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

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Objective: To evaluate whether childhood obesity is associated with infertility in women's reproductive-aged life.
Design: Prospective longitudinal study.
Setting: Not applicable.
Intervention(s): None.
Patient(s): A total of 1,544 girls, aged 7–15 years in 1985, and who completed questionnaires at follow-up in 2004-2006 and/or 2009-2011.
Main Outcome Measure(s): Infertility was defined as having difficulty conceiving (had tried for ≥12 months to become pregnant without succeeding) or having seen a doctor because of trouble becoming pregnant.
Result(s): At ages from 7–11 years, girls at both the lower and upper end of the body mass index (BMI) *z* score had increased risk of infertility. Compared with normal weight girls, those with obesity at ages 7–11 years were more likely in adulthood to report infertility (adjusted relative risk [aRR] = 2.94, 95% confidence interval [CI] 1.48–5.84), difficulty conceiving (aRR = 3.89, 95% CI 1.95–7.77), or having seen a doctor because of trouble becoming pregnant (aRR = 3.65, 95% CI 1.90–7.02) after adjusting for childhood age, follow-up length, highest parental education, and marital status.
Conclusion(s): Childhood obesity before 12 years of age appears to increase the risk of female infertility in later life. (Fertil Steril® 2018;110:596-604. ©2018 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Childhood, body mass index, infertility, body composition, waist-to-height ratio

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

Few studies have investigated the association of childhood obesity with female infertility and the findings were not consistent. In a study of 3,327 British girls, Lake and colleagues (7) reported little impact of childhood body mass index (BMI) at the age of 7 years on infertility 26 years later (defined by achieving a pregnancy after ≥12 months). However, participants were restricted to women with a live birth from their first pregnancy. The BMI cutpoints were defined using an index of relative weight (weight expressed as a percentage of the standard weight for age, height, and sex). More recently, a report (8) based on 1,061 participants in the Bogalusa Heart Study in the United States showed that girls with obesity before 12 years of age were more likely in later life to have tried to become pregnant without success. Weight status was defined according to age and gender specific BMI percentiles and based on US Centers for Disease Control and Prevention statistics (e.g., ≥95th percentile for obesity). A

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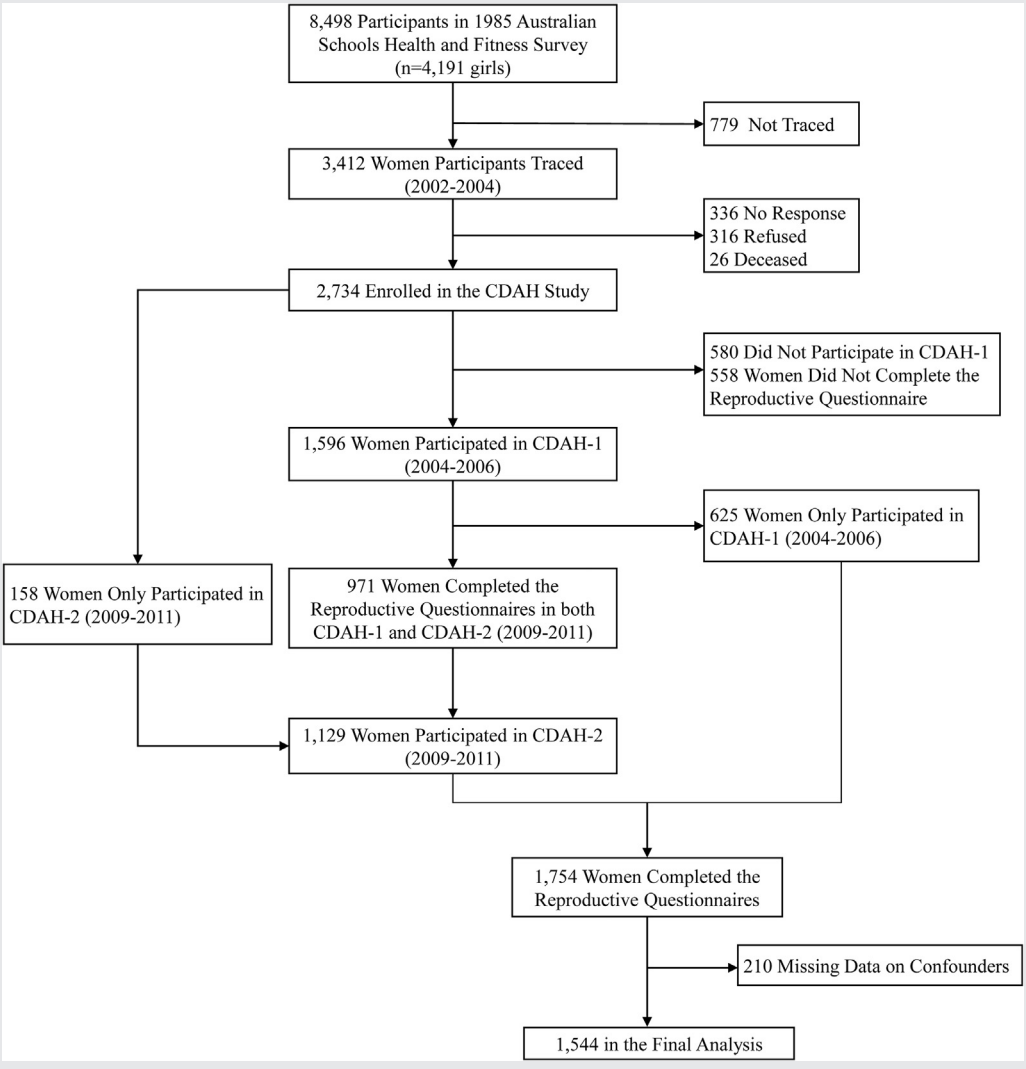
FIGURE 1



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

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limitation of this study is that it determined whether participants had "ever tried to become pregnant and were unable to" but did not specify a time interval and may 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 was able to exclude them. The aim of the present study was to examine the association between different measures of body composition at ages 7–15 years and infertility at ages 26–41 years in a large population-based sample of Australian women with consideration of a wide range of potential confounders.

MATERIALS AND 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, 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, 3,412 women participants were traced and 2,734 women agreed to participate in the CDAH study (Fig. 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 the 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

The BMI, calculated as weight (in kilograms)/height (in meters)^2, was derived from measured height and weight with weight status defined using international age- and sex-specific cutpoints (11) and was transformed into BMI *z* scores based on age- and sex-specific standardization of the full childhood cohort (n = 4,189 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 the waist circumference by height and the dichotomized into <0.5 or ≥ 0.5. Abdominal obesity was defined as WHtR ≥ 0.5 (12).

Adult Body Composition Measurement

At CDAH-1, weight and height were measured at study clinics. A subsample 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). The BMI (in kilograms per meter squared) 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. The BMI was calculated using measured height at CDAH-1, adjusted self-reported height at CDAH-1, or at enrolment.

Adult BMI was categorized into three groups (<25, 25–30, and ≥ 30 kg/m^2). Overweight was defined as 25 kg/m^2 $\leq$ BMI $\leq$29.9 kg/m^2 and obesity was defined as BMI ≥ 30 kg/m^2 (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, PCOS, hyperprolactinemia, 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 (minutes/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, exsmoker, current smoker), alcohol consumption (nondrinker, light drinker, moderate drinker, heavy/very heavy drinker), and total physical activity (minutes/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 $>10\%$ 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 factor infertility to examine whether 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 US Centers for Disease Control and Prevention norms (20) and age- and sex-specific childhood BMI in our 1985 Australian Schools Health and Fitness Survey cohort.

All analyses were performed using STATA software, version 14.2 (Stata Corp.). A P value of $<.05$ 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 cutpoints and WHtR category. The mean age at follow-up was 34 years (range, 26-41 years). There were 346 (22.4%) women who reported experiencing infertility in adulthood, including 264 (17.1%) who reported having tried for ≥12 months to become pregnant without succeeding and 281 (18.2%) who had 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; $P=.003$), had marginally lower BMI (18.2 vs. 18.4 kg/m^2; $P=.009$), and were less likely to have abdominal obesity (5.2% vs. 8.3%; $P<.001$) 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 (adjusted relative risk [aRR] = 2.94, 95% confidence interval [CI] 1.48–5.84), having ever tried for >12 months to become pregnant without succeeding (aRR = 3.89, 95% CI 1.95–7.77), and having 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 12–15 years at baseline. No significant association was found between other adiposity indicators (waist circumference, waist-to-hip ratio, and WHtR ≥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-year-old group (Fig. 2A), with the risk significantly higher in children with z scores >1.05 or < -0.80. No significant association was observed for those in the 12- to 15-year-old group (Fig. 2B).

Cause of Infertility

Most women who had seen a doctor because of trouble becoming pregnant reported one or more infertility causes and infertility investigations (Supplemental Table 1, available online). 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; $P=.10$). 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 Supplemental Figure 1 and Supplemental Table 2, both available online. 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%. Although a higher prevalence of reported infertility was observed in the persistently overweight and obese group, it did not reach statistical significance ($P=.37$). 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 years) into adulthood than those who had consistently healthy weight (Supplemental Table 3, available online).

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) for those aged 7–11 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 >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 7–11 years. Sensitivity analyses conducted by reanalyzing 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%–3.3% (Supplemental Table 4, available online). Further analysis using US Centers for Disease Control and Prevention and our cohort internal cutpoints of 85th and 95th childhood BMI percentiles showed similar significant associations of childhood obesity and infertility in the 7- to 11-year-old group (Supplemental Tables 5 and 6, available online).

TABLE 1

Characteristics of women in childhood (1985) and adulthood (2004–2011).[a]

	Tried for ≥12 mo to become pregnant without succeeding		Seen a doctor because of trouble becoming pregnant		Any fertility problem[b]	
	Yes	No	Yes	No	Yes	No
Characteristic	**(n = 264)**	**(n = 1,279)**	**(n = 281)**	**(n = 1,263)**	**(n = 346)**	**(n = 1,198)**
Childhood						
Age (y), mean ± SD	11.5 ± 2.4[c]	10.9 ± 2.5	11.4 ± 2.5[c]	10.9 ± 2.5	11.4 ± 2.4[c]	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[c]	61.9 ± 7.7	62.9 ± 8.1	62.0 ± 7.7	63.0 ± 8.0[c]	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[c]	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
<1 per wk	22.6	24.6	25.0	24.1	22.3	24.9
>1 per wk	4.5	5.9	4.8	5.9	5.2	5.8
Physical activity (min/wk), mean ± SD	384 ± 342	398 ± 376	396 ± 378	395 ± 368	388 ± 353	398 ± 375
Age at menarche (y), 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 (y), mean ± SD	33.5 ± 2.9[c]	34.2 ± 3.5	33.4 ± 2.9[c]	34.3 ± 3.5	33.4 ± 2.8[c]	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
BMI (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
Exsmoker	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[c]	47.1	46.4	46.8	45.2[c]	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[c]	22.4	2.5[c]	22.5	2.9[c]	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, %						
Nondrinkers	29.5[c]	21.4	24.5	22.3	27.2[c]	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 (min/wk), mean ± SD	755 ± 512	766 ± 495	732 ± 500	770 ± 497	743 ± 488	769 ± 501
Follow-up length (y), mean ± SD	22.6 ± 2.5		22.6 ± 2.5		22.5 ± 2.5	

Note: Childhood overweight and obesity were defined according to the international cutpoints. BMI = body mass index; SD = standard deviation; SEIFA = Socio-Economic Indexes for Areas.

[a] Sample size ranges from 873–1,543 due to missing data on some covariates.

[b] Women who answered yes to any one of the two related infertility questions.

[c] $P<.05$.

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TABLE 2

Associations between body composition measures in childhood with fertility problem in adulthood, stratified by childhood age.

	Tried for ≥12 mo to become pregnant without succeeding					Seen a doctor because of trouble becoming pregnant					Infertility[a]				
		Unadjusted		Model 1			Unadjusted		Model 1			Unadjusted		Model 1	
Body composition	**n**	**RR**	**95% CI**	**RR**	**95% CI**	**n**	**RR**	**95% CI**	**RR**	**95% CI**	**n**	**RR**	**95% CI**	**RR**	**95% CI**
Age, 7–11 y															
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, 12–15 y															
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

Note: Model 1: adjusted for age and parental education at baseline, follow-up length, and marital status at adulthood. BMI = body mass index; CI = confidence interval; RR = risk ratio.

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

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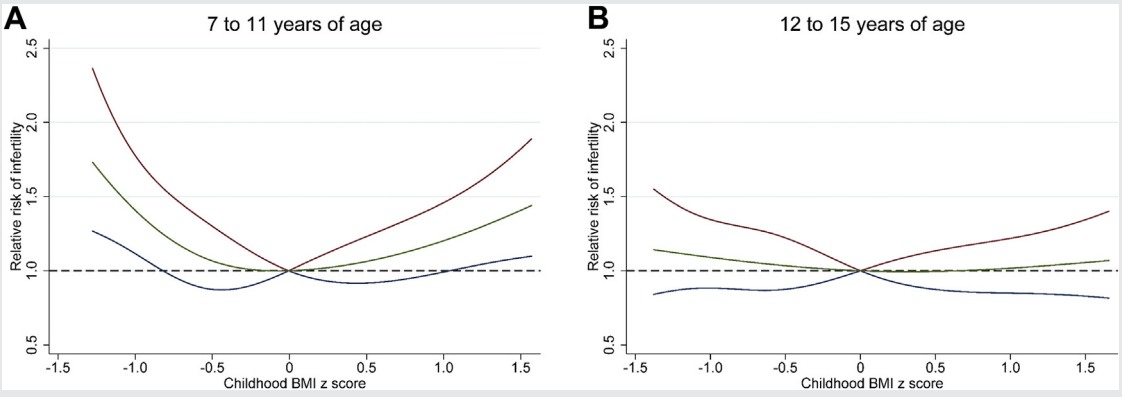
FIGURE 2



Relative risk (RR) of infertility and childhood body mass index (BMI) *z* score, adjusting for age, parental status at baseline, follow-up length, and marital status at adulthood. **(A)** 7- to 11-year-old group; **(B)** 12- to 15-year-old group. 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 7–11 years age group **(A)** and from -1.38 to 1.69 in 12–15 years age group **(B)**.

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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 (21) also suggested an inverted U-shaped between BMI in adolescence and the number of children conceived. 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 United States (8) reported that obesity before age 12 years was associated with an increased likelihood of having ever tried to become pregnant without success. In contrast, the analysis from a British cohort study (7) 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. The reasons for the inconsistent results may be the use of different methods to sample study populations (e.g., 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 prepubertal phase is a more sensitive window for the effects of high BMI on the development of reproductive capacity than later pubertal or postpubertal stages of development. A recent study (23) 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 LH surge. In humans, early-onset obesity is associated with the earlier puberty and earlier maturation of the hypothalamopituitary axis, which may impact on the development of the reproductive system in girls (24). Increased estrogen (E) produced by more body fat and accelerated aromatization of adrenal and ovarian androgens in adipose tissue promotes earlier adrenarche, pubarche, and thelarche, which may have unfavorable influences on the hypothalamopituitary 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 elevated level of 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 in the normal weight group (15.1%) was similar to findings from a recent meta-analysis (29), which pooled 11 studies of participants with ages ranging from 16–65 years and reported that more elevated BMI was associated with a lower risk of endometriosis in adulthood. Furthermore, results from our sensitivity analysis suggest that male factor 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 WHtR. In addition, our definition of having difficulty conceiving specified a time interval of having tried for ≥12 months and is more consistent with definitions used in clinical practice (30). In addition, we demonstrated associations with infertility of BMI *z* score as a continuous variable as well as obesity defined by age- and sex-specific BMI ≥95th 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 cutpoints 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 after at least one prior conception), which is important for evaluating women's ability to have children and exploring the etiology 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 ≥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 years on infertility later in life. The early prevention of childhood obesity is important for fertility, as well as disease prevention.

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Asociación de obesidad infantil con infertilidad femenina en la edad adulta: Un estudio de 25 años de seguimiento

Objetivo: Evaluar si la obesidad infantil se asocia a infertilidad en mujeres en edad reproductiva.

Diseño: Estudio prospectivo longitudinal.

Entorno: No aplica.

Intervención(es): Ninguna.

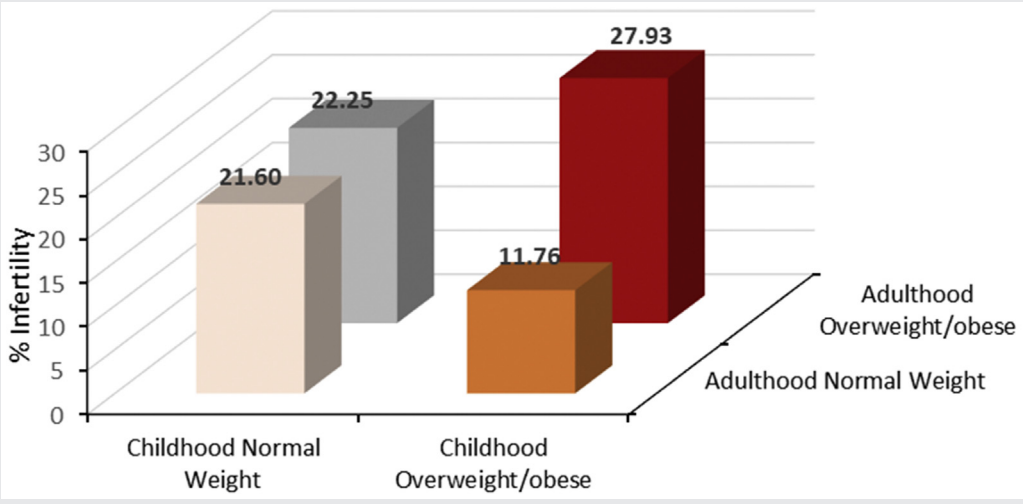
Paciente(s): Un total de 1544 niñas, con edades entre 7-15 años en 1985, y que completaron cuestionarios en seguimientos en 2004-2006 y/o 2009-2011.

Principales medidas de resultados: La infertilidad fue definida como tener dificultad para concebir (haber intentado conseguir embarazo durante $\geq$ 12 meses sin éxito), o haber visitado al médico por problemas para conseguir embarazo).

Resultado(s): A las edades de 7-11 años, las niñas en los límites inferior y superior del índice de masa corporal (IMC) tuvieron un riesgo incrementado de infertilidad. Comparadas con las niñas con peso corporal normal, aquellas con obesidad a las edades de 7-11 años fueron más propensas a reportar infertilidad en la edad adulta (riesgo relativo ajustado [aRR] = 2,94, 95% intervalo de confianza [IC] 1,48-5,84), dificultad para concebir (aRR = 3,89, 95% IC 1,95-7,77), o haber visitado a un médico por problemas para conseguir embarazo (aRR = 3,65, 95% IC 1,90-7,02) después de ajustar para edad infantil, duración del seguimiento, mayor educación de los padres y estado civil.

Conclusión: La obesidad infantil antes de los 12 años parece aumentar el riesgo de infertilidad femenina en la vida posterior.

SUPPLEMENTAL FIGURE 1



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

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