The Queen's Medical Research Institute Medical School Main Hospital

Key developments in research on reproductive endocrinology

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Arguably the most important risk factor for a shorter, unhealthier life…….

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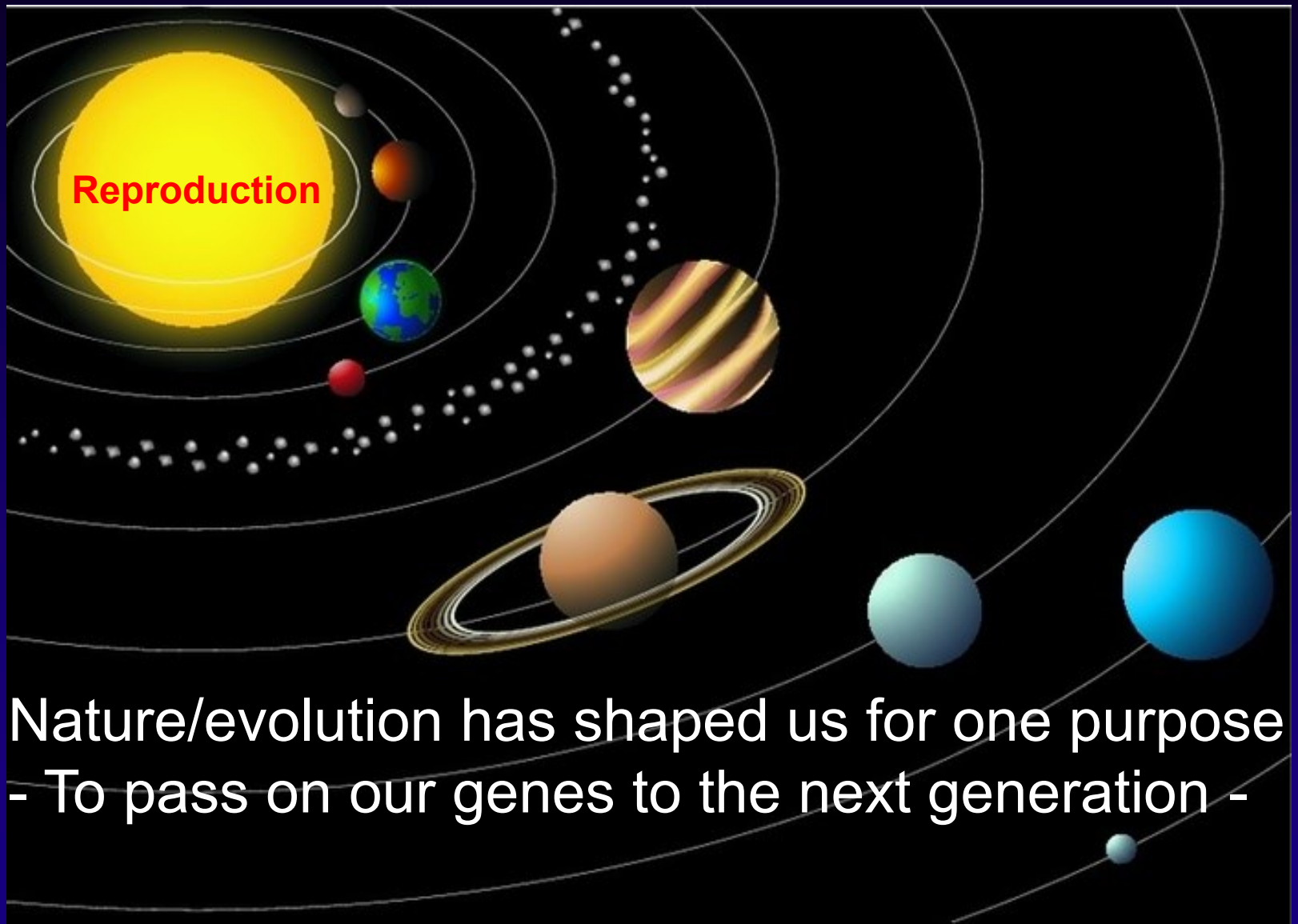
Increased risk of

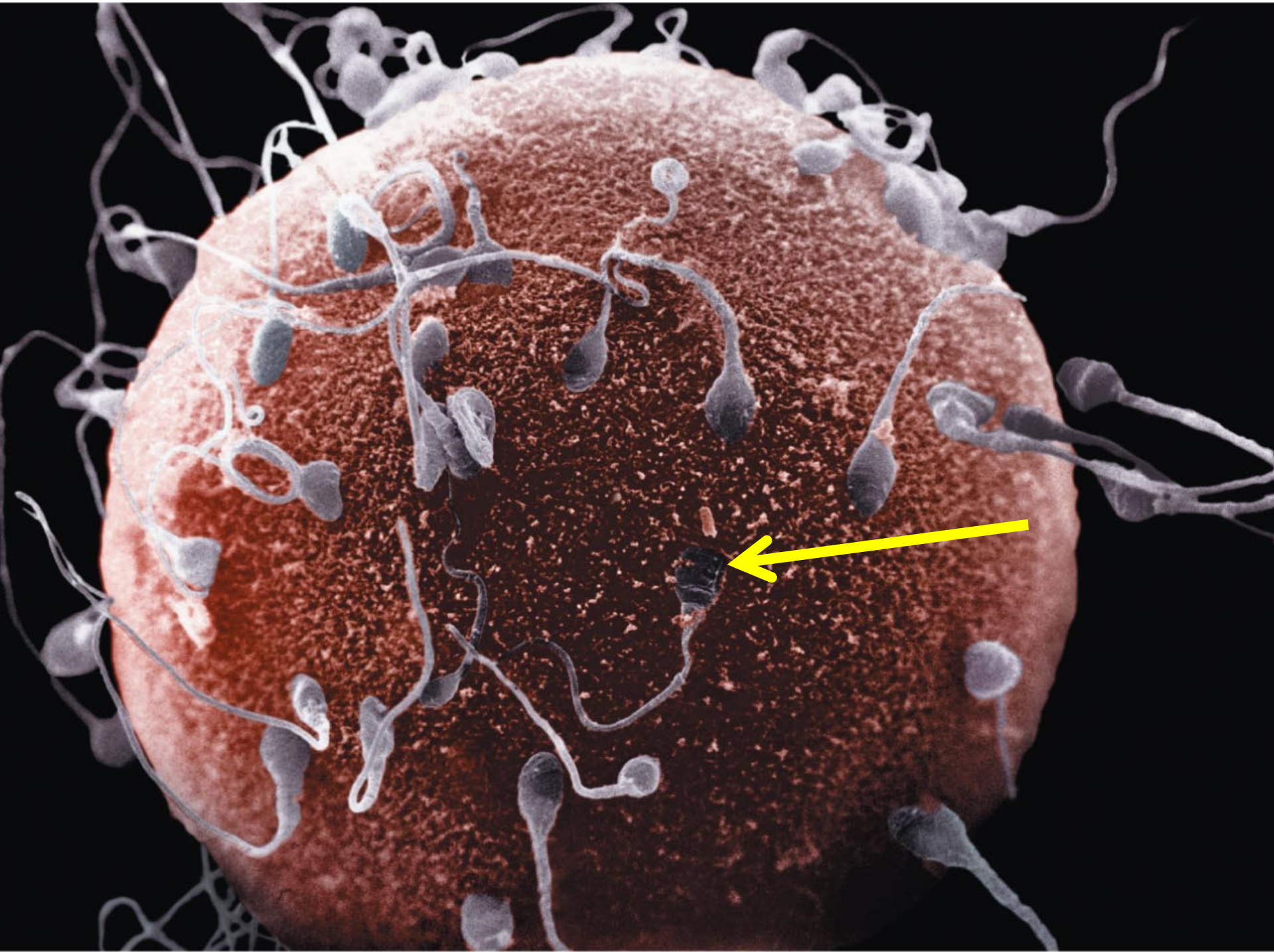
- Dying earlier
- Cardiovascular disease
- Kidney disease/hypertension
- Visceral obesity
- Most cancers
- Gastric ulcers
- Schizophrenia
- Autism spectrum disorders

The biggest question of all?

Why are we here?

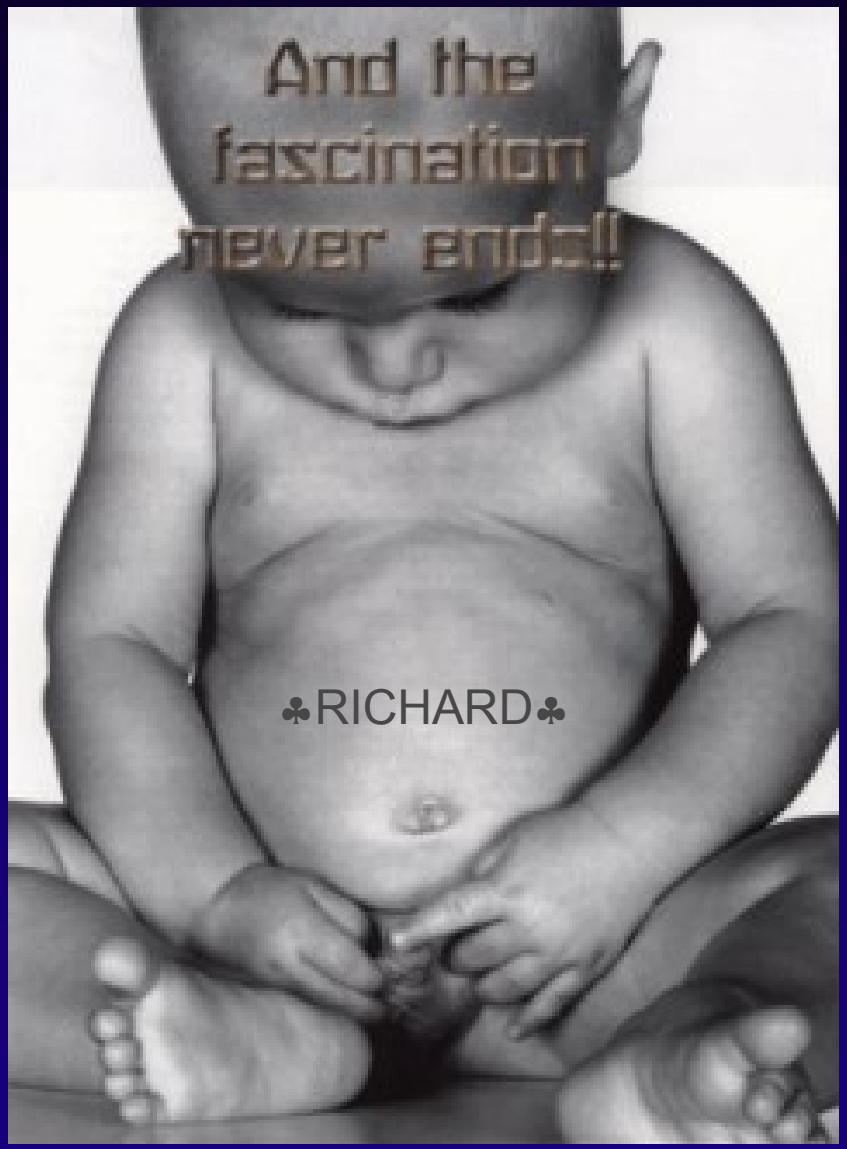


Nature/evolution has shaped us for one purpose
- To pass on our genes to the next generation -

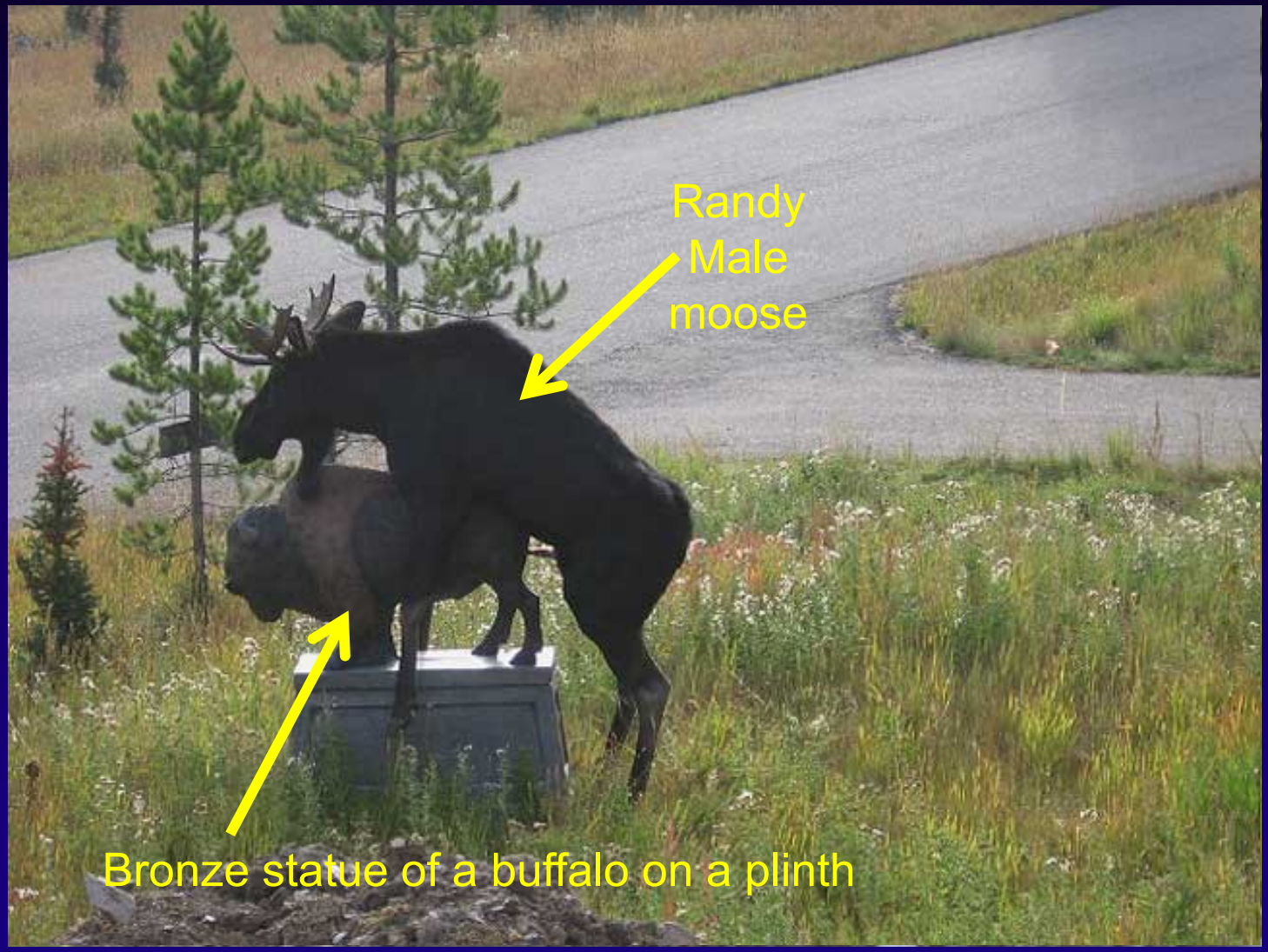


Male preoccupation with sex

It starts at an early age



When it comes to that sexual urge
Common sense is discarded in males



When it comes to that sexual urge

Common sense is discarded in males

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As Jeremy Clarkson commented

‘It should not surprise us that teenage boys are unable to keep their bedroom tidy or to have decent table manners, when all you are is a life support system for your testicles’

When to start puberty?

What says ‘Go’

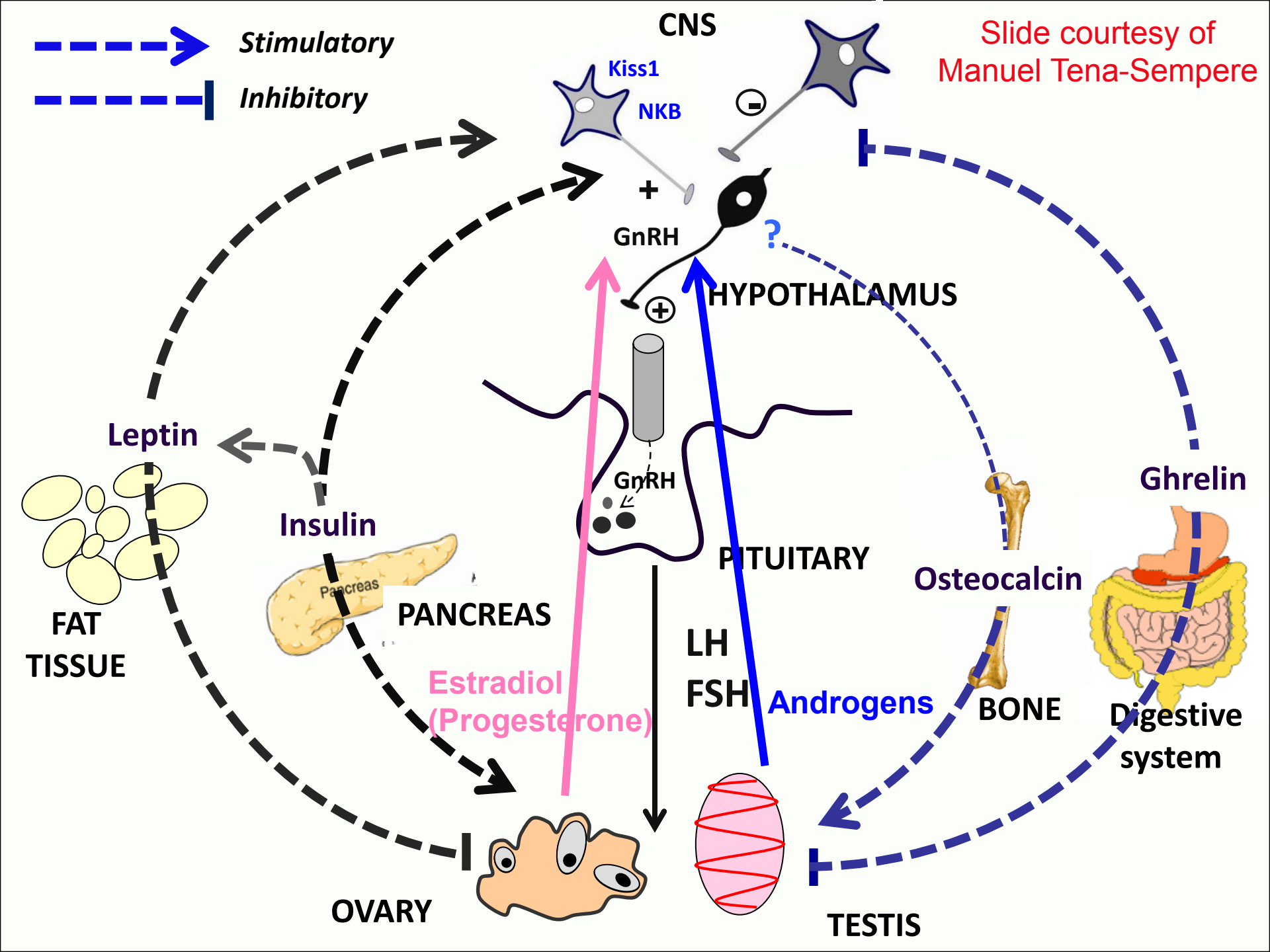
When to start puberty?
What says 'Go'

Reproduction requirements

Female (*to support pregnancy & lactation*)
- Bone and general physical development
- Energy stores/reserves

Male (*to support sperm production/sex drive*)
- Make sperm and be able to have sex
- (?fight off other interested males)

FOOD, FAT Stores, a functional reproductive system


Stimulatory
Inhibitory
CNS
Slide courtesy of
Manuel Tena-Sempere
Kiss1
NKB
+
GnRH
?
HYPOTHALAMUS
GnRH
PITUITARY
Leptin
Insulin
Ghrelin
Osteocalcin
FAT
TISSUE
Pancreas
PANCREAS
LH
FSH
Estradiol
(Progesterone)
Androgens
BONE
Digestive
system
OVARY
TESTIS

The diverse influence of reproductive hormones

Reproductive/Sex hormones regulate or modulate:

- Body appearance (male or female)
- Body growth rates and final height (skeletal effects)
- Body composition (muscle and fat amounts and distribution)
- Brain development and organisation (male or female)
- Liver, kidney, lung and cardiovascular development/function
- The immune system
- Puberty, sex drive/function and fertility

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Increased risk of

- Dying earlier
- Cardiovascular disease
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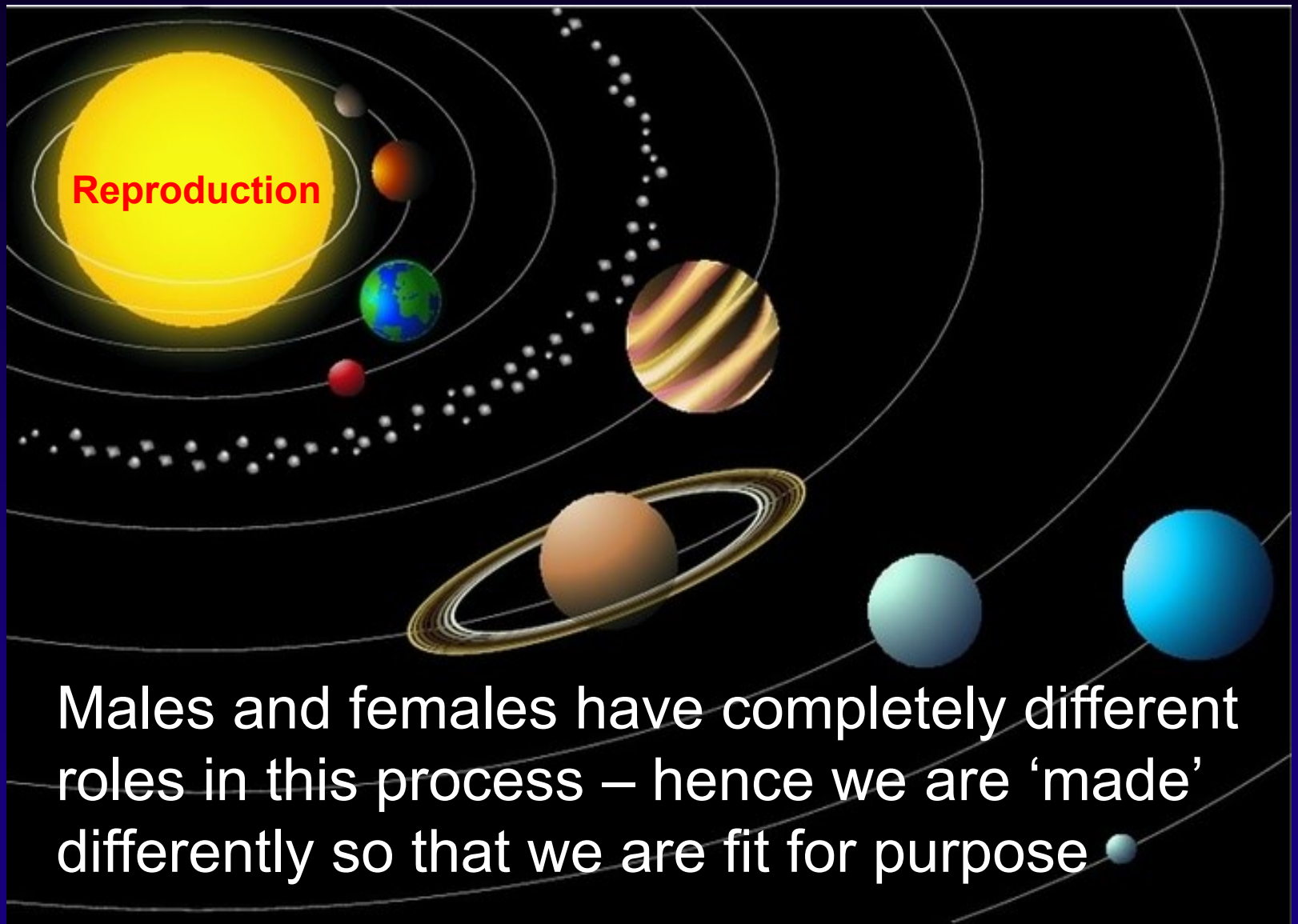
Welcome to the exclusive club of being a MALE

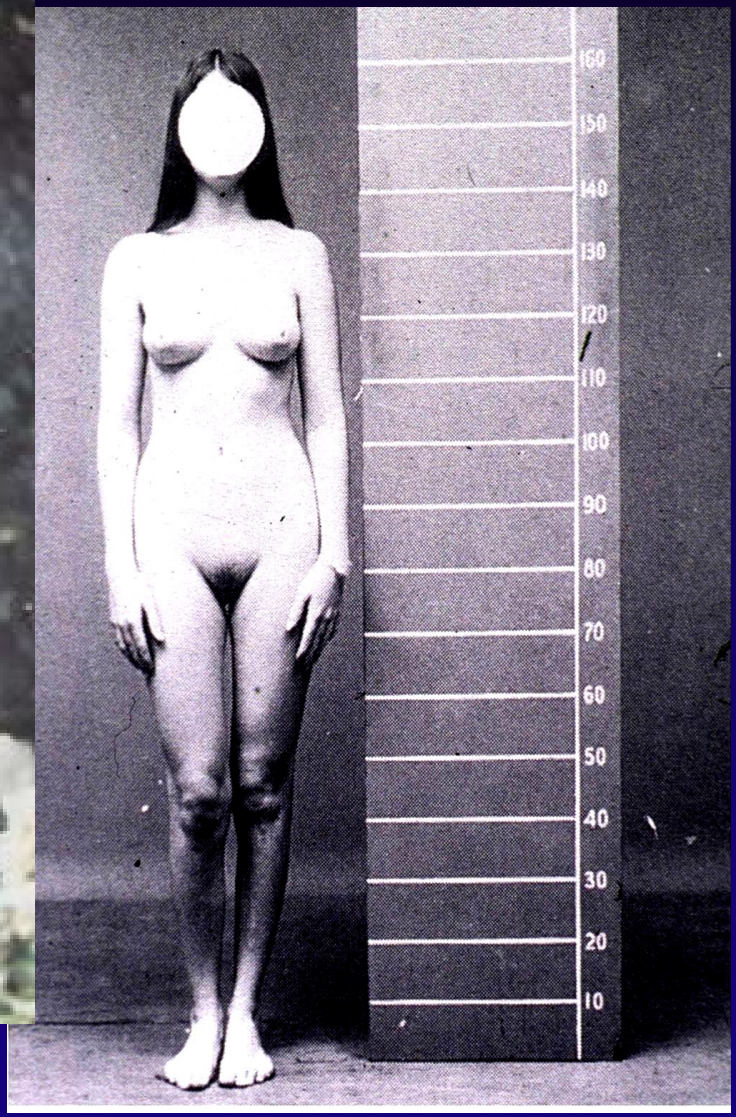
Why are we here?



Males and females have completely different roles in this process – hence we are ‘made’ differently so that we are fit for purpose

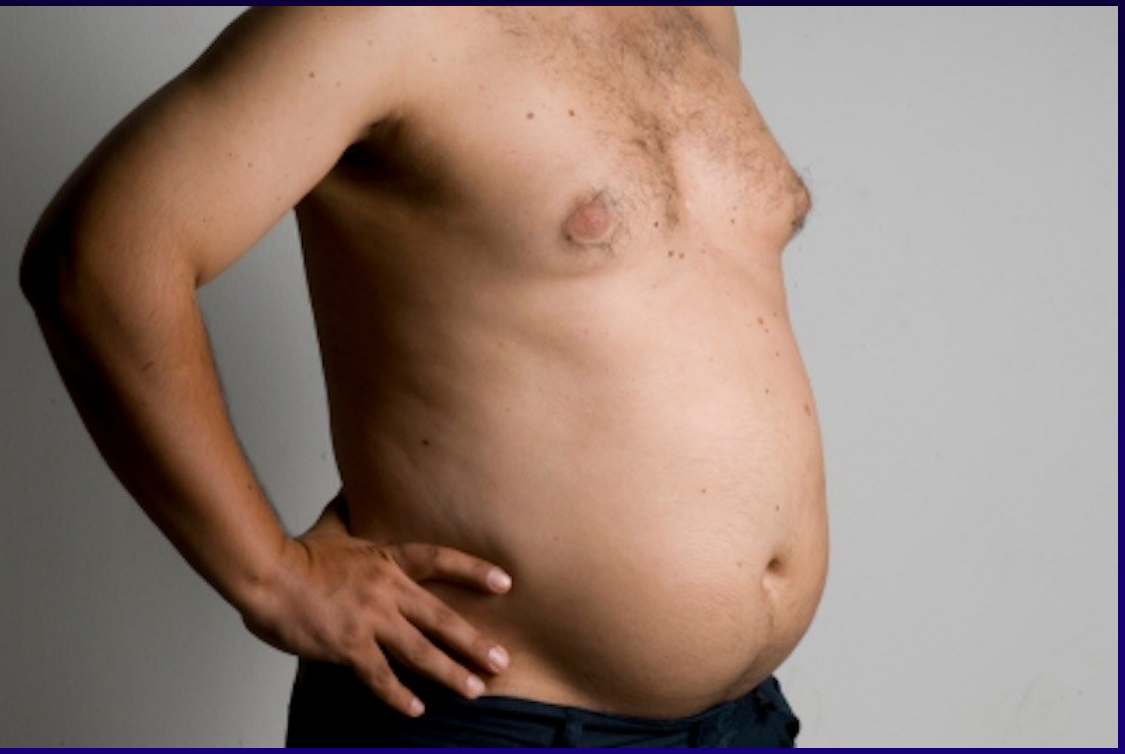
Masculinisation of males

Is it the Y chromosome or is it androgens?



Male - female differences

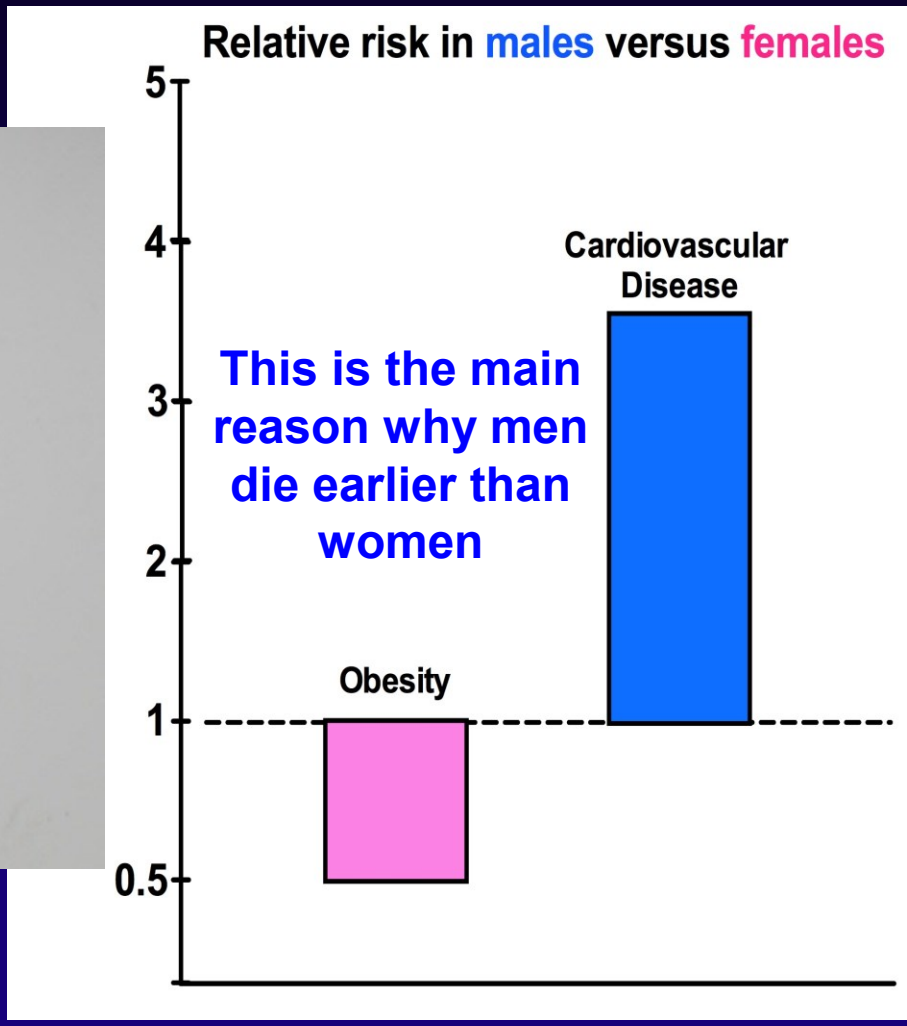
Fat deposition is fundamentally different



This is thought to reflect sex differences in energy needs/utilisation (from an evolutionary perspective)

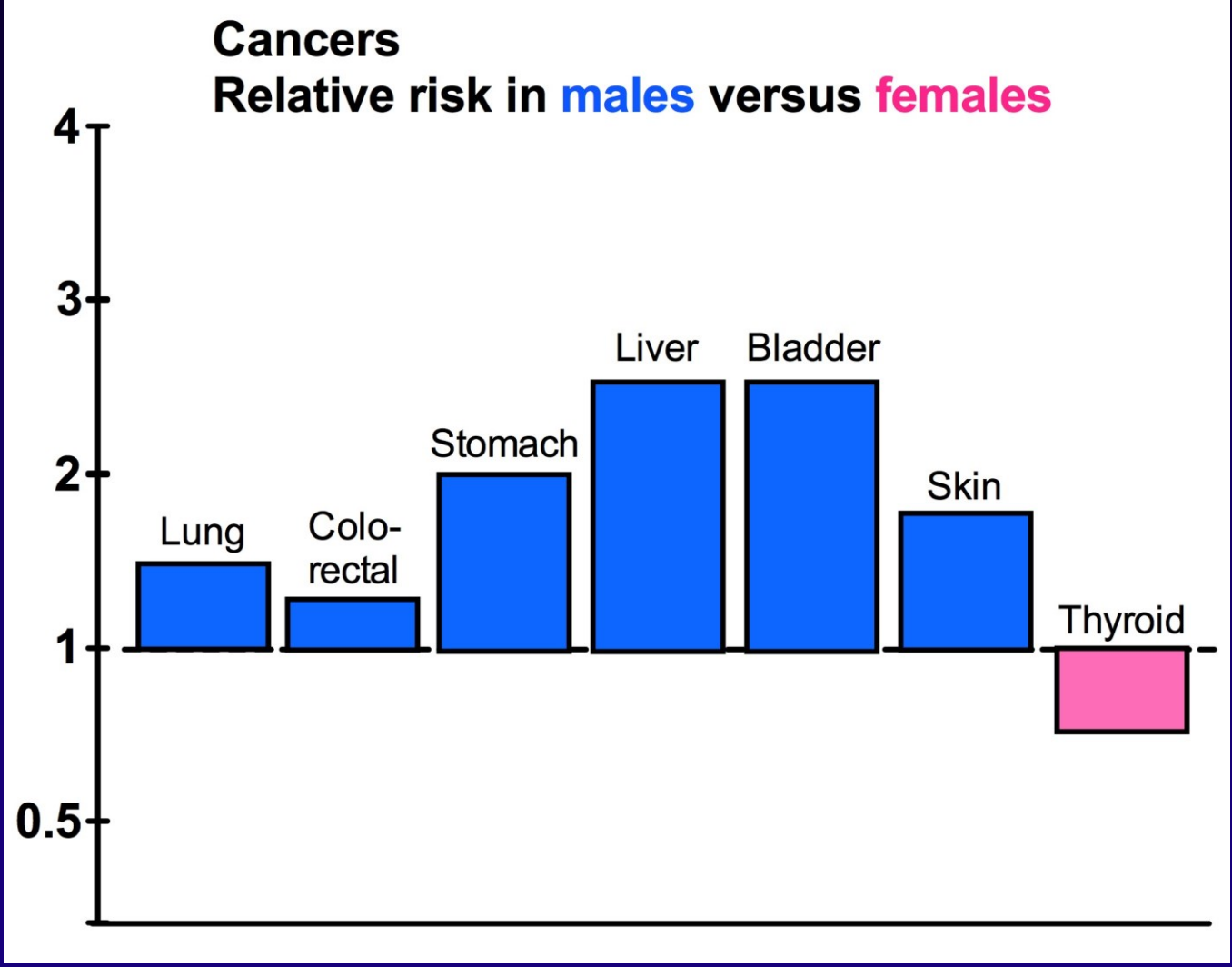
Male - female differences

Fat deposition is fundamentally different



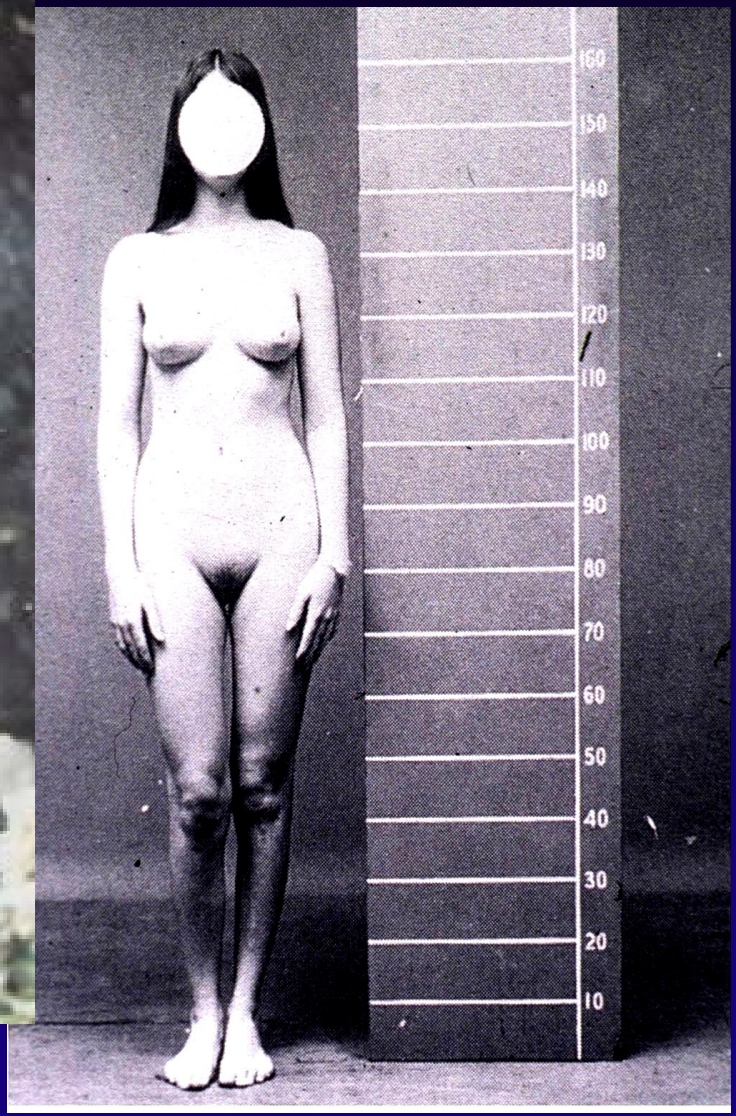
Male - female differences

Differences in disease risks



Masculinisation of males

How common are subtle disturbances of this?



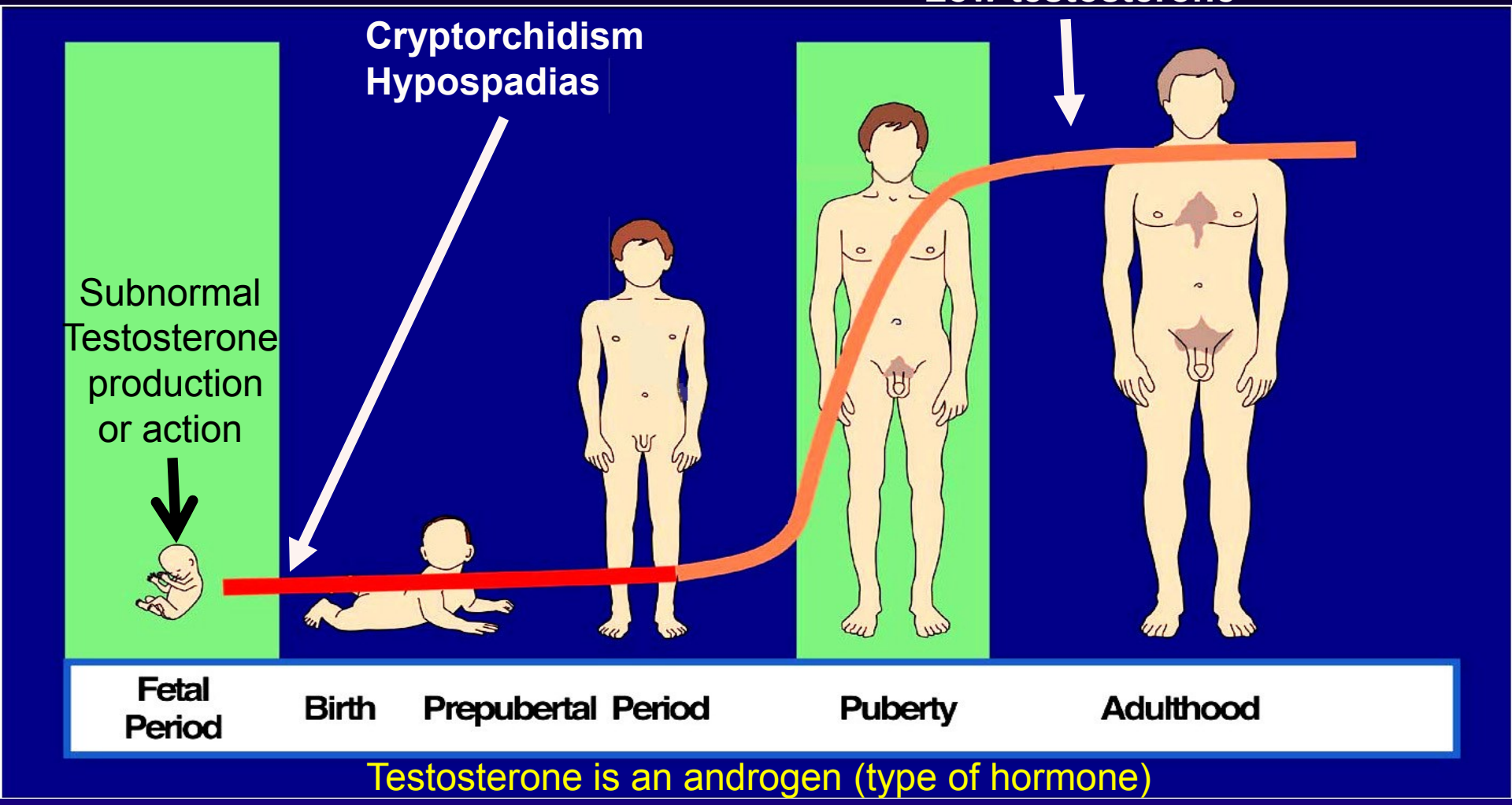
Prevalence data for reproductive disorders in newborn or young adult males

Parameter	Prevalence	Evidence
Cryptorchidism (undescended testis)	2-9%	Prospective EU studies
Hypospadias (Penis abnormality)	0.4-0.9%	Prospective EU studies
Low sperm counts	16-20%	Prospective EU studies
Testis germ cell cancer	0.45%	Registry data (reliable)
Low adult testosterone (Compensated Leydig cell failure)	~10%	Longitudinal birth cohorts

Environmental/lifestyle factors are implicated in the high/increasing prevalence of these disorders. What these factors are, is unknown

The commonest reproductive disorders of the developing and young adult male

'Testicular dysgenesis syndrome'

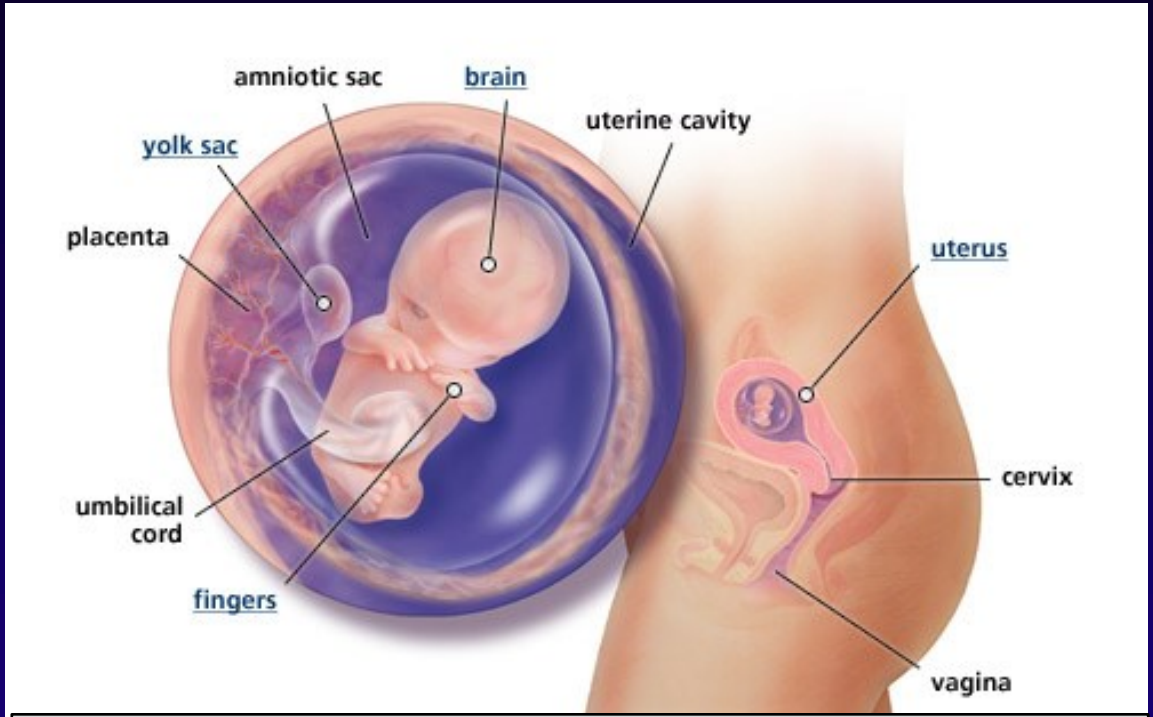


Testosterone is an androgen (type of hormone)

The ‘masculinisation programming window’ (MPW)

Studies in rodents have identified that androgen exposure within the MPW is critical for determining normal reproductive development and ultimate reproductive organ size

The available evidence suggests that TDS disorders arise because of androgen deficiency in the MPW

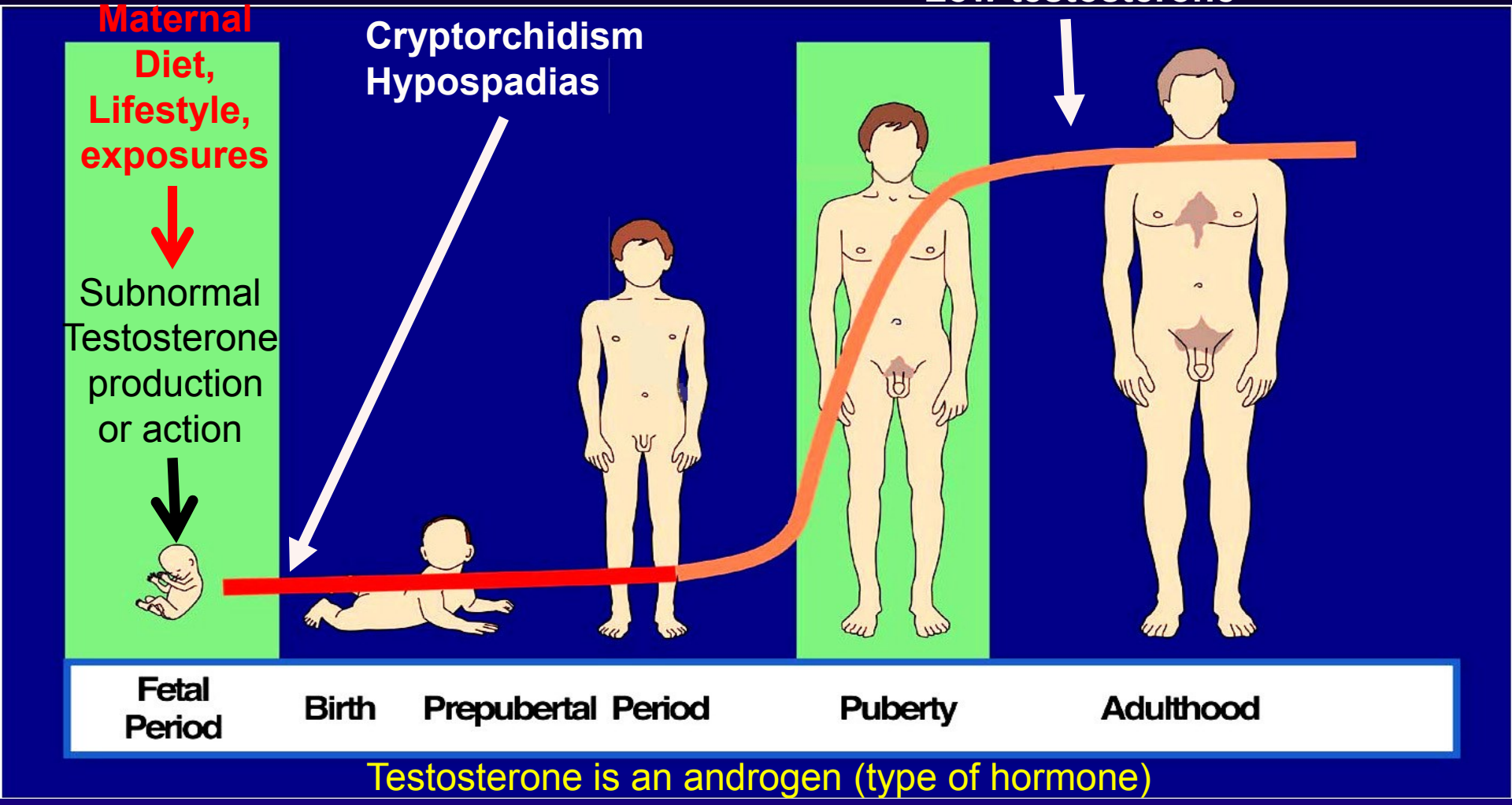


The human equivalent of the MPW is estimated to be within 8-14 weeks’ gestation

Based on: Welsh et al (2008) J Clin Invest 118: 1479-1490

The commonest reproductive disorders of the developing and young adult male

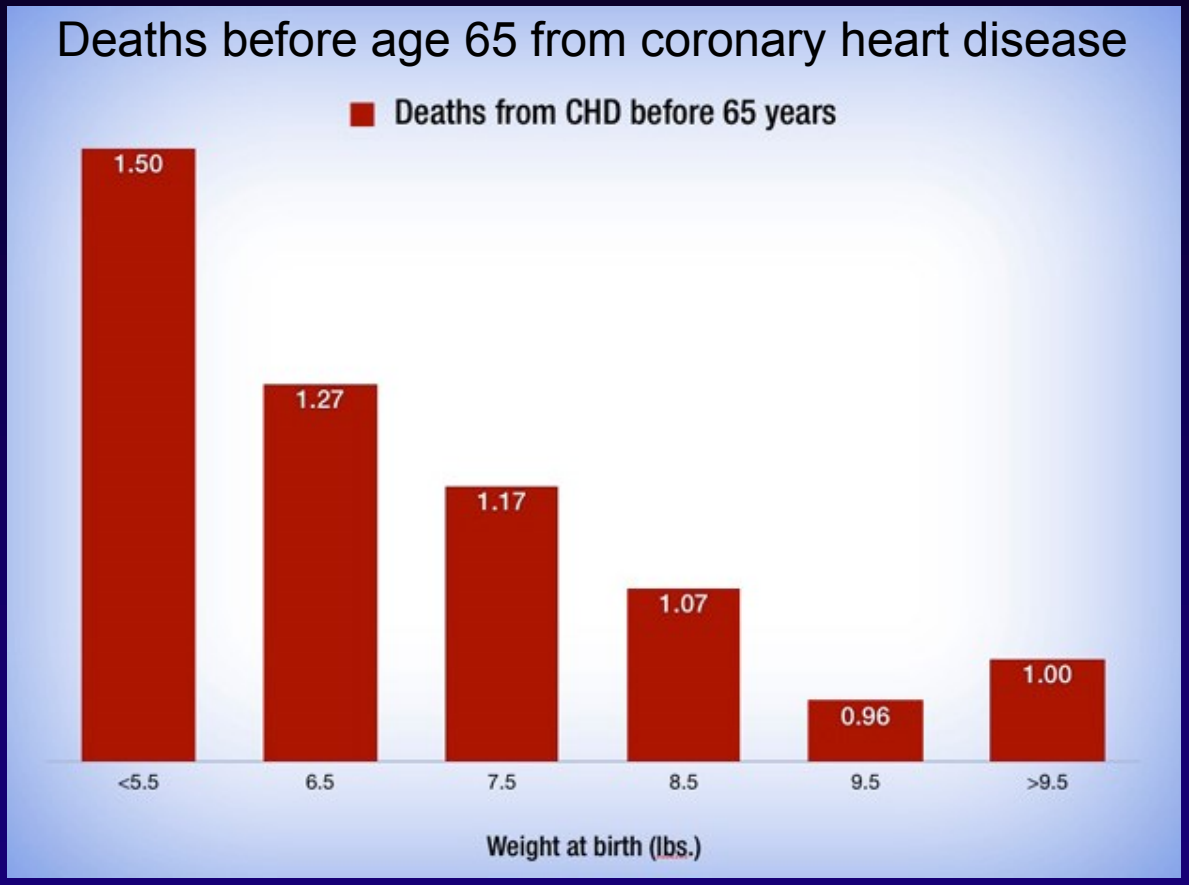
'Testicular dysgenesis syndrome'



Testosterone is an androgen (type of hormone)

Fetal programming of adult disease risk

Adult cardiovascular disease is inversely related to birth weight



The picture is similar for blood pressure – the lower your birth weight the higher is your blood pressure

The higher your birth weight the lower your adult blood pressure and the lower your risk of coronary heart disease

Birth weight is *positively* associated with adult testosterone levels (independent of adult bodyweight)

Birth Weight in Relation to Sex Steroid Status and Body Composition in Young Healthy Male Siblings

Griet Vanbillemont, Bruno Lapauw, Veerle Bogaert, Hélène De Naeyer, Dirk De Bacquer, Johannes Ruige, Jean-Marc Kaufman, and Youri E. C. Taes

Department of Endocrinology (G.V., B.L., V.B., H.D.N., J.R., J.-M.K., Y.E.C.T.), Ghent University Hospital; and Department of Public Health (D.D.B.), Ghent University, 9000 Ghent, Belgium

Context: Sex steroid concentrations have a strong genetic determination, but environmental factors and body composition play an important role. From studies in children with intrauterine growth restriction, low birth weight has been associated with altered gonadotropin concentrations.

Objective: We aim to investigate sex steroid concentrations in healthy young brothers in relation to birth weight (normal gestational age), body composition, and parental steroid concentrations.

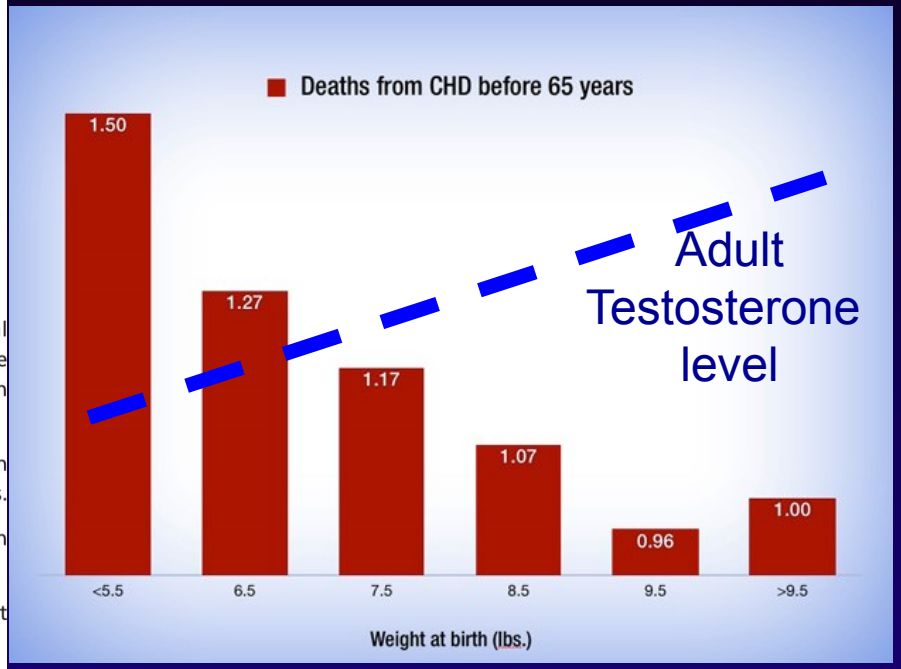
Design and Setting: We conducted a cross-sectional, population-based sibling pair study with inclusion of parental data.

Participants: A total of 677 men (25–45 yr old) were included in this study, with 296 independent pairs of brothers and 122 fathers.

Main Outcomes: We measured testosterone, estradiol, leptin, adiponectin, IGF-I (immunoassays), and free steroid hormones (calculated) in relation to birth weight and changes in body composition (dual-energy x-ray absorptiometry).

Results: Birth weight was associated with serum testosterone ($P = 0.0004$) and SHBG ($P = 0.0001$), independent from weight, age, or fat mass, whereas no association with (free) estradiol, LH, or FSH was found. Paternal testosterone ($P = 0.02$), estradiol ($P = 0.04$), and SHBG ($P = 0.0004$) were associated with the respective sex steroid concentrations in the brothers. Weight increase (population rank) during life, was associated with lower testosterone (−15%; $P < 0.001$), independent from current weight and with higher free estradiol concentrations (+8%; $P = 0.002$), whereas weight decrease was associated with higher testosterone (+13%; $P < 0.001$).

Conclusion: Birth weight and paternal steroid concentrations are associated with testosterone concentrations, independent from adult weight. These findings support the concept of *in utero* programming across the range of birth weight. (***J Clin Endocrinol Metab*** **95: 1587–1594, 2010)**



Therefore, higher birth weight is associated with reduced risk of adult obesity and cardiovascular disease AND with higher blood testosterone levels (in men)

Disorders in men associated with lowered testosterone levels

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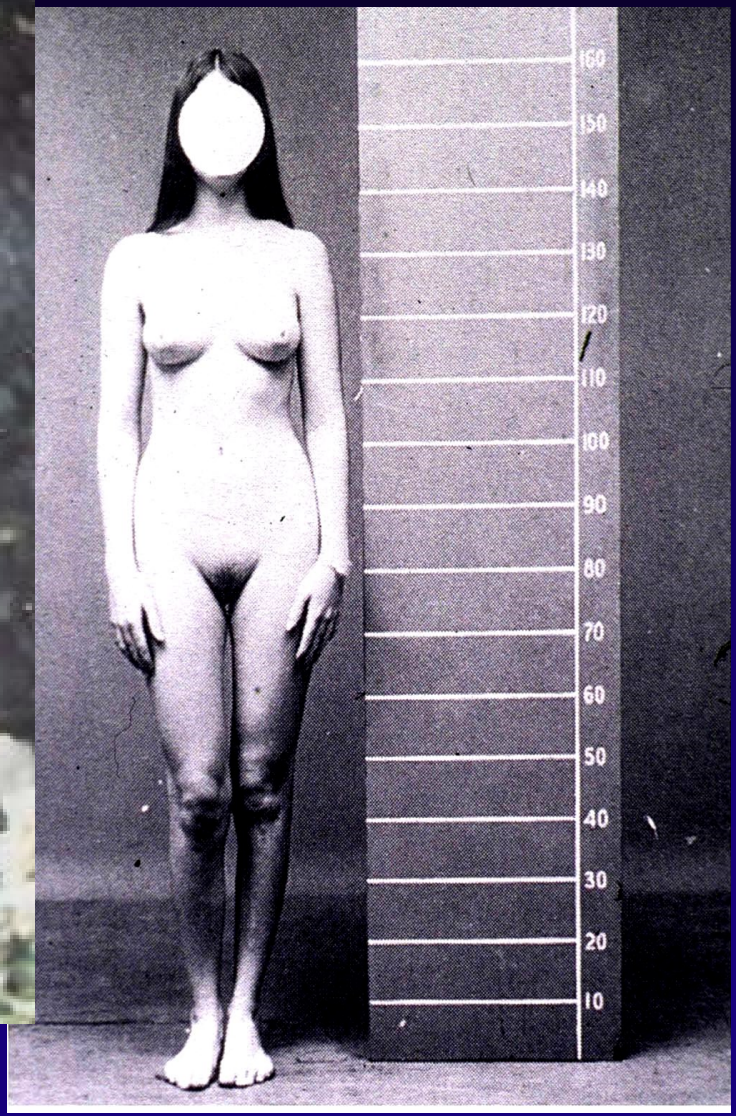
- Cardiovascular disease
- Hypertension
- Visceral obesity
- Insulin resistance
- Type II diabetes
- Fatty liver disease
- Pro-inflammatory blood profile
- **Erectile dysfunction**

Early warning alert

Normal female development

Female development is about avoiding androgens



Male - female differences

Fat deposition is fundamentally different

As intra-abdominal fat increases in men

Testosterone decreases*

Insulin resistance increases*

*Both these changes lead to more fat deposition

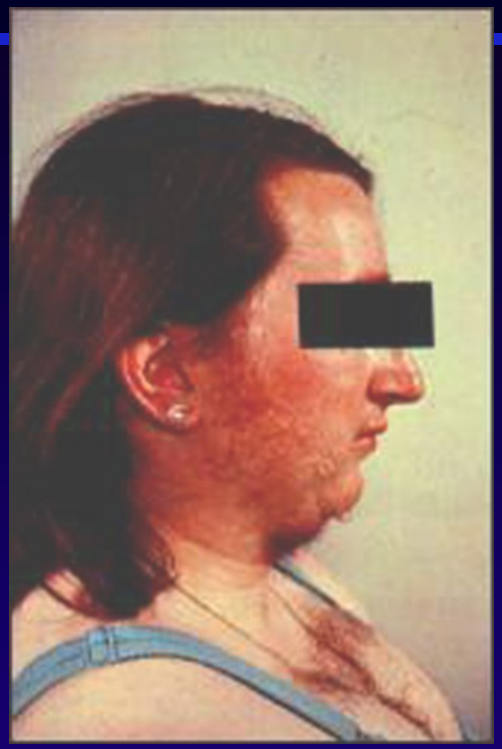
In women, it operates in exactly the opposite direction

Polycystic ovary syndrome (PCOS)

Affects 7-15% of women

In animal models (monkeys, sheep), PCOS can be induced via increased androgen exposure in fetal life

Some elements can be induced via increased androgen in adulthood



Slide courtesy of Dr Colin Duncan

PCOS Phenotype

Clinical Hormonal Ovarian Metabolic

Polycystic ovary syndrome (PCOS)

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Some elements can be induced via increased androgen in adulthood

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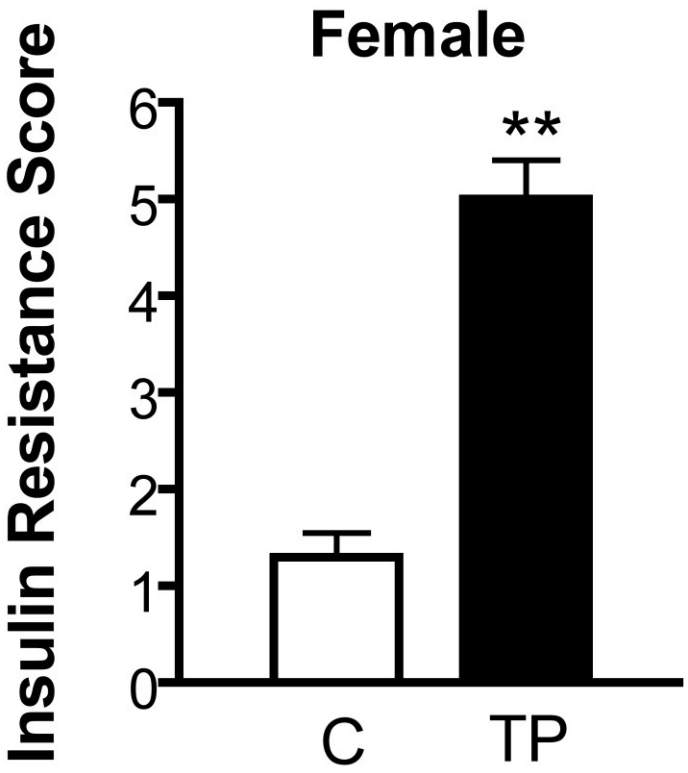
PCOS Phenotype

Clinical Hormonal Ovarian Metabolic

Effect of androgen (TP) exposure in adult female sheep and in females exposed in utero to androgens (PCOS*)



*PCOS = polycystic ovary syndrome (affects 7-15% of women of reproductive age)

Slide courtesy of Dr Colin Duncan

Male versus female
Mirror images?

- In adult men, disease risks associated with *subnormal* T levels (CVD, obesity, type 2 diabetes, liver disease) are associated with *supranormal* T levels in women

- In many instances androgens and oestrogens have different or opposite cell-specific effects in males versus females

- Many aspects of our sex-biased behaviour can be viewed as being ‘opposites’

Negative feedback!

Impacts of obesity and ‘Western’ diet on fertility

Human disorders positively associated with dietary effects

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Adults

- Obesity, waist circumference ✔
- Prediabetes & Type 2 diabetes ✔
- Cardiovascular disease ✔
- Impaired liver function, steatosis ✔
- •Altered oocyte development ✔
- •IVF outcome/success ✔
- •PCOS ✔
- •Reduced adult male testosterone ✔
- •Male libido/sexual function ✔
- •Semen Quality ✔
- •Mammary gland development/breast cancer ✔

Fetus/Babies/Children

- •Reduced fetal growth/birth outcomes ✔
- •Reduced anogenital distance ✔
- •Thyroid hormone levels ✔
- •Childhood obesity ✔
- •Kidney disease ✔
- •Behavioural disorders ✔
- •CpG methylation (girls) ?✔

✔ Association and/or causal evidence for dietary induction

A jump outside of the conventional

Out of our comfort zone

Why are we here?

Reproduction also offers us a unique opportunity to change future generations for the better – make them better adapted (Darwin)

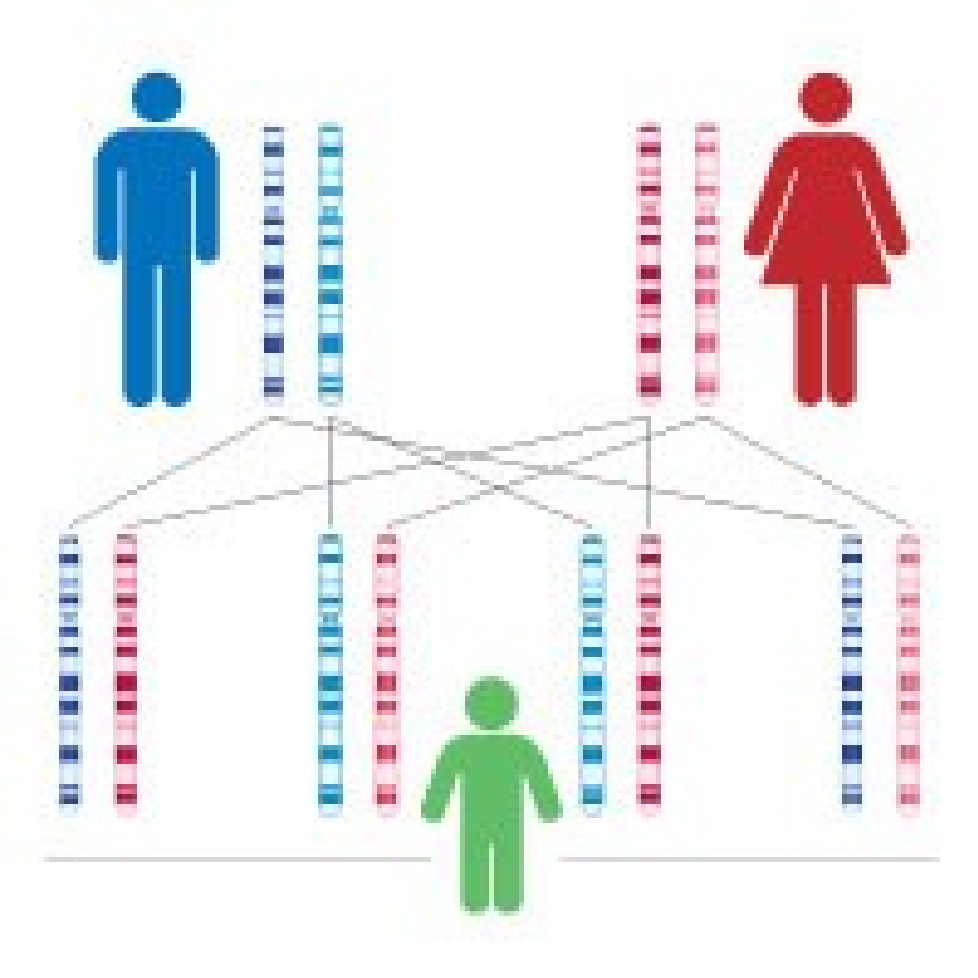
The pivotal role of reproduction

- Reproduction offers the opportunity to produce offspring that are better adapted to the prevailing environment (than their parents)

- According to natural selection, ***sexual*** reproduction offers a ***random*** way of changing the offspring ***in the hope*** that it may be better adapted to the prevailing environment. This seems awfully risky!

Genetic inheritance

DNA pattern of offspring is different from parents



Twin studies suggest that 40-70% of obesity is inherited, yet so far genetic explanations can only account for <5% of obesity

The pivotal role of reproduction

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- According to natural selection, ***sexual*** reproduction offers a ***random*** way of changing the offspring ***in the hope*** that it may be better adapted to the prevailing environment. This seems awful risky!

- But it could, in theory, be achieved by epigenetic adaptations – does this occur?

Epigenetics
Regulating how genes work

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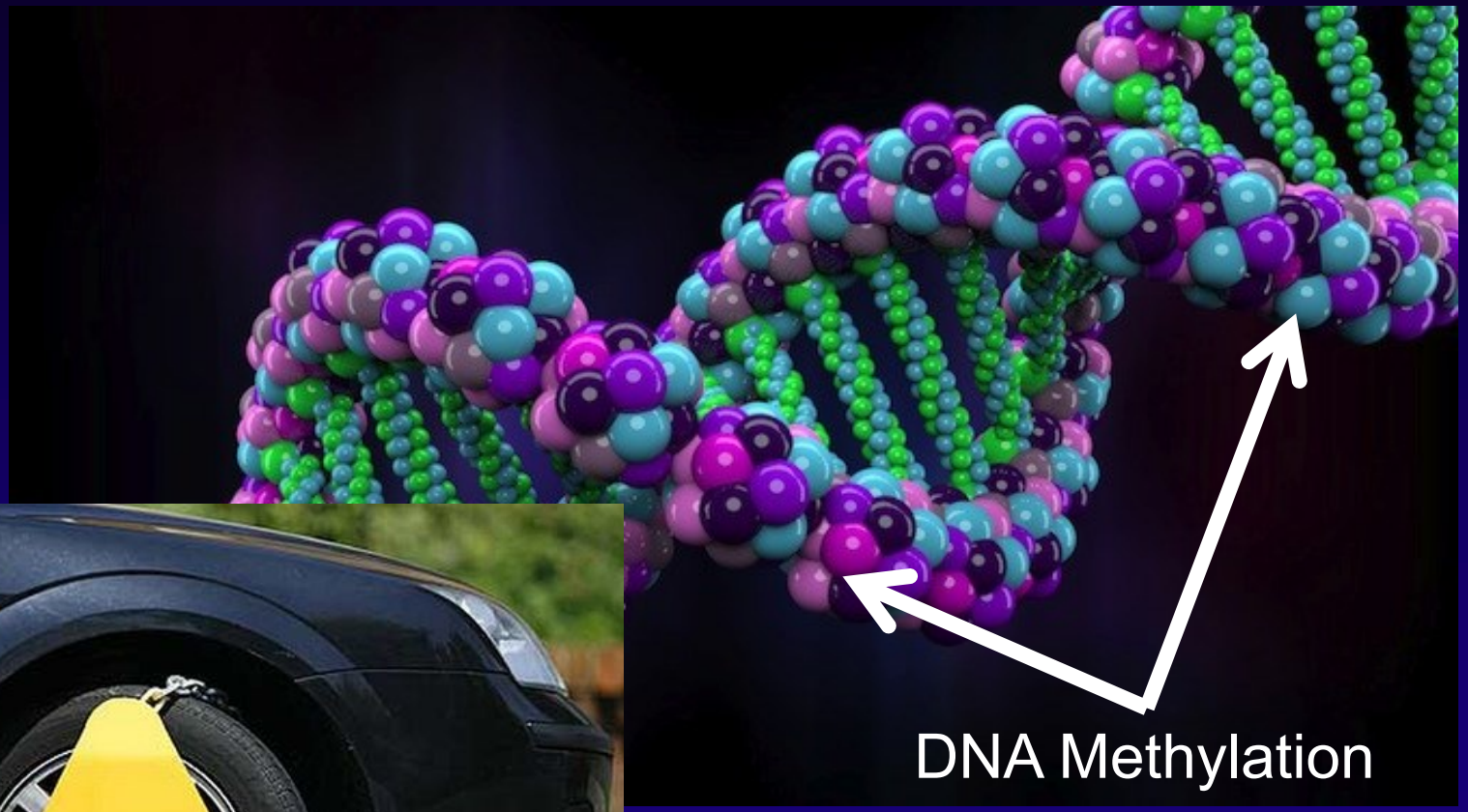
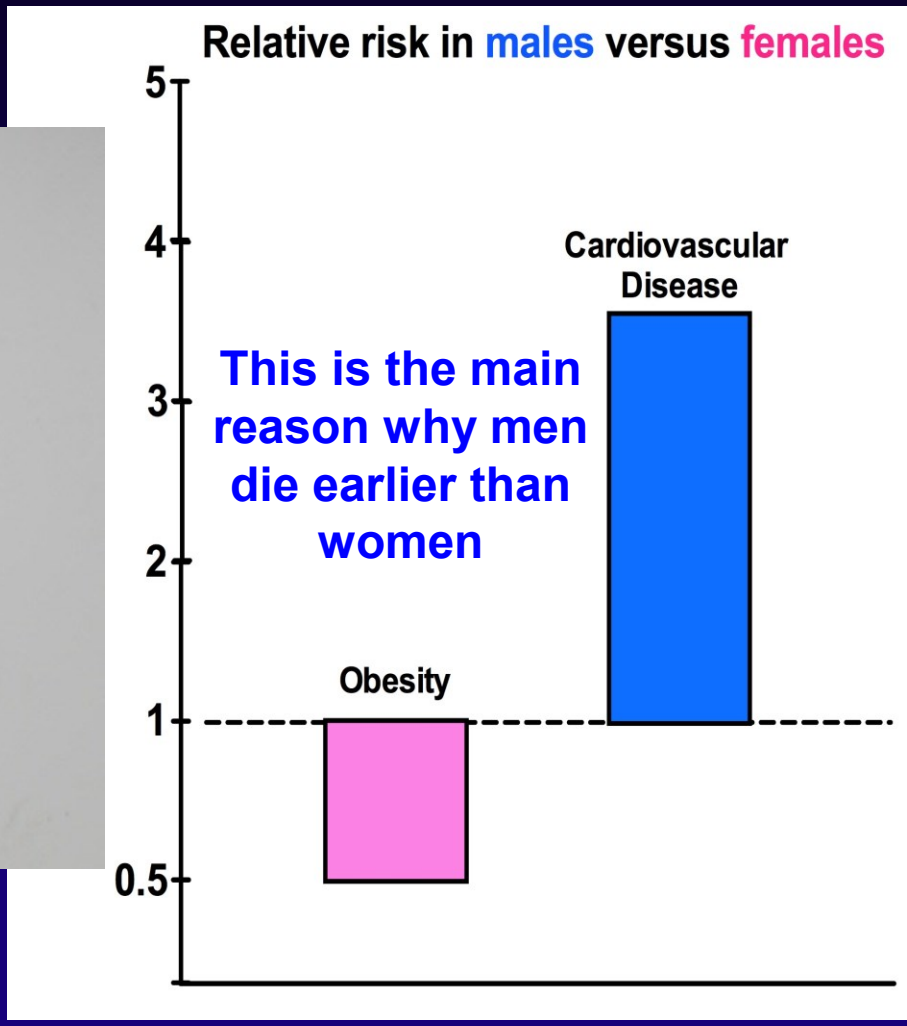


Male - female differences

Fat deposition is fundamentally different



Adverse phenotype in adult male rats

Visceral adiposity and insulin resistance

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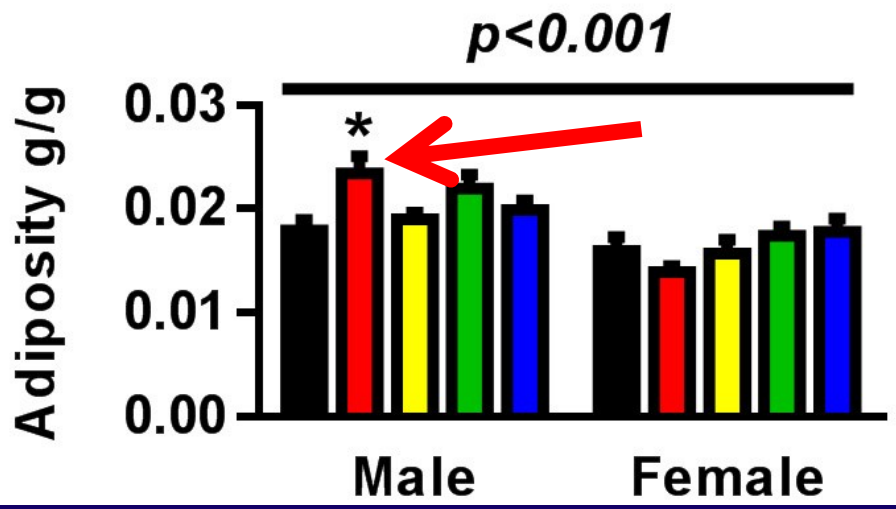
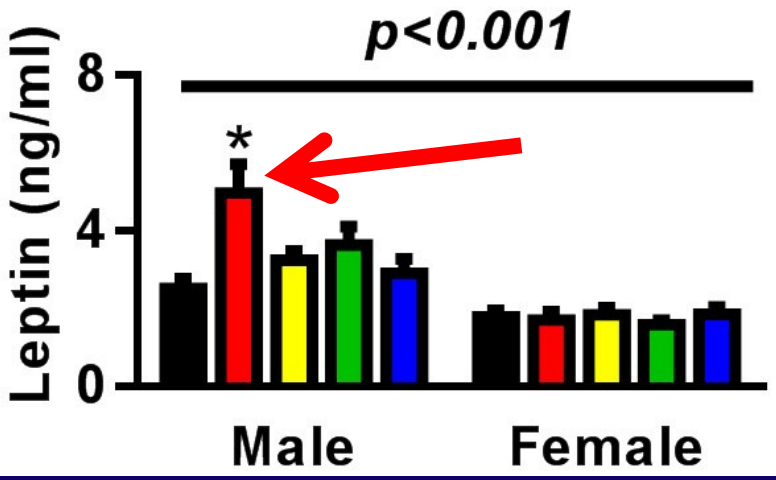
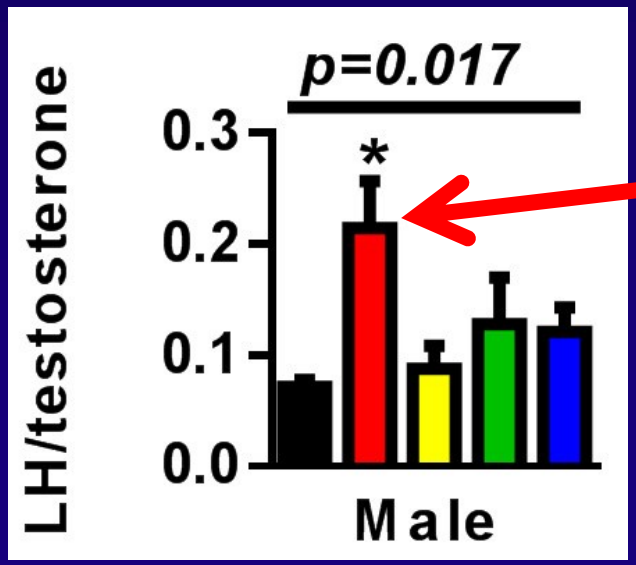
Visceral adiposity



Plasma Leptin





Primary hypogonadism

What caused this?

Tom Chambers et al – unpublished data

Male - female differences

Visceral adiposity

Over-consumption of calories is what makes us fat

But the rats that I showed you ate a normal control diet

The only intervention was in the diet of the male rats' ***grandfathers***

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For 14 weeks (from weaning onwards) the 'grandfathers' were fed a high fat diet that caused ~10% increase in bodyweight

The resulting 'effects' in the grandsons is presumed to be the result of epigenetic changes induced in the grandfathers to their sperm (or to their seminal plasma)

The pivotal role of reproduction

Sperm as a genetic and epigenetic memory transfer

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So it appears that sperm (and/or seminal plasma) are transferring epigenetic information that may modify the function of (DNA in) the resulting offspring

Thus, you are influenced both genetically and epigenetically by your grandfather (and grandmother)

Do these grandparental effects provide evidence of attempts to (epigenetically) better adapt the grandchildren to their environment?

Epigenetic remodelling of germ cells in both sexes occurs during early fetal life

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In all mammals, including humans, the **germ cell** epigenome is remodelled in fetal life

For example, DNA methylation is ‘wiped clean’ early on and is then reinstated later in gestation

Histone methylation also changes dramatically

These changes provide an opportunity for modifications to ‘adapt’ the fetus better to the perceived environment (via the mother)

Male - female differences

Visceral adiposity

Over-consumption of calories is what makes us fat

But it may also affect your children and/or your grandchildren

Thank you for your attention