



TIMING PUBERTAIRE:

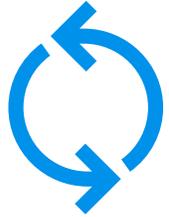
COMPREHENSION ET CONSEQUENCES

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Avril 2017

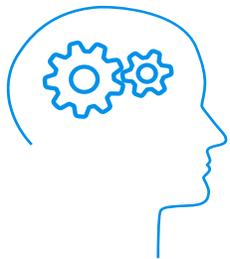
Définitions



Passage de L'ENFANT à L'ADULTE



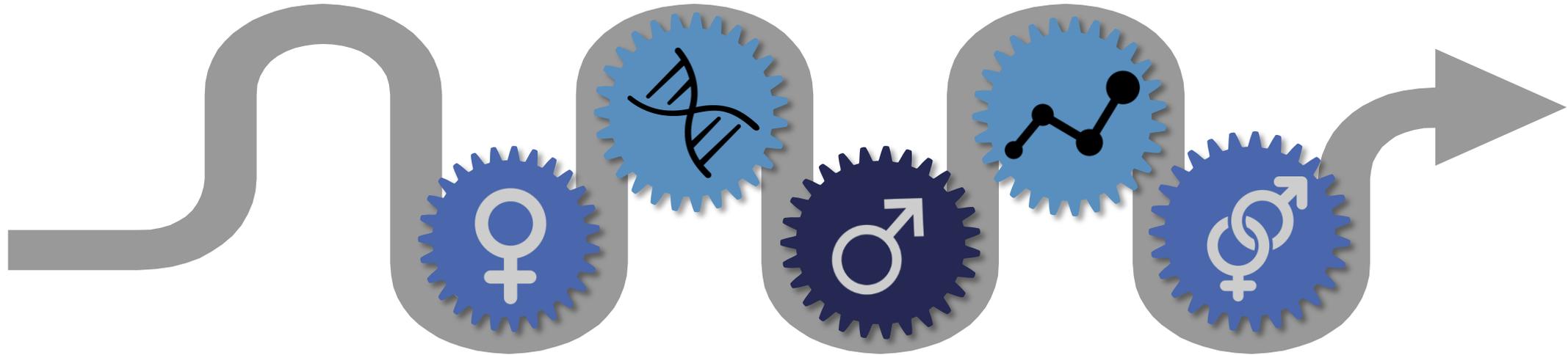
Accession à la FONCTION DE REPRODUCTION

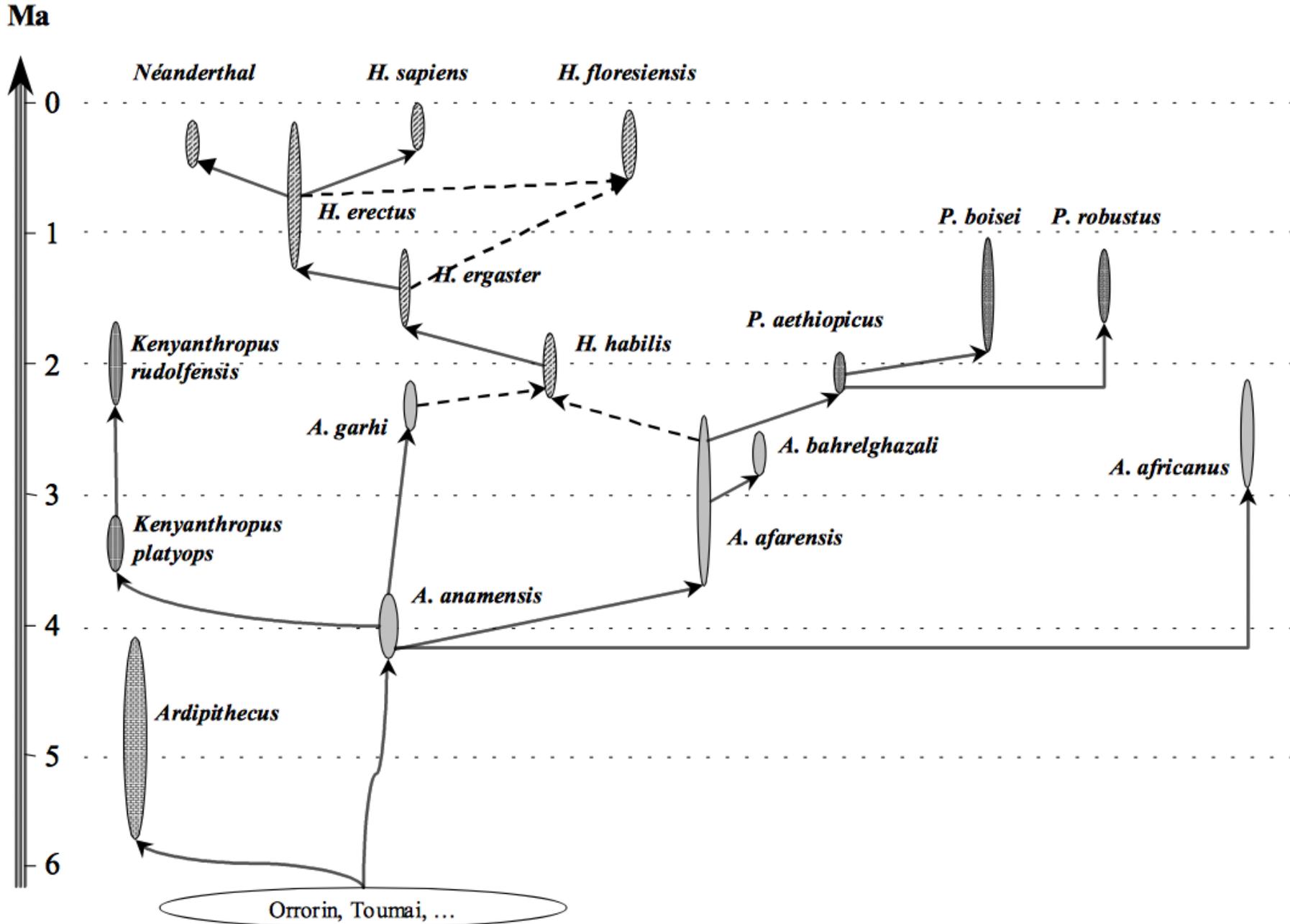


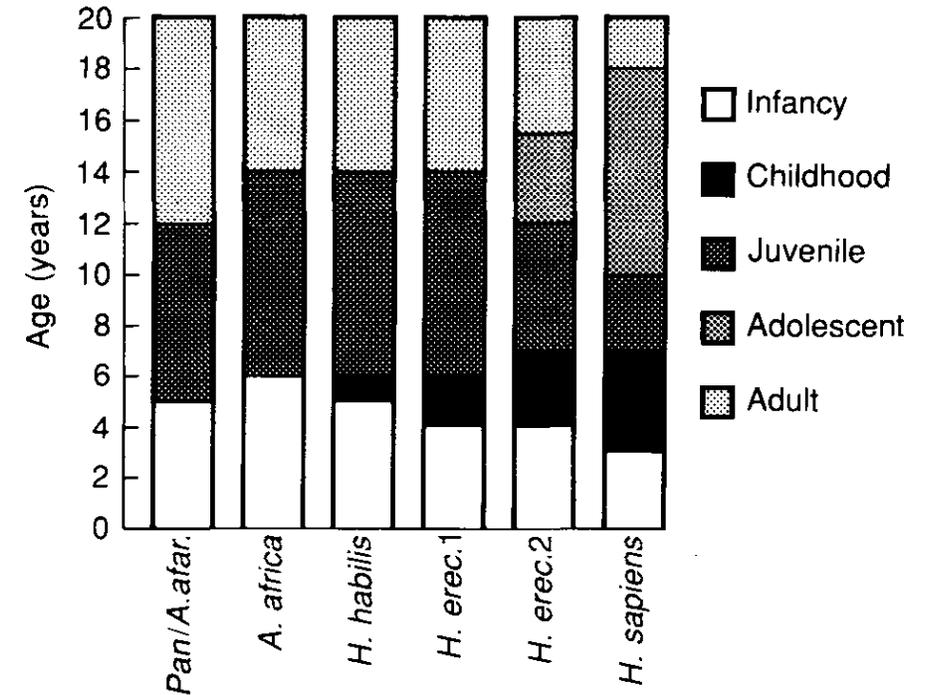
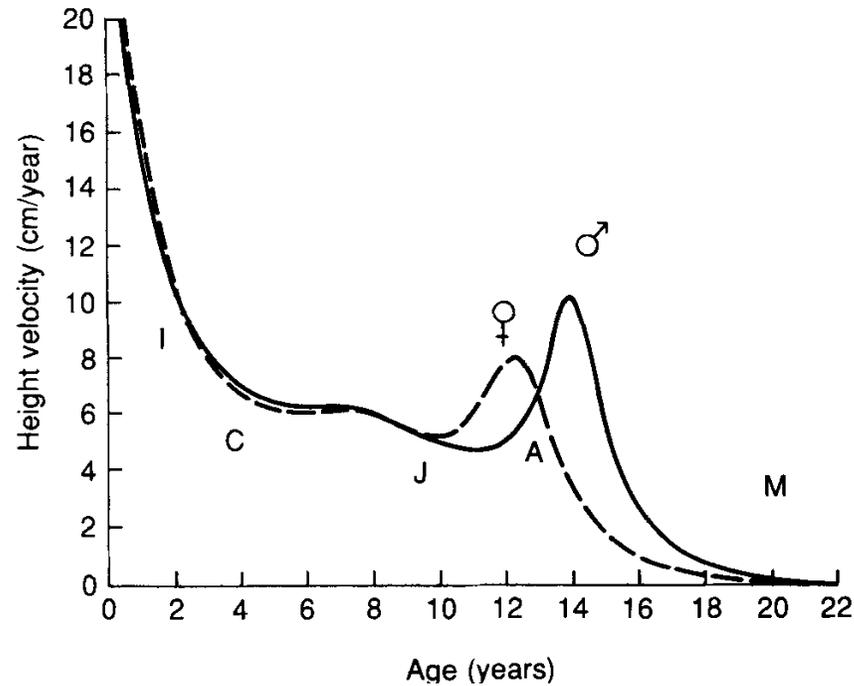
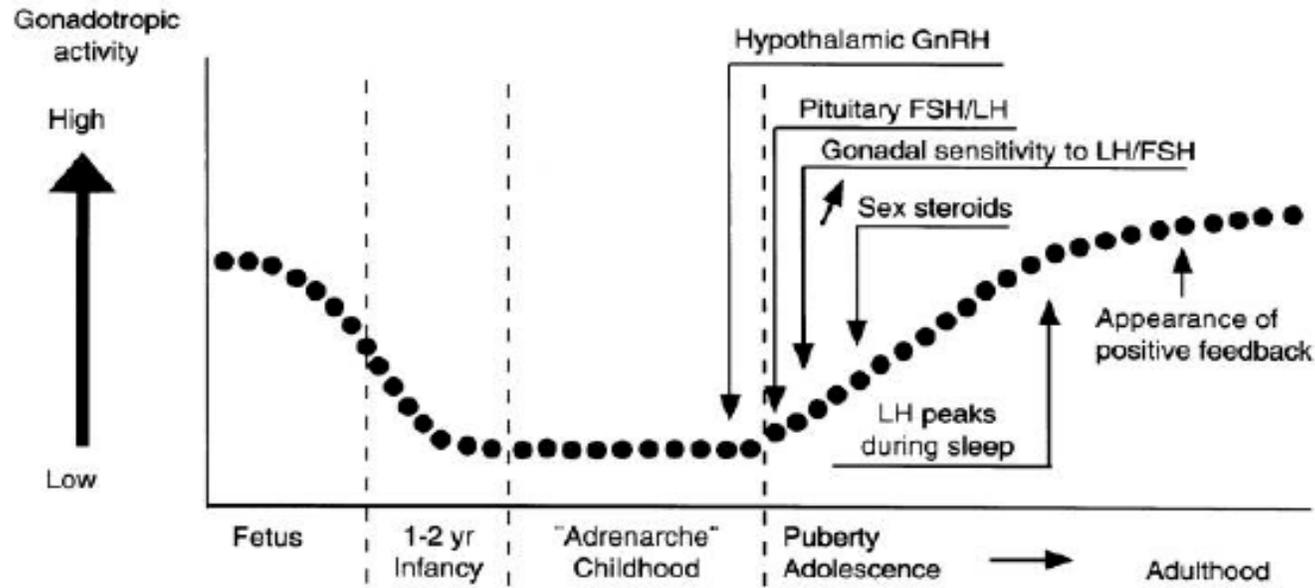
Phénomènes physiques, psychiques, mentaux, affectifs



Puberté dans le champ plus large de l'évolution







Adolescence et avantage reproductif



LES ÊTRES HUMAINS ONT UN AVANTAGE REPRODUCTIF/TOUS LES AUTRES MAMMIFÈRES



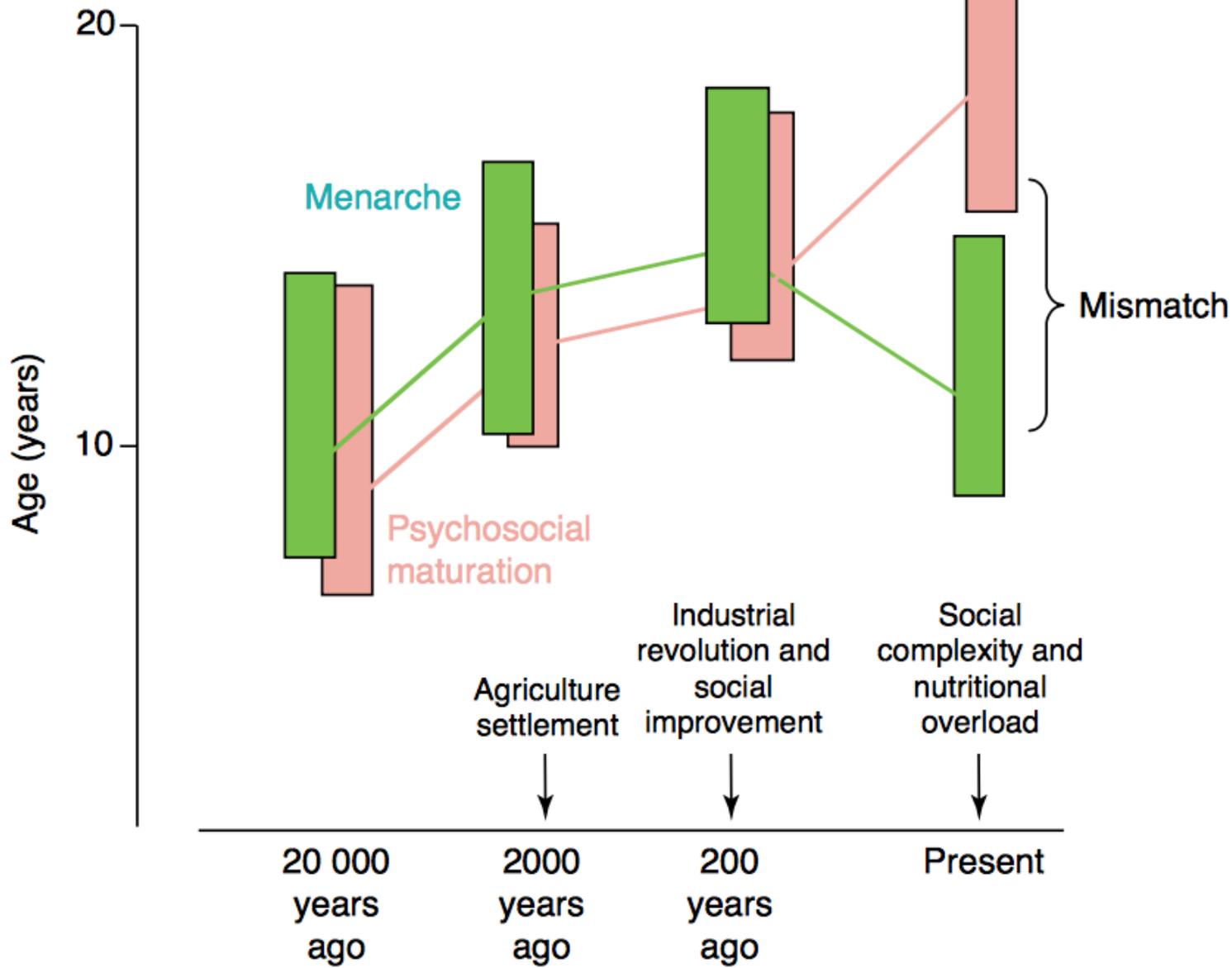
50% des enfants des êtres humains survivaient contre **35%** des enfants de chimpanzés contre **12%** des enfants de carnivores vivant en groupe



Délai entre la ménarche et la réelle capacité à se reproduire (1 à 3 ans) : apprentissage de leur rôle social alors qu'elles sont déjà perçues comme matures



Chez les garçons: production du sperme autour de **13.4 ans** en moyenne mais délai important avec la paternité (4% avant 20 ans aux USA): apprentissage de leur rôle social alors qu'ils sont perçus comme immature (signes d'imprégnation stéroïdes tardifs)



Ménarche



Hétérogénéité des données récentes européennes

1 mois/ 10 ans



7 mois/10 ans

dans les pays à rapide transformation économique

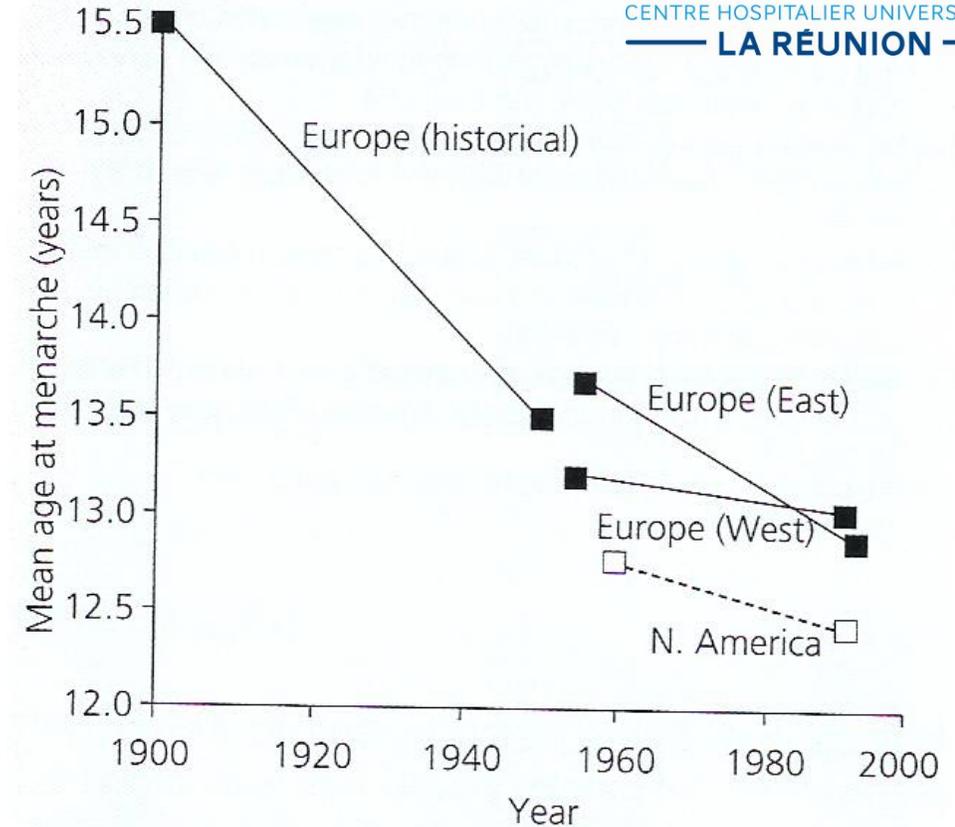
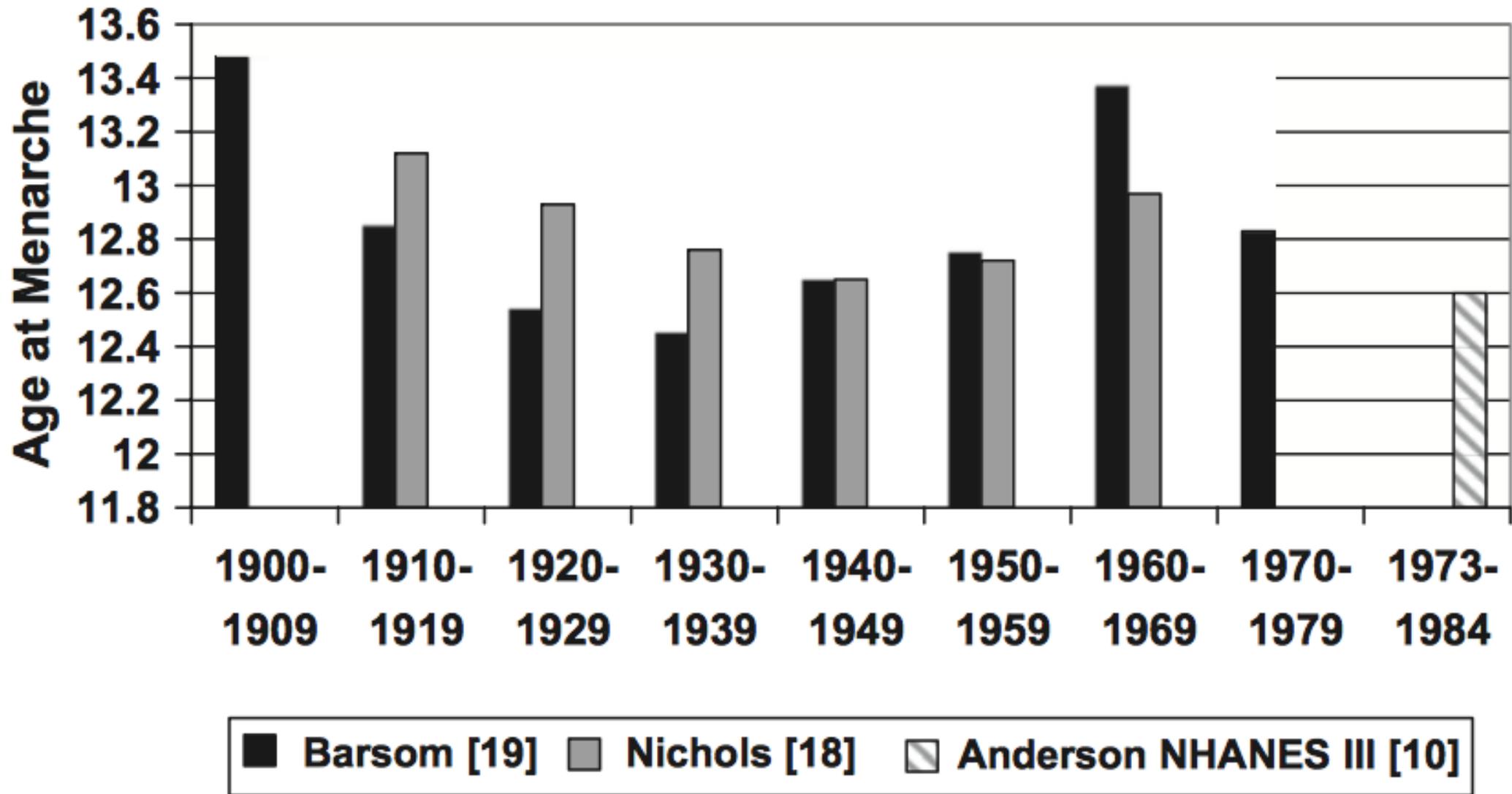


Fig. 2: Average rates of decline in age at menarche from population-based studies in Europe and North America



Données identiques en Angleterre et au Canada

Dann TC. Menarcheal age in University of Warwick young women. J Biosoc Sci 1993

Harris MA. Age at menarche in the Canadian population: Secular trends and relationship to adulthood BMI. J Adolesc Health 2008.

Et les garçons?

Studies of puberty timing in US boys

Study	Number of subjects (N)	Ages of subjects	Tanner II genitals (white/black)	Tanner V genitals (white/black)	Tanner II pubic hair (white/black)	Tanner V pubic hair (white/black)
Guidance Study 1930s–1940s [5]	92	8–18 years	11.8/–	15.2/–		
Fels Institute 1940s [7]	59	9–21 years	11.5/–	17.3/–	12.2/–	16.1/–
Lee Study 1969–1974 [22]	36	9–17 years	11.9/–	15.1/–	12.3/–	15.3/–
Bogalusa Heart Study 1973–1974 [13]	1,829	5–14 years	11.8/11.2		12.5/11.7	
NHANES III 1988–1994 [12]	1,333	8–19 years	10.0/9.2	16.0/15.0	12.0/11.2	15.7/15.3
Biro Study Late 1980s [23]	515	10–18 years	12.2 ^a (TV \geq 3 cc)		12.8	15.2

TV = testicular volume.

^a Genital staging done by testicular volume only.

Evolution variable

Le timing pubertaire évolue non pas de manière linéaire au cours du siècle précédent, mais de manière variable en fonction des décades de naissance.

Etudes danoises

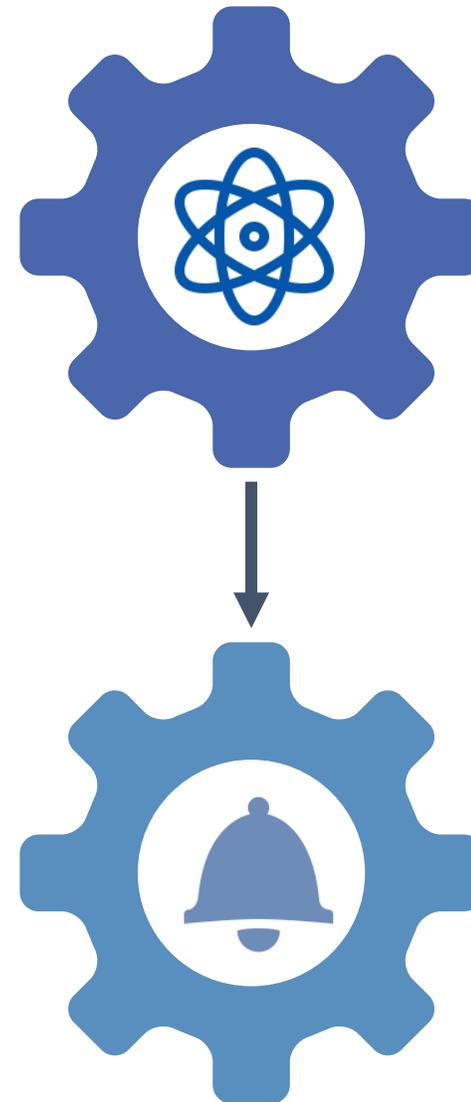
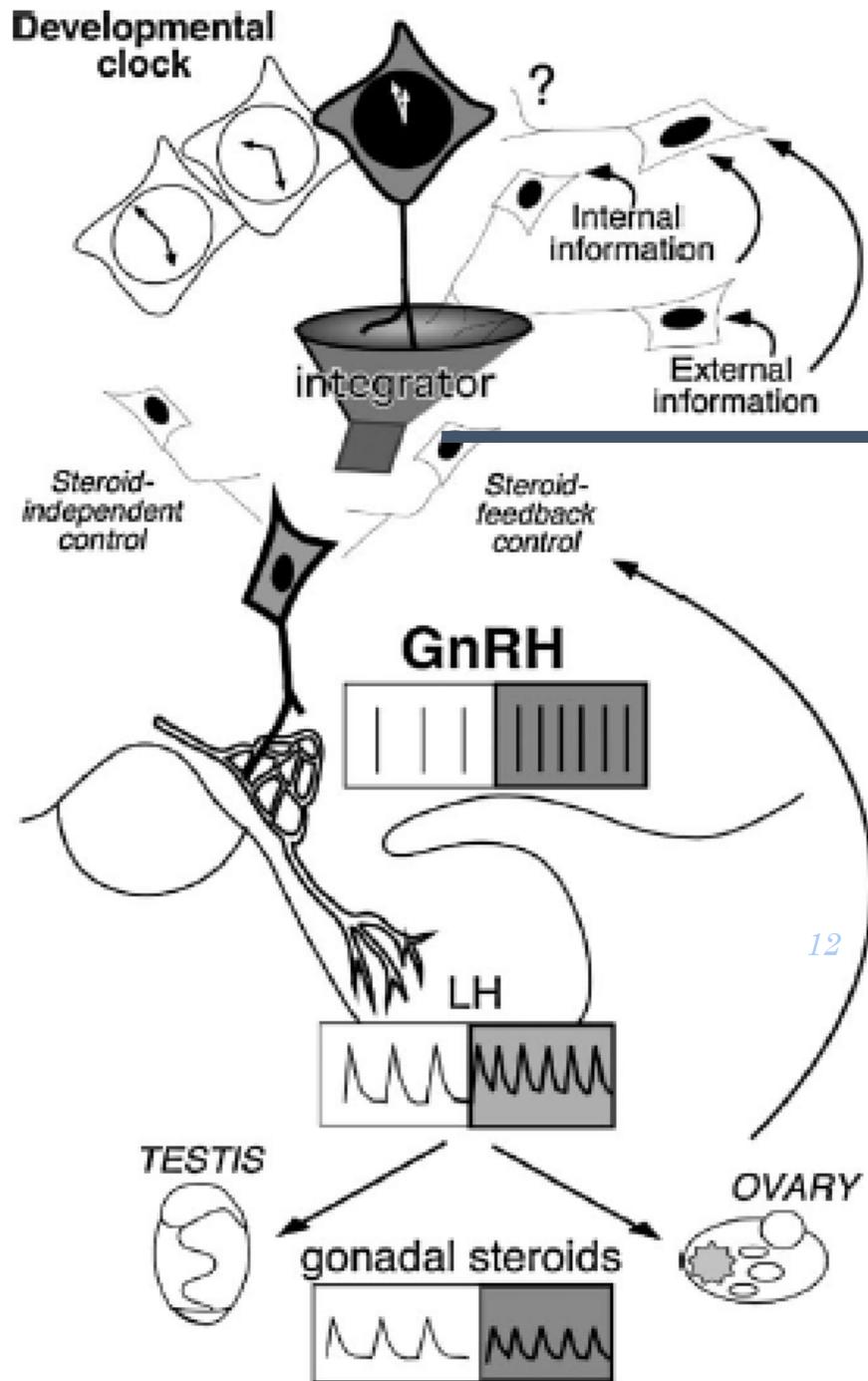
Des données récentes
Danoises (2009/2010):



Résultats

Garçons danois :
Démarrage 3 mois plus tôt mais non significatifs quand corrigés par IMC

Apparition des **seins** de manière **plus précoce** (1 an avant) à 15 ans d'intervalle 2006/1990 mais **âge de la ménarche inchangé**



GnRH

Pulse generator
Transsynaptiques
et réseau glial+++

ALARME
ET
EXPRESSION
DE CETTE
ALARME

Kiss 1 GPR 54 SYSTEM



Gene Kiss1R 2004



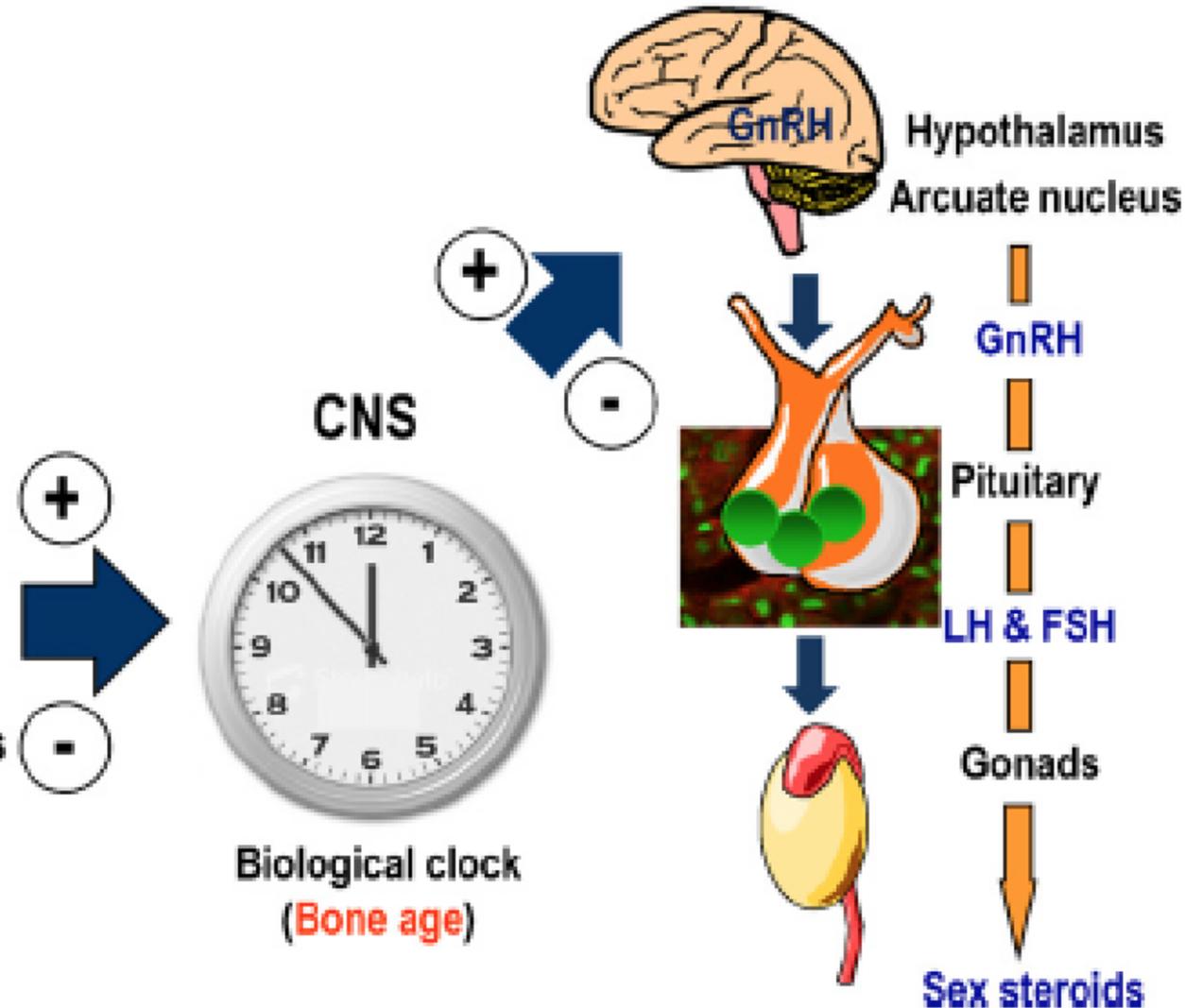
50 à 75%

de la variance tempo/timing pubertaire génétique

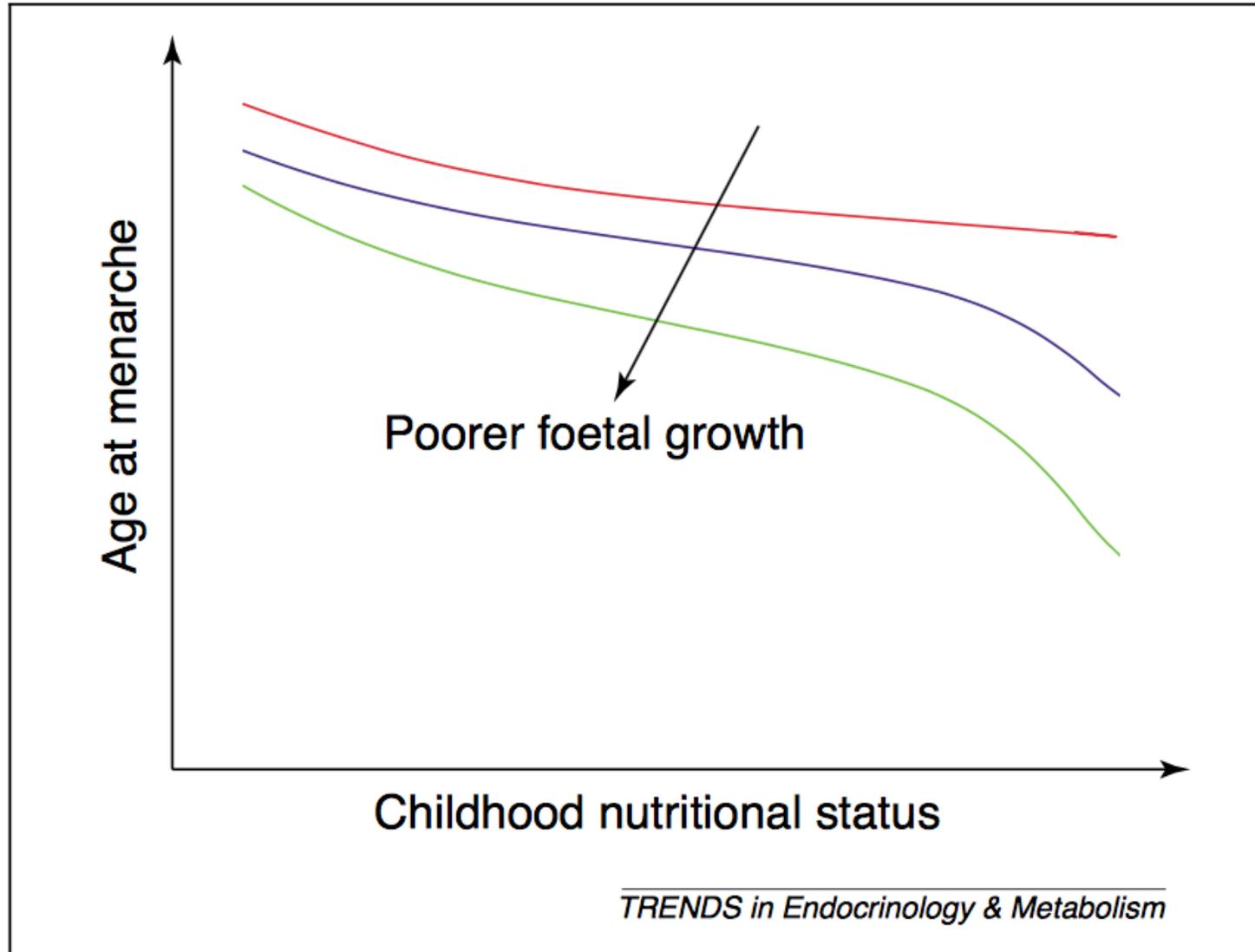
Auguste Rodin – Le baiser

Facteurs chimiques environnement

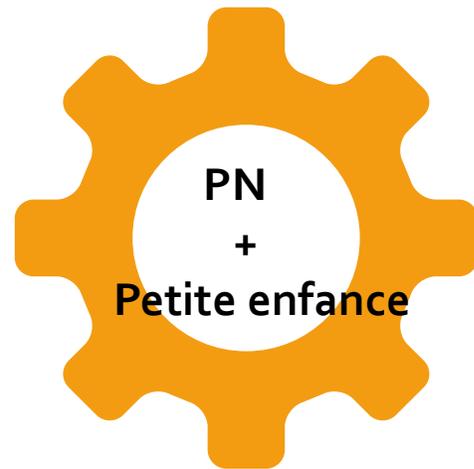
- Age (bone age)
- Sex
- Race
- Inheritance
- Timing
- Nutrition
- Stress
- Body mass
- Body fat
- Geographical factors
- Sex steroids
- Adrenarche
- Cerebral lesions



Nutrition pre et post natale



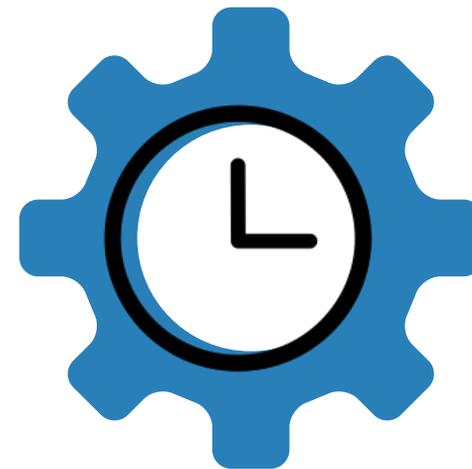
Rattrapage de la croissance



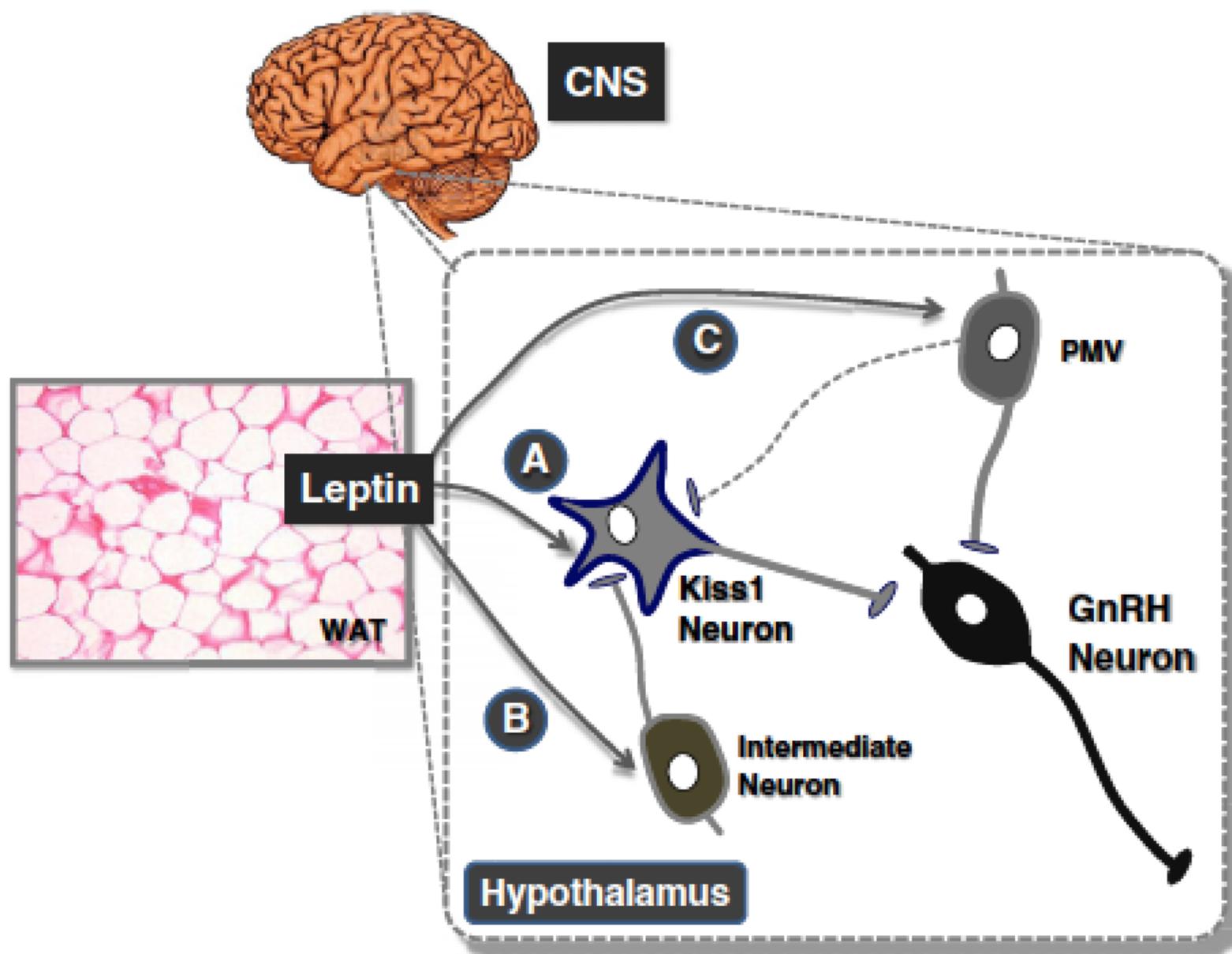
Malnutrition foetale
et/ou post natale



Rattrapage
pondéral



Timing
pubertaire



Pretermes et Puberté (very low birth weight <1500g VLBW)

Component of puberty, mean ages (sd), yr	VLBW SGA	VLBW AGA	Controls	Missing values VLBW SGA/VLBW AGA/controls
Females, n	21	44	92	
Acceleration of pubertal growth	9.6 (0.8)	9.4 (1.3)	10.1 (1.2)	3/9/33
Pubertal peak height velocity	11.8 (0.6)	11.6 (1.1)	12.0 (1.0)	1/2/4
Adult height attainment	16.2 (0.7)	15.6 (1.2)	16.3 (1.1)	9/8/28
Menarche	12.6 (1.8)	12.2 (1.2)	12.5 (1.3)	1/0/0
Males, n	14	34	54	
Acceleration of pubertal growth	11.0 (0.9)	11.3 (1.4)	12.0 (1.0)	1/5/4
Pubertal peak height velocity	13.1 (0.6)	13.5 (0.9)	13.8 (0.8)	0/8/10
Adult height attainment	16.6 (0.9)	17.4 (0.7)	17.9 (0.9)	6/22/27
Voice break	13.5 (1.0)	13.3 (1.3)	13.8 (1.2)	2/4/8

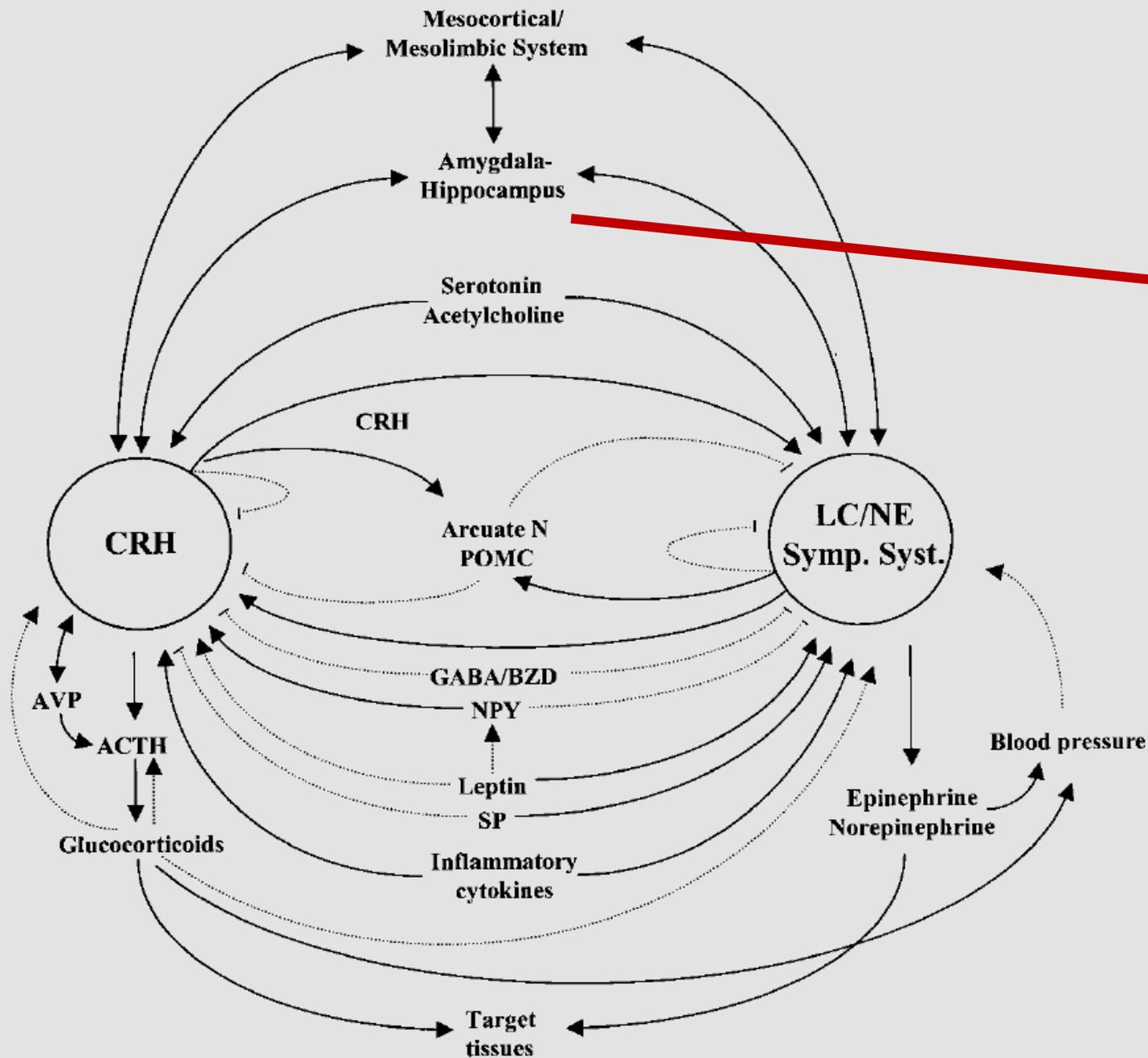
- IMC entre 5 et 7 ans
- Antécédents familiaux (âge ménarche chez la mère)

- Facteurs de risques supplémentaires

IMC : Obésité et Puberté

Cumulative logit mixed model results for Tanner pubic hair and Tanner breast

Scale	Effect	Est.	LRT	OR 95% CI
Pubic hair	θ_1	14.18	71.72	
	θ_2	16.58	77.96	
	Age	1.43	415.32	
	Sexual abuse group	1.25	6.75	3.49 (1.34–9.12)
	Ever obese ^a	-.23	.22	.79 (.30–2.08)
	Minority status ^b	1.74	12.99	5.69 (2.10–15.48)
	Biological father absence ^c	.35	.59	.70 (.58–3.50)
	σ^2_u	1.87		
Breast	θ_1	15.44	60.79	
	θ_2	18.55	66.62	
	Age	1.59	424.46	
	Sexual abuse group	1.12	4.62	3.06 (1.11–8.49)
	Ever obese ^a	1.92	11.18	6.80 (2.06–22.55)
	Minority status ^b	1.08	4.35	2.95 (1.04–8.32)
	Biological father absence ^c	.49	.98	.61 (.62–4.26)
	σ^2_u	2.42		

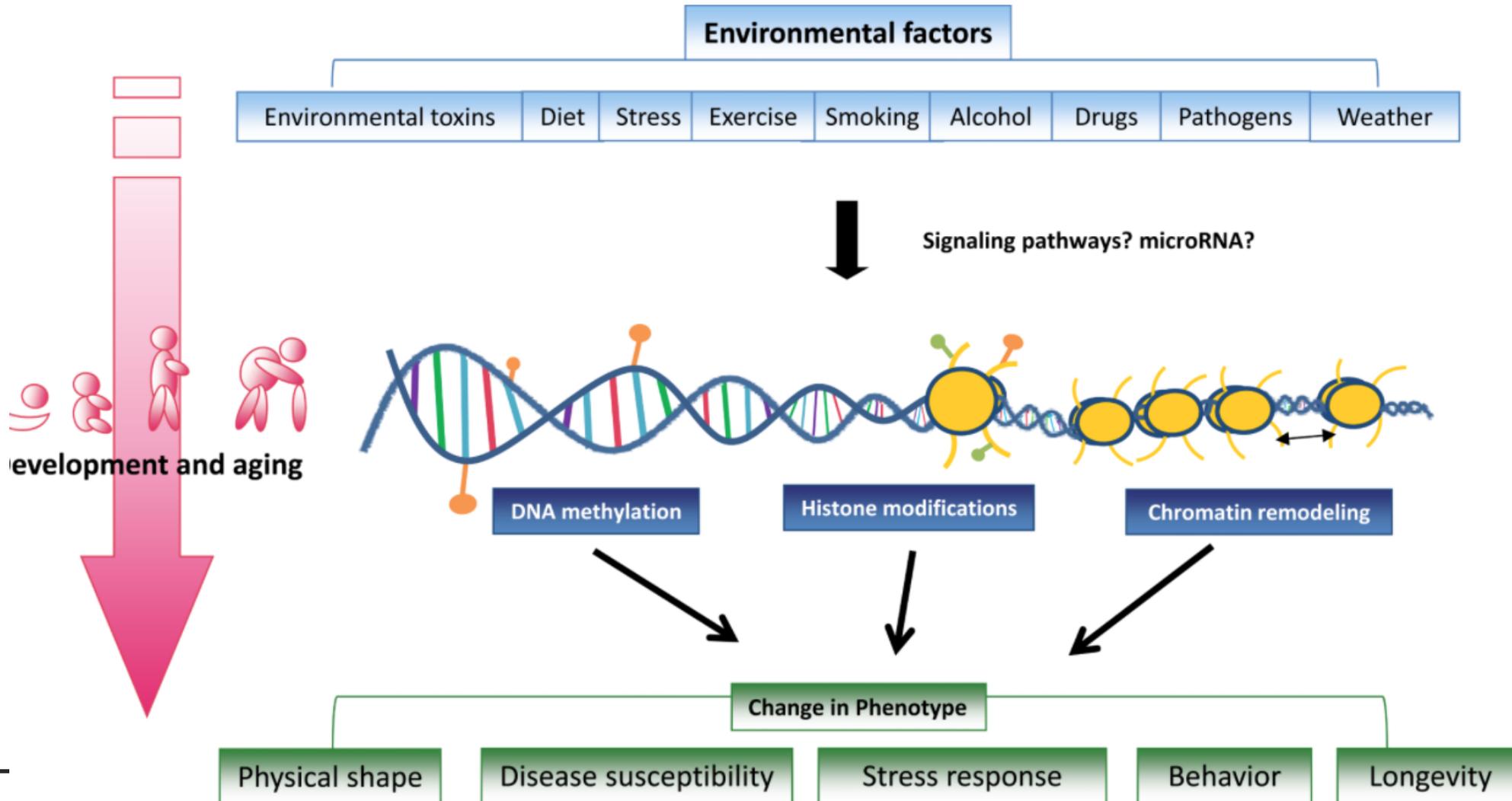


Mémoire Apprentissage

STRESS AIGU
STRESS CHRONIQUE OU PÉRIODES
CRITIQUES :

- **DEPASSEMENT DU CONCEPT FIGHT OR FLIGHT**
- **LE COMBAT OU LA FUITE (CANNON 1915) LORS DU STRESS AIGU**

Maladaptive plasticity and cognitive impairment



Environmental factor	Year	Subjects	Effect on puberty
Body weight	2008 [30]	8080 women, Canada	Older age at menarche (one year older) associated with lower BMI (0.5 less)
Body weight	2009 [32]	156,835 children, Denmark	BMI at 7 years of age is inversely correlated with the start and peak of a child's growth spurt as indicators of puberty timing
Body weight	2012 [33]	2127 girls, Croatia	Girls who achieved menarche prior to 11.98 years were of higher BMI than girls who had not
Body weight	2009 [36]	98 children, Netherlands	Peak leptin levels occurred prior to peak LH and FSH levels in girls but not in boys
Birth weight	2006 [91]	156 girls, Australia	Infants >49.3 cm and <3.325 kg achieved menarche 1 year earlier than shorter, heavier infants
Birth weight	2006 [92]	187 girls, Spain	Infants with BW -2 SD or below had earlier menarche, girls with premature adrenarche and BW -2 SD were three times as likely to reach menarche prior to 12 years
Birth weight	2001 [40]	997 girls, Philippines	BW alone did not affect timing of menarche, but being long (>49 cm) and lean (<3 kg) at birth predicted menses 6 months earlier than the opposite regardless of BMI at 8 years
Birth weight	2012 [37]	78 girls, China	SGA status was significantly associated with CPP
Social	2012 [37]	78 girls, China	Father's absence between ages 4 and 6 in a girl's life was significantly associated with CPP
Social	2006 [51]	655 children, Denmark	10–20 times increased risk of precocious puberty in internationally adopted boys and girls, with even higher risk if adopted after age 2
Social	2008 [52]	161 girls, New Zealand	Sisters who were premenstrual prior to familial dysfunction achieved menarche 11 months earlier than older sisters
Social	2011 [53]	120 children, Wisconsin	Earlier menarche was associated with higher family stress and sympathetic nervous system activation
Social	2009 [54]	35,330 women, USA	Positive association between earlier menarche and history of sexual abuse
Intrauterine environment	2011 [46]	3486 boys, Denmark	Maternal smoking during pregnancy was associated with earlier puberty
Intrauterine environment	2011 [47]	3169 girls, Denmark	Menarche occurred 2.8–4.1 months earlier in girls who were exposed to prenatal maternal smoking (10+ cigarettes/day)
Intrauterine environment	2001 [49]	589 women, Sweden	Exposure to pre-eclampsia had no effect on puberty timing
Intrauterine environment	2011 [50]	166 young adults, USA	No association of <i>in vitro</i> fertilization with puberty timing
Diet	2011 [41]	994 girls, Philippines	Girls who were exclusively breast fed longer had later onset of menarche
Diet	2011 [45]	242 girls, Columbia	Vitamin D deficient girls reached menarche 0.8 years earlier than vitamin D sufficient girls
Diet	2011 [43]	2657 women, NHANES	Increased milk intake from 5 to 12 years of age was weakly associated with earlier menarche
Diet	2010 [60]	227 children, Germany	No association with fiber intake and puberty timing (Dortmund study)
Diet	2012 [82]	112 children, Germany	Children with higher vegetable intake reached puberty 7 months later than average and ones with higher animal protein intake reached puberty 7 months earlier than average

Les disrupteurs endocriniens

Effects of natural exposures on puberty timing.

Environmental Factor	Year	Subjects	Effect on puberty
Skin lotion	2007 [61]	3 boys	Boys with gynecomastia had exposure to lavender and tea tree oils which resolved after stopping oils and <i>in vitro</i> studies confirmed estrogenic properties of both oils
Soy formula	2012 [57]	2922 girls, UK	Infant girls fed soy formula at <4 months reached menarche earlier (4 months) than girls not fed soy or fed soy later than 4 months
Soy formula	2001 [93]	811 adults, Iowa	In recall, no difference in timing of menarche or breast development in women fed exclusive soy vs. cow's milk formula in infancy
Soy formula	2004 [94]	48 children, Italy	No effect of >6 months of soy formula feeding on precocious puberty, gynecomastia, bone age, estradiol levels
Fennel	2008 [62]	4 girls, Turkey	Premature thelarche occurred in girls given <i>goeniculum vulgare</i> tea and resolved when stopped
Isoflavones	2011 [58]	108 girls, Korea	Girls with CPP showed significantly higher serum isoflavone (daidzein, genistein and total isoflavone) concentrations than controls
Phytoestrogens	2008 [59]	192 girls, New York	Higher levels of phytoestrogens (daidzein, genistein, enterolactone) were associated with later onset of breast development
Phytoestrogens	2010 [60]	227 children, Germany	Girls who had the highest urinary markers of phytoestrogen intake achieved breast development (0.7 years) and peak height velocity (0.6 years) later than girls with less phytoestrogen intake (Dortmund study)

Rien sur la puberté

1mg/kg

La limite au delà de laquelle des phénomènes de toxicité pourraient apparaître chez l'Homme, qui s'élève à **1mg/kg** de poids corporel/j d'aglycones pour les isoflavones

Possible changement

Ceci est un choix résultant de l'état actuel des connaissances sur la seule génistéine et qui peut changer avec l'évolution des connaissances.



Risques

Les risques associés à l'exposition in utero aux phytoestrogènes, et les risques associés à l'exposition des nourrissons et des enfants en bas âge aux préparations à base de protéines de soja dont la concentration est élevée en isoflavones alors qu'elle devrait être inférieure à **1 mg/L** de préparation reconstituée en équivalents aglycones, soit environ **0.15mg/kg** de poids corporel.

Effects of chemical endocrine disruptors on puberty timing.

Agent	Year	Subjects	Effect on puberty
Phthalates	2009 [73]	89 girls, Taiwan	Higher phthalate metabolite levels were seen in girls with premature thelarche
Phthalates	2000 [74]	76 girls, Puerto Rico	Premature thelarche was associated with higher phthalate levels
Phthalates	2007 [95]	210 girls, Shanghai	Higher phthalate levels are in girls with CPP
Phthalates	2010 [71]	61 pubertal boys, Turkey	Higher phthalate metabolite levels associated with pubertal gynecomastia in boys
Phthalates	2012 [68]	750 girls, 25 with precocious puberty, Denmark	No association of phthalate levels and precocious puberty
Phthalates	2010 [75]	56 girls, USA	No association with phthalate levels and CPP
Phthalates	2011 [74]	300 women, New York	Association between hair oil use and perms with earlier menarche
Bisphenol-A	2010 [79]	1151 girls, New York, Ohio, California	No effect of BPA on breast development
Bisphenol-A	2010 [80]	210 girls, Shanghai	Higher BPA levels in girls with CPP
DDE	2004 [85]	151 girls, Michigan	Increase in serum DDE of 15 mcg/l associated with decreased age at menarche by 1 year
DDE	2012 [37]	78 patients, China	Higher DDE levels slightly associated with CPP
DDT	2005 [83]	446 women, China	Higher DDT serum levels associated with earlier menarche
DDE	2001 [84]	145 children, Belgium	CPP patients who had immigrated to Belgium had higher DDE levels
DDE	2008 [59]	192 girls, New York	No association of DDE urine levels and breast advancement
DDE	2005 [86]	138 girls, New York, Canada	No association of DDE with menarche timing
DDE	2012 [96]	94 girls, Italy	No association of DDE with precocious puberty

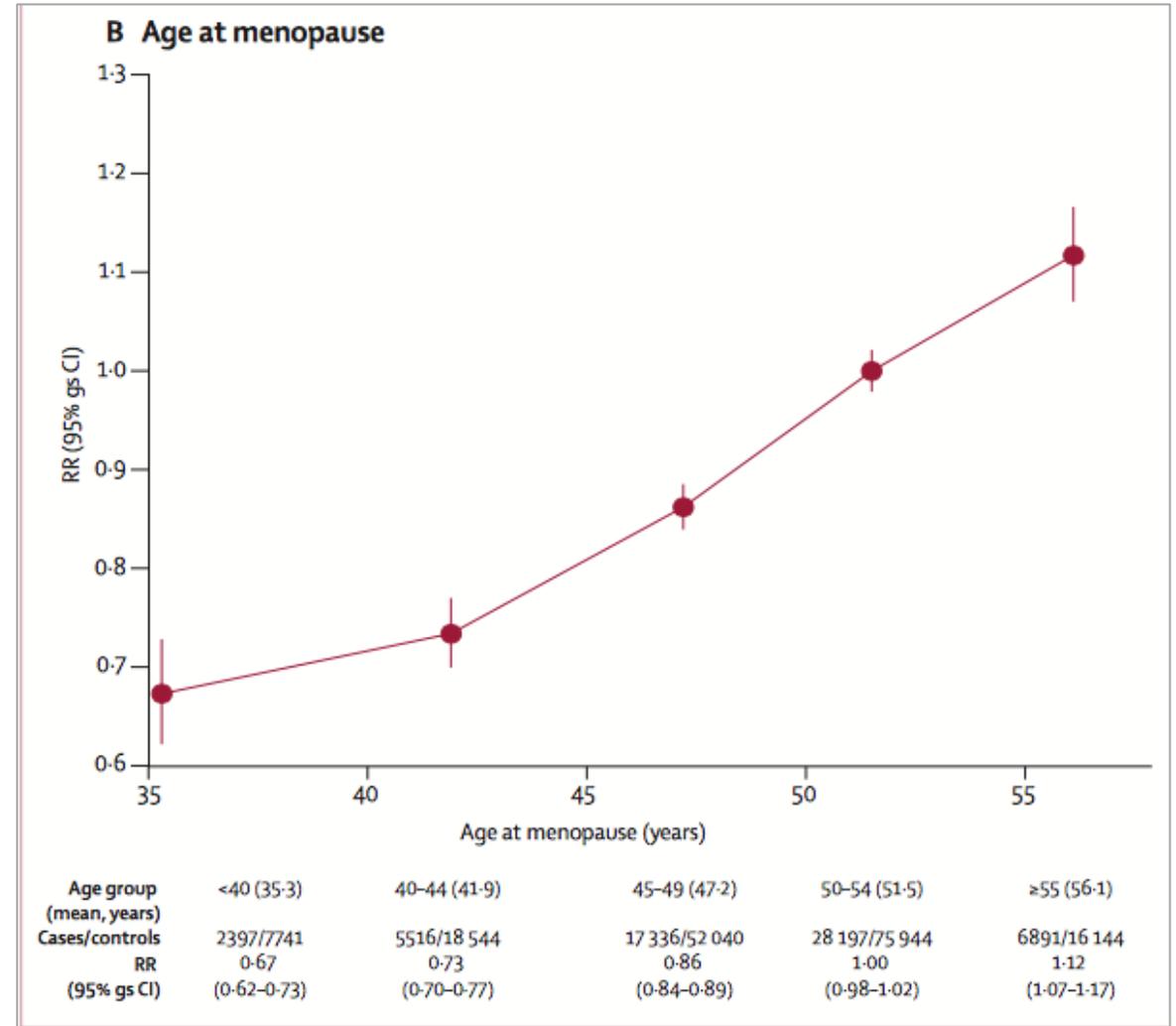
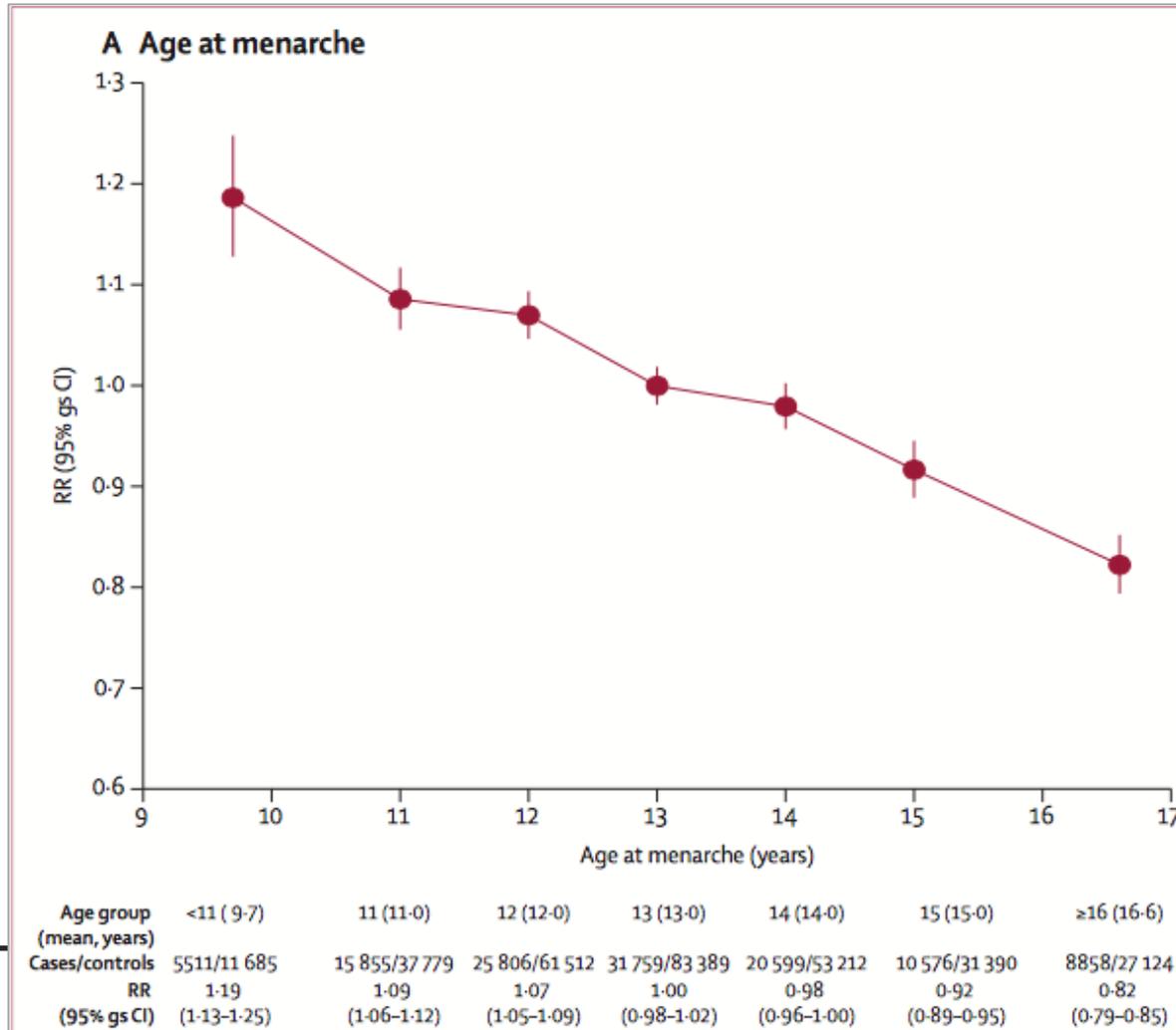
LES CONSÉQUENCES



TIMING PUBERTAIRE



Timing pubertaire et cancer



From: **Early Age at Menarche Associated with Cardiovascular Disease and Mortality**

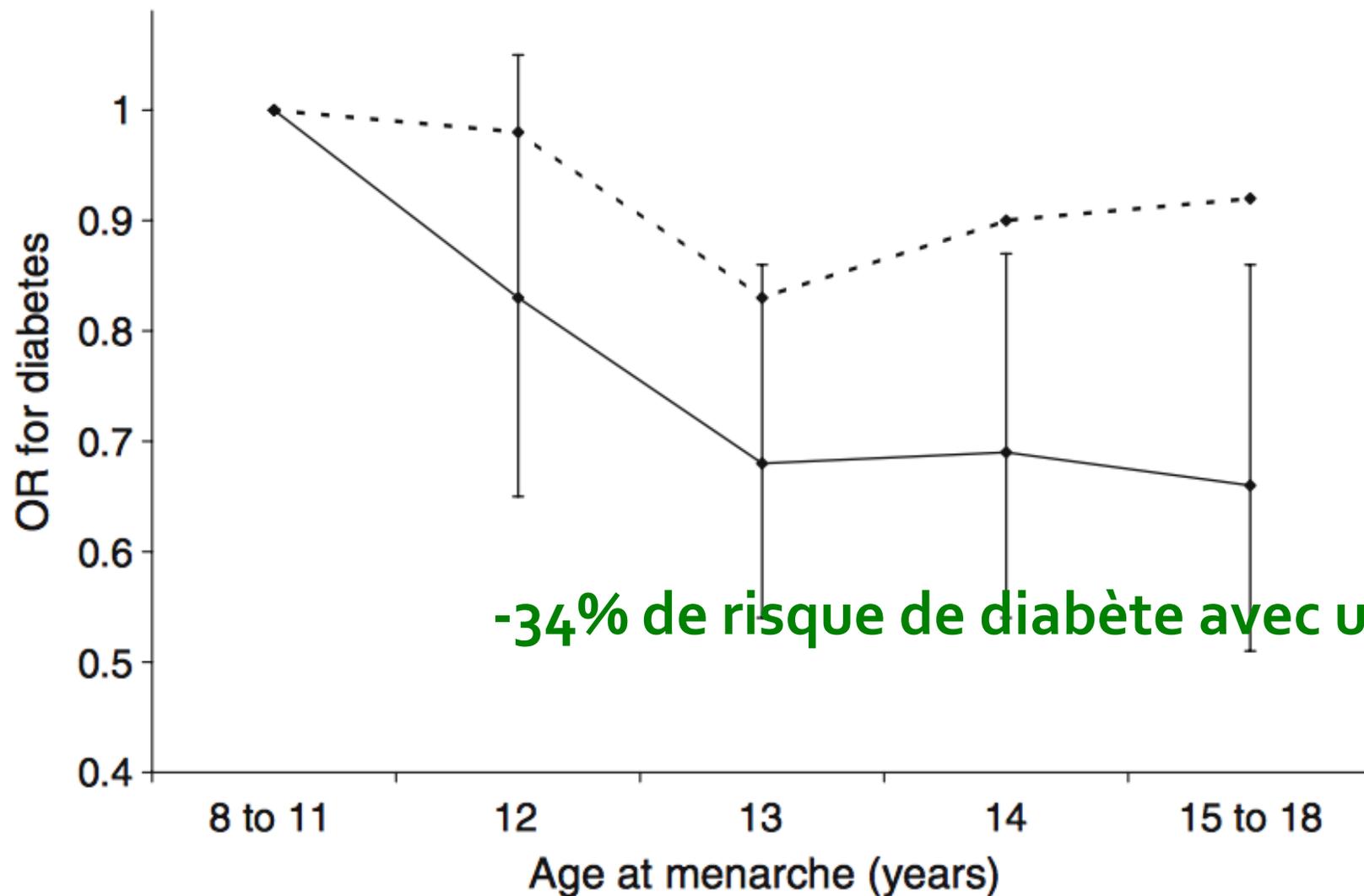
J Clin Endocrinol Metab. 2009;94(12):4953-4960. doi:10.1210/jc.2009-1789

Incident CVD	1.28 (1.13–1.34)	<0.001
Incident CHD	1.26 (1.10–1.49)	0.001
Incident stroke	1.14 (0.89–1.44)	0.297
All-cause mortality	1.21 (1.07–1.38)	0.004
CVD mortality	1.27 (1.01–1.60)	0.065
Cancer mortality	1.28 (1.06–1.57)	0.011

Figure Legend:

A, Age-adjusted percentages of CVD risk factors in adulthood by categories (approximate quintiles) of age at menarche; B, age-standardized rates of cardiovascular events and mortality in adulthood by categories (approximate quintiles) of age at menarche.

Risque de diabète de type 2



-34% de risque de diabète avec une ménarche tardive

TIMING PUBERTÉ ET IMC

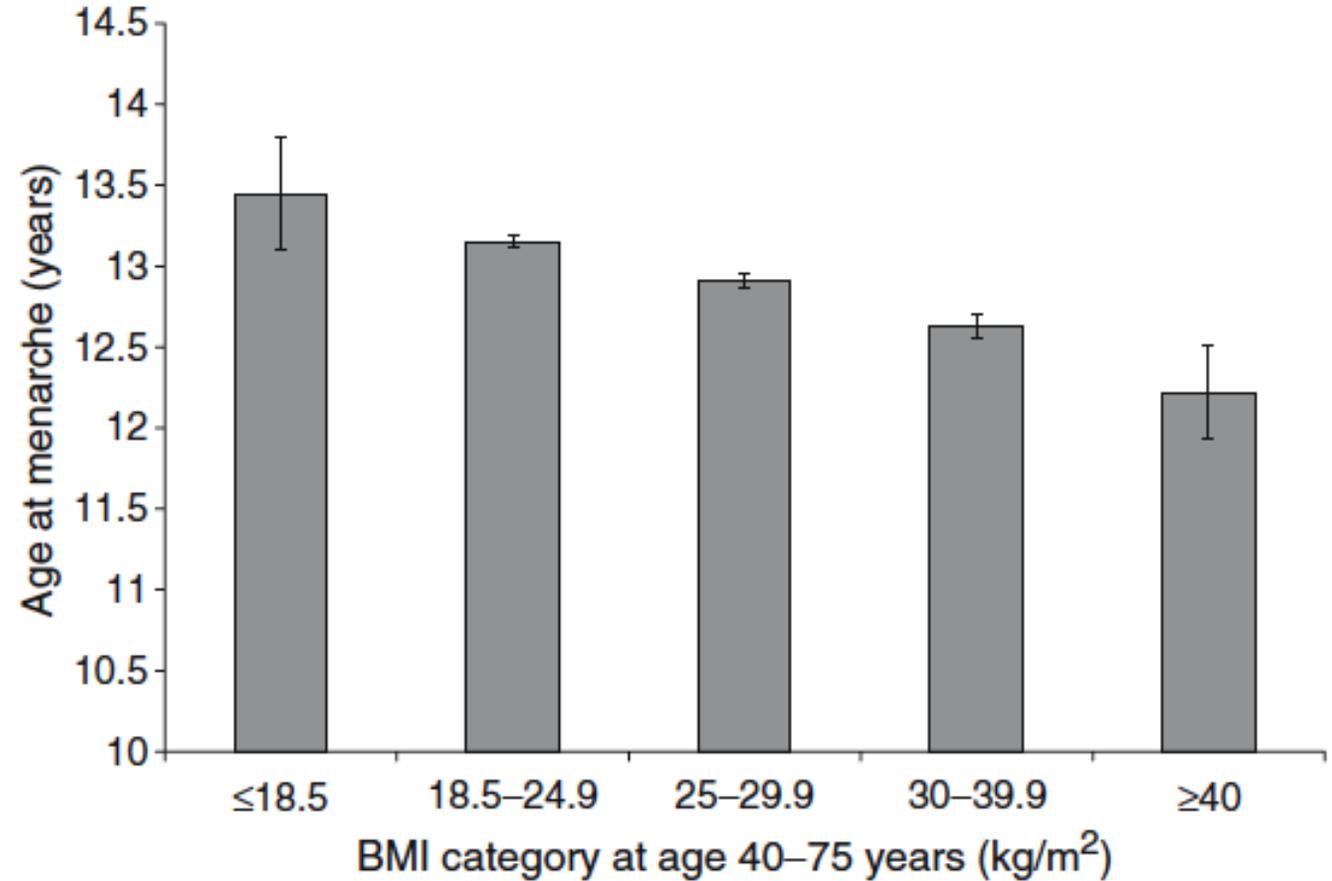
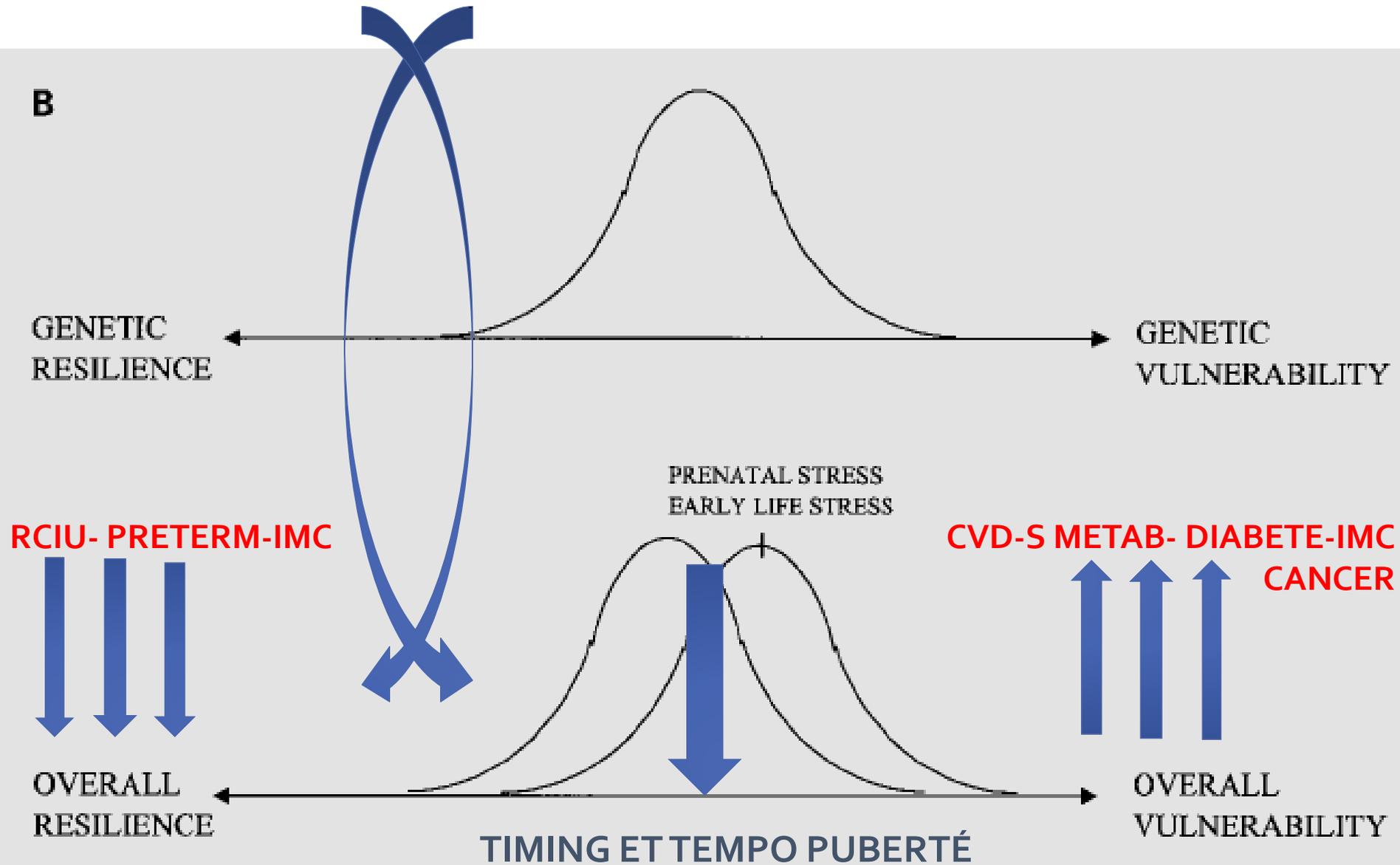


Fig. 2 Mean (95% CIs) age at menarche by adult BMI category: the EPIC-Norfolk cohort study. $p < 0.0001$ for trend

Stress +++: sévices - parents - psychosocial



**THANK
YOU.**

