

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  
40 odds 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  
45 this.

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

47

48 **Introduction**

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

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

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

72 developing osteoarthritis.[3,4] This therefore suggests that life course size may predispose to  
73 osteoarthritis later in life.

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

## 79 **Method**

### 80 *Study sample*

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

### 91 *Outcome – knee osteoarthritis*

92 During the home visit at age 53 years, trained nurses conducted clinical examinations of  
93 study participants' knees.[3] Based on these examinations, the American College of  
94 Rheumatology criteria for the clinical diagnosis of idiopathic knee osteoarthritis were used to  
95 identify those with knee pain in either knee on most days for at least 1 month in the last year

96 prior to the examination in 1999, and at least two of the following: stiffness, crepitus, bony  
97 tenderness and bony enlargement.[7]

#### 98 *Height variables*

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

#### 107 *Covariates*

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

#### 114 *Statistical analysis*

115 To address the two main aims, we used logistic regression models to test associations  
116 between: (1) height at each age (aim 1); (2) conditional changes in height during specific life  
117 periods (early childhood: 2–4 years; late childhood: 4–7 years; childhood to adolescence: 7–  
118 15 years; adolescence to young adulthood: 15–20 years) (aim 2) and; (3) each SITAR height  
119 variable (aim 2) and odds ratios (ORs) of knee osteoarthritis. In models to address aim 2, we

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

### 135 *Sensitivity analyses*

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

## 145 **Results**

### 146 Cohort characteristics

147 A total of 1437 men and 1478 women had complete data on the SITAR parameters of height  
148 and knee osteoarthritis. Descriptive statistics are described in Table 1. In this sample, the  
149 percentage of individuals with knee osteoarthritis at 53 years of age was higher in women  
150 (13.1%) than in men (7.3%).

### 151 Life course height and knee osteoarthritis

152 In sex-adjusted models, estimated associations between taller height and decreased odds of  
153 knee osteoarthritis at age 53 years were small at all ages. For example, the largest  
154 associations were an OR of knee osteoarthritis of 0.9 per 5cm increase in height at age 4,  
155 (95% CI 0.7 to 1.1 (Model 1; Table 2) and an OR of 0.9 per 5cm increase in height, (95% CI  
156 0.8 to 1.0) at age 6 (Table 2). With adjustment for early life confounding factors (Model 2)  
157 and weight (Model 3), these estimates decreased further (Table 2).

### 158 Height growth and knee osteoarthritis

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

### 165 Sensitivity analyses

166 Comparison of the characteristics of those individuals with complete data, vs those excluded  
167 are described in Tables S1.1 & S1.2. We found that higher proportions of those included were  
168 female (50.7% vs 49.3%;  $p < 0.001$ ; Tables S1.1 & S1.2). No significant differences were

169 observed in height between ages 2 – 15 years but at age 20, those included reported shorter  
170 heights (169.5 cm vs 171.0 cm) and lower weights (64.0 kg vs 65.5 kg) than those excluded  
171 (Table S1.1). When sex adjusted models were rerun on the maximum available samples  
172 including all available participants (Tables S2.1 – S2.3), there were no substantive  
173 differences in findings. When we excluded those participants with potential secondary knee  
174 osteoarthritis from our analyses, there were no substantive differences in associations  
175 between height (Table S3.1), conditional height gain (Table S3.2), or SITAR variables (Table  
176 S3.3) and primary knee osteoarthritis at 53 years, compared with the main findings presented.  
177 Sex-stratified analyses confirmed that there were consistent patterns of association in men  
178 and women (Tables S4.1 – 4.3).

## 179 **Discussion**

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

186 A major strength of our study is the availability of multiple prospectively ascertained  
187 measurements of height throughout childhood and adolescence in the NSHD, together with  
188 the already derived SITAR variables and measures of knee osteoarthritis in a relatively large  
189 sample of people in midlife.[9] This provided a unique opportunity to investigate the  
190 associations between life course longitudinal growth and knee osteoarthritis at 53 years of  
191 age. Here we used two approaches to model growth and understand its relation to knee  
192 osteoarthritis in later life. Firstly, we used a conditional change approach to enable us to  
193 determine whether there are specific sensitive period/s of growth which may be associated



194 with knee osteoarthritis. This can be interpreted as the change in height size above or below  
195 that expected given earlier height, and thus is useful in identifying accelerated or restricted  
196 growth.[14] We next chose the SITAR growth curve model since it was previously shown to  
197 effectively summarise pubertal growth based on three parameters of size, velocity and  
198 tempo.[9,10] A limitation of this approach is the use of multiple models which increases the  
199 chance of a type I error. Also, as in any longitudinal study, it is important to consider loss to  
200 follow-up over time and the impact of this on research findings. Despite losses to follow-up  
201 between birth and age 53 years, which may have introduced bias, comparisons with census  
202 data suggest that the respondent sample at age 53 were still representative of the general  
203 population born in the UK at a similar time in most respects.[24]

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

218 Primary osteoarthritis is described as naturally occurring or ageing-related osteoarthritis,  
219 while secondary osteoarthritis is associated with other causes including trauma. Our previous  
220 findings in the STR/Ort mouse examined primary murine osteoarthritis [1] and therefore to  
221 examine the influence of secondary knee osteoarthritis on the patterns of height growth in the  
222 NSHD, we ran a sensitivity analysis in which we excluded individuals who had reported  
223 consulting a Doctor about a knee injury. However, whilst we found no substantive  
224 differences in findings, this highlights the need to examine the risk of osteoarthritis in aged  
225 individuals where primary knee osteoarthritis is more prevalent.

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

243 later in life.[19] Recent evidence in the ALSPAC cohort has also identified pubertal timing,  
244 as reflected by height tempo, to be associated with hip shape.[20] Further, in the UK  
245 Biobank, early menarche is associated with higher risk for osteoarthritis.[21] However these  
246 associations were not observed in this study.

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

## 252 **Acknowledgements**

253 The authors thank all the participants of the MRC National Survey of Health and  
254 Development and all staff involved in data collection and data entry. The authors would also  
255 like to thank Dr Alex Ireland (Manchester Metropolitan University, UK) for his insightful  
256 discussions during the preparation of this manuscript.

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

## 260 **Author contributions**

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

## 266 **Role of funding source**

267 The authors would like to acknowledge the Medical Research Council for funding to KS  
268 (MR/R022240/1). The funding source was not involved in the study design, collection,  
269 analysis and interpretation of data; in the writing of the manuscript; or in the decision to  
270 submit the manuscript for publication.

#### 271 **Conflict of interest**

272 There are no conflicts of interest.

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362 **Tables**

	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	

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

365

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

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

373

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

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

382

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

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

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