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Long-term growth in offspring of infertile parents: a 20-year follow-up study

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Conflicts of interest

USK and BB reports personal fees from Merck, independent of the current study. LH, NHE, UBK and CO have no competing interests.

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ABSTRACT

Introduction: Long-term growth has been poorly investigated in boys and girls born by parents receiving fertility treatment. This study aimed to investigate the growth of children born following fertility treatment up to adulthood hypothesizing comparable growth in children born by parents receiving fertility treatment or by subfertile parents conceiving spontaneously to that of children spontaneously conceived by fertile parents.

Material and methods: In this historical long-term follow-up study the study population consisted of 4151 singletons born at term in the Aarhus Birth Cohort between 1990 and 1992. Parental lifestyle- and sociodemographic characteristics together with multiple measurements of weight and height were collected up to 20 years of age (6.1% of children contributed with at least one measurement for height or weight at age 20). The main outcome was difference in z-score for height (m) and weight (kg) between children conceived spontaneously (reference) and children conceived following fertility treatment, children conceived spontaneously by subfertile parents or unplanned. Results were adjusted for pre-pregnancy maternal and paternal body mass index, maternal educational level, smoking during pregnancy, maternal age, and parity.

Results: Singletons conceived following fertility treatment (n=164 (4.0%)) or by subfertile parents (n=271 (6.5%)) had comparable magnitude of weight estimates to children conceived spontaneously (difference in z-score per year 0.0148 (95% confidence interval (CI): 0.0026 - 0.0270) and 0.0069 (95%CI -0.0028 - 0.0165), respectively). Height estimates was also comparable between groups of children conceived following fertility treatment or by subfertile parents (difference in z-score per year 0.0022 (95% CI -0.0075 - 0.0119) compared to children conceived spontaneously (difference in z-score per year -0.0026 (95% CI -0.0103 - 0.0052). From the beginning of adolescence, we found lower weight for children born to subfertile parents and to parents receiving fertility treatment compared to spontaneously conceived children.

Conclusions: The main finding was equal long-term growth for children born at term by parents who received fertility treatment or parents waiting more than 12 months to conceive compared to spontaneously conceived children.

Keywords

Fertility treatment, growth, subfertility, infertility, child development.

Abbreviations

IVF: in vitro fertilization

CI: confidence interval

ABC Aarhus Birth Cohort

GDPR General Data Protection Regulation

ICSI intracytoplasmic sperm injection

Key message

Children born at term by subfertile parents and parents receiving fertility treatment have comparable long-term growth into adolescence.

INTRODUCTION

Although millions of children have been conceived following fertility treatment[1] the preconception handling of eggs and sperm and the potential postnatal health consequences are still a matter of concern.[2-6]

A number of meta-analyses have shown increased risk of adverse pregnancy outcomes in pregnancies achieved through fertility treatment compared with spontaneously conceived pregnancies, including low birth weight, preterm birth,[7] and congenital malformations,[8] even when taking into account the higher risk of multiples.[9]

Despite the consistent findings of low birth weight following fertility treatment studies on long-term growth of children born following fertility treatment are few and with divergent results. A recent meta-analysis by Bay et al. found lower weight in preschool children born after in vitro fertilization (IVF) compared with spontaneously conceived children.[10] However, the authors did not find differences in the weight after the age of 5 years. Only three of the 13 studies included in the meta-analysis contained growth data beyond the age of 10, [12] making the body of literature on long-term growth scarce. Since both low birth weight and early catch-up growth have been associated with risk of cardiovascular disease in adulthood in studies of spontaneously conceived children and IVF-children,[11-12] the need for research evaluating the growth pattern throughout childhood and into adulthood is essential.

This study aimed to investigate the growth of singletons born to subfertile parents or following fertility treatment up to the age of 20 years, while hypothesizing comparable growth in children born by parents receiving fertility treatment or by subfertile parents conceiving spontaneously to that of children spontaneously conceived by fertile parents.

MATERIAL AND METHODS

A cohort study was designed based on information from the Aarhus Birth Cohort (ABC). In 1989, the ABC was established at the Department of Obstetrics and Gynecology, Aarhus University Hospital to enable studies of exposures during pregnancy and adverse pregnancy outcomes.[13-14]

Danish-speaking pregnant women were included in the ABC at their routine antenatal visit in their second trimester (90% between gestational week 8-19) and completed self-administered questionnaires in the second and third trimester (90% between gestational week 27-34). The questionnaires were used to collect information on medical and obstetric history (e.g. fertility treatment) as well as maternal characteristics and lifestyle factors such as smoking and alcohol consumption. Information on the delivery and the newborn child was obtained from structured birth registration forms filled in by the attending midwife immediately after delivery. Women unable to speak Danish were not invited to participate in the ABC.

In 2001, when the children born within the ABC were 9-11 year old, their parents were asked for signed consent to collect the child's historical data from health care authorities and the school system (6-16 years old).[15] On average, all children in Denmark are offered nine routine health examinations by health visitors from birth to 16 years and seven visits at their family doctor from birth to 5 years of age. Measurement of height and weight is mandatory at these health examinations (according to guidelines by the Danish Health Authority, e.g. without shoes and outdoor clothes, empty pockets, dry nappy), and attendance is generally high.[16] Growth was measured by the general practitioner examining the child or by a nurse with calibrated equipment. Height was measured in whole cm without decimals. Weight was measured in kg with up to one decimal. In the period 2008-2012, information on all registered height and weight measurements for boys and girls up to 18-22 years of age was collected from medical records by contact to general practitioners and health visitors. Central registers were used to identify the children per general practitioner and health visitors. At the beginning of the 2008-2012-period, all the data was in paper record patient files and manually copied and subsequently transformed to electronic form, and computerized on site. From October 2011 to March 2012, mailed lists of children with missing information were sent to the general practitioners and health visitors. They were asked to feed the data electronically and an online system using SurveyXact was established for the purpose of this data collection. A log-on code to the online system was included with the list. General practitioners with more than 10 children on the list received economic compensation if they participated in the data collection. The health visitors were contacted per telephone ahead of the mailed list. We included the entire ABC cohort. Neither a priori nor post hoc power calculations were performed.

All live born children in Denmark are assigned a unique personal identification number, allowing accurate linkage of data between registries. Hence, growth measurements into adulthood were complemented for the boys by including data from the Danish Conscription Register.[17] In Denmark, all men are liable for military service, and they must register in one of the country's conscription districts, determined by their place of residence at the age of 18 years or shortly thereafter. Men providing a medical documentation for conditions that would disqualify them for military service may be exempted for the examination (approximately 15%). The conscript board examination includes standardized measurement of height and weight, and the data are recorded in the Conscription Register, available electronically since 2006. The study population was restricted to singletons born at term (>37 weeks of gestation). A flow chart of the selected study population is shown in Figure 1.

The self-reported exposure information of fertility treatment was collected antenatally and categorized into four groups: i) parents conceiving after fertility treatment (Fertility-treated), ii) fertile parents who conceived naturally within 12 months (Fertile), iii) subfertile parents taking more than 12 months before conceiving naturally (Subfertile), and a iiii) group of parents who reported the pregnancy as unplanned (Unplanned parenthood).

The weight-for-age (kg) and height-for-age (m) z-scores were standardized using the UK World Health Organization child growth standards.[18-19]

Estimates were adjusted for covariates identified a priori based on the existing scientific literature. The potential *a priori* defined confounders and covariates were collected by medical reports or questionnaires and defined as follows: maternal age (years), parity (0, ≥1), pre-pregnancy maternal height (m) and weight (kg), pre-pregnancy paternal height (m) and weight (kg), pre-pregnancy maternal level of higher education (none: <1 year, medium-long: 1-4 years and long: ≥5 years), maternal smoking status when completing the questionnaire at approximately gestational week 16 (yes/no), child height (m) and child weight (kg). Birth weight (kg) was included in a sub analysis. Due to the General Data Protection Regulation (GDPR), information of cohabitation could not be presented because of less than five observations for some of the exposure groups.

Statistical analyses

Descriptive characteristics were presented for fertility-treated parents, fertile parents, subfertile parents, and unplanned parenthood (Table 1). Independency within contingency tables was tested using chi-square test, Kruskal-Wallis test, and Bartlett's test as appropriate.

Stratified by sex, the difference in means with 95% confidence intervals (CI) over time for height and weight were modelled using restricted cubic splines in a regression and visualised for different pairs of fertility treatments using the Stata prefix command emc.[20]

A mixed effects linear regression model (random effects corresponding to intercept and slope) was used to estimate the unadjusted and adjusted difference in z-score with corresponding 95% CI for height and weight per year comparing children born by subfertile parents, fertility-treated parents and unplanned parenthood, respectively, to that of children born by fertile parents. Model validation was performed by plotting observed and fitted z-scores, inspecting QQ-plots of standardized residuals, and by comparing observed and expected correlations and standard deviations. The analysis was restricted to children born at term (n=4151) and adjusted for maternal and paternal pre-pregnancy height and weight, parity, maternal level of higher education, maternal age and maternal smoking during pregnancy. The adjusted analyses for difference in z-score for weight were additionally adjusted for child height, whereas the adjusted analyses for difference in z-score for height were additionally adjusted for child weight.

We omitted birth weight in the analysis of the overall effect of fertility treatment on growth, as we consider birth weight might be an intermediate on the pathway from exposure to outcome.[21] However, in a sensitivity analysis we adjusted for birth weight. In a sub-analysis we studied long-term growth patterns within each exposure group compared to the reference group stratified by age 0-10 year and 11-20 year, adjusted for the same covariates as in the main model.

The two-sided statistical significance level was set to 5%. The data analyses were conducted in Stata version 15.0, soft-ware (StataCorp LLC, College Station, Texas, USA).

According to Danish interpretations of the EU GDPR regulations, we may not report average values corresponding to an exact number of individuals less than five in the study (GDPR, regulation (EU), 2016/679 of 25 May 2018). Therefore, measurement contributions are listed in percentages.

Ethical approval

The follow-up study of the ABC in 2001 was approved by the Danish Central Ethics Committee on May 26, 2000 (No C-2000-15, ÅA 20000094).

RESULTS

A total of 10 907 women gave birth to singletons born 2 January 1990 to 6 May 1992 (Figure 1). Information on height and weight of 287 168 men aged 18-24 years recorded in the Conscription Register for the period January 31, 2006 to June 30, 2015 was merged to the 10 907 children in the ABC.

Among the 10 907 children, information on method of conception, including any parental fertility treatment, was available for 5033 children. Information of growth was missing for 719 children and 163 children were born preterm, leaving a final study population of 4151 children born at term with information of a least one measurement and up to 28 measurements of height and weight at various time points from birth to the age of 20 years (Supporting Information Table S1). The majority of the growth data was centralized around age 0-15 years. 91.8-93.3% (mean 92.5%) of the children had at least one measurement of height and weight in their first year of life. In the age group of 1-15 years, 28.0-55.0% (mean 42.1%) of the children had at least 1 measurement for height and weight. Only 1.1-4.4% (mean 2.6%) of the 16-17 year-olds had at least 1 measurement of growth. Due to data from the Conscription Register 15.1-26.8% (mean 20.9%) of the 18-19 year-olds contributed with at least 1 measurement of height and weight. Only 4.3-7.9% (mean 6.1%) of the 20 year-olds contributed with growth data. There were no systematic differences in the percentage of measurements in between conceptions groups. In the age group of 0-16 years, boys and girls contributed with equal number of growth measurements. For the 17-20 year-olds, girls only contributed with 3.2% of growth measurements.

Among the 4151 singletons, a total of 164 (4.0%) in the study population were conceived following fertility treatment, another 271 (6.5%) were conceived naturally but by subfertile parents, and the group of unplanned parenthood accounted for 1507 (36.2%) of the children. The remaining majority of the children eligible for the study were conceived by fertile parents N= 2209 (53.1%).

Parents reporting fertility treatment or subfertility were older at the time of conception, more often primiparous, and both parents were more often smokers compared to the group of fertile parents or parents reporting unplanned parenthood (Table 1).

Long-term growth in relation to UK World Health Organization standards

The variation in long-term growth within each exposure group and comparison to the reference group is shown in Table 2.

The change per year in z-score for weight was slightly higher for children born by fertility-treated parents compared to children born by fertile parents (Z=0.0148 (95% CI 0.0026- 0.070)). For children born by subfertile parents and unplanned parenthood, the change in growth rate for weight increased insignificantly.

The change per year in z-score for height showed no evidence of difference between the groups in either unadjusted or adjusted analyses (Table 2).

In a separate analysis, we also adjusted for birth weight. The results for all groups showed no evidence of difference between mode of conception and growth (data not shown), including the above difference in z-score for weight for children born by fertility-treated parents compared to children born by fertile parents (Z=0.0116 (95% CI -0.0009 - 0.0241)). In a sub-analysis we studied the variation in long-term growth within each exposure group and in comparison to the reference group stratified by age (Table 3). For 0-10 year olds the change per year in z-score for weight was slightly higher for children born by subfertile (Z=0.0157 (95% CI: 0.0003 - 0.0310)) and fertility-treated parents (Z=0.0206 (95% CI: 0.0011 - 0.0401)) compared to children born by fertile parents. For children born by unplanned parenthood, the change in growth rate for weight increased insignificantly in early childhood. The change per year in z-score for weight in 11-20 year olds showed no evidence of a difference between the groups in either unadjusted or adjusted analyses. The change per year in z-score for height also showed no evidence of a difference between the groups in either age groups (Table 3).

Long-term weight development

Figure 2 illustrates long-term growth from birth to 20 years of children born by subfertile parents or parents receiving fertility treatment compared to the spontaneously conceived reference group, stratified by sex. Boys born by subfertile parents had a comparable weight throughout childhood. However, from the beginning of adolescence the weight was found to be lower compared to spontaneously conceived children, and at age 20 it was approximately 2 kg lower. Similarly, boys conceived following fertility treatment had a lower weight from adolescence onward reaching a difference of approximately 4 kg at age 20. The same tendency was found in girls for both groups, although not reaching significant differences at any age.

Long-term height development

Boys and girls born by subfertile parents and parents receiving fertility treatment showed an overall equal height throughout childhood and adolescence compared to spontaneously conceived children. Girls born by parents receiving fertility treatment showed a tendency to lower height from adolescence onward compared to spontaneously conceived girls (Figure 2).

DISCUSSION

The overall finding in this long-term follow-up study of a Danish birth cohort of 4151 children was that the growth was equal in children born at term of the same sex and age irrespective of whether using absolute differences or z-score. A deviant finding from this overall trend of growth being equal was boys presenting with lower weight from adolescence onward when born by subfertile and infertile parents compared to spontaneously conceived children. The results of the girls followed the same trend.

The main study strength is the unique evaluation of 20 years long-term growth parameters in a large, historical cohort of girls and boys based on multiple individual measurements from childhood to adulthood and the statistical adjustment for strong confounding factors such as parental anthropometrics. Restricted cubic splines and the multilevel mixed-effects linear regression model took into account the contribution of measurements over time which makes our follow-up study a contribution to uncover growth all the way into adulthood for children born after fertility treatment. In our main analysis, we considered birth weight an intermediate variable and did not include it in the analysis because of the risk of underestimating a possible association.[22] However, in a sub-analysis we adjusted for birth weight and found similar trends and no clinically relevant differences in results, which indicates that birth weight is not a strong intermediate in our study.

Our study also has some limitations. First, the study population makes up 40% of the ABC cohort, which may limit the validity of the results. 54% had missing information on fertility treatment and further exclusions were due to lack of information on growth and preterm birth. This lapse can be related to the representativeness of fertility-treated or spontaneous pregnancy and introduce biased results in the case of exposure data not missing at random. However, we do not assume missing exposure information to be associated with the outcome and suspect the potential misclassification to be non-differential. A further limitation in the exposure assessment was the lack of validation of the exposure in the ABC. We trust the finding of no overall association of conception and long-term growth however we cannot rule out the possibility of type 2 error failing to reject a null hypothesis which is really false.

Second, regarding outcome measurements we only assumed a minor degree of non-differential measurement error, even though the growth measurements were not standardized. Calibrated standard equipment was used, and trained health care professionals have obtained the growth measurements independent of the exposure, and the multiple measurements of each individual have been obtained by different health care professionals. However, a considerable amount of families changed municipality or family doctor across the study period, which impeded collection of the growth data, even though central registers were used to identify these data. These missing data are assumed to be missing at random.

Third, the finding of lower weight in adulthood needs to be interpreted with caution due to the small number of children and few measurements between 16-20 years of age. In the 20th year we only had data on <10% of the cohort. Especially the girls contribute with the fewest growth measurements in this age group resulting in wide CIs.

Finally, a further limitation was that we were unable to investigate if different treatment modalities affect growth differentially. In our data, the fertility treated group consisted of couples receiving intrauterine insemination, IVF or intracytoplasmic sperm injection (ICSI), a heterogeneous group regarding etiological causes of infertility. A recent review explored IVF-ICSI differences on growth and found that evidence is lacking on long-term growth patterns -however, no growth differences were found in studies of early childhood growth.[23] In a cohort study by Hann et al. of 5200 assisted reproductive technology children, the children conceived following fresh assisted reproductive technology treatment weighed less and showed postnatal catch up growth compared to children born after frozen embryo transfer and spontaneous conception.[24]

The hypothesis of equal growth in children born by parents receiving fertility treatment compared to spontaneously conceived children has been supported in multiple studies. A number of studies have investigated the hypothesis of catch-up growth compensation for lower birth weight and reported comparable long term weight and height.[2, 4, 10, 12, 24-25] Yet, other studies have reported overall comparable growth.[26-28] In the systematic review and meta-analysis by Bay et al. from 2018 comparing 3972 children born after IVF/ICSI with 11 012 spontaneously conceived children, the pooled analyses did not reveal clinically relevant differences in growth for children above the age of 5 years, but included a limited number of studies with children beyond the age of 10 years.

In contrast to the findings of equal growth, several human and animal studies have suggested persistent influenced growth leaving room for discussion on altered metabolism and physiology of fetuses conceived by fertility treatment.[29-30] Hence, results were found for taller height of children conceived following fresh IVF-embryo transfer compared to naturally conceived children.[30] In a Finnish cohort of IVF singletons compared to a reference group examined up to the age of 3 years, IVF children weighed the least.[5] None of the studies adjusted for the potentially biasing intermediate variable birth weight.

The hypothesis of minor epigenetic changes of imprinted genes related to growth and metabolism in IVF-children has also been examined in different studies.[4-5, 29, 31] Miles et al. conducted a cohort study of 69 IVF-children aged 4-10 years. The IVF group was found to be taller with altered endocrine profiles of higher serum insulin-like growth factor (IGF)-I and IGF-II levels compared to an equally sized group of a spontaneously conceived reference group matched by age, sex, ethnicity and socioeconomic factor.[29]

In conclusion, the evidence on growth differences is still controversial and studies are difficult to compare due to methodological differences in follow-up time and confounder control and small sample sizes. However, while it is quite evident that children born following fertility treatment have a lower body weight at the time of birth and are more often born preterm, most studies show that this is compensated for at some point in the childhood. This does not, however, rule out the possibility of a more long-term effect with altered metabolism and potentially adverse growth and/or morbidity.

In our analyses, the tendency of weight being lower for boys and girls from adolescence and onwards does not seem to be associated with fertility treatment *per se* as this association is comparable for the group conceived by subfertile parents and by parents receiving fertility treatment, respectively. However, overall no trend was apparent when using z-score suggesting that any minor sex differences are most likely of little clinical importance.

Few other studies have investigated these groups separately. Bay et al. in their Danish national cohort study did not find growth differences between subfertile and fertility treatment groups up till the age of five.[25] However, Savage et al. found growth differences in children born after ovarian stimulation compared to children born by subfertile or fertile parents.[32] Still, the discussion is ongoing whether manipulation and in vitro handling of sperm and eggs cause epigenetic changes that may affect growth or if epigenetic alterations causes infertility.[23, 30, 33-36]

In the main analysis reported in Table 2 we found a significant z-score difference for the children conceived by parents receiving fertility treatment. In the stratified analysis by age we see that this difference is driven by minor growth differences in early childhood from 0-10 years, where both children by subfertile and fertility treated parents show significant results. However, the difference is not attributed any clinical significance. And we do not find growth differences between the groups from 11-20 years.

Our results speak against the hypothesis that the pathology or biology related to subfertility or infertility may influence long-term growth. The literature does not provide an unambiguous answer and more studies are needed to unfold mechanisms behind potential different growth patterns in different age groups and to test the findings in large epidemiological studies.

CONCLUSION

In this cohort, there was no association identified between height in adolescence and whether children were conceived naturally or after fertility treatment. There may be a weak but clinically unimportant association between children born after fertility treatment or to subfertile couples and their weight in childhood and a similarly weak association of weight being lower for boys in adolescence; however, further studies are warranted.

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Figure and table legends

Figure 1. Flowchart for the study population of long-term growth in offspring of infertile parents

Figure 2. Long-term weight and height in girls and boys of subfertile parents or parents receiving fertility treatment compared to children conceived spontaneous (n=4151)

___ Children spontaneous conceived (SC).
- - - Children born by subfertile parents (SC>12). Children born by parents receiving fertility treatment (FT).

Table 1. Baseline characteristics for fertile parents, subfertile parents, fertility-treated parents and unplanned parenthood and their children (n=4151)

Table 2. Unadjusted and adjusted difference in z-score (95% CI) for height and weight (0-20 years) comparing subfertile parents, fertility-treated parents and unplanned parenthood to fertile parents for children born at term (n=4,151)

Table 3. Unadjusted and adjusted difference in z-score (95% CI) for height and weight comparing subfertile parents, fertility-treated parents and unplanned parenthood to fertile parents for children born at term (n=4,151) stratified by age 0-10 years and 11-20 years.

Supporting Information legend

Table S1. Percentage of children with at least one measurement for height or weight at the specified age from 0-20 years and divided into conception groups (n=4151).

Characteristics	Fertile parents	Subfertile parents	Fertility-treated parents	Unplanned parenthood	P value
n(%)	2209 (53.2)	271 (6.5)	164 (4.0)	1507 (36.3)	
Child sex (male); n(%)	1241 (56.2)	136 (50.2)	86 (52.4)	857 (56.9)	0.17[a]
Gestational age (wk), median (iqr)	40.4 (1.7)	40.7 (2.0)	40.4 (1.7)	40.4 (1.9)	0.23[b]
Birth weight (g); mean±SD	3587 ±481	3564 ±503	3497 ±510	3588 ±504	0.26[c]
Birth length (cm); mean±SD	52.2 ±2.3	52.0 ±2.4	51.4 ±2.3	52.1 ±2.1	0.09[c]
Maternal age (years); mean±SD	29.7 ±4.6	30.7 ±4.7	32.2 ±3.9	29.4 ±5.0	<0.01[a]
Maternal parity (primiparous); n(%)	1094 (49.6)	155 (57.4)	121 (74.2)	773 (51.4)	<0.01[a]
Maternal smoking (smokers)[§]; n(%)	562 (25.4)	93 (34.3)	56 (34.2)	488 (32.4)	<0.01[a]
Maternal alcohol use (drink/wk)[§] ; n(%):					0.30[a]
< 1	1267 (58.2)	154 (57.9)	95 (58.3)	894 (61.1)	
1-4	848 (39.0)	100 (37.6)	61 (37.4)	522 (35.7)	
≥ 5	60 (2.8)	12 (4.5)	7 (4.3)	47 (3.2)	
Maternal educational level; n(%):					<0.01[a]
< 1 year	499 (25.5)	66 (26.6)	30 (21.0)	446 (35.3)	
1-4 years	1285 (65.5)	165 (66.5)	99 (69.2)	725 (57.5)	
≥ 5 years	177 (9.0)	17 (6.9)	14 (9.8)	91 (7.2)	
Maternal height (cm); mean±SD	168 ±5.9	168 ±6.2	168 ±5.7	168 ±6.0	0.43[c]
Maternal weight (kg); mean±SD	61.2 ±9.4	61.4 ±10.7	63.4 ±12.8	61.7 ±10.4	<0.01[c]
Paternal age (years); mean±SD	31.9 ±5.1	33.0 ±5.3	35.6 ±5.7	31.8 ±6.0	<0.01[c]
Paternal educational level; n(%):					0.01[a]
< 1 year	238 (13.1)	29 (12.5)	20 (14.9)	191 (17.4)	
1-4 years	1108 (60.8)	153 (66.0)	80 (59.7)	664 (60.6)	
≥ 5 years	476 (26.1)	50 (21.5)	34 (25.4)	241 (22.0)	
Paternal height (cm); mean±SD	181 ±6.3	182 ±6.2	181 ±7.0	181 ±6.5	0.31[c]
Paternal weight (kg); mean±SD	77.6 ±9.8	78.4 ±11.0	80.0 ±11.7	77.9 ±11.0	<0.01[c]
Paternal smoking (smokers)[§]; n(%)	700 (42.3)	116 (54.0)	57 (45.2)	489 (45.1)	<0.01[a]

[§] Gestational week 16

[a] Chi-square test

[b] Kruskal-Wallis test

[c] Bartletts test (Chi2)

wk: Week

iqr: Interquartile range

SD: Standard deviation

Fertile parents (conceived naturally within 12 months)

Subfertile parents (time to pregnancy >12 months before conceiving naturally)

Unplanned parenthood (the parents reported the pregnancy as unplanned)

	Unadjusted		Adjusted[§]	
	diff	(95% CI)	diff	(95% CI)
Weight[a]:				
SC>12 vs SC	0.0087	(-0.0004 - 0.0178)	0.0069	(-0.0028 - 0.0165)
FT vs SC	0.0162	(0.0048 - 0.0276)	0.0148	(0.0026 - 0.0270)
UP vs SC	0.0023	(-0.0024 - 0.0070)	0.0027	(-0.0026 - 0.0079)
Height[b]:				
SC>12 vs SC	-0.0015	(-0087 - 0.0057)	-0.0026	(-0.0103 - 0.0052)
FT vs SC	0.0078	(-0.0012 - 0.0169)	0.0022	(-0.0075 - 0.0119)
UP vs SC	0.0018	(-0.0020 - 0.0056)	0.0017	(-0.0025 - 0.0059)

[§]Adjusted for maternal height (m) and prepregnancy weight (kg), paternal height (m) and weight (kg), maternal level of higher education (<1, 1-4, ≥5 years), parity (0, ≥1), maternal age (years), maternal smoking at gestational week 16 (yes/no)

[a]Additionally adjusted for child height (m)

[b]Additionally adjusted for child weight (kg)

diff: Difference in z-score

CI: confidence interval

SC: Fertile parents (conceived naturally within 12 months)

SC>12: Subfertile parents (time to pregnancy >12 month before conceiving naturally

FT: Fertility-treated parents

UP: Unplanned parenthood (the parents reported the pregnancy as unplanned)

	Unadjusted		Adjusted[§]	
	diff	(95% CI)	diff	(95% CI)
Weight 0-10 years[a]:				
SC>12 vs SC	0.0097	(-0.0052 - 0.0247)	0.0157	(0.0003 - 0.0310)
FT vs SC	0.0232	(0.0041 - 0.0423)	0.0206	(0.0011 - 0.0401)
UP vs SC	0.0023	(-0.0055 - 0.0102)	0.0014	(-0.0070 - 0.0098)
Weight 11-20 years[a]:				
SC>12 vs SC	0.0081	(-0.0119 - 0.0281)	-0.0057	(-0.0263 - 0.0149)
FT vs SC	0.0003	(-0.0220 - 0.0286)	0.0019	(-0.0245 - 0.0284)
UP vs SC	0.0029	(-0.0075 - 0.0131)	0.0048	(-0.0063 - 0.0158)
Height 0-10 years[b]:				
SC>12 vs SC	-0.0057	(-0.0198 - 0.0083)	-0.0024	(-0.0163 - 0.0116)
FT vs SC	0.0178	(-0.0002 - 0.0358)	0.0105	(-0.0073 - 0.0283)
UP vs SC	-0.0009	(-0.0084 - 0.0065)	0.0003	(-0.0073 - 0.0080)
Height 11-20 years[b]:				
SC>12 vs SC	0.0062	(-0.0129 - 0.0253)	-0.0086	(-0.0298 - 0.0126)
FT vs SC	-0.0124	(-0.0367 - 0.0120)	-0.0232	(-0.0504 - 0.0040)
UP vs SC	0.0068	(-0.0031 - 0.0167)	0.0034	(-0.0079 - 0.0148)

[§]Adjusted for maternal height (m) and prepregnancy weight (kg), paternal height (m) and weight (kg), maternal level of higher education (<1, 1-4, ≥5 years), parity (0, ≥1), maternal age (years), maternal smoking at gestational week 16 (yes/no)

[a]Additionally adjusted for child height (m)

[b]Additionally adjusted for child weight (kg)

diff: Difference in z-score

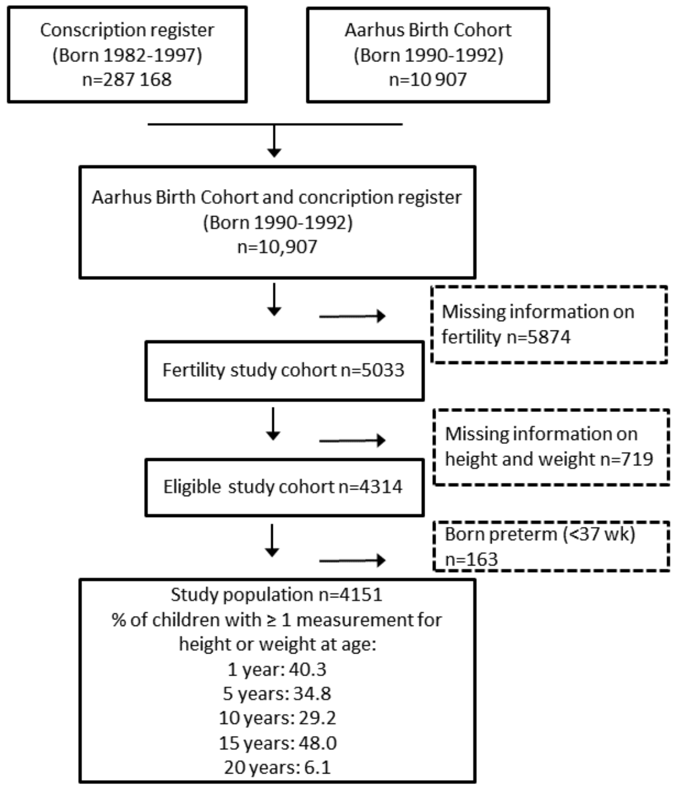
CI: confidence interval

SC: Fertile parents (conceived naturally within 12 months)

SC>12: Subfertile parents (time to pregnancy >12 month before conceiving naturally

FT: Fertility-treated parents

UP: Unplanned parenthood (the parents reported the pregnancy as unplanned)



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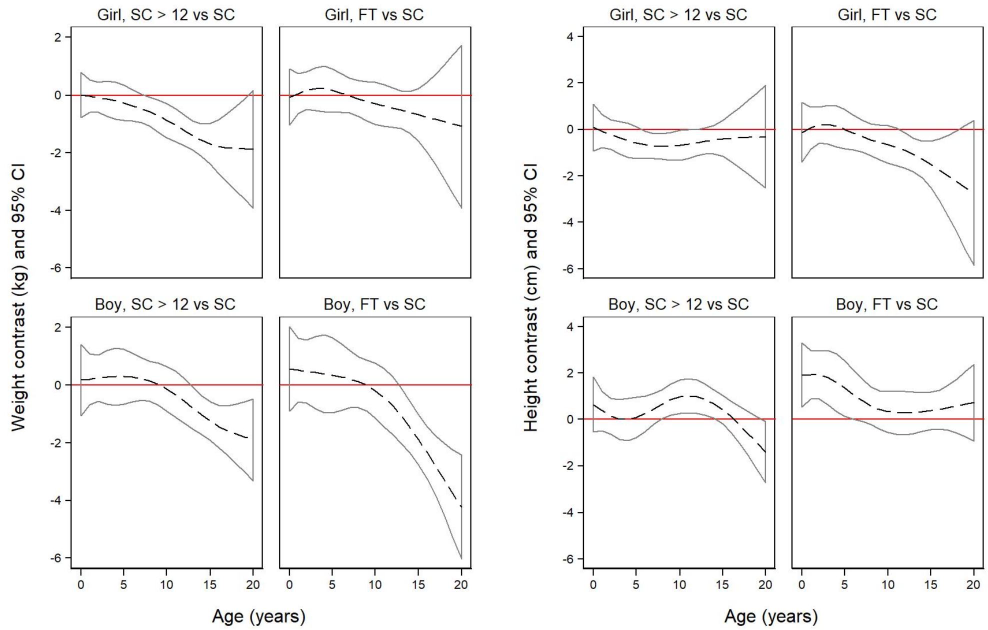

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