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Gendered Life-Cycle Approach in practice

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Genetic causes of sex differences

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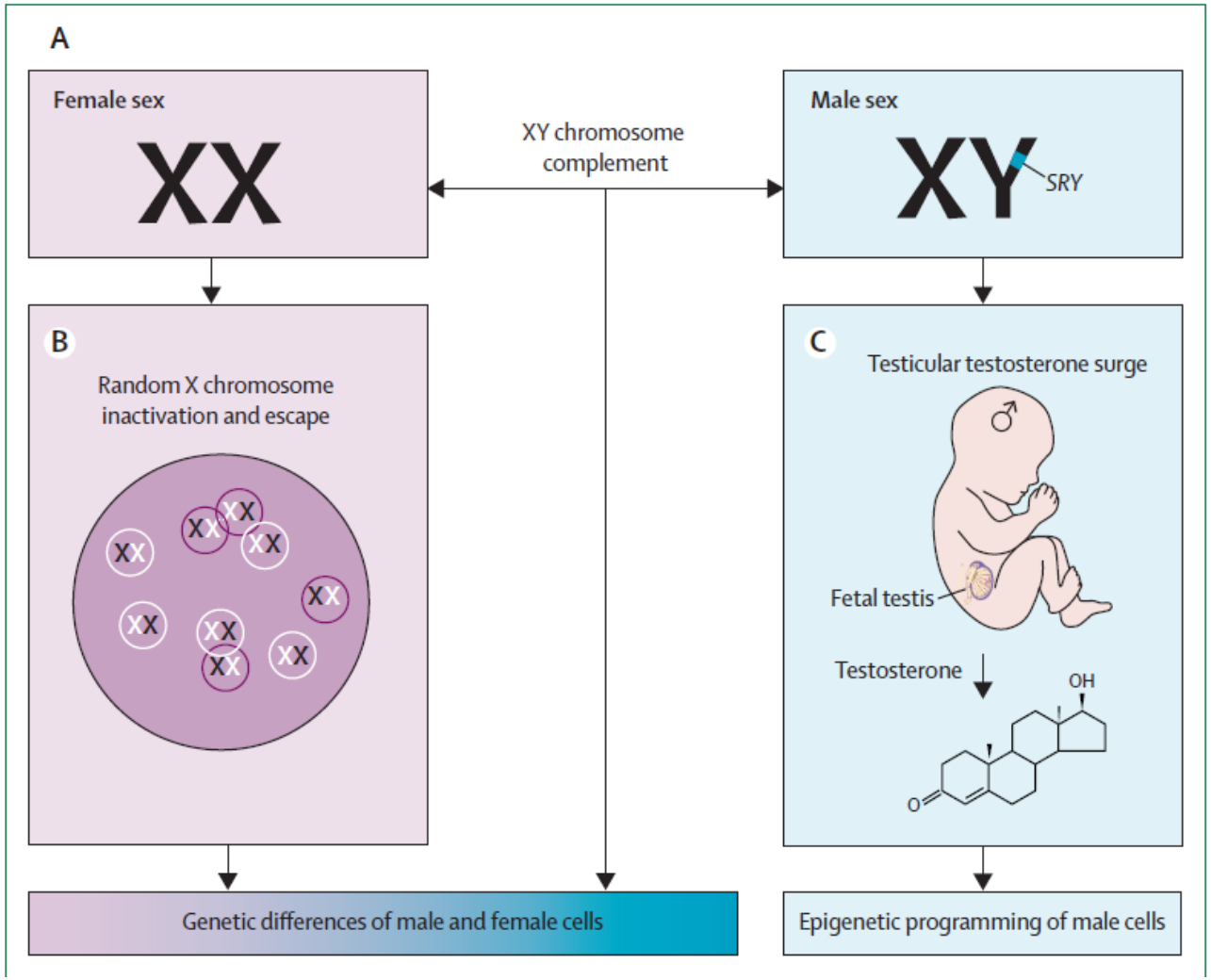
(A) Genetic sex differences start with cells carrying either XX or XY chromosome complement (eg, genes outside the testis-determining *SRY* gene), which generates ubiquitous sex differences in the molecular makeup of all male and female cells.

(B) Random inactivation of one X chromosome in female cells causes another level of sex differences in gene expression. Some X-linked genes escape inactivation in female individuals and have a higher expression in female than male individuals.

(C) The Y chromosomal *SRY* gene directs the development of a testis in male individuals, which produces a surge of testicular testosterone at the end of pregnancy. The testosterone surge programmes cellular gene expression and tissue structure in multiple organs of male individuals via epigenetic remodelling. The combination of these genetic and developmental events programmes sex differences in physiology and susceptibility to diseases that will manifest in adulthood.



Mauvais-Jarvis et al, 2020

Inter-relation between sex and gender in health, diseases, and medicine

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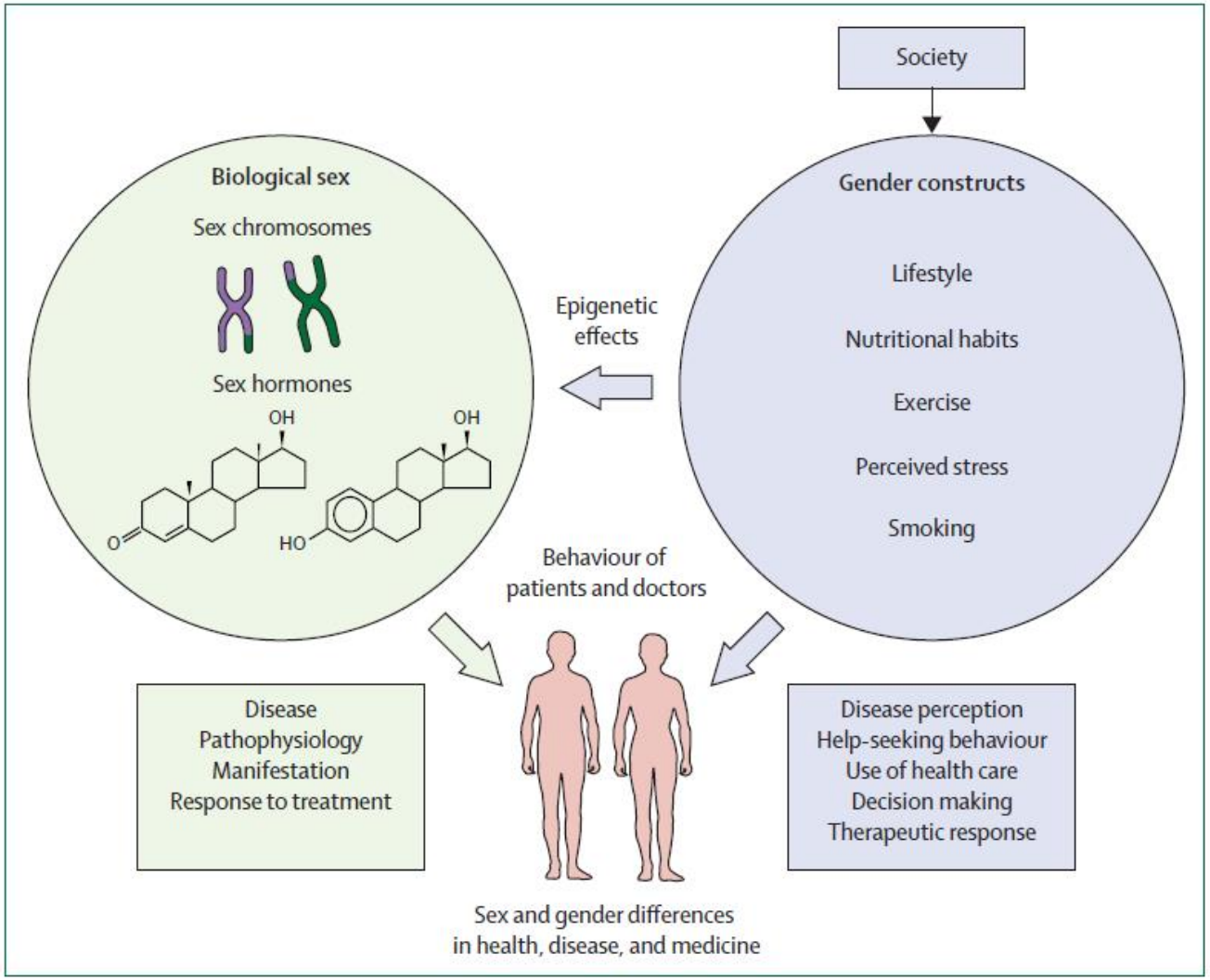
- Biological sex causes sex differences through genetic and hormonal influences in disease pathophysiology, clinical manifestations, and response to treatment.
- Sex also influences behaviours (towards more aggressive or caring phenotypes).
- On the other hand, gender-related behaviours (eg, smoking, lifestyle, perceived stress, and nutritional habits) produce epigenetic modifications that modulate the expression of biological sex.
- Gender constructs determine patients' perception of disease, help-seeking behaviour, and individual use of health care. Gender constructs also influence decision making and trigger different therapeutic responses from providers, biased by gender.



Mauvais-Jarvis et al, 2020

Sex Differences in Age-associated Genome Instability

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Type of Genome Instability	Species	Sex Differences Detected?	Sex Most Affected
DNA damage/mutations			
Nuclear	Human	Yes	Male
	Mouse	Sometimes	Mixed
	Fly	Yes	Mixed
Mitochondrial	Rat	Yes	Male
	Mouse	?	?
	Fly	?	?
Telomere attrition	Human	Yes	Male
	Mammals	Sometimes	Male
	Birds	Sometimes	Male
	Fly	No	—
	Worm	—	—
Epigenetic			
DNA methylation	Human	Sometimes	Male
	Mouse	Maybe	?
Histone modifications	Fly	Maybe	?
	Worm	Maybe	?
Nuclear architecture	Human	Maybe	?
	Mouse	Maybe	?

Fischer & Riddle, 2018

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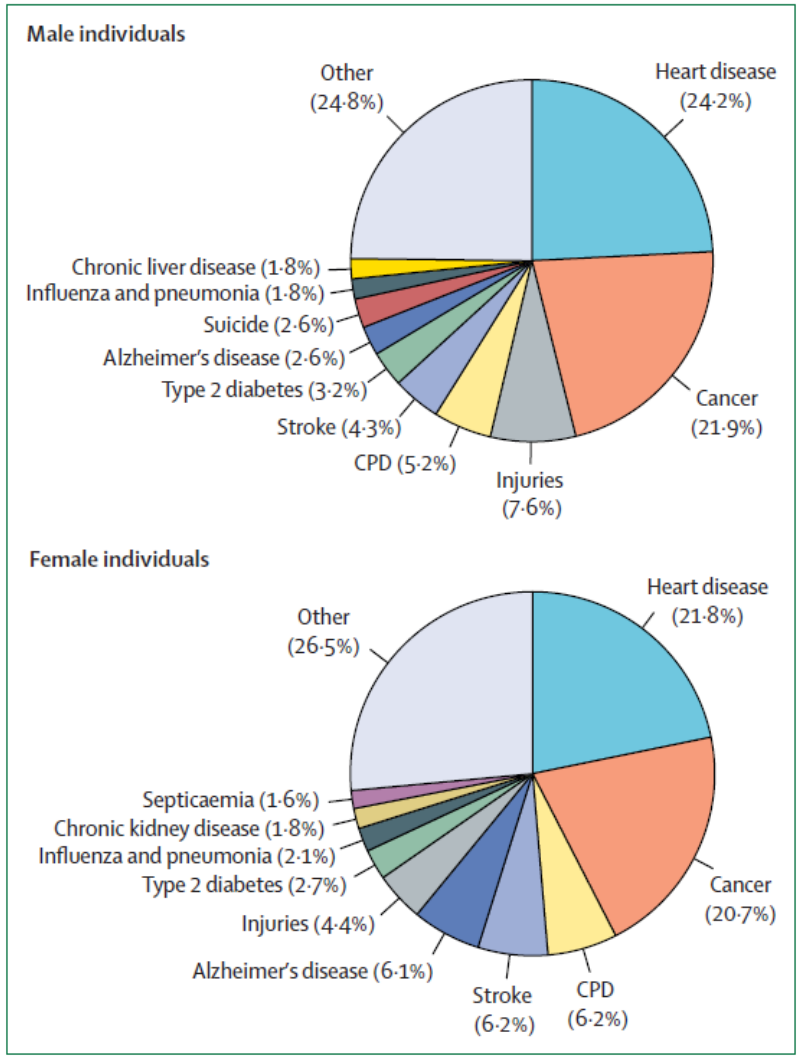
Percent distribution of the ten leading causes of death, by sex: USA, 2017



- These sex and gender disparities are relevant to other high-income countries as well as low-income and middle-income countries, where the burden of these diseases becomes increasingly like those in high-income countries.
- In most diseases, efforts to separate the effects of sex and gender are still incomplete, so that we just refer to the differences among women and men.

Mauvais-Jarvis et al, 2020

Disabling disorders with high sex influence on prevalence

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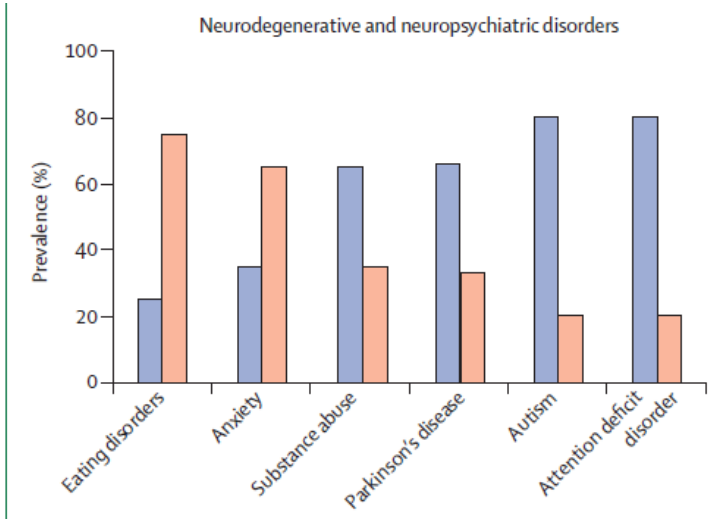

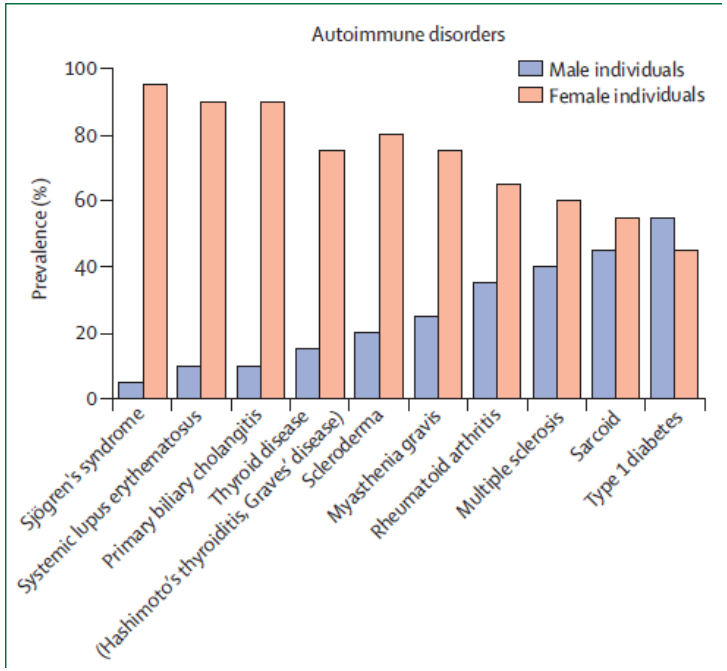

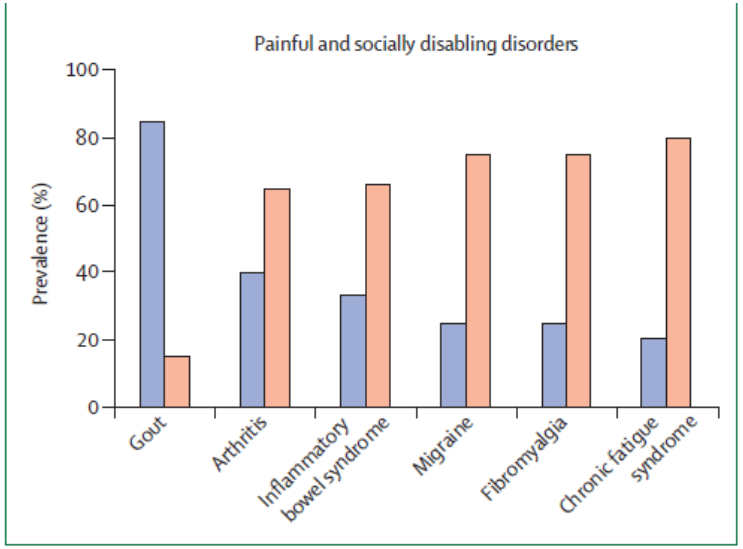

- Sex distribution of disorders that exhibit a strong sex influence.

Mauvais-Jarvis et al, 2020

Sex and gender differences in leading causes of mortality (1)

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	Sex differences		Gender differences, women compared with men
	Male sex	Female sex	
Heart disease	Younger age; more obstructive coronary artery disease; more heart failure with reduced ejection fraction	Older age; more coronary microvascular dysfunction; more heart failure with preserved ejection fraction	Underdiagnosed inflammatory airway disease; less evidence-based treatment; higher myocardial infarction mortality; fewer heart transplantations, although more frequent donors
Cancer	Higher prevalence and mortality; genetic cell autonomous predisposition; stimulatory role of testosterone after puberty in hepatocellular carcinoma	Lower prevalence and mortality for some cancers; higher expression of X-encoded tumour suppressors; protective effect of oestrogen after puberty in hepatocellular carcinoma	Not identified
COPD and asthma	COPD: higher prevalence; asthma: higher prevalence before puberty	COPD: early onset with less tobacco exposure; majority of non-smoking COPD; high exacerbation rates; immune dysregulation; decline in lung function at menopause; asthma: higher prevalence in middle-age; premenstrual asthma; improves after menopause	COPD: smoking advertisements targeting women in the 1960s; increased smoking rates; often misdiagnosed; suffer from comorbid conditions, anxiety, and depression

COPD=chronic obstructive pulmonary disease.

Mauvais-Jarvis et al, 2020

Sex and gender differences in leading causes of mortality (2)

Co-funded by the Erasmus+ Programme of the European Union

	Sex differences		Gender differences, women compared with men
	Male sex	Female sex	
Ischaemic stroke	Younger age of onset	Older age of onset; sex-specific risk factors: hypertensive disorders of pregnancy, gestational diabetes, contraception; aspirin provides greater benefit for women in primary prevention	Often undertreated; poorer outcome because of old age; higher disability, poststroke depression, and social isolation
Alzheimer's disease	Lower prevalence; more likely diagnosed with mild cognitive impairment	Higher prevalence; apolipoprotein E epsilon 4 provides four times higher risk; risk increase with pregnancy, hypertensive disorders of pregnancy, early menopause, and late initiation of menopausal hormone therapy; clinical course is faster	Better performance on verbal memory tests; often delayed or missed diagnosis; greater burden of disease caregiving
Type 2 diabetes	More frequent impaired fasting glycaemia; testosterone deficiency predisposes and testosterone therapy protects	More frequent impaired glucose tolerance; greater clustering of cardiovascular risk factors; menopause predisposes and oestrogen therapy protects	Undertreatment of type 2 diabetes in women

Mauvais-Jarvis et al, 2020

Sex and gender differences in leading causes of mortality (3)

Co-funded by the Erasmus+ Programme of the European Union

	Sex differences		Gender differences, women compared with men
	Male sex	Female sex	
Influenza	Predominant in young boys	Predominant in adults; morbidity and mortality are higher, especially in pregnant women; higher antibody titres following vaccination	Different roles and occupations lead to exposure to different strains of influenza A virus; higher vaccine hesitancy and lower vaccine receipt
Chronic kidney disease	More rapid rate of progression; testosterone might be deleterious	Higher prevalence; risk increases with hypertensive disorders of pregnancy; oestrogens might be protective	Receive fewer kidney transplants; receive fewer arteriovenous fistulas; potential dialysis overdose or administration of larger amounts of erythropoietin-stimulating agents
Chronic liver diseases	Higher risk of primary sclerosing cholangitis, chronic viral hepatitis, cirrhosis, and hepatocellular carcinoma; higher prevalence of alcoholic liver disease; higher risk of NAFLD, fibrosis, and mortality; testosterone is protective against NAFLD; NASH resolution requires moderate bodyweight reduction	Higher risk of primary biliary cholangitis and autoimmune hepatitis; higher susceptibility to alcoholic liver disease; protected from NAFLD and fibrosis before menopause but not after menopause; oestrogens are protective against NAFLD, whereas testosterone is detrimental; greater weight loss is required for NASH resolution	Greater weight loss is required for NASH resolution
Depression	Less frequent but more lethal suicide attempts; irritability, aggression, violence, substance abuse, risky behaviour, and somatic complaints	Higher prevalence; hyperphagia, weight gain, hypersomnia, anxiety; role for gonadal hormones in depression	More likely to be diagnosed

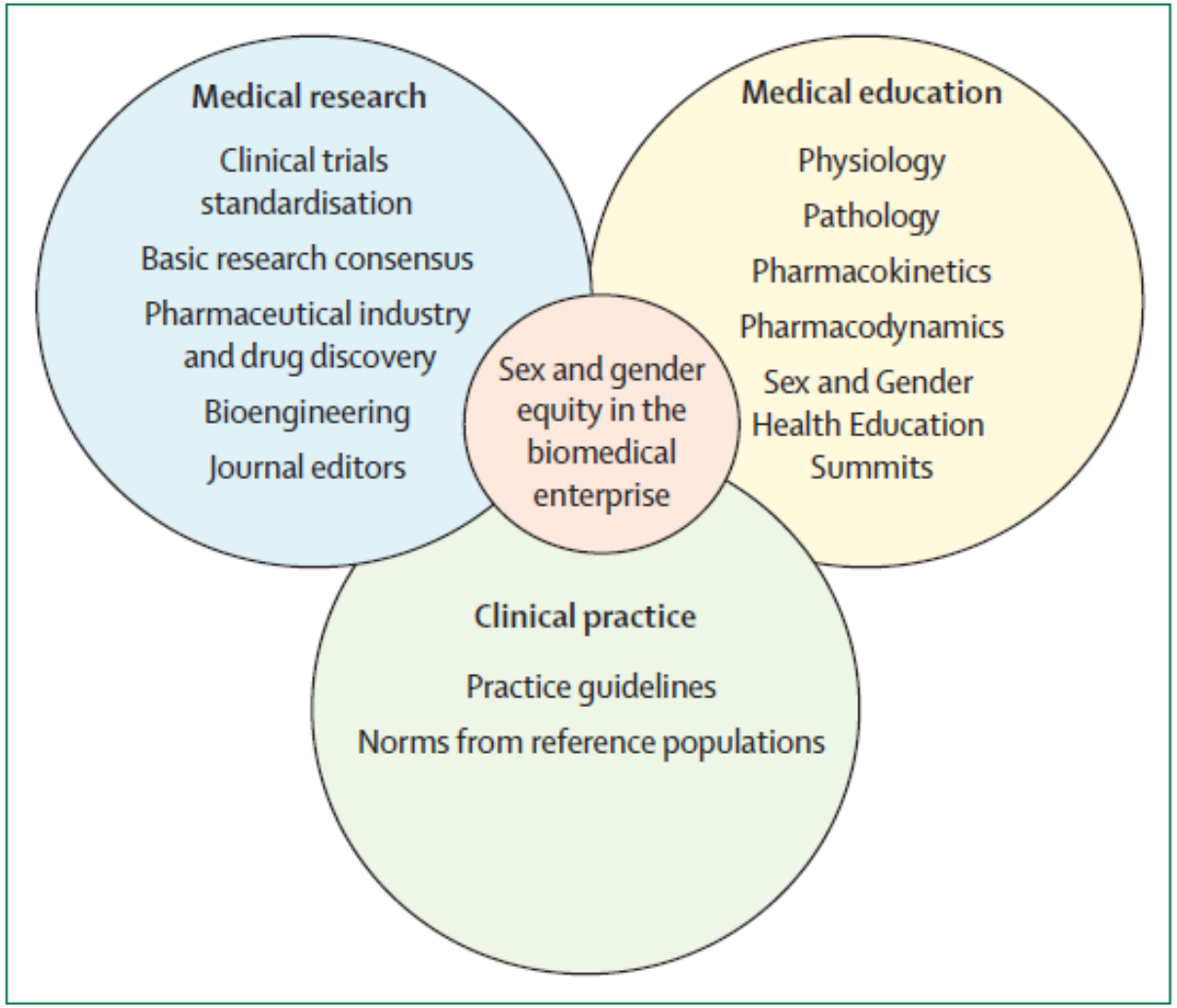
NAFLD=non-alcoholic fatty liver disease. NASH=non-alcoholic steatohepatitis.

Mauvais-Jarvis et al, 2020

Recommendations to promote sex and gender equity in the biomedical enterprise

Co-funded by the Erasmus+ Programme of the European Union

- The influence of sex and gender on human health and disease continues to be underestimated, understudied, and underutilised in medical practice.
- The beliefs, attitudes, and knowledge of clinicians and researchers regarding the importance of sex and gender in biology, disease, and medicine are key barriers in addressing these pressing issues.
- Efforts to bring sex and gender into the mainstream of modern medical research, practice, and education are urgently needed, as the lack of appreciation for sex and gender differences harms both women and men.
- Several steps can be taken to promote gender equity at all levels of the biomedical enterprise.

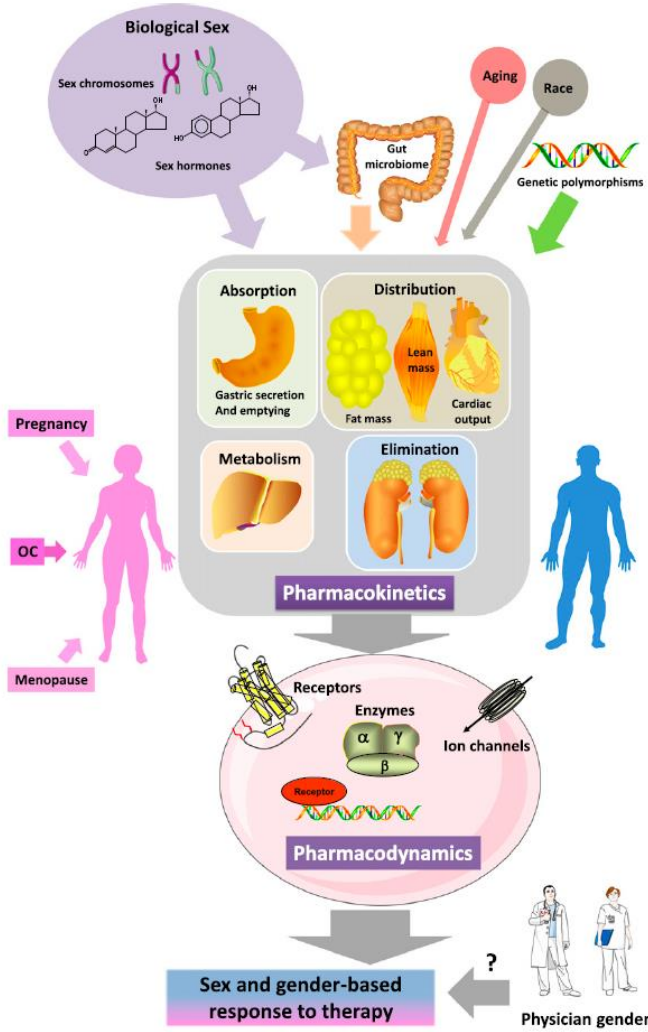


Mauvais-Jarvis et al, 2020

Sex as a genetic modifier of the pharmacological response to drugs

Co-funded by the Erasmus+ Programme of the European Union

- Biologic sex via sex-specific genetic and hormonal influences on cellular systems alters the transcriptome, proteome, and metabolome of all cells and organs as well as the gut microbiome and influences pharmacokinetics (e.g., absorption, distribution, metabolism, and elimination of drugs) and pharmacodynamics (e.g., the effect of drugs on receptors, ion channels, enzymes, and signaling pathways).
- Aging, race, and genetic polymorphism also influence pharmacokinetics and pharmacodynamics parameters in a sex-specific manner. In women, the hormonal influences of pregnancy, menopause, and the use of OCs also produce sex differences in the pharmacokinetics and pharmacodynamics of drugs.
- Finally, physician gender could add an additional level of difference in response to treatment.



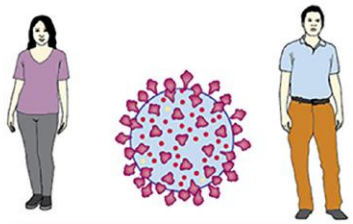
Mauvais-Jarvis et al, 2021

Gender disparities in Covid-19 pandemic

Co-funded by the Erasmus+ Programme of the European Union

Sex Differences

- Hormonal factors
- Immune response
- Inflammatory response
- ACE2 receptors
- Others



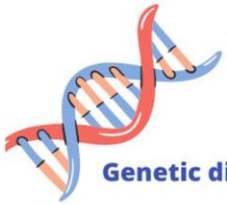
Age and co-morbidities

Morbidity and Mortality from COVID-19

Gender Differences

- Compliance with public health preventive measures
- High risk behaviors
- High risk jobs
- Others

Ya'qoub et al, 2021



Genetic differences

↑ Expression of protective X-linked immune-modulatory genes

↑ TLR-7 driven IFN response

Immunodeficiency polymorphisms

Hormonal differences

Protective role of estrogen signalling

Estrogen mediated ACE-2 downregulation → Decreased viral entry

Immunosuppressive effect of Testosterone

Immunological differences

Stronger antiviral immune response

↑ Antiviral T cell response

↑ Levels of circulating antibodies

↑ Levels of pro-inflammatory cytokines

Behavioural differences

↑ High risk behaviours
Risk of Exposure

↑ Hygiene practices
Adherence to social distancing

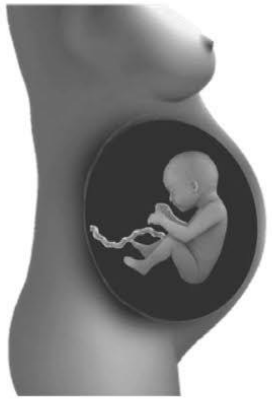
Raza et al, 2021

The Developmental Origins of Health and Disease (DOHaD) concept

Co-funded by the Erasmus+ Programme of the European Union

Maternal environmental challenges → **Developmental programming** → **Offspring outcomes in adult life**

Stress
Undernutrition
Overnutrition



Mechanisms
Placental function
Endocrine milieu
Epigenetic changes
Oxidative stress

Obesity
Diabetes
Hypertension
Behavioral problems
Fetility alterations

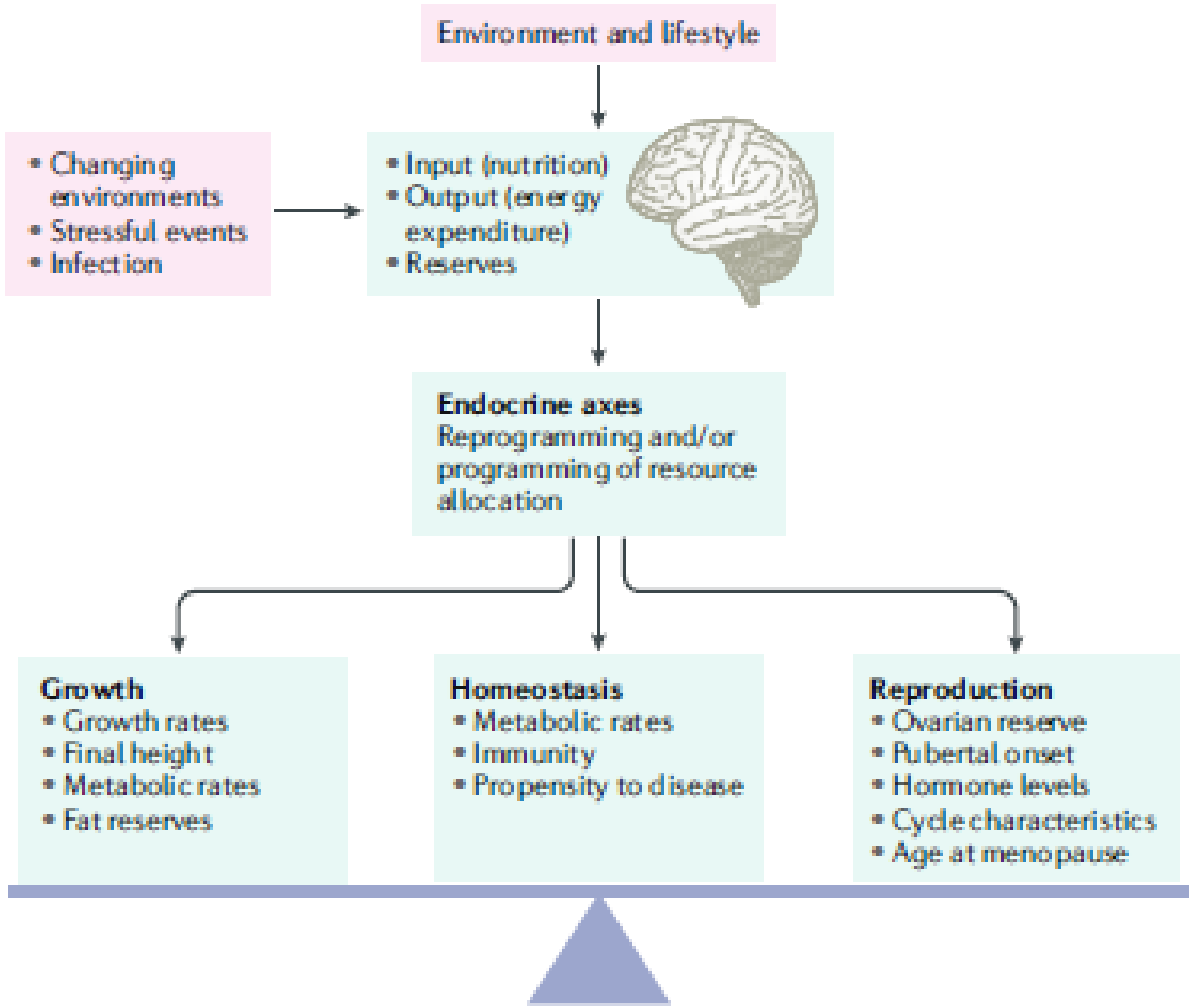
- (DOHaD) proposes that foetal and neonatal physiology and metabolism can be altered by challenges during a critical plastic time window of development in pregnancy and lactation. These alterations generate persistent structural and functional responses in the foetus that are associated with the development of diseases in the adult.
- The DoHaD concept is based on (a) epidemiological studies that associate human birth weight with the presence of cardiovascular and metabolic diseases, and (b) in animal models where nutritional restriction, obesity, overfeeding or exposure to hormonal agents such as glucocorticoids in pregnancy that predispose offspring to the development of physiological, metabolic, reproductive and endocrine dysfunction.

Zambrano et al, 2021

Unravelling the role of epigenetics in reproductive adaptations to early- life environment

Co-funded by the Erasmus+ Programme of the European Union

- In response to changing environmental conditions and in the context of existing resources, resource allocation can be reprogrammed through the endocrine system to balance or shift between growth, homeostasis and reproduction, with the brain having a central role owing to its ability to regulate all three endocrine axes.

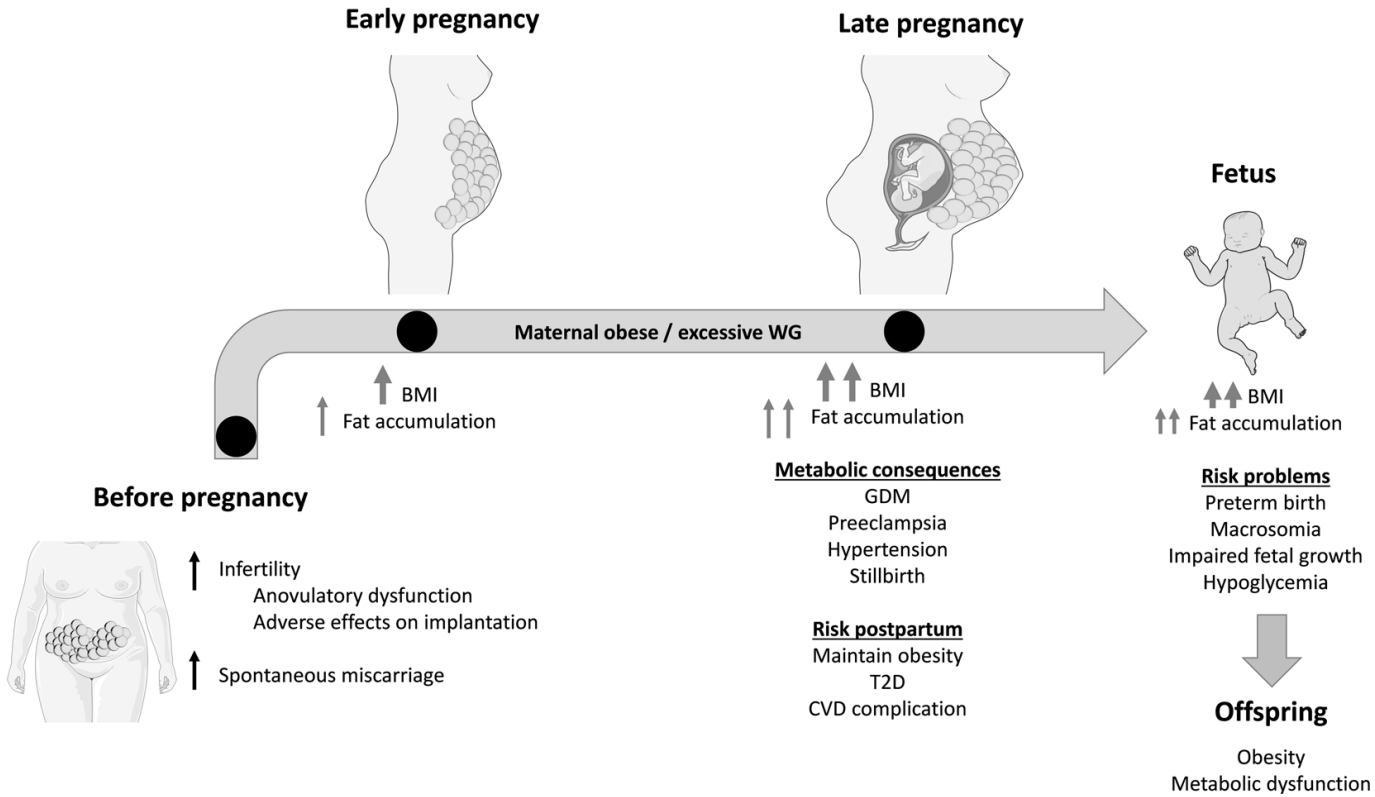


Bar- Sadeh et al, 2020

Negative consequences of obesity before pregnancy and during gestation

Co-funded by the Erasmus+ Programme of the European Union

- Obesity before pregnancy is associated with an increase of infertility due to anovulatory dysfunction, and adverse effects on implantation and, therefore, overweight/obese women have an upward trend of risks for spontaneous miscarriage.
- Maternal obesity is related to fat accumulation and high body mass index (BMI) at early pregnancy. However, it is more pronounced later during the pregnancy following obesity or excessive weight gain during gestation.
- Maternal obesity is a predictor of metabolic consequences for mother, such as gestational diabetes mellitus (GDM), preeclampsia, hypertension, and stillbirth.
- However, overweight/obese women have been related to risk postpartum to maintain obesity, develop type 2 diabetes (T2D) and other cardiovascular (CVD) complications. Furthermore, maternal obesity and excessive weight gain during pregnancy predisposes to adverse fetal outcomes as increased BMI and fat accumulation, and preterm birth, macrosomia, impaired fetal growth and hypoglycaemia.
- In addition, these problems exacerbate obesity and other metabolic dysfunctions in the future for the offspring.

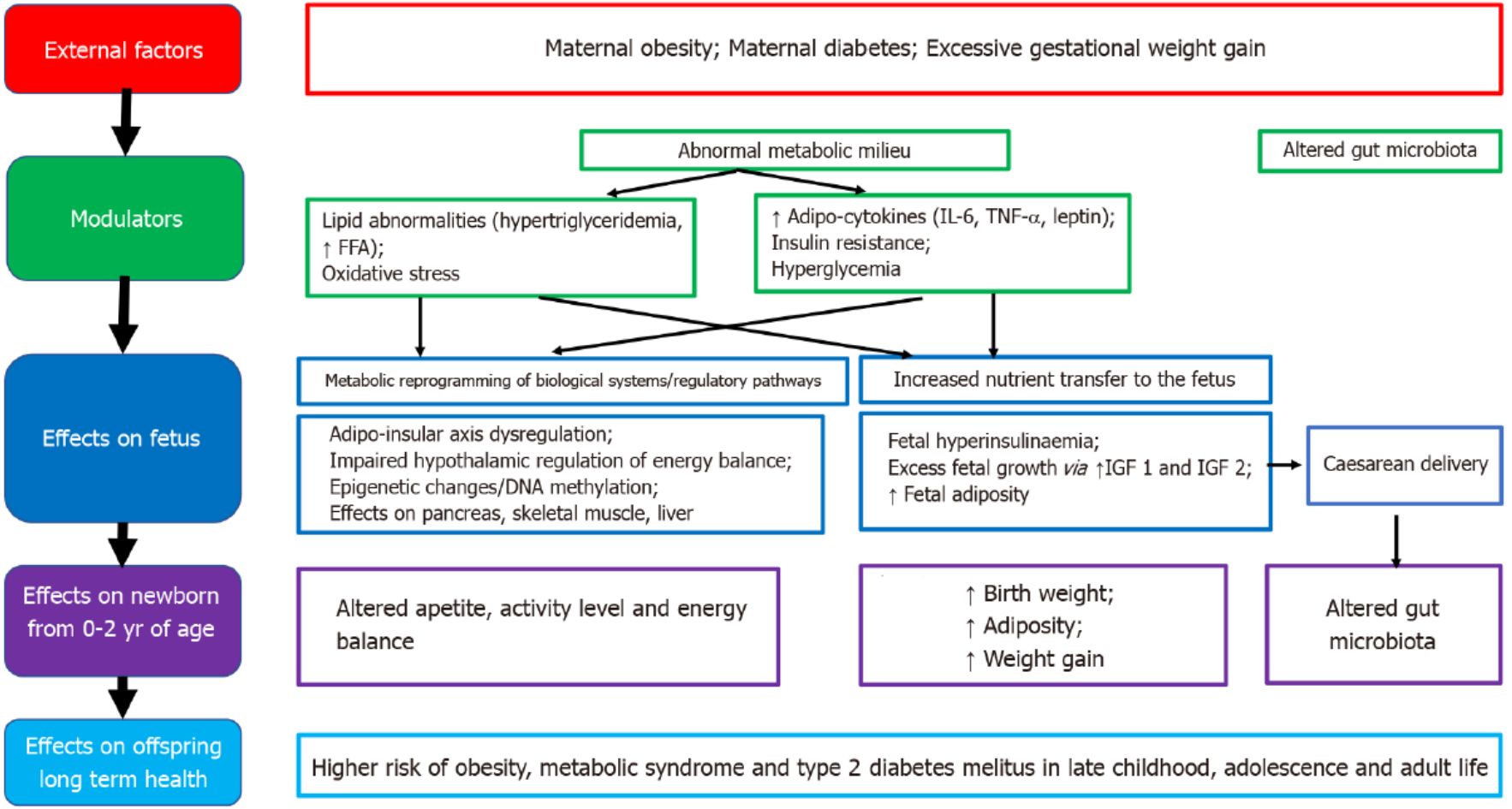


Corrales et al, 2021

Fetal programming of obesity and type 2 diabetes (1)

Co-funded by the Erasmus+ Programme of the European Union

Associations between maternal overnutrition and fetal programming of obesity/type 2 diabetes mellitus including potential modulating factors and effects on offspring health.

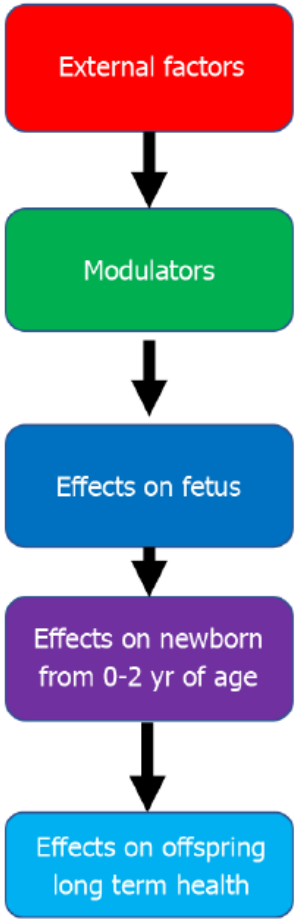


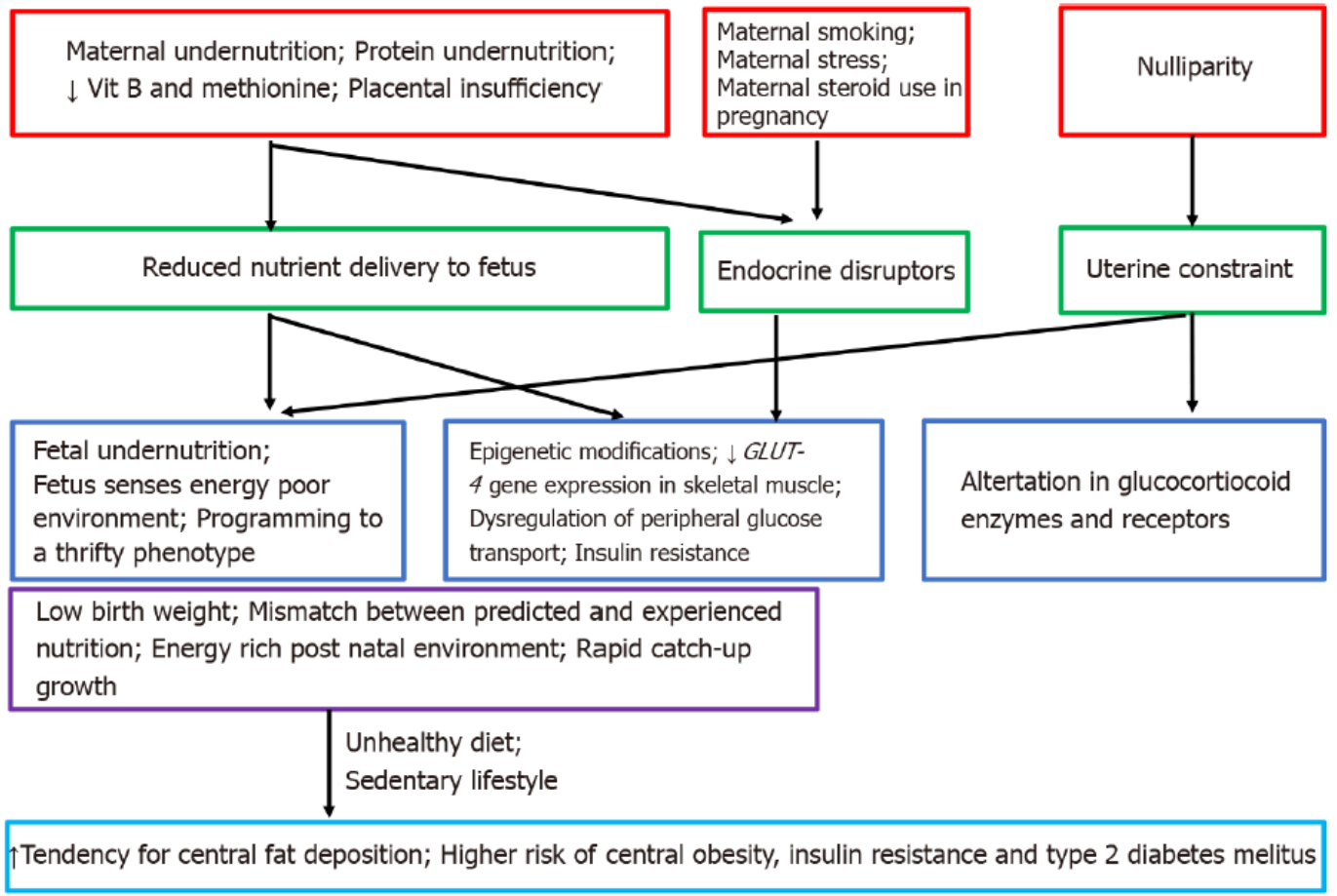
Seneviratne & Rajindrajith, 2022

Fetal programming of obesity and type 2 diabetes (2)

Co-funded by the Erasmus+ Programme of the European Union

Associations between maternal undernutrition and fetal programming of obesity/type 2 diabetes mellitus including potential modulating factors and effects on offspring health.





Seneviratne & Rajindrajith, 2022

The adverse offspring outcomes related to maternal high-fat diet

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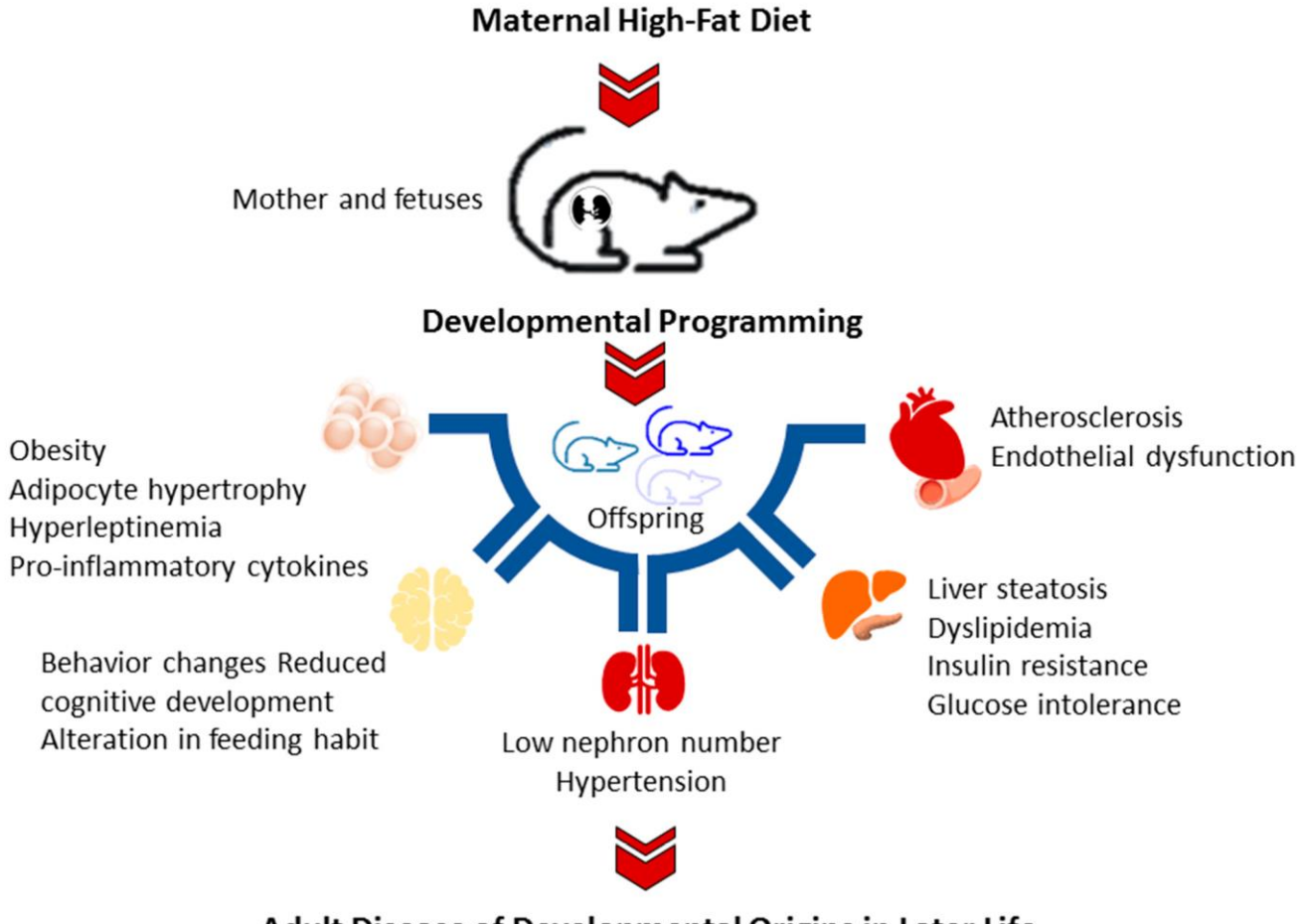

Tain & Hsu, 2022

The common mechanisms linking maternal high-fat diet to offspring hypertension

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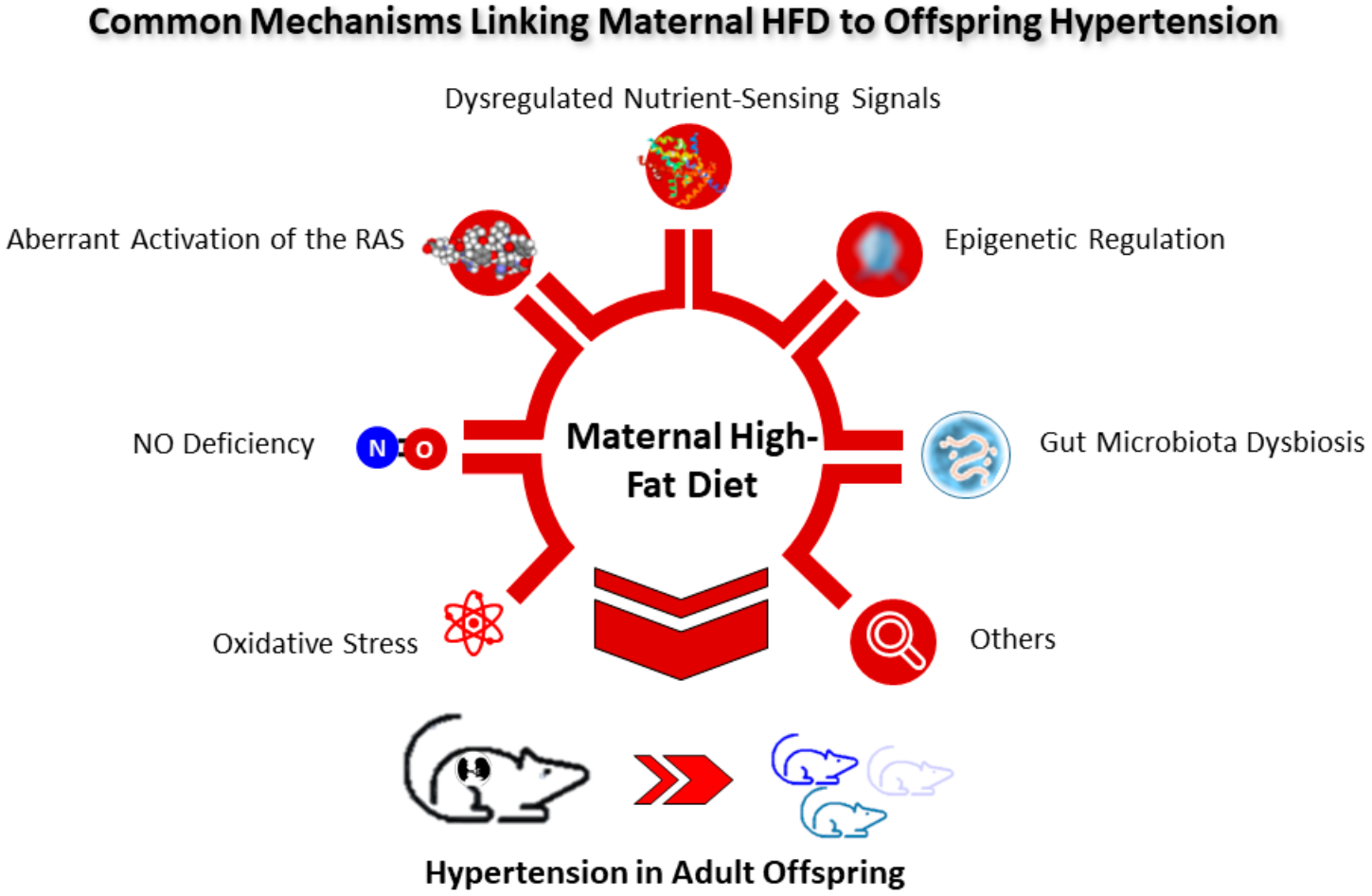
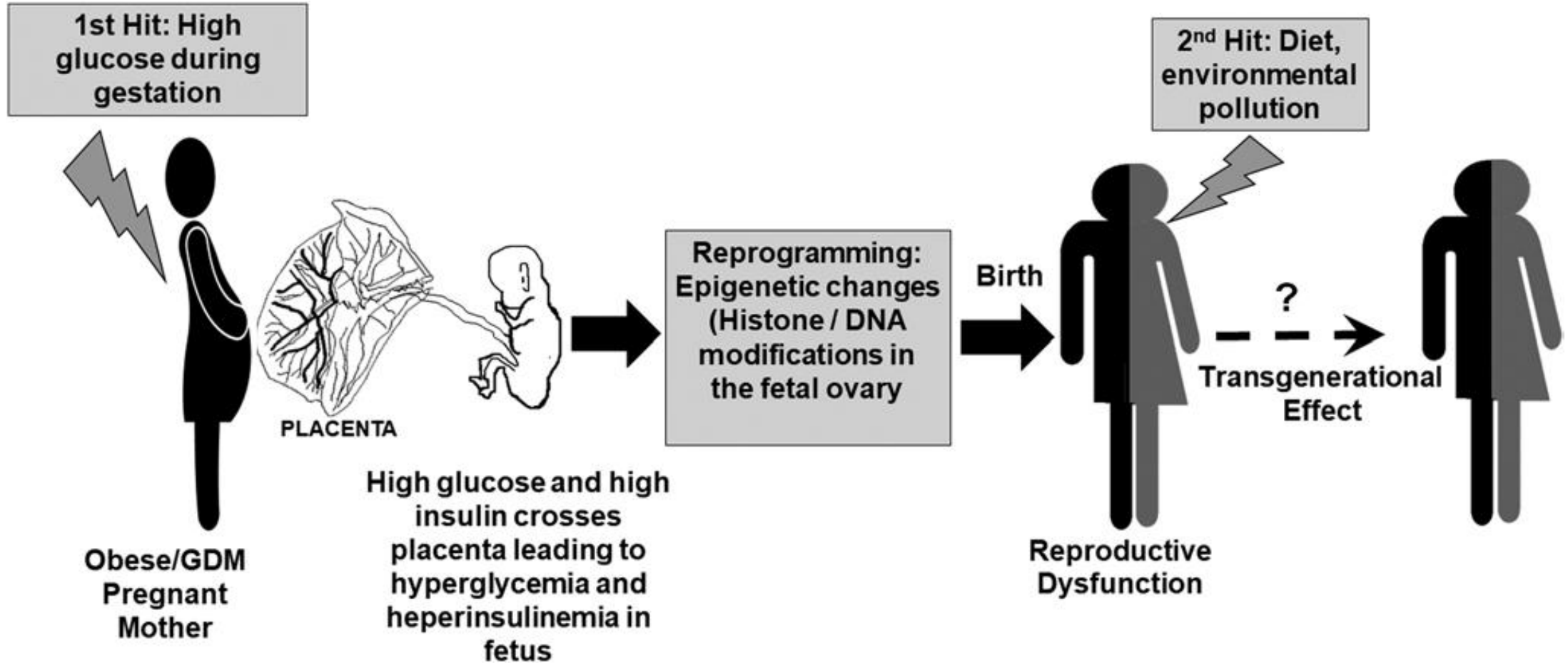


Tain & Hsu, 2022

Looking at the Future Through the Mother's Womb: Gestational Diabetes and Offspring Fertility

Co-funded by the Erasmus+ Programme of the European Union



Sinha et al, 2021

Reproductive consequences in males with maternal gestational diabetes

Co-funded by the Erasmus+ Programme of the European Union

Table 1. Modified genes/proteins associated with the reproductive health of male offspring exposed to gestational diabetes mellitus

Experimental design	Species	Reproductive phenotype	Affected genes/proteins	Ref
HFHS diet, 1 wk before conception and throughout pregnancy	C57BL/6J	Reduced epididymis weight and sperm count	–	(40)
STZ injection, before mating	Wistar rats	Low testicular weight, testosterone level, and sperm concentration Low sperm reserve and faster sperm transit time in epididymis	–	(42) (43)
STZ injection, 15 d before mating	CD-1 mice	Dysfunctional spermatogenesis	Changes in DNA methylation pattern of *H19* (paternally imprinted gene)	(44)
HFHS diet, 1 wk before mating and throughout gestation	C57B16/J	Decreased sperm motility	FGF signaling regulator 2, deleted in azoospermia-associated protein 1, septin 7, and aberrant serine/arginine-rich splicing factor	(58)

Abbreviations: FGF, fibroblast growth factor; HFHS, high-fat, high-sugar; Ref, reference; STZ, streptozotocin.

Sinha et al, 2021

Reproductive consequences in females with maternal gestational diabetes

Co-funded by the Erasmus+ Programme of the European Union

Table 2. Modified genes/proteins associated with the reproductive health of female offspring exposed to gestational diabetes mellitus

Experimental design	Species	Reproductive phenotype	Affected genes/proteins	Ref
Offspring of women with GDM	Human	Early puberty	–	(62, 63)
HFD/control diet, conception to lactation	Wistar rats	Altered estrous cyclicity Fewer oocytes in fetal stage, increased primordial follicles and follicular atresia; Early pubertal onset; abnormal reproductive cyclicity	Low *Amh* and *AmhRII* expression	(53) (54)
STZ injection, d 6.5 post conception	CD-1	Germ cells arrested at G1 stage; low primordial, primary, and secondary follicles; increased rate of apoptosis	Decreased expression of *Stra8*, *Dmc1*, and *Sycp3* in fetal (E14.5) ovaries Increased mRNA levels of *p21*, *Figla*, *Nobox*, *BMP15*, *Lhx8*, *FasL*, *Bcl2*, and Bax	(55)
STZ injection, day of conception	ICR mice	Increased germ cell cyst breakdown; accelerated primordial follicle formation	Increased activation of PI3K/Akt pathway	(56)
HFHS diet, conception throughout pregnancy STZ injection, day of conception	C57BL/6J	Subfertile; fewer ovulated oocytes; fewer preantral and antral follicles; increased atresia	Increased *Cart* expression in granulosa cells; depleted H3K27me3 and 5mC levels and high H3K27ac and 5hmC levels on *Cart* promoter	(57)
HFHS diet, 1 wk before mating and throughout gestation	C57B16/J	Altered ovarian morphology and elevated apoptosis	Differential levels of ovarian proteome	(58)
HFD following artificial insemination	Porcine	Low number of large and small follicles and increased follicular atresia; high oxidative stress	Fetal ovary, decreased expression of *Aat*, *Aap*, *Grp78*, *Gen*, *CuZn-Sod*, *Gpx*, *and Bax* Fetal and adult ovary, increased expression of *Bcl2*	(60)

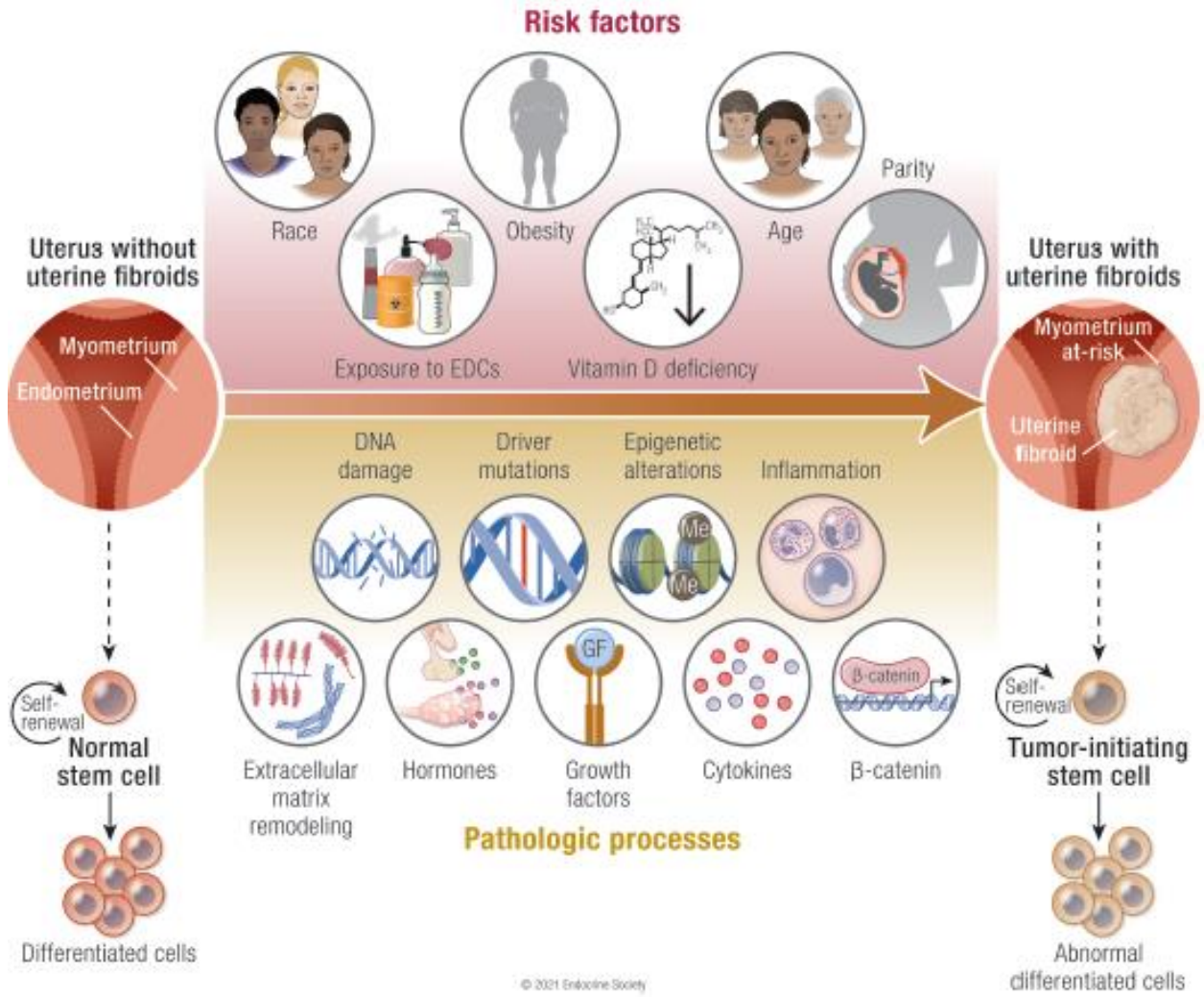
Abbreviations: GDM, gestational diabetes mellitus; HFD, high-fat diet; HFHS, high-fat, high-sugar; ICR, Institute of Cancer Research; mRNA, messenger RNA; Ref, reference; STZ, streptozotocin.

Sinha et al, 2021

Role of epigenetics pathways in uterine fibroids

Co-funded by the Erasmus+ Programme of the European Union

1. Developmental exposure to EDCs in early life reprograms myometrial stem cells, thus increasing the risk of uterine fibroids development.
2. Several risk factors such as age, race, obesity, parity, hypertension, vitamin D deficiency, and diet in late life can trigger uterine fibroids pathogenesis.
3. Pathogenic exon 2 mutations in *MED12* promote uterine fibroids formation and disrupt CDK8/19 kinase activity.
4. Several vital pathways and mechanisms such as sex hormones, ECM, Wnt/β-catenin, TGF-β, growth factors, epigenetic and epitranscriptomic regulation, YAP/TAZ, Rho/ROCK, and DNA damage repair pathways contribute to the development of uterine fibroids.
5. Fertility therapy is highly needed for the treatment of patients with uterine fibroids.

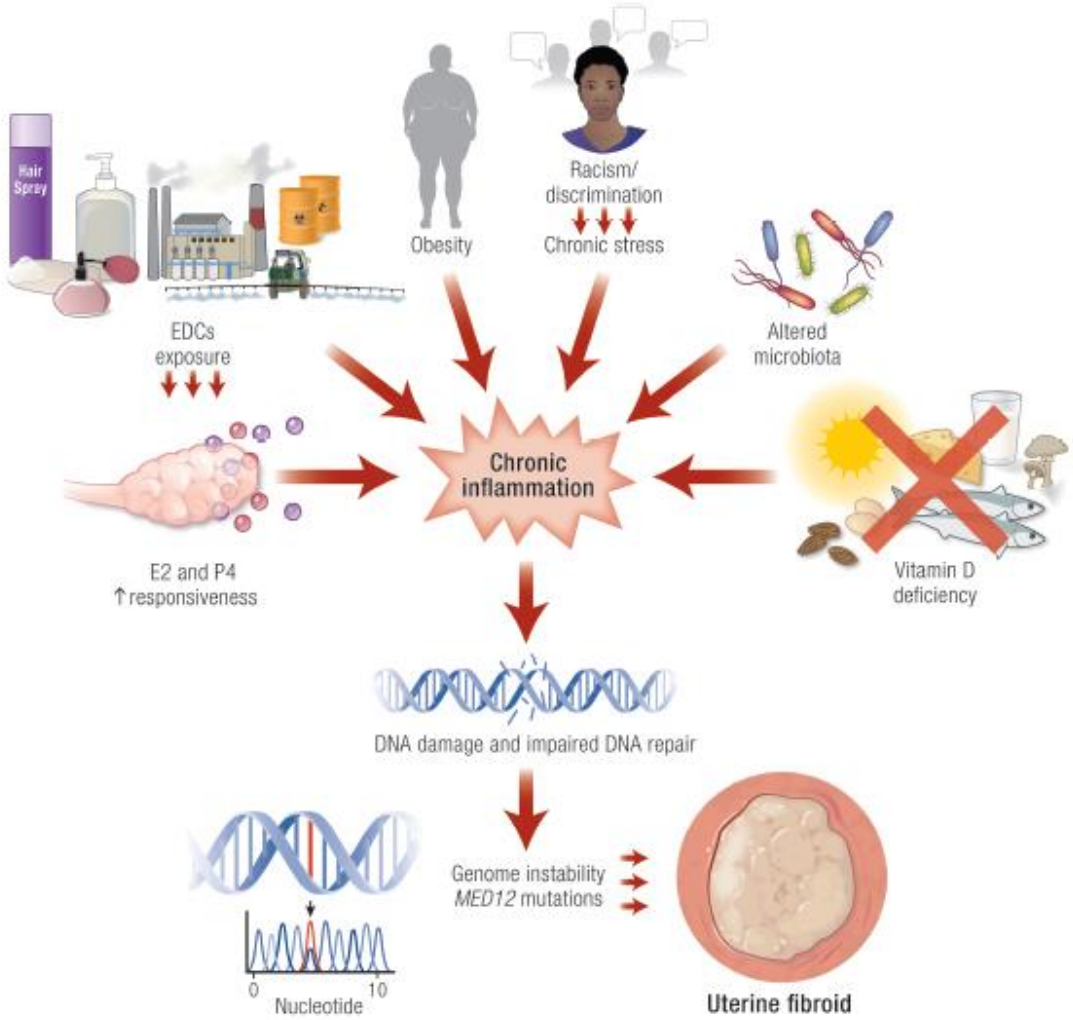


Yang et al, 2022

Risk factors for uterine fibroids affecting inflammation, DNA damage pathways, and genetic instability

Co-funded by the Erasmus+ Programme of the European Union

- External and internal factors, such as EDC exposure, hyper-responsiveness to sex steroid hormones, obesity, vitamin D deficiency, and altered reproductive tract microbiome, contribute to chronic systemic inflammation.
- The inflammatory environment, EDC exposure, and vitamin D deficiency promote DNA damage and the accumulation of mutations.
- Consequently, these genetic events may activate the pathways involved in cell proliferation, the inhibition of apoptosis, and ECM remodeling, ultimately leading to the development and growth of fibroids.



E2, estrogen; EDCs, endocrine-disrupting chemicals; *MED12*, RNA polymerase II transcriptional mediator complex subunit 12; P4, progesterone.

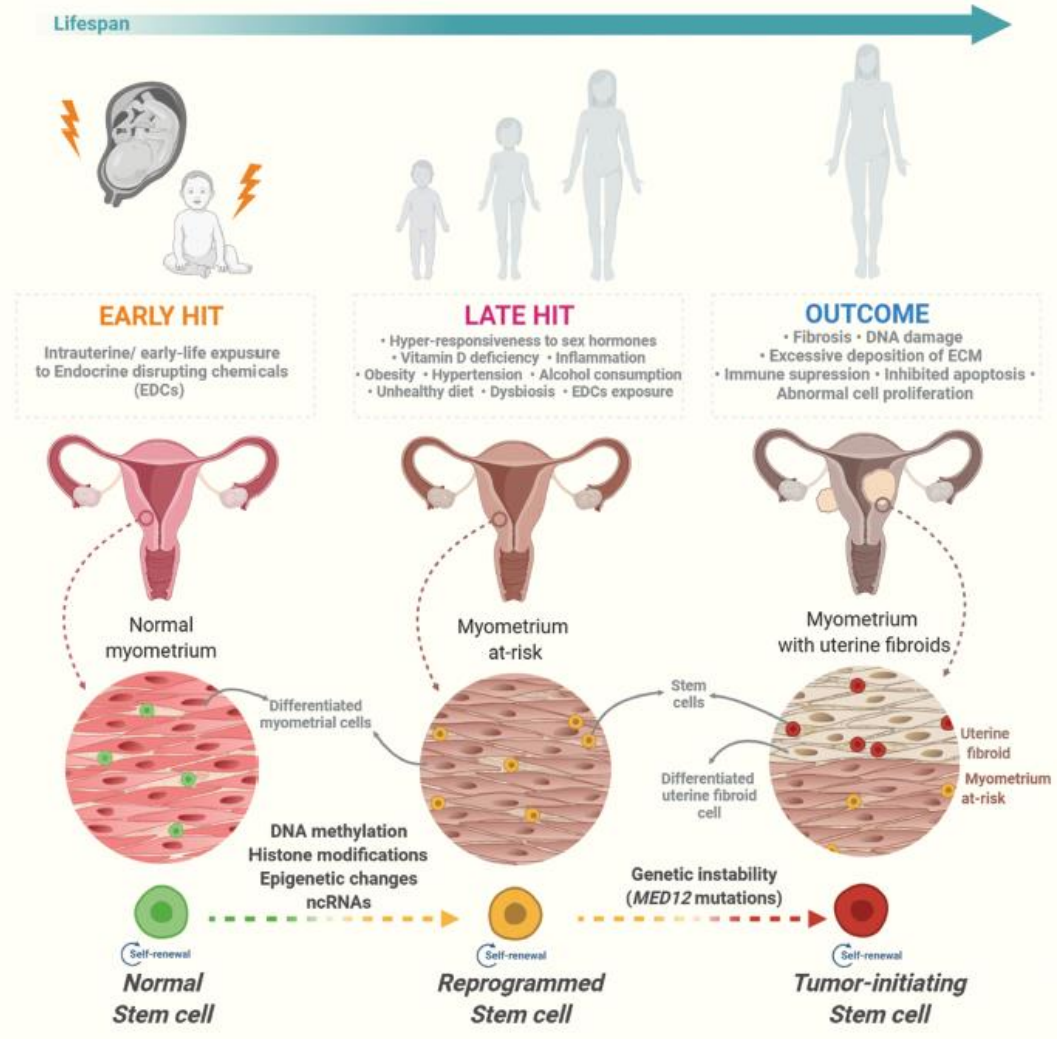
Yang et al, 2022

Developmental origin of fibroids from myometrial stem cells

Co-funded by the Erasmus+ Programme of the European Union

- Intrauterine and early-life adverse environmental exposure to endocrine disrupting chemicals may act as the early hit to induce normal myometrial stem cells' reprogramming by hijacking epigenomic plasticity.
- The plasticity of the developing epigenome is susceptible to epigenomic changes in myometrial stem cells following later-life adverse exposures, thereby leading to mutations and their transformation into tumor-initiating stem cells.
- The development and growth of fibroids are mainly characterized by abnormal cell proliferation, inhibited apoptosis, DNA instability, excessive deposition of ECM, and other critical biological pathways.

ECM, extracellular matrix; MED12, RNA polymerase II transcriptional mediator complex subunit 12; ncRNAs, non-coding RNA.

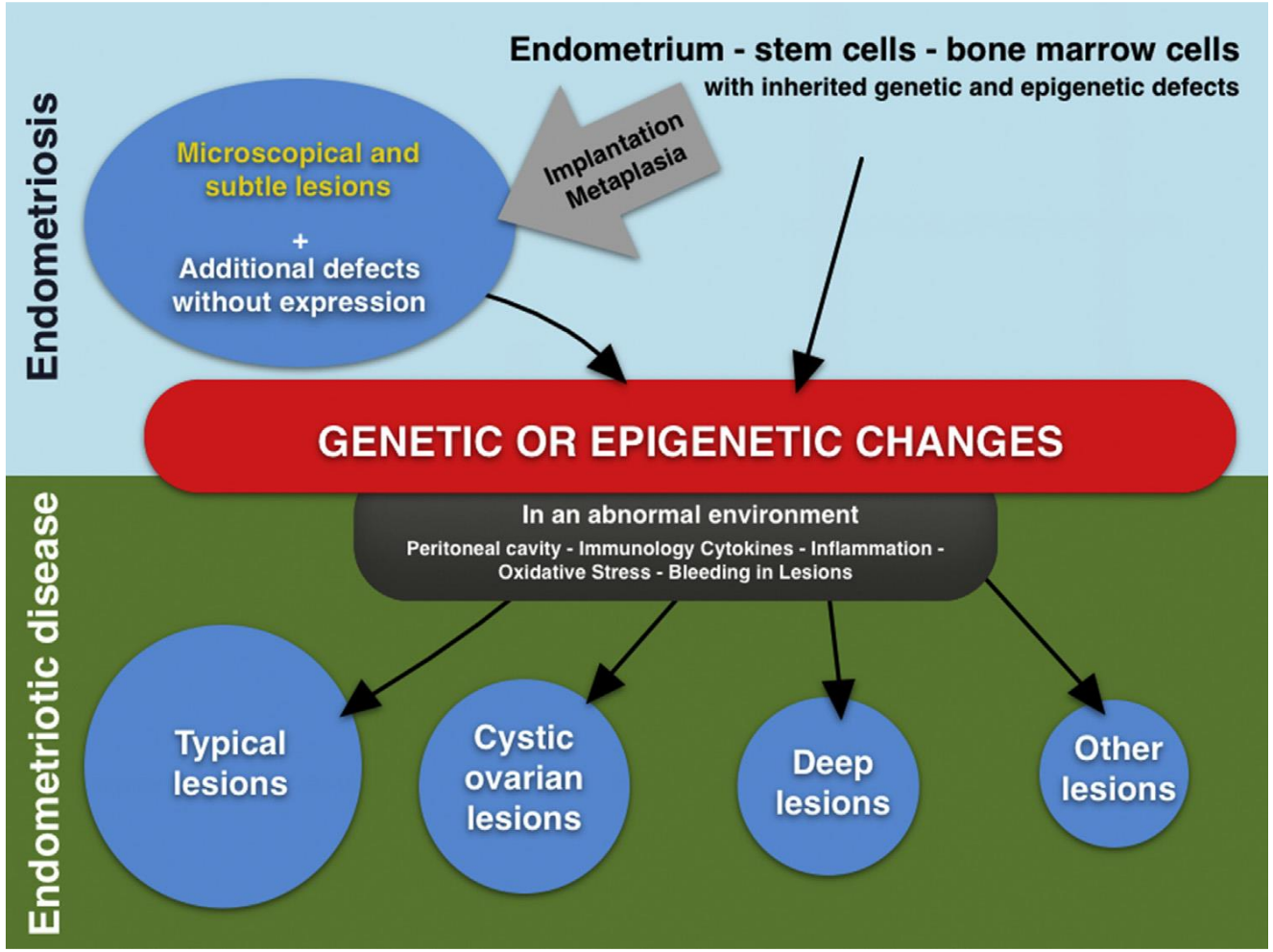


Yang et al, 2022

Pathogenesis of endometriosis: the genetic/epigenetic theory

Co-funded by the Erasmus+ Programme of the European Union

- The original cell can be an endometrial cell, a stem cell, or a bone marrow cell with their inherited genetic and epigenetic defects. These defects, together with additional acquired defects without expression constitute the predisposition.
- After implantation or metaplasia, defined as stable and transmittable changes, subtle and microscopic lesions occur. Additional genetic or epigenetic changes are required for these cells to change behavior and to progress into typical, cystic, deep, or other lesions.

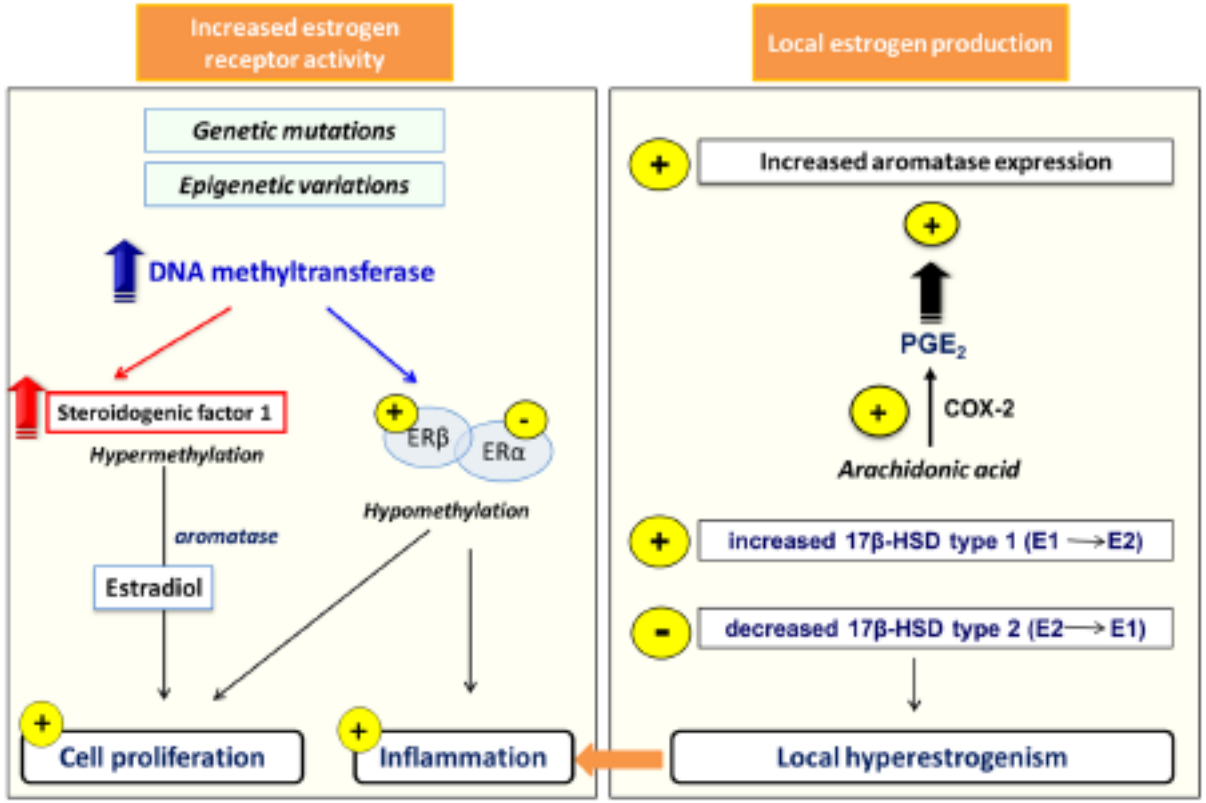


Koninckx et al, 2019

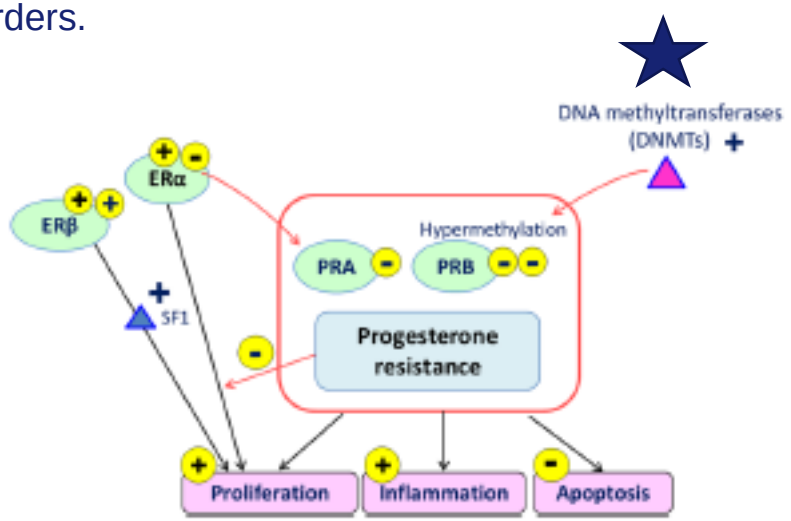
The endocrine background of inflammation in endometriosis

Co-funded by the Erasmus+ Programme of the European Union

Endocrine and inflammatory changes explain pain and infertility of this gynecological disorder, and the systemic comorbidities described in these patients, such as autoimmune (thyroiditis, arthritis, allergies), inflammatory (gastrointestinal/ urinary diseases) and mental health disorders.



Estrogen receptors activity and local estrogens production in endometriosis



The mechanisms of progesterone-resistance in endometriosis

Vannuccini et al, 2022

Immune and epithelial to mesenchymal transition involvements in adenomyosis: 2 hypotheses

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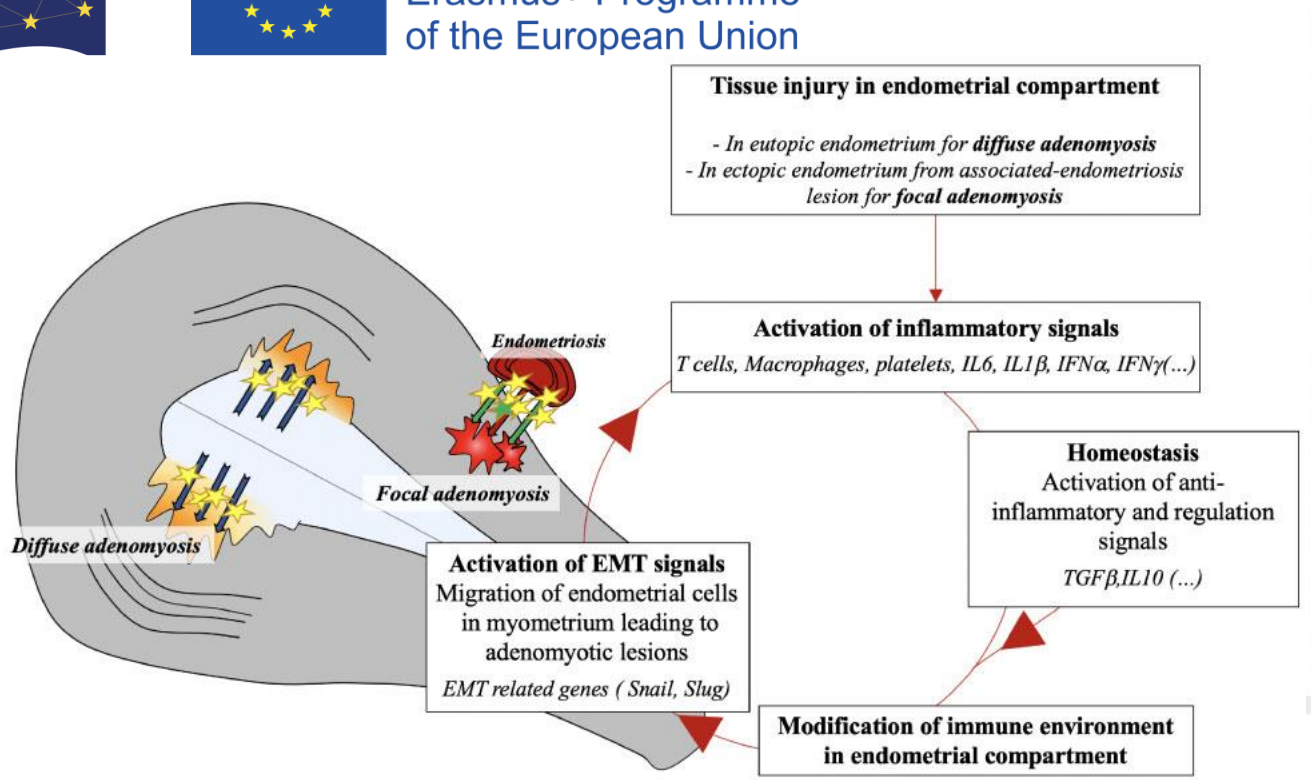

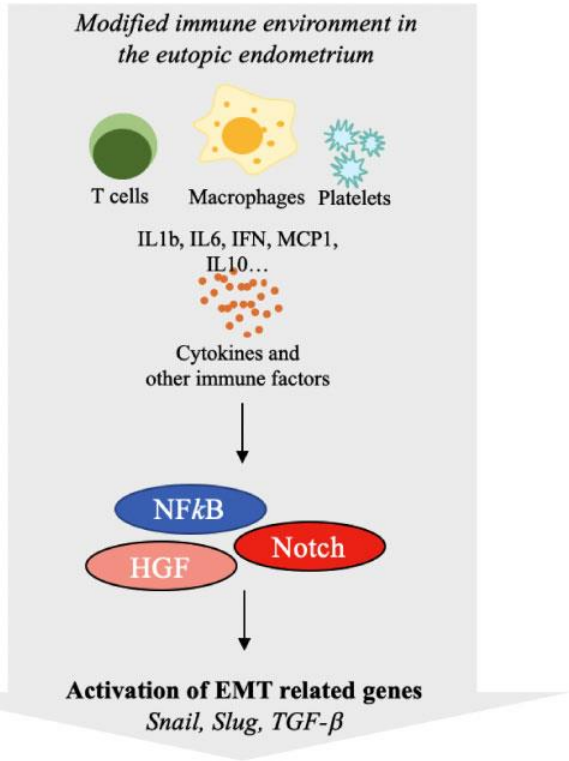

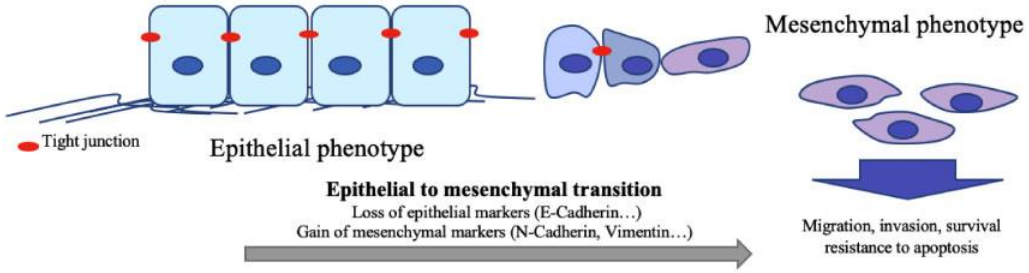

Bourdon et al, 2021

GENDER SPECIFIC CVD MORTALITY

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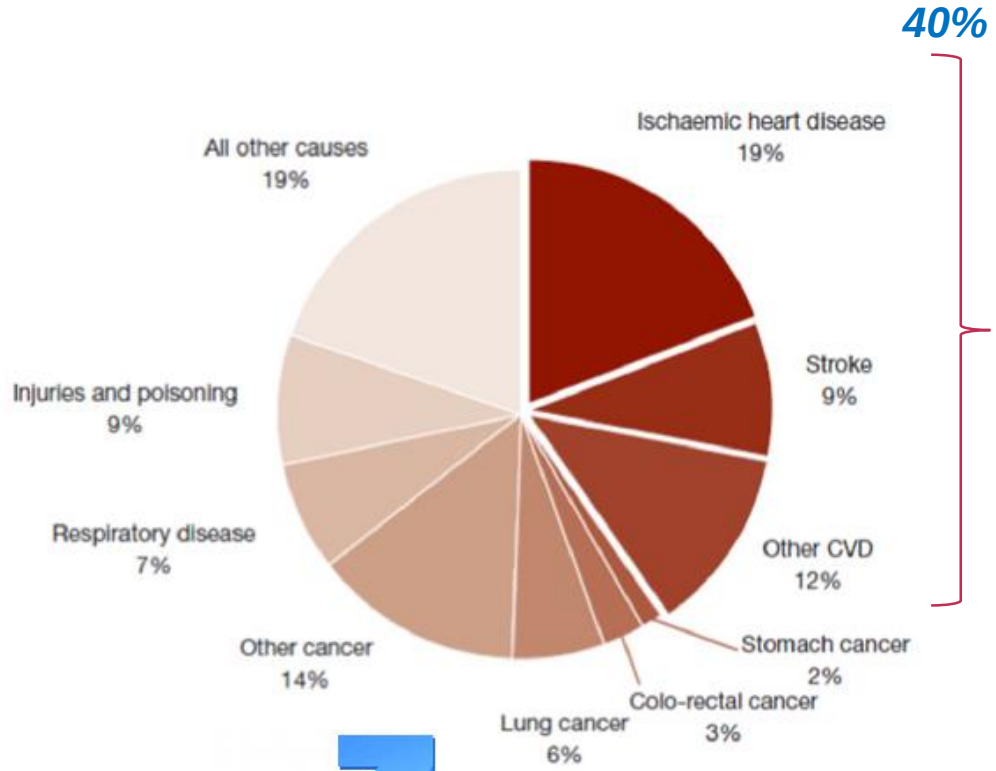

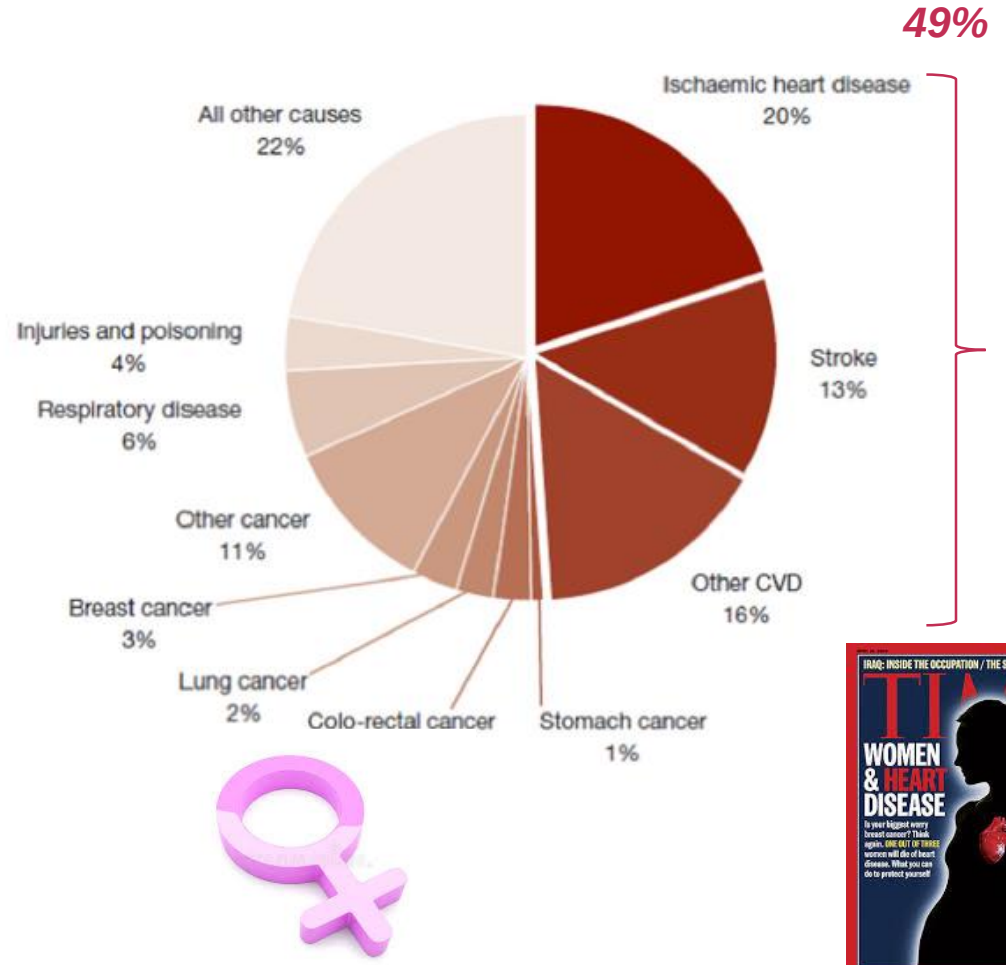

Cifkova et al, 2019

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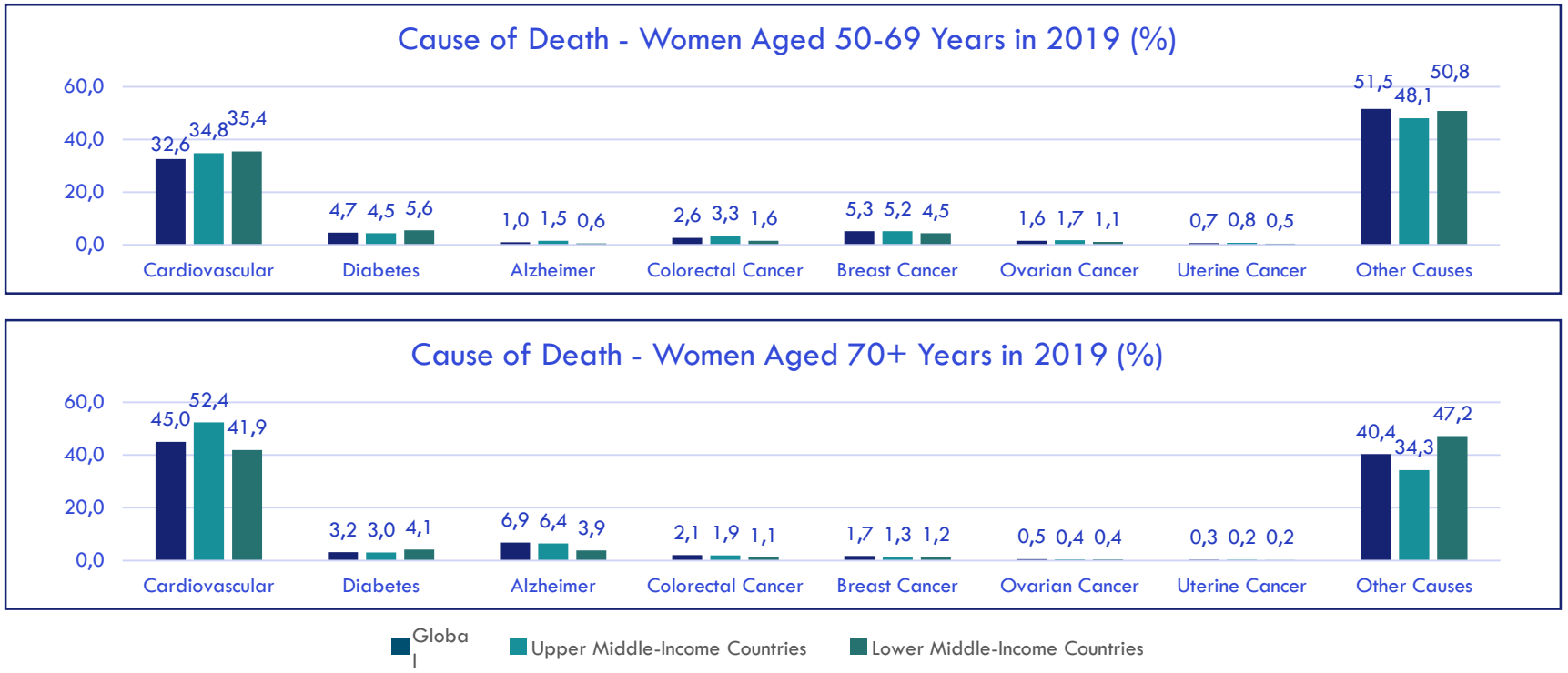
Cardiovascular disease is the leading cause of mortality in women ≥50 years

Co-funded by the Erasmus+ Programme of the European Union



IHME – Health Data. Available at: https://vizhub.healthdata.org/gbd-compare/; Accessed on July 06th, 2022.

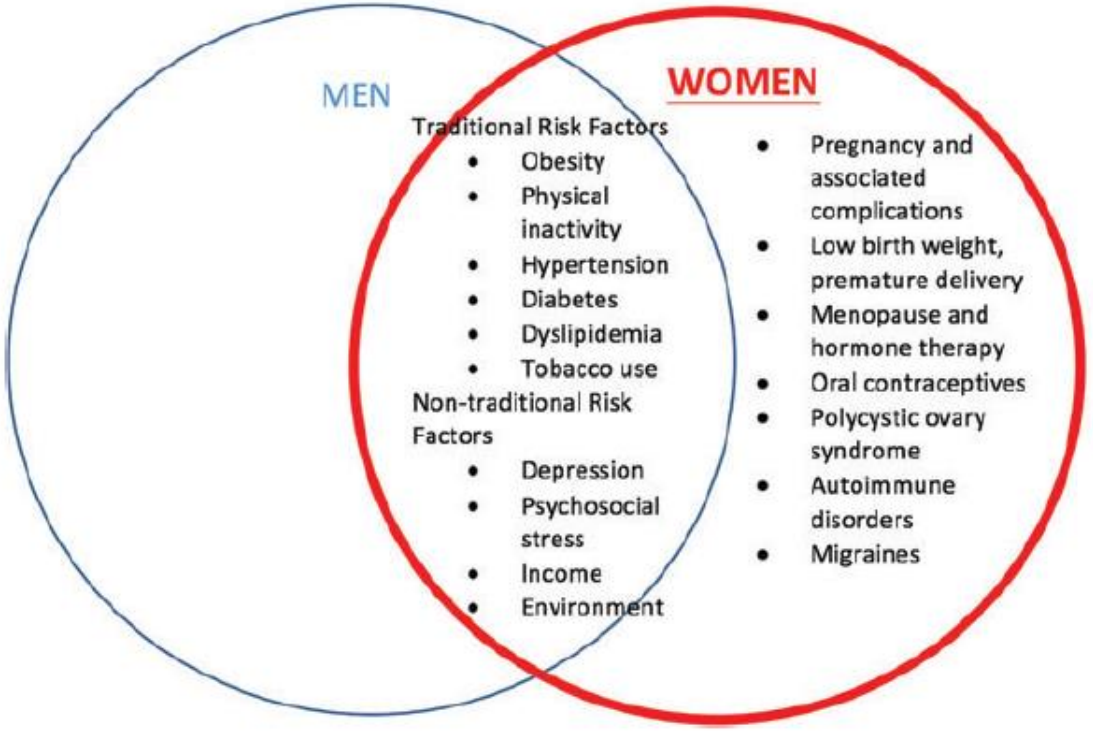
BEING A WOMAN IS A NON-MODIFIABLE CVD RISK FACTOR!

Co-funded by the Erasmus+ Programme of the European Union

Table 2 Key cardiovascular risk factors	
Non-modifiable	Modifiable
Age Gender Heredity	Hypertension[a] Dyslipidaemia[a] Obesity[a] Glucose intolerance[a] Cigarette smoking Diabetes mellitus Sedentarism

[a]Components of the metabolic syndrome.

Collins et al, 2007

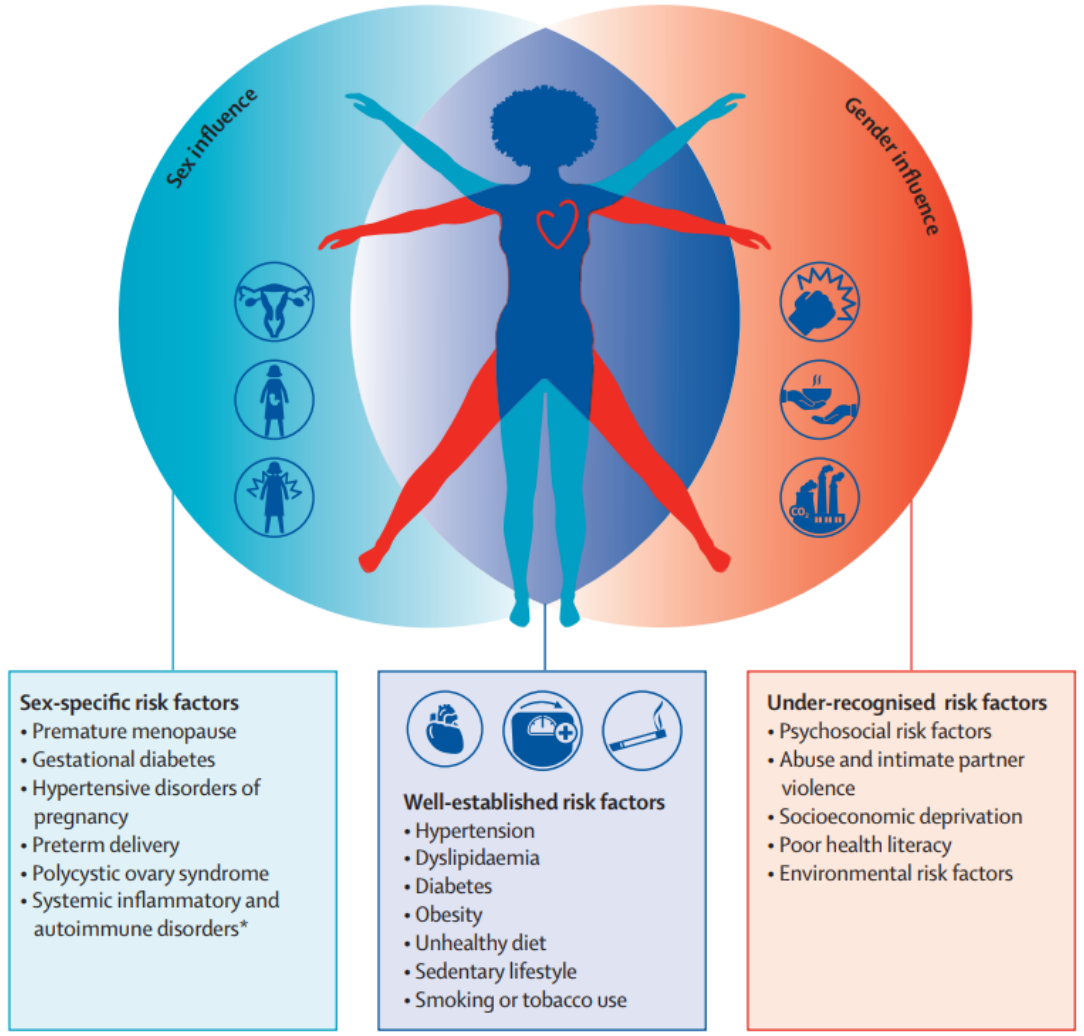


Lee et al, 2017

Cardiometabolic health in women: traditional, sex-specific and gender-specific risk factors

Co-funded by the Erasmus+ Programme of the European Union

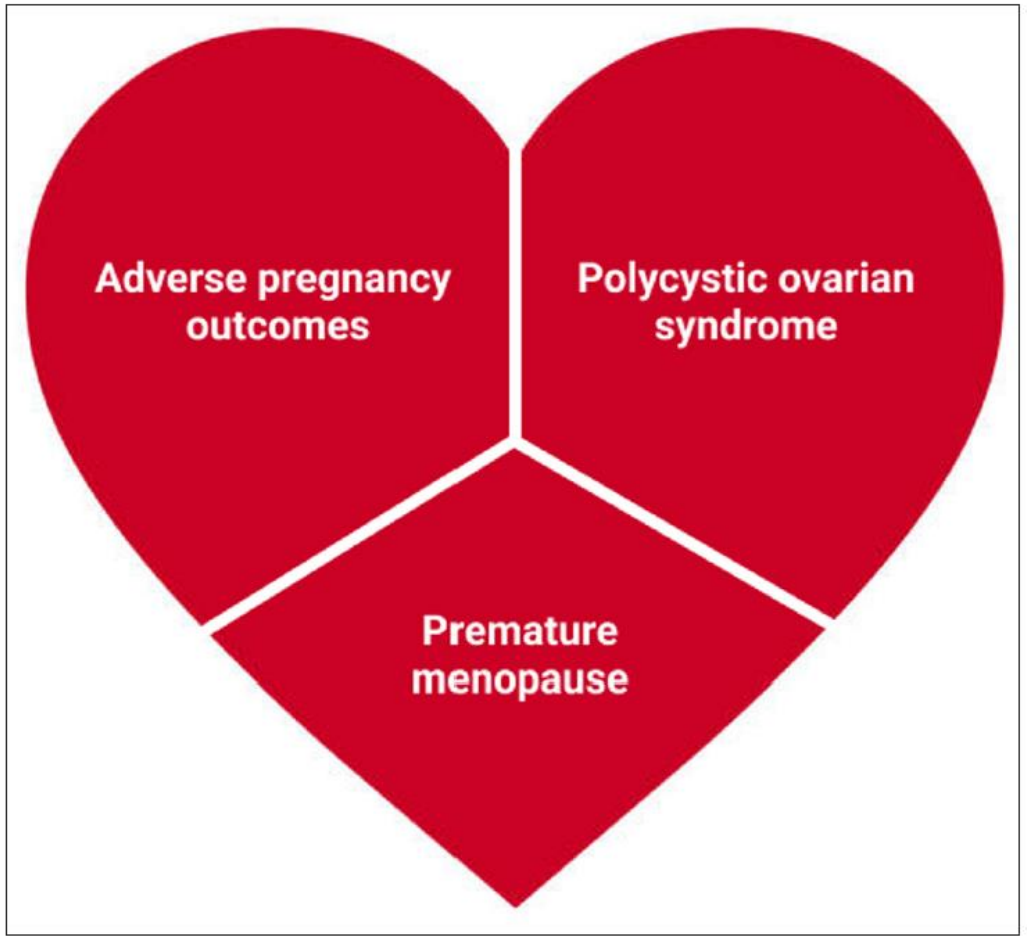
The figure categorises risk factors for cardiovascular disease in women into three categories: those that are well-established and affect both sexes but which might affect women differently to men (eg, hypertension, dyslipidaemia, and diabetes); those that are sex-specifc (eg, premature menopause and pregnancy-related disorders); and those that are under-recognised (eg, intimate partner violence or poverty) and which can be related to gender and interaction with a woman's social and physical environment. Although research is beginning to recognise how these factors might interact or increase risk, acknowledging the effects of well established, sex-specifc, and under-recognised risk factors is crucial to understanding cardiovascular disease in women.



Vogel et al, 2021

Most important sex-specific cardiovascular risk factors in women

Co-funded by the Erasmus+ Programme of the European Union



Shah et al, 2021

Cardiometabolic risk in the life cycle of women

Co-funded by the Erasmus+ Programme of the European Union

Panel 1: Main aspects of gynaecological and obstetric history in the context of cardiometabolic health

Adult life

- Functional hypothalamic amenorrhoea
- Polycystic ovary syndrome
- History of infertility, miscarriage, or stillbirth
- Other gynaecological conditions (eg, endometriosis, fibroids, heavy menstrual bleedings, or hysterectomy aged <50 years)

Pregnancy

- Hypertensive disorders of pregnancy (gestational hypertension or pre-eclampsia)
- Gestational diabetes

Midlife

- Early menopause (surgical or iatrogenic)
- Premature ovarian insufficiency

Nappi et al, 2022

Key reproductive exposures associated with future risk of cardiovascular disease in women

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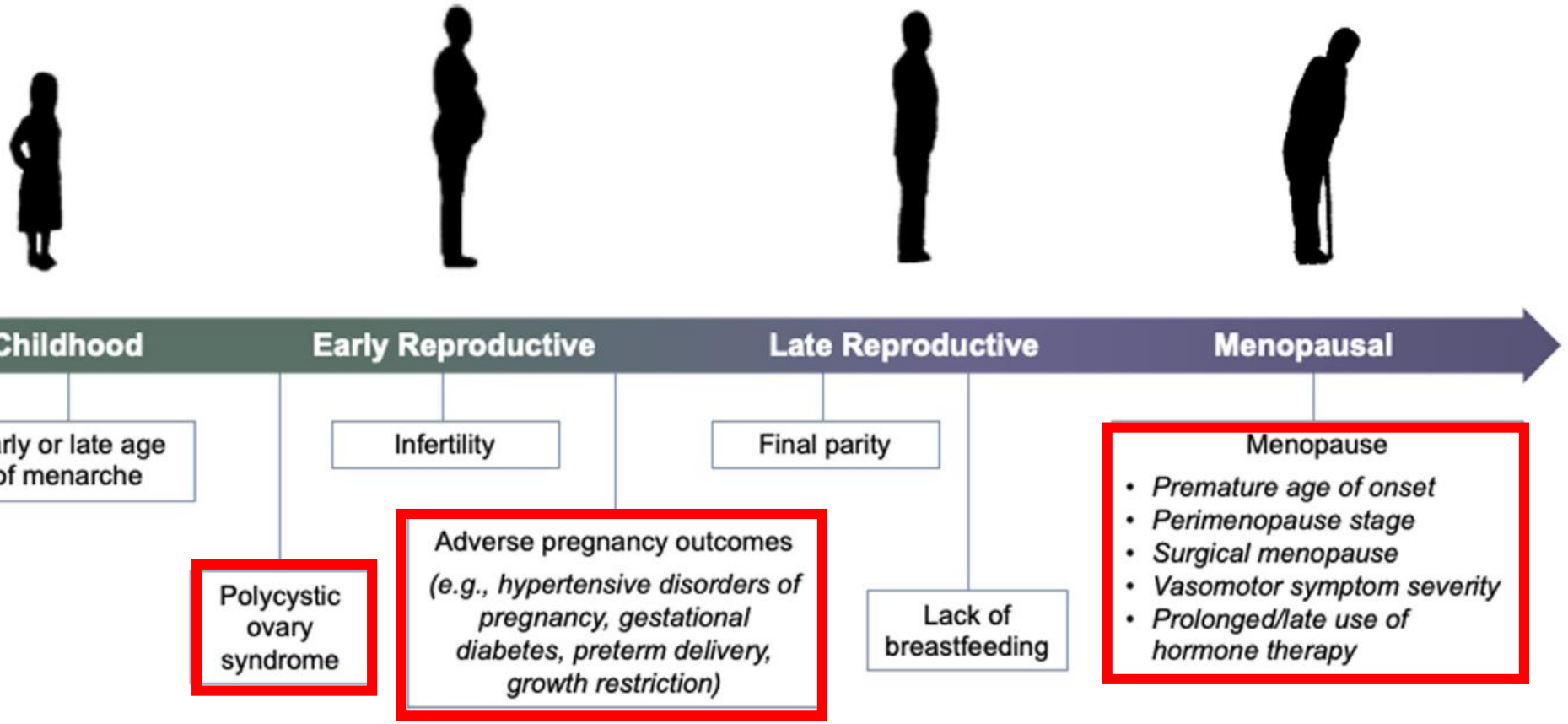
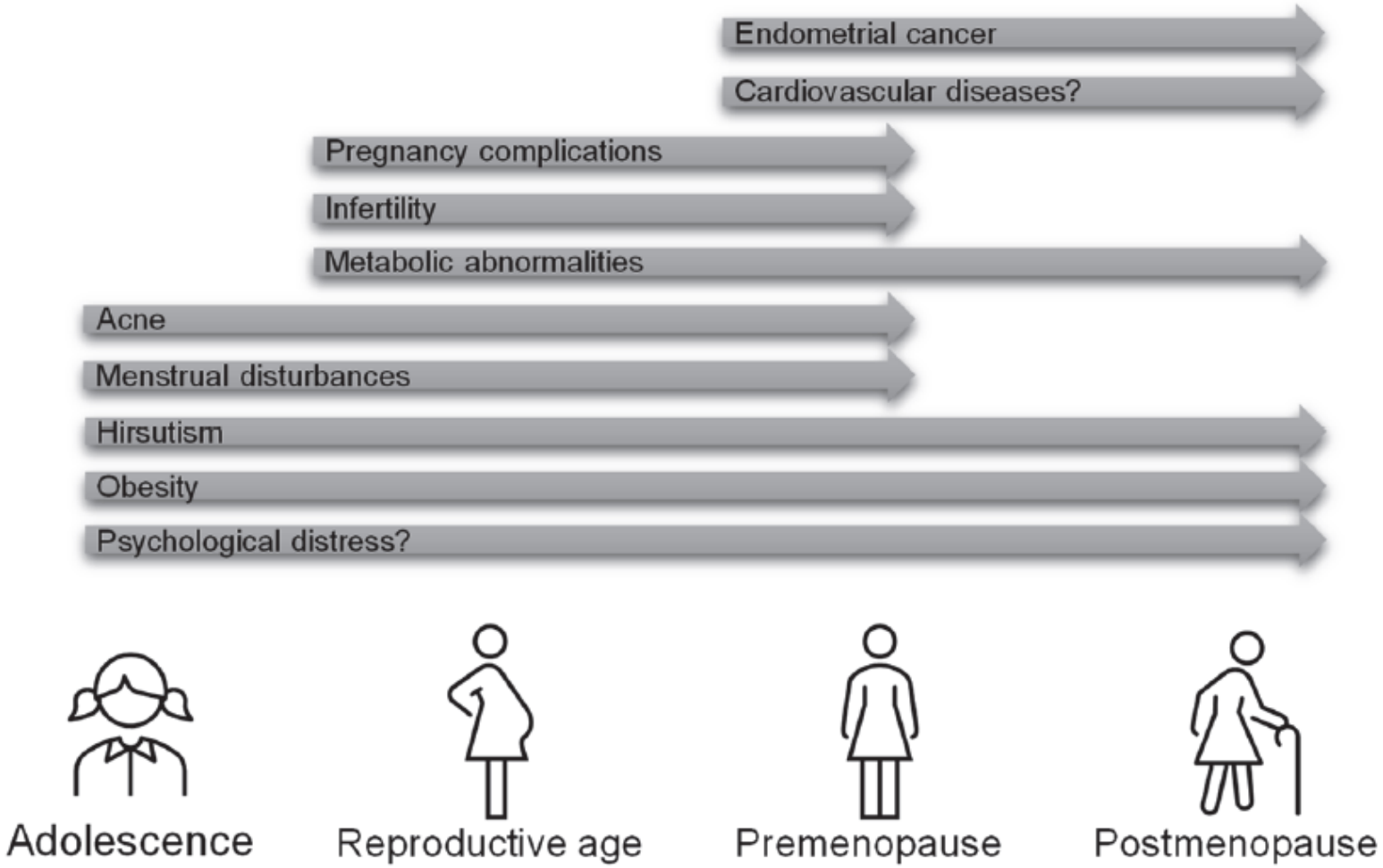


O'Kelly et al 2022

PCOS ACROSS THE LIFE SPAN OF WOMEN

Co-funded by the Erasmus+ Programme of the European Union



Karjula, 2021

Clinical characteristics of Polycystic Ovary Syndrome (PCOS)

Co-funded by the Erasmus+ Programme of the European Union

Hirsutism – excess hair growth on face, chest or upper thigh

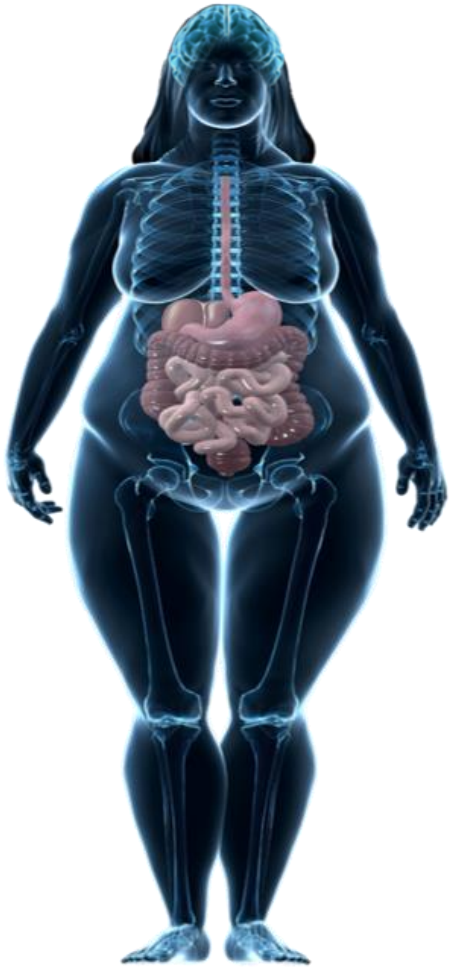
- Present in >70% of women with PCOS[1]

Irregular menstrual periods; absent, infrequent, too frequent, heavy and unpredictable periods

- Present in 80-90% of women with PCOS[1]

Infertility (most common cause of female infertility)

- Present in 40% of women with PCOS[1]



Severe Acne

- Commonly found (~33% of women with PCOS)[1]

Oily skin

- Commonly found

Acanthosis nigricans (patches of thickened, velvety, darkened skin)

- Present in 50-60% women with PCOS[2]

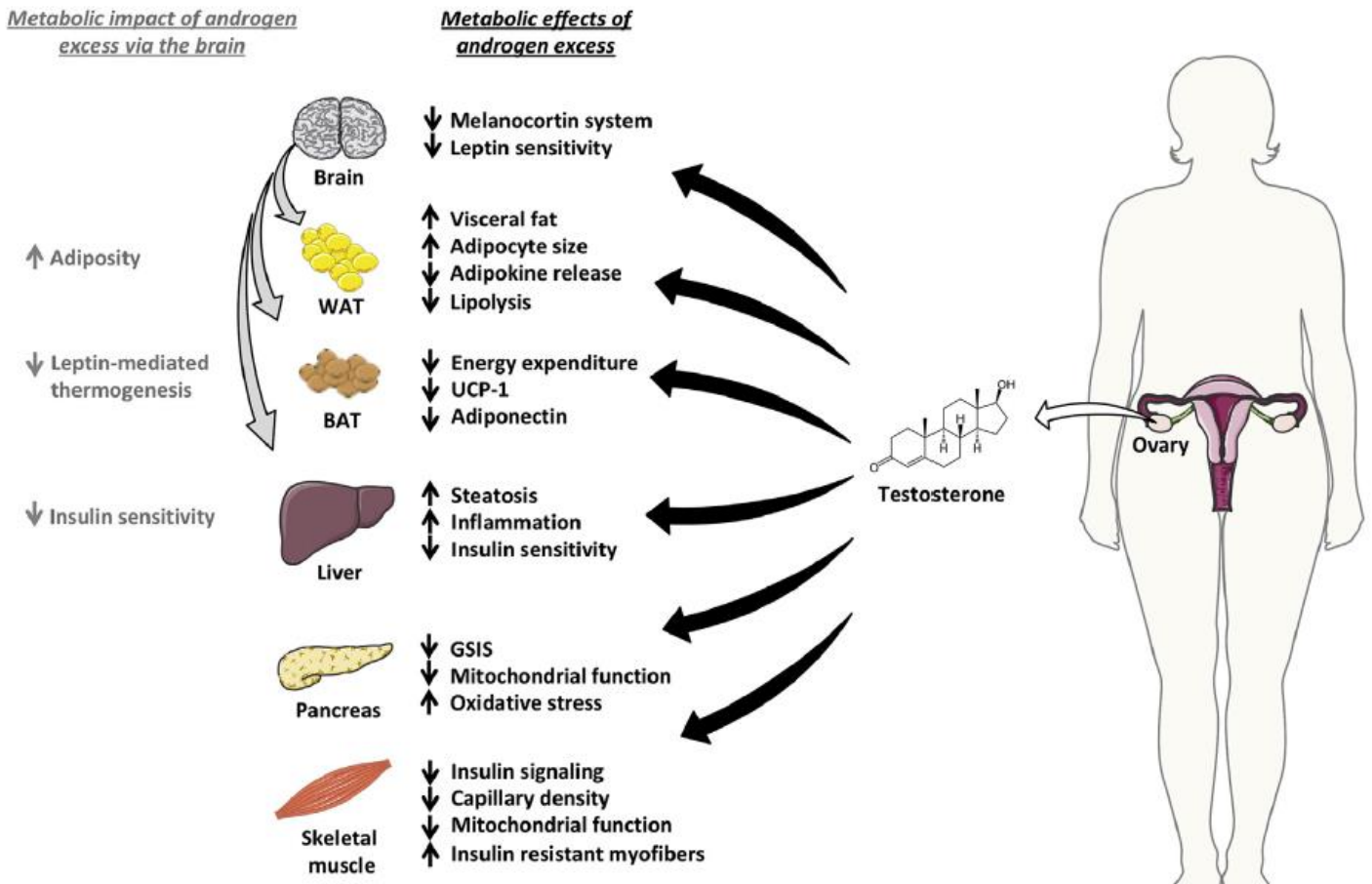
Polycystic ovarian morphology

- Present in >80% of women with PCOS[3]

[1]Teede et al, 2010; [2]Shivaprakash et al, 2013; [3]Azziz et al, 2009

Metabolic impact of hyperandrogenism in women with PCOS

Co-funded by the Erasmus+ Programme of the European Union

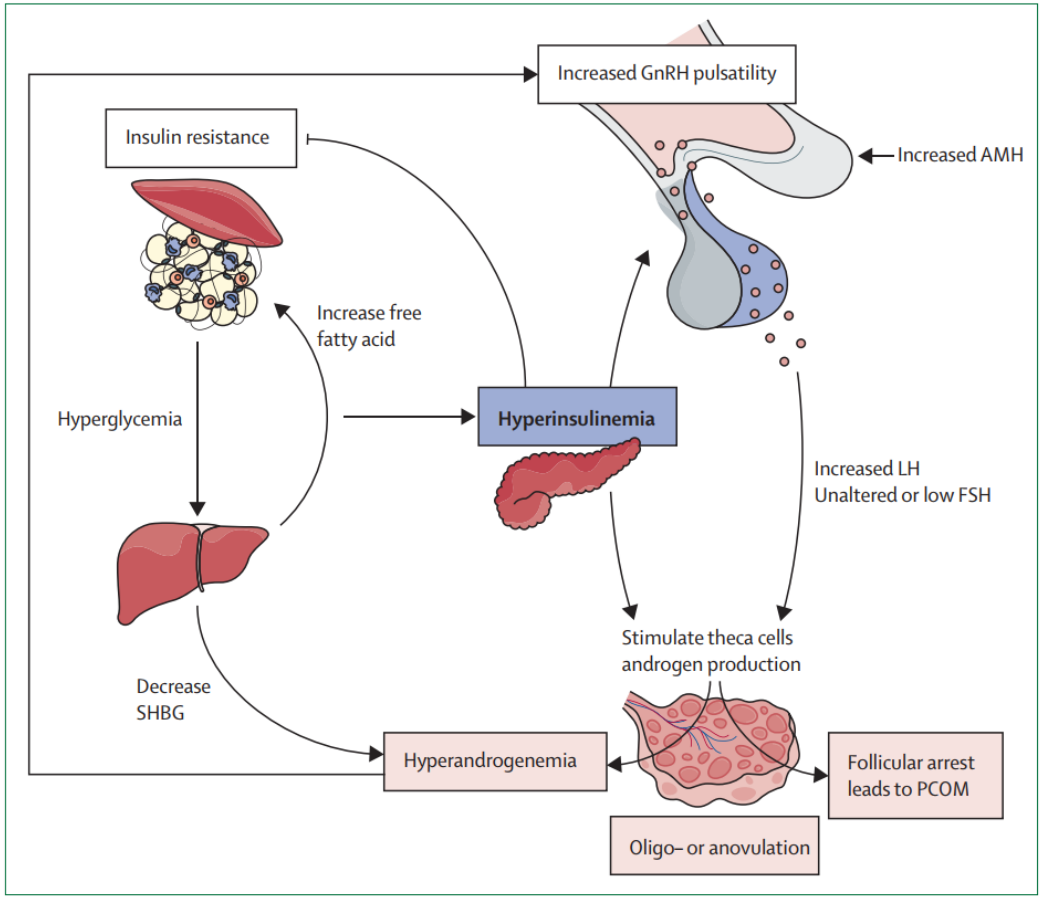


Sanchez-Garrido & Tena-Sempere, 2020

Metabolic impact of PCOS

Co-funded by the Erasmus+ Programme of the European Union

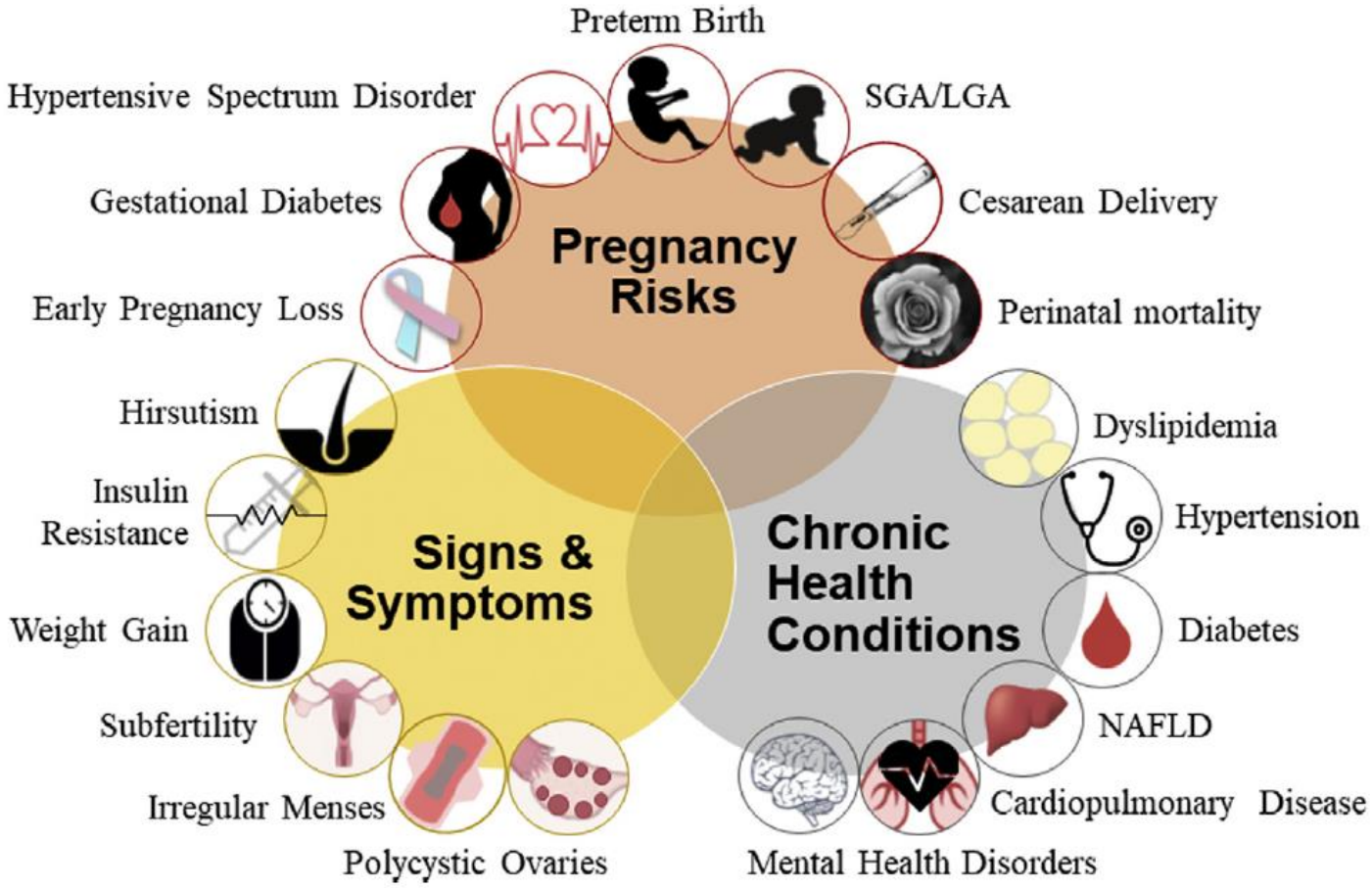
- Women with polycystic ovary syndrome (PCOS) have **high gonadotropin-releasing hormone** (GnRH) **pulse frequency** resulting in **hypersecretion of luteinizing hormone (LH)** leading to stimulation of ovarian theca cell **androgen** production.
- The unaltered (or low) follicle stimulating hormone (FSH) inhibits expansion of follicular size and maturation, leading to **follicular arrest** and **polcystic ovarian morphology** (PCOSM) and **oligoovulation** or **anovulation**. The large number of preantral and small antral follicles increase antimüllerian hormone (AMH) production.
- **Elevated AMH** levels also increase the activity of GnRH neurons and directly stimulate GnRH-dependent secretion of lutenising hormone, which may further stimulate ovarian hyperandrogenism. Moreover, **insulin resistance** results in **hyperinsulinemia** stimulating GnRH secretion and ovarian theca cell androgen production, and **decreases sex hormone binding globulin** (SHBG) production, further contributing to hyperandrogenism.



Joham et al 2022

PCOS and increased risks for perinatal complications/chronic health conditions

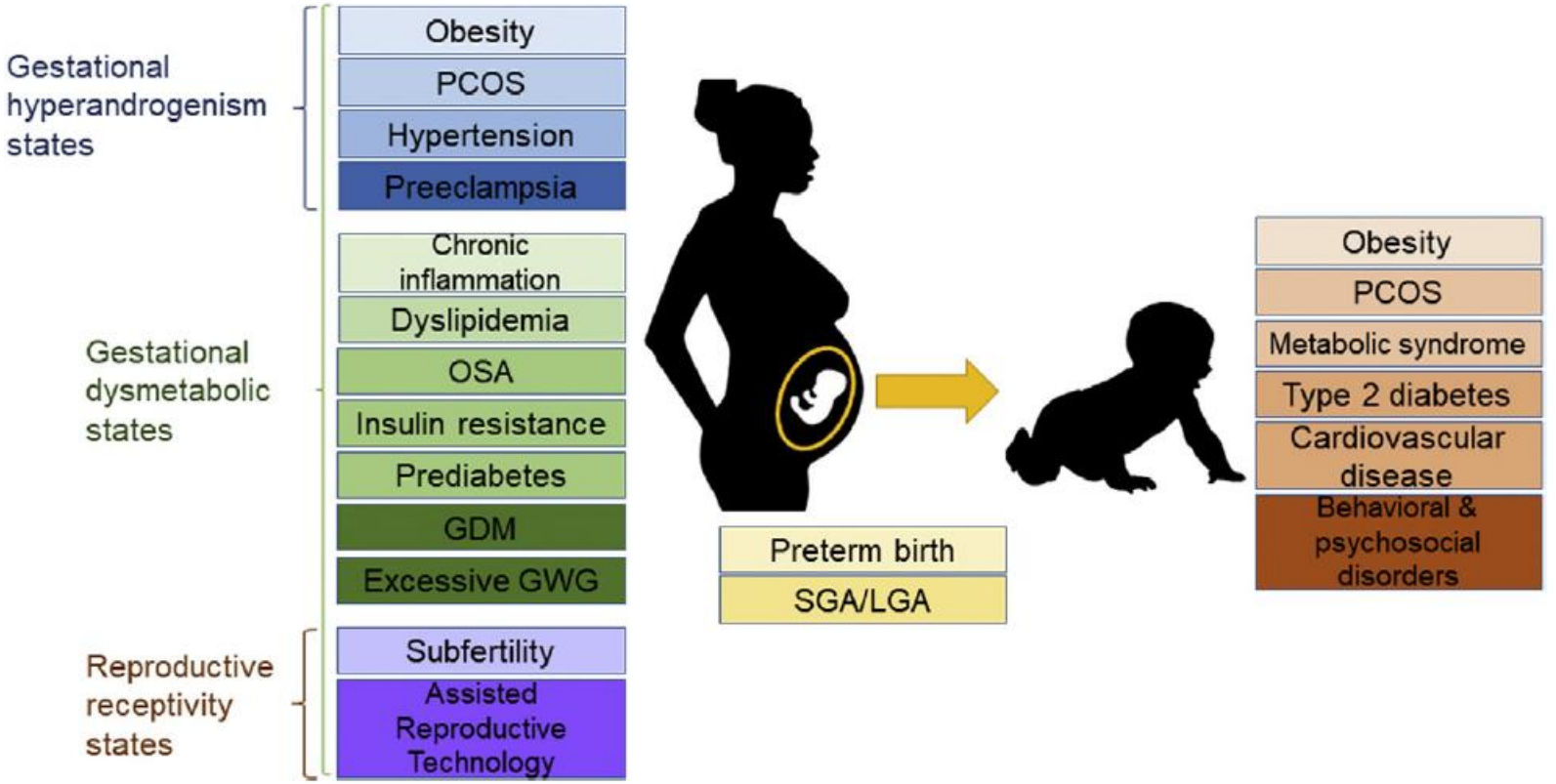
Co-funded by the Erasmus+ Programme of the European Union



Valent & Barbour, 2021

PCOS, obesity and transgenerational medicine

Co-funded by the Erasmus+ Programme of the European Union



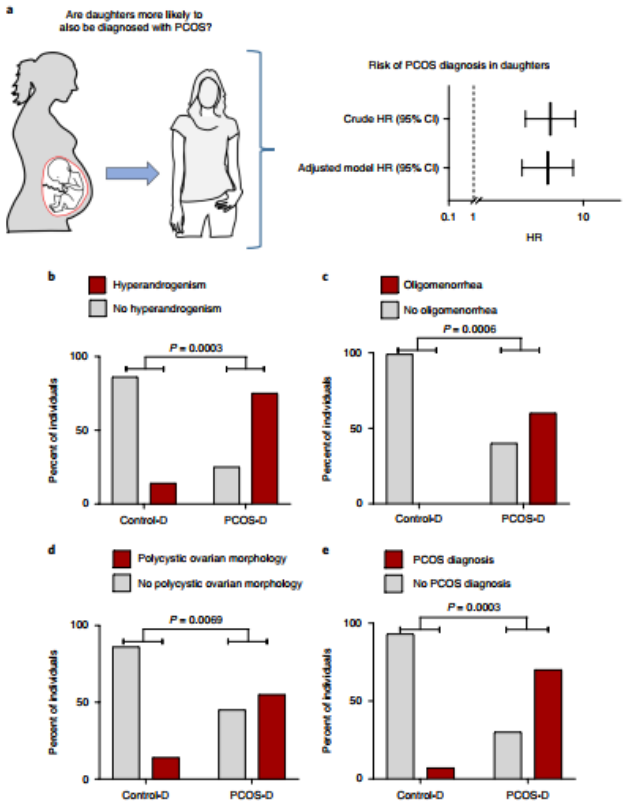
PCOS, PCOS-related conditions, and associated perinatal complications influence the intrauterine environment, leading to the developmental programming of the offspring for long-term, chronic health conditions.

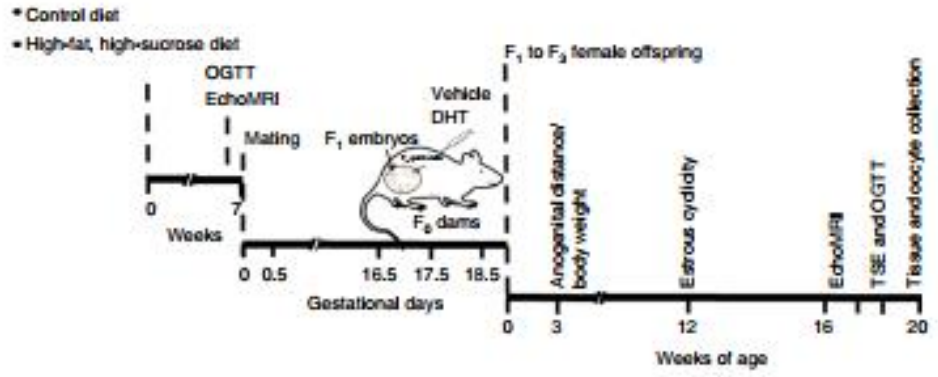
Valent & Barbour, 2021

Valent & Barbour, 2021

Prenatal androgen exposure and transgenerationl susceptibility to PCOS

Co-funded by the Erasmus+ Programme of the European Union



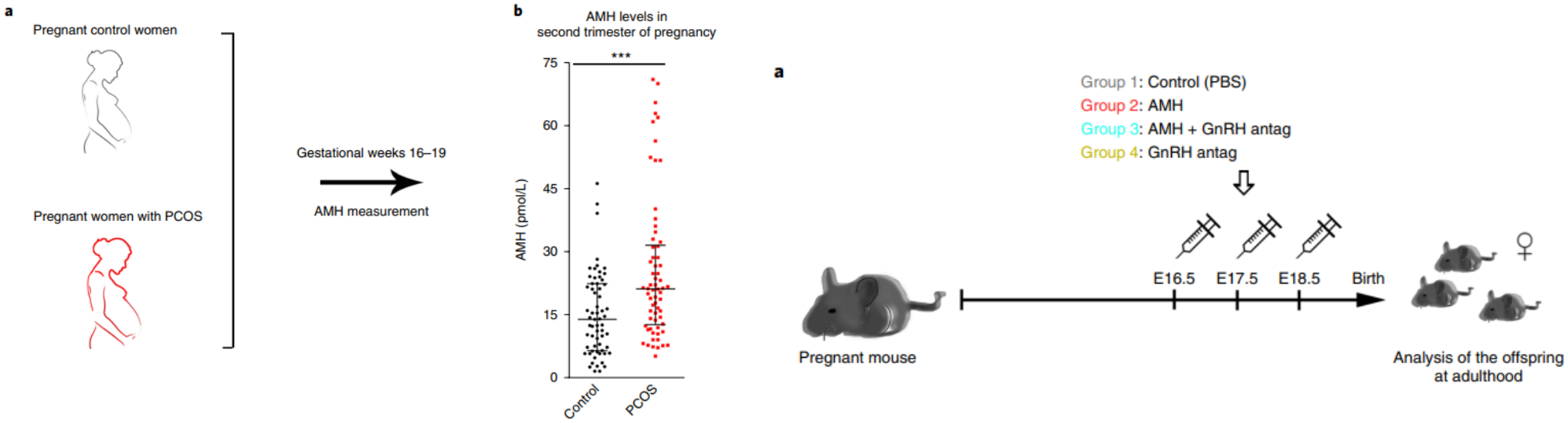


- Androgen exposure during pregnancy in a F0 mother mouse model, in association or not with high fat and sugar diet, is associated with transgenerational (F1-F3) increased anogenital distance, irregular estrous cycles, increased fat mass, larger adipocytes and disturbed adipogenesis.
- Sequencing of single metaphase II oocytes from F1–F3 offspring revealed common and unique altered gene expression across all generations.

Risal et al, 2019

Elevated antimullerian hormone reprograms the fetus and induces PCOS in adult mouse

Co-funded by the Erasmus+ Programme of the European Union



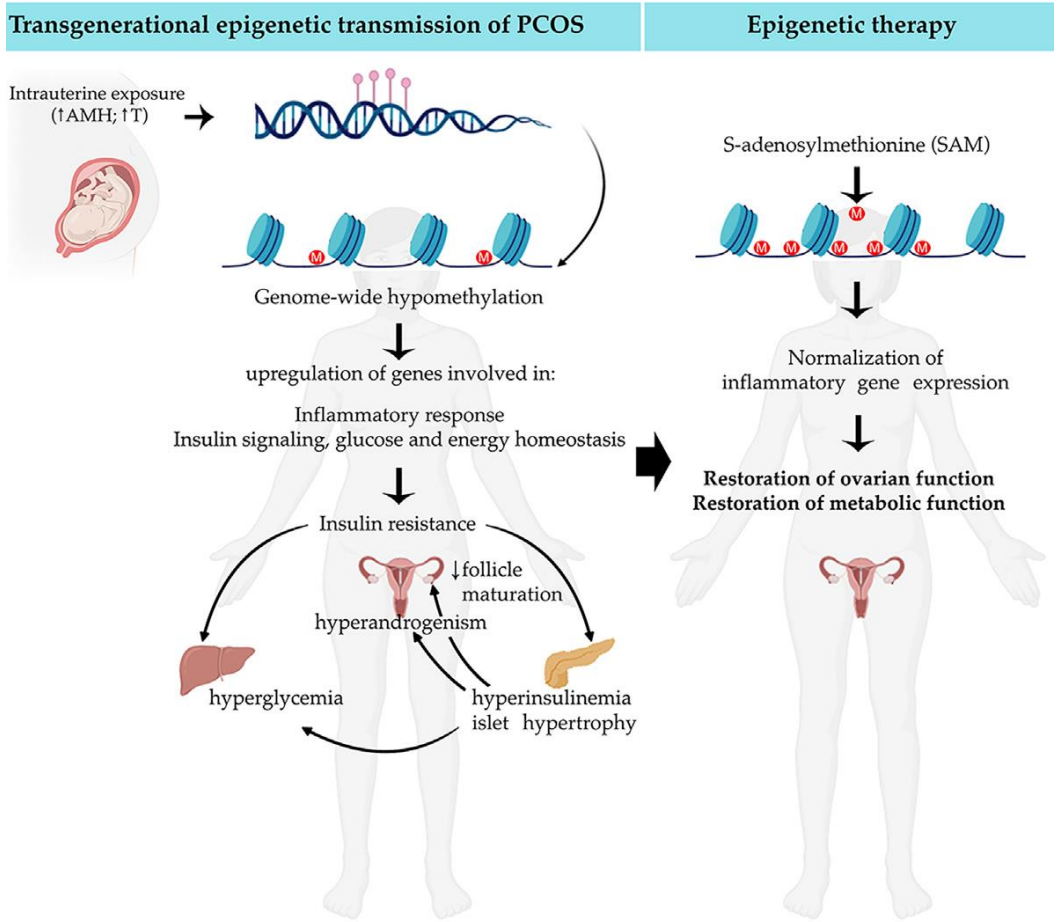
- AMH is significantly more elevated in the pregnant PCO women compared to controls.
- Treating pregnant mice with AMH resulted in maternal neuroendocrine-driven testosterone excess and diminished placental metabolism of testosterone to estradiol, leading to a masculinization of the exposed female fetus and a PCOS-like reproductive and neuroendocrine phenotype in adulthood.

Tata et al, 2018

Polycystic ovary syndrome (PCOS) is transmitted via a transgenerational epigenetic process

Co-funded by the Erasmus+ Programme of the European Union

- Transmission of PCOS-like traits to multiple generations occurs via an altered landscape of DNA methylation and transcriptome expression.
- Metabolic- and inflammatory-related pathways are dysregulated in models of PCOS
- Common hypomethylation signatures occur in a mouse model of PCOS and in humans
- Identification of a novel epigenetic-based therapeutic strategy for PCOS



Mimouni et al, 2021

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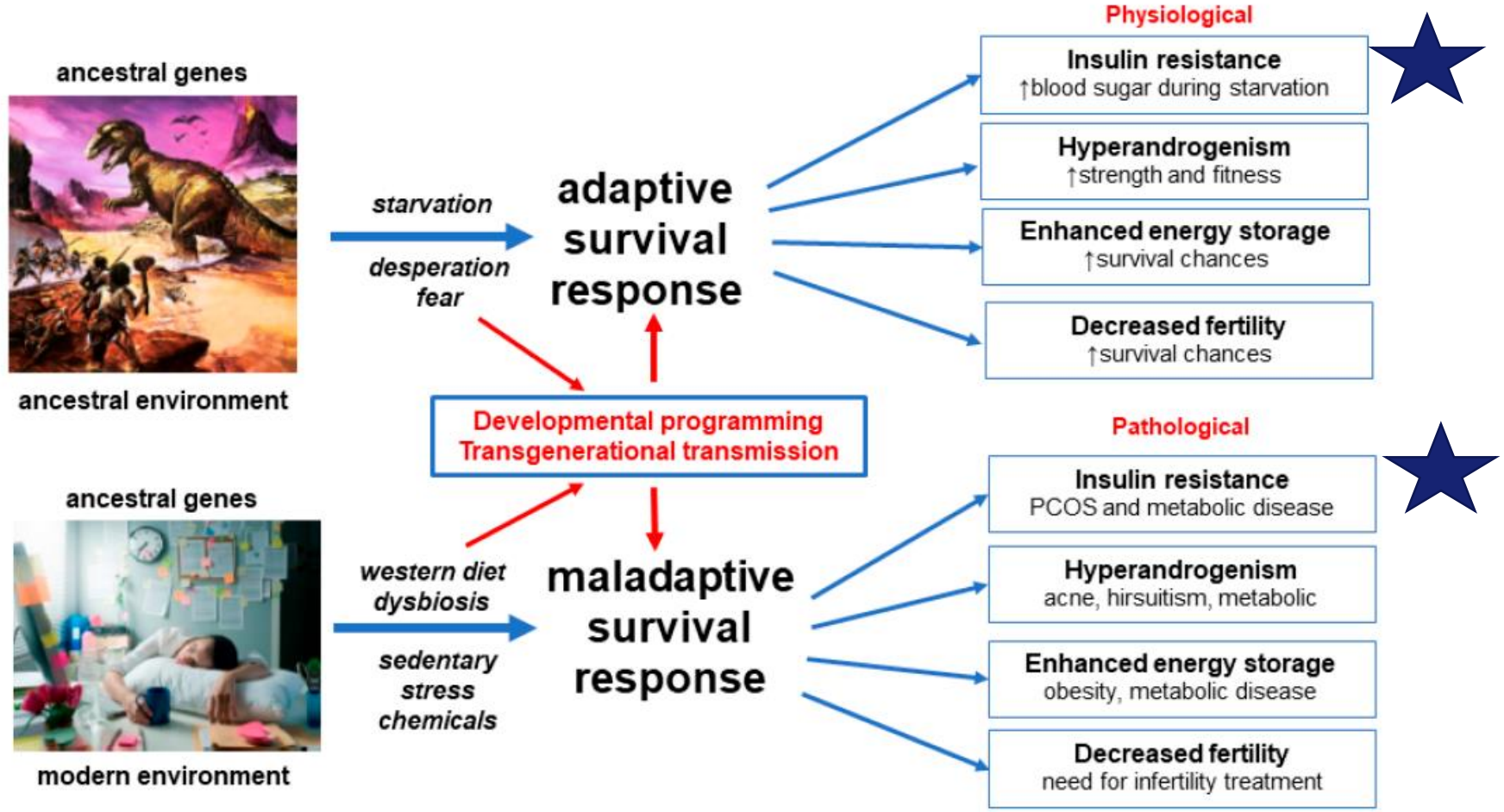
Etiopathogenetic model of PCOS in human evolution

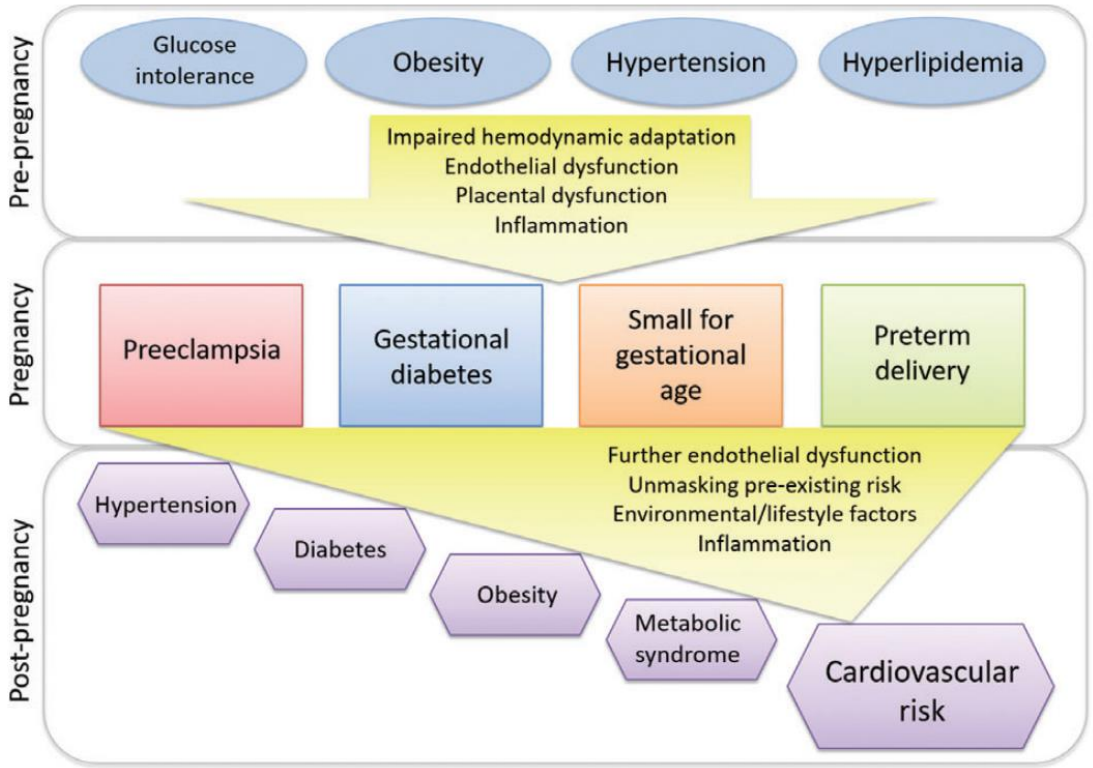
Co-funded by the Erasmus+ Programme of the European Union



Parker et al, 2022

Adverse pregnancy outcomes and future cardiovascular health

Co-funded by the Erasmus+ Programme of the European Union



- Women with a history of preeclampsia have a 71% increased risk of CVD mortality, a 2.5-fold increase in risk of CAD, and a 4-fold increase in heart failure
- Women with a history of GDM have a 7-fold increased risk of T2DM and an independent 2 folds increased risk of major cardiovascular events
- Women with SGA infants have been found to be twice as likely to experience future CVD
- Infant birth weight 2 standard deviations above the mean is associated with 26% higher risk of maternal CVD
- Preterm delivery was associated with a 38% increased risk of ischemic heart disease, 71% increased risk of stroke, and 2-fold increased risk of overall CVD.

Hauspurg et al, 2018

Co-funded by the Erasmus+ Programme of the European Union

Pregnancy as a “stress test” to the female body

Women with adverse pregnancy outcomes have maladaptive responses to pregnancy

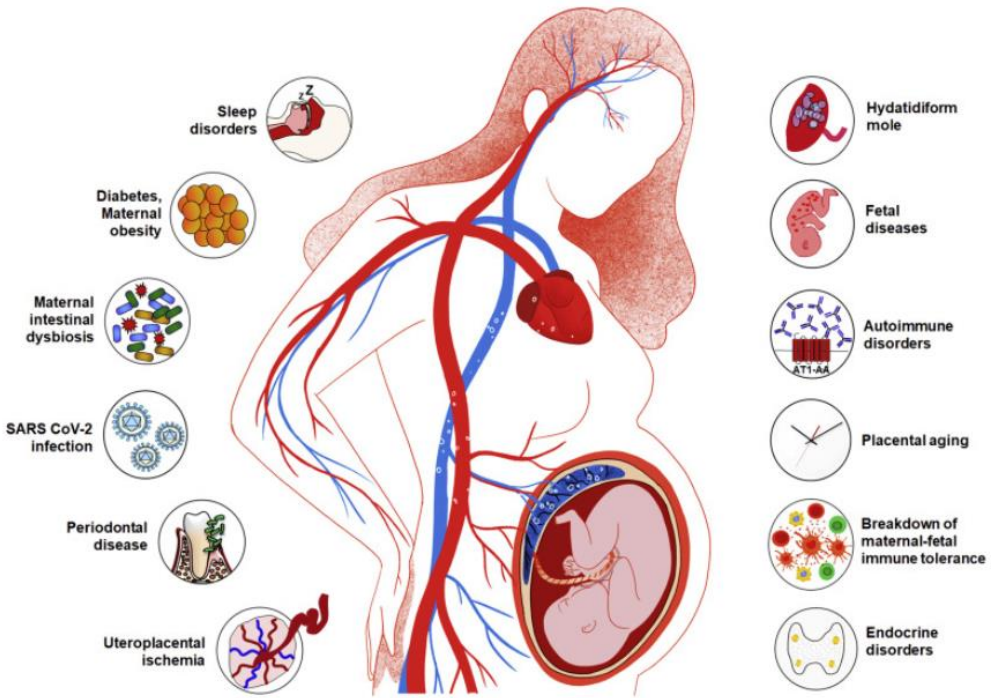
TABLE 1 Normal physiologic changes of pregnancy compared to changes in preeclampsia in select organ systems

Organ System	Changes in Normal Pregnancy[2]	Changes With Preeclampsia[3]
Cardiovascular	Increased cardiac output: 30%–50% increase (due to increased heart rate and stroke volume)	Impaired hemodynamic adaptation
	Reduced systemic vascular resistance and blood pressure	Increased mean arterial pressure, systemic vascular resistance, decreased cardiac output
Renal	75% increase in renal plasma flow with resulting 40%–50% increase in glomerular filtration rate	Compromised glomerular filtration rate
	Increased excretion of total protein, albumin and low-molecular-weight proteins	Decreased renal clearance of uric acid, leading to hyperuricemia
		Exaggerated urinary excretion of proteins
Metabolic	Increased insulin resistance to facilitate transfer of glucose to fetus	Exaggerated insulin resistance
	Two- to fourfold increase in triglycerides; ~50% increase in total cholesterol	Dyslipidemia with lower HDL, higher triglycerides, higher circulating free fatty acids
Hematologic	40%–50% increase in maternal plasma volume, increased red cell mass with resultant physiologic anemia	Subclinical activation of coagulation system
	Increase in coagulation factors overall leading to a hypercoagulable state	Decrease in concentration and lifespan of platelets

Hauspurg et al, 2018

Mechanisms linking hypertensive disorders of pregnancy to cardiovascular disease

Co-funded by the Erasmus+ Programme of the European Union



Jung et al, 2022

O'Kelly et al, 2022

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Cardiovascular risk & life cycle

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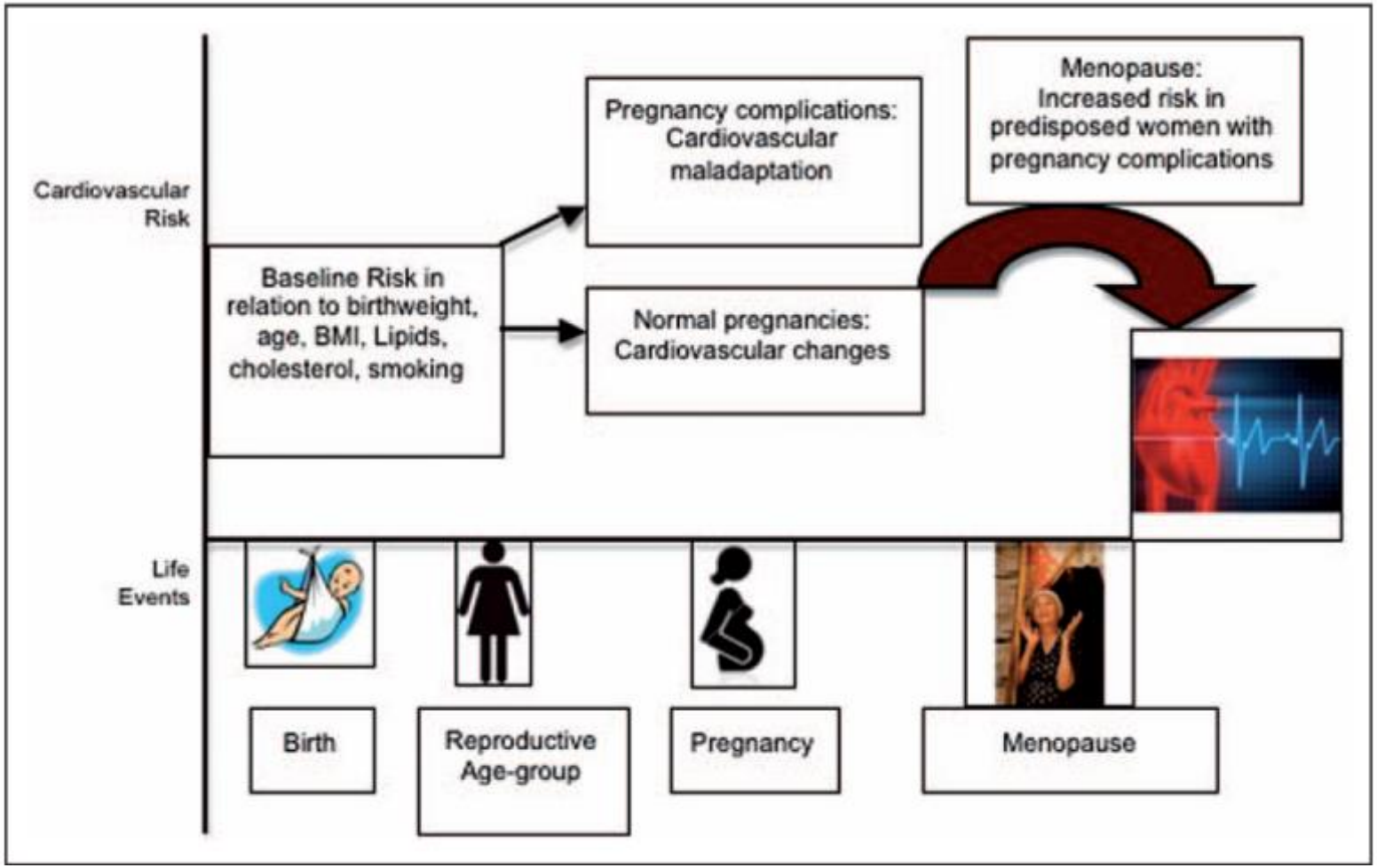

Mahendru & Morris, 2013

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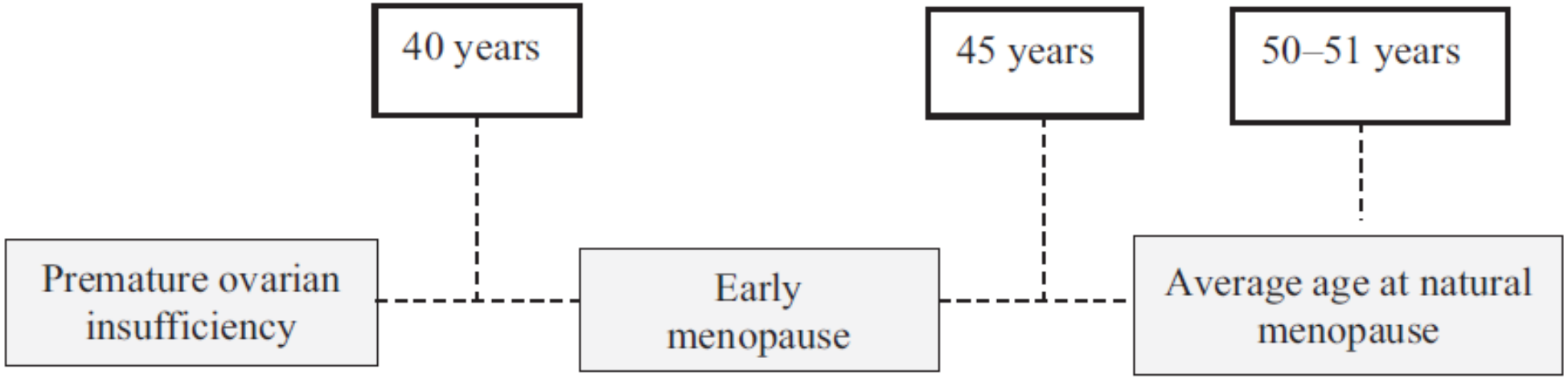
Menopause and Age



- The final menstrual period defines the menopause. The average age at natural menopause is approximately 50.5 years (95% CI: 50.2 to 50.8).
- Women with premature ovarian insufficiency experience ovarian senescence before the age of 40 years.
- Termination of menses at an age >40 years but under 45 years is defined as early menopause.

Lambrinoudaki et al, 2022

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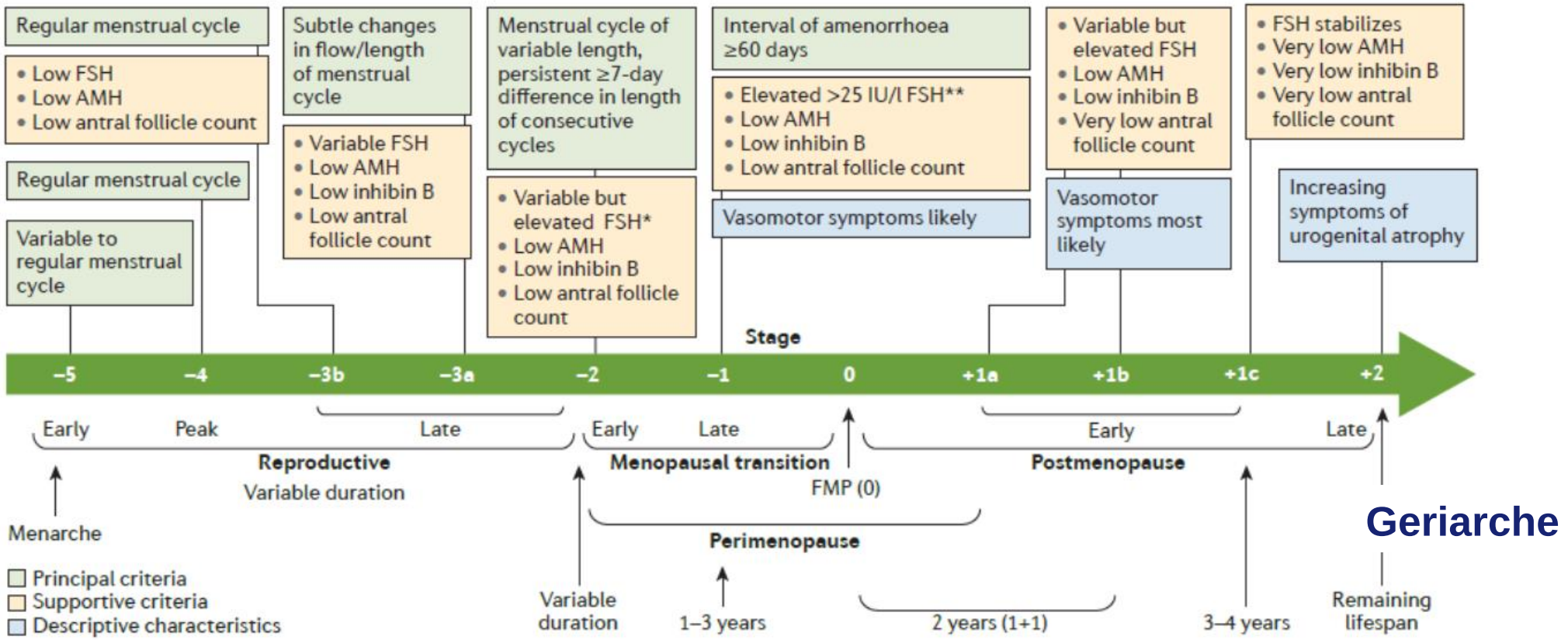
Stages of Menopause

Fertipause

Menopause



Geriarche

5-7 years

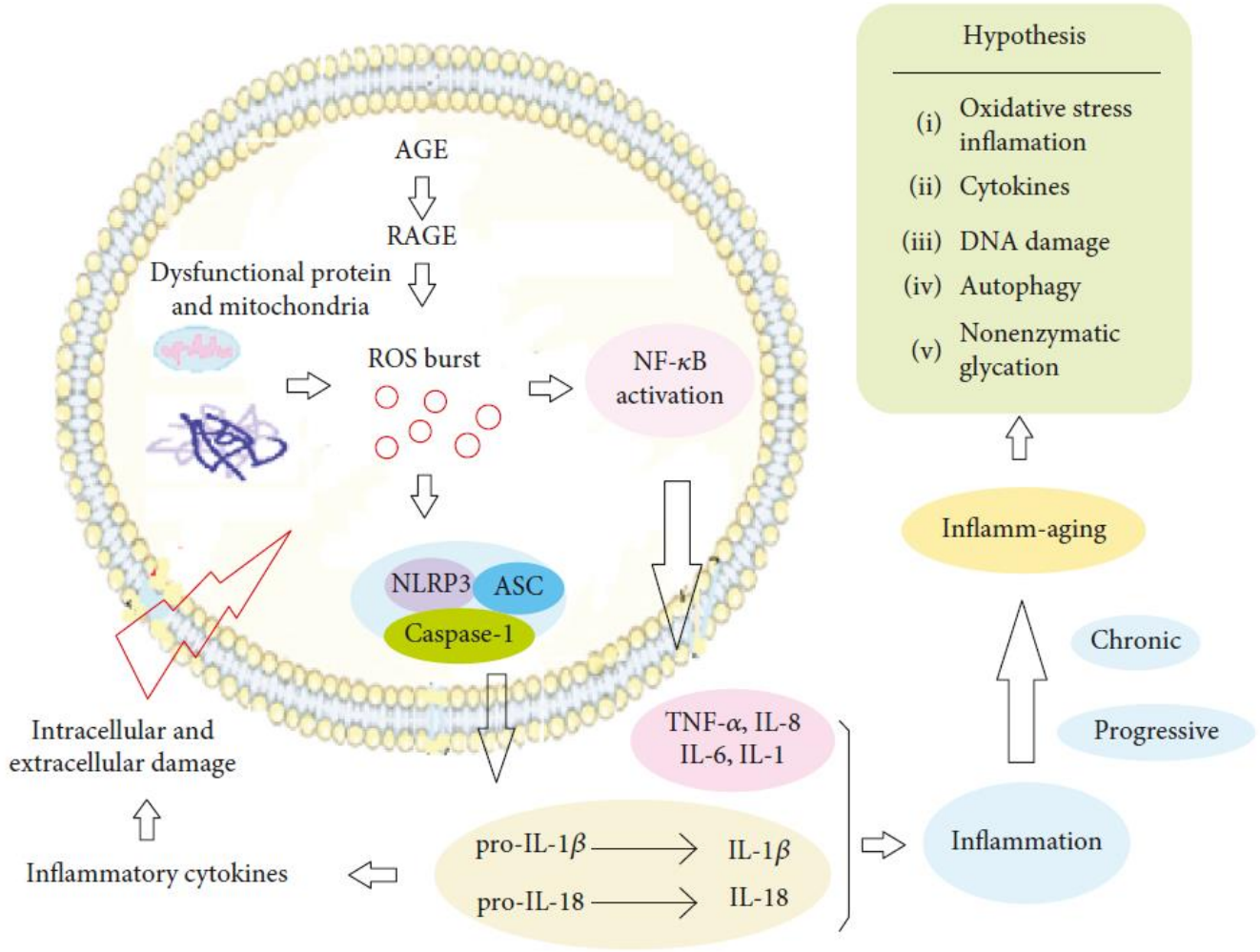
10 years

Modified from Davis et al, 2015

Inflamm-Aging: A New Mechanism Affecting Premature Ovarian Insufficiency

Co-funded by the Erasmus+ Programme of the European Union

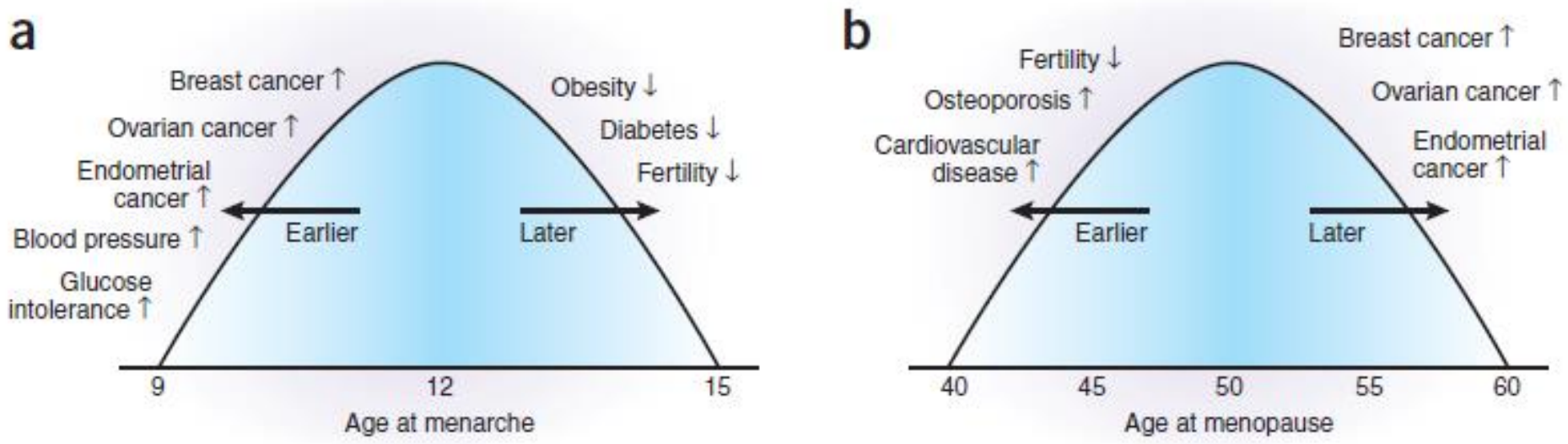
- In the process of aging, with the activation of inflammatory factors, the body appears to be in a chronic, progressively elevated proinflammatory state called inflammatory aging. ROS in the body is increased due to several factors. It causes oxidative stress and a series of inflammatory reactions activated by NLPR3 and NF-κB. It is now summarized as follows: oxidative stress inflammation, cytokines, DNA damage, autophagy, and nonenzymatic glycation.



Huang et al, 2019

POTENTIAL HEALTH IMPACT OF OVARIAN AGING

Co-funded by the Erasmus+ Programme of the European Union



- **Longer cumulative exposures to estrogen and progesterone or specific hormonal exposure during a window of susceptibility may increase or decrease some health risks**
- **Does a gene that influences menarche/menopause directly affect the risk of developing a disease?**

HORMONES, GENES OR BOTH?

P Hartge, 2009

Menopause Accelerates Biological Ageing

Co-funded by the Erasmus+ Programme of the European Union

- A highly accurate epigenetic biomarker of age (known as the “epigenetic clock”), which is based on DNA methylation levels (blood, saliva, and buccal epithelium) using data from four large studies: the Women’s Health Initiative (n = 1,864); Invecchiare nel Chianti (n = 200); Parkinson’s disease, Environment, and Genes (n = 256); and the United Kingdom Medical Research Council National Survey of Health and Development (n = 790).

- Increased epigenetic age acceleration in blood is significantly associated with earlier menopause (P = 0.00091), bilateral oophorectomy (P = 0.0018), and a longer time since menopause (P = 0.017).
- An SNP that relates to age at menopause also relates to epigenetic AgeAccel.

- This is a definitive study that shows an association between age of menopause and biological aging (measured using the epigenetic clock). Results also indicate menopause may accelerate the epigenetic aging process in blood and that age at menopause and epigenetic age acceleration share a common genetic signature

Chromosome	SNP	Base pair position	Minor/ major alleles	β-coefficient (*P* value)
19	rs11668344	55833664	G/A	0.506 (0.031)
20	rs16991615	5948227	A/G	0.151 (0.763)

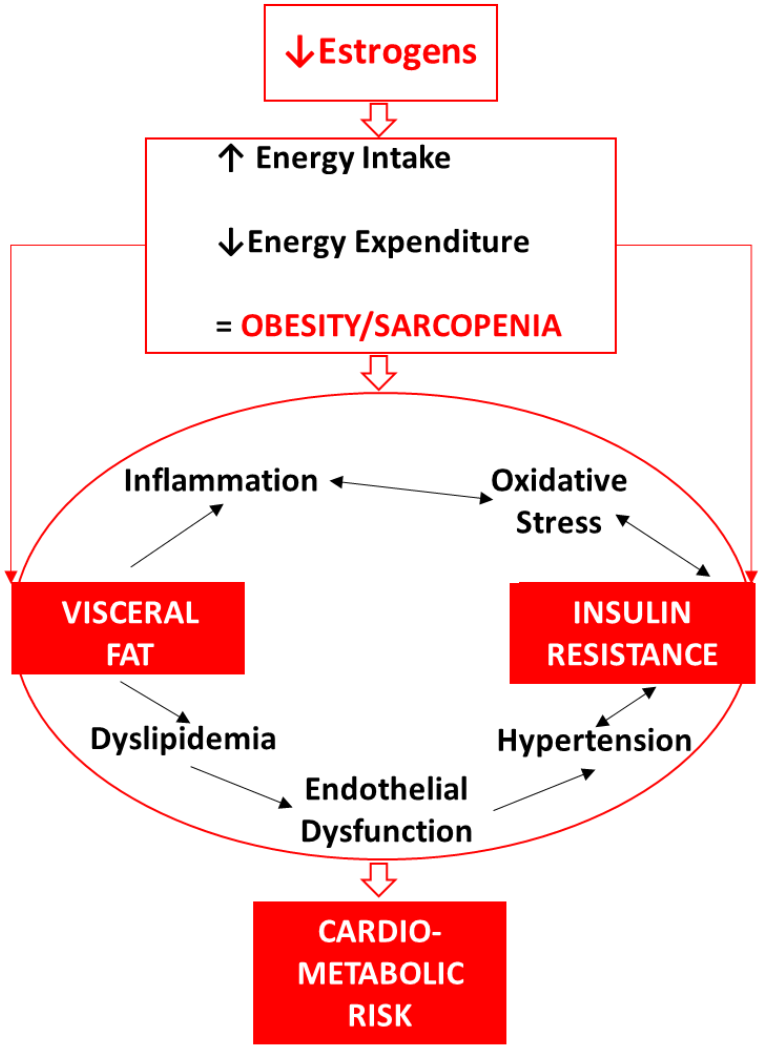
Levine et al, 2016

Multi-systemic changes related to estrogen decline leading to an increased cardio-metabolic risk

Co-funded by the Erasmus+ Programme of the European Union

Other Factors

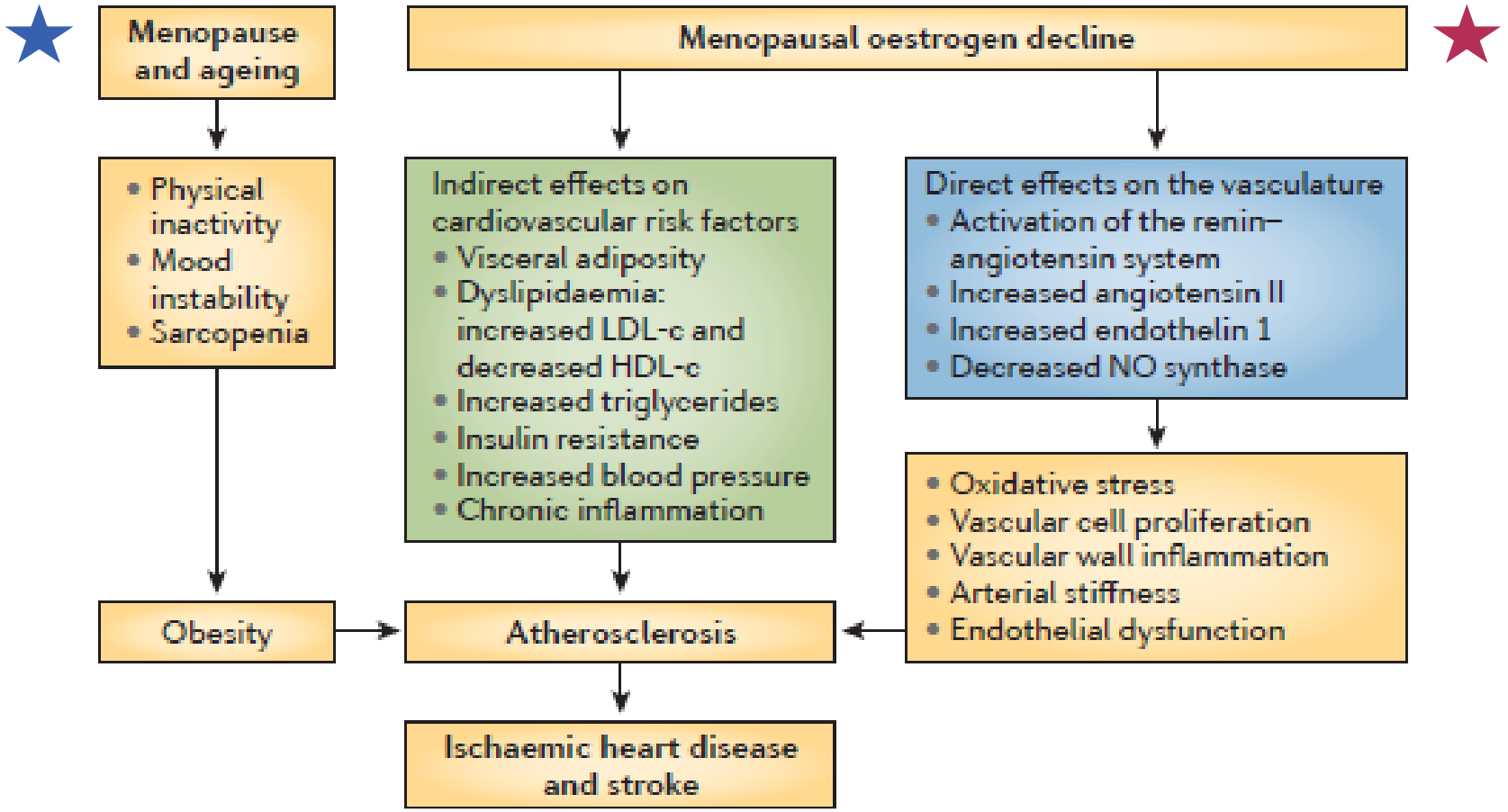
- Vitamin D deficiency
- Low physical activity
- Sedentary behavior
- **Irregular sleep**
- Smoking and alcohol intake



Nappi et al, 2022

Menopause and Ageing on Women's Health: CVD Risk

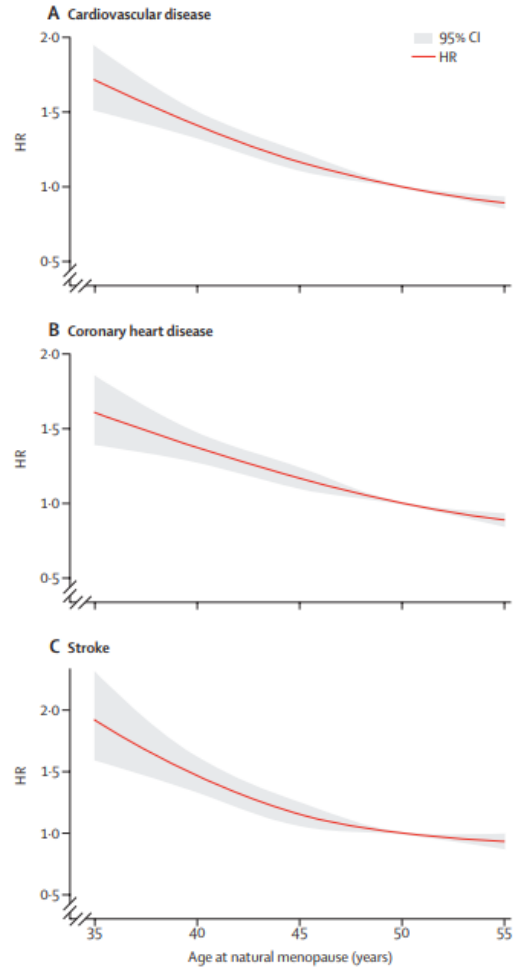
Co-funded by the Erasmus+ Programme of the European Union



Davis et al, 2015

Age at natural menopause and incident cardiovascular disease

Co-funded by the Erasmus+ Programme of the European Union



- Pooled analysis of 15 observational studies involving 301,438 women.
- This showed an increased risk of CVD (CHD and stroke) in women with POI (HR 1.55, 95% CI 1.38–1.73) and early menopause (age 40–44 years; HR 1.30, 95% CI 1.22–1.39), after adjustment for age at last follow-up, ethnicity, BMI, smoking status, educational level, hypertension status and use of hormone therapy.
- The relationship between age at menopause and incident risk of CVD was almost linear; risk of CVD increased by 3% for every year or early menopause.
- A sub-analysis of seven studies demonstrated that HRT the greatest reduction in CVD incidence was in women with POI or early menopause who used HRT for at least 10 years.
- POI who initiated HRT within 1 year of diagnosis had the lowest risk of CVD.

Zhu et al, 2019

Menopause and Ageing on Women's Health: Osteoporosis

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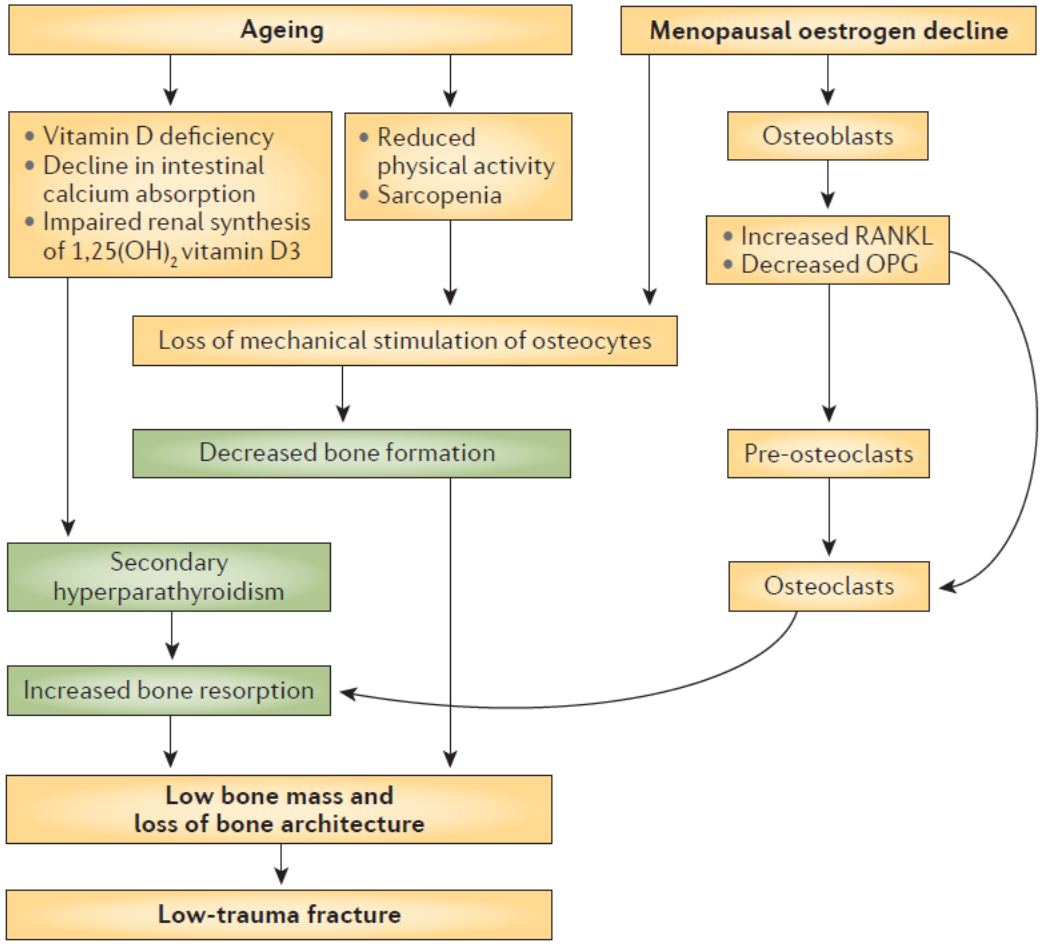

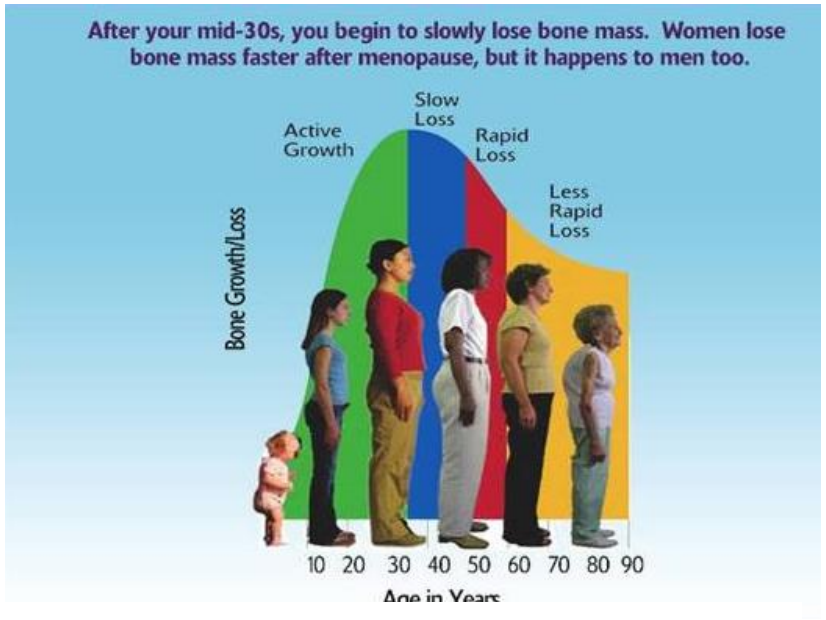

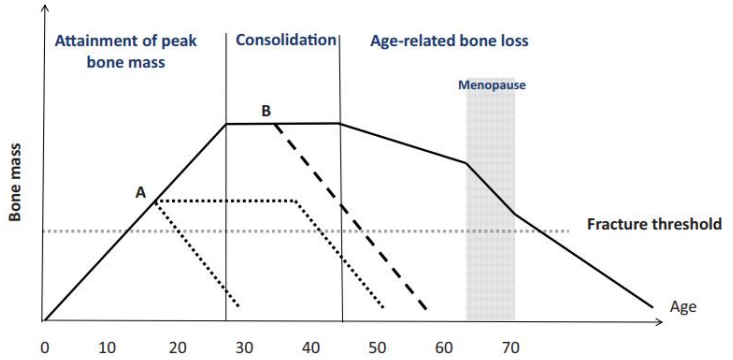

Davis et al, 2015

Gender & Sarcopenia

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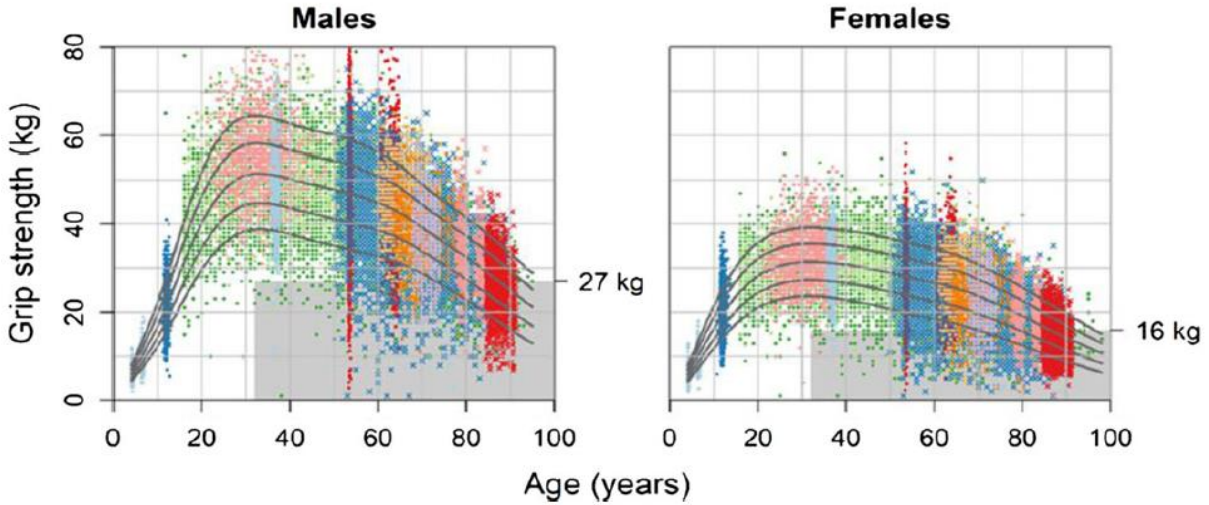
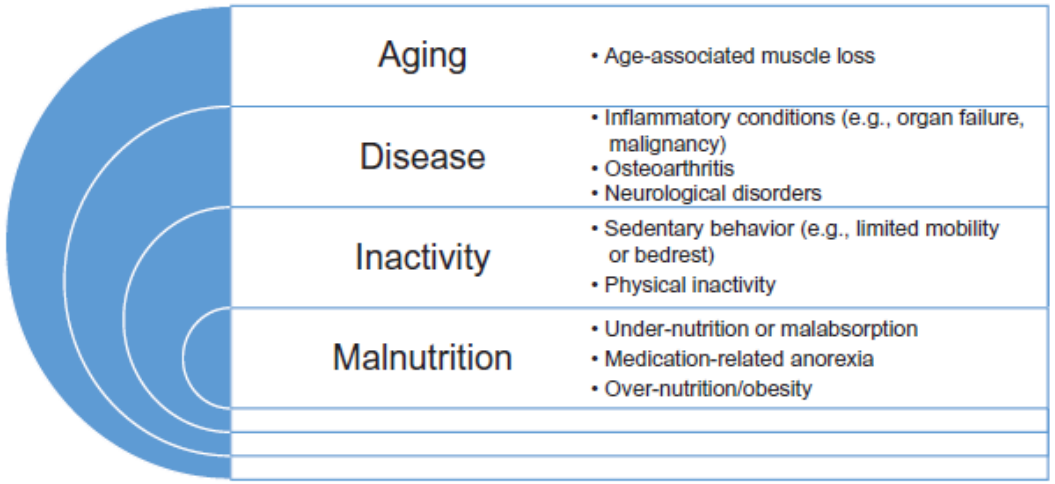
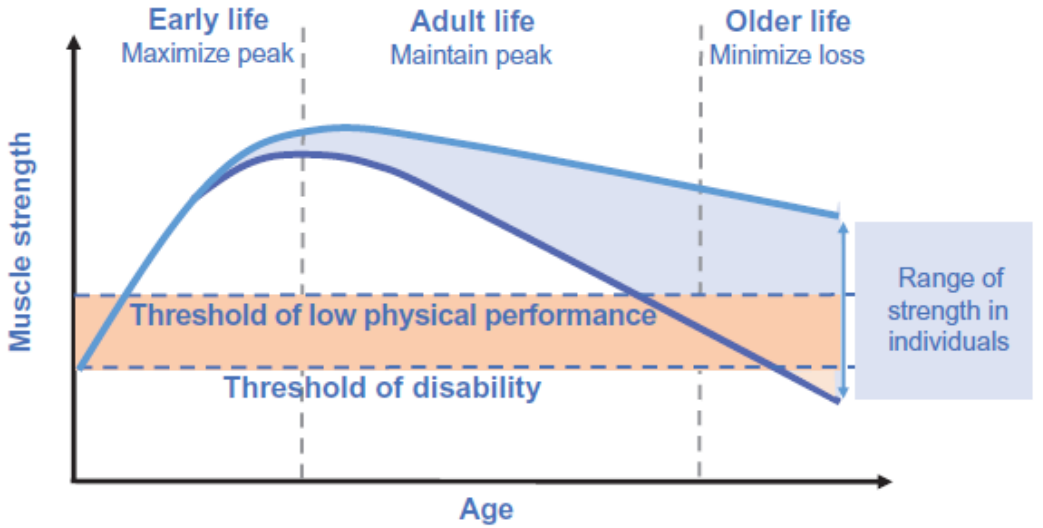
- Sarcopenia is a progressive and generalised skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability and mortality







Cruz-Jentoft et al, 2019

Osteoporotic fracture and mortality risk

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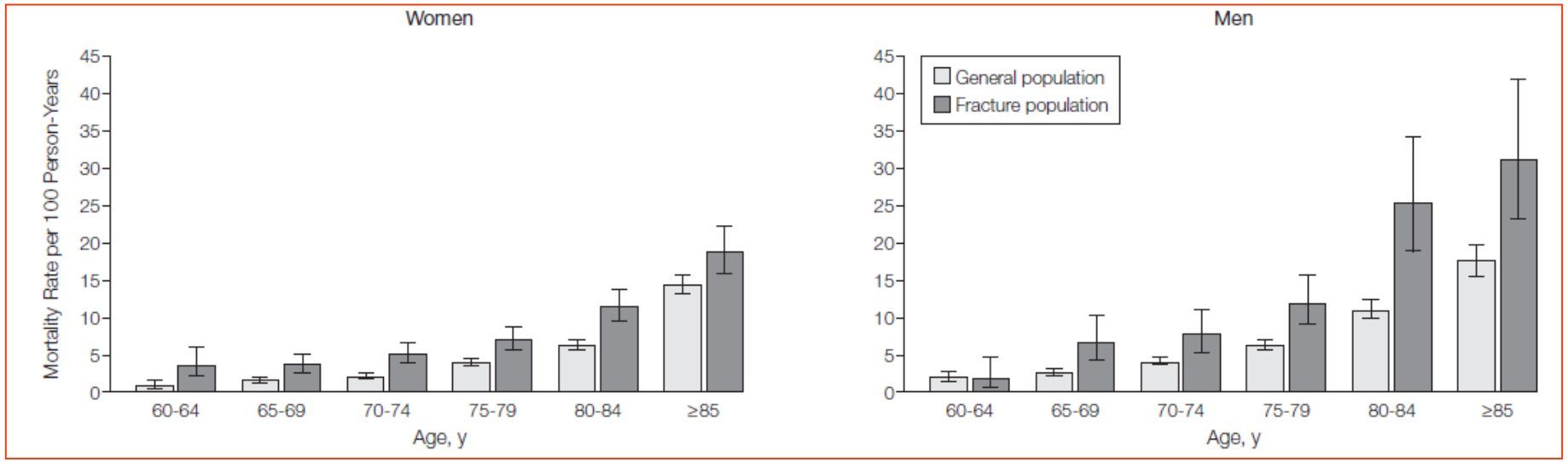


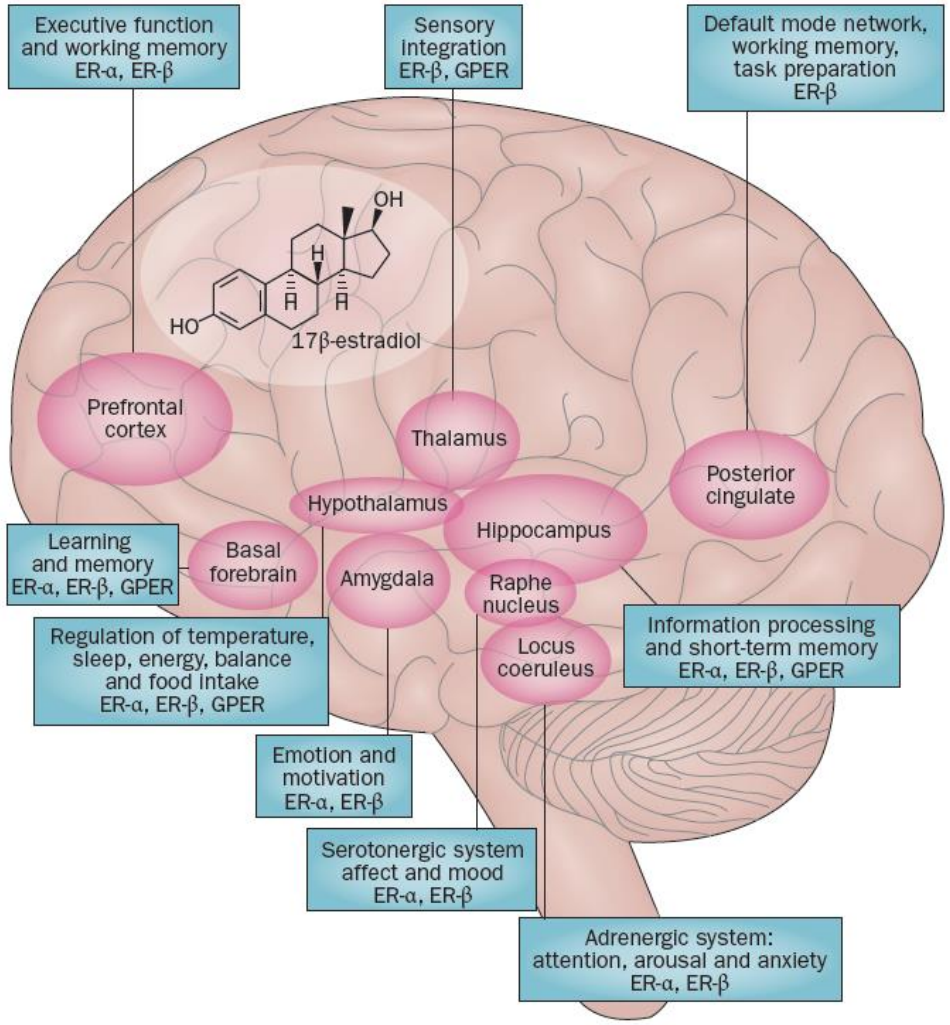
- ☑ **Mortality rates in both sexes increased with age as expected.**
- ☑ **For each age group, mortality in the fracture participants was consistently higher than that in the general population**
- ☑ **For all ages, mortality was higher for men than for women, most markedly in the older age groups.**

Bliuc et al, 2009

Perimenopause as a neurological transition state

Co-funded by the Erasmus+ Programme of the European Union

- Neurological functions affected by the perimenopausal transition. Brain regions and their corresponding functions provide a map of the neural circuits regulated by estrogen and **a neurobiological basis for the array of symptoms that can emerge during perimenopause**. Nuclear, membrane-associated and mitochondrial estrogen receptors are distributed within each of the neural circuits and can be present in both neurons and glial cells. While the complete distribution of ER-α and ER-β remains to be completely mapped in humans, in rats the location of these receptors is well documented.
- Dysregulation of estrogen signalling, either through changes in estrogen concentration or through modifications of estrogen receptor, will affect neural circuit activation and, thus, neurological function.

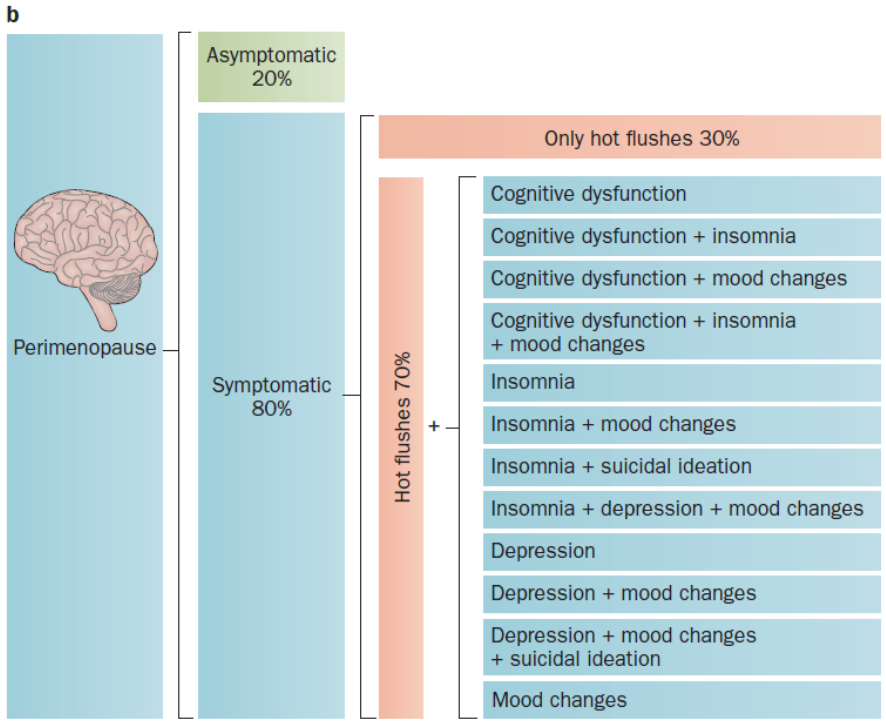


Abbreviations: ER, estrogen receptor; GPER, G protein-coupled estrogen receptor.

Brinton et al, 2015

VMS & CNS Symptoms: a Matter of Sugar!

Co-funded by the Erasmus+ Programme of the European Union



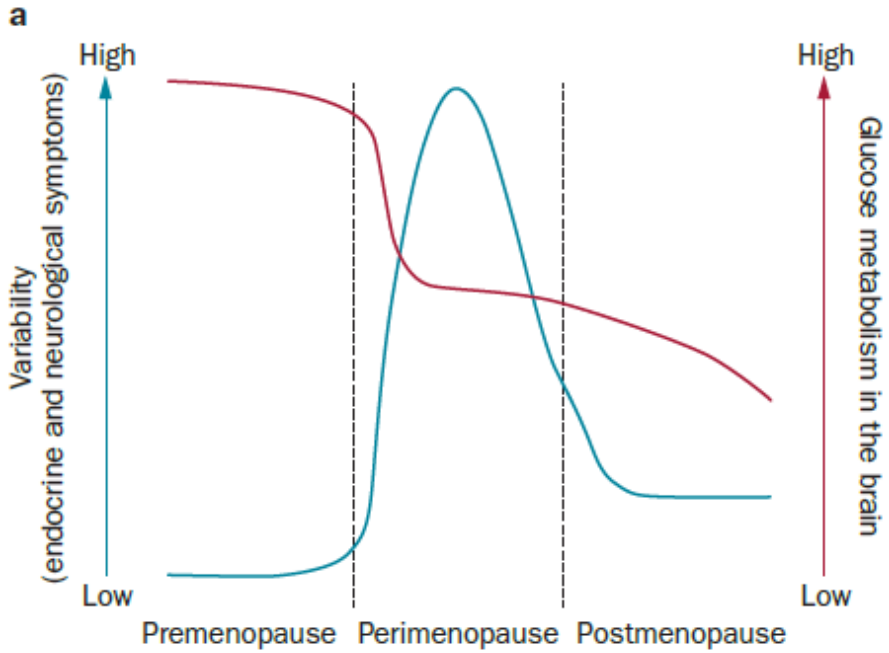


Figure 1 | Symptoms during perimenopause. Perimenopause is characterized by heightened variability in neurological symptoms, which is co-incident with a decline in glucose metabolism in the brain. **a** | Variability of symptoms in premenopause, perimenopause and postmenopause (blue line; left axis); glucose metabolism in the brain (red line; right axis). **b** | Diversity of neurological symptoms during perimenopause. The majority of women will experience neurological symptoms during perimenopause; however, a small proportion (~20%) of women will transition without symptoms.

Brinton et al, 2015

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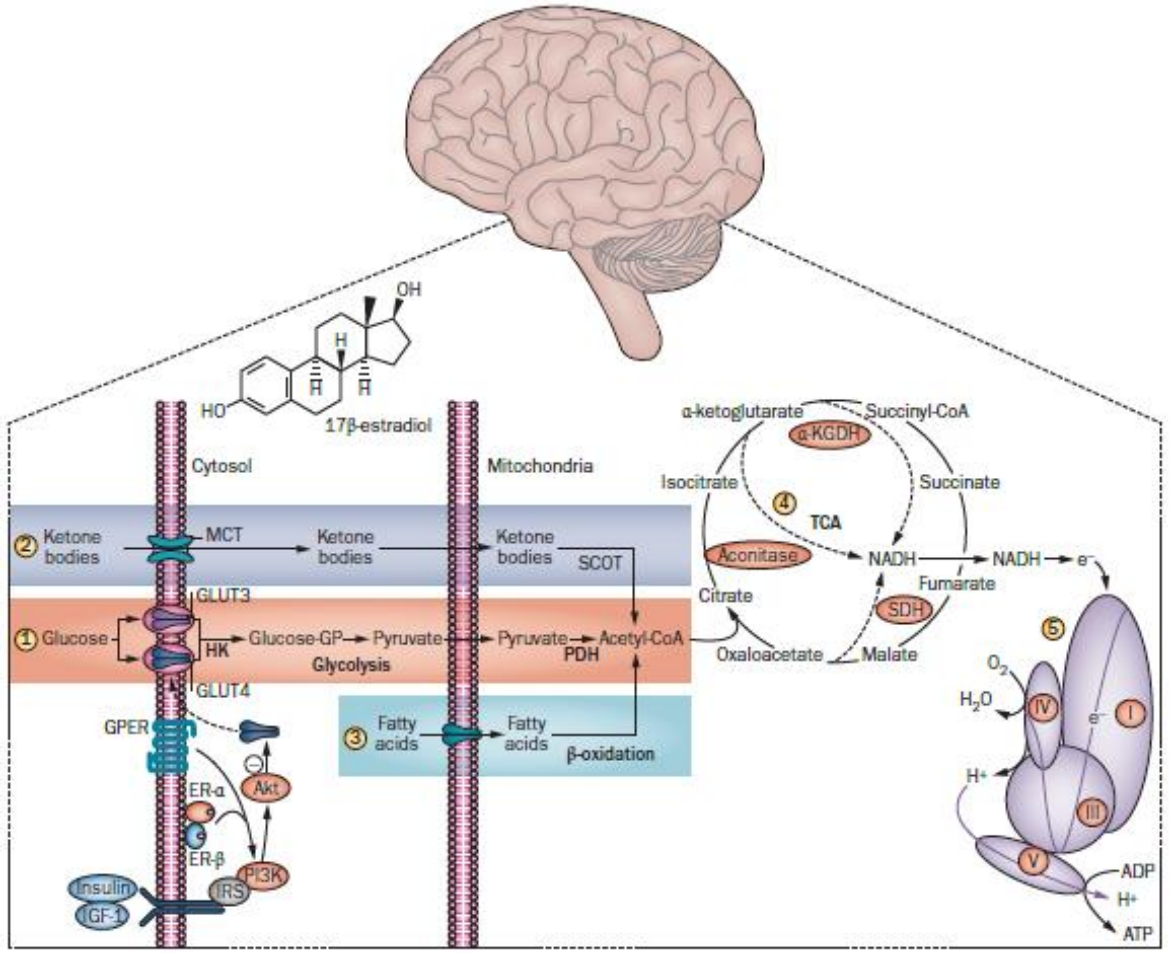
Estrogen-mediated regulation of the bioenergetic system

Co-funded by the Erasmus+ Programme of the European Union

Estrogen signalling supports and sustains glucose metabolism in the brain by regulating expression of glucose transporters, which results in increased glucose uptake, and by stimulating glucose metabolism, mitochondrial oxidative phosphorylation and ATP generation—collectively referred to as aerobic glycolysis. Glucose (1) is the primary metabolic fuel for the brain. Estrogen regulates the bioenergetic system in brain the through the estrogen receptors, GPER, ER-α and ER-β, and their activation of PI3K and downstream Akt and MAPK–ERK signalling pathways. When the glucose pathway is compromised, for example, during starvation, acetyl-CoA can be generated from ketone bodies via ketogenesis in the liver and transported through the blood to the brain through monocarboxylate transporters (2) or from fatty acid via β-oxidation (3). During the perimenopausal transition, neuronal levels of glucose transporters decline, which is co-incident with the appearance of hypometabolism in the brain.86 The brain adapts to this decline in glucose availability by increasing reliance on ketone bodies as an alternative fuel to generate acetyl-CoA required for entry to the TCA cycle (4) and ultimately generation of ATP via complexes of the mitochondrial redox carriers (5). Initially, ketone bodies are derived from the periphery by lipid metabolism in the liver. Depletion of peripheral sources of ketone bodies can result in metabolism of brain-derived fatty acids to generate ketone bodies via β-oxidation in glia cells (3).

Abbreviations: GP, glucose-6-phosphate; GPER, G protein-coupled estrogen receptor 1; ER-α, estrogen receptor α; ER-β, estrogen receptor β; HK, hexokinase; α-KGDH, α-ketoglutarate dehydrongenase, IGF-1, insulin growth factor-1; IRS, insulin receptor substrate; MCT, monocarboxylate transporter; PDH, pyruvate dehydrogenase; PI3K, phosphoinositide 3-kinase; SCOT, succinyl-CoA:3-ketoacid CoA transferase; SDH, succinate dehydrogenase; TCA, tricarboxylic acid cycle.



Brinton et al, 2015

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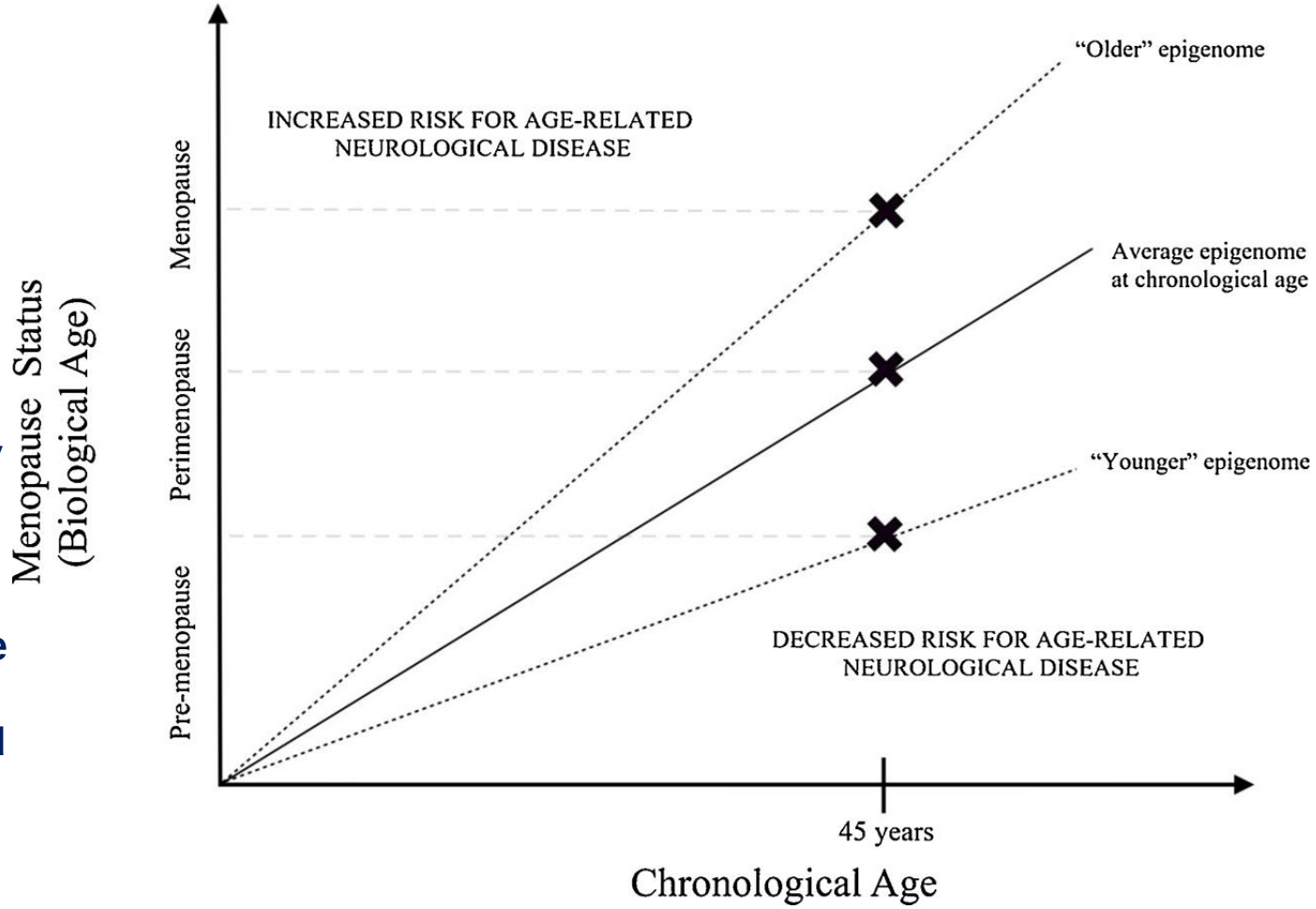
Epigenetics of the developing and aging brain

- In humans, **menopause is strongly associated with the accelerated epigenetic patterns of aging in blood**. Post-menopausal women are “biologically and epigenetically” older than pre-menopausal women of the same chronological age (hypothetically marked along each trajectory as “X”).
- **Epigenetic changes prior to and during the perimenopause transition may provide an explanation for the age-related negative health and cognitive outcomes associated with early menopause**.



Bacon & Brinton, 2021

How Women's Reproductive Health Can Drive Brain Aging

Co-funded by the Erasmus+ Programme of the European Union

- While the neurobiological consequences of reproductive history and hormonal changes on brain aging and AD risk have only begun to be understood, converging evidence supports **a role for cumulative estrogen exposure in reducing risk of AD and dementia later in life**.
- This strongly argues for continued examination of sex hormones and reproductive history factors in AD prevention strategies for women.
- There is an urgent need for prospective epidemiological, clinical and biomarkers studies with data taken at several time points starting at midlife that examine the associations between cumulative estrogen exposure and cognitive function in later life.
- **Understanding the dynamic interplay between sex, chronological aging, endocrine aging, and additional risk factors is crucial** to inform and justify primary prevention strategies targeting female-specific risk factors underlying the increased prevalence of AD in women, and for development of future personalized preventive care.

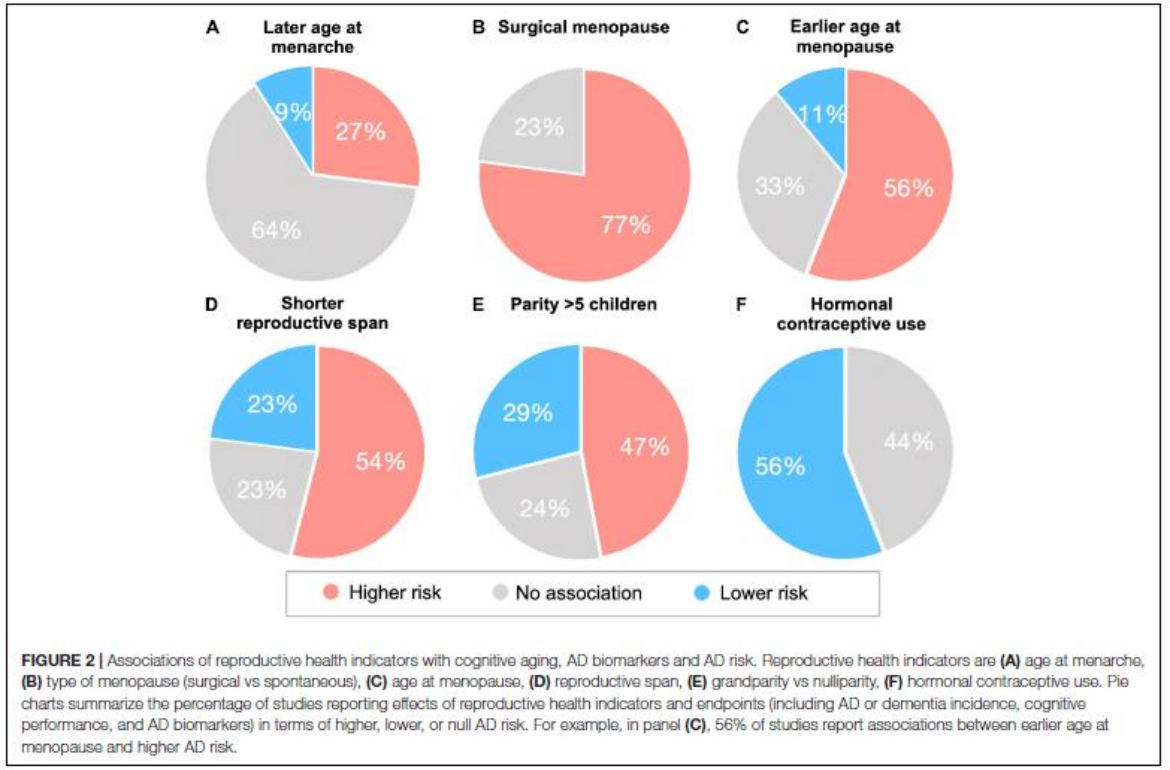


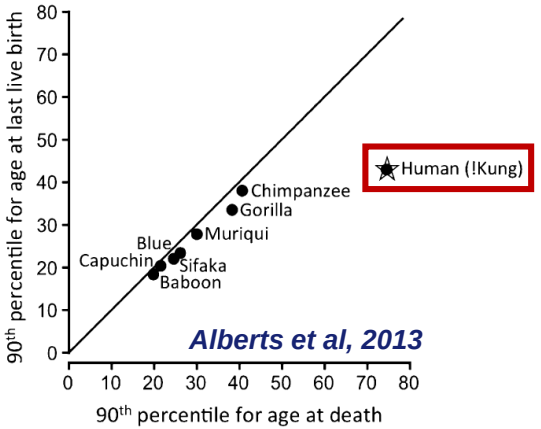
FIGURE 2 | Associations of reproductive health indicators with cognitive aging, AD biomarkers and AD risk. Reproductive health indicators are **(A)** age at menarche, **(B)** type of menopause (surgical vs spontaneous), **(C)** age at menopause, **(D)** reproductive span, **(E)** grandparity vs nulliparity, **(F)** hormonal contraceptive use. Pie charts summarize the percentage of studies reporting effects of reproductive health indicators and endpoints (including AD or dementia incidence, cognitive performance, and AD biomarkers) in terms of higher, lower, or null AD risk. For example, in panel **(C)**, 56% of studies report associations between earlier age at menopause and higher AD risk.

Jett et al, 2022

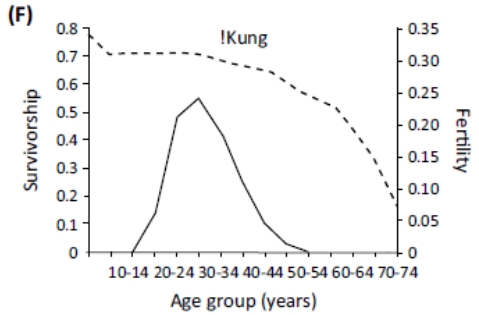
Why women live longer than menopause?

Co-funded by the Erasmus+ Programme of the European Union

The investigation of reproductive ageing in higher primates suggests human female are different.



Alberts et al, 2013



Croft et al, 2015

Panay & Fenton, 2015

<u>POSTREPRODUCTIVE LIFE</u>:
Numerous hypotheses in evolution

- **Mother/Grandmother**
- **Genetics**
- **Chance**

An explanation for menopause comes from killer whales (1)

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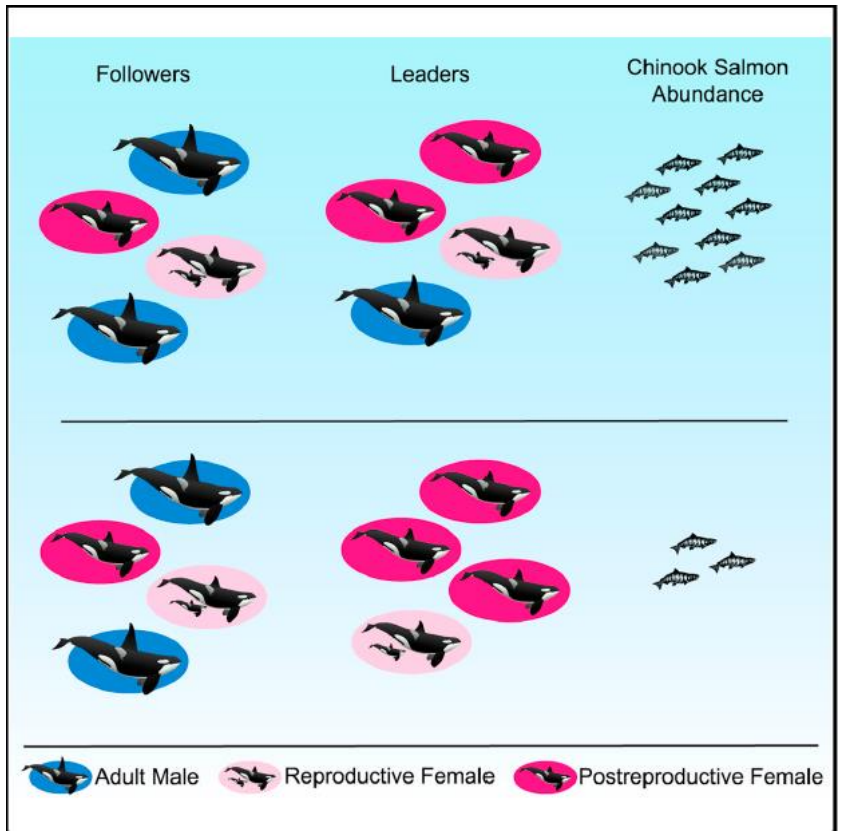

Brent et al, 2015

Ecological Knowledge, Leadership, and the Evolution of Menopause in Killer Whales

Highlights

- Postreproductively aged female resident killer whales lead collective movement
- Leadership by postreproductive females is most prominent when food abundance is low
- Sons are more likely than daughters to follow their mothers

- **Older women are relevant to help the younger!**

An explanation for menopause comes from killer whales (2)

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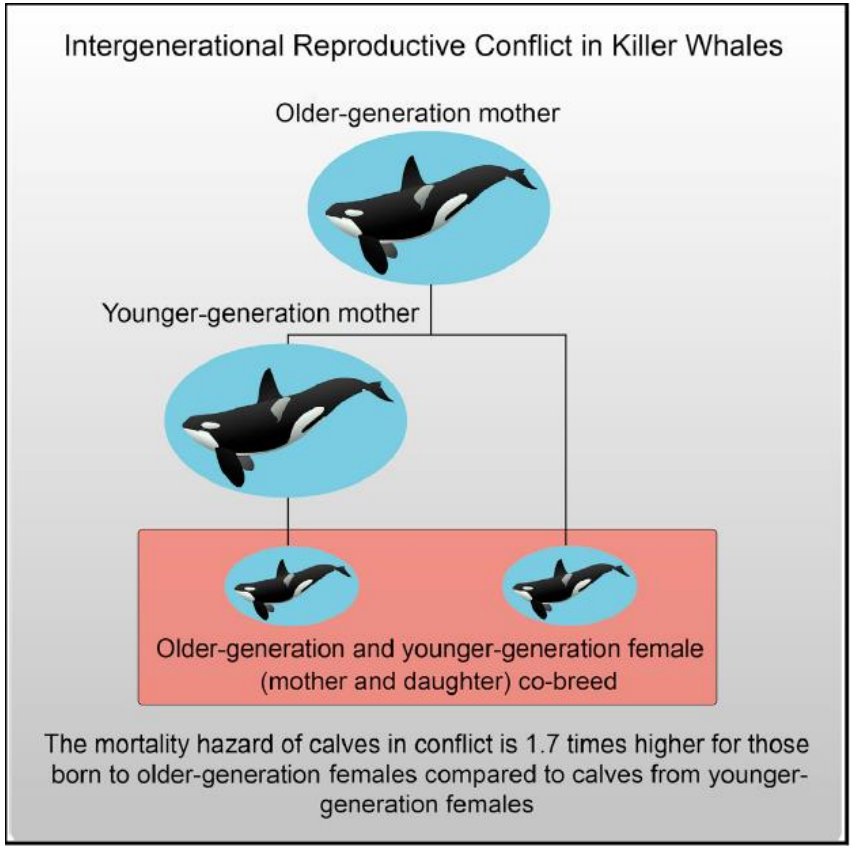
Reproductive Conflict and the Evolution of Menopause in Killer Whales



Highlights

- Local group relatedness increases with age in female killer whales
- Young females are predicted to invest more in reproductive competition
- The costs of co-breeding with kin are greater for old compared to young females

- **Late reproduction is a big risk!**

Croft et al, 2017

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Thank You!

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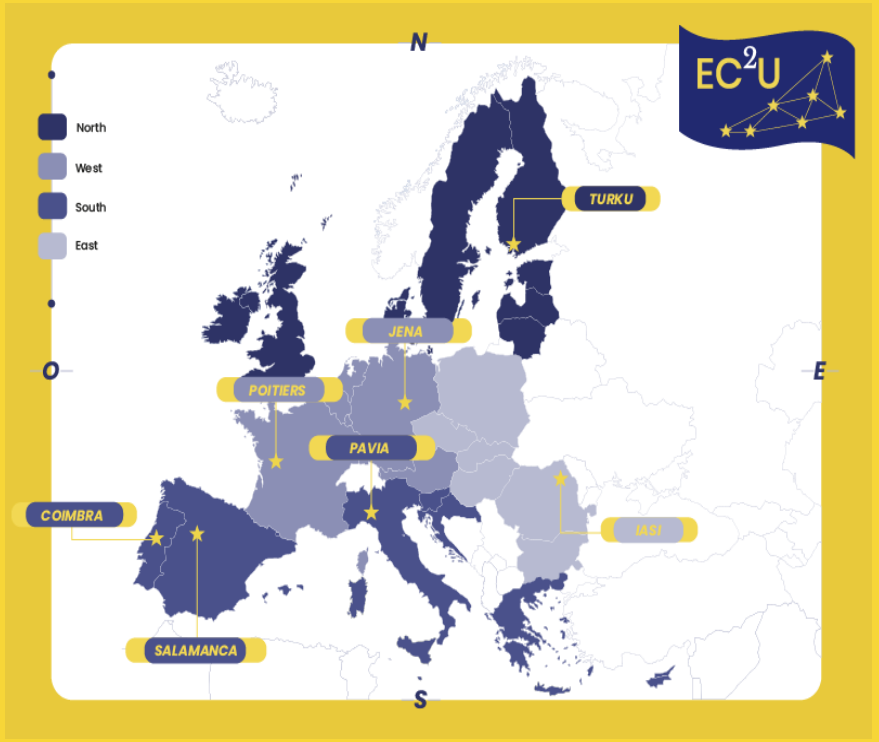

Thank you !

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