Metabolic health of young adults who were born small for gestational age and treated with growth hormone, after cessation of growth hormone treatment: a 5-year longitudinal study

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Summary

Background Growth hormone treatment reduces fat mass and insulin sensitivity and increases lean body mass. Data are only available for short-term longitudinal changes after cessation of growth hormone treatment in young adults born small for gestational age. We aimed to assess long-term changes over a 5-year period following cessation of growth hormone treatment.

Methods We did a longitudinal study of young adults born small for gestational age and previously treated with growth hormone. Individuals were followed up for 5 years after attainment of adult height, when growth hormone treatment was discontinued: assessments were done at cessation of growth hormone treatment and at 6 months, 2 years, and 5 years thereafter. Data 5 years after cessation of growth hormone were compared with untreated age-matched controls. We used dual-energy x-ray absorptiometry to assess body composition, and did frequently sampled intravenous glucose tolerance tests to assess insulin sensitivity, acute insulin response, and the disposition index (a measure of β-cell function). This study is registered with ISRCTN, numbers ISRCTN96883876 and ISRCTN65230311.

Findings Between April, 2004, and April, 2016, we followed up 199 young adults born small for gestational age and previously treated with growth hormone, during the 5 years after cessation of growth hormone treatment. Data at 5 years for these individuals were compared with those for 51 untreated adults born small for gestational age with short stature, 92 untreated adults born small for gestational age with spontaneous catch-up growth, and 142 adults born appropriate for gestational age and unexposed to growth hormone treatment. In young adults born small for gestational age and previously treated with growth hormone, 5 years after cessation of growth hormone treatment, there were increases in fat mass (estimated marginal mean 10·73 kg [95% CI 9·95–11·50] at cessation of treatment *vs* 16·12 kg [14·77–17·46] at 5 years; p<0·0001), trunk fat (5·34 kg [4·94–5·73] *vs* 7·86 kg [7·12–8·60]; p<0·0001), and limb fat (4·87 kg [4·49–5·25] *vs* 7·41 kg [6·78–8·05]; p<0·0001); furthermore, lean body mass had decreased (42·41 kg [95% CI 41·09–43·73] at cessation of treatment *vs* 41·42 kg [40·17–42·66] at 5 years; p=0·0013). Insulin sensitivity increased within 6 months of cessation and was sustained 5 years after treatment cessation (estimated marginal mean 4·14 mU/L [95% CI 3·79–4·53] at cessation of treatment *vs* 6·15 mU/L [5·21–7·24] at 5 years; p<0·0001), and acute insulin response was diminished at 6 months, which persisted at 5 year follow-up (597·63 mU/L [539·62–661·86] *vs* 393·69 mU/L [337·56–459·15]; p<0·0001). The disposition index was increased 6 months after treatment but values at 5 years were similar to those at cessation of treatment (2483·94 [95% CI 2233·43–2762·54] at cessation of treatment *vs* 2367·83 [2033·43–2757·22] at 5 years; p=0·49). 5 years after cessation of growth hormone treatment, adults born small for gestational age and previously treated with growth hormone had fat mass, insulin sensitivity, and disposition index similar to those of untreated adults born small for gestational age with short stature, but lean body mass (adjusted for sex and height) was lower (46·47 kg [44·95–48·00] in those born small for gestational age with short stature *vs* 44·32 kg [43·35–45·30] in those born small for gestational age and treated with growth hormone; p=0·007). In adults previously treated with growth hormone born small for gestational age, at 5 years after cessation of growth hormone treatment, compared with adults born small for gestational age with spontaneous catch-up growth and adults born appropriate for gestational age, lean body mass was lower and results from frequently sampled intravenous glucose tolerance tests were similar.

Interpretation Significant changes in body composition and insulin sensitivity were recorded 5 years after cessation of growth hormone treatment in adults born small for gestational age, reflecting a loss of pharmacological effects of growth hormone. 5 years after cessation of treatment, fat mass, insulin sensitivity, and β-cell function of previously treated adults were similar to untreated adults born small for gestational age with short stature, indicating that long-term growth hormone treatment in children born small for gestational age has no unfavourable effects on metabolic health in early adulthood.

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Research in context

Evidence before this study

We searched PubMed for articles published up to May 1, 2016, using terms related to small for gestational age birth, growth hormone treatment, and primary outcomes, with no language restrictions. Previous studies have shown that children born small for gestational age have a higher risk of metabolic diseases in adulthood. Growth hormone treatment has been approved to increase adult height; however, it causes changes in body composition and insulin resistance that could have long-term effects for children born small for gestational age. Data from the Safety and Appropriateness of Growth hormone treatments in Europe (SAGhE) project suggested that cardiovascular mortality might be increased in adults born small for gestational age who were treated with growth hormone during childhood. However, a limitation of the SAGhE project is that data for former patients were compared with national reference values and not with data for age-matched, untreated controls born small for gestational age. To study the effects of growth hormone treatment on risk for type 2 diabetes and cardiovascular diseases, data for previously treated adults born small for gestational age should be compared with those for untreated adults born small for gestational age.

Added value of this study

To our knowledge, our study is the first, longest, and largest follow-up study providing longitudinal data on metabolic safety into adulthood after cessation of growth hormone treatment. Fat mass increased steadily during the 5 years after cessation of growth hormone treatment, indicating a loss of benefits of growth hormone. Reassuringly, the growth hormone-induced reduction in insulin sensitivity was fully reversed within 6 months after cessation of growth hormone treatment, despite the increase in fat mass. Furthermore, to our knowledge, our study is the first to compare metabolic health at the age of 21 years with untreated controls born small for gestational age or appropriate for gestational age. Body composition and insulin sensitivity of adults born small for gestational age and treated with growth hormone were similar compared with untreated controls born small for gestational age or appropriate for gestational age.

Implications of all the available evidence

Long-term growth hormone treatment of children born small for gestational age with short stature does not have an unfavourable effect on metabolic health in young adulthood. Previous concerns are hereby diminished and growth hormone treatment can be administered safely in clinical practice.

Introduction

Approximately 10% of children born small for gestational age show insufficient catch-up growth and remain short, with a height below –2 SDS (SD score).[1,2] Growth hormone treatment induces catch-up growth and increases adult height effectively in children of short stature born small for gestational age.[3–6] It also results in a decline in fat mass, an increase in lean body mass, and a lower insulin sensitivity.[7,8]

Children born small for gestational age are at high risk of developing type 2 diabetes in adulthood.[9–11] Since growth hormone treatment induces insulin resistance,[12,13] concern has been expressed about the long-term outcomes of treatment with growth hormone in children born small for gestational age. Moreover, data from the Safety and Appropriateness of Growth hormone treatments in Europe (SAGhE) project indicated that cardiovascular mortality might be increased in adults born small for gestational age who were treated with growth hormone during childhood.[14] However, the SAGhE project is limited by the absence of an appropriate control group of untreated patients born small for gestational age. To study the effect of growth hormone treatment on risks for type 2 diabetes and cardiovascular diseases, it is important not only to address the already known increased risk for these diseases in children born small for gestational age but also to compare adults born small for gestational age and previously treated with growth hormone with untreated controls born small for gestational age.

The primary aim of our study was to investigate longitudinal changes in insulin sensitivity and body composition after cessation of growth hormone treatment. Therefore, we aimed to assess body composition and frequently sampled intravenous glucose tolerance test results in young adults born small for gestational age and previously treated with growth hormone, during the 5-year period after cessation of growth hormone treatment. We postulated that after cessation of treatment, body composition would change in line with the loss of pharmacological effects of growth hormone—ie, an increase in fat mass and a decrease in lean body mass—and that insulin resistance induced by growth hormone would be reversible. We aimed to compare data obtained for these young adults 5 years after cessation of growth hormone with those from young adults born small for gestational age with persistent short stature who were never treated with growth hormone, to assess the effect of growth hormone treatment during childhood on body composition and insulin sensitivity in early adulthood. We also postulated that body composition and frequently sampled intravenous glucose tolerance test results in adults born small for gestational age and previously treated with growth hormone would return to levels similar to those recorded in untreated adults of short stature born small for gestational age. Furthermore, to investigate whether catch-up growth induced by growth hormone has a similar effect on adult body composition as does spontaneous catch-up growth, we additionally compared

data obtained 5 years after cessation of growth hormone treatment with untreated young adults born small for gestational age with spontaneous catch-up growth to a normal stature.

Methods

Participants

We did a longitudinal study in the Netherlands, including adults born small for gestational age and previously treated with growth hormone and three different control groups. We enrolled in our study young adults born small for gestational age (below –2 SDS for birthweight, birth length, or both) who had participated in one of two similar growth hormone trials (ISRCTN96883876 and ISRCTN65230311) in which treatment was started before puberty (aged 5–8 years), with a height SDS below –2·5 and no growth failure caused by other disorders. Children with endocrine or metabolic disorders were excluded from these growth hormone trials. Children with a growth hormone deficiency (defined as maximum serum growth hormone <20 mU/L during a growth hormone stimulation test) were excluded from the growth hormone trials. Children were to continue growth hormone treatment until they reached adult height, according to the protocol of the growth hormone trials. At cessation of treatment, we invited the young adults to participate in our 5-year follow-up study. We excluded individuals who used drugs that could affect glucose homoeostasis.

For controls, we obtained data from a study cohort of age-matched healthy young adults (aged 18–24 years) who had not received growth hormone treatment. That study cohort included individuals born small for gestational age (birth length below –2 SDS) with persistent short stature (below –2 SDS) or with catch-up growth resulting in normal adult height (more than –1 SDS) and young adults born appropriate for gestational age (birth length above –1 SDS) with normal adult height (more than –1 SDS). The controls who were born small for gestational age were recruited from several hospitals in the Netherlands by reviewing hospital records from birth onwards, using the same inclusion and exclusion criteria as we did for children born small for gestational age treated with growth hormone. Healthy young adults from schools of different educational levels were randomly asked to participate as controls born appropriate for gestational age.

The medical ethics committee of the Erasmus University Medical Center approved this study and the original growth hormone trials. We obtained written informed consent from all participants and, if they were younger than 18 years at cessation of growth hormone treatment, from their parents or guardians.

Procedures

In the original growth hormone trials, participants received the approved daily dose of growth hormone (in Europe, 1 mg/m², or roughly 0·033 mg/kg), which was given subcutaneously at bedtime (Norditropin; Novo Nordisk A/S, Bagsværd, Denmark).[15] Every 3 months, the dose of growth hormone was adjusted to the calculated body surface area. Treatment with growth hormone was discontinued when adult height was attained.

To assess metabolic health at adult height, we took measurements for adults born small for gestational age and treated with growth hormone at cessation of growth hormone treatment then at 6 months, 2 years, and 5 years thereafter. We measured standing height to the nearest 0·1 cm (Harpenden stadiometer; Holtain, Crymmyth, UK) and weight to the nearest 0·1 kg on a digital scale (Servo Balance KA-20-150S; Servo Berkel

	Previously treated with growth hormone, born small for gestational age (n=199)	Untreated, born small for gestational age, short stature (n=51)	Untreated, born small for gestational age, spontaneous catch-up growth (n=92)	Untreated, born appropriate for gestational age (n=142)
Male sex	96 (48%)	18 (35%)	38 (41%)	67 (47%)
Female sex	103 (52%)	33 (65%)	54 (59%)	75 (53%)
Gestational age at birth (weeks)	36·0 (3·8)	38·1 (3·1)*	36·0 (3·4)	36·3 (4·1)
Birth length (SDS)	–3·2 (1·6)	–3·0 (0·9)	–3·0 (0·8)	0·2 (0·8)†
Birthweight (SDS)	–2·3 (1·2)	–2·1 (0·9)	–2·3 (0·8)	0·3 (1·2)†
At start of growth hormone treatment				
Age (years)	6·4 (2·0)	N/A	N/A	N/A
Height (SDS)	–3·0 (0·6)	N/A	N/A	N/A
Weight for height (SDS)	–1·5 (1·2)	N/A	N/A	N/A
At cessation of treatment				
Age (years)	16·4 (1·3)	N/A	N/A	N/A
Height (SDS)	–1·2 (0·8)	N/A	N/A	N/A
Weight for height (SDS)	–0·7 (1·1)	N/A	N/A	N/A
Weight for age (SDS)	–0·9 (0·9)	N/A	N/A	N/A
Systolic blood pressure (SDS)	0·17 (0·8)	N/A	N/A	N/A
Diastolic blood pressure (SDS)	0·02 (0·6)	N/A	N/A	N/A
Duration of growth hormone treatment (years)	10·0 (2·3)	N/A	N/A	N/A
At 5 years after cessation of treatment				
Male sex	36/88 (41%)	18/51 (35%)	38/92 (41%)	67/142 (47%)
Female sex	52/88 (59%)	33/51 (65%)	54/92 (59%)	75/142 (53%)
Age (years)	21·3 (1·5)	20·9 (1·8)	20·7 (1·7)	20·9 (1·7)
Adult height (SDS)	–1·6 (0·9)†	–2·6 (0·5)†	–0·2 (0·7)‡	0·1 (0·8)
Weight for age (SDS)	–1·4 (1·5)§	–1·4 (1·5)§	–0·02 (1·2)	0·2 (0·9)
Systolic blood pressure (SDS)	0·32 (1·0)	0·22 (1·1)	0·36 (1·0)	0·24 (0·8)
Diastolic blood pressure (SDS)	0·24 (0·7)	0·49 (0·8)	0·53 (0·7)	0·42 (0·6)
Smoking (%)	25 (28%)	13 (25%)	26 (28%)	34 (24%)
Alcohol users (%)	72 (82%)	39 (76%)	71 (77%)	116 (82%)
Low socioeconomic status	10/81 (12%)	10/45 (22%)	12/80 (15%)	6/128 (5%)
Middle socioeconomic status	47/81 (58%)	13/45 (29%)	25/80 (31%)	23/128 (18%)
High socioeconomic status	24/81 (30%)	22/45 (49%)	43/80 (54%)	99/128 (77%)

Data are number of patients (%) or mean (SD), unless otherwise stated. N/A=not applicable. SDS=SD score. *p=0·0032 compared with other groups. †p<0·0001 compared with other groups. ‡p=0·0016 compared with controls born appropriate for gestational age. §p<0·0001 compared with controls born small for gestational age with catch-up growth and those born appropriate for gestational age.

Table 1: **Clinical characteristics**

Prior, Katwijk, Netherlands). We expressed height and weight as SDS, adjusted for chronological age and sex; we expressed weight during growth hormone treatment as SDS adjusted for height and sex, with references for Dutch adults, using Growth Analyser Research Calculation Tools (Growth Analyser BV, Rotterdam, Netherlands).[16] We calculated adult height as SDS 5 years after cessation of growth hormone treatment, with references for Dutch adults (age 21 years). We measured brachial diastolic blood pressure and systolic blood pressure in the supine position on the non-dominant arm after 10 min of rest, with an automatic device every 5 min for 1 h. We took the mean of these 13 measurements to reflect resting blood pressure. We expressed blood pressure as SDS, with sex-matched and age-matched reference values.[17] Depending on education level, we scored participants' socioeconomic status between 1 (low) and 3 (high).

We measured body composition at every timepoint using one dual-energy x-ray absorptiometry scanner (Lunar Prodigy, GE Healthcare, Chalfont St Giles, UK). We did quality assurance daily. For this type of dual-energy x-ray absorptiometry, the intra-assay coefficient of variation has been reported as 0·41–0·88% for fat tissue and 1·57–4·49% for lean body mass.[18] We measured total fat mass, lean body mass, trunk fat, and limb fat.

We assessed glucose homoeostasis with the frequently sampled intravenous glucose tolerance test with tolbutamide after an overnight fast.[19] We calculated insulin sensitivity, glucose effectiveness, acute insulin response, and the disposition index using Bergman's MINMOD Millennium software (version 6.01).[20] Insulin sensitivity quantifies the capacity of insulin to stimulate glucose disposal and glucose effectiveness reflects the capacity of glucose to mediate its own disposal. Acute insulin response is an estimate of insulin secretory capacity, measured as the area under the curve from 0 min to 10 min, corrected for baseline insulin levels. The disposition index is a measure of β-cell function and is calculated as insulin sensitivity multiplied by acute insulin response.

We ascertained fasting glucose on an Architect ci8200 system (Abbott Diagnostics, Lake Forest, IL, USA). We measured fasting insulin by immunoradiometric assay (IRMA; Medgenix, Biosource Europe, Nivelles, Belgium) with an intra-assay coefficient of variation of 2·1% to 1·5% (6·6–53·3 mg equivalents [mE]/L) and interassay coefficient of variation 6·5% to 6·1% (14·4–100·4 mE/L). As described elsewhere,[21] we measured serum IGF-1 at one laboratory using specific radioimmunoassays. We expressed amounts in serum of IGF-1 as SDS, adjusting for age and sex, using reference values for healthy children with normal stature measured in the same laboratory.[22]

Outcomes

Our primary outcome was to assess changes in body composition (total fat mass, lean body mass, trunk fat, and limb fat) and frequently sampled intravenous glucose tolerance test results (insulin sensitivity, glucose effectiveness, acute insulin response, and disposition index) from cessation of treatment to 5 years. Further, we investigated blood pressure, fasting glucose, fasting insulin, and IGF-1. Our secondary outcome was to compare body composition and frequently sampled intravenous glucose tolerance test results for individuals treated with growth hormone born small for gestational age with those for untreated age-matched controls.

Statistical analysis

We did statistical analyses with SPSS version 23. We ascertained the distribution of variables with the Kolmogorov-Smirnov test and normal Q-Q-plots. We have presented clinical characteristics as mean (SD). We used ANOVA to calculate differences between subgroups. Because of skewed distributions, we log-transformed insulin sensitivity, glucose effectiveness, acute insulin response, and the disposition index. We used transformed data to calculate the differences between groups; we transformed mean data used in the figures and tables back to original units. To assess longitudinal changes in body composition and frequently sampled intravenous glucose tolerance test results, we used repeated measurements analysis with an unstructured covariance type, which takes into account the missing data. For the initial analysis of longitudinal changes in body composition, frequently sampled intravenous glucose tolerance test results, and IGF-1 concentrations, we did not use covariates. For analyses with additional adjustment for age, the covariate was age in years. With Pearson's correlation test, we calculated correlations between IGF-1

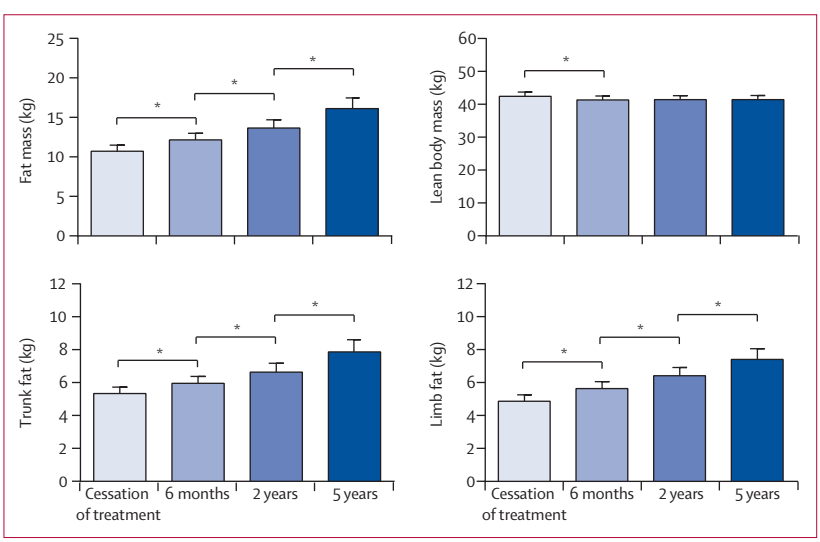

Figure 1: **Longitudinal changes in body composition variables**
Date are for adults born small for gestational age and previously treated with growth hormone. Bars represent the estimated marginal mean and error bars the upper limit of the 95% CI. *p<0·0001.

SDS and fat mass; between birthweight, birth length, and lean body mass; and between socioeconomic status and body composition. We used ANCOVA for comparisons between groups at age 21 years.

We did a power calculation to calculate the sample size. In previous studies,[23] the insulin sensitivity for adults born small for gestational age treated with growth hormone was mean 5·8 mU/L (SD 3·0) and for healthy controls (appropriate for gestational age) it was 7·4 mU/L (4·0), suggesting that healthy controls have an insulin sensitivity that is roughly 25% higher than in individuals born small for gestational age. Therefore, we used a non-inferiority margin of 25% (corresponding to an absolute margin of 1·45 mU/L). Assuming equal means and an SD of 3·45, with a non-inferiority test (one-sided, α=0·025, *t* test), a sample size of 50 participants in each group would have a power of 80%. We expressed data for longitudinal analyses and group comparisons as estimated marginal means (95% CI). We judged p less than 0·05 significant.

This study is registered with ISRCTN, numbers ISRCTN96883876 and ISRCTN65230311.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The growth hormone trials included 283 young children born small for gestational age, of whom 42 dropped out during growth hormone treatment and 241 continued with treatment until they reached adult height. Of these 241 young adults, 42 did not want to participate in our follow-up study because of the time-consuming aspect of the tests or a fear of intravenous catheters (appendix p 1). Of 285 untreated healthy young adults, 51 were born small for gestational age with persistent short stature, 92 were born small for gestational age with spontaneous catch-up growth resulting in a normal adult height, and 142 were born appropriate for gestational age (appendix p 2). Therefore, the total study group comprised 484 young adults, of whom 199 were born small for gestational age and had participated in a growth hormone trial and 285 were age-matched untreated controls.

Our study was undertaken between April, 2004, and April, 2016. Of 199 adults born small for gestational age and treated with growth hormone, not all had completed data at all four study assessments: 166 provided data at cessation of treatment; 138 participated at 6 months; 127 had data at 2 years; and 88 had available data at 5 years (table 1). 5 years after cessation of treatment, 91 patients could not participate in our study because they had discontinued growth hormone treatment for fewer than 5 years. Their baseline characteristics were

	Estimated marginal mean (95% CI)	Time period for changes	p value
Fat mass (kg)			
Cessation of treatment	10·73 (9·95 to 11·50)	0 months to 6 months	<0·0001
6 months after cessation	12·16 (11·33 to 12·99)	6 months to 2 years	<0·0001
2 years after cessation	13·65 (12·61 to 14·69)	2 years to 5 years	<0·0001
5 years after cessation	16·12 (14·77 to 17·46)	0 months to 5 years	<0·0001
Trunk fat (kg)			
Cessation of treatment	5·34 (4·94 to 5·73)	0 months to 6 months	<0·0001
6 months after cessation	5·96 (5·54 to 6·38)	6 months to 2 years	<0·0001
2 years after cessation	6·63 (6·09 to 7·18)	2 years to 5 years	<0·0001
5 years after cessation	7·86 (7·12 to 8·60)	0 months to 5 years	<0·0001
Limb fat (kg)			
Cessation of treatment	4·87 (4·49 to 5·25)	0 months to 6 months	<0·0001
6 months after cessation	5·64 (5·22 to 6·05)	6 months to 2 years	<0·0001
2 years after cessation	6·41 (5·91 to 6·92)	2 years to 5 years	<0·0001
5 years after cessation	7·41 (6·78 to 8·05)	0 months to 5 years	<0·0001
Lean body mass (kg)			
Cessation of treatment	42·41 (41·09 to 43·73)	0 months to 6 months	<0·0001
6 months after cessation	41·32 (40·10 to 42·54)	6 months to 2 years	0·49
2 years after cessation	41·43 (40·22 to 42·64)	2 years to 5 years	0·95
5 years after cessation	41·42 (40·17 to 42·66)	0 months to 5 years	0·0013
Lean body mass after adjustment for age (kg)			
Cessation of treatment	46·81 (45·38 to 48·24)	0 months to 6 months	<0·0001
6 months after cessation	44·12 (42·96 to 45·29)	6 months to 2 years	<0·0001
2 years after cessation	39·59 (38·52 to 40·67)	2 years to 5 years	<0·0001
5 years after cessation	30·42 (27·78 to 33·06)	0 months to 5 years	<0·0001
IGF-1 (SDS)			
Cessation of treatment	1·18 (1·00 to 1·37)	0 months to 6 months	<0·0001
6 months after cessation	−0·11 (−0·27 to 0·05)	6 months to 2 years	0·15
2 years after cessation	−0·24 (−0·42 to −0·07)	2 years to 5 years	0·58
5 years after cessation	−0·35 (−0·75 to 0·05)	0 months to 5 years	<0·0001
Insulin sensitivity (mU/L)			
Cessation of treatment	4·14 (3·79 to 4·53)	0 months to 6 months	<0·0001
6 months after cessation	6·30 (5·65 to 7·01)	6 months to 2 years	0·21
2 years after cessation	5·74 (4·89 to 6·76)	2 years to 5 years	0·52
5 years after cessation	6·15 (5·21 to 7·24)	0 months to 5 years	<0·0001
Glucose effectiveness (mg/dL)			
Cessation of treatment	0·017 (0·016 to 0·018)	0 months to 6 months	0·0019
6 months after cessation	0·019 (0·018 to 0·020)	6 months to 2 years	0·76
2 years after cessation	0·019 (0·017 to 0·021)	2 years to 5 years	0·32
5 years after cessation	0·020 (0·019 to 0·022)	0 months to 5 years	0·0002
Acute insulin response (mU/L)			
Cessation of treatment	597·63 (539·62 to 661·86)	0 months to 6 months	<0·0001
6 months after cessation	480·12 (430·00 to 536·09)	6 months to 2 years	0·91
2 years after cessation	476·50 (415·01 to 547·10)	2 years to 5 years	0·033
5 years after cessation	393·69 (337·56 to 459·15)	0 months to 5 years	<0·0001
Disposition index*			
Cessation of treatment	2483·94 (2233·43 to 2762·54)	0 months to 6 months	0·0002
6 months after cessation	3090·30 (2797·49 to 3413·74)	6 months to 2 years	0·11
2 years after cessation	2759·10 (2411·67 to 3156·60)	2 years to 5 years	0·087
5 years after cessation	2367·83 (2033·43 to 2757·22)	0 months to 5 years	0·49

Data are for adults born small for gestational age and previously treated with growth hormone. SDS=SD score.
*A measure of β-cell function, calculated as insulin sensitivity × acute insulin response.

Table 2: **Repeated measurements analysis of outcome measures during 5 years after cessation of treatment**

See Online for appendix

similar to those of the 88 participants who had available data 5 years after treatment cessation (data not shown), and were therefore assumed to be missing at random.

Among adults born small for gestational age and previously treated with growth hormone, mean age at the start of growth hormone treatment was 6·4 years (SD 2·0) and mean duration of treatment was 10·0 years (2·3). 5 years after cessation of treatment, mean age was 21·3 years (1·5), which was similar to that of untreated adults born small for gestational age with short stature, those born small for gestational age with catch-up growth, and those born appropriate for gestational age (table 1). In adults born small for gestational age and previously treated with growth hormone, adult height at 5 years was –1·6 SDS (0·9), which was higher than that for untreated adults born small for gestational age and of short stature (–2·6 [0·5]; p<0·0001) but lower than that for untreated adults born small for gestational age with spontaneous catch-up growth (–0·2 [0·7]; p<0·0001) and those born appropriate for gestational age (0·1 [0·8]).

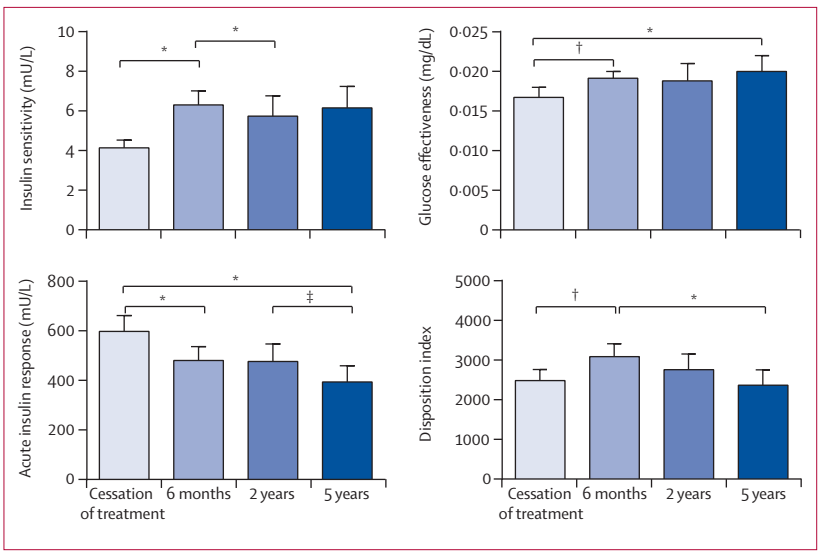

Figure 2: **Longitudinal changes in frequently sampled intravenous glucose tolerance test results**
Date are for adults born small for gestational age and previously treated with growth hormone. Bars represent the estimated marginal mean and error bars the upper limit of the 95% CI. Disposition index is a measure of β-cell function, calculated as insulin sensitivity × acute insulin response. *p<0·0001. †p=0·0002. ‡p=0·033.

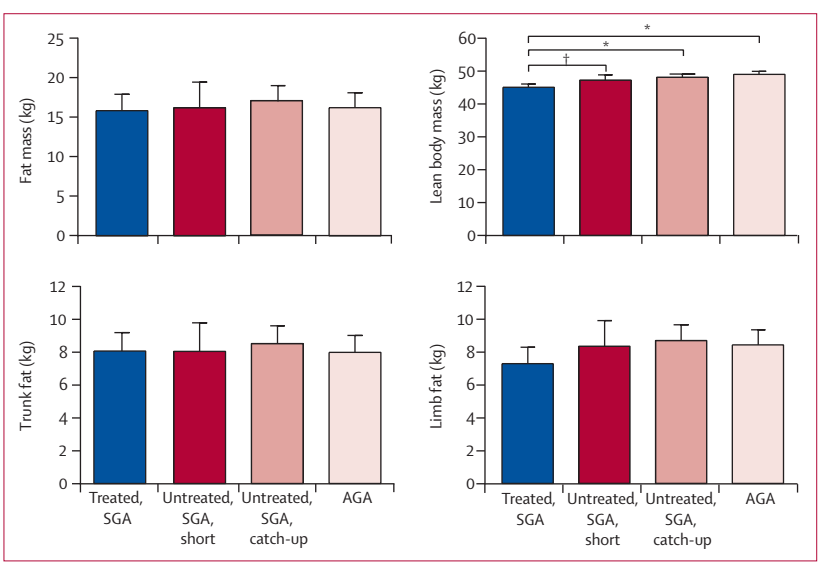

Figure 3: **Comparison of body composition variables**
Date are for adults born small for gestational age and previously treated with growth hormone, untreated adults born small for gestational age with short stature, untreated adults born small for gestational age with spontaneous catch-up growth, and adults born appropriate for gestational age. Data for treated individuals are 5 years after cessation of treatment. Bars represent the estimated marginal mean and error bars the upper limit of the 95% CI. AGA=appropriate for gestational age. SGA=small for gestational age. *p<0·0001. †p=0·0071.

Figure 1 shows the longitudinal changes in body composition in adults born small for gestational age and previously treated with growth hormone after cessation of growth hormone treatment. During the first 6 months after cessation of treatment, fat mass, trunk fat, and limb fat increased significantly (p<0·0001) and continued to steadily increase at every timepoint assessed up to 5 years (p<0·0001; table 2). Adjustment for age did not change these results (data not shown). During the first 6 months after cessation of growth hormone treatment, lean body mass declined (p<0·0001) and remained at a similar level thereafter, resulting in a lower lean body mass at 5 years after growth hormone cessation compared with at cessation of treatment (p=0·0013). After adjustment for age, lean body mass declined steadily during the 5-year period after cessation of growth hormone (p<0·0001; table 2).

IGF-1 SDS declined from 1·18 (95% CI 1·00 to 1·37) at cessation of growth hormone treatment to –0·11 SDS (–0·27 to 0·05) at 6-month follow-up (mean change –1·29, 95% CI –1·48 to –1·01; p<0·0001) and remained similar thereafter. No correlations were noted between serum IGF-1 SDS and fat mass or lean body mass at cessation of growth hormone or at 6 months, 2 years, and 5 years of follow-up (data not shown).

Figure 2 shows the longitudinal changes in insulin sensitivity, glucose effectiveness, acute insulin response, and disposition index after growth hormone cessation in adults born small for gestational age and previously treated with growth hormone (table 2). During the first 6 months after cessation of growth hormone, significant increases were recorded in insulin sensitivity (p<0·0001) and glucose effectiveness (p=0·0019), which were maintained at 5 years (p<0·0001 for both; table 2). The acute insulin response decreased during the first 6 months after cessation of growth hormone treatment (p<0·0001) and remained steady until the 2-year assessment, then fell again 5 years after cessation of treatment (p<0·0001). The disposition index (the proxy for β-cell function) increased significantly during the first 6 months after cessation of growth hormone treatment (p=0·0002), but at 5 years after cessation of growth hormone treatment, it was similar to the level recorded at treatment cessation (p=0·49). Additional adjustment for fat mass and age did not change these results (data not shown). None of the participants had

glucose intolerance or developed type 2 diabetes, neither during growth hormone treatment nor up to 5 years after treatment cessation (data not shown).

Adults born small for gestational age and previously treated with growth hormone differed from the three groups of controls with respect to male:female ratio and adult height (table 1), which are important factors for body composition; therefore, we adjusted the analyses comparing the study groups for sex and height (figure 3). 5 years after cessation of treatment, fat mass and fat distribution (trunk fat and limb fat) were similar in the four study groups (table 3). A negative correlation was recorded between socioeconomic status and trunk fat mass (r=–0·158, p=0·004). Additional adjustment for socioeconomic status did not change the results for trunk fat (data not shown). No correlation was recorded between socioeconomic status and other body composition outcomes (data not shown). Lean body mass (adjusted for sex and height) was lowest in adults born small for gestational age and previously treated with growth hormone compared with untreated controls (table 3). Positive correlations were recorded between birthweight and lean body mass (r=0·338, p<0·0001) and between birth length and lean body mass (r=0·151, p=0·006). After adjustment for birthweight and birth length, lean body mass was similar between adults born small for gestational age and previously treated with growth hormone and untreated adults born small for gestational age and of short stature, but was lower compared with untreated adults with spontaneous catch-up growth and those born appropriate for gestational age (table 3).

Because of the noted differences in male:female ratio between the four study groups, comparisons for frequently sampled intravenous glucose tolerance test results were adjusted for sex (figure 4). 5 years after cessation, adults born small for gestational age and previously treated with growth hormone had measures of insulin sensitivity, glucose effectiveness, acute insulin response, and disposition index similar to those for untreated adults of short stature. Glucose effectiveness was higher in adults born small for gestational age and previously treated with growth hormone compared with untreated adults born small for gestational age with spontaneous catch-up growth or those born appropriate for gestational age, whereas insulin sensitivity, acute insulin response, and disposition index were similar to the two control groups (table 3). Adults born small for gestational age with spontaneous catch-up growth had the lowest levels of insulin sensitivity and glucose effectiveness: the level of insulin sensitivity was lower than in adults born appropriate for gestational age (p=0·006) and glucose effectiveness was lower compared with adults born small for gestational age and previously treated with growth hormone (p=0·003).

Mean systolic and diastolic blood pressure remained within the normal range during the 5-year study period (table 1). Diastolic blood pressure SDS was lowest in adults born small for gestational age and previously treated with growth hormone (0·24 [95% CI 0·10–0·38]) compared with untreated adults of short stature (0·49 [0·31–0·68]; p=0·030), those with spontaneous catch-up growth (0·53 [0·39–0·67]; p=0·004), and adults born appropriate for gestational age (0·42 [0·31–0·53]; p=0·040). Adjustment for height did not change these results (data not shown). After adjustment for the number of cigarettes smoked per day, diastolic blood pressure was similar between all subgroups of participants (data not shown).

Discussion

Our longitudinal study during the 5-year period after cessation of growth hormone treatment is, as far as we know, the longest and largest follow-up study of young adults born small for gestational age and previously treated with growth hormone. Our findings show that cessation of growth hormone treatment in these individuals has pronounced effects on body composition, insulin sensitivity, and β-cell function, reflecting the loss of pharmacological effects of growth hormone. Insulin resistance that was induced by use of growth hormone

	Estimated marginal mean (95% CI)	p value*
Fat mass (kg) after adjustment for sex and height		
Treated with growth hormone, born small for gestational age	15·81 (13·76–17·86)	
Untreated, born small for gestational age, short stature	16·19 (12·98–19·39)	0·82
Untreated, born small for gestational age, spontaneous catch-up growth	16·98 (15·00–18·95)	0·45
Untreated, born appropriate for gestational age	16·17 (14·29–18·05)	0·82
Trunk fat (kg) after adjustment for sex and height		
Treated with growth hormone, born small for gestational age	7·99 (6·89–9·09)	
Untreated, born small for gestational age, short stature	7·97 (6·25–9·68)	0·98
Untreated, born small for gestational age, spontaneous catch-up growth	8·44 (7·39–9·50)	0·58
Untreated, born appropriate for gestational age	7·91 (6·90–8·92)	0·93
Limb fat (kg) after adjustment for sex and height		
Treated with growth hormone, born small for gestational age	7·16 (6·18–8·13)	
Untreated, born small for gestational age, short stature	8·20 (6·68–9·72)	0·19
Untreated, born small for gestational age, spontaneous catch-up growth	8·54 (7·60–9·48)	0·062
Untreated, born appropriate for gestational age	8·28 (7·38–9·17)	0·14
Lean body mass (kg) after adjustment for sex and height		
Treated with growth hormone, born small for gestational age	44·32 (43·35–45·30)	
Untreated, born small for gestational age, short stature	46·47 (44·95–48·00)	0·0071
Untreated, born small for gestational age, spontaneous catch-up growth	47·31 (46·37–48·25)	<0·0001
Untreated, born appropriate for gestational age	48·18 (47·28–49·08)	<0·0001
Lean body mass (kg) after adjustment for sex, height, birthweight, and length at birth		
Treated with growth hormone, born small for gestational age	44·95 (43·71–46·19)	
Untreated, born small for gestational age, short stature	46·38 (44·77–47·99)	0·11
Untreated, born small for gestational age, spontaneous catch-up growth	48·21 (47·23–49·20)	0·0001
Untreated, born appropriate for gestational age	48·22 (47·30–49·15)	0·0003

(Table 3 continues on next page)

	Estimated marginal mean (95% CI)	p value*
(Continued from previous page)		
Insulin sensitivity (mU/L) after adjustment for sex		
Treated with growth hormone, born small for gestational age	6·03 (5·15–7·06)	
Untreated, born small for gestational age, short stature	5·70 (4·49–7·23)	0·68
Untreated, born small for gestational age, spontaneous catch-up growth	4·85 (4·04–5·82)	0·10
Untreated, born appropriate for gestational age	6·75 (5·83–7·82)	0·14
Glucose effectiveness (mg/dL) after adjustment for sex		
Treated with growth hormone, born small for gestational age	0·020 (0·019–0·021)	
Untreated, born small for gestational age, short stature	0·019 (0·017–0·021)	0·43
Untreated, born small for gestational age, spontaneous catch-up growth	0·017 (0·015–0·018)	0·0032
Untreated, born appropriate for gestational age	0·018 (0·016–0·019)	0·018
Acute insulin response (mU/L) after adjustment for sex		
Treated with growth hormone, born small for gestational age	416·06 (352·85–490·60)	
Untreated, born small for gestational age, short stature	413·34 (322·09–530·44)	0·98
Untreated, born small for gestational age, spontaneous catch-up growth	469·09 (387·60–567·72)	0·39
Untreated, born appropriate for gestational age	376·33 (322·48–439·18)	0·24
Disposition index after adjustment for sex†		
Treated with growth hormone, born small for gestational age	2508·68 (2124·40–2962·47)	
Untreated, born small for gestational age, short stature	2355·48 (1831·40–3029·53)	0·68
Untreated, born small for gestational age, spontaneous catch-up growth	2274·76 (1876·37–2757·73)	0·47
Untreated, born appropriate for gestational age	2541·11 (2174·47–2969·57)	0·81

*Compared with individuals previously treated with growth hormone and born small for gestational age. †A measure of β-cell function, calculated as insulin sensitivity × acute insulin response.

Table 3: **Comparison of outcome measures between groups at age 21 years**

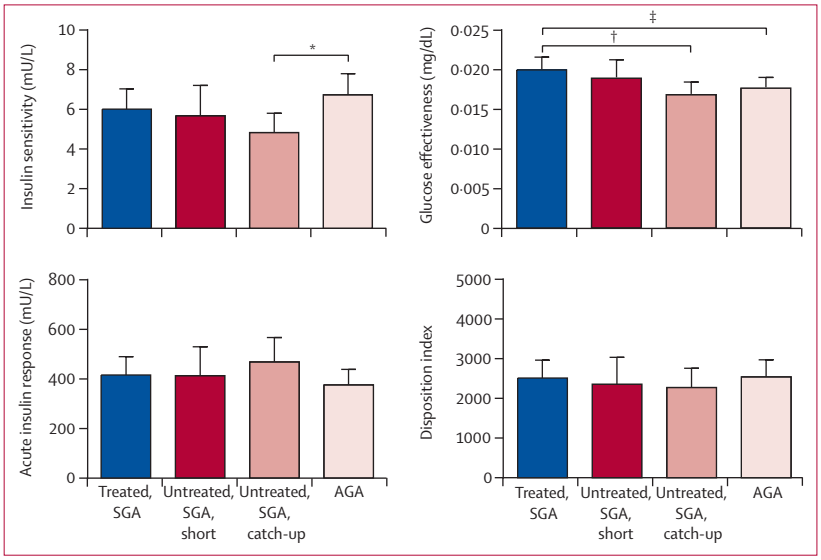

Figure 4: **Comparison of frequently sampled intravenous glucose tolerance test results**
Date are for adults born small for gestational age and previously treated with growth hormone, untreated adults born small for gestational age with short stature, untreated adults born small for gestational age with spontaneous catch-up growth, and adults born appropriate for gestational age. Data for treated individuals are 5 years after cessation of treatment. Bars represent the estimated marginal mean and error bars the upper limit of the 95% CI. Disposition index is a measure of β-cell function, calculated as insulin sensitivity × acute insulin response. AGA=appropriate for gestational age. SGA=small for gestational age. *p=0·0058. †p=0·0032. ‡p=0·018.

was reversed after cessation of treatment, despite the persistent increase in fat mass. However, at 5 years after cessation of treatment, most measures of body composition, insulin sensitivity, and β-cell function of young adults born small for gestational age and previously treated with growth hormone were similar to those for untreated age-matched adults born small for gestational age, with or without catch-up growth, and to those for individuals born at an appropriate weight and length for gestational age. The discrepant variable was lean body mass, which was lower in adults born small for gestational age and previously treated with growth hormone compared with the control groups unexposed to growth hormone treatment. Both body composition (fat mass) and insulin sensitivity changed by more than 25% from cessation of treatment until 5 years thereafter, which is more than was judged clinically relevant in the initial power calculation.

After cessation of growth hormone treatment, fat mass increased and lean body mass decreased, which is contrary to the changes that occurred during growth hormone treatment. The increase in fat mass was neither attributable to increasing age over time nor to lower amounts in serum of IGF-1, indicating that these changes reflect the loss of the lipolytic characteristics of growth hormone. Despite the substantial increase in fat mass after cessation of growth hormone, at 5 years and after adjustment for height, this variable was similar in adults born small for gestational age and previously treated with growth hormone compared with all three control groups. We, therefore, anticipate that future development of fat mass in adults born small for gestational age and previously treated with growth hormone will be similar to that for untreated adults of short stature born small for gestational age. After additional adjustment for birthweight and birth length, lean body mass was similar at 5 years after cessation of treatment in adults born small for gestational age and previously treated with growth hormone compared with those untreated and born small for gestational age of short stature; lean body mass was lower in these two groups compared with untreated adults born small for gestational age with spontaneous catch-up growth or who were born appropriate for gestational age. This finding might suggest that their body composition was reprogrammed during fetal and early life, with long-term effects on body composition persisting even into adulthood.

During the first 6 months after cessation of growth hormone treatment, insulin sensitivity, glucose effectiveness, acute insulin response, and the disposition index (β-cell function) improved in adults born small for gestational age and previously treated with growth hormone, and these improvements were sustained thereafter, despite the increase in fat mass. Since insulin sensitivity correlates strongly with fat mass, this finding indicates that the beneficial effect of cessation of

treatment—and thereby the loss of pharmacological effects of growth hormone—on insulin sensitivity is greater than is the opposite effect of gaining fat mass. At 5 years after cessation of treatment, insulin sensitivity was higher and acute insulin response was lower compared with at cessation of treatment, suggesting that insulin resistance induced by growth hormone and increased insulin secretion were reversed fully. β-cell function was similar at cessation of treatment and 5 years afterwards, which is reassuring, since particularly a reduction in β-cell function is associated with increased risk for type 2 diabetes. Since type 2 diabetes develops over a period of decades, longer follow-up studies are still needed. We used the frequently sampled intravenous glucose tolerance test with tolbutamide, which is a gold standard for measuring insulin sensitivity and β-cell function, similar to the euglycaemic-hyperinsulinaemic clamp.[24] Because the frequently sampled intravenous glucose tolerance test is more invasive, labour-intensive, and costly than other measurements of insulin sensitivity (eg, the oral glucose tolerance test and homoeostatic model assessment of insulin resistance [HOMA-IR]), no other studies (as far as we know) have done frequently sampled intravenous glucose tolerance tests in such high numbers of individuals born small for gestational age after cessation of growth hormone treatment, making our data unique.

Up to now, no longitudinal data have been available for body composition and insulin sensitivity after cessation of growth hormone treatment, with the exception of our preliminary data for 48 adolescents born small for gestational age during the first 6 months after cessation of treatment,[25] which showed similar changes to those we report here. We now show that during the subsequent 5 years after cessation of growth hormone treatment, fat mass increases steadily and acute insulin response declines further. At 5 years after cessation of treatment, fat mass, insulin sensitivity, glucose effectiveness, acute insulin response, and the disposition index (β-cell function) are similar in adults born small for gestational age and previously treated with growth hormone and in untreated adults born small for gestational age of short stature, indicating that growth hormone treatment does not impair insulin sensitivity in the long term.

We have previously shown—in a considerably smaller group of individuals born small for gestational age and previously treated with growth hormone—that measures of insulin sensitivity and β-cell function at 6·5 years after cessation of treatment were similar to those in untreated individuals born small for gestational age with short stature,[23] but in that study we made no comparison with people born small for gestational age with spontaneous catch-up growth and those born appropriate for gestational age. In the present study, measures of fat mass, lean body mass, insulin sensitivity, glucose effectiveness, acute insulin response, and the disposition index of adults born small for gestational age and previously treated with growth hormone were also compared with those for untreated adults born small for gestational age with spontaneous catch-up growth to investigate whether catch-up growth induced by growth hormone had a similar effect to spontaneous catch-up growth. Change in fat mass was similar in these two groups of people, but adults born small for gestational age with spontaneous catch-up growth had the lowest levels of insulin sensitivity and glucose effectiveness, which accords with previous findings showing that accelerated catch-up in weight for length in early life is associated with a higher risk for an unfavourable health profile in adulthood.[26–30]

In a previous study, researchers reported that adults treated with growth hormone during childhood for isolated short stature have increased cardiovascular mortality, but it is unknown whether adults severely deficient for growth hormone in that study were treated with growth hormone into adulthood or whether they stopped treatment at attainment of adult height.[14] In other studies, no deaths attributable to cardiovascular disease or cancer have been reported, indicating that patients without risk factors for cardiovascular disease and malignant diseases can expect an uneventful course after treatment.[31,32] A limitation of these previous studies was that data for adults born small for gestational age and previously treated with growth hormone were compared with national reference values and not control data from untreated individuals born small for gestational age. To study the effect of growth hormone treatment on risk for type 2 diabetes and cardiovascular diseases, it is important to address the already known increased risk for these diseases in children born small for gestational age and to compare adults born small for gestational age and previously treated with growth hormone with those left untreated, instead of only with individuals born appropriate for gestational age. Our study now provides these important and long-awaited data, which are of interest to health-care practitioners worldwide.

Our study has several limitations. First, the clinical relevance of a gain in fat mass depends on the distribution of visceral and subcutaneous fat; visceral fat is related to worse metabolic health. We could not distinguish between visceral fat and subcutaneous fat because we used dual-energy x-ray absorptiometry scans to assess body composition. However, trunk fat is known to be a proxy for visceral fat and, thus, augmented metabolic risk. Our results show that the increase in fat mass was present in both the trunk and limbs. Second, the control group of untreated children born small for gestational age of short stature lived during their childhood in a part of the Netherlands that was not yet involved in the growth hormone trials; therefore, growth hormone treatment was not proposed to these children. The reason why these children remained untreated was not related to a refusal to start treatment, preventing the possibility of confounding by indication in our study.

Of course, it could be argued that some other systematic differences might exist between the regions from which the different study groups were recruited. We find this possibility unlikely, yet, nevertheless, adjustment for socioeconomic status did not affect the comparisons between adults born small for gestational age previously treated with growth hormone and those untreated and of short stature, suggesting that our findings are unlikely to be biased by such environmental confounding.

In conclusion, our follow-up study during the 5-year period after cessation of growth hormone treatment shows pronounced longitudinal changes in insulin sensitivity, β-cell function, and body composition, notably, a steady increase in fat mass, reflecting the loss of pharmacological effects of growth hormone. Reassuringly, the changes in insulin sensitivity and β-cell function induced by growth hormone were reversed fully within 6 months of treatment cessation, despite the increase in fat mass. At 5 years after cessation of growth hormone treatment, fat mass, insulin sensitivity, and β-cell function of adults born small for gestational age and previously treated with growth hormone were comparable with untreated adults born small for gestational age and of short stature, indicating that long-term treatment of children born small for gestational age with short stature does not have an unfavourable effect on body composition, insulin sensitivity, and β-cell function in early adulthood.

Contributors

ACSH-K is the principal investigator, had the idea for and designed the study, and contributed to data collection, data interpretation, and writing of the report. MvdS contributed to data collection, data analyses, data interpretation, writing of the report, and generation of the figures. GFK contributed to data collection, and data interpretation, and critically reviewed the report. CCJS contributed to data collection and critically reviewed the report.

Declaration of interests

We declare no competing interests.

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