Adolescent idiopathic scoliosis

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Abstract | Adolescent idiopathic scoliosis (AIS) is the most common form of structural spinal deformities that have a radiological lateral Cobb angle — a measure of spinal curvature — of ≥10°. AIS affects between 1% and 4% of adolescents in the early stages of puberty and is more common in young women than in young men. The condition occurs in otherwise healthy individuals and currently has no recognizable cause. In the past few decades, considerable progress has been made towards understanding the clinical patterns and the three-dimensional pathoanatomy of AIS. Advances in biomechanics and technology and their clinical application, supported by limited evidence-based research, have led to improvements in the safety and outcomes of surgical and non-surgical treatments. However, the definite aetiology and aetiopathogenetic mechanisms that underlie AIS are still unclear. Thus, at present, both the prevention of AIS and the treatment of its direct underlying cause are not possible.

Scoliosis (skōlē-ō’sĭs), ‘Σκολίωση’, a Greek word meaning crookedness, was used by the Greek physicians Hippocrates (A.D. 460–370) and Galen (A.D. 131–201) to describe the condition and its aetiological implications approximately 2 millennia ago. Scoliosis is defined as a three-dimensional (3D) structural deformity of the spine and is diagnosed on the basis of a measurement of the major curves comprising the deformity. This measurement is traditionally done using the Cobb method and gives the Cobb angle [FIG. 1]. The measurement is carried out in the coronal plane using a standard posteroanterior radiograph, and the Cobb angle is formed between a line drawn parallel to the superior endplate of the upper vertebra included in the scoliotic curve and a line drawn parallel to the inferior endplate of the lower vertebra of the same curve. Scoliosis is diagnosed if the Cobb angle is ≥10°. In addition to spinal curves, scoliosis is frequently associated with asymmetries of the trunk and the extremities1.

Adolescent idiopathic scoliosis (AIS) is the most common type of scoliosis. The condition begins in early puberty, affects 1–4% of adolescents and disproportionately affects young women. Idiopathic scoliosis denotes curve of unknown aetiology, in contrast to congenital, neuromuscular and other types of scoliosis that have better understood underlying mechanisms. AIS can be classified according to different criteria, including age of onset and the location of the maximal curve (BOX 1; FIG. 2). In this Primer, we provide an update on the latest advances in AIS epidemiology, screening, natural history, quality of life, key concepts and hypotheses of aetiopathogenesis, as well as conservative and surgical treatment options. This update is followed by a brief discussion of the outstanding research and clinical questions in the field, along with speculation on the progress that is likely to be made in the coming decade.

Epidemiology

The prevalence of AIS is related to geography. AIS is more prevalent in areas located at high northern latitudes than in regions of lower latitude2. A 2010 meta-analysis calculated the global prevalence of AIS using 36 studies from 17 countries that had evaluated scoliosis screening3. The global pooled prevalence of spinal curves of ≥10° was 1.34% (95% CI: 0.98–1.70%). However, the prevalence might have varied across studies and countries. For instance, a prevalence range of 0.7–7.5% was found for Spain, in North America this range was 0.4–3.9%, in Asia the range was 0.4–2.5%, in Israel the prevalence was estimated to be 0.1%, the Middle East had a rate of 1.9% and the reported prevalence in Australia was 1.9%. In addition, the pooled prevalence of spinal curves of ≥20°, which defines patients in need of clinical follow-up care, was 0.22% (95% CI: 0.15–0.30%) and the prevalence of individuals who had been treated for scoliosis using either or both a brace or surgery was 0.07% (95% CI: 0–0.13%). The substantial heterogeneity in AIS prevalence across studies might be attributable to considerable differences in the age groups that were targeted in the different studies, along with whether follow-up monitoring was carried out until skeletal maturity. To date, the largest cohort study that assessed children from 10 years of age until skeletal maturity at 19 years of age was carried out in Hong Kong and reported that the prevalence of spinal curves of ≥10° during adolescence was 2.5% (95% CI: 2.4–2.6%)4. The same study reported that the
Sagittal plane

Transverse plane

Figure 1 | Measuring the Cobb angle. a | The axes and planes of the human body. b | Scoliosis curves are measured from the y-axis (coronal plane), where the Cobb angle is commonly measured by drawing a line that is parallel with the angle of the top of the top vertebra involved in the spine curve and the bottom of the bottom vertebra involved in the curve. The Cobb angle is measured where these lines intersect. In addition, the sagittal plane Cobb angle can be measured from the z-axis. c | The spine can be divided into regions comprising the cervical, thoracic, lumbar and sacral vertebral regions.
Box 1 | Current classifications and subclassification system for scoliosis

Idiopathic scoliosis can be further classified and subclassified according to the following criteria:

**Pathological type**
- Structural
- Functional, which is without demonstrable anatomical abnormalities in the spinal column

**Age of onset**
- Infantile, 0–3 years of age
- Childhood, 4–9 years of age
- Adolescent (adolescent idiopathic scoliosis), 10 years of age until closure of the growth plate. This is the most common type of scoliosis
- Adult, ≥18 years of age
- In addition, the term early-onset scoliosis is used to describe the condition when the spinal curve occurs before 10 years of age and late-onset scoliosis is used to describe the condition that begins after 10 years of age

**Curve magnitude**
- Measured using the Cobb method on standard spinal radiographs to generate the Cobb angle

**Curve level and apex**
- Either cervical, thoracic, thoracolumbar or lumbar
- Can include combinations such as right thoracic ([Fig. 2a](#)), thoracolumbar ([Fig. 2b](#)) and lumbar major curves ([Fig. 2c](#))

**Three-dimensional nature of the curve**
- Negrini[^20^] three-dimensional classification, which is based on the direction, the shift and the phase of the curve
- Poncet[^20^] classification, which is based on three distinct patterns of geometric torsion of the major curve

**Non-surgical treatment types**
- Lehnert-Schroth classification[^24^], which includes the ‘three curve pattern’ with the shoulder, thoracic and lumbo-pelvic block deviated and rotated against each other in the frontal plane
- Rigo classification[^20^], which defines specific principles of the corrections required for effective brace design and fabrication on the basis of radiological and clinical curve pattern

**Surgical treatment types**
- King classification, which defines five curve types[^7^,^20^,^2^,^2^]
- Lenke classification, which defines six curve types[^7^]
- Peking Union Medical College classification, which defines three major curve types and 13 subtypes[^20^]
- All three classifications provide more detail for the subtyping of curve patterns on the basis of static and/or dynamic bending radiographs, thus allowing better planning of the surgical approach and the fusion level of the curve

The pathomechanisms of AIS could either be primary or secondary to the scoliosis itself and might form part of the pathogenetic process that contributes to the initiation and/or progression of the spinal curve. These proposed concepts and hypotheses include multiple biological and biomechanical processes that are expressed in the upright growing human spine. Some of the classic concepts include the following: axial rotational instability[^1^]; biomechanical and neuromuscular factors[^1^]; relative anterior spinal overgrowth and asynchronous (uncoupled) spinal neuro-osseous growth (in which the growth of the spinal cord fails to keep pace with that of the vertebral column, causing the spine to ‘buckle’[^1^–^1^]; biomechanical growth modulation as a result of asymmetrical mechanical compression and reduced loading, known as the Huerter–Volkmann effect[^1^,^1^]; the thoracospinal concept, which applies to girls with right thoracic AIS[^1^]; melatonin and melatonin signalling pathway dysfunction[^1^,^1^]; and platelet calmodulin dysfunction[^1^]. New concepts on the pathogenesis of AIS have recently been developed that have been aided by advances in 3D imaging. Selected examples of these hypotheses and techniques include intrinsic dorsal (posterior) shear forces with axial rotation instability of the spine that result from bipedalism[^2^] ([Fig. 4](#)), 3D-computerized morphological reconstruction of the spine[^2^,^2^,^2^], numerical simulation of spinal deformity[^2^] and abnormal regional cerebral cortical thickness and function[^2^,^2^]. Recent results from genetic and genome-wide association studies (GWAS) have led to speculation of a potential link between AIS and newly discovered molecular biological and axonal guidance pathways. A speculative emerging concept of AIS pathogenesis[^2^] involves a cascade that links the leptin body composition effect to both the development of the CNS[^2^,^2^] and the asynchronous neuro-osseous growth mechanism[^2^] ([Fig. 4](#)).

Finally, AIS is associated with osteopenia, a lower body mass index and lower circulating leptin levels than those in individuals without AIS and other systemic abnormalities[^5^,^9^,^1^,^1^]. Therefore, it is likely that AIS shares abnormal metabolic pathways with other complex diseases[^9^], as is the case, for instance, for obesity and hypertension.

**Genetic basis**

The genetic variants that are responsible for AIS remain poorly understood, despite strong evidence that the condition has a genetic basis. The heritability of AIS is indicated by the increased risk of developing AIS in first-degree relatives of individuals with the condition (with a prevalence of 6–11%)[^1^] and by twin studies that show higher AIS concordance rates in monozygotic twins (73%) compared with dizygotic twins (36%)[^6^]. In addition, a questionnaire-based study of the large Swedish Twin Registry estimated that 38% of the variance in the risk of developing scoliosis in general is the result of additive genetic effects and 62% of the variance is the result of unique environmental effects[^6^].

Emerging views of AIS heritability favour a complex polygenic model with considerable genetic heterogeneity ([Fig. 5](#)). Although multiple large families with an over-representation of AIS have been described[^10^], only rarely have genes been identified with putative roles in pathogenesis. For instance, variants in **POC5**, which encodes a centriolar protein, and in **CHD7**, which encodes chromodomain helicase DNA-binding protein 7 and is associated with CHARGE syndrome, segregate with AIS[^11^]; a rare **POC5** variant might play a part in AIS development in some families[^1^]. However, most AIS does not follow the classic mode of Mendelian inheritance and this inability to identify causative AIS genes supports a complex polygenic mode of inheritance. An important model of inheritance proposes that genetic associations with complex traits involve different
sets of genetic and environmental factors that, in the case of AIS, could separately contribute to the initiation and/or to the progression of the spinal curve46. Results from a subsequent genetic epidemiological and hereditability study supported this model41, as did the results from another study that found that sibling risk ratios for AIS were similar to those for other well-described complex diseases, such as rheumatoid arthritis, Crohn disease and type 1 diabetes42. Polygenic inheritance of AIS is also supported by pedigree analyses showing that male patients with AIS are more likely to have siblings and children with scoliosis than female patients, which suggests that males might require a greater number of genetic risk factors to be affected by the condition43,44.

Further support for a complex polygenic mode of AIS inheritance is provided by early candidate gene-based studies. These studies focused on genes related to connective tissue structure, bone metabolism, melatonin signalling pathways, puberty, growth, axon guidance pathways and genes that encode melatonin and oestrogen receptors45. Although some of these genes were found to be associated with AIS curve severity, no associations were found with the initiation of AIS46,47. Moreover, many of these associations have not been replicated, and none of these genes have been significant in larger GWAS.

GWAS of common variants have yielded important insights into the pathogenesis of AIS. For example, GWAS identified common single-nucleotide polymorphisms (SNPs) associated with AIS near the cell adhesion molecule L1-like (CHL1) locus, which suggested a role for axonal guidance molecules in AIS pathogenesis, although these associations did not reach genome-wide significance48. In addition, large GWAS have demonstrated a strong association between AIS and SNPs near the ladybird homeobox 1 (LBX1) locus49, and this association was replicated in a meta-analysis50. LBX1 encodes a homeobox transcription factor involved in muscle cell migration and cardiac and neural tube development, although the mechanism by which the associated SNP influences AIS risk is not known. A subsequent study in the same Japanese cohort identified an association of AIS with SNPs near the adhesion G protein-coupled receptor G6 (ADGRG6; also known as GPR126) locus51, a gene that is essential for neural, cardiac and aural development. Interestingly, the protein encoded by ADGRG6 also regulates human height and binds to collagen, which are functions that support possible roles for this protein in spinal development or extracellular matrix stability. Studies of even larger AIS patient cohorts are likely to reveal additional genetic risk factors, although it is probable that most of these factors will confer small-to-moderate effects.

The basis for the female bias in AIS has not been systematically addressed, although large GWAS have identified a SNP that is associated with AIS in young women but not in young men52. This sexually dimorphic susceptibility locus is near an enhancer of paired box 1 (PAX1), which encodes a transcription factor that had previously been implicated in spinal abnormalities in mice53. Interestingly, the alleles conferring AIS susceptibility were shown in other studies to be protective for male-patterned baldness, which is another strongly sexually dimorphic trait54.

Advances in whole-genome and exome sequencing have made rare variant association studies possible for AIS. Given that rare coding variants often deleteriously alter protein function, these variants have the potential to more strongly contribute to AIS risk within an individual than common genetic variants. Rare variants in fibrillin 1 (FBN1) and FBN2 — the genes responsible for Marfan syndrome and congenital contractual arachnodactyly, respectively — were found in 7.6% of patients with AIS compared with 2.4% of controls and were also associated with progression of the spinal curve severity in these patients55. Fibrillins might influence AIS pathogenesis through their function as extracellular matrix proteins or through their role in transforming growth factor-β (TGFβ) signalling. A role for extracellular matrix protein gene variation in AIS is also supported by identification of rare variants in HSPG2, which encodes basement membrane-specific heparin sulfate proteoglycan core protein, also known as perlecan56.

CNS and neurophysiological dysfunction

Various morphological and functional abnormalities in the CNS have potential links to the aetiopathogenesis of AIS (FIG. 6). For instance, abnormal neurophysiological functions have been reported in patients with AIS. These include abnormal somatosensory-evoked potentials,

Figure 2 | Classification of scoliosis on the basis of the location of the spinal curve. Radiographs (top panels) and corresponding patient photographs (bottom panels) show three different types of scoliosis classified on the basis of the location and the apex of the major spinal curve: right thoracic (part a), thoracolumbar (part b) or lumbar (part c).
which are the electrical signals generated by neurons in response to stimuli, that have prolonged and asymmetrical latencies. These abnormalities correlate with spinal curve direction and progression. Abnormal neurophysiological functions in patients with AIS also include postural instability under both static and dynamic conditions, abnormal proprioceptive function, which is the ability to sense the relative positions of different body parts, visuo-oculomotor and vestibular dysfunction and combinations of all the above.

In addition, considerable neuromorphological abnormalities associated with AIS have been shown in the CNS at both the brain and the spinal cord. Research in this area has been aided by improvements in MRI technology that have been reinforced by advanced pulse sequences and computational techniques. Patients with AIS have reduced spinal cord to vertebral length ratios. In these individuals, the position of the spinal cord tends to be shifted to the concave side, which is accompanied by a distorted spinal cord shape at the apex of the curve and is associated with low-lying cerebellar tonsils. These observations support the hypothesis that asynchronous or uncoupled neuro-osseous growth contributes to AIS. In this context, anterior spinal overgrowth at the thoracic level relative to the slower growing spinal cord and nerve roots could lead to lordoscoliotic deformity, which involves a combination of spinal curves in the x-axis and y-axis, with maximum torsion at the apex of the spinal curve. This hypothesis also fits with microstructural damage and subclinical neurophysiological changes in patients with AIS, as revealed by diffusion tensor imaging that shows decreased fractional anisotropy values—a useful measure of connectivity within the CNS in the brainstem and in the upper cervical spinal cord. A decrease in fractional anisotropy could reflect reduced integrity of or damage to the white matter tracts of the CNS.

Brain imaging studies have shown several alterations that are associated with AIS. For example, patients with the condition have a larger regional brain volume difference, including in the brainstem and in the corpus callosum—a region that connects the motor and the premotor cortices of the two hemispheres—compared with individuals who do not have AIS. Two subsequent studies analysed the corpus callosum, showing that the 2D shape and the fractional anisotropy using diffusion tensor imaging were consistently different between patients with AIS and unaffected individuals. Using functional MRI, patients with AIS were also found to have a greater interhemispheric asymmetry index and decreased structural connectivity between hemispheres compared with individuals without the condition, which indicates that AIS might involve a primary deficit in interhemispheric coordination. Other studies have shown considerable differences in the cerebral cortical thickness maturation pattern, focal cortical thickness and regional cerebellar volume between those with and those without AIS. Moreover, abnormal patterns of brain activation were observed in secondary motor areas during movement execution in patients with AIS, which were accompanied by increased connectivity in several cortical regions. Overall, the brain regions that show abnormalities in patients with AIS coincide well with functional areas involved in motor control and the vestibular and somatosensory systems.

Disorder in the integration of the neurological systems, which have been implicated in AIS by imaging studies, might contribute to the initiation and/or progression of the condition. It is not clear whether the abnormalities detected in these systems are primary—that is, aetiopathogenetic—or secondary—that is, representative of adaptive or compensatory responses— to the development of AIS. Nonetheless, these alterations resemble several well-documented functional neurological abnormalities. In addition, some studies have shown morphological alteration of the vestibular apparatus itself with morphological abnormalities and asymmetry in the semicircular canals in patients with AIS. Specifically, these studies found that the distance between the centres of the lateral and superior canals and the angle formed between the centre-joining lines at the posterior canal were smaller in patients with AIS than in unaffected individuals. In addition, the orientation...
Figure 4 | The cascade concept of AIS pathogenesis. Adipose tissue and energy control are related to the predisposition to adolescent idiopathic scoliosis (AIS)\(^\text{16}\). As such, it is possible that leptin could be linked to the development of the central nervous system (CNS) and to the asynchronous neuro-osseous growth mechanism\(^\text{15}\). According to the cascade concept of AIS, which incorporates several existing pathogenetic concepts, during late childhood, a low body fat mass leads to low circulating leptin levels. This, in turn, leads to effects on the CNS, including impaired growth of the CNS axis, also known as the neuraxis, and the cauda equina stretch in response to the linear growth of vertebrae, creating a neuraxis tether from 10 years of age or before. This interpretation links low leptin levels to the initiation of asynchronous neuro-osseous growth with which, as the spine lengthens, tension is created in the tether. During the early adolescent growth spurt, these issues translate into changes in spinal conformation, which initially occurs in the sagittal plane by the tethering of anterior vertebral growth; this, together with tension in the tether, induces a more backward vertebral tilt. In the transverse plane of the spine, a normal developmental left-to-right anteverdbral rotation (AVR) conversion process involves asymmetrical neurocentral synchondroses (NCSs) and reflects the most prevalent curve patterns in thoracic idiopathic scoliosis at different ages. Increasing backward vertebral tilt with thoracic AVR leads to increasing spinal instability and torsion. Depending on the backward tilt, axial rotation might be aggravated to become scoliogenic for right thoracic AIS, by different putative thoracic spinal axial rotation factors that include: CNS disturbances such as contralateral cerebral hemisphere dysfunction during development, rib asymmetry and the shallow chest with hypokyphosis, aortic left shift and ribcage rotation that are all found in patients with right thoracic AIS, possibly involving cardiothoracic disproportion. These vertebral changes during adolescence, combined with various other contributing factors, lead to the relative anterior spinal overgrowth that results in the formation of a three-dimensional (3D) scoliosis deformity\(^\text{29}\).

**Skeletal growth and bone quality**

One hypothesis to explain the pathogenesis of AIS posits that dysfunctional interaction between specific genetic and multiple environmental factors could lead to abnormal regulation and modulation of systemic bone growth, bone metabolism and bone modelling and remodelling. These abnormalities might function through different biological and biomechanical pathways and might be phenotypically expressed as systemic osteopenia, abnormal bone mineralization and abnormal bone micro-architecture. These expressions could, in turn, affect mechanical bone strength and contribute to the initiation and progression of spinal deformity in patients with AIS that occurs during the rapid growth period in early puberty.

**Abnormal skeletal growth.** AIS occurs in children during their pubertal growth spurt; abnormal skeletal growth has been widely reported to be associated with the development and progression of scoliotic curves in these patients\(^\text{71}\). Patients with AIS tend to be taller than those without AIS and have longer arm spans and leg lengths, which can be transitory or persistent. Longitudinal growth studies have revealed a significant increase in the peak height velocity (the period when maximum rate of growth occurs) in patients with AIS, which also occurs at an earlier age compared with those who do not have the condition\(^\text{72}\). Disproportionate growth and asymmetric morphology of skeletal features beyond the spine, including the periapical ribs\(^\text{73}\), upper arm length, left–right symmetry and iliac height have been reported in patients with AIS and have been found to be significantly associated with apical vertebral rotation and curve severity\(^\text{74}\). Indeed, disproportionate and asynchronous neuro-osseous growth of the spinal column and spinal cord, which leads to relative anterior spinal overgrowth, has been reported to be associated with the condition and has been hypothesized to be a contributing factor in the aetiopathogenesis of AIS\(^\text{75}\).

**Abnormal body composition.** In addition to skeletal growth and height, many studies have reported that spinal curve severity in AIS correlates with abnormal body composition, with individuals with AIS having a lower body weight and lower body mass index than those without the condition\(^\text{75}\). In this context, lower body weight is caused by a decrease in both body fat and fat-free mass\(^\text{76}\). Furthermore, a large prospective cohort study reported that decreases in leptin, lean mass and fat mass were associated with an increased risk of scoliosis\(^\text{71}\). These results, along with evidence indicating that there is abnormally low free leptin bioavailability in patients...
with AIS, support the suggestion that leptin and soluble leptin receptor — with its physiological functions in regulating skeletal growth, bone metabolism and energy homeostasis — might be responsible for some of the abnormal phenotypes observed in AIS.

**Osteopenia.** Low bone mineral density (osteopenia) is defined using the z-score, which describes the number of standard deviations an individual's bone mineral density is from the mean of a reference matched ethnic population. Individuals with a z-score of < 1 are considered to have osteopenia, and in one study, this threshold was met by 36–38% of girls with AIS. This osteopenia was systemic, detected at the axial skeletal sites, such as the hip and the spine, and peripherally in the distal tibia and radius. Longitudinal studies have shown that this osteopenia can persist into adulthood if not treated and constitutes an important prognostic factor for curve progression in AIS. Advancements in bone micro-imaging technology are reflected in studies that use quantitative ultrasonography, peripheral quantitative CT, high-resolution peripheral quantitative CT and micro-CT. In one such recent study, low bone mass in patients with AIS was found to affect both cortical and trabecular bone compartments and was associated with abnormal bone mineralization, bone morphology, trabecular micro-architecture, volumetric bone density, overall bone quality and mechanical strength. In addition, histomorphometric investigations have shown that patients with AIS have a reduced bone volume fraction and trabecular bone thickness and low osteocyte and osteoblast density compared with unaffected individuals. These deficiencies might be related to abnormalities in the osteocyte lacunocanalicular system, which is a network within the mineralized bone matrix that mediates communication between osteocytes. Finally, biochemical studies have also reported markers of abnormal bone metabolism in patients with AIS (TABLE 1).

**Bipedalism and 3D spinal–pelvic deformity**

An emerging theory of how AIS could develop relates to the biomechanics associated with human bipedalism. Although spinal deformities have been observed in animals, true idiopathic scoliosis has only been diagnosed in humans. Whereas the spinal anatomy of humans and other vertebrates is very similar, the biomechanical loading of the human spine greatly differs from other species. Humans have the unique ability to simultaneously extend both hips and knees. This, in combination with a lordotic curvature that starts between the ischial and iliac bones and continues into the lumbar spine, puts the human centre of gravity directly above the pelvis. All other vertebrates, including those that are bipedal, lack these lordotic curvatures and instead walk with flexed hips and knees — putting the trunk’s centre of gravity in front of the hips.

These differences have serious consequences for the biomechanical forces that influence the human spine. For instance, in our opinion, the spine, on the basis of its anatomy, is able to withstand axial and anterior loads, but as a result of its position certain areas in the human spine are posteriorly inclined and subject to posteriorly directed loads. Research has suggested the possibility that these posterior shear loads decrease the rotational stiffness of the spine. Thus, rotational stability apparently depends on whether individual vertebrae are anteriorly or posteriorly inclined in the sagittal plane. This sagittal profile differs considerably between girls and boys, especially during their pubertal growth spurt, with girls having a larger posteriorly inclined area of the spine, and thus less rotational stability, than boys. This, in our opinion, might explain the predominance of scoliosis in girls and its development during this crucial phase of life. In further support of this hypothesis, different types of scoliosis develop on different sagittal profiles, with the posteriorly inclined segment being longer and more proximal in the spine for thoracic curves than for lumbar curves.

Once the spinal curve develops, its rotational direction follows an in-built pattern that is already present in the normal, non-scoliotic spine. The direction of this pre-existing rotation is identical to that observed in idiopathic scoliosis, but the magnitude of rotation depends on the position of the spine relative to the gravity line. This pre-existing rotation in the normal spine is significantly less severe in an individual in the quadrupedal position than in the same individual standing upright. This difference further shows that, compared with the forces on a quadrupedal spine, the loading of the upright human spine, which involves the introduction of posteriorly directed loads, leads to an increased rotation.

In summary, it is our opinion that the unique configuration in space of the human upright spinal–pelvic complex, and the way it is consequently biomechanically loaded, makes it much more prone to rotate than any other spine in nature. A slight amount of intrinsic rotation is always present in unaffected individuals,
which corresponds exactly to the direction of rotation that occurs in patients with scoliosis. Whether this pre-existent rotation will go on to exceed a certain threshold and induce the development of the scoliosis deformity depends on a multitude of factors. These factors might include, for instance, individual variations in the sagittal shape of the spine in relation to the timing of the adolescent growth spurt.

**Primary and/or secondary biomechanical factors**

Various factors are probably involved in the initiation of spinal deformity in AIS. After a certain asymmetry is achieved, the progression of this deformity is likely to be mediated by mechanical disturbance of spinal loading. Mechanical factors that could predispose individuals to the initiation of scoliosis during growth include an abnormal sagittal curvature such as hypokyphosis and a ‘slender’ spine. Spines with these features are more susceptible to ‘buckling’ in the frontal plane and rotation in the axial plane, which is greatest at the apex of the spinal curve. It is also possible that uncoupled neuro-osseous growth causes the spine to buckle into a scoliosis deformity. Ligamentous and muscular structures have also been implicated in ‘tethering’ of the spine, which could produce scoliosis and rotation of the spine. In addition, it is possible that anomalies of neuromuscular control produce asymmetrical spinal loading and hence initiation and progression of scoliosis.

Although the role of biomechanics in the initiation of AIS is unclear, the importance of mechanical factors in the progression phase of the condition is supported by the current understanding of how the mechanical environment interacts with bone growth, together with the existence of a range of animal models in which surgically induced asymmetrical loading can result in progressive spinal deformity. Furthermore, conservative management of AIS with back braces is based on this premise, and recent research that links the efficacy of bracing to compliance with brace-wearing provides empirical support for this hypothesis. Neuromuscular, idiopathic and, to some extent, congenital scoliosis have a mode of progression during adolescence that is similar to that of AIS, which is suggestive of a common underlying mechanism.

A ‘vicious cycle’ of scoliosis progression has been proposed, in which asymmetrical stresses that act on a laterally curved spine and the vertebral growth plates produce asymmetrical spinal growth. This asymmetry, in turn, leads to progression of the lateral curvature through the Hueter–Volkmann principle, in which increased compressive loading retards growth and decreased loading results in accelerated growth. In vertebrae, this would produce wedging of the vertebrae in the coronal plane. This concept is incorporated into the surgical paradigms of ‘guided growth’ and fusion-sparing surgery, as well as into conservative management approaches that use bracing. The hypothesis is supported by a quantitative analysis that includes estimates of the magnitude of stresses on the convex and concave sides of vertebrae, data from experimental studies in various mammalian species that describe the sensitivity of growth plates to compressive stress from experimental studies and geometrical changes that result from asymmetrical growth. This analysis predicted that a small curve in an adolescent human with remaining growth would experience scoliosis progression similar to that observed clinically. However, this analysis only addressed the role of vertebral growth plates in producing wedging of vertebrae in the coronal plane and assumed that synchronous development of coronal plane wedging of intervertebral discs was equal to that of the vertebrae. Analytical modelling of this mechanism of progression is limited by its assumptions and by the available data, including...
the estimates of the magnitude of spinal loading and the resulting growth modulation. Experimental evidence suggests that growth modulation by sustained static forces is similar to the response to cyclical loading at one cycle per 10 seconds\textsuperscript{109}, although the exact range of loading \textit{in vivo} is not well defined. Furthermore, the mechanism responsible for the development of discal wedging in scoliosis is unknown. It is also unclear why the dramatic slowing of scoliosis progression at skeletal maturity, defined as cessation of bony growth, is associated with the slowing of both discal and vertebral wedging. At a qualitative level, it has been suggested\textsuperscript{106} that differing trunk-muscle activation patterns might explain why some curves are progressive but others are not.

**Abnormal metabolic pathways and endophenotypes**

**Abnormal metabolic pathways in AIS.** During the past decade, several hormonal and metabolic factors have been associated with the onset and development of AIS\textsuperscript{110}. Of particular note is an association between osteopenia and AIS\textsuperscript{111}, which implies that abnormalities that affect bone metabolism could influence the development of AIS\textsuperscript{113-115}. TABLE 1 summarizes some key findings associated with selected bone metabolic markers and/or regulators. A major difficulty faced by most of the metabolic studies of AIS is the phenotypic and genetic heterogeneity of the disease, which is often further exacerbated by a lack of replication cohorts from different populations. In addition, it is difficult to define the roles of bone metabolism markers in AIS pathogenesis because they are not disease-specific and the metabolic changes they indicate could reflect the consequences of crosstalk between multiple genes and environmental factors. For example, reduced leptin concentration in the sera of patients with AIS compared with unaffected individuals could contribute to lower bone mass, which is typically observed in female patients with AIS\textsuperscript{77,78,113,114}, and could be explained by the dysregulated G\textsubscript{1} signalling activities that have been previously reported in patients with AIS\textsuperscript{119,20,115}. Indeed, Alonso-Vale and colleagues showed that increased cytosolic cyclic AMP strongly inhibited leptin synthesis, which can normally be prevented by melatonin signalling activity through its interaction with MT1-type melatonin receptors\textsuperscript{116}. This finding suggests that a reduction in circulating leptin levels in patients with AIS could be the consequence of greater metabolic dysfunction, rather than causative of the condition.

**AIS endophenotypes.** The genetic epidemiology term 'endophenotype' is used to explain symptoms associated with complex disorders. Endophenotypes can be revealed through the induction of specific conditions, such as behavioural responses triggered by specific stimuli, or through laboratory tests such as cell signalling assays. Endophenotypes can be viewed as a global approach to partition complex genetic disorders into somewhat stable phenotypes. This concept has been widely used to investigate complex psychiatric disorders such as schizophrenia\textsuperscript{117} and, more recently, has started to be reported in AIS\textsuperscript{118}.

### Table 1 | Abnormalities in bone metabolic factors associated with AIS

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<th>Biomarkers</th>
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<td><strong>OST</strong></td>
<td>• Significantly higher serum OST levels (P &lt; 0.01) were observed in adolescents with AIS than in individuals in the control group\textsuperscript{106}</td>
<td>• 15 patients with AIS and 7 matched controls \n• White patients from Romania</td>
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<td><strong>RANKL</strong></td>
<td>• Significantly higher serum RANKL levels (P &lt; 0.01) were observed in adolescents with AIS than in individuals in the control group\textsuperscript{106}</td>
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<td></td>
<td>• Significantly higher mRNA and protein expression levels of RANKL were observed in osteoblasts from patients with AIS who had osteopenia\textsuperscript{115}</td>
<td>• 72 patients with AIS and 64 matched controls \n• Asian patients from South Korea</td>
</tr>
<tr>
<td><strong>Soluble OBR</strong></td>
<td>• A decrease in circulating leptin levels were observed in Chinese girls with AIS\textsuperscript{113} \n• These patients showed an association between leptin and body weight, BMI and bone mass\textsuperscript{114} \n• A significant correlation was found between higher levels of circulating soluble OBR and free leptin with curve severity in these patients\textsuperscript{77,78}</td>
<td>Study 1: \n• 120 patients with AIS and 80 matched controls \n• Asian (Han Chinese) patients from China \nStudy 2: \n• 95 patients with AIS and 46 matched controls \n• Asian (Han Chinese) patients from China</td>
</tr>
<tr>
<td><strong>MATN1</strong></td>
<td>• Plasma MATN1 levels were reduced in patients with AIS compared with individuals in the control group (P &lt; 0.01)\textsuperscript{114} \n• The GG genotype (allele G of the MATN1 SNP rs1149048) was associated with lower MATN1 levels than the AA and AG genotypes in both patients and control groups, but this trend was stronger in patients with AIS\textsuperscript{116} \n• Plasma MATN1 levels were significantly lower in patients whose AIS progressed than for those whose AIS was stable\textsuperscript{114}</td>
<td>• 25 patients with AIS and 25 matched controls \n• Asian (Han Chinese) patients from China</td>
</tr>
<tr>
<td><strong>COMP</strong></td>
<td>• Plasma COMP levels were lower in children with idiopathic scoliosis than in children in a control cohort\textsuperscript{110} \n• In children with scoliosis, high levels of COMP modestly correlated with high growth velocity, but not with curve severity\textsuperscript{110}</td>
<td>• 105 patients with AIS and 103 matched controls \n• White patients from Sweden</td>
</tr>
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</table>

AIS, adolescent idiopathic scoliosis; BMI, body mass index; COMP, cartilage oligomeric matrix protein; MATN1, matrilin 1; OBR, leptin receptor; OST, osteocalcin; RANKL, nuclear factor-xB ligand; SNP, single-nucleotide polymorphism.
In complex genetic disorders such as AIS, endophenotypes are potentially useful for the identification of genes that confer risk and disease pathophysiology without any prior knowledge of mutations in any defective genes. For example, a common disease mechanism has been identified among all patients with AIS, based on a differential impairment of G$_i$-coupled receptor signalling activities, by comparing multiple cell types from patients and unaffected individuals$^{115,119}$. This discovery led to the classification of patients with AIS into one of three different biological endophenotypes termed FG1, FG2 and FG3. These endophenotypes resulted from a selective inhibition of one or more G$_i$ subunit isoforms (G$_i$1, G$_i$3, and G$_i$5), which was caused by subunit serine phosphorylation. These endophenotypes enable patient stratification, which has been correlated to specific molecular expression profiles and differential clinical outcomes$^{118}$. The occurrence of severe scoliosis cases, defined by curves with a Cobb angle of $\geq$45°, is different among each biological endophenotype. For instance, in a French-Canadian population, the proportion of AIS cases that were classed as severe was 13% for the FG1 endophenotype, 60% for the FG2 endophenotype and 27% for the FG3 endophenotype.

Experimental approaches have also shown the relevance of AIS endophenotypes. For example, exposure of osteoblasts and peripheral blood mononuclear cells from patients with FG2-type and FG3-type AIS in vitro to osteopontin — a cytokine with multiple functions — further exacerbates G$_i$-coupled receptor signalling impairment$^{119}$. The relevance of osteopontin in AIS pathogenesis was recently strengthened by a study by Yadav and colleagues$^{120}$, which showed the presence of increased plasma osteopontin levels in phosphatase orphan 1 (Phospho1)–knockout mice that have scoliosis and other skeletal abnormalities. Furthermore, Xie and colleagues$^{121}$ showed a possible link between osteopontin, the onset of scoliosis and the progression of spinal deformity by carrying out daily injections of recombinant osteopontin into a bipedal mouse model, which was produced by amputation of the forelimbs of male C3H mice. This treatment induced an increase in the frequency of scoliosis and severe spinal deformities in mice that received osteopontin compared with mice that received solvent alone and untreated wild-type mice.

In summary, the variability in results between metabolic studies supports the suggestion that ethnic and/or genetic heterogeneity underlies variability in the causes of AIS and in the expression of AIS symptoms. Stratification on the basis of the suggested endophenotypes provides an important approach to resolving some of this variability; however, replication of these findings in further studies from different research centres is required. The link between osteopontin and the onset and the progression of scoliosis awaits further clinical validation in human studies and, in particular, in a range of different paediatric populations.

**Diagnosis, screening and prevention**

**Diagnosis**

Several technological advances have enabled elaboration of the structural changes in the spine that characterize scoliosis. Nicoladoni's anatomy work in 1904 recognized the 3D nature of the scoliosis deformity; however, more-specific radiological descriptions of the condition did not occur until the 1980s$^{122}$. It was not until the availability of CT and, in the past decade, modern low-dose biplanar X-ray systems$^{123}$ that more-precise 3D reconstruction of the spine was possible$^{124}$. As a result of this progress, the classic description of scoliosis is evolving...
towards a 3D characterization that also includes the sagittal plane alignment and the axial rotation in the horizontal plane. These 3D parameters could be important in predicting the progression of the scoliosis curve in the early stages of the condition. However, for these emerging parameters to gain wider application in regular clinical settings, further research aiming to refine and define these 3D references along with economical and technological advances in biplanar radiography are required.

Clinically, AIS can contribute to shoulder height asymmetry, shift of the trunk with reference to the centre of the pelvis or decompensatory side bending in the coronal plane. In addition, upon forward bending, a back ‘hump’ or prominence manifests secondary to the rotational element of scoliosis. From the side, patients might have a normal appearance or a hypokyphosis of the thoracic spine. Radiographic diagnosis is made by ruling out other structural abnormalities or congenital anomalies of the spine. Typical coronal images of AIS on a standing radiograph of the entire spine include a lateral curvature of the spine with a Cobb angle of ≥10° with vertebral rotation. The lateral radiograph can determine the amount of thoracic kyphosis or lumbar lordosis. Flexibility of the deformity is usually measured before surgery through radiographs taken in supine bending, traction or fulcrum bending positions, in which the curve is bent over a bolster placed under the apex of the curve. MRI of the spine is not a routine test, as children enter their growth spurt. The most commonly used screening tests for AIS are the forward bending test (FBT), the scoliometer measurement of angle of trunk rotation (ATR), Moiré topography and low-dose roentgenography. Most screening programmes around the world have adopted the FBT alone, with or without additional ATR measurement. Moiré topography has been used in some countries in Europe and East Asia in conjunction with FBT and/or ATR measurement. In Japan, Moiré topography and low-dose roentgenography have been used in tiers.

The FBT, scoliometer ATR and Moiré topography are all measures of surface deformity and are generally safe. Of these tests, the FBT is the simplest and the cheapest. However, the observer-dependent assessment during the test could substantially increase unnecessary referral of children for radiography. Thus, additional screening tests are recommended. In particular, the tandem use of FBT, ATR measurement and Moiré topography that is used in tiers in Hong Kong has been shown to be effective in identifying patients with AIS who have curves of ≥20° that deserve clinical follow-up care. In the same Hong Kong study, the sensitivity and the positive predictive value for detecting curves of ≥20° were 56% and 37%, respectively, whereas the specificity and the negative predictive value were >95%. The corresponding cost per student screened in Hong Kong, including screening, diagnosis and medical treatment was US$56, which is highly comparable to the US$55 cost of a screening programme in North America that used FBT and ATR measurement only. Current evidence, including the US NIH study showing bracing effectiveness, supports early detection by primary care physicians and continuation or reviving of screening for AIS.

Prevention

Current evidence is inadequate to derive any robust prevention strategies. It is generally accepted that AIS is a multifactorial condition, as discussed above. Without a clear understanding of its aetiology, primary prevention of AIS is not possible. Once AIS has been diagnosed, bracing is the only treatment proven to be of value in preventing curve progression and, possibly, in avoiding future surgery. Hence, detection of AIS at an earlier stage of the clinical course through screening of high-risk adolescents is the only meaningful secondary prevention strategy. Until the aetiology or the genetic basis of the condition is determined, treatment of AIS will be limited to salvage surgeries aiming to correct the spinal deformity. It is hoped that, in the future, the natural history of AIS could be modulated without the need for surgery.

**Figure 8 | Scoliosis screening tests.**

- **a** A patient with a right thoracic and a left lumbar scoliosis is shown. Note the elevated right scapula, waist asymmetry and a mild shift of the thoracic cage to the right.
- **b** The forward bending test revealed a prominent right thoracic rib hump. The inclination of the thoracic cage or the angle of trunk rotation was measured using a scoliometer.
- **c** The Moiré topography is a photostereometric method that shows back asymmetry. A contour map of the back is created by shining a beam of light through a transparent grid marked with black vertical lines. The shadows of these lines cast on the back show the degree of asymmetry between the two sides of the back, which in turn correlates with the magnitude of the scoliosis.
The majority of clinical treatment decisions in AIS are made on the basis of spinal curve magnitude and progression, assuming that, if the curve gets worse, the patient will develop future problems such as pain, increased risk of early mortality, increasing deformity and negative psychosocial effects. Over the lifetime of patients, spinal curve magnitude generally increases. However, how much the curve actually progresses and over what time frame varies for each patient. Factors that can predict spinal curve progression include curve magnitude, age at diagnosis and maturity factors, which include spinal curve size and location, age at menarche and the amount of growth remaining as judged by either the Risser score of ossification of the iliac apophysis or the more reliable Sanders Maturity Score. Curve progression is more probable in skeletally immature patients and those with larger curve size (even after maturity) than in patients who are older and have smaller spinal curves. Curves that have a thoracic apex and a Cobb angle of >50° have the highest prevalence of progression.

Pulmonary function is the only symptom that is consistently associated with curve size in AIS. Factors other than spinal curve size that affect pulmonary function include the degree of thoracic lordosis, vertebral rotation magnitude and decreased respiratory muscle strength. Unlike in early-onset idiopathic scoliosis, which begins between 0 and 5 years of age, in AIS, pulmonary hypertension and right heart failure are rare occurrences. In AIS, large thoracic curves, defined as having a Cobb angle of >50°, are associated with reduced vital capacity and more frequent shortness of breath than that experienced by patients with smaller spinal curves. By contrast, AIS that involves large thoracic curves is only rarely associated with severe cardiopulmonary compromise.

To put the problem into perspective, approximately 50% of adults who do not have scoliosis have an episode of low back pain in any particular year and 15% report frequent back pain or pain that lasts for >2 weeks in a given year. Most long-term follow-up investigations of patients with AIS report the frequency of back pain in these individuals to be similar to that of the general population. By contrast, the Iowa 50-year natural history follow-up study of patients with AIS reported that those with the condition had a greater frequency, intensity and duration of chronic back pain than in the general population. These patients were not disabled. They were able to work and undertake everyday activities to a level that was similar to that of their unaffected peers. Although most patients with AIS will develop radiographic osteoarthritis changes, the presence or absence of radiographic osteoarthritis or curve severity does not correlate with the history of backache. This lack of correlation is also true for back tenderness to palpation, except for areas of lateral listhesis (vertebral displacement) in lumbar and thoracolumbar curves. Lumbar and thoracolumbar curves have the highest frequency of back pain compared with other spinal curve patterns.

**Management**

**Natural history and prognostic factors**

To make informed decisions about the treatment of any condition, clinicians need long-term natural history data that describe exactly what happens to untreated patients over time and, therefore, exactly what treatment should aim to prevent. In AIS, the evidence base for these decisions is heavily reliant on a small body of natural history literature and the longitudinal University of Iowa natural history studies.

The majority of patients with AIS lack marked symptoms and usually present to clinicians as a result of screening exams or because they have been found to have trunkal asymmetry. Treatment decisions are accordingly made with the aim of preventing future adverse consequences of the condition. The early so-called natural history literature of AIS presented a grim prognosis and implied that patients with AIS would become disabled by back pain, die young because of pulmonary compromise and have lower rates of marriage. These early studies were flawed as they included patients with other aetiologies of scoliosis or early-onset idiopathic scoliosis and also failed to evaluate outcomes related to spinal curve pattern.
With respect to overall function and self-esteem of those with AIS, the literature is sparse and conflicting\textsuperscript{131,155}. Patients with scoliosis compare favourably to age-matched and sex-matched controls in terms of the psychological aspects of the condition, including the presence or absence of clinical depression\textsuperscript{156}. Unfortunately, older patients with AIS who have not been treated are much less satisfied with their body image and appearance compared with individuals without the condition. One-third of these patients feel that their spinal curvature has restricted their life in some way. They express difficulty in purchasing clothing, reduced physical ability and increased self-consciousness\textsuperscript{157,158}.

Over their lifetime, untreated patients with AIS function well. As young adults they become employed, form relationships, have children and become active older adults. With increasing age, most patients with untreated AIS can have back pain and feel they have important cosmetic concerns. Accordingly, treatment recommendations such as watchful waiting, physiotherapy, bracing and surgery must be decided on an individual basis. The patient and their family should be well educated about the natural history of the disease to help them to make informed decisions.

Bracing treatment and outcomes
Patients with AIS who have immature skeletons are at the greatest risk of curve progression. For those patients with curves with a Cobb angle of <20°, watchful waiting is appropriate, whereas bracing is appropriate if the curve progresses to a Cobb angle of >20° (REFS \textsuperscript{35,157}). The role of physical therapy alone or in conjunction with bracing remains controversial\textsuperscript{158-160}. The goal of bracing is to prevent progression of the curve to a severity that requires surgery, which is defined by a Cobb angle of ≥50° in the thoracic region, before the patient reaches skeletal maturity. At this time, the risk of curve progression, and hence the risk of surgery, greatly diminishes. The most common non-operative treatment for the prevention of curve progression is the use of a rigid brace such as a thoracolumbosacral orthosis (FIG. 10). Although all braces are made of thermoplastic material their designs vary considerably. When using each brace, the objective is to restore the normal contours and alignment of the spine by means of external forces. Some designs also add stimulation of active correction as the patient moves the spine away from pressure points within the brace.

All braces function as a holding device during the high-risk growth phase. Along with a Cobb angle of ≥50°, additional features are also used to decide whether bracing is necessary. The inclusion criteria adopted by the Scoliosis Research Society are widely accepted and outline that patients 10–15 years of age who are skeletally immature, which is defined by a Risser grade of 0, 1 or 2 and as those who achieved (in girls) menarche within the past year, and who have a curve with a Cobb angle of 20–40° should receive treatment with a brace\textsuperscript{161}. Further research is underway to determine the ‘ideal’ candidate for bracing by investigating various maturity markers and skeletal maturity scoring systems\textsuperscript{162-165} to ensure that patients at low risk are not over-treated during these formative developmental years.

In terms of preventing curve progression to a surgical threshold, a completed randomized clinical trial in North America comparing bracing to observation in patients with AIS at high risk of requiring surgical intervention in the future showed that bracing was effective in preventing the need for surgery\textsuperscript{160,163}. This study also showed a ‘dose-dependent’ effect of bracing, in that the benefit of bracing increased with increasing brace wear, providing treating physicians with level I and level II evidence on the effectiveness of bracing. This study also determined that the success of bracing in preventing high-risk curves from reaching the surgical threshold was >90% if the patients wore the brace >13 hours per day; increasing brace wear beyond this point did not significantly improve the degree of success. Thus, high-risk patients with AIS are recommended to wear the brace for >13 hours per day until they reach skeletal maturity. The average time spent wearing a brace, the objective is to restore the normal contours and alignment of the spine by means of external forces. Some designs also add stimulation of active correction as the patient moves the spine away from pressure points within the brace.

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Surgical treatment and outcomes
The primary goal of surgery is to prevent scoliosis progression by achieving a spinal arthrodesis, or fusion, of the regions of the spine that are involved in the curve. Surgery is considered for patients with AIS who are thought to be at increased risk of curve progression during adult life. This generally includes patients who have scoliosis with Cobb angles, as measured using posteroanterior films, of >40–45° in the thoracolumbar region or >50° in the thoracic region. Together these represent approximately 0.1% of patients with AIS. Surgical spinal arthrodesis (fusion) aims to prevent the long-term consequences of large deformations of the spine and the thorax, which can include pain, reduced pulmonary capacity and disfigurement. Secondary goals of surgery for AIS aim to reduce the deformity and restore spinal alignment. These goals must be balanced with the risks of spinal surgery, which include partial or complete loss of neurological function in approximately 0.05% of those operated on, early or late infection in approximately 1–2% of cases, implant failure or pseudoarthrosis in approximately 1% of cases and recurrence or additional deformity in approximately 1% of cases. Adverse outcomes of this surgery can also include late effects of spinal fusion on the adjacent or remaining spinal segments that might accelerate degenerative arthritis. As such, the timing of surgery — that is, whether it should be prophylactic as an adolescent or in response to symptoms as an adult — and the magnitude of the deformity required to trigger surgery remain controversial. In addition, some patients might choose to observe curves in the ‘surgical’ range until symptoms develop, with the understanding that corrective surgery as an older adult will probably be more complex.

Figure 11 | Spinal surgery for the treatment of AIS. a | Preoperative posteroanterior and lateral radiographs of an adolescent patient with adolescent idiopathic scoliosis (AIS) that has a major thoracic and minor lumbar curve pattern. b | Postoperative radiographs following correction with posterior pedicle screw-based instrumentation of the thoracic region, sparing the motion of the lumbar spine. Note how the minor curve corrects in response to surgery on the major curve.

The principles of surgical correction in adolescence include the following: safely rebalance the trunk in space, minimize the residual deformity, create a lasting correction by fusion and limit, as much as possible, the loss of motion associated with spinal fusion. Intraoperative safety has been greatly enhanced by the use of real-time neurophysiological monitoring of sensory and motor spinal cord function, which enables rapid intervention if evoked potential signals are reduced or lost, such as by increasing blood pressure, removing implants or reducing the magnitude of the correction. Decisions regarding the ‘best’ approaches and choices of spinal levels to be fused remain controversial. Treating the largest (major) curve when there is more than one is well accepted. Defining the criteria for inclusion of lesser (minor) curves remains debated, although the classification of Lenke and colleagues provides guidelines for the treatment of minor curves on the basis of curve pattern and flexibility. One of the simplest ways to limit the extent of fusion is to spare those regions (minor curves) that will spontaneously improve in response to correction of the major curve. No matter the strategy, the patient must be left with a balanced alignment.

During surgery for AIS, 3D corrective forces are applied to the vertebral column by ‘anchors’ fixed to the bony elements that take the form of hooks, wires, cables, synthetic bands and screws. Longitudinal rods connected to the anchors span the length of the spine to be fused, providing the correction as well as the stabilization that enables the fusion bone to grow and to mature between the individual vertebrae during the ensuing 6–12 months. It is this fusion of the spine that yields the lifelong maintenance of correction, without which the metal implant might eventually fail. Bone grafting from a range of sources is used to promote fusion, and this grafting most commonly involves autologous, allogenic and demineralized bone growth factors, whereas it rarely involves recombinant bone morphogenetic protein.

The surgical access to the spine for scoliosis correction can be made by an anterior approach through the chest or abdomen or by a posterior longitudinal approach directly from behind. The anterior approach offers exposure for disectomy (removal of disc material) that is useful for increasing the mobility of the spine as well as for eliminating any remaining vertebral body growth potential, which has been attributed to loss of correction in younger adolescent and juvenile patients and might be used to enhance correction in some curves. Posterior approaches to the spine constitute the vast majority of corrective procedures for AIS. Posterior hook constructs were common from the 1960s, when the Harrington rod was introduced, through to the 1980s, when the Cotrel-Dubousset system came into use. Hooks attached to the spine were initially used only at the end of the rod to distract (extend) the spinal curve. Multiple hooks were later placed at many levels along the curve to make use of both compression and distraction. Pedicle screw fixation, which was introduced in the 1990s, has gained popularity as screws are more secure anchors than hooks and enable greater corrective forces to be applied to the spine. The introduction of
pedicle screw fixation resulted in the average correction of scoliosis deformities increasing from approximately 50% in the Harrington rod era to >70–90% \(^{172,173,174}\). Just as importantly, greater correction of the sagittal and axial plane deformities that are typical of AIS has also been realized using this modern method.

Reports on the short-term outcomes of scoliosis correction suggest high degrees of patient satisfaction using a scoliosis-specific outcomes questionnaire (SRS-22), with radiographic 3D correction of the spinal column that approaches normal alignment \(^{177}\). Not much data are available regarding the long-term outcomes of surgery for AIS \(^{178,179}\). Nonetheless, some evidence suggests that more extensive spinal fusions involving the majority of both the thoracic and lumbar spine create greater alterations in the motion of the remaining lumbar segments than less extensive fusions \(^{180}\). Adjacent segment degenerative arthritis as a result of surgery for scoliosis remains a long-term concern. Thus, the goals of scoliosis surgery are to prevent progressive deformity in those at greatest risk of progression and at the same time to minimize the adverse effects of spinal fusion both in the short term and in the long term. An emerging technology, called anterior spinal tethering, enables modulation of spinal growth from a scoliotic to a ‘straight’ conformation and introduces the possibility that a corrective non-fusion surgical option might one day replace spinal fusion surgery.

**Quality of life**

The life expectancy of patients with AIS who do not undergo treatment is similar to that of the general population \(^{181}\). Nevertheless, health issues might develop in patients who have undergone treatment for their scoliosis, which can affect their health-related quality of life (HRQOL) in the short term and the long term. The quality of life of patients with AIS who have not been treated was discussed in the previous section on the natural history and the prognostic factors involved in the disorder.

Several factors are thought to affect the quality of life of patients with AIS, of which spinal dysfunction with pain and stiffness and development of degenerative changes are the main ones \(\text{BOX 2}\). Patient-reported outcome measures have been widely used for the evaluation of general quality of life, back-related problems and mental well-being. These are complemented using a scoliosis-specific questionnaire called the Scoliosis Research Society (SRS) questionnaire \(^{182}\).

Pulmonary function was reported \(^{183}\) to improve in patients with AIS who had received treatment with either brace or surgery, and this improvement persisted in most patients for 25 years after treatment. A publication in 2001 \(\text{REF. 183}\) reported that patients who had been surgically treated showed only a slight impairment of physical function and mental health at a mean 24-year follow-up. This result was supported by results from a subsequent study published in 2006 \(\text{REF. 184}\) that evaluated patient outcomes at 10 years post surgery. A slight reduction in physical function has also been reported for patients who were treated with bracing, using the Short-Form 36 Health Survey (SF-36) questionnaire \(^{184,185}\) and the SRS questionnaire \(^{186}\).

Patients with AIS frequently report back pain, with up to 60–70% of patients admitting such pain. This back pain is seldom severe and does not cause any major disability for most individuals \(^{187,188}\). A study published in 2009 \(\text{REF. 188}\) reported that 95% of patients who had been previously treated with a Boston brace considered their back function to be excellent, good or fair, and their back function was also normal as measured by the Oswestry Disability Index, which produced a mean score of 6.4/100. HRQOL was in the normal range for most of these patients, even if large variations were found. One reason for this variation might be that co-morbidities, such as asthma, migraine and lower extremity disorders, could negatively affect HRQOL \(^{189}\).

Concerns have been raised about potential negative effects of pregnancy on both back pain and curve progression in patients with AIS \(^{190}\). However, studies have shown that during pregnancy spinal curves do not significantly increase \(^{181,191}\). In addition, back pain, which occurs in 35–55% of pregnant women who have AIS, is not usually disabling and is at the same pain level as individuals who do not have the condition. AIS does not affect complication rates for pregnancy or delivery, regardless of whether patients have been treated with bracing or surgery \(^{192}\). Both the spine deformity and the long bracing period might cause psychological stress and body image concerns \(^{194,195}\), but adults seem to have adapted to the situation and do not generally experience psychological stress. Neither curve size nor size of the rib hump have been found to correlate with the severity of the deformity perceived by patients or with their experience of pain and dysfunction \(^{184,185,186}\).

**Outlook**

**Current progress and limitations**

Considerable progress has been made in the past two decades in our understanding of the complexity of AIS. These advances relate to our concepts of AIS epidemiology, natural history and 3D pathoanatomy. In addition, improvements have also been made in our understanding of the effectiveness of properly conducted brace
Outstanding clinical research questions

For clinicians who manage patients with AIS, there are several key areas with outstanding questions of great concern. These areas include the strategies to predict who is going to develop scoliosis and how it can be prevented in these individuals. Key questions relating to this are, can we predict who among those with early scoliosis will progress further and need treatment, and how can we avoid unnecessary over-treatment? The discovery of reliable and validated molecular, genetic and functional biochemical markers would assist in addressing these questions. The issue of whether or not to carry out school-based or other forms of screening on the basis of components of body composition that are identifiable before the onset of scoliosis remains to be tackled. These relate, for instance, to epigenetic mechanisms that underlie AIS, as current evidence on the matter is fragmented. Without considerable advances in this area, we are neither able to directly target treatment towards addressing the cause of AIS nor to embark on its primary prevention.

Outstanding basic research questions

AIS is a disease of adolescence caused by a complex interaction between genetic and environmental factors that act through integrative biological and biomechanical mechanisms. As such, many outstanding research questions remain to be tackled. These relate, for instance, to epigenetic and environmental factors and lifestyle factors that interact in early life to influence AIS. These are speculative areas of endeavour that, so far, have not been well studied and are intended to stimulate further discussion. For instance, the possibility that epigenetics might have a role in the pathogenesis of AIS requires further investigation, as does the question of whether epigenetics could have clinical applications in the next 5–10 years. In addition, an important question is whether the emerging interest in and technology relating to the study of circulating microRNAs could function as the missing link to integrate metabolic abnormalities with genomic data in AIS.

Moreover, a potential new avenue of research could involve the study of early-life factors such as embryogenesis. The origin of scoliosis has been suggested to come from involvement of a cluster of cell types in early embryonic life, including adipocytes and osteoblasts derived from the same progenitor cells and also myoblasts derived from a different branch of progenitor cells (Fig. 12). Could this help to explain the association between late maternal age and trunkal asymmetry, and the potential contribution of this asymmetry to the risk of developing AIS, help to highlight maternal age as a matter of public health relevance?

The mechanism of spinal curve progression also warrants attention. Normal lateral thoracic spinal curvatures have a distribution that is similar in both sexes; the development of these normal spinal curvatures might also be related to axial rotational stability/instability, which depends on the spinal sagittal profile. Different mechanisms might produce similar phenotypes in both normal and progressive curves. Could 3D numerical simulation and modelling of scoliosis provide further insight into our understanding of the mechanism of scoliosis formation, progression and correction?
Multicentre interdisciplinary collaboration

To address the above basic and clinical research questions, more cross-disciplinary and multicentre research collaboration is needed to enable pooling of clinical cases to facilitate cross-ethnic studies with sufficient numbers of patients, covering all curve subtypes, to better define phenotypes and endophenotypes. This approach would also enable better complementary use of expertise and emerging innovative technologies and, along with wiser use of advances in other fields, could lead to improvements in research methodology and in understanding disease trajectory. In particular, further advances in AIS genetics will require collaboration among research groups to assemble the large number of cases required to identify additional genes that contribute to AIS risk.

Goals of future studies should be to synthesize algorithms that take into account both rare and common genetic variants, genomic copy number variants — which have not shown significant associations with AIS but have not been well studied — and clinical factors to predict prognosis and response to bracing.

For AIS, the ultimate hope is to derive evidence-based, affordable and effective predictive tests to be used in making prognoses, in guiding treatment and in preventing the occurrence or progression of spinal deformity by targeting identified aetiopathogenetic pathways with non-invasive biological or medical therapy. In particular, it is hoped that patients can be effectively treated, without carrying out surgical fusion and with preserved spinal mobility. 

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20. This landmark paper postulates that dorsal shear forces, acting exclusively on specific regions of the human spine, might contribute to rotational instability of the spine.
dimorphism in adolescent idiopathic scoliosis: neurological aspects of relative spinal cord tethering in AIS: Study with multiplanar reformat magnetic resonance imaging and somatosensory evoked potentials. (2014).


This is the first study to show a different thinning pattern of the cerebral cortex in girls with AIS compared with unaffected children. Focal cortical thinning was found to be different in areas related to motor and vestibular functions in these patients.


This large prospective study of 326 girls with AIS followed them longitudinally until they reached skeletal maturity. The study shows that osteopenia in the femoral neck is a pertinent factor for curve progression, with an odds ratio of 2.3.


This landmark NIH multicentre clinical trial definitively shows the efficacy of bracing in preventing high-risk patients from reaching the surgically threshold of curve with a Cobb angle of ≥50°. A significant positive association between hours of brace wear and rate of treatment success was observed.


This analytical computerized simulated spine model, modulation of vertebral growth by estimated compressive loading shows that a substantial component of vertebral growth during growth is biomechanically mediated through the vertebral growth plates.

Towards a comprehensive diagnostic assay for scoliosis.


This study describes a natural history study of a cohort of patients with AIS who had follow-up evaluation for an average of 51 years. The study shows there is an increased risk of shortness of breath associated with a thoracic Cobb angle of > 80° and an increased risk of chronic back pain in this group, although patients remained productive and functional at a high level.


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This paper describes a follow-up investigation of patients 22 years after they completed brace treatment. The study found that these patients experienced minimal back pain and dysfunction, which was comparable to what has been found in unaffected individuals.

This paper presents a follow-up investigation 23 years after patients with AIS were treated with surgery. The study found that 25% of patients reported daily pain, but analgesics were sparsely used. No major differences in back function and general HRQoL were noted between patients and unaffected individuals. The length of the fusion carried out in the lower spine did not affect the occurrence of pain.

The findings from this study indicate that maternal age at conception, considered as an environmental factor, might influence the occurrence of trunkal asymmetry and idiopathic scoliosis during growth through epigenetic mechanisms.


This study shows that patients with AIS with adolescent onset do not have increased mortality compared with the general population. The risk of respiratory failure occurs 20 years after AIS onset if the vital capacity is reduced below 45% of that predicted and the curve has a Cobb angle > 110° at skeletal maturity.


The findings from this study indicate that maternal age at conception, considered as an environmental factor, might influence the occurrence of trunkal asymmetry and idiopathic scoliosis during growth through epigenetic mechanisms.


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Author contributions


Competing interests

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