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TITLE PAGE

Association between physical activity and scoliosis: A prospective cohort study

Jon H Tobias MD PhD[1], Jeremy Fairbank MD[2], Ian Harding MD[3], Hilary J Taylor[1], Emma M Clark* MB.BS PhD[1]

[1] Musculoskeletal Research Unit, University of Bristol, UK.
[2] Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Nuffield Orthopaedic Centre, Oxford, UK.
[3] North Bristol NHS Trust, Bristol, UK.

Corresponding author: Dr Emma Clark
Consultant Senior Lecturer
Musculoskeletal Research Unit,
University of Bristol
Avon Orthopaedic Centre
Southmead Hospital
Westbury-on-Trym
Bristol, UK.
BS10 5NB

Tel: 0117 323 2283
Email: emma.clark@bristol.ac.uk

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ABSTRACT

Background: Little is understood about the causes of adolescent-onset idiopathic scoliosis (AIS). No prospective studies assessing the association between physical activity and idiopathic adolescent scoliosis have been carried out. We aimed to carry out the first prospective population-based study of this association.

Methods: The Avon Longitudinal Study of Parents and Children (ALSPAC) collected self-reported measures of physical ability/activity at aged 18 months and 10 years. Objective measures of physical activity were collected by accelerometry at aged 11 years. Scoliosis was identified using the DXA Scoliosis Method at aged 15 years. Participants with scoliosis at aged 10 years were excluded.

Results: Of 4640 participants at aged 15 years who had DXA scans, 267 (5.8%) had scoliosis. At aged 18 months, those infants who were able to stand up without being supported were 66% less likely to have developed scoliosis by aged 15 (P=0.030) compared to infants who could not. Those children whose mothers reported they did most vigorous physical activity at aged 10 years were 53% less likely to develop scoliosis (P=0.027). Those children who did more objectively measured moderate/vigorous physical activity at aged 11 were 30% less likely to have developed scoliosis (P<0.001). Results were not affected by adjustment for age, gender, lean mass, fat mass or back pain.

Conclusions: We report reduced physical ability and activity as early as aged 18 months in those who go on to develop scoliosis by aged 15 years. Further research is justified to examine the mechanisms underlying this association.

Key words
Scoliosis
ALSPAC
Cohort study
Physical activity

Key messages

- We have carried out the first prospective population-based study of the association between physical ability/activity and adolescent idiopathic scoliosis, where measures of physical ability/activity were carried out before onset of clinically identifiable scoliosis.
- Reduced physical ability and activity as early as aged 18 months was associated with increased risk of scoliosis onset between aged 10 and 15 years.
- These findings suggest that lower physical activity is a novel risk factor for scoliosis initiation, involving pathways which require further elucidation

INTRODUCTION

Scoliosis is defined as lateral curvature of the spine ≥10°, as measured using the Cobb method on a standing spinal radiograph(1). The most common form is adolescent onset idiopathic scoliosis (AIS), defined as occurring between aged 10 years and skeletal maturity(2). It is not always a benign structural abnormality, although the mortality rate for individuals with AIS is comparable to that of the general population(3). Severe AIS may result in early degenerative joint disease(4), cardiopulmonary compromise(5), negative body image(6) and psychosocial disturbances(7). Even small spinal curves in adolescents that may not have presented to spinal units are associated with an increased risk of future back pain and time off school(8). Little is known about the aetiopathology of scoliosis because of lack of prospective population-based studies, driven mainly by the problems with performing spinal radiographs on these cohorts. However, understanding the causes of scoliosis is vital, as it may lead to new, more effective means of evaluating risk of progression, which is important for prevention and treatment including planning of surgery.

There is increasing interest in the relationships between physical activity and AIS. Previous studies (9-21) have conflicting results: some suggest no association(9, 14); some that people with scoliosis do more physical activity(11, 12); and others report people with scoliosis do less physical activity(10, 13). The differing associations seen may reflect different approaches to the methods of data collection for physical activity measures and scoliosis, and the influence of failure to assess timing of physical activity measures and/or failure to account for effect modifiers or confounders.

Previous work by our group has shown that lower lean mass and lower fat mass at aged 10 years are independently associated with an increased risk of scoliosis onset by aged 15 years, based on measurement of spinal curvature on whole body DXA scans obtained in a large population-based cohort(22). It is well recognised that physical activity and exercise influence body composition, suggesting this may mediate any association between physical activity and the onset of scoliosis. Additionally, previous work by our group has identified that small spinal curves that have not presented to secondary care are nonetheless associated with back pain(8), suggesting any association between physical activity and scoliosis might be confounded by back pain.

No previous studies have used a prospective design to look at the association between physical activity and the onset of scoliosis and it is therefore unknown whether any observed association between physical activity and scoliosis reflects the fact that physical activity is a risk factor for development and/or progression of spinal curvature, or is itself impacted upon by the scoliosis.

We aimed to carry out the first prospective population-based study of the association between physical activity and the onset of scoliosis based on measurement of spinal curvature on whole body DXA scans. Physical activity was assessed at multiple time-points, using a combination of questionnaires and objective measurement with accelerometers. To identify potential causal pathways and confounders, we aimed to examine possibly modifying effects of lean mass, fat mass and back pain.

MATERIALS AND METHODS

Study population

ALSPAC is a geographically based UK cohort that recruited pregnant women residing in Avon (South-West England) with an expected date of delivery between April 1st 1991 and December 31st 1992(23). A total of 14,541 pregnancies were enrolled with 14,062 children born (see www.alspac.bris.ac.uk for more information). Please note that the study website contains details of all the data that is available through a fully searchable data dictionary http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee. Parental consent and child's assent was obtained for all measurements made. Figure 1 is a flow diagram illustrating conduct of the study.

Figure 1 here

Measurement of physical activity before onset of clinically identifiable scoliosis

Self-report data: Data on physical ability/activity were collected by questionnaire at aged 18 months and 10 years of age, all completed by the mother. At 18 months, mothers were asked questions based on the Denver Developmental Screening Test(24), namely whether their child could perform a range of motor activities including standing up without being supported or walking backwards for five steps. As previously described(25), at aged 10 years, a question was asked about the average number of times the child had participated in vigorous physical activity over the last month. Vigorous physical activity was defined as activities such as running, dance, gymnastics, netball, swimming, aerobics, or similar.

Objective data: At aged 11 years physical activity was measured objectively using an actigraph (model WAM 7164; MTI), for up to seven days. For the purposes of this study actigraph output was categorised as the daily number of minutes of moderate/vigorous activity, light activity or sedentariness. This categorisation has previously been described in detail(26) and is based on count frequencies identified during a calibration study in a subgroup of 260 children.

Measurement of scoliosis

Whole body supine DXA scans were collected at aged 10 and 15 years. The original purpose was to measure bone mass and body composition. We have recently developed a method of measuring scoliosis from DXA images(27), allowing curve identification on entire populations without exposure to high levels of ionising radiation and to address the unacceptable number of false-negative findings with the standard clinical assessment (the Adam's forward bending test)(28). As previously described(27), all total body DXA scans from the aged 15 Research Clinic were triaged into 'straight', 'possible positioning error' and 'likely scoliosis'. After validation tests, possible positioning errors were included with the straight scans. Scans triaged as likely scoliosis had angle size measured using a modified-Ferguson method. 95% of intra-observer repeat measures were within 5^o, similar to the results of the gold standard Cobb method, which is applied to erect radiographs(29). As previously described where we have compared measurements from erect radiographs and supine DXA scans on the same individuals, the presence of scoliosis using our method was defined as a curve size $\geq 6^o$, comparable with 10^o in an erect radiograph. Our method produces an approximate 30% reduction due to supine position, with an additional 10% from use of the modified-Ferguson. This suggests that a cut-off of 6^o (40% reduction of the standard cut-off of 10^o) is appropriate. Participants with scoliosis identified from DXA scans at aged 10 years (n=17) were excluded from the analysis as they do not meet the definition of AIS.

Other measures

Ethnic group was recorded by the mother on self-reported questionnaires and was categorised as white or non-white. Gender was obtained from birth notifications. Mothers highest educational qualifications were also assessed and used as a measure of socioeconomic status. Other measures of socioeconomic status such as paternal education, maternal and paternal social class, family income and housing tenure were not used in this analysis because they gave similar results to maternal education alone, as shown in previous studies on this cohort(25, 30). Puberty was assessed by self-completion questionnaires at 10 years of age using diagrams based on Tanner staging of pubic hair distribution for boys and girls and breast development for girls(31). Total body less head (TBLH) fat and lean mass were measured using a Lunar Prodigy DXA scanner at aged 10 and 15 years. Pain was assessed at aged 18 years by self-completion of a pain manikin.

Statistical analyses

All statistical analyses were performed using Stata 14.2. The outcome measure was a binary variable of presence or absence of scoliosis. Odds of exposure to the early life physical activity variables in those with and without scoliosis were calculated. Logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) to describe the association between physical activity and scoliosis. The OR Test for Trend was calculated by treating the categorical variables as continuous in the regression models i.e. the categories were assumed to be ordered and for purposes of the Test for Trend calculation continuous. To test for gender interactions as an *a-priori* planned analysis, the likelihood ratio test was used. To look for independent determinants of scoliosis, all relevant variables were included in a multivariable regression model based on previous published analyses (see first paragraph of results). Further analyses were performed using the aged 10 self-reported physical activity data with three categories to look for evidence of a dose response between amount of physical activity and risk of developing scoliosis; and between amount of physical activity and size of the spinal curvature. All analyses were rerun after adjusting for back pain, and after excluding those who were told that their Adams forward bending test was not normal (Angle of Trunk inclination ≥7 degrees, n=20), as these participants may have been aware that they had scoliosis and this could have introduced bias.

RESULTS

General description of the cohort

At aged 15 years data on scoliosis were available on 4640 participants who had DXA scans: 267 (5.8%) with new onset of scoliosis since aged 10, and 4373 without. As previously described, those with scoliosis were more likely to be female(27), and to have lower total body lean mass and fat mass(22) compared to those without scoliosis (results not shown). Also as previously described, there was no association between ethnicity, socio-economic status or pubertal stage and presence of scoliosis(22) (results not shown).

Association between self-reported physical ability at aged 18 months and scoliosis initiation by aged 15 years

Full data on self-reported physical ability at 18 months were available on 4151 participants. Those infants who were able to stand up without being supported were 66% less likely to have developed scoliosis by aged 15, even after adjustment for age, gender, lean mass and fat mass, compared to infants who were unable to stand up without being supported (see Table 1). Similarly, those infants who were able to take at least five steps unaided were 57% less likely to have developed scoliosis by aged 15, even after adjustment. The same direction of association was seen between other variables measured at 18 months and the presence of scoliosis at 15, with the exception of the ability to walk backwards five steps. Results were not changed when analyses were adjusted for lean mass and fat mass separately (results not shown).

Association between self-reported physical activity at aged 10 years and scoliosis initiation by aged 15 years

Full data on self-reported physical activity at aged 10 years were available on 2854 participants. Those children who did more episodes of vigorous physical activity per week were less likely to have developed scoliosis by aged 15, compared to those who did less, even after adjustment for age, gender, lean mass and fat mass (see Table 1). For example, after full adjustment, those children who did 4 or more episodes of vigorous physical activity per week were 53% less likely to have developed scoliosis by aged 15 years. Results were not changed when analyses were adjusted for lean mass and fat mass separately (results not shown). There was evidence of a dose response (Test for Trend P=0.004 after adjustment for age, gender, lean and fat mass): 4.1% of those doing four or more episodes of vigorous activity per week had scoliosis at aged 15; 6.5% of those doing one to three episodes; and 7.9% of those doing less than one episode of vigorous physical activity per week had scoliosis at aged 15. Furthermore, the mean spinal curve size in those who reported doing four or more episodes of vigorous activity per week was 10.3^{o} compared to 11.4^{o} in those doing one to three episodes; and 12.6^{o} in those doing less than one episode of vigorous physical activity per week (P=0.07 after adjustment for age).

Table 1 here

Association between objective physical activity variables at aged 11 years and scoliosis initiation by aged 15 years

Full data on objectively measured physical activity at aged 11 by accelerometry were available on 3861 participants. Those children who were more sedentary were 18% more likely to have developed scoliosis by aged 15 (see Table 2). However, after adjustment for age and light and moderate/vigorous physical activity no association was seen. No association was seen between light activity and scoliosis. However, those children who did more moderate/vigorous physical activity were 30% less likely to have developed scoliosis by aged 15. Adjustment for age, light activity and sedentariness slightly reduced the strength of association. Further adjustment for fat and lean mass did not change the association, with a 23% reduced risk of developing scoliosis by aged 15 per SD increase in adjusted moderate/vigorous activity. Results were not changed when analyses were adjusted for lean mass and fat mass separately. There was evidence of a dose response relationship with higher quartile of moderate/vigorous physical activity associated with lower risk of scoliosis (see Figure 2).

Table 2 here

Results were unchanged after adjusting for self-reported back pain at aged 18 years. Results were also unchanged after excluding those participants who may have been aware that they had scoliosis (results not shown). No evidence of a gender interaction for any associations analysed was seen.

Figure 2 here

DISCUSSION

We present the results of the first prospective study of the association between physical activity in childhood and subsequent onset of scoliosis in adolescence, based on analysis of spinal curvature on whole body DXA scans. Importantly, we identify an inverse association between physical ability at aged 18 months and risk of onset of scoliosis between aged 10 and 15 years. Similar associations were seen for both lower self-reported physical activity at aged 10 years, and lower objectively measured physical activity at aged 11 years. Taken together, these findings suggest that reduced physical function in early life is a novel risk factor for scoliosis initiation, perhaps because the scoliosis deformity occurs as a result of reduced loading. Alternatively, the lower physical activity identified is an early manifestation of the same underlying abnormality that eventually results in AIS.

Our results agree with previous case-control studies(10, 13), but we extend their findings by presenting the first prospective data that shows a reduction in physical ability present well before identification of spinal curvature. An explanation for the association we found is that some adolescents with scoliosis may have a mild generalised neurological co-ordination and/or development dysfunction that manifests itself as early as aged 18 months. However, as only a small proportion of those with scoliosis in our study had reduced physical ability at aged 18 months, this is clearly not the only risk factor for spinal curvature. Nonetheless, this suggestion is supported by many of the rare genetic disorders characterised by severe and often early onset scoliosis also involving neuro-developmental delay and other neurological abnormalities such as Angelman Syndrome(32). Furthermore, we have previously identified low circulating leptin in adolescents with scoliosis(22), and leptin is linked to central nervous system development in mice(33). It has been postulated that low leptin may initiate asynchronous neuro-osseous growth(34), a concept suggested for pathogenesis of AIS, and our results may provide further supporting evidence of the central role of neurological development in scoliosis initiation.

An alternative explanation for the association between low physical activity and increased risk of scoliosis is reduced muscle function. We have previously shown low lean mass is a risk factor for scoliosis initiation(22), and multiple case-control studies of adolescents and young adults have identified reduced limb muscle function in those with scoliosis(18, 20, 21), as well as reduced respiratory muscle function(15-20). Suggestions for the cause of this generalised muscle dysfunction have included reduced exercise tolerance due to deconditioning and lack of fitness because of a choice to do less physical activity. Conversely, our results may suggest that the generalised muscle dysfunction is part of the early manifestation of the underlying cause that results in scoliosis, or may be the primary underlying abnormality. However, the association between reduced physical activity and increased risk of scoliosis we identified were unaffected by adjustment for lean mass, perhaps suggesting that it is the underlying neurological abnormality that is important.

The reduced physical activity seen in people with scoliosis in previous case-control studies(10, 13) may be related to back pain, as suggested by some improvements in function with reduction in back pain(35). However, the associations we found between reduced physical ability or physical activity and scoliosis were unaffected by adjustment for back pain. This may reflect the fact that these associations are not related to back pain, or, it may be that our single measure of self-reported back pain at aged 18 years was insufficient to fully explore the role of back pain.

Our results do not agree with the results of a previous studies that either showed no association between physical activity and scoliosis (9, 14) or higher levels of gymnastics in those with scoliosis(11, 12). For the studies that showed no association, the most likely explanations include the method of collecting self-reported physical activity information, and subject selection. Findings from the two studies that reported more girls with scoliosis did gymnastics than girls without scoliosis may be explained by selection bias arising from their case-control study design.

There are limitations to our study, particularly loss to follow-up of the original cohort. There has been a preferential dropout of children from families of lower socioeconomic status (results not shown) and this may have biased the results and affected generalisability. Our DXA-based method of identification of people with scoliosis is somewhat imprecise(27), but this will have biased our results toward the null rather than producing spurious results. Additionally, this method may be difficult to accept by scoliosis clinicians who have used erect Cobb angle measures to assess scoliosis. The number of participants with scoliosis in our study is also a limitation because it is fairly low. There is the possibility that those with scoliosis may be less likely to undergo a DXA through embarrassment, although it is likely most children did not know they had a mild scoliosis. However, the disadvantage of low numbers is outweighed by the major advantages of a population-based cohort study design that provides stronger, less biased evidence than case-control studies. Other strengths include the use of accelerometers to provide objective measurements of physical activity, as well as exclusion of those with scoliosis at aged 10 years so that our analyses can focus on scoliosis initiation and potential causal pathways. Finally, in common with all observational studies, our results may be explained by confounding or chance.

In conclusion, we report reduced physical ability and activity, both by self-report and through objective measurement, as early as aged 18 months in those who go on to develop scoliosis by aged 15 years. Further research is justified to examine the mechanisms underlying this association.

Table 1: The association between self-reported physical ability/activity variables in earlier life and onset of scoliosis by aged 15 years.

Physical ability/activity variables	No scoliosis at aged 15	Scoliosis at aged 15	P value for difference	OR for onset of scoliosis Unadjusted	OR for onset of scoliosis Adjusted for age and gender	OR for onset of scoliosis Adjusted for age, gender, lean and fat mass
Reported by mothers at aged 18 months n=4151	**N (%) n=3919**	**N (%) n=232**	**P value**	**OR (95%CI), P value**	**OR (95%CI), P value**	**OR (95%CI), P value**
Stands up without being supported			**P=0.041**			
No or only just started	**33 (86.8)**	**5 (13.2)**		**1.0**	**1.0**	**1.0**
Yes	**3886 (94.5)**	**227 (5.5)**		**0.39 (0.15-0.99), P=0.049**	**0.37 (0.14-0.96), P=0.042**	**0.34 (0.13-0.90), P=0.030**
From standing can bend down and then stand			P=0.257			
No or only just started	63 (91.3)	6 (8.7)		1.0	1.0	1.0
Yes	3856 (94.5)	226 (5.5)		0.62 (0.26-1.44), P=0.262	0.59 (0.25-1.38), P=0.221	0.60 (0.25-1.42), P=0.245
Stands alone for 1 min without holding on			P=0.074			
No or only just started	59 (89.4)	7 (10.6)		1.0	1.0	1.0
Yes	3860 (94.5)	225 (5.5)		0.49 (0.22-1.09), P=0.080	0.49 (0.22-1.10), P=0.082	0.49 (0.22-1.10), P=0.083
Walks while holding someone's hand			P=0.185			
No or only just started	23 (88.5)	3 (11.5)		1.0	1.0	1.0
Yes	3896 (94.5)	229 (5.6)		0.45 (0.13-1.51), P=0.197	0.41 (0.12-1.42), P=0.161	0.39 (0.11-1.33), P=0.132
Can take 5+ steps unaided			**P=0.023**			
No or only just started	**59 (88.1)**	**8 (11.9)**		**1.0**	**1.0**	**1.0**
Yes	**3860 (94.5)**	**224 (5.5)**		**0.43 (0.20-0.91), P=0.027**	**0.43 (0.20-0.93), P=0.031**	**0.43 (0.20-0.92), P=0.030**
Can walk backwards 5 steps			P=0.635			
No or only just started	794 (94.1)	50 (5.9)		1.0	1.0	1.0
Yes	3125 (94.5)	182 (5.5)		0.93 (0.67-1.28), P=0.635	0.96 (0.70-1.33), P=0.808	0.99 (0.71-1.36), P=0.925
Reported by mothers at aged 10 years n=2854	**N (%) n=2697**	**N (%) n=157**	**P value**	**OR (95%CI), P value**	**OR (95%CI), P value**	**OR (95%CI), P value**
Episodes of vigorous activity per week			**P=0.012**			
Less than once	**139 (92.1)**	**12 (7.9)**		**1.0**	**1.0**	**1.0**
1-3 times	**1347 (93.5)**	**93 (6.5)**		**0.80 (0.43-1.50), P=0.484**	**0.74 (0.40-1.40), P=0.355**	**0.74 (0.39-1.40), P=0.351**
4+ times	**1211 (95.9)**	**52 (4.1)**		**0.50 (0.26-0.95), P=0.036**	**0.51 (0.26-0.98), P=0.043**	**0.47 (0.24-0.92), P=0.027**
				Test for Trend 0.67 (0.51-0.87), P=0.003	**Test for Trend 0.70 (0.53-0.92), P=0.011**	**Test for Trend 0.67 (0.51-0.88), P=0.004**

Table 2 Association between objectively measured physical activity at aged 11 and onset of scoliosis by aged 15 years. ORs are per SD increase in physical activity variable.

Physical activity variables	No scoliosis at aged 15 N=3637	Scoliosis at aged 15 N=224	P value for difference	OR for onset of scoliosis Unadjusted	OR for onset of scoliosis Adjusted for other activity, age and gender	OR for onset of scoliosis Adjusted for other activity, age, gender, fat and lean mass
N=3861	**Mean (SD)**	**Mean (SD)**				
Daily number of minutes of sedentariness	**429 (66)**	**440 (67)**	**P=0.016**	**1.18 (1.03-1.36), P=0.016**	1.10 (0.90-1.34), P=0.345	1.13 (0.92-1.37), P=0.924
Daily number of minutes of light activity	327 (58)	320 (56)	P=0.086	0.89 (0.77-1.02), P=0.087	1.04 (0.86-1.26), P=0.717	1.06 (0.87-1.28), P=0.575
Daily number of minutes of moderate/vigorous activity	**23 (15)**	**19 (12)**	**P<0.001**	**0.69 (0.59-0.82), P<0.001**	**0.82 (0.68-0.98), P=0.028**	**0.77 (0.64-0.92), P=0.005**

FIGURE LEGENDS

Figure 1: Flow diagram to show conduct of the study.

Figure 2: Odds ratio for presence of scoliosis at aged 15 years according to quartile of objective moderate/vigorous physical activity measured by accelerometer at aged 11 years. P value is the Test for Trend. The heavy black line indicates the null value for presence of scoliosis: above this line indicates increased odds of scoliosis and below indicates reduced odds of scoliosis. Participants with scoliosis at aged 10 have been excluded.

REFERENCES

1. Kane WJ. Scoliosis prevalence: a call for statement of terms. Clinical Orthopaedics. 1977;126:43-6.
2. Weinstein SL, Dolan LA, Cheng JCY, Danielsson A, Morcuende JA. Adolescent Idiopathic Scoliosis. Lancet. 2008;371:1527-37.
3. Weinstein SL, Ponseti IV. Curve progression in idiopathic scoliosis. Journal of Bone and Joint Surgery Am. 1983;65:447-55.
4. Miller NH. Cause and natural history of AIS. Orthopedic Clinic of North America. 1999;30(3):343-52.
5. Aaro S, Ohlund C. Scoliosis and pulmonary function. Spine. 1984;9:220.
6. Weinstein SL, Ponseti IV. Idiopathic scoliosis: Long term follow-up and prognosis in untreated patients. Journal of Bone and Joint Surgery - American Volume. 1981;63:702-11.
7. Fowles JV, Drummond DS, L'Ecuyer DS. Untreated scoliosis in the adult. Clinical Orthopaedics. 1978;134:212-7.
8. Clark EM, Tobias JH, Fairbank J. The impact of small spinal curves in adolescents that have not presented to secondary care: a population-based cohort study. Spine. 2016;41(10):E611-E7.
9. Kenanidis E, Potoupnis ME, Papavasiliou KA, Sayegh FE, Kapetanos GA. AIS and exercising: Is there truly a liaison. Spine. 2008;33(20):2160-5.
10. Parsch D, Gartner V, Brocai DR, Castens C, Schmitt H. Sports activity of patients with idiopathic scoliosis at long-term follow-up. Clinical Journal of Sports Medicine. 2002;12(2):95-8.
11. Meyer C, Cammarata E, Haumont T, Deviterne D, Gauchard GC, Leheup B, et al. Why do idiopathic scoliosis patients participate more in gymnastics? Scandinavian Journal of Medicine & Science in Sports. 2006;16:231-6.
12. Meyer C, Haumont T, Gauchard GC, Leheup B, Lascombes P, Perrin PP. The practice of physical and sporting activity in teenagers with idiopathic scoliosis is related to the curve type. Scandinavian Journal of Medicine & Science in Sports. 2008;18:751-5.
13. Lee WTK, Cheung CSK, Tse YK, Guo X, Ho SC, Lau J, et al. Generalised low bone mass of girls with AIS is related to inadequate calcium intake and weight-bearing phsyical activity in peripubertal period. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2005;16:1024-35.
14. Diarbakerli E, Grauers A, Moller H, Abbott A, Gerdhem P. Adolescents with and without idiopathic scoliosis have similar self-reported level of physical activity: a cross-sectional study. Scoliosis and Spinal Disorders. 2016;11:DOI 10.1186/s13013-016-0082-y.
15. Barrios C, Cortes S, Perez-Encinas C, Escriva DM, Benet I, Burgos J, et al. Anthropometry and body composition profile of girls with non-surgically treated AIS. Spine. 2011;36(18):1470-7.
16. Sperandio EF, Alexandre AS, Yi LC, Poletto PR, Gotfryd AO, Vidotto MC, et al. Functional aerobic exercise capacity limitation in AIS. Spine. 2014;14(10):2366-72.
17. Mohammadi P, Akbari M, Sarrafzadeh J, Moradi Z. Comparison of respiratory muscles activity and exercise capacity in patients with idiopathic scoliosis and health individuals. Physiotherapy Theory & Practice. 2014;30(8):552-6.
18. Czaprowski D, Kotwicki T, Biernat R, Urniaz J, Ronikier A. Physical capacity of girld with mild and moderate idiopathic scoliosis: influence of the size, length and number of curvatures. European Spine Journal. 2012;21(6):1099-105.
19. Kesten S, Garfinkel SK, Wright T, Rebuck AS. Impaired exercise capacity in adults with moderate scoliosis. Chest. 1991;99(3):663-6.
20. Martinez-Llorens J, Ramirez M, Colomina MJ, Bago J, Molina A, Caceres E, et al. Muscle dysfunction and exercise limitation in AIS. European Respiratory Journal. 2010;36(2):393-400.
21. Mahaudens P, Detrembleur C, Mousny M, NBanse X. Gait in AIS: energy cost analysis. European Spine Journal. 2009;18(8):1160-8.

22. Clark EM, Taylor HJ, Harding I, Hutchinson J, Nelson I, Deanfield JE, et al. Association between components of body composition and scoliosis: A prospective cohort study reporting differences identifiable before the onset of scoliosis. Journal of Bone and Mineral Research. 2014;29(8):1729-36.
23. Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, Henderson J, et al. Cohort profile: The 'Children of the 90s' - the index offspring of the Avon Longitudinal Study of Parents and Children. International Journal of Epidemiology. 2013;42(1):111-27.
24. Frankenburg WK, Dodds JB. The Denver Developmental Screening Test. The Journal of Pediatrics. 1967;71(2):181-91.
25. Clark EM, Ness AR, Tobias JH. Vigorous physical activity increases fracture risk in children irrespective of bone mass: A prospective study of the independent risk factors for fractures in healthy children. Journal of Bone and Mineral Research. 2008;23:1012-22.
26. Tobias JH, Steer CD, Mattocks CG, Riddoch C, Ness AR. Habitual levels of physical activity influence bone mass in 11-year-old children from the UK: Findings from a large population-based cohort. Journal of Bone and Mineral Research. 2007;22(1):101-9.
27. Taylor HJ, Harding I, Hutchinson J, Nelson I, Blom A, Tobias JH, et al. Identifying scoliosis in population-based cohorts: Development and validation of a novel method based on total body DXA scans. Calcified Tissue International. 2013;92(6):539-47.
28. Karachalios T, Sofianos J, Roidis N, Sapkas G, Korres D, Nikolopoulos K. Ten-year follow-up evaluation of a school screening programme for socliosis. Spine. 1999;24:2318-24.
29. Cobb J. Outline for the study of scoliosis. Am Acad Orthop Surg Instr Course Lect. 1948;5:261-75.
30. Clark EM, Ness AR, Tobias JH, the AST. Social position affects bone mass in childhood through opposing actions on height and weight. Journal of Bone and Mineral Research. 2005;20(12):2082-9.
31. Tanner JM. Physical growth and development. In: Forfar JO, Arnell CC, editors. Textbook of Pediatrics1978. p. 249-303.
32. Dagli AI, Mueller J, Williams CA. Angelman Syndrome. In: Pagon RA, Adam MP, Ardinger HH, editors. GeneReviews [Internet]. Seattle (WA): University of Eashington, Seattle: https://www.ncbi.nim.nih.gov/books/NBK1144/#; 1998 (Updated 2015).
33. Steppan CM, Swick AG. A role for leptin in brain development. Biochemical and Biophysical Research Communications. 1999;256(3):600-2.
34. Burwell RG, Clark EM, Dangerfield PH, Moulton A. Adolescent idiopathic scoliosis: a multifactorial cascade concept for pathogenesis and embryonic origin. Scoliosis and Spinal Disorders. 2016;11(8).
35. Zapata KA, Wang-Price SS, Sucato DJ, Thompson M, Trudelle-Jackson E, Lovelace-Chandler V. Spinal stabilization exercise effectiveness for low back pain in AIS: A randomized trial. Pediatr Phys Ther. 2015;27(4):396-402.