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Birth weight for gestational age and the risk of infertility: a Danish cohort study

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STUDY QUESTION: Is birth weight for gestational age associated with infertility in adulthood among men and women?

SUMMARY ANSWER: Being born small for gestational age (SGA) was associated with infertility in adulthood among men.

WHAT IS KNOWN ALREADY: Fetal growth restriction may affect fertility, but results from previous studies have been inconsistent.

STUDY DESIGN, SIZE, DURATION: In this population-based cohort study, we used data from a Danish birth cohort, including 5594 men and 5342 women born between 1984 and 1987. Information on infertility was obtained from Danish health registers during the period from the participants' 18th birthday and up until 31 December 2017.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Participants were men and women born in two Danish municipalities, Aalborg and Odense. Information on birth weight and gestational age was obtained from birth records, and information on infertility diagnoses and fertility treatment was retrieved from the Danish National Patient Registry (NPR) and the Danish *In Vitro* Fertilisation (IVF) registry. Information on potential maternal confounders was obtained from questionnaires during pregnancy and was included in adjusted analyses. Logistic regression analysis was used to estimate crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for infertility according to birth weight for gestational age.

MAIN RESULTS AND THE ROLE OF CHANCE: Men born SGA had a 55% higher risk of being diagnosed with or treated for infertility compared to men born appropriate for gestational age (AGA) (adjusted OR = 1.55, 95% CI: 1.09–2.21). The association attenuated after exclusion of men born with hypospadias or cryptorchidism (OR = 1.37, 95% CI: 0.93–2.01). No association was found between women's birth weight for gestational age and risk of infertility (adjusted OR = 1.00, 95% CI: 0.73–1.37).

LIMITATIONS, REASONS FOR CAUTION: Estimation of gestational age is associated with some uncertainty and might have caused non-differential misclassification. The study design implicitly assumed similar distribution of reproductive and health-seeking behaviour across the groups that were compared.

WIDER IMPLICATIONS OF THE FINDINGS: Men born SGA had a higher risk of infertility. Genital malformations may account for part of the observed association, but this must be explored further.

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Introduction

About 12.5% of all couples are affected by infertility, defined by unsuccessfully attempting pregnancy for a year or longer (Mascarenhas et al., 2012). There are numerous causes of infertility, but in one-third of the cases, a specific cause cannot be identified despite thorough clinical examination (Lindsay & Vitrikas, 2015). In recent years, it has been shown that fetal growth restriction may be associated with impaired development of the gonads and disturbed sex-hormone patterns in adolescence. A meta-analysis by Main et al. concluded that fetal growth restriction is associated with an approximately 2-to-3-fold increased risk of hypospadias (ventral displacement of the urethral meatus), cryptorchidism (undescended testis) and testicular cancer (Main et al., 2006). Another meta-analysis by Ibáñez et al. showed that boys born small for gestational age (SGA) were at higher risk of having high levels of follicle-stimulating hormone (FSH), low levels of inhibin B and a small testicular volume during adolescence compared to boys born appropriate for gestational age (AGA) (Ibáñez & de Zegher, 2006). The same meta-analysis concluded that age at pubertal onset and menarche was advanced by 5–10 months in girls born SGA relative to girls born AGA. Additionally, fetal growth restriction may also be associated with higher FSH levels and smaller internal genitalia (uterus and ovaries) in adolescence (Ibáñez & de Zegher, 2006). Whether these possible reproductive consequences continue into adulthood and increase the risk of infertility in individuals born SGA has been sparsely investigated. Only a few studies have investigated the possible association between birth weight for gestational age and infertility, and these have reported conflicting findings (Ekholm et al., 2005; Meas et al., 2010; deKeyser et al., 2012; Vikström et al., 2014; Liffner et al., 2017).

The objective of this study was to examine the association between birth weight for gestational age and infertility in adulthood among men and women in a Danish cohort.

Materials and Methods

Study population

The study population included singleton children, born of mothers included in the 'Healthy Habits for Two' cohort, established from April 1984 to April 1987 in two cities (Aalborg and Odense) in Denmark (Olsen et al., 1989). A total of 11 980 pregnant women participated and completed a questionnaire that was handed out by their midwives at approximately gestational week 36 (participation rate: 87%) (Olsen et al., 1989). We excluded individuals with missing information on sex, gestational age and birth weight, individuals born in the 44th gestational week or later and individuals with birth weights incompatible with the ostensible gestational age, using birth weight *z*-scores. We further excluded individuals who died during follow-up.

Exposure

Data on birth weight and gestational age was obtained from the birth records. In about half of our participants, gestational age was measured using ultrasound, and in the other half, it was based on the date of onset of the last menstrual period. The exposure of interest was categorised into the following groups based on sex and gestational age according to the sex and gestational age specific reference growth curve by Kramer et al., (2001): SGA (defined as those born with a birth weight below the 10th percentile), AGA (defined as those born with a birth weight between the 10th percentile and the 90th percentile) and large for gestational age (LGA) (defined as those born with a birth weight above the 90th percentile). The 10th and 90th percentiles were used as cut-off values based on the World Health Organization's (WHO) recommendations (WHO Expert Committee, 1995).

Outcome

We defined infertility as having received an infertility diagnosis and/or a fertility treatment. The information was obtained from the Danish National Patient Registry (NPR), which was established in 1977 (Schmidt et al., 2015). The register holds information on inpatient contacts to hospitals in Denmark since 1977 and outpatient medical contacts since 1995, including the date of admission and discharge as well as diagnostic codes and type of diagnosis (main, additional, referral, emergency). We obtained information on infertility diagnoses during the period from the participants' 18th birthday and up until 31 December 2016. We used the following *International Classification of Diseases, Tenth Revision* (ICD-10) diagnoses for female infertility: N97 (female infertility), N970 (anovulation), N971 (tubal origin), N972 (uterine origin), N973 (cervical origin), N978 (other origin), N978A (secondary female infertility), N978B (ovary origin), N978B1 (after retraction of cryopreserved ovarian tissue), N978C (multiple reasons), N978D (primary female sterility), N978E (pituitary origin), N978F (hypothalamus origin) and N979 (unspecified). We used the following ICD-10 diagnoses for male infertility: N46 (male infertility), N469 (male infertility unspecified), N469A (aspermia), N469B (azoospermia), N469C (oligospermia), N469D (oligo-teratospermia) and N469W (other reason). We obtained information on fertility treatments from the Danish *In Vitro* Fertilisation (IVF) registry from the participants' 18th birthday and up until 31 December 2017. The registry contains personal identification numbers on women and their partners (if they have one), information on fertility treatments conducted at public and private fertility clinics in Denmark and the cause of treatment, if known (Health Data Board, 2018). Men were defined as infertile if they had a female partner, who was treated for infertility on indication of a male factor according to the IVF registry (i.e. assuming that only the man was infertile). On the same terms, women were defined as infertile if they were treated for infertility on indication of a female factor according to the IVF registry (i.e. assuming that only the woman was infertile). If there was missing information concerning a couple's fertility status in the registry or if a couple was treated for infertility due to both male and female factors, both the man and the woman were defined as infertile.

Potential confounders and restriction variables

Potential confounders were selected based on the available literature of associations between gestational age at birth, and their potential effect on fertility. From the questionnaires, we had information on factors related to maternal lifestyle, health and sociodemographic status. The following potential confounders were included in the adjusted analyses: maternal age in years (continuous), the level of employment of both parents based on the highest ranking of occupational status between the mother and father at the time of

pregnancy (lowest, medium or highest), parental cohabitation status (do not live together or do live together), maternal smoking during pregnancy (non-smoker, stopped smoking before 3rd trimester, <10 cigarettes per day or ≥10 cigarettes per day), maternal weekly alcohol consumption during pregnancy (<1 drink, 1–4 drink(s) or ≥4 drinks) and maternal pre-pregnancy body mass index (BMI) (underweight (<18.5 kg/m^2), normal weight (≥18.5–<25.0 kg/m^2) or overweight/obese (≥25.0 kg/m^2)) and maternal parity (0 children or ≥1 child).

Information on the two genital malformations, cryptorchidism and hypospadias, was obtained from the NPR from the participants date of birth and until 31 December 2016. This identified male participants diagnosed with any diagnosis of hypospadias (ICD-8 codes; 75220, 75221, 75222, 75228, 75229 or ICD-10 codes; Q54, Q540, Q540A, Q541, Q542, Q543, Q548, Q549) or cryptorchidism (ICD-8 codes; 75210, 75211, 75219 or ICD-10 codes; Q53, Q531, Q531A, Q532, Q532A, Q539).

Statistical analyses

Missing information

Some participants were lost to follow-up due to death (n = 139, 1.2%). An analysis was conducted to identify if there were systematic differences according to birth weight for gestational age between participants (n = 10 936) and participants lost to follow-up (n = 139). Furthermore, many of the participants' mothers (n = 1324) did not fill in questions about 'maternal pre-pregnancy BMI' and 'parental cohabitation status', restricting the number of observations in the adjusted analyses. Two non-response analyses were performed to identify if there were systematic differences according to birth weight for gestational age and infertility between participants whose mothers did not answer questions about maternal pre-pregnancy BMI and parental cohabitation status in the baseline questionnaire (n = 1324) and those who did (n = 9612).

Data analyses

Multiple logistic regression models were performed, and crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were estimated for infertility according to birth weight for gestational age using the AGA group as the reference category. All analyses were stratified by sex. Since the data contained siblings (n = 260, 2.4%), we applied robust standard errors when calculating the CIs.

Since fetal growth restriction is associated with an increased risk of hypospadias and cryptorchidism and these two genital malformations may increase the risk of infertility in adulthood, we performed a sub-analysis, excluding boys with the genital malformations. Because of the well-known association between maternal smoking during pregnancy and semen quality in the sons, and the higher proportion of smoking mothers in the SGA groups, we performed a sub-analysis excluding men of smoking mothers. We also performed sensitivity analyses to check the robustness of the main analytical approach: first, we changed the analyses by using a different definition of SGA, AGA and LGA: SGA (birth weight below the fifth percentile), AGA (birth weight between 5th and 95th percentiles) and LGA (birth weight above the 95th percentile). Second, we performed the analyses with the growth curve by Marsál *et al.* (1996) as reference using the 10th and 90th percentiles as cut-off values. Third, we restricted the analyses to include cases with an infertility diagnosis only (i.e. excluded cases with missing information about the cause of their performance in the IVF registry (n = 78)), as we assumed that the likelihood of participants actually being infertile was higher if they were registered with an infertility diagnosis. This analysis was also performed excluding men with hypospadias and cryptorchidism.

Data were analysed in STATA version 15.1 (StataCorp, College Station, TX, USA).

Ethical approvals

The study was approved by the Danish Data Protection Agency (record number 2015-57-0002) and Aarhus University (record number 2016-051-000001, internal registration 749).

Results

Characteristics of the study population

A total of 11 144 live-born singletons were born in the 'Healthy Habits for Two' birth cohort between 1984 and 1987. We excluded individuals with missing values on sex (n = 2), gestational age and birth weight (n = 56), individuals born ≥gestational week 44 (n = 7), individuals with extreme birth weight z scores (n = 4) and individuals who died during follow-up (n = 139). The final study population cohort consisted of 10 936 individuals followed until 31 December 2017 (98% of the original birth cohort). Among these, 5342 were women (49%) and 5594 were men (51%) (Fig. 1). The mean age of the participants was 32 years at the end of follow-up.

A total of 553 (10.4%) women and 586 (10.5%) men were born SGA, 4315 (80.8%) women and 4515 (80.7%) men were born AGA and 474 (8.9%) women and 493 (8.8%) men were born LGA. Among both men and women, the exposure groups were relatively similar with respect to maternal age, level of parental employment and maternal cohabitation status (Table I). Mothers for the SGA groups had the highest level of cigarette and alcohol consumption and the lowest pre-pregnancy BMI and were more often first-time mothers (Table I).

Missing information

Among women, there were no differences between participants and participants lost to follow-up in relation to birth weight for gestational age. For men, a higher proportion was born SGA among participants lost to follow-up compared with participants (26 vs. 10%) (Supplementary Table SI). The two non-response analyses showed no systematic differences in any of the investigated variables between participating and non-participating mothers (Supplementary Table SII).

Birth weight for gestational age and infertility

Among the women, 533 (10.0%) were categorised as infertile during follow-up. Causes of female infertility were N979 (unspecified) (60.3%), N978 (other origin) (12.1%), N970 (anovulation) (8.0%), N978D (primary female sterility) (6.5%), N97 (female infertility) (5.8%), N978A (secondary female infertility) (2.7%), N978B (ovary origin) (2.7%), N971 (tubal origin) (1.7%) and N972 (uterine origin) (0.2%). Among the men, 332 (5.9%) were categorised as infertile

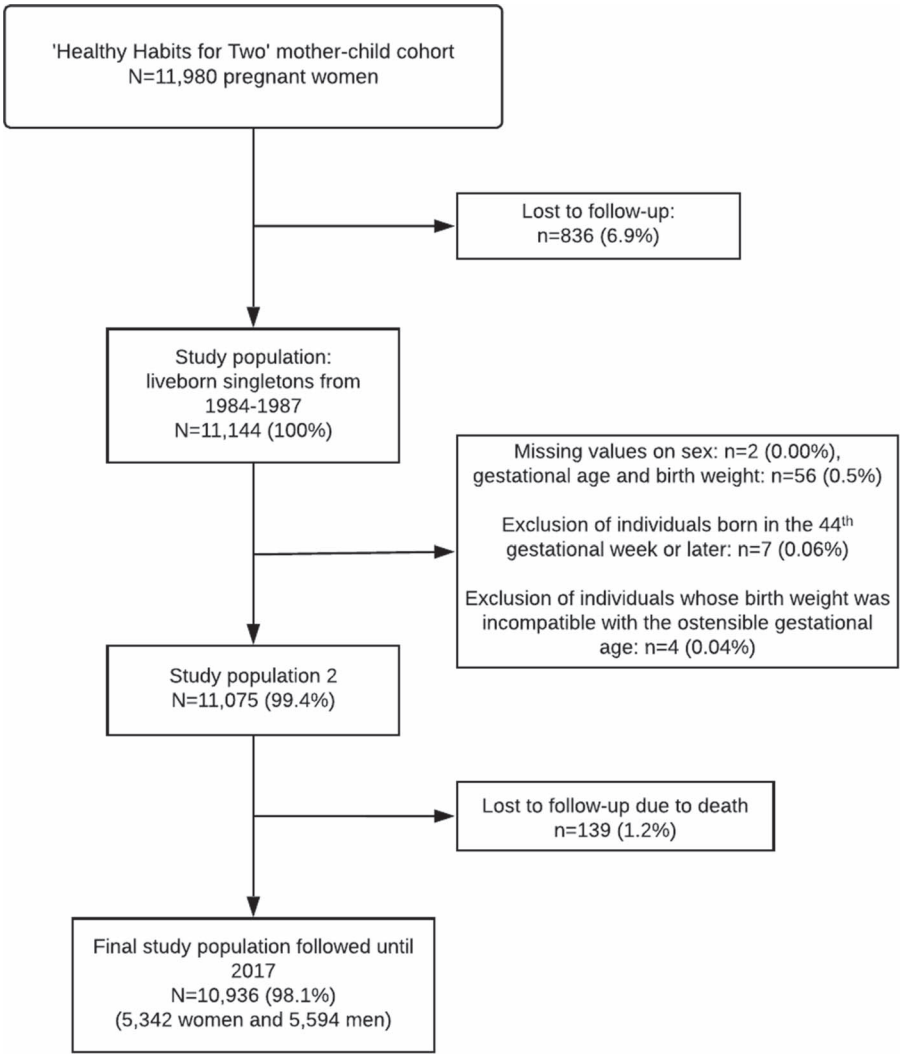

Figure 1 **Flow chart of the study population.**

during follow-up. Causes of male infertility were N469 (male infertility unspecified) (89.7%), N469C (oligospermia) (6.9%), N469B (azoospermia) (2.6%) and N469D (oligo-teratospermia) (0.9%). The mean age at infertility diagnosis or treatment was 27.5 years for men and 27.4 years for women.

Table II presents ORs of infertility according to birth weight for gestational age for each sex. Results were very similar in the unadjusted and adjusted analyses. For women, no association was found between SGA and infertility (adjusted OR = 1.00, 95% CI: 0.73–1.37). Men born SGA had 55% higher odds of being infertile (adjusted OR = 1.55, 95% CI: 1.09–2.21) compared with men born AGA. No association was found between LGA and infertility, either among men or women.

In the first sub-analysis, we excluded men with hypospadias or cryptorchidism (n = 180, 3.2%). The risk of being infertile was attenuated but still tended to be higher for men born SGA compared to men born AGA (adjusted OR = 1.37, 95% CI: 0.93–2.01) (Supplementary Table SIII). In the second sub-analysis, we excluded men whose mothers smoked during pregnancy. The risk of being infertile was higher among men born SGA compared to men born AGA (adjusted OR = 1.78, 95% CI: 1.05–3.00) (Supplementary Table SIV), and even more so.

In sensitivity analyses, we first defined SGA and LGA as the 5th and 95th percentile (Supplementary Table SV), respectively, and second, we used the growth curve by Marsál *et al.* (1996) (Supplementary Table SVI). Using these definitions did not change our results markedly. Men born SGA had 67% higher odds of being infertile (adjusted OR = 1.67, 95% CI: 1.09–2.55) compared with men born AGA when using the 5th and 95th percentiles as cut-off values (Supplementary Table SV). Finally, we restricted the analyses to include cases with an infertility diagnosis only, and the risk of infertility changed from a 55% higher risk of being infertile (adjusted OR = 1.55, 95% CI: 1.09–2.21) to an 88% higher risk (adjusted OR = 1.88, 95% CI: 1.30–2.70) among men born SGA (Supplementary Table SVII). The results remained unchanged among women. The restricted analysis was also performed excluding men with hypospadias or

Table I Descriptive characteristics according to birth weight for gestational age among men and women from the 'Healthy Habits for Two' birth cohort, Denmark, 1984–1987.

	Women ($n = 5342$)			Men ($n = 5594$)		
	SGA ($n = 553$, 10.4%)	AGA ($n = 4315$, 80.8%)	LGA ($n = 474$, 8.9%)	SGA ($n = 586$, 10.5%)	AGA ($n = 4515$, 80.7%)	LGA ($n = 493$, 8.8%)
Maternal age at gestational week 36 (mean, SD)						
Years	26.8 (4.8)	27.1 (4.6)	28.3 (4.8)	26.6 (4.5)	27.2 (4.6)	27.9 (4.7)
Parental level of employment (combined, highest level of employment) (*n*, %)						
Lowest	168 (30.4)	1142 (26.5)	119 (25.1)	165 (28.2)	1187 (26.3)	145 (29.4)
Medium	274 (49.6)	2402 (55.7)	267 (56.3)	330 (56.3)	2475 (54.8)	267 (54.2)
Highest	111 (20.1)	771 (17.9)	88 (18.6)	91 (15.5)	853 (18.9)	81 (16.4)
Parental cohabitation status during pregnancy (*n*, %)						
Do not live together	16 (3.1)	127 (3.1)	10 (2.2)	22 (4.1)	135 (3.2)	8 (1.7)
Do live together	506 (97.0)	3942 (96.9)	444 (97.8)	513 (95.9)	4147 (96.9)	463 (98.3)
Maternal smoking during pregnancy (*n*, %)						
Non-smoker	195 (35.3)	2388 (55.7)	341 (72.6)	195 (33.6)	2572 (57.5)	346 (70.5)
Stopped smoking before the 3rd trimester	19 (3.4)	229 (5.3)	39 (8.3)	19 (3.3)	236 (5.3)	29 (5.9)
<10 cigarettes per day	133 (24.1)	779 (18.2)	51 (10.6)	159 (27.4)	833 (18.6)	67 (13.7)
≥10 cigarettes per day	205 (37.1)	893 (20.8)	39 (8.3)	208 (35.8)	831 (18.6)	49 (10.0)
Maternal pre-pregnancy BMI (kg/m^2)						
<18.5 kg/m^2	74 (14.2)	423 (10.5)	16 (3.7)	85 (15.6)	362 (8.6)	18 (4.0)
≥18.5 kg/m^2 and < 25 kg/m^2	405 (77.7)	3109 (77.1)	328 (75.2)	411 (75.3)	3331 (79.4)	336 (74.2)
≥25 kg/m^2	42 (8.1)	500 (12.4)	92 (21.1)	50 (9.2)	500 (11.9)	99 (21.9)
Maternal weekly alcohol consumption during pregnancy (*n*, %)						
<1 drink	204 (37.0)	1495 (34.7)	178 (37.6)	193 (33.0)	1614 (35.8)	174 (35.3)
1–4 drink(s)	292 (52.9)	2468 (57.2)	258 (54.6)	338 (57.8)	2564 (56.8)	296 (60.0)
≥4 drinks	56 (10.1)	351 (8.1)	37 (7.8)	54 (9.2)	336 (7.4)	23 (4.7)
Maternal parity (*n*, %)						
0 children	311 (56.2)	2095 (48.6)	164 (34.6)	344 (58.7)	2180 (48.3)	176 (35.7)
≥1 child	242 (43.8)	2220 (51.5)	310 (65.4)	242 (41.3)	2335 (51.7)	317 (64.3)

Abbreviations: BMI, body mass index; *n*, number; SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age
Missing: maternal age ($n = 8$), parental cohabitation status ($n = 603$), maternal smoking ($n = 81$), maternal pre-pregnancy BMI ($n = 755$) and maternal alcohol consumption ($n = 5$)

cryptorchidism. The risk remained higher among men born SGA compared with men born AGA (adjusted OR = 1.67, 95% CI: 1.12–2.48) (Supplementary Table SVIII).

Discussion

In this cohort study, we investigated the association between birth weight for gestational age and infertility in adulthood among men and women. Being born SGA was associated with a higher risk of infertility among men compared to men born AGA. The association was attenuated when excluding those born with malformations in the genital organs. For women, no association was found between SGA and infertility.

Previous studies on this subject are sparse and show conflicting results. Consistent with our results, a Swedish population-based registry study by deKeyser *et al*. reported a 9% lower reproductive rate (the rate of having a live born child) for men born SGA, while no association was observed among women (deKeyser *et al*., 2012). However, their analyses were not adjusted for potential behavioural, nutritional and environmental confounders. In contrast, Ekholm *et al*. found an increased rate of reproduction among 25–27-year-old women born SGA, an association that had disappeared entirely by the time the women reached 31–33 years of age (Ekholm *et al*., 2005). It is well-known that SGA is associated with certain maternal lifestyle factors, including high levels of smoking and alcohol consumption. It could be speculated that girls born SGA grow up in an environment that could be associated with an increased probability of giving birth at an early age. The higher reproductive rate for the young SGA women may therefore be due to confounding. A case–control study performed by Liffner *et al*. found no difference in the use of assisted reproductive technology (ART) among men born SGA, AGA or LGA (Liffner *et al*., 2017). However, in a sensitivity analysis, they found that men becoming fathers by intracytoplasmic sperm injection (ICSI) had a doubled risk of having been born SGA compared with men who became fathers

Table II Odds ratios for infertility according to birth weight for gestational age among men and women from the 'Healthy Habits for Two' birth cohort, Denmark, 1984–1987.

Women								
Birth weight for gestational age	Unadjusted model ($N = 5342$)				Adjusted model* ($N = 4675$)			
	Total	Infertile, (n, %)	OR	95% CI	Total	Infertile, (n, %)	OR	95% CI
SGA	553	57 (10.3)	1.04	0.77–1.39	489	50 (10.2)	1.00	0.73–1.37
AGA	4315	431 (10.0)	1.00	Reference	3773	372 (9.9)	1.00	Reference
LGA	474	45 (9.5)	0.95	0.68–1.30	413	38 (9.2)	0.96	0.68–1.37
Men								
Birth weight for gestational age	Unadjusted model ($N = 5594$)				Adjusted model* ($N = 4852$)			
	Total	Infertile, (n, %)	OR	95% CI	Total	Infertile, (n, %)	OR	95% CI
SGA	586	48 (8.2)	1.48	1.07–2.04	492	41 (8.3)	1.55	1.09–2.21
AGA	4515	257 (5.7)	1.00	Reference	3929	224 (5.7)	1.00	Reference
LGA	493	27 (5.5)	0.96	0.64–1.44	431	23 (5.3)	0.90	0.57–1.41

Abbreviations: BMI, body mass index; n, number; SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age; OR, odds ratio; CI, confidence interval

*Adjusted for maternal age, parental level of employment, parental cohabitation status, maternal smoking and alcohol consumption, maternal pre-pregnancy BMI and maternal parity

by conventional IVF treatment. A case–control study performed by Vikström *et al*. found that infertile women with a known female infertility factor were almost three times more likely to have been born SGA compared with women with unexplained infertility (Vikström *et al*., 2014). The category with an unexplained cause of infertility makes interpretation of their results difficult, since this category may contain individuals where the cause of infertility has yet to be discovered. A study performed by Meas *et al*. showed no association between birth weight for gestational age and time to pregnancy (TTP) in adulthood among women nor men, but the sample size was relatively small ($N = 1282$), which increases the risk of type 2 error (Meas *et al*., 2010). Results from a follow-up study performed by Ramlau-Hansen *et al*., including male participants from the 'Healthy Habits for Two' birth cohort, did not indicate an effect of birth weight on semen quality or level of reproductive hormones in adult life (Ramlau-Hansen *et al*., 2010). However, the exposure contrast was restricted and they had limited power to detect small associations. Taken together, comparison across the existing literature is challenging due to methodological variations and solid conclusions cannot be made.

The potential mechanisms underlying the association observed among men in our study remain unresolved. Suggestions of a biological cause may be considered regarding research that shows a link between fetal growth restriction and development of hypospadias and cryptorchidism (Main *et al*., 2006; Jensen *et al*., 2012), two factors associated with impaired testicular function (Miller et al. 2001; Virtanen et al. 2007; Örtqvist et al. 2017). This is consistent with our results as exclusion of men born with hypospadias and cryptorchidism attenuated the risk of infertility among men born SGA compared with the main results, indicating that the genital malformations may be intermediate factors in the observed association. It could also be speculated that cryptorchidism, hypospadias and reduced infertility have common origins in fetal life.

Our study has strengths as well as limitations. A major strength in our study was the high participation rate (87%) among the pregnant women included in the 'Healthy Habits for Two' cohort and the availability of data from the Danish national registers, which resulted in a high follow-up rate in our birth cohort (98%). This reduces the risk of selection bias and optimises the representativeness. We found a higher proportion of men born SGA among those lost to follow-up. If non-participants have a higher risk of infertility compared with participants, the association between SGA and infertility among men may be underestimated.

Generally, the quality and completeness of the NPR and the IVF registry are considered high (Andersen *et al*., 1999; Schmidt *et al*., 2015). To our knowledge, no validation studies have been performed regarding registration of infertility diagnoses and infertility treatments in the two registers; registrations may be prone to some degree of measurement errors, which may have led to non-differential misclassification. Another strength in our study is the availability of detailed information on potential confounders from questionnaire data, such as maternal smoking, alcohol, pre-pregnancy BMI and cohabitation status. These factors had a small impact of the crude OR estimate, and the association between SGA and infertility among men would have been underestimated if not adjusting for these variables. Future studies on this subject may therefore take these confounders into account. However, there were a large number of missing registrations on maternal pre-pregnancy BMI and cohabitation status due to no reply to the baseline questionnaire among the participants' mothers. The missing information was, however, not related to our exposure or outcome of interest.

The mean age at birth of the first child in Denmark was roughly 29 years for women and 31 years for men in 2017 (Statistical Denmark, 2018). The participants were between 30 and 33 years of age at the end of our study period. We consider the cohort appropriate to study infertility; however, we acknowledge that they had not reached the end

of their reproductive lives, and thus it will be of interest to follow-up the cohort in additional 10 years' time. Furthermore, in the SGA group, a large proportion of mothers had a high level of cigarette and alcohol consumption. It could be speculated that boys born SGA grow up in an environment that could be associated with an increased probability of having a child in an early age. In our study, however, the mean age of infertility diagnosis or treatment was the same among men born SGA, AGA and LGA. Further, in a sub-analysis excluding smoking mothers, we found that men born SGA had a 78% higher risk of infertility compared to men born AGA. Despite a reduction in power, the tendency of the association is the same as in the total male population.

A limitation was the different measurement methods used to estimate the participants' gestational age. Using the date of onset of the last menstrual period as measurement method has been shown to overestimate the proportion of infants with post-term gestational ages and underestimate those born preterm compared with early ultrasound measurements (Kramer *et al*., 1988; Mongelli *et al*., 1996). However, this did not seem to be an issue in our study as the proportion of participants born preterm, term or post-term was similar, regardless of the measurement method used. Despite this, estimation of gestational age will always be associated with some uncertainty, which increases the risk of non-differentiated misclassification and an underestimation of the estimated associations.

In our study, men and women were classified as infertile, if they either had a diagnosis of infertility or were part of a couple that had received fertility treatment. As there are other reasons for seeking fertility treatment than a couple's inability to achieve a pregnancy (e.g. sexual dysfunction, being lesbian or single (only relevant for women)), we may have misclassified some men and women in our main analyses. Therefore, we performed a restriction analysis where we excluded infertile cases with missing information on the cause of their performance in the IVF registry. The increased risk of infertility changed from 55 to 88% among men born SGA. It is expected that the OR estimate from this analysis will more accurately reflect the true risk of infertility.

Our findings add to the growing literature that being born SGA may impact future fertility, at least among boys. The results are reassuring for girls born SGA, although we cannot exclude that misclassification could have led to bias toward the null. Many children are born SGA, so if SGA is causally linked to infertility, this has public health relevance. It is therefore important to focus on the underlying mechanisms that can explain the possible association between SGA and infertility as it allows a more targeted prevention strategy.

Conclusions

We found that being born SGA was associated with a higher risk of infertility among men. Two genital malformations, hypospadias and cryptorchidism, may account for a part of the association observed. For women, no association was found between birth weight for gestational age and infertility.

Authors' roles

All authors contributed to the conception and design of the study. J.O., B.H., J.P.B. and C.R.H. contributed to the acquisition of data. A.T. and J.L. performed the statistical analyses and A.T. drafted the manuscript. All authors revised the paper critically and approved the final version of the manuscript.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

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Conflict of interest

None declared.

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