

23 The purpose of the study is to investigate the characteristics of prevalence and curve severity in
24 the patients with AIS and the body composition alterations between the patients with AIS and the
25 healthy controls.

26

27 **Methods**

28 The information of the study sample was obtained from a screening database. The AIS cohort was
29 paired with an age-and-gender matched healthy cohort. The stratification of BMI and curve
30 severity were conducted according to the criteria developed by the U.S. Center for Disease Control
31 and the Scoliosis Research Society. The prevalence and curve severity of the patients with AIS
32 were investigated. Multi-group comparison of body composition parameters were conducted
33 according to BMI between the patients with AIS and healthy controls.

34

35 **Results**

36 1,202 patients with AIS and an age-and-gender matched cohort were recruited from local schools.
37 The underweighted cases had the highest prevalence of AIS and significant higher Cobb angle as
38 compared to other three BMI subgroups; despite the patients with AIS had lower body weight,
39 body fat mass, percentage of body fat and fat free mass as compared with healthy controls,
40 converse results were observed in the underweighted cases after stratification according to BMI.

41

42 **Conclusion**

43 Based on the sporadic body composition of the patients with AIS observed in the current study, it
44 is predictable that the pathophysiological alternations may be different before and after the onset
45 of scoliosis. Well-designed human or animal studies for underweighted cases would be helpful to

46 release the mechanisms of the pathophysiological alternations and better predict the development
47 of AIS.

48

49 **Keywords**

50 Adolescent idiopathic scoliosis; Body composition; Body mass index; Body weight; Underweight.

51

52 **Introduction**

53 Adolescent idiopathic scoliosis (AIS) is a complex three-dimensional spinal deformity with
54 effecting patients throughout their peripubertal growth period. The etiology of AIS appears to be
55 genetic [1], however the mechanisms by which the curves develop are still unknown. The Meta-
56 analysis by Zhang et al. reported a pooled prevalence of scoliosis was 1.02% in mainland China
57 [2]. To devise effective preventive and therapeutic management, it is important to elucidate the
58 etiopathogenesis of AIS.

59 There has been a long-term debate as to whether there is a real connection between the
60 debut of AIS and the body composition alternations. Numerous growth studies attempted to answer
61 this question with different samples [1, 3-19]. Among them, several investigators confirmed the
62 lower body weight, taller stature, larger arm span, lower body mass index (BMI), delayed
63 menarche and lower bone mass in the patients with AIS than the healthy controls. Sadat-Ali et al.
64 compared girls with AIS and their healthy siblings and found that scoliosis caused osteopenia and
65 osteoporosis among the affected girls whereas their siblings had higher BMI and bone mineral
66 density [17]. Nonetheless, some researchers failed to find any significant association. A study
67 screened 3631 children found that height and weight in non-scoliotic children were not statistically
68 different from their scoliotic counterparts [16]. In addition, Dangerfield et al. even reported an
69 inverse result that girls with scoliosis were shorter than the healthy controls [18]. The general
70 consensus as to these previously observed characteristic anthropometric alterations in the patients
71 with AIS has not been reached.

72 Despite body composition alterations in the patients with AIS are increasingly clarified, to
73 the best of our knowledge, only a few studies have investigated the difference in the body
74 composition between the patients with AIS and their non-scoliotic counterparts [20, 21].

75 Conflicting findings were reported with small sample size in these studies. Therefore, the purpose
76 of the current study aimed at investigating the differences of body composition alterations between
77 the patients with AIS and an age-and-gender matched healthy controls based on a relatively large
78 screening database, as well as the prevalence and curve severity of the patients with AIS according
79 to the BMI subgroups.

80

81 **Methods**

82 *Design*

83 The present observational, cross-sectional case control study received approval from the Chinese
84 Ethics Committee for Registering Clinical Trials.

85

86 *Study population*

87 Every primary and secondary school student undergoing nine-year compulsory education in
88 mainland China is required to receive a comprehensive medical evaluation annually granted by the
89 National Health and Family Planning Commission of the People's Republic of China. For the
90 purpose of early detection and management of AIS, a school screening of AIS was undergoing
91 parallelly with the annual medical evaluation among students aged 10-16 years in Wuxi City,
92 Jiangsu Province. All schools were enrolled with no special consideration for geographic,
93 economic or ethical representation. Ethical approval was obtained and informed written consents
94 were also obtained from all the subjects or from their legal guardians before screening.

95 Physical examinations, Adam's forward bending test (FBT) combined with determination
96 of angle of trunk inclination (ATI) by Scoliometer were performed during school-based screening
97 phase. Those who had ATIs of 5° or above were referred for X-ray examination. Participants
98 diagnosed as the patients with AIS (Cobb angle \geq 10° confirmed with the whole spine X-ray film)
99 in our hospital were enrolled in this study. An age-and-gender matched healthy control (ATI $<$ 5°
100 confirmed with the Scoliometer) was also paired from the screening database. Subjects in both
101 cohorts with history of congenital deformities, neuromuscular diseases, skeletal dysplasia,
102 endocrine diseases or cardiorespiratory dysfunctions were excluded from the study.

103

104 ***Measurements of anthropometric parameters***

105 Anthropometric parameters including body height, body weight, BMI, percentage of body fat
106 (PBF), body fat mass (BFM) and fat free mass (FFM) were measured and calculated. Body height
107 was recorded to the nearest 0.1 cm without shoes standing against a wall-mounted ruler. Body
108 weight was measured to the nearest 0.1 kg in light clothes without shoes. BMI was calculated as
109 body weight in kilograms divided by body height in meters squared. The PBF, the percentage of
110 BFM by body weight, was measured with a hand-to-hand bioelectrical impedance meter (Omron
111 Body Fat Analyzer HBF-306; Omron, Japan) [22]. The BFM is the total quantity of lipids that
112 extracted from fat and other cells and the FFM is the weight of the remaining components once
113 BFM has been excluded from body weight.

114

115 ***Measurements of Cobb angle***

116 Based on the standing posterior-anterior whole spine X-ray film, the inclination of the end
117 vertebrae, and indirectly the magnitude of the curve, is assessed by measuring the Cobb angle. The
118 Cobb angle is formed by the inclination of the upper end plate of the upper end vertebra and the
119 inclination of the lower end plate of the lower end vertebra. Final diagnosis of scoliosis, as defined
120 by the Scoliosis Research Society [23], is based on Cobb angles of 10° or more measured by two
121 independent observers (Ning Sun and Tao Wang). The intra-observer correlation coefficient in
122 measuring the Cobb angle was 0.954 (95% CI: 0.932-0.976).

123

124 ***Data stratification***

125 All the subjects enrolled in this study were classified according to the age-and-sex growth charts
126 developed by the U.S. Center for Disease Control: underweight (BMI<5th percentile), normal

127 weight (BMI \geq 5th and <85th percentile), overweight (BMI \geq 85th and <95th percentile and obesity
128 (BMI \geq 95th percentile) [24].

129 Based on the severity of spinal deformity, the patients with AIS were classified into one of
130 three subgroups. “Mild” indicated patient showed a Cobb angle of 10 to 24°; “moderate” indicated
131 patient showed a Cobb angle of 25 to 40° and “severe” indicated patient showed a Cobb angle
132 greater than 40° [23].

133

134 ***Statistical analysis***

135 Numerical data are presented as mean followed by standard deviation, and categorical data are
136 presented as frequency followed by the percentage of the total number in the sample.

137 Anthropometric data including body height, body weight, BMI, PBF, BFM and FFM were
138 compared between the patients with AIS and the healthy controls using independent samples *t-test*.

139 Gender and Risser score were compared using *Chi-square* analysis. One-way ANOVA was

140 adopted for the comparison between BMI subgroups and curve subgroups. The loss of statistical

141 power within multi-group comparison was adjusted with Bonferroni’s method. SPSS 21.0 for

142 Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. P<0.05 was considered

143 statistically significant.

144

145 **Results**

146 A total of 79,122 primary and secondary school students were screened. 1202 patients with AIS
147 were classified according to the BMI subgroups and the curve subgroups and the corresponding
148 prevalence were summarized in Table 1. The highest prevalence was found in underweighted cases
149 and it decreased gradually with the increase of BMI in each curve subgroup. When analyzed
150 according to curve severity, a similar trend was observed in each BMI subgroup.

151

152 **Table 1 Prevalence of AIS by BMI and curve severity**

153

154 Comparison of body composition parameters between curve subgroups were also performed in
155 the patients with AIS. As shown in Table 2, though the absolute value of body weight, body
156 height, BMI, BFM, PBF and FFM were higher in the severe cohort, no significant difference was
157 detected across groups. When the curve severity was compared according to BMI subgroups,
158 significant differences in Cobb angle were only found between the underweighted cases and the
159 normal weights (Figure 1).

160

161 **Table 2 Comparison of body composition parameters according to curve subgroups**

162

163 **Figure 1 Comparison of curve severity of the patients with AIS according to BMI subgroups**

164

165 1,202 patients with AIS and an age-and-gender matched cohort were recruited from local schools.
166 As shown in Table 3, the average Cobb angle in the patients with AIS was $18.68 \pm 8.16^\circ$. There are
167 919 and 269 students diagnosed as mild ($10-24^\circ$) and moderate ($25-40^\circ$) AIS respectively, only

168 fourteen patients were found as severe cases (above 40°). Data of Risser score was also provided
169 in Table 4.

170 The patients with AIS had significant lower body weight ($P<0.001$). Body height were not
171 significantly different between AIS and controls ($P=0.098$). Lower BMI was found in the patients
172 with AIS ($P<0.001$). In addition, the patients with AIS also had lower BFM (10.21 ± 3.76 kg vs.
173 12.12 ± 4.97 kg, $P<0.001$), lower PBF ($20.40\pm5.11\%$ vs. $22.48\pm6.01\%$, $P<0.001$), lower FFM
174 (39.01 ± 7.48 kg vs. 40.50 ± 8.27 , $P<0.001$) than healthy controls.

175

176 **Table 3 Comparison of demographic and clinical data between the patients with AIS and**
177 **healthy controls**

178

179 Table 4 and 5 show the comparison of body composition parameters between the patients with AIS
180 and healthy controls by BMI subgroups. The patients with AIS had higher body weight than the
181 healthy controls ($P=0.001$) in the underweight cohort, but the difference became insignificant in
182 the other three cohorts. Body height were comparable between the patients with AIS and healthy
183 controls in all BMI subgroups. Regarding BMI, underweight patients with AIS had a significant
184 higher value ($P<0.001$) while an inverse result was found in the obesity. Significant higher BFM
185 were found in the patients with AIS from underweight cohort and healthy controls from the other
186 three cohorts. Similar results were found in PBF except the comparison in the obesity cohort.

187

188 **Table 4 Comparison of body composition parameters between the patients with AIS and**
189 **healthy controls (For underweight and normal weight)**

190

191 **Table 5 Comparison of body composition parameters between the patients with AIS and**
192 **healthy controls (For overweight and obesity)**

193

194

195 **Discussion**

196 The current screening database contains relevant information either on the AIS cohort or the
197 healthy cohort so that it provides us a chance to investigate the actual prevalence of AIS according
198 to BMI and to detect the anthropometric characteristics in the patients with AIS. It also enables us
199 to compare the anthropometric alterations between the patients with AIS and their non-scoliotic
200 counterparts.

201 One of the striking findings of this study was that it demonstrated a potential association
202 between AIS and BMI. The prevalence was highest in underweighted cases and decreased across
203 the groups with the increase of the BMI (Table 1). Despite it seems the body component parameters
204 were generally higher in more severe cases (Table 2), no significant result was detected. When
205 compared between BMI subgroups, patients in the underweight group were significantly more
206 severe than patients in other groups (Figure 1). Our findings were comparable with a recent
207 published study [25], in which a similar strategy of data stratification as to BMI and the severity
208 of spinal deformity was applied in 103,249 patients. The potential explanation might be the theory
209 that the lower BMI in the patients with AIS is associated with decreased circulating leptin levels
210 followed by the increased autonomic nervous system activity as compared to the healthy controls.
211 This in turn launches the developmental disharmony between autonomic and somatic nervous
212 systems followed by the spinal deformity as an adverse response [26]. Lower BMI may have
213 interactions with decreased circulating leptin levels, increased autonomic nervous system activity
214 as to the initiation of the scoliosis. After its onset, however, the progression of the spinal deformity
215 may not be mainly attribute to the BMI. As summarized in the 2011 SOSORT guideline, there are
216 four factors that are related to the risk of curve progression: age, gender, skeletal maturity and
217 pattern of scoliotic curve presented [23]. Specifically, the pubertal growth spurt is the period of the

218 most marked progression. Female and those who has a curve greater than 30° is more likely to
219 progress. Therefore, it was not supervising that this study did not find a difference in body
220 composition parameters between curve subgroups.

221 This study also found significantly lower body weight, BMI, BFM, PBM and FFM in the
222 patients with AIS than the healthy controls (Table 3). These findings can be partially explained by
223 its correlation with the leptin bioavailable. As shown in a recent study [27], in which 148 AIS
224 female patients were studied with the body composition and leptin measurement, and they found
225 the altered free leptin bioavailability in AIS girls was associated with lower body weight, lower
226 BMI, lower BFM and lower PBM. Despite strong and positive correlations have been shown
227 between leptin and BFM and PBF in the healthy population [28, 29], correlations between body
228 composition parameters and serum leptin level, soluble leptin receptor level and free leptin index
229 in AIS girls were slightly weaker than the healthy controls [27]. The initiation of the scoliosis
230 might be due to the interactions between the production of leptin and nervous systems, however,
231 our observations also suggested that the functions of leptin could be affected under the pathological
232 conditions of AIS, and the mechanisms of leptin secretion and signaling in patients with AIS need
233 to be further explored. Although muscle strength was not tested in our study, the decreased body
234 composition parameters could also lead to a lower muscle strength in the patients with AIS [30,
235 31]. Several studies have reported that imbalanced strength of paraspinal muscle alone the concave
236 and convex sides of the spine could lead to higher chances of curve progression [32, 33]. These
237 evidence may also partial explain why the underweighted cases had the higher prevalence and
238 more severe curve in the current study.

239 When the body composition parameters were compared between the patients with AIS and
240 healthy controls according to BMI subgroups, an even more intriguing finding was that the

241 underweight patients with AIS had significant higher body weight, BMI, BFM and PBF than the
242 healthy control (Table 4), while the results in other three BMI subgroups (Table 4 and 5) were
243 consistent with the general trend in Table 3. No solid evidence can be found to support the former
244 observation and it might be due to the pathophysiological alternations at the genetic, molecular
245 and cellular levels under the conditions of AIS as well as the sample size discrepancy (290 in
246 patients with AIS vs. 74 in healthy controls). Therefore, the mechanisms behind this observation
247 can be further investigated with well-designed human and animal studies.

248 To the best of our knowledge, it was the largest study to be carried out on AIS in eastern
249 China, so that the sample can be stratified to study the characteristics of each subgroup. Another
250 strength of the current study was that the BMI and curve severity subgroups were classified
251 according to the criteria developed by the U.S. Center for Disease Control and the Scoliosis
252 Research Society respectively. This allows better data fusion and outcome comparison among
253 different studies in the future. The limitation with the current study was that some parameters (i.e.
254 leptin level in the plasma, paraspinal muscle strength and bone density) directly or indirectly
255 related to the body composition were not collected during the screening. This was mainly due to
256 the huge workload during screening, and the time should be limited as a cross-sectional study. In
257 addition, despite the AIS cohort was paired with an age-and-gender matched healthy cohort, the
258 sample size discrepancy still occurred after the sample was stratified according to BMI. Therefore,
259 it is suggested to further strict the pairing criteria so that the potential bias can be eliminated and
260 the discussion can be focused on the observation itself.

261 In summary, the current study indicated that the underweighted cases had the highest
262 prevalence of AIS and relatively more severe curve; despite the patients with AIS had sporadic
263 body composition with lower body weight, BFM, PBF and FFM as compared with age-and-gender

264 matched healthy controls, converse results were observed in the underweighted cases after
265 stratification according to BMI. In light of these results, the pathophysiological alternations may
266 be different before and after the onset of scoliosis. Based on the limitations of the current study,
267 well-designed human or animal studies on underweighted cases would be helpful to release the
268 mechanisms of the pathophysiological alternations and better predict the development of the
269 disease. Integration of the data from different research sites would also help to detail the
270 characteristics of BMI and curve severity in the patients with AIS. Furthermore, caution should be
271 taken when applying the results in the current study to a different ethnic group.

272

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274 None.

275

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287

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