

1 Running title: Childhood obesity and infertility

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Association of childhood obesity with female infertility in adulthood: a 25-year follow-up study

Ye He, Ph.D.^a

Jing Tian, Ph.D.^a

Wendy H. Oddy, Ph.D.^a

Terry Dwyer, M.D.^{a,b}

Alison J. Venn, Ph.D.^a

^a Menzies Institute for Medical Research, University of Tasmania.

^b The George Institute for Global Health, University of Oxford, Oxford, UK.

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Reprints request and corresponding Author: Alison J. Venn, PhD, Menzies Institute for Medical Research, University of Tasmania, 17 Liverpool Street, Hobart, Tasmania 7000, Australia. Telephone: 61-3-6226-7706; Fax: 61-3-6226-7704; E-mail: Alison.Venn@utas.edu.au

48 Capsule: In this 25-year follow-up study of 1,544 girls, we found childhood obesity before 12
49 years of age appears to increase the risk of female infertility in later life.

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67 **Abstract**

68 **Objectives:** To evaluate whether childhood obesity is associated with infertility in women's
69 reproductive-aged life.

70 **Design:** Prospective longitudinal study.

71 **Setting:** A childhood cohort from 1985 Australian Schools Health and Fitness Survey.

72 **Intervention(s):** None.

73 **Patient(s):** 1,544 girls aged 7 to 15 years in 1985 and completed questionnaires at follow-up
74 in 2004-2006 and/or 2009-2011.

75 **Main outcome Measure(s):** Infertility was defined as having difficulty conceiving (had ever
76 tried for 12 months or more to become pregnant without succeeding) or having ever seen a
77 doctor because of trouble becoming pregnant.

78 **Result(s):** At ages from 7 to 11 years, girls at both the lower and upper end of the BMI z-
79 score had increased risk of infertility. Compared with normal weight girls, those with obesity
80 aged 7-11 years were more likely in adulthood to report infertility (adjusted relative risk
81 (aRR): 2.94, 95% confidence interval (CI): 1.48-5.84), difficulty conceiving (aRR: 3.89, 95%
82 CI: 1.95-7.77), or having ever seen a doctor because of trouble becoming pregnant (aRR:
83 3.65, 95% CI: 1.90-7.02) after adjusting for childhood age, follow-up length, highest parental
84 education and marital status.

85 **Conclusion(s):** Childhood obesity before 12 years of age appears to increase the risk of
86 female infertility in later life.

87 **Key words:** Childhood, body mass index, infertility, body composition, waist-to-height ratio

88 **Introduction**

89 The increase in obesity among children and adolescents is of great concern around the world
90 (1). In Australia, one in four children aged 5-17 years were overweight or obese in 2014-2015
91 which is twice the recorded prevalence in 1986 (2). Substantial evidence suggests that obesity
92 in women is associated with a wide range of gynaecological disorders including infertility (3,
93 4). Obesity during childhood and adolescence has been linked with early puberty, menstrual
94 disorders and polycystic ovarian syndrome (PCOS) (5). From the life course perspective of
95 female reproductive health, it is important to determine whether childhood obesity has long-
96 term effects on infertility in adulthood, typically defined clinically as a failure to conceive
97 after regular unprotected intercourse or attempting pregnancy for 12 months or more (6).

98 Few studies have investigated the association of childhood obesity with female infertility and
99 the findings were not consistent. In a study of 3,327 British girls, Lake and colleagues (7)
100 reported little impact of childhood body mass index (BMI) at the age of 7 years on infertility
101 26 years later defined by achieving a pregnancy after more than 12 months. However,
102 participants were restricted to women with a live birth from their first pregnancy. BMI cut-
103 points were defined using an index of relative weight (weight expressed as a percentage of
104 the standard weight for age, height, and sex). More recently, a report based on 1,061
105 participants in the Bogalusa Heart Study in USA showed that girls with obesity prior to 12
106 years of age were more likely in later life to have tried to become pregnant without success.

107 Weight status was defined according to age and gender specific BMI percentiles and based on
108 USA Centers for Disease Control (CDC) and Prevention statistics (e.g. \geq 95th percentile for
109 obesity) (8). A limitation of this study is that it determined whether participants had 'ever
110 tried to become pregnant and were unable to' but did not specify a time interval and may
111 have resulted in misclassification of infertility. In addition, male factors (e.g. poor semen

quality) are commonly reported causes of infertility (9) and not the outcome of interest:
neither of these studies were able to exclude them.

The aim of the present study was to examine the association between different measures of
body composition at age 7-15 and infertility at age 26-41 in a large population-based sample
of Australian women with consideration of a wide range of potential confounders.

Methods

Participants

The Childhood Determinants of Adult Health (CDAH) Study is a follow-up of 8,498 children
which included 4,191 girls who participated in the 1985 Australian Schools Health and
Fitness Survey (ASHFS), a nationally representative sample of Australian school children
aged 7-15 years (herein referred to as “baseline”) (10). At baseline, all children had physical
assessments and those aged 9-15 years completed questionnaires. During 2002-2004, a total
of 3,412 women participants were traced and 2,734 women agreed to participate in the
CDAH Study (Figure 1). During 2004-2006, when the participants were aged 26-36 years,
1,596 women completed questions on reproductive health (CDAH-1). The second follow-up
(CDAH-2) was conducted during 2009-2011, when participants were aged 31-41 years and
1,129 women completed questions on reproductive health. After combining two follow-ups, a
total of 1,754 women who answered reproductive health questions at CDAH-1 or CDAH-2 or
both were eligible for the study.

The study was approved by the Southern Tasmania Health and Medical Human Research
Ethics Committee. Written informed consent was obtained at both time points.

Childhood body composition measurement

BMI, calculated as weight (kg)/ height (m)², was derived from measured height and weight with weight status defined using international age- and sex-specific cut-points (11) and was transformed into BMI z scores based on age- and sex-specific standardisation of the full childhood cohort (n=4189 girls). Waist circumference was taken at the level of the umbilicus to the nearest 0.1 cm. Hip circumference was measured at the level of the greatest posterior protuberance of the buttocks. Waist-to-hip ratio was calculated by dividing waist by hip circumference. Waist-to-height ratio (WHtR) was calculated by dividing waist circumference by height and dichotomized into < or \geq 0.5. Abdominal obesity was defined as WHtR \geq 0.5 (12).

Adult body composition measurement

At CDAH-1, weight and height were measured at study clinics for most. A sub-sample of these participants also self-reported their weight and height before measurements were taken to assess the accuracy of self-reported values. The difference between clinic and self-reported weight and height was used to calculate a correction factor from a linear regression model. Participants who did not visit a study clinic self-reported their weight and height, and a correction factor was applied to adjust for error (13). BMI (kg/m²) was calculated from height and weight.

Weight was self-reported at CDAH-2. Adjusted weight values were calculated using the correction factor applied at CDAH-1. BMI was calculated using measured height at CDAH-1 or adjusted self-reported height at CDAH-1 or at enrolment.

Adult BMI was categorized into three groups (<25, 25-30 and \geq 30 kg/m²). Overweight was defined as $25 \leq \text{BMI} \leq 29.9$ kg/m² and obesity was defined as BMI \geq 30 kg/m² (14).

Adult infertility measurement

In the reproductive questionnaire of CDAH-1 and CDAH-2, women were asked to answer ‘yes’ or ‘no’ to questions ‘Have you ever tried to become pregnant for 12 months or more without succeeding?’ and ‘Have you ever seen a doctor because you were having trouble becoming pregnant?’ Infertility was recorded if they responded ‘yes’ to either of the two questions. Women were further asked whether any of the following investigations had been undertaken if they reported having seen a doctor because of difficulty conceiving: hormone test, laparoscopy and partner’s semen test. Participants were also asked about any diagnosis they had been given including ovulatory problem, tubal problem, male factor, unexplained fertility problem or any other female problem with a written specified reason. We categorized the answers into tubal, male, ovulatory (including ovulatory problem, polycystic ovary syndrome, hyperprolactinaemia, hypogonadotrophic, hypergonadotrophic and premature ovarian failure), endometriosis, unexplained, other and uterine factors.

Covariate measures

Childhood factors considered as covariates included age, age at menarche (self-reported in adulthood), socioeconomic position based on area of residence (high, medium high, medium low, or low), highest parental education (reported in adulthood as high school only, vocational training, any university education), smoking experimentation (none, a few puffs, < 10 cigarettes in their life, and ≥ 10 cigarettes in their life), alcohol consumption (never, less than once per week, more than once per week) and total physical activity (mins/week). Sociodemographic characteristics were self-reported at follow-ups. Adult covariates included highest level of education attained (classified as for childhood), socioeconomic position based on area of residence (classified as for childhood), marital status (single, married/living as married, separated/divorced/widowed), smoking status (never, ex-smoker, current smoker), alcohol consumption (non-drinker, light drinker, moderate drinker, heavy/very heavy drinker),

and total physical activity (mins/week). Follow-up length was also considered as a potential confounder.

Statistical analyses

Subgroup analyses by child age (7-11 years and 12-15 years) were undertaken because of reported differences in the association of onset of obesity in childhood with later infertility (8). Univariable and multivariable log-binomial regression was used to derive risk ratio (RR) estimates for the association between body composition and infertility before and after adjustment for potential confounders. If the log binomial model failed to converge, RRs were estimated using Poisson regression with robust standard errors to correct for the misspecification of the binomial errors (15-18). Covariates kept in the final model were variables associated with the exposure and the outcome, and resulted in more than 10% change in the coefficient of the principal study factor when added into the model.

Restricted cubic regression splines based on 4 knot points were used to present associations between childhood BMI z score and infertility (19). The x-axis on the graph goes from the 5th to the 95th percentile of childhood BMI z score.

The following sensitivity analyses were conducted. First, we excluded those who reported male infertility to examine if it had biased the observed association between childhood obesity and having ever seen a doctor because of trouble becoming pregnant. Second, we restricted our sample to women who were married or living as married. Third, we considered the effect of loss to follow-up using inverse probability weighting. The completed factors available at baseline used to determine the weights were childhood age, school type and state of residence. Fourth, childhood BMI was classified alternatively as normal (<85th percentile), overweight (85th-94th percentile) or obese (\geq 95th percentile) based on age- and sex-specific USA CDC norms (20) and age- and sex-specific childhood BMI in our 1985 ASHFS cohort.

All analyses were performed using STATA software, version 14.2 (Stata Corp., College Station, TX); a p -values of <0.05 was considered statistically significant.

Results

Participant characteristics

This study included 1,754 women who reported fertility outcomes. Of these participants, 971 completed both follow-up surveys, 625 participated in only the first follow-up and 158 women participated in only the second follow-up. Participants who had missing data on confounders (210 women) were excluded, leaving 1,544 women for the final analysis.

The anthropometric and sociodemographic characteristics of participants at childhood and adulthood are shown in Table 1. At baseline, 17 (1.1%) children were obese, 116 (7.5%) were overweight and 80 (5.2%) children had abdominal obesity as defined by BMI cut-points and WHtR category, respectively. The mean age at follow-up was 34 years (range 26-41). There were 346 (22.4%) women who reported experiencing infertility in adulthood, including 264 (17.1%) who reported ever having tried for more than 12 months to become pregnant without succeeding and 281 (18.2%) who had ever seen a doctor because of trouble becoming pregnant. Participants with lower parental education in childhood and those who were married or living as married in adulthood were more likely to report infertility.

Compared with those who did not participate in the follow-up, those who did participate were slightly older (11.0 vs 10.8 years; $P=0.003$), had marginally lower BMI (18.2 vs 18.4 kg/m²; $P=0.009$) and were less likely to have abdominal obesity (5.2% vs 8.3%; $P<0.001$) at baseline.

Infertility

After adjustment for age, follow-up length, parental education and marital status, compared with women with normal childhood weight between 7 and 11 years (Table 2), those who were obese as children were more likely to report infertility (aRR=2.94, 95% CI 1.48-5.84), having ever tried for more than 12 months to become pregnant without succeeding (aRR=3.89, 95% CI 1.95-7.77) and having ever seen a doctor because of trouble becoming pregnant (aRR=3.65, 95% CI 1.90-7.02). This association was not evident for the group aged 12 to 15 years at baseline. No significant association was found between other adiposity indicators (waist circumference, waist-to-hip ratio and WHtR \geq 0.5) in childhood and infertility in adulthood, including when abdominal adiposity measures were adjusted for childhood BMI.

The association between childhood BMI z score and relative risk of infertility in adulthood is shown in Figure 2. There was a U-shaped association of BMI z score with infertility in the 7 to 11 years group (Figure 2A), with the risk significantly higher in children with z score over 1.05 or less than -0.80. No significant association was observed for those in the 12 to 15 years group (Figure 2B).

Cause of infertility

Most women who had ever seen a doctor because of trouble becoming pregnant reported one or more infertility causes and infertility investigations (Supplemental table 1). Endometriosis was a less common cause of infertility in those who were overweight or obese in childhood (15.1% in normal vs. 3.3% in overweight/obese, $p=0.10$). Similar proportions of women had infertility investigations irrespective of their childhood BMI category (Supplemental table 1).

Influence of adiposity from childhood into adulthood

The proportions and the number of women who reported infertility by adiposity status from childhood to adulthood are displayed in Supplementary figure 1 and Supplemental table 2.

For consistently normal weight participants (normal weight in childhood and adulthood), the prevalence of infertility was 21.6%, and for consistently overweight/obese participants (overweight/obese from childhood to adulthood), the corresponding figure was 27.9%. Though a higher prevalence of reported infertility was observed in the persistently overweight and obese group, it did not reach statistical significance ($P=0.37$). After adjustment for childhood age and parental education at baseline, length of follow up, adult education, marital status and alcohol consumption in adulthood, the risk of infertility was significantly higher in women who were persistently overweight or obese from childhood (ages 7-11) into adulthood than those who had consistently healthy weight (Supplemental table 3).

Sensitivity analysis

Similar results were observed after excluding women who reported infertility due to male factor ($n=20$) and endometriosis ($n=39$). Compared with those of normal weight in childhood, the risk of having ever seen a doctor because of trouble becoming pregnant in the obese group was 3.69 (95% CI 1.94-6.99) and 4.16 (95% CI 2.14-8.06) respectively for those aged 7 to 11 years at baseline. When restricting the sample to women who were married or living as married (and who it might be assumed would have a greater likelihood of becoming pregnant), the risks of infertility (aRR=3.15, 95% CI 1.37-7.25), having ever tried for more than 12 months to become pregnant without succeeding (aRR=4.12, 95% CI 1.78-9.50) and having ever seen a doctor because of trouble becoming pregnant (aRR=3.84, 95% CI 1.78-8.25) remained significantly higher in those who were obese at ages 7 to 11 years. Sensitivity analyses conducted by reanalysing the data with inverse probability weighting produced similar patterns of results as the unweighted analyses and the changes in the magnitude of significant associations were small, ranging from 1.5 to 3.3 % (Supplemental table 4). Further analysis using USA CDC and our cohort internal cut-points of 85th and 95th childhood BMI

percentiles showed similar significant associations of childhood obesity and infertility in the 7 to 11 years group (Supplemental table 5 and Supplemental table 6).

Discussion

Our findings indicate that being obese before the age of 12 years is associated with impaired fertility in later life and a U-shaped relationship between childhood BMI z score and infertility. A previous study also suggested an inverted U-shaped between BMI in adolescence and number of children (21). Some evidence suggests that body fat distribution in women may have more impact on fertility than obesity (22), but our results did not support this association in relation to children's WHtR. No appreciable differences in the associations of waist circumference, waist-to-hip ratio and abdominal obesity in childhood were found with later infertility in adulthood.

Current evidence on the association of childhood obesity and adult infertility is not consistent. Similar to our finding, a study from the USA reported that obesity before age 12 years was associated with an increased likelihood of having ever tried to become pregnant without success (8). In contrast, the analysis from a British cohort study showed that weight during childhood did not predict subsequent fecundity, but it did find that obesity at the age of 7 years was associated with increased menstrual irregularities by age 33 years (7). The reasons for the inconsistent results may be the use of different methods to sample study populations, for example, the British cohort study was limited to women with a live birth from their first pregnancy.

The explanation for the difference in associations by age group is unclear but there may be cumulative impacts of childhood obesity on adult infertility whereby girls who are obese at a younger age (i.e. 7-11 years in this study) have more impaired fertility, and/or that the pre-pubertal phase is a more sensitive window for the effects of high BMI on the development of

reproductive capacity than later pubertal or post-pubertal stages of development. A recent study in rodents suggests that early-onset obesity induces reproductive deficits in adult female rats by reducing the number of oocyte and preantral follicles and inhibiting the luteinizing hormone surge (23). In humans, early-onset obesity is associated with the earlier puberty and earlier maturation of the hypothalamo-pituitary axis which may impact on the development of the reproductive system in girls (24). Increased estrogen produced by greater body fat and accelerated aromatization of adrenal and ovarian androgens in adipose tissue promotes earlier adrenarche, pubarche and thelarche, which may have unfavourable influences on the HPO axis, ovarian function, oocyte quality, endometrial receptivity, or any combination of these factors in the long-term (25). In addition, obesity in childhood is an important factor contributing to the presence and severity of PCOS in adolescents, which may increase the risk of subsequent anovulatory infertility (26-28). In our study, we failed to detect an association between high childhood adiposity and infertility due to ovulatory dysfunction. It is plausible that obesity disrupts endocrine homeostasis with long-term effects on infertility, however, the mechanisms involved in reducing reproductive potential are still poorly understood.

Our finding that endometriosis as a cause of infertility was less common in those in the childhood overweight/obese group (3.5%) than the normal weight group (15.1%) was similar to findings from a recent meta-analysis which pooled 11 studies of participants with ages ranging from 16 to 65 years and reported that higher BMI was associated with lower risk of endometriosis in adulthood (29). Further, results from our sensitivity analysis suggest that male infertility did not bias the observed association between childhood obesity and infertility in adulthood.

The strengths of our study are a relatively contemporary cohort with childhood body composition measurements taken in 1985 and follow-ups conducted during women's

reproductive years. Although the Bogalusa Heart Study measured skinfolds in childhood, to our knowledge our study is the first to have reported the associations of various abdominal obesity indicators in childhood with adult infertility including waist circumference, waist-to-hip ratio and waist-to-height ratio. In addition, our definition of having difficulty conceiving specified a time interval of having ever tried ≥ 12 months and is more consistent with definitions used in clinical practice (30). Moreover, we demonstrated associations with infertility of BMI z score as a continuous variable as well as obesity defined by age- and sex-specific BMI ≥ 95 th percentile.

Some limitations should be acknowledged. First, the sample size in the childhood obese group is small. The prevalence of obesity in girls using international BMI cut-points was only 1.1%. However, similar findings were shown with continuous BMI z scores and sensitivity analyses in our study. Second, we could not distinguish primary infertility (no prior pregnancies) and secondary infertility (infertility following at least one prior conception), which is important for evaluating women's ability to have children and exploring the aetiology of infertility. Third, our measure of infertility relied on self-reported problems. However, the prevalence of infertility in our study is consistent with Australian estimates of approximately one in six couples experiencing a delay of greater than 12 months to achieve a planned pregnancy during their reproductive life (31, 32). Although infertility diagnoses and investigations are self-reported, these are likely to be important events for women, and women should be able to recall specific diagnoses and investigations that have been undertaken.

In conclusion, our study of a cohort of Australian women indicated a detrimental impact of childhood obesity before age 12 on infertility later in life. The early prevention of childhood obesity is important for fertility as well as disease prevention.

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Figure captions

Figure 1. Selection of participants for the Childhood Determinants of Adult Health (CDAH) Study, Australia, 1985–2011.

Figure 2 Relative risk (RR) of infertility and childhood BMI z score, adjusting for age, and parental status at baseline, follow-up length and marital status at adulthood. 7 to 11 years group (A) and 12 to 15 years group (B). The dashed line indicates an RR of 1. The green lines indicate the RR for the association between childhood BMI z score and adult infertility. The blue and red lines indicate the upper and lower bounds of the 95% confidence interval for the association. The axes on the graph go from 5th to 95th percentile of the childhood BMI z score distribution, which range from -1.28 to 1.57 in 7 to 11 years age group (Figure 2A) and from -1.38 to 1.69 in 12 to 15 years age group (Figure 2B).

Table 1 Characteristics of women in childhood (1985) and adulthood (2004–2011), Childhood Determinants of Adult Health study ^a

Characteristics	Ever tried for ≥ 12 months to become pregnant without succeeding		Ever seen a doctor because of trouble becoming pregnant		Any fertility problem ^c	
	Yes (n=264)	No (n=1279)	Yes (n=281)	No (n=1263)	Yes (n=346)	No (n=1198)
Childhood						
Age, years, Mean(SD)	11.5(2.4) ^b	10.9(2.5)	11.4(2.5) ^b	10.9(2.5)	11.4(2.4) ^b	10.9(2.5)
SEIFA disadvantage (%)						
High	24.3	27.5	28.9	26.4	25.8	27.2
Medium-high	30.3	28.7	27.6	29.4	29.7	28.8
Medium-low	37.2	38.1	36.9	38.2	37.8	38.0
Low	8.3	5.7	6.7	6.1	6.7	6.0
Waist circumference, cm, Mean(SD)	63.2(8.1) ^b	61.9(7.7)	62.9(8.1)	62.0(7.7)	63.0(8.0) ^b	61.9(7.7)
Waist-to-hip ratio, Mean(SD)	0.81(0.06)	0.81(0.06)	0.81(0.06)	0.81(0.06)	0.81(0.06)	0.82(0.06)
Body-mass index, kg/m ² , Mean(SD)	18.4(3.0)	18.1(2.7)	18.4(3.0)	18.1(2.7)	18.4(3.0)	18.1(2.7)
BMI category (%)						
Normal	90.1	91.6	89.6	91.8	89.9	91.8
Overweight	8.0	7.4	8.6	7.3	8.7	7.2
Obese	1.9	0.9	1.8	1.0	1.5	1.0
Smoking experimentation (%)						
None	55.7	59.2	57.9	58.7	57.1	59.0
A few puffs	20.8	21.9	19.7	22.2	20.2	22.2
<10 cigarettes	8.6	7.2	8.8	7.1	8.7	7.0
>10 cigarettes	14.9	11.7	13.6	12.0	13.9	11.8
Parental education (%)						
University education	20.1 ^b	29.1	23.8	28.4	22.5	29.0
Vocational training	37.1	33.0	34.9	33.5	35.3	33.3
High school	42.8	37.9	41.3	38.2	42.2	37.7
Alcohol assumption (%)						
Never	72.9	69.5	70.2	70.0	72.5	69.3
Less than once per week	22.6	24.6	25.0	24.1	22.3	24.9
More than once per week	4.5	5.9	4.8	5.9	5.2	5.8
Physical activity, mins/week, Mean(SD)	384(342)	398(376)	396(378)	395(368)	388(353)	398(375)
Age at menarche, years, Mean(SD)	13.1(1.3)	13.2(1.3)	13.1(1.3)	13.2(1.3)	13.1(1.3)	13.1(1.3)
Adulthood						
Age, years, Mean(SD)	33.5(2.9) ^b	34.2(3.5)	33.4(2.9) ^b	34.3(3.5)	33.4(2.8) ^b	34.2(3.5)
SEIFA disadvantage (%)						

High	26.9	24.1	25.6	24.9	26.0	24.4
Medium-high	25.4	22.9	19.9	23.5	23.4	23.2
Medium-low	23.9	25.2	24.9	25.2	24.0	25.3
Low	23.9	27.8	29.5	26.3	26.0	27.1
Body-mass index, kg/m ² , Mean(SD)	25.7(5.8)	25.2(5.4)	25.4(5.6)	25.3(5.5)	25.5(5.6)	25.3(5.4)
BMI category (%)						
Normal	56.2	60.2	58.1	59.7	57.5	60.1
Overweight	23.7	24.1	22.3	24.2	23.1	24.1
Obese	20.1	15.7	19.6	16.1	19.4	15.8
Smoking status (%)						
Never smoker	54.2	55.3	55.7	55.2	55.4	55.2
Ex-smoker	25.0	26.9	26.4	26.5	25.8	26.7
Current smoker	20.8	17.8	17.9	18.3	18.8	18.1
Self-education (%)						
University education	45.1 ^b	47.1	46.4	46.8	45.2 ^b	47.2
Vocational training	22.4	28.2	24.3	28.0	23.8	28.4
High school	32.6	24.7	29.3	25.2	31.0	24.5
Marital status (%)						
Single	2.7 ^b	22.4	2.5 ^b	22.5	2.9 ^b	23.5
Married/living as married	93.2	72.7	94.0	72.7	93.4	71.5
Separated/divorced/widowed	4.2	4.9	3.6	4.8	3.8	4.9
Alcohol consumption (%)						
Non-drinkers	29.5 ^b	21.4	24.5	22.3	27.2 ^b	21.5
Light drinkers	57.9	56.9	59.7	56.5	57.4	56.8
Moderate drinkers	10.3	16.2	13.2	15.8	12.4	16.2
Heavy /very heavy drinkers	2.3	5.6	2.6	5.4	3.0	5.5
Physical activity, mins/week, Mean(SD)	755(512)	766(495)	732(500)	770(497)	743(488)	769(501)
Follow-up length, years, Mean(SD)		22.6(2.5)		22.6(2.5)		22.5(2.5)

Childhood overweight and obesity were defined according to the international cutpoints;

Abbreviations: BMI, Body-mass Index; SEIFA, Socio-Economic Indexes for Areas; SD, standard deviation

^a Sample size ranges from 873-1543 due to missing data on some covariates

^b P<0.05

^c Women who answered yes to any one of the two related infertility questions.

Table 2 Associations between body composition measures in childhood with fertility problem in adulthood stratified by childhood age, Childhood Determinants of Adult Health study, 1985–2011.

Body Composition	Ever tried for≥12 months to become pregnant without succeeding					Ever seen a doctor because of trouble becoming pregnant					Infertility ^a				
	n	Unadjusted		Model 1		n	Unadjusted		Model 1		n	Unadjusted		Model 1	
		RR	95% CI	RR	95% CI		RR	95% CI	RR	95% CI		RR	95% CI	RR	95% CI
Age 7 to 11 years															
BMI category															
Normal	786	Ref.	—	Ref.	—	786	Ref.	—	Ref.	—	786	Ref.	—	Ref.	—
Overweight	69	0.80	0.41-1.57	0.85	0.45-1.61	69	1.18	0.71-1.98	1.30	0.82-2.07	69	1.12	0.70-1.80	1.21	0.80-1.84
Obese	8	2.59	1.04-6.43	3.89	1.95-7.77	8	2.36	0.95-5.85	3.65	1.90-7.02	8	1.94	0.78-4.80	2.94	1.48-5.84
Waist circumference	864	1.01	0.98-1.03	0.99	0.97-1.02	864	1.01	0.98-1.03	1.00	0.97-1.03	864	1.01	0.99-1.03	1.00	0.97-1.02
Waist-to-hip ratio	864	0.90	0.67-1.20	0.97	0.72-1.29	864	0.82	0.63-1.09	0.88	0.67-1.16	864	0.88	0.69-1.13	0.98	0.77-1.24
Waist-to-height ratio															
<0.5	814	Ref.	—	Ref.	—	814	Ref.	—	Ref.	—	814	Ref.	—	Ref.	—
≥0.5	49	0.99	0.49-2.00	1.17	0.60-2.27	49	0.87	0.43-1.75	1.02	0.52-1.99	49	1.04	0.59-1.84	1.29	0.76-2.18
Age 12 to 15 years															
BMI category															
Normal	622	Ref.	—	Ref.	—	623	Ref.	—	Ref.	—	623	Ref.	—	Ref.	—
Overweight	47	1.40	0.86-2.28	1.18	0.75-1.87	47	1.16	0.67-1.99	1.06	0.64-1.76	47	1.26	0.81-1.95	1.11	0.72-1.70
Obese	9	1.12	0.33-3.85	1.05	0.33-3.37	9	1.10	0.32-3.77	1.03	0.32-3.27	9	0.88	0.26-3.00	0.90	0.26-3.12
Waist circumference	679	1.01	0.99-1.03	1.01	0.99-1.03	680	1.01	0.99-1.03	1.00	0.98-1.02	680	1.01	0.99-1.02	1.00	0.99-1.02
Waist-to-hip ratio	679	1.18	0.91-1.53	1.18	0.90-1.53	680	1.23	0.95-1.58	1.23	0.95-1.59	680	1.15	0.92-1.43	1.14	0.91-1.43
Waist-to-height ratio															
<0.5	647	Ref.	—	Ref.	—	648	Ref.	—	Ref.	—	648	Ref.	—	Ref.	—
≥0.5	31	1.28	0.69-2.38	1.24	0.70-2.18	31	1.11	0.57-2.16	1.07	0.57-2.01	31	1.13	0.64-2.00	1.09	0.65-1.82

Model 1: adjusted for age and parental education at baseline, follow-up length and marital status at adulthood.

Abbreviations: BMI, body mass index; RR, risk ratio; CI, confidence interval.

^a Women answered yes to any one of the two related infertility questions.

Supplemental data

Supplemental table 1. Diagnoses and investigations in women who had seen a doctor because they were having trouble becoming pregnant, by body mass index category in childhood.

Supplemental table 2: Number of participants by weight status category from childhood to adulthood by adult infertility.

Supplemental table 3: Relative risks of infertility in adulthood according to adiposity group in childhood and adulthood.

Supplemental table 4: Sensitivity analysis using inverse propensity weighting technique. Associations between body composition measures in childhood with fertility problem in adulthood stratified by childhood age, Childhood Determinants of Adult Health Study, 1985–2011.

Supplemental table 5. Associations between childhood obesity and fertility problem in adulthood using USA CDC 95th percentile stratified by childhood age and sex, Childhood Determinants of Adult Health study, 1985–2011.

Supplemental table 6. Associations between childhood obesity and fertility problem in adulthood using 1985 ASHFS cohort 95th percentile stratified by childhood age and sex, Childhood Determinants of Adult Health study, 1985–2011.

Supplemental figure 1. Percentage of reported infertility across adiposity status from childhood to adulthood.

Supplemental table 1: Diagnoses and investigations in women who had seen a doctor because they were having trouble becoming pregnant, by body mass index category in childhood.

	Normal (n=251)	Overweight/obese (n=29)	<i>P value</i>
	No. (%)	No. (%)	
<i>Diagnoses</i>			
Ovulatory dysfunction	67 (26.7)	9 (31.0)	0.62
Tubal problem	22 (8.8)	3 (10.3)	0.73
Endometriosis	38 (15.1)	1 (3.5)	0.10
Uterine and other problem	13 (5.2)	3 (6.9)	0.66
Male factor	17 (6.8)	3 (10.3)	0.84
Unexplained	39 (15.5)	4 (13.8)	1.00
No diagnosis	80 (31.9)	10 (34.5)	0.78
<i>Investigations</i>			
Hormone test	206 (82.1)	24 (82.8)	0.93
Laparoscopy	104 (41.4)	11 (37.9)	0.72
Partner's semen analysed	160 (68.8)	15 (51.7)	0.21
No investigation	24 (9.6)	3 (10.3)	0.75

Supplemental table 2 Number of participants by weight status category from childhood to adulthood by adult infertility.

Adiposity status from childhood to adulthood	n	Infertility ^a		<i>P</i> value
		Yes n (%)	No n (%)	
Normal-normal	852	184 (21.6%)	668 (78.4%)	0.37
Normal-overweight/obese	481	107 (22.3%)	374 (77.8%)	
Overweight/obese-normal	17	2 (11.8%)	15 (88.2%)	
Overweight/obese-overweight/obese	111	31 (27.9%)	80 (72.1%)	

^a Women answered yes to any one of the two related infertility questions.

Supplemental table 3: Relative risks of infertility in adulthood according to changes in weight status from childhood to adulthood.

Changes in weight status from childhood to adulthood		n	Infertility ^a			
			Unadjusted		Model 1	
			RR	95% CI	RR	95% CI
<i>Aged 7 to 15 years</i>						
	Normal to normal	831	Ref.	—	Ref.	—
	Normal to overweight/obese	469	1.00	0.81-1.24	1.07	0.88-1.31
	Overweight/obese to normal	17	0.54	0.15-1.99	0.64	0.18-2.28
	Overweight/obese to overweight/obese	107	1.24	0.88-1.73	1.23	0.90-1.68
<i>Aged 7-11 years</i>						
	Normal to normal	476	Ref.	—	Ref.	—
	Normal to overweight/obese	257	1.03	0.75-1.40	1.08	0.80-1.46
	Overweight/obese to normal	14	0.38	0.06-2.52	0.42	0.07-2.73
	Overweight/obese to overweight/obese	56	1.42	0.88-2.27	1.60	1.04-2.48
<i>Aged 12-15 years</i>						
	Normal to normal	355	Ref.	—	Ref.	—
	Normal to overweight/obese	212	0.96	0.72-1.29	1.08	0.82-1.42
	Overweight/obese to normal	3	1.29	0.26-6.43	2.29	0.14-36.15
	Overweight/obese to overweight/obese	51	1.06	0.66-1.71	1.01	0.64-1.60

Model 1: adjust for age and parental education at baseline, follow-up length, adult education, marital status and alcohol consumption at adulthood.

^a Women answered yes to any one of the two related infertility questions.

Supplemental table 4 Sensitivity analysis using inverse propensity weighting technique. Associations between body composition measures in childhood with fertility problem in adulthood stratified by childhood age, Childhood Determinants of Adult Health Study, 1985–2011.

Body Composition		Ever tried for ≥12 months to become pregnant without succeeding				Ever seen a doctor because of trouble becoming pregnant				Infertility ^a					
	n	Unadjusted		Model 1			Unadjusted		Model 1			Unadjusted		Model 1	
		RR	95% CI	RR	95% CI		RR	95% CI	RR	95% CI		RR	95% CI	RR	95% CI
Age 7 to 11 years															
BMI category															
Normal	786	Ref.	—	Ref.	—	786	Ref.	—	Ref.	—	786	Ref.	—	Ref.	—
Overweight	69	0.78	0.40-1.54	0.84	0.44-1.60	69	1.15	0.68-1.93	1.27	0.79-2.03	69	1.09	0.68-1.75	1.19	0.78-1.82
Obese	8	2.55	1.01-6.40	3.77	1.93-7.37	8	2.31	0.92-5.79	3.53	1.88-6.65	8	1.91	0.76-4.77	2.86	1.46-5.58
Waist circumference	864	1.01	0.98-1.03	0.99	0.96-1.02	864	1.00	0.98-1.03	1.00	0.97-1.03	864	1.01	0.99-1.23	1.00	0.97-1.02
Waist-to-hip ratio	864	0.90	0.67-1.20	0.97	0.72-1.29	864	0.82	0.60-1.10	0.87	0.65-1.16	864	0.88	0.67-1.16	0.97	0.75-1.25
Waist-to-height ratio															
<0.5	814	Ref.	—	Ref.	—	814	Ref.	—	Ref.	—	814	Ref.	—	Ref.	—
≥0.5	49	0.97	0.47-1.97	1.15	0.59-2.26	49	0.81	0.40-1.65	0.95	0.48-1.88	49	1.00	0.56-1.78	1.23	0.72-2.12
Age 12 to 15 years															
BMI category															
Normal	622	Ref.	—	Ref.	—	623	Ref.	—	Ref.	—	623	Ref.	—	Ref.	—
Overweight	47	1.36	0.83-2.24	1.18	0.73-1.91	47	1.13	0.65-1.95	1.03	0.62-1.72	47	1.22	0.78-1.91	1.08	0.69-1.67
Obese	9	1.11	0.32-3.84	1.07	0.31-3.74	9	1.09	0.32-3.77	1.00	0.31-3.24	9	0.87	0.25-2.99	0.87	0.25-3.05
Waist circumference	679	1.01	0.99-1.03	1.01	0.98-1.03	680	1.00	0.97-1.03	1.00	0.98-1.02	680	1.01	0.99-1.02	1.00	0.99-1.02
Waist-to-hip ratio	679	1.16	0.89-1.50	1.15	0.87-1.51	680	1.20	0.93-1.54	1.19	0.91-1.56	680	1.13	0.91-1.39	1.11	0.88-1.40
Waist-to-height ratio															
<0.5	647	Ref.	—	Ref.	—	648	Ref.	—	Ref.	—	648	Ref.	—	Ref.	—
≥0.5	31	1.27	0.68-2.37	1.23	0.69-2.17	31	1.07	0.54-2.12	1.04	0.55-1.97	31	1.10	0.62-1.96	1.05	0.62-1.78

Model 1: adjusted for age and parental education at baseline, follow-up length and marital status at adulthood.

Abbreviations: BMI, body mass index; RR, risk ratio; CI, confidence interval.

^a Women answered yes to any one of the two related infertility questions.

Supplemental table 5: Associations between childhood obesity and fertility problem in adulthood using USA CDC 95th percentile stratified by childhood age and sex, Childhood Determinants of Adult Health study, 1985–2011^a.

Body Composition	Ever tried for≥12 months to become pregnant without succeeding					Ever seen a doctor because of trouble becoming pregnant					Infertility ^b				
	n	Unadjusted		Model 1		n	Unadjusted		Model 1		n	Unadjusted		Model 1	
		RR	95% CI	RR	95% CI		RR	95% CI	RR	95% CI		RR	95% CI	RR	95% CI
Age 7 to 11 years															
BMI category															
Normal	760	Ref.	—	Ref.	—	760	Ref.	—	Ref.	—	760	Ref.	—	Ref.	—
Overweight	76	0.63	0.30-1.29	0.63	0.31-1.27	76	0.90	0.51-1.59	0.93	0.54-1.60	76	0.87	0.52-1.46	0.90	0.56-1.47
Obese	27	1.51	0.73-3.12	1.60	0.83-3.09	27	1.85	1.01-3.38	2.10	1.25-3.52	27	1.52	0.83-2.76	1.69	1.00-2.87
Age 12 to 15 years															
BMI category															
Normal	611	Ref.	—	Ref.	—	612	Ref.	—	Ref.	—	612	Ref.	—	Ref.	—
Overweight	53	1.33	0.83-2.15	1.21	0.76-1.93	53	1.12	0.66-1.88	1.05	0.64-1.71	53	1.11	0.71-1.74	1.05	0.67-1.63
Obese	14	1.08	0.39-2.99	1.13	0.43-2.94	14	1.06	0.38-2.92	1.10	0.43-2.84	14	1.12	0.48-2.59	1.13	0.52-2.48

Model 1: adjusted for age and parental education at baseline, follow-up length and marital status at adulthood

Abbreviations: BMI, body mass index; RR, risk ratio; CI, confidence interval.

^a Normal defined as <85th percentile childhood BMI; overweight defined as 85th-94th percentile childhood BMI; obese defined as ≥ 95 th percentile childhood BMI

^b Women answered yes to any one of the two related infertility questions.

Supplemental table 6: Associations between childhood obesity and fertility problem in adulthood using 1985 ASHFS cohort 95th percentile stratified by childhood age and sex, Childhood Determinants of Adult Health study, 1985–2011^a.

Childhood BMI	Ever tried for≥12 months to become pregnant without succeeding					Ever seen a doctor because of trouble becoming pregnant					Infertility ^b				
	n	Unadjusted		Model 1		n	Unadjusted		Model 1		n	Unadjusted		Model 1	
		RR	95% CI	RR	95% CI		RR	95% CI	RR	95% CI		RR	95% CI	RR	95% CI
Age 7 to 11 years															
Normal	765	Ref.	—	Ref.	—	765	Ref.	—	Ref.	—	765	Ref.	—	Ref.	—
Overweight	67	0.51	0.21-1.19	0.55	0.24-1.27	67	0.64	0.31-1.32	0.71	0.36-1.43	67	0.60	0.31-1.18	0.67	0.35-1.29
Obese	31	1.53	0.78-2.30	1.39	0.76-2.55	31	1.99	1.17-3.40	2.20	1.40-3.46	31	1.80	1.10-2.95	1.81	1.19-2.78
Age 12 to 15 years															
Normal	601	Ref.	—	Ref.	—	602	Ref.	—	Ref.	—	602	Ref.	—	Ref.	—
Overweight	48	1.10	0.65-1.87	1.05	0.59-1.84	48	0.82	0.43-1.58	0.85	0.45-1.59	48	0.98	0.59-1.64	0.98	0.60-1.60
Obese	29	1.54	0.90-2.66	1.39	0.82-2.35	29	1.53	0.87-2.69	1.37	0.82-2.27	29	1.36	0.81-2.28	1.21	0.75-1.97

Model 1: adjusted for age and parental education at baseline, follow-up length and marital status at adulthood

Abbreviations: BMI, body mass index; RR, risk ratio; CI, confidence interval.

^a Normal defined as <85th percentile childhood BMI; overweight defined as 85th-94th percentile childhood BMI; obese defined as ≥ 95 th percentile childhood BMI

^b Women answered yes to any one of the two related infertility questions.