Body composition and metabolism in adults with molecularly-confirmed Silver-Russell syndrome

Authors

Oluwakemi Lokulo-Sodipe (1,2,) Hazel M. Inskip (1,4,5), Christopher D. Byrne (1,5), Jenny Child (7), Emma L. Wakeling (6), Deborah J.G. Mackay (1,8), I. Karen Temple (1,3), Justin H. Davies[1] (1,2).

*corresponding author. ORCiD: https://orcid.org/0000-0001-7560-6320

Author affiliations

1. Department of Human Development and Health, Faculty of Medicine, University of Southampton
2. Regional Paediatric Endocrinology Service, University Southampton Hospitals NHS Foundation Trust, Southampton
3. The Wessex Clinical Genetics Service, University Hospitals Southampton NHS Foundation Trust, Southampton
4. MRC Epidemiology Unit, Faculty of Medicine, University of Southampton, Southampton
5. NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust
6. North East Thames Regional Genetic Service, Great Ormond Street Hospital for Children NHS Foundation Trust, Great Ormond Street London WC1N 3JH

[1] Justin H. Davies is corresponding author; Department of Human Development and Health, Faculty of Medicine, University of Southampton, University Hospital Southampton, Tremona Road, Southampton SO16 6YD; email: justin.davies@uhs.nhs.uk

7. Child Growth Foundation, c/o Kinnair Associates Limited, Aston House, Redburn Road, Newcastle, NE5 1NB, UK (affiliation at the time of this work)
8. Wessex Regional Genetics Laboratory, Salisbury Health Care Trust, Salisbury.

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Disclaimer

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Disclosure summary

JHD has received travel bursaries from Pfizer, Ipsen, SANDOZ and NovoNordisk.

JC assisted with recruitment to the study, providing a family perspective on study design and reviewed the manuscript in preparation. OLS submitted and defended a PhD thesis, including data from her work on this study, to the University of Southampton. HMI, CDB, ELW, DJGM and IKT have nothing to declare.

Abstract

Context

Low birth weight, as seen in Silver-Russell syndrome (SRS), is associated with later cardiometabolic disease. Data on long term outcomes and adult body composition in SRS are limited.

Objective

To evaluate body composition and metabolic health in adults with SRS.

Design.

This was an observational study. Body composition and metabolic health were assessed at a single appointment. Individuals with SRS were compared with unaffected men and women (from the Southampton Women's Survey (SWS)).

Setting

Clinical research facilities across the UK.

Participants

25 individuals with molecularly-confirmed SRS aged ≥18 years.

Main Outcome Measures

Fat mass, lean mass, bone mineral density (BMD), blood pressure, lipids, and blood glucose were measured.

Results

25 adults with SRS were included (52% female). The median age was 32.9 years (range 22.0-69.7). Fat percentage was greater in the SRS group than the SWS cohort (44.1% vs 30.3%, p<0.001). Fat mass index was similar (9.6 vs 7.8, p=0.3). Lean mass percentage (51.8% vs 66.2%, p<0.001) and lean mass index (13.5 kg/m^2 vs 17.3 kg/m^2, p<0.001) were lower in the SRS group than the SWS cohort. BMD was lower in the SRS group than the SWS cohort (1.08 vs 1.24, p<0.001) (all median values). Total cholesterol was ≥5mmol/L in 52.0%. Triglyceride levels were ≥1.7mmol/L in 20.8%. Fasting blood glucose levels were ≥6.1mmol/L in 25.0%. Hypertension was present in 33.3%.

Conclusions

Adults with SRS have an unfavourable body composition and predisposition to cardiometabolic disease. These results support the need for a health surveillance strategy to mitigate adverse outcomes.

Introduction

Silver-Russell syndrome (SRS) is characterised by pre- and post-natal growth failure resulting in small-for-gestational age (SGA) at birth, short stature, body asymmetry, relative macrocephaly at birth, a protruding forehead, and feeding difficulties during childhood. SRS can be diagnosed clinically using the Netchine-Harbison clinical scoring system (1,2). In ~50% of SRS cases, loss of methylation at the intergenic H19/IGF2 (H19/IGF2 LOM) differentially-methylated region (DMR) at 11p15.5 has been identified (3,4). In 5-10% of cases maternal uniparental disomy for chromosome 7 (matUPD7) has been detected (4,5). Sporadic or familial mutations in *IGF2*, *CDKN1C* and the *PLAG1/HMGA2* pathway are estimated to account for ~1% of cases.

Lower weight at birth is associated with higher blood pressure, insulin resistance, type 2 diabetes (T2D) (6) and an increased rate of ischaemic heart disease (7) in later life. Thinness at birth is associated with later death from cardiovascular disease (8). Lower abdominal circumference is associated with high levels of cholesterol (9). These associations led to the 'Barker hypothesis', which postulates that developmental changes resulting from the intra-uterine environment later result in enhanced risk of adult diseases. As SGA is a key feature of SRS, adult cardiovascular and/or metabolic disease may develop. There has been increasing focus on the long-term outcomes of individuals with SRS – both in relation to metabolic health (10,11) and in relation to height, (12), the lived experience (13) and adult phenotype (14). There are case reports of individuals with molecularly-confirmed SRS who have developed: 1) excessive weight gain (body mass index SDS 2.1 at age 20 years) and type 2 diabetes mellitus; 2) hypercholesterolaemia and fatty liver disease; 3)

glomerulonephritis and hypertension (15) and; 4) hypertension and dilated cardiomyopathy (16). A 69 year old with SRS has been reported with type 2 diabetes mellitus, hypercholesterolaemia, osteopenia and low testosterone levels (17). This individual is also included within our cohort.

In addition to weight, additional anthropometry (such as body mass index, BMI), and assessment of body composition could enhance understanding of the cardio-metabolic profile observed in SRS. In early reports, children with SRS were noted to have low subcutaneous fat (18) and an extremely lean appearance (19). In three studies of children with SRS, mean or median BMI SDS varied between -2.2 and -2.8 before any intervention (4,20,21). The cohorts included in these studies were not independent and they reported BMI at a single time point or before and after a short-term intervention. However, they demonstrate that BMI in SRS is generally low in childhood.

To the authors' knowledge, dual energy x-ray absorptiometry (DXA) assessment of body composition in SRS has been reported in two papers. In a case series of seven adults with molecularly-confirmed SRS, the BMI SDS ranged from -2.8 to 2.5 (corresponding to absolute BMI of 16.3-32.3 kg/m^2) providing some evidence that BMI could increase considerably in adulthood (11). The results showed high fat body mass percentage (mean 38.2%, SD 10.2), high fat mass index (mean of 8.37 kg/m^2, SD 4.47), high trunk/limb fat ratio (mean 0.93 ± 0.45), low lean body mass (mean 25.84 kg ± 2.16), normal bone mineral density (L1-L4 spine Z-score 0.1 ± 1.2, mean total body Z-score 0.44 ± 0.9) and no cases of metabolic syndrome. Another study, of children and adults treated with GH (with both clinical SRS (n=9) and molecularly-confirmed SRS (n=20)) included DXA measurements and showed fat mass

percentage SDS was -0.51 and mean lean body mass SDS was -1.63 at baseline. Lean body mass was lower in SRS than non-SRS individuals who had been born SGA. Final measurements showed relatively elevated fat mass percentage SDS and a lower mean lean body mass SDS. BMI SDS were not reported (12).

We previously studied a cohort of older individuals with exclusively molecularly-confirmed SRS. The inclusion of exclusively molecularly-confirmed cases of SRS was important as the clinical features of SRS overlap with other conditions, and historical cohorts included those born small for gestational age (SGA) along with SRS (22,23). Growth parameters and some aspects of metabolic health (height, weight, BMI, obesity, waist circumference, waist-to-hip ratios, fat percentage, hypertension, and glucose, triglyceride and cholesterol levels) were reported for all 33 individuals in the study. Median BMI was above average (SDS 0.53) with a high total fat percentage (41.3%). Abnormal glycaemic control was found in 25% (n=6) with three cases of impaired fasting glycaemia and three cases of type 2 diabetes mellitus. High triglyceride levels, hypercholesterolaemia and hypertension were also prevalent (14). The data for all 33 individuals in the study were included in a multi-centre study on 71 individuals with SRS and the effects of previous growth hormone treatment. The larger number of participants in the multi-centre cohort, provides greater statistical power and showed significant differences in BMI in later life (24).

In this paper, we present the results for the 25 individuals aged ≥18 years with exclusively molecularly-confirmed SRS. The age of this cohort is appropriate for assessment of adult conditions, including the diagnostic criteria for metabolic syndrome. Our results provide detailed information on body composition and metabolic outcomes and contribute to a

greater understanding of the cardiometabolic profile in adults with SRS, the underlying mechanisms and may help inform a health surveillance strategy during adulthood.

Materials and methods

Study design

Research and Development approval was granted at University Hospital Southampton (study sponsor) and the NIHR UK Rare Genetic Disease Research Consortium Agreement ('Musketeers' memorandum') at other genetics centres in the UK. Ethics approval was granted by the NHS Research Ethics Committee South Central – Hampshire B (REC reference: 13/SC/0630).

Study recruitment

Individuals with SRS aged ≥18 years with molecularly-confirmed matUPD7 or H19/IGF2 LOM were recruited via: 1) involvement in prior genetic research studies with the Wessex Imprinting Group, 2) following referral to diagnostic NHS Genetics Services or tertiary Paediatric Endocrine Centres within the UK, 3) through the Child Growth Foundation (Newcastle-upon-Tyne, NE5 1NB, UK), 4) via the research study website.

Participants attended a single study appointment (OL-S). Clinical information was recorded using a standardised in-depth interview framework. All examination procedures were standardised as far as possible. Additional information on each participant was gathered from hospital records and from their parent(s) using a standard questionnaire.

Molecular testing

Molecular genetic testing was performed on genomic DNA extracted from peripheral blood leucocytes. Methylation-specific polymerase chain reaction (MS-PCR) and methylation-

189 specific multiplex ligation-dependent probe amplification (MS-MLPA) were performed as
190 previously reported (25,26).
191
192 *Anthropometric measurements*
193 Height and weight measurements were documented at a single study visit or from case note
194 review of the most recent follow-up appointment. BMI was calculated as: weight [kg]
195 divided by height [m] squared. Standard deviation scores (SDS) were calculated for heights,
196 weights and BMI using the age- and sex-specific reference data (the UK 1990 standard).
197 Where the age of the individual was greater than the upper age limit, the data for the
198 maximum age available (23 years) was used. Weight status was categorised by BMI using
199 the World Health Organisation classification (27): Underweight = BMI <18.5 kg/m^2; Ideal
200 weight = BMI 18.5 to 24.99 kg/m^2; overweight = BMI 25 to 29.99 kg/m^2; obese = BMI ≥30
201 kg/m^2; obese class I = BMI 30 to 34.99 kg/m^2; obese class II = BMI 35 to 39.99 kg/m^2; obese
202 class III = BMI ≥40 kg/m^2. An elevated waist circumference was defined as >94 cm in males
203 and >80 cm in females (28).
204
205 *Assessment of body composition*
206 For participants attending their study appointment at University Hospital Southampton,
207 body composition was evaluated by DXA scan of the whole body, spine, and hip on the non-
208 dominant (smaller side in cases of asymmetry) using a Hologic Horizon W instrument
209 (Hologic Inc, Bedford, MA, USA) with APEX v 5.5.3.1 software. Fat mass index was
210 calculated from fat mass (kg)/height $(m)^2$. Fat percentage was calculated from (fat mass
211 (kg)/weight (kg))x100. Lean mass index was calculated from lean mass (kg)/height $(m)^2$.
212 Lean percentage was calculated from (lean mass (kg)/weight (kg))x100. Fat/lean mass

indices and percentages were included as the former use height as a variable, which would be influenced by short stature, whereas percentage does not. Spine bone mineral apparent density was calculated as described by Ward et al (2007) and using reference data from that study, age- and sex-specific SDS were also calculated (29).

Hand grip strength measurement

Muscle function was assessed using a JAMAR hand dynamometer (JAMAR, Patterson Medical Holdings Incorporated, Sammons Preston, Rolyan, Bolingbrook, Illinois, USA) to measure grip strength in the hands according to a standardised approach (30).

Biochemical analyses

Fasted blood samples (following 12 hours fasting) were taken at the study appointment. The samples were tested in NHS pathology laboratories for full blood count, renal function, liver function, thyroid function, insulin and c-peptide levels. Serum and plasma were centrifuged and frozen at -70^{o}C within two hours for specialised testing. Bone-specific alkaline phosphatase and adiponectin were tested on defrosted samples. Vitamin D levels were considered sufficient if ≥50 nmol/L.

Assessment of cardio-metabolic status

Metabolic syndrome and hypertension were evaluated using the harmonised definition agreed by the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Metabolic syndrome was diagnosed where three or more of five

criteria were present: elevated waist circumference, elevated triglycerides (or drug treatment for elevated triglycerides), reduced HDL cholesterol (or treatment for reduced HDL cholesterol), elevated blood pressure (systolic ≥ 130 mmHg and/or diastolic ≥ 85 mmHg, or antihypertensive drug treatment), elevated fasting glucose (or drug treatment of elevated glucose) (28). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting insulin [mU/L] x fasting glucose [mmol/L]/22.5 (31). The quantitative insulin sensitivity check index (QUICKI) was calculated as 1/(log fasting insulin [mU/ml]+log fasting glucose [mg/dl]) (32). Impaired fasting glycaemia and diabetes mellitus were diagnosed if the blood glucose level were 6.1-6.9 mmol/L and ≥7 mmol/L respectively.

Comparison group

In order to compare the SRS group to unaffected individuals, a comparison group was needed. There are few datasets containing DXA and grip strength measurements in the general population and UK normative data for the Hologic Horizon W instrument was not available either for adults or specifically for individuals with short stature. However, we identified the Southampton Women's Survey (SWS) as having DXA data on women and their partners aged 19 to 63 years, broadly representative of the general population and scanned with the same Hologic Horizon W instrument as used in the study presented here. For the SWS cohort, there were no data available on molecular genetic testing, hand grip strength or biochemical analyses.

Statistical analyses

Comparisons were made between the SRS group who underwent DXA scanning and with: 1) the whole SWS cohort; 2) individuals in the SWS cohort aged 22.0 to 69.7 years and with

heights 130.6-171.9 cm (i.e. limited to ages and heights matching the SRS group); 3) sex and age-matched individuals – using the closest ages. Two individuals in the SWS were included for every one individual with SRS. These subanalyses were included with the aim of reducing effects from age- or height differences between the comparison groups.

The SRS group was also stratified on the basis of any prior GH treatment and GH-treated vs GH-untreated individuals were compared.

Continuous variables were compared using the Mann-Whitney U test or independent samples t-test as appropriate. Fisher's exact test or Chi square tests were used to compare categorical variables. Statistical significance was initially set as $p<0.05$. However, in line with recent discussion, P values were not considered purely dichotomously (i.e. significant vs not significant) (33). Data analysis was performed using SPSS Statistics versions 24 to 26 (International Business Machines Corporation, Armonk, New York, United States of America).

Results

Clinical characteristics

Data were available for 25 individuals (13 female) with SRS. Loss of methylation at H19/IGF2 was found in 22 (88%) cases and matUPD7 in 3 (12%). The median age was 32.9 years (range 22.0-69.7). The median height SDS, weight SDS and BMI SDS were -3.13 (interquartile range, IQR -3.83 to -1.31), -1.83 (IQR -3.76 to -0.11) and -0.47 (-1.83 to 1.53) respectively. Within the SRS group, there were no marked differences in age, height, weight

285 or BMI between those treated with GH in childhood (n=15) and those not treated (n=10).
286 Those who had been treated with GH received treatment for a median of 10.13 years (IQR
287 6.55 to 13.00).
288
289 *DXA measurements*
290 Clinical characteristics of the SRS –individuals who underwent DXA (n=19) and full SWS
291 cohort of 820 men and women are shown in Table 1. Individuals with SRS were younger
292 than those in the SWS cohort and had lower median height, weight and BMI. Table 2 shows
293 the SRS group compared with 362 individuals in the SWS cohort aged 22.0 to 69.7 years and
294 with heights 130.6-171.9 cm (i.e. limited to the ranges seen in the SRS group). Again,
295 individuals with SRS were younger with lower median height, weight and BMI than the SWS
296 cohort. Table 3 shows the SRS group compared with 38 individuals in the SWS cohort.
297 Individuals with SRS had lower median height and weight than those 38 individuals in the
298 SWS cohort. The 38 individuals from the SWS cohort were matched for sex and with ages as
299 close as possible to the individuals with SRS. There was no significant difference in age
300 between the SRS group and the 38 individuals from the SWS cohort. The range of difference
301 in age between pairings was 0-9.9 years (mean 2.2 years and median 0.6 years).
302
303 *Fat mass*
304 The median total fat percentage was 44.45% (IQR 31.45 to 46.88). The median fat mass
305 index was 9.33 kg/m^2 (IQR 5.29 to 13.53). Fat percentage was greater in the SRS group than
306 the whole SWS cohort (median 44.1% vs 30.3%, p<0.001) (Table 1). Greater fat percentage
307 was found in SRS in both sub-analyses of the SWS cohort (Table 2). In the SRS group
308 compared with the SWS cohort, fat mass (19.9 vs 22.8 respectively, p=0.3) and fat mass

index (9.6 vs 7.8 respectively, p=0.3) were similar despite lower weight (55.5 vs 79.1, p<0.001) and BMI (22.3 vs 26.1, p=0.03) in the SRS group (Table 1). There was a suggestion that trunk/limb fat ratio was greater in SRS than in the whole SWS cohort (median 1.2 vs 1.0, p=0.06) (Table 1). This difference was more apparent in the sub-analyses of the SWS cohort; median 1.2 vs 0.94, p=0.002 (Table 2) when the age and height ranges were matched and median 1.2 vs 0.88, p=0.01 in the sex- and age-matched SWS cohort. In GH-treated (n=10) vs GH-untreated groups (n=9) respectively in the SRS group, fat percentage (median 40.7% vs 44.5%, p=0.6) and fat mass index (median 7.9 vs 11.42, p=0.17) were similar. No participants in the GH-treated group had a BMI ≥30 kg/m^2 compared with three in the GH-untreated group.

Lean mass and hand grip strength

The median lean mass index was 13.5 kg/m^2 (IQR 12.0 to 15.1). The median maximum hand grip strength was 22.5 kg (IQR 16.0 to 29.8), which corresponds to a median hand grip strength SDS of -2.12 (IQR -2.90 to -1.57) (n=22). Hand grip strength positively correlated with lean mass index (Spearman rho 0.694, p=0.004). Correlation of creatinine to lean mass index was 0.311 (p=0.159). Comparing the SRS group with the SWS cohort, lean body mass (30.8 kg vs 52.5 kg, p<0.001), lean percentage (51.8% vs 66.2%, p<0.001) and lean mass index (13.5 kg/m^2 vs 17.3 kg/m^2, p<0.001) were all lower (Table 1). This difference was also apparent in the two sub-analyses comparing the SRS group with the SWS cohort (Table 2 and Table 3). In the SRS group, GH-treated (n=10) vs GH-untreated groups (n=9) respectively, lean mass index (median 11.7 vs 14.0, p=0.2) were not markedly different.

Bone mineral density

The median whole-body BMD T-score was -0.65 (IQR -1.65 to -0.30). BMD was lower in the SRS group compared with the SWS cohort (median 1.08 vs 1.24, p<0.001) (Table 1). This difference remained in the two sub-analyses of the SWS cohort (Table 2). There was no difference in BMD between GH treated and GH untreated individuals with SRS.

Biochemical analysis

Biochemical investigations were performed in the SRS group (n=25). Total cholesterol ≥5 mmol/L was present in 52.0%. Triglyceride levels ≥1.7 mmol/L were present in 20.8%. Blood glucose levels were ≥6.1 mmol/L) in 25.0%. Of these participants, three had type 2 diabetes mellitus; one was diagnosed as a result of the study and two were already on treatment. Three individuals had impaired fasting glycaemia. Triglyceride levels were lower in the GH-treated group compared with the GH-untreated group (median 0.90 (IQR 0.7 to 1.2) vs 1.50 (IQR 1.00 to 2.15) p=0.041).

Elevated ALT and GGT levels were found in 16.0% (4/25) and 12.5% (3/24) respectively. Low creatinine levels (by laboratory reference range) were found in 68.0% (17/25). Low vitamin D levels were found in 32.0% (n=24). High bone turnover was reported from bone-specific ALP in 88.2% (15/17). No relationship was identified between adiponectin levels with fat percentage or fat mass index.

Metabolic syndrome and insulin resistance

Metabolic syndrome was present in 18.2% (4/22) of the cohort where all five criteria were available for scoring. There was no difference in prevalence of metabolic syndrome between GH-treated and GH-untreated individuals with SRS (7.7% vs 33.3%, p=0.264).

Hypertension was present in 33.3% (8/24). There was no difference in prevalence of hypertension between GH-treated and GH-untreated individuals with SRS (35.7% vs 30.0%, p=1.0).

Discussion

To our knowledge, this is the largest study describing body composition in adults with molecularly-confirmed SRS. SGA is associated with later cardiovascular risk factors, such as type 2 diabetes, hyperlipidaemia and hypertension (34). In SRS, some long-term health problems, including cardiometabolic disease, have been described (11,12,14). However, only one of these studies reported detailed body composition and this was a small cohort of seven molecularly-confirmed cases. The international consensus on the management of SRS advocated a healthy lifestyle and diet in SRS in order to avoid excessive or rapid weight gain and to avoid insulin resistance. The consensus also recommended consideration of medical follow-up of adolescents and young adult patients with SRS (2). Our study supports the need for long-term follow-up and we would recommend that surveillance for hypertension, diabetes mellitus, hypercholesterolaemia and hypertriglyceridaemia should continue throughout adulthood in individuals with SRS.

Further research on the long-term effects of GH on body composition in SRS was also suggested. Our study contributes towards increasing information on adult outcomes in SRS, where a lack of data has been highlighted (2). Exclusively molecularly-confirmed cases have been included to minimise heterogeneity and the majority (88%) of cases resulted from ICR1/H19 LOM, as is typically seen in SRS. We provide data on individuals with SRS who have not been treated with GH. As treatment with GH is increasingly more widely given, the natural history of SRS will be more difficult to evaluate.

In this study, the median height SDS was -3.13, which is lower than reported previously in other adult SRS cohorts (10,35) and in a larger cohort of exclusively molecularly-confirmed

SRS (24). The median body mass index was 21.2 kg/m^2 with a corresponding BMI SDS of -0.47. The prevalence of obesity in the adults in this study was greater (12%) than in a previous report of children and adults with SRS (7.0%) (24). The adult phenotype and heights and weights of individuals from the SRS group presented here have previously been reported (14,24).

Fat mass percentage, fat mass index and trunk to limb fat ratios were all greater in SRS than the comparison group. Despite lower body weight in SRS, total fat mass was similar to the comparison group. The median total fat percentage of 44.45% and the median fat mass index of 9.33 kg/m^2 in this study were high, consistent with a previous study (11). Our study provides supporting data that increased body fat and particularly central adiposity (demonstrated by high trunk to limb fat ratios) is seen in adults with SRS. Areal BMD is dependent on bone size therefore smaller bones result in a lower BMD. A similar size effect may be possible with other DXA parameters such as calculations of fat and lean mass. However, our results demonstrating greater fat mass in SRS are particularly reliable as this relationship is in the opposite direction to potential size effects (i.e. smaller size in SRS could yield smaller results).

Lean mass percentage and lean mass index were lower in the SRS group than the comparison group. We report lean mass percentage and lean mass index to reduce the potential influence of size effects. Reduced lean body mass has been reported previously in SRS (11) and median LMI of 13.5 kg/m^2 is comparable to that study. Low creatinine levels were found in 68.0% but there was no correlation with hand grip strength, therefore this does not appear to be a useful marker to relate to function.

Total cholesterol ≥5 mmol/L was present in 52.0%. Triglyceride levels ≥1.7 mmol/L were present in 20.8% (5/24). Diabetes mellitus or impaired fasting glycaemia were present in 25.0% (6/24). Metabolic syndrome was present in 18.2% of the cohort compared with two previous studies, in which metabolic syndrome was not found (11,12), although those studies used different criteria for diagnosis and in one study, the participants were much younger. The global prevalence of metabolic syndrome was estimated to be 25% in 2015 (36). However, the prevalence is likely to have risen. The results of our study demonstrate that hypercholesterolaemia, hypertriglyceridaemia and dysglycaemia are present in adults with SRS. Therefore, lifestyle modification to mitigate against the cardiometabolic risk profile is likely to be prudent.

In SRS, GH treatment is associated with lower BMI and lower gain in BMI SDS from childhood to adulthood (24). As a result of the small sample number, this study lacked statistical power to assess growth hormone effects. However there was a suggestion that a greater proportion of the GH-treated group were an ideal weight compared with the GH-untreated group and obesity was only present in the GH-untreated group. Triglyceride levels were lower in the GH-treated group compared with the GH-untreated group. These results suggest there may be benefits from GH treatment, in addition to height gain, and that further research is needed. No differences were seen in body fat or lean mass and larger studies of body composition in SRS would be beneficial. The natural history data presented here could serve as a useful comparison in future evaluation of the long-term effects of GH on body composition in SRS.

In adults born SGA, chronic hypertension has been reported in 3-4%, diabetes mellitus in 0.7-1.9% and obesity in 10.2-13.7% (37). Metabolic syndrome has been observed in 2.3% of adults with SGA (38). The results from our study suggest that individuals with SRS may have a higher prevalence of hypertension (33.3%) and metabolic syndrome (18.2%) but similar prevalence of obesity (12%). However, the definitions may have varied.

There were limitations to this study including the small number of participants and the wide age range in the SRS group. The ideal control group would be matched for age, sex and short stature. Furthermore, owing to variability between DXA scanners, it is important that results obtained from the same type of scanner are used for comparison. Comparison data fulfilling the above criteria for an ideal control group were not available. The SWS cohort was the best available option, as the participants were scanned using the same Hologic scanner as the SRS group, and represented healthy adults. However, the SWS represents a self-selected group of individuals who have committed to a long-term study, and as such may be less representative of the general population than is ideal for this comparison. It was not possible to ascertain or exclude prior GH treatment in individuals in the SWS cohort. Individuals with SRS were younger than those in the comparison group and had lower, median height, weight and BMI as expected (Table 1). These differences in median height, weight and BMI persisted in the sub-analyses of the SWS group (Table 2). Limiting the SWS cohort to age and height ranges matching the SRS cohort resulted in a greater proportion of women being included in the SWS cohort (74.9%) compared with the SRS group (52.6%). However, the comparisons showed similar results to those between SRS and the whole SWS cohort, therefore this did not appear to affect the results obtained. Although the cases were sex-matched, there was some variability in difference in age within

the pairings. This was accepted pragmatically so that two SWS cases could be used for each individual with SRS.

In conclusion, adults with SRS have central adiposity, greater body fat and lower lean mass than unaffected individuals. They may be at higher risk of cardiometabolic problems than adults born SGA. Counselling for children, young people and adults with SRS should emphasise lifestyle modification to avoid weight gain in order to ameliorate the cardiometabolic profile in later life. We advocate that formal surveillance or screening of adults with SRS for hypertension, diabetes mellitus, hypercholesterolaemia and hypertriglyceridaemia should be instituted to allow early intervention.

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Data Availability

Some or all datasets generated during and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Table 1. Characteristics of the SRS group compared with individuals from the Southampton Women's Survey cohort. BMI = body mass index. Dual energy x-ray absorptiometry data (DXA) for the SRS cohort (n=18 unless indicated * where n=19). Results presented as median (interquartile range) unless otherwise indicated in the first column. BMD = bone mineral density.

	SRS	**SWS**	p value
Number, n	19	820	
Clinical characteristics			
Male, n (%)	9 (47.4)	507 (61.8)	0.2
Female, n (%)	10 (52.6)	313 (38.2)	
Age, years	33.9 (28.6-39.1)	40.4 (19.1-63.1)	0.001
Height, cm	150.3 (144.1-159.3)	173.0 (165.1-179.0)	<0.001
Weight, kg	55.5 (44.1-65.2)	79.1 (68.4-89.9)	<0.001
BMI, kg/m^2	22.3 (19.5-28.3)	26.1 (23.6-29.4)	0.03
DXA total body BMD, g/cm^2	1.08 (1.04-1.14)	1.24 (1.18-1.32)	<0.001
DXA total fat mass, kg	19.9 (15.4-30.7)	22.8 (18.1-29.2)	0.3
DXA total fat percentage, %	44.4 (31.5-46.9)	30.3 (24.5-36.6)	<0.001
DXA fat mass index, kg/m^2	9.6 (6.3-13.0)	7.8 (6.1-10.0)	0.1
DXA total lean mass, kg	30.8 (25.0-38.9)	52.5 (41.7-60.2)	<0.001
DXA total lean percentage, %	51.8 (50.0-64.4)	66.2 (60.1-72.0)	<0.001
DXA lean mass index, kg/m^2	13.5 (12.0-15.1)	17.3 (15.1-19.0)	<0.001
DXA Trunk limb fat mass ratio (trunk /limb fat ratio)	1.2 (0.9-1.4)	1.0 (0.8-1.3)	0.06

Table 2. Characteristics of the SRS group compared with individuals from the Southampton Women's Survey cohort aged 22.0 to 69.7 years and with heights 130.6-171.9 cm. BMI = body mass index. Dual energy x-ray absorptiometry data (DXA) for the SRS cohort (n=18 unless indicated * where n=19). Results presented as median (interquartile range) unless otherwise indicated in the first column. BMD = bone mineral density.

	SRS	**SWS**	p value
Number, n	19	362	
Clinical characteristics			
Male, n (%)	9 (47.4)	91 (25.1)	0.085
Female, n (%)	10 (52.6)	271 (74.9)	
Age, years	33.9 (28.6-39.1)	41.2 (38.6-44.1)	<0.001
Height, cm	150.3 (144.1-159.3)	164.7 (160.8-168.2)	<0.001
Weight, kg	55.5 (44.1-65.2)	69.4 (61.7-80.2)	<0.001
BMI, kg/m^2	22.3 (19.5-28.3)	25.7 (23.1-29.4)	0.03
DXA whole body BMD, g/cm^2	1.08 (1.04-1.14)	1.22 (1.16-1.28)	<0.001
DXA total fat mass, kg	19.9 (15.4-30.7)	23.0 (18.8-30.0)	0.4
DXA total fat percentage, %	44.4 (31.5-46.9)	35.5 (29.5-41.2)	0.005
DXA fat mass index, kg/m^2	9.6 (6.3-13.0)	8.7 (6.8-11.6)	0.48
DXA total lean mass, kg	30.8 (25.0-38.9)	41.2 (37.1-48.5)	<0.001
DXA total lean percentage, %	51.8 (50.0-64.4)	60.9 (55.6-66.5)	0.003
DXA lean mass index, kg/m^2	13.5 (12.0-15.1)	15.5 (14.1-17.6)	0.001
DXA Trunk limb fat mass ratio (trunk /limb fat ratio)	1.2 (0.9-1.4)	0.94 (0.76-1.11)	0.002

Table 3. Characteristics of the SRS group compared with age- and sex matched individuals from the Southampton Women's Survey cohort. BMI = body mass index. Dual energy x-ray absorptiometry data (DXA) for the SRS cohort (n=18 unless indicated * where n=19). Results presented as median (interquartile range) unless otherwise indicated in the first column. BMD = bone mineral density.

	SRS	**SWS**	**p value**
Number, n	19	38	
Clinical characteristics			
Male, n (%)	9 (47.4)	18 (47.4)	1.00
Female, n (%)	10 (52.6)	20 (52.6)	
Age, years	33.9 (28.6-39.1)	34.1 (32.6-39.1)	0.6
Height, cm	150.3 (144.1-159.3)	171.0 (164.9-177.6)	<0.001
Weight, kg	55.5 (44.1-65.2)	77.7 (67.4-90.8)	<0.001
BMI, kg/m^2	22.3 (19.5-28.3)	26.1 (23.6-29.0)	0.07
DXA whole body BMD, g/cm^3	1.08 (1.04-1.14)	1.24 (1.18-1.33)	<0.001
DXA total fat mass, kg	19.9 (15.4-30.7)	25.3 (17.7-30.0)	0.4
DXA total fat percentage, %	44.4 (31.5-46.9)	32.1 (23.5-39.1)	0.002
DXA fat mass index, kg/m^2	9.6 (6.3-13.0)	8.3 (5.6-10.6)	0.3
DXA total lean mass, kg	30.8 (25.0-38.9)	48.1 (39.5-61.2)	<0.001
DXA total lean percentage, %	51.8 (50.0-64.4)	65.1 (57.5-72.4)	0.001
DXA lean mass index, kg/m^2	13.5 (12.0-15.1)	16.5 (14.2-19.5)	<0.001
DXA Trunk limb fat mass ratio (trunk /limb fat ratio)	1.2 (0.9-1.4)	0.88 (0.74-1.10)	0.01