پلی‌کلینیک ژنتیک
نسل فردا

Environmental & Molecular factors in human infertility

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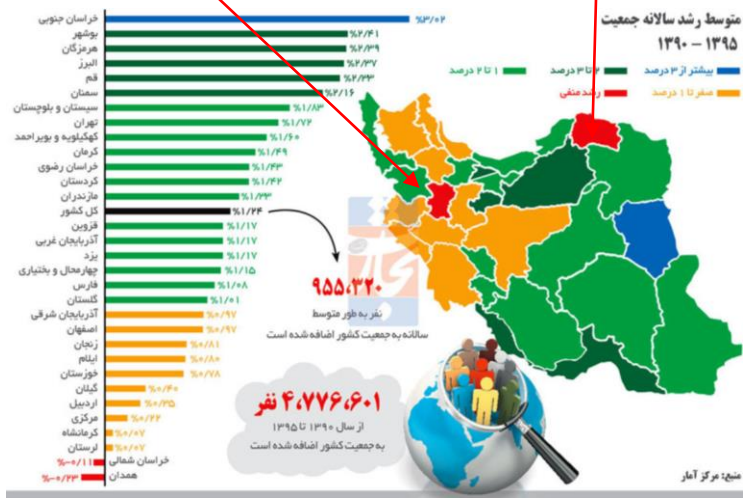
Next Generation Genetic Polyclinic

Overview

✓Industrialized regions have birth rates so low that their populations cannot be sustained; declines in birth rates are generally ascribed to socioeconomic and cultural factors, although human infertility is widespread.

همدان

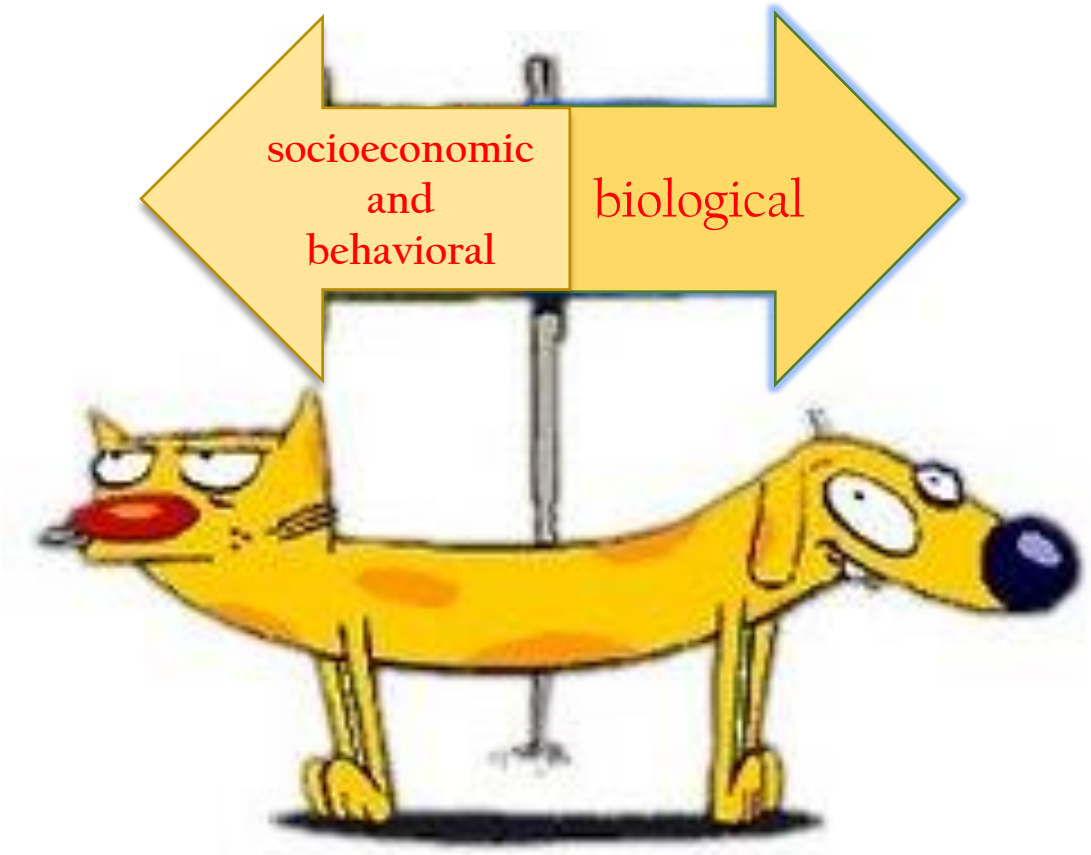
خراسان شمالی



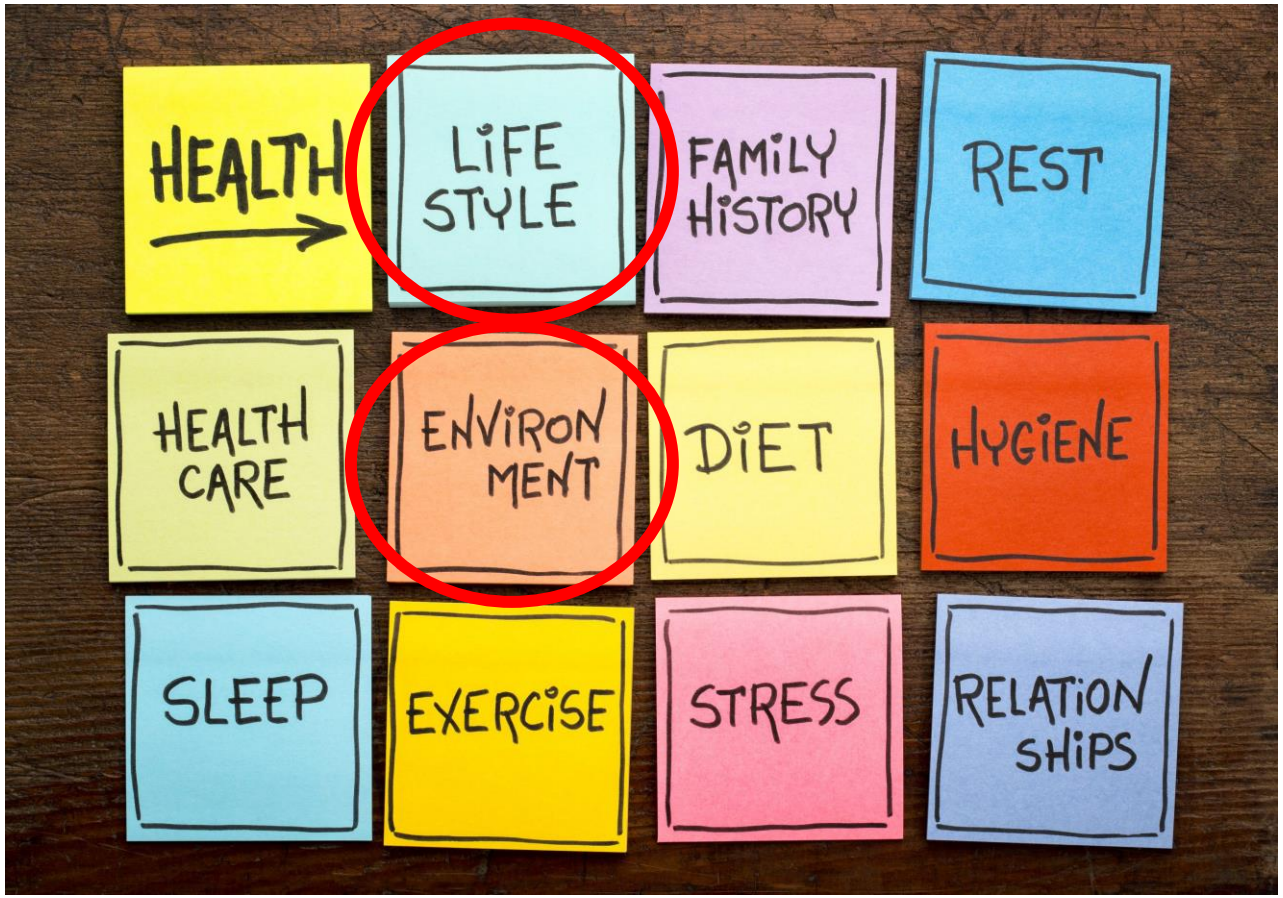
✓Decreasing fertility rates were already recorded in the world, a few decades after the beginning of utilization of fossil fuels that were, and still are, drivers of modern industrialization and wealth.

✓We hypothesize that declines in fertility rates might be linked to exposures to chemicals originating from fossil fuels causing human reproductive problems and cancer; early gestation might be a sensitive period.

A key research challenge remains:
How to distinguish biological from socioeconomic and behavioral factors?

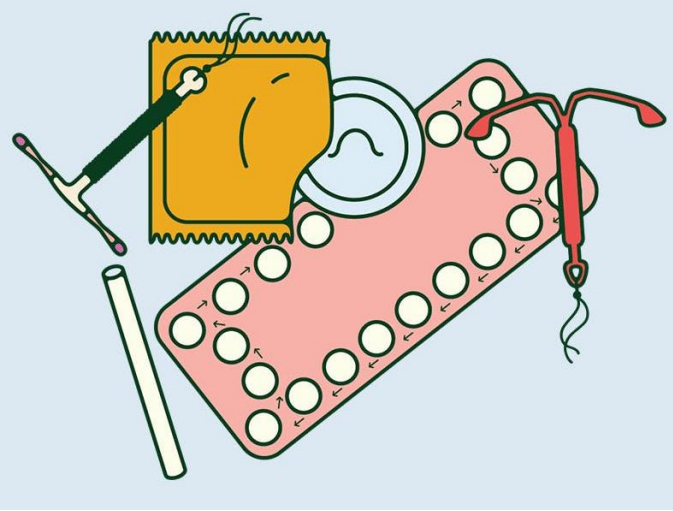


Lifestyles and environmental exposures



Factors that influence birth rates

Contraception, unplanned pregnancies and abortions

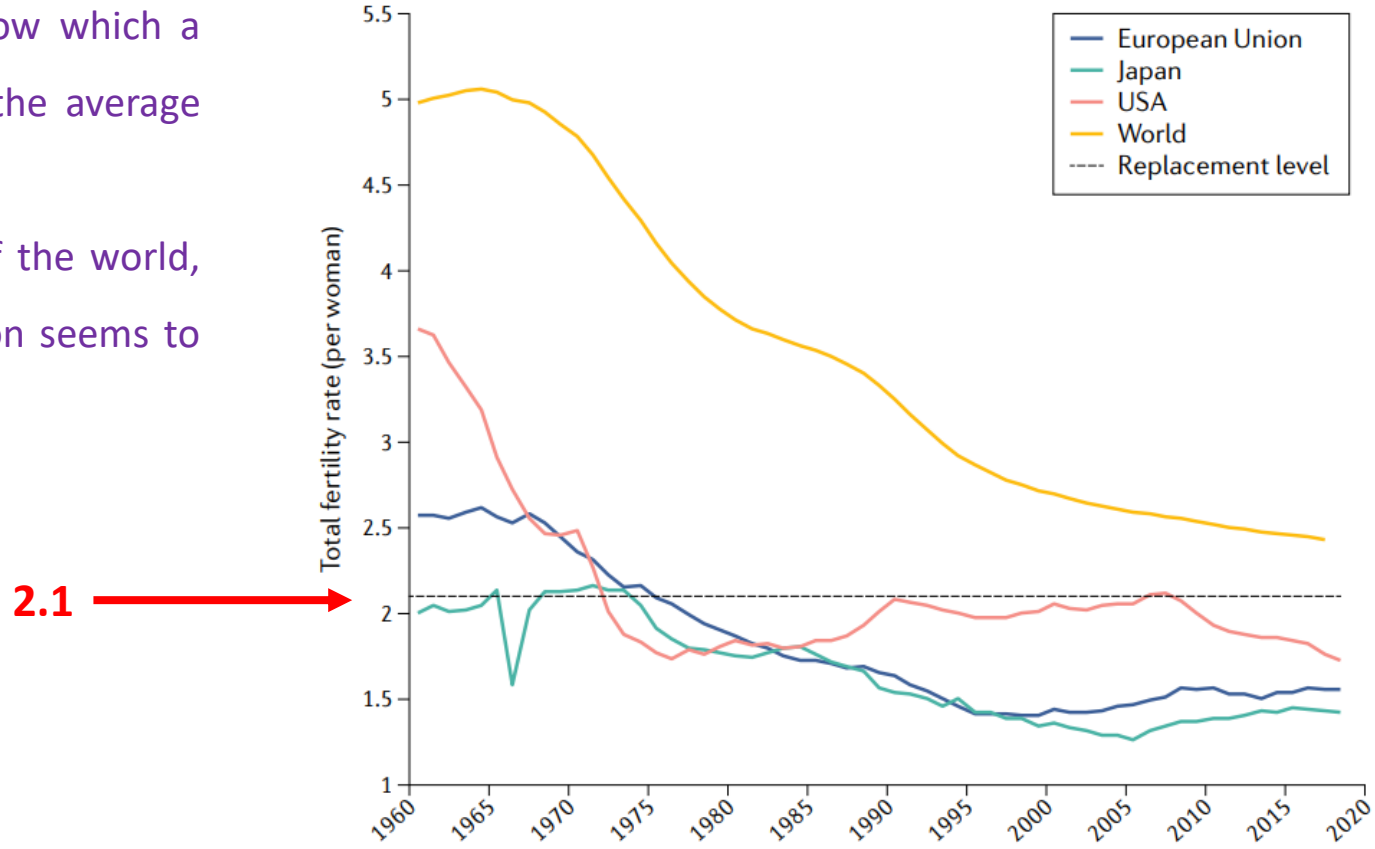


Spontaneous pregnancy loss

Twinning rates

Total fertility rates in the European Union, Japan and the USA, 1960–2018.

- The dashed line represents a fertility rate of **2.1**, below which a population cannot be sustained (total fertility rate is the average number of children per woman).
- Despite higher birth rates in non-industrialized parts of the world, even the total fertility rate of the total world population seems to be declining towards 2.1.



Couple infertility and MAR

- **Pregnancy planning**

✓ Women to have more control over their reproductive choices.

✓ Estimated: 120 million new users of the oral contraceptive pill by 2020 (Family Planning 2020).

✓ The consequent risk from postponing family initiation is that the family size might ultimately be smaller than in previous generations due to the age-related decrease in fecundity.


selection
sexual
male
female
traitss
evolution
mating
ageing
reproductive
offspring
heredity
conflict
condition
species
rate
theory
variation
effects
size
reduced
evidence
reproduction
mortality
genetic
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ecological
paternal
population
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net

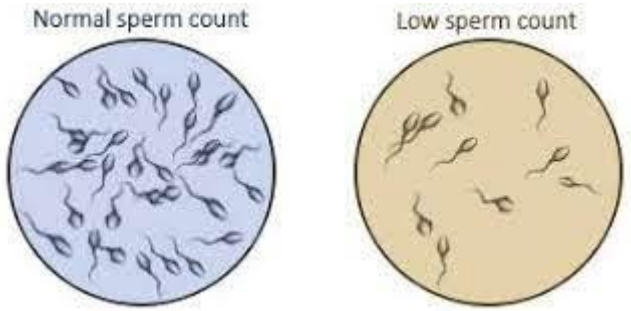
Male reproductive disorders

Poor human spermatogenesis

- Sperm count is linked to the **quality** of spermatogenesis in the seminiferous tubules.
- Compared with other mammalian species belonging to different orders, human spermatogenesis is uniquely **poor**

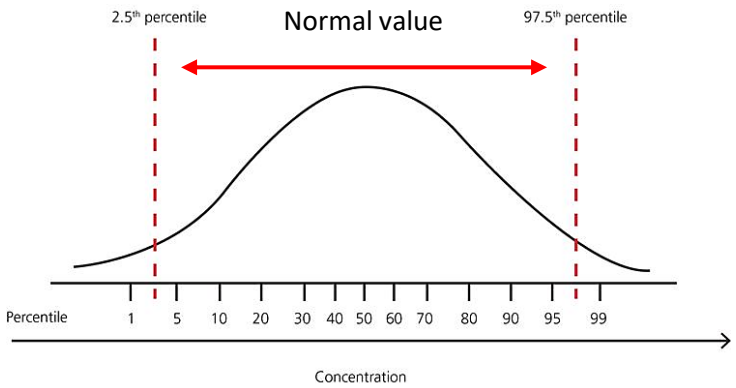
Semen quality

- With the level observed today, a large proportion of young men have a sperm concentration in the **suboptimal** range below the threshold of 40 million per milliliter and a longer time to pregnancy or need for fertility treatment could be expected.



Significance of changes in reference ranges for human semen quality.

- Normality in medicine: 2.5 and 97.5 percentiles in a random sample from the general population.
- The most recent WHO guidelines for analysis of semen adhere to this principle.



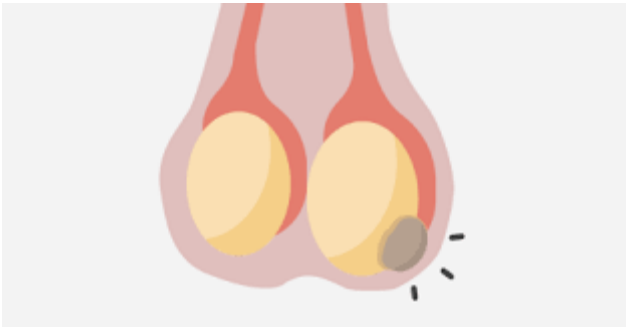
Male reproductive disorders

Testicular cancer

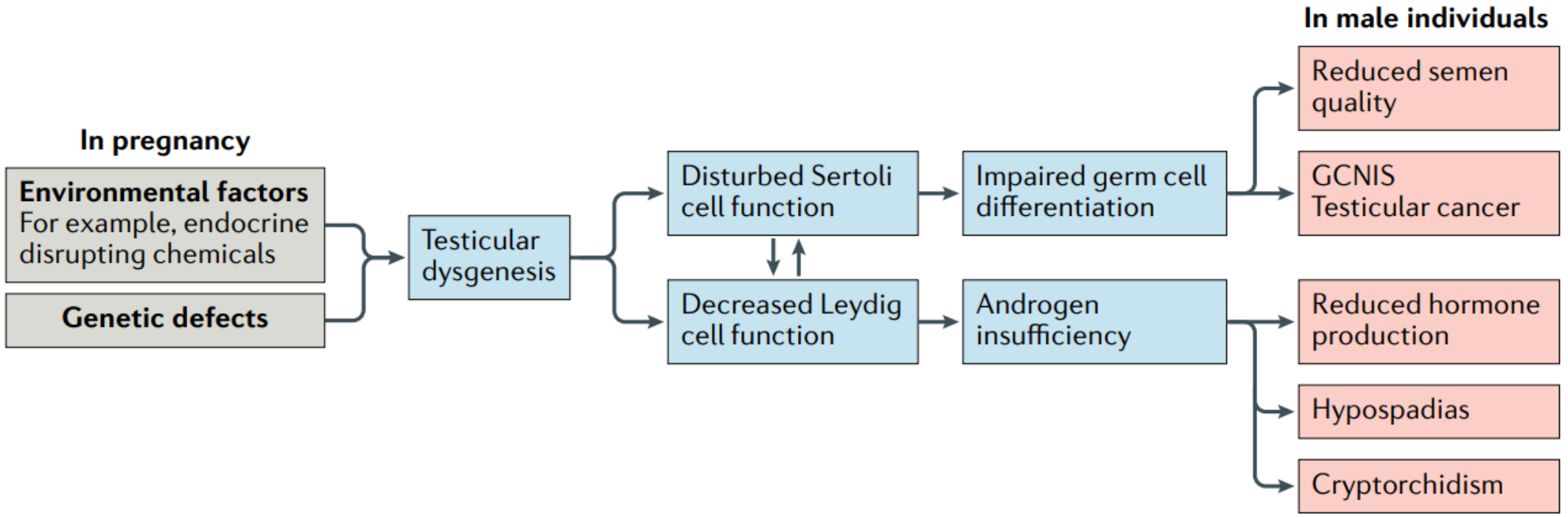
- mainly occurs in young men

It is associated with:

- undescended testis
- decreased semen quality
- infertility and childlessness
- 74,500 estimated new testicular cancer cases per year globally



Testicular dysgenesis syndrome



- The hypothesis shown here links **fetal maldevelopment of the male gonads** to congenital malformations visible at birth and late-onset symptoms occurring in adulthood, including GCNIS (germ cell neoplasia in situ) that develops into germ cell cancer (seminoma and non-seminoma), and/or infertility and/or decreased testosterone production.

  Some patients with testicular dysgenesis syndrome have all symptoms others only one or two.

Possible biological mechanisms

Roles of genetic and epigenetic factors

- To our knowledge, no single genetic or epigenetic factor has been shown to affect fertility on a population scale.
- Obviously, genetic or epigenetic factors negatively affecting fertility are not likely to survive in the population
- the increased use of MAR, and especially ICSI, bypasses the natural negative selection pressure, and enables the accumulation of genetic and epigenetic variants with subtle effects on fertility in the population.

Epigenetics at a glance

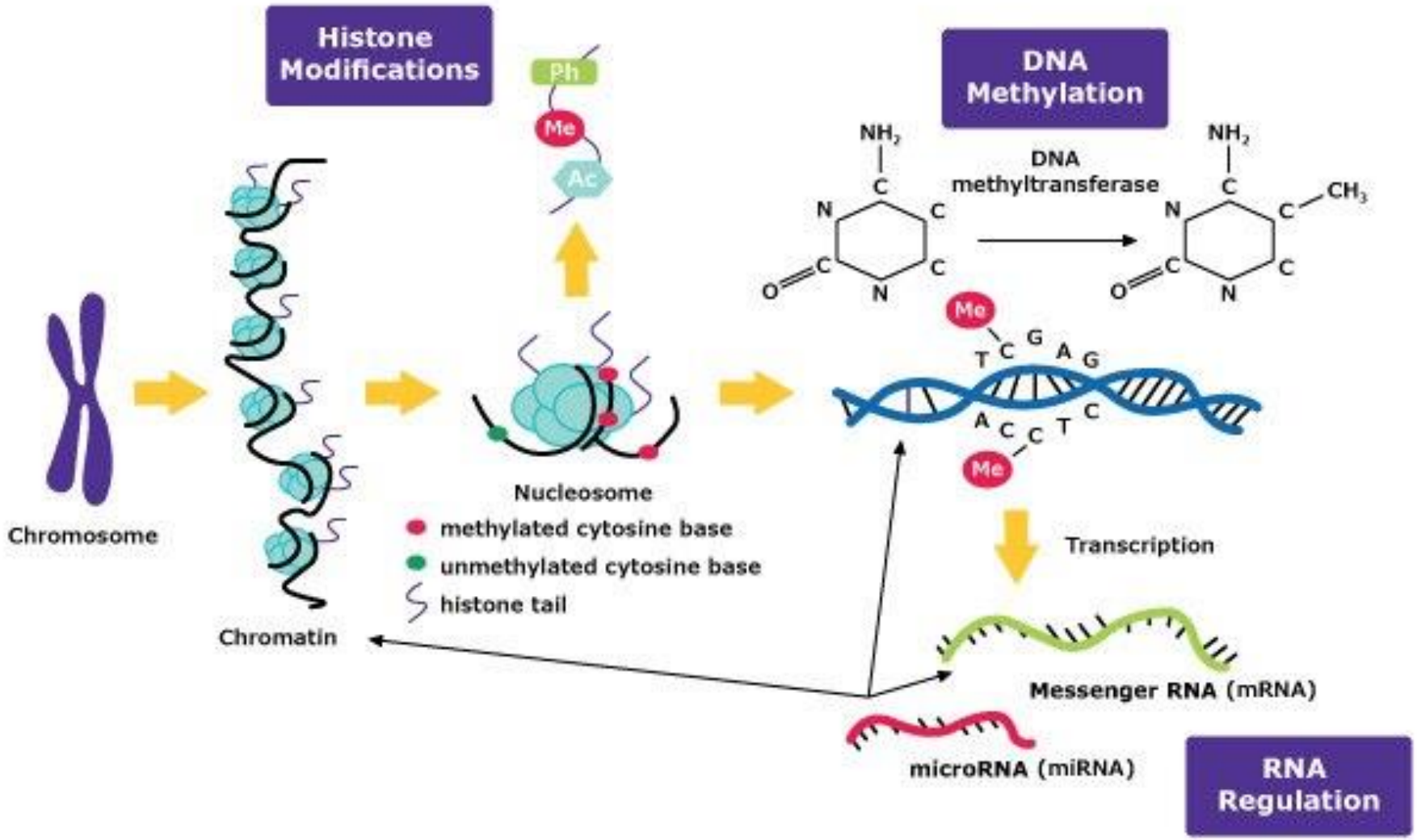
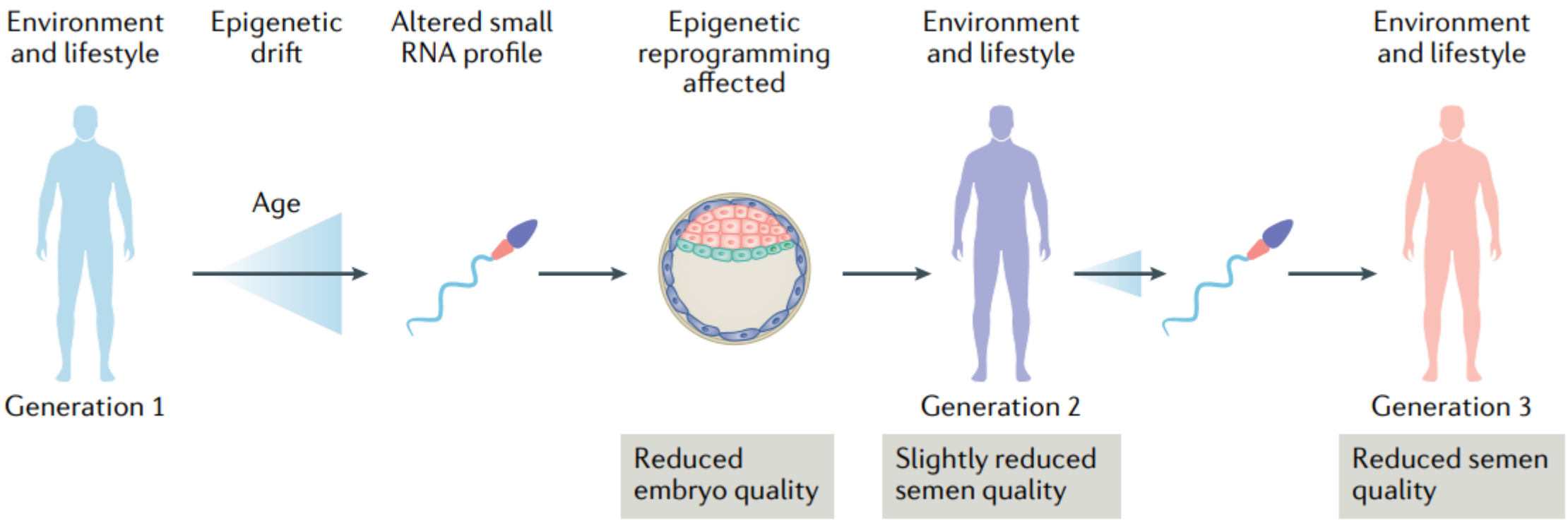


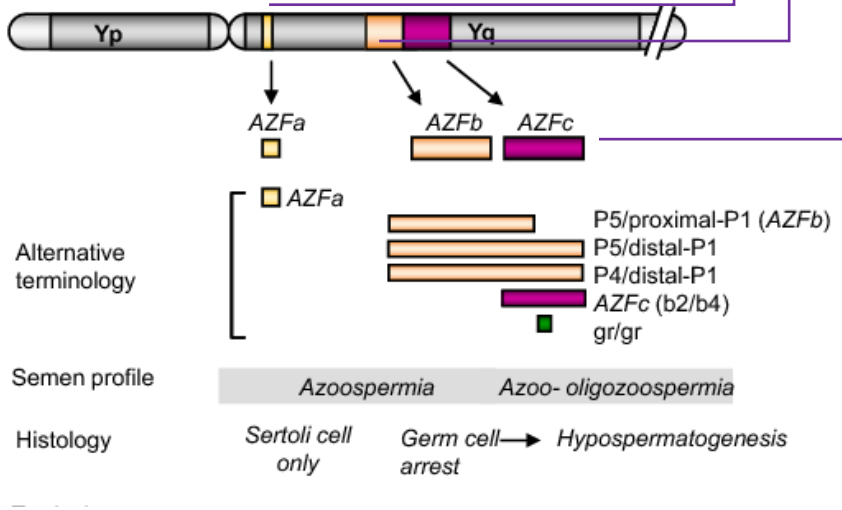
illustration of epigenetic drift



Environment-mediated and lifestyle-mediated epigenetic drift in the germline might be passed on by **small RNAs** to subsequent generations. With **increasing age** of the individual, the sperm epigenome is likely to **acquire a range of epigenetic alterations** that can be passed on to subsequent generations. Although the concept has been established in animal models, it remains to be validated in humans.

AZF Microdeletions

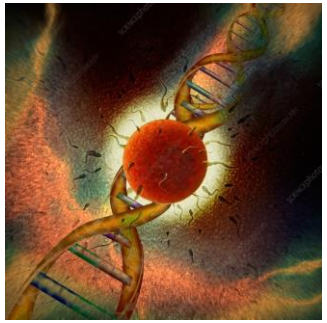
The largest known genetic effect on male fertility still relates to the sex chromosomes, **X** and **Y**, including **microdeletions** in the **AZF regions** on the **Y chromosome** and the presence of **supernumerary X chromosomes**, as found among men with **Klinefelter** syndrome.



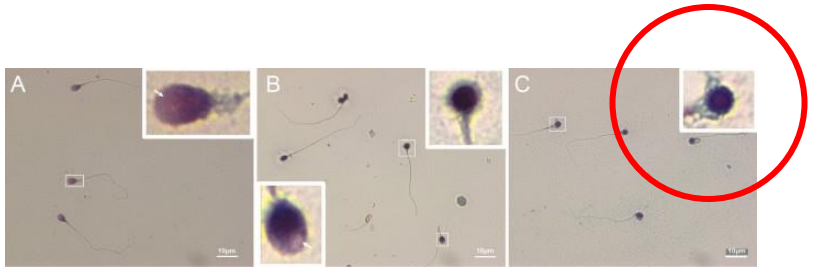
Deletion	Deletions are known to correspond to:
AZFa deletion	Complete *AZFa* deletions: severe testicular phenotype, SCOS and spermatogenic arrest
	Partial *AZFa* deletions: extremely rare
AZFb deletion	Complete *AZFb* deletions: spermatogenic arrest
	Partial AZFb deletions: variable phenotypes from hypospermatogenesis to SCOS extremely rare
AZFc deletion	Complete *AZFc* deletions: variable phenotype which may range from mild oligospermia to azoospermia and SCOS
Partial *AZFc* deletion	Variable phenotypes from hypospermatogenesis to the SCOS
AZFbc deletion	SCOS/spermatogenic arrest
AZFabc deletion	SCOS

AZF; Azoospermia factor **and SCOS; Sertoli cell-only syndrome.**

Possible biological mechanisms



Genetic variants with effects on reproduction



- ***DPY19L2*** and ***SPATA16*** :associated with globozoospermia.
- **GWAS** in men with oligospermia or azoospermia: quite inconclusive.
- Multifactorial
- New studies: Sequencing non-obstructive azoospermia
- Mutations causing non-obstructive azoospermia have been identified in several genes, but can only explain non-obstructive azoospermia in a small fraction of all cases.

Springer Link

Original Investigation | Published: 27 October 2020

Genetic analyses of a large cohort of infertile patients with globozoospermia, *DPY19L2* still the main actor, GGN confirmed as a guest player

Tristan Celse, Caroline Cazin, ... Pierre F. Ray + Show authors

Human Genetics **140**, 43–57 (2021) | Cite this article

554 Accesses | **10** Citations | **1** Altmetric | Metrics

Take Home Message...

biological systems

behavioral socioeconomic changes

Reasons

- Genetic variations
  - Aneuploidy
  - Copy number variants
  - Microsatellite instability
  - Single-gene allelic variants
  - Activation of retrotransposons
- Repair system defects and genome instability
  - Replication errors
  - Mismatch repair genes
  - Defects of DNA mitotic and meiotic recombination genes
- Epigenetic changes
  - DNA methylation
  - Histone modifications
  - Regulation via ncRNAs (PIWI/piRNA pathway)
- Aging and cellular senescence
  - Eroded telomeres and fragile DNA hotspots
  - Accumulation of DNA strandbreaks
- Environment and lifestyle factors
  - Alcohol
  - Smoking
  - Other agents (phthalates, etc.)

GENOME INSTABILITY
Hallmark: DNA strandbreaks, aneuploidy/mosaicism

Consequences

General:
- Increased testicular and other (colorectal, melanoma, prostate) cancer risk
- Increased morbidity
- Shorter life span

Reproductive:
- Impaired spermatogenesis (azo / oligozoospermia) and infertility
- Failure in assisted reproduction (impaired embryo development and placentation)

Detection

In sperm:
- Sperm chromatin structure assays (SCSA, etc.)
- Direct assessment of sperm DNA breaks (Comet assay, TUNEL, etc.)
- ALU/LINE transcription

In peripheral blood lymphocytes:
- Micronucleation test
- COMET assay test
- Karyotyping
- Genetic methods to detect microdeletions, allelic variants in target genes (PCR, sequencing, exome analysis)
- ALU/LINE transcription
- piRNA analysis

+

environmental exposures

modern lifestyles


Thank
you

Transdisciplinary research needed

- Broad collaboration between researchers in life sciences and social sciences, including anthropology and demography, is needed to answer important questions.
- How can we establish methods to distinguish between voluntary and non-voluntary childlessness in populations with unsustainable reproduction?
- How can we develop new methods to distinguish between the role of male and female factors in couple fecundity?
- Can we identify novel biomarkers in early life that predict the adult reproductive capacity of an individual?
- What are the biological mechanisms that link testicular cancer to poor spermatogenesis and other reproductive disorders in young men?
- Why are there multiple reports on adverse trends in male reproductive health, but not similar reports on female reproduction?
- Is it possible that exposures to industrial endocrine-disrupting chemicals are more harmful for the male than the female reproductive organs, due to the anti-androgenic and estrogenic properties of many of these chemicals?
- Why is human spermatogenesis much poorer than spermatogenesis of most other mammals?
- Why have serum levels of testosterone in human males declined during the past generation? Is it due to environmental exposures or does the obesity epidemic have a role as well?
- What can we learn from scientists studying reproduction of endangered wildlife species?
- Is it possible that human fertility rates will return to sustainable levels in countries/regions where they have been below sustainable levels for decades?