BMJ Open

EARLYBIRD: catching the earliest changes of the bone and intervertebral discs in children at increased risk for scoliosis development with MRI – study protocol of a prospective observational cohort study

Peter P G Lafranca ,[1] Hilde W Stempels,[1] Steven de Reuver,[1] Michiel L Houben,[2] Joeri Kok,[3] Moyo C Kruyt,[1] René M Castelein,[1] Peter R Seevinck,[4] Tijl van der Velden,[4] Yulia M Shcherbakova,[4] Keita Ito,[1,3] Tom P C Schlösser[1]

To cite: Lafranca PPG, Stempels HW, de Reuver S, *et al*. EARLYBIRD: catching the earliest changes of the bone and intervertebral discs in children at increased risk for scoliosis development with MRI – study protocol of a prospective observational cohort study. *BMJ Open* 2025;**15**:e098929. doi:10.1136/bmjopen-2025-098929

► Prepublication history for this paper is available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2025-098929).

Received 06 January 2025
Accepted 09 June 2025

For numbered affiliations see end of article.

Correspondence to
Dr Tom P C Schlösser;
t.p.c.schlosser@umcutrecht.nl

ABSTRACT

Introduction Adolescent idiopathic scoliosis (AIS) is an acquired deformity that develops in 2–4% of otherwise healthy children during adolescent growth, substantially reducing their quality of life and creating a life-long burden of disease. Despite many years of dedicated research, the cause and mechanism of AIS are still unknown and no effective curative treatments are available for children suffering from this spinal and chest deformity. To date, all etiological studies focused on children with an already established scoliosis. EARLYBIRD aims to uncover the earliest pathoanatomical changes in AIS, by studying longitudinal spinal growth in children at increased risk for scoliosis development with MRI, starting before adolescence.

Methods and analysis This prospective observational cohort study will follow two groups: 60 adolescent girls (8–10 years old) who have an older sibling or parent diagnosed with AIS (cohort 1) and 60 adolescents with 22q11.2 deletion syndrome, a genetic microdeletion associated with 50% scoliosis prevalence (cohort 2). Data collection will be completely radiation-free and occur at baseline and yearly during adolescence up to 15 years of age in girls and up to 16 in boys. A comprehensive physical examination, a dedicated spine and chest MRI as well as a standing three-dimensional (3-D) spinal ultrasound will be obtained at each time point. The main parameter will be the longitudinal changes in segmental axial rotation during growth in subjects that do and do not develop AIS. Secondary endpoints are longitudinal changes in 3-D morphology of the bone and intervertebral discs (IVDs) during normal spinal development and during scoliosis development, determining biomarkers for bone growth, implementing radiation-free imaging methods for spinal monitoring in adolescent patients at risk for scoliosis development and use these for spinal skeletal maturity and patient-specific spinal biomechanical analyses.

Ethics and dissemination This protocol has been approved by the Medical Ethics Committee NedMed and is registered on clinicaltrials.gov (NCT05924347). Written informed consent will be obtained from all parents/legal representatives. Key findings will be disseminated via peer-reviewed journals and presentation at conferences. This study is funded by the European Research Council.

STRENGTH AND LIMITATIONS OF THIS STUDY

⇒ Prospective study in children with an increased risk for scoliosis development for identification of the earliest changes in scoliosis development.
⇒ The study is designed to follow spinal development from before adolescence to after the peak of the growth spurt.
⇒ Three-dimensional (3-D) MRI scans and Artificial Intelligence (AI)-generated MRI-based synthetic CT (sCT) provide extensive detailed images of osseous and non-osseous spinal pathoanatomy.
⇒ Generalisability of 'normal' spinal growth in the non-scoliotic subjects to the broader context of the general pediatric population of various ethnicities cannot be assured.
⇒ As baseline measurements could potentially be obtained after the disease onset and the non-experimental setup, definitive cause-and-effect conclusions cannot be drawn.

INTRODUCTION

Idiopathic scoliosis is a three-dimensional (3-D) deformity of the spine affecting 2–4% of previously healthy children, substantially reducing their quality of life and creating a life-long burden of disease.[1 2] Historical epidemiological and natural history studies showed that most are diagnosed at adolescence and that adolescent idiopathic scoliosis (AIS) is three to four times more prevalent in girls.[3] Although the disease

has been identified since the time of Hippocrates (400 B.C.), we have not been able to rationally develop effective treatments and provide a cure for AIS patients because its cause and mechanism of disease are still unknown.

The cause and disease mechanism of AIS has remained unsolved partly because of its multifactorial nature, but also because all etiological studies to date have focused on children with already established scoliosis or on animal models. AIS, however, is definitely related to paediatric spinal growth and seems to occur in girls that were previously healthy. Furthermore, AIS is unique to humans and is believed to be related to our fully upright posture making our spinal columns an inherently rotationally unstable stack of vertebral blocks. Recently, it was shown that this curvature is actually characterised by deformation that mostly begins in the intervertebral discs (IVDs).[4] We hypothesise that AIS is a rotatory decompensation of the spine that starts with torsion of the IVDs in the posteriorly inclined region of the spine (in between the apex of the thoracic kyphosis and lumbar lordosis) and that there is already an increase in segmental axial torsion before the clinical diagnosis of AIS, in adolescents that develop scoliosis as compared with adolescents that do not develop scoliosis.[5–7]

The biggest limitation for understanding AIS aetiology is that, to date, scoliosis patients have been studied after its onset, as clinicians treating patients with scoliosis only see patients once the spinal deformity is evident. Moreover, normal longitudinal growth of spinal osseous and non-osseous tissues during adolescence has not been clearly defined. To study the pre-stage of AIS, children who will and will not develop scoliosis during the adolescent growth spurt need to be studied longitudinally to assess functional spine anatomy at various stages of skeletal maturity. For ethical reasons, this can only be done in a non-harmful way, with minimal risk and burden to the participating children. Therefore, repeated full spine radiographs or CT should be avoided since their acquisition requires ionising radiation.[8] Although the image quality from radiation-free alternatives such as 3-D ultrasound or surface tomography is sufficient for global spinal alignment, they are insufficient for assessment of growth of specific spinal tissues. Therefore, for this longitudinal study, we developed a specific MRI protocol, which incorporates traditional MRI contrasts as well as BoneMRI, an artificial intelligence method to create synthetic CT (sCT) images of the vertebral column from multi-gradient-echo MRI sequence datasets using deep learning.[9–13] While the spine is relieved from gravity, structural deformities can be seen more clearly compared with positional deformities. Although in a relaxed supine position without active spine loading, by combining BoneMRI and IVD-specific MRI sequences into clinically manageable sessions, a new skeletal imaging protocol is applied in this group of children. This provides a non-invasive method, that allows for repeated use over their growth period and quantification of growth of various spinal tissues.

AIS has a familiar component, as the prevalence in girls with relatives affected by the same disorder is 11–51% and has a concordance of 36–63% in dizygotic twins.[14–19] Therefore, younger sisters and daughters of scoliosis patients are at increased risk for scoliosis development. Another patient group with an increased scoliosis prevalence is the 22q11.2 deletion syndrome (22q11.2DS) population, previously known as DiGeorge syndrome and velocardiofacial syndrome. 22q11.2DS is the most prevalent microdeletion syndrome in humans, with many phenotypical expressions, including cardiovascular abnormalities, immunodeficiency, developmental disabilities and several orthopaedic disorders.[20] Approximately half of the 22q11.2DS population develops a syndromic scoliosis that is idiopathic-like.[21–24] These curves resemble the AIS curve morphology, making it a possible ‘human biomechanical model’ for AIS.[23 25]

A prospective, observational cohort study in individuals with an increased risk of scoliosis development, could provide a unique database that can hopefully clarify scoliosis aetiology. The primary aim of EARLYBIRD is to longitudinally evaluate the substantial differences in anatomical changes in the spine during early adolescent growth in individuals who do and do not develop AIS. Secondary objectives of the study are to develop spine-specific maturity assessment grading, implement radiation-free imaging methods for spinal monitoring in adolescent patients at risk for scoliosis development, create a longitudinal dataset for patient-specific adolescent spinal biomechanical assessment and determine biomarkers for bone growth to guide the early diagnosis of scoliosis and clinical decision making.

This study will provide a necessary contribution to the field for several reasons. First, it will study human subjects before disease development and longitudinal track them non-invasively through disease initiation and progression, creating for the first time a comprehensive dataset of healthy and AIS female human spines that can be used for early detection and treatment of paediatric spine conditions. Second, it will help in understanding AIS aetiology by demonstrating its first pathoanatomical changes, and it can serve as the input for biomechanical modelling whereby predictive triggers for initial axial rotation can be identified. Third, it will implement safe non-radiographic accurate imaging of the growing spine and chest wall, which can become the standard for diagnosis and monitoring of spinal and chest deformation.

Methods and analysis

This a single centre observational cohort study, performed at the University Medical Centre Utrecht, Utrecht, the Netherlands, with subjects recruited through scoliosis patient platforms, local scoliosis exercise therapists and clinicians involved in scoliosis treatment or 22q11.2DS care.

Study population

This study will include two cohorts of individuals with increased risk for scoliosis development:

- **Cohort 1:** 60 younger sisters or daughters of patients diagnosed with AIS, that have to be 8–10 years old at inclusion.
- **Cohort 2:** 60 22q11.2DS patients with genetic confirmed 22q11.2DS. Girls have to be 8–10 years old at inclusion and boys 9–11 years old.

Exclusion criteria are:

- Contraindications for MR imaging.
- Pre-existent diagnosis of early-onset scoliosis or other spinal deformities.
- Other syndromes or neuromuscular disease associated with scoliosis.[26]
- Clinical signs of >1 cm leg length discrepancy.
- Other diseases or injuries, that are related to abnormal spinal growth, posture, activity levels or scoliosis development.

Individuals will be screened for the in- and exclusion criteria, and after written informed consent by the parents/legal representatives, participants will be screened including the forward bending test (FBT) for screening for pre-existent scoliosis with a cut-off value ≤7°. Participation in the EARLYBIRD biobank, involving a one-time blood draw, is optional and registered on the informed consent form. No formal scoliosis screening programme exists in our country, and therefore participation in this study can be advantageous for both cohorts.

Data collection

Inclusion started in July 2023 and is expected to end in December 2025. At every visit, demographics, a physical examination, a 3-D spinal ultrasound in a standing position as well as a dedicated spine and chest MRI will be obtained by a trained clinical researcher. Baseline data are collected at 8–10 years for girls, and 9–11 years for boys. Boys and girls are followed at specific timepoints (figure 1) with the same combination of examinations up to 15 and 16 years of age, respectively. A window of 3 months will be accepted for planning purposes. In addition to the MRI and ultrasound imaging, at the second follow-up, an additional hand radiograph for skeletal maturity assessment and a venous puncture for 5 mL plasma and 5 mL serum will be obtained. Plasma and serum will be stored in the central biobank of the academic hospital for 15 years. Demographics and physical examination parameters collected for this study are shown in table 1.

3-D spinal ultrasound: 3-D spinal ultrasound (ScolioScan system, Telefield Medical Imaging Limited, Hong Kong) consists of a linear ultrasound probe and a sensor to detect probe position. Patients are positioned in natural standing, weight-bearing position with arms resting by their side.

In addition, the system has a chest and hip board with supporters to minimise patient motion during ultrasound scanning.[27] The procedure of acquiring the ultrasound takes less than a minute. Previously, 3D spinal ultrasound

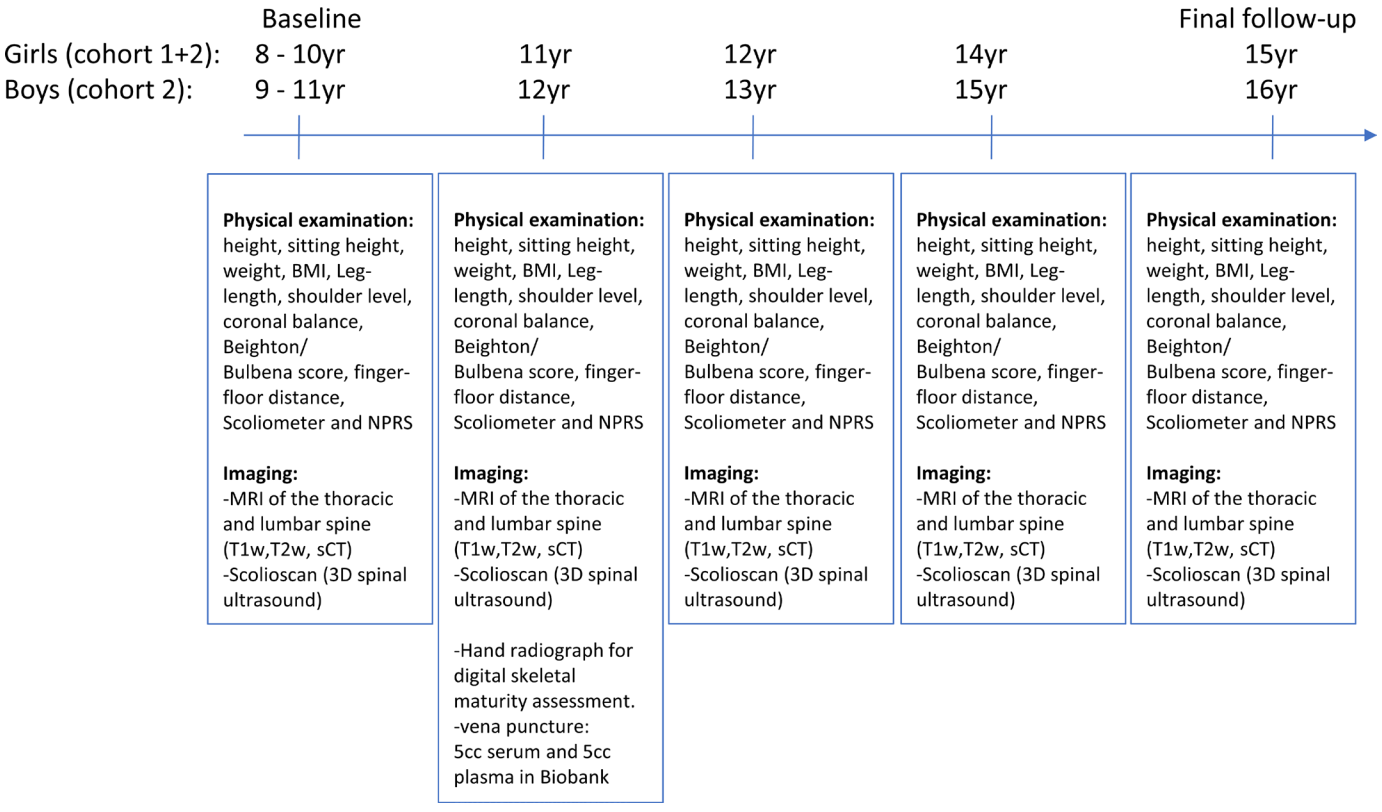

Figure 1 Overview of follow-up moments for both cohorts and sexes and what data collection are performed.

Table 1 Demographics and physical examination parameters collected for this study

	Parameters
Demographics	Age, menarche and NPRS for back pain, medical history (including spinal and neuromuscular diseases), family medical history, previous signs of scoliosis, medication
Anthropometrics	Height, sitting height, weight, BMI
Postural parameters	Leg length discrepancy, shoulder level asymmetry, coronal balance, thorax asymmetry
Hyperlaxity	Beighton and Bulbena score, finger-floor distance
Scoliosis	Bunnell Scoliometer with Adams FBT

BMI, Body Mass Index; FBT, Forward Bending Test; NPRS, Numeric Pain Rating Scale.

has been validated for coronal, sagittal and axial measurements of regional spinal alignment.[27–29]

Spine and chest MRI: MRI is a non-ionising imaging modality, which provides currently the best visualisation of spinal soft tissues in vivo. With conventional sequences, the composition of the IVD can be assessed as well as gross growth plate abnormalities. A disadvantage of MRI, is that it is not appropriate for accurate bone visualisation. To solve this issue, BoneMRI can be used to create Artificial Intelligence (AI)-generated, MRI-based sCT of the spine and pelvis.[9 10 30 31] In the workup for EARLYBIRD, also in idiopathic scoliosis patients it has been successfully applied, using a 42 cm BoneMRI of the major part of the thoracic and lumbar spine.[11 13] The MRI protocol used in this study is shown in table 2 and an example of the MRI output in figure 2. The 3-D morphological analyses of the spine will be performed semi-automatically, using in-house developed software (ScoliosisAnalysis 7.0; Image Sciences Institute, Utrecht, the Netherlands, developed with MeVisLab, MeVis Medical Solutions AG, Bremen, Germany).

Patient and public involvement

Patient and members of the public were actively involved in the design and conduct of this study. All study procedures were designed to minimise patient burden. The procedures and imaging methods are already used in the clinic for scoliosis patients and therefore could be easily adapted to maximise patient comfort. The patient associations have been involved from the start of the study and are regularly informed about progress. Participants are also partly recruited by promoting our study at these associations. The principal investigator visits the patient association meetings on a regular basis to discuss and explain

Table 2 Complete description of the MRI protocol used in the EARLYBIRD study (1.5 Tesla MRI scanner)

Sequence	Region of interest	Acquisition time (minutes)	Purpose
3-D Sag T2-w TSE-spine.	T1–L4	4:59	3-D morphological changes of annulus fibrosis and nucleus pulposus.
3-D Sag RF-spoiled multi-echo gradient-echo 'BoneMRI'.	T1–L4	4:48	Global alignment, input for biomechanical modelling, visualisation of posterior elements.
3-D Sag T1-w TSE.	T1–L4	4:43	General abnormality screening.
Quick Cor T2-w TSE.	Thoracic and lumbar spine.	0:52	Scoliosis development screening.
Axial T2 TSE, big coverage gap 25 mm.	Starting from T1, 17 slices with spacing of 2 cm.	2:05	Quantification of chest size and chest wall morphology.
Axial ME-TSE for T2 mapping six echoes.	IVD of T6–T7 up to and including T12–L1.	2:38	Quantification of disc hydration.([37])

Cor, Coronal, mm = millimetre, T = thoracic, L = lumbar; 3-D, Three-dimensional; IVD, Intervertebral Disc; ME-TSE, Multi-Echo Turbo Spin Echo; RF, Radio Frequency; Sag, Sagittal; TSE, Turbo Spin Echo; w, Weighted.

the study to patients and their families. During the study, we continuously assess each inclusion and adapt the methods if any discomfort is experienced by participants. We intend to share results and findings of this study with patients and the public in an accessible manner.

Based on predefined criteria, subjects are referred for scoliosis diagnosis and potential treatment through regular care. These criteria are:

- If there is a positive Adams FBT (Scoliometer>5°):
  - Curve angle on MRI<10° and Scolioscan<12°, no radiograph needed, continue follow-up according to study protocol.
  - Curve angle on MRI>10° or Scolioscan>12°, spinal radiograph indicated, continue follow-up according to study protocol.

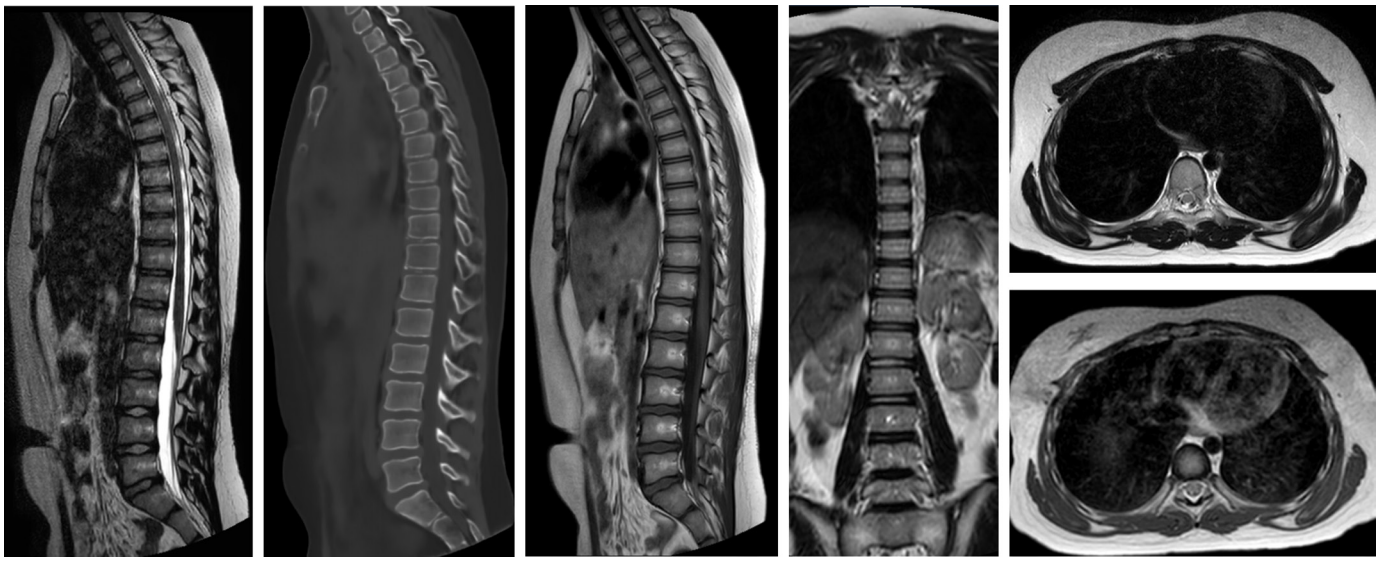

Figure 2 Example of the output of the used MRI protocol. From left to right: 3-D (Three-dimensional) Sagittal (Sag) T2-weighted (w) Turbo Spin Echo (TSE)-spine, synthetic CT created from 3-D Sag radio frequency-spoiled multi-echo gradient-echo 'BoneMRI', 3-D Sag T1-w TSE, Quick Coronal T2-w TSE, upper right: axial T2 TSE, lower right: axial Multi-Echo (ME) TSE for T2 mapping.

- If there is a negative Adams FBT (Scoliometer<5°):
  - Curve angle on MRI<15° and Scolioscan<15°, continue follow-up according to study protocol.
  - Curve angle on MRI>15° or Scolioscan>15°, spinal radiograph indicated, continue follow-up according to study protocol.

Subjects will be classified as 'potential scoliosis development' when they have an abnormal FBT (cut-off value of 7°), and as 'confirmed scoliosis' when they have obtained a spinal radiograph with a curve angle>10 degrees.[32–36] In the case of scoliosis development during the study, follow-up will continue as initially planned. If (early) brace treatment is initiated, MRIs will be obtained without the brace. If scoliosis surgery is being performed, patients will be excluded from further follow-up. All obtained data will be stored in an online electronic data capture system (Castor EDC, Castor, Amsterdam, The Netherlands).

Study outcomes and parameters

The main study parameter will be the longitudinal changes in segmental axial rotation on MRI of the thoracic and lumbar spine (T6–L3) in subjects that do and do not develop AIS.

The following secondary study parameters will also be assessed:

1. Changes in bone and intervertebral disc morphology (anterior-posterior ratio, left-right ratio, torsion, volumes, shift of the nucleus pulposus) during growth.
2. Changes in spinal alignment during growth.
3. Spine-specific (IVD/endplates) maturity assessment grading.
4. Spine-specific maturity assessment grading in relation to:

- Skeletal maturity (Greulich and Pyle digital skeletal age).
- Biological maturity (age, menarche, as well as potential markers for endochondral ossification identified in the future that can be measured on the samples in the concurrent biobank of this study population (eg, vitamin D, serum collagen X matrix, osteopontin).
- Generalised joint hypermobility (Beighton and Bulbena score).
- Spinal alignment and length in the upright position and supine position.
- Spinal cord morphology changes (conus level) during growth.
- Chest wall shape development (shape, size and volume)

5. Individual spinal biomechanical modelling for quantification of rotational instability (in silico).

In silico testing of spinal stability and IVD strain

To investigate spinal stability and IVD strain, subject-specific finite element (FE) models will be created based on the T2-weighted (w) MRI and sCTs. In these FE models, physiological loading will be simulated in each subject at each timepoint. For the vertebrae, we will use the sCTs as input, and for the IVD and facet joints the T2-w MRI scans. Using these subject-specific FE models of the growing spine in the standing position, it will be investigated first if rotational instability can be detected and if this is significantly higher in cases than controls. Second, it will be investigated what the peak strains are in the IVD and in the anterior annulus fibrosus (AF) in particular, if these are related to rotational instability, and if these are higher in cases than controls. Finally, it will be investigated if the expected positive feedback loop (overstraining the disc leads to more deformation) can be observed.

Statistical analysis

All data will be analysed with the use of SPSS software (SPSS, Chicago, Illinois). First, we will perform a descriptive analysis of the epidemiological and morphological parameters including 95% confidence interval (CI). For testing the hypothesis that AIS is a spinal deformity that starts with rotatory decompensation in the IVD, the axial torsion of the thoracolumbar IVDs (T6–L3) at baseline will be compared between subjects that do and do not develop scoliosis using an independent sample t-test. Second, repeated measures ANOVA will be performed with variable categorisation, for example, scoliosis yes/no, age, skeletal maturity, growth and menarche to search for other relevant relations. If multiple comparisons in post hoc analyses or other exploratory investigations are done, corrections for multiple testing will be performed. The level of significance will be set at 0.05 unless otherwise specified.

Sample size calculation

According to Danish data (n=1463), 21% of the daughters and 9% of the sons of patients develop a scoliosis.[14] In a study in Utah, the recurrent risk among sisters was as high as 31%.[16] In China (n=531), a female-sibling specific recurrent risk of 23.0% has been reported.[15] This prevalence was at least double that of male siblings, and 9-fold compared with younger sisters of non-scoliotic siblings. In 22q11.2DS patients (both boys and girls), the risk for scoliosis development is 48%.[24]

Based on the hypothesis that AIS is a spinal deformity that starts with rotatory decompensation and the objective to longitudinally evaluate the substantial differences in anatomical changes in the spine during adolescent growth in adolescents that do and do not develop AIS, the sample size calculation is based on the rotatory differences between subjects with and without scoliosis. Because this study is a longitudinal study with multiple MRI parameters, for which no previous pilot data is available, we believe an accurate sample size calculation is not possible on other data then the axial rotation. In adolescent girls, the mean (± SD) rotation of the most common apical level (Thoracic vertebra 9) is +2 ± 2°. Based on clinical experience and a study on mild AIS, in AIS patients with mild scoliosis the axial apical vertebral rotation is expected to be on average +5 ± 5°. Assuming a pooled SD of 2.5 units, with an independent sample t-test, the study would require a sample size of 11 for each group, to achieve a power of 80% and a level of significance of 5% (two-sided), for detecting a true difference in means. Furthermore, the collection duration must be clinically manageable for these subjects, and the datasets accurate enough for conversion to quantitative computer models. The average number of imaging will be five per study participant. In order to account for lost-to-follow-up (10%), and the expected risk of scoliosis development (20–25%), we will enrol a total of 60 subjects in each cohort. This will provide approximately 12 subjects who develop AIS in cohort 1, and 29 who develop idiopathic-like scoliosis in cohort 2.

ETHICS AND DISSEMINATION

Ethical considerations

This protocol has been approved by the Medical Ethics Review Committee (Medisch Ethische Toetsings Commissie, METC) NedMed - NL82419.041.22 - 22–999/X-G and registered at clinicalstrials.gov (NCT05924347). The study will be conducted according to the principles of the Declaration of Helsinki (2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts like 'gedragscode gezondheidsonderzoek' and Algemene Verordering Gegevensbescherming (AVG). The study will be conducted according to the codes of conduct for minors (as accepted by the Board of the Netherlands Association for Paediatric Medicine (NVK) on 21 May 2001). Written informed consent will be obtained from all parents/legal representatives.

Safety reporting

In accordance with local regulations, the study will be suspended if there is sufficient ground that continuation of the study will jeopardise the health or safety of participants. Considering the observational nature of this study, we do not expect any adverse events or untoward patient safety issues to arise. However, if an unanticipated safety issue does present, we will notify the accredited review board without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

Monitoring

An independent qualified external monitor will be appointed to monitor the study at the start of the study, after 1 year and at the end of the study.

Data depositions

Data handling and protection is conducted according to applicable laws and regulations (ie, Good Clinical Practice (GCP), General Data Protection Regulation (GDPR) and International Organization for Standardization (ISO) 27001, 9001 compliant standards). Confidentiality will be maintained at all times. More details can be found in the Data Management Plan (https://dmponline.dcc.ac.uk/plans/99983).

Publications

Findings will be disseminated via appropriate peer-reviewed journals and presentation at conferences.

Author affiliations
[1]Orthopaedic Surgery, UMC Utrecht, Utrecht, Utrecht, The Netherlands
[2]Department of Pediatrics, Wilhelmina Children's Hospital, Utrecht, Utrecht, Netherlands

[3]Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands
[4]Department of Radiology, UMC Utrecht, Utrecht, The Netherlands

Contributors PPGL: data curation, formal analysis, investigation, project administration, visualisation, writing original draft. HWS: responsible for project administration, review and editing original draft. SdR: conceptualisation, methodology, validation, review and editing original draft. MLH: methodology, review and editing original draft. JK: methodology, software, review and editing original draft. MCK: methodology, review and editing original draft. RMC: conceptualisation, methodology, supervision, funding acquisition, review and editing original draft. PRS: methodology, software, supervision, review and editing original draft. TvdV: data curation, methodology, software review and editing original draft. YMS: data curation, methodology, software, review and editing original draft. KI: supervision, conceptualisation, funding acquisition, review and editing original draft. TPCS: conceptualisation, data curation, methodology, resources, supervision, funding acquisition, review and editing original draft. All authors read and approved the final manuscript. TPCS is the guarantor.

Funding This research was financially supported by the European Research Council (Grant no: 101020004).

Competing interests PRS: cofounder MRIguidance, minority shareholder MRIguidance. TvdV: employee at MRIguidance. RMC: advisory board MRIguidance. Others: no competing interests.

Patient and public involvement Patients and/or the public were involved in the design, conduct, reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Peter P G Lafranca http://orcid.org/0000-0002-6612-1986

REFERENCES

1 Weinstein SL. The Natural History of Adolescent Idiopathic Scoliosis. *J Pediatr Orthop* 2019;39:S44–6.
2 BMJ Best Practice. Aetiology: Adolescent idiopathic scoliosis [internet]. London: BMJ Publishing Group; 2025. Available: https://bestpractice.bmj.com/topics/en-gb/979/aetiology
3 Riseborough EJ, Wynne-Davies R. A genetic survey of idiopathic scoliosis in Boston, Massachusetts. *J Bone Joint Surg Am* 1973;55:974–82.
4 Schlösser TPC, van Stralen M, Brink RC, *et al*. Three-dimensional characterization of torsion and asymmetry of the intervertebral discs versus vertebral bodies in adolescent idiopathic scoliosis. *Spine (Phila Pa 1976)* 2014;39:E1159–66.
5 Castelein RM, Pasha S, Cheng JC, *et al*. Idiopathic Scoliosis as a Rotatory Decompensation of the Spine. *J Bone Miner Res* 2020;35:1850–7.
6 Schlösser TPC, Colo D, Castelein RM. Etiology and pathogenesis of adolescent idiopathic scoliosis. *Semin Spine Surg* 2015;27:2–8.
7 Schlösser TP, Tsirikos AI, Castelein RM. Aetiological process of idiopathic scoliosis: from a normal growing spine into a complex 3D spinal deformity. *Orthop Trauma* 2021;35:321–7.
8 Simony A, Hansen EJ, Christensen SB, *et al*. Incidence of cancer in adolescent idiopathic scoliosis patients treated 25 years previously. *Eur Spine J* 2016;25:3366–70.
9 Slotman D (Jorik, Nijholt IM, *et al*. Bone visualization of the cervical spine with deep learning-based synthetic CT compared to conventional CT: A single-center noninferiority study on image quality. *Eur J Radiol* 2022;154:110414.
10 Morbée L, Chen M, Herregods N, *et al*. MRI-based synthetic CT of the lumbar spine: Geometric measurements for surgery planning in comparison with CT. *Eur J Radiol* 2021;144:109999.
11 Costa L, Velden T, Castelein R, *et al*. Radiation-free assessment of the 3D morphology of the adolescent scoliotic spine: a feasibility study in synthetic CT. *EPOS Radiologist (Scientific)* 2024.
12 Costa L, Schlosser TPC, Seevinck P, *et al*. The three-dimensional coupling mechanism in scoliosis and its consequences for correction. *Spine Deform* 2023;11:1509–16.
13 Shcherbakova YM, Lafranca PPG, Foppen W, *et al*. A multipurpose, adolescent idiopathic scoliosis-specific, short MRI protocol: A feasibility study in volunteers. *Eur J Radiol* 2024;177:111542.
14 Grauers A, Danielsson A, Karlsson M, *et al*. Family history and its association to curve size and treatment in 1,463 patients with idiopathic scoliosis. *Eur Spine J* 2013;22:2421–6.
15 Tang NLS, Yeung H-Y, Hung VWY, *et al*. Genetic epidemiology and heritability of AIS: A study of 415 Chinese female patients. *J Orthop Res* 2012;30:1464–9.
16 Ward K, Ogilvie J, Argyle V, *et al*. Polygenic inheritance of adolescent idiopathic scoliosis: a study of extended families in Utah. *Am J Med Genet A* 2010;152A:1178–88.
17 Kesling KL, Reinker KA. Scoliosis in Twins. *Spine (Phila Pa 1986)* 1997;22:2009–14.
18 Lowe TG, Edgar M, Margulies JY, *et al*. Etiology of Idiopathic Scoliosis: Current Trends in Research*. *The Journal of Bone and Joint Surgery-American Volume* 2000;82:1157–68.
19 Hadley Miller N. Genetics of Familial Idiopathic Scoliosis. *Spine (Phila Pa 1986)* 2000;25:2416–8.
20 McDonald-McGinn DM, Sullivan KE, Marino B, *et al*. 22q11.2 deletion syndrome. *Nat Rev Dis Primers* 2015;1:15071.
21 Bassett AS, Chow EWC, Husted J, *et al*. Clinical features of 78 adults with 22q11 Deletion Syndrome. *Am J Med Genet A* 2005;138:307–13.
22 Homans JF, de Reuver S, Heung T, *et al*. The role of 22q11.2 deletion syndrome in the relationship between congenital heart disease and scoliosis. *Spine J* 2020;20:956–63.
23 de Reuver S, Homans JF, Schlösser TPC, *et al*. 22q11.2 Deletion Syndrome as a Human Model for Idiopathic Scoliosis. *JCM* 2021;10:4823.
24 Homans JF, Baldew VGM, Brink RC, *et al*. Scoliosis in association with the 22q11.2 deletion syndrome: an observational study. *Arch Dis Child* 2019;104:19–24.
25 Homans JF, de Reuver S, Breetvelt EJ, *et al*. The 22q11.2 deletion syndrome as a model for idiopathic scoliosis - A hypothesis. *Med Hypotheses* 2019;127:57–62.
26 Williams BA, Matsumoto H, McCalla DJ, *et al*. Development and Initial Validation of the Classification of Early-Onset Scoliosis (C-EOS). *The Journal of Bone and Joint Surgery* 2014;96:1359–67.
27 Lee TT-Y, Lai KK-L, Cheng JC-Y, *et al*. 3D ultrasound imaging provides reliable angle measurement with validity comparable to X-ray in patients with adolescent idiopathic scoliosis. *J Orthop Translat* 2021;29:51–9.
28 Lee TY, Yang D, Lai KK-L, *et al*. Three-dimensional ultrasonography could be a potential non-ionizing tool to evaluate vertebral rotation of subjects with adolescent idiopathic scoliosis. *JOR Spine* 2023;6:e1259.
29 Lee TT-Y, Jiang WW, Cheng CLK, *et al*. A Novel Method to Measure the Sagittal Curvature in Spinal Deformities: The Reliability and Feasibility of 3-D Ultrasound Imaging. *Ultrasound Med Biol* 2019;45:2725–35.
30 Florkow MC, Willemsen K, Zijlstra F, *et al*. MRI-based synthetic CT shows equivalence to conventional CT for the morphological assessment of the hip joint. *J Orthop Res* 2022;40:954–64.
31 Zijlstra F, Willemsen K, Florkow MC, *et al*. CT synthesis from mr images for orthopedic applications in the lower arm using a conditional generative adversarial network. In: Angelini ED, Landman BA, eds. *Medical imaging 2019: image processing*; San Diego, United States, 2019:54.
32 Bunnell WP. Outcome of Spinal Screening. *Spine (Phila Pa 1986)* 1993;18:1572–80.
33 Huang SC. Cut-off Point of the Scoliometer in School Scoliosis Screening. *Spine (Phila Pa 1986)* 1997;22:1985–9.
34 Komang-Agung IS, Dwi-Purnomo SB, Susilowati A. Prevalence Rate of Adolescent Idiopathic Scoliosis: Results of School-based Screening in Surabaya, Indonesia. *Malays Orthop J* 2017;11:17–22.
35 SRS. Glossary. SRS; 1994. Available: https://www.srs.org/Education/Glossary#term20
36 Altaf F, Gibson A, Dannawi Z, *et al*. Adolescent idiopathic scoliosis. *BMJ* 2013;346:bmj.f2508.
37 Watanabe A, Benneker LM, Boesch C, *et al*. Classification of intervertebral disk degeneration with axial T2 mapping. *AJR Am J Roentgenol* 2007;189:936–42.