A Infertilidade Masculina como Indicador da Saúde do Homem

Edson Borges Jr.
FERTGROUP
Fertility Medical Group
Instituto Sapientiae

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Associação Instituto Sapientiae

Declaração

Sem conflito de interesse para divulgar relacionado ao assunto desta palestra

Resolução do Conselho Federal de Medicina
nº 1.595/2.000

Agenda

- Infertilidade Masculina e repercuções no sistema reprodutor
- Relação com a saúde, câncer e mortalidade
- Epigenética
- Idade e Obesidade

Global fertility in 204 countries and territories, 1950–2021, with forecasts to 2100: a comprehensive demographic analysis for the Global Burden of Disease Study 2021

*GBD 2021 Fertility and Forecasting Collaborators**

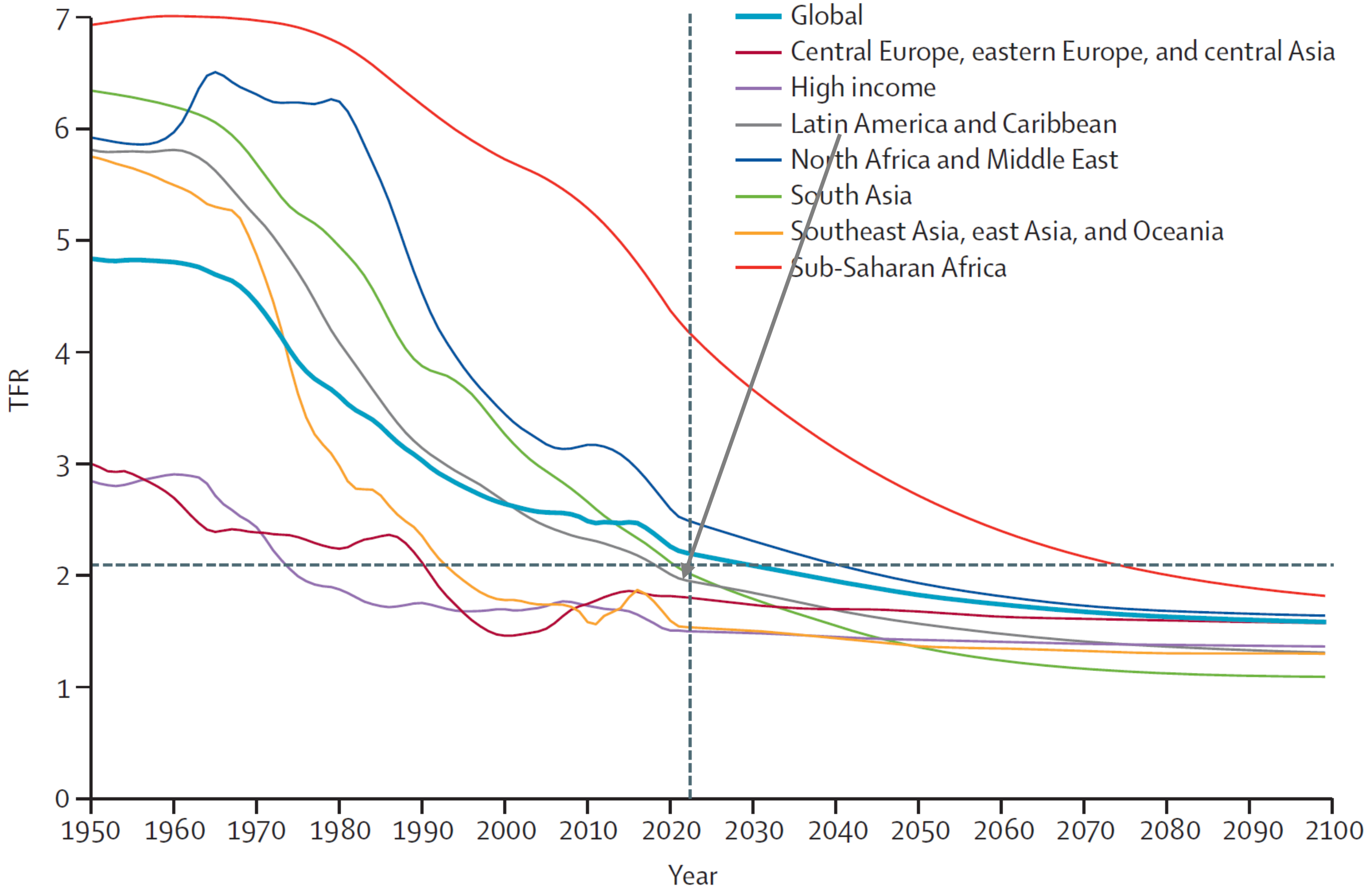

Figure 1: **TFR, globally and by GBD super-region, 1950–2100**

The dashed horizontal line indicates replacement TFR (2·1), and the dashed vertical line indicates the year 2022 (the first forecast year). GBD=Global Burden of Diseases, Injuries, and Risk Factors Study. TFR=total fertility rate.

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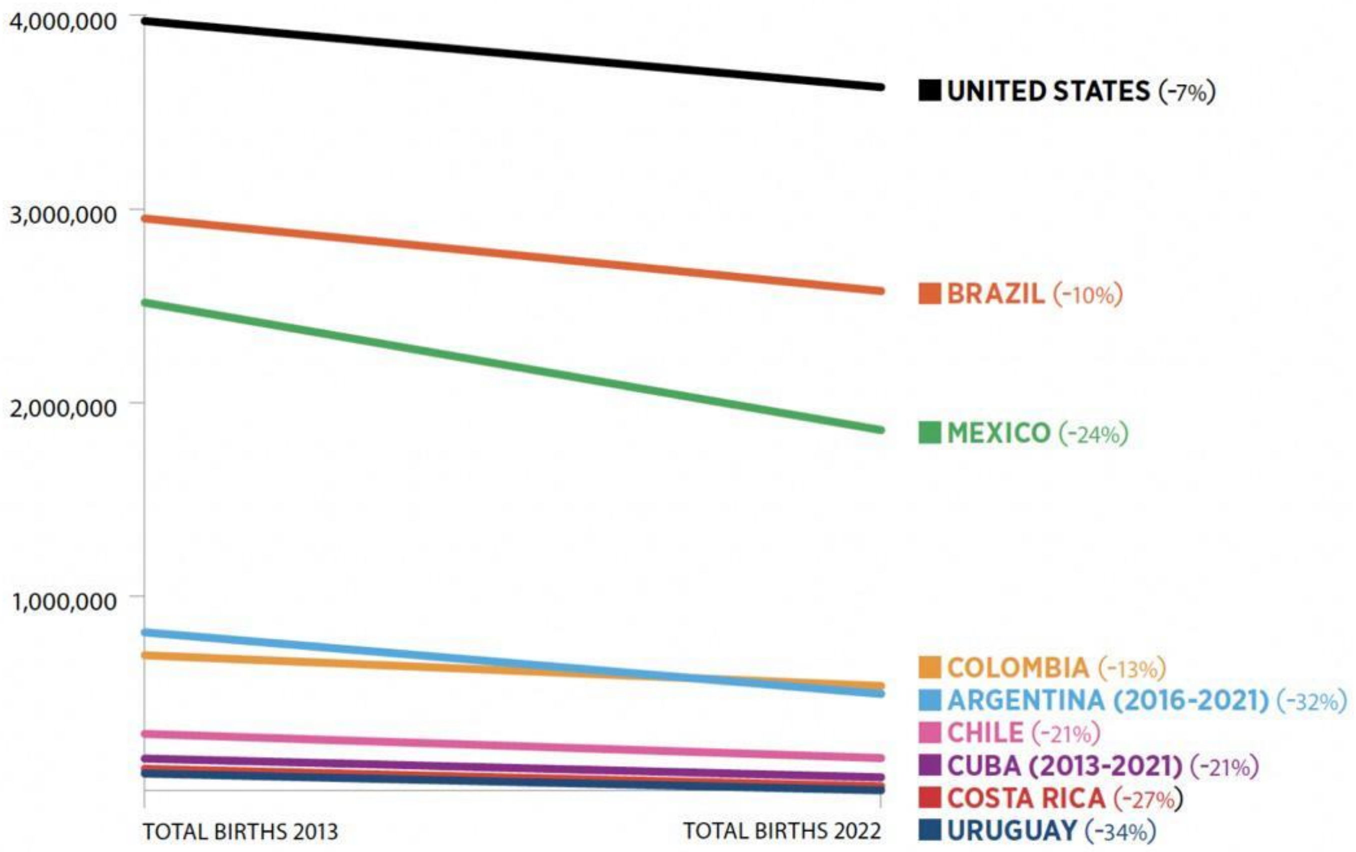
www.thelancet.com **Published online March 20, 2024 https://doi.org/10.1016/S0140-6736(24)00550-6**

The decline in fertility is a regional trend

In one decade, eight LAC countries had steeper drops in total births than the U.S.



SOURCES: MSP (URUGUAY); DEIS (ARGENTINA); INEC (COSTA RICA); INEGI (MEXICO); INE (CHILE); ONEI (CUBA); DANE (COLOMBIA); IBGE (BRAZIL); CDC (U.S.)

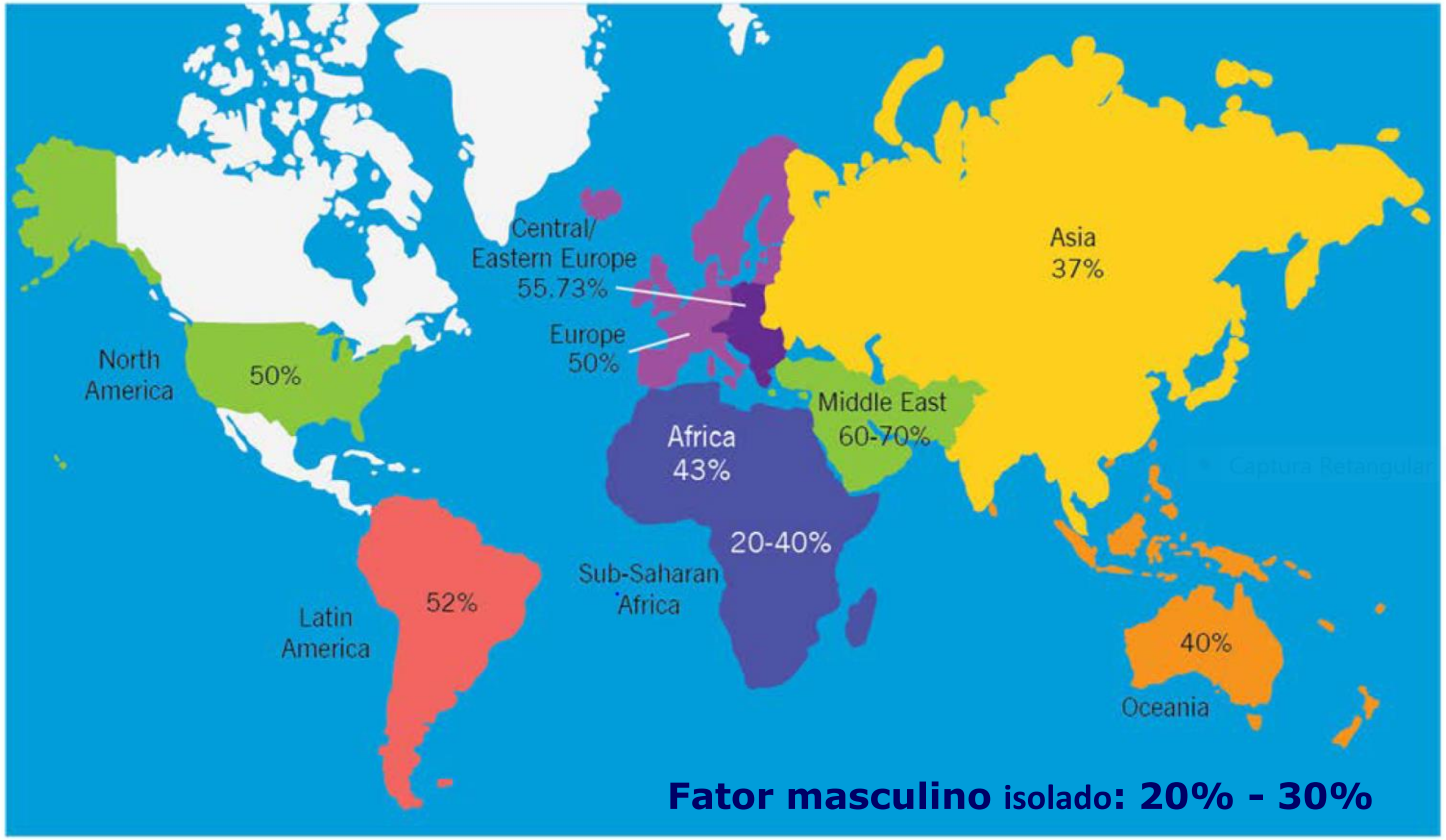


Figure 2 World map containing percentages of infertility cases per region that are due to male factor. This figure demonstrates rates of infertility cases in each region studied (North America, Latin America, Africa, Europe, Central/Eastern Europe, Middle East, Asia, and Oceania) due to male factor involvement.

RB&E REPRODUCTIVE BIOLOGY AND ENDOCRINOLOGY

Agarwal *et al. Reproductive Biology and Endocrinology* (2015) 13:37
DOI 10.1186/s12958-015-0032-1

Physiol Rev 96: 55–97, 2016
Published November 18, 2015; doi:10.1152/physrev.00017.2015

MALE REPRODUCTIVE DISORDERS AND FERTILITY TRENDS: INFLUENCES OF ENVIRONMENT AND GENETIC SUSCEPTIBILITY

Niels E. Skakkebaek, Ewa Rajpert-De Meyts, Germaine M. Buck Louis, Jorma Toppari, Anna-Maria Andersson, Michael L. Eisenberg, Tina Kold Jensen, Niels Jørgensen, Shanna H. Swan, Katherine J. Sapra, Søren Ziebe, Lærke Priskorn, and Anders Juul

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Incidência de Criptorquidia

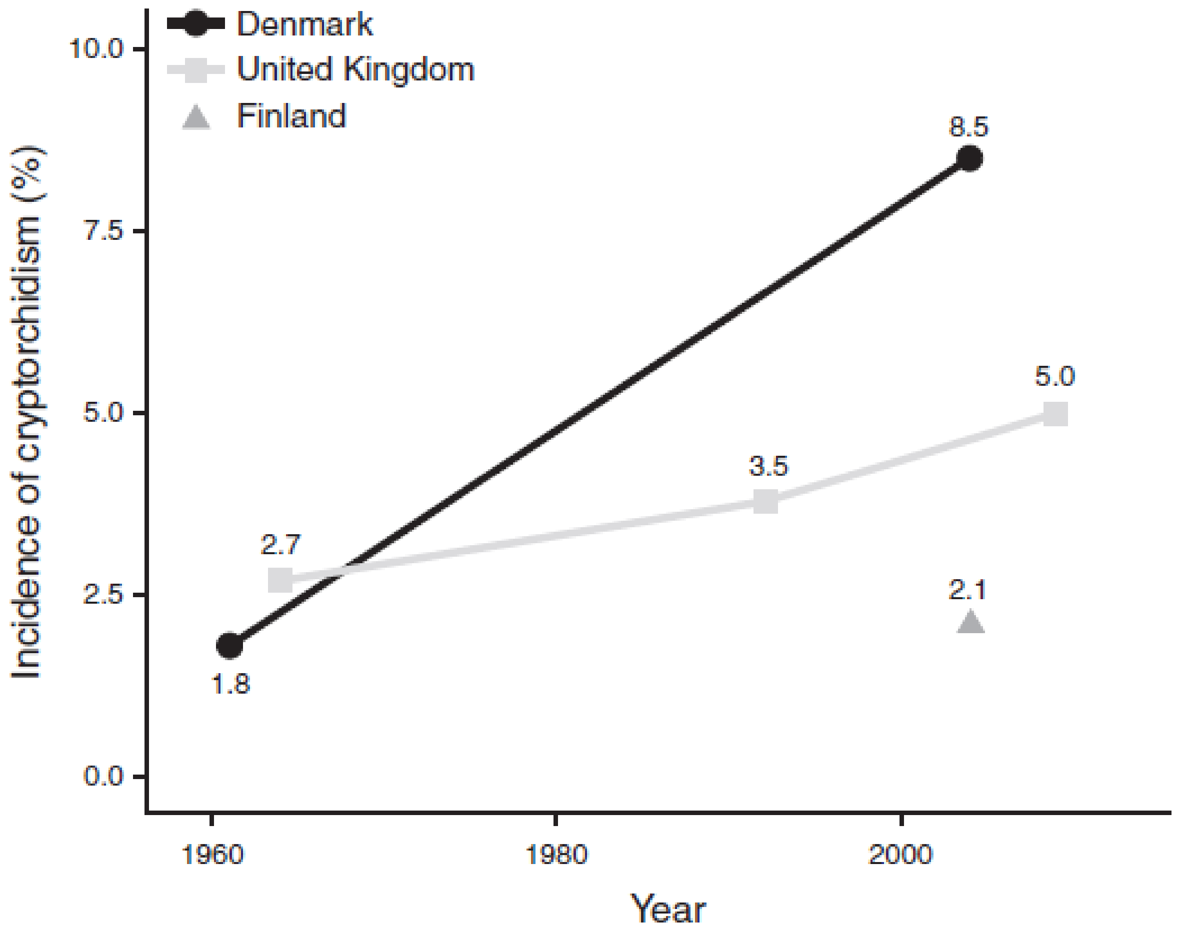

FIGURE 7. Incidence of cryptorchidism at birth on the basis of prospective clinical studies from the 1950s to the 2000s in Denmark, Finland, and United Kingdom. The data points are marked on the year of the publication of the study which represents the preceding incidence rate (3, 47, 61, 184, 377).

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Idade da Puberdade

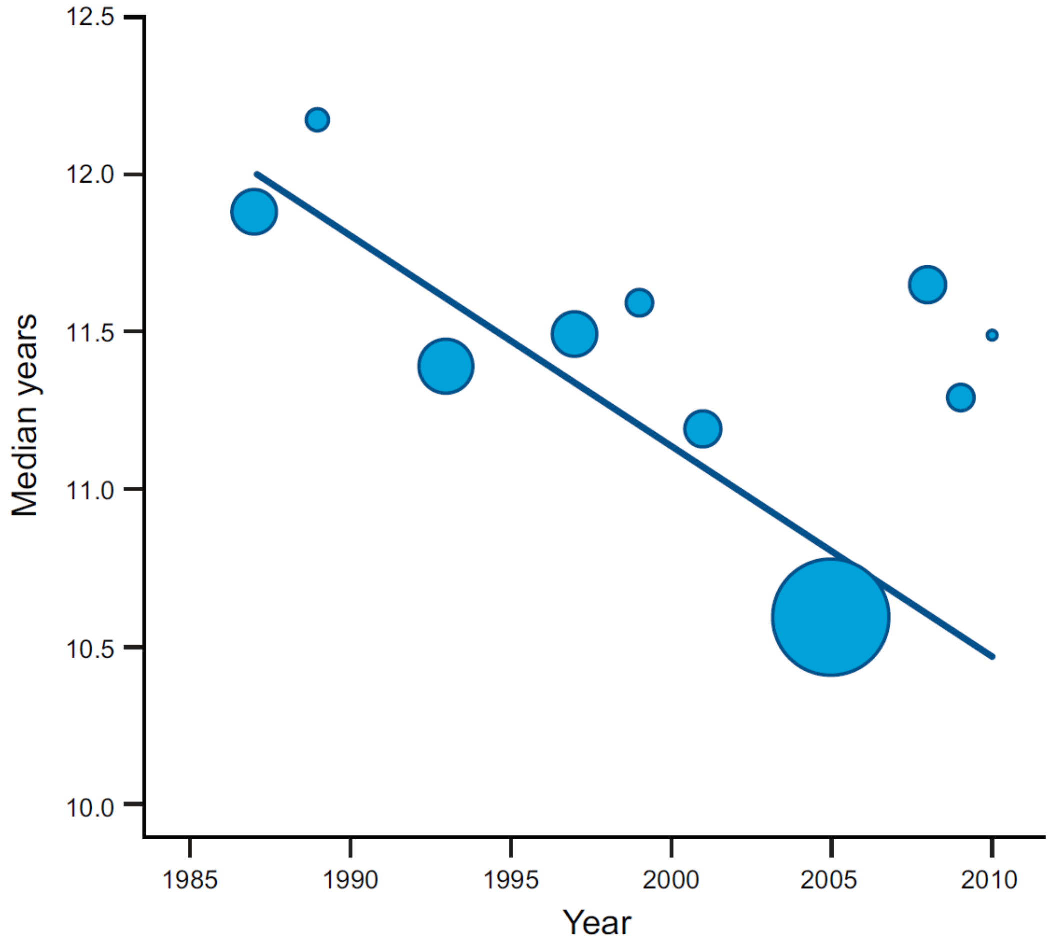

FIGURE 8. Recent changes in male pubertal timing. Testicular volume was >3 ml. [From Mouritsen et al. (293).]

Incidência de Câncer de Testículo

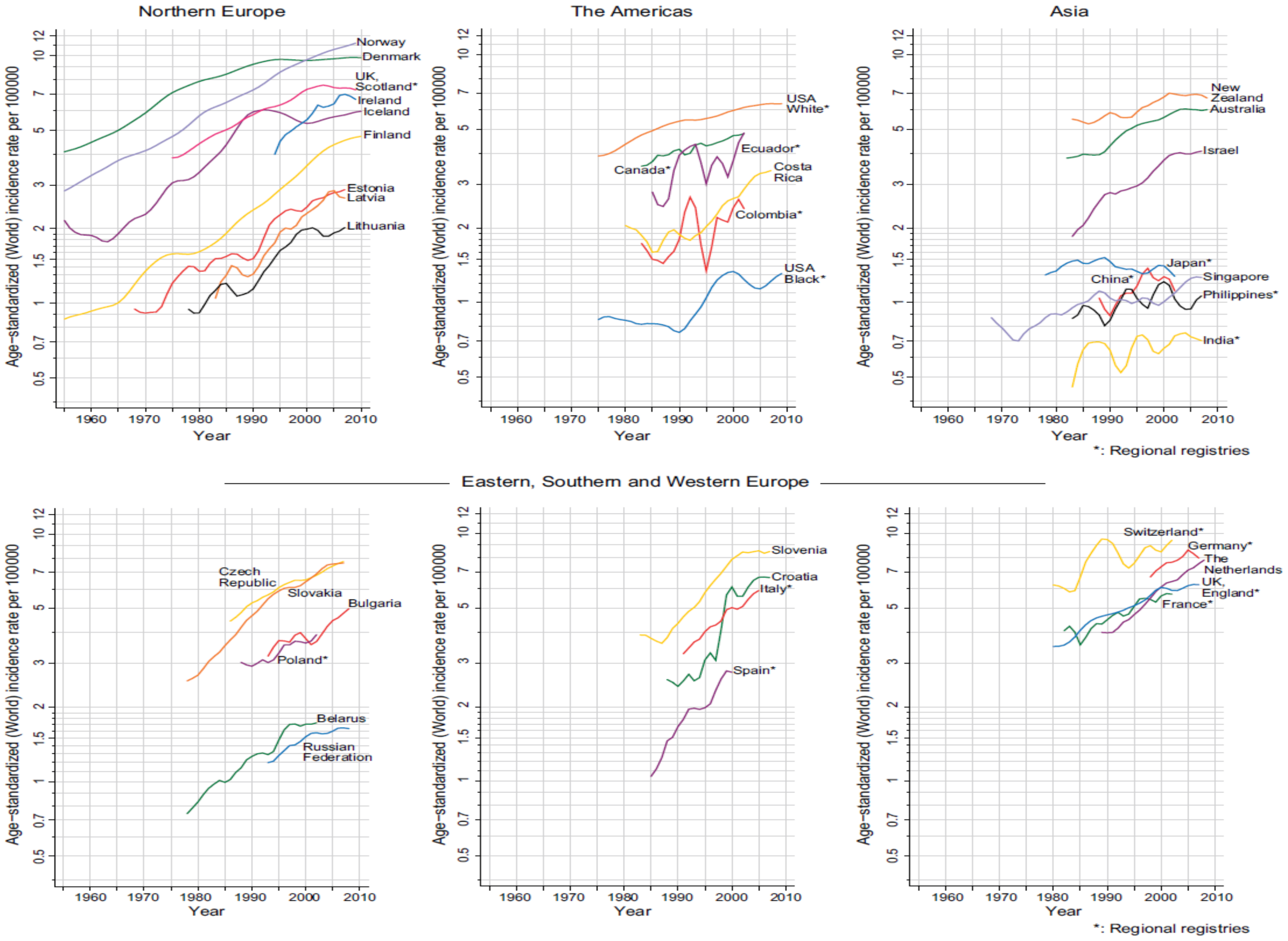

FIGURE 4. Trends in testicular cancer; age-standardized (world) incidence (regional or national), all ages. [Modified from Znaor et al. (481). Courtesy of Dr. Arinana Znaor and statistician Mathieu Laversanne, M.Sc., WHO, International Agency for Research in Cancer (IARC), Lyon, France.]

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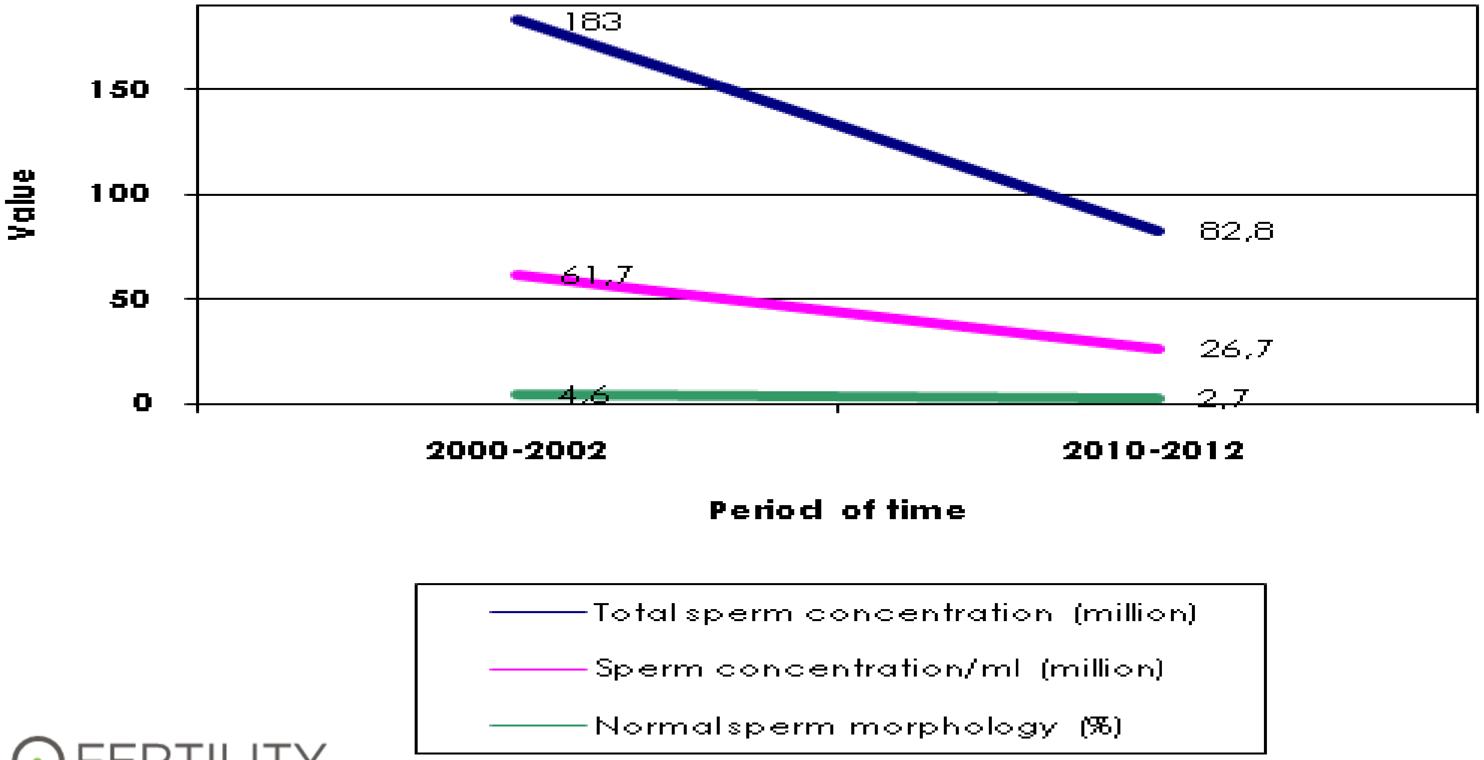
ORIGINAL ARTICLE

Vol. 41 (4): 757-763, July - August, 2015
doi:10.1590/S1677-5538.IBJU.2014.0186

Decline in semen quality among infertile men in Brazil during the past 10 years

Edson Borges Jr. [1,2], Amanda Souza Setti [1,2], Daniela Paes de Almeida Ferreira Braga [1,2], Rita de Cassia Savio Figueira [1], Assumpto Iaconelli Jr. [1,2]



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ORIGINAL ARTICLE

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Variable	2000 - 2002 (n=764)	2010 - 2012 (n=1536)	p
Azoospermia	4.9%	8.5%	<0.001
Severe oligozoospermia	15.7%	30.3%	<0.001

Article

Human and Experimental Toxicology
1–9
© The Author(s) 2017
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sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/0960327117703690
journals.sagepub.com/home/het
SAGE

Decline in sperm count in European men during the past 50 years

P Sengupta[1,2], E Borges Jr[3], S Dutta[4] and E Krajewska-Kulak[2]

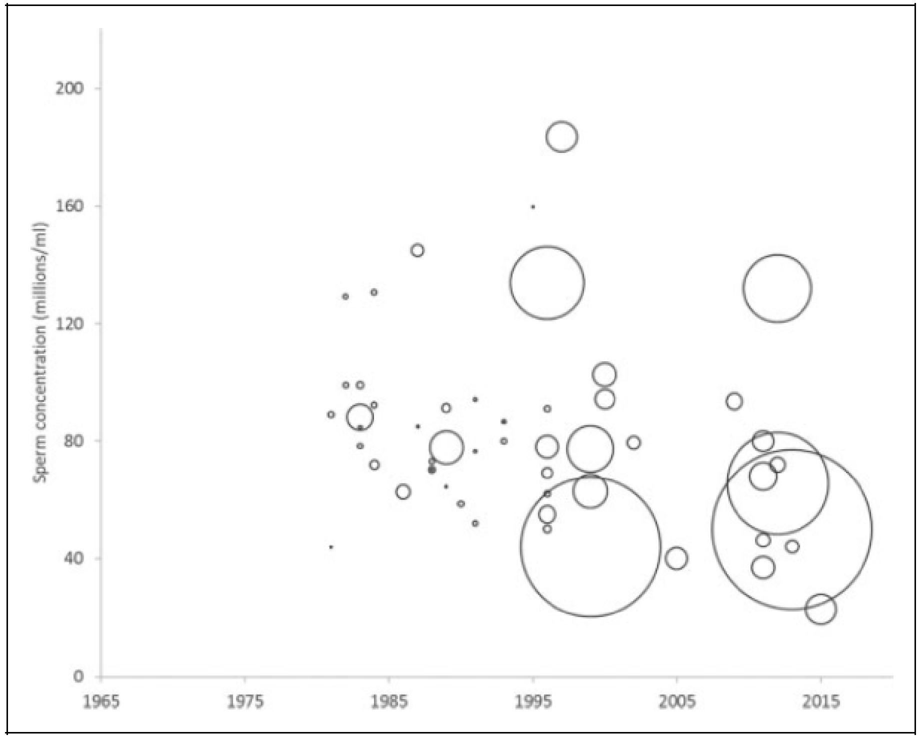

Figure 1. Temporal decline in sperm concentration ($\times 10^6$/ml) from 1965 to 2015, bubble size corresponds to the number of men in the study.

A time dependent decline in sperm concentration was observed from 1965 to 2015 (r=0.307, p=0.02)

An overall 32.5% decrease in mean sperm concentration

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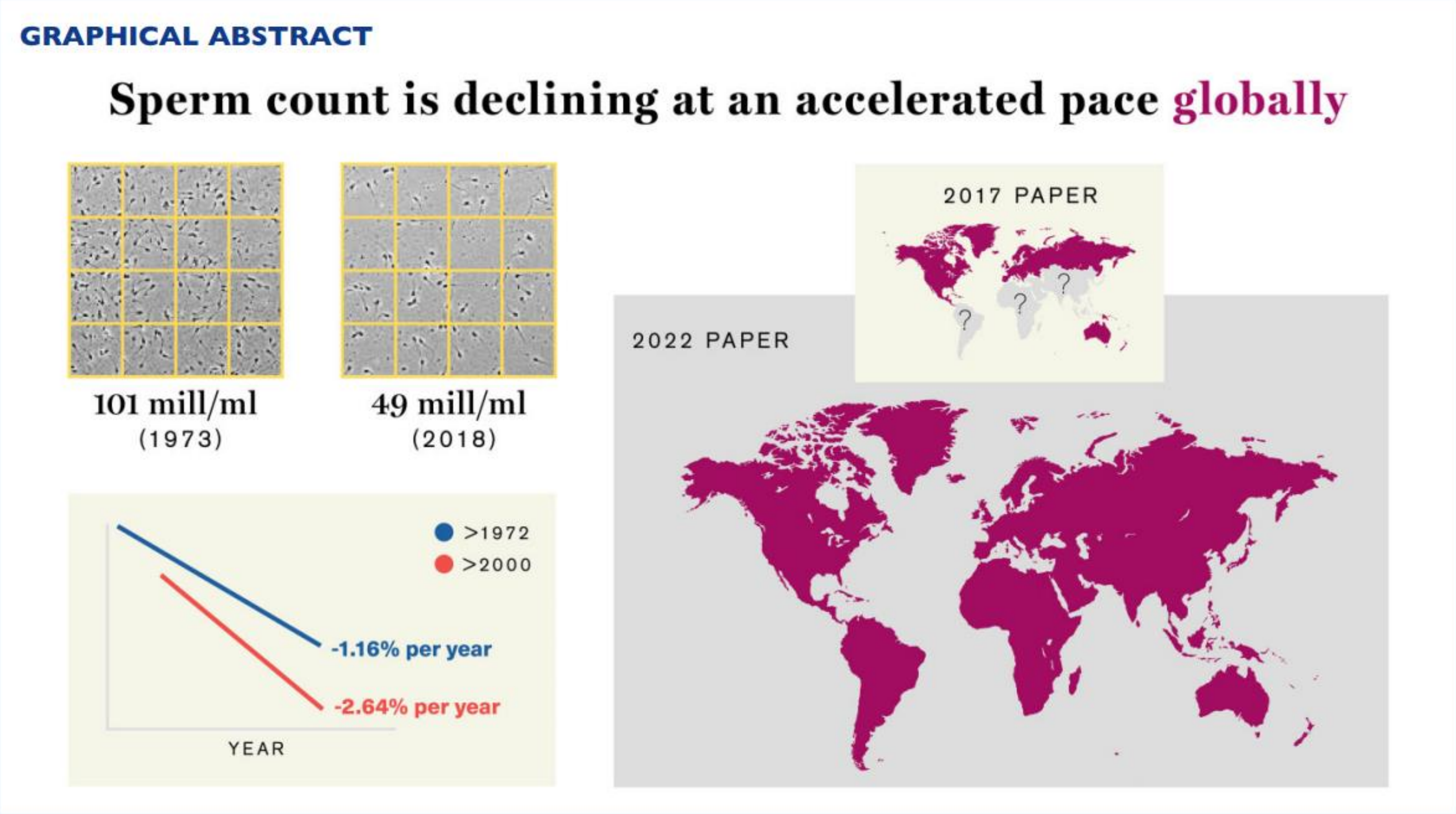

Sperm count is declining at an accelerated pace globally.

Human Reproduction Update, Vol.29, No.2, pp. 157–176, 2023
Advance Access Publication on November 15, 2022 https://doi.org/10.1093/humupd/dmac035

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Lesão do Sistema Reprodutor Masculino

FATORES AMBIENTAIS
(AÇÃO ENDÓCRINA)

Disgenesia Testicular

DEFEITO GENÉTICO

Disfunção cel. Sertoli → Prejuízo da diferenciação das cel. germinativas → Redução da qualidade seminal; CIS - Câncer Testicular

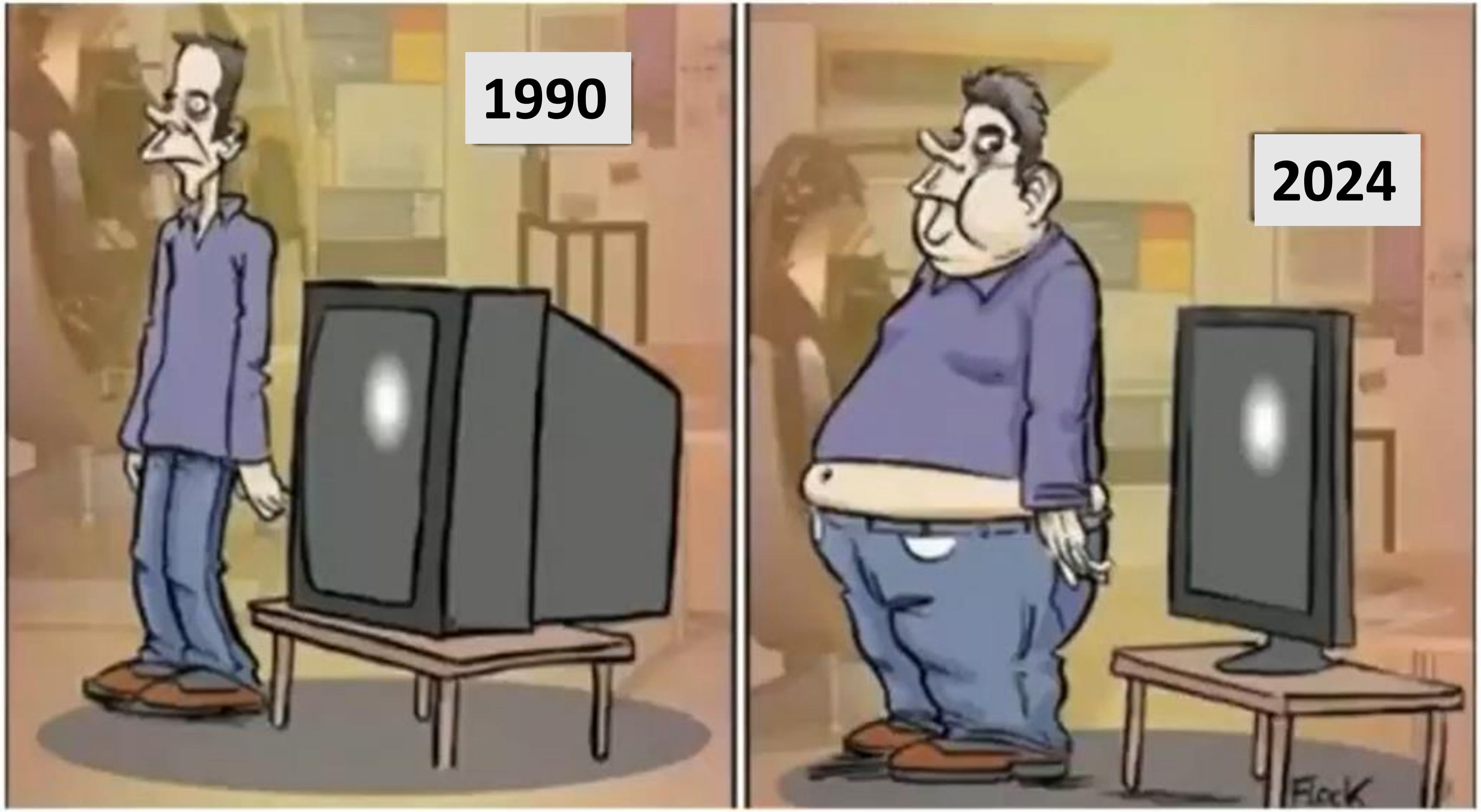
Disfunção cel. Leydig → Insuficiência androgênica → Hipospádia; Distopia testicular

Skakkebaek NE. Hum Rep 16(5): 972-8, 2001

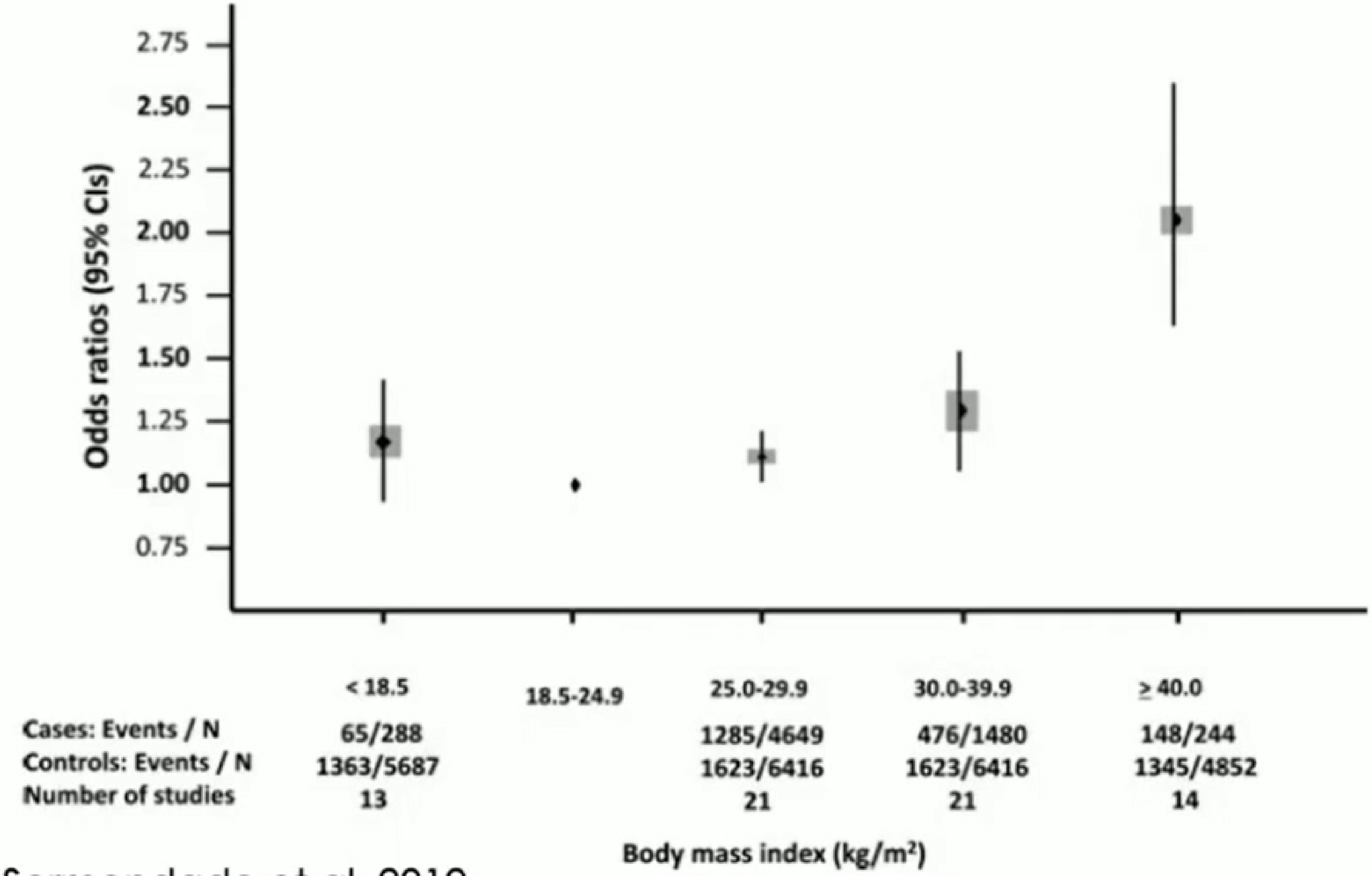
O sexto sinal vital:

O que o espermatozoide está tentando nos dizer?

Entendendo a relação...


1990
2024
Flock

IMC e concentração espermática



Sermondade et al, 2012

FERTGR

Human Reproduction Update Advance Access published December 12, 2012
Human Reproduction Update, Vol.0, No.0 pp. 1–11, 2012
doi:10.1093/humupd/dms050
human reproduction update

BMI in relation to sperm count: an updated systematic review and collaborative meta-analysis

N. Sermondade[1,2], C. Faure[1,2], L. Fezeu[2], A.G. Shayeb[3], J.P. Bonde[4], T.K. Jensen[5], M. Van Wely[6], J. Cao[7], A.C. Martini[8], M. Eskandar[9], J.E. Chavarro[10,11], S. Koloszar[12], J.M. Twigt[13], C.H. Ramlau-Hansen[14], E. Borges Jr[15], F. Lotti[16], R.P.M. Steegers-Theunissen[13], B. Zorn[17], A.J. Polotsky[18], S. La Vignera[19], B. Eskenazi[20], K. Tremellen[21], E.V. Magnusdottir[22], I. Fejes[23], S. Hercberg[2,24], R. Lévy[1,2†], and S. Czernichow[25,26,*†]

- ***21 estudos, 13.077 homens da população geral e em investigação de infertilidade***

- ***Estudo da relação entre BMI e incidência de oligozoospermia / azoospermia***

- ***Comparados com homens com peso normal:***

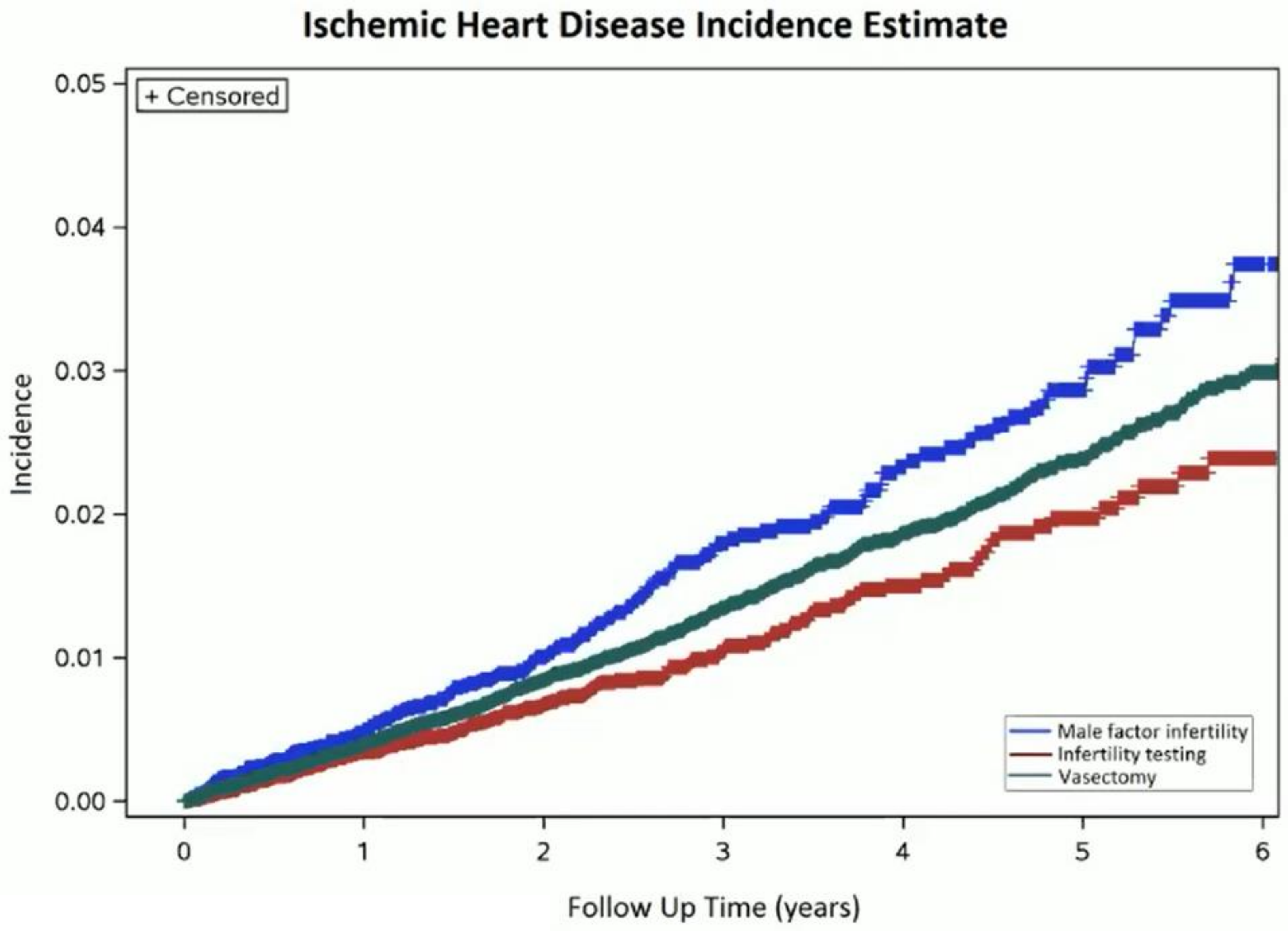
❖ Sobpeso: OR= 1,15 (0,93-1,43)

❖ Sobrepeso: OR= 1,11 (1,01-1,21)

❖ Obeso: OR= 1,28 (1,06-1,55)

❖ Obeso mórbido: OR= 2,04 (1,59-2,62)

Doenças metabólicas e vasculares



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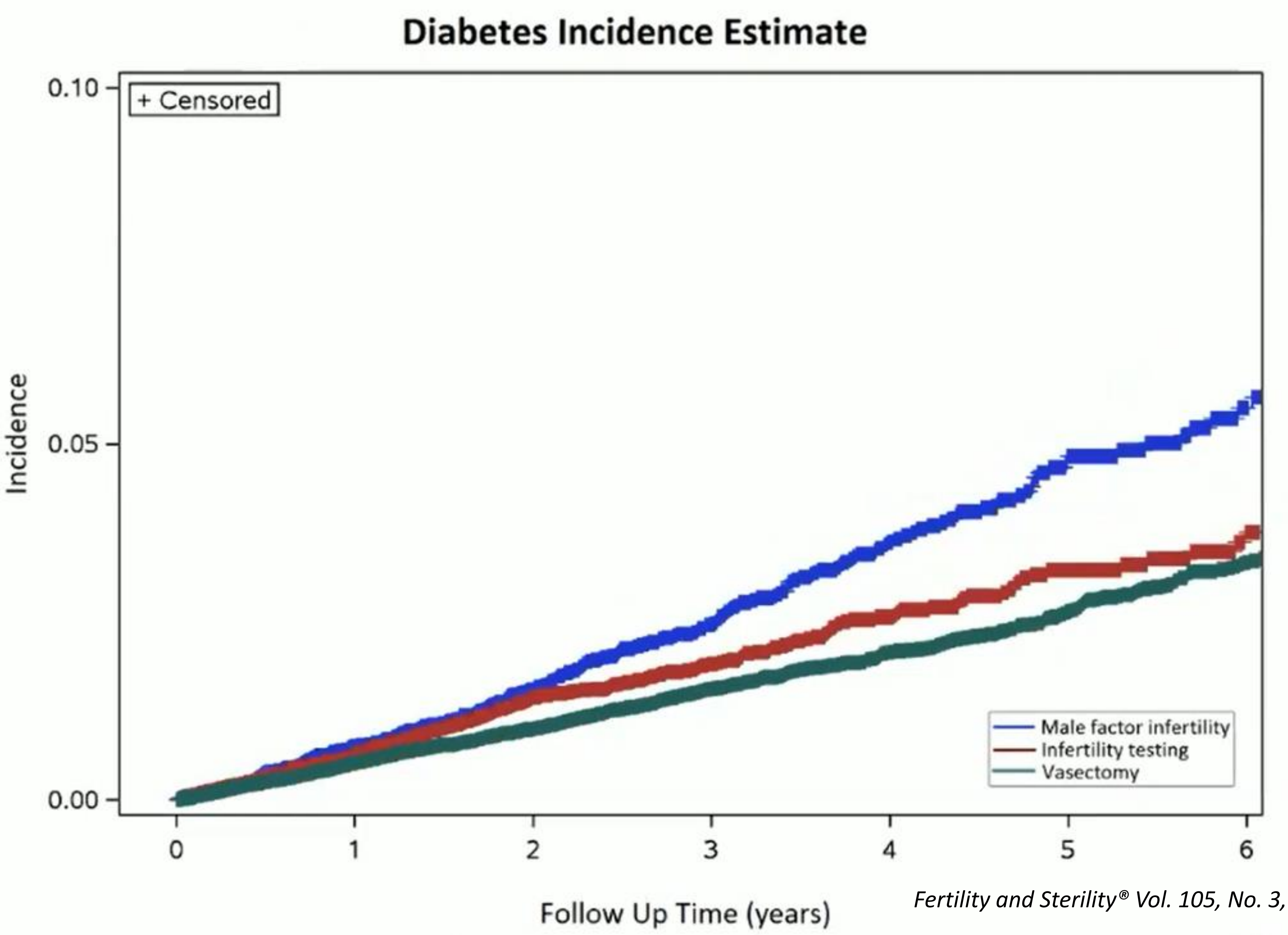
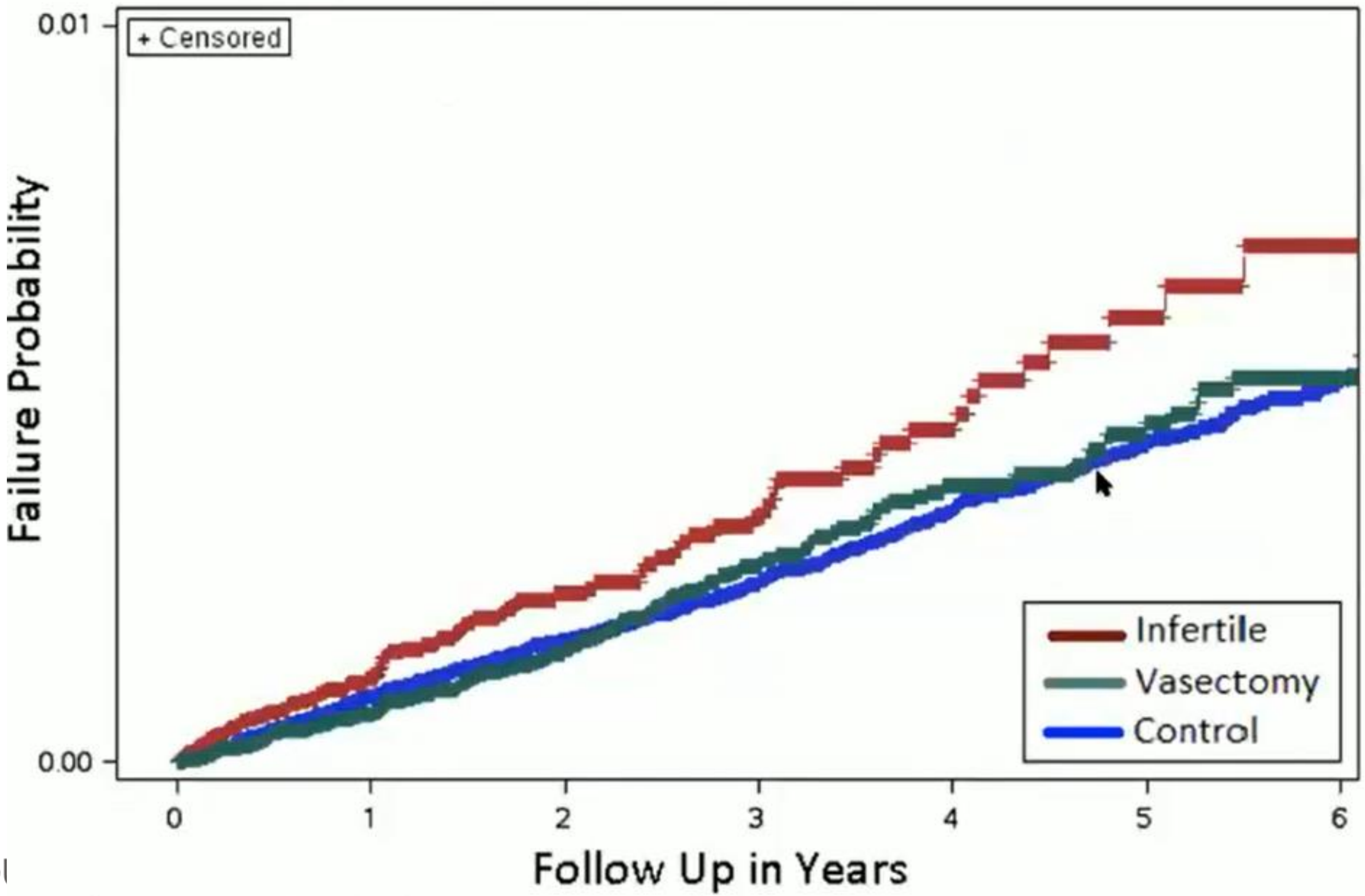


FER

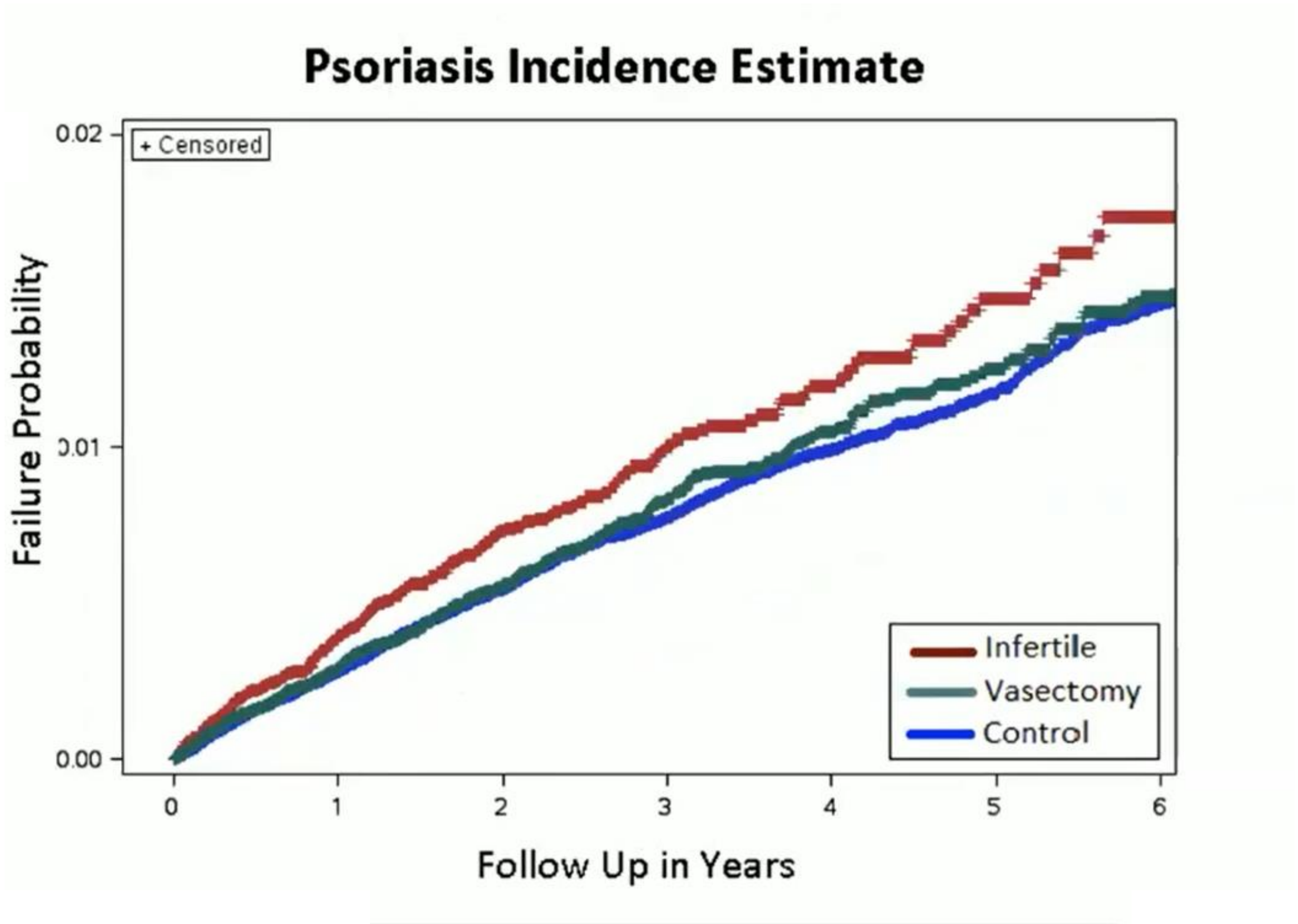
Fertility and Sterility® Vol. 105, No. 3, March 2016

Rheumatoid Arthritis & Other Inflammatory Polyarthropathies Incidence Estimate



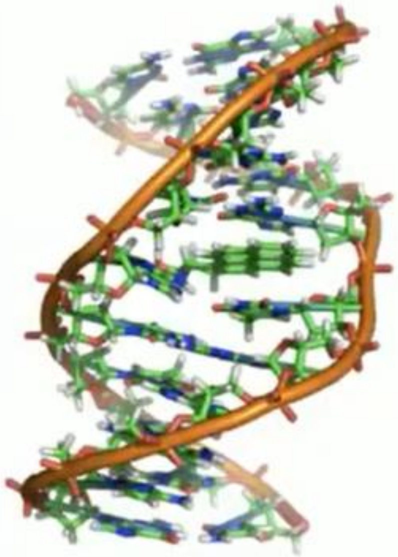
FERTGRO

W. D. Brubaker *et al., 2018;* doi: 10.1111/andr.12436



W. D. Brubaker *et al., 2018;* doi: 10.1111/andr.12436

Infertilidade risco de câncer



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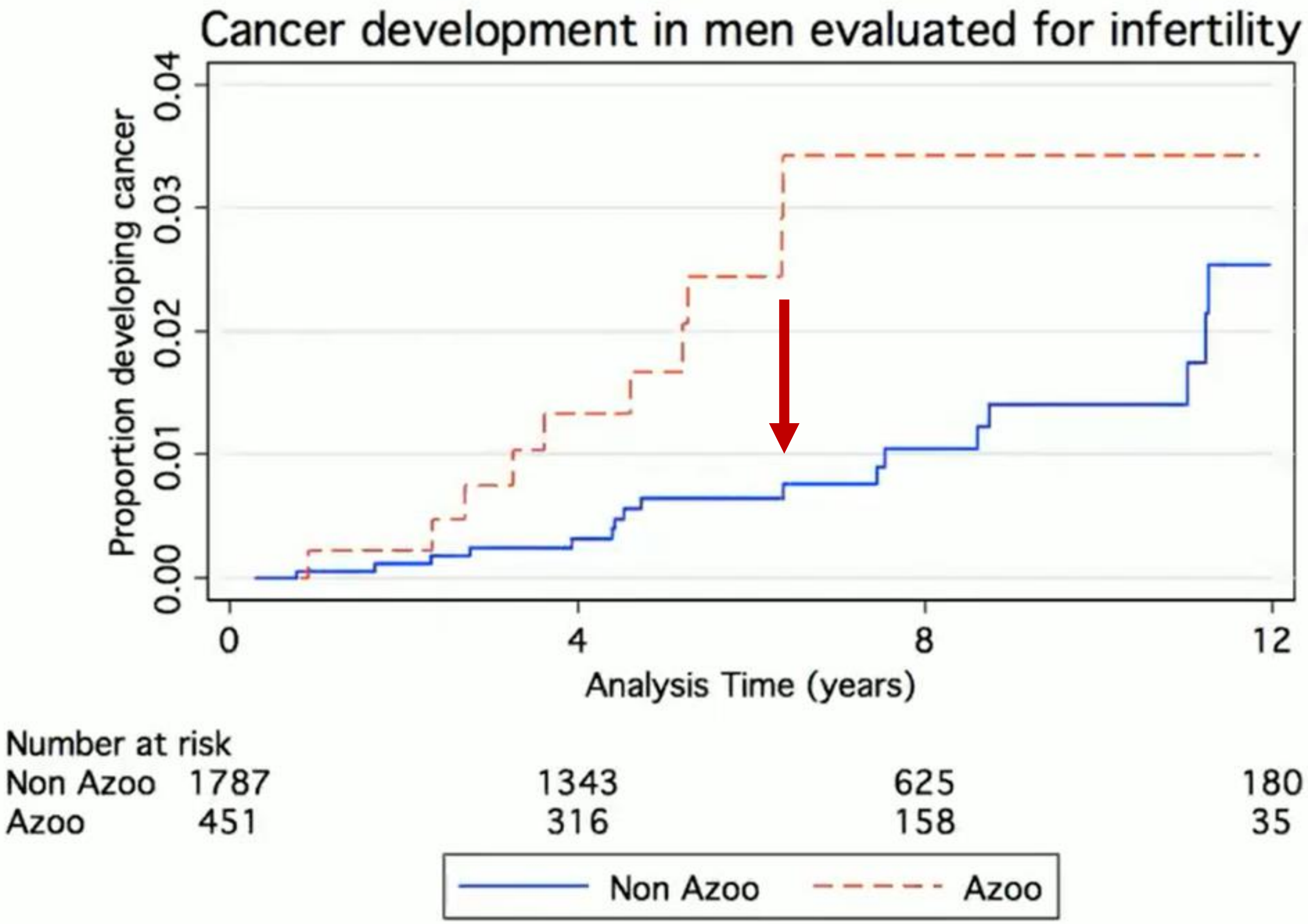

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Eisenberg *et al*.Fertil Steril . 2013 Sep;100(3):681-5.
doi: 10.1016/j.fertnstert.2013.05.022. Epub 2013 Jun 21

Infertilidade e câncer de testículo

- Examined >30,000 men who had a semen analysis in Copenhagen from 1963-1995
- Linked to Danish Cancer Registry

Jacobsen et al.BMJ. 2000 Sep 30;321(7264):789-92.
doi: 10.1136/bmj.321.7264.789

Infertilidade e câncer de testículo

Semen parameter		n	Observed cases	Expected cases	SIR
Concentration	0-20	10,509	33	14.4	**2.3 (1.6,3.2)**
	>20	18,668	42	36.9	1.1 (0.8, 1.5)
Motility	Poor	1,312	7	2.8	**2.5 (1.0, 5.2)**
	Good	19,362	44	28	1.6 (1.1, 2.1)
Morphology (% abnormal)	>75	528	4	1.4	**3.0 (0.8, 7.6)**
	0-75	27,618	64	47.8	1.3 (1.0, 1.7)

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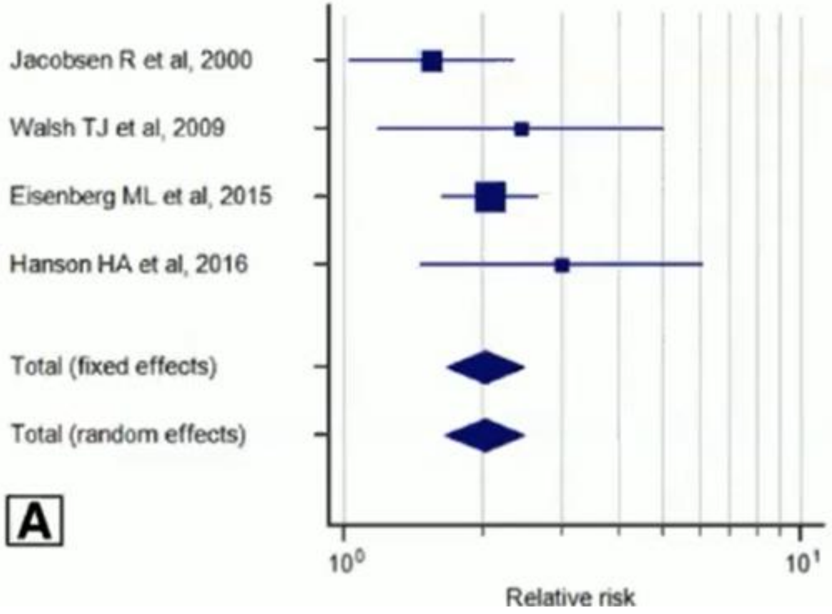
Jacobsen *et al*. BMJ. 2000 Sep 30;321(7264):789-92.
doi: 10.1136/bmj.321.7264.789

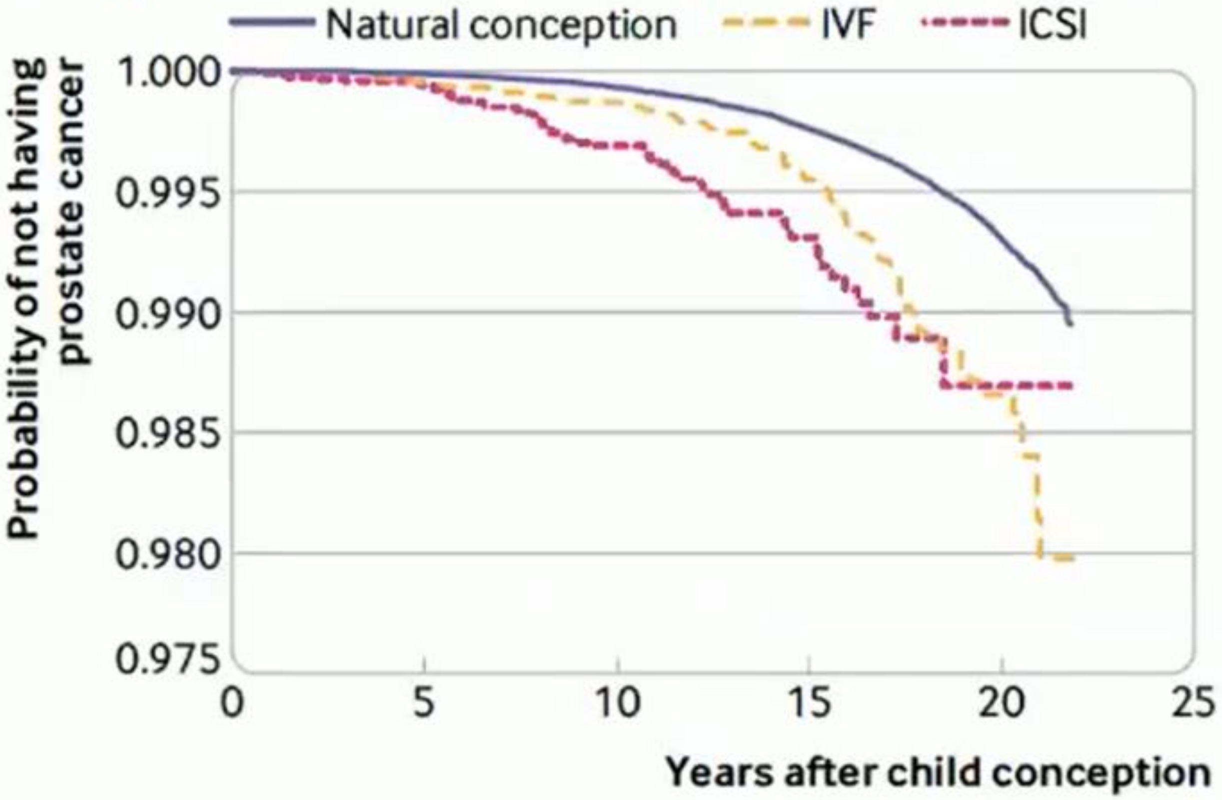
Infertilidade e câncer de testículo

Author, Year,	Infertile	Controls	Relative risk	95% CI	p value
Jacobsen R et al[37], 2000	46/13184	42/18667	1.551	1.021 to 2.355	
Walsh TJ et al[38], 2009	13/4549	17/14556	2.447	1.189 to 5.034	
Eisenberg ML et al[19], 2015	85/123467	251/760829	2.087	1.632 to 2.669	
Hanson HA et al[39], 2016	30/20432	10/20432	3.000	1.467 to 6.135	
Total (fixed effects)	174/161632	320/814484	2.033	1.671 to 2.474	<0.001
Total (random effects)	174/161632	320/814484	2.033	1.665 to 2.481	<0.001



Del Giudice *et al*. Fertil Steril. 2020 Nov;114(5):984-996.
doi: 10.1016/j.fertnstert.2020.04.042

Infertilidade e câncer de próstata



Natural conception					
	1 145 962	940 084	692 333	454 698	181 249
IVF					
	20 617	15 274	9504	5007	1535
ICSI					
	14 873	10 509	6099	2593	184

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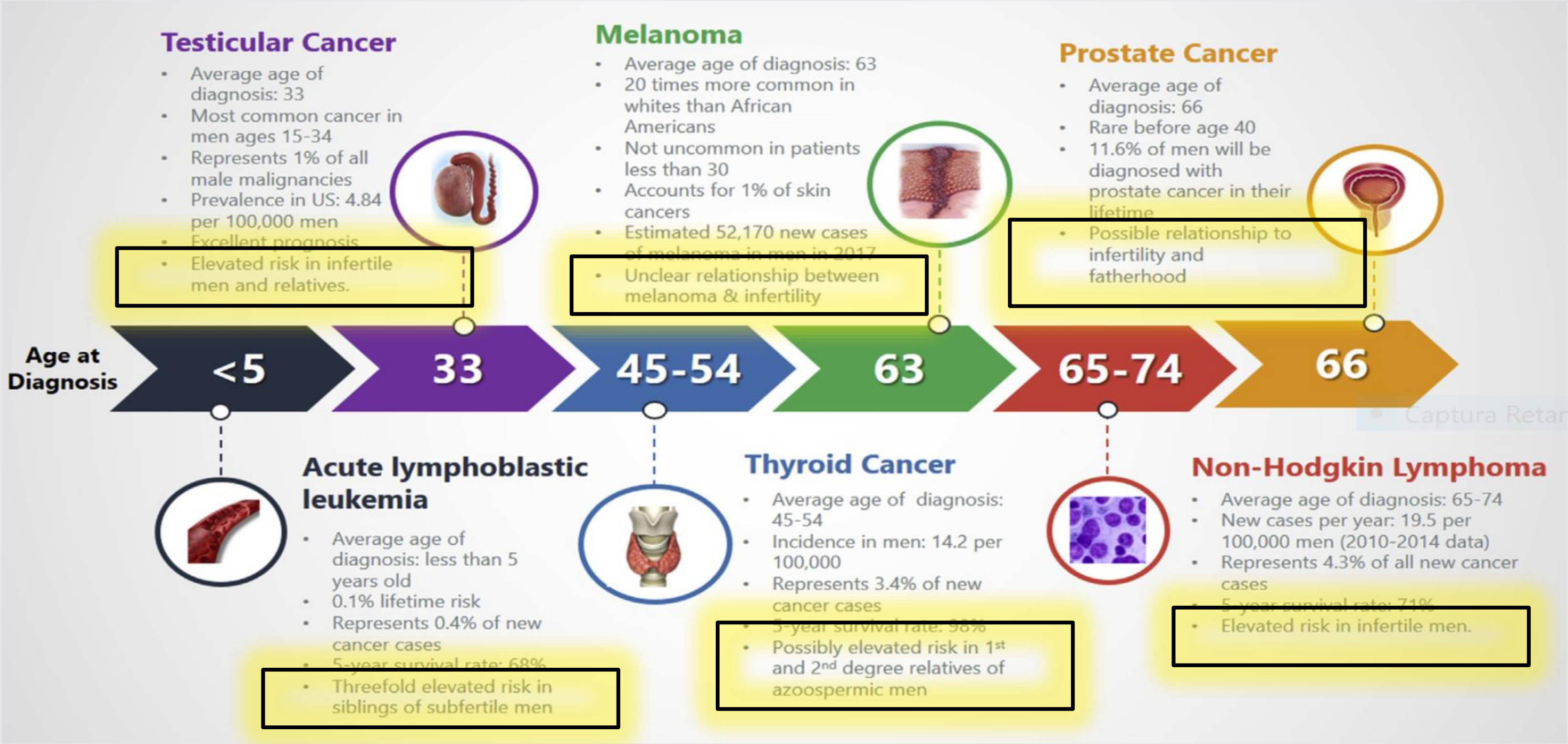
Al-Jebari *et al.* BMJ, 2019 Sep 25:366:l5214.
doi: 10.1136/bmj.l5214

Male infertility: a biomarker of individual and familial cancer risk

Brent M. Hanson, M.D.,[a] Michael L. Eisenberg, M.D.,[b] and James M. Hotaling, M.D., M.S., F.E.C.S.M.[c]

[a] Department of Obstetrics and Gynecology, University of Utah, Salt Lake City, Utah; [b] Male Reproductive Medicine and Surgery Program, Departments of Urology and Obstetrics and Gynecology, Stanford University, Stanford, California; and [c] Center for Reconstructive Urology and Men's Health, Department of Surgery–Urology, University of Utah, Salt Lake City, Utah

Fertility and Sterility® Vol. 109, No. 1, January 2018



Specific malignancies associated with infertile men and their family members by average age at diagnosis.

Hanson. Male infertility and cancer risk. Fertil Steril 2017.

Pais & Filhos

- Cohabitiation lowers mortality
- Children lower mortality

All Cause Mortality

Male characteristics	HR (95% CI)
Cohabiting custodial fathers	Reference

G. Ringback Weitoft et al. / Social Science & Medicine 59 (2004) 1449–1459

Pais & Filhos

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All Cause Mortality

Male characteristics	HR (95% CI)
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Lone custodial fathers	1.6 (1.4-1.9)

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G. Ringback Weitoft et al. / Social Science & Medicine 59 (2004) 1449–1459

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Male characteristics	HR (95% CI)
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G. Ringback Weitoft et al. / Social Science & Medicine 59 (2004) 1449–1459

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Lone non custodial fathers	2.7 (2.5-2.8)
Cohabiting childless men	1.6 (1.5-1.7)

G. Ringback Weitoft et al. / Social Science & Medicine 59 (2004) 1449–1459

Pais & Filhos

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Male characteristics	HR (95% CI)
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Lone childless	2.9 (2.8-3.0)

G. Ringback Weitoft et al. / Social Science & Medicine 59 (2004) 1449–1459

Infertilidade mortalidade

Relação entre qualidade seminal e mortalidade

American Journal of Epidemiology
Vol. 170, No. 5
DOI: 10.1093/aje/kwp168
Advance Access publication July 27, 2009
© The Author 2009. Published by the Johns Hopkins Bloomberg School of Public Health.
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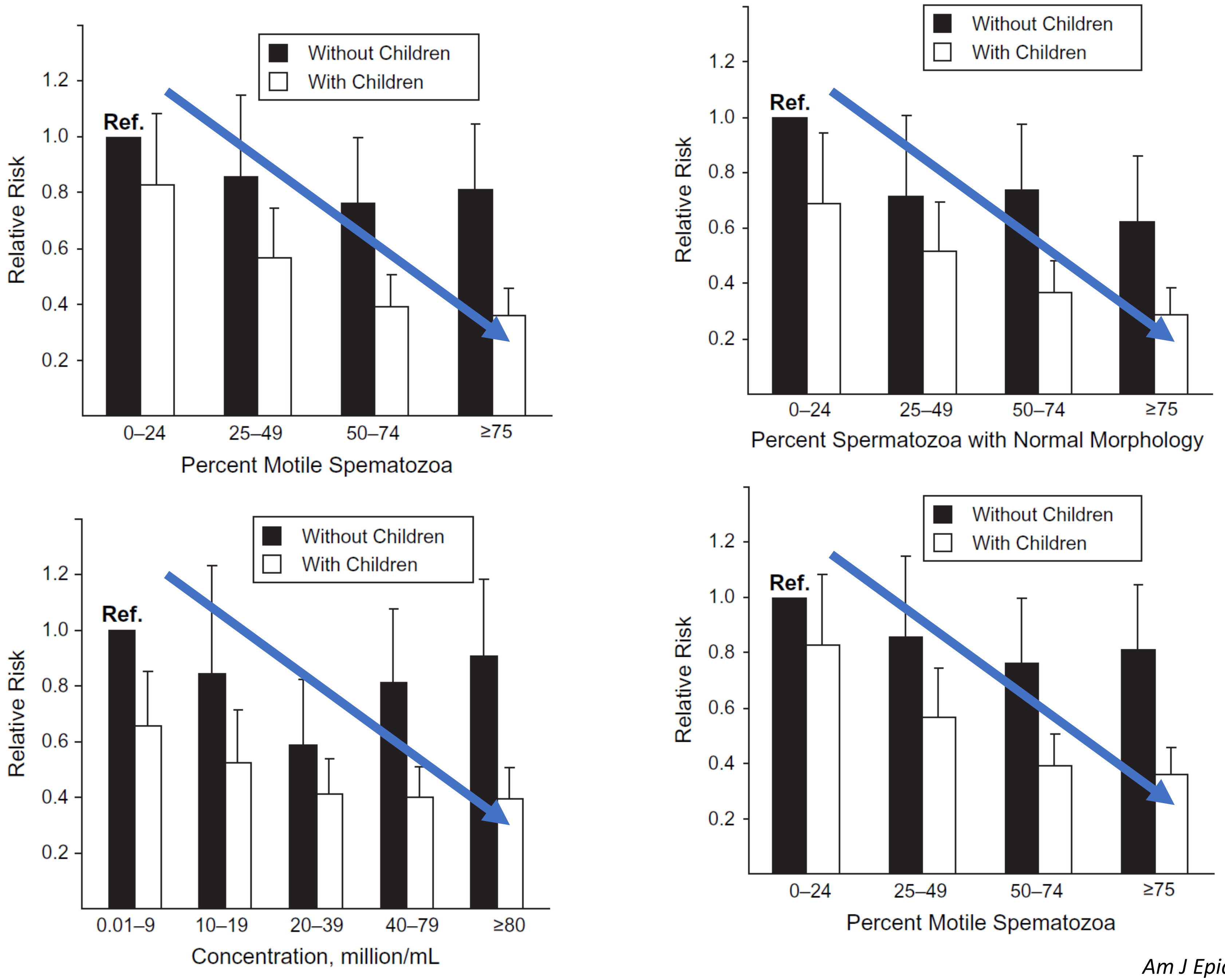
Original Contribution

Good Semen Quality and Life Expectancy: A Cohort Study of 43,277 Men

Tina Kold Jensen, Rune Jacobsen, Kaare Christensen, Niels Christian Nielsen, and Erik Bostofte

Initially submitted March 11, 2009; accepted for publication May 26, 2009.



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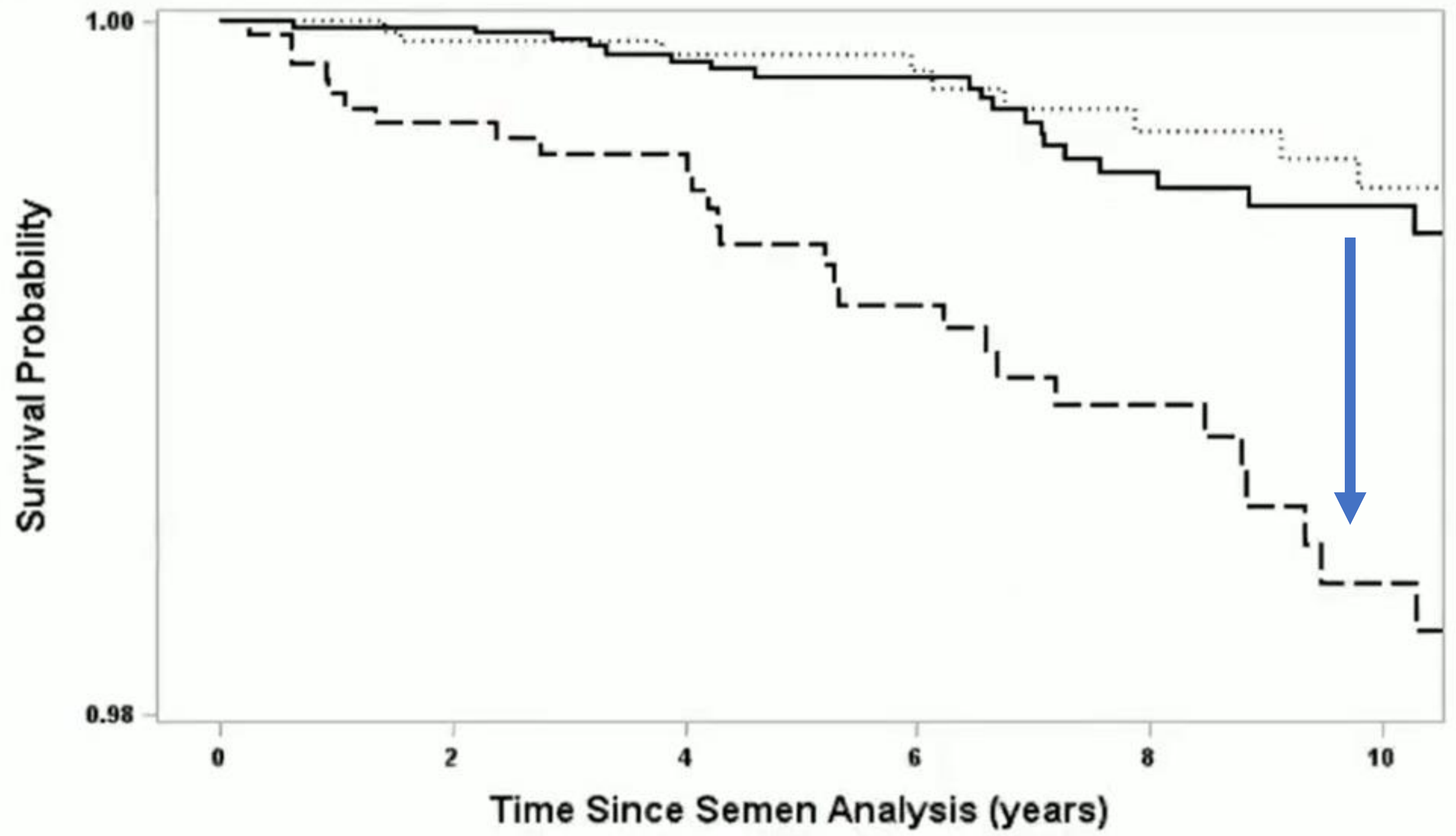
Am J Epidemiol 2009;170:559–565



Life Table of Number of Abnormalities —— 0 ······ 1 – – – 2+

0	5687	5539	4581	3470	2285	1356
1	3318	3235	2675	2023	1504	1104
2+	2391	2311	1952	1529	1110	790

Am J Epidemiol 2009;170:559–565

Human Reproduction, Vol.34, No.11, pp. 2266–2273, 2019
Advance Access Publication on November 4, 2019 doi:10.1093/humrep/dez189

human reproduction
ORIGINAL ARTICLE ***Reproductive epidemiology***

Male factor infertility and risk of death: a nationwide record-linkage study

Clara Helene Glazer[1,2,*], Michael L. Eisenberg[2], Sandra Søgaard Tøttenborg[1], Aleksander Giwercman[3], Esben Meulengracht Flachs[1], Elvira Vaclavik Bräuner[4,5], Ditte Vassard[6], Anja Pinborg[7], Lone Schmidt[6], and Jens Peter Bonde[1]

- Homens submetidos a TRA na Dinamarca (coorte MAR; n=64.563); ***população final de 384.419 homens***

- ***Homens com azoospermia*** tiveram o maior risco de morte, que persistiu tanto na comparação interna [*HR, 2,30*; 95% CI, 1,54–3,41] como na comparação externa [*HR, 3,32*; IC 95%, 2,02–5,40]

Human Reproduction, Vol.32, No.1 pp. 239–247, 2017
Advanced Access publication on December 6, 2016 doi:10.1093/humrep/dew289

human reproduction | ORIGINAL ARTICLE *Reproductive epidemiology*

Risk of childhood mortality in family members of men with poor semen quality

Heidi A. Hanson[1,2,*], Erik N. Mayer[3], Ross E. Anderson[3], Kenneth I. Aston[3,4,5], Douglas T. Carrell[3,5], Justin Berger[2], William T. Lowrance[3], Ken R. Smith[2,6], and James M. Hotaling[3,4]

- **Risco aumentado de morte devido a Malformações Congênitas em descendentes de 1º grau de homens com <u>alterações dos parâmetros seminais</u>**

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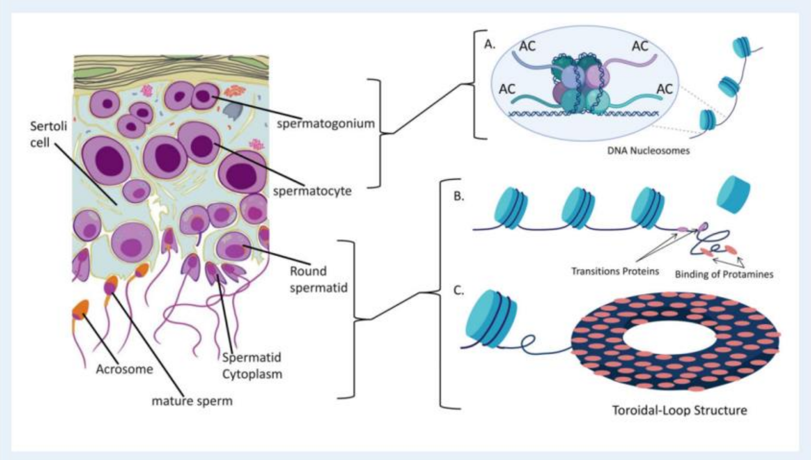
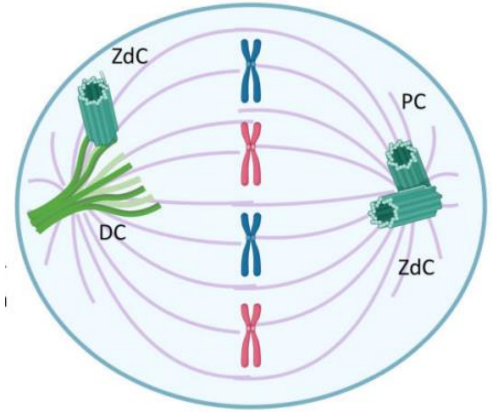
Contribuição do SÊMEN na fertilização e divisão embrionária

- *Plasma seminal - vesículas extracelulares:* epididimossomos e prostatossomos, com influência na gametogênese, fertilização, embriogênese e receptividade endometrial

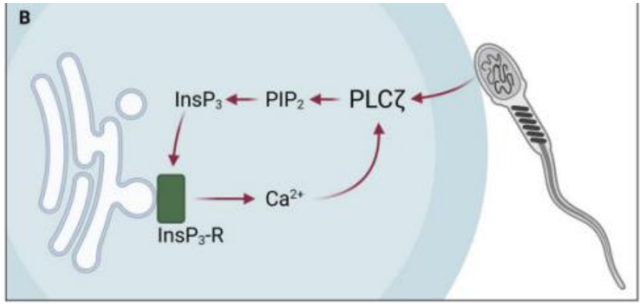


- *Espermatogênese:* material genético e influência epigenética (histonas/protaminas)

- *Centríolos*: divisão embrionária



- *Fertilização:* PLC zeta



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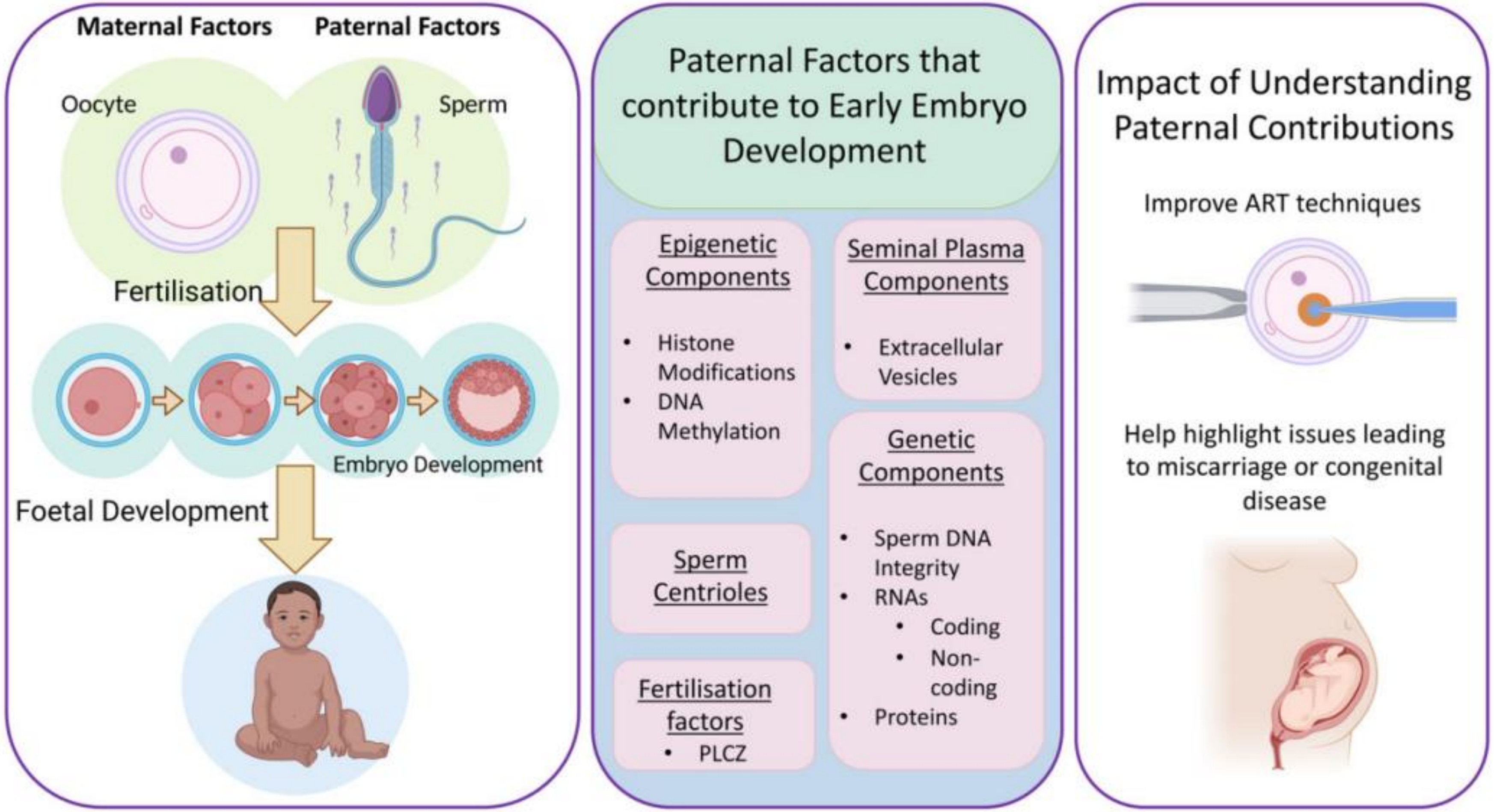
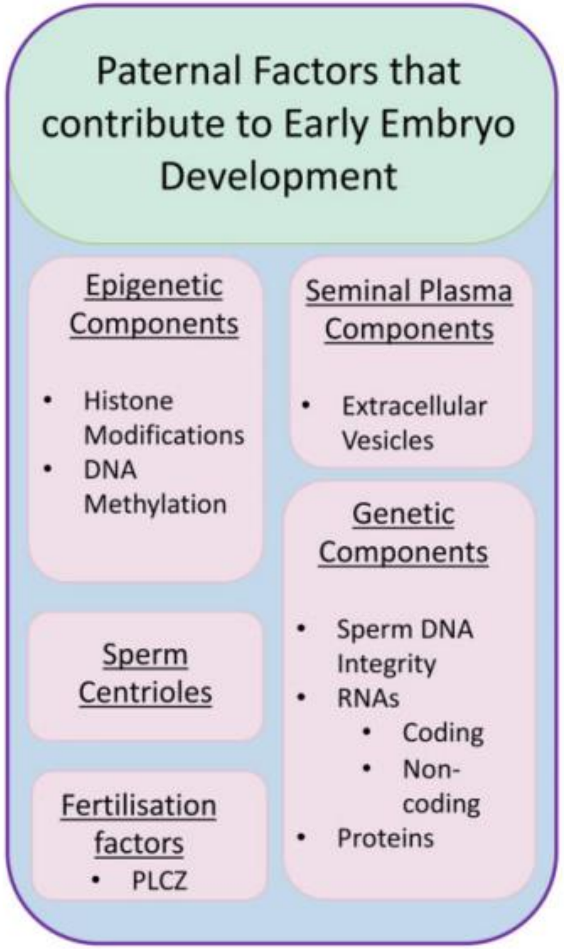


Human Reproduction Update, Vol.29, No.4, pp. 395–433, 2023

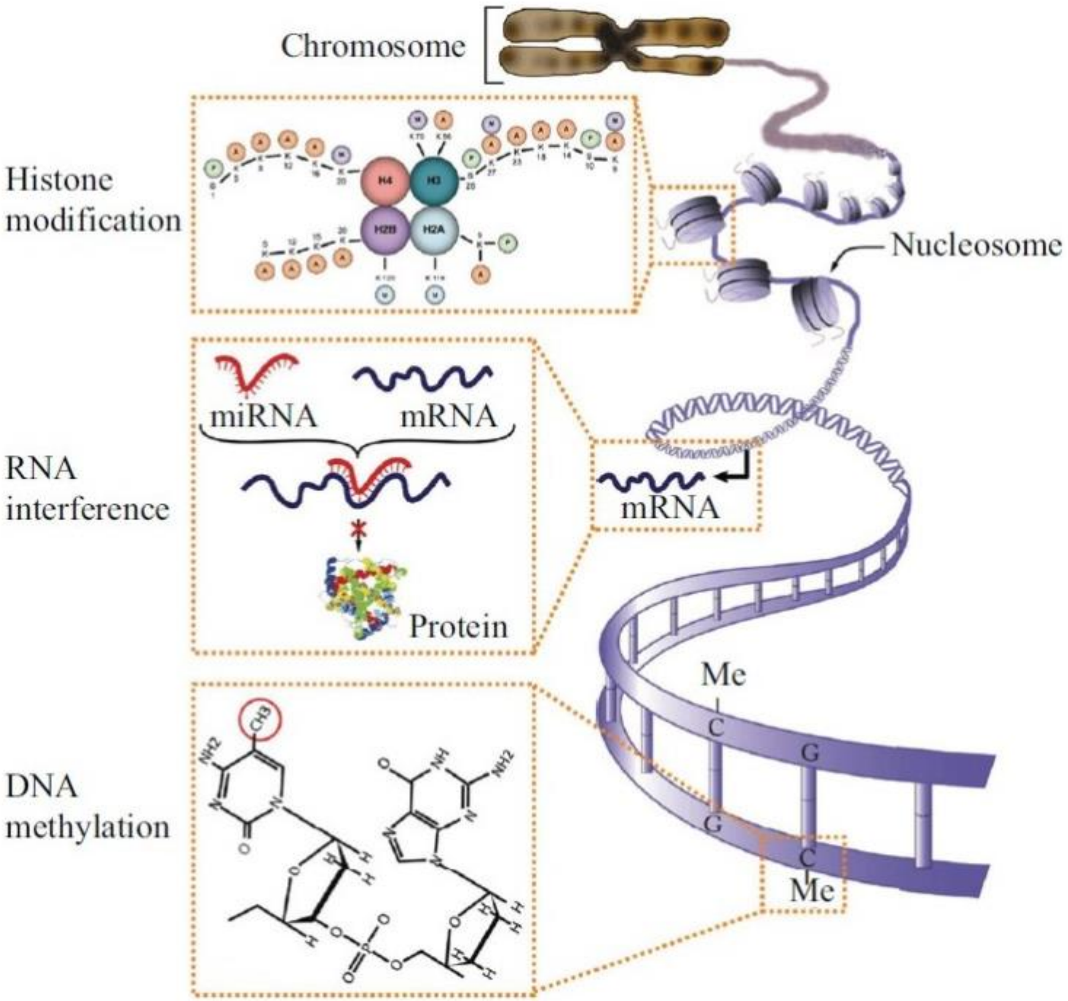


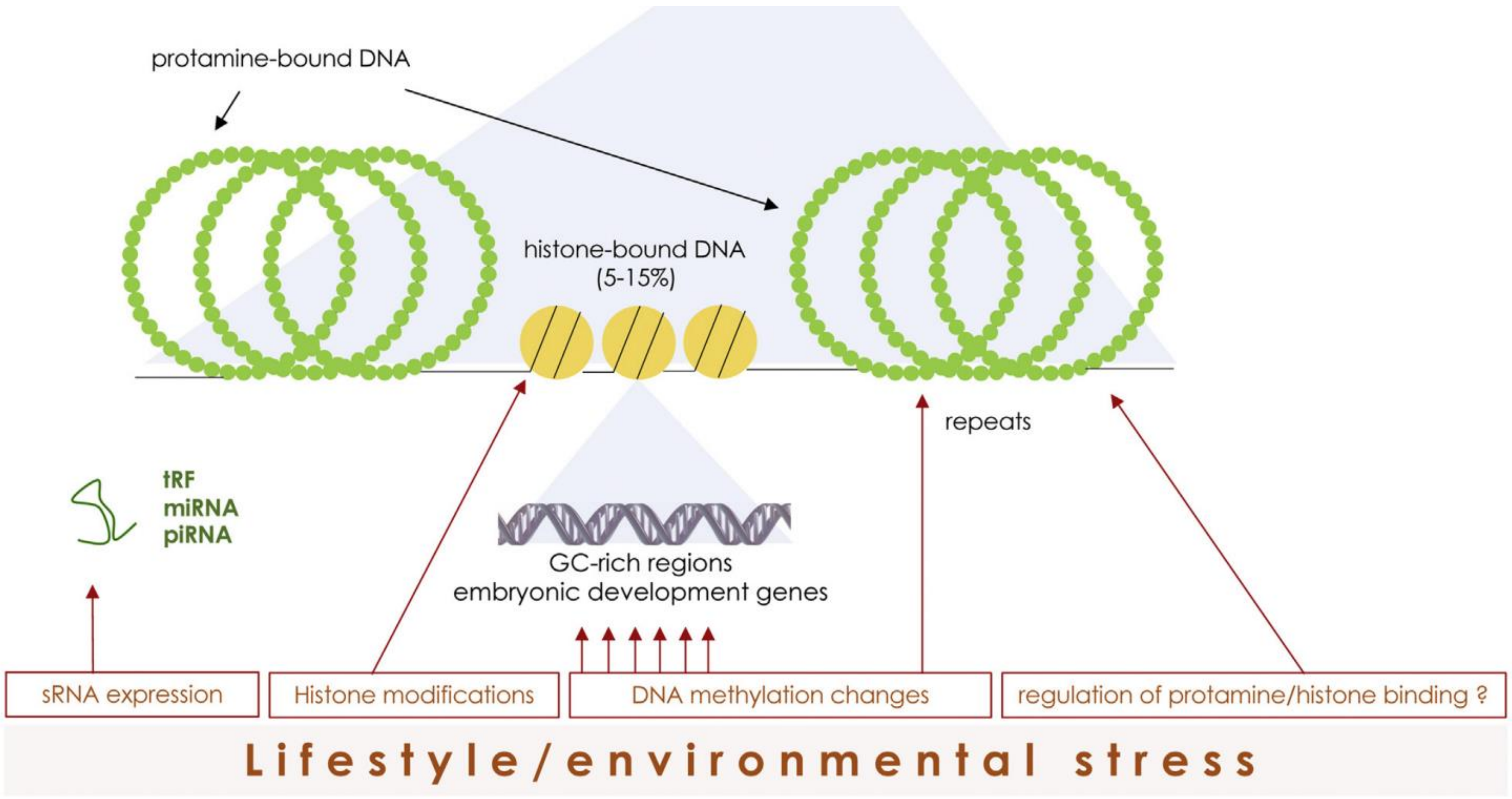
Human Reproduction Update, Vol.29, No.4, pp. 395–433, 2023

EPIGENÉTICA

A epigenética refere-se ao processo de regulação gênica sem alterações na sequência do DNA e inclui:

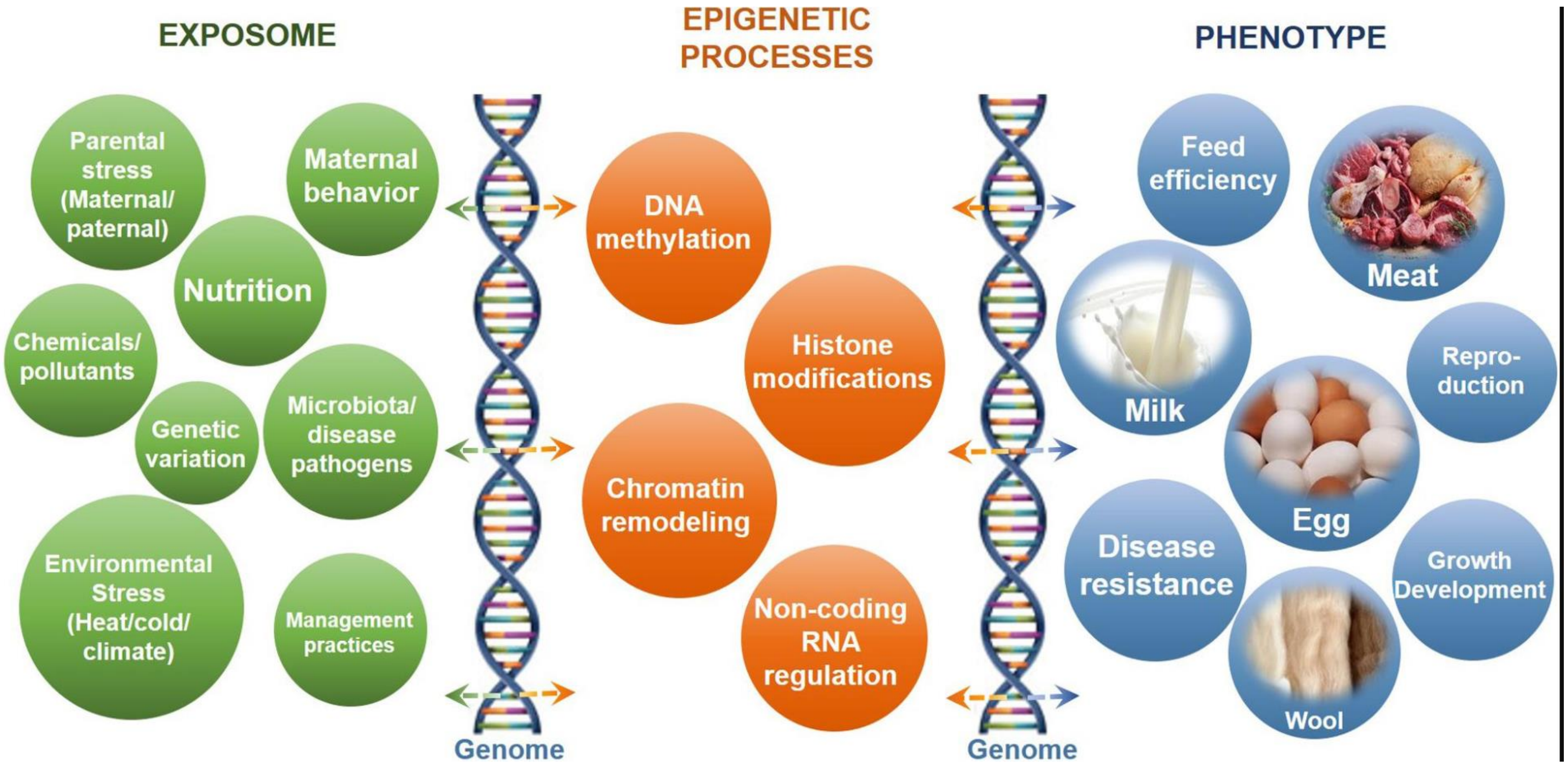
- ❑ DNA methylation
- ❑ Posttranslational histone modifications
- ❑ MicroRNA (miRNA) regulation



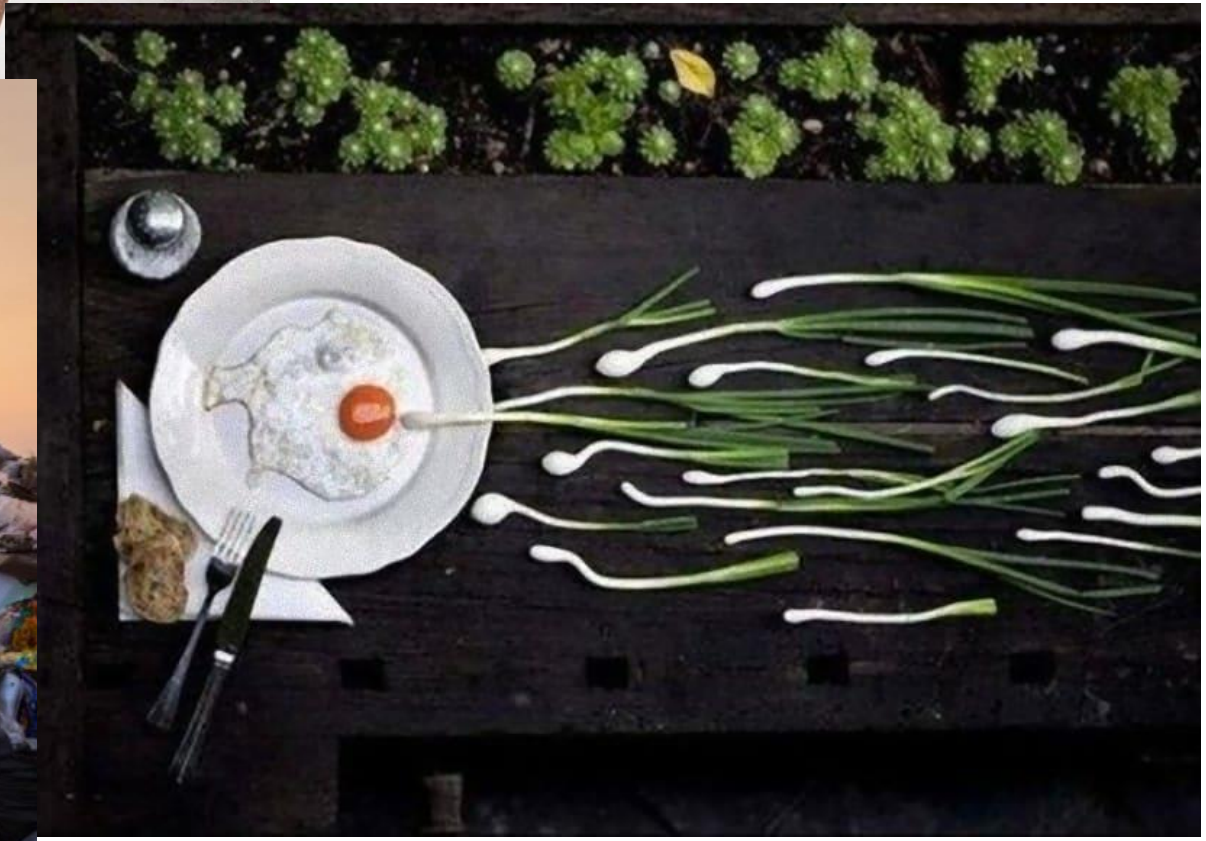


Existem fortes evidências *de fatores epigenéticos causados pelo ambiente e transmitidos pelos espermatozoides*, capazes de *alterar o fenótipo da próxima geração*

MOLECULAR METABOLISM 14 (2018) 1e11
https://doi.org/10.1016/j.molmet.2018.02.006


EXPOSOME
EPIGENETIC PROCESSES
PHENOTYPE
Parental stress (Maternal/ paternal)
Maternal behavior
Nutrition
Chemicals/ pollutants
Genetic variation
Microbiota/ disease pathogens
Environmental Stress (Heat/cold/ climate)
Management practices
Genome
DNA methylation
Histone modifications
Chromatin remodeling
Non-coding RNA regulation
Genome
Feed efficiency
Meat
Milk
Repro- duction
Egg
Disease resistance
Growth Development
Wool





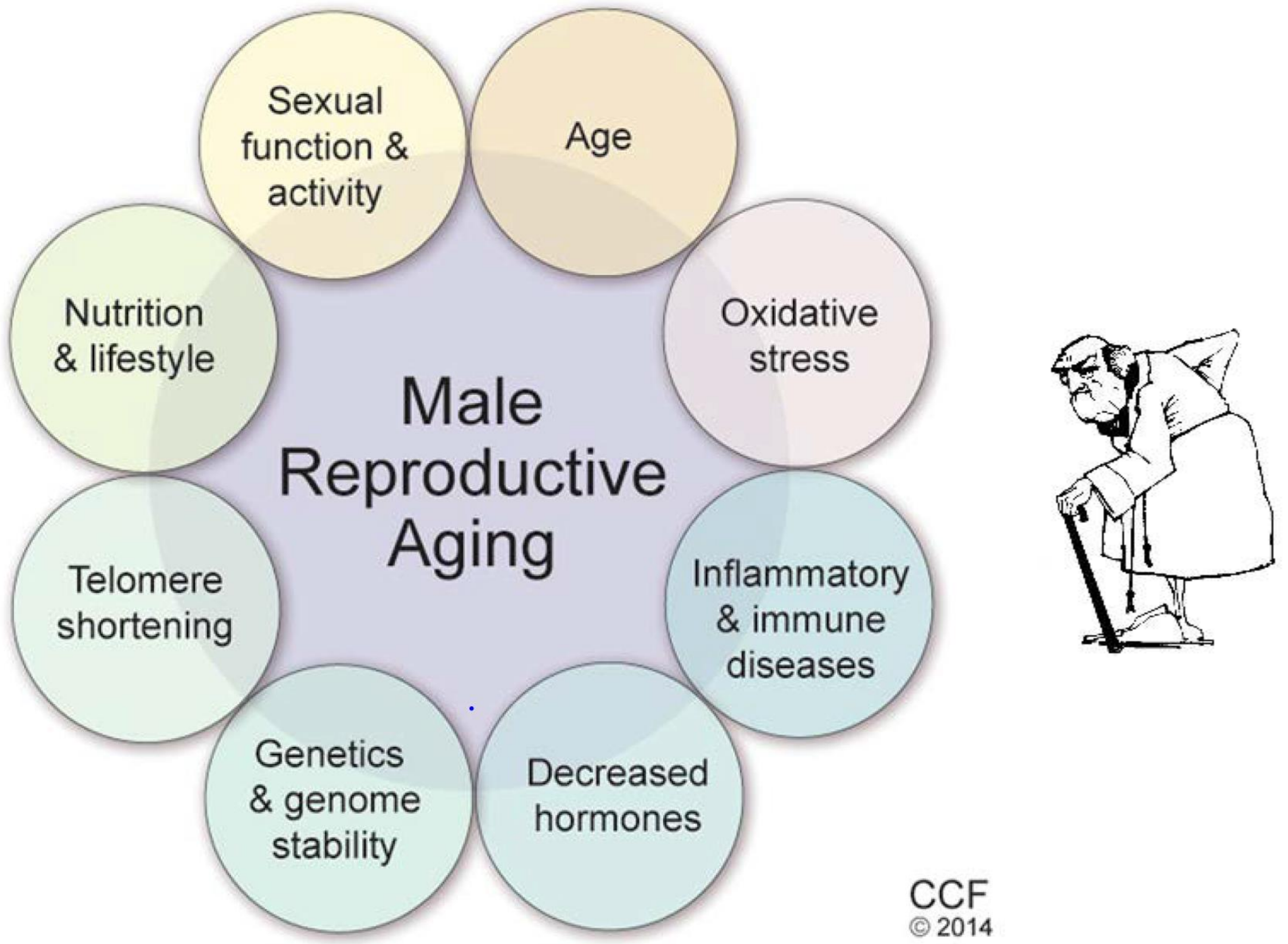
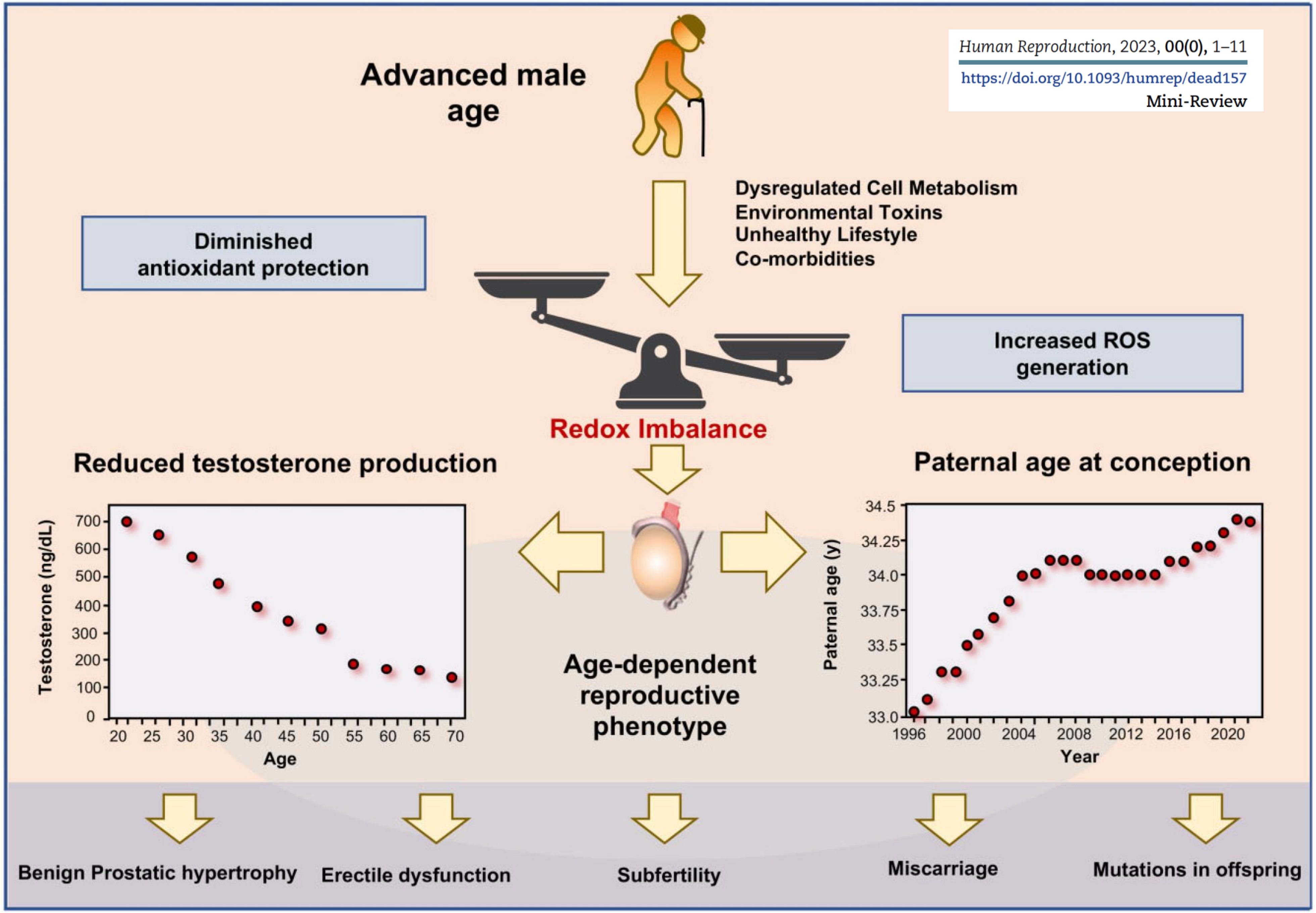


Figure 1 Main factors involved in impaired male infertility due to reproductive aging.

Sharma *et al. Reproductive Biology and Endocrinology* (2015) 13:35
DOI 10.1186/s12958-015-0028-x


Human Reproduction, 2023, 00(0), 1–11
https://doi.org/10.1093/humrep/dead157
Mini-Review
Advanced male age
Dysregulated Cell Metabolism
Environmental Toxins
Unhealthy Lifestyle
Co-morbidities
Diminished antioxidant protection
Increased ROS generation
Redox Imbalance
Reduced testosterone production
Testosterone (ng/dL)
Age
Paternal age at conception
Paternal age (y)
Year
Age-dependent reproductive phenotype
Benign Prostatic hypertrophy
Erectile dysfunction
Subfertility
Miscarriage
Mutations in offspring

Human Reproduction Update, Vol.24, No.3 pp. 320–389, 2018
Advanced Access publication on February 15, 2018 doi:10.1093/humupd/dmy005

human reproduction update

The effect of paternal factors on perinatal and paediatric outcomes: a systematic review and meta-analysis

Nan B. Oldereid[1,*], Ulla-Britt Wennerholm[2], Anja Pinborg[3], Anne Loft[4], Hannele Laivuori[5,6,7,8], Max Petzold[9], Liv Bente Romundstad[10,11], Viveca Söderström-Anttila[12], and Christina Bergh[13]

[1]Livio IVF-klinikken Oslo, Sørkedalsveien 10A, 0369 Oslo, Norway [2]Department of Obstetrics and Gynaecology, Institute of Clinical Sciences, Sahlgrenska Academy, Gothenburg University, Sahlgrenska University Hospital East, SE 416 85 Gothenburg, Sweden [3]Department of Obstetrics and Gynecology, Hvidovre Hospital, Institute of Clinical Medicine, Copenhagen University Hospital, Copenhagen, Denmark [4]Fertility Clinic, Section 4071, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, DK–2100 Copenhagen, Denmark [5]Department of Obstetrics and Gynecology, Tampere University Hospital, Teiskontie 35, FI-33521 Tampere, Finland [6]Faculty of Medicine and Life Sciences, University of Tampere, Arvo Ylpön katu 34, FI-33520 Tampere, Finland [7]Medical and Clinical Genetics, University of Helsinki and Helsinki University Hospital, Haartmaninkatu 8, FI-00290 Helsinki, Finland [8]Institute for Molecular Medicine Finland, Helsinki Institute of Life Science, University of Helsinki, Tukhomankatu 8, FI-00290 Helsinki, Finland [9]Swedish National Data Service and Health Metrics Unit, University of Gothenburg, 405 30 Gothenburg, Sweden [10]Spiren Fertility Clinic, Norwegian University of Science and Technology, Trondheim NO-7010, Norway [11]Department of Public Health, Norwegian University of Science and Technology, Trondheim, Norway [12]Mehiläinen Felicitas, Mannerheimintie 20A, 00100 Helsinki, Finland [13]Department of Obstetrics and Gynaecology, Institute of Clinical Sciences, Sahlgrenska Academy, Gothenburg University, Reproductive Medicine, Sahlgrenska University Hospital, SE-413 45 Gothenburg, Sweden

- **14.371 artigos, 238 incluídos, 81 para a meta-análise**
- **Idade, estilo de vida, peso, altura, gordura corporal, cigarro**

Human Reproduction Update, Vol.24, No.3 pp. 320–389, 2018
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human reproduction update

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Table XI Summary results of the meta-analyses of the association between paternal factors and perinatal and paediatric outcomes.

Exposure	Outcome	Pooled estimate (with 95% CI)	Certainty of evidence GRADE
Paternal age	PTB	1.02 (1.00–1.05)	⊕⊕○○
	Low BW	1.00 (0.97–1.03)	⊕⊕○○
	Stillbirth	1.19 (1.10–1.30)	⊕⊕○○
	Children with any birth defects	1.05 (1.02–1.07)	⊕⊕⊕○
	CHDs	1.03 (0.99–1.06)	⊕⊕⊕○
	Orofacial clefts	0.99 (0.95–1.04)	⊕⊕○○
		1.14 (1.02–1.29)*	
	Gastroschisis	0.88 (0.78–1.00)	⊕⊕⊕○
	Spina bifida	0.97 (0.90–1.04)	⊕⊕⊕○
	Trisomy 21	1.13 (1.05–1.23)	⊕⊕⊕○
	Acute lymphoblastic leukaemia	1.08 (0.96–1.21)	⊕⊕⊕○
	Autism and ASDs	1.25 (1.20–1.30)	⊕⊕⊕○
	Schizophrenia	1.31 (1.23–1.38)	⊕⊕⊕○
Paternal BMI	No meta-analysis		
Paternal smoking	PTB	1.16 (1.00–1.35)	⊕⊕○○
	Low BW	1.10 (1.00–1.21)	⊕⊕○○
	SGA	1.22 (1.03–1.44)	⊕⊕○○
	CHDs	1.75 (1.25–2.44)	⊕⊕○○
	Orofacial clefts	1.51 (1.16–1.97)	⊕⊕○○
	Brain tumours	1.12 (1.03–1.22)	⊕⊕○○

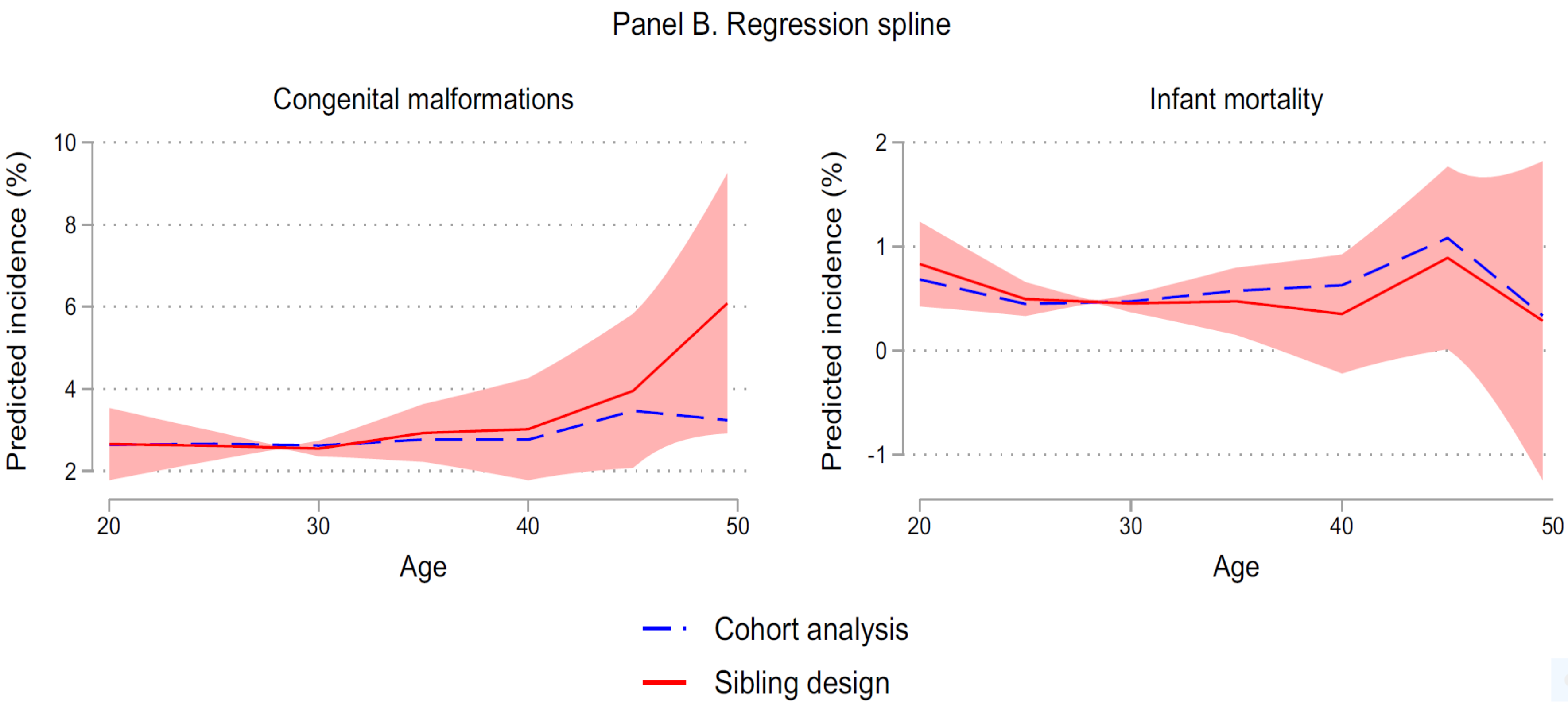
*Exposure: Paternal age >45 years.

European Journal of Epidemiology (2021) 36:849–860
https://doi.org/10.1007/s10654-021-00734-8

REPRODUCTIVE EPIDEMIOLOGY

Parental age and birth defects: a sibling study

Hans K. Hvide[1,2,3] · Julian Johnsen[4] · Kjell G. Salvanes[2,5,6,7,8]



FERTGROUP | FERTILITY

Age-related alterations in the genetics and genomics of the male germ line

Amin S. Herati, M.D.,[a,b] Boryana H. Zhelyazkova, B.A.,[c] Peter R. Butler, B.A.,[a,b] and Dolores J. Lamb, Ph.D.[a,b,c]

Fertility and Sterility® Vol. 107, No. 2, February 2017

Offspring genetic conditions associated with advanced paternal age.

Condition	Paternal age (y)	Relative risk	Population risk	Adjusted risk
Achondroplasia	>50	7.8	1/15,000	1/1,923
Apert syndrome	>50	9.5	1/50,000	1/5,263
Pfeiffer syndrome	>50	6	1/100,000	1/16,666
Crouzon syndrome	>50	8	1/50,000	1/6,250
Neurofibromatosis I	>50	3.7	1/3,000–1/4,000	[illegible]
Retinoblastoma	>45	3	1/15,000–1/20,000	[illegible]
Down syndrome	40–44	1.37	1/1,200[a]	1/876[a]
Epilepsy	40–45	1.3	1/100	1/77.0
Breast cancer	>40	1.6	1/8.5	1/5.3
Childhood leukemia	>40	1.14	1/25,000	1/21,930
Childhood central nervous system tumor	>40	1.69	1/36,000	1/21,302

[a] Maternal age 20–29 years.

Note: Adapted with permission from Ramasamy et al. (10).
[a] Maternal age 20–29 years.

Herati. Paternal aging and the male germ line. Fertil Steril 2017.

FERTGROUP | FERTILITY

Influence of paternal age on assisted reproductive technology cycles and perinatal outcomes

Audrey M. Marsidi, M.D.,[a] Lauren M. Kipling, M.P.H.,[b] Jennifer F. Kawwass, M.D.,[a] and Akanksha Mehta, M.D.[c]

[a] Division of Reproductive Endocrinology and Infertility, Department of Gynecology and Obstetrics, Emory Reproductive Center, Atlanta, Georgia; [b] Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, Georgia; and [c] Department of Urology, Emory University School of Medicine, Atlanta, Georgia

Fertil Steril 2021;116:380-7

- 77,209 fresh nondonor cycles
- Compared with paternal age $\leq$ 45 years, paternal age $\geq$ 46 years was associated with:
  - **a lower likelihood of pregnancy per cycle** (adjusted risk ratio [aRR] 0.81; 95% confidence interval [CI] 0.76–0.87) **and per transfer** (aRR 0.85; 95% CI 0.81–0.90);
  - **a lower likelihood of live birth per cycle** (aRR 0.76; 95% CI 0.72–0.84) **and per transfer** (aRR 0.82; 95% CI 0.77–0.88),
    (after controlling for maternal age and other confounders).

Received: 6 September 2019 | Revised: 19 November 2019 | Accepted: 19 November 2019
DOI: 10.1111/andr.12737

ORIGINAL ARTICLE

ANDROLOGY WILEY

Increasing paternal age and ejaculatory abstinence length negatively influence the intracytoplasmic sperm injection outcomes from egg-sharing donation cycles

Amanda S. Setti[1,2] | Daniela Paes Almeida Ferreira Braga[1,2] | Assumpto Iaconelli Junior[1,2] | Edson Borges Junior[1,2]

Paternal variable	Fertilization (%)	D3 high-quality embryos (%)	D3 normal embryo development (%)	Blastocyst development (%)	High-quality blastocysts (%)	Implantation (%)	Pregnancy chance	Miscarriage chance	Live birth chance
Age									
B	−0.276	−0.040	−2.750	−0.070	−44.058	−0.060	Exp(B) 0.664	Exp(B) 1.019	Exp(B) 0.812
SE	0.085	0.017	0.8625	0.035	20.248	0.007	0.187	0.052	0.100
CI	−0.44 to −0.11	−0.07 to −0.01	−4.44 to −1.06	−0.14 to −0.002	−84.07 to −4.05	−0.08 to −0.05	0.457 to 0.967	0.918 to 1.131	0.665 to 0.991
P	.001	.021	.001	.043	.031	<.001	.033	.718	.041
EA									
B	−0.083	−0.003	−0.300	−0.589	13.8125	−0.012	Exp(B) 0.051	Exp(B) 0.861	Exp(B) 0.169
SE	0.847	0.015	0.014	0.243	88.143	0.003	1.803	0.190	1.195
CI	−0.44 to −0.11	−0.01 to −0.001	−0.06 to −0.02	−1.07 to −0.11	−160.34 to 187.97	−0.20 to −0.35	0.001 to 1.870	0.589 to 1.258	0.015 to 1.851
P	.765	.028	.036	.016	.876	<.001	.103	.435	.142

FERTGROUP | FERTILITY

Received: 31 March 2021 | Revised: 29 July 2021 | Accepted: 30 July 2021

DOI: 10.1111/and.14211

ORIGINAL ARTICLE

First International Journal of Andrology
ANDROLOGIA WILEY

Early and late paternal contribution to cell division of embryos in a time-lapse imaging incubation system

Amanda Souza Setti[1,2] | Daniela Paes de Almeida Ferreira Braga[1,2] | Livia Vingris[3] | Assumpto Iaconelli Jr.[2,4] | Edson Borges Jr.[2,4]

FERTGROUP | FERTILITY

RESULTS

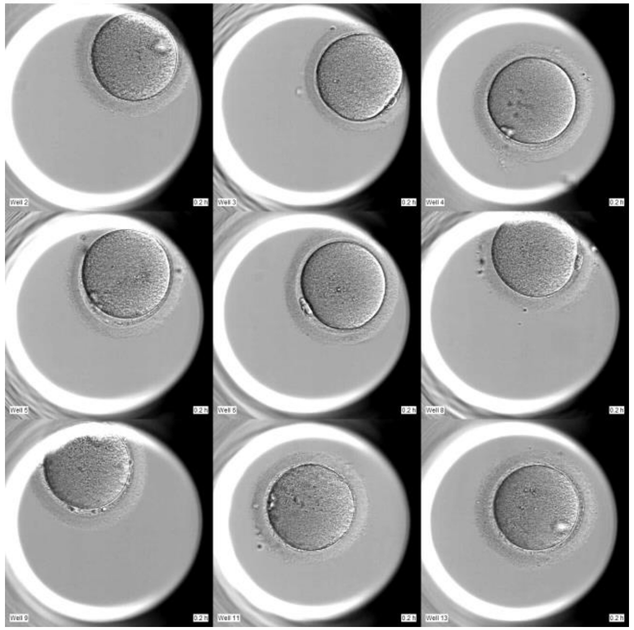
Paternal age

t2	B: 0.043, CI: 0.006 – 0.081, p: 0.043
t3	B: 0.056, CI: 0.001 – 0.110, p: 0.044
t4	B: 0.066, CI: 0.014 – 0.118, p: 0.012
t6	B: 0.080, CI: -0.002 – 0.163, p: 0.046
tB	B: 0.195, CI: 0.003 – 0.387, p: 0.046
MN	Exp(B): 1.027, CI: 1.043 – 1.203, p: 0.004
ACP	Exp(B): 1.116, CI: 1.034 – 1.205, p: 0.005
IR	B: -1.933, CI: -2.426 – -1.441, p<0.001
CP	Exp(B): 0.899, CI: 0.860 – 0.940, p<0.001

First International Journal of Andrology
ANDROLOGIA

Early and late paternal contribution to cell division of embryos in a time-lapse imaging incubation system

FERTILITY MEDICAL GROUP



FERTGROUP | FERTILITY

Received: 14 February 2022 | Revised: 20 April 2022 | Accepted: 9 May 2022

DOI: 10.1111/and.14485

ORIGINAL ARTICLE

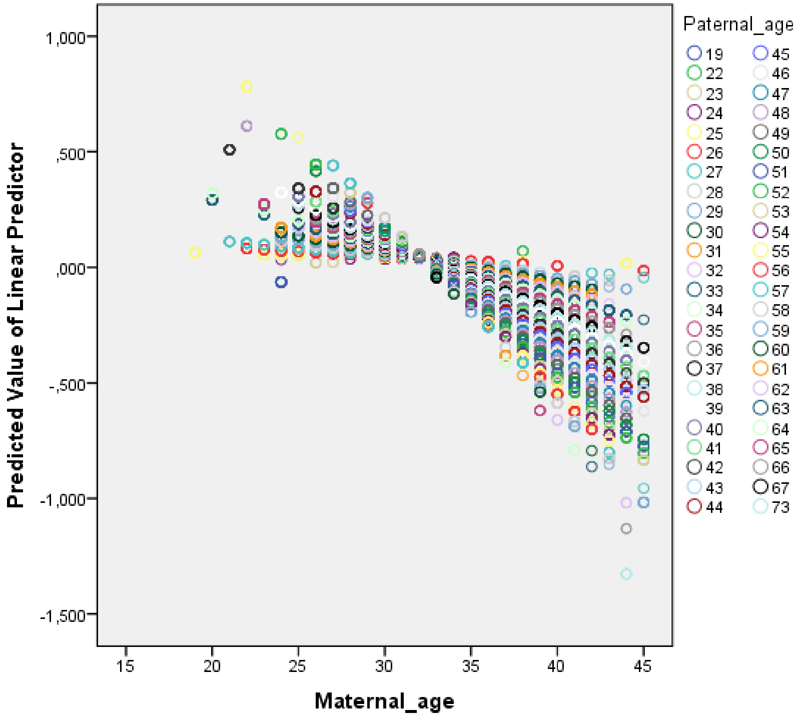
ANDROLOGIA WILEY

Paternal ageing impacts blastulation and the outcomes of pregnancy at different levels of maternal age: A clustering analysis of 21,960 oocytes and 3837 ICSI cycles

Amanda Souza Setti[1,2] | Daniela Paes de Almeida Ferreira Braga[1,2] | Patricia Guilherme[1] | Livia Vingris[1] | Assumpto Iaconelli Jr[1,2] | Edson Borges Jr[1,2]

Predective value of the interation term

Dependent variable	B	OR	CI	p-value
Blastocyst development	- 0.005	0.995	0.994 – 0.996	< 0.001



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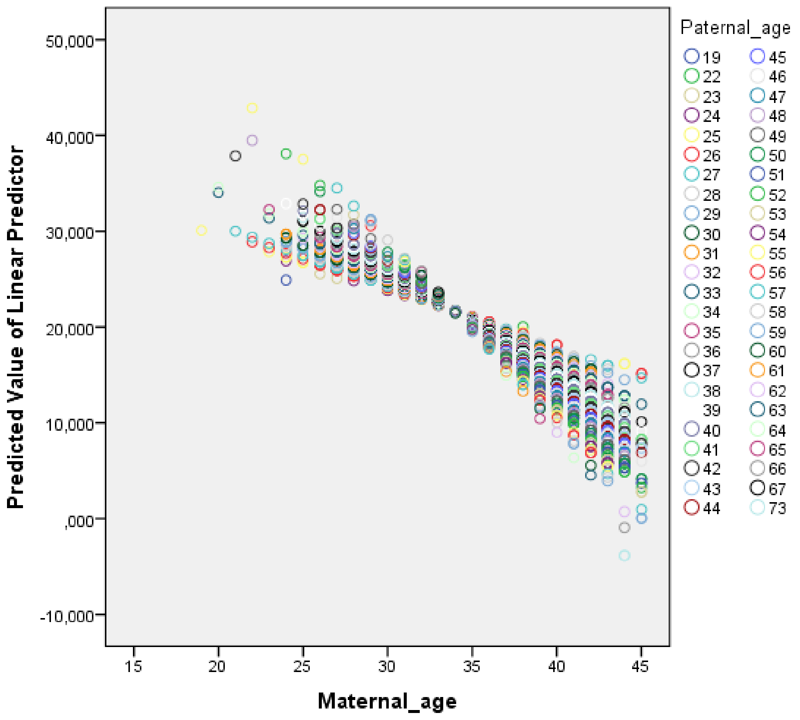
Andrologia. 2022;e14485.
https://doi.org/10.1111/and.14485

Predective value of the interation term

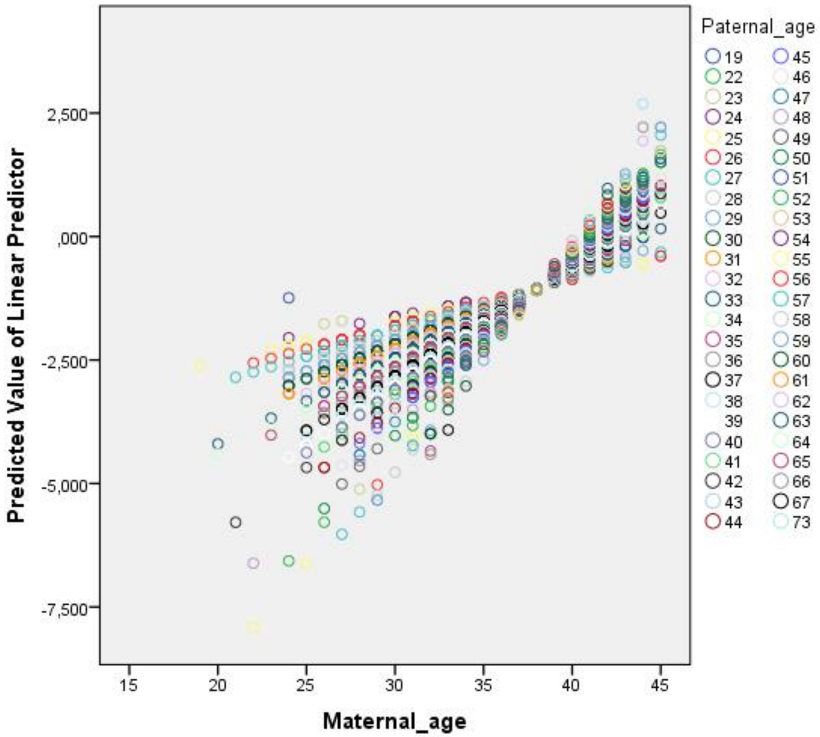
Dependent variable	B	OR	CI	p-value
Implantation rate	- 0.041	0.960	0.947 – 0.973	< 0.001



Andrologia. 2022;e14485.
https://doi.org/10.1111/and.14485

Predective value of the interation term

Dependent variable	B	OR	CI	p-value
Miscarriage rate	0.011	1.012	1.005 – 1.018	0.001



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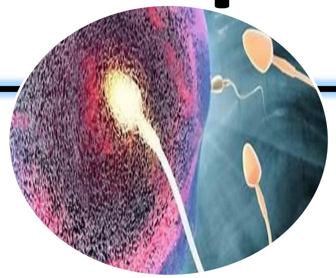
Andrologia. 2022;e14485.
https://doi.org/10.1111/and.14485

For every ***1-year increase in paternal age***, the odds ratio of live-birth reduces by:

- **1%** in females aged 37 years,
- **1.6%** in those aged 38 years,
- **2.4%** in 39-year-old females,
- **5%** in 42-year-old females and so on.

Misleading concept



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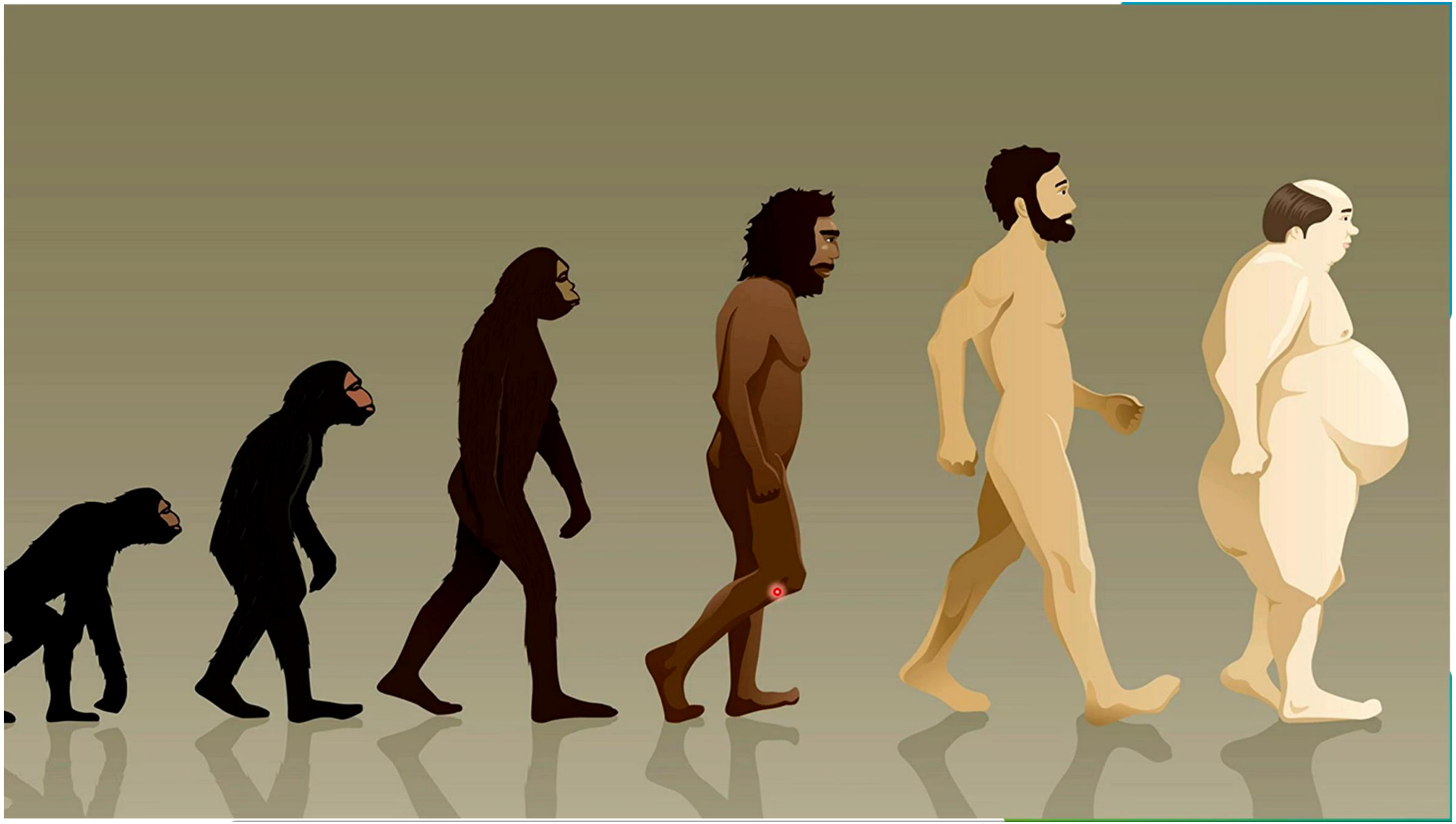
Andrologia. 2022;e14485.
https://doi.org/10.1111/and.14485



European Society of Human Reproduction and Embryology

Influence of Diet and Exercise on Sperm and its Epigenome

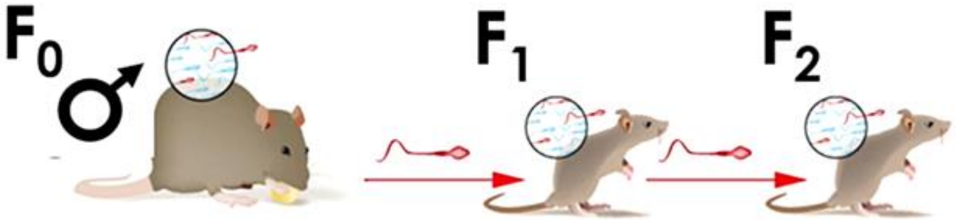
ESHRE Annual Conference 2023, Copenhagen

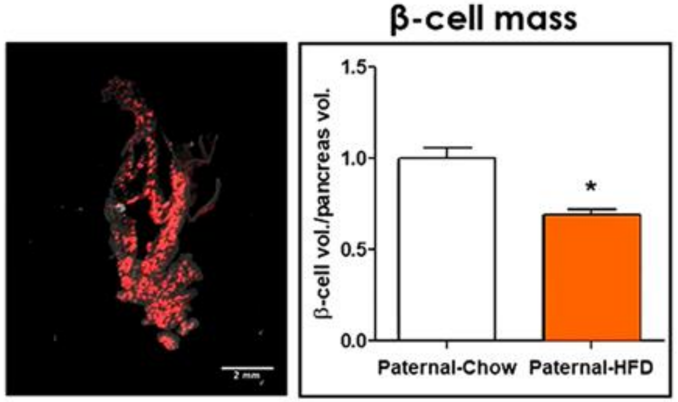
Prof. Romain Barrès

Center for Basic Metabolic Research (CBMR)
University of Copenhagen

Institut de Pharmacologie Moléculaire et Cellulaire
Université Côte d'Azur

Western style diet before conception is associated with epigenetic changes in sperm and an altered metabolic phenotype in the offspring

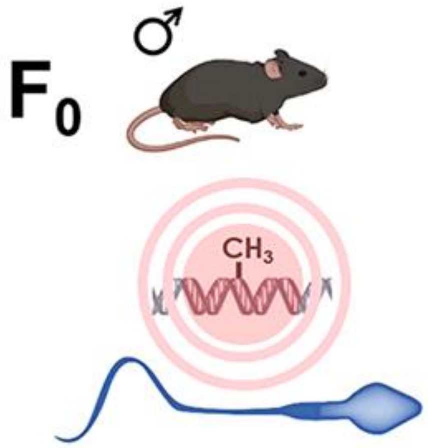


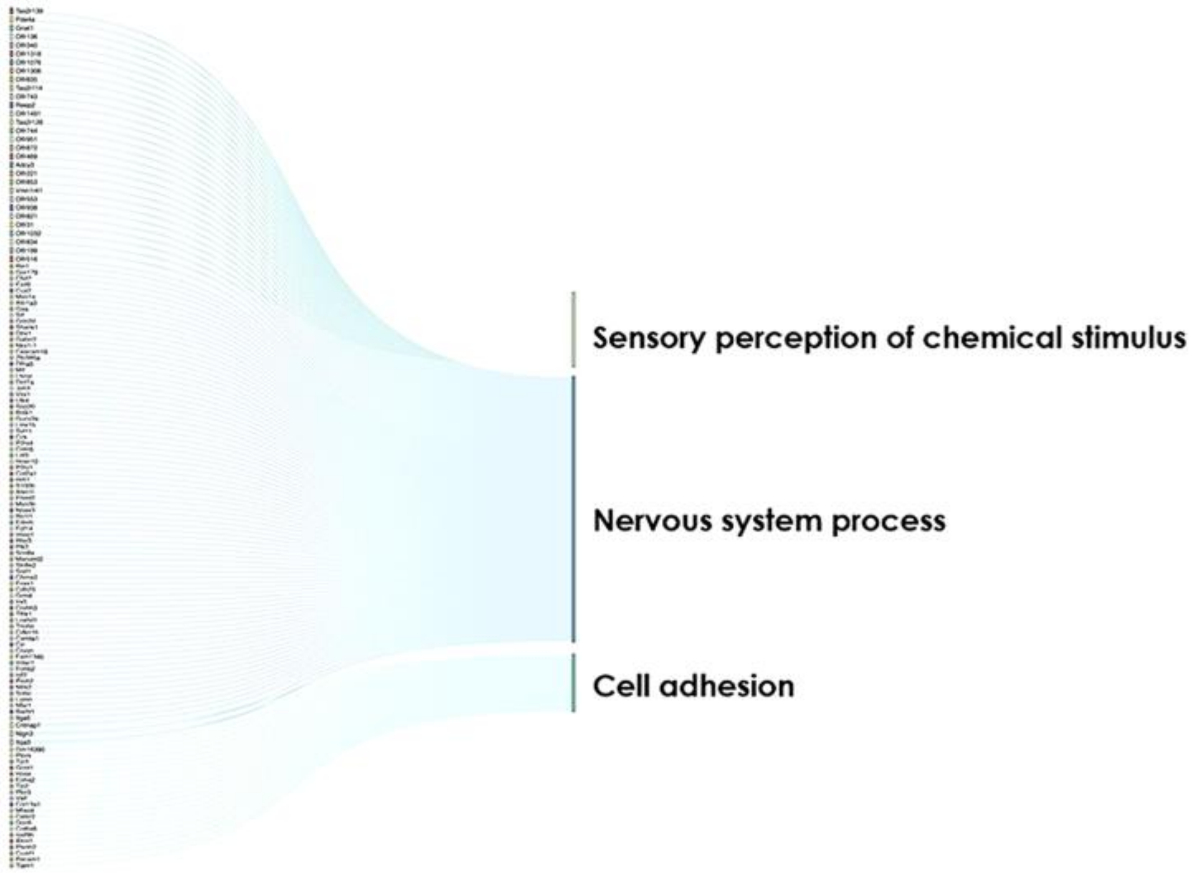


Ng […], Barrès, […], and Morris, ***Nature***, 2010.
De Castro Barbosa […] and Barrès, ***Molecular Metabolism***, 2015.

FERTGROUP | FERTILITY

Low protein diet remodels the DNA methylation profile of spermatozoa





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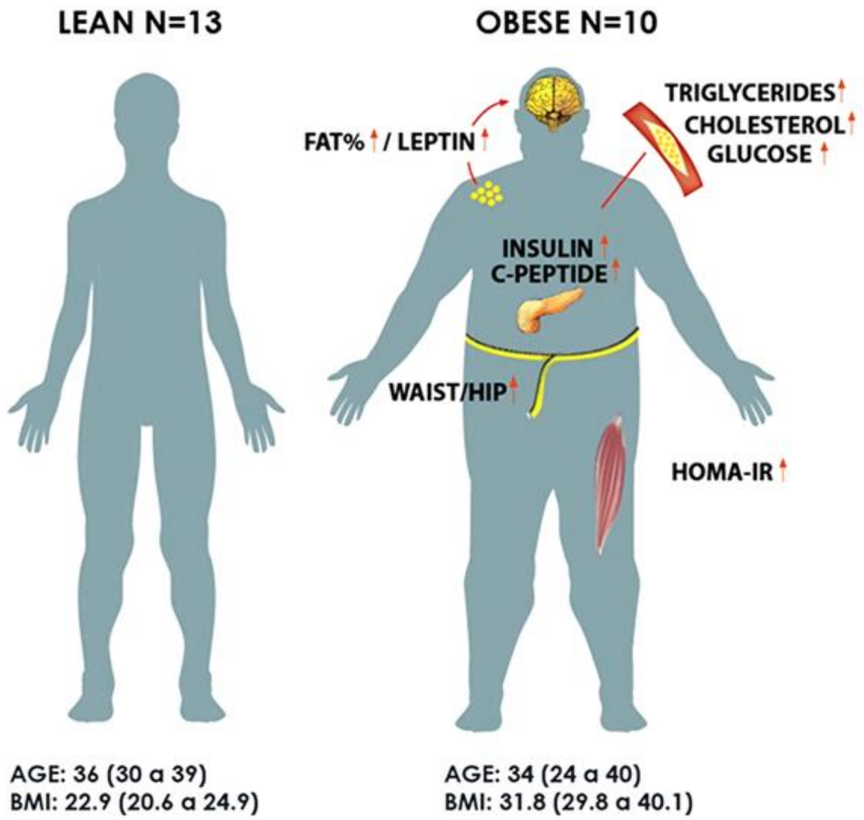
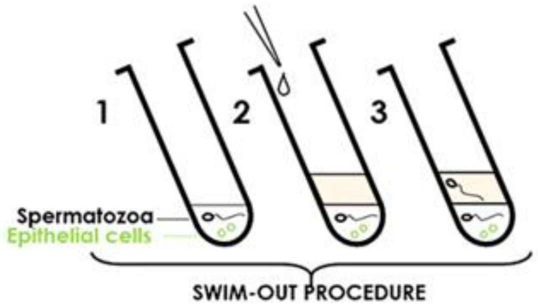
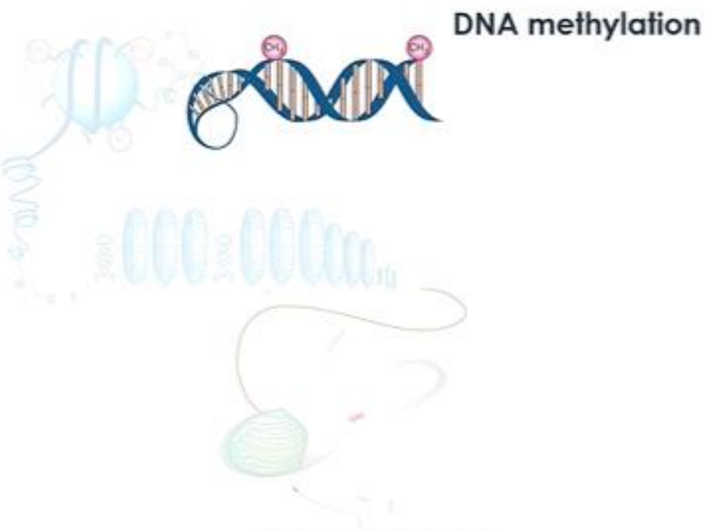
EPIGENETIC PROFILING OF SPERMATOZOA







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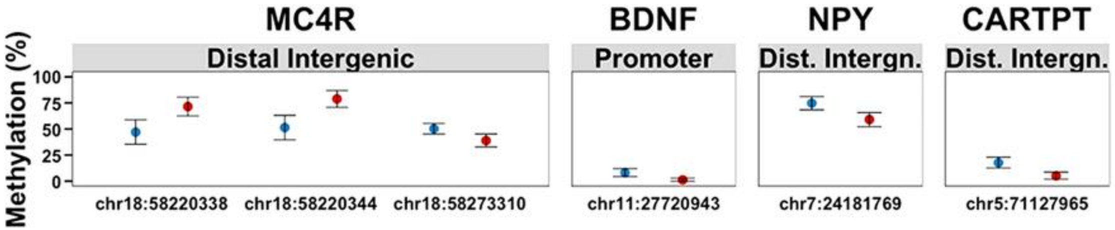
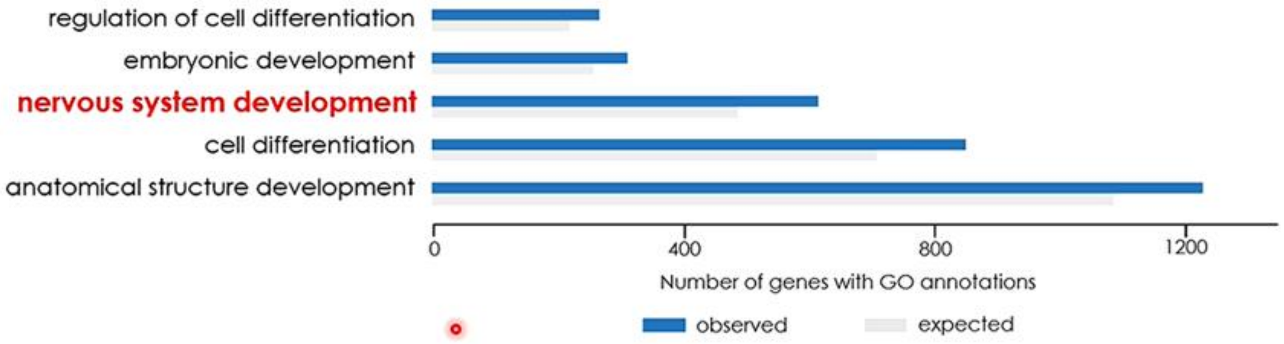
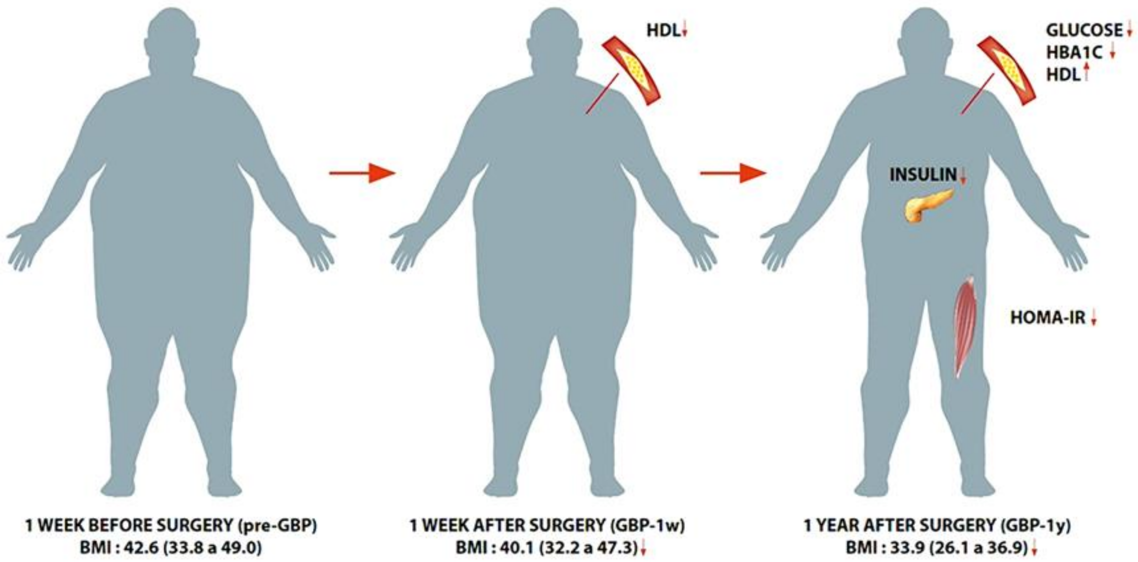


Methylation gens:

- **Brain function**
- **Central regulation of appetite**

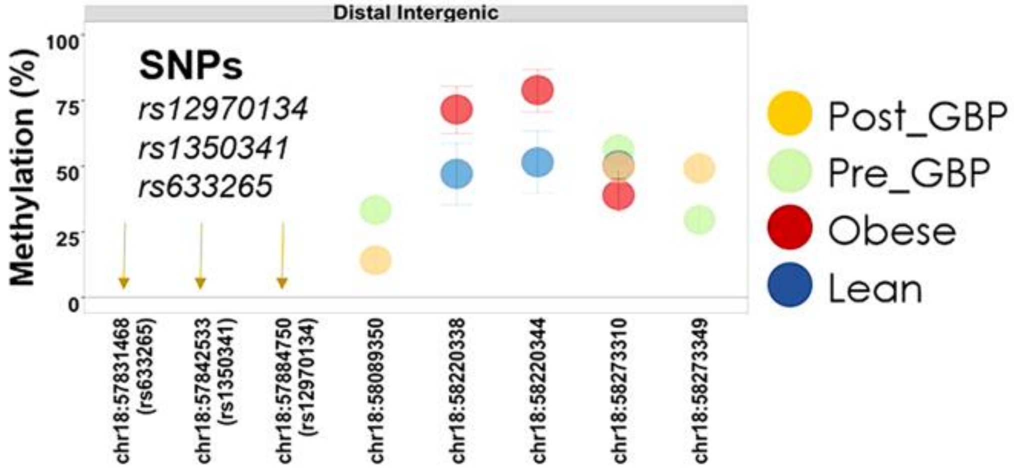


Donkin and Versteyhe, […] and Barrès. ***Cell Metabolism***, 2016.



Sperm DNA metylation response

MC4R



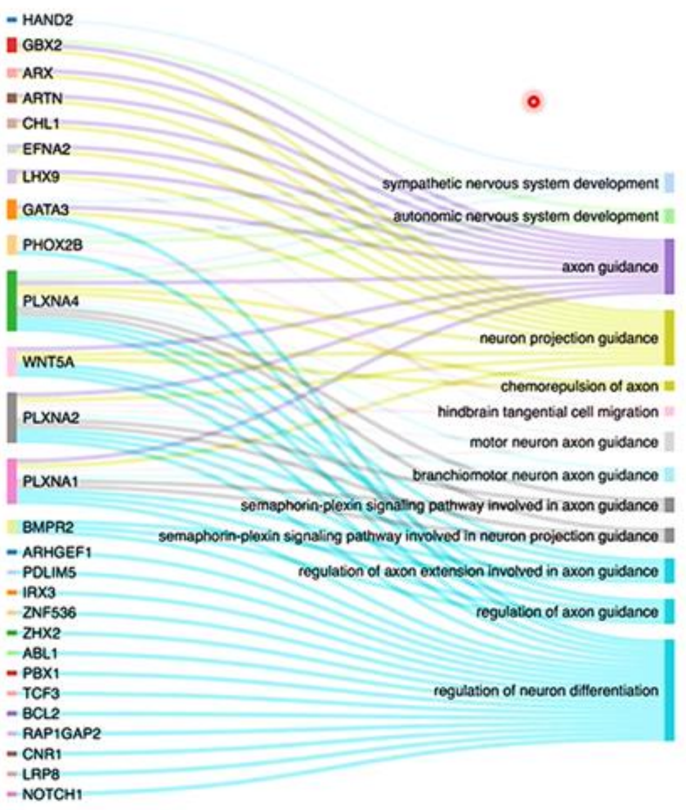
Metylation response: environment can change the epigenome sperm in the same individual

FERTGROUP | FERTILITY

Donkin and Versteyhe, [...] and Barrès. ***Cell Metabolism***, 2016.

DNA methylation variation after exercise training affects brain development genes

Trained | **Detrained**



Ingerslev and Donkin, […] and Barrès. **Clinical Epigenetics**, 2018.

- **Environmental factors that lead to epigenetic variation**
- **Gens related to the brain: hotspots of genetic variation**

Genes related to neurogenesis expressed in the brain and CNS are more susceptible to epigenetic variation

Paternal sperm DNA methylation associated with early signs of autism risk in an autism-enriched cohort

Jason I Feinberg,[1,2] Kelly M Bakulski,[1,2,3] Andrew E Jaffe,[4,11] Rakel Tryggvadottir,[2] Shannon C Brown,[1,3] Lynn R Goldman,[5,6] Lisa A Croen,[7] Irva Hertz-Picciotto,[8] Craig J Newschaffer,[9,10] M Daniele Fallin[1,11,*] and Andrew P Feinberg[2,12,*]

Int J Epidemiol. 2015

The epigenetic signature of these fathers (DNA metylation) was striking overlap between those with gastric bypass an obese individuals.

Feinberg et al., **Int J Epidemiol**, 2015.

OBESITY

Paternal obesity—a risk factor for autism?

Susan K. Murphy

The aetiology of autism-spectrum disorders is partly explained by genetic factors, but a substantial component is attributed to environmental exposures. New evidence suggests that paternal obesity increases the risk of having a child with autism, which raises the possibility that obesity-driven, autism-related shifts in epigenetic reprogramming occur during spermatogenesis.

Murphy, S. K. *Nat. Rev. Endocrinol.* **10**, 389–390 (2014); published online 3 June 2014;
doi:10.1038/nrendo.2014.81

"**Paternal obesity** was associated with a **73% increased risk** (OR 1.73, 95% CI 1.07–2.82) of having a child diagnosed with autism, compared with the risk of autism in children of **non obese fathers** (BMI ≤25 kg/m2)."

Strongest form of autism!!

Murphy, **Nat Rev Endocrinol**, 2014

Garrido et al. Clin Epigenet (2021) 13:6
https://doi.org/10.1186/s13148-020-00995-2

Clinical Epigenetics

RESEARCH Open Access

Sperm DNA methylation epimutation biomarker for paternal offspring autism susceptibility

Nicolás Garrido[1], Fabio Cruz[1], Rocio Rivera Egea[1], Carlos Simon[2,3], Ingrid Sadler-Riggleman[4], Daniel Beck[4], Eric Nilsson[4], Millissia Ben Maamar[4] and Michael K. Skinner[4*]

- *Exposições paternas ou dos ancestrais no início da vida que alteram a epigenética da linhagem germinativa*

- *Componente molecular da etiologia do TEA.*

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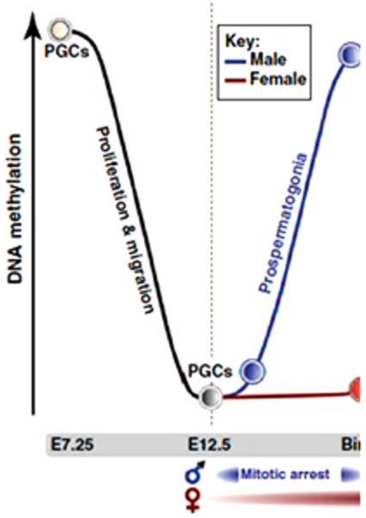
A Unique Gene Regulatory Network Resets the Human Germline Epigenome for Development

Walfred W.C. Tang,[1,2,3,5] Sabine Dietmann,[3,5] Naoko Irie,[1,2,3] Harry G. Leitch,[3] Vasileios I. Floros,[4] Charles R. Bradshaw,[1] Jamie A. Hackett,[1,2,3] Patrick F. Chinnery,[4] and M. Azim Surani[1,2,3,*]



Region escaping reprogramming were related to "[…] genes expressed in brain and participated in neural development. Comparison of the escapee geneswith the NHGRI GWAS catalog revealed characteristic trait and disease associations, such as "obesity-related traits," "schizophrenia," […]"

Tang et al., **Cell**, 2015.

Considerações

- FERTILIDADE = SAÚDE
- INFERTILIDADE relacionada com ... futuro
  - câncer
  - doenças metabólicas, c... lares, autoimunes
  - mortalidade
- Pior prognóstic
- Idade do h... cionada aos desfechos perinatais e a saúde de sua prole
- ... elacionada com mutações epigenéticas do espermatozoide, ... ações das células do cérebro e do SNC

...oblemas futuros???

Male infertility as a window to health

Obrigado!

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