

Association of childhood adiposity measures with adulthood knee cartilage defects and bone marrow lesions: a 25-year cohort study

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Abstract

Objective To describe the associations between childhood adiposity measures and adulthood knee cartilage defects and bone marrow lesions (BMLs) measured 25 years later.

Methods 327 participants from the Australian Schools Health and Fitness Survey of 1985 (aged 7-15 years) were followed up 25 years later (aged 31-41 years). Childhood measures (weight, height and skinfolds) were collected in 1985. Body mass index (BMI), overweight status and fat mass were calculated. Participants underwent 1.5T knee magnetic resonance imaging (MRI) during 2008-2010, and cartilage defects and BMLs were scored from knee MRI scans. Log binomial regressions were used to examine the associations.

Results Among 327 participants (47.1% females), 21 (6.4%) were overweight in childhood. Childhood adiposity measures were associated with the increased risk of adulthood patellar cartilage defects (Weight relative risk (RR) 1.05/kg, 95% confidence interval (CI) 1.01 to 1.09; BMI 1.10/kg/m², 1.01 to 1.19; Overweight 2.22/yes, 1.21 to 4.08; fat mass 1.11/kg, 1.01 to 1.22), but not tibiofemoral cartilage defects. Childhood adiposity measures were not significantly associated with adulthood knee BMLs except for the association between childhood overweight status and adulthood patellar BMLs (RR 2.87/yes, 95% CI 1.10 to 7.53). These significant associations persisted after adjustment for corresponding adulthood adiposity measure.

Conclusion Childhood adiposity measures were associated with the increased risk of adulthood patellar cartilage defects and, to a lesser extent, BMLs, independent of adulthood adiposity measures. These results suggest that adiposity in childhood has long-term effects on patellar structural abnormalities in young adults.

Key words: Childhood; Adiposity; Cartilage defects; Bone marrow lesions

Introduction

Osteoarthritis (OA) is the most common joint disease, which is characterised by joint structural changes including cartilage degradation and subchondral bone abnormalities [1]. About 13% of women and 10% of men aged 60 years or older have symptomatic knee OA [2], with no approved disease modifying treatments available. Thus, identifying modifiable factors that can prevent knee OA is critically important.

Cartilage defects and bone marrow lesions (BMLs) are important imaging biomarkers for the incidence and progression of knee OA. They are common in both healthy individuals and symptomatic OA patients [3-5], and are associated with knee pain [6, 7] knee cartilage volume loss [8, 9] and subsequent knee replacement surgery [10, 11] in most studies, although not all associations were consistent [12-15]. However, little is known about factors that are associated with cartilage defects and BMLs in young adults, who may not yet have established knee OA. This information may help develop intervention during early life to reduce the burden of knee OA in later life [16].

Obesity has long been recognized as a risk factor for the incidence and progression of knee OA [17], but the role of childhood adiposity in knee OA in later life is not well studied as most of current evidence is derived from middle-aged or older adults [18]. Wills et al. reported that body mass index (BMI) as early as 11 years in females and 20 years in males was independently associated with knee OA at the age of 53 [19]. Similarly, Gelber et al. reported that BMI in young men, aged 20 to 29 years, was associated with the increased risk of subsequent knee OA [20]. In addition, we reported that the childhood adiposity measures were associated with higher risk of knee pain in adulthood 25 years later [21]. These findings suggest that adiposity measures during early life may have long-term effects on knee joint in

later life. This comes particularly important as the prevalence of overweight and obesity has increased in children and adolescents in both developed and developing countries during 1980-2013 [22]. However, there is a paucity of information about the effects of childhood adiposity measures on adulthood cartilage defects and BMLs. Therefore, we aimed to describe longitudinal associations between adiposity measures in childhood and knee cartilage defects and BMLs in adulthood 25 years later.

Materials and Methods

Participants

The Australian Schools Health and Fitness Survey (ASHFS) was completed in 1985 on a nationwide sample of schoolchildren (n=8498, aged 7-15 years), and a wide range of health-related measures were collected through field and technical tests. The Childhood Determinants of Adult Health (CDAH) Study was a 20-year follow-up (n=2410, aged 26-36 years) of children who participated in ASHFS and was completed during 2004-2006, adulthood health-related measures were collected during the CDAH Study. The CDAH Knee Cartilage Study (n=330, aged 31-41 years) was a sub-study of the CDAH Study and the participants completed knee magnetic resonance imaging (MRI) scans during 2008-2010.

We used the following strategy to recruit participants from the CDAH Study. The CDAH Study participants (n=764) residing in metropolitan Melbourne and Sydney were contacted by mail and invited to participate in the CDAH Knee Cartilage Study. Participants who agreed to participate (n=529, response percentage 69%) were assessed for their eligibility. Exclusion criteria for this study were being pregnant, having had diseases that might affect knee cartilage such as rheumatoid arthritis, or having a contraindication for MRI. Eighty participants were excluded either because of the exclusion criteria or because they changed

their mind. The remaining 449 participants were asked to complete a short computer-assisted telephone interview (CATI). History of knee injury or surgery was not collected in childhood in the ASHFS study and, therefore, telephone interviews included history of knee injury in childhood. Knee injury was recorded in response to the question, “Have you had a knee injury requiring non-weight-bearing treatment for more than 24 hours or surgery?” Participants were requested to have an MRI scan at Epworth Hospital in Melbourne or North Shore Private Hospital in Sydney. Some participants (n=119) did not undergo MRI after enrolling in the study due to the long distance, work or family commitments, moving interstate, becoming pregnant by the time of MRI, or changing their mind. Eight MRI scans were not readable for cartilage defects and three for BMLs due to the absence of adequate sequences. Therefore, these MRI scans were not included for cartilage defects or BMLs assessments. There are 322 participants included in analyses for cartilage defects and 327 for BMLs. A flow chart of the selection of participants for this study is shown in Figure 1.

This study was approved by the Southern Tasmania Health and Medical Human Research Ethics Committee (HREC), the Monash University HREC and the Northern Sydney and Central Coast Area HREC. All participants provided written informed consent. At baseline, all children provided assent and parents provided written informed consent.

Anthropometric measurements

Weight was measured to the nearest 0.5 kg in 1985 and 0.1 kg during follow-up, with shoes, socks and bulky clothing removed. Height was measured to the nearest 0.1 cm (with shoes and socks removed) using a stadiometer. BMI was calculated as weight in kilograms divided by height in meters squared, at both time points. Overweight status in childhood was defined

according to age and sex-specific cut-off points [23]. Adulthood overweight status was defined as a BMI $>25 \text{ kg/m}^2$.

Triceps, biceps, subscapular, and supra-iliac skinfolds were measured at locations determined by reference to anatomical landmarks [24] to the nearest 0.1 mm by using Holtain Skinfold Calipers in 1985 and Slim Guide Skinfold Calipers (SPRI Products) during CDAH Study. Body density was estimated from the log of the sum of four skinfolds using age-specific regression equations [24-26]. Estimate of percent body fat was derived from body density [27], and fat mass was estimated by percent body fat in kilograms: fat mass=fat% \times weight.

MRI measurements

Participants had an MRI scan of their knees in the CDAH Knee Cartilage Study. MRI scans were obtained from 2 hospitals, which used the same type of machine (General Electric Medical Systems, Milwaukee, WI, USA). Knees were imaged on a 1.5T whole-body magnetic resonance unit with use of a commercial transmit-receive extremity coil. The following image sequences were used: (1) a T1-weighted, fat-suppressed 3-dimensional (3D) spoiled gradient-recalled acquisition in the steady state; flip angle 55° ; repetition time 58 msec; echo time 12 msec; field of view 16 cm; 60 partitions; 512×512 -pixel matrix; acquisition time 11 minutes, 56 seconds; 1 acquisition. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of $0.31 \times 0.31 \text{ mm}$ (512×512 pixels). (2) Proton density-weighted fat-suppressed two-dimensional fast spin-echo coronal images at a partition thickness of 3.3 mm and an in-plane resolution of $0.31 \times 0.31 \text{ mm}$ (512×512 pixels); repetition time 3800 msec; echo time 45 msec.

Knee cartilage defects were measured as previously reported [28] in an ordinal scale using the T1-weighted spoiled gradient-recalled sagittal MR images and proton density-weighted fast spin-echo coronal MR images together. Grade 0 indicated a normal cartilage, and Grade 1 indicated focal blistering and low-signal intensity area in T1-weighted sagittal images or high-signal intensity area in proton density-weighted images with intact surface/bottom. Grade 2 indicated a loss of thickness of <50% on surface/bottom of the cartilage. Grade 3 represented a loss of thickness >50%, and Grade 4 indicated a full-thickness chondral wear with exposure of subchondral bone. A prevalent cartilage defect was defined as a cartilage defect score of ≥ 2 at any site within that compartment. Intraobserver reliability expressed as an intraclass correlation coefficient (ICC) ranged from 0.89 to 0.94.

BMLs were identified using the sagittal images reformatted from coronal proton density-weighted images and then scored as the increased signal intensity area in the subchondral bone adjacent to the osteochondral junction. BMLs were scored in the tibia, femur and patella using the ordinal scoring system previously described [29]. Participants with no BMLs were scored as grade 0 and then the participants with BMLs were graded according to the percentage of area of occupancy of BML in each compartment: grade 1: $\leq 25\%$ of area; grade 2: >25% to <50%; grade 3: >50%. A prevalent BML was defined as a BML score of ≥ 1 at any site within that compartment. Intraobserver reliability expressed as an ICC ranged from 0.89 to 1.00.

Meniscal tear was graded in medial and lateral menisci separately based on a modified International Society of Arthroscopy, Knee Surgery, and Orthopaedic Sports Medicine (ISAKOS) meniscal tear classification system [30] using proton density-weighted coronal and T1-weighted sagittal images. Grade 0 indicated a normal meniscus; grade 1 indicated

181 mucoid degeneration; grade 2 indicated mild tear; grade 3 indicated displaced tear and grade
182 4 indicated macerated meniscus. A prevalent meniscal tears was defined as a meniscal tear
183 score of ≥ 2 at any site within that compartment. Intraobserver reliability expressed as an ICC
184 ranged from 0.81 to 1.00.

186 The grading was done by a clinical radiologist (ST) with 2 years of experience under the
187 supervision from an experienced radiologist with >10 years of experience (AH).

189 **Cholesterol and plasma glucose measures**

190 Venous blood samples were collected from the antecubital vein after a 12-hour fast in CDAH
191 study approximately 5 years prior to CDAH Knee study. Serum total cholesterol was
192 determined enzymatically (Olympus AU5400 automated analyzer, Olympus Optical, Tokyo,
193 Japan). Fasting plasma glucose levels were measured by the Olympus AU5400 automated
194 analyser (Olympus, Southend-on-Sea, UK).

196 **Statistical analyses**

197 Mean (standard deviation) or number (percentage) was used to describe characteristics of the
198 participants. Student's t-tests or Chi-square tests were used to assess the differences in
199 continuous and categorical variables, respectively, between groups of participants.

200 Univariable and multivariable log binomial regressions were used to estimate relative risk
201 (RR) for the associations between childhood adiposity measures and adulthood knee cartilage
202 defects or BMLs before and after adjustment for potential confounders. If the log binomial
203 model failed to converge, RR was estimated by using a Poisson distribution and robust
204 standard errors. Multivariable ordinal logistic regressions were used to estimate odds ratio
205 (OR) for the associations between childhood adiposity measures and adulthood knee cartilage

defects or BMLs grades after adjustment for potential confounders. Interactions between gender and adiposity measures on cartilage defects or BMLs were investigated by regressing cartilage defects or BMLs on the product term of gender and each exposure of interest (e.g., gender \times BMI).

Childhood age, duration of follow-up, gender, height (if weight or fat mass was the predictor), childhood knee injury, meniscal tears, cholesterol and plasma glucose were examined as potential confounders. We further adjusted for the corresponding adulthood adiposity measure to explore the independent association of each childhood adiposity measure with adulthood knee cartilage defects and BMLs. A p-value less than 0.05 (2-tailed) was considered as statistical significance. All statistical analyses were performed in STATA, version 14.2.

Results

Characteristics of the participants

A sample of 327 participants with MRI was included in this analysis. A subset (n=108) of these participants, who were aged 9, 12 or 15 years in 1985, had fat mass measure in childhood. Characteristics of the participants based on the presence of cartilage defects or BMLs are shown in Table 1. Prevalence of any cartilage defect and BML in the knee joint was 37.9% and 25.7%, respectively. The following variables were comparable between participants with and without cartilage defects or those with and without BMLs: gender, BMI, overweight, fat mass and knee injury in childhood and BMI, body weight, overweight status and knee injury in adulthood. However, participants with cartilage defects had significantly higher childhood body weight and adulthood fat mass than those without cartilage defects,

and participants with BMLs had significantly higher childhood body weight and older age than those without BMLs (Table 1).

Childhood adiposity measures and adulthood cartilage defects

Childhood body weight, BMI, overweight status and fat mass were significantly associated with higher risks of adulthood patellar cartilage defects in univariable analyses (Table 2) and these associations remained significant after adjustment for childhood age, duration of follow-up, gender, childhood height (if weight or fat mass was the predictor), childhood knee injury (Weight RR 1.05/kg, 95% CI 1.02 to 1.09; BMI 1.10/kg/m², 1.02 to 1.19; Overweight 2.04/yes, 1.12 to 3.74; fat mass 1.13/kg, 1.03 to 1.23) (Table 2). After further adjustment for corresponding adulthood measure, these associations were largely unchanged (Weight RR 1.05/kg, 95% CI 1.01 to 1.09; BMI 1.10/kg/m², 1.01 to 1.19; Overweight 2.22/yes, 1.21 to 4.08; fat mass 1.11/kg, 95% CI 1.01 to 1.22) (Table 2, Figure 2). There were no significant associations between childhood adiposity measures and adulthood tibiofemoral cartilage defects in either univariable or multivariable analyses (Table 2). Above associations remained large unchanged after adjustment for metabolic risk factors (cholesterol or glucose) or meniscal tears (data not shown).

Childhood adiposity measures and adulthood BMLs

Childhood body weight, BMI and fat mass were not associated with adulthood BMLs in patellar compartments in either univariable or multivariable analyses (Table 3); however, childhood overweight status was significantly associated with adulthood patellar BMLs after adjustment for childhood age, duration of follow-up, gender, childhood knee injury and adulthood overweight status (RR: 2.87/kg, 95% CI: 1.10 to 7.53) (Table 3). There were no significant associations between childhood adiposity measures and adulthood tibiofemoral

BMLs in multivariable analyses (Table 3); however, there was an interaction between childhood fat mass and gender on adulthood tibiofemoral BMLs ($p=0.052$), so we separated males and females to analyse the associations between childhood fat mass and adulthood tibiofemoral BMLs. Childhood fat mass was associated with a higher risk of adulthood tibiofemoral BMLs in males (RR: 1.19/kg, 95% CI: 1.07 to 1.32) (Figure 3), but not in females (RR: 1.01, 95% CI: 0.87 to 1.18). The association in males persisted after adjustment for childhood age, duration of follow-up, childhood height, childhood knee injury and adulthood fat mass (Male RR: 1.16/kg, 95% CI: 1.01 to 1.37; female RR: 1.10/kg, 95% CI: 0.93 to 1.30). Above associations remained large unchanged after adjustment for metabolic risk factors (cholesterol or glucose) or meniscal tears (data not shown).

Discussion

To the best of our knowledge, this is the first study describing the longitudinal associations between childhood adiposity measures and adulthood knee cartilage defects and BMLs. We found that childhood adiposity measures were significantly associated with the increased risk of adulthood patellar, but not tibiofemoral cartilage defects, 25 years later. In addition, childhood overweight status was significantly associated with the increased risk of adulthood patellar BMLs. These significant associations remained largely unchanged or even increased after adjustment for the corresponding adulthood adiposity measure, suggesting childhood adiposity may have independent effects on adulthood patellar structural abnormalities.

Cartilage defects indicate an early stage of cartilage damage and can predict the development of radiographic knee OA [31]. Previous studies reported that adiposity measures are consistently associated with the increased risk of knee cartilage defects among middle-aged adults [32] and obese populations [33]. A recent systematic review concluded that there is a

consistently detrimental association between adiposity measures and cartilage defects, although it also stated the strength of evidence for these findings was limited as there were lack of high-quality longitudinal studies [34]. However, all previous studies were conducted among middle-aged or older populations, and there are no studies describing the relationships between adiposity measures in childhood and cartilage defects in young adults, even though early life adiposity may play an important role in adulthood knee OA [16].

In this study, we found significant associations between childhood adiposity measures and adulthood cartilage defects in the patellar compartment, even though body weight in most children was normal. The underlying mechanisms are unclear, while evidence from research among adults suggests that mechanical and metabolic factors could play roles in the detrimental effects of adiposity. Firstly, the increased load caused by excess weight might be one of the underlying mechanisms for these significant associations, as every pound increase of body weight was associated with 4-fold increase in the load exerted on the knee during daily activities in adults [35]. This is particularly important for patella as it bears around 3 times of body weight during activities requiring knee extension, such as stair climbing, sit-to-stand and squatting [36]. Moreover, Eckstein et al. reported that the patellar cartilage was more sensitive to physical stress compared to tibiofemoral cartilage [37]. These are also consistent with the previous finding that chronic overloading is a dominant factor of anterior knee pain in adolescents [38]. Secondly, increasing evidence suggest that the association between obesity and knee cartilage could be mediated by adipocytokines [39], as the adipocytokines released by adipose tissue would play important roles in cartilage degradation [40].

While we observed consistent associations between childhood adiposity measures and patellar cartilage defects in young adults, we found no significant associations between childhood adiposity measures and adulthood tibiofemoral cartilage defects. The reasons are unclear. A recent systematic review reported that the prevalence of patellofemoral OA is high, with 39% in symptom-based cohorts [41]. We previously reported that the prevalence and severity of cartilage defects increased with age and the prevalence of patellar cartilage defects was higher than that of tibiofemoral cartilage defects in middle-aged adults (mean aged 45 years) [42]. Similarly, in this young sample, we found that the prevalence of patellar cartilage defect (24.2%) was higher than that in tibiofemoral compartment (14.6% excluding trochlear region). Based on these observations, we speculate that cartilage defects may occur in the patella prior to the tibiofemoral compartment, and patellar cartilage may be more sensitive and vulnerable to physiological stress.

BMLs correspond to several histopathological changes including bone marrow necrosis, bone marrow fibrosis and abnormal trabeculae [43]. Adiposity is associated with detrimental effects on BML both cross-sectionally and longitudinally. Cross-sectionally, BMI [10, 44] and total body fat mass [45] are associated with higher prevalence of BMLs among older adults or community-based adults. Longitudinally, increased BMI was a risk factor for the incidence of BMLs over 2 years [46] and change in BMI over 10 years was positively associated with the increased risk of BMLs [47]. Moreover, a recent systematic review concluded that obesity was a moderate risk factor for BMLs in the knee [48]. In the current study, we found that the associations of childhood adiposity measures with adulthood BMLs were less consistent than those with adulthood cartilage defects; only childhood overweight status was significantly associated with adulthood patellar BMLs. This may be due to the low prevalence of BMLs in this young population-based sample. However, our findings still

suggest a detrimental effect of overweight status on patellar BMLs, which may result from the excessive loading of the joint as well as the adiposity-related metabolic mechanisms [49, 50]. In addition, we found that childhood fat mass was significantly associated with tibiofemoral BMLs in males, but not females. This is consistent with our previous finding that childhood adiposity measures were significantly associated with adulthood knee symptoms in men, but not in women [21]. The reason for the sex difference is unclear, but may suggest the different roles of fat mass in the development of BMLs between genders.

Strengths of our study include the use of 25-year prospective data from childhood to adulthood, knee MRI scans in young adults, and the objective measures of adiposity. Limitations include the modest retention of participants from the original cohort (ASHFS), representing <5% of the original participants in the ASHFS. Reassuringly, characteristics, including age, gender and BMI, between those included in current study and the remainder of the original cohort were similar, suggesting no selection bias introduced. We used adiposity measures in childhood to predict MRI abnormalities in adulthood, which could be affected by adulthood fat measures as childhood adiposity is predictive of adulthood adiposity [51]. Reassuringly, the associations remained largely unchanged after further adjusting for corresponding adulthood adiposity measure. T1-weighted MRI assessment of cartilage defects may be susceptible to artefacts resulting from calcifications within the cartilage, but it has been validated as accurate and reproducible [52], and has been used in epidemiological studies widely [53].

In conclusion, childhood adiposity measures were associated with the increased risk of adulthood patellar cartilage defects and, to a lesser extent, BMLs, independent of adulthood

353 adiposity measures. These results suggest that adiposity in childhood has long-term effects on
354 patellar structural abnormalities in young adults.

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515 Table 1. Characteristics of the participants

	Cartilage defects		Bone marrow lesions	
	No	Yes	No	Yes
Childhood	(n=200)	(n=122)	(n=243)	(n=84)
Age (years)	10.8 (2.7)	11.2 (2.6)	10.8 (2.6)	11.4 (2.5)
Female, n (%)	88 (44.0)	64 (52.5)	111 (45.7)	43 (51.2)
Weight (kg)	38.5 (12.5)	41.8 (14.0)	38.6 (12.7)	43.0 (13.8)
BMI (kg/m ²)	17.9 (2.3)	18.4 (2.9)	18.0 (2.5)	18.5 (2.8)
Overweight, n (%)	11 (5.5)	10 (8.3)	15 (6.2)	6 (7.2)
Fat mass ^a (kg)	8.8 (3.7)	9.3 (4.9)	8.6 (3.9)	10.1 (4.9)
Adulthood				
Weight (kg)	75.1 (14.6)	77.4 (16.0)	76.2 (14.8)	75.3 (15.8)
BMI (kg/m ²)	25.0 (3.9)	25.9 (4.4)	25.4 (4.1)	25.1 (4.2)
Overweight, n (%)	86 (44.6)	58 (48.7)	109 (46.6)	36 (43.4)
Fat mass ^a (kg)	19.8 (6.5)	23.9 (9.7)	21.2 (8.1)	22.7 (8.7)

516 Values are mean (SD) unless otherwise stated.

517 ^aFat mass was measured among the children aged 9, 12 and 15 years in 1985; n=62, 45, 79

518 and 29, respectively.

519 BMI, body mass index.

520

521 Table 2. Associations between childhood adiposity measures and adulthood cartilage defects

	Univariable	Multivariable ^a	Multivariable ^b
	RR (95% CI)	RR (95% CI)	RR (95% CI)
Patellar			
Weight (kg)	1.02 (1.00 to 1.03)	1.05 (1.02 to 1.09)	1.05 (1.01 to 1.09)
BMI (kg/m ²)	1.12 (1.04 to 1.20)	1.10 (1.02 to 1.19)	1.10 (1.01 to 1.19)
Overweight (yes)	1.89 (1.11 to 3.23)	2.04 (1.12 to 3.74)	2.22 (1.21 to 4.08)
Fat mass (kg)	1.10 (1.01 to 1.19)	1.13 (1.03 to 1.23)	1.11 (1.01 to 1.22)
Tibiofemoral			
Weight (kg)	1.01 (1.00 to 1.03)	0.98 (0.92 to 1.04)	0.97 (0.91 to 1.03)
BMI (kg/m ²)	1.03 (0.93 to 1.14)	0.96 (0.83 to 1.10)	0.91 (0.78 to 1.06)
Overweight (yes)	0.97 (0.33 to 2.88)	1.10 (0.37 to 3.23)	1.00 (0.34 to 2.94)
Fat mass (kg)	1.07 (0.98 to 1.18)	1.13 (0.98 to 1.29)	1.08 (0.96 to 1.20)

522 Bold denotes statistical significance, p<0.05.

523 ^aAdjusted for childhood age, duration of follow-up, gender, height (if weight or fat mass was
524 the predictor), childhood knee injury.

525 ^bFurther adjusted for corresponding adulthood measure.

526 BMI, body mass index; CI, confidence interval; RR, relative risk.

527 Table 3. Associations between childhood adiposity measures and adulthood BMLs

	Univariable	Multivariable ^a	Multivariable ^b
	RR (95% CI)	RR (95% CI)	RR (95% CI)
Patellar			
Weight (kg)	1.01 (0.99 to 1.03)	1.02 (0.96 to 1.10)	1.04 (0.97 to 1.12)
BMI (kg/m ²)	1.05 (0.93 to 1.18)	1.06 (0.92 to 1.23)	1.11 (0.95 to 1.28)
Overweight (yes)	2.00 (0.78 to 5.17)	2.43 (0.95 to 6.23) ^c	2.87 (1.10 to 7.53)
Fat mass (kg)	1.05 (0.93 to 1.18)	0.96 (0.78 to 1.19)	0.94 (0.76 to 1.16)
Tibiofemoral			
Weight (kg)	1.02 (1.01 to 1.04)	1.01 (0.96 to 1.06)	1.01 (0.96 to 1.06)
BMI (kg/m ²)	1.07 (0.98 to 1.16)	1.02 (0.91 to 1.14)	1.03 (0.91 to 1.18)
Overweight (yes)	0.56 (0.15 to 2.14)	0.71 (0.19 to 2.75)	0.74 (0.19 to 2.86)
Fat mass (kg)	1.07 (0.98 to 1.17)	1.06 (0.95 to 1.19)	1.07 (0.95 to 1.20)

528 Bold denotes statistical significance, p<0.05.

529 ^aAdjusted for childhood age, duration of follow-up, gender, height (if weight or fat mass was
530 the predictor), childhood knee injury.

531 ^bFurther adjusted for corresponding adulthood measure.

532 BMI, body mass index; BMLs, bone marrow lesions; CI, confidence interval; RR, relative
533 risk.

534 ^cp = 0.064

Figure legends

Figure 1. Flowchart showing selection of the participants for current study from previous studies. BMLs, bone marrow lesions; CDAH Study, Childhood Determinants of Adult Health Study; MRI, magnetic resonance imaging.

Figure 2. Mean childhood weight (A), mean childhood BMI (B), childhood overweight prevalence (C) and mean childhood fat mass (D) for participants classified by patellar cartilage defect grades. ORs and 95% CIs were from multivariable ordinal logistic regressions, which included childhood age, duration of follow-up, gender, height (if weight or fat mass was the predictor), childhood knee injury as confounders. BMI, body mass index; CI, confidence interval; OR, odds ratio.

Figure 3. Mean childhood fat mass for males classified by tibiofemoral BMLs grades. OR and 95% CI were from multivariable ordinal logistic regressions, which included childhood age, duration of follow-up, gender, height, childhood knee injury as confounders. BMLs, bone marrow lesions; CI, confidence interval; OR, odds ratio.