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# Perinatal factors associate with vertebral size and shape but not lumbar lordosis in 10-year-old children.

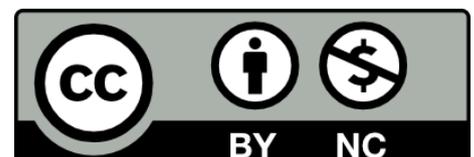
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1 **Perinatal factors associate with vertebral size and shape but not lumbar**  
2 **lordosis in 10-year-old children**

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5 Anastasia V. Pavlova<sup>1,2</sup>, Janet E. Jeffrey<sup>1</sup>, Rebecca J. Barr<sup>1,3</sup>, Richard M. Aspden<sup>1\*</sup>

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7 <sup>1</sup> Centre for Arthritis and Musculoskeletal Health, School of Medicine, Medical Sciences and  
8 Nutrition, University of Aberdeen, Aberdeen, UK.

9 <sup>2</sup> Current address: School of Health Sciences, Robert Gordon University, Aberdeen, UK.

10 <sup>3</sup> Current address: Medicines Monitoring Unit (MEMO), Division of Molecular & Clinical Medicine,  
11 School of Medicine, University of Dundee, Dundee, UK

12

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14

15 **\*Corresponding author**

16 Professor Richard M. Aspden

17 Centre for Arthritis and Musculoskeletal Health,

18 University of Aberdeen,

19 School of Medicine, Medical Sciences and Nutrition,

20 IMS Building

21 Foresterhill

22 Aberdeen, AB25 2ZD

23 UK

24 E-mail: [r.aspden@abdn.ac.uk](mailto:r.aspden@abdn.ac.uk)

25

## 26 **Abstract**

27 The intrauterine environment is known to influence foetal development and future health. Low  
28 birthweight has been linked to smaller vertebral canals in children and decreased adulthood spine  
29 bone mineral content. Perinatal factors affecting lumbar spine curvature have not yet been  
30 considered but could be important for adult spinal health as lumbar movement during lifting, a risk  
31 factor for backpain, is associated with lordosis. To investigate this, lumbar spine magnetic resonance  
32 images at age 10 years and perinatal and maternal data (birthweight, placental weight, gestation  
33 length, crown-heel length, maternal age, height, weight and smoking status) from 161 children born  
34 in Aberdeen in 1988-1989 were acquired. Statistical shape modelling, using principal component  
35 analysis, quantified variations in lumbar spine shape and resulting modes of variation were assessed  
36 in combination with perinatal data using correlations and analyses of covariance, adjusted for  
37 potential confounders. Spine modes 1-3 (SM1-SM3) captured 75% of the variation in lumbar spine  
38 shape. The first and third modes described the total amount (SM1) and evenness of curvature  
39 distribution (SM3). SM2 accounted for variations in antero-posterior vertebral diameter relative to  
40 vertebral height; increasing positive scores representing a larger relative diameter. Adjusting for  
41 gestation length and sex, SM2 positively correlated with birthweight ( $r=0.25$ ,  $P<0.01$ ), placental  
42 weight ( $r=0.20$ ,  $P=0.04$ ), crown-heel length ( $r=0.36$ ,  $P<0.001$ ) and maternal weight ( $r=0.19$ ,  $P=0.04$ )  
43 and negatively with maternal age ( $r=-0.22$ ,  $P=0.02$ ). SM2 scores were lower in girls ( $P<0.001$ ) and in  
44 the low birthweight group ( $P=0.02$ ). There were no significant differences in SM1 and SM3 scores  
45 between birthweight groups, boys and girls or children of smokers (31%) and non-smokers (69%). In  
46 conclusion, some perinatal factors were associated with vertebral body morphology but had little  
47 effect on lumbar curvature.

48

49 Keywords: Lumbar spine, perinatal factors, antenatal, lordosis, statistical shape modelling

## 50 **Introduction**

51 The antenatal period is a crucial time for a developing foetus and, as hypothesized by Barker for  
52 ischaemic heart disease (Barker, 2007), disruptions to the processes occurring during this period can  
53 have long lasting consequences (Bagnall et al., 1977, Strauss, 1997). Although antenatal factors and  
54 intrauterine environment are suggested to have short- and long-term effects on musculoskeletal  
55 health (Javaid and Cooper, 2002, Pasco et al., 2008), little is known about their influence on the  
56 spine. We previously demonstrated, in a study of lumbar magnetic resonance images (MRI) in  
57 children, that low birthweight and maternal smoking were associated with a reduced vertebral canal  
58 size (Jeffrey et al., 2003), which is related to spinal stenosis, leg and back pain later in life (Porter et  
59 al., 1980). In other studies using vertical MRI we have shown that each individual has a characteristic  
60 lumbar spine shape that is present to some degree in all positions of flexion and extension (Meakin  
61 et al., 2009a, Pavlova et al., 2014). This intrinsic shape affected the way the same individuals chose to  
62 lift a weight from the ground (Pavlova et al., 2018a); those with 'curvier' spines preferred to stoop  
63 whereas those with straighter spines found stooping difficult and chose to squat. The relationship  
64 between lumbar lordosis and low back pain is unclear but some studies have found that those with  
65 chronic low back pain were less lordotic (Chaleat-Valayer et al., 2011). A study of 13-year-olds found  
66 that increasing backpack load did not change lumbar lordosis in either those with idiopathic low back  
67 pain or controls but they noted that children with low back pain experienced significantly less lumbar  
68 lordosis with backpack load compared with controls but that it was unclear whether this related to  
69 their back pain (Shymon et al., 2013). These uncertainties indicate the need for a better  
70 understanding of the factors affecting the development of the lumbar lordosis.

71

72 One of the greatest contributors to low birthweight is short gestational length (<37 weeks (Mohsin et  
73 al., 2003)). Low maternal height and weight are suggested to place physical limitations on placental  
74 and foetal growth, either genetically or environmentally (Kramer, 1987, Spencer and Logan, 2002).  
75 Other factors associated with low birthweight include female sex, maternal age (both low (12-19  
76 years) and high (>35 years)), maternal smoking and socioeconomic status, which can itself influence

77 some of the aforementioned maternal factors (Kramer, 1987, Mohsin et al., 2003, Spencer and  
78 Logan, 2002). Furthermore, at age 10 years, a child's height is around 78% of their adult standing  
79 height for boys and 83% for girls (Dimeglio et al., 2010) and sex differences in spine morphology  
80 might be expected. The relationship between perinatal factors and pre-pubertal spinal shape and  
81 curvature is unknown but could be important for load bearing capability and future back health  
82 (Aspden, 1988, Livshits et al., 2011, Meakin and Aspden, 2012, Stone et al., 2015).

83

84 Comparisons of spinal curvature are often done from measures of the lumbar spine angle (usually  
85 between the first lumbar to first sacral vertebrae, L1-S1) or intersegmental angles between vertebrae  
86 (Cil et al., 2005, Masharawi et al., 2012). However, statistical shape modelling (SSM) provides a  
87 simpler yet more effective way to quantify spine shape and enable analysis of relationships with  
88 other factors (Meakin et al., 2009b, Meakin et al., 2008). Statistical shape modelling (SSM) uses  
89 Principal Component Analysis to describe variation in complicated shapes (Cootes et al., 1995). SSMs  
90 have previously been applied to images taken from a number of different sites within the human  
91 body using a variety of different imaging modalities; these include the heart (Cootes et al., 1995),  
92 brain (Cootes and Taylor, 2004), spine (Meakin et al., 2009b, Pavlova et al., 2014), hip (Barr et al.,  
93 2012, Goodyear et al., 2013) and leg (Varzi et al., 2015). In the context of this study SSM is a relatively  
94 new methodology and was not available at the time of the original Jeffrey et al. (2003) study.

95

96 We hypothesised that spinal shape would be associated with birthweight and possibly maternal  
97 smoking or other antenatal factors. The primary objective of this study, therefore, was to  
98 characterise lumbar spine shape using SSM in a cross-section of 10-year-old children, then relate  
99 these shape characteristics to perinatal factors and compare spine shapes between normal and low  
100 birthweight children (as defined by the World Health Organisation (Wardlaw, 2004)). A secondary  
101 objective was to explore potential differences in the shape of the lumbar spine between pre-pubertal  
102 girls and boys.

## 103 **Materials and Methods**

104 The cohort for this cross-sectional study comprised children born in 1988-1989 at the Aberdeen  
105 Maternity Hospital (United Kingdom) and included normal- and low-birthweight children. This was an  
106 existing cohort so recruitment and data collection are described in detail elsewhere (Jeffrey et al.,  
107 2003). In brief, two cohorts of children, born during 1988 or 1989 and aged 10 (standard deviation  
108 (SD) 0.6) years, were invited to take part in an MRI study to investigate antenatal factors affecting  
109 the development of the lumbar vertebral canal (Jeffrey et al., 2003). The first cohort were children  
110 born to mothers taking part in a study investigating dietary advice on pregnancy nutrition and living  
111 within Aberdeen (Anderson et al., 1995). The second cohort was recruited using the Aberdeen  
112 Maternity and Neonatal Databank. Children were identified by birthweight and gestational age; two  
113 thirds of the children classed as “small for gestational age” (standardised birthweight score < -2SD) as  
114 defined in Jeffrey et al. (Jeffrey et al., 2003). In the current study all children were reclassified using  
115 current World Health Organisation (WHO) reference values and placed into low (<2500 g) or normal  
116 ( $\geq$ 2500 g) birthweight groups (Wardlaw, 2004).

117 Magnetic resonance images (MRI) of the lumbar spine and retrospective antenatal data were  
118 available for all 161 children (77 male, 84 female) who took part in the original study. Supine, sagittal  
119 images of the lumbar spine were obtained using a 0.2 T Open Magnetom Viva MRI Scanner (Seimens,  
120 Erlangen, Germany). Historical data included birthweight and placental weight measured at birth;  
121 crown-heel length measured supine at birth from crown to sole (Fok et al., 2003); gestation period;  
122 maternal age, height, weight and smoking status (smoker/non-smoker). The children’s sex, age,  
123 height and weight at the time of imaging were also available.

124

125 The detailed methodology of statistical shape modelling (SSM) has been described in detail  
126 elsewhere (Cootes and Taylor, 2004, Cootes et al., 1995) and its application to the spine, including a  
127 sensitivity analysis, has been described by Meakin et al. (Meakin et al., 2009b, Meakin et al., 2008).  
128 Briefly, marker points were placed on mid-sagittal images according to a 168-point lumbar spine

129 template (Meakin et al., 2009b) constructed using the Active Appearance Modelling software tools  
130 from the University of Manchester  
131 ([http://personalpages.manchester.ac.uk/staff/timothy.f.cootes/software/am\\_tools\\_doc/index.html](http://personalpages.manchester.ac.uk/staff/timothy.f.cootes/software/am_tools_doc/index.html));  
132 a software program that runs within MATLAB (The Math Works Inc, Natick, United states) software  
133 environment. Further analysis was done using custom made software (SHAPE, Aberdeen University,  
134 Aberdeen, UK) and involved Procrustes transformation, to remove the overall effects of size, before  
135 principal components analysis generated a set of orthogonal modes that describe the variations in  
136 shape found within that set of images. Mode scores for the whole image set are scaled to have a  
137 mean of zero and unit standard deviation. Each image then received a score for each mode  
138 quantifying, in standard deviations, how much the shape in that image deviated from the mean. A  
139 lumbar lordosis angle was calculated between lines tangential to the superior vertebral endplates of  
140 L1 to S1 using a custom programme written in MATLAB 2008a (The MathWorks Inc., Natick,  
141 Massachusetts). Intra-rater repeatability was tested on 10 images, marked up by the same observer  
142 (AVP) on two separate occasions.

143

144 Statistical analyses were performed in SPSS 22 (SPSS, Inc., Chicago, IL, USA). Intra-rater repeatability  
145 for point placement was assessed by calculating intra-class correlation coefficients (ICC) from a two-  
146 way random effects (absolute agreement) analysis of variance (ANOVA) model (Bland, 2000). Data  
147 normality was tested using Shapiro-Wilk statistics and statistical significance was taken as  $P < 0.05$ .  
148 Where historical data were missing, correlations and other tests were performed by omitting the  
149 individual from that analysis.

150

151 Descriptive statistics are presented as mean values (standard deviations), with differences in group  
152 means assessed using Student's *t*-test. Associations between mode scores and other measures were  
153 first explored using Pearson correlation (Spearman correlation where data were not normally  
154 distributed). Since birthweight is strongly associated with gestation length and sex (Lesiński, 1962)

155 we performed further, partial, correlations to account for these factors. Analysis of covariance  
156 (ANCOVA) was used to test for differences in mode scores between low and normal birthweight  
157 groups, adjusting for sex, gestation length, and maternal height and weight. Differences in mode  
158 scores between children of smokers and non-smokers were also explored using ANCOVA, with  
159 birthweight as a covariate. Modes scores are presented in units of standard deviations (SD).  
160 Differences in mode scores between boys and girls were assessed using the independent samples *t*-  
161 test in the first instance and ANCOVA was used to check whether adjusting for potential confounders  
162 (infant bodyweight, crown-heel length, maternal weight, child weight and height at 10 years) would  
163 attenuate any results.

## 164 **Results**

165 The cohort characteristics are presented in Table 1. The ICC's for *x* and *y* coordinates of repeated  
166 point placements in SSM were 0.99, demonstrating good intra-rater point placement repeatability.

167  
168 A scree plot of the variance explained by each mode versus the mode number (Cattell, 1966) was  
169 used to select the first three modes for further analysis, as the point at which the slope of the curve  
170 changes markedly. These first three spine modes (SM1-SM3) explained 75% of the overall variance in  
171 shape (Fig 1 and supporting information). SM1 (54% of total variance) described the overall curvature  
172 within the lumbar spine, from straight spines with little lordosis (positive scores) to curvy lordotic  
173 spines (negative scores). SM2 (13% variance) captured differences in vertebral morphology, positive  
174 scores describing vertebrae with greater anterior-posterior diameters relative to vertebral height  
175 (aspect ratio) and negative scores indicating smaller aspect ratios. Finally, SM3 (8% variance)  
176 described the distribution of sagittal curvature along the lumbar spine, whether evenly distributed  
177 throughout (C-shaped curve, positive scores) or uneven (S-shaped curve, negative scores).  
178 Subsequent modes each explained less than 5% of the total variance.

179

180 No correlations were found between SM1 or SM3 with any of the maternal or perinatal variables,  
181 including birthweight. Partial correlations controlling for sex and gestation length revealed positive  
182 associations between SM2 scores and birthweight, placental weight, crown-heel length and maternal  
183 weight and a negative association with maternal age (Table 2). This suggests that children with  
184 smaller vertebral aspect ratios at age 10 were overall smaller at birth and were born to lighter and  
185 older mothers. Adjusting for potential confounders, ANCOVA results revealed significant differences  
186 in SM2 scores between normal and low birthweight groups ( $P=0.02$ ); children with a lower  
187 birthweight having smaller vertebral aspect ratios at age 10.

188

189 Data on maternal smoking were available for 150 (93%) of the participants, of whom 31% were born  
190 to mothers who smoked during pregnancy. Mode scores were not different between children of  
191 smokers and non-smokers (difference(non-smoker – smoker): SM1 -0.13,  $P = 0.48$ , SM2 0.10,  $P =$   
192 0.58, SM3 -0.03,  $P= 0.86$ ).

193

194 No significant differences were found in SM1 or SM3 scores between boys and girls, even though  
195 lumbar lordosis angle was, on average,  $3^\circ (\pm 1^\circ)$  greater in girls than boys ( $P<0.01$ ) (Table1). Boys had  
196 higher SM2 scores (0.119) than girls (-0.109) with the difference between the means being 0.228  
197 [95%CI: 0.190, 0.226] indicating larger vertebral aspect ratios (Fig 2 and Supporting Information). This  
198 difference in SM2 remained significant ( $P<0.001$ ) after accounting for possible confounders. Partial  
199 correlations controlling for sex and gestation period revealed a negative association between SM3  
200 and height at age 10 ( $r=-0.21$ ,  $P=0.02$ ), taller children having a more uneven curvature in their lumbar  
201 spine (Table 2).

## 202 Discussion

203 Perinatal factors, including low birthweight and maternal smoking, have previously been associated  
204 with the presence of a narrow spinal canal in childhood (Jeffrey et al., 2003), thus increasing

205 susceptibility to back pain, sciatica and spinal stenosis in adulthood. Here we used SSM to  
206 characterise lumbar spine shape and found associations between perinatal and maternal factors and  
207 the shape of individual vertebrae, but not overall lumbar curvature, in sagittal MR images of the  
208 lumbar spine from 10-year-old children.

209

210 The primary three modes identified by SSM were similar to those found in SSM studies of healthy  
211 adult spines (Meakin et al., 2009b, Pavlova et al., 2014, Pavlova et al., 2017). SM1 describes the  
212 overall 'curviness' of the lumbar spine and, in this study, SM3 describes the 'evenness' of the  
213 curvature; whether the curvature is located lower in the spine or distributed along the lumbar region  
214 (Meakin et al., 2008). The order of modes is in descending order of variance explained and may vary  
215 between studies, reflecting the variation between different models. Accordingly, in adults we have  
216 found the order of SM2 and SM3 is sometimes reversed but the features identified are very similar  
217 (Meakin et al., 2009b, Pavlova et al., 2017). In this study, associations between SM3 and height at  
218 age 10 years indicated that taller children had a more uneven lumbar curvature. However, overall  
219 lumbar spine shape (SM1 and SM3) at age 10 was not related to perinatal factors and not  
220 significantly different between low and normal birthweight groups. Thus, the intrauterine  
221 environment appears to have little influence on lumbar lordosis, perhaps because curvature has a  
222 greater capacity to change with the advent of walking and rapid spinal growth between 0-5 years of  
223 age and again from 10 years until adulthood (Dimeglio et al., 2010).

224

225 Lumbar lordosis has a heritability of 42-72% (Stone et al., 2015) and although Moore and colleagues  
226 (2011) proposed that curvature is primarily influenced by genetics they suggest that it is exaggerated  
227 by mechanical stimuli. The primary cervical and thoracic curves of the spine develop in the foetal  
228 period but less is known about secondary lumbosacral curves (Been and Kalichman, 2014) which  
229 develop during childhood. The spine starts to form *in utero* in the third week of gestation and at  
230 around 6 weeks the foetus begins to move (Birnholtz et al., 1978, Moore et al., 2011), which is known

231 to play a mechanical role in the formation of tissue, including bone, (Andrew and Bassett, 1971) and  
232 joints (Pitsillides and Ashhurst, 2008). Nowlan has reviewed the effects of mechanical stimulation on  
233 multiple aspects of skeletal development and showed that reduced foetal movement leads to  
234 altered shapes of limb rudiments, abnormal ossification patterns and loss of tissue definition in joint  
235 regions (Nowlan, 2015). Recent studies of the developing chick spine from that group, in which  
236 paralysis was produced for short or prolonged periods during gestation, resulted in fusion of  
237 vertebrae and gross alterations in spinal curvature (Levillain et al., 2019, Rolfe et al., 2017). The  
238 variations we found were much more subtle, as might be expected, but these laboratory studies do  
239 show that the foetal environment can play an essential role in spine formation. Interestingly, Stone  
240 et al. (2015) found no differences in lumbar lordosis between different zygosities of twins. The  
241 relative contributions of environmental (especially mechanical) and genetic factors on lumbar  
242 curvature remain unclear and pose a challenge for future research.

243

244 Vertebral body shape (SM2) appeared to be under some influence from ante- and perinatal factors.  
245 Heavier babies grew to have larger vertebral a-p diameters relative to vertebral height at age 10  
246 years while a lighter birthweight was associated with narrower vertebrae. Shorter babies and those  
247 with lighter and older mothers also tended to have relatively narrower vertebrae in childhood. These  
248 results agree with our previous findings in adults, showing that shorter and lighter individuals had  
249 smaller vertebral aspect ratios (Pavlova et al., 2017) and results from an adult cohort in which high  
250 BMI throughout the life-course was associated with larger aspect ratios (Pavlova et al., 2018b). This  
251 could prove important for future spine health as we recently found smaller aspect ratios to be  
252 associated with lower spine bone mineral density (BMD) at age 60-64 (Pavlova et al., 2017). In this  
253 same cohort, a separate study showed that later age at walking was associated with lower BMD and  
254 smaller bone area in later life (Ireland et al., 2017). Although not strong, these associations suggest  
255 that antenatal factors may have some influence on the processes involved in vertebral growth and  
256 ossification. Vertebrae begin to ossify at around 8 weeks (Moore and Dalley, 1999) and Bagnall and

257 colleagues (1977) argue that mechanical stimuli could affect osteoblast and osteoclast activity in the  
258 spine, determining the course and sequence of ossification. Since intrauterine environmental factors,  
259 including smoking, have been associated with reduced foetal movement (Birnholtz et al., 1978,  
260 Manning et al., 1975) and growth retardation (Strauss, 1997), these may also have consequences for  
261 the dimensions and shape of individual vertebrae (Vialle et al., 2005).

262

263 Studies comparing lumbar curvature in boys and girls have produced conflicting results (Cil et al.,  
264 2005, Lee et al., 2012, Mac-Thiong et al., 2007, Mac-Thiong et al., 2011, Masharawi et al., 2012,  
265 Poussa et al., 2005). Here we found that although girls were, on average, 3° more lordotic than boys  
266 this difference was not reflected in SM1 or SM3 scores, describing overall and distribution of lumbar  
267 curvature. The boys did, however, have a larger vertebral aspect ratio. These results compare with a  
268 study of over 1500 adults in which significant differences were found between men and women in  
269 overall lumbar curvature, which then disappeared on adjusting for the height of the individual. Men  
270 also had larger vertebral aspect ratios than women, although evenness was not related to sex  
271 (Pavlova et al., 2017).

272

273 Whereas smoking was previously associated with a smaller lumbar spine canal (Jeffrey et al., 2003),  
274 in this study we found no relationships between smoking and lumbar spine shape modes. Expanding  
275 on previous work (Jeffrey et al., 2003) we investigated relationships between spine shape modes and  
276 dimensions of the lumbar spine canal (midsagittal diameter, interpedicular diameter, canal shape,  
277 cross-sectional area and perimeter), but only found a few weak correlations (not reported here)  
278 which might be explained by effects of multiple testing. The lack of association with SM2, vertebral  
279 aspect ratio, was somewhat surprising but may indicate that load bearing is a key driver of vertebral  
280 body dimensions whereas other factors control the morphology and size of the posterior elements  
281 and, hence, the canal size.

282

283 The imaging in this study was limited to MRI scans of individuals in a supine posture, which are less  
284 representative of natural weight bearing postures. On average the lumbar spine angle (L1-S1) is  
285 smaller in supine lying than during standing (Lee et al., 2014) and this might be why our sample had a  
286 smaller average lordosis angle ( $38\pm 6^\circ$ ) compared with other cohorts (41 to  $54^\circ$ , (Lee et al., 2012,  
287 Mac-Thiong et al., 2007, Mac-Thiong et al., 2011, Masharawi et al., 2012) ). While a supine posture is  
288 a limitation, imaging children is not easy and imaging them in a standing posture is even harder and  
289 the technology to do this was not available at the time. Here we make use of an existing resource  
290 and, while there are differences in spine shapes between standing and supine postures, we have  
291 shown previously that these shapes are highly correlated and that each individual has an intrinsic  
292 shape that is detectable in all postures (Meakin et al., 2009b, Pavlova et al., 2014). All the  
293 participants were imaged in the same supine posture and comparisons, therefore, should still be  
294 informative. Pelvic incidence, measured from radiographs, is useful in describing sagittal spine  
295 alignment (Roussouly et al., 2005) but this was not possible here due to its absence from the images  
296 available to us. The pitfalls of using low birthweight in association studies have been discussed at  
297 length (Joseph and Kramer, 2004, Wilcox, 2001), especially that a strong association does not imply  
298 causality or that low birthweight is preventable (Wilcox, 2001). We do not wish to add to the long list  
299 of risk variables related to low birthweight or to encourage interference with foetal growth during  
300 pregnancy but to improve our understanding of the relationships between factors during growth and  
301 the structure of the spine.

302

303 To the best of our knowledge, this is the first study of its kind to investigate relationships between  
304 perinatal and maternal factors and lumbar spinal shape in childhood. Contrary to our hypothesis,  
305 perinatal and maternal factors appear to have no relationship with overall lumbar curvature,  
306 although there is some relationship with lumbar vertebral body size at age 10 years. Sex differences  
307 were seen in sagittal vertebral shapes but not the amount or distribution of lumbar curvature.

308 Further investigation is warranted into the roles of mechanical stimuli and environmental factors on  
309 spinal curvature development.

310

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318 publication of this study and the authors have no interests to declare

319

## 320 **Author Contributions**

321 Anastasia V. Pavlova contributed to the concept and design of the study, to the formal analysis of the  
322 data, drafted the manuscript, and contributed to critical revision of the manuscript and approval of  
323 the final article.

324 Janet E. Jeffrey contributed to the concept and design of the study, the acquisition of data, to the  
325 formal analysis of the data and approval of the final article.

326 Rebecca J. Barr contributed to the concept and design of the study, to the formal analysis of the data,  
327 to critical revision of the manuscript and approval of the final article.

328 Richard M. Aspden contributed to the concept and design of the study, the acquisition of funding for  
329 the project, the acquisition of data, to the formal analysis of the data, to drafting of the manuscript,  
330 to critical revision of the manuscript and approval of the final article.

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467

468 Table 1. Characteristics of the study sample, by birthweight and sex. Shown as mean (SD) except for  
 469 the sample size, *n*, where brackets indicate the percentage of the cohort).

|                                    | All          | Low<br>Birthweight | Normal<br>Birthweight | Boys          | Girls          |
|------------------------------------|--------------|--------------------|-----------------------|---------------|----------------|
| <i>n</i> (%)                       | 161          | 39 (24)            | 122 (76)              | 77 (48)       | 84 (52)        |
| Birthweight (g)                    | 3072 (644)   | <b>2227 (276)</b>  | <b>3342 (469)**</b>   | 3048 (704)    | 3094 (585)     |
| Low birthweight ( <i>n</i> )       | 39           | 39                 | -                     | 22            | 17             |
| Normal birthweight ( <i>n</i> )    | 122          | -                  | 122                   | 55            | 67             |
| Gestation period ( <i>weeks</i> )  | 38.8 (2.3)   | <b>37 (3)</b>      | <b>39 (1)**</b>       | 38.5 (2.5)    | 39.1 (2.1)     |
| Placenta weight (g)                | 591 (133)    | <b>456 (92)</b>    | <b>635 (113)**</b>    | 580 (146)     | 602(120)       |
| Crown to heel length ( <i>cm</i> ) | 48.5 (2.7)   | <b>45.5 (2.4)</b>  | <b>49.5 (2.1)**</b>   | 48.7 (3.0)    | 48.4 (2.5)     |
| Child weight at scan ( <i>kg</i> ) | 37.8 (8.9)   | 38.3 (7.8)         | 37.6 (9.3)            | 37.2 (8.4)    | 38.4 (9.4)     |
| Child height at scan ( <i>cm</i> ) | 143.5 (7.4)  | 144.5 (6.9)        | 143.2 (7.6)           | 143.4 (6.9)   | 143.7 (7.9)    |
| Lumbar angle at scan (°)           | 38 (6)       | 38.4 (6.5)         | 38.3 (6.3)            | <b>37 (6)</b> | <b>40 (6)*</b> |
| range (°)                          | 25-54        | 26 - 53            | 25 – 54               | 25-49         | 27-54          |
| Maternal age ( <i>years</i> )      | 28 (5)       | 28 (6)             | 29 (5)                | 29 (5)        | 27.9 (5.4)     |
| Maternal weight ( <i>kg</i> )      | 61.7 (9.4)   | 62.3 (10.5)        | 61.5 (8.9)            | 62.8 (9.9)    | 60.6 (8.7)     |
| Maternal height ( <i>cm</i> )      | 160.9 (5.9)  | 161.8 (7.0)        | 160.6 (5.5)           | 161.1 (6.3)   | 160.6 (5.4)    |
| Maternal smoking                   | (11 missing) | (5 missing)        | (6 missing)           | (6 missing)   | (5 missing)    |
| - smokers ( <i>n</i> (%))          | 46 (31)      | 15 (44)            | 85 (73)               | 21 (30)       | 25 (32)        |
| - non-smokers ( <i>n</i> (%))      | 104 (69)     | 19 (56)            | 31 (27)               | 50 (70)       | 54 (68)        |

470 Bold text denotes significant differences between group means (low/normal birthweight,  
 471 male/female) at  $P < 0.05$  (\*) and  $P \leq 0.001$  (\*\*).  
 472

473 Table 2 Partial correlations and *P*-values between infant and maternal data and sagittal spine shape  
 474 mode scores at age 10 years, adjusting for gestation length and sex of baby, except <sup>a</sup>controlled for  
 475 sex only. Mode 1 (curviness), mode 2 (aspect ratio) and mode 3 (evenness). Significant associations  
 476 shown in bold.

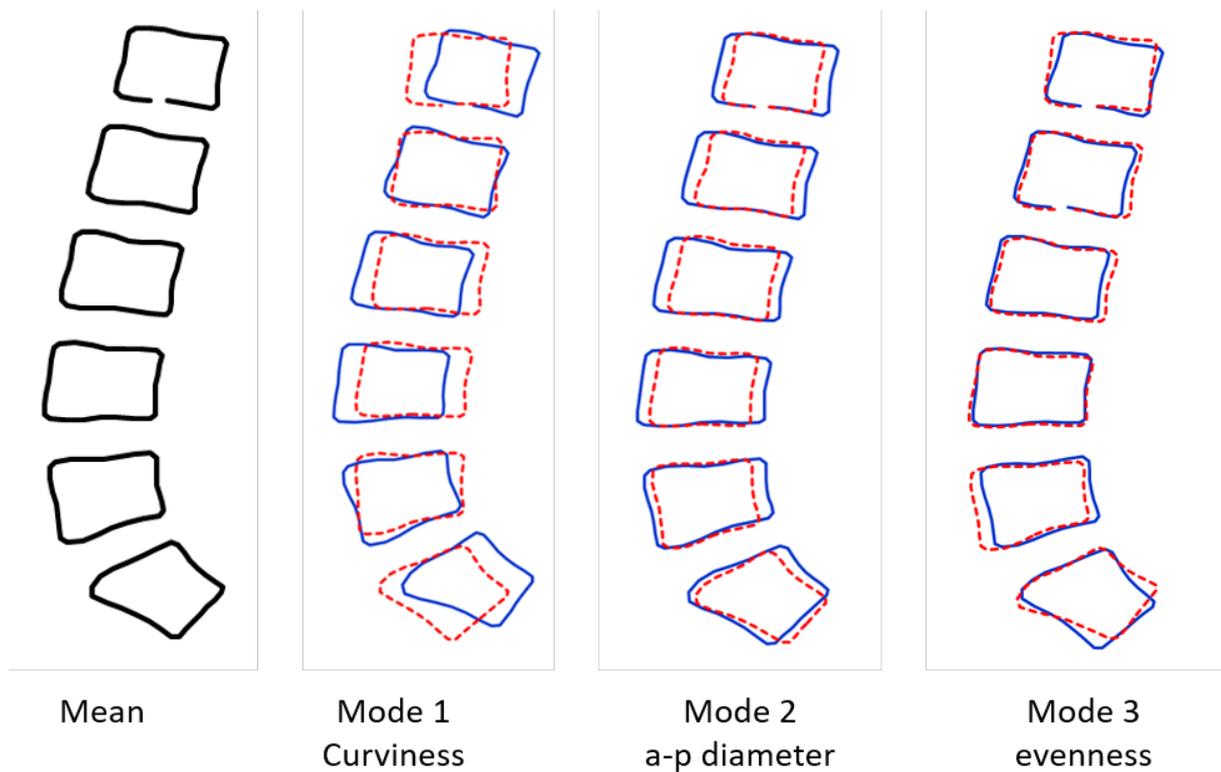
|                          | Mode 1                    | Mode 2                   | Mode 3                   |
|--------------------------|---------------------------|--------------------------|--------------------------|
|                          | <i>r</i> ( <i>P</i> )     | <i>r</i> ( <i>P</i> )    | <i>r</i> ( <i>P</i> )    |
| Birthweight (g)          | 0.06 (0.51)               | <b>0.25 (&lt;0.01)</b>   | 0.02 (0.85)              |
| Placenta weight (g)      | 0.07 (0.47)               | <b>0.20 (0.04)</b>       | -0.01 (0.94)             |
| Gestation length (weeks) | 0.001 (0.99) <sup>a</sup> | 0.11 (0.27) <sup>a</sup> | 0.03 (0.80) <sup>a</sup> |
| Crown-heel length (cm)   | -0.02 (0.86)              | <b>0.36 (&lt;0.001)</b>  | -0.11 (0.26)             |
| Weight at scan (kg)      | -0.01 (0.89)              | 0.09 (0.35)              | -0.18 (0.06)             |
| Height at scan (cm)      | 0.01 (0.95)               | 0.08 (0.40)              | <b>-0.21 (0.02)</b>      |
| Lumbar angle at scan (°) | <b>-0.83 (&lt;0.001)</b>  | -0.09 (0.32)             | 0.01 (0.93)              |
| Mother's weight (kg)     | -0.1 (0.31)               | <b>0.19 (0.04)</b>       | -0.03 (0.75)             |
| Mother's height (kg)     | 0.13 (0.16)               | 0.12 (0.21)              | -0.05 (0.62)             |
| Mother's age (years)     | 0.12 (0.22)               | <b>-0.22 (0.02)</b>      | -0.07 (0.45)             |

477

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480

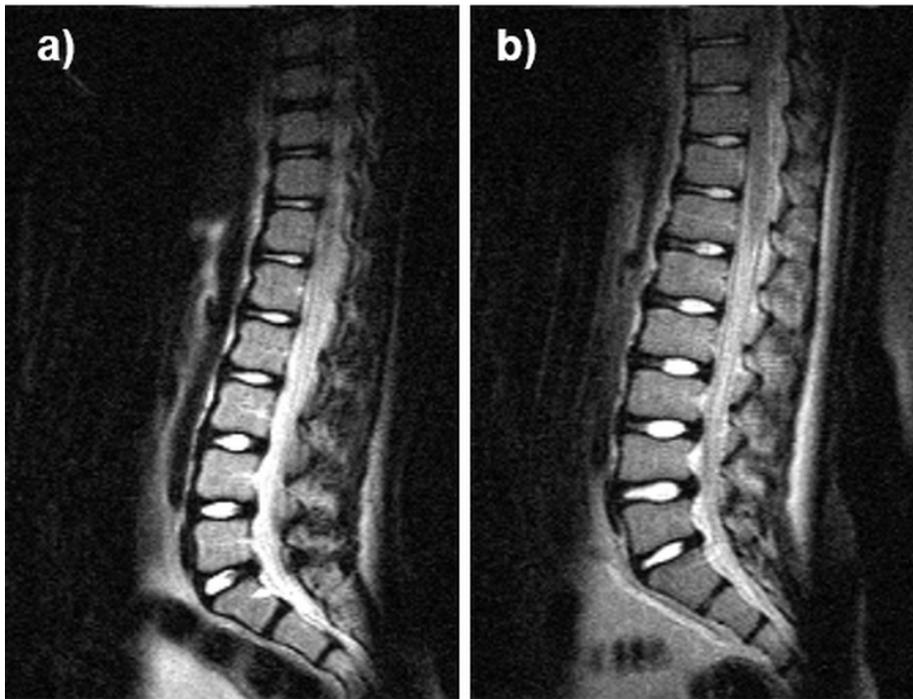


481

482 **Fig 1.** Statistical shape model of the lumbar spine (L1-S1) in 161 children, showing the average spine  
483 shape (Mean) and when each mode separately is varied by plus (solid, blue line) and minus (dashed,  
484 red line) two standard deviations (2 SD). These modes describe variations in overall lumbar curvature  
485 (SM1), anteroposterior vertebral diameter relative to height or 'vertebral aspect ratio' (SM2) and the  
486 distribution of curvature along the lumbar spine (SM3).

487

488



500

501 **Fig 2.** Supine magnetic resonance images demonstrating the shape variation described by mode 2  
502 (vertebral aspect ratio) in two 10-year-old children with the lowest (a) and highest (b) mode 2 scores.  
503 Lower scores had relatively narrower vertebral bodies (image (a)) compared with the relatively wider  
504 vertebrae in image (b).

**Perinatal factors associate with vertebral size and shape but not  
lumbar lordosis in 10-year-old children**

Anastasia V. Pavlova, Janet E. Jeffrey, Rebecca J. Barr, Richard M. Aspden

**Supplementary Information**

## Appendix A

Scatter plots for significant associations between mode scores and perinatal or maternal measurements

1. Mode 2 and birthweight
2. Mode 2 and placental weight
3. Mode 2 and Crown-heel length
4. Mode 2 and Maternal weight
5. Mode 2 and Maternal age
6. Mode 3 and child's height at age 10

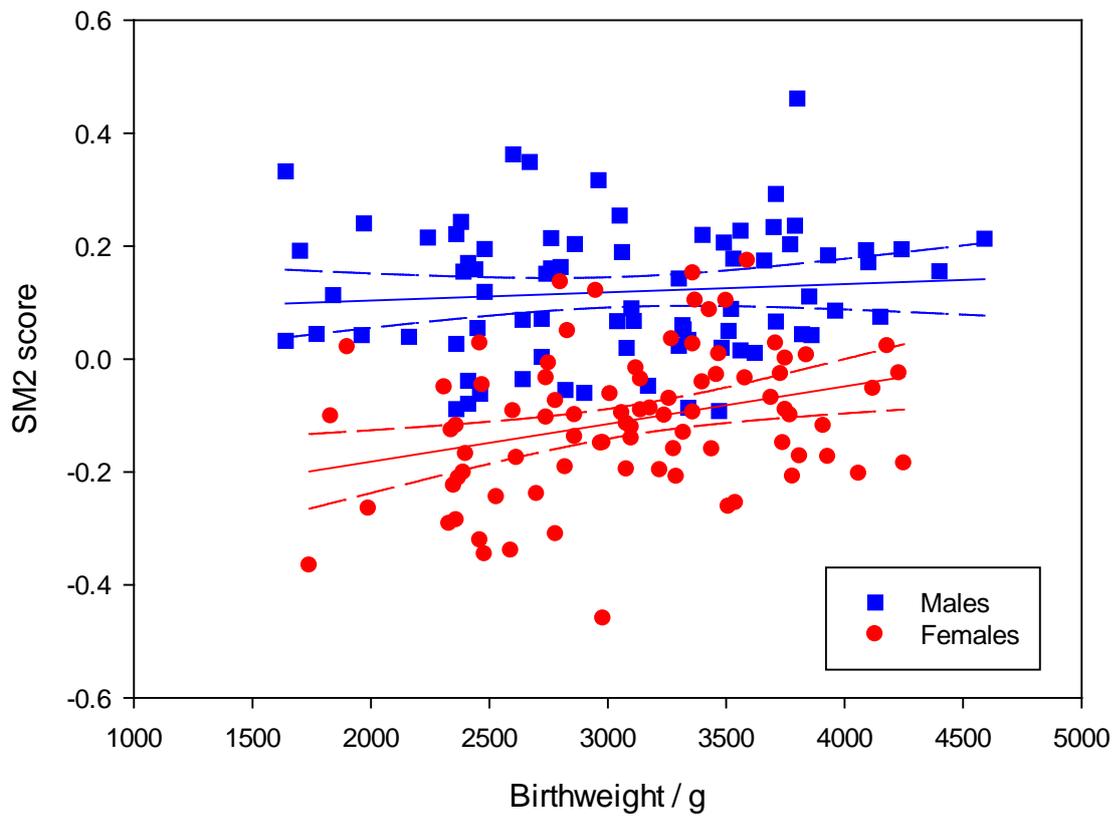
## Appendix 2

Box plot of mode scores for modes 1-3 by sex

Regression line coefficients are given as value (standard deviation)

## Appendix 1

### Mode 2 versus birthweight



#### Females

$r^2$  0.096

Coefficients:

Intercept -0.316 (0.079)

Slope  $6.67 \times 10^{-5}$  ( $2.25 \times 10^{-5}$ )

#### Males

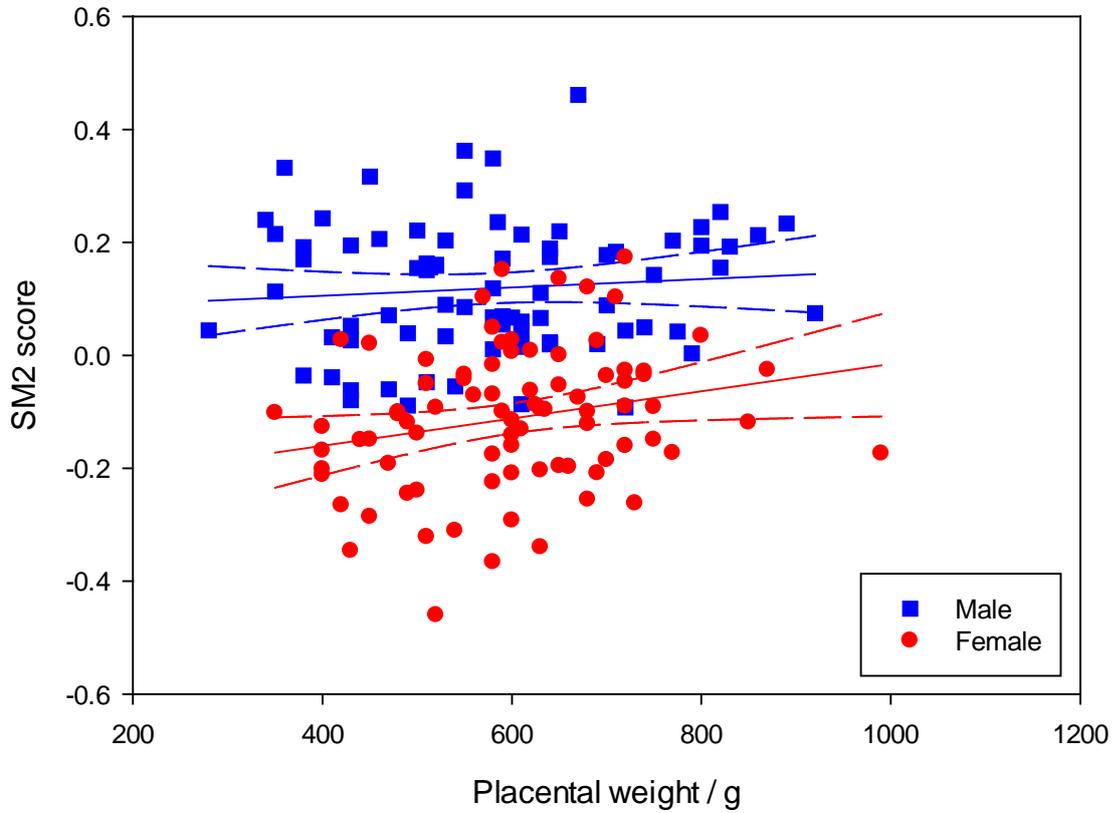
$r^2$  0.0077

Coefficients:

Intercept 0.075 (0.060)

Slope  $1.46 \times 10^{-5}$  ( $1.91 \times 10^{-5}$ )

## Mode 2 versus placental weight



### Females

$r^2$  0.054

Coefficients:

Intercept -0.257 (0.069)

Slope  $2.42 \times 10^{-4}$  ( $1.13 \times 10^{-4}$ )

### Males

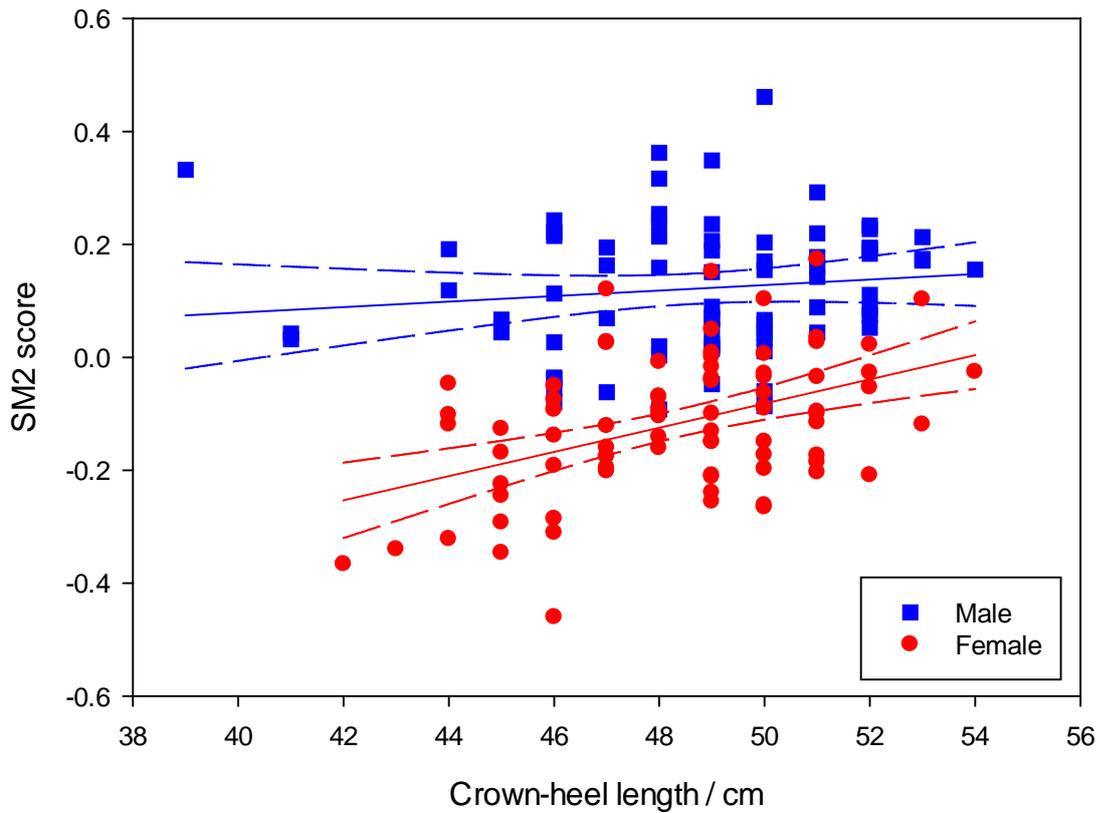
$r^2$  0.0084

Coefficients:

Intercept 0.076 (0.055)

Slope  $7.36 \times 10^{-5}$  ( $9.25 \times 10^{-5}$ )

## Mode 2 versus Crown-heel length



### Female

$r^2$  0.196

Coefficients:

Intercept -1.15 (0.24)

Slope 0.0215 (0.0049)

Standard Errors:

### Male

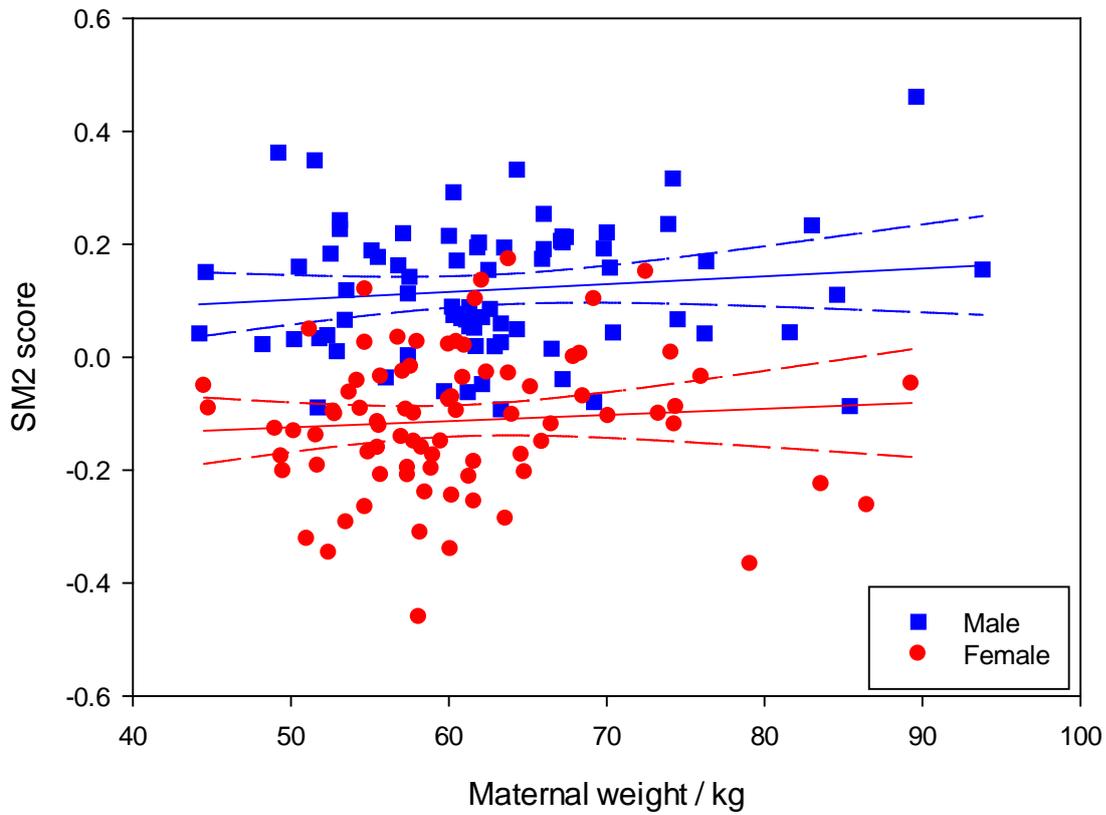
$r^2$  0.0149

Coefficients:

Intercept -0.12 (0.23)

Slope 0.0049 (0.0047)

## Mode 2 versus Maternal weight



### Female

$r^2$   $5.74 \times 10^{-3}$

Coefficients:

Intercept -0.179 (0.098)

Slope 0.0011 (0.0016)

### Male

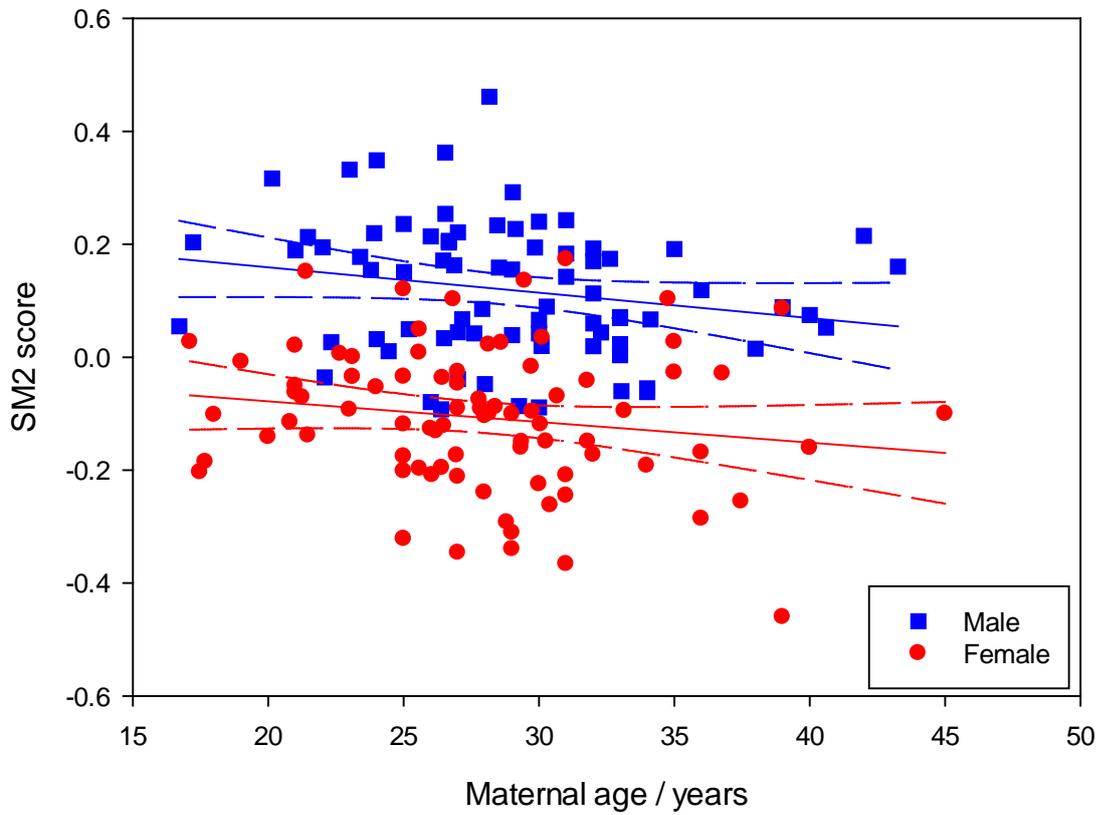
$r^2$  0.0142844

Coefficients:

Intercept 0.032 (0.086)

Slope 0.0014 (0.0013)

## Mode 2 versus Maternal age



### Female

$r^2$  0.025

Coefficients:

Intercept -0.0053 (0.072)

Slope -0.0037 (0.0025)

### Male

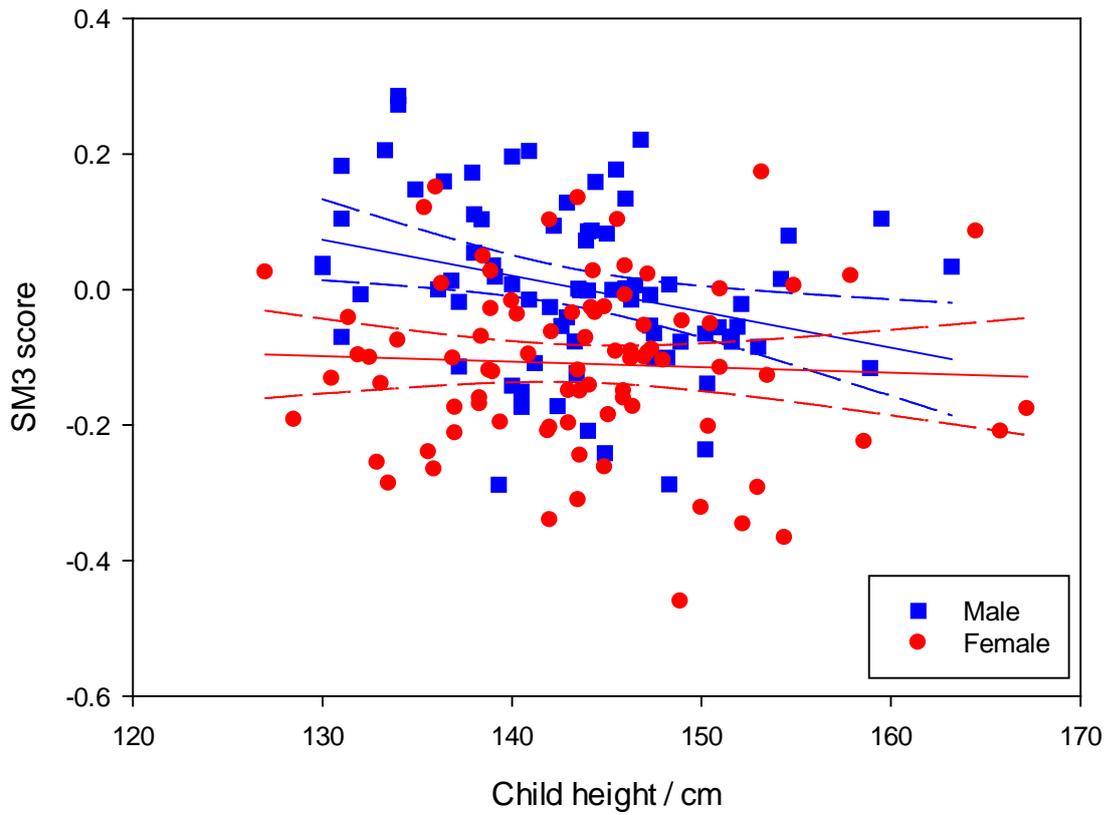
$r^2$  0.0404223

Coefficients:

Intercept 0.249 (0.075)

Slope -0.0045 (0.0025)

### Mode 3 versus Child height



Female

$r^2$   $2.57 \times 10^{-3}$

Coefficients:

Intercept 0.0074 (0.25)

Slope  $-8.1 \times 10^{-4}$  ( $17.6 \times 10^{-4}$ )

Male

$r^2$  0.086

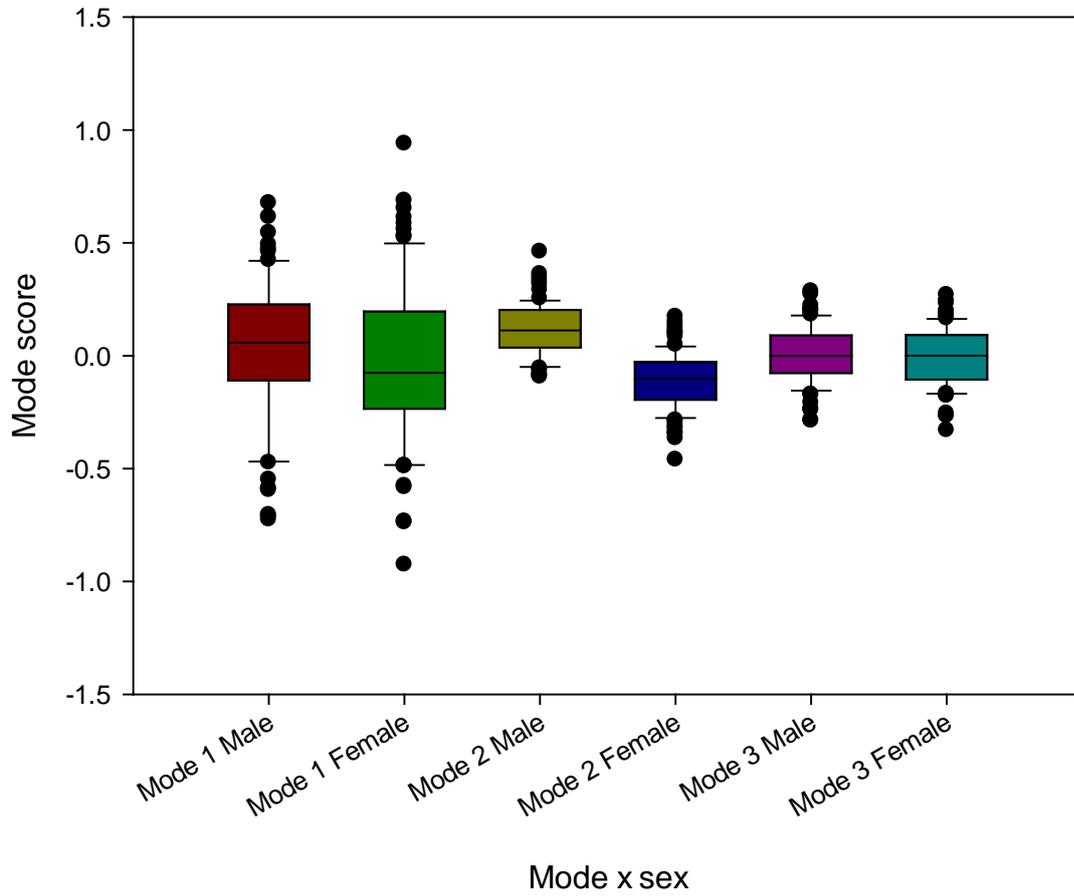
Coefficients:

Intercept 0.76 (0.29)

Slope  $-5.31 \times 10^{-3}$  ( $1.99 \times 10^{-3}$ )

Appendix 2

Mode scores



Scores for modes 1 to 3 for each sex. Only mode 2, representing the aspect ratio (vertebral a-p diameter relative to vertebral height) was significantly different between the sexes.