

PAVLOVA, A.V., JEFFREY, J.E., BARR, R.J. and ASPDEN, R.M. 2019. Perinatal factors associate with vertebral size and shape but not lumbar lordosis in 10-year-old children. *Journal of anatomy* [online], Early View. Available from: <https://doi.org/10.1111/joa.13024>

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

PAVLOVA, A.V., JEFFREY, J.E., BARR, R.J., ASPDEN, R.M.

2019

This is the peer reviewed version of the following article: PAVLOVA, A.V., JEFFREY, J.E., BARR, R.J. and ASPDEN, R.M. 2019. Perinatal factors associate with vertebral size and shape but not lumbar lordosis in 10-year-old children. *Journal of Anatomy* [online], Early View, which has been published in final form at <https://doi.org/10.1111/joa.13024>. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions.

 OpenAIR
@RGU

This document was downloaded from
<https://openair.rgu.ac.uk>



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

3
4

5 Anastasia V. Pavlova^{1,2}, Janet E. Jeffrey¹, Rebecca J. Barr^{1,3}, Richard M. Aspden^{1*}

6

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

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

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

12

13 Short title: Antenatal factors and spine shape in children

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

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);
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° , (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

311 **Acknowledgements**

312 Ethical approval for this study was granted by the North of Scotland Research Ethics Committees
313 (13/NS/0162). We would like to thank the authors and radiographers and participants involved in the
314 original study from which MR images and data were used. We thank Dr Onyedikachi Eseonu for his
315 contribution to data generation and marking up spinal images. AVP was supported by a PhD
316 studentship kindly donated by Roemex Ltd. to the Aberdeen Centre of the Oliver Bird Rheumatism
317 Programme at the Nuffield Foundation. The funders played no part in the design, execution or
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.

References

- 331
332
333 **Anderson, AS, Campbell, DM, Shepherd, R** (1995) The influence of dietary advice on nutrient intake
334 during pregnancy. *Br J Nutr* **73**, 163-177.
- 335 **Andrew, C, Bassett, L** (1971) CHAPTER 1 - Biophysical Principles Affecting Bone Structure*. *In:*
336 Bourne, GH (ed.) *Development and Growth (Second Edition)*. Academic Press.
- 337 **Aspden, RM** (1988) A new mathematical model of the spine and its relationship to spinal loading in
338 the workplace. *Applied Ergonomics* **19**, 319-323.
- 339 **Bagnall, KM, Harris, PF, Jones, PR** (1977) A radiographic study of the human fetal spine. 2. The
340 sequence of development of ossification centres in the vertebral column. *Journal of anatomy*
341 **124**, 791.
- 342 **Barker, DJP** (2007) The origins of the developmental origins theory. *J Intern Med* **261**, 412-417.
- 343 **Barr, RJ, Gregory, JS, Reid, DM, Aspden, RM, Yoshida, K, Hosie, G, et al.** (2012) Predicting
344 osteoarthritis progression to total hip replacement: can we do better than risk factors alone
345 using active shape modelling as an imaging biomarker? *Rheumatology (Oxford)* **51**, 562-570.
- 346 **Been, E, Kalichman, L** (2014) Lumbar Lordosis. *Spine Journal* **14**, 87-97.
- 347 **Birnholtz, JC, Stephens, JC, Faria, M** (1978) Fetal movement patterns: a possible means of defining
348 neurologic developmental milestones in utero. *American Journal of Roentgenology* **130**, 537-
349 540.
- 350 **Bland, M** (2000) *An introduction to medical statistics*, New York, Oxford University Press.
- 351 **Cattell, RB** (1966) The Scree Test For The Number Of Factors. *Multivariate Behav Res* **1**, 245-276.
- 352 **Chaleat-Valayer, E, Mac-Thiong, JM, Paquet, J, Berthonnaud, E, Siani, F, Roussouly, P** (2011) Sagittal
353 spino-pelvic alignment in chronic low back pain. *Eur Spine J* **20 Suppl 5**, 634-640.
- 354 **Cil, A, Yazici, M, Uzumcugil, A, Kandemir, U, Alanay, A, Alanay, Y, et al.** (2005) The evolution of
355 sagittal segmental alignment of the spine during childhood. *Spine* **30**, 93-100.
- 356 **Cootes, TF, Taylor, CJ** (2004) Anatomical statistical models and their role in feature extraction. *British*
357 *Journal of Radiology* **77**, S133-S139.

358 **Cootes, TF, Taylor, CJ, Cooper, DH, Graham, J** (1995) Active Shape Models- Their Training and
359 Application. *Computer Vision and Image Understanding* **61(1)**, 38-59.

360 **Dimeglio, A, Bonnel, F, Canavese, F** (2010) Normal Growth of the Spine and Thorax. *In: Akbarnia, B,*
361 *Yazici, M & Thompson, G (eds.) The Growing Spine.* Springer Berlin Heidelberg.

362 **Fok, TF, So, HK, Wong, E, Ng, PC, Chang, A, Lau, J, et al.** (2003) Updated gestational age specific birth
363 weight, crown-heel length, and head circumference of Chinese newborns. *Archives of*
364 *Disease in Childhood - Fetal and Neonatal Edition* **88**, F229-F236.

365 **Goodyear, SR, Barr, RJ, McCloskey, E, Alesci, S, Aspden, RM, Reid, DM, et al.** (2013) Can we improve
366 the prediction of hip fracture by assessing bone structure using shape and appearance
367 modelling? *Bone* **53**, 188-193.

368 **Ireland, A, Muthuri, S, Rittweger, J, Adams, JE, Ward, KA, Kuh, D, et al.** (2017) Later Age at Onset of
369 Independent Walking Is Associated With Lower Bone Strength at Fracture-Prone Sites in
370 Older Men. *J Bone Miner Res* **32**, 1209-1217.

371 **Javaid, MK, Cooper, C** (2002) Prenatal and childhood influences on osteoporosis. *Best Practice and*
372 *Research: Clinical Endocrinology and Metabolism* **16**, 349-367.

373 **Jeffrey, JE, Campbell, DM, Golden, MHN, Smith, FW, Porter, RW** (2003) Antenatal factors in the
374 development of the lumbar vertebral canal: A magnetic resonance imaging study. *Spine* **28**,
375 1418-1423.

376 **Joseph, KS, Kramer, MS** (2004) Should we intervene to improve fetal and infant growth? *In: Kuh, D &*
377 *Shlomo, YB (eds.) A Life Course Approach to Chronic Disease Epidemiology.* Oxford: OUP.

378 **Kramer, MS** (1987) Determinants of low birth weight: methodological assessment and meta-analysis.
379 *Bulletin of the World Health Organization* **65**, 663-737.

380 **Lee, CS, Noh, H, Lee, DH, Hwang, CJ, Kim, H, Cho, SK** (2012) Analysis of sagittal spinal alignment in
381 181 asymptomatic children. *J Spinal Disord Tech* **25**, E259-263.

382 **Lee, E, Ko, C, Suh, S, Kumar, S, Kang, I, Yang, J** (2014) The effect of age on sagittal plane profile of the
383 lumbar spine according to standing, supine, and various sitting positions. *J Orthop Surg Res* **9**,
384 1-10.

385 **Lesiński, J** (1962) Relationship between length of gestation, birth weight and certain other factors: A
386 statistical study. *Bulletin of the World Health Organization* **26**, 183-191.

387 **Levillain, A, Rolfe, RA, Huang, Y, Iatridis, JC, Nowlan, NC** (2019) Short-term foetal immobility
388 temporally and progressively affects chick spinal curvature and anatomy and rib
389 development. *Eur Cell Mater* **37**, 23-41.

390 **Livshits, G, Popham, M, Malkin, I, Sambrook, PN, Macgregor, AJ, Spector, T, et al.** (2011) Lumbar
391 disc degeneration and genetic factors are the main risk factors for low back pain in women:
392 The UK Twin Spine Study. *Annals of the Rheumatic Diseases* **70**, 1740-1745.

393 **Mac-Thiong, J-M, Labelle, H, Berthonnaud, E, Betz, R, Roussouly, P** (2007) Sagittal spinopelvic
394 balance in normal children and adolescents. *European Spine Journal* **16**, 227-234.

395 **Mac-Thiong, J-M, Labelle, H, Roussouly, P** (2011) Pediatric sagittal alignment. *European Spine*
396 *Journal* **20**, 586-590.

397 **Manning, F, Pugh, EW, Boddy, K** (1975) Effect of cigarette smoking on fetal breathing movements in
398 normal pregnancies. *British medical journal* **1**, 552.

399 **Masharawi, Y, Kjaer, P, Manniche, C, Bendix, T** (2012) Lumbar sagittal shape variation vis-à-vis sex
400 during growth: A 3-year follow-up magnetic resonance imaging study in children from the
401 general population. *Spine* **37**, 501-507.

402 **Meakin, JR, Aspden, RM** (2012) Modelling the effect of variation in sagittal curvature on the force
403 required to produce a follower load in the lumbar spine. *Journal of Mechanics in Medicine*
404 *and Biology* **12**, 1250013-1250011-1250013-1250010.

405 **Meakin, JR, Gregory, JS, Aspden, RM, Smith, FW, Gilbert, FJ** (2009a) The intrinsic shape of the
406 human lumbar spine in the supine, standing and sitting postures: characterization using an
407 active shape model. *J Anat* **215**, 206-211.

408 **Meakin, JR, Gregory, JS, Aspden, RM, Smith, FW, Gilbert, FJ** (2009b) The intrinsic shape of the
409 human lumbar spine in the supine, standing and sitting postures: characterization using an
410 active shape model. *J Anat* **215**, 206-211.

411 **Meakin, JR, Gregory, JS, Smith, FW, Gilbert, FJ, Aspden, RM** (2008) Characterizing the shape of the
412 lumbar spine using an active shape model: reliability and precision of the method. *Spine*
413 (*Phila Pa 1976*) **33**, 807-813.

414 **Mohsin, M, Wong, F, Bauman, A, Bai, J** (2003) Maternal and neonatal factors influencing premature
415 birth and low birth weight in Australia. *Journal of Biosocial Science* **35**, 161-174.

416 **Moore, KL, Agur, AMR, Dalley, AF** (2011) *Essential Clinical Anatomy*, Philadelphia, Lippincott
417 Williams & Wilkins/Wolters Kluwer.

418 **Moore, KL, Dalley, AF** (1999) *Clinically Oriented Anatomy*, Lippincott Williams & Wilkins.

419 **Nowlan, NC** (2015) Biomechanics of foetal movement. *Eur Cell Mater* **29**, 1-21.

420 **Pasco, JA, Wark, JD, Carlin, JB, Ponsonby, A-L, Vuillermin, PJ, Morley, R** (2008) Maternal vitamin D
421 in pregnancy may influence not only offspring bone mass but other aspects of
422 musculoskeletal health and adiposity. *Medical Hypotheses* **71**, 266-269.

423 **Pavlova, AV, Meakin, JR, Cooper, K, Barr, RJ, Aspden, RM** (2014) The lumbar spine has an intrinsic
424 shape specific to each individual that remains a characteristic throughout flexion and
425 extension. *Eur Spine J* **23 Suppl 1**, 26-32.

426 **Pavlova, AV, Meakin, JR, Cooper, K, Barr, RJ, Aspden, RM** (2018a) Variation in lifting kinematics
427 related to individual intrinsic lumbar curvature: an investigation in healthy adults. *BMJ Open*
428 *Sport & Exercise Medicine* **4**.

429 **Pavlova, AV, Muthuri, SG, Cooper, R, Saunders, FR, Gregory, JS, Barr, RJ, et al.** (2018b) Body mass
430 index and waist circumference in early adulthood are associated with thoracolumbar spine
431 shape at age 60-64: The Medical Research Council National Survey of Health and
432 Development. *PLoS One* **13**.

433 **Pavlova, AV, Saunders, FR, Muthuri, SG, Gregory, JS, Barr, RJ, Martin, KR, et al.** (2017) Statistical
434 shape modelling of hip and lumbar spine morphology and their relationship in the MRC
435 National Survey of Health and Development. *J Anat* **231**, 248-259.

436 **Pitsillides, AA, Ashhurst, DE** (2008) A critical evaluation of specific aspects of joint development.
437 *Developmental Dynamics* **237**, 2284-2294.

438 **Porter, RW, Hibbert, C, Wellman, P** (1980) Backache and the lumbar spinal canal. *Spine* **5**, 99-105.

439 **Poussa, MS, Heliovaara, MM, Seitsamo, JT, Kononen, MH, Hurmerinta, KA, Nissinen, MJ** (2005)
440 Development of spinal posture in a cohort of children from the age of 11 to 22 years. *Eur*
441 *Spine J* **14**, 738-742.

442 **Rolfe, RA, Bezer, JH, Kim, T, Zaidon, AZ, Oyen, ML, Iatridis, JC, et al.** (2017) Abnormal fetal muscle
443 forces result in defects in spinal curvature and alterations in vertebral segmentation and
444 shape. *J Orthop Res* **35**, 2135-2144.

445 **Roussouly, P, Gollogly, S, Berthonnaud, E, Dimnet, J** (2005) Classification of the normal variation in
446 the sagittal alignment of the human lumbar spine and pelvis in the standing position. *Spine*
447 **30**, 346-353.

448 **Shymon, SJ, Yaszay, B, Dwek, JR, Proudfoot, JA, Donohue, M, Hargens, AR** (2013) Altered Disc
449 Compression in Children With Idiopathic Low Back Pain: An Upright MRI Backpack Study.
450 *Spine (Phila Pa 1976)* **39**, 243-248.

451 **Spencer, N, Logan, S** (2002) Social influences on birth weight. *Journal of Epidemiology and*
452 *Community Health* **56**, 326.

453 **Stone, MA, Osei-Bordom, DC, Inman, RD, Sammon, C, Wolber, LE, Williams, FM** (2015) Heritability
454 of spinal curvature and its relationship to disc degeneration and bone mineral density in
455 female adult twins. *Eur Spine J* **24**, 2387-2394.

456 **Strauss, RS** (1997) Effects of the intrauterine environment on childhood growth. *British Medical*
457 *Bulletin* **53**, 81-95.

458 **Varzi, D, Coupaud, SA, Purcell, M, Allan, DB, Gregory, JS, Barr, RJ** (2015) Bone morphology of the
459 femur and tibia captured by statistical shape modelling predicts rapid bone loss in acute
460 spinal cord injury patients. *Bone* **81**, 495-501.

461 **Vialle, R, Levassor, N, Rillardon, L, Templier, A, Skalli, W, Guigui, P** (2005) Radiographic Analysis of
462 the Sagittal Alignment and Balance of the Spine in Asymptomatic Subjects. *Journal of Bone*
463 *and Joint Surgery* **87**, 260-267.

464 **Wardlaw, TM** (2004) *Low Birthweight: Country, regional and global estimates*, UNICEF.

465 **Wilcox, AJ** (2001) On the importance—and the unimportance— of birthweight. *International Journal*
466 *of Epidemiology* **30**, 1233-1241.

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 Birthweight	Normal Birthweight	Boys	Girls
<i>n</i> (%)	161	39 (24)	122 (76)	77 (48)	84 (52)
Birthweight (g)	3072 (644)	2227 (276)	3342 (469)**	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)	37 (3)	39 (1)**	38.5 (2.5)	39.1 (2.1)
Placenta weight (g)	591 (133)	456 (92)	635 (113)**	580 (146)	602(120)
Crown to heel length (<i>cm</i>)	48.5 (2.7)	45.5 (2.4)	49.5 (2.1)**	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)	37 (6)	40 (6)*
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 ^acontrolled for
 475 sex only. Mode 1 (curviness), mode 2 (aspect ratio) and mode 3 (evenness). Significant associations
 476 shown in bold.

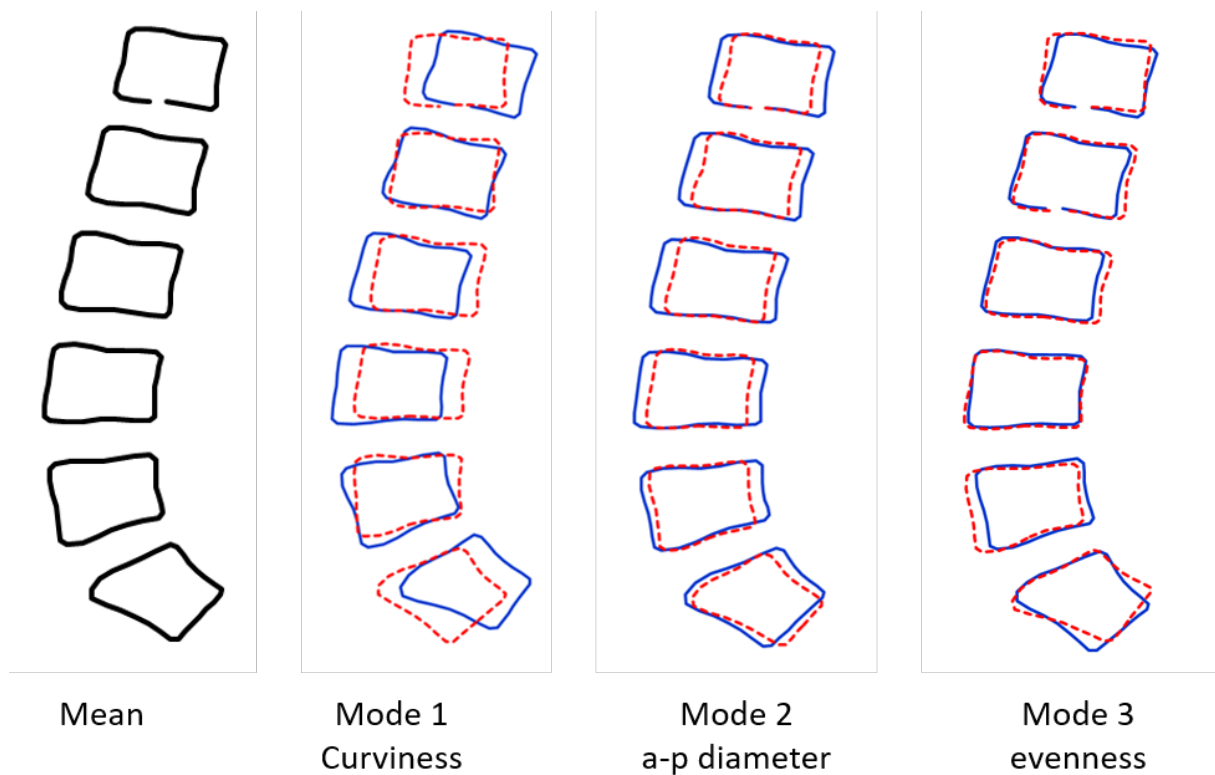
	Mode 1	Mode 2	Mode 3
	<i>r</i> (<i>P</i>)	<i>r</i> (<i>P</i>)	<i>r</i> (<i>P</i>)
Birthweight (g)	0.06 (0.51)	0.25 (<0.01)	0.02 (0.85)
Placenta weight (g)	0.07 (0.47)	0.20 (0.04)	-0.01 (0.94)
Gestation length (weeks)	0.001 (0.99) ^a	0.11 (0.27) ^a	0.03 (0.80) ^a
Crown-heel length (cm)	-0.02 (0.86)	0.36 (<0.001)	-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)	-0.21 (0.02)
Lumbar angle at scan (°)	-0.83 (<0.001)	-0.09 (0.32)	0.01 (0.93)
Mother's weight (kg)	-0.1 (0.31)	0.19 (0.04)	-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)	-0.22 (0.02)	-0.07 (0.45)

477

478

479

480

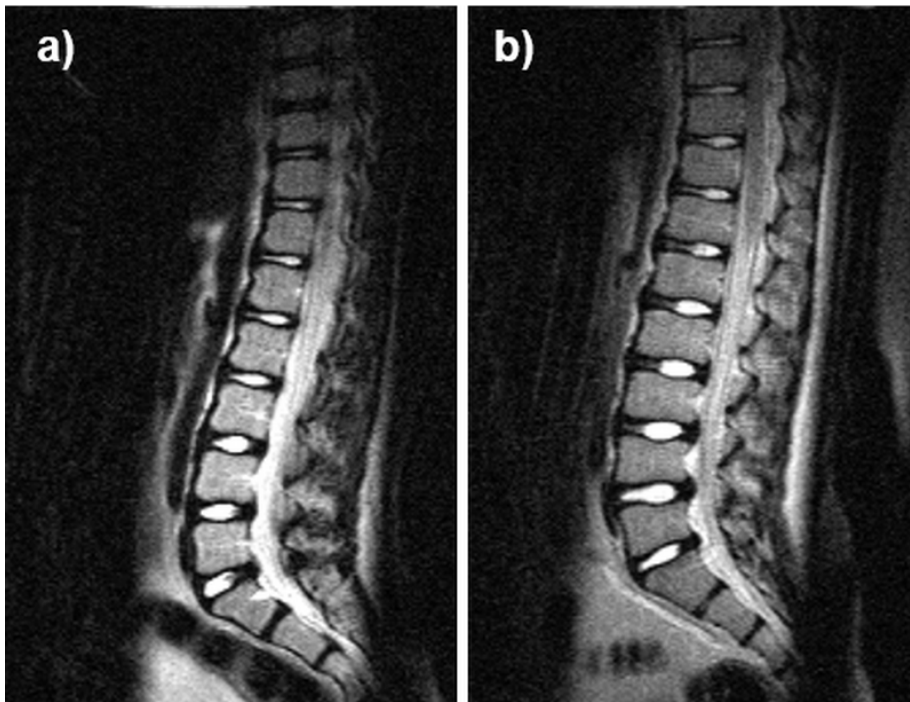


481

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

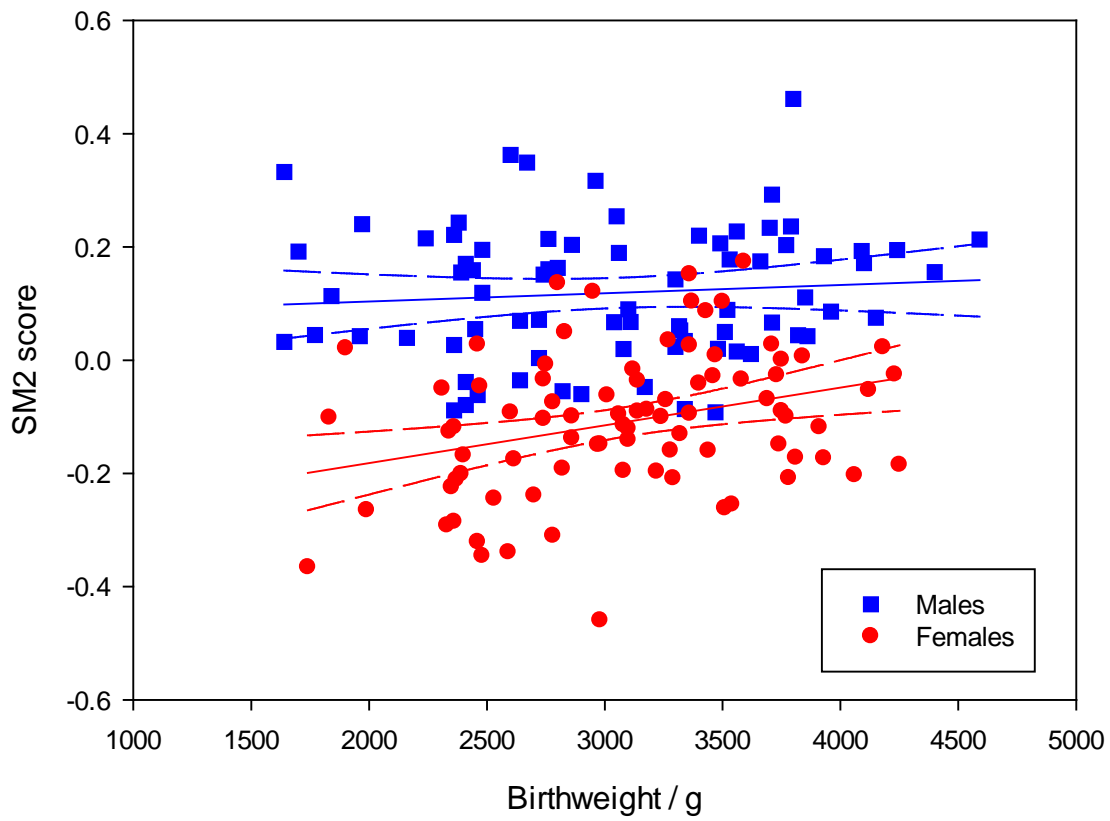
Appendix 2

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 6.67×10^{-5} (2.25×10^{-5})

Males

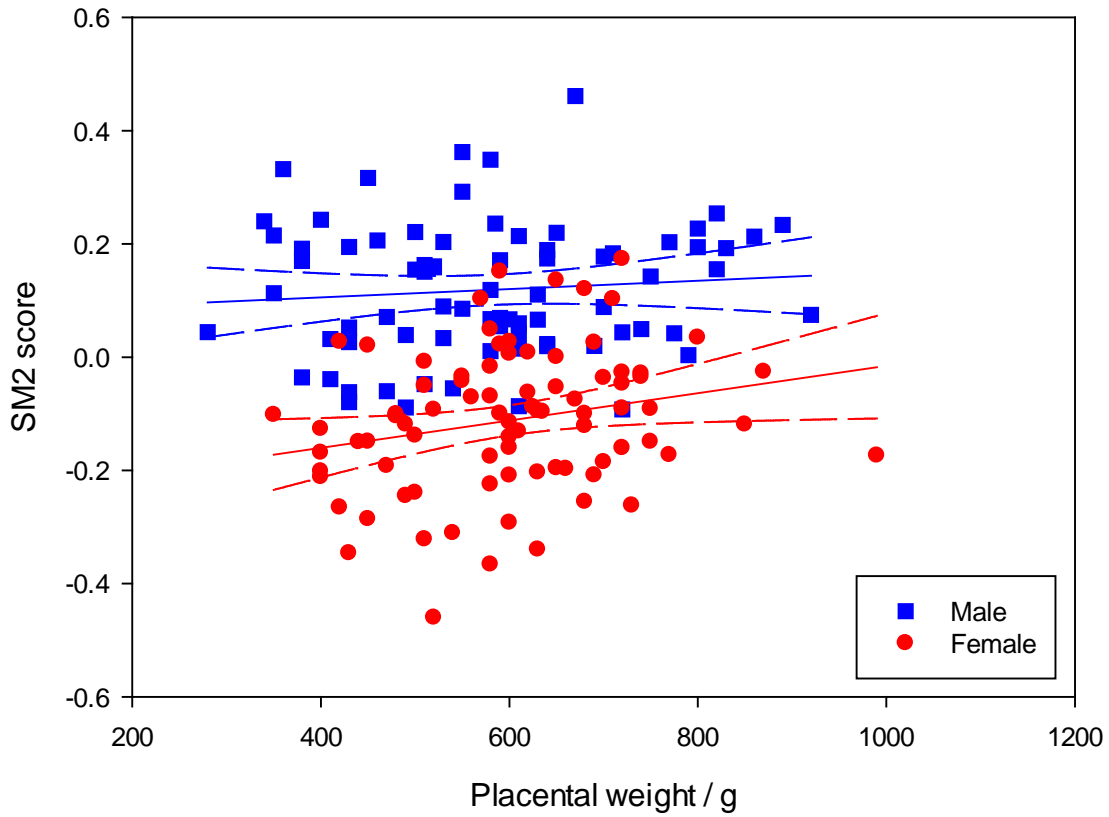
r^2 0.0077

Coefficients:

Intercept 0.075 (0.060)

Slope 1.46×10^{-5} (1.91×10^{-5})

Mode 2 versus placental weight



Females

r^2 0.054

Coefficients:

Intercept -0.257 (0.069)

Slope 2.42×10^{-4} (1.13×10^{-4})

Males

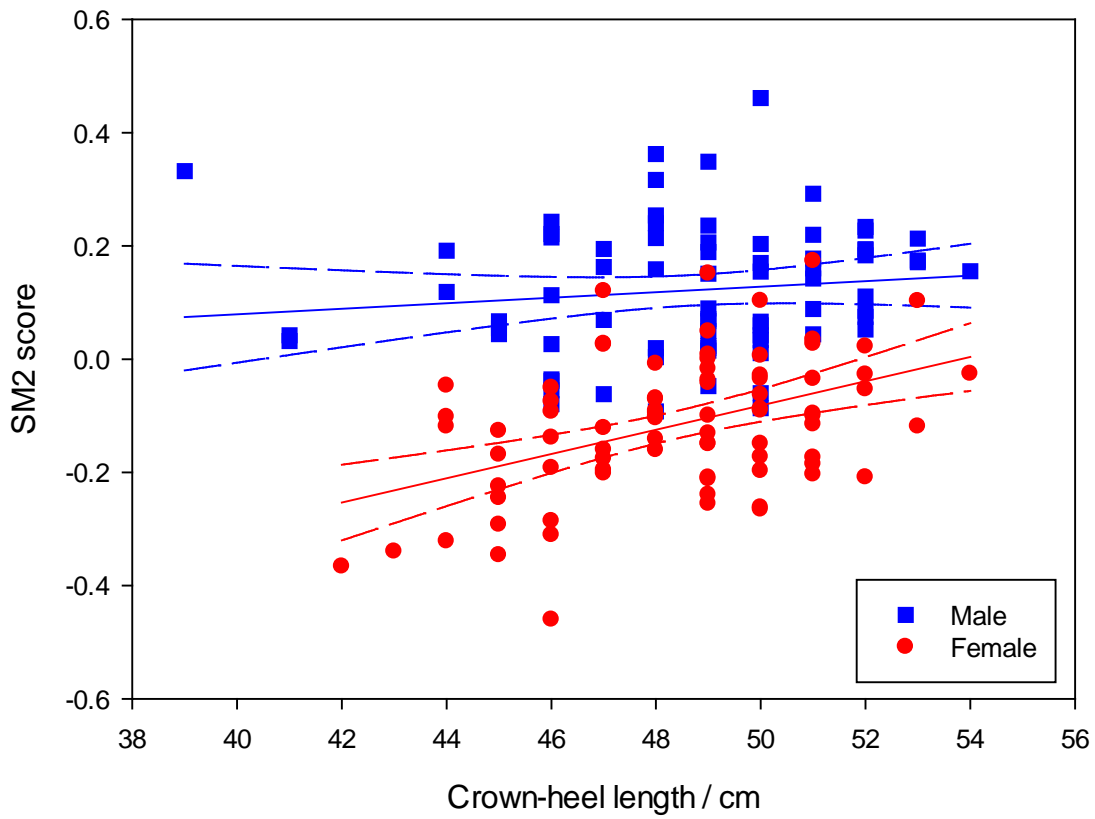
r^2 0.0084

Coefficients:

Intercept 0.076 (0.055)

Slope 7.36×10^{-5} (9.25×10^{-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

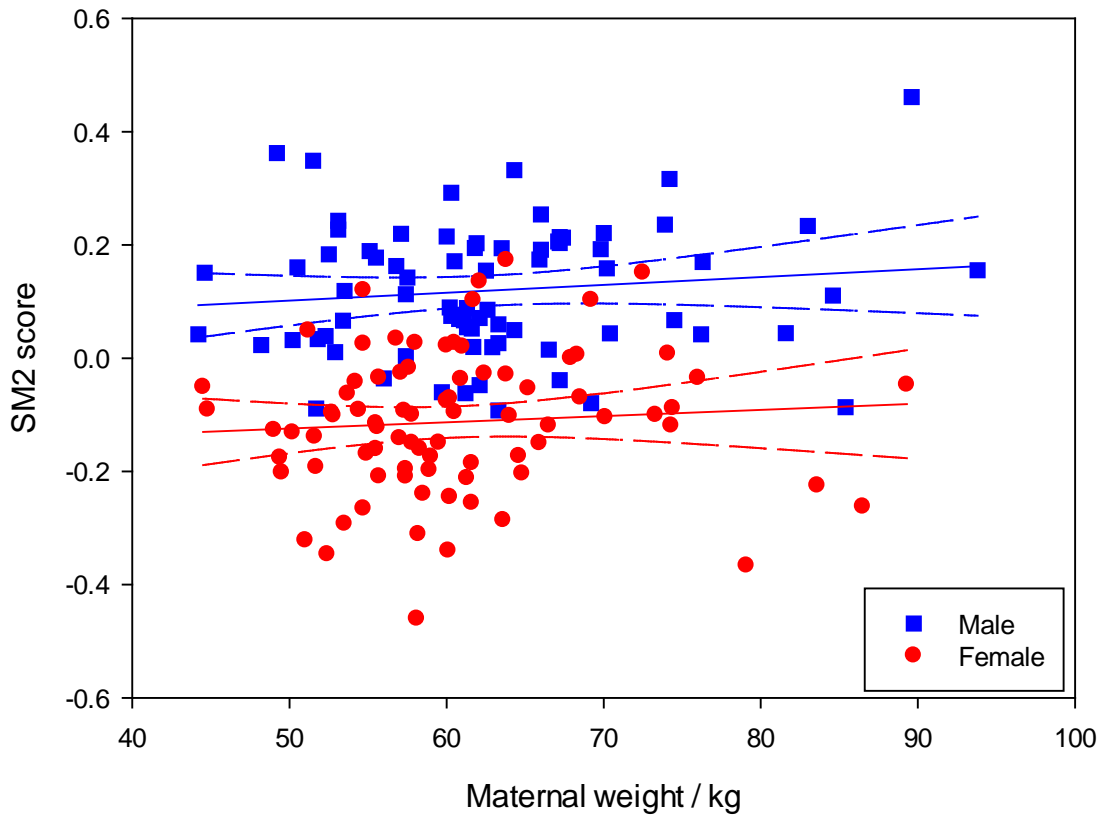
r^2 0.0149

Coefficients:

Intercept -0.12 (0.23)

Slope 0.0049 (0.0047)

Mode 2 versus Maternal weight



Female

r^2 5.74×10^{-3}

Coefficients:

Intercept -0.179 (0.098)

Slope 0.0011 (0.0016)

Male

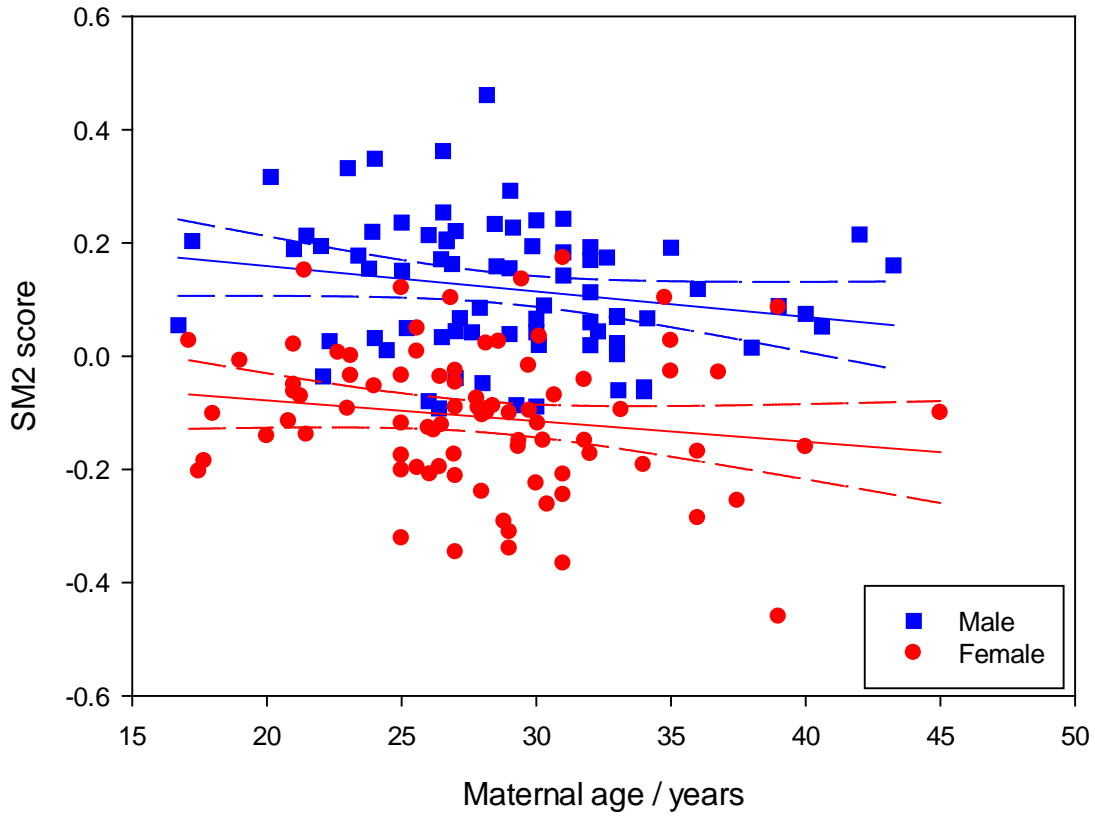
r^2 0.0142844

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

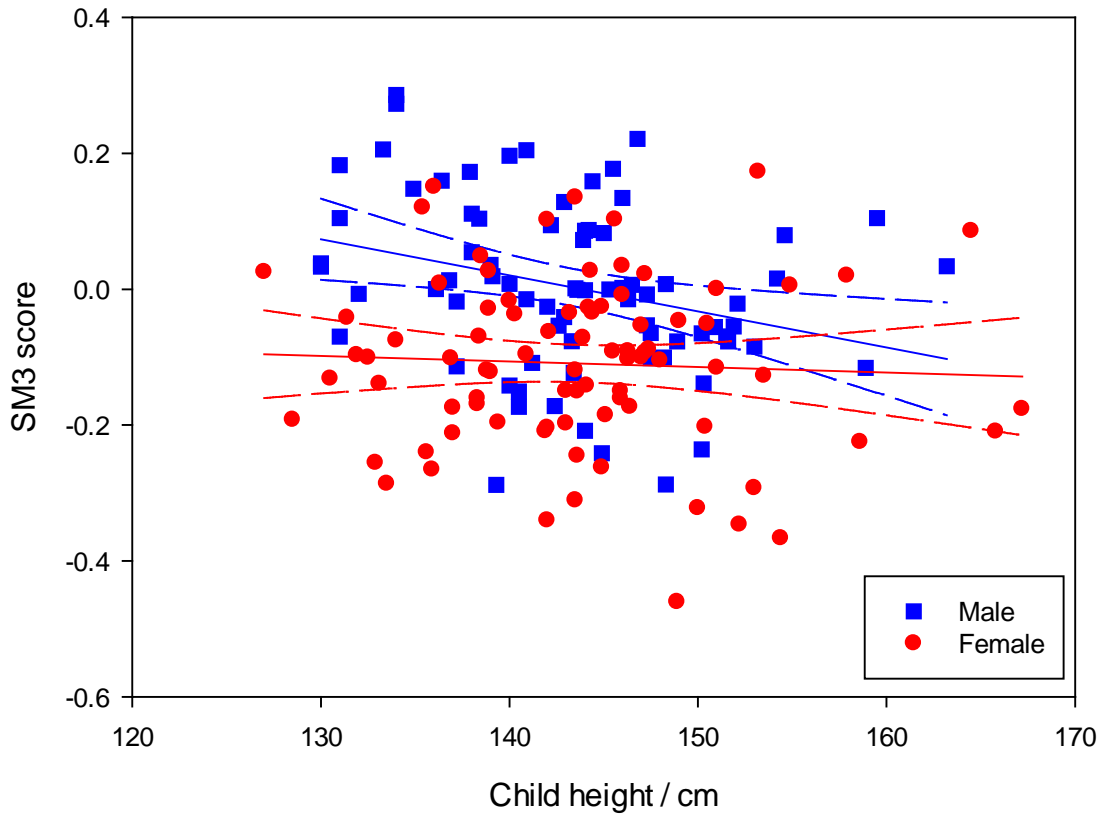
r^2 0.0404223

Coefficients:

Intercept 0.249 (0.075)

Slope -0.0045 (0.0025)

Mode 3 versus Child height



Female

r^2 2.57×10^{-3}

Coefficients:

Intercept 0.0074 (0.25)

Slope -8.1×10^{-4} (17.6×10^{-4})

Male

r^2 0.086

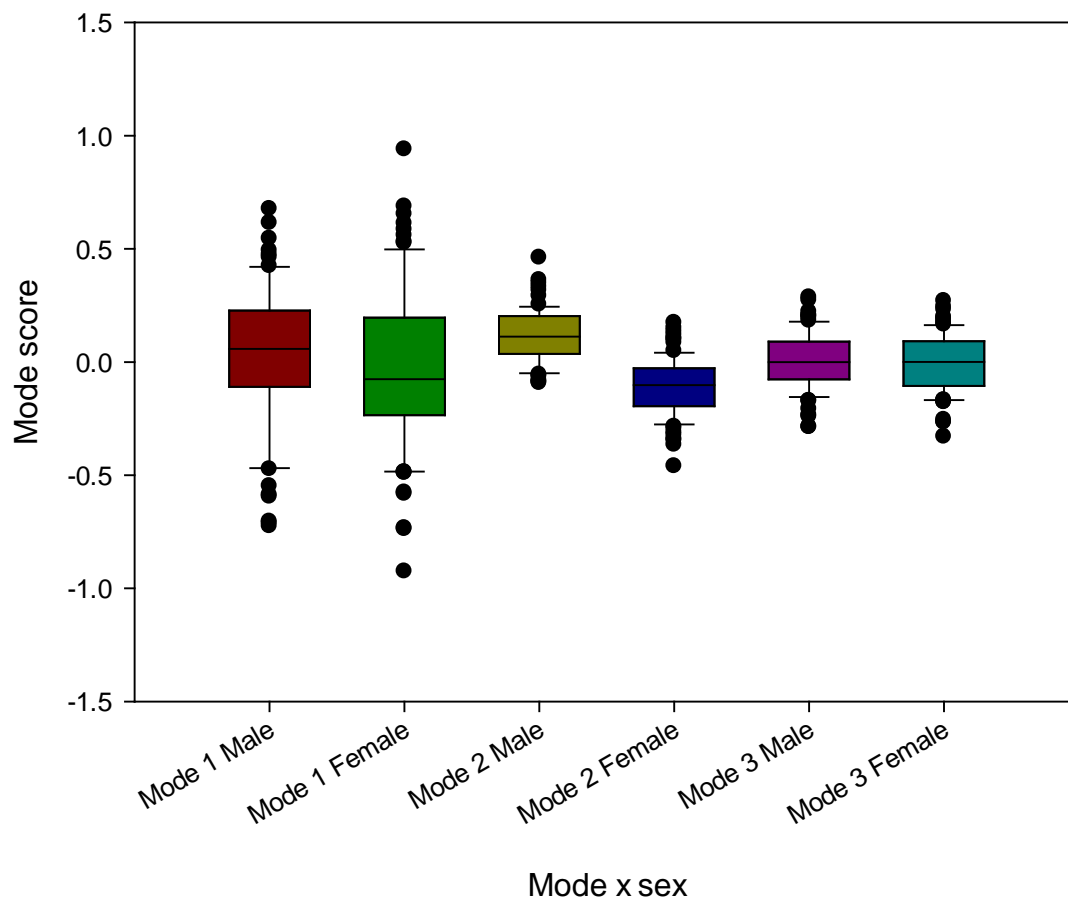
Coefficients:

Intercept 0.76 (0.29)

Slope -5.31×10^{-3} (1.99×10^{-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.