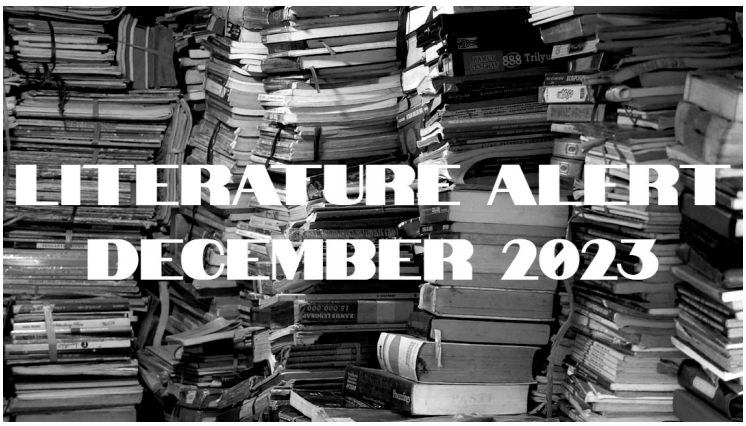


EUROPEAN ACADEMY OF ANDROLOGY

Dear EAA Members,

Your librarian spent some of the holiday break to select the most interesting andrology articles published at the end of 2023. There are also two very interesting books *(scroll to the end)*. The topics include: PDE5 inhibitors and fatherhood, Cushing syndrome, prevalence of male infertility, hypospadias and urogenital cancers, sleep and fecundity, prostate cancer, sperm DNA fragmentation, reproductive education of young men, hypogonadism, infertility-causing mutations, Y-chromosome deletions, radial spokes in sperm, anoikis in Sertoli cells, testicular macrophages, endocrine disrupters, and more.

Clinical andrology and epidemiology

thebmj

Datasets from two large UK biobanks were used to investigate the association of genetically proxied inhibition of phosphodiesterase 5 (PDE5), with fertility and sexual behaviour.

The results provided genetic support for PDE5 inhibition potentially increasing the number of children fathered by male (but not female) individuals. Sustained and robust penile erections are a potential underlying mechanism.

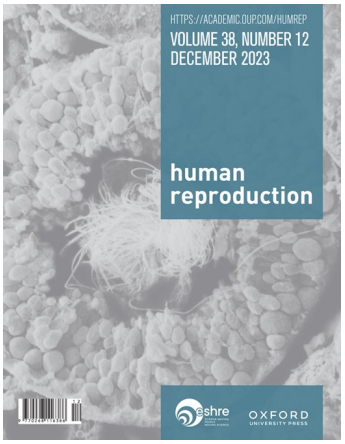
Woolf B, Rajasundaram S, Cronjé HT, Yarmolinsky J, Burgess S, Gill D. A drug target for erectile dysfunction to help improve fertility, sexual activity, and wellbeing: mendelian randomisation study. ***BMJ***. 2023 Dec 12; 383:e076197. PMID: 38086555.
https://doi.org/10.1136/bmj-2023-076197

Testicular functions were studied in men with Cushing's syndrome (CS), and the findings demonstrated varying degrees of hypogonadotropic hypogonadism with altered spermatogenesis in men with intense hypercortisolism associated with paraneoplastic/ectopic adrenocorticotrophic hormone (ACTH) secretion.

Papadakis GE, de Kalbermatten B, Dormoy A, Salenave S, Trabado S, Vieira-Pinto O, Richa C, Kamenicky P, Chanson P, Maione L, Pitteloud N, Young J. Impact of Cushing's syndrome on the gonadotrope axis and testicular functions in men. ***Hum Reprod***. 2023 Dec 4;38(12):2350-361.
https://doi.org/10.1093/humrep/dead187

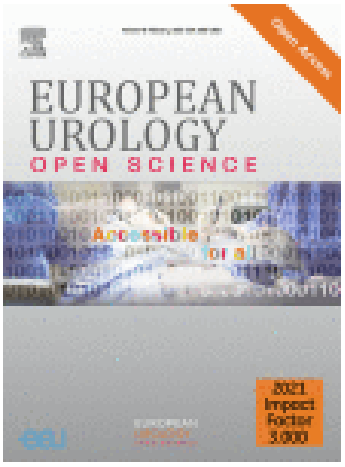
This study analysed the global burden of male infertility. The rise in prevalence of male infertility is a pervasive global trend, with a concerning recent rise in Western Sub-Saharan Africa. The current status of male infertility poses a substantial threat to reproductive health and necessitates heightened attention from researchers.

Huang, B., Wang, Z., Kong, Y. et al. Global, regional and national burden of male infertility in 204 countries and territories between 1990 and 2019: an analysis of global burden of disease study. ***BMC Public Health***, 2195 (2023).
https://doi.org/10.1186/s12889-023-16793-3



This large prospective cohort study from Denmark found that prolonged time-to-pregnancy (TTP) is associated with increased mortality in both mothers and fathers in a dose-response manner, suggesting that fecundity in men and women reflects their health and survival potential.

Lindahl-Jacobsen R, Tavlo Petersson M, Priskorn L, Skakkebæk NE, Juul A, Kristensen DM, Eisenberg ML, Jensen TK. Time to pregnancy and life expectancy: a cohort study of 18796 pregnant couples. ***Hum Reprod.*** 2023 Dec 16: Epub ahead of print.
https://doi.org/10.1093/humrep/dead260



In this Swedish population-based study, hypospadias was associated with a greater risk of testicular cancer but without any clear familial coaggregation. Hypospadias was also associated with Wilms' tumour, bladder and urethral cancers, but not prostate cancer.

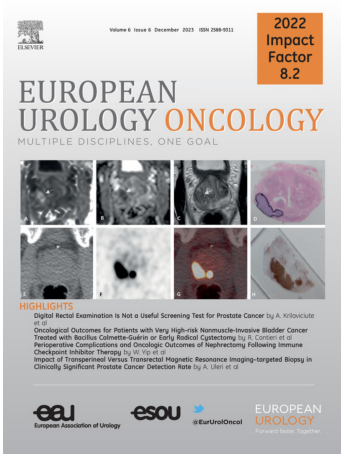
Phillips L, Lundholm C, Almqvist C, Skarin Nordenvall A, Nordenskjöld A. Risk of Urological Cancer Among Boys and Men Born with Hypospadias: A Swedish Population-based Study. ***Eur Urol Open Sci***. 2023 Sep 28;57:51-59.
https://doi.org/10.1016/j.euros.2023.09.009

This study investigated a possible association between sleep quality and fertility and found that sleep duration was associated with some biomarkers of fecundity in young men. Maintaining a recommended sleep duration may be beneficial for young men with regard to reproductive health.

Gaml-Sørensen A, Frølich MK, Brix N, Ernst A, Bonde JPE, Hougaard KS, Tøttenborg SS, Clemmensen PJ, Toft G, Ramlau-Hansen CH. Sleep duration and biomarkers of fecundity in young men: a cross-sectional study from a population-based cohort. ***Andrology***. 2023 Nov 20. Epub ahead of print.
https://doi.org/10.1111/andr.13560

Can one prevent dying from prostate cancer? This study looked at 10,396 men of the Health Professionals Follow-up Study who had an initially negative prostate biopsy, and 18.5% of whom developed prostate cancer during 20-years. Coffee, lycopene intake and statin use tended to be associated with lower rates of lethal prostate cancer.

Feng X, Zhang Y, Vaselkiv JB, Li R, Nguyen PL, Penney KL, Giovannucci EL, Mucci LA, Stopsack KH. Modifiable risk factors for subsequent lethal prostate cancer among men with an initially negative prostate biopsy. ***Br J Cancer.*** 2023 Dec;129(12):1988-2002.
https://doi.org/10.1038/s41416-023-02472-y



The previously recommended - but disliked by patients - digital rectal examination (DRE) was found NOT useful if performed alone to screen for prostate cancer (PCa). The multicentric, randomized PROBASE trial, which enrolled >46 000 men to test the screening methods for PCa, has documented the poor performance of DRE in comparison to the PSA test.

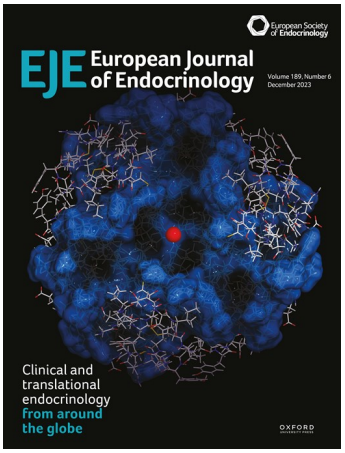
Krilaviciute A, Becker N, Lakes J, Radtke JP, Kuczyk M, Peters I, Harke NN, Debus J, Koerber SA, Herkommer K, Gschwend JE, Meissner VH, Benner A, Seibold P, Kristiansen G, Hadaschik B, Arsov C, Schimmöller L, Giesel FL, Antoch G, Makowski M, Wacker F, Schlemmer HP, Kaaks R, Albers P. Digital Rectal Examination Is Not a Useful Screening Test for Prostate Cancer. ***Eur Urol Oncol***. 2023 Dec;6(6):566-573.
https://doi.org/10.1016/j.euo.2023.09.008

This study examined various semen quality parameters in men with poor sperm motility (asthenozoospermia) and found a much greater risk for sperm DNA fragmentation (SDF) and oxidative stress in these patients. These abnormalities can decrease the sperm fertilizing capability under both natural and medically assisted reproduction conditions.

Gill K, Machałowski T, Harasny P, Grabowska M, Duchnik E, Piasecka M. Low human sperm motility coexists with sperm nuclear DNA damage and oxidative stress in semen. ***Andrology***. 2023 Nov 28.
https://doi.org/10.1111/andr.13556

Serum testosterone (T) is largely bound to the SHBG and human serum albumin (hSA). This study investigated the possible impact of PFAS molecules on T binding in vitro, and suggested that PFOA could possibly compete with T for albumin binding, but any significant effect is unlikely.

Pavan A, Cendron L, Di Nisio A, Pedrucci F, Sabovic I, Scarso A, Ferlin A, Angelini A, Foresta C, De Toni L. In vitro binding analysis of legacy-linear and new generation-cyclic perfluoro-alkyl substances on sex hormone binding globulin and albumin, suggests low impact on serum hormone kinetics of testosterone. ***Toxicology***. 2023 Dec;500:153664.
https://doi.org/10.1016/j.tox.2023.153664



Symptomatic hypogonadism discourages men from stopping anabolic-androgenic steroids (AAS). Some men illicitly take drugs following post-cycle therapy to lessen hypogonadal symptoms. Only half of men had complete biochemical testicular recovery after stopping AAS.

Grant B, Campbell J, Pradeep A, Burns AD, Bassett P, Abbara A, Saket P, Minhas S, Dhillo WS, McVeigh J, Bhasin S, Jayasena CN. Factors predicting normalization of reproductive hormones after cessation of anabolic-androgenic steroids in men: a single center retrospective study. ***Eur J Endocrinol.*** 2023 Dec 6;189(6):601-610. https://doi.org/10.1093/ejendo/lvad164

Four animations on testicular health and fertility, informed by andrologists, academics, designers, boys, and young men, were developed. Adolescent boys (and girls) were subjected to pre- and post-animation questionnaires, and exhibited substantial interest in the material, so boys and men should be considered as being a relevant target population for fertility education, not just girls and women.

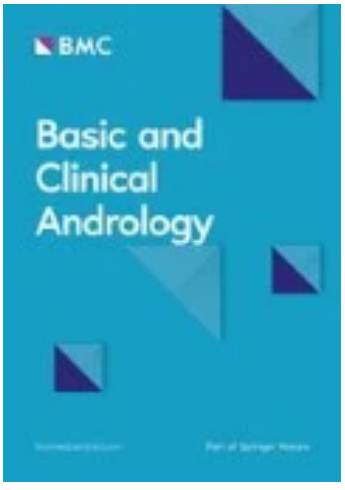
Harrison C, Greves G, Barnard E, Davies A, McEleny K, Gordon U, Lucky M, Woodward B, Pacey A, Heatley M, Boivin J. The effect of an educational animation on knowledge of testicular health and fertility of adolescents. ***Hum Reprod.*** 2023 Dec 4;38(12):2470-2477. https://doi.org/10.1093/humrep/dead195

Androgenetics

LRRC23 is a radial spoke (RS3) component essential for the flagellar motility in mammalian spermatozoa. A splice site variant of LRRC23 was identified in a man with defective sperm motility.

Cryo-electron tomography revealed the absence of the RS3 head and the sperm-specific RS2-RS3 bridge structure in LRRC23 mutant spermatozoa.

Hwang JY, Chai P, Nawaz S, Choi J, Lopez-Giraldez F, Hussain S, Bilguvar K, Mane S, Lifton RP, Ahmad W, Zhang K, Chung JJ. LRRC23 truncation impairs radial spoke 3 head assembly and sperm motility underlying male infertility. ***eLife***. 2023 Dec 13;12:RP90095. https://doi.org/10.7554/eLife.90095.3



Men with azoospermia have a relatively high frequency of loss of Y chromosome material. This study confirmed that structural abnormal Y chromosomes are unstable and therefore often lost. Men with 45,X cell lines are often small in stature, which may be due to a reduced number of SHOX genes.

Fedder J, Fagerberg C, Jørgensen M. et al. Complete or partial loss of the Y chromosome in an unselected cohort of 865 non-vasectomized, azoospermic men. ***Basic Clin. Andrology***, 37 (2023). https://doi.org/10.1186/s12610-023-00212-z

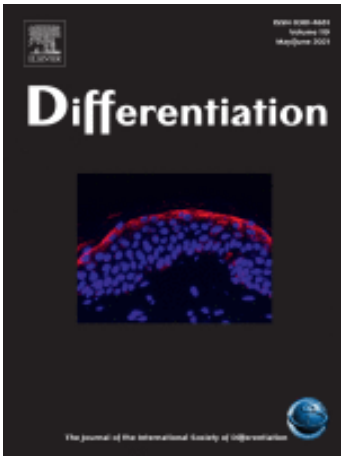
This study showed that patients with Y chromosome AZFc microdeletions exhibited reduced normal fertilization rate, reduced blastocyst formation rate and increased incidence of aneuploid embryos. The patients should be informed about these risks.

Jiang W, Xie Q, Li X. et al. Y chromosome AZFc microdeletion may have negative effect on embryo euploidy: a retrospective cohort study. ***BMC Med Genomics*** 16, 324 (2023).
https://doi.org/10.1186/s12920-023-01760-z

Translational and basic andrology

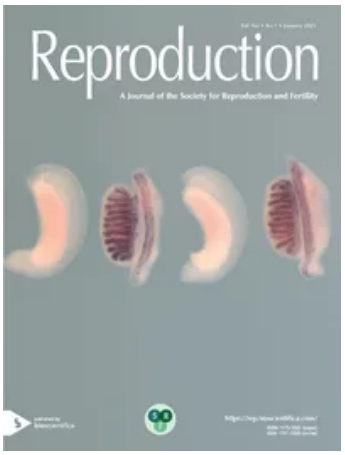
Mice with ablated NR5A1 in Sertoli cells (SCs) after sex differentiation, displayed SC death through an anoikis-like mechanism, and death of germ cells due to the premature meiotic entry. Some SCs acquired a 'pre-granulosa-like' cell identity or were 'intersex'. The adult males had persistent Müllerian duct derivatives, decreased anogenital distance and reduced penis length.

Souali-Crespo S, Condrea D, Vernet N, Féret B, Klopfenstein M, Grandgirard E, Alunni V, Cerciat M, Jung M, Mayere C, Nef S, Mark M, Chalmel F, Ghyselinck NB. Loss of NR5A1 in mouse Sertoli cells after sex determination changes cellular identity and induces cell death by anoikis. ***Development***. 2023 Dec 15;150(24):dev201710.
https://doi.org/10.1242/dev.201710



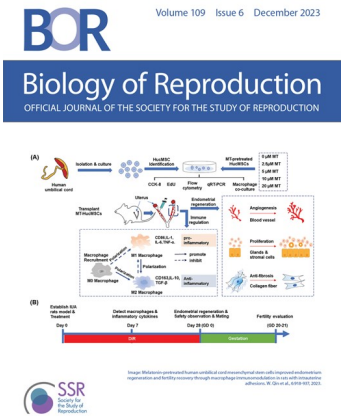
Adult male Sertoli cell-specific Connexin43 knockout mice (SCCx43KO) exhibit increased Sertoli cell (SC) numbers. This study found prolonged period of SC proliferation in the KO mice into adulthood.

Hüneke H, Langeheine M, Rode K, Jung K, Pilatz A, Fietz D, Kliesch S, Brehm R. Effects of a Sertoli cell-specific knockout of Connexin 43 on maturation and proliferation of postnatal Sertoli cells. ***Differentiation***. 2023 Nov-Dec;134:31-51.
https://doi.org/10.1016/j.diff.2023.09.002



In mice with spcar3 phenotype (spermatocytic arrest) a mutation in *Setx* was identified. The gene encodes senataxin, a DNA/RNA helicase that regulates transcription termination by resolving DNA/RNA hybrid R-loop structures. The Setxspcar3 mutant spermatocytes display defective formation of the sex body and arrest of meiosis in mid-prophase.

Fujiwara Y, Saito K, Sun F, Petri S, Inoue E, Schimenti J, Okada Y, Handel MA. New allele of mouse DNA/RNA helicase senataxin causes meiotic arrest and infertility. ***Reproduction***. 2023 Nov 6;166(6):437-450.
https://doi.org/10.1530/rep-23-0166



A frameshift mutation of *BNC1* (basonuclin 1) was identified in Chinese patients with primary ovarian insufficiency and in males with nonobstructive azoospermia. This study showed mitochondrial dysfunction and apoptosis of spermatogonia in mice with a *Bnc1* mutation, which was reversed by administration of nicotinamide riboside or metformin.

Ni F, Wang F, *et al* et Zhang D. BNC1 deficiency induces mitochondrial dysfunction-triggered spermatogonia apoptosis through the CREB/SIRT1/FOXO3 pathway: the therapeutic potential of nicotinamide riboside and metformin. ***Biol Reprod.*** (BOR) 2023 Dec 11:ioad168.
https://doi.org/10.1093/biolre/ioad168

The authors identified numerous sperm acrosome glycoproteins by an in-silico screen. Phenotypic analyses revealed that the knockout males showed normal testis and epididymis histology, normal sperm morphology and motility, and the knockout male mice could sire pups with normal litter sizes when paired with wild-type females.

Ogawa Y, Lu Y, Kiyozumi D, Chang HY, Ikawa M. CRISPR/Cas9-mediated genome editing reveals seven testis-enriched transmembrane glycoproteins dispensable for male fertility in mice. ***Andrology***. 2023 Dec 12.
https://doi.org/10.1111/andr.13564

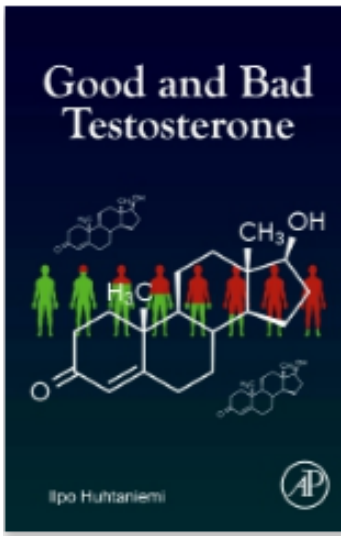
An in vitro model was used to study the function of mouse testicular macrophages. The data indicates that macrophage CSF is a likely inducer of high *Irf7* expression levels, confirming that local intrinsic signals govern the phenotypes and functions of mouse tissue resident macrophages by inducing specific transcription factors.

Yang Y, Kumar V, Peng W, Fijak M, Gabriela M, Cai W, Meinhardt A, Bhushan S. Role of macrophage colony stimulating factor and interferon regulatory factor 7 in modulating the immune profile of mouse testicular macrophages. ***J Reprod Immunol.*** 2023 Nov 21;161:104169.
https://doi.org/10.1016/j.jri.2023.104169

Non-steroidal anti-inflammatory drugs (NSAIDs) and 17 alpha-ethinylestradiol (EE2) are considered endocrine disrupters. This study investigated in mice the outcomes of chronic exposure to mixtures of NSAIDs and EE2 and found intergenerational adverse effects on male and female fertility.

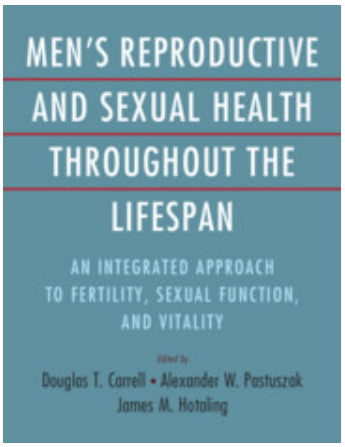
Philibert P, Stévant I, Déjardin S, Girard M, Sellem E, Durix Q, Messager A, Gonzalez AA, Mialhe X, Pruvost A, Poulat F, Boizet-Bonhoure B. Intergenerational effects on fertility in male and female mice after chronic exposure to environmental doses of NSAIDs and 17α-ethinylestradiol mixtures. ***Food Chem Toxicol.*** 2023 Dec;182:114085.
https://doi.org/10.1016/j.fct.2023.114085

Books of the month



A unique reference to understand and learn about the biology and psychophysical aspects of testosterone.

Good and Bad Testosterone
1st Edition, November 2023
Author: Ilpo Huhtaniemi
Hardback ISBN: 9780443134326
eBook ISBN: 9780443134319
https://shop.elsevier.com/books/good-and-bad-testosterone/huhtaniemi/978-0-443-13432-6



Men's Reproductive and Sexual Health Throughout the Lifespan:

An Integrated Approach to Fertility, Sexual Function, and Vitality
Editors: Carrell DT, Pastuszak AW and Hotaling JM, Utah Center for Reproductive Medicine, USA
Publisher: Cambridge University Press
Online publication date: December 2023
Print publication year: 2023
Online ISBN: 9781009197533
DOI: https://doi.org/10.1017/9781009197533

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