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Body Composition in Children and Adolescents Born after *in Vitro* Fertilization or Spontaneous Conception

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Context: Increasing evidence suggests that adverse conditions during prenatal life are associated with the development of chronic diseases in adult life. It is still unclear whether *in vitro* fertilization (IVF) conception could affect the vulnerable developmental processes in humans occurring during early prenatal development with long-term perturbations of developmental pathways.

Objective: Our objective was to examine body composition in 8- to 18-yr-old IVF singletons and spontaneously conceived controls born from subfertile parents.

Design and Setting: This follow-up study was conducted at the VU University Medical Center in Amsterdam, The Netherlands.

Participants: Participants included 233 IVF children (139 pubertal children) and 233 age- and gender-matched control children (143 pubertal children).

Main Outcome Measures: Body composition measures were assessed by anthropometry and dual-energy x-ray absorptiometry in the pubertal subpopulation.

Results: IVF children had a significantly lower subscapular-triceps skinfold ratio and a significantly higher sum of peripheral skinfolds, peripheral body mass, and percentage of peripheral body fat as compared with controls. Although not reaching statistical significance, both dual-energy x-ray absorptiometry and skinfold measurements suggested that total body fat in IVF children is increased. Neither current and early risk factors nor parental factors, such as subfertility cause, could explain the differences in peripheral fat assessed by anthropometry between IVF children and controls. No differences in bone mineral composition between IVF children and controls were found.

Conclusions: Our observations indicate that body fat composition in IVF children is disturbed. Follow-up of IVF children to monitor body fat pattern and potentially related health problems from adolescence into adulthood is of great importance. (***J Clin Endocrinol Metab* 92: 3417–3423, 2007**)

IN VIEW OF THE rising public health problems with regard to obesity and osteoporosis in adult life, the need to elicit determinants of body fat composition and skeletal architecture is compelling. Accumulating evidence indicates that environmental influences during prenatal life are associated with changes in adult body composition including altered fat distribution and low bone mineral content (BMC) (1–3). These associations are thought to be the consequence of programming of physiological, metabolic, and endocrine key systems whereby adaptive responses to environmental stimuli during critical or sensitive periods in early life may have long-lasting consequences (4).

The period around fertilization appears to be one of the critical time windows during which the developing conceptus is susceptible to environmentally induced changes. It has been demonstrated in animal models that poor periconceptional and preimplantational conditions can disturb both prenatal and postnatal developmental potential (5). It is still largely unclear whether developmental trajectories such as skeletal development and adipogenesis can irreversibly be perturbed by periconceptional insults. Nevertheless, the Dutch famine study demonstrated that exposure to undernutrition in early pregnancy is associated with an increased risk for obesity in adult life (6, 7). Periconceptional undernutrition was also found to increase fetal adiposity in sheep twins, suggesting the importance of environmental influences during early prenatal life for adipose tissue development (8). The number of children born after *in vitro* fertilization (IVF) treatment is steadily growing as nowadays approximately 1–3% of the current births in developed countries are established after IVF (9). Growing and convincing evidence suggests that IVF children are at increased risk of low birth weight, preterm birth, and perinatal death (10, 11). Several animal studies demonstrated that embryo manipulation techniques are linked to long-term alterations in the characteristics of fetal and postnatal growth and development (12, 13). Intriguingly, embryo culture conditions during the preimplantation period in mice were found to have detrimental influences on body mass and adiposity in adult progeny (14). It is still unclear whether the IVF process in humans could affect the vulnerable developmental processes occurring during early prenatal development with long-term perturbations of developmental pathways. Therefore, we in-

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Abbreviations: BMC, Bone mineral content; BMD, bone mineral density; BMI, body mass index; DXA, dual-energy x-ray absorptiometry; IVF, *in vitro* fertilization; SDS, SD score.

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vestigated postnatal growth and development in 8- to 18-yr-old children born from subfertile parents who were either successfully treated with IVF or conceived spontaneously after all. In the current study, we examined whether postnatal body composition is influenced by method of conception by measuring bone mass, bone density, body fat mass, and lean mass using dual-energy x-ray absorptiometry (DXA) and anthropometry in IVF children and control children. Based on the above-mentioned studies regarding prenatal programming of body composition, we hypothesized that IVF children may be at increased risk for elevated body fat mass and low bone mass.

Subjects and Methods

Study population

The OMEGA study is a Dutch retrospective cohort study aimed to examine long-term health effects of hormone stimulation. The cohort consists of 26,428 women diagnosed with subfertility problems in one of the 12 IVF clinics between 1980 and 1995; 19,840 women received IVF treatment and 6,588 women did not (15–17). Eligible women had not achieved conception after at least 1 yr of frequent unprotected intercourse at the time of their first visit to the fertility clinic. Risk factor questionnaires to the women and detailed data collection from the medical records provided information on the children born from the OMEGA participants up to 1996–1997. The questionnaire response rate was 73% among subfertile women with children. The present study was restricted to IVF and spontaneously conceived children born from OMEGA participants who were treated for subfertility in the VU medical center (VUmc). IVF children born from women treated in the VUmc who did not participate in the OMEGA study were also eligible for recruitment.

From the 553 eligible singletons born after standard IVF treatment, we invited 95% of IVF children born between 1986–1991, 74% of IVF children born between 1992–1993, and 41% of IVF children born between 1994–1995 to achieve equal representation of all 1-yr age categories. For each participating IVF child, one spontaneously conceived child of similar gender and age (≤3 months age difference) born from subfertile parents was searched. In case this control child did not want to participate, the control recruitment process was repeated until an appropriate control child was found who agreed to participate. The study protocol was approved by the ethics committee of the VUmc and by the National Medical Ethics Committee known as the Centrale Commissie Mensgebonden Onderzoek located in The Hague, The Netherlands.

Approach of eligible study subjects

Between March 2003 and March 2006, children and their parents were informed by letter about our study on growth and development of IVF children (n = 354 IVF children and n = 454 control children). By means of a reply form and a prestamped envelope, parents were able to inform us whether they were willing to participate in our study. Address information of the families was checked and/or obtained using extensive tracing techniques. After 4–8 wk, nonresponders were approached by telephone. Inclusion results are summarized in Fig. 1. In total, 72% of the IVF responders (n = 246) and 55% of the control responders (n = 233) agreed to participate, resulting in 233 matched pairs. Children and their parents gave written informed consent to participate in the study. Those children who were in the pubertal stage were recruited for additional research including DXA measurements [female criterion for puberty was at least stage 2 of breast development; male criterion was at least stage 2 of genital development and/or testis volume ≥ 4 ml, assessed according to Tanner *et al.* (18)]. In total, 85% of the pubertal children underwent DXA scanning.

Families who refused to participate in the study received a single questionnaire regarding health, education, and other characteristics of the respective child (n = 283). Nonparticipation analysis yielded no significant differences between participants and nonparticipants regarding children's current height, weight, and body mass index (BMI). On average, nonparticipating children were significantly older (12.9 ± 2.6 *vs.* 12.0 ± 2.6 yr, $P = 0.002$) and their mothers were less often highly

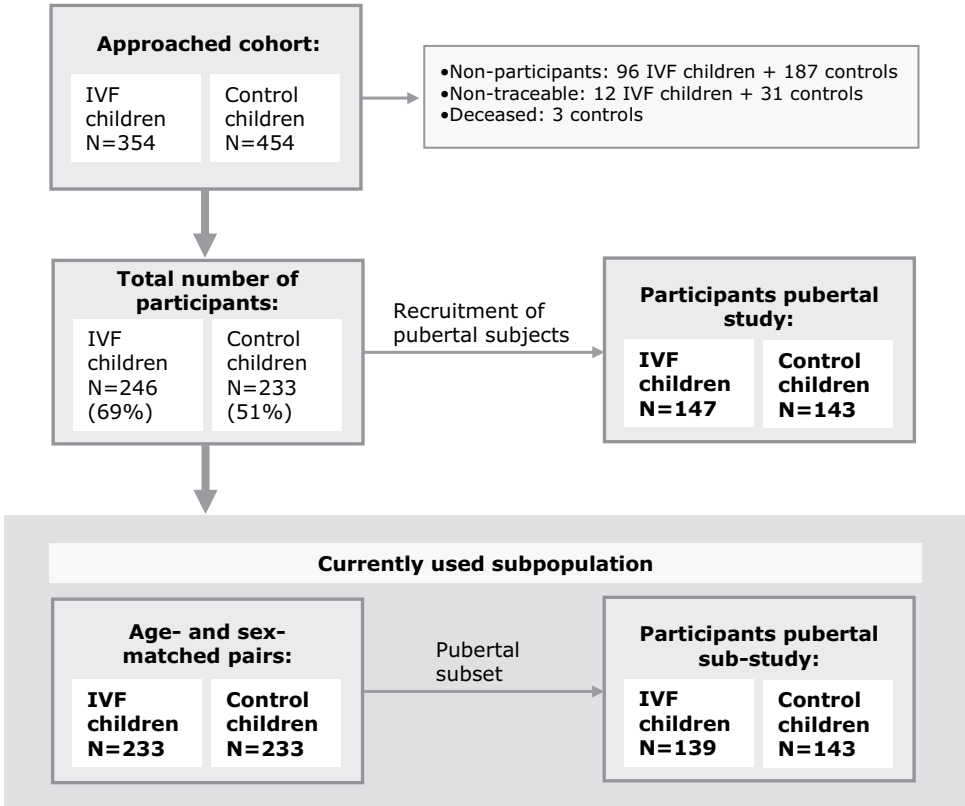

FIG. 1. Overview of the inclusion process and study population.

educated (26 *vs.* 37%, $P = 0.015$), but these differences were similar in the IVF and control population.

Data collection and measurements

Height to the nearest 0.1 cm and body weight to the nearest 0.1 kg were measured using a stadiometer with children dressed only in underwear. From these measurements, the BMI was calculated as weight divided by height squared (kilograms per square meter). SD scores (SDS) for weight, height, and BMI were calculated using a Dutch reference population (19, 20). Skinfold thickness measurements (triceps, biceps, subscapular, and suprailiac) were collected in triplicate on the nondominant side of the body by means of a Harpenden caliper. Coefficients of variation for repeated skinfold measurements at the different locations were 3.4, 4.3, 2.6, and 3.8%, respectively. The sum of the triceps and biceps skinfold was used as a measure of peripheral adiposity, the sum of the subscapular and suprailiac as an index of truncal adiposity, and the subscapular to triceps skinfold ratio was calculated as an measure of truncal to peripheral adiposity (21). The sum of the four measured skinfold thicknesses was used as an index of total adiposity. Waist circumference was measured using a tape measure (22). Pubertal maturity was assessed using breast developmental stages or genital developmental stages according to Tanner (18). The majority (94%) of the anthropometric measurements were performed by one observer (M.C.).

BMC (grams) and bone mineral density (BMD, grams per square centimeter) of the L1–L4 region of the lumbar spine, the nondominant side of the femur (femoral neck, femoral trochanter, and femoral intertrochanter, separately, and combined as total hip) and the total body were determined using the Hologic QDR-4500 bone densitometer operated in the fan beam mode (Hologic Inc., Waltham, MA). Body fat and lean mass measures were estimated from the total body scan to investigate body fat patterning. Body regions were delineated with the use of specific anatomical landmarks. All scans were analyzed using Hologic software version 12.3 and were subsequently evaluated by a single blinded investigator (J.B.).

Information regarding various demographic, lifestyle, and medical factors was obtained by questionnaire. Birth weight was either extracted from birth certificates of the VUmc (49%) or outpatient clinic reports (37%) or self-reported by the parents (14%) and were expressed as SDS to correct for gestational age and gender (23). Socioeconomical status was defined as the highest level of education completed by either parent, categorized as low (primary school, low occupational training), medium (high school, medium occupational training), and high (university, high occupational training). Other relevant outcomes, such as blood pressure levels, have been reported elsewhere.

Statistical analysis

In the present study, characteristics of 233 matched IVF control pairs were compared using the paired *t* test for continuous variables and the McNemar test for dichotomous variables (SPSS version 12.0; SPSS Inc., Chicago, IL). Differences in DXA measures between the unmatched pubertal subpopulations, consisting of 139 IVF children and 143 control subjects, were compared after correction for age and gender. Odds ratios associated with method of conception for being in the highest quartile of sum of peripheral skinfolds and in the lowest quartile of subscapular-triceps skinfold ratio were estimated by logistic regression analysis. Furthermore, linear regression analysis was carried out to explore the relation between method of conception and postnatal body composition measures after correction for current risk factors (age, sex, pubertal stage, and height), early life factors (maternal smoking during pregnancy, birth weight, and gestational age), and parental factors (parental education, maternal BMI at follow-up, and subfertility cause). The square root of height was used to adjust for body size as suggested by VanItallie *et al.* (24). Skewed-distributed variables were log-transformed before analysis. P value of <0.05 was considered to be statistically significant, based on two-sided testing.

Results

Birth weight, birth weight SDS, and gestational age were significantly lower in children conceived by IVF compared with controls (3.2 ± 0.6 *vs.* 3.4 ± 0.6 kg, $P < 0.001$; -0.15 ± 1.00 *vs.* 0.08 ± 1.08, $P = 0.025$; 38.9 ± 2.5 *vs.* 39.5 ± 1.8 wk, $P = 0.004$, respectively). Age at follow-up of IVF children and controls was 12.2 ± 2.6 yr. Table 1 presents various fat and lean mass measures of the IVF children and controls. IVF children had a significantly higher sum of peripheral skinfolds (21.9 ± 10.4 *vs.* 19.7 ± 8.9 mm, $P = 0.014$) and a significantly lower subscapular-triceps skinfold ratio com-

TABLE 1. Body fat and lean mass measurements assessed by anthropometry at follow-up in IVF-conceived subjects and control subjects

	IVF population	Control population	*P* value[a]
No. of subjects	233	233	
Age at follow-up (yr)	12.2 ± 2.6	12.2 ± 2.6	0.323
Gender (% male)	49	49	1.000
Height (cm)	156.1 ± 15.0	155.4 ± 15.6	0.297
Height SDS	0.17 ± 1.02	0.06 ± 1.01	0.232
Weight (kg)	47.5 ± 15.9	46.3 ± 14.7	0.158
Weight SDS	0.28 ± 1.08	0.14 ± 1.05	0.162
BMI (kg/m^2)	19.0 ± 3.6	18.7 ± 3.2	0.238
BMI SDS	0.28 ± 1.04	0.15 ± 1.09	0.234
Pubertal stage 1	62 (27%)	67 (29%)	0.628
Pubertal stage 2	52 (23%)	48 (21%)	
Pubertal stage 3	25 (11%)	28 (12%)	
Pubertal stage 4	43 (19%)	47 (20%)	
Pubertal stage 5	49 (21%)	41 (18%)	
Anthropometry			
Peripheral measures			
Sum of peripheral skinfolds (mm)	21.9 ± 10.4	19.7 ± 8.9	0.014
Central measures			
Sum of truncal skinfolds (mm)	18.5 ± 10.7	17.3 ± 9.6	0.190
Waist circumference (cm)	66.6 ± 9.0	66.1 ± 8.8	0.449
Central-peripheral measures			
Subscapular-triceps skinfold ratio	0.72 ± 0.22	0.77 ± 0.25	0.010
Total-body measures			
Total sum skinfolds (mm)	40.4 ± 20.3	37.1 ± 17.5	0.054

Data represent mean ± SD unless indicated otherwise.

[a] Continuous variables were analyzed using paired *t* test; dichotomous variables were analyzed using McNemar test.

pared with control children (0.72 ± 0.22 *vs.* 0.77 ± 0.25, $P = 0.010$). Likewise, children born after IVF treatment were 1.8 times more likely to be in the highest quartile of peripheral skinfold sum (≥25 mm) than control children (95% confidence interval, 1.1–3.1). Similarly, IVF-conceived children were 1.9 times more likely to be in the lowest subscapular-triceps skinfold ratio quartile (≤0.57) compared with controls (95% confidence interval, 1.2–3.3). Total sum of skinfolds appeared to be higher in IVF children, although this observation did not reach statistical significance (40.3 ± 20.3 *vs.* 37.1 ± 17.5 mm, $P = 0.054$). No differences in other anthropometric measurements such as height, weight, BMI, pubertal Tanner stage, and central fat measures between IVF children and control children were found.

Comparison of fat and lean mass measures assessed by DXA in the pubertal subset of children demonstrated that peripheral body fat mass and percentage of peripheral body fat were significantly higher in IVF children (7.59 ± 4.22 *vs.* 6.69 ± 3.15 kg, $P = 0.039$; 27.5 ± 9.0 *vs.* 25.8 ± 8.3%, $P = 0.030$, respectively) (Table 2). Absolute peripheral lean mass did not differ between IVF children and controls, whereas percentage of peripheral lean mass was significantly lower among IVF children (69.0 ± 8.7 *vs.* 70.5 ± 8.0%, $P = 0.023$). No differences in central fat and lean mass measures were found between IVF and control children. Although not statistically significant, IVF children had a different total body fat mass, percentage of total body fat, and percentage of total body lean mass compared with controls. Linear regression analysis was used to investigate whether differences in body fat composition between IVF children and controls could be explained by current risk factors, early life factors, and/or parental factors (Table 3). After correction for these potential confounding factors, differences in subscapular-triceps skinfold ratio and sum of peripheral skinfolds between IVF children and controls remained statistically significant. Total sum of skinfolds and peripheral and total body fat mass assessed by DXA seemed to be increased in IVF children after correction for potentially confounding variables, although these differences did not reach statistical significance. Variation in central body fat measures was predominantly explained by maternal smoking during pregnancy, gender, and/or height. Pearson correlation analyses demonstrated that skinfold measurements and DXA were highly correlated for sum of peripheral skinfolds and DXA peripheral body fat ($r = 0.868$; $P < 0.001$), sum of central skinfolds and DXA central body fat ($r = 0.927$; $P < 0.001$), and total sum of skinfolds and DXA total body fat ($r = 0.921$; $P < 0.001$).

Comparison of BMC and BMD between the pubertal IVF subjects and the control subjects revealed no statistically significant differences in skeletal status (Table 4). However, there seemed to be a trend toward a higher total-body BMD in IVF children (0.97 ± 0.11 *vs.* 0.95 ± 0.11 g/cm^2, $P = 0.064$). Linear regression analysis was performed to examine whether confounding variables obscured a potential association between method of conception and bone composition. After correction for sex, age, height, pubertal stage, birth weight SDS, and parental education, method of conception appeared to have no significant influence on bone mineral composition. Variation in BMC and BMD was predominantly caused by age, height, and gender.

Discussion

In the present study, we compared body composition among 8- to 18-yr-old IVF singletons and spontaneously conceived controls born from subfertile parents. Peripheral adipose tissue mass assessed by skinfold measurements and DXA was significantly higher in IVF children compared with

TABLE 2. Body fat and lean mass measurements assessed by DXA at follow-up in pubertal IVF-conceived subjects and control subjects

	IVF population	Control population	*P* value[a]
No. of subjects	136	143	
Age at follow-up (yr)	13.7 ± 2.1	13.5 ± 2.1	0.634
Gender (% male)	48	48	0.913
Pubertal stage 2	34 (25%)	36 (25%)	0.557
Pubertal stage 3	19 (14%)	27 (19%)	
Pubertal stage 4	39 (29%)	43 (30%)	
Pubertal stage 5	44 (32%)	37 (26%)	
DXA measurements			
Peripheral measures			
Peripheral fat mass (kg)	7.59 ± 4.22	6.69 ± 3.15	0.039
Peripheral fat percentage	27.5 ± 9.0	25.8 ± 8.3	0.030
Peripheral lean mass (kg)	18.27 ± 5.17	17.85 ± 4.87	0.679
Peripheral lean percentage	69.0 ± 8.7	70.5 ± 8.0	0.023
Central measures			
Central fat mass (kg)	4.80 ± 3.19	4.34 ± 2.71	0.166
Central fat percentage	18.6 ± 7.7	17.7 ± 7.2	0.180
Central lean mass (kg)	19.11 ± 4.97	18.62 ± 4.88	0.501
Central lean percentage	79.5 ± 7.5	80.4 ± 7.0	0.123
Total-body measures			
Total body fat mass (kg)	13.26 ± 7.37	11.89 ± 5.74	0.075
Total-body fat percentage	23.1 ± 7.6	21.8 ± 7.0	0.078
Total-body lean mass (kg)	40.42 ± 10.22	39.46 ± 9.91	0.555
Total-body lean percentage	73.7 ± 7.3	74.9 ± 6.7	0.060
Total-body weight (kg)	55.48 ± 15.43	53.08 ± 13.82	0.167

Data represent mean ± SD unless indicated otherwise; three children did not undergo a total-body scan.
[a] Body composition measures were corrected for age and gender.

TABLE 3. Associations between method of conception and peripheral and total-body fat measures adjusted for potential confounders

	Association with IVF after adjusting for current risk factors		Association with IVF after adjusting for current risk and early life factors		Association with IVF after adjusting for current risk, early life, and parental factors	
	β	*P* value	β	*P* value	β	*P* value
Peripheral body fat measures						
Subscapular-triceps skinfold ratio	−0.114	0.007	−0.151	<0.001	−0.143	0.001
Sum of peripheral skinfolds (mm)	0.125	0.005	0.119	0.007	0.121	0.006
DXA peripheral fat mass (kg)	0.105	0.037	0.089	0.074	0.083	0.098
Total-body fat measures						
Total sum of skinfolds (mm)	0.100	0.021	0.085	0.054	0.081	0.057
DXA total-body fat mass (kg)	0.091	0.073		NS[a]		NS[a]

Data represent standardized regression coefficients (β) describing the association between IVF conception and several body fat composition measures after correction for the following variables when appropriate: current risk factors (age, sex, height, and pubertal stage), early life factors (maternal smoking during pregnancy, birth weight, and gestational age), and parental factors (parental education, maternal BMI, and subfertility cause).

[a] Not significant; $P \geq 0.100$.

controls. Conversely, a significant lower percentage of peripheral lean tissue was observed among IVF children. Although not statistically significant, both DXA and skinfold measurements suggested that total body fat is higher in IVF children compared with controls. Differences in peripheral body fat assessed by anthropometry could not be explained either by current and early life factors or by parental factors such as subfertility cause and socioeconomic status. These observations suggest that the IVF procedure unfavorably affects body fat composition of children conceived by IVF, irrespective of potentially confounding variables.

Concerns about potential significant lifelong implications for health in IVF children have recently been expressed (25–27). Many epidemiological studies demonstrated that prenatal events can permanently program metabolic processes in the fetus that cause chronic diseases in adult life (4, 28). Because body fatness is recognized as a major risk indicator of cardiovascular disease (29), our data demonstrating a disturbed body fat composition in IVF children confirm the importance of long-term research after IVF conception. It has to be taken into account that especially peripheral adipose tissue was increased in IVF children, whereas increased risk for cardiovascular health problems has been suggested to be primarily associated with a central body fat deposition (30). On the other hand, in view of our other findings demonstrating elevated blood pressure and fasting glucose levels in IVF children compared with controls (31) (Ceelen, M., M. M. van Weissenbruch, J. P. W. Vermeiden, F. E. van Leeuwen, and H. A. Delemarre-van de Waal, submitted for publication), continued body fat monitoring in IVF children is of great importance. In addition, current knowledge regarding fat patterning development in childhood and adolescence as well as their relative contributions to the development of diseases in later life is fairly limited. There are indications that central fat deposition is increasing from adolescence into adulthood, in particular in males, due to an increase in truncal fat mass and a decrease in peripheral fat mass (32, 33).

It has been proposed that developmental plasticity after exposure to early prenatal insults can lead to irreversible changes in imprinted gene expression, nutrient and stress-related signaling pathways, and/or cell cycle and apoptotic rates (12). Especially the role of epigenetics in developmental

TABLE 4. Bone mineral measurements at various skeletal regions in adolescents according to method of conception

	IVF children (n = 139)	Control children (n = 143)	*P* value[a]
Lumbar spine			
BMC (g)	45.67 ± 14.81	44.30 ± 15.41	0.436
BMD (g/cm^2)	0.82 ± 0.16	0.80 ± 0.17	0.156
Femoral neck			
BMC (g)	3.97 ± 0.93	3.87 ± 0.94	0.504
BMD (g/cm^2)	0.78 ± 0.13	0.78 ± 0.13	0.796
Femoral trochanter			
BMC (g)	6.98 ± 2.74	6.89 ± 2.69	0.864
BMD (g/cm^2)	0.69 ± 0.13	0.69 ± 0.14	0.787
Femoral intertrochanter			
BMC (g)	18.79 ± 6.31	18.31 ± 6.47	0.583
BMD (g/cm^2)	0.99 ± 0.18	0.96 ± 0.18	0.195
Total hip			
BMC (g)	29.86 ± 9.51	29.08 ± 9.75	0.691
BMD (g/cm^2)	0.87 ± 0.14	0.86 ± 0.15	0.444
Total body			
BMC (g)	1790.2 ± 456.1	1723.9 ± 485.1	0.199
BMD (g/cm^2)	0.97 ± 0.11	0.95 ± 0.11	0.064

Data represent mean ± SD.

[a] BMC and BMD are corrected for age and gender.

plasticity is increasingly recognized. During the periconceptional period, important events including the transition of maternal to embryonic control and epigenetic reprogramming of the genome make the developing embryo highly susceptible to environmentally induced changes (34). Increasing evidence suggests that manipulation of gametes and embryos inherent to assisted reproductive technologies can perturb these important epigenetic processes causing altered expression of important genes related to fetal growth and development with both pre- and postnatal consequences (35). Additional research is necessary to investigate whether similar epigenetic mechanisms contribute to the disturbed body fat composition observed among IVF children in the present study.

With regard to skeletal status, no differences in bone mineral composition between IVF children and control children were observed in the present study. Method of conception was demonstrated to have no significant influence on BMC and BMD. There is growing evidence that environmental influences during prenatal life have long-term consequences on bone composition, which influences fracture risk in later life (36). For instance, a relation between maternal diet during pregnancy and bone mass in childhood has been found (37). Despite the lack of evidence of disturbed skeletal development in IVF children in the present study, investigation of other important processes, including the amount of attained peak bone mass during early adulthood and subsequent rate of bone loss in late adult life, are warranted.

When interpreting our results, potential limitations need to be considered. First, our study was based on 58% (n = 466) of the total number of subjects approached (n = 808). However, no differences in anthropometric measures such as height, weight, and BMI were found between the participants and nonparticipants who returned the questionnaire. Second, it must be acknowledged that both DXA and skinfold thickness measurements do not distinguish between different types of adipose tissue. Especially visceral fat has been shown to be related to several metabolic disease risk factors (30). However, skinfold measurements, which measure only sc body fat, and body fat measured by DXA, which comprises all internal and sc body fat, were highly correlated in the present study. These findings are in line with other studies, which suggested that during childhood and adolescence, most of the total body fat is deposited sc (38, 39).

In conclusion, this is the first study addressing body composition in IVF children and adolescents and controls using DXA and anthropometric measures. Although underlying mechanisms remain to be identified, the periconceptional period might represent a critical time window in humans during which environmental influences can perturb developmental pathways leading to aberrant fat distribution in postnatal life. It is of great importance that follow-up of IVF children is continued to monitor physiological changes in fat distribution from adolescence into adulthood and to address potential related health problems.

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