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Motor development in infancy and spine shape in early old age: findings from a British birth cohort study

3 Fiona R Saunders, Aberdeen Centre for Arthritis and Musculoskeletal Health, School of

4 Medicine, Medical Sciences & Nutrition, University of Aberdeen, Institute of Medical

- 5 Sciences, Foresterhill, Aberdeen, AB25 2ZD, UK
- 6 Jennifer S Gregory, Aberdeen Centre for Arthritis and Musculoskeletal Health, School of
- 7 Medicine, Medical Sciences & Nutrition, University of Aberdeen, Institute of Medical
- 8 Sciences, Foresterhill, Aberdeen, AB25 2ZD, UK
- 9 Anastasia V Pavlova, Aberdeen Centre for Arthritis and Musculoskeletal Health, School of

10 Medicine, Medical Sciences & Nutrition, University of Aberdeen, Institute of Medical

11 Sciences, Foresterhill, Aberdeen, AB25 2ZD, UK and School of Health Sciences, Robert

12 Gordon University, Ishbel Gordon Building, Garthdee Road, Aberdeen, AB10 7QE, UK.

Stella G Muthuri, MRC Unit for Lifelong Health and Ageing at UCL, 1-19 Torrington Place,
London, WC1E 7HB, UK

15 Rebecca J Hardy, MRC Unit for Lifelong Health and Ageing at UCL, 1-19 Torrington Place,

16 London, WC1E 7HB, UK and Cohort and Longitudinal Studies Enhancement Resources

17 (CLOSER), UCL Institute of Education, 20 Bedford Way, Bloomsbury, London WC1H 0AL,
18 UK

- 19 Kathryn R Martin, Aberdeen Centre for Arthritis and Musculoskeletal Health, School of
- 20 Medicine, Medical Sciences & Nutrition, University of Aberdeen, Institute of Medical
- 21 Sciences, Foresterhill, Aberdeen, AB25 2ZD, UK
- 22 Rebecca J Barr, Aberdeen Centre for Arthritis and Musculoskeletal Health, School of
- 23 Medicine, Medical Sciences and Nutrition, University of Aberdeen, AB25 2ZD,

24	UK and Medicines Monitoring Unit (MEMO), Division of Molecular & Clinical Medicine,
25	School of Medicine, University of Dundee, Mailbox 2 Level 7, Ninewells Hospital &
26	Medical School, Dundee DD1 9SY
27	Judith E Adams †, Manchester Academic Health Science Centre and Radiology, Central
28	Manchester University Hospitals NHS Foundation Trust and University of Manchester,
29	Manchester Royal Infirmary, Oxford Road, Manchester, M13 9WL, UK
30	Diana Kuh, MRC Unit for Lifelong Health and Ageing at UCL, 1-19 Torrington Place,
31	London, WC1E 7HB, UK
32	Richard M Aspden, Aberdeen Centre for Arthritis and Musculoskeletal Health, School of
33	Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, AB25 2ZD,
34	UK
35	Rachel Cooper, Research Centre for Musculoskeletal Science & Sports Medicine,
36	Department of Sport and Exercise Sciences, Manchester Metropolitan University,
37	Manchester, M15 6BH
38	Alex Ireland, Research Centre for Musculoskeletal Science & Sports Medicine, Department
38 39	Alex Ireland, Research Centre for Musculoskeletal Science & Sports Medicine, Department of Life Sciences, Manchester Metropolitan University, Manchester, M1 5GD
38 39 40	Alex Ireland, Research Centre for Musculoskeletal Science & Sports Medicine, Department of Life Sciences, Manchester Metropolitan University, Manchester, M1 5GD Corresponding Author: Fiona Saunders, University of Aberdeen, Institute of Medical
38 39 40 41	Alex Ireland, Research Centre for Musculoskeletal Science & Sports Medicine, Department of Life Sciences, Manchester Metropolitan University, Manchester, M1 5GD Corresponding Author: Fiona Saunders, University of Aberdeen, Institute of Medical Sciences, Foresterhill, Aberdeen, AB25 2ZD <u>f.r.saunders@abdn.ac.uk</u> . +44 (0)1224 437454
 38 39 40 41 42 	Alex Ireland, Research Centre for Musculoskeletal Science & Sports Medicine, Department of Life Sciences, Manchester Metropolitan University, Manchester, M1 5GD Corresponding Author: Fiona Saunders, University of Aberdeen, Institute of Medical Sciences, Foresterhill, Aberdeen, AB25 2ZD <u>f.r.saunders@abdn.ac.uk</u> . +44 (0)1224 437454
 38 39 40 41 42 43 	Alex Ireland, Research Centre for Musculoskeletal Science & Sports Medicine, Department of Life Sciences, Manchester Metropolitan University, Manchester, M1 5GD Corresponding Author: Fiona Saunders, University of Aberdeen, Institute of Medical Sciences, Foresterhill, Aberdeen, AB25 2ZD <u>f.r.saunders@abdn.ac.uk</u> . +44 (0)1224 437454 Running Title: (5 words): Developmental Milestones and Spine Shape

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- 49 of the data analysis
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51 Abstract:

Spine shape changes dramatically in early life, influenced by attainment of developmental 52 milestones such as independent walking. Whether these associations persist across life is 53 unknown. Therefore, we investigated associations between developmental milestones and 54 spine shape, as determined using statistical shape models (SSMs) of lumbar spine from DXA 55 56 scans in 1327 individuals (688 female) at 60-64y in the MRC National Survey of Health and Development. Lumbar lordosis angle (L4 inferior endplate to T12 superior endplate) was 57 measured using the two-line Cobb method. In analyses adjusted for sex, height, lean and fat 58 mass, socioeconomic position and birthweight, later walking age was associated with greater 59 lordosis described by SSM1 (regression coefficient 0.023, 95%CI 0.000-0.047, p=0.05) and 60 direct angle measurement. Modest associations between walking age and less variation in 61 62 anterior-posterior vertebral size caudally (SSM6) were also observed (0.021, 95%CI -0.002-0.044, p=0.07). Sex interactions showed that later walking was associated with larger relative 63 vertebral anterior-posterior dimensions in men (SSM3; -0.043, 95%CI -0.075-0.01, p=0.01) 64 but not women (0.018, 95%CI -0.0007-0.043, p=0.17). Similar associations were observed 65 between age at independent standing and SSMs but there was little evidence of association 66 67 between sitting age and spine shape. Unadjusted associations between walking age and SSMs 1 and 6 remained similar after adjustment for potential confounders and mediators. This 68 69 suggests that these associations may be explained by altered mechanical loading of the spine 70 during childhood growth, although other factors could contribute. Early life motor development, particularly walking, may have a lasting effect on features of spine morphology 71 with clinical significance. 72

73 Keywords: Growth, mechano-adaptation, loading

74 Introduction

Infancy and early childhood represent key periods for the development of spine shape and 75 structure. Lordosis (indicated by the lumbosacral angle) increases from 20° to 70° in the first 76 five years of life¹, followed by slower growth in both lordosis and thoracic kyphosis up to 77 adulthood². In contrast, cervical lordosis increases until 9-10 years of age before decreasing 78 throughout adolescence³. Vertebral height and width increase dramatically in the first two 79 years of life, after which time more modest growth continues until adulthood ⁴. These growth 80 patterns are highly dependent on vertebral location, with greater growth in lumbar than 81 thoracic and in turn cervical bodies⁴ in line with the loading they experience. Due to these 82 increases in both vertebral size and bone mineral density, lumbar spine bone mass increases 83 fivefold between the ages of 1 to 36 months 5 . 84

85 A key factor in the development of spine shape during this period is attainment of motor milestones at 6-24 months of age. This development coincides with a large increase in 86 lordosis, and this angle is closely associated with stages of motor development such as 87 standing, walking and running¹. The influence of early life motor development on spine 88 shape can also be examined through comparison with groups where attainment of motor 89 90 skills is impaired. Children with cerebral palsy display impaired growth of vertebral bodies, with these deficits emerging after typical walking age at around 2 years ⁴. In children with 91 osteogenesis imperfecta, earlier attainment of independent sitting is associated with delayed 92 development of scoliosis ⁶. However, it is unknown whether associations between early life 93 motor development and spine shape persist into adulthood. 94

Development of spine shape involves simultaneous but discordant regional changes in
vertebral size and shape, as well as overall curvature ^{7; 8}. Studies of spine shape have typically
described only a small number of these variables. Statistical shape modelling (SSM) can

provide an objective description of variation in these and other aspects of spine shape (such
as degree of variation in vertebral size within an individual's spine). SSM has been shown to
be more reliable and accurate than traditional measurements of spinal curvature ^{9; 10}.

Therefore, our primary aim was to examine whether early childhood motor development, as 101 indicated by age of attainment of independent walking is associated with spine shape in older 102 age using data from the MRC National Survey of Health and Development (NSHD), a British 103 birth cohort study. Walking age was selected as the motor milestone of primary interest 104 because of the large loads experienced during this movement ¹¹ and previous reports of strong 105 associations between walking age and bone health throughout life ¹²⁻¹⁴. Whilst spine shape 106 was our primary outcome, as a secondary aim we also examined associations between 107 walking age and osteoarthritis of the spine to assess whether there was any evidence that our 108 109 main findings have clinical consequences that are detectable in early old age. As age at attainment of sitting and standing have also been associated with skeletal development ^{1;6}, 110 and are highly correlated with age at walking, associations between these exposures and spine 111 shape were also assessed as secondary analyses. It was hypothesised that the age at which 112 independent walking was attained would be associated with variation in spine shape features 113 114 in early old-age.

115 Methods

117

116 *Study Population*

births in 1 week in March 1946 in England, Scotland and Wales. These participants have 118 been prospectively followed regularly since birth ¹⁵. Between 2006-2010, eligible participants 119 known to be alive and living in England, Scotland and Wales were invited for an assessment 120 at one of six clinical research facilities (CRF). Of 2856 individuals invited, 1690 attended a 121 CRF and 539 received a home visit from a research nurse. Ethical approval for this data 122 collection was obtained from the Central Manchester Research Ethics Committee 123 (07/H1008/245) and the Scottish A Research Ethics Committee (08/MRE00/12). 124 125 Spine DXA images During the CRF assessment, images of the total body and spine were obtained using a QDR 126 127 4500 Discovery dual-energy X-ray absorptiometry (DXA) scanner (Hologic, Inc., Bedford, MA). In five centres, scanners had rotating C-arms allowing participants to lie supine for all 128 scans, whilst one centre used a scanner with a fixed C-arm requiring participants to be 129 130 scanned in a lateral decubitus position. In both cases, participants were scanned with hips and knees flexed, and with arms raised so as not to obscure the scanned region. Judith E Adams's 131 laboratory performed quantitative analysis of all scans and assessments for image quality. A 132 manufacturer-provided phantom was scanned daily prior to participant scanning; once a 133 month, these results were sent to the coordinating centre for scrutiny. 134

The NSHD is a birth cohort study consisting of a socially-stratified sample of 5,362 singleton

135 Statistical shape modelling

Of the 1690 participants who attended a CRF, 1601 had a spine DXA scan. 72 images were
excluded from analysis: in 41 images vertebral outlines could not be clearly determined, 23
had scanning artefacts, five did not include all vertebrae of interest, two included metalwork

139 and excessive axial rotation was observed in one image. This left 1529 images which were used to build the SSM; this process has been described in detail previously ¹⁶. Briefly, 140 custom-made Shape software (University of Aberdeen) was used to create a template of 89 141 points including all vertebrae from the tenth thoracic vertebra (T10) to the superior endplate 142 of the fifth lumbar vertebrae. These eight vertebrae were chosen for analysis as they were 143 visible on all scans. Following an automatic search and placement of points, all images were 144 manually checked and where necessary points were adjusted. Mean intra- and inter-rater 145 repeatability for this technique is 1.4 and 2.2 pixels respectively ¹⁶, which represents a small 146 147 error considering an average spine image size of 1200 x 400 pixels and a typical vertebra size of approximately 80 x 60 pixels. Procrustes transformation was used to translate, rotate and 148 scale the images to remove influences of size and alignment. Principal component analysis 149 150 was then performed to generate independent orthogonal modes of variation, describing in descending order of percentage variation standardised to a mean of 0 and standard deviation 151 of 1. Eight modes (SM1 to SM8) were identified which each accounted for >1% spine shape 152 variation ranging from SM1 which accounted for 53.0% of variation to SM8 which accounted 153 for 1.2%; in total these eight modes accounted for 84.9% of the total variance ¹⁶. Lumbar 154 lordosis angle was measured using the two-line Cobb method ¹⁷ between the inferior endplate 155 of L4 and the superior endplate of T12. For each endplate we used the statistical shape model 156 point co-ordinates for the vertebral 'corners' to plot a line and calculate the slope of that line. 157 158 Using custom-written code in MATLAB (R2018a, The Mathworks, Natick, MA) the angle of intersection of the two lines was calculated in degrees for each image in the dataset. 159

160 Age at Onset of Independent Walking

161 The age in months at which their child first walked unaided was recalled by participants'

162 mothers during an assessment at age 2 years.

163 *Covariates*

Potential confounders and mediators of the main associations between walking age and each 164 spine shape mode were selected *a priori* based on existing literature ^{12; 16; 18}. The potential 165 confounders were birthweight, childhood socioeconomic position (SEP), adult SEP and 166 height, and the potential mediators were appendicular lean mass and appendicular fat mass. 167 Birthweight was extracted from medical records within a few days of birth, and 168 169 measurements to the nearest quarter-pound (113 g) were converted to kilograms. As indicators of socioeconomic position (SEP), father's occupation at age 4 years (or at age 11 170 171 or 15 if missing at age 4) and own occupation at age 53 years (or if not available, the most recent measure in adulthood) were both categorized into six groups (I [professional], II 172 [managerial and technical], IIINM [skilled non-manual], IIIM [skilled manual], IV [partly 173 skilled], and V [unskilled]) using the Registrar General's Social Classification ¹⁹. During the 174 CRF visit, height was measured to the nearest mm and recorded in cm, and appendicular lean 175 and fat mass in kilograms were estimated from total body DXA scans. 176

177 Statistical Analysis

We include 1327 participants (688 women) in our models; of the 1529 participants with spine 178 shape mode data, 106 had missing data on age of independent walking and a further 96 had 179 missing data on covariates. Complete case analysis was undertaken using the R statistical 180 environment (version 3.2.2, www.r-project.org). Associations between age at onset of 181 independent walking and each spine shape mode were assessed using multiple linear 182 regression models. There was no evidence of deviation from linearity when quadratic terms 183 were included, so walking age was modelled as a continuous linear variable. Walking 184 age*sex interactions were examined given previous findings of sex-specific associations of 185 walking age with bone outcomes 12 . Where sex interactions were identified (P < 0.1), 186 subsequent models were sex-stratified. Model 1 was adjusted for sex (unless sex-stratified) 187

and CRF location (as one CRF used a scanner with a fixed C-arm requiring participants to be
moved between scans). The impact of adjustment for each of the confounders and mediators
identified above was then examined in turn before all covariates were entered into a final
model (Model 2) simultaneously. Associations between walking age and lumbar lordosis
angle were assessed using the same model structures.

In addition to describing associations between walking age and individual mode scores, we wanted to examine how overall spine shape described by these modes varied between earlier and later walkers. Therefore, we combined mean mode scores for early walkers (defined as -2SD below the mean walking age (i.e. 9.0 months)) and late walkers (defined as +2SD above the mean walking age (i.e. 18.5 months)) for both women and men to generate mean spine shapes.

199 Sensitivity Analyses

Whilst the prevalence of radiographic spine osteoarthritis in the NSHD cohort is low, we
investigated whether there were any associations between walking age and osteoarthritis of
the spine at age 60-64. DXA images were graded using a validated atlas scoring system ²⁰,
with grades of 0-3 for each vertebra (T10-L4) summed to give a Total Lane Grade (TLG).
We also assessed associations between sitting (mean 6.5±1.4 months) and standing age (mean
11.4±2.1 months) obtained at the same maternal interview as walking age, and spine shape
modes using models described above.

207 **Results**

Characteristics of the participants in this study are detailed in Table 1 and spine shapes
described by each mode are presented in Supplementary Figure S-1. Scores for SM1, SM3
and SM8 were greater in women than men, whereas men had a higher score for SM6. Lumbar
lordosis angle was also greater in women than men.

Later age at onset of independent walking was weakly associated with greater SM1 scores in
Model 1 (regression coefficient 0.019, 95%CI -0.004 to 0.041), this association was
strengthened in fully-adjusted Model 2 (0.023, 95%CI 0.000-0.047). This suggests that
associations in Model 1 were obscured by negative confounding, although further analyses of
individual factors suggested that this was not attributable to any one single covariate (Table
217 2).

There was some evidence to suggest that later walking age was also weakly associated with greater SM6 scores in Model 1 (0.021, 95%CI -0.002 to 0.043); this association was similar in Model 2. Sex interactions were evident for SM3 in Model 1, with later walking age modestly associated with lower scores in men and higher scores in women. In Model 2, the interaction was stronger due to a strengthening of the negative association in males. There was no evidence of associations between walking age and SM 2, 4, 5, 7 or 8.

When taking findings for SM1, 3 and 6 together, in later walkers these modes describe greater lumbar and thoracic lordosis (SM1), and more uniform anterior-posterior vertebral body diameter relative to vertebral height throughout the spine (SM6). Sex interactions in SM3 indicated greater relative anterior-posterior vertebral size in late-walking men but not women. In support of features described by associations with SM1, walking age was also associated with greater lumbar angle corresponding to an increase in lordosis of 0.57° (95% CI 0.36° to 0.78°, P = 0.007) for every 1 SD (around two months) increase in walking age in

Model 2. Mean spine shapes generated for early and late-walking men and women are shownin Figure 1.

233 Sensitivity Analyses

Prevalence and severity of radiographic OA was low in this cohort; 301 individuals (23%) 234 had no evidence of degeneration (grade 0) at any vertebrae, and 898 individuals (68%) had 235 only mild degeneration (grade ≤ 1) at any vertebrae. No associations were observed between 236 walking age and TLG when the latter was modelled either as a continuous or dichotomous 237 variable (based on a TLG > 0 as cut-off) (P > 0.4 in both cases). Sitting age was weakly 238 positively associated with walking age ($r^2 = 0.18$, P < 0.001), and was weakly negatively 239 associated with spine shape mode 5 only (Supplementary Table 1, P = 0.06). There was a 240 strong positive association between standing age and walking age ($r^2 = 0.64$, P < 0.001). 241 Standing age was weakly positively associated with SM1 scores in Model 2 only (regression 242 coefficient 0.022, 95%CI -0.004 to 0.047), and with SM6 scores in both models. There was 243 evidence of sex interactions for SM3 with later standing age associated with lower scores in 244 men and higher scores in women, and for SM5 with later standing age associated with lower 245 scores in women only 246

247 **Discussion**

The aim of this study was to investigate associations between early life motor development and components of spine shape described by statistical shape models in early old age. In fully-adjusted models, later walking age was modestly associated with greater lordosis and more even vertebral size along the spine, and with greater relative vertebral size in men but not women. Similar associations were observed for later standing age but not for sitting age.

253 Comparison with previous findings

254 To our knowledge, this is the first study to investigate associations between early life motor development and spine shape in adulthood. Previous studies have shown associations 255 between attainment of motor development milestones and lordosis in early childhood¹. 256 257 Impaired or delayed motor development has previously been shown to be associated with spine development. Children with cerebral palsy are at risk of developing excessive lordosis 258 of the lumbar spine²¹, similar to observations of greater lordosis in late walkers in this study. 259 We have previously reported associations between walking age and spine area in males only 260 in this cohort ¹², which would initially seem to contradict findings of smaller vertebral size in 261 262 males in this study. However, as can be seen in Figure 1 and Supplementary Figure S-1 these differences are subtle and unlikely to have a substantial influence on overall vertebral area. 263 More importantly, images are scaled prior to generation of shape modes thereby removing 264 265 differences in overall size. Greater vertebral size in SM6 therefore represents the relative anterior-posterior to cranial-caudal proportions of vertebral bodies, which could result from 266 narrower and/or taller vertebrae. As walking age is positively associated with height in this 267 268 cohort, greater vertebral height could explain these apparently conflicting associations. Similar associations to those observed between walking age and spine shape were observed 269 for standing age, which was highly correlated with walking age, but there was little evidence 270

of associations between sitting age and spine shape. This is similar to findings of previous

studies in younger children, where walking age but not crawling or standing age was

273 associated with tibia mass and geometry 14 .

274 Possible explanation of findings

Walking is associated with lumbosacral loads of around 1.6 times bodyweight, which is 60% 275 greater than those achieved during standing¹¹. Therefore, attainment of independent walking 276 exposes the spine to large increases in loading at a time of rapid development. The smaller 277 loads associated with static activities may explain the lack of association between sitting age 278 and spine shape. The importance of larger locomotory loads for spine health is supported by 279 the large bone losses associated with loss of ambulation such as in long-term spaceflight ²². 280 Initially, vertebral size is similar throughout the spine ²³ but differences between lumbar and 281 thoracic vertebrae emerge around onset of walking ⁴. Reduced variation in relative vertebral 282 size in late walkers may therefore reflect reduced loading variation throughout the spine 283 during this period. Greater back extensor muscle size has previously been associated with 284 greater lumbar lordosis ²⁴, but there was little evidence of associations between lean mass and 285 spine shape modes in this study, and adjustment for lean mass did not attenuate association 286 between walking age and spine shape modes. 287

288 Significance and implications

Greater lumbar lordosis, described by SM1 and the lumbar angle, identified in late walkers in
the current study have been shown to be associated with spondylolysis and isthmic
spondylolisthesis in other studies ²⁵. A recent study also found that smaller relative anteriorposterior size, observed in late-walking women in this study, was also associated with
spondylolysis ²⁶. A number of clinical groups with delayed ambulation including Down
syndrome ²⁷, osteogenesis imperfecta ²⁸ and dyskinetic cerebral palsy ²⁹ have increased risk

295 of spondylolysis and/or isthmic spondylolisthesis, therefore motor deficits in early life may contribute to these problems. If delayed motor development is shown to influence 296 spondylolysis risk in late walkers, there may be interventional opportunities to minimise 297 298 these effects. Parent-led walking training can lead to earlier walking onset in the general population ³⁰ and clinical cohorts such as children with Down syndrome ³¹. In children with 299 myelomeningocele, these interventions appear effective in reducing deficits in bone mass ³². 300 Whilst the effects of walking training on joint shape are unknown, future interventional 301 studies investigating these effects could establish motor development as a modifiable factor 302 303 influencing lifelong spine health. There is conflicting evidence as to whether lumbar lordosis is associated with other types of lower back pain and osteoarthritis ²⁵, but these associations 304 were not found in the cohort examined in this study ³³. We found no evidence of associations 305 between walking age and radiographic OA, although the incidence of OA was very low in 306 307 this cohort. In addition, to our knowledge there have been no previous investigations of associations between the reduced curvature in the lower thoracic region observed in late 308 309 walkers in this study and clinical outcomes. Previous observations of lower bone mass in male late walkers in this cohort ¹² suggest an increased risk of fracture, but it is not clear 310 whether spine shape features identified in the current study could influence this risk. Future 311 studies examining associations between motor development and spine pathologies could help 312 reveal the clinical consequences of delayed attainment of motor milestones. 313

314 *Strengths and weaknesses*

The cohort examined in this study is broadly representative of the British-born population of the same age ³⁴, which allows us to generalise these results to this population. In addition, the cohort have been followed for over six decades since birth, allowing us to adjust for potential confounders which were obtained prospectively. Most importantly, details of early life motor development were obtained six decades previously by maternal recall at two years, which has

been shown to be highly reliable ^{35; 36}. Previous studies have shown that associations between 320 early life motor development and adolescent bone outcomes are mediated by childhood 321 physical activity ¹². Due to limited information on physical activity in early life we were 322 323 unable to explore this potential mediating pathway, although walking age is not associated with adult physical activity in this cohort ³⁷. As an observational study we cannot attribute 324 causality, and residual confounding and bias due to drop out and missing data in this cohort ³⁸ 325 may have influenced the results. Caution is required in interpreting these findings and 326 considering their implications, because evidence suggests that some of the associations we 327 328 have observed in this study are modest. In addition, the overall shape differences between early and late walkers described by statistical shape models are quite subtle. However, even 329 these small differences (0.2-0.4SD) are similar to those identified between individuals with 330 and without long-term back pain in the same cohort ³³ suggesting that they may prove to be 331 clinically relevant with increasing age. Spine images were taken with participants in a supine 332 position with hips and knees flexed which would result in differences in spine morphology 333 compared to standing. However, we have shown previously that inter-individual variation in 334 spine shape is preserved throughout a full range of extension to flexion and in a range of 335 postures ^{39; 40} therefore the current results likely reflect spine shape variation independent of 336 position. In addition, we could only measure down to inferior endplate of vertebra L4 as the 337 inferior endplate of vertebra L5 was not consistently visible, so measures of lumbar angle 338 339 from T12 to L4 are surrogate measures of the full lumbar lordosis angle.

340 *Conclusions*

Later age at onset of independent walking in early childhood is modestly associated with features of spine shape in early old age, namely with greater lordosis and less variation in vertebral size along the spine, and relative vertebral size is greater in male later walkers but not females. These associations were also observed with standing but not sitting age and were

345 independent of a number of potential confounders and mediators, which suggests that they could result from altered mechanical loading during a key phase of growth in early 346 childhood. Clinically, greater lumbar lordosis and smaller vertebral size are associated with 347 348 spondylolysis and isthmic spondylolisthesis and a number of clinical populations with delayed motor development have greater incidence of these conditions. Early life motor 349 development, in particular walking onset age, appears to have a small persisting effect on 350 features of spine morphology with clinical relevance throughout life. Given that training 351 interventions can promote earlier walking onset, age at onset of independent walking may 352 represent a novel modifiable factor to improve spine development particularly in populations 353 in which delayed motor development and spine problems are common. 354

355

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371 Data used in this publication are available to bona fide researchers upon request to the NSHD

372 Data Sharing Committee via a standard application procedure. Further details can be found at

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Variable	Women (n=688)		Men (n=639)		Sex difference	
	Mean	SD	Mean	SD	P-value	
Walking Age (mo	13.7	2.4	13.7	2.3	0.6	
Birthweight (k	3.39	0.63	3.45	0.57	0.05	
	n	%	n	%		
	Ι	51	7.4%	58	9.1%	
	II	158	23.0%	141	22.1%	
Father's	IIINM	130	18.9%	125	19.6%	0.72
(age 4y)	IIIM	195	28.3%	184	28.8%	0.72
(age +y)	IV	122	17.7%	97	15.2%	
	V	32	4.7%	34	5.3%	
	Ι	14	2.0%	86	13.5%	
	II	293	42.6%	303	47.4%	
Own Occupational	IIINM	246	35.8%	71	11.1%	<0.01
Class (age 53y)	IIIM	39	5.7%	136	21.3%	<0.01
	IV	73	10.6%	35	5.5%	
	V	23	3.3%	8	1.3%	
N	lusculosk	celetal as	sessments	at 60-64	у	
	Mean	SD	Mean	SD		
Age at time of asses (y)	63.2	1.1	63.1	1.2	0.09	
Height (m)	1.62	0.06	1.75	0.06	< 0.01	
Weight (kg)		71.4	12.3	84.9	12.6	< 0.01
Appendicular Lean (kg)	16.1	2.4	24.6	3.3	< 0.01	
Appendicular Fat Ma	14.3	4.1	10.0	2.8	< 0.01	
Lumbar lordosis an	13.1	7.7	11.5	7.2	< 0.01	
	SM1	0.07	1.02	-0.05	0.96	0.03
	SM2	-0.03	0.99	0	1	0.62
	SM3	0.47	0.78	-0.49	0.98	< 0.01
Spine Shape Mode	SM4	-0.05	1.02	0.03	0.98	0.12
(SM) Scores	SM5	-0.04	0.97	0.05	1	0.1
	SM6	-0.18	0.98	0.19	0.96	< 0.01
	SM7	-0.01	0.96	0.05	1.03	0.28
	SM8	0.23	0.92	-0.27	1	< 0.01

477 Table 1. Characteristics of the MRC National Survey of Health and Development stratified

478 by sex (sample restricted to those with complete spine shape mode data and covariates).

Table 2. Associations between age at onset of independent walking and spine shape mode outcomes in the MRC National Survey of Health and Development. Regression coefficients are the difference in mean SM score per 1 month increase in walking age. Where sex interactions were evident (*P* for interaction < 0.1), sex-specific associations are presented.

Mode	Group	Model	Regression coefficient	95% CI		Р	Sex Interaction P
SM1	Combined	1	0.019	-0.004	0.041	0.1	0.28
		2	0.023	0.000	0.047	0.05	0.36
SMO	Combined	1	-0.002	-0.025	0.021	0.88	0.76
51112		2	-0.014	-0.037	0.010	0.25	0.79
	Men	1	-0.024	-0.056	0.008	0.15	0.03
SM2	Women		0.021	-0.004	0.046	0.09	0.03
51115	Men	2	-0.043	-0.075	-0.010	0.01	< 0.01
	Women		0.018	-0.007	0.043	0.17	
SM4	Combined	1	-0.013	-0.037	0.010	0.25	0.14
5114		2	-0.006	-0.030	0.017	0.6	0.14
SM5	Combined	1	-0.011	-0.034	0.012	0.35	0.34
51115		2	-0.017	-0.040	0.007	0.17	0.45
SM6	Combined	1	0.021	-0.002	0.043	0.07	0.94
SIVIO		2	0.021	-0.002	0.044	0.07	0.91
SM7	Combined	1	0.007	-0.016	0.030	0.54	0.56
SIVI /		2	0.006	-0.018	0.030	0.63	0.39
SMO	Combined	1	0.002	-0.020	0.024	0.84	0.19
51110	Combined	2	0.010	-0.012	0.033	0.36	0.24

Footnote: Model 1 adjusted for Sex (if men and women are combined) and Clinic, Model 2:
Model 1 + Birthweight + Father's occupational Class + Adult Occupational Class + Height +
Appendicular Fat Mass + Appendicular Lean Mass. Only results from basic and fully-adjusted
models are presented for brevity. When each set of covariates were adjusted for in turn there
was no evidence that any one specific set of factors was responsible for the attenuations
observed between the models shown here.

- 490 Figure 1. Mean spine shapes described by statistical shape models in early (-2SD of the mean
- 491 age) and late-walking (+2SD of the mean age) men and women.
- 492 Footnote: The mean age of walking in this cohort was 13.7±2.3 months with no sex
- 493 difference. Therefore, early and late walking as described above corresponded to walking at
- 494 9.0 months and walking at 18.5 months respectively.