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1 **Life course longitudinal growth and risk of knee osteoarthritis at age 53 years: evidence**
2 **from the 1946 British birth cohort study**

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22 **Running headline:** Life course growth and knee osteoarthritis

23

24 **Abstract**

25 *Objective*

26 To examine the relationship between height gain across childhood and adolescence with knee
27 osteoarthritis in the MRC National Survey of Health and Development (NSHD).

28 *Materials and methods*

29 Data are from 3035 male and female participants of the NSHD. Height was measured at ages
30 2, 4, 6, 7, 11 and 15 years, and self-reported at ages 20 years. Associations between (i) height
31 at each age (ii) height gain during specific life periods (iii) Super-Imposition by Translation
32 And Rotation (SITAR) growth curve variables of height size, tempo and velocity, and knee
33 osteoarthritis at 53 years were tested.

34 *Results*

35 In sex-adjusted models, estimated associations between taller height and decreased odds of
36 knee osteoarthritis at age 53 years were small at all ages - the largest associations were an OR
37 of knee osteoarthritis of 0.9 per 5cm increase in height at age 4, (95% CI 0.7-1.1) and an OR
38 of 0.9 per 5cm increase in height, (95% CI 0.8-1.0) at age 6. No associations were found
39 between height gain during specific life periods or the SITAR growth curve variables and odds
40 of knee osteoarthritis.

41 *Conclusions*

42 There was limited evidence to suggest that taller height in childhood is associated with
43 decreased odds of knee osteoarthritis at age 53 years in this cohort. This work enhances our
44 understanding of osteoarthritis predisposition and the contribution of life course height to this.

45 **Key words:** osteoarthritis, SITAR, growth, life course, birth cohort

46

47 **Introduction**

48 Joint health is reliant upon the preservation of the articular cartilage and, its degradation is one
49 of the main hallmarks of the degenerative joint disease osteoarthritis. Osteoarthritis,
50 characterised by articular cartilage loss, subchondral bone thickening and osteophyte
51 formation, is a major health care burden throughout the world. It is estimated that worldwide
52 at least 10% of men and 18% of women aged over 60 years have symptomatic osteoarthritis.
53 Osteoarthritis causes much pain and disability, and yet its underlying molecular mechanisms
54 are not fully understood. Indeed, even the precipitating pathology remains a matter of debate
55 and we are still unable to identify those at most risk of developing the disease.

56 Our previous work in a spontaneous murine model of ageing-related osteoarthritis, the STR/Ort
57 mouse, revealed accelerated long bone growth, increased growth plate chondrocyte
58 differentiation, and widespread abnormal expression of chondrocyte markers in osteoarthritis-
59 prone mice.[1] Furthermore, we revealed enriched growth plate bridging, indicative of
60 advanced and thus premature growth plate closure, in these mice.[1] Together this suggested
61 that osteoarthritis development is associated with an accelerated growth phenotype and
62 advanced pubertal onset.

63 Consistent with this finding, canine hip dysplasia (a hereditary predisposition to degenerative
64 osteoarthritis) is more common in certain breeds, in particular larger breeds which tend to grow
65 more rapidly.[2] However, associations between lifetime linear growth, i.e. height gain during
66 specific life periods up to the attainment of adult height, and knee osteoarthritis development
67 in human populations have, to our knowledge, not yet been studied. Previous epidemiological
68 analyses of the Hertfordshire Cohort Study and the Medical Research Council National Survey
69 of Health and Development (MRC NSHD) have found associations between low birth weight
70 and high body mass index across life and increased risk of developing osteoarthritis.[3,4] This
71 therefore suggests that life course size may predispose to osteoarthritis later in life.

72 Herein, we use one of these studies, the MRC NSHD, to examine the relationship between
73 childhood and adolescent height growth and knee osteoarthritis at 53 years. Our aims were to:
74 (1) test associations between height at different ages in early life and knee osteoarthritis in
75 adulthood; (2) assess how patterns of height growth during childhood and adolescence are
76 associated with knee osteoarthritis.

77 **Method**

78 *Study sample*

79 The MRC NSHD is a birth cohort study, which includes a nationally representative sample of
80 2815 men and 2547 women born in England, Scotland, and Wales during 1 week in March
81 1946. The cohort has been followed prospectively across life with outcome data for these
82 analyses drawn from a data collection in 1999, when participants were 53 years old.[5] At 53,
83 3035 participants (1472 men, 1563 women) participated, the majority (n=2989) were
84 interviewed and examined in their own homes by research nurses with others completing a
85 postal questionnaire (n=46). The responding sample at age 53 is in most respects representative
86 of the national population of a similar age.[6] The data collection at age 53 years received
87 ethical approval from the North Thames Multi-centre Research Ethics Committee, and written
88 informed consent was given by all respondents.

89 *Outcome – knee osteoarthritis*

90 During the home visit at age 53 years, trained nurses conducted clinical examinations of study
91 participants' knees.[3] Based on these examinations, the American College of Rheumatology
92 criteria for the clinical diagnosis of idiopathic knee osteoarthritis were used to identify those
93 with knee pain in either knee on most days for at least 1 month in the last year prior to the
94 examination in 1999, and at least two of the following: stiffness, crepitus, bony tenderness and
95 bony enlargement.[7]

96 *Height variables*

97 Height was measured by nurses using standardised protocols at ages 2, 4, 7, 11, and 15 years,
98 and self-reported at age 20. Individual patterns of height growth during puberty were estimated
99 using the SuperImposition by Translation and Rotation (SITAR) model of growth curve
100 analysis, as previously described by Cole et al.[9,10] The SITAR model estimates the mean
101 growth curve and three individual-specific parameters: size (reflecting differences in mean
102 height), tempo (reflecting differences in the timing of the pubertal growth spurt) and velocity
103 (reflecting differences in the duration of the growth spurt), each expressed relative to the mean
104 curve.

105 *Covariates*

106 Factors that may potentially confound the main associations of interest were selected *a priori*
107 based on previous findings in the literature.[3] These were birth weight, father's occupational
108 class in childhood (categorised as non-manual vs manual) and sporting ability at 13 years
109 (categorised as above average, average, or below average according to teacher reports of their
110 sporting ability). [11] [12] Weight was measured by nurses using standardised protocols at ages
111 2, 4, 7, 11, and 15 years, and self-reported at age 20.

112 *Statistical analysis*

113 To address the two main aims, we used logistic regression models to test associations between:
114 (1) height at each age (aim 1); (2) conditional changes in height during specific life periods
115 (early childhood: 2–4 years; late childhood: 4-7 years; childhood to adolescence: 7–15 years;
116 adolescence to young adulthood: 15–20 years) (aim 2) and; (3) each SITAR height variable
117 (aim 2) and odds ratios (ORs) of knee osteoarthritis. In models to address aim 2, we generated
118 conditional changes in height by regressing each height measure on the earlier height measure
119 for each sex and calculating the residuals.[13] The residuals were standardized (to have mean

120 0 and SD of 1) to ensure their comparability and these were included as the main independent
121 variables. In initial models, we formally tested for interactions between sex and each main
122 independent variable and where no evidence of interaction was found based on statistical
123 significance ($P < 0.05$), models were fitted with men and women combined and adjusted for sex.
124 We also tested for deviations from linearity by including quadratic terms, but there was no
125 evidence of this. In each set of models we first adjusted for sex (where there was no evidence
126 of interaction), before then also adjusting for early life factors (birth weight + sporting ability
127 at 13 years + father's occupational class in childhood). In our final model, we adjusted for
128 weight at each age for aim 1, conditional weight gain (aim 2) and the SITAR weight variables
129 (aim 2) to assess the contribution of weight during growth. To maximise statistical power, each
130 set of models were run on the sample with valid data for the outcome, the specified independent
131 variable and the covariates for that analysis. Data were analysed using Stata statistical software
132 (version SE 14.2).

133 *Sensitivity analyses*

134 To assess the potential impact of having to exclude those participants lost to follow-up before
135 age 53 years and with missing data, comparisons were made between those included and those
136 excluded from the main analyses. In addition, the sex-adjusted analyses were rerun in the
137 maximum available samples including all available participants rather than being restricted to
138 the sample with valid data on all measures. To assess the influence of potential secondary
139 osteoarthritis on our findings the main analyses were repeated after excluding those participants
140 with knee osteoarthritis who had reported ever seeing a doctor about an injury to the knee in
141 which osteoarthritis was diagnosed. Finally, sex stratified analyses were run.

142 **Results**

143 Cohort characteristics

144 A total of 1437 men and 1478 women had complete data on the SITAR parameters of height
145 and knee osteoarthritis. Descriptive statistics are described in Table 1. In this sample, the
146 percentage of individuals with knee osteoarthritis at 53 years of age was higher in women
147 (13.1%) than in men (7.3%).

148 Life course height and knee osteoarthritis

149 In sex-adjusted models, estimated associations between taller height and decreased odds of
150 knee osteoarthritis at age 53 years were small at all ages. For example, the largest associations
151 were an OR of knee osteoarthritis of 0.9 per 5cm increase in height at age 4, (95% CI 0.7 to
152 1.1 (Model 1; Table 2) and an OR of 0.9 per 5cm increase in height, (95% CI 0.8 to 1.0) at age
153 6 (Table 2). With adjustment for early life confounding factors (Model 2) and weight (Model
154 3), these estimates decreased further (Table 2).

155 Height growth and knee osteoarthritis

156 No associations were found between height gains during any of the four periods assessed and
157 odds of knee osteoarthritis at 53 years (Table 3). There was also no evidence of associations
158 between height size, tempo or velocity (SITAR variables) and knee osteoarthritis at 53 years
159 in models adjusted for sex and early life confounding factors (Models 1 & 2; Table 4).
160 Increased SITAR height size and height tempo were marginally associated with lower odds of
161 knee osteoarthritis at 53 years after additional adjustment SITAR weight size (Table 4).

162 Sensitivity analyses

163 Comparison of the characteristics of those individuals with complete data, vs those excluded
164 are described in Tables S1.1 & S1.2. We found that higher proportions of those included were
165 female (50.7% vs 49.3%; $p < 0.001$; Tables S1.1 & S1.2). No significant differences were
166 observed in height between ages 2 – 15 years but at age 20, those included reported shorter
167 heights (169.5 cm vs 171.0 cm) and lower weights (64.0 kg vs 65.5 kg) than those excluded

168 (Table S1.1). When sex adjusted models were rerun on the maximum available samples
169 including all available participants (Tables S2.1 – S2.3), there were no substantive differences
170 in findings. When we excluded those participants with potential secondary knee osteoarthritis
171 from our analyses, there were no substantive differences in associations between height (Table
172 S3.1), conditional height gain (Table S3.2), or SITAR variables (Table S3.3) and primary knee
173 osteoarthritis at 53 years, compared with the main findings presented. Sex-stratified analyses
174 confirmed that there were consistent patterns of association in men and women (Tables S4.1 –
175 4.3).

176 **Discussion**

177 In this nationally representative British birth cohort study, associations between greater height
178 at ages 4 and 6 years and marginally lower odds knee osteoarthritis at age 53 were observed in
179 sex-adjusted models, but these were attenuated after adjustment for early life factors. No
180 associations were observed between height changes during early childhood, late childhood,
181 childhood to adolescence or adolescence to young adulthood or SITAR parameters and knee
182 osteoarthritis.

183 A major strength of our study is the availability of multiple prospectively ascertained
184 measurements of height throughout childhood and adolescence in the NSHD, together with the
185 already derived SITAR variables and measures of knee osteoarthritis in a relatively large
186 sample of people in midlife.[9] This provided a unique opportunity to investigate the
187 associations between life course longitudinal growth and knee osteoarthritis at 53 years of age.
188 Here we used two approaches to model growth and understand its relation to knee osteoarthritis
189 in later life. Firstly, we used a conditional change approach to enable us to determine whether
190 there are specific sensitive period/s of growth which may be associated with knee osteoarthritis.
191 This can be interpreted as the change in height size above or below that expected given earlier
192 height, and thus is useful in identifying accelerated or restricted growth.[14] We next chose the

193 SITAR growth curve model since it was previously shown to effectively summarise pubertal
194 growth based on three parameters of size, velocity and tempo.[9,10] A limitation of this
195 approach is the use of multiple models which increases the chance of a type I error. Also, as
196 in any longitudinal study, it is important to consider loss to follow-up over time and the impact
197 of this on research findings. Despite losses to follow-up between birth and age 53 years, which
198 may have introduced bias, comparisons with census data suggest that the respondent sample at
199 age 53 were still representative of the general population born in the UK at a similar time in
200 most respects.[24]

201 Our previous work explored associations between growth dynamics and osteoarthritis onset in
202 a spontaneous murine model of osteoarthritis, the STR/Ort mouse.[1] We revealed accelerated
203 long bone growth, aberrant expression of growth plate markers and enriched growth plate
204 bridging, indicative of advanced and thus premature growth cessation, in these osteoarthritis-
205 prone mice.[1] Together this suggested that these accelerated growth dynamics in young
206 osteoarthritis-prone mice may underpin their osteoarthritis onset. However, whether these
207 observations are unique to osteoarthritis in the STR/Ort mouse or are characteristic of human
208 osteoarthritis in general had yet to be established. This study suggests that in the NSHD,
209 associations between greater gains in height, indicative of accelerated growth, are not
210 associated with increased odds of knee osteoarthritis. Rather, the modest associations found
211 suggest the opposite. It is however important to note that this was examined in midlife when
212 the cohort are still relatively young, and osteoarthritis prevalence (7.3% in men; 13.1% in
213 women) is lower than that seen currently in primary care at this age. It would therefore be of
214 interest to further examine these potential associations in older individuals.

215 Primary osteoarthritis is described as naturally occurring or ageing-related osteoarthritis, while
216 secondary osteoarthritis is associated with other causes including trauma. Our previous
217 findings in the STR/Ort mouse examined primary murine osteoarthritis [1] and therefore to

218 examine the influence of secondary knee osteoarthritis on the patterns of height growth in the
219 NSHD, we ran a sensitivity analysis in which we excluded individuals who had reported
220 consulting a Doctor about a knee injury. However, whilst we found no substantive differences
221 in findings, this highlights the need to examine the risk of osteoarthritis in aged individuals
222 where primary knee osteoarthritis is more prevalent.

223 Our study extends a previous study examining this British birth cohort in which prolonged
224 exposure to high BMI through adulthood increased risk of development of knee osteoarthritis
225 at age 53.[3] This is consistent with our sensitivity analyses in which adjustment for weight
226 strengthened the associations between SITAR height size and odds of knee osteoarthritis. Wills
227 et al., also found that BMI increases from childhood to adolescence (7–15 years) were
228 positively associated with knee osteoarthritis, however this was in women only.[3] In our
229 analyses, we found no evidence of differences in association by sex. We did find that in our
230 cohort with complete data, women had a higher prevalence of knee osteoarthritis, similar to
231 that reported previously in the NSHD, and in primary care.[3,15] Wills et al., concluded that
232 the excessive weight during this period may result in altered mechanical loading to the knee
233 joint. Similarly, it is likely that periods of accelerated growth will also impact on the
234 biomechanics of the joint. The shape of the hip joint is largely determined in childhood, and
235 previous studies have identified that in the NSHD, this is associated with (i) age of onset of
236 walking in infancy [16] (ii) higher BMI at all ages and greater gains in BMI [17] and (iii)
237 height, weight, BMI and BMD at ages 60-64 years.[18] Similarly, in the Avon Longitudinal
238 Study of Parents and Children (ALSPAC) cohort, hip shape in perimenopausal women is
239 associated with hip osteoarthritis susceptibility loci and may contribute to hip osteoarthritis
240 later in life.[19] Recent evidence in the ALSPAC cohort has also identified pubertal timing, as
241 reflected by height tempo, to be associated with hip shape.[20] Further, in the UK Biobank,

242 early menarche is associated with higher risk for osteoarthritis.[21] However these associations
243 were not observed in this study.

244 In conclusion, in this relatively large population-based cohort study, there was limited evidence
245 to suggest that height in childhood is associated with odds of knee osteoarthritis at age 53 years.
246 Further, there were no associations with height gain during specific periods of growth, or with
247 the SITAR height growth variables. This work enhances our understanding of osteoarthritis
248 predisposition and the contribution of life course height to this.

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253 the preparation of this manuscript.

254 Data used in this publication are available to bona fide researchers upon request to the NSHD
255 Data Sharing Committee via a standard application procedure. Further details can be found at
256 <http://www.nshd.mrc.ac.uk/data>. doi: 10.5522/NSHD/Q101

257 **Author contributions**

258 All authors contributed to the conception and design of the study, or acquisition of data, or
259 analysis and interpretation of data; drafting the article or revising it critically for important
260 intellectual content and the final approval of the version to be submitted. KS
261 (k.staines@brighton.ac.uk) takes responsibility for the integrity of the work as a whole, from
262 inception to finished article.

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267 manuscript for publication.

268 **Conflict of interest**

269 There are no conflicts of interest.

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	Men			Women		
	N	Mean	SD	n	Mean	SD
Height 2 years (cm)	1211	85.91	5.24	1197	84.72	4.57
Height 4 years (cm)	1288	103.51	5.10	1307	102.84	5.05
Height 6 years (cm)	1238	114.46	5.25	1255	113.74	5.26
Height 7 years (cm)	1249	120.35	5.65	1303	119.65	5.50
Height 11 years (cm)	1230	140.62	6.73	1257	141.16	6.94
Height 15 years (cm)	1135	162.04	8.86	1156	158.65	6.22
Height 20 years (cm)	1155	176.76	6.72	1231	162.62	6.24
Weight 2 years (kg)	1225	13.22	1.46	1244	12.61	1.49
Weight 4 years (kg)	1313	17.50	2.12	1338	17.00	2.16
Weight 6 years (kg)	1232	20.87	2.54	1267	20.34	2.61
Weight 7 years (kg)	1203	23.05	2.95	1257	22.56	3.17
Weight 11 years (kg)	1221	34.28	5.96	1247	34.98	6.81
Weight 15 years (kg)	1135	51.74	9.36	1151	51.84	8.28
Weight 20 years (kg)	1155	70.59	9.27	1229	57.81	8.19
Birthweight (kg)	1432	3.46	0.53	1473	3.32	0.48
	N	%		n	%	
Knee osteoarthritis at 53 years:	105	7.31		193	13.06	
Sporting ability at 13 years:	Above average	235	18.98	220	17.31	
	Average	793	64.05	902	70.97	
	Below average	210	16.96	149	11.72	
Father's occupational class in childhood:	Manual	605	43.71	600	42.43	
	Non-manual	779	56.29	814	57.57	

360 **Table 1:** Characteristics of the sample from the MRC National Survey of Health and Development with
 361 complete data on the SITAR height parameters and the outcome, knee osteoarthritis.

362

Height (per 5cm)	n	Model	Odds ratio	95% CI	
2 years	1986	1	0.96	0.82	1.12
		2	0.98	0.84	1.14
		3	1.01	0.85	1.20
4 years	2211	1	0.85	0.74	0.98
		2	0.87	0.75	1.01
		3	0.88	0.74	1.04
6 years	2116	1	0.89	0.78	1.02
		2	0.91	0.79	1.05
		3	0.88	0.72	1.08
7 years	2085	1	0.98	0.88	1.09
		2	1.01	0.91	1.12
		3	1.02	0.89	1.18
11 years	2259	1	0.99	0.97	1.01
		2	1.00	0.98	1.02
		3	0.99	0.96	1.01

15 years	2102	1	0.96	0.87	1.06
		2	0.98	0.89	1.09
		3	0.90	0.79	1.02
20 years	2082	1	0.93	0.83	1.04
		2	0.95	0.85	1.07
		3	0.88	0.77	1.00

363 **Table 2:** Associations between height (per 5cm) at different ages throughout childhood, adolescence
364 and young adulthood and odds ratios of knee osteoarthritis at age 53 years. Each set of models were
365 run on the sample with valid data for knee osteoarthritis, height at the specific age and the confounders.
366 Logistic regression Model 1: adjusted for sex; Model 2: further adjusted for birth weight, sporting
367 ability and Father's occupational class in childhood; Model 3: further adjusted for weight at each age.
368 Sex interactions: 2 years – $p=0.7$; 4 years – $p=0.7$; 6 years – $p=1.0$; 7 years – $p=0.8$; 11 years – $p=0.7$;
369 15 years – 0.8 ; 20 years – $p=0.09$.

370

Conditional change	n	Model	Odds ratio	95% CI	
2 - 4 years	1876	1	0.91	0.78	1.07
		2	0.94	0.80	1.10
		3	0.91	0.77	1.08
4 - 7 years	1689	1	0.94	0.80	1.10
		2	0.95	0.81	1.11
		3	0.95	0.80	1.13
7 - 15 years	1710	1	1.09	0.93	1.30
		2	1.09	0.93	1.28
		3	0.99	0.83	1.18
15 - 20 years	1611	1	1.05	0.89	1.23
		2	1.05	0.90	1.24
		3	0.99	0.84	1.17

371 **Table 3:** Associations of conditional height gain (per standard deviation) during different periods of
372 growth (early childhood: 2–4 years; late childhood: 4-7 years; childhood to adolescence: 7–15 years;
373 adolescence to young adulthood: 15–20 years) with knee osteoarthritis at 53 years. Each set of models
374 were run on the sample with valid data for knee osteoarthritis, conditional height gain during each life
375 period, and the confounders. Logistic regression Model 1: adjusted for sex; Model 2: further adjusted
376 for birth weight, sporting ability and Father's occupational class in childhood; Model 3: further
377 adjusted for weight at each age. Sex interactions: 2-4 years – $p=0.2$; 4-7 years – $p=0.6$; 7-15 years –
378 $p=0.3$; 15-20 years – $p=0.1$.

379

SITAR variable (n=2470)	Model	Odds ratio	95% CI	
Size (cm)	1	0.98	0.96	1.01
	2	0.99	0.97	1.01
	3	0.96	0.93	0.99
Tempo (%)	1	1.00	0.98	1.02
	2	0.99	0.98	1.01
	3	0.97	0.95	0.99
Velocity (%)	1	1.00	0.99	1.01
	2	1.00	0.99	1.02
	3	0.99	0.98	1.01

380 **Table 4:** Associations between each parameter of the SITAR model of growth curve analysis (height
381 size, tempo and velocity) and odds of knee osteoarthritis. Each set of models were run on the sample
382 with valid data for knee osteoarthritis, each SITAR variable and the confounders. Logistic regression
383 Model 1: adjusted for sex; Model 2: further adjusted for birth weight, sporting ability and Father's
384 occupational class in childhood; Model 3: further adjusted for weight at each age. Sex interactions:
385 size – $p=0.5$; tempo – $p=0.8$; velocity – $p=0.8$.