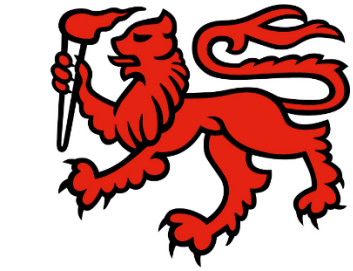

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Association between factors in early life and knee structures in young adults

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MBBS, MMed

Submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy (Medical research)

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Declaration of Originality

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We, the undersigned, endorse the above stated contribution of work undertaken for each of the published (or submitted) peer-reviewed manuscripts contributing to this thesis:

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Date:	6 April 2020	6 April 2020	6 April 2020

Statement of Ethical Conduct

The research associated with this thesis abides by the international and Australian codes on human and animal experimentation, the guidelines by the Australian Government's Office of the Gene Technology Regulator and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University.

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Other Publications during Candidature

1. Chang J, Liao Z, Lu M, **Meng T**, Han W, Ding C. Systemic and local adipose tissue in knee osteoarthritis. Osteoarthritis and Cartilage. 2018 Jul; 26(7):864-871.

2. Chang J, Zhu Z, Liao Z, **Meng T**, Zheng S, Cicuttini F, et al. A novel method for assessing proximal tibiofibular joint on MR images in patients with knee osteoarthritis. Osteoarthritis and Cartilage. 2018 Dec; 26(12):1675-1682.

3. Zheng S, Tu L, Cicuttini F, Han W, Zhu Z, Antony B, Wluka A, Winzenberg T, **Meng T**, et al. Effect of Vitamin D Supplementation on Depressive Symptoms in Patients with Knee Osteoarthritis. Journal of the American Medical Directors Association. 2019 Dec; 20(12):1634-1640.

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2018 October

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List of Abbreviations

3D	three-dimensional
AAOS	American Academy of Orthopaedic Surgeons
ACR	American College of Rheumatology
ASHFS	Australian Schools Health and Fitness Survey
BLOKS	Boston-Leeds Osteoarthritis Knee Score
BMI	body mass index
BMLs	bone marrow lesions
CDAH	Childhood Determinants of Adult Health
CI	confidence interval
DM	diabetes mellitus
ESCEO	European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases
EULAR	European League Against Rheumatism
HDL-C	high-density lipoprotein cholesterol
HOMA2-β	homeostatic model assessment 2-beta cell function
HOMA2-IR	homeostatic model assessment 2-insulin resistance
HOMA2-S	homeostatic model assessment 2-insulin sensitivity
HR	Hazard ratio
HREC	Human Research Ethics Committee
ICC	intraclass correlation coefficient
IPAQ-L	long version of the International Physical Activity Questionnaire
JSN	joint space narrowing
K-L	Kellgren-Lawrence

LFTC	lateral femorotibial compartment
MD	mean difference
MetS	metabolic syndrome
MFTC	medial femorotibial compartment
MRI	magnetic resonance imaging
MRI-OPs	magnetic resonance imaging-detected early osteophytes
NSAIDs	nonsteroidal anti-inflammatory drugs
OA	osteoarthritis
OARSI	Osteoarthritis Research Society International
OR	odds ratio
PTFJ	proximal tibiofibular joint
PWC170	physical work capacity at a heart rate of 170 bpm
RCTs	randomised controlled trials
RR	relative risk
SMD	standardised mean difference
WHR	waist-hip ratio
WORMS	Whole-Organ Magnetic Resonance Imaging Score
YLDs	years lived with disability

Abstract

Osteoarthritis (OA) is the most common form of arthritis worldwide, and mostly affects knee joint. The patients with knee OA usually suffer from severe knee symptoms and may even live with disability. There is no approved disease-modifying treatment available for knee OA, and existing management may only have limited effects or even have a range of side-effects. Thus, developing the preventive strategies of knee OA may be an effective way in reducing the disease burden. Magnetic resonance imaging (MRI) is an advanced technique which can detect early knee osteoarthritic changes. Several studies reported the associations between modifiable risk factors and MRI-based biomarkers in middle-aged or older adults, but few studies identified the relationships in young adults, who are the ideal target population for knee OA prevention. Therefore, this thesis aimed to describe associations between factors in early life and knee structures in young adults.

This thesis used data from an Australian-based cohort study. In 1985, the Australian Schools Health and Fitness Survey (ASHFS) was conducted to provide benchmark data on the health and fitness of Australian school children using a nationally representative sample. A total of 8498 children (aged 7-15 years) participated in ASHFS with childhood measurements collected. During 2004-2006, the Childhood Determinants of Adult Health (CDAH) study were conducted as a 20-year follow-up of ASHFS. 2410 participants (aged 26-36 years) completed a clinic visit with adult measurements collected. During 2008-2010, the participants residing in metropolitan Melbourne and Sydney were invited to participated in the CDAH Knee Cartilage study, which is a sub-study of the CDAH study. 330 participants (aged 31-41 years) completed the knee MRI scans and their knee structures were measured using MRI.

Chapter 3 described the associations between childhood adiposity measures and adult knee cartilage defects and bone marrow lesions (BMLs). Childhood adiposity measures, including weight, body mass index (BMI), overweight status and fat mass, were associated with the higher risk of adult patellar cartilage defects. Childhood overweight status was associated with the higher risk of adult patellar BMLs. These associations persisted after further adjusting for corresponding adiposity measure in adulthood. No associations identified in femorotibial compartment. These findings suggested adiposity in childhood may have long-term and independent effects on patellar structural abnormalities in young adults.

Chapter 4 described the associations of adiposity measures in childhood and adulthood with knee cartilage thickness, volume and bone area in young adults. Childhood weight and BMI were negatively associated with adult patellar bone area, suggesting the long-term detrimental effects of childhood adiposity on adult patellar morphology. Adult weight was positively associated with bone area in femorotibial compartments, which may be the response to mechanical stress from excess adiposity. Adult waist-hip ratio (WHR) and the change of WHR from childhood to adulthood were negatively associated with cartilage thickness, volume, and bone area, suggesting central obesity during early life could be detrimental to knee cartilage and bone morphology in young adults.

Chapter 5 described associations of body composition, physical activity and physical performance with knee cartilage thickness and subchondral bone area in young adults. Lean mass was positively associated with knee cartilage thickness and subchondral bone area, whereas no significant associations were found for fat mass. Physical activity, including walking, moderate activity, vigorous activity, and total physical activity, were not associated with cartilage thickness or bone area. Long jump, hand grip strength, and physical work

capacity, but not leg strength, were positively associated with cartilage thickness. All the physical performance measures (Long jump, hand grip strength, physical work capacity, and leg strength) were positively associated with subchondral bone area. The significant associations for physical performance were largely disappeared after further adjusting for lean mass, and the mediation analysis confirmed the mediating effects of lean mass. These findings suggest that lean mass may play an important role in maintaining knee joint health in young adults.

Chapter 6 described the associations of glucose homeostasis and metabolic syndrome (MetS) measures with knee cartilage defects and cartilage volume in young adults. Most glucose homeostasis measures, including fasting insulin, homeostatic model assessment 2 (HOMA2)-insulin resistance, HOMA2-beta cell function, HOMA2-insulin sensitivity, but not fasting glucose, were associated with tibiofemoral cartilage defects. No associations were identified between glucose homeostasis measures and knee cartilage volume. MetS was not associated with knee cartilage defects or cartilage volume. However, two MetS components (high waist circumference and low high-density lipoprotein cholesterol) were associated with the higher risk of tibiofemoral cartilage defects. These results suggested glucose homeostasis and some MetS components may affect early cartilage damage in young adults.

In conclusion, this thesis indicates that early life factors may affect knee joint health in young adults. Our findings may be useful in developing preventive strategies for knee OA, though further confirmatory studies are needed.

Chapter 1: Introduction

1.1 Overview of knee osteoarthritis (OA)

1.1.1 What is knee OA

OA is a common form of arthritis, and knee is the most commonly affected joint. The hallmark of knee OA is the breakdown of articular cartilage; however, knee OA also involves several other alterations in surrounding joint structures, including subchondral bone [1]. Pain is the primary symptom of knee OA and is usually the reason for seeking medical support [2]. With the disease progression, knee OA patients may suffer from joint stiffness, dysfunction, and even disability [1].

The definition of knee OA was evolving in the past decades. Kellgren-Lawrence (K-L) grading system was the first criteria for defining knee OA [3]. The system was an ordinal 5-point grading system, based on the joint characters in radiographs. The criteria were then accepted by the World Health Organization and were widely used in epidemiological studies. The details of K-L grading system are presented in Table 1.1.

Table 1.1 Kellgren-Lawrence grading system

Grade	Description
0, none	No changes.
1, doubtful	Doubtful narrowing of joint space, possible osteophytic lipping.
2, minimal	Definite osteophytes, little or mild narrowing of joint space.
3, moderate	Multiple osteophytes, definite narrowing of joint space, some sclerosis, and possible deformity of bone ends.
4, severe	Large osteophytes, marked narrowing of joint space, severe sclerosis, and definite deformity of bone ends.

Some other systems were also developed for defining knee OA. For example, the Osteoarthritis Research Society International (OARSI) atlas system [4] used semi-quantitative scores to assess joint space narrowing (JSN) and osteophytes in each knee compartment. As these systems were based on radiographs, the diagnosed knee OA was usually called radiographic knee OA.

Although the definition of radiographic knee OA was well developed, there is a major discordance between radiographic alterations and knee symptoms. Previous studies reported that only 15-76% patients with knee pain met the definition of radiographic knee OA [5]. To account for those without definite radiographic changes, the concept of clinical knee OA was developed by the American College of Rheumatology (ACR) [6]. The diagnosis of clinical knee OA can only utilise knee symptoms and clinical signs, such as pain, crepitus and stiffness. This innovation largely expanded the scope of knee OA and provided a cheap and convenient way in knee OA diagnosis. This innovation comes particularly important and useful for epidemiologic studies, which usually include larger populations with less costs.

The European League Against Rheumatism (EULAR) also developed the criteria for diagnosis of clinical knee OA [7]. The criteria suggested that 3 symptoms (persistent knee pain, limited morning stiffness and reduced function) and 3 clinical signs (crepitus, restricted movement and bony enlargement) are mostly important and useful in diagnosis. The number of positive symptoms and clinical signs is positively related to the probability of having radiographic knee OA. When a patient has all the 3 symptoms and 3 clinical signs, the probability of having radiographic knee OA could be 99%. Thus, the criteria suggested that thorough clinical assessment alone can provide a confident rule in diagnosis of knee OA.

1.1.2 Epidemiology and burden

The prevalence of knee OA could be various, as the definitions of knee OA, countries of origin, and age and sex composition of study population are different. The Global Burden of Disease 2010 study estimated that the global prevalence of radiographically confirmed symptomatic knee OA in 2010 was 3.8% [8]. OA is a major contributor to global disability. The total years of life lived with disability (YLDs) associated with OA were over 12 million in 2013, which ranked the 13th leading cause of YLDs [9]. Moreover, OA was the 4th fastest increasing cause of YLDs, with a 75% increase of total YLDs from 1990 to 2013 [9]. The specific amount of global economic cost of knee OA is unclear. However, the amount was estimated to be large as both direct costs (e.g. pharmacological treatments, surgery, and caregiver payment) and indirect costs (e.g. loss of productivity, disability compensation, and potential depression/anxiety) were high [10].

In Australia, OA affects over 2.2 million people (prevalence: 9.3%). In particular, the prevalence increased sharply from the age of 45 years [11]. The prevalence of self-reported poor health, severe bodily pain, and high psychological distress were twice among Australians over 45 years and with OA compared to those over 45 years and without OA [11]. OA cost Australian health system $3.5 billion in 2015-2016, representing 28% of disease expenditure on musculoskeletal disorders and 3% of total disease expenditure [12]. The major expenditure was the cost of knee replacement. Over 53,000 knee replacement procedures with a principal diagnosis of knee OA were performed in Australian hospitals during 2016-17, with a total cost of over $1.1 billion [11, 12]. With the aging of population and the increase of overweight/obesity rate, the incidence of knee replacement was estimated to rise by 50% by 2030, and the total cost was estimated to be $1.6 billion [13].

1.1.3 Management

Given the heavy social and economic burden of knee OA, several disease management guidelines were developed by professional associations, including ACR [14], OARSI [15], European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) [16] and American Academy of Orthopaedic Surgeons (AAOS) [17]. Among these guidelines, the non-pharmacologic treatments (exercise, weight loss and education) were consistently suggested as the foundation of knee OA management. A Cochrane systematic review included 54 high-quality randomised clinical trials (RCTs) and reported that land-based therapeutic exercise provided benefits on reducing pain, improving joint function, and enhancing quality of life among knee OA patients [18]. Similarly, a recent systematic review summarized the findings from 12 RCTs and reported that resistance training improved pain and physical function in knee OA patients [19]. However, due to heterogeneity of the studies, the optimal exercise prescription (including the recommended kinds of exercise, the optimal duration, intensity, and frequency) is unavailable. Moreover, the long-term effectiveness of exercise is unclear as the adherence and compliance may be a barrier to gain an approving result [20]. For the knee OA patients who are overweight or obese, weight loss is important. A meta-analysis summarized the findings from 9 RCTs and reported that weight loss induced by diet and exercise could reduce knee pain and improve joint function in overweight/obese knee OA patients; however, the diet-only induced weight loss did not achieve a significant pain relief [21], suggesting the methods of weight loss may affect the effectiveness. Moreover, the degree of weight loss may be also important, as a post-hoc analysis of an RCT reported clear dose-responses to weight loss for knee pain, joint function and quality of life, and suggested that at least 10% weight loss should be obtained to get an evident result [22]. Patient education is an approach with potential benefits and minimal risks. Disease knowledge, principles of management, and effects and side effects of interventions are the key messages

which were suggested to be delivered to patients [23]. However, the effect size from the education program is small [24].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most common medications in knee OA management. Two recent meta-analyses assessed the efficacy and safety of the use of topical NSAIDs and oral NSAIDs on knee OA respectively. In the one about topical NSAIDs, results from 36 RCTs suggested that topical NSAIDs can reduce pain and improve function, without increased local or systemic adverse effects compared to placebo [25]. In the other one about oral NSAIDs, results from 72 RCTs suggested that the effects from oral NSAIDs peaked at 2 weeks on pain remission and function improvement [26] . However, the magnitude of oral NSAIDs effects would decrease after the peak time, and the incidence of gastrointestinal adverse events would increase by 38% when using the medication for 4 weeks [26] . Thus, the oral NSAIDs were recommended to be used with the lowest doses and the shortest duration as possible. The mechanism of NSAIDs use is that the suppression of cyclooxygenase enzymes can reduce the synthesis of prostaglandins and then have the analgesic effects. Therefore, NSAIDs cannot slow or halt the development or progression of knee OA.

The efficacy and safety of other pharmacologic options are controversial. For example, intra-articular corticosteroids are strongly recommended in ACR guideline, but a Cochrane systematic review argued that the benefits from corticosteroids were short-term and the overall quality of previous evidence was low [27]. Moreover, a recent high-quality RCT used intra-articular injection of 40 mg of triamcinolone acetonide every 3 months among symptomatic knee OA patients with ultrasonic features of synovitis, and reported that 2 years of intra-articular triamcinolone (compared with intra-articular saline) cannot reduce the knee pain but lead to a significantly greater cartilage volume loss [28]. Thus, the effectiveness of intra-

articular corticosteroids is still unclear. There are some other pharmacologic interventions suggested by the guidelines, whereas the recommendations were not consistent (Table 1.2).

When knee OA patients cannot get satisfied results from all the appropriate non-surgical treatments, surgery would be considered. Total knee replacement was associated with greater symptom relief than non-surgical management among patients who were eligible for surgery [29]. However, the knee replacement surgery may cause a range of adverse events, including bleeding, infection, post-surgery chronic pain. Moreover, a study using data from two large OA-specific cohorts (the Osteoarthritis Initiative Study and the Multicentre Osteoarthritis Study) reported that, due to the high cost of surgery, current practice of total knee replacement for knee OA has extremely limited cost-effectiveness on improving quality of life of knee OA patients at the group level [30].

Although there is a broad spectrum of interventions available for knee OA management, all of them have either small-moderate effects, adverse event risk or high cost, and none of them have disease-modifying effects which can stop or slow the structural progression of knee OA. Primary prevention of knee OA among healthy adults may be an ideal way, as it can effectively and efficiently relieve the disease burden. However, it is not well-developed due to little available evidence. Identifying the modifiable risk factors of knee osteoarthritic changes may be helpful in developing the preventive strategies. The details of imaging biomarkers and modifiable risk factors of knee OA focused in this thesis are shown in the following sections.

Table 1.2 Pharmacologic recommendations from OARSI, AAOS, ACR and ESCEO guidelines.

Guideline	Oral NSAID	Topical NSAID	Intra-articular corticosteroids	Acetaminophen/ paracetamol	Glucosamine/ chondroitin	Opioids	Duloxetine	Intra-articular hyaluronic acid
OARSI[a]	1B	1A	1B	4A	4A	4A	3	2
AAOS[b]	S	S	I	I	NR	I	NR	NR
ACR[c]	SR	SR	SR	CR	SRA	CRA	CR	CRA
ESCEO[d]	SR	SR	WR	WRA	SR	WR	WR	WR

[a]OARSI: Level 1A- ⩾75% in favour & >50% strong, Level 1B- ⩾75% in favour & >50% conditional, Level 2- 60%-74% in favour, Level 3- 41%–59% in favour, Level 4A- 60–74% against, Level 4B- ⩾75% against & >50% conditional, Level 5- 75-100% against & >50% strong.

[b]AAOS: Strong (S), Moderate (M), Limited (L), Inconclusive (I), Consensus (C), NR (not recommended).

[c]ACR: Strong Recommendation (SR), Conditional Recommendation (CR), Conditionally Recommended Against (CRA), Strongly Recommended Against (SRA).

[d]ESCEO recommendation grades: Strong recommendation (SR), Weak recommendation (WR), Weak recommendation against (WRA), Strong recommendation against (SRA).

Source: Adapted from Cao et al. Pharmacotherapy for knee osteoarthritis: current and emerging therapies. Expert Opinion on Pharmacotherapy. 2020. doi: 10.1080/14656566.2020.1732924

1.2 Knee structures measured using MRI

1.2.1 The advantages of MRI

Radiography was traditionally used to diagnose knee OA based on osteophytes and JSN. In the recent EULAR recommendations, radiography is still the first-choice imaging modality in knee OA clinical management [31]. Despite the high availability and low cost, radiography has several limitations. The main disadvantage is that radiography cannot assess most of osteoarthritic features. Knee OA is a disease involving the while-joint pathologic changes, the disease process is complex with multiple structural alterations, such as cartilage defects, BMLs and meniscal damage. However, radiography cannot depict the overall circumstance of disease as it can only indirectly assess the knee cartilage loss using the JSN. Moreover, the radiographic appearance of tibiofemoral joint space is heavily dependent on knee positioning and the angle of joint flexion, so the reproducibility of this measure is limited and the comparison between multiple time points may be not accurate.

MRI is an advanced technique with several advantages over radiography. The major advantage is it can evaluate most osteoarthritic features in both articular cartilage and periarticular structures including subchondral bone, meniscus and ligaments. In particular, a recent meta-analysis reported that the prevalence of MRI-based knee OA features among asymptomatic uninjured knees were 4-14% in adults aged <40 years [32], suggesting MRI is important in assessing early knee OA changes in young adults who are the ideal target in knee OA prevention. Moreover, as the validity and reliability of MRI measures have been approved, the longitudinal changes of knee structures can be accurately assessed using MRI with the development and progression of knee OA. Thus, MRI has been recommended as the most important imaging modality for knee OA research [33]. The details of the use, advantages, and disadvantages of radiography and MRI for knee OA are summarised in Table 1.3.

Table 1.3 Summary of use, advantages and disadvantages of radiography and MRI.

Modality	Use	Advantages	Disadvantages
Radiography	a. First line imaging modality for routine clinical care of osteoarthritis b. Assess osteophytes and joint space narrowing c. Severity classification based on Kellgren-Lawrence grading or Osteoarthritis Research Society International Atlas	a. Widely available b. Low cost	a. Minimal radiation b. Unable to depict most of osteoarthritis features including cartilage defects, meniscal damage, bone marrow lesions, synovitis, ligamentous damage c. Problem with reproducibility when comparing multiple time points because joint space width can changes depending on the positioning of the knee joint d. Limited sensitivity to change
MRI	a. Most important imaging modality for research b. Evaluation of all articular and periarticular structures including cartilage, meniscus, ligaments, bone marrow lesions, subchondral cysts, osteophytes, synovitis, effusion c. Contrast enhanced MRI can accurate evaluate synovitis d. Currently limited clinical role in routine patient care of osteoarthritis	a. Detailed morphologic analysis using semiquantitative and quantitative techniques b. Pre-morphologic analysis (biochemical composition of articular tissues) using compositional techniques c. No radiation	a. Costly b. Advanced compositional techniques may be limited to academic institutions with specialised software and hardware c. May be contraindicated in some patients (e.g. cardiac pacemaker)

Source: Adapted from Hayashi et al. Recent advances in research imaging of osteoarthritis with focus on MRI, ultrasound and hybrid imaging. Clinical and Experimental Rheumatology 2018; 36 Suppl 114(5):43-52.

As MRI has several advantages in assessing knee OA, some MRI-based knee structures were set as imaging biomarkers and have been widely used in clinical trials and observational studies [34]. The following sections highlighted the MRI-based pathologic changes (cartilage defects and BMLs) and morphological measures (cartilage volume, cartilage thickness and bone area) which were focused in this thesis.

1.2.2 Cartilage defects

Cartilage defects refer to the focal damage of articular cartilage, which is usually assessed using semi-quantitative scoring system. It is an indicator of early cartilage damage, with a prevalence of 24% in asymptomatic uninjured knees [32]. The predictive value of cartilage defects to knee pain has been examined in several studies. A nested case-control study reported that the baseline cartilage defects were associated with a 3-fold odd of incident knee pain over 48 months [35]. A population-based cohort reported that baseline cartilage defects can predict a 2-fold risk of "moderate pain" trajectory over 10.7 years (pain scored about 15 out of 45) [36]. Moreover, a dose-response association between number of sites having severe cartilage defects and severity of knee pain was found among a community-based study [37].

Cartilage defects were also associated with knee structural alterations. A nested case-control study reported that both partial- and full-thickness cartilage defects increased the risk of developing new cartilage damage in middle-aged to older adults with or at high risk of knee OA [38]. A population-based study reported that baseline cartilage defects could predict site-specific BMLs progression over 2.7 years and vice versa, suggesting cartilage defects and BMLs are interconnected [39]. Moreover, a cohort study among older adults reported that baseline cartilage defect grade predicted cartilage volume loss at the medial tibia, lateral tibia and patella over 2.9 years (β=-1.78% to -1.27% per annum per 1 grade increase) [40]. These

findings were consistent with the evidence which suggested a relationship between cartilage defects and subsequent total knee replacement surgery. Data from the Osteoarthritis Initiative Cohort reported that baseline cartilage defect scores assessed using either the Whole-Organ Magnetic Resonance Imaging Score (WORMS) system or the Boston-Leeds Osteoarthritis Knee Score (BLOKS) system were significantly and independently predictive of subsequent knee replacement (BLOKS: Hazard ratio (HR) 3.02/score, 95% confidence interval (CI) 1.07-8.52 ; WORMS HR 2.60/score, 95% CI 1.18-5.68) [41]. Another prospective study among older adults using a validated classification system (Grade 0-4) reported that per 1 grade increase of cartilage defects was associated a 1.73 odd of knee replacement over 5 years [40].

1.2.3 Bone marrow lesions

BMLs represent a wide variety of early lesions in subchondral bone with high signals in MRI. The histopathology of BMLs has not been fully understood, but it could contain remodelled trabeculae, bone marrow fibrosis, bone marrow necrosis [42]. BMLs are the most important subchondral bone abnormalities in knee OA and have been found in asymptomatic uninjured adults with a prevalence of 18% [32]. The relationship between BMLs and knee pain has been suggested in previous studies. A recent population-based study among older adults reported that the presence of BMLs was associated with more severe knee pain cross-sectionally and knee pain progression longitudinally [43]. A prospective study reported that BML size has a dose-responsive relationship with the severity of knee pain in older adults [44]. In particular, a study in young adults reported that BMLs were cross-sectionally associated with more severe knee pain, suggesting the clinic significance of BMLs during early life [45].

BMLs are also related to knee OA structural progression. The data from Osteoarthritis Initiative cohort reported that presence of baseline BMLs was associated with accelerated cartilage

volume loss over 2 years (medial tibia: β=-2.1% per annum; lateral tibia: β=-1.9% per annum) [46]. Similarly, another cohort among older adults reported that baseline patellar BMLs were associated with larger patellar cartilage volume loss over 2.6 years (β=-2.1% per annum) [47]. Moreover, in older adults, baseline BMLs were related to the higher risk of progression of radiographic OA, which was defined by a baseline K-L grade of 2 or 3 changing to a higher grade by 48-month follow-up [46]. These findings were consistent with the studies suggesting the predictive value of BMLs to knee replacement. A longitudinal study among symptomatic knee OA patients reported that per 1 BML score higher (out of 4 in total) at baseline was associated with a 1.57-fold odd of knee replacement over 4 years [48]. A cohort study among radiographic knee OA patients (K-L grade $\geqslant$2) reported that the presence of baseline BMLs was associated with the higher risk of knee replacement over 3 years (odds ratio (OR) range 1.5-2.4) [46]. In particular, a follow-up of knee OA patients who participated in a clinical trial about intra-articular injections of hyaluronic acid reported that baseline BMLs were associated with a 2.3-fold odd of subsequent knee replacement over 15 years, suggesting BMLs may be the long-term risk of following knee replacement surgery [49].

1.2.4 Cartilage volume, cartilage thickness and bone area

Cartilage volume loss is the most representative hallmark of knee OA. It was previously indicated by JSN in radiography and now can be quantitatively measured using MRI. Some studies identified the correlation between knee cartilage volume loss in MRI and JSN in radiography. Cicuttini et al reported that, in knee OA patients, the total of tibial and femoral cartilage volume had a modest correlation with joint space width (r=0.64), but the cartilage volume loss was not associated with JSN over 2 years [50]. Similarly, a prospective study did not find a significant correlation between cartilage volume loss and JSN over a 10-year follow-up [51]. However, a nested case-control study reported that medial femoral cartilage volume

loss was strongly associated with radiographic progression (defined by medial tibiofemoral JSN >0.7 mm) in those with or at high risk of knee OA [52]. The inconsistent findings may be due to the limitation of radiography in assessing structural changes as we discussed in Section 1.2.1. The association between cartilage volume loss and knee replacement has also been described in several studies. A study among knee OA patients reported that every 1% increase of the rate of tibial cartilage volume loss was independently predicted a 20% increase risk of undergoing a knee replacement at 4 years [53]. Moreover, a narrative review concluded that cartilage volume loss was a viable MRI parameter, which could predict knee replacement in a continuous manner [54]. Thus, the cartilage volume loss assessed in MRI has been suggested as a better indicator of knee OA progression and was usually set as a primary outcome in clinical trials [28, 55].

Despite the wide use of cartilage volume in knee OA research, it can be greatly affected by subchondral bone area [56]. Several studies assessed the predictive value of cartilage thickness in knee OA, which is independent of bone area. A nested case-control study reported that loss of medial femorotibial cartilage thickness was strongly associated with radiographic progression (OR 4.0, 95% CI 2.9, 5.3) and weakly associated with pain progression (OR 1.3, 95% CI 1.1, 1.6) [57]. A longitudinal study extended these findings and reported that the concurrent cartilage thickness loss (occurred in the 2-year follow-up) was associated with the radiographic progression (OR 3.4, 95% CI 2.6, 4.3) and symptomatic progression (OR 1.5, 95% CI 1.2, 1.7) over 2 years, whereas the preceding cartilage thickness loss (occurred in the past 2 years before baseline) was only associated with the radiographic progression (OR 1.3, 95% CI 1.1, 1.5) but not the symptomatic progression [58]. Moreover, a recent study identified the trajectories of medial femorotibial cartilage thickness at baseline, 1 and 2 years in those with or at high risk of knee OA, and determined the optimal model with 3 distinct trajectories: stable

(mean change = -0.08 mm), moderate decline (mean change = -0.75 mm), and greatest decline (mean change = -1.38mm) [59]. The study suggested that the two progression trajectories combined was associated with knee pain progression over 2 years (OR 1.99, 95% CI 1.34, 2.97) and incidence of knee replacement over 4 years (OR 4.34, 95% CI 1.62, 11.62) [59]. Thus, the measurement of cartilage thickness has also been accepted as an imaging biomarker and was used in clinical trials [60, 61].

Subchondral bone area may also play a role in knee OA. A prospective study in older adults reported that baseline tibial bone area predicted the incidence of following cartilage defects (OR 1.6-2.4 per z-score increase) and medial tibial cartilage volume loss (β -34.9 mm^3 per z-score increase) over 2.7 years [62]. Similarly, a nested case-control study in knees with mild-to-moderate radiographic OA reported that the 24-month change of bone area across all the compartments (including medial and lateral femur, tibia and patella) were associated with the combination of radiographic and pain progression over 48 months (OR 1.28-1.71 per z-score increase) [63]. However, larger bone area in childhood or young adults has been suggested having physiologic benefits, as the physiological accrual can distribute joint loading over a larger surface [64].

1.3 Modifiable risk factors of knee OA

1.3.1 Obesity/overweight

Obesity/overweight has long been recognized as a risk factor of knee OA. A meta-analysis of cohort studies in older adults (⩾50 years) reported that being overweight/obese was associated higher risk of the onset of knee pain (Overweight: OR 1.98, 95% CI 1.57, 2.20; obesity: OR 2.66, 95% CI 2.15, 3.28) [65]. Similarly, another meta-analysis reported that, compared to healthy participants, the BMI was higher in adults with patellofemoral pain (standardised mean difference (SMD) 0.24, 95% CI 0.12 to 0.36) and patellofemoral OA (SMD 0.73, 95% CI 0.46 to 0.99) [66]. Recent studies provided further evidence which confirmed that obesity is a major risk of knee OA. A longitudinal study reported that baseline obesity was associated with higher risk of incident radiographic knee OA over 5 years among community-dwelling older adults (Relative risk (RR) 1.87, 95% CI 1.46, 2.40) [67]. Similarly, a nested case-control study reported that BMI was associated with higher risk of incident radiographic knee OA over 2 years (OR 1.51/kg/m^2, 95% CI 1.20, 1.90) [68].

The effects of obesity/overweight on MRI-based knee structures were also identified in previous studies. A systematic review of observational study examined the relationships between obesity and knee cartilage, and reported that BMI has a consistent detrimental effect on cartilage defects and a modest detrimental effect on cartilage volume loss [69]. A recent cross-sectional analysis among asymptomatic people (40-79 years) reported that people of overweight status (BMI⩾25) had a 3-fold increased odd of having cartilage defects [70]. Collins et al. evaluated the in vivo data of knee cartilage mechanics and composition under the influence of obesity, and reported that the strains and T1ρ relaxation times in tibiofemoral cartilage were increased in obese people, which resulted in the reduction of tibial cartilage thickness [71]. Similarly, there was a systematic review reported the moderate evidence from

observational studies supporting the relationship between BMI and the prevalence and incidence of knee BMLs [72]. A recent longitudinal study reported that, in overweight/obese women without clinical knee OA, participants with weight gain (average 8.6 kg) over 2.5 years would have a 1.62 odd of the progression of patellofemoral BMLs compared to those with stable weight [73].

Although there is a well-established link between obesity and knee OA, most of previous studies were conducted among middle-aged to older adults, with few studies identified the relationships during early life. A population-based British birth cohort reported that the association between BMI and later clinical knee OA (assessed by ACR criteria) became significant at 20 years in men and 15 years in women [74]. In addition, Gelber et al. reported that higher BMI in young men (aged 20-29 years) was associated with higher risk of subsequent knee OA (self-reported) during a median follow-up of 36 years [75]. These findings suggested that obesity/overweight in young adults could be a risk of knee OA development. However, no study identified the associations between obesity/overweight and MRI-based knee structures in young adults. Moreover, a longitudinal study reported that childhood overweight was independently associated with higher risk of adult knee pain in young men (RR 1.68, 95% CI 1.06, 2.65), suggesting childhood overweight may have long-term detrimental effects on knee joint health [76]. However, no study reported the effects of overweight in childhood on knee structures in young adults.

1.3.2 Body composition

In addition to obesity, body composition also attracted attention in knee OA research, as it can distinguish the effects from different components of body weight (fat mass and lean mass). A recent meta-analysis of observational studies examined the association between fat mass and

knee OA (including radiographic, symptomatic and self-reported knee OA) [77]: fat mass was consistently associated with higher risk of knee OA in either case-control studies, cross-sectional studies or cohort studies, with the fat mass in those with knee OA being higher than in the those without knee OA (mean difference (MD) 4.38, 95% CI 2.84, 5.92); in particular, the higher risk of knee OA for fat mass was consistently reported in cohort studies (RR ranged 1.03-1.88). The meta-analysis also reported that the lean mass in those with knee OA was slightly higher than that in those without knee OA (MD 0.95, 95% CI -0.44, 2.34); this result may be due to the insufficient adjustment for body size in most studies, as the lean mass percentage was significantly and negatively associated with the risk of knee OA (pooled OR 0.65, 95% CI: 0.46–0.92).[77].

The relationship between body composition and knee cartilage was also identified in some studies. A community-based cohort (participants aged 40-69 years) reported that baseline fat mass predicted the higher risk of knee cartilage defects over 10 years (OR 1.04/kg, 95% CI 1.00, 1.07) [78]. A prospective study among older adults (aged 51-81 years) reported that baseline fat mass was associated with higher medial tibial cartilage volume loss over 2.9 years (β -0.10% per annum/kg, 95% CI -0.17, -0.03) [79]. On the contrary, lean mass has been associated with higher tibial cartilage volume cross-sectionally (β 46.0 mm^3/kg, 95% CI 23.0, 69.0) [80], higher tibial cartilage volume 10 years later (β 48.4 mm^3/kg, 95% CI 27.9, 68.9) [78] and lower cartilage volume loss in lateral tibia over 2.9 years (β -0.13% per annum/kg, 95% CI 0.04, 0.22) [79]. Most of previous studies were conducted among middle-aged to older adults, with only one study described the association between body composition and tibia cartilage volume in young adults. In that study, fat mass was negatively (β -11.8 mm^3/kg, 95% CI -22.2, -1.4) but lean mass was positively (26.4 mm^3/kg, 95% CI 13.6, 39.1) associated with tibial cartilage volume measured 5 years later [81]. However, that study was only focusing on

the tibia site, but not the whole knee joint (including tibia, femur and patella), and only used the cartilage volume, but not the other independent parameters (cartilage thickness and bone area) of knee joint morphology.

1.3.3 Physical activity and physical performance

Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure above resting (basal) levels, including all the activities done during exercise, daily living, occupation, leisure and active transportation. A recent umbrella review evaluated the evidence from systematic reviews, meta-analyses and pooled analyses during 2011-2018 regarding the effects of physical activity on knee OA, and reported that, among a total of 24,583 participants from 240 studies, physical activity was consistently associated with the reductions in pain (SMD 0.53) and improvements in physical function (SMD 0.76) and health-related quality of life (SMD 0.28) for knee OA [82]. An updated systematic review summarized the results from 33 RCTs which were published in 2018-2019, and reported that exercise intervention can effectively improve clinical symptoms in knee OA [83]. Moreover, in the 2018 EULAR recommendations for physical activity in people with knee OA, promoting physical activity was strongly recommended to be an integral part of standard care throughout the course of disease [84]. In contrast, the associations between physical activity and knee structures are remaining undetermined. Bricca et al. reported that female knee OA patients with moderate physical activity (defined by the Physical Activity Scale for the Elderly) had less cartilage thickness loss over 4 years compared to those with low physical activity (MD 0.09 mm, 95% CI 0.02, 0.16) [85]. However, another prospective study did not find associations between daily walking and radiographic worsening or MRI-based cartilage loss over 2 years in people at risk or with mild knee OA (K-L grade $\leqslant$2, aged 50-79 years) [86]. Moreover, a recent meta-analysis of RCTs investigated the effects of long-term exercise therapy (>6 months) for

people with knee OA, and did not find significant treatment effects from exercise on tibiofemoral radiographic disease severity or knee cartilage morphology [87].

Physical performance, defined as one's ability to carry out activities requiring specific physical actions, may also be associated with knee OA. A longitudinal analysis reported that, among people with medial meniscal pathology but without knee OA, those in the highest tertile of knee extensor strength had lower risk of the incident radiographic knee OA compared to those in the lowest tertile over 2 years (RR 0.52-0.56) [88]. A prospective study among the women with frequent knee pain reported that higher baseline knee extensor strength was associated with lower risk of following knee replacement over 7 years (HR 0.99/Nm, $p<0.0001$) and the poorer baseline stand performance (time of 5 chair standing without using hands) predicted the incident knee replacement within 2-2.5 years (OR 1.04/s, 95% CI 1.00, 1.08) [89]. Moreover, a recent nested case-control study investigated the association between physical performance and knee cartilage, and reported that a series of performance measures, including 20-m walk test, 5-min walk test, stair ascending and stair descending test, and timed up & go test, were significantly associated with MRI-defined knee cartilage degeneration (graded by the MRI Osteoarthritis Knee Score) [90].

A few studies identified the effects of physical activity and physical performance on knee cartilage during early life. A study among adolescents (9-18 years) reported that higher physical activity was associated with higher knee cartilage accrual over 1.6 years [91]. Van-Ginckel et al. reported that a 10-week moderate running intervention could improve the glycosaminoglycan content of knee cartilage among young women (average aged 25 years) [92]. Moreover, a longitudinal study reported that physical activities measured 5 years prior using the long version of International Physical Activity Questionnaire were consistently

associated with tibial cartilage volume in young adults (β 0.30-0.54 mm^3/min/week) [93]. In the same cohort, both childhood and adult physical performance measures (physical work capacity, 1.6-km long-run, 50-m short-run, sit-ups, and leg strength in childhood; physical work capacity, long jump, and leg strength in adulthood) were associated with higher tibial cartilage volume in young adults (31-41 years) [93, 94]. However, the magnitude of the associations with cartilage volume decreased dramatically after adjusting for bone area, suggesting the cartilage accrual may depend on the bone development. Thus, using both cartilage thickness and bone area may be required to accurately assess the associations of physical activity and physical performance with knee cartilage and bone morphology in young adults.

1.3.4 Diabetes and metabolic syndrome (MetS)

Diabetes and knee OA are commonly existing, whereas their relationship is not clear yet. Although a systematic review, which included the observational studies published before October 2016, reported that there was little evidence that impaired glucose metabolism was a risk factor for knee OA [95], recent studies indicated the potential detrimental effects from diabetes. A cross-sectional study compared the knee pain measured using the Knee injury and Osteoarthritis Outcome Score (0=worst pain, 100=no pain) between knee OA participants (K-L grade $\geqslant$1) with and without diabetes, and reported that individuals with diabetes experienced higher pain intensity (β=-4.73, 95% CI -7.22, -2.23) [96]. Driban et al. reported that high glycated serum protein was associated higher risk of the K-L grade increase (OR 3.21, 95% 1.07, 9.62) over 48 months among healthy participants (baseline K-L grade <2) [97]. The effects of diabetes on knee cartilage have also been identified in recent studies. Neumann et al. reported that diabetes was associated with more severe cartilage lesions (assessed using the WORMS) over 4 years among participants with K-L grade $\leqslant$2 [98]. Another study in the same

cohort reported that the increase of cartilage T2 relaxation time over 24 months in participants with diabetes was twice that in those without diabetes, suggesting diabetes may accelerate the knee cartilage degeneration [99]. Moreover, a cross-sectional study among older adults (averaged 63 years) reported that diabetes status was consistently associated with higher cartilage T2 texture parameters (including variance, contrast, and entropy), which are the indicators of early articular cartilage degeneration [100]. However, there is no recent evidence regarding the knee cartilage morphology. In addition, all the previous studies were conducted among middle to older adults, but no studies were in young adults.

The MetS is characterised as central obesity, dyslipidaemia, impaired fasting glucose, and hypertension. Emerging evidence from basic research indicated the theoretical links between MetS and knee OA and suggested that related metabolic pathways and mediators could be potential targets for knee OA treatment [101, 102]. Recent epidemiological studies also extended the understanding of the role of MetS in knee OA. A population-based cohort study reported that MetS and its components were associated with a 2-fold risk of belonging to the worse pain trajectory (consistently moderate pain) over 10 years [103]. The secondary analysis of that study suggested that the results were similar in those with radiographic knee OA. This was consistent with other three case-control studies, where MetS and its components were associated more severe knee pain in knee OA patients [104-106]. However, the association between MetS and the onset of knee OA has not been established. A recent systematic review summarised the published literature up to May 2018, and reported that the causal relations between MetS and knee OA cannot be determined due to the limited quality of available evidence and insufficient data [107]. After that, Lee et al. used the cross-sectional data (n=8491) from a national survey of South Korea, and reported that MetS was significantly associated with radiographic knee OA in women (OR 1.61, 95% CI 1.38, 1.87), but not in men [108]. In

contrast, the other cross-sectional data among British women (n=952, aged 45-65 years) did not find significant associations for MetS and knee OA [109]. Moreover, a nationally representative population sample of Finland (n=6274) reported that neither MetS nor its components increased the incident knee OA during a 32-year follow-up [110]. There are only two studies regarding the association between MetS and MRI-based knee cartilage measures. Jungmann et al. reported that MetS was cross-sectionally associated with higher T2 relaxation time (MD 1.2 ms, 95% CI 0.3, 2.1) among adults without knee OA (45-60 years) [111]. In the other study, MetS was associated with medial tibial cartilage volume loss over 10.7 years (β -0.30% per annum, 95% CI -0.46, -0.13) among a population-based sample (57-69 years) [112]. However, both of the studies were conducted among middle-aged to older adults, with no evidence in young adults.

1.4 Research questions and hypotheses

Given the background reviewed above, this thesis aimed to describe the associations between the modifiable factors in early life and the MRI-based knee structural measures in young adults. The detailed research questions and hypotheses are listed below.

Chapter 3: To describe the associations between childhood adiposity measures and adult knee cartilage defects and BMLs measured 25 years later.

Research questions:

a) Are childhood adiposity measures associated with adult cartilage defects or BMLs?

b) If present, are the associations independent of adult adiposity?

Hypotheses:

a) Childhood adiposity measures are associated with adult cartilage defects and BMLs.

b) The present associations are independent of adult adiposity.

Chapter 4: To describe the associations of adiposity measures in childhood and adulthood with knee cartilage thickness, volume and bone area in young adults.

Research questions:

a) Are childhood adiposity measures associated with adult knee cartilage thickness, volume and bone area?

b) Are adult adiposity measures associated with adult knee cartilage thickness, volume and bone area?

c) Are the changes of adiposity measures from childhood to adulthood associated with adult knee cartilage thickness, volume and bone area?

Hypotheses:

a) Childhood adiposity measures are associated with adult knee cartilage thickness, volume and bone area.

b) Adult adiposity measures are associated with adult knee cartilage thickness, volume and bone area.

c) The changes of adiposity measures from childhood to adulthood are associated with adult knee cartilage thickness, volume and bone area.

Chapter 5: To describe associations of body composition, physical activity and physical performance with knee cartilage thickness and bone area in young adults.

Research questions:

a) Is body composition associated with knee cartilage thickness and bone area in young adults?

b) Is physical activity associated with knee cartilage thickness and bone area in young adults?

c) Is physical performance associated with knee cartilage thickness and bone area in young adults?

d) Are the significant associations independent of each other?

Hypotheses:

a) Body composition is associated with knee cartilage thickness and bone area in young adults.

b) Physical activity is associated with knee cartilage thickness and bone area in young adults.

c) Physical performance is associated with knee cartilage thickness and bone area in young adults.

d) The significant associations may be not independent of each other.

Chapter 6: To describe the associations of glucose homeostasis and MetS measures with knee cartilage defects and cartilage volume in young adults.

Research questions:

a) Are glucose homeostasis measures associated with knee cartilage defects or cartilage volume?

b) Are MetS measures associated with knee cartilage defects or cartilage volume?

Hypotheses:

a) Glucose homeostasis measures are associated with knee cartilage defects and cartilage volume.

b) MetS measures are associated with knee cartilage defects and cartilage volume.

Chapter 2: Methods

2.1 Participants

In 1985, the Australian Schools Health and Fitness Survey (ASHFS) was conducted to provide benchmark data on the health and fitness of Australian school children using a nationally representative sample. Two-stage probability sampling was used for the ASHFS to randomly select schools and then children within age groups in the schools. The details of enrolment of the ASHFS was published elsewhere [113]. 8498 children (aged 7-15 years) were selected in ASHFS. All the children provided assent and parents provided written informed consent. ASHFS was approved by the State Directors General of Education. The childhood measures in this thesis were collected in ASHFS.

During 2004-2006, the participants of ASHFS were invited to participated in the Childhood Determinants of Adult Health (CDAH) study, which is the 20-year follow-up of ASHFS. The details of enrolment of the CDAH study was published elsewhere [114]. Participants attended clinics which were located at sites in major cities and regional centres around Australia. 2410 participants (aged 26-36 years) completed the clinic visit. All the participants provided written informed consent. The study was approved by the Southern Tasmania Health and Medical Human Research Ethics Committee (HREC) (Ethics Approval Number: H0008152). The adult measures in this thesis were collected during the CDAH clinic visit.

During 2008-2010, the participants of CDAH study were invited to participated in the CDAH Knee Cartilage study, which is a sub-study of the CDAH study. Participants residing in metropolitan Melbourne and Sydney were invited by mail. Participants who agreed to participate were assessed for eligibility. Exclusion criteria included being pregnant, having diseases that might affect knee cartilage (including rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and psoriatic arthritis) or having magnetic resonance

imaging (MRI) contraindications. The remaining participants were asked to complete a computer-assisted telephone interview, with knee injury history recorded. Childhood knee injury history was recorded in response to the question “Have you had a knee injury requiring non-weight bearing treatment more than 24 hours or surgery during childhood?”. Adult knee injury history was recorded in response to the question “Have you had a knee injury requiring non-weight bearing treatment more than 24 hours or surgery in your adult life?”. Then the participants were requested to have the knee MRI scan at Epworth Hospital in Melbourne or North Shore Private Hospital in Sydney. 330 participants (aged 31-41 years) completed the knee MRI scans. All the participants provided written informed consent. The study was approved by the Southern Tasmanian Health and Medical HREC, the Monash University HREC and the Northern Sydney and Central Coast Area HREC (Ethics Approval Number: H0009828). The knee structural measures in this thesis were measured from the knee MRI scans.

The flowchart of the selection of participants for this thesis is shown in Figure 2.1.

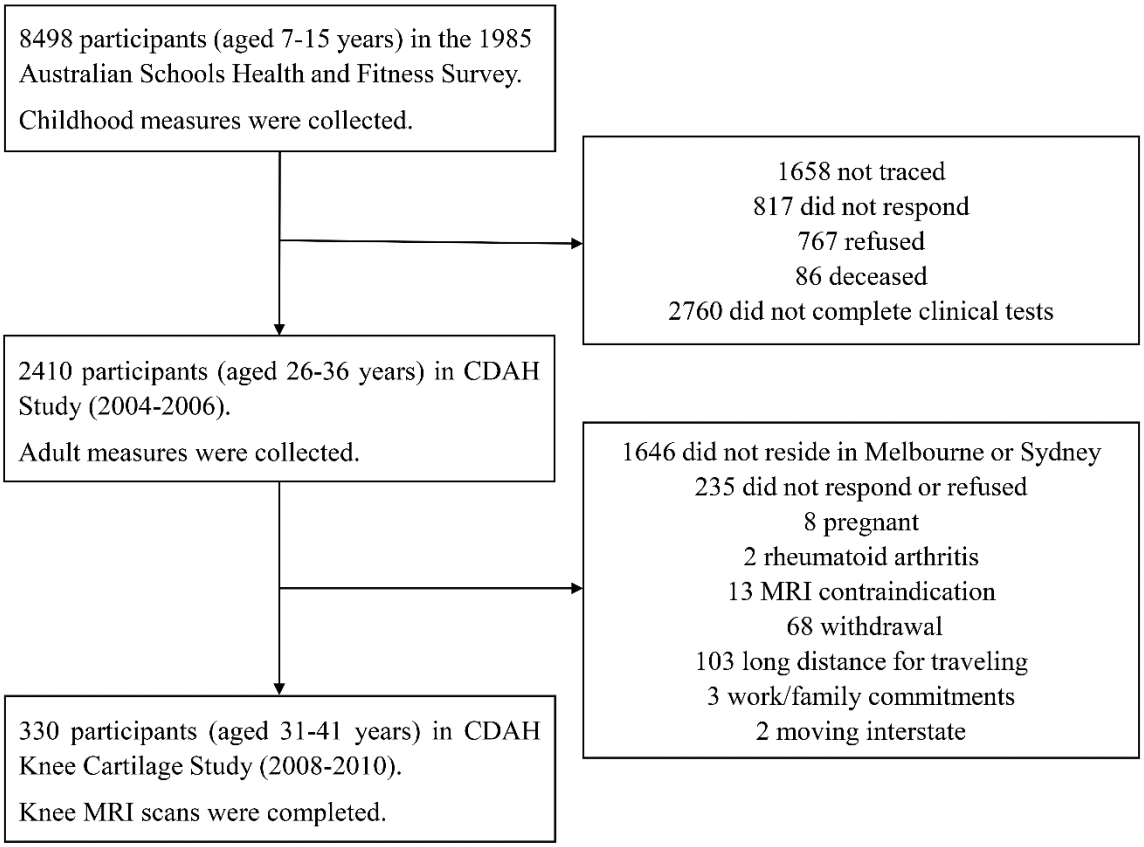

Figure 2.1 Flowchart showing selection of the participants in this thesis

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

2.2 Anthropometric measurements

2.2.1 Childhood anthropometric measurements

In ASHFS, weight was measured to the nearest 0.5 kg using regularly calibrated scales with shoes, socks and bulky clothing removed. Height was measured to the nearest 0.1 cm using a Kawe height tape with shoes and socks removed. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Childhood overweight status was defined according to age and sex-specific cut-off points [115].

Triceps, biceps, subscapular, and supra-iliac skinfolds were measured at locations determined by reference to anatomical landmarks [116] to the nearest 0.1 mm using Holtain Skinfold Calipers. All the data collectors were trained. Body density was estimated from the log of the sum of four skinfolds using age-specific regression equations [116, 117]. Estimate of percent body fat was derived from body density [118], Fat mass and lean mass were estimated by the percent body fat: fat mass = fat (%) × weight (kg); lean mass = weight - fat (%) × weight (kg).

Waist circumference and hip circumference were measured to the nearest 0.1 cm using a constant tension tape. Waist-hip ratio (WHR) was calculated by dividing waist circumference in centimetre by hip circumference in centimetres.

2.2.2 Adult anthropometric measurements

In the CDAH study, weight was measured to the nearest 0.1 kg using digital Heine portable scales (Heine, Dover, NH, USA) with shoes, socks and bulky clothing removed. Height was measured to the nearest 0.1 cm using a stadiometer (Invicta, Leicester, UK) with shoes and socks removed. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Adult overweight status was defined as a BMI $\geqslant$25 kg/m^2.

Triceps, biceps, subscapular, and supra-iliac skinfolds were measured at locations determined by reference to anatomical landmarks [117, 119] to the nearest 0.1 mm using Slim Guide Skinfold Calipers (SPRI Products). All the data collectors were trained. Body density was estimated from the log of the sum of four skinfolds using Durnin's equation; the slope and intercept of the equations for each age- and sex-specific group have been published elsewhere [117, 119]. An estimate of the percent body fat was derived from body density using Siri's equation: fat (%) = (4.95/density-4.50) × 100 [118]. Fat mass and lean mass were estimated by the percent body fat: fat mass = fat (%) × weight (kg); lean mass=weight - fat(%) × weight (kg).

Waist circumference and hip circumference were measured to the nearest 0.1 cm using a constant tension tape. WHR was calculated by dividing waist circumference in centimetre by hip circumference in centimetres.

2.3 Physical activity measurements

The physical activity measurements were collected during the CDAH study. Physical activity was assessed using the long version of the International Physical Activity Questionnaire. Participants were asked to report the total time (minutes) and frequency (times/week) of occupational, commuting, domestic and leisure activity during the past week. Physical activities were calculated by multiplying frequency by duration to represent the minutes per week of vigorous, moderate and walking activity. Time spent in each domain was summed to provide the estimate of total minutes of physical activity.

2.4 Physical performance measurements

The physical performance measurements were collected during the CDAH study. All the measurements were collected by the trained data collectors based on a documented protocol. All the participants were shown how to complete the measurements before the formal collections. The participants were asked to perform with their maximal effort during the formal collections. The standing long jump was measured by asking the participants to stand on the gym mat with toes behind the line and with feet slightly apart. A two-foot take-off and landing was used, with the participants swinging the arms and bending the knees to provide the drive for jump. The landing point at the closest part of the heel to the starting line was marked and the distance to the starting line was measured. Right and left hand grip strength was measured as participants gripped the dynamometer (Smedley dynamometer, TTM, Tokyo, Japan) with maximum force in one hand, with the higher of two measurements recorded. Hand grip strength was determined by calculating the average of right and left hand grip strength. Leg strength was measured using a leg-back dynamometer (Muscle Meter, TTM, Tokyo, Japan) by standing flat-footed on a platform with a straight back flat against a wall. A hand bar was held with an overhand grip and knees were flexed at an angle of 115°, at which point the bar was attached to the dynamometer by a chain. The bar was then pulled as far upwards as possible by sliding the body up the wall. Physical work capacity at a heart rate of 170 bpm (PWC170) was assessed using a Monark bicycle ergometer. Participants were asked to cycle at a constant 60 rpm for 3 min each at three successively increasing but submaximal workloads. Heart rate was recorded at 1 min intervals at each workload using an electronic heart rate monitor. PWC170 was calculated by linear regression with extrapolation of the line of best fit to a heart rate of 170 bpm.

2.5 Glucose homeostasis measurements

Glucose homeostasis measurements were collected in the CDAH study. Fasting glucose and insulin levels were measured using venous blood samples collected from the antecubital vein after a 12-hour fast. An Olympus AU5400 automated analyser (Olympus Optical, Tokyo, Japan) was used to enzymatically measure fasting glucose. A microparticle enzyme immunoassay kit (AxSYM; Abbot Laboratories, Abbot Park, IL) or an electrochemiluminescence immunoassay (Elecsys Modular Analytics E170; Roche Diagnostics, Mannheim, Switzerland) with inter-assay standardisation was used to measure fasting insulin. Glucose homeostasis measures, including homeostatic model assessment 2-insulin resistance (HOMA2-IR), HOMA2-beta cell function (HOMA2-β) and HOMA2-insulin sensitivity (HOMA2-S), were calculated by a homeostasis model assessment calculator (version 2.2.3 available from http://www.dtu.ox.ac.uk/homacalculator) using fasting glucose and fasting insulin.

2.6 Metabolic syndrome (MetS) measurements

MetS measurements were collected in the CDAH study. MetS was defined using the harmonized definition [120]. Five components of MetS and their thresholds were proposed in the definition. MetS was diagnosed when at least three of the five components were present. The details of MetS definition and thresholds of MetS components have been published elsewhere [120]. We use the following methods to collect the MetS measures: Waist circumference was measured at the narrowest point between the lower costal border and the iliac crest to the nearest 0.1 cm using a constant tension tape; high waist circumference was defined as waist circumference $\geqslant$102 cm in males or $\geqslant$88 cm in females. Fasting glucose was measured as described in glucose homeostasis measurements; hyperglycaemia was defined as fasting glucose of $\geqslant$5.6 mmol/L. Triglyceride and high-density lipoprotein cholesterol (HDL-C) were measured enzymatically using an Olympus AU5400 automated analyser (Olympus Optical, Tokyo, Japan). Hypertriglyceridemia was defined as serum triglycerides $\geqslant$ 1.7 mmol/L, and low HDL-C was defined as HDL-C <1.03 mmol/L in males or <1.3 mmol/L in females. Resting systolic and diastolic blood pressure readings were recorded after 5 min of quiet sitting using an OMRON HEM907 Digital Automatic Blood Pressure Monitor (Omron Healthcare Co., Ltd., Kyoto, Japan), and the mean of three recordings was used. Hypertension was defined as blood pressure $\geqslant$ 130/85 mmHg.

2.7 MRI measurements

2.7.1 MRI collections

Knee MRI scans were collected 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 1.5 T 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 min, 56 s; 1 acquisition. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31×0.31 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 0.31×0.31 mm (512×512 pixels); repetition time 3800 msec; echo time 45 msec. In each structural measurement, we randomly selected 20 participants and re-measured their scans, so as to assess the intraclass correlation coefficient (ICC). There were at least 2 weeks between the two measurements.

2.7.2 Cartilage defects

Knee cartilage defects were measured as previously reported [121] in an ordinal scale using the T1-weighted spoiled gradient-recalled sagittal MRI scans and proton density-weighted fast spin-echo coronal MRI scans 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 ICC ranged from 0.89 to 0.94.

2.7.3 Bone marrow lesions (BMLs)

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 [39]. 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: ⩽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.

2.7.4 Meniscal tears

Meniscal tear was graded in medial and lateral menisci separately based on a modified International Society of Arthroscopy, Knee Surgery, and Orthopaedic Sports Medicine meniscal tear classification system [122] using proton density-weighted coronal and T1-weighted sagittal images. Grade 0 indicated a normal meniscus; grade 1 indicated mucoid degeneration; grade 2 indicated mild tear; grade 3 indicated displaced tear and grade 4 indicated macerated meniscus. A prevalent meniscal tears was defined as a meniscal tear score of ⩾2 at any site within that compartment. Intraobserver reliability expressed as an ICC ranged from 0.81 to 1.00.

2.7.5 Cartilage thickness, cartilage volume and bone area

In Chapter 4 and Chapter 5, cartilage thickness, cartilage volume and subchondral bone area were measured in the medial/lateral femorotibial compartment (MFTC/LFTC) and in the patella as previously reported [123] by a quantitative approach, using the T1-weighted spoiled gradient-recalled sagittal MRI scans. 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 3D 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 coefficient of variation 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 [124]. In chapter 4, the cartilage thickness and bone area in MFTC and LFTC were calculated as the sum of the area. In chapter 5, the cartilage thickness in MFTC, LFTC and the whole knee joint were calculated as the weighted average of the thickness of each compartment according to the bone area size; the bone area was calculated as the sum of the area of each compartment.

In Chapter 6, cartilage volume was determined by means of 3D image processing on an independent work station using software program OsiriX (Geneva, Switzerland). Individual plates were isolated by manually drawing disarticulation contours around the cartilage boundaries on a section-by-section basis. These data were then re-sampled by means of bilinear and cubic interpolation (area of 312×312 μm^2 and thickness of 1.5 mm, continuous sections) for the final 3D rendering. The coefficients of variation for cartilage volume measures were 2.1-2.6%. Femoral cartilage volume was not measured, as it strongly correlates with tibial cartilage volume [125].

2.8 Statistical analyses

Histograms and Q–Q plots were used to assess the normality of continuous variables. Mean (standard deviation), median (interquartile range) and number (percentage) were used to describe the characteristics of the participants. T-tests, Wilcoxon rank-sum test and Chi-square tests were used to assess differences in normally distributed variables, skewed variables and categorical variables between groups, respectively.

Linear regression models were used to estimate β coefficients when the outcomes were continuous. For each final model, we checked whether the assumptions of linear regression were satisfied. Where necessary to reduce heteroscedasticity and skewness of the residuals, the variable was transformed (e.g. by taking logarithms). Additionally, we paid careful attention to the scaling of the covariates. Log binomial regression models were used to estimate relative risk when the outcomes were binary. Ordinal logistic regression models were used to estimate odds ratio when the outcomes were ordinal. In multivariable analyses, we retained the confounders that had important biological plausibility or changed the estimated coefficient by >10% [126].

A 95% confidence interval not including the null point or a p-value <0.05 (two-tailed) was considered statistically significant. All statistical analyses were performed in Stata (Version 14.2/15.0, StataCorp, College Station, TX, USA).

In Chapter 4, 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.

In Chapter 5, when significant associations disappeared and effect sizes decreased dramatically after adjusting for a potential mediator, we performed mediation analysis. We used the Stata command medeff to separate the total effect into direct effect and indirect effect. This generated an estimate of the proportion of total effect that is mediated [127].

Chapter 3: Association of childhood adiposity measures with adulthood knee cartilage defects and bone marrow lesions

(Meng T et al. Osteoarthritis and Cartilage. 2018 Aug; 26(8):1055-1062.)

3.1 Introduction

Osteoarthritis (OA) is the most common joint disease, which is characterised by joint structural changes including cartilage degradation and subchondral bone abnormalities [128]. About 13% of women and 10% of men aged 60 years or older have symptomatic knee OA [129], 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 [130-132], and are associated with knee pain [37, 133], knee cartilage volume loss [134, 135] and subsequent knee replacement surgery [136, 137] in most studies, although not all associations were consistent [41, 138-140]. 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 [141].

Obesity has long been recognized as a risk factor for the incidence and progression of knee OA [142], 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 [143]. 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 [74]. Similarly, Gelber et al. reported that BMI in young men, aged 20-29 years, was associated with the increased risk of subsequent knee OA [75]. In addition, we reported that the childhood adiposity measures were associated with higher risk of knee pain in adulthood 25 years later [76]. 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 [144]. 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.

3.2 Methods

3.2.1 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. 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 flowchart of the selection of participants for this study is shown in Figure. 3.1.

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.

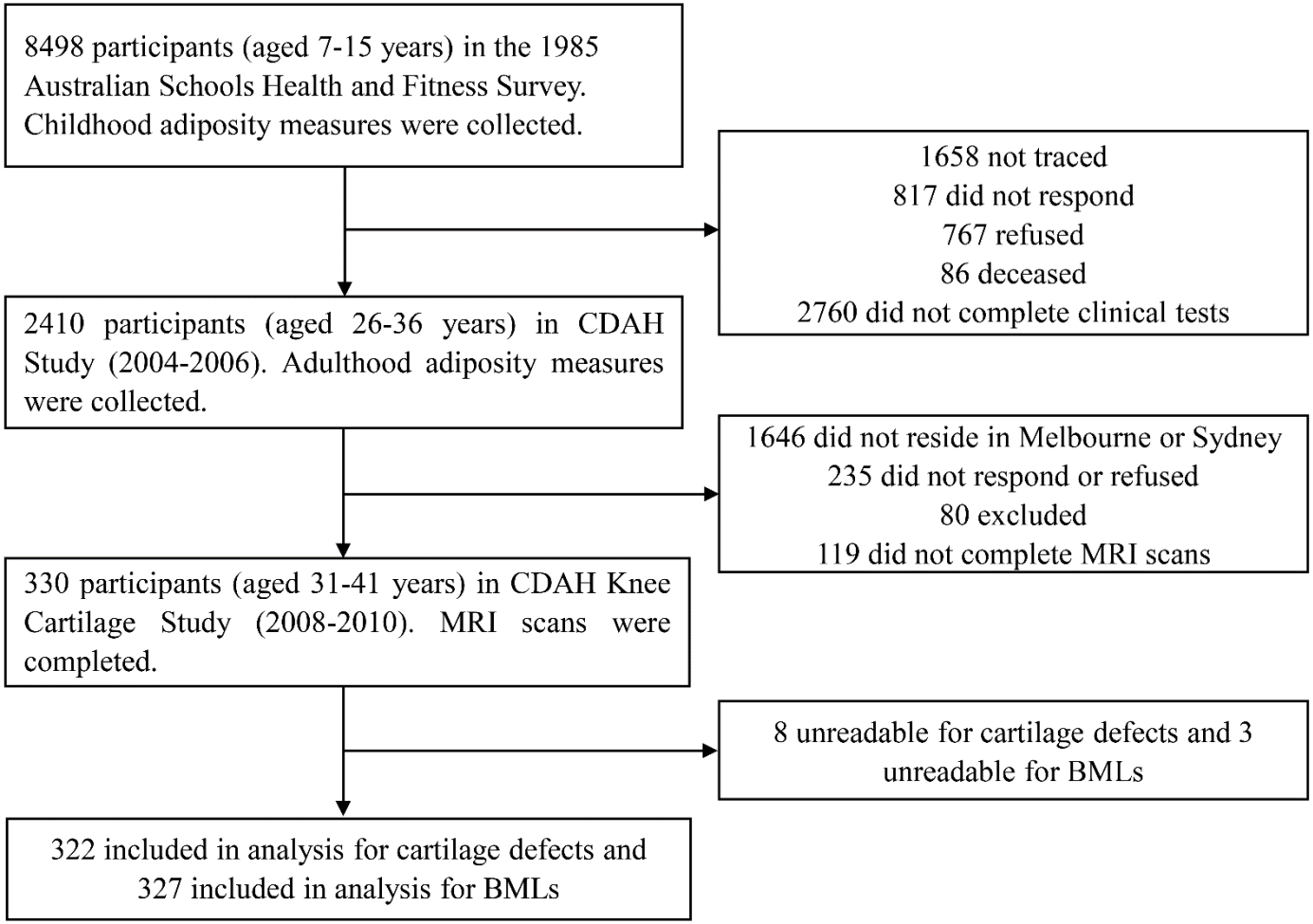

Figure 3.1 Flowchart showing selection of the participants in Chapter 3

BMLs, bone marrow lesions; CDAH Study, Childhood Determinants of Adult Health Study; MRI, magnetic resonance imaging.

3.2.2 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 [115]. Adulthood overweight status was defined as a BMI $\geqslant$25 kg/m^2.

Triceps, biceps, subscapular, and supra-iliac skinfolds were measured at locations determined by reference to anatomical landmarks [119] 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 [116, 117, 119]. Estimate of percent body fat was derived from body density [118], and fat mass was estimated by percent body fat in kilograms: fat mass=fat%×weight.

3.2.3 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 1.5 T 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 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 min, 56 s; 1 acquisition. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31×0.31 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 0.31×0.31 mm (512×512 pixels); repetition time 3800 msec; echo time 45 msec.

Knee cartilage defects were measured as previously reported [121] in an ordinal scale using the T1-weighted spoiled gradient-recalled sagittal MRI scans and proton density-weighted fast spin-echo coronal MRI scans 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 [39]. 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: ⩽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

meniscal tear classification system [122] using proton density-weighted coronal and T1-weighted sagittal images. Grade 0 indicated a normal meniscus; grade 1 indicated mucoid degeneration; grade 2 indicated mild tear; grade 3 indicated displaced tear and grade 4 indicated macerated meniscus. A prevalent meniscal tears was defined as a meniscal tear score of $\geqslant 2$ at any site within that compartment. Intraobserver reliability expressed as an ICC ranged from 0.81 to 1.00.

3.2.4 Cholesterol and plasma glucose measures

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

3.2.5 Statistical analyses

Mean (standard deviation) or number (percentage) was used to describe characteristics of the participants. Student's t-tests or Chi-square tests were used to assess the differences in continuous and categorical variables, respectively, between groups of participants. Univariable and multivariable log binomial regressions were used to estimate relative risk (RR) for the associations between childhood adiposity measures and adulthood knee cartilage defects or BMLs before and after adjustment for potential confounders. If the log binomial model failed to converge, RR was estimated by using a Poisson distribution and robust standard errors. Multivariable ordinal logistic regressions were used to estimate odds ratio (OR) for the associations between childhood adiposity measures and adulthood knee cartilage defects or BMLs grades after adjustment for potential confounders. Interactions between sex and

adiposity measures on cartilage defects or BMLs were investigated by regressing cartilage defects or BMLs on the product term of sex and each exposure of interest (e.g., sex×BMI).

Childhood age, duration of follow-up, sex, 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.

3.3 Results

3.3.1 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 3.1. Prevalence of any cartilage defects and BMLs 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: sex, 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 3.1).

Table 3.1 Characteristics of the participants in Chapter 3

	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)

Values are mean (standard deviation) unless otherwise stated.

[a]Fat mass was measured among the children aged 9, 12 and 15 years in 1985; n=62, 45, 79 and 29, respectively.

BMI, body mass index.

3.3.2 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 3.2) and these associations remained significant after adjustment for childhood age, duration of follow-up, sex, childhood height (if weight or fat mass was the predictor), childhood knee injury (Weight RR 1.05/kg, 95% confidence interval (CI) 1.02-1.09; BMI 1.10/kg/m^2, 1.02-1.19; Overweight 2.04/yes, 1.12-3.74; fat mass 1.13/kg, 1.03-1.23) (Table 3.2). After further adjustment for corresponding adulthood measure, these associations were largely unchanged (Weight RR 1.05/kg, 95% CI 1.01-1.09; BMI 1.10/kg/m^2, 1.01-1.19; Overweight 2.22/yes, 1.21-4.08; fat mass 1.11/kg, 95% CI 1.01-1.22) (Table 3.2, Figure 3.2). There were no significant associations between childhood adiposity measures and adulthood tibiofemoral cartilage defects in either univariable or multivariable analyses (Table 3.2). Above associations remained large unchanged after adjustment for metabolic risk factors (cholesterol or glucose) or meniscal tears.

Table 3.2 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)

Bold denotes statistical significance, $p<0.05$.

[a]Adjusted for childhood age, duration of follow-up, sex, height (if weight or fat mass was the predictor), childhood knee injury.

[b]Further adjusted for corresponding adulthood measure.

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

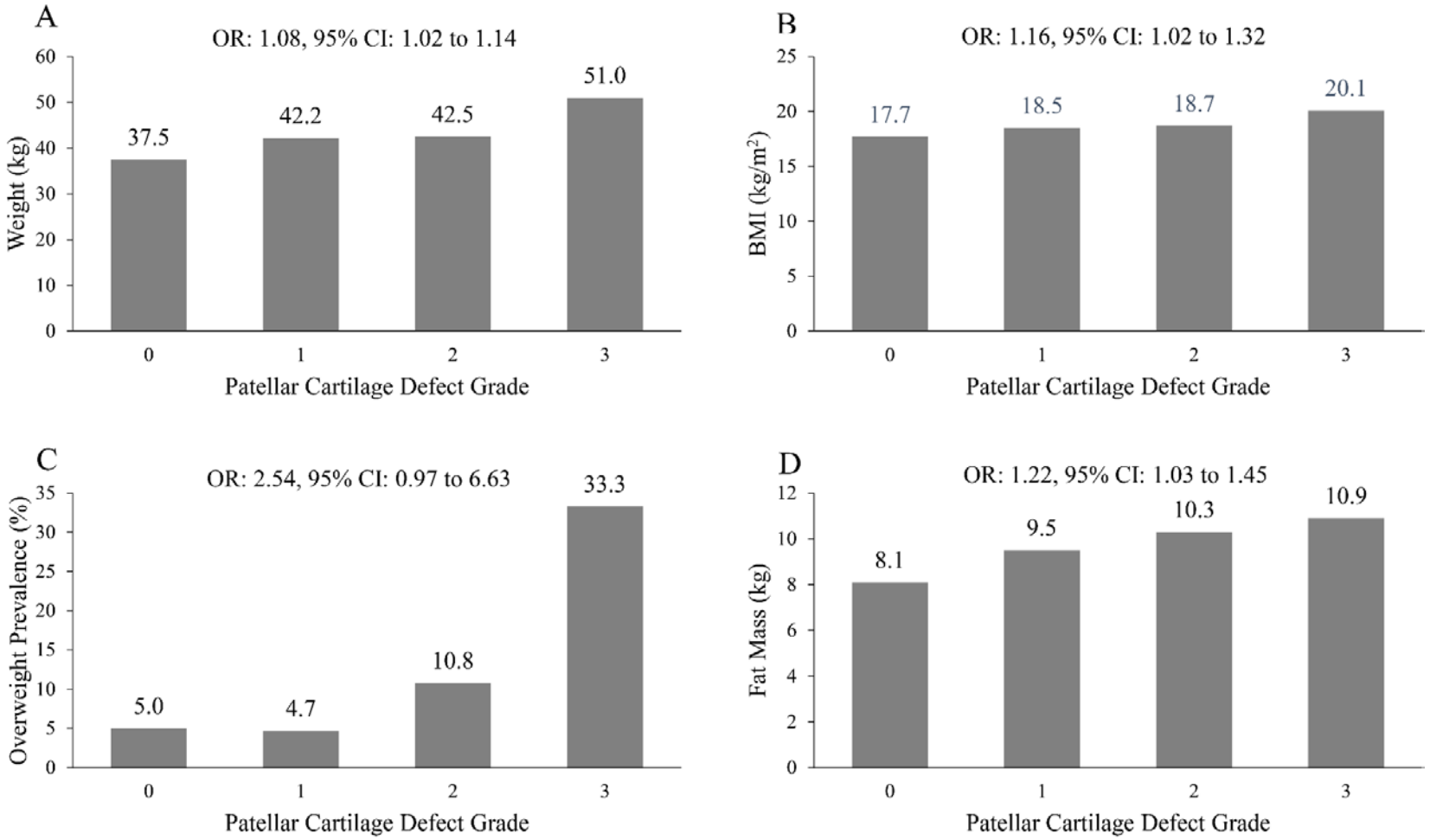

Figure 3.2 Mean childhood weight, mean childhood BMI, childhood overweight prevalence and mean childhood fat mass for participants classified by patellar cartilage defect grades

ORs and 95% CIs were from multivariable ordinal logistic regressions, which included childhood age, duration of follow-up, sex, height (if weight or fat mass was the predictor), childhood knee injury as confounders.

BMI, body mass index; CI, confidence interval; OR, odds ratio.

3.3.3 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 3.3); however, childhood overweight status was significantly associated with adulthood patellar BMLs after adjustment for childhood age, duration of follow-up, sex, childhood knee injury and adulthood overweight status (RR: 2.87/kg, 95% CI: 1.10-7.53) (Table 3.3). There were no significant associations between childhood adiposity measures and adulthood tibiofemoral BMLs in multivariable analyses (Table 3.3); however, there was an interaction between childhood fat mass and sex 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: 1.07-1.32) (Figure 3.3), but not in females (RR: 1.01, 95 % CI: 0.87e1.18). 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: 1.01-1.37; female RR: 1.10/kg, 95% CI: 0.93-1.30). Above associations remained large unchanged after adjustment for metabolic risk factors (cholesterol or glucose) or meniscal tears.

Table 3.3 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)

Bold denotes statistical significance, $p<0.05$.

[a]Adjusted for childhood age, duration of follow-up, sex, height (if weight or fat mass was the predictor), childhood knee injury.

[b]Further adjusted for corresponding adulthood measure.

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

[c]$p=0.064$.

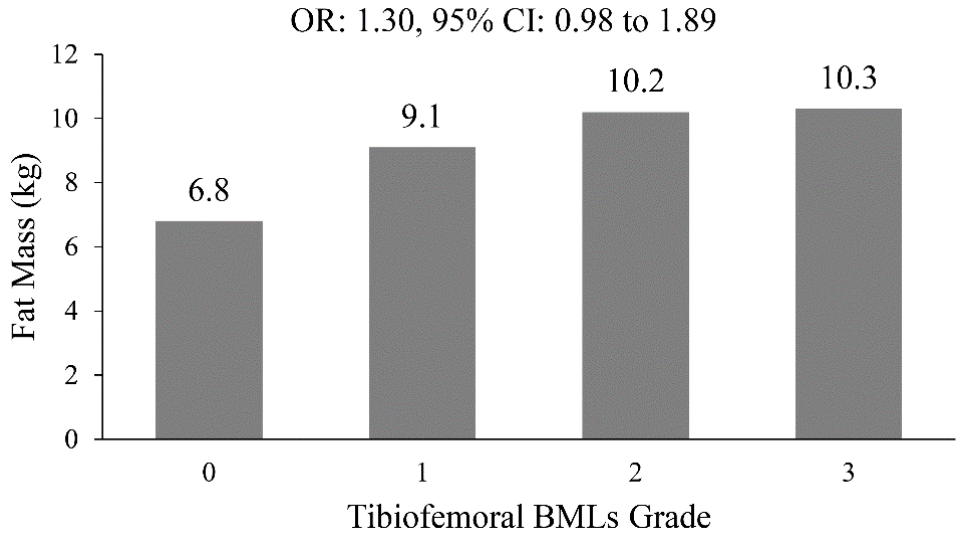

Figure 3.3 Mean childhood fat mass for males classified by tibiofemoral BMLs grades OR and 95% CI were from multivariable ordinal logistic regressions, which included childhood age, duration of follow-up, sex, height, childhood knee injury as confounders. BMLs, bone marrow lesions; CI, confidence interval; OR, odds ratio.

3.4 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 [40]. Previous studies reported that adiposity measures are consistently associated with the increased risk of knee cartilage defects among middle-aged adults [145] and obese populations [146]. 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 [69]. 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 [141].

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 [147]. 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 [148]. Moreover, Eckstein et al. reported that the patellar cartilage was more sensitive to physical stress compared to tibiofemoral cartilage [149]. These are also consistent with the previous finding that chronic overloading is a dominant factor of anterior knee pain in adolescents [150]. Secondly, increasing evidence suggest that the association between obesity and knee cartilage could be mediated by adipocytokines [151], as the adipocytokines released by adipose tissue would play important roles in cartilage degradation [152].

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 [153]. 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) [154]. 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 [155]. Adiposity is associated with detrimental effects on BML both cross-sectionally and longitudinally. Cross-sectionally, BMI [136, 156] and total body fat mass [80] 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 [157] and change in BMI over 10 years was positively associated with the increased risk of BMLs [158]. Moreover, a recent systematic review concluded that obesity was a moderate risk factor for BMLs in the knee [72]. 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 [159, 160]. 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 [76]. The reason for the sex difference is unclear, but may suggest the different roles of fat mass in the development of BMLs between sexs.

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, sex 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 [161]. 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 [162], and has been used in epidemiological studies widely [163]. We did not collect knee injury information in childhood, but asked the participants to recall the childhood knee injury history. The accuracy of this information may be limited. Moreover, the types of injuries were not available, which has the potential to affect our results.

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

Chapter 4: Association of adiposity measures in childhood and adulthood with knee cartilage thickness, volume and bone area in young adults

(Meng T, et al. International Journal of Obesity. 2019 Jul; 43(7):1411-1421.)

4.1 Introduction

Knee osteoarthritis (OA) is a common joint disease worldwide and a major source of knee pain and dysfunction in older people [164]. 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) [164]. 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 [69, 130]. Reductions in cartilage volume and thickness were found to be associated with knee pain [165, 166], joint space narrowing [165, 167] and subsequent knee replacement surgery [54], and regarded as major outcome measures in MRI-based clinical trials [168, 169]. Subchondral bone underlying the cartilage is also an important knee joint structure, as this region functionally adapts to physiological or pathological mechanical stress [64, 130, 170]. Expansion of tibial bone area in older populations has been shown to predict cartilage damage [62] and knee replacement surgery [53]; 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 [141], indicating the importance of addressing early risk factors of the disease. We reported that physical performance measures and physical activity levels in childhood [94] and young adults [93] 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 have 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 [69, 145]. However, there are no studies describing the effects of adiposity during early life on knee cartilage and bone morphology in adulthood. We hypothesised 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.

4.2 Methods

4.2.1 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 flowchart of the selection of participants for this study is shown in Figure 4.1.

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.

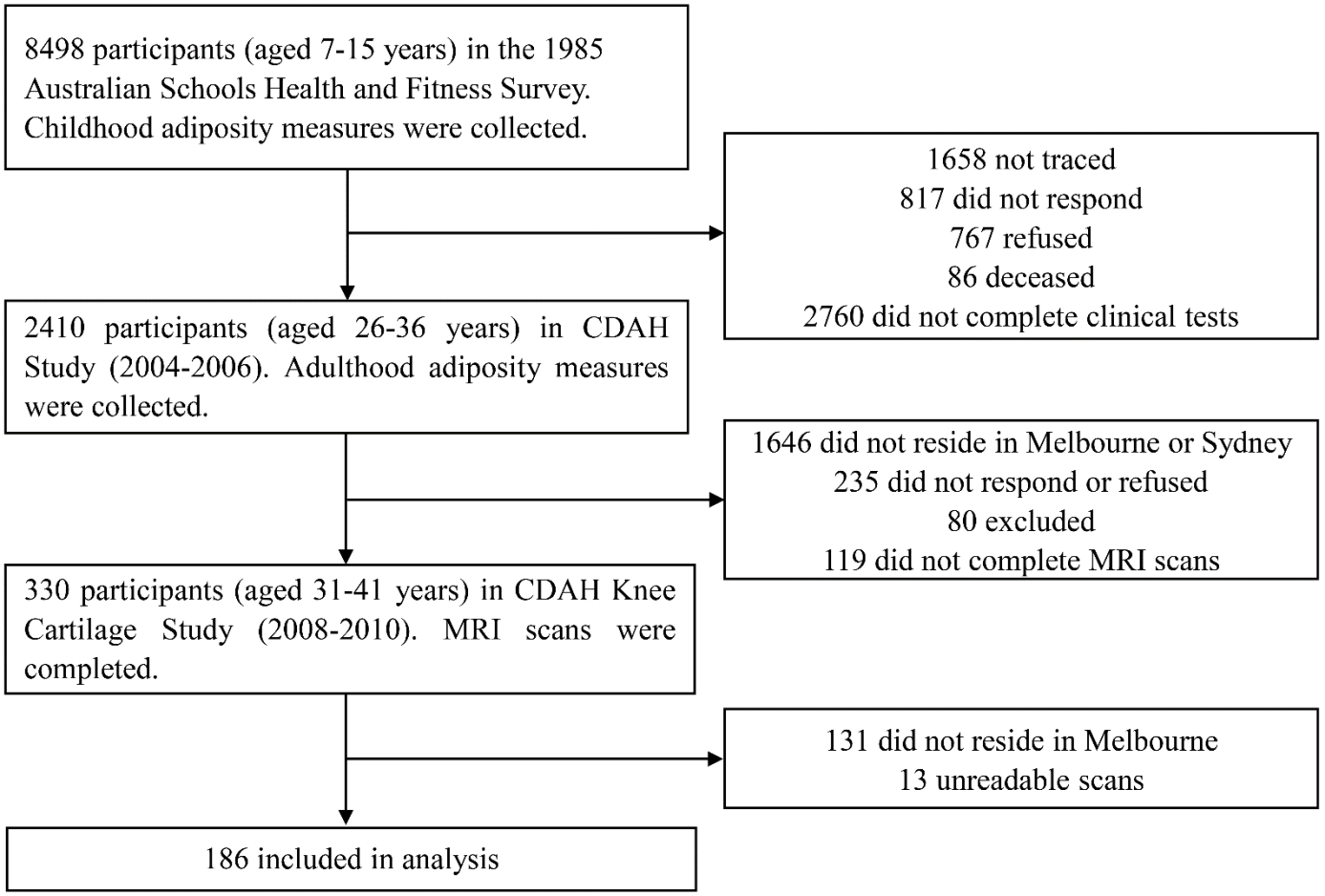

Figure 4.1 Flowchart showing selection of the participants in Chapter 4

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

4.2.2 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. Body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared. Overweight status in childhood was defined according to age- and sex-specific cut-off points, as previously published [115]. Adult overweight status was defined as a BMI $\geqslant$25 kg/m^2. Waist-hip ratio (WHR) was calculated by dividing waist circumference in centimetre by hip circumference in centimetres.

4.2.3 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 three-dimensional (3D) spoiled gradient-recalled acquisitions in the steady state (flip angle 55°, repetition time 58 ms, echo time 12 ms, field of view 16 cm, 60 partitions, 512 × 512-pixel matrix, acquisition time 11 min, 56 s, 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/lateral femorotibial compartment (MFTC/LFTC) and in the patella as previously reported [123] by a quantitative approach, using the T1-weighted spoiled gradient-recalled sagittal MRI scans. 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 3D 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 coefficient of variation 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 [124].

4.2.4 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 sex 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 < 0.05 (two-tailed) was considered statistically significant. All statistical analyses were performed in Stata, version 15.0.

4.3 Results

4.3.1 Characteristics of the participants

A sample of 186 participants with MRI was included in this analysis. Characteristics of study participants are given in Table 4.1. 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, sex, weight, BMI and overweight status in childhood. However, WHR was lower in the current sample than that in the remainder of original cohort (Table 4.1). 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.

Table 4.1 Characteristics of the participants in Chapter 4

	MRI quantitative measures		P value
	Yes	No	
Childhood	(n=186)	(n=8312)	
Female, n (%)	90 (48.4)	4101 (49.3)	0.797
Age (years)	10.9 (2.7)	10.9 (2.5)	0.887
Weight (kg)	39.7 (13.6)	39.9 (13.0)	0.872
BMI (kg/m^2)	18.1 (2.7)	18.2 (2.9)	0.469
Overweight[a] (yes), n (%)	14 (7.6)	975 (11.9)	0.069
WHR (unit)	0.82 (0.05)	0.84 (0.06)	0.001
Adulthood		(n=2144)	
Weight (kg)	75.8 (15.0)	77.2 (17.4)	0.291
BMI (kg/m^2)	25.1 (4.1)	25.8 (4.9)	0.080
Overweight[b] (yes), n (%)	77 (42.1)	1075 (50.1)	0.038
WHR (unit)	0.79 (0.08)	0.80 (0.07)	0.051
Cartilage thickness (mm)			
Patella	2.47 (0.36)		
MFTC	3.65 (0.47)		
LFTC	4.15 (0.51)		
Cartilage volume (mm^3)			
Patella	2843 (714)		
MFTC	3363 (799)		
LFTC	4041 (1035)		
Bone area (mm^2)			
Patella	1081 (170)		
MFTC	1798 (260)		
LFTC	1825 (299)		

Values are mean (standard deviation) unless otherwise stated.

BMI, body mass index; LFTC, lateral femorotibial compartment; MFTC, medial femorotibial compartment; WHR, waist-hip ratio.

[a]Childhood overweight status was defined according to the age and sex-specific cut-off points;

[b]Adulthood overweight status was defined as a BMI $\geqslant$25 kg/m^2.

4.3.2 Childhood adiposity measures and adult knee structures

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 compartments in multivariable analyses, after adjustment for childhood age, sex and height (if weight was the predictor) (Table 4.2). 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 4.2). The significant associations of childhood weight and BMI with adult patellar bone area were persistent after further adjustment 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 β-values (14.7% and 8.1%, respectively).

Table 4.2 Associations between childhood adiposity measures and knee cartilage thickness, cartilage volume and subchondral bone area

	Cartilage thickness (mm) β (95% CI)	Cartilage volume (mm^3) β (95% CI)	Bone area (mm^2) β (95% CI)
Patella			
Weight, kg	0.003 (-0.008 to 0.013)	-13.13 (-30.18 to 3.92)	**-5.57 (-9.27 to -1.87)**
BMI, kg/m^2	0.009 (-0.015 to 0.033)	-23.68 (-63.88 to 16.51)	**-11.55 (-20.37 to -2.73)**
Overweight, yes	0.092 (-0.102 to 0.286)	-111.46 (-438.07 to 215.14)	-71.66 (-143.73 to 0.42)[a]
WHR, 0.01 unit	-0.003 (-0.015 to 0.009)	-2.30 (-21.83 to 17.23)	-0.17 (-4.49 to 4.15)
MFTC			
Weight, kg	0.009 (-0.003 to 0.020)	5.79 (-9.76 to 21.34)	-1.07 (-5.62 to 3.48)
BMI, kg/m^2	0.021 (-0.006 to 0.048)	25.03 (-13.07 to 63.14)	3.97 (-7.88 to 15.82)
Overweight, yes	0.031 (-0.188 to 0.251)	50.81 (-256.63 to 358.25)	-0.39 (-95.72 to 94.94)
WHR, 0.01 unit	0.003 (-0.010 to 0.016)	3.07 (-15.66 to 21.81)	-1.65 (-7.43 to 4.13)
LFTC			
Weight, kg	0.006 (-0.007 to 0.018)	3.08 (-15.57 to 21.74)	-0.15 (-4.61 to 4.32)
BMI, kg/m^2	0.017 (-0.013 to 0.047)	25.97 (-20.53 to 72.47)	6.99 (-4.92 to 18.90)
Overweight, yes	-0.046 (-0.287 to 0.194)	-50.95 (-425.66 to 323.77)	10.10 (-85.94 to 106.13)
WHR, 0.01 unit	-0.005 (-0.020 to 0.010)	-1.64 (-24.47 to 21.20)	0.03 (-5.81 to 5.88)

Bold denotes statistical significance, $p<0.05$.

Adjusted for childhood age, sex, height (if weight was the predictor).

BMI, body mass index; CI, confidence interval; LFTC, lateral femorotibial compartment; MFTC, medial femorotibial compartment; WHR, waist-hip ratio.

[a]$p=0.051$.

4.3.3 Adult adiposity measures and adult knee structures

Adult BMI and overweight status were largely not associated with knee cartilage thickness, cartilage volume and subchondral bone area measured 4-5 years later in multivariable analyses, including adult age and sex as confounders (Table 4.3). However, adult weight was positively associated with cartilage volume in MFTC and bone area in MFTC and LFTC (Table 4.3). 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 4.3, Figure 4.2). 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 4.3). 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 4.3).

Table 4.3 Associations between adulthood adiposity measures and knee cartilage thickness, cartilage volume and subchondral bone area

	Cartilage thickness (mm) β (95% CI)	Cartilage volume (mm^3) β (95% CI)	Bone area (mm^2) β (95% CI)
Patella			
Weight, kg	-0.001 (-0.005 to 0.004)	-0.45 (-7.10 to 6.20)	-0.37 (-1.71 to 0.97)
BMI, kg/m^2	-0.005 (-0.018 to 0.008)	-11.52 (-32.88 to 9.85)	-3.66 (-8.37 to 1.04)
Overweight, yes	0.027 (-0.081 to 0.135)	-15.86 (-196.54 to 164.82)	-26.72 (-66.42 to 12.99)
WHR, 0.01 unit	-0.009 (-0.018 to 0.000)[a]	**-20.97 (-36.35 to -5.60)**	**-4.39 (-7.79 to -0.98)**
MFTC			
Weight, kg	0.002 (-0.003 to 0.006)	**8.51 (2.47 to 14.54)**	**3.37 (1.73 to 5.00)**
BMI, kg/m^2	0.002 (-0.013 to 0.017)	16.13 (-4.23 to 36.49)	**6.62 (0.37 to 12.87)**
Overweight, yes	0.085 (-0.037 to 0.207)	**174.22 (4.51 to 343.93)**	40.45 (-12.21 to 93.11)
WHR, 0.01 unit	**-0.011 (-0.021 to -0.001)**	-12.86 (-27.60 to 1.89)[b]	-1.97 (-6.55 to 2.61)
LFTC			
Weight, kg	0.001 (-0.004 to 0.006)	4.85 (-2.45 to 12.16)	**2.08 (0.46 to 3.71)**
BMI, kg/m^2	0.002 (-0.014 to 0.018)	4.45 (-20.52 to 29.42)	2.57 (-3.82 to 8.97)
Overweight, yes	0.077 (-0.057 to 0.211)	93.46 (-115.28 to 302.20)	13.17 (-40.41 to 66.75)
WHR, 0.01 unit	**-0.012 (-0.023 to -0.001)**	**-21.71 (-39.54 to -3.88)**	-4.45 (-9.05 to 0.15)[c]

Bold denotes statistical significance, $p<0.05$.

Adjusted for adulthood age, sex, height (if weight was the predictor).

BMI, body mass index; CI, confidence interval; WHR, waist-hip ratio; MFTC, medial femorotibial compartment; LFTC, lateral femorotibial compartment.

[a]$p=0.060$; [b]$p=0.087$; [c]$p=0.058$.

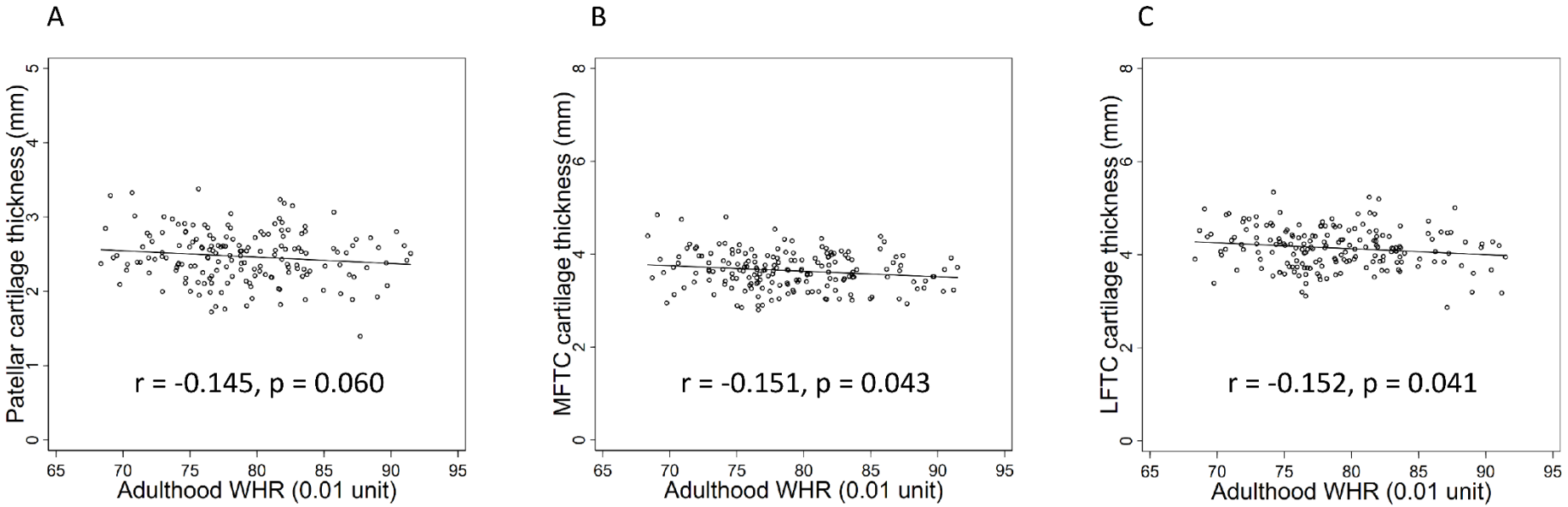

Figure 4.2 Scatter plots and linear regression lines for associations between adulthood WHR and knee cartilage thickness.

Linear regression lines are from models adjusted for adult age and sex.

LFTC, lateral femorotibial compartment; MFTC, medial femorotibial compartment; WHR, waist-hip ratio.

4.3.4 The change of adiposity measures from childhood to adulthood and adult knee structures

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 4.4). 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 4.4). The effect sizes for the negative associations between WHR z-score change and cartilage volume in MFTC and between WHR z-score change and bone area in LFTC were relatively large, although they did not reach statistical significance (p=0.059 and 0.053, respectively) (Table 4.4). 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 (β=-26.22 mm^3, 95% CI: -82.03 to 29.58) after adjustment for corresponding bone area.

Table 4.4 Associations of the change of adiposity measures from childhood to adulthood with knee cartilage thickness, cartilage volume and subchondral bone area

	Cartilage thickness (mm) β (95% CI)	Cartilage volume (mm^3) β (95% CI)	Bone area (mm^2) β (95% CI)
Patella			
Weight z-score change	-0.055 (-0.120 to 0.010)	-36.91 (-138.17 to 64.36)	-1.25 (-21.75 to 19.25)
BMI z-score change	-0.036 (-0.092 to 0.021)	15.30 (-80.37 to 110.96)	11.49 (-9.69 to 32.66)
WHR z-score change	-0.029 (-0.075 to 0.018)	**-89.95 (-166.26 to -13.64)**	**-20.74 (-37.52 to -3.97)**
MFTC			
Weight z-score change	-0.041 (-0.117 to 0.034)	-1.66 (-97.19 to 93.86)	11.33 (-14.97 to 37.62)
BMI z-score change	-0.035 (-0.101 to 0.031)	-10.23 (-82.08 to 102.54)	16.37 (-12.13 to 44.87)
WHR z-score change	**-0.056 (-0.108 to -0.005)**	-69.69 (-142.10 to 2.72)[a]	-7.18 (-29.72 to 15.35)
LFTC			
Weight z-score change	-0.042 (-0.123 to 0.040)	-70.78 (-183.79 to 42.22)	-13.75 (-38.89 to 11.40)
BMI z-score change	-0.025 (-0.097 to 0.047)	-31.30 (-143.73 to 81.14)	-4.88 (-33.73 to 23.97)
WHR z-score change	-0.037 (-0.094 to 0.020)	**-93.98 (-182.02 to -5.93)**	-22.29 (-44.88 to 0.31)[b]

Bold denotes statistical significance, $p<0.05$.

Adjusted for childhood and adulthood age, sex, childhood and adulthood height (if weight z-score change is the predictor).

BMI, body mass index; CI, confidence interval; LFTC, lateral femorotibial compartment; MFTC, medial femorotibial compartment; WHR, waist-hip ratio.

[a]$p=0.059$; [b]$p=0.053$.

4.4 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) [171]. However, another study reported baseline BMI did not predict change in tibial cartilage volume longitudinally over 2 years in healthy middle-aged men [172]. Similarly, weight loss slowed loss of knee cartilage thickness over 12-month among participants in a randomised clinical trial of a weight loss programme [173] 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 [174, 175]; in contrast, no significant difference in change of cartilage thickness over 1 year were observed between participants who were overweight and those who were of normal weight [176], 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 trial [177]. 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 [69]. 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 [178, 179] or adults [145], 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 [145]. 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 from 3 to 7 years [178]. Similarly, Goulding et al. [179] reported that overweight or obese children had lower bone mass and total bone area than their predicted values calculated from body weight during growth. 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 [180] and people with knee OA patients [181], and have been shown to depend on the mechanical stress distribution and alignment [170]. Such changes in subchondral bone could be maladaptive, as an outcome of remodelling of subchondral trabeculae (with increased extracellular matrix deposition) due to loading [130]. However, bone accrual during childhood or young adulthood is likely to be a physiologic rather than a pathologic process, as the enlargement of bone area could be an adaptive change to load-bearing stimuli and enable distribution of loads over a larger surface [64, 170]. This is consistent with our previous studies, which reported positive associations between childhood physical performance measures and knee tibial bone area [94] and bone mass [182] in young

adults, suggesting tibial bone accrual from childhood to early adulthood may be a physiological process.

In this study, childhood body weight and 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 [76]. 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, e.g., higher on MFTC/LFTC than on patella [170], 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 [183], whereas the abdominal adiposity was more readily to mobilise free fatty acids [184]. In addition to higher WHR being indicative of central adiposity, it also indicates less muscle mass in the thigh region [185], which will result in reduced leg strength and thereby lead to potential knee joint structural damages [186].

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 [187-189] and can be reversible [187-190]. 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 [187]. Cardiovascular disease and OA have shared pathophysiology [191]; therefore, the effects of childhood adiposity on adult knee cartilage and bone morphology may only have a few residual effects. In addition, this may be due to the low prevalence of overweight status (7.6%) in childhood, whereas around 40% were overweight in adulthood [175]. 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 peripubertal 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 healthier participants and these may not bias our results as normal-weight children and young adults are less likely to report knee joint alterations [175, 192]. 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.

Chapter 5: Association of body composition, physical activity and physical performance with knee cartilage thickness and bone area in young adults

(Meng T et al. Rheumatology. 2020 Jul; 59(7):1607-1616.)

5.1 Introduction

Osteoarthritis (OA) is one of the most prevalent joint disorders worldwide. However, there are no proven therapies to arrest or delay disease progression. Therefore, identifying modifiable factors that can prevent OA is critically important.

Magnetic resonance imaging (MRI) is a sensitive method for detecting early structural changes in knee OA [163]. Cartilage loss, as viewed on MRI, is regarded as the signature feature of knee OA [34]. Thinning of cartilage predicts knee pain and joint space narrowing over 6 months [165] and knee replacement surgery over 4 years [193]. Subchondral bone is also important in knee OA. Changes in bone area over24 months are associated with the combination of radiographic and pain progression over 48 months [63]. In young adults, bone area enlargement could be a physiological adaption to mechanical stimulation, as the enchondral ossification process to form larger metaphyses could distribute the stress over a larger area [64, 93]. Therefore, thicker cartilage and larger subchondral bone may be beneficial to maintain knee joint health.

Body composition is associated with physical function and quality of life among OA patients, even among those with normal body mass index (BMI) [194]. However, body composition has shown inconsistent associations with knee cartilage morphology in previous studies [69]. We reported that fat mass was negatively associated with cartilage volume and lean mass was positively associated with cartilage volume in both young [81] and older adults [79], whereas fat mass was not associated with cartilage volume in other studies [80, 195]. Exercise is recommended for managing knee OA, as it improves patient outcomes related to symptoms, mobility, quality of life and psychological health [196, 197]. However, a systematic review reported that there were only a few studies that reported a positive relationship between

physical activity and cartilage volume among healthy participants (ages 19-79 years) [198]. Physical performance is a product of both muscular performance and cardiorespiratory performance and has been set as an important target for disease preventive strategies [199]. Hand grip strength is the most important indicator of whole-body muscular fitness. Lower hand grip strength has been associated with more severe knee radiographic OA among people >50 years of age [200]. Similarly, physical work capacity at a heart rate of 170 bpm (PWC170) is a good indicator of cardiorespiratory fitness, and previous studies have reported that higher PWC170 is associated with higher knee cartilage volume in both young and older adults [93, 201]. In addition to the indicators reflecting the whole-body condition, leg strength and long jump are important indicators of strength and power, respectively, in the lower limbs. Both leg strength and leg power have been associated with knee symptoms in knee OA patients [202-204] and higher cartilage volume in young adults [93].

As bone area is a key driver of cartilage volume [56], assessing both cartilage thickness and bone area may be required to accurately assess knee cartilage and bone morphology. In addition, cartilage thickness has a close association with early knee OA [205] and has been reported as an imaging biomarker [34]. However, few studies have identified factors associated with cartilage thickness in young adults, who are the important target population for OA prevention. Therefore, we aimed to describe associations of body composition, physical activity and physical performance with knee cartilage thickness and bone area in young adults.

5.2 Methods

5.2.1 Participants

In 1985, the Australian Schools Health and Fitness Survey (ASHFS) was conducted to provide benchmark data on the health and fitness of Australian school children using a nationally representative sample. Two-stage probability sampling was used for the ASHFS to randomly select schools and then children within age groups in the schools. The Childhood Determinants of Adult Health (CDAH) study was a 20-year follow-up of children who participated in the ASHFS. From 2004 to 2006, participants attended clinics that were located at sites in major cities and regional centres around Australia, and anthropometric measurements, physical activity measurements and physical performance measurements were collected during the clinic visit. The details of enrolment of the ASHFS and CDAH study have been published elsewhere [113, 114]. The CDAH Knee Cartilage Study was a sub-study of the CDAH study where participants completed knee MRI scans during 2008–2010. The current study is a subset of the CDAH Knee Cartilage Study. Due to limited funding, we measured cartilage and bone morphology among the participants residing in Melbourne.

We used the following strategy to recruit participants from the CDAH study. Participants residing in metropolitan Melbourne and Sydney were invited by mail to participate in the CDAH Knee Cartilage Study. Participants who agreed to participate were assessed for eligibility. Exclusion criteria included being pregnant, having diseases that might affect knee cartilage (including rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and psoriatic arthritis) or having MRI contraindications. The remaining participants were asked to complete a computer-assisted telephone interview, with knee injury history recorded. Then the participants were requested to have an MRI scan at Epworth Hospital in Melbourne or North Shore Private Hospital in Sydney.

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 Health HREC. All participants provided written informed consent.

5.2.2 Anthropometric measurements

The anthropometric measurements were collected during the CDAH study. Weight was measured to the nearest 0.1 kg, with shoes, socks and bulky clothing removed. Height was measured to the nearest 0.1 cm, with shoes and socks removed. BMI was calculated as weight (kg) divided by height squared (m^2). Triceps, biceps, subscapular and supra-iliac skinfolds were measured at locations determined by reference to anatomical landmarks [119] to the nearest 0.1 mm using Slim Guide Skinfold Callipers (SPRI Products). Body density was estimated from the log of the sum of four skinfolds using Durnin's equation; the slope and intercept of the equations for each age- and sex-specific group have been published elsewhere [117, 119]. An estimate of the percent body fat was derived from body density using Siri's equation: fat (%) = (4.95/density-4.50) × 100 [118]. Fat mass and lean mass were estimated by the percent body fat (kg): fat mass = fat (%) × weight (kg); lean mass = weight - fat (%) × weight (kg).

5.2.3 Physical activity measurements

The physical activity measurements were collected during the CDAH study. Physical activity was assessed using the long version of the International Physical Activity Questionnaire (IPAQ-L). Participants were asked to report the total time (minutes) and frequency (times/week) of occupational, commuting, domestic and leisure activity during the past week. Physical activities were calculated by multiplying frequency by duration to represent the minutes per

week of vigorous, moderate and walking activity. Time spent in each domain was summed to provide the estimate of total minutes of physical activity.

5.2.4 Physical performance measurements

The physical performance measurements were collected during the CDAH study. Physical performance measurements included long jump, hand grip strength, leg strength and PWC170. The standing long jump was measured by asking the participants to stand on the gym mat with toes behind the line and with feet slightly apart. A two-foot take-off and landing was used, with the participants swinging the arms and bending the knees to provide the drive for jump. The landing point at the closest part of the heel to the starting line was marked and the distance to the starting line was measured. Right and left hand grip strength was measured as participants gripped the dynamometer (Smedley dynamometer, TTM, Tokyo, Japan) with maximum force in one hand, with the higher of two measurements recorded. Hand grip strength was determined by calculating the average of right and left hand grip strength. Leg strength was measured using a leg-back dynamometer (Muscle Meter, TTM, Tokyo, Japan) by standing flat-footed on a platform with a straight back flat against a wall. A hand bar was held with an overhand grip and knees were flexed at an angle of 115°, at which point the bar was attached to the dynamometer by a chain. The bar was then pulled as far upwards as possible by sliding the body up the wall. PWC170 was assessed using a Monark bicycle ergometer. Participants were asked to cycle at a constant 60 rpm for 3 min each at three successively increasing but submaximal workloads. Heart rate was recorded at 1 min intervals at each workload using an electronic heart rate monitor. PWC170 was calculated by linear regression with extrapolation of the line of best fit to a heart rate of 170 bpm.

5.2.5 MRI measurements

The MRI scans were collected during the CDAH Knee Cartilage Study. Knees were imaged on a 1.5 T whole-body MRI unit (General Electric Medical Systems, Milwaukee, WI, USA) with the use of a commercial transmit–receive extremity coil. Sagittal, T1-weighted, fat-suppressed three-dimensional 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 min 56 sec, 1 acquisition) were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31×0.31 mm for cartilage morphometric analysis.

Cartilage thickness and subchondral bone area were measured in the medial and lateral femorotibial compartment (MFTC/LFTC) and in the patella as previously reported [123] by a quantitative approach. Manual segmentation of knee cartilage surfaces (i.e. articular surface and subchondral bone interface) was performed in all 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 and subchondral bone area, using Chondrometrics 3.0 software (Chondrometrics GmbH, Ainring, Germany). The total knee joint cartilage thickness was calculated as the weighted average of the thickness of each compartment according to the bone area size and the total knee joint bone area was calculated as the sum of the area of each compartment. The absolute reliability of these measures has been assessed in young adults (ages 22–27 years), with a coefficient of variation of 2.5–3.9% for cartilage thickness and 1.5–4.5% for bone area [206]. We used the same measurement system, same rater and similar population in the current study.

5.2.6 Statistical analyses

Histograms and Q–Q plots were used to assess the normality of continuous variables. Mean (standard deviation), median (interquartile range) and number (percentage) were used to describe the characteristics of the participants. T-tests, Wilcoxon rank-sum test and Chi-square tests were used to assess differences in normally distributed variables, skewed variables and categorical variables between groups, respectively. Linear regression analysis was used to estimate β-values for associations of body composition, physical activity and physical performance with knee cartilage thickness and subchondral bone area. We retained the confounders that had important biological plausibility or changed the estimated coefficient by >10% [126]. Age (in the CDAH study), sex, height (if fat mass or lean mass was a predictor), BMI (if physical activity or physical performance measures were predictors), duration of follow-up and knee injury history were included in the analysis models. For each model, we checked whether the assumptions of linear regression were satisfied. Where necessary to reduce heteroscedasticity and skewness of the residuals, the variable was transformed (e.g. by taking logarithms). Additionally, we paid careful attention to the scaling of the covariates.

We further adjusted for lean mass or total physical activity to explore independent associations of physical performance measures with knee cartilage thickness and subchondral bone area. When significant associations disappeared and effect sizes decreased dramatically after adjusting for a potential mediator, we performed mediation analysis to confirm the associations. We used the Stata (Stata version 15.0, StataCorp, College Station, TX, USA) command medeff to separate the effect of physical performance on cartilage thickness and bone area into direct effect (independent effect of physical performance on knee structures) and indirect effect (effect of physical performance on knee structures mediated by lean mass). This generated an estimate of the proportion of the total effect that is mediated [127].

A 95% confidence interval not including the null point or a p-value <0.05 (two-tailed) was considered statistically significant. All statistical analyses were performed in Stata version 15.0.

5.3 Results

5.3.1 Characteristics of the participants

A total of 2410 participants completed a clinic visit during the CDAH study and 330 participants completed MRI scans during the CDAH Knee Cartilage Study. Nonparticipation in the CDAH Knee Cartilage Study was related to the following: not residing in Melbourne or Sydney (n=1646), not responding or refusing (n=235), pregnant (n=8), rheumatoid arthritis (n=2), MRI contraindication (n=13), withdrawal (n=68), long distance for travelling to imaging site (n=103), work/family commitments (n=3) and moving interstate (n=2). A total of 186 MRI scans were measured for the current study, as 131 scans were not from Melbourne and 13 scans were unreadable.

In the current study, participants were 31–41 years of age (mean 35.3) when the MRI was acquired and 48% were female. The time between exposure measurements and MRI scanning ranged from 4.01 to 5.43 years (mean 4.77). Participants in the current study were younger and had less fat mass, less moderate activity and greater long jump performance than those in the remainder of the CDAH study, whereas other characteristics were comparable (Table 5.1). Additionally, participants in the current study were younger and had less knee injury than those in the remainder of the CDAH Knee Cartilage Study (data not shown).

Table 5.1 Characteristics of the participants in Chapter 5 and the remainder of CDAH Study

	MRI quantitative measures		P value
	Yes (n=186)	No (n=2144)	
Age[a] (years)	30.4 (2.8)	31.1 (2.6)	0.002
Sex (female), n (%)	90 (48.4)	1092 (51.0)	0.369
BMI (kg/m^2)	25.1 (4.1)	25.8 (4.9)	0.080
Knee injury history, n (%)	21 (11.3)		
Body composition (kg)			
Lean mass	54.4 (11.3)	54.4 (12.2)	0.981
Fat mass	21.4 (7.6)	22.8 (9.3)	0.043
Physical activity (hours/week), median (IQR)			
Walking	3.3 (1.3, 6.0)	3.0 (1.0, 6.3)	0.609
Moderate activity	3.8 (1.8, 6.8)	4.8 (2.2, 8.6)	0.009
Vigorous activity	1.0 (0.0, 3.7)	1.0 (0.0, 3.3)	0.381
Total activity	10.5 (5.9, 16.2)	11.0 (6.2, 17.8)	0.176
Physical performance measures			
Long jump (cm)	170.9 (32.6)	162.5 (36.6)	0.005
Hand grip strength[b] (kg)	39.3 (10.4)	38.2 (11.6)	0.149
Leg strength (kg)	136.0 (47.0)	128.7 (51.7)	0.062
PWC170 (watt)	170.5 (53.0)	164.2 (51.8)	0.130
Cartilage thickness (μm)			
Total[c]	2073 (237)		
MFTC	1801 (221)		
LFTC	2100 (260)		
Patella	2473 (361)		
Bone area (mm^2)			
Total[d]	4704 (674)		
MFTC	1798 (260)		
LFTC	1825 (299)		
Patella	1081 (170)		

Values are mean (standard deviation) unless otherwise stated.

CDAH Study, the Childhood Determinants of Adult Health Study; MRI, magnetic resonance imaging; BMI, body mass index; IQR, interquartile range; MFTC, medial femorotibial compartment; LFTC, lateral femorotibial compartment; PWC170, physical work capacity.

[a]Age during the CDAH Study.

[b]Calculated as the average of right and left hand grip strength.

[c]Calculated as the weighted-average according to the bone area of each compartment.

[d]Calculated as the sum of each compartment.

5.3.2 Body composition and knee structures

Lean mass was positively associated with cartilage thickness in the whole knee joint and in the MFTC and LFTC, but not the patella (Table 5.2, Figure 5.1). Fat mass was not associated with cartilage thickness in any sites (Table 5.2). Lean mass was positively associated with bone area in the whole knee joint, MFTC and LFTC, but not the patella (Table 5.2). Fat mass was not associated with bone area, except for the positive association between fat mass and bone area in the MFTC (Table 5.2).

Table 5.2 Association of body composition (kg) with knee cartilage thickness and bone area in young adults

	Cartilage thickness (μm)	Bone area (mm^2)
	β (95% CI)	β (95% CI)
Total		
Lean mass	**6.52 (0.86 to 12.18)**	**13.37 (5.43 to 21.31)**
Fat mass	-2.83 (-6.94 to 1.28)	3.20 (-2.68 to 9.08)
MFTC		
Lean mass	**7.13 (1.96 to 12.31)**	**8.37 (4.80 to 11.94)**
Fat mass	-1.68 (-5.49 to 2.12)	**3.48 (0.80 to 6.16)**
LFTC		
Lean mass	**6.86 (0.91 to 12.81)**	**7.34 (3.79 to 10.88)**
Fat mass	-3.34 (-7.66 to 0.99)	0.87 (-1.80 to 3.55)
Patella		
Lean mass	9.00 (-0.73 to 18.72)	-0.26 (-3.36 to 2.84)
Fat mass	-3.33 (-10.36 to 3.71)	-0.58 (-2.80 to 1.65)

Bold denotes statistical significance, $p<0.05$.

Adjusted for baseline age, sex, duration of follow-up, knee injury history and height.

CI, confidence interval; MFTC, medial femorotibial compartment; LFTC, lateral femorotibial compartment.

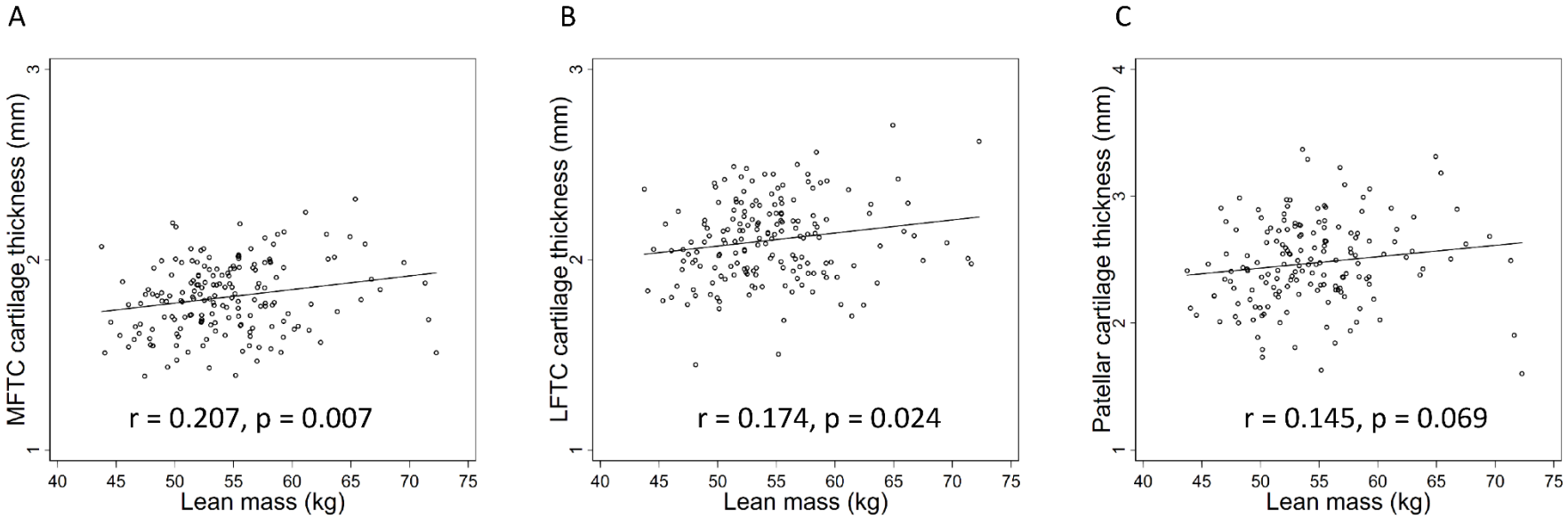

Figure 5.1 Scatter plots and linear regression lines for associations between lean mass and knee cartilage thickness

r and p values are from models adjusted for baseline age, sex, duration of follow-up, knee injury history, and height.

MFTC, medial femorotibial compartment; LFTC, lateral femorotibial compartment.

5.3.3 Physical activity and knee structures

Associations between physical activity measures (including walking, moderate activity, vigorous activity and total physical activity) and cartilage thickness and bone area in the whole knee or individual compartments were not statistically significant (Table 5.3).

Table 5.3 Association of physical activity (hours/week) with knee cartilage thickness and bone area in young adults

	Cartilage thickness (μm)	Bone area (mm^2)
	β (95% CI)	β (95% CI)
Total		
Walking	0.09 (-7.91 to 8.08)	0.06 (-16.59 to 16.72)
Moderate activity	2.77 (-4.88 to 10.41)	-5.14 (-21.11 to 10.83)
Vigorous activity	4.48 (-5.32 to 14.28)	-1.70 (-22.24 to 18.84)
Total physical activity	1.54 (-2.49 to 5.58)	-1.69 (-10.12 to 6.74)
MFTC		
Walking	1.79 (-5.20 to 8.77)	2.89 (-3.56 to 9.33)
Moderate activity	0.30 (-6.71 to 7.30)	-2.30 (-8.77 to 4.18)
Vigorous activity	3.33 (-5.43 to 12.10)	-3.98 (-12.12 to 4.17)
Total physical activity	1.10 (-2.49 to 4.69)	-0.50 (-3.83 to 2.83)
LFTC		
Walking	3.99 (-4.08 to 12.05)	1.30 (-5.79 to 8.38)
Moderate activity	5.53 (-2.52 to 13.58)	-1.94 (-9.04 to 5.17)
Vigorous activity	9.41 (-0.64 to 19.46)	0.09 (-8.87 to 9.05)
Total physical activity	4.07 (-0.03 to 8.17)	-0.15 (-3.80 to 3.50)
Patella		
Walking	-0.72 (-14.16 to 12.72)	-1.20 (-6.41 to 4.00)
Moderate activity	3.08 (-9.80 to 15.96)	-2.47 (-7.45 to 2.51)
Vigorous activity	-0.86 (-17.43 to 15.72)	-2.55 (-8.99 to 3.89)
Total physical activity	0.53 (-6.27 to 7.33)	-1.42 (-4.05 to 1.21)

Adjusted for baseline age, sex, duration of follow-up, body mass index, knee injury history. CI, confidence interval; MFTC, medial femorotibial compartment; LFTC, lateral femorotibial compartment.

5.3.4 Physical performance and knee structures

Long jump, hand grip strength and PWC170 were associated with greater knee cartilage thickness in the whole joint and in most compartments (except long jump in the LFTC and PWC170 in the patella) (Table 5.4). These associations were largely unchanged after further adjustment for total physical activity (data not shown). However, most associations disappeared after further adjustment for lean mass, with only associations between long jump and knee cartilage thickness in the whole joint and patella remaining statistically significant (Table 5.4). There were no associations between leg strength and cartilage thickness in any sites (Table 5.4). All physical performance measures were positively associated with subchondral bone area in the whole knee joint and most individual compartments (except for long jump in the MFTC and hand grip strength and leg strength in the patella) (Table 5.4). These associations were largely unchanged after further adjustment for total physical activity (data not shown). However, all the significant associations disappeared after further adjustment for lean mass, with large reductions in the effect sizes (Table 5.4).

In mediation analysis, associations between physical performance and total knee cartilage thickness and bone area were largely mediated by lean mass. All the indirect effects (mediated by lean mass) were statistically significant, whereas most of the direct effects were not significant (except the association between long jump and cartilage thickness) (Table 5.5). The percentage of the total effect mediated by lean mass ranged from 27 to 95% (Table 5.5).

Table 5.4 Associations of physical performance with knee cartilage thickness and bone area in young adults

	Cartilage thickness (μm)		Bone area (mm^2)	
	Model 1 β (95% CI)	Model 2 β (95% CI)	Model 1 β (95% CI)	Model 2 β (95% CI)
Total				
Long jump (cm)	**2.44 (0.70 to 4.18)**	**1.78 (0.10 to 3.46)**	**3.99 (0.64 to 7.34)**	1.26 (-1.20 to 3.72)
Hand grip strength (kg)	**7.74 (1.50 to 13.98)**	3.53 (-2.81 to 9.87)	**19.06 (7.21 to 30.92)**	1.70 (-7.69 to 11.09)
Leg strength (kg)	0.66 (-0.46 to 1.78)	-0.15 (-1.27 to 0.97)	**3.18 (1.09 to 5.28)**	0.19 (-1.46 to 1.84)
PWC170 (watt)	**1.07 (0.29 to 1.85)**	0.37 (-0.47 to 1.20)	**3.15 (1.70 to 4.60)**	0.27 (-0.97 to 1.50)
MFTC				
Long jump (cm)	**1.76 (0.21 to 3.31)**	1.20 (-0.29 to 2.69)	1.05 (-0.30 to 2.40)	0.11 (-0.95 to 1.18)
Hand grip strength (kg)	**6.33 (0.89 to 11.77)**	2.08 (-3.55 to 7.71)	**7.71 (3.06 to 12.35)**	0.59 (-3.47 to 4.64)
Leg strength (kg)	0.62 (-0.38 to 1.62)	-0.12 (-1.13 to 0.88)	**1.27 (0.42 to 2.12)**	0.13 (-0.59 to 0.85)
PWC170 (watt)	**0.83 (0.13 to 1.53)**	0.17 (-0.59 to 0.92)	**1.01 (0.41 to 1.61)**	-0.17 (-0.71 to 0.37)
LFTC				
Long jump (cm)	1.43 (-0.36 to 3.22)	0.80 (-0.93 to 2.52)	**1.51 (0.11 to 2.91)**	0.47 (-0.58 to 1.51)
Hand grip strength (kg)	**9.87 (3.71 to 16.03)**	5.39 (-1.03 to 11.81)	**10.28 (5.53 to 15.02)**	2.39 (-1.54 to 6.33)
Leg strength (kg)	0.66 (-0.49 to 1.81)	-0.21 (-1.36 to 0.95)	**1.62 (0.75 to 2.49)**	0.34 (-0.37 to 1.04)
PWC170 (watt)	**1.32 (0.53 to 2.11)**	0.66 (-0.21 to 1.52)	**1.52 (0.92 to 2.12)**	0.27 (-0.25 to 0.80)
Patella				
Long jump (cm)	**5.35 (2.43 to 8.27)**	**4.51 (1.61 to 7.40)**	**1.13 (0.07 to 2.19)**	0.54 (-0.41 to 1.49)
Hand grip strength (kg)	**10.57 (0.19 to 21.33)**	4.94 (-6.22 to 16.11)	2.89 (-0.98 to 6.75)	-1.05 (-4.70 to 2.60)
Leg strength (kg)	1.19 (-0.73 to 3.10)	0.13 (-1.84 to 2.10)	0.34 (-0.35 to 1.02)	-0.36 (-1.00 to 0.28)
PWC170 (watt)	1.12 (-0.24 to 2.47)	0.05 (-1.42 to 1.53)	**0.79 (0.32 to 1.26)**	0.19 (-0.29 to 0.68)

Bold denotes statistical significance, $p<0.05$.
Model 1 = adjusted for baseline age, sex, duration of follow-up, body mass index, knee injury history.
Model 2 = model 1 + further adjusted for lean mass.
CI, confidence interval; MFTC, medial femorotibial compartment; LFTC, lateral femorotibial compartment; PWC170, physical work capacity.

Table 5.5 Mediation analysis of associations between physical performance measures and knee structures (mediated by lean mass)

	Total knee cartilage thickness (μm) Estimates (95% CI)	Total knee bone area (mm^2) Estimates (95% CI)
Long jump (cm)		
Indirect effect	**0.65 (0.10 to 1.40)**	**2.68 (0.45 to 5.14)**
Direct effect	**1.75 (0.15 to 3.40)**	1.22 (-1.12 to 3.63)
Total effect	**2.40 (0.72 to 4.16)**	**3.90 (0.59 to 7.17)**
Total effect mediated, %	**27 (16 to 90)**	**68 (35 to 100)**
Hand grip strength (kg)		
Indirect effect	**4.17 (1.81 to 7.31)**	**17.21 (9.37 to 26.21)**
Direct effect	3.41 (-2.60 to 9.63)	1.53 (-7.37 to 10.74)
Total effect	**7.58 (1.53 to 14.08)**	**18.74 (7.17 to 30.40)**
Total effect mediated, %	**55 (29 to 100)**	**92 (57 to 100)**
Leg strength (kg)		
Indirect effect	**0.80 (0.37 to 1.39)**	**2.97 (1.58 to 4.56)**
Direct effect	-0.17 (-1.23 to 0.93)	0.16 (-1.41 to 1.78)
Total effect	0.63 (-0.42 to 1.79)	**3.13 (1.09 to 5.19)**
Total effect mediated, %	98 (-14 to 100)	**95 (57 to 100)**
PWC170 (watt)		
Indirect effect	**0.70 (0.32 to 1.16)**	**2.87 (1.92 to 4.03)**
Direct effect	0.35 (-0.45 to 1.17)	0.24 (-0.93 to 1.46)
Total effect	**1.05 (0.31 to 1.86)**	**3.11 (1.71 to 4.54)**
Total effect mediated, %	**67 (37 to 100)**	**92 (63 to 100)**

Bold denotes statistical significance, $p<0.05$.

CI, confidence interval; PWC170, physical work capacity.

Covariates: baseline age, sex, duration of follow-up, body mass index, knee injury history.

All estimates obtained using causal mediation analysis with Stata's medeff command.

Direct effects: independent effects of physical performance on knee structures.

Indirect effect: effects of physical performance on knee structures mediated by lean mass.

5.4 Discussion

This is the first study describing associations of body composition, physical activity and physical performance with knee cartilage thickness and subchondral bone area in young adults. We found that greater lean mass and physical performance, but not physical activity, were associated with greater knee cartilage thickness and subchondral bone area. Associations between physical performance and cartilage thickness and bone area were largely mediated by lean mass and were independent of total physical activity.

Our finding that lean mass was positively associated with cartilage thickness and bone area in the MFTC and LFTC is consistent with studies looking at lean mass and cartilage volume loss, where lean mass was associated with greater tibial cartilage volume cross-sectionally in young to middle-aged adults (ages 25-60 years) [80, 195] and over 5 years in young adults [81]. Lean mass was also associated with reduced cartilage volume loss over 2.9 years in older adults [79]. Additionally, loss of muscle mass was associated with greater cartilage volume loss over 2 years [195]. Environmental factors could play important roles; for example, exercise may elicit the lean mass gains [207] and then provide greater stability in the knee joint, which is a protective mechanical factor for OA [208].

We did not identify any consistent associations between fat mass and cartilage thickness or subchondral bone area. This is similar to literature on cartilage volume, where no association between fat mass and cartilage volume loss was found in two studies of middle-aged to older adults [80, 195], but this is inconsistent with a third study looking exclusively at young adults [81]. While we looked at fat mass globally, adipose tissue in different locations may have different effects: subcutaneous, visceral and intramuscular adipose tissues may be detrimental to the knee joint, while local adipose tissues, for example, normal infrapatellar fat pad (without

signal intensity alteration on MRI), could have protective effects on knee OA, and the role of intermuscular adipose tissue in knee OA remains unclear [209].

We did not find associations between physical activity and cartilage thickness or bone area. This is not consistent with other reports, where physical activity was associated with tibial cartilage volume in young adults (total activity) [93] and healthy middle-aged women (sports participation) [210]. This may be due to the inability of our questionnaire to distinguish between weight-bearing and non-weight-bearing activities [64]; alternatively, this may suggest cartilage thickness and bone area in the whole joint are not responsive to physical activities in young adults.

We found muscular strength (hand grip strength), power (long jump) and cardiorespiratory performance (PWC170) were positively associated with cartilage thickness and bone area. These were consistent with our previous study on tibial cartilage volume and bone area in young adults [93]. The significant associations largely disappeared after adjustment for lean mass, suggesting the effects of physical performance was mediated by lean mass; further mediation analysis confirmed this. Although lean mass explained most of the effects of hand grip strength and PWC170 on knee cartilage thickness, it only had moderate mediating effects on the association between long jump and cartilage thickness, suggesting other factors such as motor coordination may play roles in this association [211]. The association between leg strength and cartilage thickness was not significant, maybe due to leg strength being less strongly associated with lean muscle mass in the thigh compared with leg power [212].

Strengths of our study include that knee MRI was acquired in young adults (usually older adults are studied), cartilage thickness and subchondral bone area were studied rather than cartilage

volume and objective measures of physical performance were used. Some limitations of our study should be considered. First, we only had a modest sample size from one urban centre in Australia (as opposed to coverage of the whole Australia in the CDAH study), so the generalizability of study results may be limited. We compared characteristics between participants in the current study and in the remainder of CDAH study and the remainder of the CDAH Knee Cartilage Study. The current sample was comprised of younger and healthier participants. These differences have the potential to lead results towards the null, but not statistical significance, as healthier participants were less likely to report knee joint alterations [93, 192]. Second, we did not collect body composition, physical activity and physical performance measures during follow-up and MRI at baseline, so we were unable to describe longitudinal changes in exposure measures and knee cartilage and bone morphology. The changes in exposure measures and knee cartilage and bone morphology are important properties in knee OA research and are worthy of future studies. Third, body composition estimates based on skinfolds may not be as accurate as those based on dual-energy X-ray absorptiometry. Reassuringly, our measures have been validated [119, 213]. Fourth, physical activity measures, based on self-reported answers, were not objective. Reassuringly, previous studies have reported that the IPAQ-L has acceptable reliability and validity when assessing levels of physical activity among healthy adults (18–65 years) [214, 215]. Fifth, we did not have synovitis or cartilage composition measures, and the effects from these parameters should be identified in future studies.

In conclusion, greater lean mass and better physical performance measured 4-5 years prior were associated with greater knee cartilage thickness and subchondral bone area in young adults, and the associations of physical performance were largely mediated by lean mass. These

findings suggest lean mass may play an important role in maintaining knee joint health in young adults.

Chapter 6: Association of glucose homeostasis and metabolic syndrome with knee cartilage defects and cartilage volume in young adults

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6.1 Introduction

Knee osteoarthritis (OA) is a common joint disease worldwide, which causes severe knee pain, stiffness and dysfunction [164]. Currently, there are no proven therapies which can arrest or delay disease progression. Thus, identifying the risk factors of knee OA in early life could be important for disease prevention [141].

Magnetic resonance imaging (MRI) is a sensitive technique for examining early structural changes in knee joint [163], including imaging biomarkers of knee OA such as cartilage defects and loss of cartilage volume [34]. Cartilage defects and loss of cartilage volume have been associated with knee pain [37, 166] and subsequent knee replacement surgery [54, 137] in observational studies, and were set as important endpoints in clinical trials [55, 216]. Therefore, preventing knee cartilage defects and loss of cartilage volume may be an effective way to prevent knee OA.

Diabetes mellitus (DM) and OA coexist in the general population [217]. Experimental studies demonstrated that hyperglycaemia can decrease transport of dehydroascorbate into chondrocytes, which then compromises synthesis of type II collagen and leads to cartilage destruction [218]. Additionally, hyperglycaemia is associated with higher inflammatory responses in OA chondrocytes [219], which is detrimental to articular cartilage. A recent systematic review reported that there is limited evidence from epidemiological studies to support an independent association between DM and knee OA. However, the review stressed the requirement for prospective studies, which use objective and appropriate measures for both DM and OA and account for important confounding factors, such as age, sex and body mass index (BMI), to examine the independent associations [95].

Metabolic syndrome (MetS), defined as central obesity, dyslipidaemia, impaired fasting glucose and hypertension, has recently attracted interest in knee OA research as MetS shares many causal pathways with knee OA [191]. Although previous narrative reviews summarised several potential pathophysiologic pathways between MetS and knee OA [220-222], a recent systematic review found insufficient data from epidemiological studies to confirm the links between MetS and knee OA [107]. The systematic review suggested the need for future studies, which account for weight or BMI and examine early stage of disease [107].

Therefore, using data from a cohort of young adults with knee structures measured by MRI, we aimed to describe the associations of glucose homeostasis and MetS measures with knee cartilage defects and cartilage volume.

6.2 Methods

6.2.1 Participants

The Childhood Determinants of Adult Health (CDAH) Study was conducted on a nationwide sample of young adults in Australia. During 2004-2006, participants attended clinics which were located at sites in major cities and regional centres around Australia. Measures of anthropometrics, glucose homeostasis, metabolic syndrome and physical activity were collected during the clinic visit [114]. The CDAH Knee Cartilage Study was a subsequent sub-study of the CDAH study where participants completed knee MRI scans during 2008-2010.

We used the following strategy to recruit participants from the CDAH study. Participants residing in metropolitan Melbourne and Sydney were contacted by mail and were invited to participate in the CDAH Knee Cartilage Study. Participants who agreed to participate were assessed for eligibility. Exclusion criteria included being pregnant, having had diseases that might affect knee cartilage (including rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and psoriatic arthritis), or having MRI contraindications. The remaining participants were asked to have an MRI scan at Epworth Hospital in Melbourne or North Shore Private Hospital in Sydney.

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 Health HREC. All participants provided written informed consent.

6.2.2 Anthropometric measurements

Weight was measured to the nearest 0.1 kg (with shoes and bulky clothing removed) using Heine scales (Heine, Dover, NH). Height was measured to the nearest 0.1 cm (with shoes and

socks removed) using a stadiometer (Invicta, Leicester, UK). BMI was calculated as weight in kilograms divided by height in meters squared.

6.2.3 Glucose homeostasis measurements

Fasting glucose and insulin levels were measured using venous blood samples collected from the antecubital vein after a 12-hour fast. An Olympus AU5400 automated analyser (Olympus Optical, Tokyo, Japan) was used to enzymatically measure fasting glucose. A microparticle enzyme immunoassay kit (AxSYM; Abbot Laboratories, Abbot Park, IL) or an electrochemiluminescence immunoassay (Elecsys Modular Analytics E170; Roche Diagnostics, Mannheim, Switzerland) with inter-assay standardisation was used to measure fasting insulin. Glucose homeostasis measures, including homeostatic model assessment 2-insulin resistance (HOMA2-IR), HOMA2-beta cell function (HOMA2-β) and HOMA2-insulin sensitivity (HOMA2-S), were calculated by a homeostasis model assessment calculator (version 2.2.3 available from http://www.dtu.ox.ac.uk/homacalculator) using fasting glucose and fasting insulin.

6.2.4 MetS measurements

MetS was defined using the harmonized definition [120]. Five components of MetS and their thresholds were proposed in the definition. MetS was diagnosed when at least three of the five components were present. The details of MetS definition and thresholds of MetS components have been published elsewhere [120]. We use the following methods to collect the MetS measures: Waist circumference was measured at the narrowest point between the lower costal border and the iliac crest to the nearest 0.1 cm using a constant tension tape; high waist circumference was defined as waist circumference $\geqslant$102 cm in males or $\geqslant$88 cm in females. Fasting glucose was measured as described above; hyperglycaemia was defined as fasting

glucose of ⩾5.6 mmol/L. Triglyceride and high-density lipoprotein cholesterol (HDL-C) were measured enzymatically using an Olympus AU5400 automated analyser (Olympus Optical, Tokyo, Japan). Hypertriglyceridemia was defined as serum triglycerides ⩾1.7 mmol/L, and low HDL-C was defined as HDL-C <1.03 mmol/L in males or <1.3 mmol/L in females. Resting systolic and diastolic blood pressure readings were recorded after 5 min of quiet sitting using an OMRON HEM907 Digital Automatic Blood Pressure Monitor (Omron Healthcare Co., Ltd., Kyoto, Japan), and the mean of three recordings was used. Hypertension was defined as blood pressure ⩾ 130/85 mmHg.

6.2.5 Physical activity measurements

Physical activity was assessed using the long version of the International Physical Activity Questionnaire. Participants were asked to report the total time (minutes) and frequency (times/week) of occupational, commuting, domestic and leisure activity during the past week. Physical activities were calculated by multiplying frequency by duration to represent minutes per week of vigorous, moderate and walking activity. Time spent in each domain was summed to provide the estimate of total minutes of physical activity.

6.2.6 MRI measurements

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 1.5 T 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 min, 56 s; 1 acquisition. Sagittal images were obtained at a partition thickness of 1.5 mm

and an in-plane resolution of 0.31×0.31 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 0.31×0.31 mm (512×512 pixels); repetition time 3800 msec; echo time 45 msec.

Knee cartilage defects were measured as previously reported [223] 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. 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%. 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 $\geqslant 2$ at any site within that compartment. Intraobserver reliability expressed as an intraclass correlation coefficient ranged from 0.89 to 0.94.

Cartilage volume was determined by means of 3D image processing on an independent work station using software program OsiriX (Geneva, Switzerland). Individual plates were isolated by manually drawing disarticulation contours around the cartilage boundaries on a section-by-section basis. These data were then re-sampled by means of bilinear and cubic interpolation (area of 312×312 μm^2 and thickness of 1.5 mm, continuous sections) for the final 3D rendering. The coefficients of variation for cartilage volume measures were 2.1-2.6%. Femoral cartilage volume was not measured, as it strongly correlates with tibial cartilage volume [125].

6.2.7 Statistical analyses

Histograms and Q-Q plots were used to assess the normality of continuous variables. Mean (standard deviation), median (interquartile range), and number (percentage) were used to describe normally-distributed variables, skewed variables and categorical variables, respectively. T-tests, Wilcoxon rank-sum test and Chi-square tests were used to assess differences in normally-distributed variables, skewed variables and categorical variables between groups, respectively. Univariable and multivariable log binomial regression models were used to estimate relative risk (RR) for associations of glucose homeostasis and MetS measures with knee cartilage defects before and after adjustment for potential confounders. Univariable and multivariable linear regression models were used to estimate β coefficients for associations of glucose homeostasis and MetS measures with knee cartilage volume before and after adjustment for potential confounders. Age, sex, BMI (except when high waist circumference was the predictor) and total physical activity were included as potential confounders based on biological plausibility. A p-value less than 0.05 (2-tailed) was considered statistically significant. All statistical analyses were performed in Stata (Texas, USA), version 15.0.

6.3 Results

6.3.1 Characteristics of the participants

A total of 2410 participants completed clinic visit during the CDAH Study and 330 participants completed MRI scans during the CDAH Knee Cartilage Study. The follow-up time was 4-5 years. Nonparticipation in the CDAH Knee Cartilage Study was related to the following: not residing in Melbourne or Sydney (n=1646), not responding or refusing (n=235), pregnant (n=8), rheumatoid arthritis (n=2), MRI contraindication (n=13), withdrawal (n=68), long distance for traveling to the imaging site (n=103), work/family commitments (n=3), moving interstate (n=2). In the current study, 322 participants were included in analyses for cartilage defects and 328 for cartilage volume, as 8 scans were unreadable for cartilage defects and 2 for cartilage volume.

Participants were aged 31-41 (mean 35.4) years when MRI was acquired, 155 (47%) were female. 40 (12.7%) participants had hyperglycaemia and 21 (6.7%) had MetS. Participants included in the current study did less physical activity and had higher fasting glucose and lower HOMA2-β than those in the remainder of the CDAH Study, whereas other characteristics were comparable (Table 6.1).

Table 6.1 Characteristics of the participants in Chapter 6 and the remainder of CDAH study

	MRI measures		P value
	Yes (n=328)	No (n=2002)	
Age [a] (years)	30.8 (2.7)	31.1 (2.6)	0.138
Female, n (%)	155 (47.3)	1037 (51.5)	0.150
BMI (kg/m^2)	25.3 (4.1)	25.8 (4.9)	0.090
Total physical activity (hour/week), median (IQR)	9.6 (5.6, 15.7)	11.1 (6.3, 17.9)	0.017
Glucose homeostasis measures, median (IQR)			
Fasting glucose (mmol/L)	5.1 (4.8, 5.3)	5.0 (4.7, 5.3)	0.017
Fasting insulin (mU/L)	5.8 (4.2, 7.9)	6.0 (4.3, 8.7)	0.207
HOMA2-IR (unit)	0.80 (0.60, 1.10)	0.80 (0.60, 1.20)	0.146
HOMA2-β (unit)	0.79 (0.66, 1.00)	0.85 (0.68, 1.06)	0.005
HOMA2-S (unit)	1.27 (0.95, 1.69)	1.23 (0.86, 1.67)	0.168
MetS measures, n (%)			
MetS	21 (6.7)	136 (7.2)	0.744
High waist circumference [b]	36 (11.3)	293 (14.6)	0.121
Hyperglycaemia [c]	40 (12.7)	195 (10.3)	0.192
Hypertriglyceridemia [d]	49 (15.6)	280 (14.8)	0.716
Low HDL-C [e]	52 (16.5)	371 (19.6)	0.201
Hypertension [f]	60 (18.4)	436 (21.7)	0.169
Cartilage defects, n (%)			
Patellar	78 (24.2)		
Tibiofemoral	47 (14.6)		
Cartilage volume (mm^3)			
Patellar	2939 (752)		
Tibial	3896 (1005)		

Values are mean (standard deviation) unless otherwise stated.

MRI, magnetic resonance imaging; BMI, body mass index; CDAH, Childhood Determinants of Adult Health Study HOMA2-IR, homeostatic model assessment 2-insulin resistance; HOMA2-β, homeostatic model assessment 2-beta cell function; HOMA2-S, homeostatic model assessment 2-insulin sensitivity; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; MetS, metabolic syndrome.

[a]Age in the CDAH study.

[b]Defined as waist circumference ≥102 cm in males or ≥88 cm in females.

[c]Defined as fasting glucose ≥5.6 mmol/L.

[d]Defined as serum triglycerides ≥1.7 mmol/L.

[e]Defined as HDL-C <1.03 mmol/L in males or <1.3 mmol/L in females.

[f]Defined as blood pressure ≥130/85 mm Hg.

6.3.2 Glucose homeostasis and knee cartilage defects

Higher fasting insulin, HOMA2-IR and HOMA2-β were significantly associated with higher risk of tibiofemoral cartilage defects and higher HOMA2-S was associated with lower risk of tibiofemoral cartilage defects before and after adjustment for age, sex, BMI and physical activity (Table 6.2). Fasting glucose was not associated with tibiofemoral cartilage defects. Glucose homeostasis measures, including fasting glucose, fasting insulin, HOMA2-IR, HOMA2-β and HOMA2-S, were not associated with patellar cartilage defects in either univariable or multivariable analyses (Table 6.2).

Table 6.2 Associations between glucose homeostasis measures and knee cartilage defects

	Univariable RR (95% CI)	Multivariable[a] RR (95% CI)
Patellar		
Fasting glucose, mmol/L	0.62 (0.37 to 1.03)	0.55 (0.29 to 1.04)
Fasting insulin, mU/L	0.99 (0.94 to 1.04)	0.95 (0.88 to 1.02)
HOMA2-IR, per unit	0.90 (0.61 to 1.33)	0.60 (0.32 to 1.14)
HOMA2-β, per unit	1.10 (0.61 to 1.96)	0.87 (0.38 to 1.99)
HOMA2-S, per unit	1.01 (0.70 to 1.45)	1.15 (0.76 to 1.75)
Tibiofemoral		
Fasting glucose, mmol/L	1.31 (0.72 to 2.40)	0.89 (0.41 to 1.93)
Fasting insulin, mU/L	**1.05 (1.02 to 1.07)**	**1.05 (1.01 to 1.08)**
HOMA2-IR, per unit	**1.42 (1.15 to 1.76)**	**1.44 (1.08 to 1.92)**
HOMA2-β, per unit	**2.13 (1.24 to 3.65)**	**2.59 (1.33 to 5.07)**
HOMA2-S, per unit	**0.46 (0.27 to 0.78)**	**0.36 (0.18 to 0.72)**

Bold denotes statistical significance, $p<0.05$.

[a]Adjusted for age, sex, body mass index and physical activity.

CI, confidence interval; HOMA2-IR, homeostatic model assessment 2-insulin resistance; HOMA2-β, homeostatic model assessment 2-beta cell function; HOMA2-S, homeostatic model assessment 2-insulin sensitivity; RR, relative risk.

6.3.3 Glucose homeostasis and knee cartilage volume

Glucose homeostasis measures were not significantly associated with cartilage volume in univariable analyses, except for the positive associations between fasting glucose and cartilage volume in patella and tibia, and the negative association between HOMA2-β and tibial cartilage volume (Table 6.3). Associations were no longer significant after adjustment for age, sex, BMI and physical activity (Table 6.3).

Table 6.3 Associations between glucose homeostasis measures and knee cartilage volume (mm^3)

	Univariable β (95% CI)	Multivariable[a] β (95% CI)
Patellar		
Fasting glucose, mmol/L	**255.2 (60.6 to 449.7)**	-92.9 (-293.3 to 107.4)
Fasting insulin, mU/L	-2.6 (-21.3 to 16.1)	-6.3 (-25.1 to 12.4)
HOMA2-IR, per unit	1.1 (-154.6 to 156.9)	-40.6 (-195.9 to 114.7)
HOMA2-β, per unit	-228.8 (-513.6 to 56.0)	-48.0 (-330.5 to 234.5)
HOMA2-S, per unit	9.5 (-151.9 to 171.0)	32.4 (-125.6 to 190.4)
Tibial		
Fasting glucose, mmol/L	**561.2 (307.6 to 814.8)**	-22.0 (-280.0 to 236.1)
Fasting insulin, mU/L	-4.9 (-29.7 to 19.9)	-17.5 (-41.5 to 6.6)
HOMA2-IR, per unit	-15.3 (-221.5 to 190.8)	-127.8 (-323.1 to 67.6)
HOMA2-β, per unit	**-463.2 (-838.1 to -88.4)**	-236.8 (-592.0 to 118.4)
HOMA2-S, per unit	19.8 (-193.9 to 233.6)	64.9 (-134.3 to 264.1)

Bold denotes statistical significance, $p<0.05$.

[a]Adjusted for age, sex, body mass index and physical activity.

CI, confidence interval; HOMA2-IR, homeostatic model assessment 2-insulin resistance; HOMA2-β, homeostatic model assessment 2-beta cell function; HOMA2-S, homeostatic model assessment 2-insulin sensitivity.

6.3.4 MetS and knee cartilage defects

MetS and its components were not associated with patellar cartilage defects in univariable analyses, except hypertriglyceridemia was associated with higher risk of patellar cartilage defects (Table 6.4); however, this association was no longer statistically significant after adjustment for age, sex, BMI and physical activity (Table 6.4). MetS and its components were not associated with tibiofemoral cartilage defects in univariable analyses, except for the association between low HDL-C and higher risk of tibiofemoral cartilage defects (Table 6.4). The significant association persisted and the association between high waist circumference and higher risk of tibiofemoral cartilage defects became significant after adjustment for confounders (Table 6.4).

Table 6.4 Associations between metabolic syndrome measures and knee cartilage defects

	Univariable RR (95% CI)	Multivariable[a] RR (95% CI)
Patellar		
MetS	1.37 (0.72 to 2.60)	1.38 (0.60 to 3.21)
High waist circumference [b]	1.44 (0.86 to 2.39)	1.13 (0.59 to 2.15)
Hyperglycaemia [c]	0.91 (0.50 to 1.68)	0.76 (0.32 to 1.78)
Hypertriglyceridemia [d]	**1.66 (1.08 to 2.55)**	1.66 (0.97 to 2.84)
Low HDL-C [e]	0.93 (0.55 to 1.60)	0.88 (0.48 to 1.61)
Hypertension [f]	1.15 (0.72 to 1.84)	1.23 (0.70 to 2.17)
Tibiofemoral		
MetS	2.06 (0.99 to 4.29)	1.39 (0.58 to 3.32)
High waist circumference [b]	1.86 (0.98 to 3.54)	**2.32 (1.18 to 4.54)**
Hyperglycaemia [c]	1.24 (0.60 to 2.57)	0.90 (0.37 to 2.14)
Hypertriglyceridemia [d]	1.32 (0.68 to 2.56)	0.89 (0.40 to 1.96)
Low HDL-C [e]	**2.45 (1.43 to 4.19)**	**1.99 (1.08 to 3.69)**
Hypertension [f]	1.57 (0.86 to 2.84)	1.50 (0.77 to 2.95)

Bold denotes statistical significance, $p<0.05$.

[a]Adjusted for age, sex, body mass index (except when high waist circumference was the predictor) and physical activity.

[b]Defined as waist circumference ≥102 cm in males or ≥88 cm in females.

[c]Defined as fasting glucose ≥5.6 mmol/L.

[d]Defined as serum triglycerides ≥1.7 mmol/L.

[e]Defined as HDL-C <1.03 mmol/L in males or <1.3 mmol/L in females.

[f]Defined as blood pressure ≥130/85 mmHg.

CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome; RR, relative risk.

6.3.5 MetS and knee cartilage volume

MetS and its components were not significantly associated with cartilage volume in univariable analyses, except for the positive associations of hyperglycaemia and hypertension with tibial cartilage volume (Table 6.5). After adjustment for age, sex, BMI and physical activity, the significant associations disappeared (Table 6.5).

Table 6.5 Associations between metabolic syndrome measures and knee cartilage volume (mm^3)

	Univariable β (95% CI)	Multivariable[a] β (95% CI)
Patellar		
MetS	131.1 (-205.0 to 467.3)	-116.2 (-432.4 to 199.9)
High waist circumference [b]	-82.7 (-345.9 to 180.4)	20.1 (-213.0 to 253.2)
Hyperglycaemia [c]	212.8 (-37.3 to 462.9)	-64.1 (-306.5 to 178.2)
Hypertriglyceridemia [d]	119.7 (-111.5 to 350.9)	-52.0 (-170.9 to 275.0)
Low HDL-C [e]	-33.1 (-259.2 to 192.9)	-20.5 (-221.7 to 180.8)
Hypertension [f]	90.2 (-121.1 to 301.5)	-188.7 (-380.4 to 3.1)
Tibial		
MetS	210.1 (-234.8 to 655.1)	-255.7 (-660.2 to 148.8)
High waist circumference [b]	-218.2 (-566.4 to 130.0)	-120.7 (-418.9 to 177.4)
Hyperglycaemia [c]	**438.5 (108.4 to 768.6)**	-55.8 (-367.5 to 255.9)
Hypertriglyceridemia [d]	165.9 (-140.2 to 472.0)	-154.0 (-439.3 to 131.4)
Low HDL-C [e]	2.4 (-297.0 to 301.8)	-109.2 (-366.9 to 148.6)
Hypertension [f]	**333.7 (53.6 to 613.7)**	-38.4 (-285.4 to 208.6)

Bold denotes statistical significance, $p<0.05$.

[a]Adjusted for age, sex, body mass index (except when high waist circumference was the predictor) and physical activity.

[b]Defined as waist circumference ≥102 cm in males or ≥88 cm in females.

[c]Defined as fasting glucose ≥5.6 mmol/L.

[d]Defined as serum triglycerides ≥1.7 mmol/L.

[e]Defined as HDL-C <1.03 mmol/L in males or <1.3 mmol/L in females.

[f]Defined as blood pressure ≥130/85 mmHg.

CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome; RR, relative risk.

6.4 Discussion

This is the first study describing associations of glucose homeostasis and MetS measures with knee cartilage defects and cartilage volume in young adults. Our major findings were that higher levels of fasting insulin, HOMA2-IR and HOMA2-β were associated with an increased risk of tibiofemoral cartilage defects, and higher level of HOMA2-S was associated with a decreased risk of tibiofemoral cartilage defects. In addition, high waist circumference and low HDL-C were associated with higher risk of tibiofemoral cartilage defects.

Most previous studies describing the association between serum glucose and knee OA have focused on the incidence of radiographic OA (according to Kellgren-Lawrence grade) [95], except for two studies setting T2-relaxation time [111] or cartilage volume [224] as the outcome by using MRI. In one study, self-reported DM was associated with higher baseline T2 (more severe cartilage degradation), but not progression of T2 over 2 years [111]. In the other study, serum glucose (measured 10-14 years prior to baseline MRI) was associated with higher annual loss of tibial cartilage volume over 2 years in females but not in males [224]. Both studies used inaccurate glucose measures (self-reported or measured a long time ago) and did not measure serum insulin. In addition, the populations of interest in these studies were middle-aged or older-aged (40-69 years), whereas no studies were conducted in young adults.

In our study, we used both fasting glucose and fasting insulin, and calculated measures of insulin resistance, beta cell function and insulin sensitivity using the HOMA2 calculator, which is an effective tool to assess glucose homeostasis in clinical and epidemiological studies [225]. We collected MRI-based cartilage measures from young adults, which can predict knee OA and even joint replacement surgery in later life. Our findings that worse glucose homeostasis measures (except for fasting glucose) were associated with higher risk of tibiofemoral cartilage

defects suggested the detrimental effects of insulin resistance on knee cartilage. The lack of association for fasting glucose may be due to the age of our cohort. Young adults may have increased insulin secretion and insulin resistance, whereas their fasting glucose levels could still be in healthy range [226]. Furthermore, we only found significant associations in the tibiofemoral compartment, but not in the patella. The underlying reason was unclear, but may reflect the fact that pathological mechanisms involved in patellofemoral OA and tibiofemoral OA are different [227]. We did not find consistent associations between glucose homeostasis measures and knee cartilage volume; this may be due to knee cartilage defects occurring prior to cartilage volume loss in early knee OA [121].

Previous studies did not find independent associations between MetS and radiographic knee OA cross-sectionally [228] or longitudinally [229]. There is only one study that used an MRI-based outcome (compositional MRI outcome but not structural MRI outcome), which reported participants with $\geqslant 3$ metabolic components (versus <3) had higher baseline T2-relaxation time (more severe cartilage degradation) [111]. However, the study used self-reported DM and fat consumption (calculated from food questionnaire) to represent impaired glucose tolerance and dyslipidaemia; in addition, though the study selected the younger half of the source cohort, the participants were middle-aged or older-aged (45-60 years).

Our study addressed the issues in the previous study by using MRI-based structural outcomes in young adults and objective measures of MetS components. We found high waist circumference and low HDL-C were associated with higher risk of tibiofemoral cartilage defects. These results are consistent with previous studies, where central obesity was associated with thinner cartilage thickness in young adults [230] and reduced HDL was associated with knee OA in mice models [231]. We did not find associations between MetS and cartilage

defects or cartilage volume. The reason may be that our participants were young adults (31-41 years) and the prevalence of MetS was low (6.7%). We speculate that MetS will be associated with knee OA when the prevalence of MetS increases with ageing, though this needs to be confirmed by future studies.

Strengths of our study include the selection of a population-based sample of young adults and the use of knee MRI-based structural measures of cartilage. We also used objective measures of glucose homeostasis and MetS. Some limitations of our study should be considered. First, we only had a modest sample size from two urban centres in Australia (as opposed to the coverage of all Australian states/territories in CDAH study), so the generalizability of study results may be limited. We compared characteristics between participants in current study and in the remainder of CDAH Study: the current sample did less physical activity and had higher fasting glucose and lower HOMA2-β. The effects of these differences on our results were unknown though the differences were relatively small. Second, we did not acquire baseline MRI, so we were unable to describe longitudinal changes in knee cartilage defects and cartilage volume. Third, we did not collect knee alignment data, so we were unable to assess its potential effects on our findings.

In conclusion, insulin resistance, high waist circumference and low HDL-C were associated with higher risk of tibiofemoral cartilage defects, suggesting glucose homeostasis and some MetS components may affect early cartilage damage in young adults.

Chapter 7: Summary and future directions

7.1 Summary

Given the heavy disease burden of knee osteoarthritis (OA) and the lack of effective therapies, the prevention of knee OA is critically important. Although knee OA mostly affects middle-aged or older adults, young adults are the ideal target population in knee OA prevention. Several potential risk factors and protective factors of knee joint health in young adults were explored in this thesis.

In Chapter 3, we described the associations between adiposity measures in childhood and knee cartilage defects and bone marrow lesions (BMLs) in adulthood. We found that childhood adiposity measures, including body weight, body mass index (BMI), overweight status and fat mass, were associated with the increased risk of patellar cartilage defects 25 years later. We also found childhood overweight status was associated with the increased risk of patellar BMLs 25 years later. These results existed after adjusting for adult adiposity measures, suggesting these associations were independent. The long-term detrimental effects of childhood adiposity on adult patella addressed the importance of knee OA prevention on an early stage.

In Chapter 4, we described the associations between adiposity measures in childhood and adulthood and knee cartilage thickness, volume and bone area in young adults. We found childhood body weight and BMI were negatively associated with adult patellar bone area. Bone accrual during early life is a physiologic process, as it could distribute loads on a larger surface. Thus, this finding suggests the long-term detrimental effects of childhood adiposity on patellar bone morphology. We found adult weight was positively associated with bone area in both medial and lateral femorotibial compartments, indicating the natural response of weight-bearing joint to additional mechanical stress. We found that adult waist-hip ratio (WHR) was negatively associated with cartilage thickness, cartilage volume and bone area measured 4-5

years later; these results indicated the detrimental effects of central obesity on knee cartilage and bone morphology in young adults. Moreover, the z-score change of WHR from childhood to adulthood was negatively associated with knee cartilage thickness, cartilage volume and bone area, suggesting the track of central obesity during early life could affect knee structures in young adults.

In Chapter 5, we described associations of body composition, physical activity and physical performance with knee cartilage thickness and subchondral bone area in young adults. We found lean mass was positively associated with cartilage thickness and bone area, suggesting the protective effects of lean mass on knee structures. We did not find associations between physical activity and cartilage thickness or bone area. We found most physical performance measures were positively associated with knee cartilage thickness and bone area. However, the associations of physical performance were largely disappeared after further adjusting for lean mass, suggesting lean mass may be an important mediator, and the results from mediation analyses confirmed the mediation effects of lean mass. Thus, higher lean mass may be beneficial to maintain knee joint health in young adults.

In Chapter 6, we described the associations of glucose homeostasis and metabolic syndrome (MetS) measures with knee cartilage defects and cartilage volume in young adults. We found insulin resistance other than fasting glucose was associated with the higher risk of tibiofemoral cartilage defects. Moreover, some MetS components (high waist circumference and low high-density lipoprotein cholesterol (HDL-C)), but not MetS, were associated with the higher risk of tibiofemoral cartilage defects. The lack of association of fasting glucose or MetS may be due to the young age of our cohort: The prevalence of hyperglycaemia and MetS were low so we had little power to find significant results. We did not find associations about cartilage

volume; this may be due to knee cartilage defects occurring prior to cartilage volume loss in early knee OA. Nonetheless, our findings suggested that metabolic factors may involve in early cartilage damage in young adults.

In summary, the findings from this thesis indicate that early life factors may affect knee joint health in young adults. Our findings may be useful in developing preventive strategies for knee OA. However, our findings need to be confirmed and extended in future studies. The potential future directions are suggested in the following section.

7.2 Future directions

7.2.1 Further follow-up

Our findings provided important and novel information for maintaining knee joint health and preventing knee OA during early life. However, our studies were limited by the magnetic resonance imaging (MRI) scans as they were only collected once. The longitudinal changes of knee structures are important in knee OA research. Some knee structural abnormalities, including cartilage defects and BMLs, can be reversible [157, 232]. Reversing these abnormalities may relieve the knee symptoms and slow down the structural progression of knee OA. Moreover, knee cartilage loss is the hallmark of knee OA. Knee cartilage loss rather than cartilage volume per se has been predictive of total knee replacement [53]. Furthermore, the expansion of tibial bone area in adulthood can lead to the development of cartilage defects and predict the following cartilage loss and joint replacement [130]. Thus, the effects of early life factors on these structural changes are worthy of exploring in future studies.

Further follow-up will also provide the unique opportunity to observe the transition from healthy knees to osteoarthritic knees. Evidence suggested that knee cartilage loss became evident at about 40 years old [233]. Similarly, the prevalence of knee cartilage defects and BMLs were higher in middle-aged adults than those in young adults [233]. Our participants are now aged 43-53 years, so the osteoarthritic characteristics in their knee joints are becoming evident. Further follow-up will enable us to describe the nature of knee OA onset and identify the long-term effects of early life factors on knee osteoarthritic changes in middle-aged adults.

7.2.2 Large cohort studies

The participants in our studies were residing in Sydney and Melbourne, as opposed to coverage of the whole Australia in the original cohort. Although we compared the characteristics of our

participants and the remainder in the original cohort and the slight differences may not bias our results, the generalizability of our findings still needs to be evaluated carefully. Moreover, the original cohort mainly targeted cardiovascular disease and type 2 diabetes, and we can only conduct the secondary analyses using the data in the main study. In childhood, we did not collect the data about knee joint health, for example, the knee injury history (though we asked the participants to recall that in adulthood), which may affect our results. Therefore, our findings need to be confirmed in future studies. Ideally, the large prospective studies, which have the representative sample of the whole population and mainly focus on knee joint health, should be conducted.

7.2.3 Intervention studies

The findings of this thesis suggested several potential interventions for knee OA prevention. The well-designed randomized controlled trials (RCTs) may confirm our findings and provide strong empirical evidence of the interventions' efficacy on knee OA prevention.

Weight management in childhood

We reported childhood adiposity was associated with adult patellar abnormalities (cartilage defects and BMLs) in Chapter 3 and childhood adiposity was detrimental to adult patellar bone morphology (bone area) in Chapter 4, suggesting the long-term effects of childhood adiposity on patella. In 2017-18, about 25% (1.2 million) Australian children and adolescents (aged 2-17 years) were overweight or obese [234], so the effective management in preventing/ameliorating excess weight gain in childhood may have significant effects in keeping patellar health. Several RCTs have been conducted to develop the intervention strategies for childhood obesity. A meta-analysis included 85 RCTs, which aimed the primary prevention of childhood obesity and related hypertension, and reported that the combination of

parental involvement, physical activity, health education, and eating habits could be effective in reducing children's BMI and blood pressure [235]. Moreover, a recent systematic review, which summarised the school-based weight management interventions targeting children aged 4-12 years, concluded that increasing physical activity and reducing sedentary behaviour were the most effective interventions, and healthy diet and involving pupils' parents and family could enhance the effectiveness [236].

Preventing/reducing central obesity and increasing lean mass in young adults

We reported adult WHR and increasing WHR z-score from childhood to adulthood were negatively associated with cartilage thickness, volume and bone are in Chapter 4, and adult high waist circumference ($\geqslant$102 cm in males or $\geqslant$88 cm in females) was associated with the higher risk of tibiofemoral cartilage defects in Chapter 6, suggesting the detrimental effects from central obesity. Given the prevalence of high waist circumference was 41% (8.1 million) among Australian adults in 2017-18 [234], preventing/reducing central obesity could be critically important. Though current approaches for obesity management largely focus on general obesity (defined by BMI) [237], they may be also effective in central obesity. Apart from pharmacotherapy and bariatric surgery which should be considered carefully because of their safety and cost-effectiveness, the lifestyle interventions (diet and exercise) remain the foundation of obesity management [237]. Reducing 15-30% energy intake from habitual intake may be sufficient and appropriate to decrease waist circumference [238]. Aerobic exercise may also be effective as it will notably enhance the energy expenditure [239]. However, the kinds of aerobic exercise should be selected carefully, as they should avoid causing knee injury or increasing the joint loading.

In Chapter 5, we reported that lean mass may be protective to knee cartilage and bone morphology. Thus, resistance training, which can increase lean mass, may also be helpful in knee OA prevention [240]. A combination program of diet, aerobic exercise and resistance training, which can reduce waist circumference and increase lean mass, may be reasonable. Previously, an RCT investigated the effects of diet and exercise on knee mechanistic loading and symptoms among older knee OA patients [241]. The results suggested that diet combined with aerobic and strength training could remarkably reduce knee compressive forces and improve knee symptoms in the participants over 18 months However, no similar studies have been done in young adults. Thus, further studies are needed to determine the optimal prescription of the combination program and explore its effects on knee OA prevention.

Relieving insulin resistance and dyslipidaemia in young adults

We reported that insulin resistance was associated with the higher risk of tibiofemoral cartilage defects in Chapter 6. This is consistent with a recent research hotspot, where metformin may be effective in treating knee OA. Metformin is an oral medication used in the treatment of type 2 diabetes. Basic research has reported that metformin can limit the development and progression of knee OA in mice models through activating AMP-activated protein kinase signalling [242]. This finding may also apply to humans, as a prospective study reported that metformin use could reduce the cartilage volume loss over 4 years among knee OA patients with obesity [243]. However, no RCTs have confirmed whether metformin would protect knee cartilage and be a disease-modifying drug for obese knee OA patients. Our finding suggested the potential effects of metformin on knee OA prevention, as it may lower insulin resistance and prevent early cartilage damage. Future RCTs are needed to confirm our hypothesis.

We also reported that low HDL-C was associated with the higher risk of tibiofemoral cartilage defects in Chapter 6. Dyslipidaemia may affect knee cartilage through the shared pathophysiologic pathways between cardiovascular disease and knee OA [191]. Several studies explored the effects of lipid-lowing drugs on knee OA. A longitudinal study reported that using statins for >5 years was associated with the lower risk of developing knee pain over the following 4 years [244]. However, statin use did not reduce the risk of subsequent knee joint replacement in other cohorts [245, 246]. All the previous studies were observational studies and were conducted among older adults or knee OA patients. The effects of stains intervention in knee OA prevention among young adults are unclear.

7.2.4 Other MRI measures

In addition to the MRI measures used in this thesis, some other imaging biomarkers for early knee OA or novel MRI measures may be useful in knee OA prevention. Among these, we highlight compositional MRI, MRI-detected early osteophytes (MRI-OPs), and proximal tibiofibular joint (PTFJ) in this section.

Compositional MRI

The compositional MRI (T1ρ and T2 relaxation time) is able to detect early biochemical changes of knee cartilage prior to the morphologic changes [247]. T1ρ describes the spin-lattice relaxation in the rotating frame, higher T1ρ indicates the loss of proteoglycan in cartilage. T2 reflects the ability of free water protons to move and to exchange energy inside the cartilage matrix, higher T2 indicates the damage of collagen and increase of water content in cartilage. Thus, higher T1ρ and T2 are important indicators of early cartilage degeneration. A recent meta-analysis reported that healthy people with higher T1ρ and T2 relaxation time were under higher risk of subsequent knee OA [248]. Using our unique longitudinal data to identify the

risk factors of higher T1ρ and T2 during early life may provide the new information about knee OA prevention.

MRI-OPs

Osteophyte is a typical osteoarthritic structure and traditionally detected by radiograph. However, a cohort of Australian older adults (aged 50-80 years) reported that 85% of participants had MRI-detected osteophytes while only 10% of participants had radiographically-detected osteophytes [249]. The researchers later named the osteophytes, which can only be detected by MRI but not by radiograph, as MRI-OPs [250]. The MRI-OPs were dynamic in older adults from that cohort, with 46% worsened, 53% stable and 1% decreased over 2.6 years [251]. In the same setting, baseline MRI-OPs were associated with the higher risk of cartilage defects and BMLs in a site-specific manner and were suggested as an indicator of early-stage osteoarthritic progression [250]. However, neither the prevalence nor the natural history of MRI-OPs was described in young adults. The role of MRI-OPs in knee OA prevention during early life needs further exploration.

PTFJ

PTFJ is the joint located between lateral tibial condyle and fibular head. Recently, a novel method for measuring the morphological parameters of PTFJ using MRI have been developed and validated among older adults [252]. The parameters of the measure system include the contacting area on the PTFJ surface plane (S), the projection of S onto the horizontal plane (Sτ), the projection of S onto the sagittal plane (Sφ), and the projection of S onto the coronal plane (Sυ). The different parameters represent different mechanical loadings: S bears total force of the fibula from the tibia, Sτ carries load-bearing force to the fibula from the tibia in an upward direction, Sφ bears lateral stress-bolstering force of fibula from tibia in the inward direction,

and Sυ bears posterior stress-bolstering force of fibula from tibia in the forward direction. A nested matched case-control study has reported that S, Sτ and Sυ were associated with the higher risk of incident radiographic knee OA among older adults (average aged 60 years), suggesting their predictive value of knee OA [253]. However, no research identified the role of these parameters in knee joint health among young adults.

Appendix: Published Manuscripts

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

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SUMMARY

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 (ASHFS) 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 1.5 T 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) 1.01–1.09; BMI 1.10/kg/m^2, 1.01–1.19; Overweight 2.22/yes, 1.21–4.08; fat mass 1.11/kg, 1.01–1.22), 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 1.10–7.53). 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.

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

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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 20–29 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 h 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 flowchart of the selection of participants for this study is shown in Fig. 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 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% × 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 1.5 T 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 min, 56 s; 1 acquisition. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31 × 0.31 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 × 0.31 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

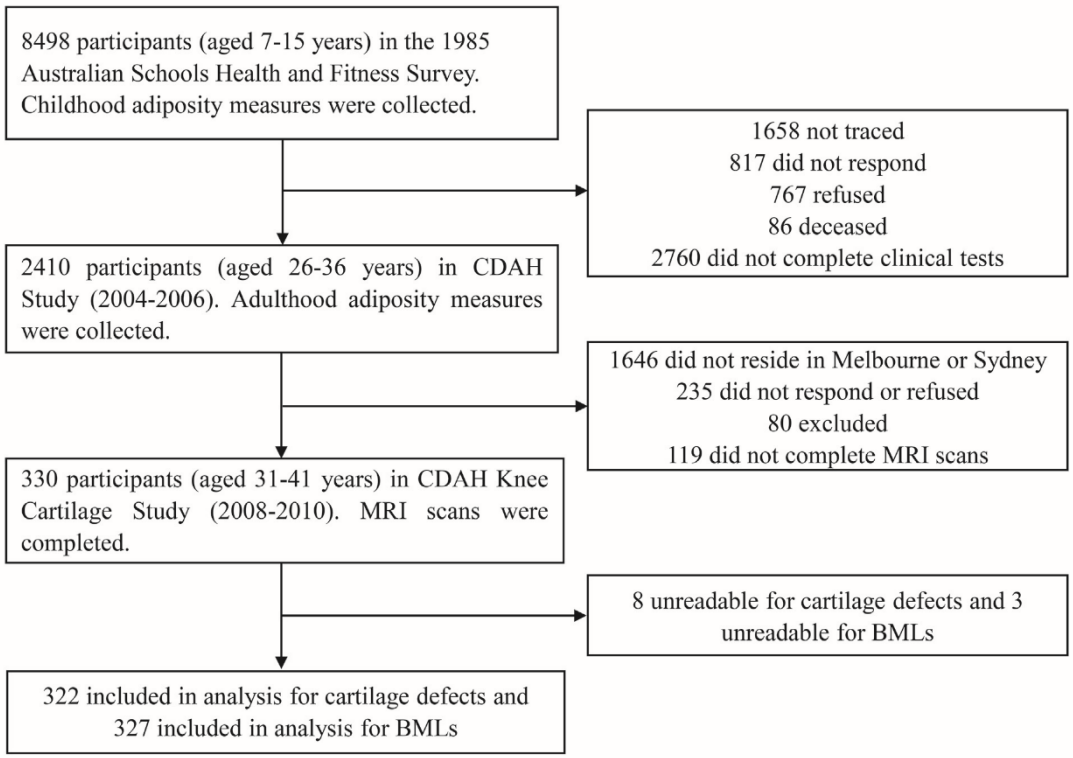

Fig. 1. Flowchart showing selection of the participants for current study from previous studies. BMLs, bone marrow lesions; CDAH Study, Childhood Determinants of Adult Health Study; MRI, magnetic resonance imaging.

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

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

Cholesterol and plasma glucose measures

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

Statistical analyses

Mean (standard deviation) or number (percentage) was used to describe characteristics of the participants. Student's *t*-tests or Chi-square tests were used to assess the differences in continuous and categorical variables, respectively, between groups of participants. Univariable and multivariable log binomial regressions were used to estimate relative risk (RR) for the associations between childhood adiposity measures and adulthood knee cartilage defects or BMLs before and after adjustment for potential confounders. If the log binomial model failed to converge, RR was estimated by using a Poisson distribution and robust standard errors. Multivariable ordinal logistic regressions were used to estimate odds ratio (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 × 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 I. 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 I).

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 II) 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% confidence interval (CI) 1.02–1.09; BMI 1.10/kg/m^2, 1.02–1.19; Overweight 2.04/yes, 1.12–3.74; fat mass 1.13/kg, 1.03–1.23) (Table II). After further adjustment for corresponding adulthood measure, these associations were largely unchanged (Weight RR 1.05/kg, 95% CI 1.01–1.09; BMI 1.10/kg/m^2, 1.01–1.19; Overweight 2.22/yes, 1.21–4.08; fat mass 1.11/kg, 95% CI 1.01–1.22) (Table II, Fig. 2). There were no significant associations between childhood adiposity measures and adulthood tibiofemoral cartilage defects in either univariable or multivariable analyses (Table II). Above associations remained large unchanged after adjustment for metabolic risk factors (cholesterol or glucose) or meniscal tears (data not shown).

Table I
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* (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* (kg)	19.8 (6.5)	23.9 (9.7)	21.2 (8.1)	22.7 (8.7)

BMI, body mass index.
Values are mean (SD) unless otherwise stated.
* Fat mass was measured among the children aged 9, 12 and 15 years in 1985; $n = 62$, 45, 79 and 29, respectively.

Table II
Associations between childhood adiposity measures and adulthood cartilage defects

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

BMI, body mass index; CI, confidence interval; RR, relative risk.
Bold denotes statistical significance, $P < 0.05$.
* Adjusted for childhood age, duration of follow-up, gender, height (if weight or fat mass was the predictor), childhood knee injury.
† Further adjusted for corresponding adulthood measure.

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 III); 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: 1.10–7.53) (Table III). There were no significant associations between childhood adiposity measures and adulthood tibiofemoral BMLs in multivariable analyses (Table III); 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: 1.07–1.32) (Fig. 3), but not in females (RR: 1.01, 95 % CI: 0.87–1.18). 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: 1.01–1.37; female RR: 1.10/kg, 95% CI: 0.93–1.30). 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

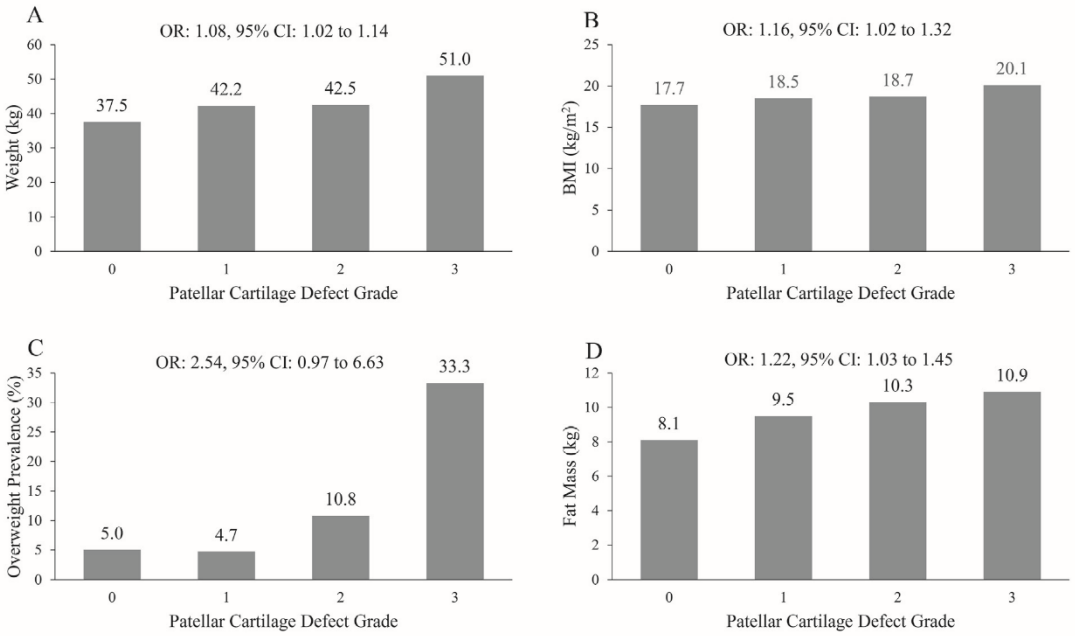

Fig. 2. Mean childhood weight (A), mean childhood BMI (B), childhood overweight prevalence (C) and mean childhood fat mass (D) for participants classified by patellar cartilage defect grades. ORs and 95% CIs were from multivariable ordinal logistic regressions, which included childhood age, duration 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.

Table III
Associations between childhood adiposity measures and adulthood BMLs

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

BMI, body mass index; BMLs, bone marrow lesions; CI, confidence interval; RR, relative risk.
Bold denotes statistical significance, $P < 0.05$.
* Adjusted for childhood age, duration of follow-up, gender, height (if weight or fat mass was the predictor), childhood knee injury.
† Further adjusted for corresponding adulthood measure.
‡ $P = 0.064$.

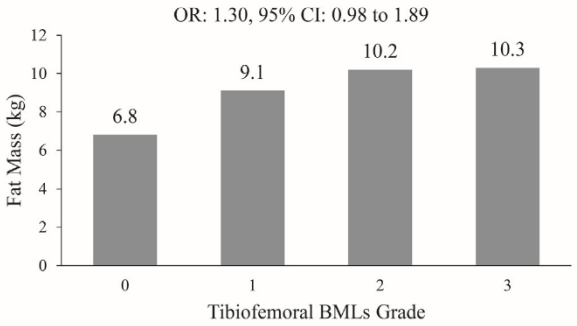

Fig. 3. Mean childhood fat mass for males classified by tibiofemoral BMLs grades. OR and 95% CI were from multivariable ordinal logistic regressions, which included childhood age, duration of follow-up, gender, height, childhood knee injury as confounders. BMLs, bone marrow lesions; CI, confidence interval;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

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

Author contributions

CD (Changhai.Ding@utas.edu.au) had full access to all the data in the study and takes responsibility for its integrity and the accuracy of the data analysis. Study conception and design: AV, FC, LM, TD, GJ and CD; acquisition of data: ST, AV, FC, LM, TD, AH, MC, GJ, CD and BA; analysis and interpretation of data: TM, AV, FW, LL, GJ, CD and BA. All authors helped the preparation of manuscript and approved the manuscript for submission.

Competing interest statement

The authors have no conflicts of interest relevant to this article to disclose.

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ARTICLE

Pediatrics

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

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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 ($\beta = -5.57$ mm^2/kg) and body mass index (BMI) ($\beta = -11.55$ mm^2/kg/m^2) were negatively associated with adult patellar bone area, whereas adult weight was positively associated with bone area in medial femorotibial compartment (MFTC) ($\beta = 3.37$ mm^2/kg) and lateral femorotibial compartment (LFTC) ($\beta = 2.08$ mm^2/kg). Adult waist–hip ratio (WHR) was negatively associated with cartilage thickness (MFTC: $\beta = -0.011$; LFTC: $\beta = -0.012$ mm/0.01 unit), volume (Patella: $\beta = -20.97$; LFTC: $\beta = -21.71$ mm^3/0.01 unit) and bone area (Patella: $\beta = -4.39$ mm^2/0.01 unit). The change in WHR z-scores from childhood to adulthood was negatively associated with cartilage thickness (MFTC: $\beta = -0.056$ 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.

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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

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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 have 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 hypothesised 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 substudy 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 flowchart of the selection of participants for this study is shown in Fig. 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

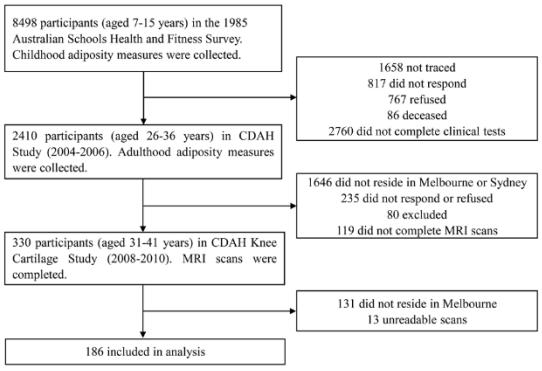

Fig. 1 Flowchart showing selection of the participants for current study from previous studies. CDAH Study, Childhood Determinants of Adult Health Study; MRI, magnetic resonance imaging

metres squared. Overweight status in childhood was defined according to age- and sex-specific cutoff points, as previously published [18]. Adult overweight status was defined as a BMI ≥ 25 kg/m^2. 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 three-dimensional (3D) spoiled gradient-recalled acquisitions in the steady state (flip angle 55°, repetition time 58 ms, echo time 12 ms, field of view 16 cm, 60 partitions, 512 × 512-pixel matrix, acquisition time 11 min, 56 s, 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 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 3D 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 coefficient of variation 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 (SD) or number (percentage) was used to describe characteristics of the participants. T-tests or χ^2-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 < 0.05 (two-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 adjustment for adult BMI (Weight: $\beta = -4.75$ 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 β-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

Table 1 Characteristics of participants

	MRI quantitative measures		*P*-value
	Yes	No	
Childhood	($n = 186$)[a]	($n = 8312$)	
Female, *n* (%)	90 (48.4)	4101 (49.3)	0.797
Age (years)	10.9 (2.7)	10.9 (2.5)	0.887
Weight (kg)	39.7 (13.6)	39.9 (13.0)	0.872
BMI (kg/m^2)	18.1 (2.7)	18.2 (2.9)	0.469
Overweight[b] (yes), *n* (%)	14 (7.6)	975 (11.9)	0.069
WHR (unit)	0.82 (0.05)	0.84 (0.06)	0.001
Adulthood		($n = 2144$)	
Weight (kg)	75.8 (15.0)	77.2 (17.4)	0.291
BMI (kg/m^2)	25.1 (4.1)	25.8 (4.9)	0.080
Overweight[c] (yes), *n* (%)	77 (42.1)	1075 (50.1)	0.038
WHR (unit)	0.79 (0.08)	0.80 (0.07)	0.051
Cartilage thickness (mm)			
Patella	2.47 (0.36)	NA	
MFTC	3.65 (0.47)	NA	
LFTC	4.15 (0.51)	NA	
Cartilage volume (mm^3)			
Patella	2843 (714)	NA	
MFTC	3363 (799)	NA	
LFTC	4041 (1035)	NA	
Bone area (mm^2)			
Patella	1081 (170)	NA	
MFTC	1798 (260)	NA	
LFTC	1825 (299)	NA	

Values are mean (SD) unless otherwise stated

BMI body mass index, *LFTC* lateral femorotibial compartment, *MFTC* medial femorotibial compartment, *WHR* waist–hip ratio

[a]The quantitative measures were only done in a subsample ($n = 186$) of the participants who underwent MRI scans ($n = 330$); [b]Childhood overweight status was defined according to the age and sex-specific cutoff points; [c]Adulthood overweight status was defined as a BMI ≥ 25 kg/m^2

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 ($\beta = 0.06$ 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, Fig. 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, although 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 ($\beta = -22.47$ 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 programme [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 1 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

Table 2 Associations between childhood adiposity measures and knee cartilage thickness, cartilage volume and subchondral bone area

	Cartilage thickness (mm)		Cartilage volume (mm^3)		Bone area (mm^2)	
	Univariable β (95% CI)	Multivariable[a] β (95% CI)	Univariable β (95% CI)	Multivariable[a] β (95% CI)	Univariable β (95% CI)	Multivariable[a] β (95% CI)
Patella						
Weight, kg	0.002 (− 0.002 to 0.006)	0.003 (− 0.008 to 0.013)	2.10 (− 5.92 to 10.11)	− 13.13 (− 30.18 to 3.92)	0.05 (− 1.85 to 1.95)	**− 5.57 (− 9.27 to − 1.87)**
BMI, kg/m^2	0.006 (− 0.014 to 0.026)	0.009 (− 0.015 to 0.033)	− 18.07 (− 57.81 to 21.67)	− 23.68 (− 63.88 to 16.51)	− 9.11 (− 18.53 to 0.31)	**− 11.55 (− 20.37 to − 2.73)**
Overweight, yes	0.092 (− 0.111 to 0.295)	0.092 (− 0.102 to 0.286)	− 97.77 (− 503.17 to 307.63)	− 111.46 (− 438.07 to 215.14)	− 65.54 (− 161.98 to 30.89)	− 71.66 (− 143.73 to 0.42)[b]
WHR, 0.01 unit	0.007 (− 0.004 to 0.017)	− 0.003 (− 0.015 to 0.009)	**29.80 (9.64 to 49.96)**	− 2.30 (− 21.83 to 17.23)	**8.36 (3.63 to 13.10)**	− 0.17 (− 4.49 to 4.15)
MFTC						
Weight, kg	**0.006 (0.001 to 0.011)**	0.009 (− 0.003 to 0.020)	**13.31 (5.01 to 21.60)**	5.79 (− 9.76 to 21.34)	**3.89 (1.17 to 6.61)**	− 1.07 (− 5.62 to 3.48)
BMI, kg/m^2	0.023 (− 0.002 to 0.048)	0.021 (− 0.006 to 0.048)	35.14 (− 7.69 to 77.96)	25.03 (− 13.07 to 63.14)	6.72 (− 7.35 to 20.79)	3.97 (− 7.88 to 15.82)
Overweight, yes	0.044 (− 0.212 to 0.300)	0.031 (− 0.188 to 0.251)	86.42 (− 351.45 to 524.29)	50.81 (− 256.63 to 358.25)	15.53 (− 127.66 to 158.73)	− 0.39 (− 95.72 to 94.94)
WHR, 0.01 unit	**0.017 (0.004 to 0.030)**	0.003 (− 0.010 to 0.016)	**37.10 (15.27 to 58.94)**	3.07 (− 15.66 to 21.81)	**11.62 (4.48 to 18.75)**	− 1.65 (− 7.43 to 4.13)
LFTC						
Weight, kg	**0.006 (0.001 to 0.011)**	0.006 (− 0.007 to 0.018)	**14.52 (3.70 to 25.35)**	3.08 (− 15.57 to 21.74)	**3.98 (0.84 to 7.11)**	− 0.15 (− 4.61 to 4.32)
BMI, kg/m^2	0.018 (− 0.009 to 0.046)	0.017 (− 0.013 to 0.047)	31.77 (− 23.85 to 87.38)	25.97 (− 20.53 to 72.47)	6.98 (− 9.14 to 23.10)	6.99 (− 4.92 to 18.90)
Overweight, yes	− 0.027 (− 0.306 to 0.253)	− 0.046 (− 0.287 to 0.194)	14.63 (− 552.14 to 581.40)	− 50.95 (− 425.66 to 323.77)	33.57 (− 130.38 to 197.51)	10.10 (− 85.94 to 106.13)
WHR, 0.01 unit	0.013 (− 0.001 to 0.028)	− 0.005 (− 0.020 to 0.010)	**50.53 (22.34 to 78.71)**	− 1.64 (− 24.47 to 21.20)	**16.88 (8.83 to 24.94)**	0.03 (− 5.81 to 5.88)

Bold denotes statistical significance, $p < 0.05$. *BMI* body mass index, *CI* confidence interval, *LFTC* lateral femorotibial compartment, *MFTC* medial femorotibial compartment, *WHR* waist–hip ratio

[a]Adjusted for childhood age, gender, height (if weight was the predictor)

[b]$p = 0.051$

Table 3 Associations between adulthood adiposity measures and knee cartilage thickness, cartilage volume and subchondral bone area

	Cartilage thickness (mm)		Cartilage volume (mm^3)		Bone area (mm^2)	
	Univariable β (95% CI)	Multivariable[a] β (95% CI)	Univariable β (95% CI)	Multivariable[a] β (95% CI)	Univariable β (95% CI)	Multivariable[a] β (95% CI)
Patella						
Weight, kg	**0.005 (0.001 to 0.008)**	− 0.001 (− 0.005 to 0.004)	**18.81 (12.11 to 25.50)**	− 0.45 (− 7.10 to 6.20)	**4.89 (3.34 to 6.44)**	− 0.37 (− 1.71 to 0.97)
BMI, kg/m^2	− 0.001 (− 0.014 to 0.013)	− 0.005 (− 0.018 to 0.008)	5.76 (− 20.55 to 32.07)	− 11.52 (− 32.88 to 9.85)	0.86 (− 5.34 to 7.07)	− 3.66 (− 8.37 to 1.04)
Overweight, yes	0.086 (− 0.024 to 0.196)	0.027 (− 0.081 to 0.135)	196.80 (− 19.16 to 412.77)	− 15.86 (− 196.54 to 164.82)	29.66 (− 21.54 to 80.86)	− 26.72 (− 66.42 to 12.99)
WHR, 0.01 unit	0.007 (− 0.001 to 0.014)	− 0.009 (− 0.018 to 0.000)[b]	**28.26 (15.13 to 41.39)**	**− 20.97 (− 36.35 to − 5.60)**	**7.84 (4.81 to 10.87)**	**− 4.39 (− 7.79 to − 0.98)**
MFTC						
Weight, kg	**0.011 (0.006 to 0.015)**	0.002 (− 0.003 to 0.006)	**30.21 (23.83 to 36.59)**	**8.51 (2.47 to 14.54)**	**10.95 (8.99 to 12.90)**	**3.37 (1.73 to 5.00)**
BMI, kg/m^2	0.013 (− 0.004 to 0.030)	0.002 (− 0.013 to 0.017)	**41.29 (13.26 to 69.33)**	16.13 (− 4.23 to 36.49)	**15.19 (6.13 to 24.26)**	**6.62 (0.37 to 12.87)**
Overweight, yes	**0.210 (0.075 to 0.345)**	0.085 (− 0.037 to 0.207)	**465.16 (239.56 to 690.76)**	**174.22 (4.51 to 343.93)**	**140.31 (66.40 to 214.21)**	40.45 (− 12.21 to 93.11)
WHR, 0.01 unit	**0.017 (0.008 to 0.025)**	**− 0.011 (− 0.021 to − 0.001)**	**45.21 (32.01 to 58.40)**	− 12.86 (− 27.60 to 1.89)[c]	**16.62 (12.48 to 20.76)**	− 1.97 (− 6.55 to 2.61)
LFTC						
Weight, kg	**0.012 (0.007 to 0.016)**	0.001 (− 0.004 to 0.006)	**37.04 (28.55 to 45.54)**	4.85 (− 2.45 to 12.16)	**12.05 (9.74 to 14.36)**	**2.08 (0.46 to 3.71)**
BMI, kg/m^2	0.014 (− 0.005 to 0.032)	0.002 (− 0.014 to 0.018)	**39.68 (2.91 to 76.45)**	4.45 (− 20.52 to 29.42)	**13.48 (2.93 to 24.04)**	2.57 (− 3.82 to 8.97)
Overweight, yes	**0.214 (0.066 to 0.362)**	0.077 (− 0.057 to 0.211)	**499.63 (202.57 to 796.68)**	93.46 (− 115.28 to 302.20)	**139.41 (53.60 to 225.23)**	13.17 (− 40.41 to 66.75)
WHR, 0.01 unit	**0.018 (0.009 to 0.027)**	**− 0.012 (− 0.023 to − 0.001)**	**60.11 (43.09 to 77.12)**	**− 21.71 (− 39.54 to − 3.88)**	**19.76 (15.06 to 24.47)**	− 4.45 (− 9.05 to 0.15)[d]

Bold denotes statistical significance, $p < 0.05$. *BMI* body mass index, *CI* confidence interval, *LFTC* lateral femorotibial compartment, *MFTC* medial femorotibial compartment, *WHR* waist–hip ratio

[a]Adjusted for adulthood age, gender, height (if weight was the predictor)

[b]$p = 0.060$; [c]$p = 0.087$; [d]$p = 0.058$

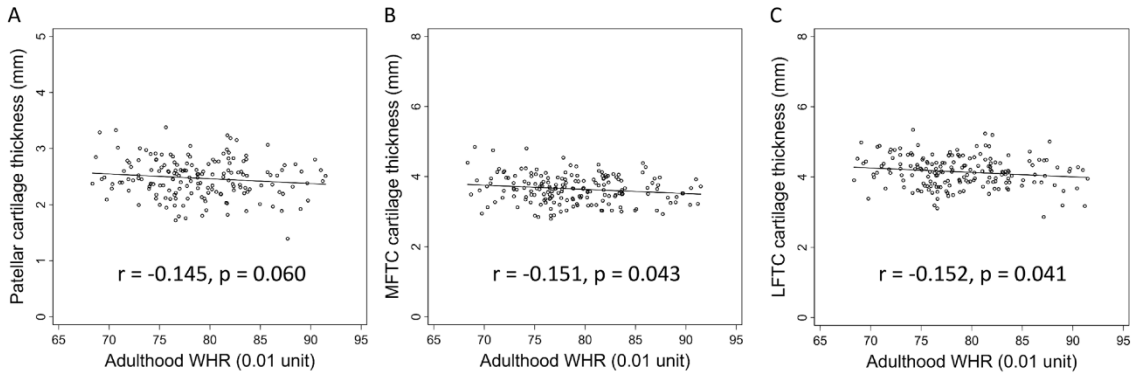

Fig. 2 Scatter plots and linear regression lines for associations between adulthood WHR and knee cartilage thickness (**a**: patella; **b**: MFTC; **c**: LFTC). Linear regression lines are from models adjusted for adult age and gender. LFTC lateral femorotibial compartment, MFTC medial femorotibial compartment, WHR waist–hip ratio

structural outcomes was detected during the 18-month Intensive Diet and Exercise for Arthritis 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 from 3 to 7 years [28]. Similarly, Goulding et al. [29] reported that overweight or obese children had lower bone mass and total bone area than their predicted values calculated from body weight during growth. 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, as 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, e.g., 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

Table 4 Associations of the change of adiposity measures from childhood to adulthood with knee cartilage thickness, cartilage volume and subchondral bone area

	Cartilage thickness (mm)		Cartilage volume (mm^3)		Bone area (mm^2)	
	Univariable β (95% CI)	Multivariable[a] β (95% CI)	Univariable β (95% CI)	Multivariable[a] β (95% CI)	Univariable β (95% CI)	Multivariable[a] β (95% CI)
Patella						
Weight *z*-score change	− 0.042 (− 0.105 to 0.021)	− 0.055 (− 0.120 to 0.010)	5.81 (− 118.18 to 129.79)	− 36.91 (− 138.17 to 64.36)	11.50 (− 17.68 to 40.68)	− 1.25 (− 21.75 to 19.25)
BMI *z*-score change	− 0.040 (− 0.099 to 0.019)	− 0.036 (− 0.092 to 0.021)	− 3.83 (− 121.17 to 113.50)	15.30 (− 80.37 to 110.96)	6.40 (− 21.44 to 34.24)	11.49 (− 9.69 to 32.66)
WHR *z*-score change	− 0.021 (− 0.070 to 0.028)	− 0.029 (− 0.075 to 0.018)	− 65.55 (− 161.01 to 29.92)	**− 89.95 (− 166.26 to − 13.64)**	− 14.91 (− 37.41 to 7.59)	**− 20.74 (− 37.52 to − 3.97)**
MFTC						
Weight *z*-score change	− 0.050 (− 0.130 to 0.029)	− 0.041 (− 0.117 to 0.034)	− 33.60 (− 169.54 to 102.34)	− 1.66 (− 97.19 to 93.86)	− 1.04 (− 45.32 to 43.23)	11.33 (− 14.97 to 37.62)
BMI *z*-score change	− 0.054 (− 0.129 to 0.022)	− 0.035 (− 0.101 to 0.031)	− 31.82 (− 161.04 to 97.40)	− 10.23 (− 82.08 to 102.54)	2.43 (−39.80 to 44.67)	16.37 (− 12.13 to 44.87)
WHR *z*-score change	− 0.035 (− 0.095 to 0.026)	**− 0.056 (− 0.108 to − 0.005)**	− 22.72 (− 125.44 to 80.00)	− 69.69 (− 142.10 to 2.72)[b]	7.44 (− 26.01 to 40.88)	− 7.18 (− 29.72 to 15.35)
LFTC						
Weight *z*-score change	− 0.050 (− 0.137 to 0.037)	− 0.042 (− 0.123 to 0.040)	− 101.49 (− 277.44 to 74.46)	− 70.78 (− 183.79 to 42.22)	− 24.31 (− 75.10 to 26.48)	− 13.75 (− 38.89 to 11.40)
BMI *z*-score change	− 0.046 (− 0.128 to 0.037)	− 0.025 (− 0.097 to 0.047)	− 88.30 (− 255.54 to 78.95)	− 31.30 (− 143.73 to 81.14)	− 21.75 (− 70.04 to 26.55)	− 4.88 (− 33.73 to 23.97)
WHR *z*-score change	− 0.015 (− 0.081 to 0.051)	− 0.037 (− 0.094 to 0.020)	− 34.25 (− 167.60 to 99.09)	**− 93.98 (− 182.02 to − 5.93)**	− 5.03 (− 43.49 to 33.44)	− 22.29 (− 44.88 to 0.31)[c]

Bold denotes statistical significance, $p < 0.05$. *BMI* body mass index, *CI* confidence interval, *LFTC* lateral femorotibial compartment, *MFTC* medial femorotibial compartment, *WHR* waist–hip ratio

[a]Adjusted for childhood and adulthood age, gender, childhood and adulthood height (if weight *z*-score change is the predictor)

[b]$p = 0.059$; [c]$p = 0.053$

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], whereas the abdominal adiposity was more readily to mobilise 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. In adition, this may be due to the low prevalence of overweight status (7.6%) in childhood, whereas 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 peripubertal 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 $\alpha = 0.05$ and $\beta = 0.20$. 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 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.

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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.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Original article

Association of body composition, physical activity and physical performance with knee cartilage thickness and bone area in young adults

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Abstract

Objective. To describe associations of body composition, physical activity and physical performance with knee cartilage thickness and subchondral bone area in young adults.

Methods. Body composition, physical activity and physical performance were measured 4–5 years prior to knee MRI. Cartilage thickness and bone area were measured quantitatively from MRI. Associations were assessed using linear regression analysis, with mediators being identified using mediation analysis.

Results. Participants ($n = 186$) were 31–41 years of age when the MRI was acquired and 48% were female. Greater lean mass was positively associated with cartilage thickness [$\beta = 6.52$ μm/kg (95% CI 0.86, 12.18)] and bone area [$\beta = 13.37$ mm^2/kg (95% CI 5.43, 21.31)]. Physical performance measures were positively associated with cartilage thickness [long jump: $\beta = 2.44$ μm/cm (95% CI 0.70, 4.18); hand grip strength: 7.74 μm/kg (95% CI 1.50, 13.98); physical work capacity: 1.07 μm/W (95% CI 0.29, 1.85)] and bone area [long jump: $\beta = 3.99$ mm^2/cm (95% CI 0.64, 7.34); hand grip strength: 19.06 mm^2/kg (95% CI 7.21, 30.92); leg strength: 3.18 mm^2/kg (95% CI 1.09, 5.28); physical work capacity: 3.15 mm^2/W (95% CI 1.70, 4.60)]. Mediation analysis suggested these associations were mediated by lean mass (effect mediated: 27–95%).

Conclusion. Greater lean mass and better physical performance measured 4–5 years prior were associated with greater knee cartilage thickness and subchondral bone area in young adults, and the associations of physical performance were largely mediated by lean mass. These findings suggest lean mass may play an important role in maintaining knee joint health in young adults.

Key words: osteoarthritis, knee, cartilage, epidemiology, MRI

Rheumatology key messages

- Lean mass may play an important role in maintaining knee health in young adults.
- The beneficial effects in the knee of physical performance are largely mediated by lean mass.

Introduction

OA is one of the most prevalent joint disorders worldwide. However, there are no proven therapies to arrest or delay disease progression. Therefore, identifying modifiable factors that can prevent OA is critically important.

MRI is a sensitive method for detecting early structural changes in knee OA [1]. Cartilage loss, as viewed on MRI, is regarded as the signature feature of knee OA [2]. Thinning of cartilage predicts knee pain and joint space narrowing over 6 months [3] and knee replacement surgery over 4 years [4]. Subchondral bone is also important in knee OA. Changes in bone area over 24 months are associated with the combination of

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radiographic and pain progression over 48 months [5]. In young adults, bone area enlargement could be a physiological adaption to mechanical stimulation, as the enchondral ossification process to form larger metaphyses could distribute the stress over a larger area [6, 7]. Therefore, thicker cartilage and larger subchondral bone may be beneficial to maintain knee joint health.

Body composition is associated with physical function and quality of life among OA patients, even among those with normal BMI [8]. However, body composition has shown inconsistent associations with knee cartilage morphology in previous studies [9]. We reported that fat mass was negatively associated with cartilage volume and lean mass was positively associated with cartilage volume in both young [10] and older adults [11], whereas fat mass was not associated with cartilage volume in other studies [12, 13]. Exercise is recommended for managing knee OA, as it improves patient outcomes related to symptoms, mobility, quality of life and psychological health [14, 15]. However, a systematic review reported that there were only a few studies that reported a positive relationship between physical activity and cartilage volume among healthy participants (ages 19–79 years) [16]. Physical performance is a product of both muscular performance and cardiorespiratory performance and has been set as an important target for disease prevention strategies [17]. Hand grip strength is the most important indicator of whole-body muscular fitness. Lower hand grip strength has been associated with more severe knee radiographic OA among people >50 years of age [18]. Similarly, physical work capacity at a heart rate of 170 bpm (PWC170) is a good indicator of cardiorespiratory fitness, and previous studies have reported that higher PWC170 is associated with higher knee cartilage volume in both young and older adults [6, 19]. In addition to the indicators reflecting the whole-body condition, leg strength and long jump are important indicators of strength and power, respectively, in the lower limbs. Both leg strength and leg power have been associated with knee symptoms in knee OA patients [20–22] and higher cartilage volume in young adults [6].

As bone area is a key driver of cartilage volume [23], assessing both cartilage thickness and bone area may be required to accurately assess knee cartilage and bone morphology. In addition, cartilage thickness has a close association with early knee OA [24] and has been reported as an imaging biomarker [2]. However, few studies have identified factors associated with cartilage thickness in young adults, who are the important target population for OA prevention. Therefore we aimed to describe associations of body composition, physical activity and physical performance with knee cartilage thickness and bone area in young adults.

Methods

Participants

In 1985, the Australian Schools Health and Fitness Survey (ASHFS) was conducted to provide benchmark data on the health and fitness of Australian school children using a nationally representative sample. Two-stage probability sampling was used for the ASHFS to randomly select schools and then children within age groups in the schools. The Childhood Determinants of Adult Health (CDAH) study was a 20 year follow-up of children who participated in the ASHFS. From 2004 to 2006, participants attended clinics that were located at sites in major cities and regional centres around Australia, and anthropometric measurements, physical activity measurements and physical performance measurements were collected during the clinic visit. The details of enrolment of the ASHFS and CDAH study have been published elsewhere [25, 26]. The CDAH Knee Cartilage Study was a substudy of the CDAH study where participants completed knee MRI scans during 2008–2010. The current study is a subset of the CDAH Knee Cartilage Study. Due to limited funding, we measured cartilage and bone morphology among the participants residing in Melbourne.

We used the following strategy to recruit participants from the CDAH study. Participants residing in metropolitan Melbourne and Sydney were invited by mail to participate in the CDAH Knee Cartilage Study. Participants who agreed to participate were assessed for eligibility. Exclusion criteria included being pregnant, having diseases that might affect knee cartilage (including RA, AS, JIA and PsA) or having MRI contraindications. The remaining participants were asked to complete a computer-assisted telephone interview, with knee injury history recorded. Then the participants were requested to have an MRI scan at Epworth Hospital in Melbourne or North Shore Private Hospital in Sydney.

This study was approved by the Southern Tasmania Health and Medical Human Research Ethics Committee, the Monash University Human Research Ethics Committee and the Northern Sydney and Central Coast Area Health Human Research Ethics Committee. All participants provided written informed consent.

Anthropometric measurements

The anthropometric measurements were collected during the CDAH study. Weight was measured to the nearest 0.1 kg, with shoes, socks and bulky clothing removed. Height was measured to the nearest 0.1 cm, with shoes and socks removed. BMI was calculated as weight (kg) divided by height squared (m^2). Triceps, biceps, subscapular and supra-iliac skinfolds were measured at locations determined by reference to anatomical landmarks [27] to the nearest 0.1 mm using Slim Guide Skinfold Callipers (SPRI Products). Body density was estimated from the log of the sum of four skinfolds using Durnin's equation; the slope and intercept of the

equations for each age- and sex-specific group have been published elsewhere [27, 28]. An estimate of the percent body fat was derived from body density using Siri's equation: fat (%) = (4.95/density − 4.50) × 100 [29]. Fat mass and lean mass were estimated by the percent body fat (in kilograms): fat mass = fat (%) × weight (kg); lean mass = weight − fat (%) × weight (kg).

Physical activity measurements

The physical activity measurements were collected during the CDAH study. Physical activity was assessed using the long version of the International Physical Activity Questionnaire (IPAQ-L). Participants were asked to report the total time (minutes) and frequency (times/week) of occupational, commuting, domestic and leisure activity during the past week. Physical activities were calculated by multiplying frequency by duration to represent the minutes per week of vigorous, moderate and walking activity. Time spent in each domain was summed to provide the estimate of total minutes of physical activity.

Physical performance measurements

The physical performance measurements were collected during the CDAH study. Physical performance measurements included long jump, hand grip strength, leg strength and PWC170. The standing long jump was measured by asking the participants to stand on the gym mat with toes behind the line and with feet slightly apart. A two-foot take-off and landing was used, with the participants swinging the arms and bending the knees to provide the drive for jump. The landing point at the closest part of the heel to the starting line was marked and the distance to the starting line was measured. Right and left hand grip strength was measured as participants gripped the dynamometer (Smedley dynamometer, TTM, Tokyo, Japan) with maximum force in one hand, with the higher of two measurements recorded. Hand grip strength was determined by calculating the average of right and left hand grip strength. Leg strength was measured using a leg-back dynamometer (Muscle Meter, TTM, Tokyo, Japan) by standing flat-footed on a platform with a straight back flat against a wall. A hand bar was held with an overhand grip and knees were flexed at an angle of 115°, at which point the bar was attached to the dynamometer by a chain. The bar was then pulled as far upwards as possible by sliding the body up the wall (Supplementary Fig. S1, available at *Rheumatology* online). PWC170 was assessed using a Monark bicycle ergometer. Participants were asked to cycle at a constant 60 rpm for 3 min each at three successively increasing but submaximal workloads. Heart rate was recorded at 1 min intervals at each workload using an electronic heart rate monitor. PWC170 was calculated by linear regression with extrapolation of the line of best fit to a heart rate of 170 bpm.

MRI measurements

The MRI scans were collected during the CDAH Knee Cartilage Study. Knees were imaged on a 1.5 T whole-body MRI unit (General Electric Medical Systems, Milwaukee, WI, USA) with the use of a commercial transmit–receive extremity coil. Sagittal, T1-weighted, fat-suppressed three-dimensional 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 min 56 sec, 1 acquisition) were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31 × 0.31 mm for cartilage morphometric analysis.

Cartilage thickness and subchondral bone area were measured in the medial and lateral femorotibial compartment (MFTC/LFTC) and in the patella as previously reported [30] by a quantitative approach. Manual segmentation of knee cartilage surfaces (i.e. articular surface and subchondral bone interface) was performed in all 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 and subchondral bone area, using Chondrometrics 3.0 software (Chondrometrics GmbH, Ainring, Germany). The total knee joint cartilage thickness was calculated as the weighted average of the thickness of each compartment according to the bone area size and the total knee joint bone area was calculated as the sum of the area of each compartment. The absolute reliability of these measures has been assessed in young adults (ages 22–27 years), with a coefficient of variation of 2.5–3.9% for cartilage thickness and 1.5–4.5% for bone area [31]. We used the same measurement system, same rater (Felix Eckstein) and similar population in the current study.

Statistical analyses

Histograms and Q–Q plots were used to assess the normality of continuous variables. Mean (standard deviation), median (interquartile range) and number (percentage) were used to describe the characteristics of the participants. T-tests, Wilcoxon rank-sum test and χ^2 tests were used to assess differences in normally distributed variables, skewed variables and categorical variables between groups, respectively. Linear regression analysis was used to estimate β-values for associations of body composition, physical activity and physical performance with knee cartilage thickness and subchondral bone area. We retained the confounders that had important biological plausibility or changed the estimated coefficient by >10% [32]. Age (in the CDAH study), sex, height (if fat mass or lean mass was a predictor), BMI (if physical activity or physical performance measures were predictors), duration of follow-up and knee injury history were included in the analysis models. For each model, we checked whether the assumptions of linear

regression were satisfied. Where necessary to reduce heteroscedasticity and skewness of the residuals, the variable was transformed (e.g. by taking logarithms). Additionally, we paid careful attention to the scaling of the covariates.

We further adjusted for lean mass or total physical activity to explore independent associations of physical performance measures with knee cartilage thickness and subchondral bone area. When significant associations disappeared and effect sizes decreased dramatically after adjusting for a potential mediator, we performed mediation analysis to confirm the associations. We used the Stata (Stata version 15.0, StataCorp, College Station, TX, USA) command medeff to separate the effect of physical performance on cartilage thickness and bone area into direct effect (independent effect of physical performance on knee structures) and indirect effect (effect of physical performance on knee structures mediated by lean mass). This generated an estimate of the proportion of the total effect that is mediated [33].

A 95% CI not including the null point or a *P*-value <0.05 (two-tailed) was considered statistically significant. All statistical analyses were performed in Stata version 15.0.

Results

A total of 2410 participants completed a clinic visit during the CDAH study and 330 participants completed MRI scans during the CDAH Knee Cartilage Study. Non-participation in the CDAH Knee Cartilage Study was related to the following: not residing in Melbourne or Sydney ($n=1646$), not responding or refusing ($n=235$), pregnant ($n=8$), RA ($n=2$), MRI contraindication ($n=13$), withdrawal ($n=68$), long distance for travelling to imaging site ($n=103$), work/family commitments ($n=3$) and moving interstate ($n=2$). A total of 186 MRI scans were measured for the current study, as 131 scans were not from Melbourne and 13 scans were unreadable.

In the current study, participants were 31–41 years of age (mean 35.3) when the MRI was acquired and 48% were female. The time between exposure measurements and MRI scanning ranged from 4.01 to 5.43 years (mean 4.77). Participants in the current study were younger and had less fat mass, less moderate activity and greater long jump performance than those in the remainder of the CDAH study, whereas other characteristics were comparable (Table 1). Additionally, participants in the current study were younger and had less knee injury than those in the remainder of the CDAH Knee Cartilage Study (Supplementary Table S1, available at *Rheumatology* online).

Lean mass was positively associated with cartilage thickness in the whole knee joint and in the MFTC and LFTC, but not the patella (Table 2, Fig. 1). Fat mass was not associated with cartilage thickness in any sites (Table 2). Lean mass was positively associated with bone area in the whole knee joint, MFTC and LFTC, but not the patella (Table 2). Fat mass was not associated with bone area, except for the positive association between fat mass and bone area in the MFTC (Table 2).

Associations between physical activity measures (including walking, moderate activity, vigorous activity and total physical activity) and cartilage thickness and bone area in the whole knee or individual compartments were not statistically significant (Table 3).

Long jump, hand grip strength and PWC170 were associated with greater knee cartilage thickness in the whole joint and in most compartments (except long jump in the LFTC and PWC170 in the patella) (Table 4). These associations were largely unchanged after further adjustment for total physical activity (data not shown). However, most associations disappeared after further adjustment for lean mass, with only associations between long jump and knee cartilage thickness in the whole joint and patella remaining statistically significant (Table 4). There were no associations between leg strength and cartilage thickness in any sites (Table 4). All physical performance measures were positively associated with subchondral bone area in the whole knee joint and most individual compartments (except for long jump in the MFTC and hand grip strength and leg strength in the patella) (Table 4). These associations were largely unchanged after further adjustment for total physical activity (data not shown). However, all the significant associations disappeared after further adjustment for lean mass, with large reductions in the effect sizes (Table 4).

In mediation analysis, associations between physical performance and total knee cartilage thickness and bone area were largely mediated by lean mass. All the indirect effects (mediated by lean mass) were statistically significant, whereas most of the direct effects were not significant (except the association between long jump and cartilage thickness) (Table 5). The percentage of the total effect mediated by lean mass ranged from 27 to 95% (Table 5).

Discussion

This is the first study describing associations of body composition, physical activity and physical performance with knee cartilage thickness and subchondral bone area in young adults. We found that greater lean mass and physical performance, but not physical activity, were associated with greater knee cartilage thickness and subchondral bone area. Associations between physical performance and cartilage thickness and bone area were largely mediated by lean mass and were independent of total physical activity.

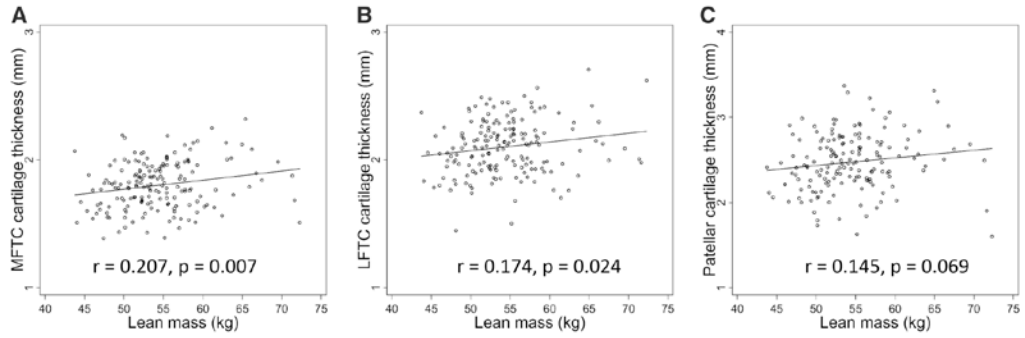
Our finding that lean mass was positively associated with cartilage thickness and bone area in the MFTC and LFTC is consistent with studies looking at lean mass and cartilage volume loss, where lean mass was associated with greater tibial cartilage volume cross-sectionally in young to middle-aged adults (ages 25–60 years) [12, 13] and over 5 years in young adults [10].

TABLE 1 Characteristics of the participants in the current study and the remainder of CDAH study

Characteristics	MRI quantitative measures		*P*-value
	Yes ($n = 186$)	No ($n = 2144$)	
Age[a], years	30.4 (2.8)	31.1 (2.6)	**0.002**
Sex, female, *n* (%)	90 (48.4)	1092 (51.0)	0.369
BMI, kg/m^2	25.1 (4.1)	25.8 (4.9)	0.080
Knee injury history, *n* (%)	21 (11.3)		
Body composition, kg			
Lean mass	54.4 (11.3)	54.4 (12.2)	0.981
Fat mass	21.4 (7.6)	22.8 (9.3)	**0.043**
Physical activity, hours/week, median (IQR)			
Walking	3.3 (1.3–6.0)	3.0 (1.0–6.3)	0.609
Moderate activity	3.8 (1.8–6.8)	4.8 (2.2–8.6)	**0.009**
Vigorous activity	1.0 (0.0–3.7)	1.0 (0.0–3.3)	0.381
Total activity	10.5 (5.9–16.2)	11.0 (6.2–17.8)	0.176
Physical performance measures			
Long jump, cm	170.9 (32.6)	162.5 (36.6)	**0.005**
Hand grip strength[b], kg	39.3 (10.4)	38.2 (11.6)	0.149
Leg strength, kg	136.0 (47.0)	128.7 (51.7)	0.062
PWC170, watts	170.5 (53.0)	164.2 (51.8)	0.130
Cartilage thickness, μm			
Total[c]	2073 (237)		
MFTC	1801 (221)		
LFTC	2100 (260)		
Patella	2473 (361)		
Bone area, mm^2			
Total[d]	4704 (674)		
MFTC	1798 (260)		
LFTC	1825 (299)		
Patella	1081 (170)		

Values are mean (S.D.) unless stated otherwise. Bold denotes statistical significance, $P < 0.05$. [a]Age during the CDAH study. [b]Calculated as the average of right and left hand grip strength. [c]Calculated as the weighted average according to the bone area of each compartment. [d]Calculated as the sum of each compartment. IQR, interquartile range.

FIG. 1 Scatter plots and linear regression lines for associations between lean mass and knee cartilage thickness



(**A**) MFTC, (**B**) LFTC, (**C**) patella. R- and P-values are from models adjusted for baseline age, sex, duration of follow-up, knee injury history and height.

Lean mass was also associated with reduced cartilage volume loss over 2.9 years in older adults [11]. Additionally, loss of muscle mass was associated with greater cartilage volume loss over 2 years [13]. Environmental factors could play important roles; for example, exercise may elicit the lean mass gains [34] and then provide greater stability in the knee joint, which is a protective mechanical factor for OA [35].

Table 2 Association of body composition (kg) with knee cartilage thickness and bone area in young adults

Body composition	Cartilage thickness, μm, β (95% CI)	Bone area, mm^2, β (95% CI)
Total		
Lean mass	**6.52 (0.86, 12.18)**	**13.37 (5.43, 21.31)**
Fat mass	−2.83 (−6.94, 1.28)	3.20 (−2.68, 9.08)
MFTC		
Lean mass	**7.13 (1.96, 12.31)**	**8.37 (4.80, 11.94)**
Fat mass	−1.68 (−5.49, 2.12)	**3.48 (0.80, 6.16)**
LFTC		
Lean mass	**6.86 (0.91, 12.81)**	**7.34 (3.79, 10.88)**
Fat mass	−3.34 (−7.66, 0.99)	0.87 (−1.80, 3.55)
Patella		
Lean mass	9.00 (−0.73, 18.72)	−0.26 (−3.36, 2.84)
Fat mass	−3.33 (−10.36, 3.71)	−0.58 (−2.80, 1.65)

Adjusted for baseline age, sex, duration of follow-up, knee injury history and height. Bold denotes statistical significance, $P < 0.05$.

Table 3 Association of physical activity (h/week) with knee cartilage thickness and bone area in young adults

Physical activity	Cartilage thickness, μm, β (95% CI)	Bone area, mm^2, β (95% CI)
Total		
Walking	0.09 (−7.91, 8.08)	0.06 (−16.59, 16.72)
Moderate activity	2.77 (−4.88, 10.41)	−5.14 (−21.11, 10.83)
Vigorous activity	4.48 (−5.32, 14.28)	−1.70 (−22.24, 18.84)
Total physical activity	1.54 (−2.49, 5.58)	−1.69 (−10.12, 6.74)
MFTC		
Walking	1.79 (−5.20, 8.77)	2.89 (−3.56, 9.33)
Moderate activity	0.30 (−6.71, 7.30)	−2.30 (−8.77, 4.18)
Vigorous activity	3.33 (−5.43, 12.10)	−3.98 (−12.12, 4.17)
Total physical activity	1.10 (−2.49, 4.69)	−0.50 (−3.83, 2.83)
LFTC		
Walking	3.99 (−4.08, 12.05)	1.30 (−5.79, 8.38)
Moderate activity	5.53 (−2.52, 13.58)	−1.94 (−9.04, 5.17)
Vigorous activity	9.41 (−0.64, 19.46)	0.09 (−8.87, 9.05)
Total physical activity	4.07 (−0.03, 8.17)	−0.15 (−3.80, 3.50)
Patella		
Walking	−0.72 (−14.16, 12.72)	−1.20 (−6.41, 4.00)
Moderate activity	3.08 (−9.80, 15.96)	−2.47 (−7.45, 2.51)
Vigorous activity	−0.86 (−17.43, 15.72)	−2.55 (−8.99, 3.89)
Total physical activity	0.53 (−6.27, 7.33)	−1.42 (−4.05, 1.21)

Adjusted for baseline age, sex, duration of follow-up, BMI and knee injury history.

We did not identify any consistent associations between fat mass and cartilage thickness or subchondral bone area. This is similar to literature on cartilage volume, where no association between fat mass and cartilage volume loss was found in two studies of middle-aged to older adults [12, 13], but this is inconsistent with a third study looking exclusively at young adults [10]. While we looked at fat mass globally, adipose tissue in different locations may have different effects: subcutaneous, visceral and intramuscular adipose tissues may be detrimental to the knee joint, while local adipose tissues, for example, normal infrapatellar fat pad (without signal intensity alteration on MRI), could have protective effects on knee OA, and the role of intermuscular adipose tissue in knee OA remains unclear [36].

We did not find associations between physical activity and cartilage thickness or bone area. This is not consistent with other reports, where physical activity was associated with tibial cartilage volume in young adults (total activity) [6] and healthy middle-aged women (sports participation) [37]. This may be due to the inability of our questionnaire to distinguish between weight-bearing and non-weight-bearing activities [7]; alternatively, this may suggest cartilage thickness and bone area in the whole joint are not responsive to physical activities in young adults.

TABLE 4 Associations of physical performance with knee cartilage thickness and bone area in young adults

Physical performance	Cartilage thickness, μm, β (95% CI)		Bone area, mm^2, β (95% CI)	
	Model 1	Model 2	Model 1	Model 2
Total				
Long jump (cm)	**2.44 (0.70, 4.18)**	**1.78 (0.10, 3.46)**	**3.99 (0.64, 7.34)**	1.26 (−1.20, 3.72)
Hand grip strength (kg)	**7.74 (1.50, 13.98)**	3.53 (−2.81, 9.87)	**19.06 (7.21, 30.92)**	1.70 (−7.69, 11.09)
Leg strength (kg)	0.66 (−0.46, 1.78)	−0.15 (−1.27, 0.97)	**3.18 (1.09, 5.28)**	0.19 (−1.46, 1.84)
PWC170 (watts)	**1.07 (0.29, 1.85)**	0.37 (−0.47, 1.20)	**3.15 (1.70, 4.60)**	0.27 (−0.97, 1.50)
MFTC				
Long jump (cm)	**1.76 (0.21, 3.31)**	1.20 (−0.29, 2.69)	1.05 (−0.30, 2.40)	0.11 (−0.95, 1.18)
Hand grip strength (kg)	**6.33 (0.89, 11.77)**	2.08 (−3.55, 7.71)	**7.71 (3.06, 12.35)**	0.59 (−3.47, 4.64)
Leg strength (kg)	0.62 (−0.38, 1.62)	−0.12 (−1.13, 0.88)	**1.27 (0.42, 2.12)**	0.13 (−0.59, 0.85)
PWC170 (watts)	**0.83 (0.13, 1.53)**	0.17 (−0.59, 0.92)	**1.01 (0.41, 1.61)**	−0.17 (−0.71, 0.37)
LFTC				
Long jump (cm)	1.43 (−0.36, 3.22)	0.80 (−0.93, 2.52)	**1.51 (0.11, 2.91)**	0.47 (−0.58, 1.51)
Hand grip strength (kg)	**9.87 (3.71, 16.03)**	5.39 (−1.03, 11.81)	**10.28 (5.53, 15.02)**	2.39 (−1.54, 6.33)
Leg strength (kg)	0.66 (−0.49, 1.81)	−0.21 (−1.36, 0.95)	**1.62 (0.75, 2.49)**	0.34 (−0.37, 1.04)
PWC170 (watts)	**1.32 (0.53, 2.11)**	0.66 (−0.21, 1.52)	**1.52 (0.92, 2.12)**	0.27 (−0.25, 0.80)
Patella				
Long jump (cm)	**5.35 (2.43, 8.27)**	**4.51 (1.61, 7.40)**	**1.13 (0.07, 2.19)**	0.54 (−0.41, 1.49)
Hand grip strength (kg)	**10.57 (0.19, 21.33)**	4.94 (−6.22, 16.11)	2.89 (−0.98, 6.75)	−1.05 (−4.70, 2.60)
Leg strength (kg)	1.19 (−0.73, 3.10)	0.13 (−1.84, 2.10)	0.34 (−0.35, 1.02)	−0.36 (−1.00, 0.28)
PWC170 (watts)	1.12 (−0.24, 2.47)	0.05 (−1.42, 1.53)	**0.79 (0.32, 1.26)**	0.19 (−0.29, 0.68)

Model 1 was adjusted for baseline age, sex, duration of follow-up, BMI and knee injury history. Model 2 was model 1 + adjusted for lean mass. Bold denotes statistical significance, $P < 0.05$.

TABLE 5 Mediation analysis of associations between physical performance measures and knee structures (mediated by lean mass)

Physical performance	Total knee cartilage thickness (μm), estimate (95% CI)	Total knee bone area (mm^2), estimate (95% CI)
Long jump (cm)		
Indirect effect	**0.65 (0.10, 1.40)**	**2.68 (0.45, 5.14)**
Direct effect	**1.75 (0.15, 3.40)**	1.22 (−1.12, 3.63)
Total effect	**2.40 (0.72, 4.16)**	**3.90 (0.59, 7.17)**
Total effect mediated, %	**27 (16, 90)**	**68 (35, 100)**
Hand grip strength (kg)		
Indirect effect	**4.17 (1.81, 7.31)**	**17.21 (9.37, 26.21)**
Direct effect	3.41 (−2.60, 9.63)	1.53 (−7.37, 10.74)
Total effect	**7.58 (1.53, 14.08)**	**18.74 (7.17, 30.40)**
Total effect mediated, %	**55 (29, 100)**	**92 (57, 100)**
Leg strength (kg)		
Indirect effect	**0.80 (0.37, 1.39)**	**2.97 (1.58, 4.56)**
Direct effect	−0.17 (−1.23, 0.93)	0.16 (−1.41, 1.78)
Total effect	0.63 (−0.42, 1.79)	**3.13 (1.09, 5.19)**
Total effect mediated, %	98 (−14, 100)	**95 (57, 100)**
PWC170 (watts)		
Indirect effect	**0.70 (0.32, 1.16)**	**2.87 (1.92, 4.03)**
Direct effect	0.35 (−0.45, 1.17)	0.24 (−0.93, 1.46)
Total effect	**1.05 (0.31, 1.86)**	**3.11 (1.71, 4.54)**
Total effect mediated, %	**67 (37, 100)**	**92 (63, 100)**

Covariates: baseline age, sex, duration of follow-up, BMI and knee injury history. All estimates obtained using causal mediation analysis with Stata's medeff command. Direct effects: independent effects of physical performance on knee structures. Indirect effects: effects of physical performance on knee structures mediated by lean mass. Bold denotes statistical significance, $P < 0.05$.

We found muscular strength (hand grip strength), power (long jump) and cardiorespiratory performance (PWC170) were positively associated with cartilage thickness and bone area. These were consistent with our previous study on tibial cartilage volume and bone area in young adults [6]. The significant associations largely disappeared after adjustment for lean mass, suggesting the effects of physical performance was mediated by lean mass; further mediation analysis confirmed this. Although lean mass explained most of the effects of hand grip strength and PWC170 on knee cartilage thickness, it only had moderate mediating effects on the association between long jump and cartilage thickness, suggesting other factors such as motor coordination may play roles in this association [38]. The association between leg strength and cartilage thickness was not significant, maybe due to leg strength being less strongly associated with lean muscle mass in the thigh compared with leg power [39].

Strengths of our study include that knee MRI was acquired in young adults (usually older adults are studied), cartilage thickness and subchondral bone area were studied rather than cartilage volume and objective measures of physical performance were used. Some limitations of our study should be considered. First, we only had a modest sample size from one urban centre in Australia (as opposed to coverage of the whole Australia in the CDAH study), so the generalizability of study results may be limited. We compared characteristics between participants in the current study and in the remainder of CDAH study and the remainder of the CDAH Knee Cartilage Study. The current sample was comprised of younger and healthier participants. These differences have the potential to lead results towards the null, but not statistical significance, as healthier participants were less likely to report knee joint alterations [6, 40]. Second, we did not collect body composition, physical activity and physical performance measures during follow-up and MRI at baseline, so we were unable to describe longitudinal changes in exposure measures and knee cartilage and bone morphology. The changes in exposure measures and knee cartilage and bone morphology are important properties in knee OA research and are worthy of future studies. Third, body composition estimates based on skinfolds may not be as accurate as those based on dual-energy X-ray absorptiometry. Reassuringly, our measures have been validated [27, 41]. Fourth, physical activity measures, based on self-reported answers, were not objective. Reassuringly, previous studies have reported that the IPAQ-L has acceptable reliability and validity when assessing levels of physical activity among healthy adults (18–65 years) [42, 43]. Fifth, we did not have synovitis or cartilage composition measures, and the effects from these parameters should be identified in future studies.

In conclusion, greater lean mass and better physical performance measured 4–5 years prior were associated with greater knee cartilage thickness and subchondral bone area in young adults, and the associations of physical performance were largely mediated by lean mass. These findings suggest lean mass may play an important role in maintaining knee joint health in young adults.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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Clinical vignette

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Ossification of the ligamentum flavum

A 29-year-old male patient was referred to the Rheumatology Department due to chronic intermittent thoracic back pain. His past medical history was unremarkable except for acne, which has been treated with oral isotretinoin for 5 years. Clinical examination was normal, without restriction of spinal mobility. Because of the inflammatory characteristics of the pain and unremarkable conventional radiography, we performed an MRI and a CT of the thoracic spine. The MRI showed a hypointense linear 'mass' within the ligamentum flavum. The CT scan revealed curvilinear hyperdense thickening of the ligamentum flavum in the sagittal (Fig. 1A) and transverse planes (Fig. 1B) and corresponding ossification of the ligamentum flavum (OLF) (Fig. 1, arrow). We started symptomatic treatment with non-steroidal anti-rheumatic drugs.

OLF is a rare and often asymptomatic phenomenon that is most frequently described in the elderly and male East Asian ethnic groups [1]. The lower thoracic spine is the most affected region, where OLF can occasionally cause myelopathy. Retinoids are known to induce spinal and extraspinal hyperostosis (spurs) and calcification of tendons and ligaments [2], which could explain the occurrence of OFL in this young patient from Switzerland. Retinoid-induced changes of the spine often persist and only symptomatic treatment is possible.

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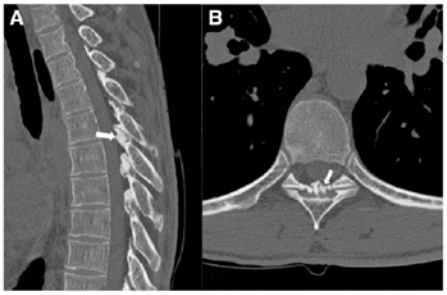
Fig. 1 CT scan of the thoracic spine. Ossification of the ligamentum flavum in the **(A)** sagittal and **(B)** transverse planes



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Association of glucose homeostasis and metabolic syndrome with knee cartilage defects and cartilage volume in young adults

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ABSTRACT

Objective: To describe the associations of glucose homeostasis and metabolic syndrome (MetS) measures with knee cartilage defects and cartilage volume in young adults.
Methods: Fasting blood biochemistry, waist circumference and blood pressure measures were collected 4–5 years prior to knee magnetic resonance imaging (MRI) scans. Blood measures included levels of glucose, insulin, triglyceride and high-density lipoprotein cholesterol (HDL-C). Homeostatic model assessment 2-insulin resistance (HOMA2-IR), HOMA2-beta cell function (HOMA2-β), HOMA2-insulin sensitivity (HOMA-S) and MetS were calculated or defined. Knee cartilage defects and cartilage volume were measured from MRI scans. Data were analysed using log binomial or linear regressions.
Results: Among 328 participants (47.3% were females, aged 26–36 years at baseline), 40 (12.7%) had hyperglycaemia and 21 (6.7%) had MetS. Glucose homeostasis measures (except fasting glucose) were associated with tibiofemoral cartilage defects (fasting insulin: relative risk (RR) 1.05, 95% confidence interval (CI) 1.01 to 1.08; HOMA2-IR: 1.44, 1.08 to 1.92; HOMA2-β: 2.59, 1.33 to 5.07; HOMA2-S: 0.36, 0.18 to 0.72), but not patellar cartilage defects. There were no associations between glucose homeostasis measures and knee cartilage volume. High waist circumference (RR 2.32, 95% CI 1.18 to 4.54) and low HDL-C (RR 1.99, 95% CI 1.08 to 3.69) were associated with tibiofemoral cartilage defects, but no other associations were observed between MetS or its components and cartilage defects or volume.
Conclusion: Insulin resistance, high waist circumference and low HDL-C were associated with higher risk of tibiofemoral cartilage defects, suggesting glucose homeostasis and some MetS components may affect early cartilage damage in young adults.

Introduction

Knee osteoarthritis (OA) is a common joint disease worldwide, which causes severe knee pain, stiffness and dysfunction [1]. Currently, there are no proven therapies which can arrest or delay disease progression. Thus, identifying the risk factors of knee OA in early life could be important for disease prevention [2].

Magnetic resonance imaging (MRI) is a sensitive technique for examining early structural changes in knee joint [3], including imaging biomarkers of knee OA such as cartilage defects and loss of cartilage volume [4]. Cartilage defects and loss of cartilage volume have been associated with knee pain [5, 6] and subsequent knee replacement surgery [7, 8] in observational studies, and were set as important endpoints in clinical trials [9, 10]. Therefore, preventing knee cartilage defects and loss of cartilage volume may be an effective way to prevent knee OA.

Diabetes mellitus (DM) and OA coexist in the general population [11]. Experimental studies demonstrated that hyperglycaemia can decrease transport of dehydroascorbate into chondrocytes, which then compromises synthesis of type II collagen and leads to cartilage destruction [12]. Additionally, hyperglycaemia is associated with higher inflammatory responses in OA chondrocytes [13], which is detrimental to articular cartilage. A recent systematic review reported that there is limited evidence from epidemiological studies to support an independent association between DM and knee OA. However, the review stressed the requirement for prospective studies, which use objective and appropriate measures for both DM and OA and account for important confounding factors, such as age, sex and body mass index (BMI), to examine the independent associations [14].

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Metabolic syndrome (MetS), defined as central obesity, dyslipidaemia, impaired fasting glucose and hypertension, has recently attracted interest in knee OA research as MetS shares many causal pathways with knee OA [15]. Although previous narrative reviews summarised several potential pathophysiologic pathways between MetS and knee OA [16–18], a recent systematic review found insufficient data from epidemiological studies to confirm the links between MetS and knee OA [19]. The systematic review suggested the need for future studies, which account for weight or BMI and examine early stage of disease [19].

Therefore, using data from a cohort of young adults with knee structures measured by MRI, we aimed to describe the associations of glucose homeostasis and MetS measures with knee cartilage defects and cartilage volume.

Methods

Participants

The Childhood Determinants of Adult Health (CDAH) Study was conducted on a nationwide sample of young adults in Australia. During 2004–2006, participants attended clinics which were located at sites in major cities and regional centres around Australia. Measures of anthropometrics, glucose homeostasis, metabolic syndrome (MetS) and physical activity were collected during the clinic visit [20]. The CDAH Knee Cartilage Study was a subsequent sub-study of the CDAH study where participants completed knee MRI scans during 2008–2010.

We used the following strategy to recruit participants from the CDAH study. Participants residing in metropolitan Melbourne and Sydney were contacted by mail and were invited to participate in the CDAH Knee Cartilage Study. Participants who agreed to participate were assessed for eligibility. Exclusion criteria included being pregnant, having had diseases that might affect knee cartilage (including rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and psoriatic arthritis), or having MRI contraindications. The remaining participants were asked to have an MRI scan at Epworth Hospital in Melbourne or North Shore Private Hospital in Sydney.

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 Health HREC. All participants provided written informed consent.

Anthropometric measurements

Weight was measured to the nearest 0.1 kg (with shoes and bulky clothing removed) using Heine scales (Heine, Dover, NH). Height was measured to the nearest 0.1 cm (with shoes and socks removed) using a stadiometer (Invicta, Leicester, UK). BMI was calculated as weight in kilograms divided by height in meters squared.

Glucose homeostasis measurements

Fasting glucose and insulin levels were measured using venous blood samples collected from the antecubital vein after a 12-hour fast. An Olympus AU5400 automated analyser (Olympus Optical, Tokyo, Japan) was used to enzymatically measure fasting glucose. A microparticle enzyme immunoassay kit (AxSYM; Abbot Laboratories, Abbot Park, IL) or an electrochemiluminescence immunoassay (Elecsys Modular Analytics E170; Roche Diagnostics, Mannheim, Switzerland) with inter-assay standardisation was used to measure fasting insulin. Glucose homeostasis measures, including homeostatic model assessment 2-insulin resistance (HOMA2-IR), HOMA2-beta cell function (HOMA2-β) and HOMA2-insulin sensitivity (HOMA-S), were calculated by a homeostasis model assessment (HOMA2) calculator (version 2.2.3 available from http://www.dtu.ox.ac.uk/homacalculator) using fasting glucose and fasting insulin.

MetS measurements

MetS was defined using the harmonized definition [21]. Five components of MetS and their thresholds were proposed in the definition. MetS was diagnosed when at least three of the five components were present. The details of MetS definition and thresholds of MetS components have been published elsewhere [21]. We use the following methods to collect the MetS measures: Waist circumference was measured at the narrowest point between the lower costal border and the iliac crest to the nearest 0.1 cm using a constant tension tape; high waist circumference was defined as waist circumference ≥102 cm in males or ≥88 cm in females. Fasting glucose was measured as described above; hyperglycaemia was defined as fasting glucose of ≥5.6 mmol/L. Triglyceride and high-density lipoprotein cholesterol (HDL-C) were measured enzymatically using an Olympus AU5400 automated analyser (Olympus Optical, Tokyo, Japan). Hypertriglyceridemia was defined as serum triglycerides ≥1.7 mmol/L, and low HDL-C was defined as HDL-C <1.03 mmol/L in males or <1.3 mmol/L in females. Resting systolic and diastolic blood pressure readings were recorded after 5 min of quiet sitting using an OMRON HEM907 Digital Automatic Blood Pressure Monitor (Omron Healthcare Co., Ltd., Kyoto, Japan), and the mean of three recordings was used. Hypertension was defined as blood pressure ≥130/85 mmHg.

Physical activity measurements

Physical activity was assessed using the long version of the International Physical Activity Questionnaire. Participants were asked to report the total time (minutes) and frequency (times/week) of occupational, commuting, domestic and leisure activity during the past week. Physical activities were calculated by multiplying frequency by duration to represent minutes per week of vigorous, moderate and walking activity. Time spent in each domain was summed to provide the estimate of total minutes of physical activity.

MRI measurements

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 1.5 T 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 min, 56 s; 1 acquisition. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31 × 0.31 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 × 0.31 mm (512 × 512 pixels); repetition time 3800 msec; echo time 45 msec.

Knee cartilage defects were measured as previously reported [22] 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. 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%. 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 ranged from 0.89 to 0.94.

Cartilage volume was determined by means of 3D image processing on an independent work station using software program OsiriX

(Geneva, Switzerland). Individual plates were isolated by manually drawing disarticulation contours around the cartilage boundaries on a section-by-section basis. These data were then re-sampled by means of bilinear and cubic interpolation (area of 312×312 μm^2 and thickness of 1.5 mm, continuous sections) for the final 3D rendering. The coefficients of variation for cartilage volume measures were 2.1–2.6%. Femoral cartilage volume was not measured, as it strongly correlates with tibial cartilage volume [23].

Statistical analyses

Histograms and Q–Q plots were used to assess the normality of continuous variables. Mean (standard deviation), median (interquartile range), and number (percentage) were used to describe normally-distributed variables, skewed variables and categorical variables, respectively. T-tests, Wilcoxon rank-sum test and Chi-square tests were used to assess differences in normally-distributed variables, skewed variables and categorical variables between groups, respectively. Univariable and multivariable log binomial regression models were used to estimate relative risk (RR) for associations of glucose homeostasis and MetS measures with knee cartilage defects before and after adjustment for potential confounders. Univariable and multivariable linear regression models were used to estimate β coefficients for associations of glucose homeostasis and MetS measures with knee cartilage volume before and after adjustment for potential confounders. Age, sex, BMI (except when high waist circumference was the predictor) and total physical activity were included as potential confounders based on biological plausibility. A p-value less than 0.05 (2-tailed) was considered statistically significant. All statistical analyses were performed in Stata (Texas, USA), version 15.0.

Results

2410 participants completed clinic visit during the CDAH Study and 330 participants completed MRI scans during the CDAH Knee Cartilage Study. The follow-up time was 4–5 years. Nonparticipation in the CDAH Knee Cartilage Study was related to the following: not residing in Melbourne or Sydney (1646), not responding or refusing (235), pregnant (8), rheumatoid arthritis (2), MRI contraindication (13), withdrawal (68), long distance for traveling to the imaging site (103), work/family commitments (3), moving interstate (2). In the current study, 322 participants were included in analyses for cartilage defects and 328 for cartilage volume, as 8 scans were unreadable for cartilage defects and 2 for cartilage volume.

Participants were aged 31–41 (mean 35.4) years when MRI was acquired, 155 (47%) were female. 40 (12.7%) participants had hyperglycaemia and 21 (6.7%) had MetS. Participants included in the current study did less physical activity and had higher fasting glucose and lower HOMA2-β than those in the remainder of the CDAH Study, whereas other characteristics were comparable (Table 1).

Higher fasting insulin, HOMA2-IR and HOMA2-β were significantly associated with higher risk of tibiofemoral cartilage defects and higher HOMA2-S was associated with lower risk of tibiofemoral cartilage defects before and after adjustment for age, sex, BMI and physical activity (Table 2). Fasting glucose was not associated with tibiofemoral cartilage defects. Glucose homeostasis measures, including fasting glucose, fasting insulin, HOMA2-IR, HOMA2- β and HOMA2-S, were not associated with patellar cartilage defects in either univariable or multivariable analyses (Table 2).

Glucose homeostasis measures were not significantly associated with cartilage volume in univariable analyses, except for the positive associations between fasting glucose and cartilage volume in patella and tibia, and the negative association between HOMA2-β and tibial cartilage volume (Table 3). Associations were no longer significant after adjustment for age, sex, BMI and physical activity (Table 3).

MetS and its components were not associated with patellar cartilage defects in univariable analyses, except hypertriglyceridemia was associated with higher risk of patellar cartilage defects (Table 4); however, this association was no longer statistically significant after adjustment for age, sex, BMI and physical activity (Table 4). MetS and its components were not associated with tibiofemoral cartilage defects in univariable analyses, except for the association between low HDL-C and higher risk of tibiofemoral cartilage defects (Table 4).

Table 1
Characteristics of the participants in current study and the remainder of original study.

	MRI measures		P value
	Yes (n = 328)	No (n = 2002)	
Age[a] (years)	30.8 (2.7)	31.1 (2.6)	0.138
Female, n (%)	155 (47.3)	1037 (51.5)	0.150
BMI (kg/m^2)	25.3 (4.1)	25.8 (4.9)	0.090
Total physical activity (hour/week), median (IQR)	9.6 (5.6, 15.7)	11.1 (6.3, 17.9)	**0.017**
Glucose homeostasis measures, median (IQR)			
Fasting glucose (mmol/L)	5.1 (4.8, 5.3)	5.0 (4.7, 5.3)	**0.017**
Fasting insulin (mU/L)	5.8 (4.2, 7.9)	6.0 (4.3, 8.7)	0.207
HOMA2-IR (unit)	0.80 (0.60, 1.10)	0.80 (0.60, 1.20)	0.146
HOMA2-β (unit)	0.79 (0.66, 1.00)	0.85 (0.68, 1.06)	**0.005**
HOMA2-S (unit)	1.27 (0.95, 1.69)	1.23 (0.86, 1.67)	0.168
MetS measures, n (%)			
MetS	21 (6.7)	136 (7.2)	0.744
High waist circumference[b]	36 (11.3)	293 (14.6)	0.121
Hyperglycaemia[c]	40 (12.7)	195 (10.3)	0.192
Hypertriglyceridemia[d]	49 (15.6)	280 (14.8)	0.716
Low HDL-C[e]	52 (16.5)	371 (19.6)	0.201
Hypertension[f]	60 (18.4)	436 (21.7)	0.169
Cartilage defects, n (%)			
Patellar	78 (24.2)		
Tibiofemoral	47 (14.6)		
Cartilage volume (mm^3)			
Patellar	2939 (752)		
Tibial	3896 (1005)		

Values are mean (SD) unless otherwise stated.
Bold denotes statistical significance, $p < 0.05$.
MRI, magnetic resonance imaging; BMI, body mass index; HOMA2-IR, homeostatic model assessment 2-insulin resistance; HOMA2-β, homeostatic model assessment 2-beta cell function; HOMA2-S, homeostatic model assessment 2-insulin sensitivity; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; MetS, metabolic syndrome.
[a] Age in Childhood Determinants of Adult Health Study.
[b] Defined as waist circumference ≥102 cm in males or ≥88 cm in females.
[c] Defined as fasting glucose ≥5.6 mmol/L.
[d] Defined as serum triglycerides ≥1.7 mmol/L.
[e] Defined as HDL-C <1.03 mmol/L in males or <1.3 mmol/L in females.
[f] Defined as blood pressure ≥130/85 mm Hg.

Table 2
Associations between glucose homeostasis measures and knee cartilage defects.

	Univariable RR (95% CI)	Multivariable[a] RR (95% CI)
Patellar		
Fasting glucose, mmol/L	0.62 (0.37 to 1.03)	0.55 (0.29 to 1.04)
Fasting insulin, mU/L	0.99 (0.94 to 1.04)	0.95 (0.88 to 1.02)
HOMA2-IR, per unit	0.90 (0.61 to 1.33)	0.60 (0.32 to 1.14)
HOMA2-β, per unit	1.10 (0.61 to 1.96)	0.87 (0.38 to 1.99)
HOMA2-S, per unit	1.01 (0.70 to 1.45)	1.15 (0.76 to 1.75)
Tibiofemoral		
Fasting glucose, mmol/L	1.31 (0.72 to 2.40)	0.89 (0.41 to 1.93)
Fasting insulin, mU/L	**1.05 (1.02 to 1.07)**	**1.05 (1.01 to 1.08)**
HOMA2-IR, per unit	**1.42 (1.15 to 1.76)**	**1.44 (1.08 to 1.92)**
HOMA2-β, per unit	**2.13 (1.24 to 3.65)**	**2.59 (1.33 to 5.07)**
HOMA2-S, per unit	**0.46 (0.27 to 0.78)**	**0.36 (0.18 to 0.72)**

Bold denotes statistical significance, $p < 0.05$.
CI, confidence interval; HOMA2-IR, homeostatic model assessment 2-insulin resistance; HOMA2-β, homeostatic model assessment 2-beta cell function; HOMA2-S, homeostatic model assessment 2-insulin sensitivity; RR, relative risk.
[a] Adjusted for age, sex, body mass index and physical activity.

Table 3
Associations between glucose homeostasis measures and knee cartilage volume (mm^3).

	Univariable β (95% CI)	Multivariable[a] β (95% CI)
Patellar		
Fasting glucose, mmol/L	**255.2 (60.6 to 449.7)**	−92.9 (−293.3 to 107.4)
Fasting insulin, mU/L	−2.6 (−21.3 to 16.1)	−6.3 (−25.1 to 12.4)
HOMA2-IR, per unit	1.1 (−154.6 to 156.9)	−40.6 (−195.9 to 114.7)
HOMA2-β, per unit	−228.8 (−513.6 to 56.0)	−48.0 (−330.5 to 234.5)
HOMA2-S, per unit	9.5 (−151.9 to 171.0)	32.4 (−125.6 to 190.4)
Tibial		
Fasting glucose, mmol/L	**561.2 (307.6 to 814.8)**	−22.0 (−280.0 to 236.1)
Fasting insulin, mU/L	−4.9 (−29.7 to 19.9)	−17.5 (−41.5 to 6.6)
HOMA2-IR, per unit	−15.3 (−221.5 to 190.8)	−127.8 (−323.1 to 67.6)
HOMA2-β, per unit	**−463.2 (−838.1 to −88.4)**	−236.8 (−592.0 to 118.4)
HOMA2-S, per unit	19.8 (−193.9 to 233.6)	64.9 (−134.3 to 264.1)

Bold denotes statistical significance, $p<0.05$.
CI, confidence interval; HOMA2-IR, homeostatic model assessment 2-insulin resistance; HOMA2-β, homeostatic model assessment 2-beta cell function; HOMA2-S, homeostatic model assessment 2-insulin sensitivity.
[a] Adjusted for age, sex, body mass index and physical activity.

Table 4
Associations between metabolic syndrome measures and knee cartilage defects.

	Univariable RR (95% CI)	Multivariable[a] RR (95% CI)
Patellar		
MetS	1.37 (0.72 to 2.60)	1.38 (0.60 to 3.21)
High waist circumference[b]	1.44 (0.86 to 2.39)	1.13 (0.59 to 2.15)
Hyperglycaemia[c]	0.91 (0.50 to 1.68)	0.76 (0.32 to 1.78)
Hypertriglyceridemia[d]	**1.66 (1.08 to 2.55)**	1.66 (0.97 to 2.84)
Low HDL-C[e]	0.93 (0.55 to 1.60)	0.88 (0.48 to 1.61)
Hypertension[f]	1.15 (0.72 to 1.84)	1.23 (0.70 to 2.17)
Tibiofemoral		
MetS	2.06 (0.99 to 4.29)	1.39 (0.58 to 3.32)
High waist circumference[b]	1.86 (0.98 to 3.54)	**2.32 (1.18 to 4.54)**
Hyperglycaemia[c]	1.24 (0.60 to 2.57)	0.90 (0.37 to 2.14)
Hypertriglyceridemia[d]	1.32 (0.68 to 2.56)	0.89 (0.40 to 1.96)
Low HDL-C[e]	**2.45 (1.43 to 4.19)**	**1.99 (1.08 to 3.69)**
Hypertension[f]	1.57 (0.86 to 2.84)	1.50 (0.77 to 2.95)

Bold denotes statistical significance, $p<0.05$.
CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome; RR, relative risk.
[a] Adjusted for age, sex, body mass index (except when high waist circumference was the predictor) and physical activity.
[b] Defined as waist circumference ≥102 cm in males or ≥88 cm in females.
[c] Defined as fasting glucose ≥5.6 mmol/L.
[d] Defined as serum triglycerides ≥1.7 mmol/L.
[e] Defined as HDL-C <1.03 mmol/L in males or <1.3 mmol/L in females.
[f] Defined as blood pressure ≥130/85 mmHg.

The significant association persisted and the association between high waist circumference and higher risk of tibiofemoral cartilage defects became significant after adjustment for confounders (Table 4).

MetS and its components were not significantly associated with cartilage volume in univariable analyses, except for the positive associations of hyperglycaemia and hypertension with tibial cartilage volume (Table 5). After adjustment for age, sex, BMI and physical activity, the significant associations disappeared (Table 5).

Discussion

This is the first study describing associations of glucose homeostasis and MetS measures with knee cartilage defects and cartilage volume in young adults. Our major findings were that higher levels of fasting insulin, HOMA2-IR and HOMA2-β were associated with an increased risk of tibiofemoral cartilage defects, and higher level of HOMA2-S was associated with a decreased risk of tibiofemoral

Table 5
Associations between metabolic syndrome and knee cartilage volume (mm^3).

	Univariable β (95% CI)	Multivariable[a] β (95% CI)
Patellar		
MetS	131.1 (−205.0 to 467.3)	−116.2 (−432.4 to 199.9)
High waist circumference[b]	−82.7 (−345.9 to 180.4)	20.1 (−213.0 to 253.2)
Hyperglycaemia[c]	212.8 (−37.3 to 462.9)	−64.1 (−306.5 to 178.2)
Hypertriglyceridemia[d]	119.7 (−111.5 to 350.9)	−52.0 (−170.9 to 275.0)
Low HDL-C[e]	−33.1 (−259.2 to 192.9)	−20.5 (−221.7 to 180.8)
Hypertension[f]	90.2 (−121.1 to 301.5)	−188.7 (−380.4 to 3.1)
Tibial		
MetS	210.1 (−234.8 to 655.1)	−255.7 (−660.2 to 148.8)
High waist circumference[b]	−218.2 (−566.4 to 130.0)	−120.7 (−418.9 to 177.4)
Hyperglycaemia[c]	**438.5 (108.4 to 768.6)**	−55.8 (−367.5 to 255.9)
Hypertriglyceridemia[d]	165.9 (−140.2 to 472.0)	−154.0 (−439.3 to 131.4)
Low HDL-C[e]	2.4 (−297.0 to 301.8)	−109.2 (−366.9 to 148.6)
Hypertension[f]	**333.7 (53.6 to 613.7)**	−38.4 (−285.4 to 208.6)

Bold denotes statistical significance, $p<0.05$.
CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome; RR, relative risk.
[a] Adjusted for age, sex, body mass index (except when high waist circumference was the predictor) and physical activity.
[b] Defined as waist circumference ≥102 cm in males or ≥88 cm in females.
[c] Defined as fasting glucose ≥5.6 mmol/L.
[d] Defined as serum triglycerides ≥1.7 mmol/L.
[e] Defined as HDL-C <1.03 mmol/L in males or <1.3 mmol/L in females.
[f] Defined as blood pressure ≥130/85 mmHg.

cartilage defects. In addition, high waist circumference and low HDL-C were associated with higher risk of tibiofemoral cartilage defects.

Most previous studies describing the association between serum glucose and knee OA have focused on the incidence of radiographic OA (according to Kellgren-Lawrence grade) [14], except for two studies setting T2-relaxation time [24] or cartilage volume [25] as the outcome by using MRI. In one study, self-reported DM was associated with higher baseline T2 (more severe cartilage degradation), but not progression of T2 over 2 years [24]. In the other study, serum glucose (measured 10–14 years prior to baseline MRI) was associated with higher annual loss of tibial cartilage volume over 2 years in females but not in males [25]. Both studies used inaccurate glucose measures (self-reported or measured a long time ago) and did not measure serum insulin. In addition, the populations of interest in these studies were middle-aged or older-aged (40–69 years), whereas no studies were conducted in young adults.

In our study, we used both fasting glucose and fasting insulin, and calculated measures of insulin resistance, beta cell function and insulin sensitivity using the HOMA2 calculator, which is an effective tool to assess glucose homeostasis in clinical and epidemiological studies [26]. We collected MRI-based cartilage measures from young adults, which can predict knee OA and even joint replacement surgery in later life. Our findings that worse glucose homeostasis measures (except for fasting glucose) were associated with higher risk of tibiofemoral cartilage defects suggested the detrimental effects of insulin resistance on knee cartilage. The lack of association for fasting glucose may be due to the age of our cohort. Young adults may have increased insulin secretion and insulin resistance, whereas their fasting glucose levels could still be in healthy range [27]. Furthermore, we only found significant associations in the tibiofemoral compartment, but not in the patella. The underlying reason was unclear, but may reflect the fact that pathological mechanisms involved in patellofemoral OA and tibiofemoral OA are different [28]. We did not find consistent associations between glucose homeostasis measures and knee cartilage volume; this may be due to knee cartilage defects occurring prior to cartilage volume loss in early knee OA [29].

Previous studies did not find independent associations between MetS and radiographic knee OA cross-sectionally [30] or longitudinally

[31]. There is only one study that used a MRI-based outcome (compositional MRI outcome but not structural MRI outcome), which reported participants with ≥3 metabolic components (versus <3) had higher baseline T2-relaxation time (more severe cartilage degradation) [24]. However, the study used self-reported DM and fat consumption (calculated from food questionnaire) to represent impaired glucose tolerance and dyslipidaemia; in addition, though the study selected the younger half of the source cohort, the participants were middle-aged or older-aged (45–60 years).

Our study addressed the issues in the previous study by using MRI-based structural outcomes in young adults and objective measures of MetS components. We found high waist circumference and low HDL-C were associated with higher risk of tibiofemoral cartilage defects. These results are consistent with previous studies, where central obesity was associated with thinner cartilage thickness in young adults [32] and reduced HDL was associated with knee OA in mice models [33]. We did not find associations between MetS and cartilage defects or cartilage volume. The reason may be that our participants were young adults (31–41 years) and the prevalence of MetS was low (6.7%). We speculate that MetS will be associated with knee OA when the prevalence of MetS increases with ageing, though this needs to be confirmed by future studies.

Strengths of our study include the selection of a population-based sample of young adults and the use of knee MRI-based structural measures of cartilage. We also used objective measures of glucose homeostasis and MetS. Some limitations of our study should be considered. First, we only had a modest sample size from two urban centres in Australia (as opposed to the coverage of all Australian states/territories in CDAH study), so the generalizability of study results may be limited. We compared characteristics between participants in current study and in the remainder of CDAH Study: the current sample did less physical activity and had higher fasting glucose and lower HOMA2-β. The effects of these differences on our results were unknown though the differences were relatively small. Second, we did not acquire baseline MRI, so we were unable to describe longitudinal changes in knee cartilage defects and cartilage volume. Third, we did not collect knee alignment data, so we were unable to assess its potential effects on our findings.

In conclusion, insulin resistance, high waist circumference and low HDL-C were associated with higher risk of tibiofemoral cartilage defects, suggesting glucose homeostasis and some MetS components may affect early cartilage damage in young adults.

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Declaration of Competing Interest

None.

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Author contributions

Study conception and design: TM, BA, AV, FC, LM, TD, GJ and CD; acquisition of data: TM, BA, AV, FB, FC, LM, MC, TD, GJ and CD; analysis and interpretation of data: TM, BA, AV, FB, FC, LM, MC, TD, GJ, LL and CD. 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.

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