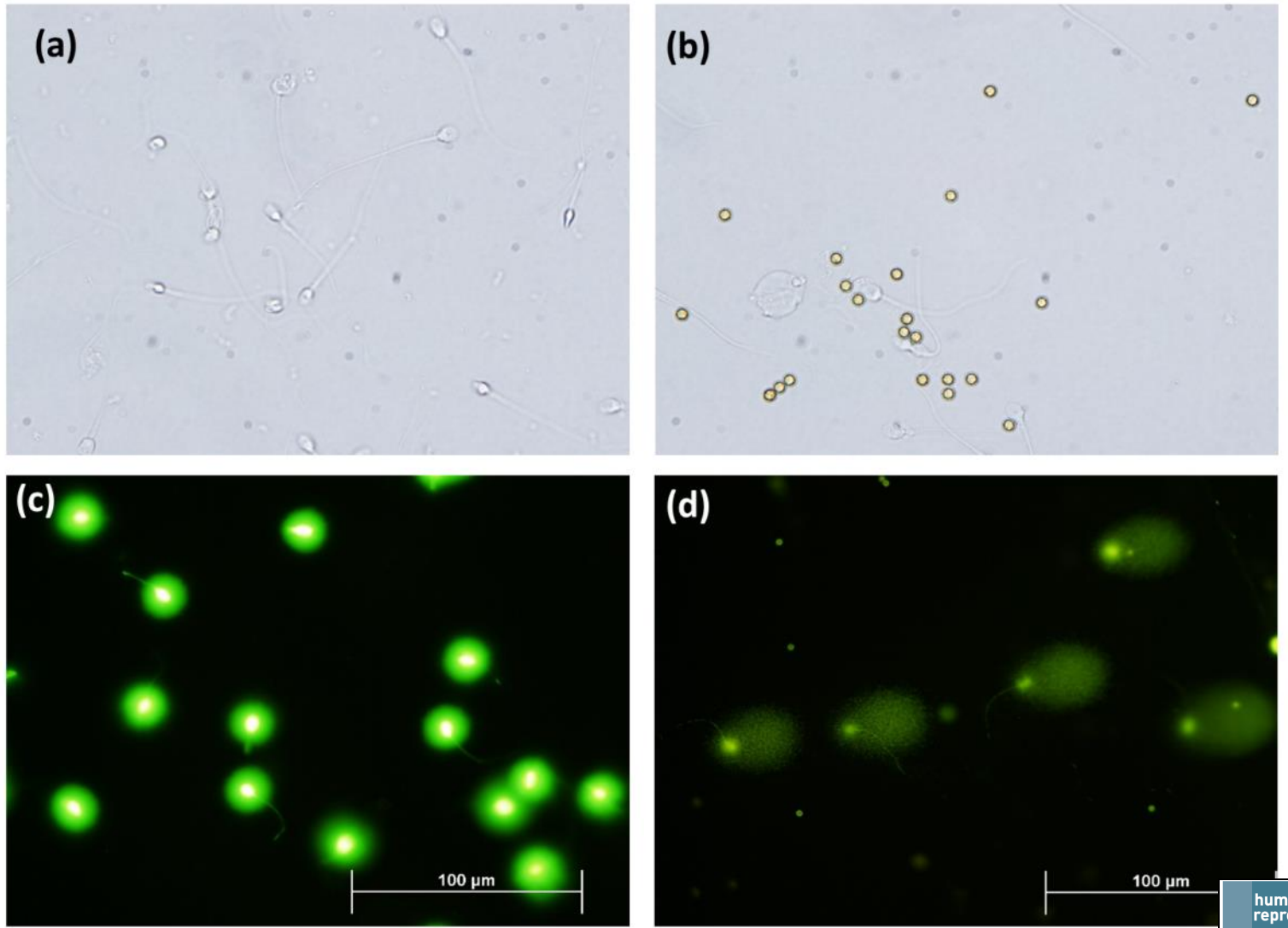
In sperm

- ↑ ELSPBP1

Unraveling the sperm proteome and post-genomic pathways associated with sperm nuclear DNA fragmentation

Paula Intasqui · Mariana Camargo · Paula T. Del Giudice · Deborah M. Spaine · Valdemir M. Carvalho · Karina H. M. Cardozo · Agnaldo P. Cedenho · Ricardo P. Bertolla

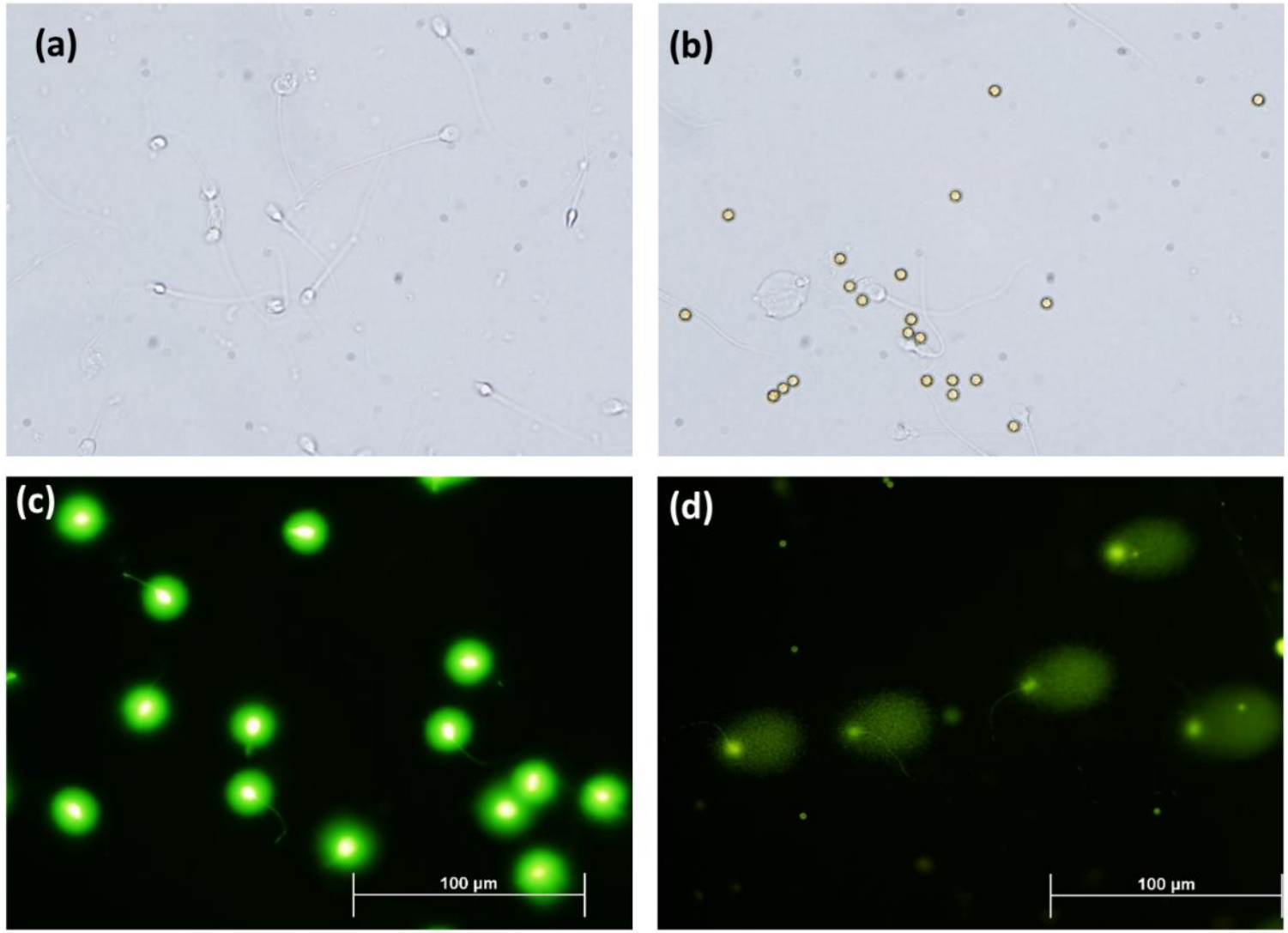




human reproduction ORIGINAL ARTICLE *Andrology*

Separating the chaff from the wheat: antibody-based removal of DNA-fragmented sperm

L.B. Belardin[1], M.P. Antoniassi [1], M. Camargo[1], P. Intasqui[1], and R.P. Bertolla [1,2*]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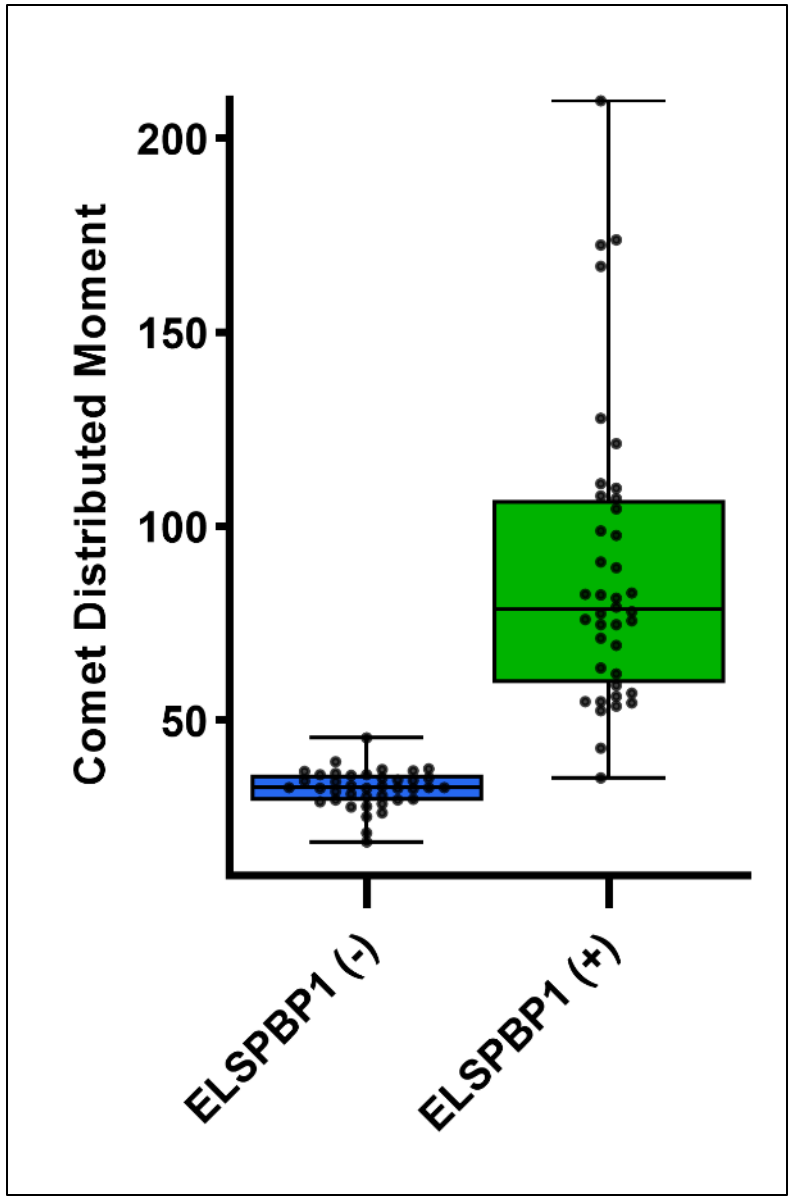
(b)
(c)
(d)
100 µm
100 µm


Comet Distributed Moment
200
150
100
50
ELSPBP1 (-)
ELSPBP1 (+)

- High DFI group proteins - oxidative stress response, protein misfolding, mitochondrial dysfunction, ferroptosis, cellular senescence, and the tricarboxylic acid cycle

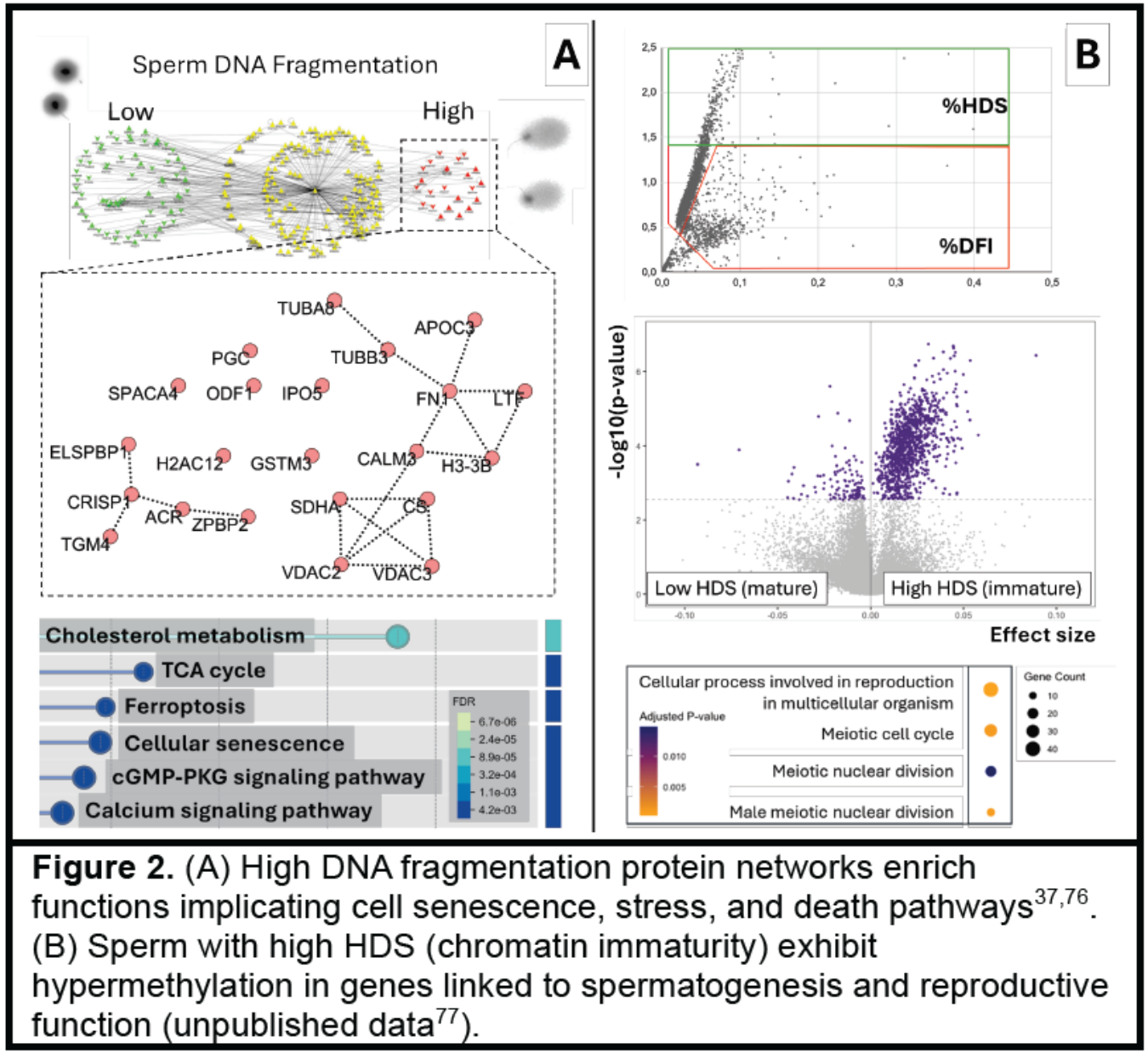
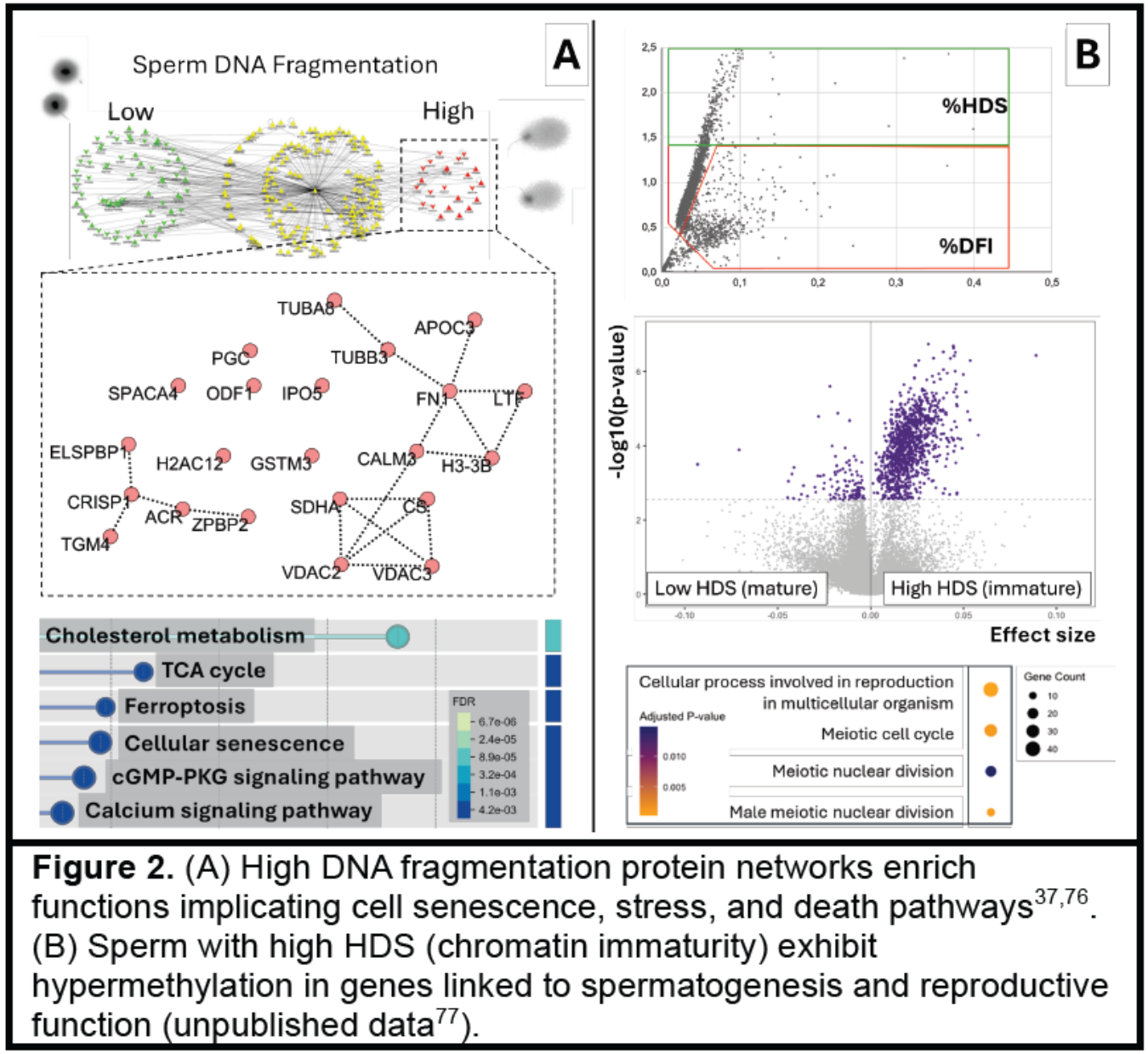


Figure 2. (A) High DNA fragmentation protein networks enrich functions implicating cell senescence, stress, and death pathways[37,76]. (B) Sperm with high HDS (chromatin immaturity) exhibit hypermethylation in genes linked to spermatogenesis and reproductive function (unpublished data[77]).

- Several fertilization-related proteins were also detected in both groups, suggesting that sperm with substantial DNA damage may retain fertilizing capacity yet potentially compromise embryonic development.



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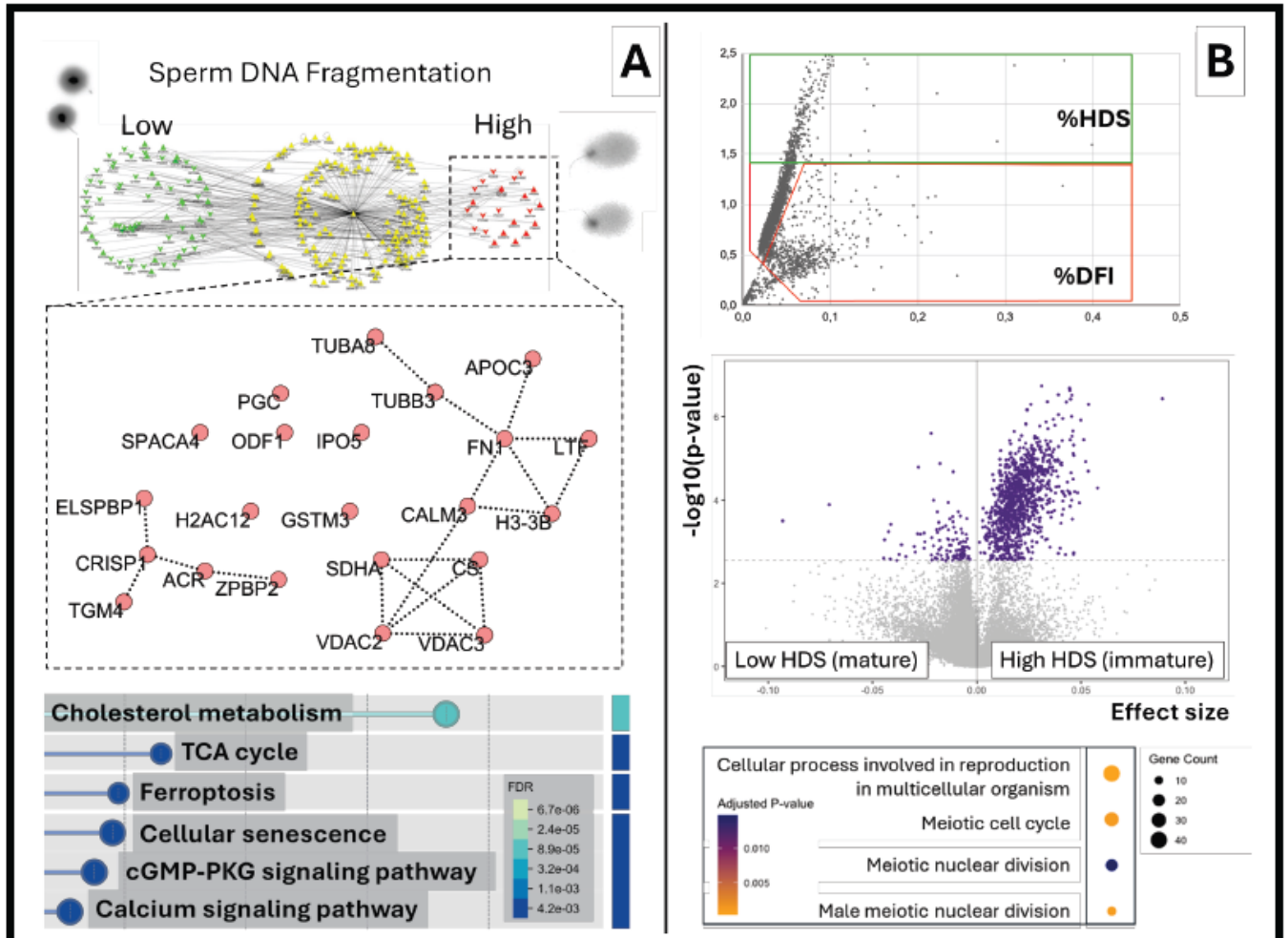
- Multiple hyper and hypomethylated CpG regions
- Genes involved in meiotic cell division, spermatogenesis-related transcriptional regulation.



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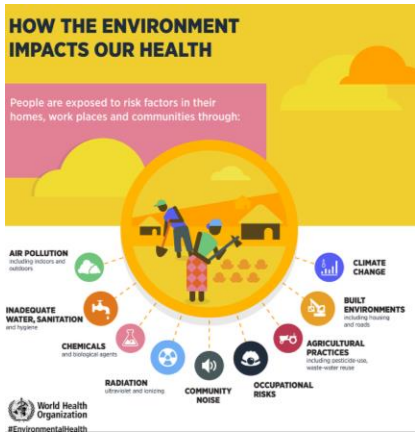
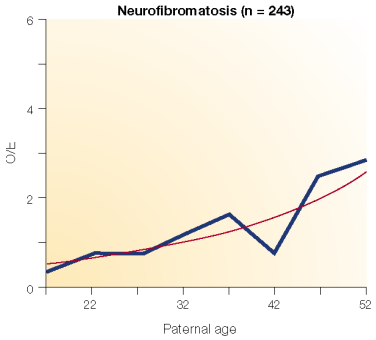
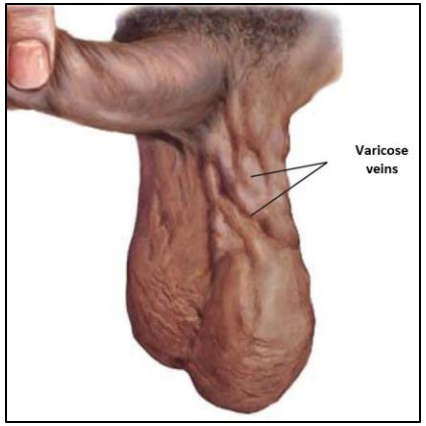
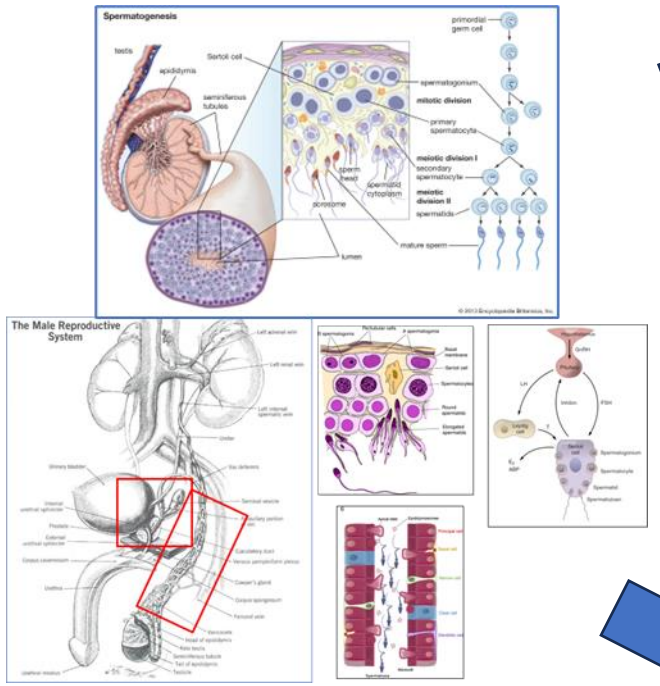
What don't we know/where do we need to get to?





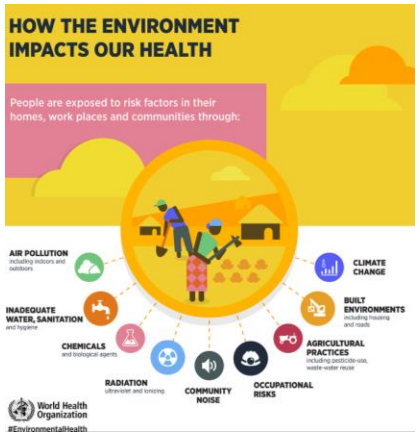




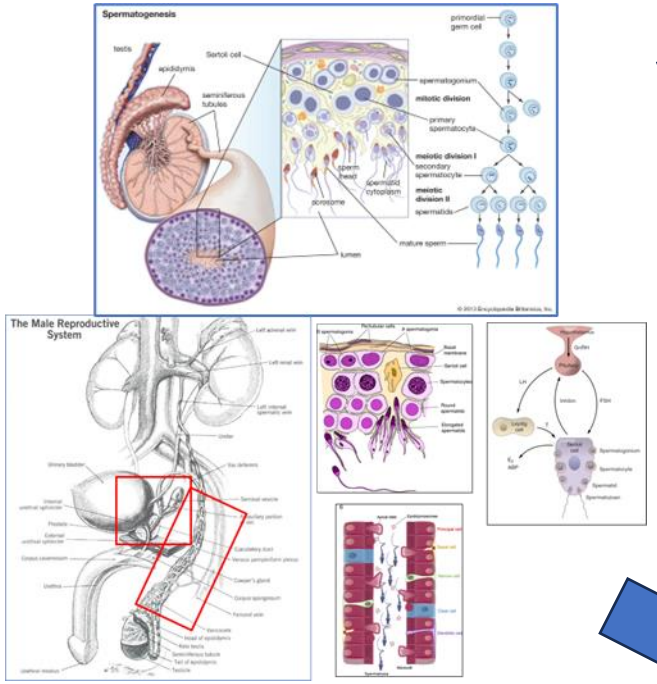
Semen quality
Infertility
Sperm function

Obstetric health and outcomes

Development



What don't we know/where do we need to get to?



Semen quality
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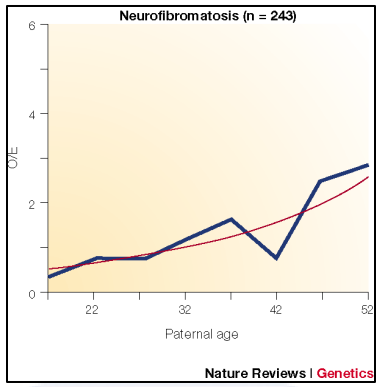
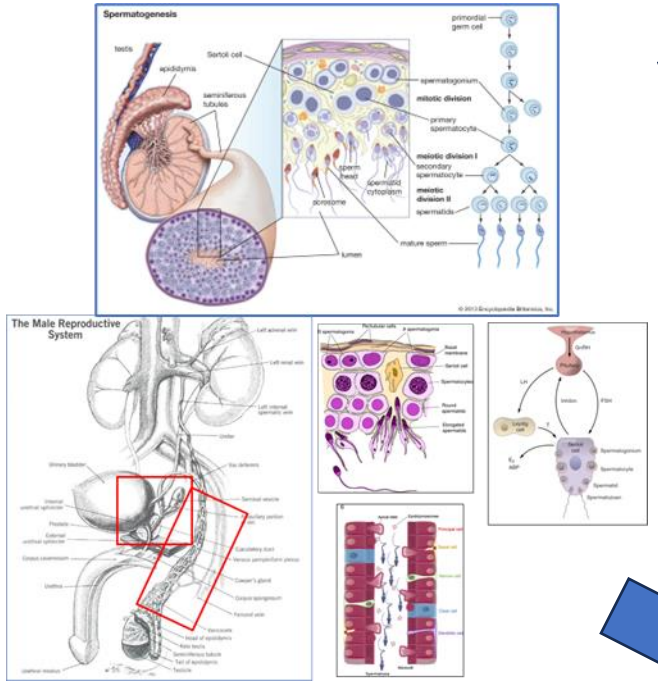
What don't we know/where do we need to get to?





Semen quality
Infertility
Sperm function

Obstetric health and outcomes

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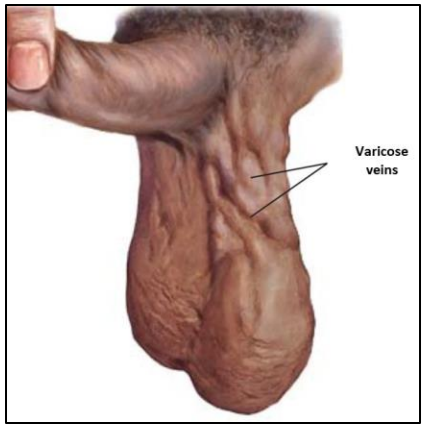
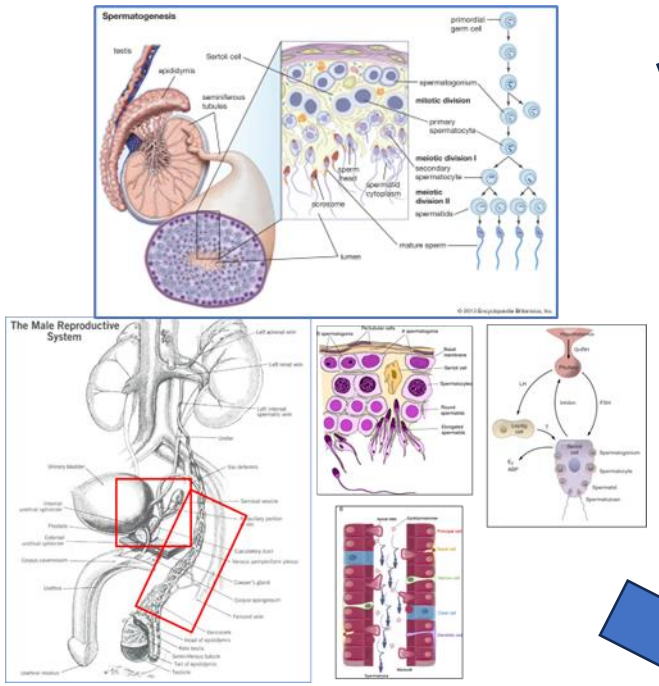
What don't we know/where do we need to get to?





Semen quality
Infertility
Sperm function

Obstetric health and outcomes

Development

Summary II

- Paternal age is increasing, and it is linked to obstetric outcomes and to child health;
- Paternal health is linked to obstetric outcomes;
- Sperm DNA fragmentation is associated to obstetric outcomes;
  - Animal data – and to increased risk of cancer;
- Environmental exposure is associated to altered semen and altered sperm DNA methylation profiles;
- Some treatable clinical conditions are associated to increased sperm DNA fragmentation.

What don't we know/where do we need to get to?

- Critical gaps:
  - For most paternal data:
    1. Need to collect more data on evidence;
    2. Need to collect more data on pre-conceptional cohorts (without infertility);
    3. What are the effects?
    4. What are the mechanisms? Metabolomics, exposomics, DNA methylation, sperm quality (functional integrity)?
    5. Do clinical conditions affect the observed effects (varicocele, obesity)?
    6. Do lifestyle factors? Alcohol, diet, exercise, smoking?

  - Paternal effects are potentially modifiable/preventable – they represent a window of prevention before conception.

Acknowledgements

Students
Paula T. Del Giudice
Barbara F. da Silva
Rhayza Andretta
Paula Lopes
Juliana Stevanato
Amanda Victorino
Luana N. G. Adami
Patrícia Porciúncula
Sophia Costa Araújo
Thais S. de Paula
Juliana Pariz
Larissa Belardin
Bruna T. de Lima
Aram Minas
Raquel Guilharducci
Mika Miyazaki
Gabrielly Alves
Larissa Rodrigues

Lab techs
Valéria Barradas
Carolina Homsi

Agnaldo Cedenho
Renato Fraietta
Matheus Gröner
Mariana Antoniassi
Mariana Camargo
Paula Intasqui
Tiago Silva

Robert Sullivan
Sylvie Breton

Nancy Brackett
Charles Lynne
Emad Ibrahim

Karina Cardozo
Valdemir Melechco

Ricardo Cavalli
Rosana Reis

J. Richard Pilsner, PhD
Amanda Paskavitz
Karolina Novak, PhD

UG3OD023285
1R01HD110462
1R01ES036537

Questions?

- rbertolla@wayne.edu