Birmingham Women's and Children's NHS Foundation Trust

National Institute for Health Research

SSSA 2024

Sotos syndrome in adults

Dr Alison Foster MRCPCH PhD
Consultant in Clinical Genetics at Royal Devon University Hospitals and
Honorary Consultant at Birmingham Women's and Children's Hospitals

Introduction

Birmingham Women's and Children's NHS Foundation Trust

Most of the medical literature focuses on the features of Sotos syndrome in children

Limited information on Sotos syndrome in adult life

Need to study the clinical features of Sotos syndrome in adults to generate evidence to inform clinical practice

The phenotype of Sotos syndrome in adulthood: a review of 44 individuals

Alison Foster,[1,2] Anna Zachariou,[3] Chey Loveday,[3] Tazeen Ashraf,[4] Ed Blair,[5] Jill Clayton-Smith,[6,7] Huw Dorkins,[8] Alan Fryer,[9] Blanca Gener,[10] David Goudie,[11] Alex Henderson,[12] Melita Irving,[4] Shelagh Joss,[13] Vaughan Keeley,[14] Nayana Lahiri,[15] Sally Ann Lynch,[16] Sahar Mansour[15, 17] Emma McCann,[9] Jenny Morton,[2] Nicole Motton,[18] Alex Murray,[19] Katie Riches,[14], Debbie Shears,[5] Zornitza Stark,[20,21] Elizabeth Thompson,[22,23] Julie Vogt,[2] Michael Wright,[12] Trevor Cole,[2] and Katrina Tatton-Brown[3,15, 17]

American Journal of Medical Genetics Part C 2019

Adult study

Birmingham Women's and Children's NHS Foundation Trust

Eligibility:

Age 18 or over

Diagnosis of Sotos syndrome confirmed on molecular genetic testing - intragenic variant or deletion *NSD1*

Participation identification:

Previous involvement in a research study as children (Tatton-Brown et al. 2005) – 26 individuals

Additional participants identified through clinical genetics centres in the UK – 18 individuals

Data collection:

Clinic appointment - 23 individuals

Standardized clinical proforma completed either by clinical geneticist or individual/family member - 21 individuals

Participants

Birmingham Women's and Children's NHS Foundation Trust

44 adults with Sotos syndrome

17 men and 27 women

Age range 18-48 years

Mean age of 30 years

Areas of interest

Intellectual (learning) disability

Neurodevelopment and mental health

Growth – final height and head circumference

Puberty and reproduction

Medical problems

- ongoing from childhood
- new adult onset

Intellectual disability

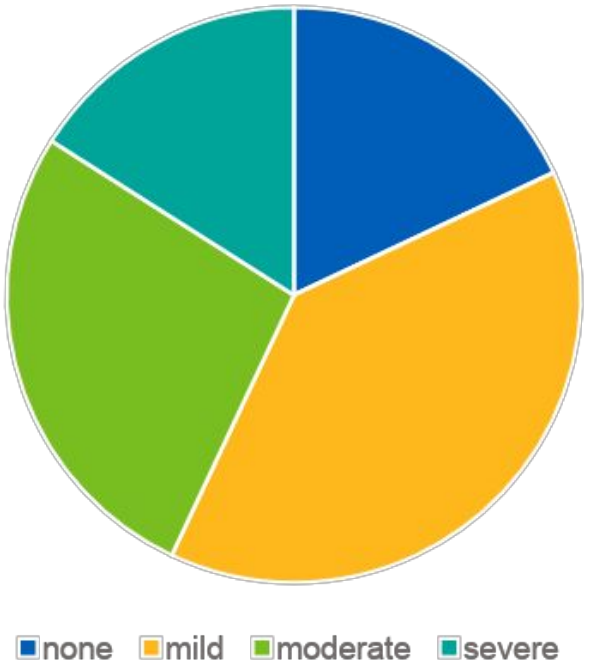
NHS
Birmingham Women's and Children's
NHS Foundation Trust

8/44 individuals (18%) no ID

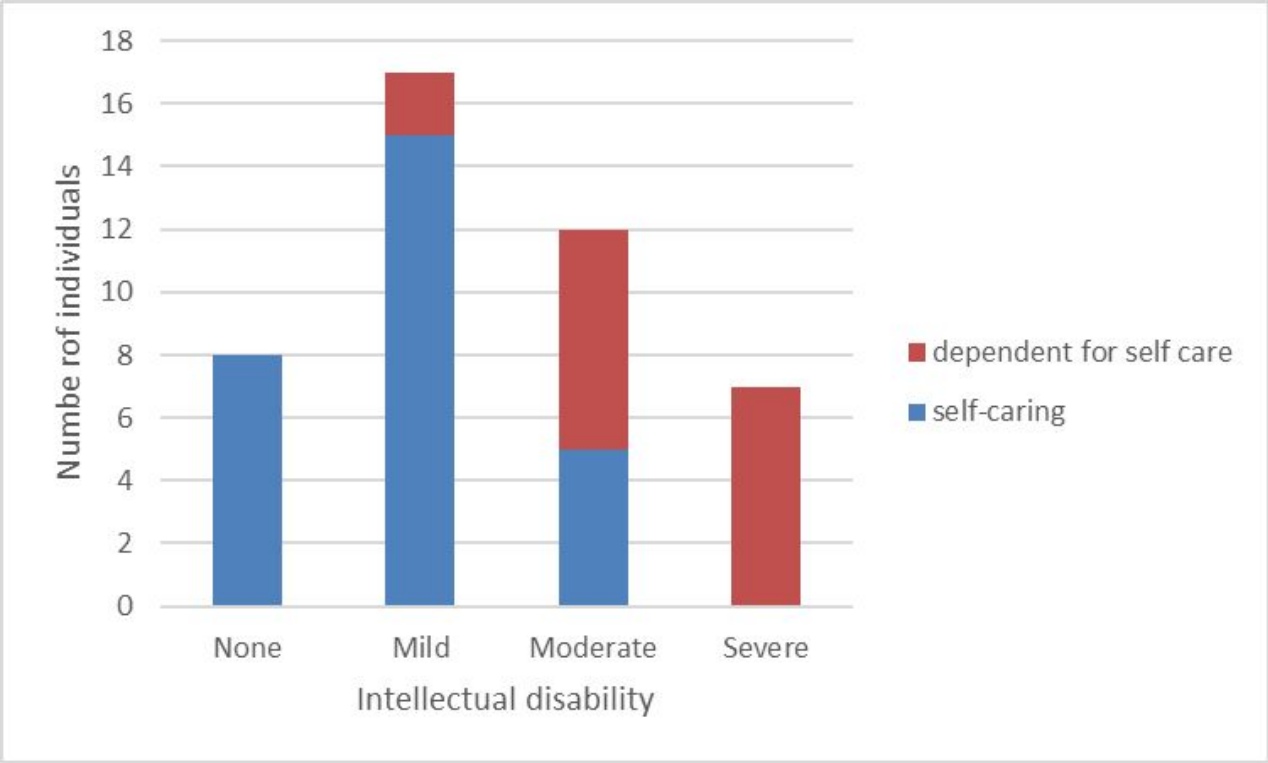
17/44 (39%) had a mild ID

12/44 (27%) a moderate ID

7/44 (16%) a severe ID



Intellectual disability and self-care (activities of daily living)



Participants with no ID and mild ID

Birmingham Women's and Children's NHS Foundation Trust

No ID

All were employed or in vocational training courses (carer, barber, sales clerk, information technology, nursing and business studies)

Mild ID

Most were employed or in vocational training (retail, painting/ decorating, waitressing, health and social care, air stewarding and cleaning)

Most felt unable or did not want to live away from the support of their families

Managing money and finances was an area of difficulty

Participants with moderate ID and severe ID

Birmingham Women's and Children's NHS Foundation Trust

Moderate intellectual disability

Two were in supported employment (shop assistant and office assistant)

Severe intellectual disability

Seven attended special educational needs colleges or day care and one was receiving 24 hour care

Neurodevelopment and mental health: themes

Birmingham Women's and Children's NHS Foundation Trust

Autism spectrum disorder:
nine individuals (20%)
all with a moderate or severe intellectual disability

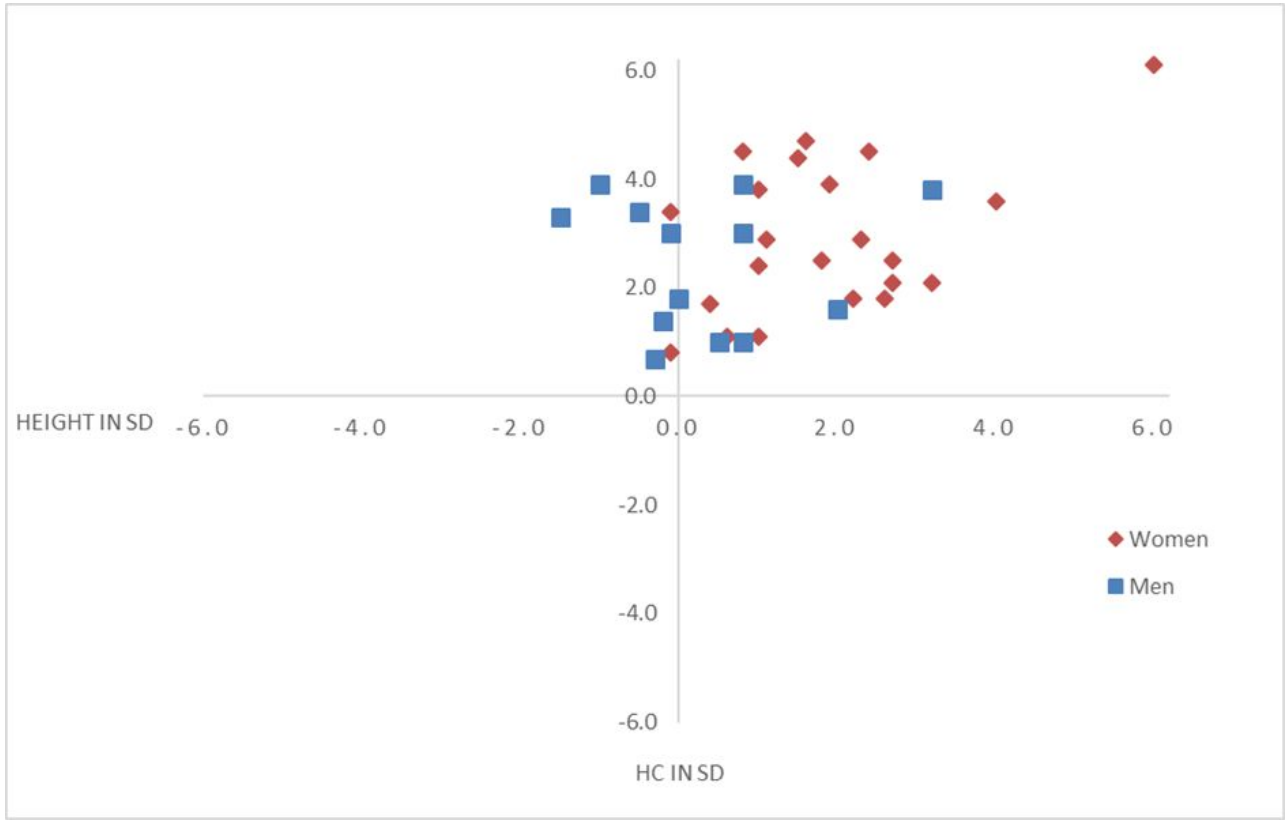
Anger/aggression
seven individuals (16%)

Anxiety (panic attacks and/or social avoidance)
six individuals (14%)

one adult with anxiety had co-existing depression and an episode of psychosis

Growth parameters

Birmingham Women's and Children's NHS Foundation Trust



Height in women:
range 5'4" to 6'5"
median of 5'9"

Height in men:
range from 5'5" to 6'5"
median 5'11"

HC in women:
range +0.8 SD to +6.1 SD
median of +2.7 SD

HC in men:
range +0.7 SD to +3.9 SD
median of +2.4 SD

Weight

Women:

Weight range 117lb-281lb (median of 165lb)

BMI range 19.6-44.1 (median of 26.3)

Men:

Weight range 124lb-249lb (median 181lb)

BMI range 19-33.4 (median of 26.8)

Puberty and reproduction

Birmingham Women's and Children's NHS Foundation Trust

Age at puberty

Women: 7-16 years, median 13 years

Men: 11-17 years, median 14 years

Four women in our cohort had children

- First - two children without Sotos syndrome
- Second – three children including identical twins with Sotos and older sibling without Sotos (mother diagnosed as an adult following diagnosis in the twins)
- Third - one child with Sotos (IVF for subfertility)
- Fourth - four children, one with Sotos syndrome and three without Sotos

No men in our cohort had children

- One had a low sperm count

Medical problems

Overall, adults with Sotos syndrome were in good health

Ongoing medical problems reported in Sotos in childhood – scoliosis, renal, dental, hearing

Scoliosis

NHS
Birmingham Women's and Children's
NHS Foundation Trust

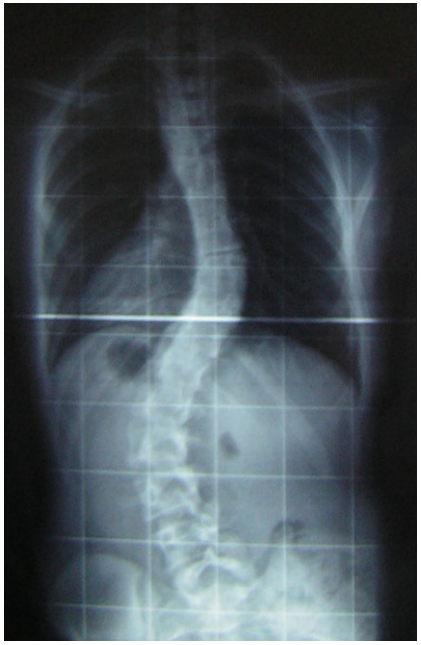
One of the most common medical problems in Sotos, previously reported in one third of individuals

Over half the adults (24/44, 55%) had scoliosis and/or kyphosis

All but one diagnosed before age 16

Eleven individuals (11/24, 46%) required surgery

- Three adults with surgically treated scoliosis had chronic pain



Renal anomalies

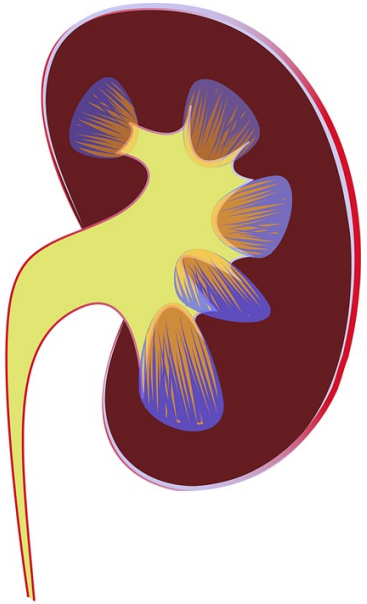
Minority of individuals (8/44, 18%) had congenital renal anomalies

Two with congenital renal anomalies developed hypertension

- first diagnosed in his early 20s. History of absent right kidney and left sided hydronephrosis and hydroureter
- second in her late 40s. History duplicated left ureter (surgically repaired) and recurrent urinary tract infections

One individual with posterior urethral valves required a long-term indwelling catheter

No individuals in the current study known to have chronic renal impairment

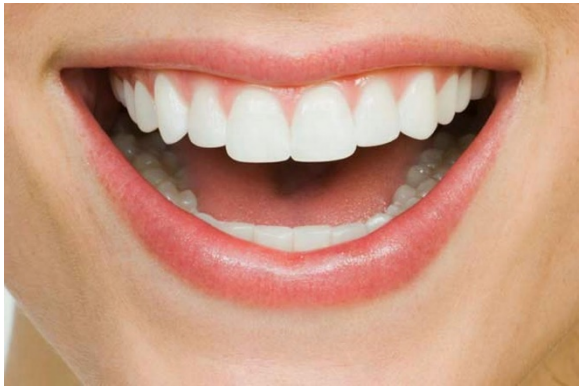


Dental problems

Birmingham Women's and Children's NHS Foundation Trust

Dental problems were reported in seven adults (7/44, 16%)

- soft, worn or crumbling teeth (three individuals)
- absent and/or abnormal secondary dentition (four individuals)

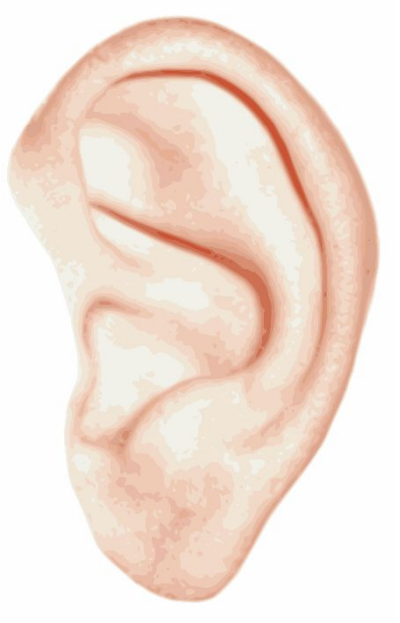


Hearing loss

Seven adults (7/44, 16%)

- two - recurrent ear infections
- one - cholesteatoma diagnosed age 25
- one - degenerative changes of the eardrum
- three - hearing loss of unspecified cause

Four individuals wore hearing aids



New medical problems in adults

Birmingham Women's and Children's NHS Foundation Trust

Small number of adults with new medical problems of adult onset

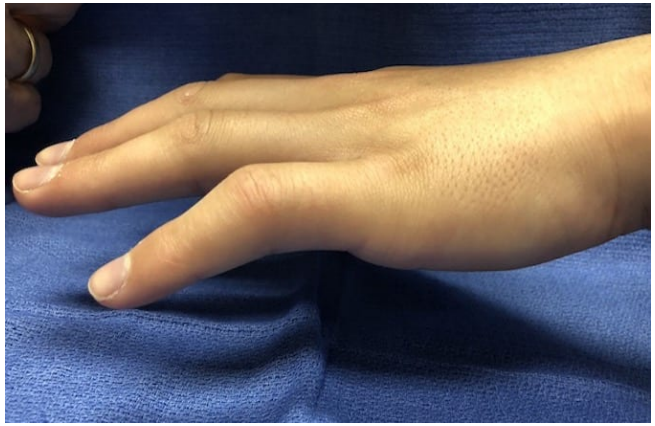
Medical issues reported in two or more adults:

- contractures
- tremor
- lymphoedema/pericardial effusion
- (aortic dilatation)

Contractures

Four adults

- one individual developed mild contractures of both elbows
- one developed hip and ankle contractures
- two developed bilateral camptodactyly (finger contractures)



Tremor

Three individuals developed progressive essential tremor

Two of these individuals also had contractures of the fingers

- Impacted their ability to undertake everyday tasks such as eating, drinking, and dressing.
- One receiving symptomatic treatment with propranolol and clonidine

Third individual developed a progressive tremor in her early 30s with no current impact on function

Lymphedema and pericarditis

NHS
Birmingham Women's and Children's
NHS Foundation Trust

Three individuals developed lower limb lymphedema in adulthood

- One individual age 21 treated with compression stockings and a lymphedema pump three hours per day

Two also developed pericardial effusion/pericarditis

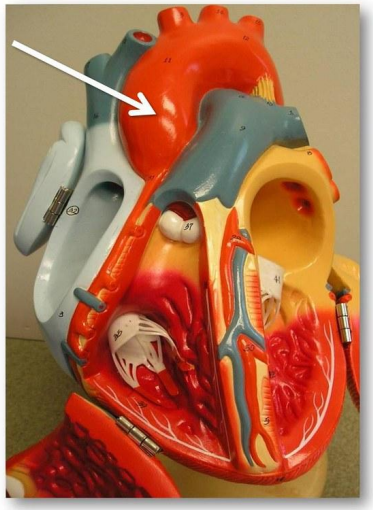
- One individual required admission to critical care age 21 for pericarditis with effusion then developed lymphedema
- Second individual had onset of lymphedema age 16 then myopericarditis age 20

Aortic dilatation

Four individuals had borderline/non-progressive dilatation of the aortic root or ascending aorta

- two individuals: the dilatation had resolved by their 30s/40s
- third had a mild diffuse non-progressive dilatation of the ascending aorta treated with prophylactic beta blocker therapy
- fourth diagnosed with borderline enlargement of the aortic sinus at the age of 47

No reports of complications of aortic dilatation



Take home messages

Wide spectrum of intellectual ability

Final height in men and women is variable

Few adults with Sotos have children

Adults with Sotos were generally well - small numbers with new medical problems

No tumors in any adults in the study

Management guidelines for adults with Sotos

NHS
Birmingham Women's and Children's
NHS Foundation Trust

General healthy lifestyle advice as for general population

Annual blood pressure monitoring

Routine dental check ups

Be alert to potential hearing problems

Pre-pregnancy obstetric review and genetic counselling if considering having children

Pre-pregnancy planning

NHS
Birmingham Women's and Children's
NHS Foundation Trust

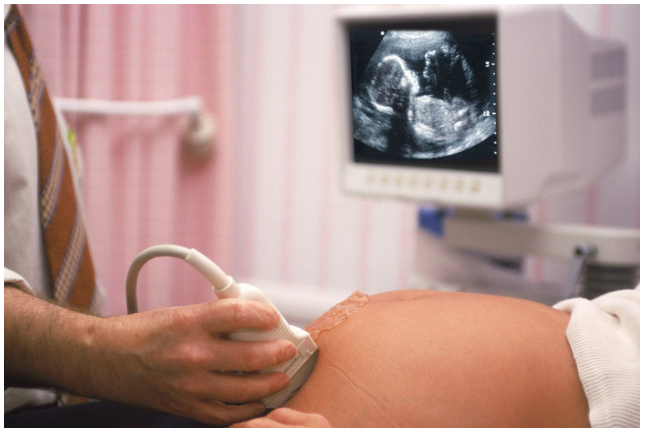
Consideration of existing medical conditions - congenital heart disease, kidney disease, scoliosis, epilepsy etc

Increased chance of pre-eclampsia

Antenatal scans for congenital anomalies, fetal echocardiogram, growth

Plan for delivery and neonatal care

Parenting support



Genetic counselling

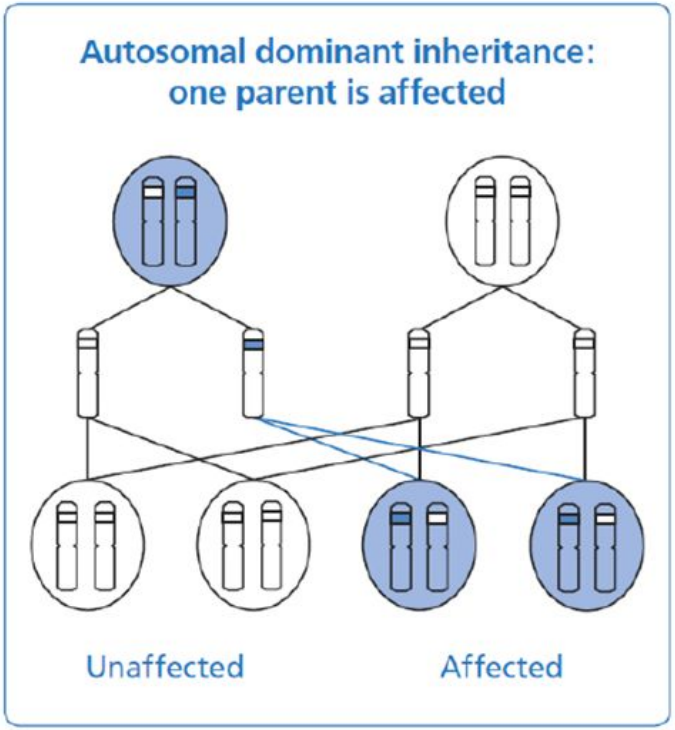
Birmingham Women's and Children's NHS Foundation Trust

If a parent has Sotos:

1 in 2 chance (50%) for each child of inheriting the variant in NSD1 and having Sotos syndrome

Medical and learning issues may be different between individuals with Sotos in the same family

Reproductive options available e.g. pre-implantation genetic testing (PGT)



Molecular genetic testing

NHS
Birmingham Women's and Children's
NHS Foundation Trust

The diagnosis of Sotos syndrome is usually clear from clinical features

However, there are other rare genetic overgrowth disorders with similar features

If no known NSD1 variant, revisit genetic testing

Genetic testing technology has improved exponentially

- whole genome sequencing (WGS) now first line test

Genome-wide methylation testing for a Sotos DNA methylation profile 'episignature' may be helpful if a no variant / variant of uncertain significance is identified

Future work

Birmingham Women's and Children's NHS Foundation Trust

Unanswered questions remain regarding the features of Sotos throughout life

Many participants in the study were young adults

- only 19 individuals (43%) were over 30 years old
- only seven (16%) were over 40 years old

We need to continue to follow the current cohort of individuals

Identify new or evolving medical issues to enable us to provide the best possible medical care

Acknowledgments

Thank you to the adults and their families for their active participation in this study

SSSA

Colleagues

Wellcome Trust (100210), the Child Growth Foundation (GR01/13), the Institute of Cancer Research, and the NIHR Rare Diseases Translational Research Collaboration.

Questions

NHS
Birmingham Women's and Children's
NHS Foundation Trust