Association of adiposity measures in childhood and adulthood with knee cartilage thickness, volume and bone area in young adults

Running title: Adiposity and knee cartilage and bone morphology

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Competing Interests: The authors declare no competing financial interests

Word count: 3512

Abstract

Objective To describe the associations of childhood and adulthood adiposity measures with knee cartilage thickness, volume and bone area in young adults.

Methods Childhood and adulthood adiposity measures (weight, height, waist circumference and hip circumference) of 186 participants were collected in 1985 (aged 7-15 years) and during 2004-2006 (aged 26-36 years). Knee magnetic resonance imaging was conducted during 2008-2010 (aged 31-41 years), and cartilage thickness, volume and bone area were measured using a quantitative approach (Chondrometrics, Germany). Linear regressions were used to examine the above associations.

Results The prevalence of overweight was 7.6% in childhood and 42.1% in adulthood. Childhood weight (β=-5.57 mm^2/kg) and body mass index (BMI) (β=-11.55 $mm^2/kg/m^2$) were negatively associated with adult patellar bone area, while adult weight was positively associated with bone area in medial femorotibial compartment (MFTC) (β=3.37 mm^2/kg) and lateral femorotibial compartment (LFTC) (β=2.08 mm^2/kg). Adult waist-hip ratio (WHR) was negatively associated with cartilage thickness (MFTC: β=-0.011; LFTC: β=-0.012 mm/0.01 unit), volume (Patella: β=-20.97; LFTC: β=-21.71 mm^3/0.01 unit) and bone area (Patella: β=-4.39 mm^2/0.01 unit). The change in WHR z-scores from childhood to adulthood was negatively associated with cartilage thickness (MFTC: β=-0.056 mm), volume (patella: -89.95; LFTC: -93.98 mm^3) and bone area (patella: -20.74 mm^2). All p values < 0.05.

Conclusions Childhood weight and BMI were negatively but adult weight was positively associated with adult bone area. Adult WHR and the change in WHR from childhood to adulthood were negatively associated with cartilage thickness, volume and bone area. These suggest early life adiposity measures may affect knee structures in young adults.

Introduction

Knee osteoarthritis (OA) is a common joint disease worldwide, and a major source of knee pain and dysfunction in older people [1]. There are no approved disease-modifying treatments for knee OA; thus, identifying the early life risk factors is an ideal strategy for preventing the incidence of knee OA in later life.

Knee OA involves multifarious changes in the joint structures, which eventually result in joint dysfunction. Early changes in knee joint structure can be identified using magnetic resonance imaging (MRI) [1]. Studies using MRI have reported that quantitative morphologic measures, including changes in knee cartilage thickness, cartilage volume and subchondral bone area, are associated with knee OA [2, 3]. Reductions in cartilage volume and thickness were found to be associated with knee pain [4, 5], joint space narrowing [4, 6] and subsequent knee replacement surgery [7], and regarded as major outcome measures in MRI-based clinical trials [8, 9]. Subchondral bone underlying the cartilage is also an important knee joint structure as this region functionally adapts to physiological or patholological mechanical stress [3, 10, 11]. Expansion of tibial bone area in older populations has been shown to predict cartilage damage [12] and knee replacement surgery [13]; however, the effects of knee subchondral bone area on knee OA in young adults are not yet studied.

Previous studies have reported that early life factors, including obesity and physical activity, are associated with knee OA status in adulthood [14], indicating the importance of addressing early risk factors of the disease. We reported that physical performance measures and physical activity levels in childhood [15] and young adults [16] were associated with tibial bone area and tibial cartilage volume in young adults, suggesting that early life factors influence knee structural morphology in adulthood, which play important roles in development of knee

OA. Existing evidence among middle-aged or older adults reported detrimental effects of adiposity on the morphology of knee cartilage and subchondral bone [2, 17]. However, there are no studies describing the effects of adiposity during early life on knee cartilage and bone morphology in adulthood. We hypothesized that the childhood and adult adiposity would have detrimental effects on knee cartilage and bone morphology in adulthood. Therefore, we aimed to describe associations between adiposity measures in childhood and adulthood and knee cartilage thickness, cartilage volume and subchondral bone area in young adults.

Participants 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. A range of health-related factors were measured. The CDAH Knee Cartilage Study (n=330, aged 31-41 years) was a sub-study of the CDAH Study and the participants completed knee MRI scans during 2008-2010. We measured the cartilage and bone morphological parameters among 186 participants who were residing in Melbourne in CDAH Knee Cartilage Study.

We used the following strategy to recruit participants from the CDAH study. CDAH 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 included being pregnant, having had diseases that might affect knee

cartilage, including rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and psoriatic 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 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 required to travel to have the MRI, work or family commitments, moving interstate, becoming pregnant by the time of MRI, or changing their mind. 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 at 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. Waist circumference and hip circumference were measured to the nearest 0.1 cm using a constant tension tape. BMI was calculated as weight in kilograms divided by height in meters squared. Overweight status in childhood was defined according to age and sex-specific cut-off points, as previously published [18]. Adult overweight status was defined as a BMI ≥25 kg/m^2. Waist-hip ratio (WHR) was calculated by dividing waist circumference in centimetre by hip circumference in centimetres.

MRI measurements

In the CDAH Knee Cartilage study, knees were imaged on a 1.5T whole-body magnetic resonance unit with the use of a commercial transmit-receive extremity coil. Sagittal, T1-weighted, fat-suppressed 3-dimensional (3D) spoiled gradient-recalled acquisitions 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) were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31×0.31 mm (512×512 pixels) for the morphometric analysis.

Cartilage thickness, cartilage volume and subchondral bone area were measured in the medial and lateral femorotibial compartment (MFTC/LFTC) and in the patella as previously reported [19] by a quantitative approach, using the T1-weighted spoiled gradient-recalled sagittal MR images. A manual segmentation of knee cartilage surfaces (i.e. articular surface and subchondral bone interface) was performed in all of the slices depicting the respective cartilage structure. From the segmented voxels and three-dimensional reconstruction of the cartilage surface areas, quantitative parameters of cartilage and bone morphology were derived, including cartilage thickness, cartilage volume and subchondral bone area, using Chondrometrics 3.0 Platform software (Chondrometrics GmbH, Ainring, Germany). The reproducibility of these measures reported in previous studies were high, with root mean square (rms) coefficient of variation (CV) values ranging from 1.6% to 3.2% for cartilage thickness, 1.6% to 3.4% for cartilage volume and 1.0% to 2.1% for bone area [20].

Statistical analyses

Weight, BMI and WHR z-scores were calculated using the entire dataset (ASHFS for childhood and CDAH for adulthood). The z-score changes were calculated as sex-specific z-

score in adulthood minus age- and sex-specific z-score in childhood. Mean (standard deviation) or number (percentage) was used to describe characteristics of the participants. T-tests or Chi-square tests were used to assess the differences in continuous and categorical variables, respectively, between groups of participants. Linear regressions were used to estimate β-values for the associations of adiposity measures in childhood/adulthood or the changes of adiposity measures with knee cartilage thickness, cartilage volume and subchondral bone area in adulthood before and after adjustment for potential confounders.

Age and gender were included as confounders as they were associated with the predictors (adiposity measures) and outcomes (cartilage and bone morphology). We further adjusted for height, if weight or weight z-score change was the predictor, to remove the influence of height on weight and bone and cartilage morphology. A p-value less than 0.05 (2-tailed) was considered statistically significant. All statistical analyses were performed in STATA, version 15.0.

Results

A sample of 186 participants with MRI was included in this analysis. Characteristics of study participants are given in Table 1. The mean childhood and adult ages of the participants were 10.9 and 30.4 years, respectively, with 90 (48.4%) participants in the sample being female. The prevalence of overweight status was 7.6% in childhood and 42.1% in adulthood. There were no significant differences between those in current study and the reminder of original cohort (ASHFS) in terms of age, gender, weight, BMI and overweight status in childhood. However, WHR was lower in the current sample than that in the remainder of original cohort (Table 1). The characteristics, including weight, BMI and WHR, in current sample and the

reminder of the CDAH Study were comparable, except the lower prevalence of overweight status in the current sample than that in the remainder of the CDAH Study.

No associations were identified between childhood adiposity measures (including weight, BMI, overweight status and WHR) and adult knee cartilage thickness and cartilage volume in any knee compartment in multivariable analyses, after adjustment for childhood age, gender and height (if weight was the predictor) (Table 2). However, childhood body weight and BMI were negatively associated with adult patellar bone area, and the association of childhood overweight status with adult patellar bone area was of borderline significance ($p = 0.051$) (Table 2). The significant associtions of childhood weight and BMI with adult patellar bone area were persistent after futher adjustiment for adult BMI (Weight: β=-4.75 mm^2/kg, 95% confidence interval (CI): -8.83 to -0.68; BMI: -10.61 $mm^2/kg/m^2$, -20.58 to -0.65), with a reduction in beta values (14.7% and 8.1%, respectively).

Adult BMI or overweight status was not significantly associated with knee cartilage thickness, cartilage volume and subchondral bone area measured 4-5 years later in any compartment in multivariable analyses, including adult age and gender as confounders (Table 3). However, adult weight was positively associated with cartilage volume in MFTC and bone area in MFTC and LFTC (Table 3). The significant association between adult weight and cartilage volume in MFTC disappeared after further adjusting for corresponding bone area (β=0.06 mm^3/kg, 95% CI: -4.58 to 4.71). In addition, WHR was significantly and negatively associated with cartilage thickness measured 4-5 years later in both MFTC and LFTC, and the negative association between adult WHR and patellar cartilage thickness was of borderline statistical significance ($p=0.060$) (Table 3, Figure 2). Moreover, adult WHR was significantly and negatively associated with cartilage volume in both patella and LFTC, and

the negative association between adult WHR and cartilage volume in MFTC approached statistical significance (p=0.087) (Table 3). Furthermore, adult WHR was significantly and negatively associated with subchondral bone area in patella, and the negative association between adult WHR and bone area in LFTC was of borderline statistical significance (p=0.058) (Table 3).

The change of weight z-scores or BMI z-scores from childhood to adulthood was not significantly associated with cartilage thickness, cartilage volume or bone area in young adults (Table 4). However, increased WHR z-score from childhood to adulthood was negatively associated with cartilage thickness in MFTC, cartilage volume in patella and LFTC, and bone area in patella (Table 4). The effect sizes for the negative associations between WHR z-score chage and cartilage volume in MFTC and between WHR z-score change and bone area in LFTC were relatively large, though they did not reach statistical significance (p=0.059 and 0.053, respectively) (Table 4). The significant associations between the change of WHR z-score and cartilage volume disappeared in patella (β=-22.47 mm^3, 95% CI: -76.94 to 31.99) and LFTC (-26.22 mm^3, 95% CI: -82.03 to 29.58) after adjustment for corresponding bone area.

Discussion

To the best of our knowledge, this is the first study describing associations between adiposity measures during early life and knee cartilage thickness, cartilage volume and subchondral bone area in young adults. We found childhood body weight and BMI were negatively associated with adult patellar bone area but adult body weight was positively associated with bone area in MFTC and LFTC, and adult WHR and the WHR change from childhood to

adulthood were negatively associated with knee cartilage thickness, cartilage volume and subchondral bone area.

Associations between adiposity measures and knee cartilage morphology reported in the literature have been inconsistent. A cross-sectional study observed that BMI was negatively associated with knee cartilage volume in older adults (range 52-78 years old) [21]. However, another study reported baseline BMI did not predict change in tibial cartilage volume longitudinally over 2 years in healthy middle-aged men [22]. Similarly, weight loss slowed loss of knee cartilage thickness over 12-month among participants in a randomised clinical trial of a weight loss program [23], and studies reported that morbidly obese children and adolescents had increased knee cartilage lesions while normal weight children and adolescents did not typically show knee joint alterations [24, 25]; in contrast, no significant difference in change of cartilage thickness over one year were observed between participants who were overweight and those who were of normal weight [26], and no effect of diet-induced weight loss, with and without combination with exercise, on a large set of knee joint structural outcomes was detected during the 18 month Intensive Diet and Exercise for Arthritis (IDEA) trial [27]. A recent systematic review concluded that there is limited evidence for the detrimental effects of obesity on knee cartilage, and highlighted the paucity of evidence from high-quality cohort studies [2]. Most of previous studies were conducted among middle-aged or older people, and there were no studies describing the association of early life adiposity measures with knee cartilage morphology in young adults. Furthermore, all the obesity measures used in the included studies were focusing on general obesity such as BMI, body weight and fat mass, whereas no studies have explored the effects of central obesity.

Associations between adiposity measures and bone area were examined in a few studies in either children [28, 29] or adults [17], with conflicting findings being reported. A cross-sectional study reported that higher BMI was associated with tibial bone enlargement among participants aged from 26 to 61 years [17]. However, Wosje et al. reported that higher baseline fat mass was associated with smaller increase in total body bone area (except for the skull) over 3.5 years among children aged form 3 to 7 years [28]. Similarly, Goulding et al. reported that overweight or obese children had lower bone mass and total bone area than their predicted values calculated from body weight during growth [29]. Subchondral bone is a dynamic structure, and the increased bone area may play different roles in the development of knee joint during different stages of life. In older populations, increases in the tibial plateau bone area occur over time in both healthy people [30] and people with knee OA patients [31], and have been shown to depend on the mechanical stress distribution and alignment [10]. Such changes in subchondral bone could be maladaptive, as an outcome of remodelling of subchondral trabeculae (with increased extracellular matrix deposition) due to loading [3]. However, bone accrual during childhood or young adulthood is likely to be a physiologic rather than a pathologic process, since the enlargement of bone area could be an adaptive change to load-bearing stimuli and enable distribution of loads over a larger surface [10, 11]. This is consistent with our previous studies, which reported positive associations between childhood physical performance measures and knee tibial bone area [15] and bone mass [32] in young adults, suggesting tibial bone accrual from childhood to early adulthood may be a physiological process.

In this study, childhood body weight amd BMI were independently and negatively associated with adult patellar bone area; this suggests the potential long-term detrimental effects of childhood adiposity on patellar bone morphology. These results are consistent with our

previous findings, which indicated childhood adiposity measures were associated with adult knee symptoms [33]. We also found that the adult weight was positively associated with bone area in MFTC and LFTC, but not patella; the reason for the different results between patella and MFTC/LFTC in adulthood are unclear but could be related to the different mechanical stress induced by obesity on different compartment, for example, higher on MFTC/LFTC than on patella [10], which may result in larger bone area.

We found that adult WHR, but not general obesity measures, was significantly associated with thinner cartilage in MFTC and LFTC, smaller cartilage volume in patella and LFTC, and smaller bone area in patella measured 4-5 years later. The associations of adult WHR with cartilage thickness in patella, cartilage volume in MFTC and bone area in LFTC were of borderline significance. These results indicate the detrimental effects of central obesity on knee cartilage and bone morphology in young adults. Moreover, the change of WHR from childhood to adulthood was negatively associated with knee cartilage and bone morphology measures. The significant associations of WHR changes with cartilage volume largely disappeared after further adjusting for corresponding bone area, suggesting the detrimental effects of WHR changes on cartilage may be mediated by subchondral bone area. Current findings suggest that in context of its impact on joint structures, the specific location of the adipose tissue is important, as gluteofemoral adiposity is associated with higher level of leptin and adiponectin and lower levels of inflammatory cytokines [34], while the abdominal adiposity was more readily to mobilize free fatty acids [35]. In addition to higher WHR being indicative of central adiposity, it also indicates less muscle mass in the thigh region [36], which will result in reduced leg strength and thereby lead to potential knee joint structural damages [37].

We observed that the associations between adiposity measures and cartilage and bone morphology were largely evident in adulthood. The lack of association of childhood adiposity may be explained in line with the cardiovascular studies among early life participants, which reported that the effect of childhood adiposity measures on cardiovascular outcomes are lower in magnitude [38-40] and can be reversible [38-41]. The results from a childhood consortium study, conducted among four prospective cohorts, reported that the participants who were overweight or obese in childhood and obese as adults had the highest risk on adult cardiovascular outcomes and those who became normal weight from being overweight in childhood had almost similar risks of cardiovascular events as to those who were never obese [38]. Cardiovascular disease and OA have shared pathophysiology [42]; therefore, the effects of childhood adiposity on adult knee cartilage and bone morphology may only have a few residual effects. Additionally, this may be due to the low prevalence of overweight status (7.6%) in childhood while around 40% were overweight in adulthood [25]. We also reported that childhood weight and BMI were negatively associated with patellar bone area, but adult weight was positively associated with bone area in MFTC and LFTC. The underlying reasons for these differences were unclear, but may reflect that the adiposity have different effects on different compartments of knee joint (weight bearing and non-weight bearing) between peri-pubertal period and adulthood. Nevertheless, our results still suggested that preventing obesity in both childhood and adulthood and maintaining normal weight from childhood to adulthood were potentially helpful in maintaining knee joint health.

Strengths of our study include the 25-year prospective data from childhood to adulthood, knee MRI scans in young adults, and the objective measures of adiposity. Some limitations of our study should be considered. First, the 186 MRI scans measured for the cartilage and bone morphology, representing <5% of the original participants in the ASHFS, gave us only a

modest sample size. A formal power calculation was not performed for this study because it was a secondary analysis of the data collected in the main study. The key finding of scientific interest in this study was the negative association between adult WHR and knee cartilage thickness, and we performed power calculations on the analysed model with the assumption of α=0.05 and β=0.20. The results showed that we needed 349 participants in MFTC, 346 participants in LFTC and 382 participants in patella to have 80% power, and our current sample size was lower. Therefore, the lack of statistical associations in our model should be interpreted carefully as we did not have enough power. Reassuringly, we still found statistically significant or of borderline significant associations, indicating these associations were valid. Second, the WHR was lower in current sample than that in the remainder of the original cohort (ASHFS) and the prevalence of overweight status was lower in current sample than that in the remainder of the CDAH Study. The lower WHR and overweight prevalence may indicate that the current sample comprised of healthier participants, and these may not bias our results as normal weight children and young adults are less likely to report knee joint alterations [25, 43]. Third, we did not perform MRI scans among the participants at baseline, so we were unable to describe the longitudinal changes of knee cartilage and bone morphology over time. Fourth, we did not collect knee injury information in childhood, which would have impact on knee cartilage in later life. Thus, we were unable to adjust childhood knee injury status when we analysed the effects of change of adiposity measures from childhood to adulthood on knee cartilage thickness, volume and bone area in young adults.

In conclusion, childhood weight and BMI were negatively but adult weight was positively associated with adult bone area. Adult WHR and the change in WHR from childhood to adulthood were negatively associated with cartilage thickness, volume and bone area. These suggest early life adiposity measures may affect knee structures in young adults.

Acknowledgements Special thanks go to the participants who made this study possible. The roles of Liz O'Loughlin, Judy Hankin in collecting the data, Marita Dalton in managing the database and Professor Leigh Blizzard in data analysis are gratefully acknowledged.

Author contributions Study conception and design: TM, AV, FC, LM, TD, GJ and CD; acquisition of data: TM, AV, FE, WW, FC, LM, TD, MC, GJ, CD and BA; analysis and interpretation of data: TM, AV, FE, WW, FC, LL, GJ, CD and BA. All authors participated in the preparation of manuscript, approved the manuscript for submission and publication, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding The National Health and Medical Research Council of Australia (Grant number: 490006) funded this study. The funders had no role to play in the study design, data collection and analysis, decision to publish or preparation of the manuscript.

Competing Interests The authors declare no competing financial interests

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Figure legends

Figure 1. Flowchart showing selection of the participants for current study from previous studies.

CDAH Study, Childhood Determinants of Adult Health Study; MRI, magnetic resonance imaging.

Figure 2. Scatter plots and linear regression lines for associations between adulthood WHR and knee cartilage thickness (A: patella; B: MFTC; C: LFTC). Linear regression lines are from models adjusted for adult age and gender. WHR, waist-hip ratio; MFTC, medial femorotibial compartment; LFTC, lateral femorotibial compartment.