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Johanna Laru

ASSOCIATION OF GROWTH FROM BIRTH UNTIL MIDDLE AGE WITH SEX HORMONE PARAMETERS AND REPRODUCTIVE FUNCTION IN THE NORTHERN FINLAND BIRTH COHORT 1966

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
FACULTY OF MEDICINE;
MEDICAL RESEARCH CENTER OULU;
OULU UNIVERSITY HOSPITAL

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Abstract

Obesity predisposes people to numerous morbidities and less well-known reproductive problems. In women, obesity increases the risk of infertility and polycystic ovary syndrome (PCOS). In men, obesity impairs reproductive health and is associated with testosterone (T) deficiency. Since the above-mentioned problems affect a significant proportion of the population, this study focuses on the association between early risk factors and reproductive problems, providing a great opportunity to identify the sensitive time periods for preventive actions.

The aim of this study was to assess the impact of prenatal factors, birth weight (BW), and BMI, from birth until middle age, on sex hormone levels and reproductive function in both women and men. The study populations (women and men with impaired reproductive function, women with PCOS and men with low T at age 31) were derived from the Northern Finland Birth Cohort 1966 with additional data from the Finnish Medical Birth Register. Multiple confounding factors, such as socioeconomic and lifestyle factors, marital status, attempts to have children, and adult obesity, could be considered.

The results revealed that in girls, obesity in mid-childhood and especially in puberty - and in boys, low BMI in early childhood - predicted impaired reproductive function, as well as an increased risk of childlessness regardless of confounding factors. In boys, overweight and obesity in early childhood was associated with a decreased risk of infertility, but BMI from mid-childhood onwards did not affect their subsequent reproductive function. Both women with PCOS and men with low T at age 31 already had higher weight gain from childhood onwards; their weight gain began earlier, and their BMIs remained higher until age 46. In boys, maternal obesity was associated significantly with later T deficiency, suggesting that metabolic factors during pregnancy affect boys' endocrine function later in life. Lower BW and prematurity in girls were associated with PCOS later in life.

Given the well-known health risks related to obesity and the steadily rising prevalence of maternal obesity, the study results emphasize the importance of preventing obesity, maintaining an optimal growth during childhood, and preventing maternal obesity, as all these factors affect reproductive health later in life.

Keywords: adiposity rebound, androgen, birth weight, childhood growth, childlessness, infertility, male hypogonadism, obesity, overweight, PCOS, reproductive function, underweight

Laru, Johanna, Painon kehityksen yhteys hormonaalisiin muuttujiin ja lisääntymisterveyteen syntymästä keski-ikään Pohjois-Suomen syntymäkohortissa 1966.
Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Medical Research Center Oulu; Oulun yliopistollinen sairaala
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Tiivistelmä

Lihavuus aiheuttaa monien sairauksien lisäksi myös merkittäviä lisääntymisterveyden ongelmia ja lisää riskiä lapsettomuudelle. Lihavuus lisää naisilla munasarjojen monirakkulaoireyhtymän (PCOS) ja miehillä mieshormonivajeen riskiä. Nämä ongelmat koskettavat merkittävää osaa väestöstä. Tämä tutkimus antaa mahdollisuuden tunnistaa varhaisten riskitekijöiden yhteyksiä lisääntymisterveyden ongelmiin ja siten löytää keinoja oikea-aikaisiin ennaltaehkäiseviin toimiin.

Tässä tutkimuksessa arvioitiin raskauden aikaisten tekijöiden, syntymäpainon ja painoindeksin (BMI) kehityksen vaikutusta hormonaalisiin muuttujiin ja lisääntymisterveyteen sekä naisilla että miehillä keski-ikään saakka. Tutkimuspopulaatiot (lapsettomuudesta kärsivät naiset ja miehet, PCOS-naiset sekä miehet, joilla todettiin mieshormonivaje 31-vuotiaana) koostuivat Pohjois-Suomen syntymäkohortista 1966, johon yhdistettiin Terveyden ja hyvinvoinninlaitoksen syntymärekisterin tietoja. Tutkimusaineisto mahdollisti useiden sekoittavien tekijöiden, kuten sosioekonomisen aseman, elintapojen, siviilisäädyn, lapsitoiveen ja aikuisiän lihavuuden, huomioimisen analyyseissa.

Tutkimuksessa havaittiin, että keskilapsuuden ja murrosiän lihavuus tytöillä ja varhaislapsuuden matala BMI pojilla olivat yhteydessä lapsettomuusongelmiin ja riskiin jäädä myöhemmin lapsettomaksi siviilisäädystä riippumatta. Toisaalta poikien ylipaino ja lihavuus varhaislapsuudessa, mutta ei enää sen jälkeen, vähensivät lapsettomuusongelmien riskiä. Sekä PCOS-naisilla että 31-vuotiaana mieshormonivajeesta kärsivillä miehillä todettiin suurempi painon kertyminen jo varhaislapsuudessa, ja BMI pysyi korkeampana kuin kontrolleilla aina keski-ikään saakka. Pojilla äidin lihavuus liittyi merkittävästi itsenäisenä riskitekijänä myöhempään mieshormonivajeeseen viitaten siihen, että raskauden aikaiset aineenvaihdunnalliset tekijät vaikuttavat merkittävästi myöhempään hormonaalisen toimintaan. Tytöillä matalampi syntymäpaino ja ennenaikaisuus lisäsivät riskiä PCOS:lle.

Tämän tutkimuksen tulokset korostavat synnyttäjien ylipainon ja lapsuusiän lihavuuden ehkäisemisen sekä optimaalisen kasvun tukemisen tärkeyttä, varsinkin kun otetaan huomioon lihavuuteen liittyvät muut terveysriskit ja synnyttäjien ylipainon jatkuva lisääntyminen, koska nämä kaikki vaikuttavat myöhempään lisääntymisterveyteen.

Asiasanat: alipaino, hedelmällisyys, lapsettomuus, lapsuusiän kasvu, lihavuus, lisääntymisterveys, mieshormoni, mieshormonivaje, munasarjojen monirakkulaoireyhtymä, painon kehitys, PCOS, ylipaino

To Leevi, Eelis, Saimi and Lauri

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Oulu April 2023 *Johanna Laru*

Abbreviations

ACTH	Adrenocorticotropic hormone
AE-PCOS	Androgen Excess and Polycystic Ovary Syndrome
AFC	Antral follicle count
AGA	Appropriate for gestational age
AMH	Anti-Müllerian hormone
AP	Adiposity peak
AR	Adiposity rebound
ASRM	American Society for Reproductive Medicine
BMI	Body mass index
BW	Birth weight
CDC	Center for Disease Control and Prevention
cFT	Calculated free testosterone
CI	Confidence interval
DAG	Directed acyclic graph
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandrosterone sulfate
E	Estrogens
EAU	European Association of Urology
e.g.	exempli gratia, for example
ESHRE	European Society of Human Reproduction and Embryology
E1	estrone
E2	estradiol
E3	estriol
FAI	Free androgen index
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone
H	Hirsutism
HA	Hyperandrogenism
HC	Hip circumference
HPA	Hypothalamus-pituitary-adrenal
HPG	Hypothalamus-pituitary-gonadal
HPO	Hypothalamus-pituitary-ovary
HPT	hypothalamic-pituitary-testicular
i.e.	id est, that is
IR	Insulin resistance

IVF	*In vitro* fertilization
KS	Klinefelter syndrome
LBW	Low birth weight
LGA	Large for gestational age
LH	Luteinizing hormone
MeS	Metabolic syndrome
NFBC66	Northern Finland Birth Cohort 1966
NFBC86	Northern Finland Birth Cohort 1986
NIH	National Institutes of Health
NW	Normal weight
OA	Oligo-amenorrhea
OB	Obese
OR	Odds ratio
OW	Overweight
pc	Percentile
PCOM	Polycystic ovary morphology
PCOS	Polycystic ovary syndrome
SD	Standard deviation
SES	Socioeconomic status
SGA	Small for gestational age
SHBG	Sex hormone-binding globulin
STD	Sexually transmitted disease
T	Testosterone
T2DM	Type II diabetes mellitus
TTP	Time to get pregnant
UW	Underweight
WC	Waist circumference
WHO	World Health Organization
WHR	Waist-to-hip ratio

List of original publications

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:

I Koivuaho E., Laru J., Ojaniemi M., Puukka K., Kettunen J., Tapanainen J. S., Franks S., Järvelin M-R., L. Morin-Papunen L., Sebert S. & Piltonen T. T. (2019). Age at adiposity rebound in childhood is associated with PCOS diagnosis and obesity in adulthood - longitudinal analysis of BMI data from birth to age 46 in cases of PCOS. *International Journal of Obesity, 43*(1), 1370–1379. https://doi.org/10.1038/s41366-019-0318-z.

II Laru, J., Nedelec, R., Koivuaho, E., Ojaniemi, M., Järvelin, M-R., Tapanainen, J. S., Franks, S., Tolvanen, M., Piltonen, T. T., Sebert, S. & Morin-Papunen, L. (2021). BMI in childhood and adolescence is associated with impaired reproductive function - A population-based cohort study from birth to age 50 years. *Human Reproduction, 36*(11), 2948–2961. https://doi.org/10.1093/humrep/deab164.

III Laru, J., Ojaniemi, M., Franks, S., Järvelin, M-R., Piltonen, T. T., Korhonen, E., Sebert, S., Tapanainen, J. S. & Morin-Papunen, L. (2022). An optimal growth pattern during pregnancy and early childhood associates with better fertility in men. *European Journal of Endocrinology, 187*(6):847–858. https://doi.org/10.1530/EJE-22-0385.

IV Laru, J., Pinola, P., Ojaniemi, M., Korhonen, E., Laikari, L., Franks, S., Tapanainen, J. S., Niinimäki, M. & Morin-Papunen, L. (2023). Low testosterone at age 31 associates with maternal obesity and higher BMI from adiposity rebound in childhood until middle age — a birth cohort study. (*Submitted manuscript*).

Contents

1 Introduction

Obesity has reached epidemic proportions worldwide, and its association with the risk of metabolic syndrome (MeS), insulin resistance, type 2 diabetes mellitus (T2DM), and coronary artery disease is well-recognized (Perez, 2013; Simmonds et al., 2015). Obesity also has many effects on women's and men's hormonal balance and on fertility (Craig et al., 2017; Katib, 2015; Nelson & Fleming, 2007). The association between obesity and polycystic ovary syndrome (PCOS), the most common endocrine disorder in women of reproductive age and the most frequent cause of anovulatory infertility, is also well-recognized (Teede et al., 2018). In men, obesity in adulthood has become one of the main causal factors of hypogonadism, i.e., low androgen levels in adulthood (Calderón et al., 2016; Fernandez et al., 2019; Kelly & Jones, 2015).

Infertility is defined as the inability to conceive after 12 months of regular, unprotected sexual intercourse (Zegers-Hochschild et al., 2017). It is estimated to affect 9–18% of couples of reproductive age (Boivin et al., 2007; Hanson et al., 2017; Herbert et al., 2012; Vander Borght & Wyns, 2018). Female infertility accounts solely for 20–35%, and male factor infertility for 20–30% of all infertility causes. In combination with female factors, male factors contribute to another 30%, and no cause is found in 10–20% of couples (Agarval et al., 2021; Anderson et al., 2009; Zegers-Hochschild et al., 2017).

Obesity has been shown to be associated with infertility via multiple mechanisms in both sexes. In women, PCOS has an important role, whereas secondary hypogonadism, impaired spermatogenesis and erectile dysfunction are strongly associated with obesity in men (Craig et al., 2017; Eisenberg et al., 2014; Katib, 2015). Previous studies have shown an inverted J-shaped association between body mass index (BMI) during adolescence and the number of children later in life (Jokela et al., 2007, 2008), but there are very few follow-up studies throughout the reproductive lifespan where all confounding factors have been considered.

Obesity in adolescence and increased weight gain, especially in early adulthood, are associated with an increased incidence of PCOS (de Zegher et al., 2017; Laitinen et al., 2003; Ollila et al., 2016). Consequently, weight management – especially during adolescence and early adulthood – plays a critical role in the prevention and treatment of the syndrome (Barber et al., 2007). However, it remains unclear whether the birth weight (BW) of women who later develop PCOS differs

from that of the general population, and more studies are needed to investigate the relationships between BMI from birth to adolescence with PCOS.

Androgen levels in men decline moderately with age. Lower androgen levels (i.e., hypogonadism) have been associated with a higher risk of MeS, T2DM, and cardiovascular diseases (Antonio et al., 2015; Bhasin, 2003; Hart et al., 2019; Ottarsdottir et al., 2018). Also, some studies have described an association between low androgen levels and abdominal obesity (Camacho et al., 2013; Gyawali et al., 2018; Sovio et al., 2011; Vaidya et al., 2012). However, most studies are cross-sectional or relatively short-lasting with a typical follow-up time period of under 10 years. In addition, there are very limited studies with data on prenatal factors or early growth and their relationship with low androgen levels in adulthood.

Recent studies on the association between childhood obesity and metabolic disorders in adulthood have focused on childhood growth trajectory data rather than on BMI (Koyama et al., 2015; Péneau et al., 2016; Silverwood et al., 2009). In newborns, BMI increases from birth and reaches a maximum at the age of 7–9 months (adiposity peak, AP), after which it decreases, reaching its nadir at the age of 5–7 years. The second rise in BMI, the adiposity rebound (AR), occurs after this increase and lasts until adulthood. Early AR has been associated with the development of obesity and a poor metabolic profile in adulthood, both in men and women (Koyama et al., 2014; Péneau et al., 2016), but there are no studies on its relationship with reproductive function later in life.

In summary, not only is obesity a worldwide epidemic causing metabolic diseases, but it also affects the population's reproductive capacity. In particular, childhood obesity is increasing (Perez, 2013; Ward et al., 2017), highlighting the importance of long-lasting population-based follow-up studies on the relationship between childhood growth and infertility. Obesity-related hormonal disturbances, such as PCOS and male hypogonadism, represent major health issues among fertile-aged women and men, and the need for infertility assessments and treatments is rising (Sun et al., 2019). Early identification of these high-risk individuals is essential for timely intervention and support. This thesis study was designed to identify early risk factors for the development of impaired reproductive capacity in both sexes, PCOS in females and androgen deficiency in males.

2 Review of the literature

2.1 Milestones of childhood growth

2.1.1 Birth weight and prenatal environment

'The developmental origins of health and disease hypothesis' was first described by Barker in 1986. In this hypothesis, impaired fetal growth is thought to be associated with an increased risk of developing adult morbidities and higher cardiovascular disease-related mortality. The fetuses exposed to undernourishment in utero are prepared for undernourishment later in life, putting them at a greater risk for metabolic complications in a normal growth environment (Barker, 2007; Barker & Osmond, 1986). The majority of infants with low BW or who are small for gestational age (SGA) will experience 'catch-up' growth before age two (Garn, 1985; Lee et al., 2003; Saenger et al., 2007), and are at a higher risk for obesity, insulin resistance (IR), MeS, and cardiovascular diseases in adulthood (Barker, 2007; Barker & Osmond, 1986; Eriksson et al., 2002; Jornayvaz et al., 2016; Risnes et al., 2011; Stein et al., 2005).

At the other end of the scale, maternal obesity with overnourishment and the hormonal changes related to obesity strongly affect developmental programming in utero. This overnourishment induces permanent changes in the fetus' molecular, cellular, metabolic, neuroendocrine and physiological functions (Lin et al., 2017; Şanlı & Kabaran, 2019), resulting in increased susceptibility to health problems in adulthood (Desai et al., 2015; Kitsiou-Tzeli & Tzetis, 2017).

The association between low BW or overnourishment during pregnancy and adverse metabolic outcomes later in life are most likely linked to prenatal epigenetic changes (Jornayvaz et al., 2016; Risnes et al., 2011; Şanlı & Kabaran, 2019). In addition, the mother's obesity alters hormonal concentrations in the placenta, cord blood, and the fetus, which have shown to affect not only growth during pregnancy, but also growth in infancy and childhood (Karakosta et al., 2016; Kim et al., 2020; Parker et al., 2011; Simpson et al., 2017; Stefaniak et al., 2019; Walsh et al., 2014). In previous studies, mothers' obesity were associated strongly with their offspring's obesity later in life, but many confounders, such as nutrition, paternal obesity, and socioeconomic status (SES), must be taken into account (Chen et al., 2021; Drake & Reynolds, 2010; Eriksson et al., 2015; Pirkola et al., 2010; Reynolds, 2013; Whitaker et al., 1997).

The mother's smoking during pregnancy places adverse effects on the fetus; preterm delivery, birth defects, SGA, and IUGR are more common (United States Public Health Service Office of the Surgeon General & National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health, 2020). Smoking during pregnancy has also shown to increase childhood obesity (Riedel et al., 2014; Timmermans et al., 2014), in addition to its association with lower height and higher BMI in adulthood (Ravnborg et al., 2011; Storgaard et al., 2003) and a higher risk for cardio-metabolic diseases later in life (Kataria et al., 2019; Parmar et al., 2018).

2.1.2 Mini-puberty

Postnatal activation of the hypothalamus-pituitary-gonadal (HPG) axis is called mini-puberty. Soon after birth, follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels increase, peaking between one week and three months, and result in high levels of sex steroids (testosterone (T) and estrogens (E)), which induce the maturation of sexual organs in both sexes (Kuiri-Hänninen et al., 2014; Lucaccioni et al., 2020; Renault et al., 2020). In boys, LH and FSH levels decrease by 6–9 months of age; in girls, FSH levels remain elevated much longer, up to 3–4 years of life (Bizzarri & Cappa, 2020; Kuiri-Hänninen et al., 2014; Lanciotti et al., 2018) (Fig.1). The T peak is associated with penile and testicular growth, and with the proliferation of gonadic cells (Boas 2006; Kuiri-Hänninen 2011). The E levels are rather fluctuant and decrease gradually at the second year of life, causing enlargement of the uterus and breasts in girls (Kuiri-Hänninen et al., 2013; Schmidt et al., 2002).

This mini-puberty, first described in the 1970s (Forest et al., 1973), has been demonstrated to represent a "window of opportunity' to evaluate the HPG axis before puberty (Kiviranta et al., 2016; Lanciotti et al., 2018), and to be putatively related to reproductive capacity later in adulthood (Boas et al., 2006; Cortes et al., 1987; Kuiri-Hänninen et al., 2011; Nordenström, 2022). The postnatal activity of the HPG axis has been reported to be more pronounced and protracted in preterm infants (Kuiri-Hänninen et al., 2011).

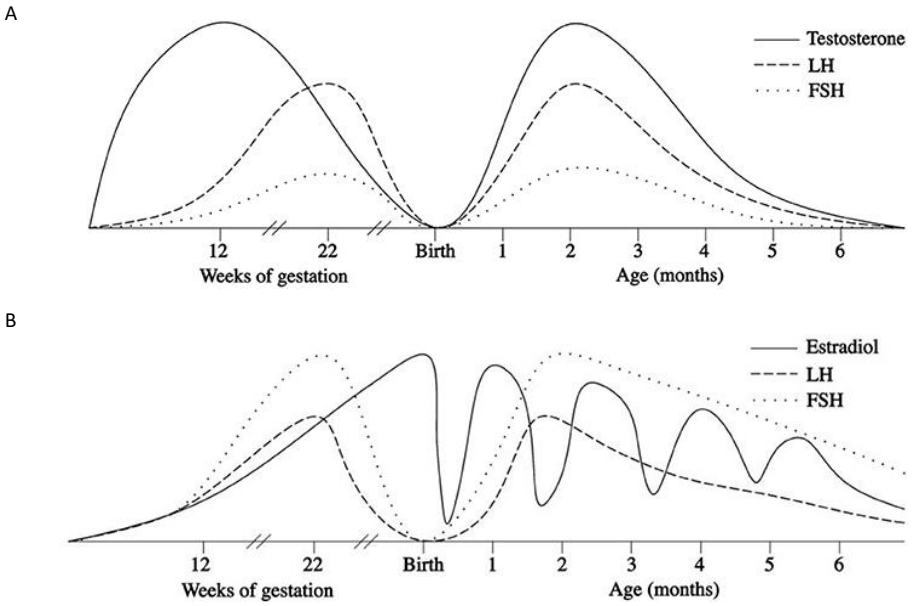

Fig. 1. Mini-puberty in boys (A) and in girls (B). © 2018 Lanciotti, Cofini, Leonardi, Penta and Esposito.

In both sexes, higher T levels, but not E, in mini-puberty have shown a positive correlation with growth velocity in infancy and early childhood (Becker et al., 2015; Kiviranta et al., 2016; Varimo et al., 2016), but there is no data on their correlation with later growth and the association with later fecundability is not known (Nordenström, 2022).

The differences in sex hormones during mini-puberty are important for sex differentiation regarding linear growth and body composition: boys have a greater growth velocity, and they accumulate more lean mass compared to girls. Moreover, mini-puberty and early childhood are complex developmental stages marked by nutritional, genetic, and epigenetic factors, which all have consequences concerning later growth (de Onis & Branca, 2016; Kuiri-Hänninen et al., 2014; Kyle et al., 2015; Stein et al., 2005).

2.1.3 Infant and childhood growth trajectories

In addition to age-specific BMI measures and percentiles, childhood BMI growth trajectory data have been an area of interest when evaluating the association

between childhood obesity and metabolic disorders in adulthood. According to growth trajectories, BMI first increases from birth and reaches a maximum approximately at the age of 9 months (AP), and decreases thereafter to reach a nadir at the age of 4–7 years (AR) (Koyama et al., 2014; Péneau et al., 2016; Silverwood et al., 2009) (Fig. 2).

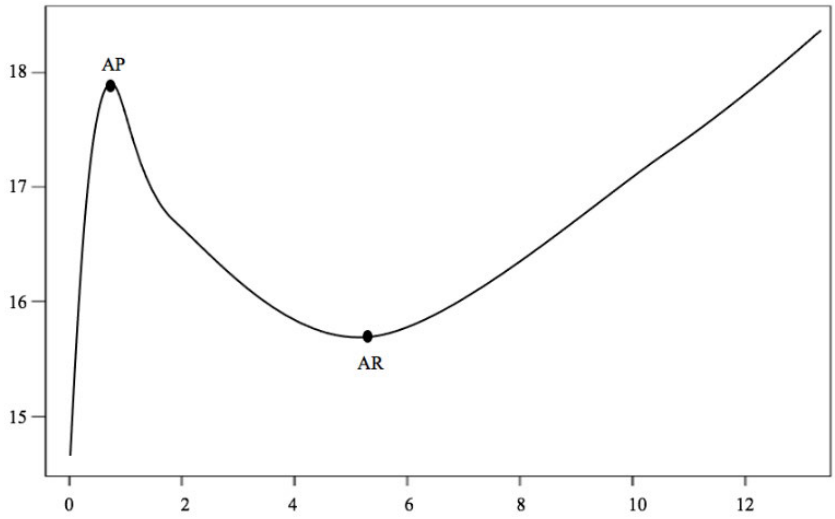

Fig. 2. Typical BMI trajectory in infancy and childhood. Adiposity peak (AP) and rebound (AR) are marked as dots.

Adiposity peak

AP (i.e., infancy peak) requires several BMI measurements in infancy to determine the age of its occurrence. A later timing and a higher BMI at AP have been associated with childhood and adulthood obesity. An increased magnitude of AP has been associated with greater BMI (Hof et al., 2013; Silverwood et al., 2009; Sovio et al., 2014) and higher blood pressure levels later in life (Sovio et al., 2014). Children without AP are especially at risk for metabolic disturbances later in life (Aris et al., 2019). No studies concerning AP and later fertility, or the sex hormone function, have been published.

Adiposity rebound

AR is defined as the second increase in BMI in the childhood growth trajectory following its nadir. In 1984, a study revealed for the first time the association between early AR and higher adiposity later in life (Rolland-Cachera et al., 1984). Later, this finding has been replicated in numerous studies (Aris et al., 2019; Dorosty et al., 2000; Hughes et al., 2014; Koyama et al., 2014; Ohlsson et al., 2012; Péneau et al., 2016; Taylor et al., 2004, 2011; Whitaker et al., 1998; Williams, 2005). Early AR (i.e., occurring before the age of 5 years) has also been associated with increased risks of metabolic disorders (Bhargava et al., 2004; Eriksson et al., 2003; González et al., 2014; Koyama et al., 2014; Mo-Suwan et al., 2017; Péneau et al., 2016; Sovio et al., 2014), higher blood pressure (Koyama et al., 2014; Péneau et al., 2016), and impaired cardiac function in middle age (Korpela et al., 2020).

Early AR has been shown to be associated with an increased fat mass by gaining adiposity faster than fat free mass. Early rebounders accumulate fat mass three times faster than late rebounders (Campbell et al., 2011; Hughes et al., 2014; Taylor et al., 2011). Studies on PCOS have previously shown a similar fat accumulation in women with PCOS (de Zegher et al., 2017; Laitinen et al., 2003; Ollila et al., 2016). Early adiposity rebounders experience earlier menarche for girls (Williams & Dickson, 2002), and for boys, earlier puberty (Ohlsson et al., 2012), but no studies concerning AR and later fertility or the sex hormone function have been published.

2.1.4 Adrenarche

Adrenarche is the period before puberty when the innermost zone of the adrenal cortex (zone reticularis) begins to produce sex hormones. It typically starts between the ages of 6 and 8 when dehydroepiandrosterone sulfate (DHEAS) concentrations become detectable (Witchel et al., 2020). Further activation of the steroid metabolism pathways also leads to an increase of T and E levels, which also become detectable in the blood (Auchus & Rainey, 2004; Miller, 2009; Rege & Rainey, 2012). The first signs of puberty emerge during adrenarche, characterized by the development of pubic and axillary hair, adult apocrine aroma, oiliness of the skin and hair, and acne (Auchus & Rainey, 2004; Miller, 2009; Rege & Rainey, 2012; Witchel et al., 2020). Adrenarche also occurs in individuals with hypogonadotropic hypogonadism or primary gonadal failure (Sklar et al., 1980),

suggesting that the mechanism behind the activation of the HPG axis on one side, and the onset of adrenarche on the other side, are different (Cutler et al., 1978).

Premature adrenarche, i.e., the appearance of pubic or axillary hair before age 8 in girls and age 9 in boys, has been shown to be associated with PCOS (Kuiri-Hänninen et al., 2014; Stein et al., 2005) and hyperinsulinemia in women (Kaya et al., 2018; Utriainen et al., 2015), and in some studies with dyslipidemia in both sexes (Voutilainen & Jääskeläinen, 2015), but not with MeS (Liimatta et al., 2019). Premature adrenarche is associated with childhood obesity (Rosenfield et al., 2009; Sopher et al., 2011), advanced skeletal maturation (Sopher et al., 2011), and an increased velocity of length growth (Pere et al., 1995; Sopher et al., 2011). Obesity at this age has been shown to accelerate the skeleton maturation via increased insulin, insulin-like growth factor 1, and leptin concentrations (Klein et al., 2016; Sopher et al., 2011).

2.1.5 Puberty and menarche age

In puberty, the HPG axis activates and maturates. Sex-specific features start to develop and growth velocity increases. Normal puberty occurs at the ages between 10 and 14 in girls and 11–15 in boys. Obesity in childhood has been shown to prepone puberty in both boys and girls, while being underweight does the opposite (Aghaee et al., 2022; Baker, 1985; Tomova et al., 2015).

Menstrual irregularities are common in adolescence, and it takes 2–5 years for menstruation to become regular and for the hypothalamus-pituitary-ovary (HPO) axis to reach its maturation (Apter, 1980; Welt & Carmina, 2013). Earlier menarche age has been linked with childhood (Rosenfield et al., 2009) and adulthood obesity, and a worse metabolic profile (Adair & Gordon-Larsen, 2001; Bleil et al., 2012), as well as menstrual disorders and PCOS (Carroll et al., 2012; Dramusic et al., 1997; Rosenfield et al., 2009; van Hooff et al., 2004), but opposite results have also been published (Pinola et al., 2012). Later menarche age has been associated with higher androgen levels (Dramusic et al., 1997).

The peripubertal age seems to be a decisive period regarding later metabolic and reproductive health. Physiological IR increases after the first signs of puberty, and normally returns to its prepubertal level when puberty is completed (Lindgren et al., 1990; Moran et al., 1999). In obese girls, IR is more pronounced and lasts longer, and is a strong predictor of obesity and impaired metabolic profile in adulthood (Maffeis et al., 2002; Moran et al., 1999; van Hooff et al., 2000). IR in

adulthood is also strongly associated with PCOS and anovulatory infertility (Coviello et al., 2006; Ollila et al., 2017; Palmert et al., 2002).

2.2 Underweight, overweight and obesity

2.2.1 Classification of underweight, overweight and obesity

The continually rising prevalence of obesity has doubled during the last ten years (Perez, 2013). In Finland, almost half of the men and one third of the women were overweight or obese in early adulthood in 2017 (Jääskeläinen et al., 2019). Childhood obesity is especially a huge increasing health problem, but the prevalence seems to plateau in children and adolescents in high-income countries (World Health Organization (WHO). Regional Office for Europe, 2021). The rate of childhood obesity varies considerably (from 6% to 22%): in Europe with the highest rates in the Mediterranean region, and the lowest in Central Asia (WHO. Regional Office for Europe, 2021). In Finland, 9% of girls and 12% of boys aged 7−9 years were obese in 2017 (WHO. Regional Office for Europe, 2021), and in 2020, 4% of girls and 9% of boys aged 2−16 years were obese (Vuorenmaa et al., 2021). In most countries, boys have higher rates of overweight and obesity than girls (Perez, 2013).

BMI is currently used in clinical practice to evaluate underweight (UW), overweight (OW), and obese (OB) categories. In adulthood, exact BMI limits are used for classification: BMI < 18.50 kg/m^2 = UW, BMI 18.50–24.99 kg/m^2 = normal weight (NW), BMI 25.00–29.99 kg/m^2 = OW, and BMI ≥ 30.00 kg/m^2 = OB (WHO Consultation on Obesity, 2000).

In children, BMI classification are based on percentiles (pc) at each age, and are classified as follows: UW BMI < 5th pc, NW BMI 5th–85th pc, OW BMI 85th–95th pc, and OB BMI > 95th pc according to the criteria from the WHO and the Center for Disease Control and Prevention (CDC) (Kuczmarski et al., 2000). In addition, the so-called ISO-BMI classification is used to adjust children's BMI for age and sex. ISO-BMI converts children's BMI to the adult equivalent values, allowing the use of adulthood BMI limits. BMI does not remain constant throughout life, and is especially prone to fluctuations from birth until the age of AR (Couto Alves et al., 2019).

Waist circumference (WC) and waist-hip-ratio (WHR) are often used to estimate the distribution of adiposity and depict abdominal obesity. WC is

measured midway between the lowest palpable rib and iliac crest and hip circumference (HC) at the widest trochanters. WC over 80 cm in females and 94 cm in males, and WHR over 0.86 and 1.0 both increase the risk of metabolic complications (WHO Expert Consultation, 2011).

2.2.2 The hypothalamic-pituitary axis and the effects of underweight, overweight and obesity (Fig. 3)

The gonadal axis is regulated by the hypothalamus where hypothalamic neurons are secreting gonadotropic releasing hormone (GnRH) by pulses every 60–90 minutes (Crowley 1985, Santoro 1986). The secretion of GnRH is regulated by kisspeptins, which are downregulated by sex hormones via negative feedback. In addition, the Anti-Müllerian Hormone (AMH) (see also: Chapter 5.2.1 PCOS definition and pathogenesis) has been shown to have a role in GnRH regulation (Cimino et al., 2016; Malone et al., 2019). Other hormones, such as the energy homeostasis regulators leptin and ghrelin, also modulate the secretion of GnRH via kisspeptins (Navarro, 2020). In the pituitary, GnRH releases FSH and LH into the systemic circulation to target the gonads.

Ovarian steroidogenesis

Ovarian steroidogenesis occurs in two different cell lines: the theca cells stimulated by LH to produce androgens and the granulosa cells where LH triggers the ovulation, whereas FSH stimulates the production of inhibin B and estradiol (E2) (Fig. 3). E2 is produced via aromatization of the androgens produced in the theca cells. E2 exerts negative feedback on the hypothalamus and the pituitary, and inhibin B on the pituitary.

During the follicular phase, FSH also stimulates growth of the follicles. The concentration of E2 increases, causing negative feedback to the pituitary, which decreases FSH and LH secretion. This induces the selection of the dominant follicle, whereas the other growing follicles are driven to apoptosis. At the time of ovulation, rapidly increasing levels of E2 in the growing dominant follicle cause the surge of LH especially and FSH through positive feedback. The LH surge causes the release of the oocyte, and the luteinization of the granulosa cells to form the corpus luteum. The corpus luteum then starts to secrete progesterone and E2. During the luteal phase of the menstrual cycle, the negative feedback of E2 returns.

Testicular steroidogenesis

Testicular steroidogenesis occurs in Leydig cells, which are stimulated by LH. FSH stimulates spermatogenesis together with T in Sertoli cells. T has negative feedback on both the pituitary and hypothalamus. Inhibin B is secreted in Sertoli cells, and exerts negative feedback on the pituitary. Small amounts of E2 are secreted by both the Sertoli and the Leydig cells, and exert negative feedback on the hypothalamus and pituitary (Fig. 3).

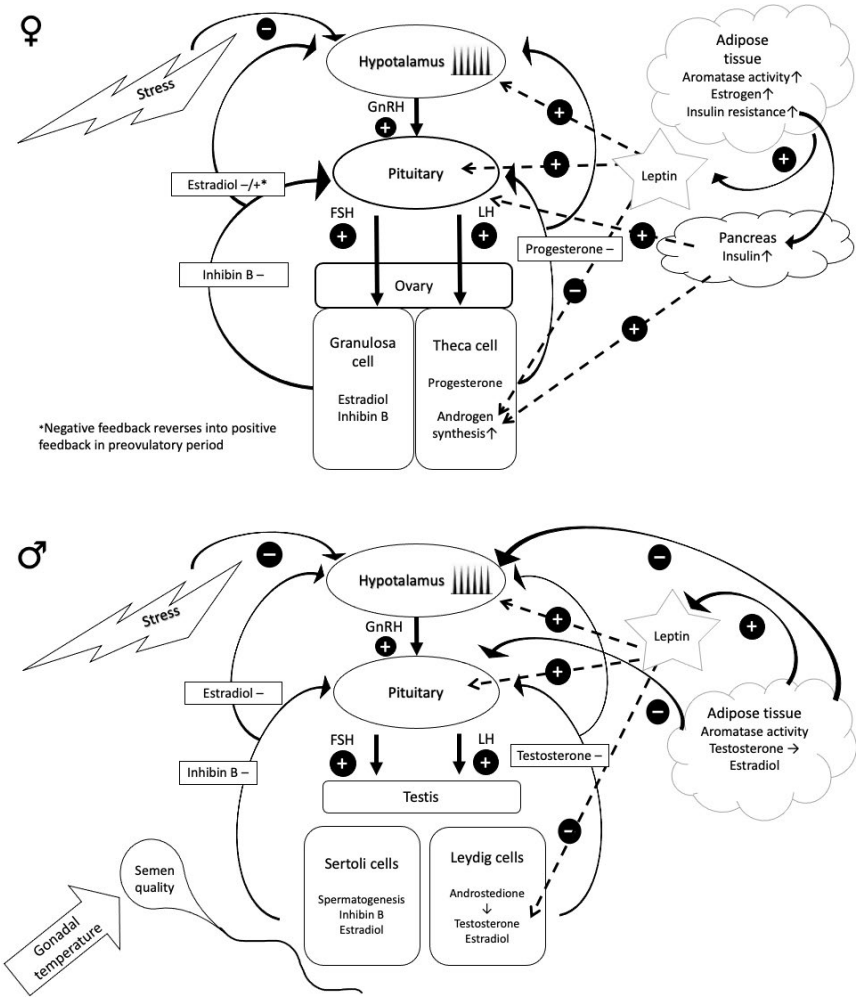

Fig. 3. The signaling pathways regulating HPG axis in women and men.

OB and UW affect these pathways in both sexes, and adipose tissue exerts an active role in it. In particular, visceral fat is an active metabolic organ secreting numerous factors, such as leptins and adiponectins, complement components, proteins of the renin-angiotensin system, as well as sex steroid hormones. This complex regulating system and its interaction with different hormone concentrations are presented in more detail below.

Estrogens

There are three major forms of E: estrone (E1), 17β-estradiol (E2), and estriol (E3). E2 is the most common and potent form of E in humans. Adipose tissue is the major source of circulating E (mainly E1) after the gonads both in men and women, and its contribution as a source for E increases with advancing age (Barakat et al., 2016).

In women, adipose and skin tissues aromatize the circulating androstenedione to E1, but the ovaries are the main source of E from puberty to menopause. E is responsible for the typical fat accumulation in females, i.e., increased gluteofemoral subcutaneous adipose tissue and reduced central adipose tissue (Frank et al., 2019; Puder et al., 2006; Tao et al., 2018).

In men, high E concentrations are associated with a negative impact on male gonadal function, and obesity in men has been shown to increase the concentration of E (Carrageta et al., 2019; Schulster et al., 2016), but controversial results have also been published (Hammoud et al., 2010; Huhtaniemi et al., 2012). In addition to the testicular secretion of E2, adipose tissue aromatizes T to E2. Conversely, weight reduction decreases E levels and increases T levels (Corona et al., 2013; Stanik et al., 1981); in some studies, weight loss did not affect E concentrations and not all OB men have elevated E levels (Dhindsa et al., 2011; Huhtaniemi et al., 2012). There are many possible explanations for this phenomenon. T is a substrate for aromatase, and lowered T levels decrease E levels via this mechanism (Huhtaniemi et al., 2012). Increased adipose tissue inflammation and IR also affect aromatization (Carrageta et al., 2019; Grossmann, 2018). Additionally, aromatase polymorphism has been found to be associated with E levels after weight loss (Hammoud et al., 2010).

Testosterone (T)

Androgens are mainly produced in the gonads, but adrenal secretion and peripheral tissues also participate in androgen secretion. Adrenal secretion is regulated by the adrenocorticotropic hormone (ACTH) secreted by the pituitary. Dehydroepiandrosterone (DHEA) and DHEAS are the main hormones secreted by the adrenal gland cortex (zone reticularis), but DHEA is also secreted by ovaries and testes. In addition to androgen secretion, the adrenal gland is also responsible for cortisol secretion, which exerts negative feedback on the HP axis in contrast to the adrenal androgens, which do not exert any negative feedback. Other peripheral tissues also produce androgens, for example (e.g.), the liver, the lungs, the skin, and most importantly, the adipose tissue (Longcope et al., 1986). The adiposity tissue converts peripheral E to T (Kershaw & Flier, 2004), and aromatizes T to E (Barakat et al., 2016; Carrageta et al., 2019).

In men, T is the main hormone responsible for the male phenotype differentiation. Decreased T levels are strongly associated with obesity (Fernandez et al., 2019; Hofstra et al., 2008; Kelly & Jones, 2015). Obesity and low T levels have a bidirectional association: obesity directly affects the HPT axis by reducing T levels, but T deficiency itself, e.g., after androgen deprivation therapy or surgical castration, induces adipogenesis and visceral obesity (Saylor & Smith, 2013; Tsai et al., 2000). Conversely, weight loss has been shown to improve T levels (Corona et al., 2013).

In women, the adrenals and the ovaries produce androgens, which are the substrates for E biosynthesis in the ovary. In women, circulating T concentrations are 1/10 of those in men. 25% of androgens are secreted by the ovaries, 25% by the adrenal glands, and the rest, 50% in peripheral tissue where E is converted to T. Androgen secretion does not exert negative feedback on the HPO axis; therefore, the control of ovarian androgen synthesis is weak (Santoro & Wierman, 2021). Although androgens do not appear to be essential for the female human's survival and health, they have a positive effect on libido (Lasley et al., 2011; Santoro & Wierman, 2021). Less desirable effects of androgens are hirsutism and acne.

Sex hormone binding globulin (SHBG)

Sex hormone binding globulin (SHBG) is produced in the liver in the hepatocytes. In the blood, sex hormones are mostly bound to SHBG or albumin, and only a small portion is in free active form (Hammond & Bocchinfuso, 1996). SHBG production

is regulated by sex hormones, dietary components, cytokine levels, thyroid hormones, liver diseases, and alcohol consumption (Thaler et al., 2015). Hyperinsulinemia, IR, cytokines, and obesity - and more precisely, liver fat content - reduce the production of SHBG (Pasquali et al., 1995; Simó et al., 2015; Singh et al., 1990; Yasui et al., 2007). Low SHBG levels are associated with a higher risk of MeS (Bhasin et al., 2011a), T2DM (Gyawali et al., 2018; Lakshman et al., 2010), and cardiovascular diseases (Gyawali et al., 2019). Importantly, weight loss has been strongly associated with increased SHBG levels (Carrageta et al., 2019; Corona et al., 2013; Escobar-Morreale et al., 2017; Simó et al., 2015; Stárka et al., 2020).

Free androgen index (FAI) and calculated free testosterone (cFT)

In women, hyperandrogenism (HA), and in men, hypoandrogenism, are defined based on the circulating level of T or calculated parameters describing androgenicity, such as free androgen index (FAI) and calculated free testosterone (cFT) (Rosner et al., 2007; Vermeulen et al., 1999). Determining the biological active free testosterone has been shown to be extremely challenging and expensive, so calculation formulas have been generated to describe the circulating free testosterone activity (Table 1). In women, FAI is more commonly used because of its simplicity and good correlation with bioactive T, but in men, it is not recommended due to its strong SHBG dependency and poor correlation with physiological active T levels (Hackett et al., 2017; Rosner et al., 2007). In men, cFT is more accurate, as it also takes albumin levels into account. If albumin is missing, a value of 43 g/L has been shown to be the most accurate in clinical evaluations (Garcia-Banigan et al., 2014; Guay et al., 2013).

Table 1. Calculation formulas used for evaluation androgenicity.

Androgen indices	Equation
Free androgen index (FAI)	$100 * \frac{total\ T}{SHBG}$
Calculated free testosterone (cFT)[1]	$cFT = \frac{-b + \sqrt{b^2 + 4a[TT]}}{2a}$
	$a = k_{at} + k_t + (k_{at} + k_t)([SHBG] + [albumin] - [T])$
	$b = 1 + k_t[\mathrm{SHBG}] + k_{at}[albumin] + (k_{at} + k_t)[T]$
	where k_t and k_{at} are association constants for T binding to $SHBG$ (10×10^8 L/mol) and $albumin$ (3.6×10^4 L/mol)

[1] Vermeulen et al., 1999

Leptin and ghrelin

Adipokine hormones like leptin are secreted by the adipocytes. Leptin regulates energy intake, and has an important role regarding sex hormone function and reproduction. It also seems to be an essential link between adequate energy homeostasis, optimal adiposity, and reproductive function (Grossmann, 2018; Moschos et al., 2002). Leptin accelerates GnRH pulsatility and secretion, and directly stimulates LH, and at a lesser degree, FSH secretion (Carrageta et al., 2019; Childs et al., 2021; Grossmann, 2018; Moschos et al., 2002). Leptin also directly affects the gonads by inhibiting steroidogenesis in Leydig cells in men, and in granulosa cells in women (de Medeiros et al., 2021; Grossmann, 2018; Ishikawa et al., 2007; Moschos et al., 2002).

Ghrelin is a peptide hormone secreted mainly by the stomach. Ghrelin levels increase during fasting and decrease after eating (Dupont et al., 2010). Ghrelin has been shown to inhibit GnRH, LH, and FSH secretion, as well as steroidogenesis and germ cell production (Schalla & Stengel, 2021).

Obesity increases leptin concentration and promotes leptin resistance. Increased leptin concentrations can lead to disorders in sex hormone production and impair reproductive function (Carrageta et al., 2019; de Medeiros et al., 2021; Grossmann, 2018). Also, UW and especially eating disorders are associated with an impairment in leptin secretion (Kim et al., 2020; Miller, 2011; Moschos et al., 2002), and low leptin concentrations are associated with amenorrhea (Boutari et al., 2020; Moschos et al., 2002).

Kisspeptins

Kisspeptins regulate the secretion of GnRH by directly affecting the GnRH secretion and pulsatility in neurons (Xie et al., 2022; Zeydabadi Nejad et al., 2017) (Fig. 4). Kisspeptin neurons adapt to the nutritional status as a link between energy homeostasis and reproductive function (Ahima et al., 2000; de Roux et al., 2003; Navarro, 2020). The pulse frequencies and amplitudes affect the secretion of FSH and LH differently, which further affects the secretion of sex hormones and reproductive function (Xie et al., 2022). Kisspeptins, along with multiple peripheral signals, also play an important role in determining the timing of puberty onset (Ahima, 2011; Donato et al., 2011).

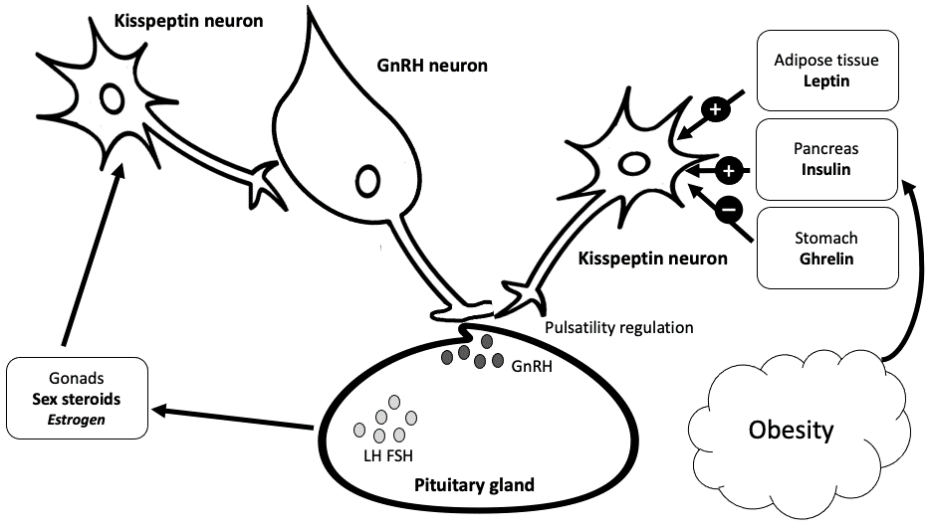

Fig. 4. Kisspeptin signaling pathways and their association with obesity.

2.2.3 Hypogonadism in men and women

In primary hypogonadism (primary defect of testis or ovary function), FSH and LH levels are high (hypergonadotropic hypogonadism), and in secondary hypogonadism, (disorder in the stimulation of testis or ovary function), they are low (hypogonadotropic hypogonadism). The etiologies behind these two entities are shown in Table 2. In primary hypogonadism, the impairment of gamete production is generally greater than the impairment of sex hormone production, whereas in secondary hypogonadism, both functions are affected equally (Basaria, 2014; Richard-Eaglin, 2018; Rothman & Wierman, 2008). Obesity is the main etiology for secondary hypogonadism in men by causing suppression of the HPG axis via multiple ways. UW has a similar effect via different mechanisms.

Table 2. The causes of primary and secondary hypogonadism in women and men (Modified based on Basaria 2014, Rothmann 2008, Richard-Eaglin 2018).

Hypogonadism	Congenital		Acquired	
Primary i.e., hyper-gonadotropic	Male - Klinefelter syndrome - Y-chromosome microdeletions - Anorchia - Cryptorchidism	Female - Turner's syndrome - Ovarian agenesis	Male - Testicular torsion, trauma, or radiation - Varicocele - Orchitis	Female - Ovarian torsion, trauma, or radiation - Premature ovarian failure
	Both - Mutations in LH and FSH receptors		Both - Chemotherapy with alkylating agents - Autoimmune diseases (Addison's disease, hyperparathyroidism) - Infiltrative disease (hemochromatosis) - Medications (androgen / estrogen synthesis inhibitors) - Hepatic cirrhosis	
Secondary i.e., hypo-gonadotropic	Male	Female	Male - Severe obesity	Female
	Both - Empty sella syndrome - Kallmann's syndrome - Prader-Willi syndrome - Mutations in β-subunit of LH and FSH		Both - Chronic systematic illness - Hyperprolactinemia (from any cause) - Pituitary or hypothalamus tumors - Medications (opioids, anabolic steroids, glucocorticoids) - Infection (tuberculosis) - Iron overload syndromes - Nutritional deficiency / excessive exercise	

2.3 Female infertility

2.3.1 Definition, prevalence, and etiology

According to the WHO definition, infertility is the inability to conceive after 12 months of normal unprotected sexual intercourse (i.e., time to pregnancy (TTP) > 12 months) (Zegers-Hochschild et al., 2017). Infertility affects approximately 9–18% of the couples trying to conceive, causes psychological

stress in patients, and leaves an economic burden on both the patients and healthcare systems (Boivin et al., 2007; Herbert et al., 2012; Vander Borght & Wyns, 2018). The prevalence of infertility has increased during recent years, and has been reported to raise as much as 0.37% every year (Sun et al., 2019).

Figure 5 presents the main factors associated with reproductive capacity and infertility. In 20−30% of the cases, infertility is caused by males, 20−30% by females, and by both sexes in 20−30%. The cause of infertility remains unexplained in 10−20% of the cases (Boivin et al., 2007; Hanson et al., 2017; Herbert et al., 2012; Vander Borght & Wyns, 2018). The most common causes of female infertility are anovulation (25%), endometriosis (15%), pelvic adhesions (12%), tubal damage (11%), other tubal abnormalities (11%), and hyperprolactemia (7%) (Thonneau et al., 1991; Vander Borght & Wyns, 2018). About 5–10% of infertile patients may have underlying genetic abnormalities (chromosome variation, gene mutations, polymorphisms) (Hanson et al., 2017; Tarín et al., 2015). Environmental factors, endocrine disruptions, and hormonal imbalances also affect fertility (Tarín et al., 2015).

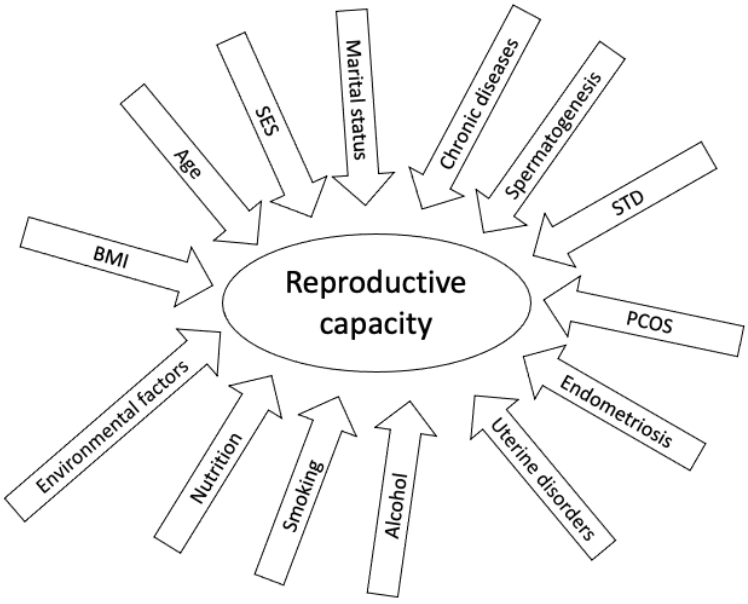

Fig. 5. Factors associated with reproductive capacity. STD: sexually transmitted disease.

It is estimated that only 30–40% of women with anovulation have PCOS because hypothalamic disorders are more of a common cause for amenorrhea, but PCOS is the main reason for anovulatory infertility (70–90% of the cases) (Azziz, 2018; Sirmans & Pate, 2013; Teede et al., 2010, Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2008). Women with PCOS commonly have infertility problems and decreased fertility, and this association is at least partly independent of the BMI (Boomsma et al., 2006; Joham et al., 2014, 2015; Palomba et al., 2014; Roos et al., 2011) (Please see Chapter 2.5.6).

2.3.2 Infertility and obesity

Some OB women conceive without difficulty and proceed through pregnancy without complications, while others may suffer from serious problems with both issues. The pathophysiological mechanisms involved in the association between obesity and reproductive disorders are still not fully clarified. It is well-known that OW and obesity affect reproductive function in many ways: anovulation, menstrual disorders and infertility, difficulties in assisted reproduction treatments, increased miscarriage rates, and adverse pregnancy outcomes (Brewer & Balen, 2010; Crujeiras & Casanueva, 2015; Hahn et al., 2014; Rich-Edwards et al., 1994). OW and OB women have a three times higher risk of anovulatory subfertility or infertility compared to those with a normal BMI, and the probability of pregnancy is reduced by 5% per one extra unit of BMI over 29 kg/m^2 (van der Steeg et al., 2008). Obesity is strongly associated with an abnormal function of the HPO-axis (see Chapter 2.2.2 and Fig. 3) by directly affecting the hypothalamic-pituitary function, and causing disorders of gonadotropin secretion and further ovulation dysregulation (Adashi et al., 1981; Nelson & Fleming, 2007).

OB women are also more likely to experience pregnancy loss and elevated miscarriage rates following either natural or assisted conception (Hahn et al., 2014; Hamilton-Fairley et al., 1992; Wang et al., 2002). Obesity also reduces uterine receptivity to implantation, and decreases pregnancy rates in assisted reproductive technology, but the histopathological and molecular effects of obesity on the endometrium are still not fully clarified (Bellver et al., 2018). Lastly, assortative mating may accentuate the influence of BMI on fertility in obese couples (Nelson & Fleming, 2007).

Whereas adulthood obesity is a well-known risk factor for infertility and childlessness (Brewer & Balen, 2010; Nelson & Fleming, 2007), there is only

limited data concerning the effect of UW, OW, and obesity during childhood and adolescence on reproductive function.

2.3.3 Infertility and birth weight

Studies on the association between BW and later fertility have displayed controversial results (Table 3). A Danish cohort following 2773 pregnancy planners showed no correlation between BW and fertility problems later in life (Wildenschild et al., 2014), but prematurity seemed to be associated with lower fecundability (Wildenschild et al., 2015).

Table 3. Previous studies on the association between birth weight and women's fertility.

Study	Study design	Participants (n)	Age of the study population (y)	Adjustments	Results	
Ekholm et al., 2005	Population based register study from Sweden	148 281	25–27	Index person: SES, marital status Their mothers: SES, age, parity, marital status	Reproductive capacity: Very low BW Prematurity: SGA and LGA[1]	 ↓ – –
Swamy et al., 2008	Population based register study from Norway	283 457	27–37	Index person	Reproductive capacity: Prematurity (< 32gw[2])	 ↓
Nohr et al, 2009	National birth cohort study from Denmark	21 786		Age, prepregnancy BMI, smoking in pregnancy, SES	TTP[3] > 12 months: BW < 2 500 g BW > 4 500 g	 ↑ ↑
deKeyser et al., 2012	Population based register study from Sweden	494 692	23–33	Index person: SES Their mothers: SES, age, parity, marital status	Reproductive capacity: Very low BW Very premature LGA SGA had earlier reproducing age	 ↓ ↓ –
Wildenschild et al., 2014	Prospective cohort study from Denmark	2 773	18–40	All were planning pregnancy	Reproductive capacity: BW	 –
Wildenschild et al., 2015	Prospective cohort study from Denmark	2 773	18–40	All were planning pregnancy	TTP > 12 months: Prematurity	 ↑

[1] large for gestational age, [2] gestational week, [3] time to pregnancy

Some studies have shown that very low birth weight (LBW) (deKeyser et al., 2012; Ekholm et al., 2005; Nohr et al., 2009) was associated with reduced reproductive function, whereas some other results have suggested that gestation age under 32 weeks was associated with impaired fertility (deKeyser et al., 2012; Swamy et al., 2008). In the studies where BW or gestational age correlated with childlessness, many confounding factors, such as the index person´s marital status, were not considered (deKeyser et al., 2012; Nohr et al., 2009; Swamy et al., 2008). This may have biased the results, as in a register study from Sweden where marital status was considered, the probability to have children was strongly associated with the probability to have a partner (Ekholm et al., 2005).

2.3.4 Infertility and childhood BMI

Only a few longitudinal studies have investigated the association between childhood growth and reproductive capacity in adulthood, and these studies have shown divergent results (Table 4). A previous Finnish cohort study has shown an inverted J-shaped relationship between adolescent BMI and parity in adulthood (Jokela et al., 2007). Another study in young adults (aged 17−24) found similar results (Jokela et al., 2008). In another prospective cohort study, OB girls in pre-menarche with higher adiposity before age 18 displayed an increased risk of involuntary childlessness and infertility in adulthood, partly independently of the presence of PCOS (Jacobs et al., 2017). Inversely, a study from Australia did not find differences between weight groups in puberty and later infertility (TTP > 12 months or the need for an infertility assessment), but OB and UW girls at ages 7−11 had an increased risk of infertility (He et al., 2018). There are only two studies investigating the relationship between obesity before age 7 and reproductive capacity in adulthood with conflicting results: one study including women born in 1958 showed no association between obesity at age 7 and later infertility (Lake et al., 1997), but in a more recent study, obesity at ages 5–9 was associated with an increased risk of childlessness (Jacobs et al., 2017).

Table 4. Previous studies on the association between childhood growth and women's fertility.

Study	Study design	Participants (n)	Age of the study population (y)	Adjustments	Results	
Lake et al., 1997	Birth cohort study from Great Britain	5 799	33	SES, smoking status 23y	TTP > 12 months: BMI 7y	 –
Jokela et al., 2007	Prospective population-based cohort study from Finland	715	33–39	Partnership, adulthood BMI	Number of children: UW, OB at age 12–18y	 ↓
Jokela et al, 2008	Prospective national longitudinal cohort study from the United States	5 982	47	Urban residence, race, number of children desired	Number of children and achieved fertility: OW, OB at age 17–24y	 ↓
Jacobs et al. 2017	Prospective cohort study from the United States	1 061	45	Race, education, smoking, financial situation, current BMI, PCOS	Any infertility problems: OB at age 9–12y OB at age 13–18y High adiposity < age 18y Childlessness: OB 5–9y OB < age 12y	 ↑ – ↑ ↑ ↑
He et al., 2018	Prospective longitudinal study from Australia	1 544	31–41	Follow-up length, parental education, marital status	TTP > 12 months, infertility assessment / treatment: OB at age 7–11y OB at age 12–15y Self-reported infertility: UW at age 7–11y	 ↑ – ↑

2.3.5 Infertility and menarche age

Starting puberty at an early age has been linked to both adult obesity and adverse metabolic profiles (Adair & Gordon-Larsen, 2001; Bleil et al., 2012; Lee et al., 2007), but the results concerning fertility are conflicting. In a retrospective American study, early menarche age was associated with a decreased ovarian reserve in infertility patients, independently of adulthood BMI (Weghofer et al., 2013). Inversely, a Chinese cross-sectional study showed a significant correlation

between higher menarche age and the risk for infertility later in life (Chen et al., 2015), and a similar result was obtained from a Danish birth cohort study (Guldbrandsen et al., 2014). In a Finnish study, menarche age was associated with childlessness, and surprisingly, women with early or late menarche had more children than those with an average age (Jokela et al., 2007). However, studies from Denmark showed no correlation between menarche age and overall fertility (Helm et al., 1995; Wise et al., 2011).

2.4 Male infertility

2.4.1 Definition, prevalence, and etiology

Male infertility accounts for 20–30% of all infertility causes and contributes, in combination with female factors, to another 30% (Agarval et al., 2021; Anderson et al., 2009). Most factors presented in Figure 5 are also associated with reproductive capacity and infertility in men. The prevalence of male infertility has increased between 1990 and 2017 by 0.29% per year (Sun et al., 2019). Men with infertility have also a worse general health status (Salonia et al., 2009), a higher risk for cancer (Hanson et al., 2018), and even increased mortality (Ventimiglia et al., 2017). Thus, early detection of the risks linked to male subfertility would be a great opportunity to identify these men and try to improve their overall health.

There are three main causes of male infertility (Agarval et al., 2021; Krausz, 2011):

1. Obstruction of seminal outflow (obstructive azoospermia)
2. Hypothalamic-pituitary disease (causing secondary hypogonadism)
3. Testicular dysfunction (may be associated with primary hypogonadism)

Adulthood obesity is associated with hypogonadism, testicular dysfunction, and impaired spermatogenesis, and is a risk factor for infertility and childlessness in men (Craig et al., 2017; Eisenberg et al., 2014; Katib, 2015). However, it is still under debate whether there is an association between low BMI and fertility in men (Guo et al., 2019; Sermondade et al., 2013).

2.4.2 Infertility and birth weight

There are only a few studies on the association between BW and later fertility or semen quality in men (Table 5). Some studies, but not all (Whitcomb et al., 2017), have also shown an association between low BW or SGA with subfertility (Boeri et al., 2016; deKeyser et al., 2012; Faure et al., 2015; Francois et al., 1997). Studies on the association between BW and testicular function have shown that unfavorable fetal growth patterns, especially SGA, are associated with impaired sperm quality (Boeri et al., 2016; Faure et al., 2015; Kahn et al., 2019) and decreased testis volume (Cicognani et al., 2002), but conflicting results have again been published, showing no relationship between SGA and sperm count (Francois et al., 1997; Hart et al., 2016; Jensen et al., 2007; Olsen et al., 2000; Ramlau-Hansen et al., 2010; Whitcomb et al., 2017). Prematurity has also been shown to be associated with impaired reproductive function (deKeyser et al., 2012). These conflicting results may result from differences in SES, and especially in a decreased opportunity to establish a relationship and therefore to have children (deKeyser et al., 2012).

Table 5. Previous studies on birth weight and childhood growth patterns and their association with fertility and semen quality.

Study	Study design	Participants (n)	Age of the study population (y)	Results	
Francois et al., 1997	Cross-sectional study in infertile patients from Belgium	206	24–57	Unexplained subfertility: LBW	↑
				Semen outcomes: BW	–
Olsen et al., 2000	Cross-sectional study in first pregnancy planners from Denmark	296	19–42	Semen parameters: BW	–
Cicognani et al., 2002	Follow-up study from Italy	49	1–18	Testis volume: SGA	↓
Jensen et al., 2007	Follow-up study from Denmark	52	16–18	Testicular size or morphology: SGA	–
Ramlau-Hansen et al., 2010	Follow-up study from a birth cohort from Denmark	347	18–21	Semen parameters: BW	–
				Prepubertal BMI	–
deKeyser et al., 2012	Population-based register study from Sweden	522 216	23–33	Reproductive rate: Very LBW and SGA	↓
				Very premature	↓
				LGA	–

Study	Study design	Participants (n)	Age of the study population (y)	Results	
Faure et al., 2015	Cross-sectional study in infertile patients from France	92 + 91	23–45	Subfertility: LBW	↑
				Total semen count: LBW	↓
				Sperm DNA fragmentation: LBW	↑
Hart et al., 2016	Randomized controlled trial from Australia	382	20–22	Semen parameters:	
				Maternal smoking	↓
				Favorable growth pattern in utero	↑
				SGA	–
				Prematurity	–
				Testicular volume:	
				Favorable growth pattern in childhood	↑
				Consistent height > 50th pc	↑
Boeri et al., 2016	Cross-sectional study in primary infertile patients from Italy	1 200	18–60	Infertility: LBW	↑
				Semen quality and concentration: LBW	↓
				Testicular volume: LBW	↓
Whitcomb et al., 2017	Population-based prospective cohort from the United States	427	25–40	Semen quality: BW	–
				Infertility: BW	–
Kahn et al., 2019	Longitudinal population-based cohort from the United States	193	38–47	Sperm concentration: LBW for gestational age	↓

Maternal smoking is associated with adverse prenatal outcomes, such as lower BW, SGA, and prematurity (Di et al., 2022; Hofhuis et al., 2003; Horta et al., 1997; Suter et al., 2013; Weisberg, 1985), and can induce permanent epigenetic changes of the fetus (Cosin-Tomas et al., 2022). It has also shown an association with lower sperm count (Hart et al., 2016; Jensen et al., 2005; Ramlau-Hansen et al., 2007a; Ravnborg et al., 2011; Storgaard et al., 2003; Virtanen et al., 2012) and reduced testicular volume (Jensen et al., 2004).

2.4.3 Infertility and childhood BMI

There are only a few studies with conflicting results on the relationship between early childhood BMI and later fecundability or testicular function (Table 5). In one

study, non-optimal growth and high adiposity in childhood were associated with impaired testicular function in young adulthood (Hart et al., 2016), but another study revealed no difference between semen parameters and prepubertal BMI (Ramlau-Hansen et al., 2010). A consistent height above 50th pc through childhood was shown to be associated with higher testis volume (Hart et al., 2016). Only two previous studies have been conducted in adolescent boys (12–18y) and young adult men (17–24y), and both showed an inverted J-shaped relationship between childhood BMI and the number of children in adulthood. However, the number of children was strongly associated with the probability of having ever been in a relationship (Jokela et al., 2007, 2008).

2.5 Polycystic ovary syndrome (PCOS)

PCOS is a multifactorial disorder affecting 8–18% of women of reproductive age depending on the diagnostic criteria. It is associated with increased morbidity, and is an economic burden on society (Azziz et al., 2016; Brakta et al., 2017; Teede et al., 2018). Women with PCOS suffer from HA, oligo-amenorrhea (OA), infertility, and adverse cardio-metabolic and psychological morbidity (Franks et al., 1985; Karjula et al., 2017; Ollila et al., 2017, 2019; Pinola et al., 2017; Puurunen et al., 2011; Teede et al., 2018; West et al., 2014b), as well as a decrease in satisfaction regarding their lives (Karjula et al., 2020; Ozcan Dag et al., 2017; Panico et al., 2017).

PCOS is strongly associated with obesity: 50–70% of women with PCOS are OW or OB (Alvarez-Blasco et al., 2006; Gambineri et al., 2002; Ollila et al., 2016). Although the syndrome is typically identified during the reproductive period, it seems to originate as early as the prenatal period, where prenatal androgen excess is thought to cause predisposition for the syndrome (Abbott et al., 2002; Bruns et al., 2007; Ibáñez et al., 2011).

2.5.1 PCOS definition and pathogenesis

The PCOS definition varies according to different guidelines: National Institutes of Health (NIH) 1992, Rotterdam 2004 and Androgen Excess and PCOS (AE-PCOS) Society 2006 (Azziz et al., 2006; Rotterdam European Society of Human Reproduction and Embryology (ESHRE) / American Society for Reproductive Medicine (ASRM) -Sponsored PCOS consensus workshop group, 2004; Zawadzki & Dunaif, 1992) (Table 6). The new International PCOS Guideline supports using

the Rotterdam criteria for diagnosis, but emphasizes the evaluation of individual diagnostic criteria (HA, OA, polycystic ovary morphology (PCOM)) more precisely (Table 6) (Teede et al., 2018).

Table 6. Diagnostic criteria for PCOS according to the different guidelines.

Diagnostic criteria	HA[1]	OA[2]	PCOM[3]
NIH	+	+	-
Rotterdam			
Phenotype A	+	+	+
Phenotype B	+	+	-
Phenotype C	+	-	+
Phenotype D	-	+	+
AE-PCOS Society			
Either	+	+	+
Or	+	+	-
Or	+	-	+

[1] Clinical sign of HA (acne, alopecia and hirsutism), biochemical HA (cFT, FAI, liquid chromatography / mass spectrometer with extraction of free testosterone). For adolescents: severe acne and hirsutism.
[2] 1–3 years post menarche: cycle < 21 or > 45 days, > 3 years post menarche: < 21 or > 35 days, > 1 year post menarche: any cycle > 90 days, primary amenorrhea at age 15 or > 3 years after thelarche
[3] ≥ 12 follicles (diameter 2–9 mm) and/or increased ovarian volume (> 10 mL) in at least one ovary. If a transvaginal high-resolution ultrasound is used, the follicle count per ovary should be ≥ 20 or ovarian volume ≥ 10 mL. Ultrasound should not be used in those < 8 years post menarche (Teede et al., 2018).

Menses disorders in PCOS can be classified as oligomenorrhea (menstrual cycle length ≥ 35 days more than twice a year or < 10 menstruations per year) or chronic amenorrhea (absent menses for three months or more) (Azziz et al., 2006; Teede et al., 2018). Oligomenorrhea and/or amenorrhea, i.e., OA, is a typical symptom in women with PCOS. It is crucial that primary and secondary amenorrhea and OA stemming from other causes (e.g., congenital malformations or genetic disorders, thyroid dysfunction, eating disorders, congenital adrenal hyperplasia, Cushing's syndrome, androgen-secreting tumors, hyperprolactinemia, hypogonadotropic hypogonadism, and premature ovarian insufficiency) should be excluded (Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004; Teede et al., 2018). Based on NIH criteria, OA is required for the diagnosis of PCOS, but according to the Rotterdam and AE-PCOS criteria, a PCOS diagnosis can be set without disturbances in the menstrual pattern. The prevalence of PCOS among women with menstrual disturbances is estimated to be 60–90%, depending

on the diagnostic criteria and the age and ethnicity of the study population (Kumarapeli et al., 2008; Taponen et al., 2004).

PCOS and hyperandrogenism

HA is a typical disorder associated with PCOS. Clinical signs of HA are acne, excessive male-type hair growth, i.e., hirsutism (H), and female-pattern hair loss, i.e., alopecia. Biochemical HA is defined based on elevated levels of total serum T, cFT, FAI, androstendione, or DHEAS. PCOS guidelines recommend the use of cFT, FAI, or calculated bioavailable T (Teede et al., 2018).

In women with PCOS, the development of obesity aggravates the vicious circle of androgen excess, abdominal adiposity, adipose tissue dysfunction, and IR (Escobar-Morreale & San Millán, 2007). PCOS women also exhibit worse adipose profiles, increased visceral fat accumulation (Carmina et al., 2007; Yildirim et al., 2003), and larger adipocytes (Mannerås-Holm et al., 2011). Weight loss has been shown to normalize androgen levels in women with PCOS (Escobar-Morreale et al., 2017; Norman et al., 2002; Sirmans & Pate, 2013). It has been speculated that NW women with PCOS, i.e., lean-PCOS, have the most disturbed ovarian steroidogenesis and the highest androgen levels, whereas women with milder disturbances also need to have other predisposed factors, such as obesity, to develop the syndrome (Azziz et al., 2016; Escobar-Morreale et al., 2017; Escobar-Morreale & San Millán, 2007).

The origin of HA in PCOS is complex. The secretion of hypothalamic and pituitary hormones (GnRH, FSH, LH) is disturbed. In addition, recent studies have shown that increased AMH levels accelerate the frequency of GnRH pulsatile secretion, causing an increase in LH but not FSH levels (Barbotin et al., 2019; Dewailly et al., 2020). Obesity further exacerbates the dysregulation of gonadotropin secretion by affecting the secretion of kisspeptins via leptin, ghrelin, and insulin (Fig. 4). All of this leads to increased LH concentrations and increased T secretion in ovarian theca cells (Daniels & Berga, 1997; Ehrmann et al., 1995). There is also evidence that theca cells in women with PCOS exhibit an increase in intrinsic steroidogenic synthesis activity, as they convert androgen precursors to T more efficiently (Rosenfield & Ehrmann, 2016). IR and hyperinsulinemia also aggravate HA by increasing T production and inhibiting the hepatic synthesis of SHBG (Ehrmann et al., 2005). The roles of adrenal androgen excess and its mechanisms are still not fully clarified, but ACTH and cortisol production might have some role (Baskind & Balen, 2016).

Anti-Müllerian hormone (AMH)

AMH, i.e., Müllerian inhibiting substance, has an important role in sexual differentiation during organogenesis by inducing the regression of the Müllerian ducts in male fetuses. In females, AMH is secreted by the granulosa cells of the ovarian follicles until the antral stage. The serum AMH levels and antral follicle count (AFC) are well-correlated with each other, both in healthy women and women with PCOS (Pigny et al., 2006; Weenen et al., 2004). AMH has multiple functions: inhibition of the initiation of primordial follicle growth, decrease of the sensitivity of the antral follicles to FSH, disruption of the pulsative secretion of GnRH and the secretion of LH via the HP axis (Cimino et al., 2016; Dewailly et al., 2020; Durlinger et al., 2002; Gruijters et al., 2003).

AMH levels strongly correlate with HA (Pigny et al., 2006; Piltonen et al., 2005), as well as in adolescence (Pinola et al., 2014). It has been suggested to use a AMH cut-off over 35 pm/l as a diagnostic criterion of PCOS because of its good correlation with AFC (Dewailly et al., 2020), but this has not still been validated as an official diagnostic criterion for PCOM (Azziz et al., 2006; Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004; Teede et al., 2018; Zawadzki & Dunaif, 1992). Excess prenatal AMH exposure and subsequent aberrant GnRH receptor signaling have also been recently shown to play a critical role in the neuroendocrine dysfunctions of PCOS (Tata et al., 2018).

2.5.2 PCOS during reproductive age

During puberty, normal physiological changes overlap with PCOS symptoms: menstrual irregularities are normal during the first two to five years after menarche age, and an ultrasound diagnosis of PCOM should not be made during the first eight years after menarche (Apter, 1980; Carmina et al., 2010; Mortensen et al., 2009; Teede et al., 2018). HA symptoms like acne are also physiological in puberty, and for this reason, it is recommended to determine the actual androgen levels (Blank et al., 2008). In the last international guidelines, an ultrasound of the ovaries was not recommended for the diagnosis of PCOS in adolescents, but both oligo-anovulation and HA are required (Teede et al., 2018).

Along with aging, the clinical symptoms of PCOS usually improve, at least partly: menstrual cycles become more regular (Dahlgren et al., 1992; Elting et al., 2001) and androgen levels decrease (Piltonen et al., 2004; Pinola et al., 2015; Welt & Carmina, 2013). Also, the AFC of PCOS women and their AMH levels, despite

the decrease with age, remain higher compared to those of control women (Piltonen et al., 2005; Tehrani et al., 2010). Some studies have shown that women with PCOS reach menopause later than control women (Forslund et al., 2019; Li et al., 2016; Tehrani et al., 2010).

2.5.3 PCOS, prenatal factors and birth weight

Intrauterine environment has important life-long consequences, and affects susceptibility to health problems in adulthood (Barker & Osmond, 1986; Desai et al., 2015). Epigenetic changes, i.e., the modifications of DNA that alter gene expression without changing the gene sequence, are one possible mechanism connecting early development with a future risk of an adverse metabolic and hormonal phenotype like PCOS (Longo et al., 2013; Şanlı & Kabaran, 2019; Wells et al., 2011). The domination of a fetal catabolic process during the intrauterine period due to placental insufficiency or maternal malnutrition leads to IUGR and SGA in the newborn. Poor placental circulation and deficient energy lead to the increased production of glucocorticoids and hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis (Lin et al., 2017; Longo et al., 2013, 2013; Zambrano et al., 2014). An overactive HPA axis in the intrauterine environment supports the hypothesis of the association between IUGR/SGA and hyperandrogenemia in PCOS: fetal malnutrition and hypoxia cause the increased production of glucocorticoids and a hyperactive HPA axis, leading to increased levels of androgens and an increased risk of developing PCOS later in life (Longo et al., 2013; Meuwese et al., 2010; Wells et al., 2011).

In addition to the intrauterine stress related to IUGR, a strong genetic background might be behind the association between low BW, prematurity, and PCOS (Bahri Khomami et al., 2019; Castillo-Higuera et al., 2021; de Wilde et al., 2017). Pregnant women with PCOS have higher androgen levels during pregnancy, which is often worsened by obesity and IR (Filippou & Homburg, 2017). They also have higher risks for preterm delivery and pregnancy complications, such as hypertension, pre-eclampsia, and gestational diabetes mellitus (Yu et al., 2016). Together with the genetic background of women with PCOS, prenatal stress factors and exposure to intrauterine HA increase the risk for permanent changes in the HPO axis and expose these fetuses to PCOS later in life.

Low BW, SGA (Davies et al., 2012; de Zegher et al., 2017; Melo et al., 2010; Minooee et al., 2016; Pandolfi et al., 2008; Sadrzadeh et al., 2017; Stracquadanio & Ciotta, 2017), and LGA (Mumm et al., 2013) have been associated with an

increased risk of PCOS, but many studies have also failed to find any significant association (Aarestrup et al., 2021; Cresswell et al., 1997; Laitinen et al., 2003; Legro et al., 2010; Paschou et al., 2015; Sadrzadeh et al., 2003, 2016; Sverrisdóttir et al., 2008). Girls with SGA have developed earlier menarche, and PCOS in some (Ibanez et al., 2007), but not all studies have shown similar results (Laitinen et al., 2003; Legro et al., 2010). On the contrary, higher BW has been associated with isolated HA (Davies et al., 2012), PCOM, and larger ovarian volume (Ibáñez et al., 2008; Michelmore et al., 2001) (Table 7). Women with PCOS have been reported to have more preterm births (Bahri Khomami et al., 2019; de Wilde et al., 2017; Yu et al., 2016), but previous studies have shown diverging results concerning the index person's own prematurity and the risk of PCOS later in life: in studies from Italy and Finland, prematurity was associated with an increased risk of PCOS (Paalanne et al., 2021; Pandolfi et al., 2008), but in a Swedish population, it did not (Sverrisdóttir et al., 2008). Women born preterm had similar AMH levels compared to full-term born women (Sydsjö et al., 2019), but their levels of adrenal androgens were increased (Meuwese et al., 2010). The maturation of the HPO axis in preterm infants is not fully understood. Girls born preterm have elevated FSH and LH levels during mini-puberty, suggesting disturbances in their hormonal secretion already began at an early age (Kuiri-Hänninen et al., 2018).

2.5.4 PCOS and childhood obesity

In previous studies, obesity and deviation in growth patterns, i.e., increased weight gain in adolescence, have been shown to associate with PCOS later in life (de Zegher et al., 2017; Laitinen et al., 2003; Ollila et al., 2016), and the change in weight z-score from birth to adolescence was greater in girls who were diagnosed with PCOS later in adulthood (de Zegher et al., 2017). A longitudinal population-based study revealed that moderately rising and high rising BMI trajectories were associated with an increased risk of PCOS, but the follow-up time started as late as 18 years of age (Kakoly et al., 2017). It has been speculated that a greater weight gain in early childhood could be a triggering factor of PCOS. Supporting this hypothesis, four studies on the association of obesity before puberty and later PCOS have been published. In two of them, obesity at age 7 was associated with an increased risk of menstrual irregularity (Lake et al., 1997) and PCOS (Li et al., 2017) in adulthood.

Table 7. Representative studies on PCOS and birth weight.

Study	Study design	Participants (n)	Age of the study population (y)	Study population	Results – risk of PCOS / PCOM	
PCOS						
Cresswell et al., 1997	Cohort study from United Kingdom	235	40–42	Birth cohort born 1952–53	BW	–
Sadrzadeh et al., 2003	Infertility cohort study from Netherlands	991	30–42	IVF patients in 1980–1995	BW	–
Laitinen et al., 2003	Birth cohort study from Finland	2 007	31	Birth cohort born 1966	BW	–
Pandolfi et al., 2008	Case-control study from Italy	70	19–23	Randomly selected women with LBW	SGA and prematurity	↑
Sverrisdottir et al., 2008	Case control study from Sweden	38	23–33	PCOS outpatients and controls from hospital records or advertisement	BW Gestational age	– –
Melo et al., 2010	Birth cohort study from Brazil	165	29	Birth cohort born 1978–1979	SGA	↑
Legro et al., 2010	Case control study from United States	553	22–34	PCOS outpatients, control selection not descripted	BW and SGA	–
Davies et al., 2012	Cohort study from Australia	948	30	Birth control born 1973–1975	Low BW	↑
Mumm et al., 2013	Register-based study from Denmark	523 757	15–40	Women from national health register born in 1973–1991	LGA and BW > 4500 g	↑
Paschou et al., 2015	Case control study from Greece	344	19–32	PCOS outpatients and students or hospital staff as controls	BW Low BW associated with hyperandrogenism	–
Minooee et al., 2016	Case control study from Iran	140	18–45	PCOS outpatients and students or hospital staff as controls	BW < 2500 g	↑

Study	Study design	Participants (n)	Age of the study population (y)	Study population	Results – risk of PCOS / PCOM	
Sadrzadeh et al., 2016	Case control study from Netherlands	161	mean age 39 (case) 45 (control)	PCOS outpatients and hospital controls	BW	–
Stracquadanio et al., 2017	Case control study from Italy	373	unknown	PCOS outpatients and hospital controls	Low BW	↑
Sadrzadeh et al., 2017	Meta-analysis	528 892	15–45	Meta-analysis	BW < 2500 g (only Rotterdam, not NIH criteria)	↑
de Zagher et al., 2017	Case control study from Spain and Germany	554	13–18	PCOS outpatients and healthy controls from Spain	BW NW PCOS girls had lower BW z-score	–
Valgeirsdottir et al., 2019	National registry-based cohort study from Sweden	681 123	15–28	National health register data on women born in 1982–1995	SGA, association was mediated by maternal factors	↑
Aarestrup et al., 2021	Population-based cohort from Denmark	200 977	15–50	National health register data on women born in 1960–1996	BW	–
Paalanne et al., 2021	Population-based cohort from Finland	385	23	Birth cohort data on women born in 1985–86	Prematurity	↑
PCOM						
Michelmore et al., 2001	Cross-sectional study from United Kingdom	224	18–24	Recruited female volunteers from Oxford universities	High BW	↑
Ibanez et al., 2008	Cohort study from Spain	86	17	Included only girls who had precocious pubarche in 2005–2006	Low BW	↓

Another study from Australia showed that girls with higher adiposity between ages 7−15 (mean age: 11.0 years) had a higher risk for PCOS and menstrual problems in adulthood (He et al., 2020).

Lastly, a study from Denmark showed that girls with OW or obesity at ages 7 and 13 had a higher risk of PCOS later in life, and that the risk was the highest in those who were OB or OW at both ages (Aarestrup et al., 2021). However, these studies did not investigate the association of AR characteristics (age and BMI) with the diagnosis of PCOS.

Women with PCOS are more likely to undergo earlier or later menarche (Carroll et al., 2012). As mentioned before, obesity and UW are associated with menarche age (Aghaee et al., 2022; Baker, 1985; Tomova et al., 2015). In women with PCOS, obesity is strongly associated with earlier menarche, and higher androgen levels with later menarche (Dramusic et al., 1997; Rosenfield et al., 2009), and conversely, idiopathic central precocious puberty was associated with an increased risk of developing PCOS later in adulthood (Franceschi et al., 2010).

2.5.5 PCOS and adulthood obesity

PCOS is strongly associated with obesity in adulthood (Alvarez-Blasco et al., 2006; Franks et al., 1985; Ollila et al., 2016). The prevalence of OW and obesity varies depending on ethnicity. In a previous study conducted in the NFBC66, 20–25% of women with PCOS were OB at age 31 and 35–40% of them at age 46 (Ollila et al., 2016). Studies from the Mediterranean areas have shown obesity to be less associated with PCOS (Diamanti-Kandarakis et al., 1999; Targher et al., 2009), whereas in a study from the United States, the prevalence of obesity was as high as 74% in the PCOS population, and it increased during the follow-up (Yildiz et al., 2008).

As mentioned before, excess weight gain in early adulthood, but not in later adulthood, is associated with PCOS (Laitinen et al., 2003; Ollila et al., 2016; Teede et al., 2013), even though women with PCOS still have larger WC and an increased risk of abdominal obesity until middle age (Ollila et al., 2016). The smaller increase in later weight gain may be due to a better recognition of health recommendations in this group of women at metabolic risks.

2.5.6 PCOS and infertility

PCOS is the most common cause of anovulatory infertility (Brewer & Balen, 2010; Nelson & Fleming, 2007; Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2008). The selection of the dominant follicle is impaired in PCOS due to the inappropriate responsiveness of antral follicles to LH, disturbed folliculogenesis by AMH, and excessively high estrogen production by the granulosa cells, which inadequately suppress FSH secretion and disturb dominant follicle maturation (Franks et al., 2008; Lujan et al., 2010).

Previous studies on lifetime fertility in women with PCOS have shown that their overall fecundability is decreased, but that these women deliver at least once as often as control women, suggesting that their fertility can be restored with infertility treatments (Boomsma et al., 2006; Hudecova et al., 2009; Joham et al., 2014, 2015; Koivunen et al., 2008; Rees et al., 2016; West et al., 2014a; West et al., 2014b). Nevertheless, women with PCOS have a smaller family size (Koivunen et al., 2008; West et al., 2014b), and women with both PCOS and obesity have the smallest family size (West et al., 2014b).

Only a few studies have shown that PCOS independently impairs fecundability (Rees et al., 2016; Roos et al., 2011), and a large meta-analysis has suggested that lean women with PCOS have significantly better ovulation and pregnancy rates than OB women with PCOS (Baghdadi et al., 2012). Weight management is the most important treatment for anovulatory infertility in women with PCOS and obesity (Teede et al., 2018): a weight loss of only 5% improves menstrual irregularity, as well as insulin sensitivity and glucose metabolism, and decreases the number of ovarian follicles (Norman et al., 2002; Pasquali et al., 2006). Women with PCOS seem to have better *in vitro* fertilization (IVF) results at a more advanced age compared to other infertile women (Li et al., 2019; Mellembakken et al., 2011; Tannus et al., 2018). Together with the higher age of menopause in women with PCOS, these findings suggest that women with PCOS might sustain fertility longer than controls.

The results of studies on the risk of miscarriages and PCOS are controversial. In some studies, women with PCOS have an increased risk of miscarriages (Glueck et al., 1999; Palomba et al., 2014; Rees et al., 2016; Tulppala et al., 1993; Wang et al., 2001), but opposing results exist (Heijnen et al., 2006; Joham et al., 2014; Koivunen et al., 2008; West et al., 2014b). Studies in this field include very heterogenic populations, and the variation of possible confounding factors is considerable.

2.6 Male hypogonadism

Male hypogonadism, i.e., hypoandrogenism or T deficiency, is caused by testicular failure to produce enough testosterone. It can be caused either by a central disorder or by a primary secretion deficiency. Secondary hypogonadism is strongly associated with obesity, especially in men;in fact, obesity is nowadays a major cause of male hypogonadism (Carrageta et al., 2019; Fernandez et al., 2019; Grossmann, 2018). The association is bidirectional: obesity directly affects the HPT axis and reduces T synthesis (Fig. 3). Conversely, T deficiency after androgen deprivation therapy or surgical castration has been shown to induce increased adipogenesis and visceral obesity (Saylor & Smith, 2013; Tsai et al., 2000).

Lower T levels have been associated with a higher risk of abdominal obesity (Camacho et al., 2013; Hall et al., 2008; Shi et al., 2013; Vaidya et al., 2012), MeS (Antonio et al., 2015; Bhasin, 2003; Hart et al., 2019), T2DM (Joyce et al., 2017; Lakshman et al., 2010; Ottarsdottir et al., 2018; Tully et al., 2016), and cardiovascular diseases (Gyawali et al., 2019; Haring, 2012; Hart et al., 2019). However, most of these studies are cross-sectional or relatively short-lasting with a follow-up time period of less than 10 years.

2.6.1 Definition of hypogonadism in men

Low androgen levels in men are associated with several symptoms: sexual, such as delayed puberty, small testes, reduced sexual desire, erectile dysfunction, delayed ejaculation, decreased volume of ejaculation, and decreased morning or night-time erections; physical, such as decreased body hair, gynecomastia, hot flushes, decreased muscle mass, decreased strength, osteoporosis, and sleep disturbances; and psychological, such as irritability, depression, poor self-related health, and decreased cognitive function (Carrageta et al., 2019; Fernandez et al., 2019; Grossmann, 2018; Hackett et al., 2017; Kelly & Jones, 2015).

The decline in physiological T occurs especially after age 40 (Haren et al., 2002; Swerdloff & Wang, 2004), and men in their 80s have 35–50% lower T levels compared to men in their 20s (Vermeulen et al., 1999). More recently, the onset of T decline has been recognized to occur even earlier in life (Carrageta et al., 2019; Lokeshwar et al., 2021) with declining T levels occurring already in adolescent males and young men (Coccia, 2019; Peterson et al., 2018).

T deficiency is a medical diagnosis defined by clinical symptoms and biochemical markers. According to the different guidelines, low T has been defined

as serum T levels below 8–12 nmol/l; the cut-off levels are also dependent on men's age (Bhasin et al., 2011b; Bhasin et al., 2018; European Association of Urology (EAU) Guidelines, 2022; Hackett et al., 2017; Khera et al., 2016; Lunenfeld et al., 2021; Mulhall et al., 2018; Nieschlag et al., 2005; Wang et al., 2008). In clinical use, the diagnosis of T deficiency should not be confirmed based on only one measurement (EAU Guidelines, 2022; Lunenfeld et al., 2021), and the blood tests should be drawn in the morning when the physiological T levels are higher (Diver et al., 2003). Most of the guidelines (Table 8) recommend 12.1 nmol/l as a cut-off value for low T (EAU Guidelines, 2022; Khera et al., 2016; Lunenfeld et al., 2021). Some guidelines have a "grey zone" of T values between 8 and 12 nmol/l (Corona et al., 2020; Hackett et al., 2017; Wang et al., 2008). In this zone, repeated measurements are needed, and SHBG and cFT calculations should be considered (Bhasin et al., 2011b; Bhasin et al., 2018; EAU Guidelines, 2022; Hackett et al., 2017; Khera et al., 2016; Lunenfeld et al., 2021; Mulhall et al., 2018; Nieschlag et al., 2005; Wang et al., 2008). If T levels are under 6 nmol/l, a magnetic resonance imaging (MRI) of the pituitary should be performed (EAU Guidelines, 2022).

Table 8. Definition of hypogonadism based on different guidelines.

Guideline	Limit for low T
American Urology Association (AUA) (Mulhall et al., 2018)	10.4 nmol/l
British Society for Sexual Medicine (Hackett et al., 2017)	8–12 nmol/l
Endocrine Society - Clinical Practice Guideline (Bhasin et al., 2018)	9.2 nmol/l
European Academy of Andrology (EAA) (Corona et al., 2020)	8–12 nmol/l
European association of Urology (EAU) (EAU Guidelines, 2022)	12.1 nmol/l
International Society of Andrology (ISA) (Wang, 2008)	8–12 nmol/l
International Society for Sexual Medicine (ISSM) (Khera et al., 2015)	12.1 nmol/l
International Society for the Study of the Aging Male (ISSAM) (Lunenfeld et al., 2021)	12.1 nmol/l

Hypogonadism can be divided into primary and secondary hypogonadism (Table 2). In the literature, LH 9.4 U/l has been used as a cut-off value to categorize hypogonadism according to its etiology (Ishikawa et al., 2007; Tajar et al., 2010; Ventimiglia et al., 2017). Primary (low T and high LH) and compensated hypogonadism (normal T and high LH) are rare entities compared to secondary hypogonadism. Primary hypogonadism is associated with congenital conditions like Klinefelter syndrome (KS), Y-chromosome microdeletion, or anorchia (Basaria, 2014; Richard-Eaglin, 2018). Compensated hypogonadism is related to similar findings on primary hypogonadism: smaller testis size, decreased sperm,

more frequent findings of azoospermia, and karyotype abnormalities (Ventimiglia et al., 2017).

2.6.2 Hypogonadism and prenatal factors in men

Maternal smoking

Some studies have shown significant associations between maternal smoking and lower T levels in adulthood (Ramlau-Hansen et al., 2007a; Ravnborg et al., 2011; Storgaard et al., 2003), but there are some published results that did not show an association (Jensen et al., 2004; Ratcliffe et al., 1992; Richthoff et al., 2008).

Maternal obesity

Maternal obesity has been shown to increase the risk of offspring obesity (Drake & Reynolds, 2010; Eriksson et al., 2015; Gaillard, 2015; Pirkola et al., 2010). Further, extreme weight loss after bariatric surgery reduced the risk of offspring obesity in boys, but not in girls, compared to their siblings born before bariatric surgery (Kral et al., 2006). This finding might suggest that the expression of obesity genes in offspring can be modulated by the mother´s weight loss.

Very limited data exists on the association between maternal obesity and reproduction function in male offspring. In one study from Denmark, maternal obesity was associated with lower inhibin B concentration, but not with semen parameters or other sex hormone levels (Ramlau-Hansen et al., 2007b). Earlier puberty has been associated with maternal obesity both in boys (Hounsgaard et al., 2014) and girls (Deardorff et al., 2013; Keim et al., 2009). Animal models have revealed that the offspring of OB mothers have lower T and LH levels compared to the offspring of NW mothers, but no differences in reproductive function or semen quality were seen (Rodríguez-González et al., 2015).

One putative mediator of this association is leptin, the level of which has been shown to be affected by maternal obesity and nutrition during pregnancy. Leptin concentrations are higher in the circulation, as well as in the cord blood of OB mothers (Kim et al., 2020; Walsh et al., 2014), and children exposed to higher leptin levels prenatally have a higher BW (Stefaniak et al., 2019; Walsh et al., 2014). Paradoxically, higher leptin levels have been associated with slower weight gain in infancy and early childhood (Karakosta et al., 2016; Parker et al., 2011), but a

positive correlation between cord leptin levels and adiposity in later childhood and adolescence has been detected (Simpson et al., 2017). Moreover, increased leptin levels and leptin resistance are associated with obesity later in life (Grossmann, 2018; Kim et al., 2020), and high leptin levels have been shown to act directly on testis function by inhibiting steroidogenesis (Carrageta et al., 2019; Fernandez et al., 2019; Grossmann, 2018; Kelly & Jones, 2015).

2.6.3 Hypogonadism and birth weight

Previous studies have shown divergent results concerning BW or SGA and later T levels in men (Table 9). SGA (Cicognani et al., 2002; Scaramuzzo et al., 2010) and low BW (Boeri et al., 2016; Thompson & Lampl, 2013; Vanbillemont et al., 2010) have shown an association with low T in some, but not all studies (Hart et al., 2016; Jensen et al., 2007; Kerkhof et al., 2009).

Table 9. Previous studies on the association between testosterone levels and birth weight / childhood growth.

Study	Study design	Participants (n)	Age of the study population (y)	Results
Cicogcnani et al., 2002	Follow-up study from Italy	49	15−22	SGA: T ↓, LH ↓, FSH –
Jensen et al., 1997	Follow-up study from Denmark	52	16−18	SGA: T –, SHBG –, LH –
Kerkfof et al., 2009	Preterm cohort study and randomly selected controls from Netherlands	207	18−24	SGA, low BW: T –, SHBG –, LH –, FSH –, Inhibin B –, AMH –
Scaramuzzo et al., 2010	Observation study of premature boys from Italy	50	0−2 days	SGA: T ↓
Vanbillemont et al., 2010	Cross-sectional, population-based sibling pair study from Belgium	677	28−40	Low BW: T ↓ , SHBG ↓, LH –, FSH –
Ramlau-Hansen et al., 2010	Follow-up study from a birth cohort from Denmark	347	18−21	BW: sex hormones – Prepubertal (5–8y) high BMI: T ↓, SHBG ↓, FSH ↓, LH –
Thompson and Lampl, 2013	Prospective, mixed-longitudinal growth study from the United States	15	1	Low BW: T ↓, Low GA: T ↓

Study	Study design	Participants (n)	Age of the study population (y)	Results
Hart et al., 2016	Randomized controlled trial from Australia	382	20−22	Prematurity: T ↓ SGA / LGA: T – Growth trajectory 'rising to high': T ↓ OB at age 20 y: T ↓
Boeri et al., 2016	A Cross-Sectional Study in Primary Infertile Patients from Italy	1 200	18−60	Low BW: T ↓, FSH ↓, SHBG –, LH –

2.6.4 Hypogonadism and BMI development

Men with hypogonadism are more OB, and they have more metabolic abnormalities than men with a normal gonadal function (Antonio et al., 2015; Bhasin, 2003). Studies concerning the association between childhood growth trajectories or BMI development and T deficiency are very limited (Table 9). An Australian cohort study has shown that an optimal BMI trajectory during childhood and adolescence was associated with higher serum inhibin B and T in adulthood (Hart et al., 2016). Another study from Denmark found an association between high BMI at prepubertal age and low T in early adulthood (Ramlau-Hansen et al., 2010).

The growth of boys with hypogonadotropic hypogonadism seems to already differ before puberty. Boys with congenital hypogonadotropic hypogonadism appear to have a decreased linear growth during mini-puberty (Varimo et al., 2016), and boys with KS seem to accelerate their length growth velocity after ages 3–6 onwards, resulting into a significantly taller stature than expected (Davis et al., 2016). Abdominal fat accumulation, decreased lean body mass, and increased fat mass is common in KS patients, both in children (Davis et al., 2016; Zitzmann & Rohayem, 2020) and adults (Chang et al., 2015; Salzano et al., 2016). Studies have shown that T substitution increases total body mass and fat free mass, and reduces fat mass in both children (Davis et al., 2019) and adults with KS (Chang et al., 2015; Kanakis & Nieschlag, 2018). Also, higher levels of T after birth are associated with a more beneficial body composition in later childhood (Becker et al., 2015).

Weight loss has been shown to improve T levels in men with obesity. Lower LH levels, together with higher T levels, have predicted better results for maintaining weight after weight loss in OB middle-aged men compared to men with higher LH levels (Wang et al., 2013). Weight loss by increasing physical

activity and diet changes had limited effect on T levels (Carrageta et al., 2019; Grossmann, 2018), but bariatric surgery has shown promising results, and it seems to be even more efficient in men with hypogonadism compared to eugonadal men (Samavat et al., 2014). These studies raise the question on the complex interrelationship between low T levels, obesity, and metabolic risks: which comes first, and what are the underlying mechanisms?

3 Aims of the study

In addition to metabolic diseases, obesity causes significant reproductive health problems. The hormonal changes linked to obesity lead to menstrual disorders, and OB women have a more than three times increased risk of infertility. The underlying mechanisms are not fully clarified, but one explanation could be that PCOS is more common in OB women. In men, obesity also has been found to impair reproductive health through its effect on hormonal factors. More specifically, androgen deficiency is strongly associated with obesity in men. By investigating childhood growth trajectories, certain stages of growth have been found to be relevant for the subsequent development of obesity and metabolic problems. Previous studies have also shown that obesity, OW, and UW in childhood and adolescence contribute to later infertility in both women and men, but the results are partly conflicting and very limited. In addition to weight, infertility is associated with numerous socioeconomic and psychological factors that make it difficult to assess the independent effect of BMI.

The Northern Finland birth cohort (NFBC66) provides an excellent opportunity to assess the impact of prenatal factors, BW, and childhood and adulthood weight gain on hormonal and reproductive problems at a population level, by considering several confounding factors, such as prenatal factors, marital status, SES, smoking, and attempts to have a child.

The specific aims of this project were:

1. To investigate the nature of the association between prenatal factors, birth weight, childhood and adolescence BMI, and reproductive capacity until the end of the reproductive lifespan in women.
2. To evaluate the association between prenatal factors, birth weight, childhood and adolescence BMI, and reproductive capacity in men until age 50.
3. To examine whether birth weight, age at adiposity rebound, and BMI trajectories from childhood until middle age differ between women with and without PCOS.
4. To examine whether prenatal factors, birth weight, the age at adiposity rebound, and BMI trajectories from childhood until middle age differ between men with low T and normal T at age 31.

4 Materials and methods

4.1 Study population Northern Finland Birth Cohort 1966 (NFBC66) and data collection

The study is based on the NFBC66, a large prospective general-population-based longitudinal birth cohort, including 12 055 women in the two northernmost provinces in Finland (Oulu and Lapland) whose estimated date of delivery was determined between January 1st and December 31st 1966. The study population comprised 96.3% of all individuals born alive in 1966 (12 058 births, 5 889 females and 6 169 males) (Rantakallio, 1988). The study was approved by the Ethics Committee of the Northern Ostrobothnia Hospital District. All participants provided informed consents. The study followed the principles of the Declaration of Helsinki.

Recruitment to this database began at the 24th gestational week; so far, it has been followed at birth, and at ages 1, 14, 31, and 46. Postal questionnaires were sent at ages 1, 14, 31, and 46, and clinical examinations were performed at ages 31 and 46 (Fig. 6).

In 1967, at age 1, a postal questionnaire was sent to 5 800 girls' and 6 069 boys' child health and welfare nurses. Of them, 91% (n = 5 279) of girls and 91.3% (n = 5 542) of boys participated. In 1980, at age 14, a postal questionnaire was sent to 5 764 girls and 6 022 boys and their families. Of them, 95% (n = 5 455) and 92.2% (n = 5 555) responded.

In 1997, at age 31, a postal questionnaire was sent to 5 608 women and 5 174 men; and 4 523 (81%) and 4 285 (75%) of them responded. In addition, those living in Northern Finland or in the Helsinki metropolitan area (4 074 women and 4 429 men) were invited to a clinical examination. Of these, 77% (n = 3 127) of women and 66% (n = 2 906) of men participated in a clinical examination including anthropometric measurements and a collection of blood samples for the assessment of hormonal and metabolic parameters.

In 2012, at age 46, a postal questionnaire was sent to all individuals alive and with known addresses (5 123 women and 5 190 men). Of these, 72% (n = 3 706) of women and 61% (n = 3 162) of men responded to the questionnaire. Of those who had received the questionnaire, 64% (n = 3 280) of women and 53% (n = 2 742) of men participated in the clinical examination.

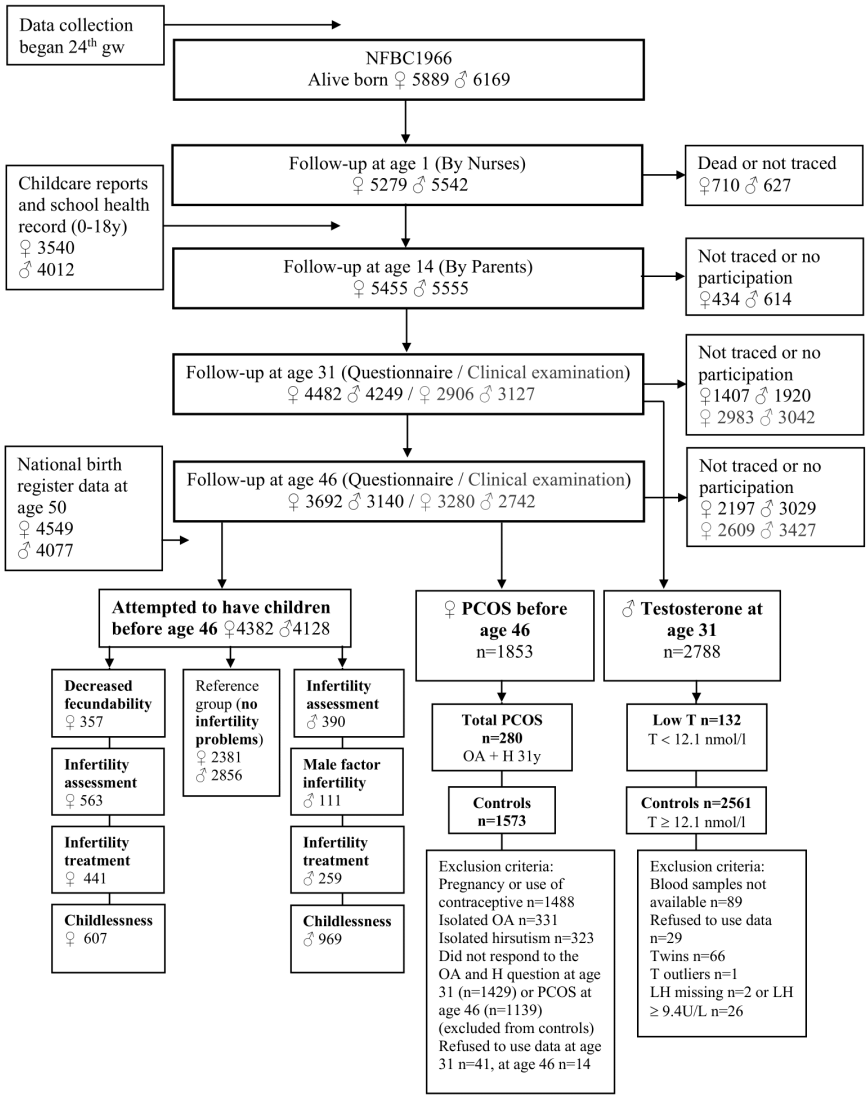

Fig. 6. Flowchart of the study populations.

4.1.1 Anthropometric measurements

The height and weight at ages 31 and 46 were measured at the clinical examination by experienced research nurses. If measurements were not available, self-reported data reported in the postal questionnaires were used. BMI was calculated as the ratio of weight (kg) to height squared (m^2). There was no statistically significant difference between self-reported and clinically measured BMIs. WC and HC were measured at the 31y and 46y clinical examinations. WC (cm) was measured midway between the lowest palpable rib and iliac crest, and HC (cm) at the widest points of both trochanters. WHR was calculated as the ratio WC/HC.

Growth data

Data on weight and height from infancy to adolescence were collected from measurements reported by the child health and welfare nurses, and later by the school nurses, as part of the national child health program, which is free for all children in Finland.

As the annual measurements of weight and height were not available for all participants, three different age groups were created: early childhood (from end of the infancy to adrenarche: 3.00–6.99 years (y)), mid-childhood (juvenile stage: 7.00–10.99y) and puberty (adolescence: 11.00–15.99y), according to the literature regarding childhood growth (Hochberg & Albertsson-Wikland, 2008; Tanner & Whitehouse, 1976). If participants had more than one measurement per year, the mean BMI for that year was calculated. The median numbers of measurements per age period (range) were: in early childhood, two (0–12); in mid-childhood, two (0–12); and in puberty, three (0–18). For each age group, the participants were stratified into UW (below 5^{th} percentile (pc)), NW (5^{th}–85^{th} pc), OW (85^{th}–95^{th} pc), and OB (over 95^{th} pc) categories according to the criteria of the WHO and the CDC (Kuczmarski et al., 2000). Being OB or UW in any of the specified age groups was defined by the occurrence of at least one BMI value over the 95^{th} pc or under the 5^{th} pc, respectively.

BMI and the timing of AP and AR were derived from fitted growth curves, as previously described (Sovio et al., 2011). The age and BMI at AP and AR were derived from cubic models in age for the two age groups separately, with random effects for the intercept and slope terms. The normal changes observed in childhood BMI required the data to be split into two age windows: infancy (2 weeks to 1.5y) and childhood (1.5 to 13y). For each participant, the predicted BMI at AP and AR

(on a grid of every 0.05y in infancy and every 0.1y in childhood) was calculated using the estimated fixed and random coefficients. The age at AP was defined as the age at maximum BMI between 0.25 and 1.25y, and the age at AR as the age at minimum BMI between 2.5 and 8.5y. To account for uncertainty in the derived parameters, each person's BMI data were weighted by the number of measurements within the age window, and those with fewer than three measurements were excluded. There were on average seven measurements during infancy, and sixteen during childhood for each child.

Height and weight at age 14 were all measured and reported by the parents. BMIs at menarche were estimated from the fitted BMI curves.

4.1.2 Blood samples and laboratory methods

At ages 31 and 46, the serum levels of total T were measured using Agilent triple quadrupole 6410 LC/MS equipment with an electrospray ionization source operating in positive-ion mode (Agilent Technologies, Wilmington, DE, USA). Multiple reaction monitoring was used to quantify T, using d3-T, with the following transitions: m/z 289.2 to 97 and 289.2 to 109 for T and 292.2 to 97 and 292.2 to 109 for d3-T.

At age 31, SHBG was assayed by fluoroimmunoassay (Wallac, Inc. Ltd., Turku, Finland), and at age 46, by chemiluminometric immunoassay (Immulite 2000, Siemens Healthcare, Lanberis, UK). As the SHBG analysis method changed over the course of the study, the SHBG values from age 31 were transformed to be comparable with the SHBG values analyzed at age 46 using the formula: 0.7615 x old method age 31 SHBG + 0.7088, and the results are reported according to this method (Ollila et al., 2017). The FAI was calculated as described previously (Table 1). FSH at age 46, and LH at ages 31 and 46 were determined using an immunochemiluminometric method (Advia Centaur; both Siemens Healthcare Diagnostics, Tarrytown, NY).

In addition, cFT was assessed at ages 31 and 46 by using albumin concentrations. As albumin was not measured at age 31, a standardized albumin level 43.0 g/l was used according to the literature (Guay et al., 2013), and SHBG and T concentrations according to the method described by Vermeulen et al (Vermeulen et al., 1999).

4.2 Definition of infertility and childlessness in the study population (Studies II and III)

4.2.1 Female infertility (Study II)

The study population was defined by the following question: 'Have you ever attempted to have children?'. At age 31, 4 386 women, and at age 46, 3 588 women answered the question. Of these, 3 639 and 3 379 reported that they had attempted to have children by age 31 or 46, respectively.

The outcomes concerning fertility were defined based on the answers to the 31y- and 46y-questionnaires (Table 10). TTP in months was asked only at age 31, and calculated from the beginning of unprotected intercourse until the first pregnancy. Decreased fecundability was defined as active exposure to pregnancy (i.e., not using contraception) for at least one year without getting pregnant (Koivunen et al., 2008). The other outcomes were the following: infertility assessment, infertility treatment, childlessness, and the number of children. The number of deliveries until the end of 2016 (when the women turned 50y) was obtained from the Finnish Medical Birth Register founded in 1987. The birth data before 1987 were collected from the Population Register Centre live births to make the birth data complete. The women without decreased fecundability, infertility assessment, infertility treatment, and childlessness formed the reference group. Women with missing data regarding decreased fecundability were also excluded from the reference group.

The final study population included 4382 women who had attempted to achieve pregnancy before age 46: women with decreased fecundability (n = 357), infertility assessment (n = 563), infertility treatment (n = 441), and childlessness (n = 607), and the reference group including the women without any infertility problem (n = 2 381) (Fig. 6).

Table 10. Questions concerning infertility at age 31 and 46

Question	Answer options	Numbers	
		Female	Male
Age 31, only women			
How many months did it take you to get pregnant (time without contraception)?	Under 12 months = Normal	2 654	
	Over 12 months = Decreased fecundability	357	
Age 31 both sexes			
Have you been assessed for infertility?	Yes	393	207
	No	3 172	3 374
Was the infertility due to you or to your partner (or both)?	Yes, me or my partner and me	191	60
	Yes, from my partner	41	94
	No reason found	171	140
Have you been treated for infertility?	Yes	288	57
	No	3 353	3 317
Age 46 both sexes			
Have you been assessed for infertility?	Yes	439	305
	No	2 424	3 074
Was the infertility due to you or to your partner (or both)?	Yes, me or my partner and me	192	88
	Yes, from my partner	65	71
	No reason found	250	214
Have you been treated for infertility?	Yes	307	230
	No	3 074	2 451

4.2.2 Male infertility (Study III)

The study population was defined by the following question: 'Have you ever attempted to have children?'. At age 31, 4 026 men, and at age 46, 3 012 men answered the question. Of these, 3 372 and 2 802 reported they had attempted to have children by age 31 or 46, respectively, and the final study population included 4 128 men who had attempted to have children by age 46.

The outcomes concerning fertility were defined based on the answers to the 31y- and 46y-questionnaires (Table 10). Male factor infertility was defined based on the question: 'Was the infertility due to you or to your partner (or both)?'. Other outcomes were as follows: infertility assessment, infertility treatment, childlessness, and number of children. The number of childbirths was recorded until the end of 2016 (when the men turned 50y), and obtained from the Finnish Medical Birth Register founded in 1987. The birth data before 1987 were collected from the Population Register Centre live births to make the birth data complete.

The final study population included 4 128 men who attempted to have children before age 46 and was divided in four groups: infertility assessment (n = 390), male factor infertility (n = 111), infertility treatment (n = 259), and childlessness (n = 969). The reference group included men without any infertility problem (n = 2 856) (Fig. 6).

4.3 Definition of PCOS (Studies I and II)

The 31y-questionnaire included a two-question screening for PCOS: 1) OA: 'Is your menstrual cycle often (more than twice a year) longer than 35 days?' and 2) H: 'Do you have bothersome, excessive body hair growth?'. Both symptoms (OA+H) were reported in 4.2% of the participants (n = 125) after the exclusion of pregnant women, women using hormonal preparations (n = 1 488), and those not permitting the use of their data for the analysis (n = 41). The reliability of the identification of women with PCOS by these questions had been validated in previous studies in the same cohort; the women with both OA+H presented the typical hormonal, metabolic, and psychological characteristics of the syndrome (Karjula et al., 2017; Laitinen et al., 2003; Ollila et al., 2016, 2017; Taponen et al., 2004).

The 46y-questionnaire included the question: 'Have you ever been diagnosed as having polycystic ovaries and/or polycystic ovary syndrome (PCOS)?', to which 181 responded "yes." Consequently, women who reported both OA+H at age 31 and/or a diagnosis of PCOS by age 46 were classified as women with PCOS (n = 280). Women without any PCOS symptoms at age 31 and without a diagnosis of PCOS by age 46 were classified as controls (n = 1 573) (Fig. 6).

4.4 Definition of low T at age 31 (Study IV)

A serum level of T < 12.1 nmol/l at age 31 was defined as a cut-off for low T levels per the recommendations of EAU, ISSAM and ISSM (EAU Guidelines, 2022; Khera et al., 2016; Lunenfeld et al., 2021). The use of testosterone, statin and opioid medications were asked at age 31; there were no testosterone or statin users, and nine opioids' users. They were not excluded, but their exclusion did not change the results.

The male participants were divided into two groups: men with low T (n = 136, 5% of the whole study population) and control men with normal T (n = 2 584, 95% of the whole study population). Luteinizing hormone (LH, cut-off value 9.4 U/l)

and T were used to classify functional hypogonadism according to the literature (Ishikawa et al., 2007; Tajar et al., 2010; Ventimiglia et al., 2017). Primary (T < 12.1 nmol/l and LH > 9.4 U/l, n = 3) and compensated hypogonadism (T ≥ 12.1 nmol/l and LH > 9.4 U/l, n = 23) were excluded from the analyses due to their small number and different etiology. This exclusion did not change the results. As twins' growth pattern differ from single born babies, they were excluded from the analyses (n = 66). Finally, the outlier values of T were excluded using the first quartile cutoff, –1.5 × IQR (interquartile range), for the lower limit and the third quartile cutoff, +1.5 × IQR, for the upper limit. According to this, only one measurement (T > 50.5 nmol/l) was excluded as an outlier.

The final study population included 2 693 men: 132 men with low T at age 31 and 2 561 men with normal T (Fig. 6).

4.5 Confounding variables

The NFBC66 questionnaires at ages 1, 14, 31, and 46 included multiple covariates, which have been used as confounders (Table 11).

Table 11. Covariates used for Studies I–IV.

Covariate	Reported	Method	Notes	Study
Mother's pre-pregnancy BMI	kg/m^2	Collected by midwives in antenatal clinics	Categorized as UW, NW, OW and OB	II–IV
Mother's age	years	Collected by midwives in antenatal clinics		II–IV
Mother's smoking end of pregnancy	yes / no	Collected by midwives in antenatal clinics		II–V
Mother's weight gain during pregnancy	kg	Collected by midwives in antenatal clinics		IV
Birth weight	g	Collected by midwives in antenatal clinics		I–IV
Gestational age	gw	Collected by midwives in antenatal clinics		I–IV
Size for gestational age		Collected by midwives in antenatal clinics	Categorized as SGA, AGA, LGA	I–IV
BMI 6 months	kg/m^2	1y-questionnaire answered by nurses		II–III
BMI 1y	kg/m^2	1y-questionnaire answered by nurses		II–III
Age AP	months	Timing of AP was calculated from fitted BMI curves	Data was collected by childcare and school nurses.	I–IV
BMI AP	kg/m^2	Predicted BMI was calculated using the estimated fixed and random coefficients	Data was collected by childcare and school nurses.	I–IV
Age AR	year	Timing of AR was calculated from fitted BMI curves	Data was collected by childcare and school nurses.	I–IV
BMI AR	kg/m^2	Predicted BMI was calculated using the estimated fixed and random coefficients	Data was collected by childcare and school nurses.	I–IV
BMI 3–6y, 7–10y and 11–15y	kg/m^2	Calculated by measured weight and height. Participants were stratified into UW<5^{th} pc, NW 5^{th}–85^{th} pc, OW 85^{th}–95^{th} pc and OB >95^{th} pc	Data was collected by childcare and school health nurses.	II–III
BMI 14y	kg/m^2	Self-reported by parents at 14y-questionnaire		I–IV
Age at menarche	years	Self-reported at 31y-questionnaire		I–II

Covariate	Reported	Method	Notes	Study
BMI menarche	kg/m^2	BMIs at menarche were estimated from the fitted BMI curves.		I–II
BMI 31y	kg/m^2	Measured weight: digital scale (kg), height: stadiometer (cm)	Study II–III: If measurement was not available, self-reported was used.	I–IV
WC 31y	cm	Measured midway between the lowest palpable rib and iliac crest		I
WHR 31y		Calculated HC / WC (Measured at the widest points of both trochanters)		IV
BMI 46y	kg/m^2	Measured weight: digital scale (kg), height: stadiometer (cm)	Study I and III–IV: If measurement was not available, self-reported was used.	I, III–IV
WC 46y	cm	Measured midway between the lowest palpable rib and iliac crest		I
WHR 46y		Calculated HC / WC (Measured at the widest points of both trochanters)		IV
Testosterone 31y and 46y	nmol/l		T at age 46 was used only in Study I	I, IV
Contraceptive use 31y	yes / no	“Have you ever used any hormonal contraception?”	Additional: “Are you currently using contraception?”	I–II
Medication 31y	yes / no	“Write down the medicines that you are taking at the present.”	Use of testosterone, statin and opioids was considered	IV
Alcohol use 31y	g/day	“Do you use alcohol, and if so, what kind, how often and how much?”		III–IV
Smoking 31y and 46y	active / former or occasional / non-smoker	“Have you ever smoked? / Do you currently smoke?”	Smoking at age 46 was used only in Study I	I–IV
Education level 31y and 46y	basic / secondary / tertiary	“Your basic education?” and “Your occupational education?"	Depicts SES. Education at age 46 was used only in Study I	I–IV
Marital status 31y and 46y	ever been in a relationship / single	“Your marital status: married, cohabiting, single, divorced, widowing?”	Being married or cohabiting with the same sex were excluded	II–III

4.6 Data analysis and statistical methods

IBM SPSS Statistics for Windows, Version 22.0 and 25.0. (Armonk, NY: IBM Corp.) was used to assess differences between the study groups, and to perform the regression analyses. RStudio version 3.3.2 was used for the longitudinal modeling and derivation of BMI trajectories from birth to 17 months, and from 18 months to 13 y of age (*Study I* and *IV*). Modeling was carried out separately in infancy and childhood. Briefly, the longitudinal BMI linear mixed-effect model was fitted using logarithmically transformed BMI as the outcome, and the predicted timing of AP and AR was calculated using estimated fixed and random coefficients.

Differences in the continuous variables were analyzed by an independent t-test, a Mann–Whitney U test, a one-way analysis of variance or a Kruskal–Wallis test, as appropriate. Continuous data was presented as means ± standard deviations (SD). To assess differences in the categorical parameters, a chi-square test was used. For these tests, the results were reported as prevalence (%), and odds ratios (OR) with a 95% confidence interval (95% CI), respectively. A p-value < 0.05 was considered statistically significant. A Bonferroni correction was used for additional analyses in different age groups, when needed (*Study III*).

Multivariable analyses were conducted using binary logistic regression modeling. The results were reported as OR with 95% CI. Variables for the adjustment models were selected according to the directed acyclic graph (DAG) in *Study II* and *III* (Fig. 7) (www.dagitty.net). The results were adjusted for the following variables: *Study I*: mother's pre-pregnancy BMI and smoking at the end of pregnancy, gestational age, BMI at ages 31 and 46, WC and testosterone at age 31; *Study II*: marital status during the reproductive age, smoking and education at age 31 and PCOS; *Study III*: birth weight, marital status during the reproductive age, and smoking and education at age 31; and *Study IV:* mother's pre-pregnancy BMI and smoking at the end of pregnancy, birth weight and gestational age, alcohol consumption, education, smoking and WHR at age 31.

Linear and quadratic associations between the number of children (the birth of the 6th or any subsequent child was not considered since only 2.9% of the participants had more than 6 children), and birth weight (*Study III*) and BMI at 14 years (*Study II* and *III*) were assessed with regression models. Results were adjusted for birth weight, marital and smoking status, as well as the educational level at age 31 (*Study III*).

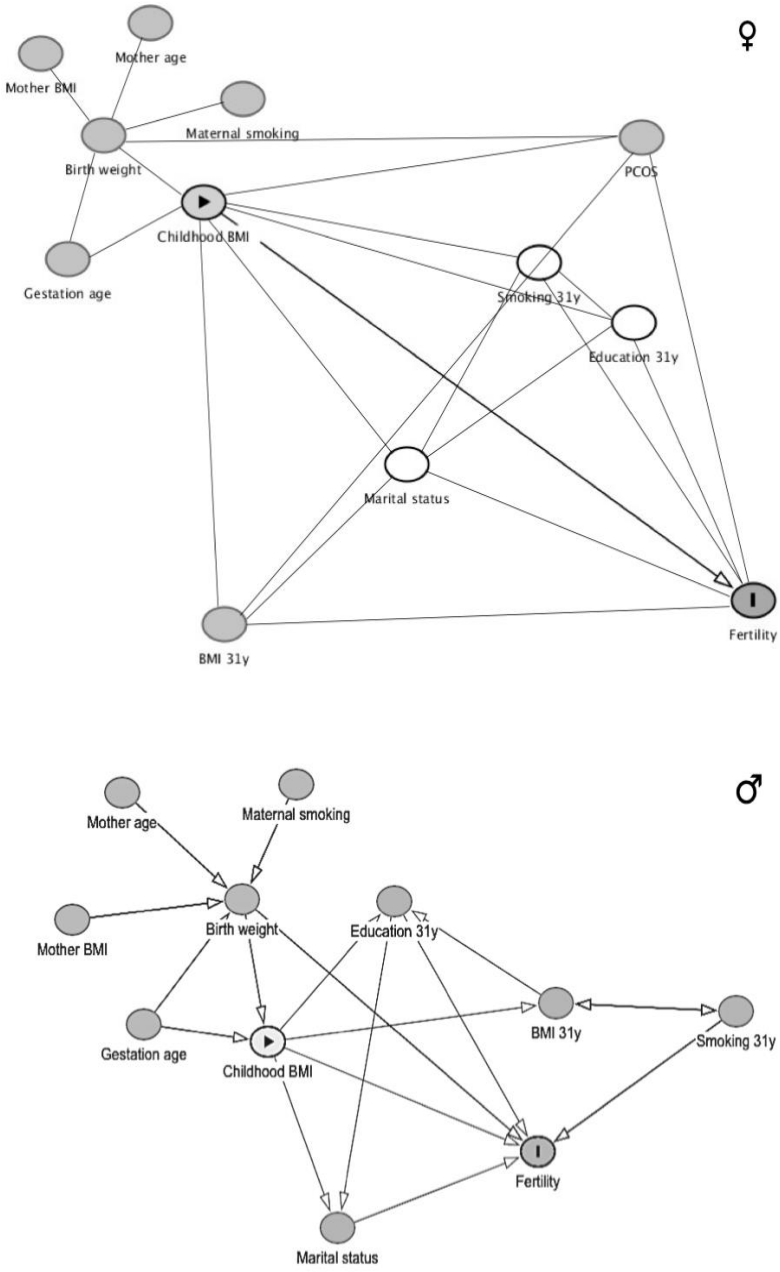

Fig. 7. DAG in the NFBC66: Fertility was considered as the outcome and childhood BMI as the primary exposure.

Table 12. Subjects, main study parameters and main results of Studies I–IV.

Study details	Study I	Study II	Study III	Study IV
Number of subjects	Women with PCOS, i.e., OA+H, at age 31 and/or self-reported PCOS diagnosis by age 46 (n = 280), controls (n = 1 573)	Female: decreased fecundability (n = 357), infertility assessment (n = 563), infertility treatment (n = 441) and childlessness (n = 607), controls (n = 2 381)	Male: infertility assessment (n = 390), male factor infertility (n = 111), infertility treatment (n = 259) and childlessness (n = 969), controls (n = 2 856)	Men with low T (T < 12.1 nmol/l) at age 31 (n = 132), controls (n = 2 561)
Main study parameters	BW, age and BMI at AP and AR, BMI trajectory from birth until age 46y	BW, UW, OW, and OB at ages 3–6, 7–10, and 11–15, age and BMI at AP and AR	BW, UW, OW, and OB at ages 3–6, 7–10, and 11–15, age and BMI at AP and AR	Prenatal outcomes, BW, age and BMI at AP and AR, BMI trajectory from birth until age 46
Main results	BW was lower; there was more prematurity, and AR age was earlier in women with PCOS independently of adulthood BMI. BMI from AR onwards was higher in women with PCOS.	Girls with obesity at mid-childhood and pubertal age had an increased risk of infertility and childlessness independently of marital status or the presence of PCOS.	Lower BMI in early childhood was associated with an increased risk of infertility and childlessness independently of marital status. OW/OB in early childhood was associated with a decreased risk of infertility.	Mothers' obesity and earlier age at AR were associated with an increased risk of low T independently of adulthood abdominal obesity. BMI from AR onwards was higher in men with low T.

5 Results and Discussion

5.1 Infertility in the NFBC66 (Studies II and III)

In the whole study population, 4 382 women and 4 128 men reported that they had attempted to have children before age 46, and 4 549 women and 4 077 men were registered with at least one offspring (Fig. 6). In all, 1 104 (25%) women and 1 272 (31%) men reported some fertility problems (decreased fecundability (only women), infertility assessment or infertility treatment) or remained childless.

Due to a significant overlap between fertility outcomes, most of the subjects were included in several infertility outcome groups. The overlap between infertility assessment and treatment was particularly extensive. On the other hand, only 18% of women and 8% of men who remained childless had been treated for infertility, and only 23% and 29% of those who received treatment, remained childless, depicting that these subgroups have different backgrounds: childless men and women were more often without any long relationship (Table 13) and therefore had a lower probability of achieving pregnancy. Male factor infertility was diagnosed in 28.5% of the cases who had undergone infertility assessments, which is in line with the literature (Agarval et al., 2021; Anderson et al., 2009).

5.1.1 Baseline characteristics of the participants (Studies II and III)

Smoking and lower education were less common in men with infertility problems. Smoking was also less common in men who had remained childless by age 50. Women and men with infertility assessment and treatment were more often higher educated. However, childlessness was more common in the low education group in men, whereas women with higher education were more often childless. These differences may be explained by socio-psychological factors and would deserve specific analyses for further studies. In men, BMI at age 31 or 46 was not associated with infertility parameters or childlessness, whereas in women, higher BMI at age 31 and 46 were associated with decreased fecundability, but not with other parameters. These differences are in line with previous studies showing that OB women were at a higher risk of infertility and prolonged TTP (Brewer & Balen, 2010; Crujeiras & Casanueva, 2015; Hahn et al., 2014; Rich-Edwards et al., 1994).

Table 13. Characteristics of the infertility study population of NFBC66.

Parameters (mean ± SD or %)	Female					Male				
	No Infertility (controls)	Decreased fecunda-bility	Infertility assessment	Infertility treatment	Childless	No infertility (controls)	Infertility assessment	Male factor infertility	Infertility treatment	Childless
	n = 2381	n = 357	n = 563	n = 441	n = 607	n = 2856	n = 390	n = 111	n = 259	n = 969
Maternal										
Pre-pregnancy BMI *kg/m²*	23.0 ± 3.1	22.9 ± 3.1	23.0 ± 3.3	22.0 ± 3.2	23.3 ± 3.2	23.9 ± 9.8	23.4 ± 9.6	22.7 ± 10.8	24.0 ± 9.6	23.6 ± 9.2
Age *year*	27.7 ± 6.6	27.6 ± 6.7	27.6 ± 6.6	27.3 ± 6.4	28.1 ± 6.9	27.9 ± 7.1	28.3 ± 7.2	26.9 ± 6.9	28.1 ± 6.9	28.5 ± 6.9
Smoking in pregnancy *%*	15.5	17.4	16.3	17.2	15.0	14.5	14.1	19.6	17.8	16.8
Index person: Childhood										
Birth weight *g*	3396 ± 496	3380 ± 496	3394 ± 507	3409 ± 496	3399 ± 522	3548 ± 536	3555 ± 540	3524 ± 559	3560 ± 564	**3495 ± 559**
Gestational age *week*	38.6 ± 7.9	38.7 ± 7.2	38.6 ± 7.8	38.6 ± 7.7	38.7 ± 7.6	40.0 ± 1.9	40.0 ± 1.8	39.9 ± 1.9	40.1 ± 1.8	39.9 ± 1.9
Age AP *month*	9.1 ± 0.43	9.1 ± 0.37	9.1 ± 0.35	9.1 ± 0.37	9.1 ± 0.39	9.1 ± 0.43	9.1 ± 0.37	9.1 ± 0.39	9.1 ± 0.38	9.1 ± 0.35
BMI AP *kg/m²*	17.8 ± 0.78	17.8 ± 0.88	17.7 ± 0.85	17.7 ± 0.86	**17.7 ± 0.81**	18.2 ± 0.79	18.2 ± 0.75	18.2 ± 0.74	**18.1 ± 0.75**	**18.1 ± 0.77**
Age AR *year*	5.57 ± 0.81	**5.4 ± 0.95**	5.54 ± 0.94	5.55 ± 0.95	**5.48 ± 0.96**	5.72 ± 0.81	5.68 ± 0.78	5.7 ± 0.80	5.70 ± 0.81	**5.67 ± 0.92**
BMI AR *kg/m²*	15.3 ± 1.1	15.3 ± 1.3	15.3 ± 1.2	15.3 ± 1.1	15.3 ± 1.1	15.5 ± 0.94	15.5 ± 0.94	15.4 ± 0.86	15.4 ± 0.90	15.4 ± 1.00
BMI 14y *kg/m²*	19.4 ± 2.3	**19.8 ± 1.3**	19.5 ± 2.6	19.6 ± 2.6	**19.7 ± 2.6**	19.3 ± 2.5	19.3 ± 2.2	19.2 ± 2.6	19.2 ± 2.1	19.4 ± 2.8
Menarche age *year*	12.9 ± 1.3	12.8 ± 1.3	13.0 ± 1.4	13.0 ± 1.4	12.8 ± 1.3	-	-	-	-	-
Index person: Adulthood										
Ever been in relationship	94.4	96.1	**96.3**	**97.3**	**66.7**	94.6	**97.9**	96.7	**97.7**	**50.1**
PCOS	4.7	**16.1**	**16.8**	**18.1**	**6.8**	-	-	-	-	-
BMI 31y *kg/m²*	23.9 ± 4.2	**24.6 ± 4.9**	24.2 ± 4.8	24.2 ± 4.8	24.0 ± 5.0	25.4 ± 3.5	25.1 ± 3.2	25.5 ± 3.7	25.1 ± 3.0	25.4 ± 4.1
BMI 46y *kg/m²*	26.4 ± 5.1	**27.2 ± 4.9**	26.7 ± 5.4	26.7 ± 5.5	26.5 ± 6.2	27.3 ± 4.2	27.0 ± 3.3	27.9 ± 5.2	27.2 ± 4.1	27.6 ± 4.7

Parameters (mean ± SD or %)	Female					Male				
	No Infertility (controls)	Decreased fecunda-bility	Infertility assessment	Infertility treatment	Childless	No infertility (controls)	Infertility assessment	Male factor infertility	Infertility treatment	Childless
	n = 2381	n = 357	n = 563	n = 441	n = 607	n = 2856	n = 390	n = 111	n = 259	n = 969
Smoking 31y %										
Non-smoker	48.5	53.1	51.5	52.2	49.0	35.0	**44.2**	36.3	**44.3**	**40.8**
Former / occasional	27.2	23.4	24.6	25.9	**22.4**	28.6	27.8	25.5	30.3	**22.6**
Active smoker	24.8	23.4	23.9	21.9	**28.6**	36.4	**28.0**	38.2	**25.4**	36.6
Education 31y %										
Basic	9.1	7.3	7.3	7.5	7.5	12.2	**6.4**	**9.6**	**7.3**	14.2
Secondary	73.9	75.1	69.7	70.1	67.7	71.8	71.1	71.3	68.2	73.1
Tertiary	17.0	17.6	**23.0**	**22.4**	**24.8**	15.9	**22.4**	**19.1**	**24.5**	**12.7**
Number of children	2.7 ± 1.7	**1.9 ± 1.6**	**1.6 ± 1.5**	**1.6 ± 1.4**	NA	2.7 ± 1.7	**1.6 ± 1.5**	**1.6 ± 1.6**	**1.6 ± 1.5**	NA

p < 0.05, compared to controls

5.1.2 Prenatal factors and birth weight

Prenatal parameters or gestational age did not correlate with any fertility outcomes in women or in men (Table 13). In women, BW did not associate with fertility outcomes, but in men, lower BW and SGA were associated with an increased risk of childlessness: OR_{BW} 0.98, 95% Cl 0.97–0.99, p = 0.009 (Table 13) and OR_{SGA} 1.39, 95% Cl 1.06–1.83, p = 0.019 (Fig. 8). After adjusting for marital status, however, the associations between BW, SGA, and childlessness in men (adjusted aOR_{BW} 0.98, 95% Cl 0.97–1.01, p = 0.124 and aOR_{SGA}, 1.23, 95% Cl 0.88–1.72, p = 0.210) lost their significance. A linear trend for a positive association between BW and the number of children remained, even after adjusting for marital status in the regression analysis (p_{crude} = 0.002, $p_{adj.}$ = 0.068) (Fig. 9).

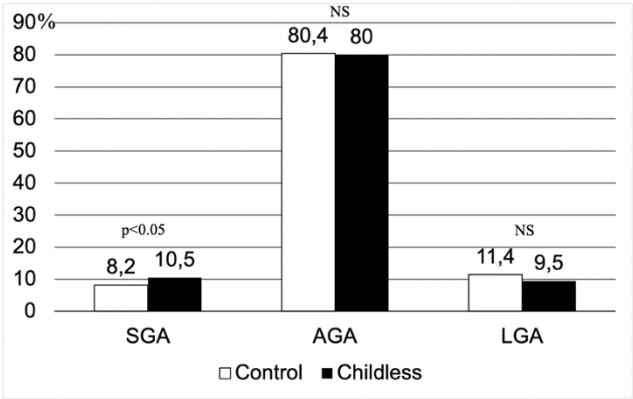

Fig. 8. Proportion of SGA, AGA, and LGA in men with childlessness and controls (men without any infertility problems) at age 50. Men who reported never having attempted to have children were excluded.

The finding that lower BW and SGA in men, but not in women, were associated with childlessness and a lower number of children is partly in line with previous results. A Danish cohort study following women trying to conceive showed no association between infertility problems and BW (Wildenschild et al., 2014). In contrast, a Swedish register-based study showed a lower probability for having children in both men and women born premature and with low BW (deKeyser et al., 2012).

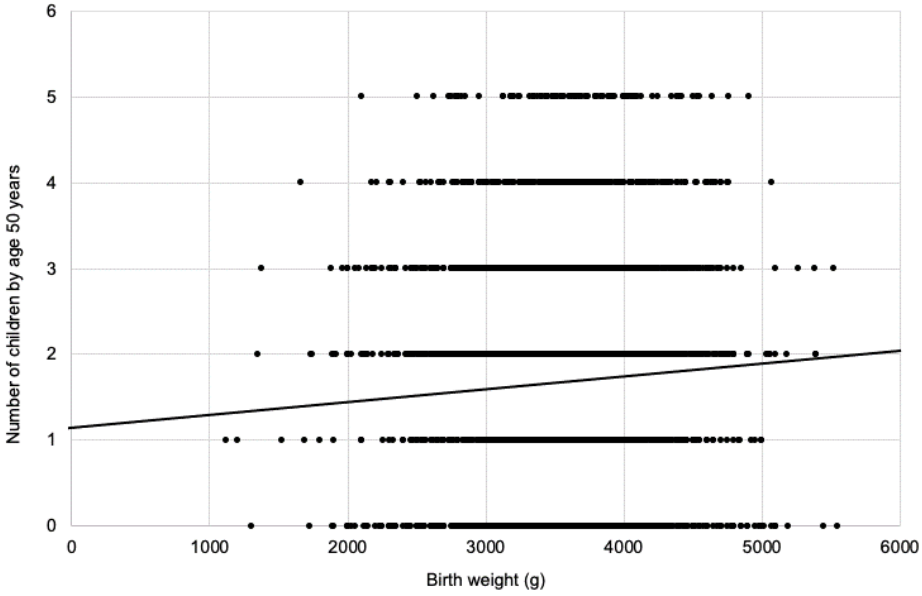

Fig. 9. Curve estimation between BW and the number of children by age 50 in men. Men who reported never having attempted to have children were excluded. © 2022 Laru et al. Written permission to reuse.

In men, many studies have shown that unfavorable fetal growth patterns in utero, especially SGA, is associated with decreased sperm counts (Boeri et al., 2016; Faure et al., 2015; Francois et al., 1997; Hart et al., 2016; Kahn et al., 2019) and decreased fertility (Boeri et al., 2016; deKeyser et al., 2012; Faure et al., 2015; Francois et al., 1997). However, contradicting results have been published, in which there was no association with decreased sperm counts and decreased fertility (Jensen et al., 2007; Ramlau-Hansen et al., 2010; Whitcomb et al., 2017). These discrepancies may be explained by differences in the study design, study populations, and lack of adjustments in some studies for confounding factors, such as marital status or attempts to have children. Biological mechanisms behind this association have been speculated. Barker's hypothesis proposes that impaired fetal growth is associated with later morbidities (Barker & Osmond, 1986), and some of the above-mentioned studies have shown that there is also a link with intrauterine environment and further infertility (Boeri et al., 2016; Faure et al., 2015; Francois et al., 1997; Hart et al., 2016; Kahn et al., 2019).

The association between lower BW and SGA with childlessness in men was lost after adjusting for marital status, which may indicate that this finding was

rather influenced by socioeconomic factors and the probability of establishing a long relationship. Marital status had a major impact on childlessness, as 33% of women and 50% of men who remained childless had never been in a long relationship. The reason for the difference between men and women remains to be clarified in further studies, as the correlation between BW and overall fertility appears to be a complex phenomenon wherein socioeconomic factors have a major impact (deKeyser et al., 2012; Ekholm et al., 2005; Swamy et al., 2008; van der Pal et al., 2021). It should be noted that, as the improvement of neonatal intensive care during the recent decades might have decreased the impact of SGA on social factors (Wildenschild et al., 2015), further studies are needed to clarify whether the present results remain true in younger cohorts.

5.1.3 Early childhood and adiposity peak & rebound

BMI at the age of AP was inversely associated with childlessness in women (OR: 0.84 [0.71–0.99]) and men (OR: 0.84 [0.71–0.99]) in the crude analyses, but the significances were lost in both sexes after adjusting for marital status. This may again suggest that the association between childlessness and lower BMI at the age of AP could be connected to psychosocial factors, and to the fact of either having or not having a partner. The age at AP had no effect.

The age at AR was earlier in women with decreased fecundability (5.57y ± 0.81 vs. 5.41y ± 0.95, p = 0.001), and in participants of both sexes with childlessness (Fig. 10). The significance concerning decreased fecundability and AR was vanished after the exclusion of women with PCOS (aOR 0.87, 95% Cl 0.72–1.05), but earlier AR remained as an independent risk factor for childlessness in both men and women (aOR_{women} 0.84, 95% Cl 0.73–0.97, aOR_{men} 0.85, 95% Cl 0.74–0.97) after adjustments, and the result did not change after excluding women with PCOS.

This is an important and novel finding. Early AR has been previously associated with adverse metabolic outcomes in adulthood (Hughes et al., 2014; Koyama et al., 2015; Péneau et al., 2016), which can affect fertility. Another possible explanation may be that early AR was also associated with PCOS in women and low T in men (see Chapter 5.2.3), which have been shown to associate with fertility problems (Brewer & Balen, 2010; Carrageta et al., 2019; Hackett et al., 2017; Koivunen et al., 2008; Nelson & Fleming, 2007; Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2008, Rees et al., 2016; Roos et al., 2011; West et al., 2014a; West et al., 2014b), but the association

persisted in women after the exclusion of PCOS cases. In men, fertility was not associated with T levels at age 31 (data not shown). Further studies are needed to confirm these findings and clarify the underlying mechanisms.

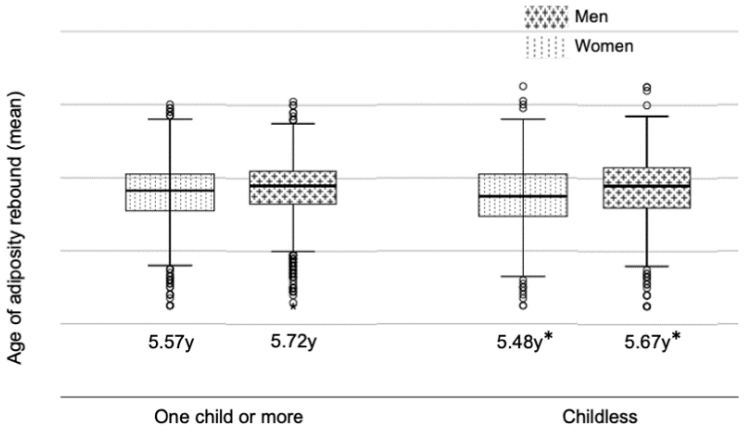

Fig. 10. Age at AR was associated with childlessness in both sexes. *p<0.001

In early childhood, 3.9% / 9.4% of the girls and 10.1% / 10.4% of the boys were classified as UW / OB; of those, 6.8% / 5.4% and 36.9% / 23% remained UW / OB at age 31, respectively. Interestingly, the prevalence of obesity (BMI > 95th pc) was the highest at age three in both sexes and decreased over time. In boys, being UW was significantly associated with an increased risk of infertility assessment and treatment, and childlessness (Fig. 11), and with a tendency for having fewer children later in life (UW 1.58 vs. normal weight 2.06, p = 0.068). In contrast, OW and OB boys in early childhood had a decreased risk of both infertility assessment, male factor infertility, and infertility treatment (Fig. 11).

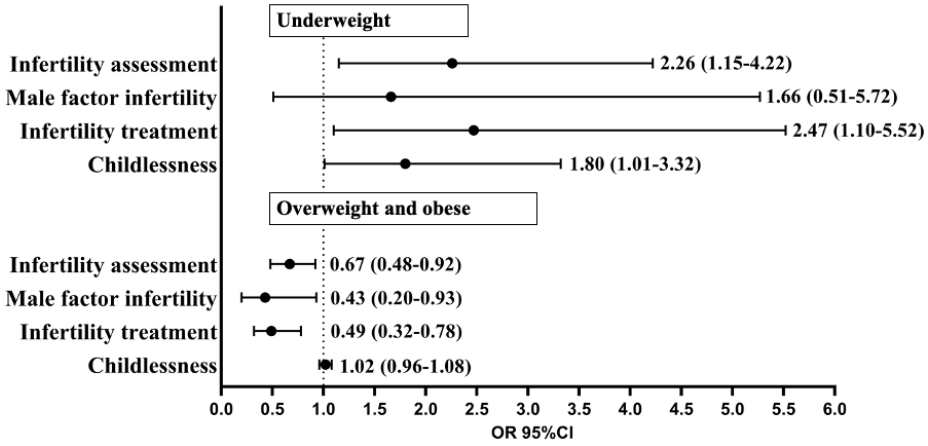

Fig. 11. Risk of later childlessness and infertility problems in UW and OW / OB boys in early childhood compared with NW boys. The analyses were made by using binary logistic regression modeling. Results are reported OR (95% CI). All parameters were adjusted for: BW, BW for gestational age, mother's smoking status, marital status, educational level, and smoking status. Men who reported never having attempted to have children were excluded from the analyses.

In girls, their weight class in early childhood was not significantly associated with later reproductive function, but interestingly, higher BMI at the age of AR seemed to be associated with a lower risk of infertility assessment (aOR 0.87, 95% Cl 0.76–0.98) and a tendency for a lower risk of infertility treatment (aOR 0.88, 95% Cl 0.75–1.01) in women without PCOS. This finding is similar with the findings in boys, for which higher BMI in early childhood seemed to be beneficial.

In two previous studies in girls, the association of high BMI in early childhood (aged 7 and aged 5 to 9) with reproductive performance has shown either a higher risk of childlessness but not infertility in obese girls (Jacobs et al., 2017) or no association (Lake et al., 1997). In boys, an Australian study showed that an optimal BMI trajectory through childhood was associated with better testicular function in adulthood (Hart et al., 2016), but another study showed no association between prepubertal BMI and semen parameters (Ramlau-Hansen et al., 2010). This is the first study on the association between early childhood BMI and infertility outcomes in men showing that especially in boys, higher BMI in early childhood was beneficial for reproductive function.

The mechanisms behind these findings may be multifactorial. Mini-puberty has shown to have an impact on reproductive capacity later in life (Boas et al.,

2006; Cortes et al., 1987; Kuiri-Hänninen et al., 2018), and growth in infancy and early childhood, especially in boys (Becker et al., 2015; Davis et al., 2019; Kiviranta et al., 2016; Varimo et al., 2016). In boys, previous studies have shown that a higher growth velocity in infancy and early childhood correlated with higher T levels in mini-puberty (Becker et al., 2015; Davis et al., 2019; Kiviranta et al., 2016; Varimo et al., 2016). In line with these findings, T substitution in early months in boys with KS has been shown to increase the total body mass and reduce fat mass (Davis et al., 2019). In girls, the nature of the association between female hormonal changes in mini-puberty and later growth has not been yet fully clarified (Kiviranta et al., 2016).

BMI in early childhood may not be the best tool to depict adiposity. The beneficial role of higher BMI might be due to higher fat-free / lean body mass rather than higher adiposity. Optimal steroid hormone function in mini-puberty may have a positive impact on early growth, and especially on the fat free body mass in childhood and later with better reproductive function in adulthood.

Early childhood is a complex developmental stage, marked by nutritional, genetic, and epigenetic factors (Kuiri-Hänninen et al., 2014; Stein et al., 2005). BMI during childhood is influenced by chronic illnesses and psychosocial environments that can strongly affect growth (de Onis & Branca, 2016; Kyle et al., 2015) and exert a negative impact on later fecundability (de Sanctis et al., 2013; Kenney et al., 2012). Childhood growth restriction increases the likelihood of IR, MeS, and cardiovascular diseases in adulthood (Barker & Osmond, 1986; Eriksson, 2011; Stein et al., 2005), which again are associated with infertility and disorders in sex hormone levels (Choy & Eisenberg, 2018; Eisenberg et al., 2014). More studies are needed to confirm these interesting novel findings, and to understand the relationship between hormonal changes in infancy, adipose accumulation later in life and their association with later reproductive function.

5.1.4 Mid-childhood and puberty

In mid-childhood, 7.0% / 6.7% of the girls and 5.8% / 7.3% of the boys were classified as UW / OB; of those, 4.9% / 56.8% and 4.5% / 31.7% remained UW / OB at age 31, respectively. In puberty, 10.0% / 5.6% of the girls and 10.1% / 7.2% of the boys were classified as UW / OB; of those, 7.3% / 74.6% and 43.5% / 41.1% remained UW / OB at age 31, respectively.

In boys, BMI classes in mid-childhood or puberty showed no significant association with any infertility parameters, childlessness, or the number of children.

In girls, OB in mid-childhood and puberty was associated with decreased fecundability at age 31 (mid-childhood: NW 11.7% vs. OB 20.7%, aOR 2.05, 95% Cl 1.26–3.35, puberty: NW 11.8% vs. OB 21.1%, aOR 2.04, 95% Cl 1.21–3.44). After excluding PCOS women, UW in puberty was associated with a tendency for higher risks of infertility assessment and infertility treatment (Fig. 12).

OB and OW girls in puberty were more often childless, independently of marital status and PCOS (Fig. 12). OW girls in mid-childhood and OB girls in puberty also had fewer children than normal weight girls (Fig. 13).

To clarify the type of association between BMI in adolescence and the number of children, curve estimation analyses were performed to explore linear, cubic, and quadratic associations between BMI at age 14 as a continuous variable and the number of children.

In girls, the number of children decreased linearly along with an increase in BMI at age 14 (number of children (y) = 2.88 – 0.03 × BMI, p = 0.033), but there was no cubic or quadratic association. In boys, the association showed an inverse J-shaped (i.e., quadratic) association (number of children (y) = -0.00465 × BMI^2 + 0.189 × BMI – 0.073, p = 0.002): UW, OW, and OB boys had less children compared to normal weight boys. After adjusting for marital status, the difference vanished in boys (p = 0.564) but not in girls (p = 0.041) (Fig. 14).

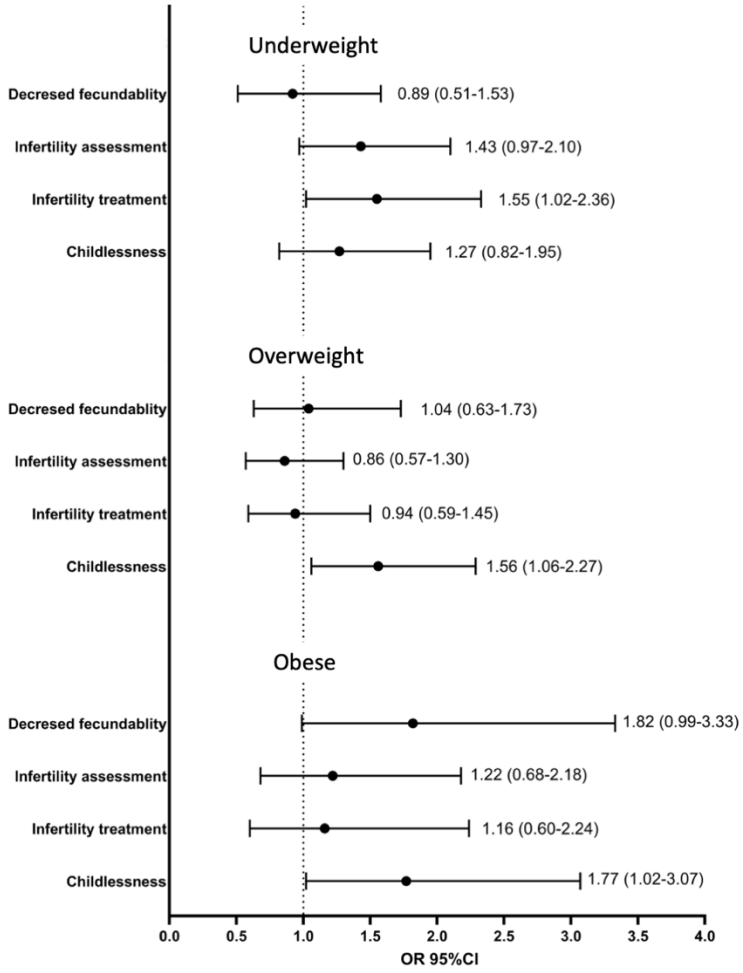

Fig. 12. Risk for later childlessness and infertility problems in UW, OW, and OB girls in puberty compared with NW girls. The analyses were made by using binary logistic regression modelling. Results are reported as OR (95% CI). All parameters were adjusted for: marital status, educational level, and smoking status at age 31. Women with PCOS and who reported to have never attempted to achieve pregnancy were excluded from the analyses.

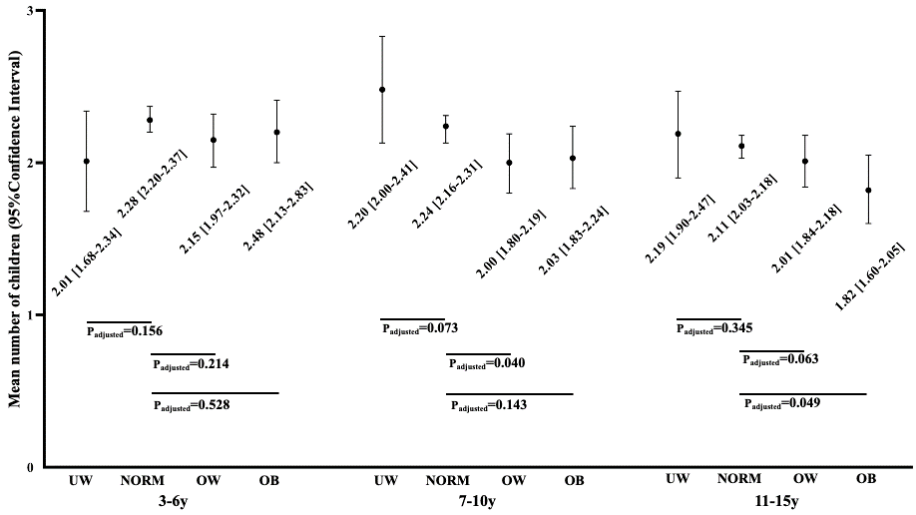

Fig. 13. Total number of children by age 50 in the female population in different weight groups at ages 3–6 (early childhood), 7–10 (mid-childhood), and 11–15 (puberty). The results were adjusted for: marital status during reproductive age, education and smoking at age 31. Women who reported to have never attempted to achieve pregnancy were excluded from the analyses. Normal weight was used as a reference group. © 2021 Laru et al. Written permission to reuse.

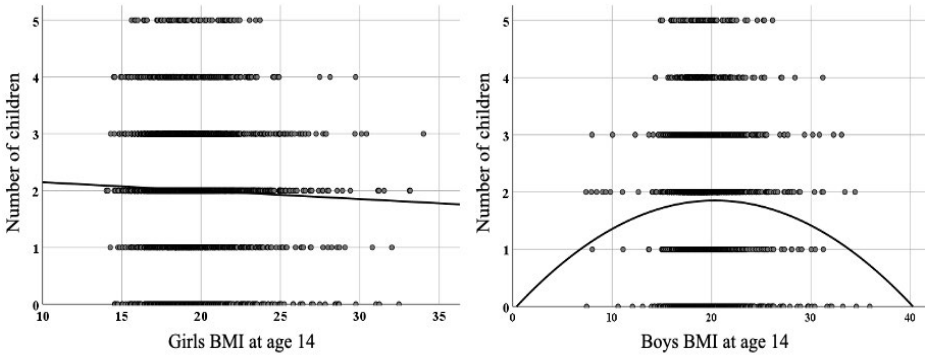

Fig. 14. Curve estimation between BMI at age 14 and the number of children.

Previous studies concerning girls' BMI in mid-childhood / puberty and later fertility have shown partly conflicting results. A recent study from Australia suggested that obesity, but not OW, at ages 7–11, but not at ages 12–15 increased the risk of

decreased fecundability and infertility assessments by age 34 (He et al., 2018). Moreover, in a study from the United States, girls with high adiposity before age 18 displayed more self-reported infertility problems and childlessness, independently of PCOS. In that study, obesity before age 12, but not between age 12 and 18, was associated with an increased risk of childlessness and infertility, but the difference vanished after excluding women with PCOS (Jacobs et al., 2017). These results differ partly from the present results, which may be due to differences of the study populations. Also, the numbers of participants were lower in previous studies compared to the present study, which may have decreased the statistical significance in previous studies.

In this study, there was an inverse linear association between the number of children and BMI at age 14 in women, and a tendency for UW girls in mid-childhood to have more children (Fig. 13), instead of the inverse J-shaped association detected in two previous Finnish studies (Jokela et al., 2007, 2008). Furthermore, in earlier studies, girls with eating disorders have exhibited an increased risk for later reproductive problems, especially an increased need for infertility assessment and treatment (Easter et al., 2011; Tabler et al., 2018), a lower number of children, or even childlessness (Jokela et al., 2007; Tabler et al., 2018). However, some studies have shown that girls UW in puberty or adolescence might have an even higher reproductive rate (Bulik et al., 1999; Easter et al., 2011). In the present study, girls´ UW in puberty was associated with more infertility assessment and treatment, but not with childlessness, suggesting that the reproductive capacity of UW girls can be restored with infertility treatments.

This pattern did not occur among adolescent boys, for which an inverse J-shaped correlation was found, in line with previous results (Jokela et al., 2007, 2008), i.e., boys with low and high BMI at age 14 had fewer children than normal weight boys. The significance was lost after adjusting for marital status, indicating that in men, growth patterns from adolescence onwards are strongly associated with their worse possibilities of establishing a long relationship and therefore their later reproductive performance. There are no other previous studies in men concerning the association between BMI and later reproductive function in these later age periods.

The peripubertal age has shown to be a decisive period regarding later metabolic and reproductive health, especially in girls. Physiological IR increases after the first signs of puberty, and normally returns to its prepubertal level when puberty is completed (Lindgren et al., 1990; Moran et al., 1999). In OB girls, IR is more pronounced and lasts longer, and is a strong predictor of adulthood obesity

and impaired metabolic profile (Maffeis et al., 2002; Moran et al., 1999; van Hooff et al., 2000). IR in adulthood is also strongly associated with PCOS and anovulatory infertility (Coviello et al., 2006; Ollila et al., 2017; Palmert et al., 2002). In the present study population, this association could not be assessed due to the lack of data on insulin resistance or HA during adolescence as possible hallmarks of PCOS.

In this study, OB girls had less children compared to controls after PCOS was considered. Previous studies have shown that women with PCOS deliver at least once as often as healthy women, and some population-based studies have even shown similar reproductive rates compared to control populations (Joham et al., 2015; Rees et al., 2016), suggesting that the impaired fertility linked to PCOS can be compensated by infertility treatments. However, their family size seemed to be smaller in some studies (Koivunen et al., 2008; West et al., 2014b). In the present study population, the association between obesity at mid-childhood or puberty and later infertility remained, even after excluding women with PCOS and after adjusting for marital status. This suggests that obesity in adulthood is causing infertility with various mechanisms (Brewer & Balen, 2010; Crujeiras & Casanueva, 2015; Hahn et al., 2014; Rich-Edwards et al., 1994). Unfortunately, there was no data on the participants´ BMIs at the time of conceiving.

The difference between boys' and girls' regarding reproductive function is interesting, and might depict some differences behind the causes of childlessness. In boys, lower and higher BMI might be associated with more problems in establishing a long relationship, whereas in girls, obesity may affect reproductive capacity more directly in adulthood. More studies are needed to explore the mechanism behind these phenomena and the impact of BMI in younger, more OB generations.

5.1.5 Menarche age

The mean age at menarche was 12.9y and the median was 13y (range: 9–18) in the entire female population. OB girls in each age group had earlier menarche than normal weight girls: early childhood: 12.4y, 95% Cl 12.1–12.6 vs. 12.9y, 95% Cl 12.8–12.9, $p < 0.001$; mid-childhood: 12.0y, 95% Cl 11.8–12.3 vs. 12.9y, 95% Cl 12.8–13.0, $p < 0.001$; puberty: 12.1y, 95% Cl 11.9–12.4 vs. 12.9y, 95% Cl 12.8–12.9, $p < 0.001$. Being UW or OW in early childhood was not associated with the age at menarche, but UW girls in mid-childhood and puberty experienced later menarche (mid-childhood: 13.3y, 95% Cl 13.0–13.5, $p = 0.015$; puberty: 13.6y, 95% Cl 13.4–13.8, $p < 0.001$) and OW girls experienced earlier (mid-childhood:

12.3y, 95% Cl 12.1–12.6, p < 0.001; puberty: 12.1y, 95% Cl 11.9–12.3, p < 0.001) menarche. There was no statistical evidence supporting that the age at menarche was associated with any of the measured outcomes regarding reproductive capacity (Table 13).

Early age of puberty has been associated with obesity and many metabolic disturbances later in life (Bleil et al., 2012; Lee et al., 2007), but the results concerning fertility are conflicting (Chen et al., 2015; Guldbrandsen et al., 2014; Jokela et al., 2007; Weghofer et al., 2013; Wise et al., 2011). The present study strengthens earlier findings that OB girls have earlier menarche and UW girls have later menarche, but there was no association between the age at menarche and later fertility, which is in line with results in some European populations (Helm et al., 1995; Wise et al., 2011). However, the association between higher menarche age and worse reproductive function have been detected in the Chinese population (Chen et al., 2015), and in studies from the United States (Weghofer et al., 2013) and Denmark (Guldbrandsen et al., 2014). The timing of menarche seems to be a complex factor to predict overall fertility because of differences in ethnicity, and because UW, chronic illnesses, and eating disorders in adolescence are also linked with the timing of menarche (Bosch et al., 2008; Fraser et al., 1988; Jacobi et al., 2004; Pereira et al., 2015).

5.2 Association of growth parameters with the development of PCOS in women and low T in men (Studies I and IV)

5.2.1 Characteristics of the study populations of the Studies I and IV

Table 14. Characteristics of the women with PCOS and men with low T.

Parameters (mean ± SD or %)	PCOS women n = 280	Control women n = 1 573	Low T men n = 132	Control men n = 2 561
Birth weight *g*	**3 357 ± 477**	**3 445 ± 505**	3 590 ± 534	3 581 ± 522
Gestational age *weeks*	38 ± 8	39 ± 7	39 ± 6	39 ± 7
Prematurity (born before 37th GW) *%*	**11.4**	**7.8**	5.3	6.9
Size for gestational age *%*				
SGA	7.8	8.6	7.9	6.7
AGA	83.2	79.9	76.4	82.8
LGA	9.0	11.5	15.7	10.5
Age AP *month*	9.1 ± 0.4	9.1 ± 0.4	8.9 ± 0.8	8.9 ± 0.7
BMI AP *kg/m*^{2}	17.7 ± 0.9	17.8 ± 0.8	18.2 ± 1.2	18.3 ± 1.1

Parameters (mean ± SD or %)	PCOS women n = 280	Control women n = 1 573	Low T men n = 132	Control men n = 2 561
Age AR *year*	**5.2 ± 1.0**	**5.6 ± 0.9**	**5.3 ± 1.0**	**5.8 ± 0.9**
BMI AR *kg/m²*	**15.6 ± 1.5**	**15.3 ± 1.5**	**15.8 ± 1.2**	**15.4 ± 1.0**
Age menarche *year*	12.7 ± 1.4	12.9 ± 1.2	-	-
BMI menarche *kg/m²*	**18.9 ± 3.1**	**17.9 ± 2.5**	-	-
BMI 14y *kg/m²*	**20.3 ± 2.8**	**19.4 ± 2.4**	**20.6 ± 3.0**	**19.3 ± 2.4**
BMI 31y *kg/m²*	**24.2 ± 5.6**	**22.6 ± 3.9**	**28.9 ± 5.2**	**25.1 ± 3.4**
BMI 46y *kg/m²*	**27.3 ± 6.3**	**25.3 ± 5.3**	**29.7 ± 5.8**	**27.1 ± 4.0**
WC 31y *cm*	**81.5 ± 15.9**	**76.0 ± 11.4**	**98.3 ± 13.1**	**88.5 ± 9.5**
WC 46y *cm*	**88.5 ± 14.8**	**84.0 ± 13.0**	**103.0 ± 11.2**	**97.1 ± 11.2**
WHR 31y	**0.84 ± 0.09**	**0.81 ± 0.08**	**0.95 ± 0.06**	**0.91 ± 0.06**
WHR 46y	**0.88 ± 0.06**	**0.86 ± 0.06**	**0.99 ± 0.05**	**0.97 ± 0.06**
Smoking 31y %				
Non-smoker	50.0	51.2	43.1	37.8
Former / occasional	23.3	26.4	24.6	26.9
Active smoker	26.7	22.4	32.3	35.2
Education 31y %				
Basic	12.9	8.5	13.1	11.4
Secondary	73.4	73.7	70.0	73.5
Tertiary	13.7	17.8	16.9	15.1

p < 0.05

5.2.2 Birth weight (Study I and IV) and prenatal parameters (Study IV)

Women with PCOS had lower BW (with a mean difference of 100 g) compared with controls, and they were more often born preterm, but the gestational age did not differ significantly between the two groups (p = 0.221) (Table 14). The difference remained after making adjustments for the mother's pre-pregnancy BMI and smoking during pregnancy, and gestational age (BW: aOR 1.03, 95% Cl 1.01−1.07). Mean GA, SGA, or LGA did not associate with PCOS. Prenatal parameters were not analyzed in this study.

In men, low T at age 31 was not associated with the mother's age, smoking at the end of pregnancy, and participants' own BW or GA. However, mothers' pre-pregnancy BMIs (23.2 vs. 24.0 kg/m^2, p = 0.022, aOR 1.06, 95% Cl 1.01−1.11) and obesity (aOR 2.43, 95% Cl 1.19−4.98) (Fig. 15) were associated independently (i.e., after adjusting for adulthood obesity of the index person) with low T. However, there was not a significant association with mothers' weight gain during pregnancy (Table 14). SGA did not associate with low T (SGA vs. AGA: OR 1.36,

95% Cl 0.71−1.25), but there was a trend for an association between LGA and low T (OR 1.63, 95% Cl 0.99–2.68, p = 0.052).

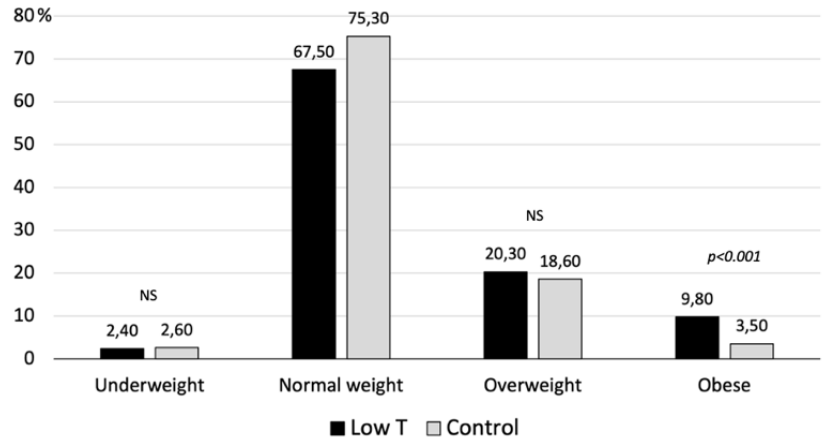

Fig. 15. Rates of maternal weight classes for the men with or without low T at age 31. Comparisons are done with the normal weight group as a reference group.

Low BW and especially IUGR have been shown to associate with adverse metabolic profiles in adulthood, both in men and women (Barker, 2007; Barker & Osmond, 1986; Eriksson et al., 2002; Jornayvaz et al., 2016; Risnes et al., 2011; Stein et al., 2005). In the present study, women with PCOS had a lower BW compared to controls. Previous results concerning women have shown conflicting results, as several studies (Davies et al., 2012; de Zegher et al., 2017, p. 201; Melo et al., 2010; Minooee et al., 2016; Pandolfi et al., 2008; Sadrzadeh et al., 2017; Stracquadanio & Ciotta, 2017), but not all (Aarestrup et al., 2021; Cresswell et al., 1997; Laitinen et al., 2003; Legro et al., 2010; Paschou et al., 2015; Sadrzadeh et al., 2003, 2016; Sverrisdóttir et al., 2008) are in line with the findings of this study. The strength of this study was that several factors associated with fetal growth were considered. However, the association was relatively weak, and no association between very low BW or SGA and PCOS was found.

In women, prematurity was more common in the PCOS group, but the mean gestational age did not differ between the groups. One previous study from Italy and one study from Finland (North Finland Birth Cohort 1986 (NFBC86)) have shown an association between prematurity and PCOS (Paalanne et al., 2021; Pandolfi et al., 2008), but another study from Sweden found no association (Sverrisdóttir et al., 2008). It has also been shown that women with PCOS have

more preterm births (de Wilde et al., 2017; Yu et al., 2016). As BW and gestational age are sensitive to numerous pregnancy-related factors, more studies regarding the association between prenatal outcomes and PCOS are needed.

BW or gestational age did not associate with low T levels in men, but there was a weak trend for LGA and low T levels. In previous studies, low BW (Boeri et al., 2016; Vanbillemont et al., 2010), SGA (Cicognani et al., 2002), and prematurity (Hart et al., 2016) have been shown to associate with decreased serum T levels in adulthood, although opposite results with no association have also been published (Ramlau-Hansen et al., 2010).

An important and novel finding was that maternal obesity was associated with low T in adult men, independently of adulthood SES, smoking, and abdominal obesity. Maternal obesity has been previously shown to be strongly associated with the offspring's obesity later in life, but many confounding factors (like socioeconomic aspects and lifestyle) also affect the risk of obesity (Drake & Reynolds, 2010; Eriksson et al., 2015; Kislal et al., 2020; Pirkola et al., 2010). The main biological mechanism behind this finding has been suggested to be the developmental programming occurring *in utero* (Desai et al., 2015; Kitsiou-Tzeli & Tzetis, 2017). Epigenetic changes are one possible mechanism connecting early development of excess adiposity with the future risk of adverse metabolic and hormonal phenotype (Şanlı & Kabaran, 2019). The elevated leptin concentrations associated with obesity and overnutrition during pregnancy might also explain this finding. Leptin concentrations have been shown to be higher in the cord blood of OB mothers, therefore exposing fetuses to higher leptin levels *in utero* (Eriksson et al., 2015; Kim et al., 2020). Children exposed to higher leptin levels prenatally had higher BW (Stefaniak et al., 2019; Walsh et al., 2014). Paradoxically, higher leptin levels have been associated with slower weight gain in infancy and early childhood (Karakosta et al., 2016; Parker et al., 2011), but in later childhood and adolescence, a positive correlation between cord leptin levels and adiposity has been shown (Simpson et al., 2017). More studies are needed to confirm these findings, and studies of the mechanism behind these phenomena are needed as well. Also, new studies to assess the role of prenatal factors in women with PCOS should be done in the future.

5.2.3 Adiposity peak and adiposity rebound

No differences were found between women with PCOS or men with low T and the control groups at the age of AP, whereas the longitudinal childhood BMI trajectory

data revealed earlier AR timing and higher BMI from the AR timing onwards until age 46, both in women with PCOS and in men with low T (Table 14, Fig. 16).

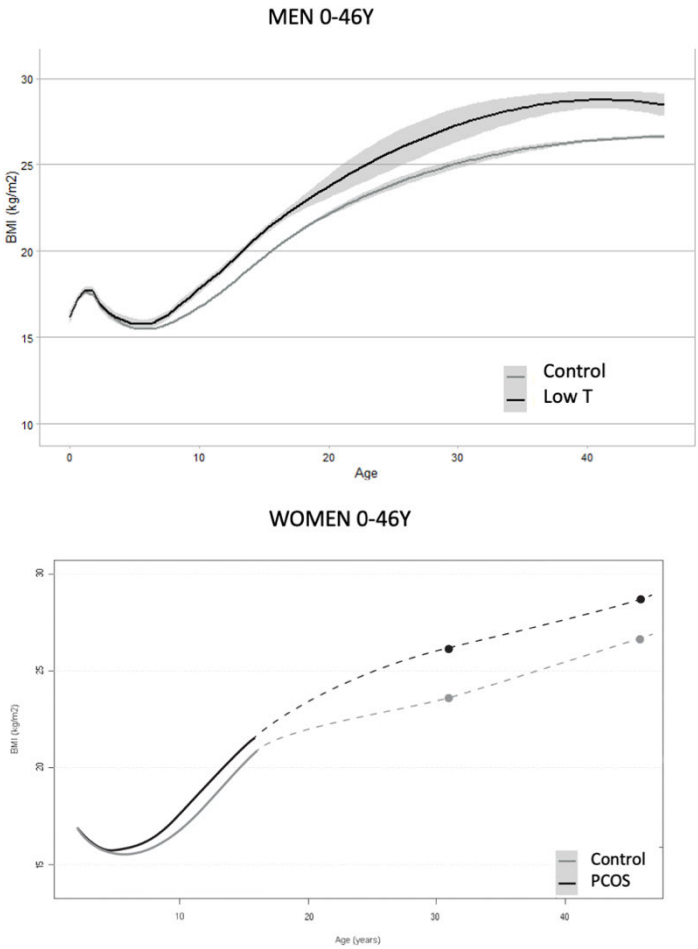

Fig. 16. BMI trajectories in women with PCOS and in men with low T, and controls.

Furthermore, women with PCOS (25.2% vs. 12.1%, $p < 0.001$) and men with low T (9.3% vs. 3.5%, $p < 0.001$) were overrepresented in the lowest AR quartile (AR under 5.1y in women and under 5.2y in men). The results did not change after adjustments: aOR_{PCOS} 2.46, 95% Cl 1.76−3.39 (adjusted for the mother's pre-pregnancy BMI, smoking at the end of pregnancy, gestational age, BMI at ages 31 and 46, and WC and T levels at age 31) and aOR_{lowT} 1.54 1.02−2.56 (adjusted for

the mother's pre-pregnancy BMI and smoking at the end of pregnancy, own BW and gestational age, alcohol consumption, education, smoking and WHR at age 31). In women with PCOS, the age at AR was the earliest in the group of women with the worse PCOS phenotype (OA+H) (Fig. 17). In women, no correlation between T levels at ages 31 (r = -0.07, p = 0.401) or 46 (r = -0.06, p = 0.504) and the timing of AR was found.

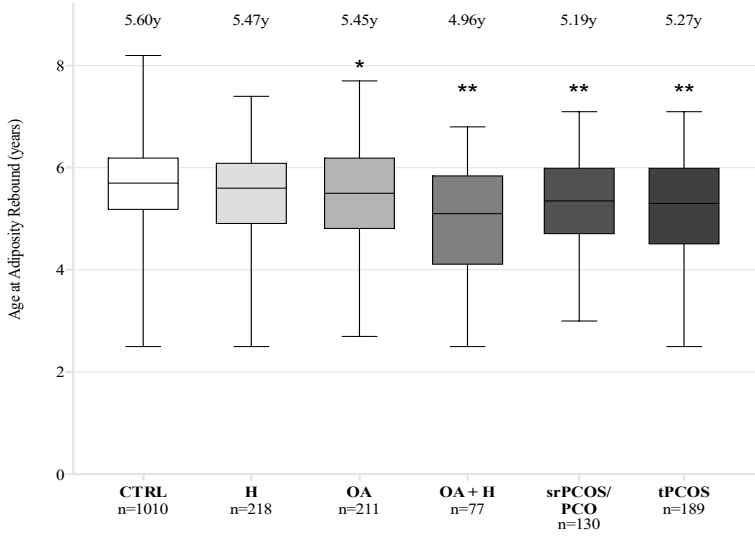

Fig. 17. Age at AR in control women, women with only one PCOS-symptom (OA, H), women with both PCOS-symptoms (OA+H), women who self-reported PCOS (srPCOS / PCO), and all women with PCOS by age 46 (tPCOS; includes women with OA+H at age 31 and self-reported PCOS at age 46). *p < 0.05, **p < 0.001 compared with controls.

Supporting these findings, early AR has previously been linked to adverse metabolic outcomes and obesity in adulthood, both in women and men (Hughes et al., 2014; Koyama et al., 2014; Péneau et al., 2016; Whitaker et al., 1997; Williams & Dickson, 2002). Similarly, PCOS in women (Franks et al., 1985; Ollila et al., 2016, 2017; Pinola et al., 2017; Puurunen et al., 2011; Teede et al., 2010; Teede et al., 2013) and low T levels in men (Antonio et al., 2015; Bhasin et al., 2011a; Camacho et al., 2013; Gyawali et al., 2018; Hall et al., 2008; Hart et al., 2019; Joyce et al., 2017; Ottarsdottir et al., 2018; Shi et al., 2013; Vaidya et al., 2012) have been associated with later metabolic abnormalities. The women reporting OA+H at age 31 and presenting a more severe PCOS phenotype had an even earlier

AR compared to the women reporting PCOS at age 46 or only one symptom, supporting the independent association between AR and PCOS.

These novel findings suggest that early AR and the deviation of BMI trajectories from the time of AR onwards may be the first sign of developmental processes towards PCOS in women and low T phenotype in men, independently of adulthood obesity. Low AR was also associated independently with childlessness both in men and women, implicating its role in the development of human reproductive function. More studies are needed to confirm these findings, and to explore triggering mechanisms especially during the prenatal period in women.

5.2.4 BMI at menarche and at age 14

Women with PCOS had a higher BMI at menarche than controls, but menarche age itself did not differ between the groups (Table 14). Also, in men, low T at age 31 was associated with higher BMI in puberty (Table 14). Previous studies have shown controversial results with an association of earlier menarche (Carroll et al., 2012; Dramusic et al., 1997; Rosenfield et al., 2009), later (Sadrzadeh et al., 2003), or the lack of any association (Ma et al., 2010; Pinola et al., 2012; Rajaeieh et al., 2014) with the development of PCOS.

The significant association between higher BMI at the age of menarche and later development of PCOS is in line with the former results of studies in this same population, where obesity at age 14 was associated with later PCOS (Laitinen et al., 2003; Ollila et al., 2016). Similar results also have been shown in other study populations (Aarestrup et al., 2021; He et al., 2020). In men, previous cross-over studies have shown an association between higher BMI in adolescence or early adulthood and low T at that age (Hart et al., 2015; Kerkhof et al., 2009), but this is the first follow-up study on this topic. Overall, the timing of menarche in women or puberty in men is a complex issue linked to ethnic differences, the mixing effect of weight, chronic illnesses, and eating disorders in adolescence (Bosch et al., 2008, Fraser et al., 1988, Jacobi et al., 2004, Pereira et al., 2015).

5.2.5 BMI change from childhood to adulthood

In men, the prevalence of OW and OB at ages 14 and 31, and of obesity at age 46, were higher in those with low T levels (Fig. 18). A similar finding was published earlier in women with PCOS in this same cohort population (Ollila et al., 2016), as well as in another study (Kakoly et al. 2017).

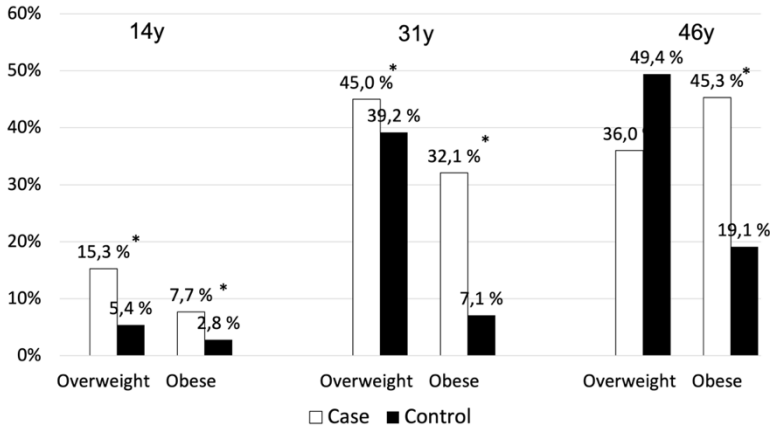

Fig. 18. Prevalence of overweight and obesity at ages 14, 31, and 46 in men with low T and controls. *p < 0.05, compared to normal weight group.

Women with PCOS and early AR had the highest BMI at ages 31 and 46, but not at the age of AR or at the age of menarche (Fig. 19). Men with low T and with early AR had the highest BMI at all ages, the greatest weight gain between ages 14 and 31, and the highest WC and WHR at ages 31 and 46 (Table 15). Cases with normal/late AR compared to control women and men with normal/late AR also had a higher BMI at ages 31 and 46 (Fig. 19).

Table 15. Characteristics depicting abdominal obesity in different AR groups in women with PCOS and men with low T at age 31.

Group	Early AR			Normal/late AR				
	PCOS	Control	p^1	PCOS T	Control	p^1	p^2	p^3
WC 31y *cm*	87.0 ± 17.1	83.0 ± 13.5	**0.016**	78.0 ± 11.9	74.5 ± 11.1	0.028	**< 0.001**	**< 0.001**
WC 46y *cm*	98.0 ± 14.6	90.8 ± 14.8	**0.014**	85.0 ± 11.1	83.0 ± 11.9	0.001	**< 0.001**	**< 0.001**
WHR 31y	0.86 ± 0.09	0.84 ± 0.08	**0.028**	0.81 ± 0.08	0.80 ± 0.07	0.398	**0.021**	**0.004**
WHR 46y	0.90 ± 0.06	0.87 ± 0.06	**0.005**	0.86 ± 0.06	0.86 ± 0.06	0.878	**0.002**	**0.003**
	Low T	Control	p^1	Low T	Control	p^1	p^2	p^3
WC 31v *cm*	102.8 ± 11.1	93.8 ± 10.4	**< 0.001**	93.7 ± 13.3	86.8 ± 8.2	**< 0.001**	**< 0.0001**	**< 0.001**
WC 46y *cm*	110.6 ± 13.6	102.6 ± 12.4	**0.003**	98.4 ± 13.4	95.6 ± 10.2	0.148	**< 0.001**	**< 0.001**
WHR 31y	0.98 ± 0.05	0.93 ± 0.06	**< 0.001**	0.94 ± 0.07	0.90 ± 0.05	**< 0.001**	**< 0.001**	**< 0.001**
WHR 46y	1.02 ± 0.06	1.00 ± 0.06	0.150	0.98 ± 0.06	0.97 ± 0.06	0.482	**< 0.001**	**< 0.001**

[1] Case *vs.* control in the early AR or normal/late AR groups, [2] Case + early AR *vs.* case + normal/late AR, [3] Control + early AR *vs.* control + normal/late AR

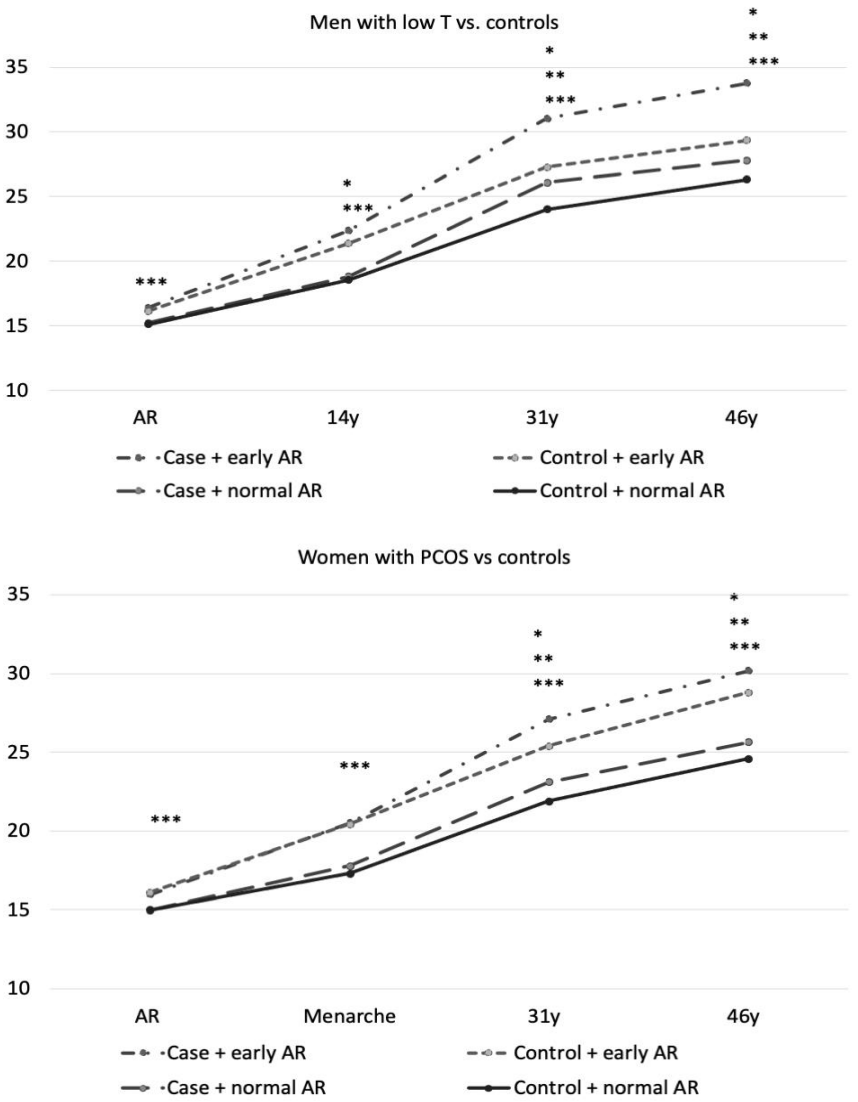

Fig. 19. BMI at the ages of AR, menarche / age 14 and ages 31 and 46 in men with low T at age 31 or women with PCOS (cases and controls). The study population was divided into four groups according to the occurrence of early or normal/late AR. The AR was considered early when it occurred before age 5.2 in boys and 5.1 in girls, as defined in this study population. p < 0.05 * Case vs. controls in the early AR groups, ** Case vs. controls in the normal/late AR groups, * Case + early AR vs. case + normal/late AR groups.**

The present results show that although early AR is related to adverse body composition, as well as in controls, the growth trajectories already deviate more significantly from the AR onwards in women with PCOS and in men with low T levels. Moreover, long-term outcomes, such as higher BMI and abdominal obesity in adulthood, were more severe in the participants with early AR. The association between metabolic disturbances and early AR has shown to be mainly driven by obesity (Hughes et al., 2014; Koyama et al., 2014; Péneau et al., 2016), but early growth trajectories may also be related to long-term metabolic outcomes, independently from adulthood BMI (Whitaker et al., 1998; Williams & Dickson, 2002). In line with this hypothesis, the association between early AR and PCOS or low T remained after adjusting for adulthood obesity in men and women, suggesting a strong positive interaction between early AR and these later disorders. There are probably numerous mechanisms affecting the relationship between the timing of AR, childhood growth, and hormonal function, independently of obesity.

Surprisingly, weight gain between ages 31 and 46 was smaller in men with low T levels compared to controls. A similar finding has been published concerning women with PCOS in this same cohort (Ollila et al., 2016). One explanation could be the loss of skeletal muscle mass in late adulthood in men with hypogonadism, as shown previously in men with functional hypogonadotropic hypogonadism (Dwyer et al., 2019). Another explanation may also be a better awareness of the metabolic risks linked to hypogonadism in these men or PCOS in women, at least in those aware of the diagnosis. More studies are needed to confirm these findings and the hypothetical underlying mechanisms.

5.3 Strengths and limitations of the study

The main strength of the present project is that it is conducted in an unselected large population-based cohort with a follow-up of growth data from the prenatal time to the end of the reproductive lifespan. This provides a unique opportunity to investigate the association between prenatal outcomes and early growth with fertility outcomes and sex hormone disorders later in life. The study population is also remarkably homogeneous regarding ethnicity. All measurements, except BMI at age 14, have been performed by trained professionals at all stages. The BMI growth data have been obtained from health registers of child health programs and school health care, which are available and free for all families. Data on deliveries are reliable due to the use of the Finnish Medical Birth Register and Population Register Centre, which together cover 100% of births in Finland. In studies

concerning reproductive capacity, all women and men, who had never attempted pregnancy, have been excluded. Childhood BMI growth trajectory data (such as the age at AR), which has shown its value as a tool to predict BMI and metabolic risks in adulthood (Koyama et al., 2014; Péneau et al., 2016), were analyzed separately.

This study also has some limitations. Despite the high participation rates throughout all collection points, children's growth data were not available for all participants. Gestational ages were not determined by means of an ultrasound, which may have affected the detection of differences between the study groups (e.g., size for gestational age). In different age groups in childhood, obesity was defined by the presence of at least one BMI value over the 95th pc in an age group, which might have caused over-diagnosis. According to recent literature, BMI does not remain constant through life, especially at the period from birth until the age of AR (Couto Alves et al., 2019; Koyama et al., 2014; Rolland-Cachera et al., 2006). In this study population, the prevalence of obesity between 6 months and 3 years was higher than expected. From AP to AR, the children are in a transitory phase between infancy and childhood, characterized by quick changes in BMIs when children are gradually losing "baby fat." Higher BMI at some points of this period might be normal and transient (Couto Alves et al., 2019; Koyama et al., 2014; Rolland-Cachera et al., 2006). This limitation may have decreased the significance of the association between childhood obesity and fertility outcomes.

In infertility studies (*Study II* and *III*), it was not possible to adjust the results for the BMI at the exact time of trying to conceive, as the BMI data was available only at age 31 when most of the women and men had already had their first child at that period (in 1997). It was neither possible to consider the partner´s BMI in the analyses. Infertility outcomes were self-reported, which can be considered as a limitation. Nonetheless, previous studies have indicated a good correlation between self-reported fertility treatments and medical records (Herbert et al., 2012; Stern et al., 2016), and the estimates are in line with previous data from developed countries showing an infertility prevalence of 5–15% (Anderson et al., 2009; Boivin et al., 2007; Herbert et al., 2012; Sun et al., 2019).

Another potential limitation of this study is that the diagnosis of PCOS was self-reported, as both the documentation of PCOS symptoms at age 31 and the assessment of a PCOS diagnosis at age 46 were based on questionnaires. Hirsutism might be over-reported by self-estimation, but it has been shown previously that the co-existence of self-reported OA and H can identify women with the typical endocrine, metabolic, and psychological profiles of PCOS (Karjula et al., 2017; Laitinen et al., 2003; Ollila et al., 2016, 2017; Taponen et al., 2003, 2004). Ovarian

ultrasonography was not performed at age 31, and it is possible that women with PCOM have been included into the control population, which may have decreased the differences between the groups.

T levels were assessed only by a single T sample for each participant. According to the general recommendations, at least two samples are recommended for a reliable determination of a T serum concentration (Bhasin et al., 2018; Bhasin et al., 2011a; EAU Guidelines, 2022; Khera et al., 2016, 2016; Lunenfeld et al., 2021; Mulhall et al., 2018; Nieschlag et al., 2005; Wang et al., 2008). However, to minimize potential bias, all blood tests were drawn in the morning when the physiologically higher T levels occur (Diver et al., 2003). Further, the LH values to evaluate the functional hypogonadism categories could be considered.

6 Conclusions and further study plans

1. In women, obesity in mid-childhood was associated with decreased fecundability at age 31, but not with a higher risk of other fertility problems or with childlessness. OW girls in mid-childhood had fewer children than their NW counterparts. The women who were OB in puberty were more likely to remain childless, to have fewer children, and to suffer more often from decreased fecundability compared to their NW counterparts, independently of marital status and PCOS. In addition, lower BMI in infancy was associated with childlessness and low BMI in early childhood and adolescence, along with an increased risk of later infertility treatment. Prenatal factors were not associated with infertility.
2. Men with lower BW, who were born SGA, and those who were UW during early childhood had an increased risk of childlessness and had fewer children in adulthood. In particular, the association between BW/SGA and childlessness was highly influenced by the decreased probability of having a partner. In contrast, being OW or OB during early childhood was independently associated with a decreased risk of infertility assessment, male factor infertility, and infertility treatments in adulthood. BMI after mid-childhood was not associated with infertility after marital status was considered.
3. In women, lower BW, prematurity, and higher BMI growth trajectory in childhood were associated with an increased risk of developing PCOS in adulthood. In women with PCOS, AR occurred earlier, BMI growth trajectories started to deviate early on from the age of AR, and the mean BMI remained higher thereafter until age 46. In this cohort, an AR drop of 1 year was associated with a 1.6-fold greater OR for a PCOS diagnosis by age 46, and the risk was independent of prenatal factors and adulthood obesity. Furthermore, women with PCOS and early AR presented the highest BMI, WC, and WHR at ages 31 and 46 compared with controls with early AR.
4. In men, low T at age 31 was strongly associated with maternal obesity, independently of other prenatal factors and adulthood abdominal obesity. The BMI growth trajectories deviated from the time of AR onwards, and remained higher than those of men with normal T levels until age 46; similar results were seen in women with PCOS. Weight gain was faster in men with low T until age 31. Men with both early AR and low T were at the highest risk of developing obesity in adulthood, suggesting a more severe phenotype in this group of men.

These findings suggest that early AR timing may be the first sign of a developmental process towards the impairment of reproductive function and hormonal disturbances in adulthood in both sexes. Given the well-known health risks related to OW and abdominal obesity, and the rising prevalence of maternal obesity, the results of this thesis study emphasize the importance of preventing obesity and the associated endocrine dysfunction that may also affect the offspring's reproductive health later in life. Optimal growth during early childhood seems to be very important for life-long fertility, especially in boys.

According to these results, OW and obesity in puberty have a strong influence on fertility, but only in girls. This study did not allow for clarification why this association is seen only in girls, but not in boys. There was not a possibility to clarify the effect of physiological IR in puberty and the mechanisms by which obesity modulates the hormonal system in this sensitive age, especially in girls. In boys, socioeconomic factors seemed to strongly affect fertility and the family size from adolescence onwards, as the association between the number of children and BMI in puberty was lost after the consideration of marital status. More follow-up studies are needed to understand the underlying mechanisms in these findings, and to investigate more deeply the causes behind these differences between sexes.

Especially in boys, the importance of optimal growth during the early years of life should be better recognized. The beneficial effect of higher BMI during early childhood on later reproductive function in boys needs further clarification. What are the mechanisms behind this finding? Are they associated with hormonal changes in mini-puberty? What is the role of a socioeconomic environment? Also, more research on the association between BMI in childhood, the quality of life, mental disorders, and SES is needed.

PCOS in women and low T at age 31 in men were associated with higher BMI already from childhood onwards. Further studies are also needed to clarify the less studied association between low T in men and the development of metabolic disturbances, glucose metabolism disorders, and cardiovascular diseases in adulthood. The NFBC66 offers a good opportunity to study these associations, and to perform a follow-up until senescence. Also, studies in younger cohorts, such as the NFBC86, could bring new information in populations with higher BMI and more metabolic risk factors. Lastly, the adverse effects of maternal obesity on later hormonal disturbances in men and women should be kept in mind.

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Original publications

I Koivuaho E., Laru J., Ojaniemi M., Puukka K., Kettunen J., Tapanainen J. S., Franks S., Järvelin M-R., L. Morin-Papunen L., Sebert S., Piltonen T. T. (2019). Age at adiposity rebound in childhood is associated with PCOS diagnosis and obesity in adulthood—longitudinal analysis of BMI data from birth to age 46 in cases of PCOS. *International Journal of Obesity, 43*(1), 1370–1379. https://doi.org/10.1038/s41366-019-0318-z.

II Laru, J., Nedelec, R., Koivuaho, E., Ojaniemi, M., Järvelin, M-R., Tapanainen, J. S., Franks, S., Tolvanen, M., Piltonen, T. T., Sebert, S., & Morin-Papunen, L. (2021). BMI in childhood and adolescence is associated with impaired reproductive function—A population-based cohort study from birth to age 50 years. *Human Reproduction, 36*(11), 2948–2961. https://doi.org/10.1093/humrep/deab164.

III Laru, J., Ojaniemi, M., Franks, S., Järvelin, M-R., Piltonen, T. T., Korhonen, E., Sebert, S., Tapanainen, J. S. & Morin-Papunen, L. (2022). An optimal growth pattern during pregnancy and early childhood associates with better fertility in men. *European Journal of Endocrinology, 187*(6):847–858. https://doi.org/10.1530/EJE-22-0385.

IV Laru, J., Pinola, P., Ojaniemi, M., Korhonen, E., Laikari, L., Franks, S., Tapanainen, J. S., Niinimäki, M. & Morin-Papunen, L. (2023). Low testosterone at age 31 associates with maternal obesity and higher BMI from adiposity rebound in childhood until middle age — a birth cohort study. (*Submitted manuscript*).

Original publications are not included in the electronic version of the dissertation.

1704. Stoor, Katri (2023) Comparative studies in the Northern Finland Birth Cohort eye study

1705. Laukka, Elina (2023) Leadership in the context of digital health services : a hypothetical model

1706. Kauppila, Janna (2023) Sudden cardiac arrest in nonischemic heart disease : role of medication, substance abuse and initial rhythm

1707. Lanning, Katriina (2023) Pulmonary artery catheter compared with less invasive hemodynamic assessment in cardiac surgical patients

1708. Shakya, Bijay Ratna (2023) Fourier Transform Infrared spectroscopy for the assessment of skin cancer : a potential tool in cancer diagnostics

1709. Majuri, Tuomas (2023) Occupational and other outcomes in schizophrenia and other psychoses

1710. Koskenranta, Miro (2023) Sosiaali- ja terveysalan opettajien kollegiaalisuus ja kollegiaalisuusosaaminen ammatillisessa oppilaitoksessa sekä ammattikorkeakoulussa

1711. Hosio, Mayu (2023) The role of antidiabetic medication, statins, and menopausal hormone therapy in breast cancer among women with type 2 diabetes

1712. Säkkinen, Hanna (2023) Novel molecular factors in cardiac hypertrophic response

1713. Terho, Anna (2023) Frozen embryo transfer : long-term growth and health of singleton offspring

1714. Onnela, Anna (2023) Mental health promotion in comprehensive schools

1715. Myllyaho, Toni (2023) Association of adoptive family functioning and genetic liability for broad schizophrenia spectrum disorders with adoptees' psychiatric morbidity : special focus on duration of preadoption out-of-home care, parental loss and familial socioeconomic status

1716. Kujanpää, Linda (2023) Comorbidity, work ability, and disability retirement among women with polycystic ovary syndrome (PCOS) : a population-based analysis in the Northern Finland Birth Cohort 1966

1717. Luukkainen, Laura (2023) Epidemiology of early-onset frontotemporal dementia and molecular genetics of early-onset neurodegenerative dementia

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