Made available through Montana State University's ScholarWorks

Unraveling sex-specific risks of knee osteoarthritis before menopause: Do sex differences start early in life?

Paula A. Hernandez, John Churchill Bradford, Priyanka Brahmachary, Sophia Ulman, Jennifer L. Robinson, Ronald K. June, Magali Cucchiarini

Accessibility Disclaimer:

For a more accessible version of this document, please submit an accessibility request form through the Montana State University Library website.

Osteoarthritis and Cartilage 32 (2024) 1032–1044

Osteoarthritis and Cartilage

Review

Unraveling sex-specific risks of knee osteoarthritis before menopause: Do sex differences start early in life?

Paula A. Hernandez # † *, John Churchill Bradford ‡, Priyanka Brahmachary §, Sophia Ulman # ¶, Jennifer L. Robinson ‖ ## ††, Ronald K. June §, Magali Cucchiarini ‡‡

Department of Orthopaedic Surgery, University of Texas Southwestern Medical Center, Dallas, TX, 75390, USA
† Department of Biomedical Engineering, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA
‡ Department of Bioengineering, University of Washington, Seattle, WA 98195, USA
§ Department of Mechanical & Industrial Engineering, Montana State University, Bozeman, MT 59717, USA
¶ Movement Science Laboratory, Scottish Rite for Children, Frisco, TX 75034, USA
‖ Department of Mechanical Engineering, University of Washington, Seattle, WA 98195, USA
Department of Orthopaedics and Sports Medicine, University of Washington, Seattle, WA 98195, USA
†† Institute for Stem Cell and Regenerative Medicine, University of Washington, Seattle, WA 98109, USA
‡‡ Center of Experimental Orthopaedics, Saarland University Medical Center, Homburg/Saar D-66421, Germany

ARTICLE INFO

Article history:
Received 19 September 2023
Accepted 24 April 2024

Keywords:
Cartilage
Meniscus
Anterior cruciate ligament
Metabolomics
Sex differences
Estrogen

SUMMARY

Objective: Sufficient evidence within the past two decades have shown that osteoarthritis (OA) has a sex-specific component. However, efforts to reveal the biological causes of this disparity have emerged more gradually. In this narrative review, we discuss anatomical differences within the knee, incidence of injuries in youth sports, and metabolic factors that present early in life (childhood and early adulthood) that can contribute to a higher risk of OA in females.
Design: We compiled clinical data from multiple tissues within the knee joint—since OA is a whole joint disorder—aiming to reveal relevant factors behind the sex differences from different perspectives.
Results: The data gathered in this review indicate that sex differences in articular cartilage, meniscus, and anterior cruciate ligament are detected as early as childhood and are not only explained by sex hormones. Aiming to unveil the biological causes of the uneven sex-specific risks for knee OA, we review the current knowledge of sex differences mostly in young, but also including old populations, from the perspective of (i) human anatomy in both healthy and pathological conditions, (ii) physical activity and response to injury, and (iii) metabolic signatures.
Conclusions: We propose that to close the gap in health disparities, and specifically regarding OA, we should address sex-specific anatomic, biologic, and metabolic factors at early stages in life, as a way to prevent the higher severity and incidence of OA in women later in life.
© 2024 The Author(s). Published by Elsevier Ltd on behalf of Osteoarthritis Research Society International. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

The concepts of "sex" and "gender" are distinct. "Sex" is a biological variable determined by factors such as genetics (with variations such as intersex[1]), physiology, and anatomy, while "gender" is a social variable determined by identity, roles, culture, and relations.[2] These two concepts have often and wrongly been used interchangeably, unfortunately confounding the correct interpretation of valuable research data. Although our search terms included both "sex" and "gender", in this review we focus on sex (as wrongly interchanged by gender in many articles), unless we specifically clarify that we are referring to gender. Here, we expose sex differences in the knee mostly in young individuals, but also including old populations, aiming to understand if important factors present earlier in life are not being considered enough to close the gap in sex disparities in knee osteoarthritis (OA).

Sex-related health disparities in the musculoskeletal system may originate from multiple sources. Knee and hand are the joints with

* Corresponding author at: Department of Orthopaedic Surgery, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA.
E-mail addresses: Paula.Hernandez2@utsouthwestern.edu (P.A. Hernandez), jcb207@uw.edu (J.C. Bradford), Priyanka.Brahmachary@montana.edu (P. Brahmachary), Sophia.Ulman@tsrh.org (S. Ulman), jrobins1@uw.edu (J.L. Robinson), rjune@montana.edu (R.K. June), mmcucchiarini@hotmail.com (M. Cucchiarini).

https://doi.org/10.1016/j.joca.2024.04.015
1063-4584/© 2024 The Author(s). Published by Elsevier Ltd on behalf of Osteoarthritis Research Society International. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

the highest global prevalence of OA and with the most marked sex differences.[3] Sex hormones may be one of the most relevant factors for the development of OA as the sex differences in knee and hand OA incidence become predominant after menopause.[3–7] Interestingly, these two joints contrast in their weight-bearing function, indicating that contributors other than biomechanical factors are involved.

For knee OA, a significant decrease in sex hormone levels do not account for all the observed differences as menopausal age is not the only life period with health disparities in the musculoskeletal system. In fact, young women are more likely to suffer from anterior cruciate ligament (ACL) injuries than men,[8,9] which result in a higher probability for post-traumatic OA.[10,11] In addition, as shown in this review, the shape of the bones in the knee, gait, and the accompanying volume of knee articular cartilage is sex-specific, even in young and healthy individuals.[12–18]

The latest advancements of science, medicine, and especially social ethics related to diversity and inclusion have highlighted that most of the current approaches to treat musculoskeletal conditions have been designed mostly for White men. There is still much-needed improvement to consider and account for the physiological and anatomical variances intrinsic to race and ethnicity. However, the inclusion of sex as a biological variable is an initial step towards understanding, designing, and delivering tailored interventions.

In this review, we focus on knee as a multi-tissue organ exposing sex differences from the perspective of (i) human anatomy in both healthy and pathological conditions, (ii) physical activity and response to injury, and (iii) metabolic signatures. As this is not a systematic review, we acknowledge that there may be additional scientific evidence of sex differences pertinent to our discussion that was not included in this review.

Anatomical differences

Shape of the long bones and the knee

Long bones vary not only due to biological sex, but also depending on race and ethnicity.[19] Several factors including socioeconomic status, proper nutrition, and physical activity may affect bone growth and remodeling. Therefore, for sex comparison of long bones, additional measurements are included. Some studies have focused on the morphological features of the knee such as depth, width, height, and aspect ratio of the femoral condyles.[20] Han et al. used anthropometric data from magnetic resonance imaging (MRI) scans from a non-OA Korean population (20–79 years old) to identify changes in knee structure with age. By grouping their data on three age ranges (20–39, 40–59, and 60–79 years old) they found significant interactions between sex and age in several geometrical parameters of the knee. Females had lower values for transepicondylar width, and lateral and medial posterior condylar offset.[21] Similar results were observed in Chinese and Caucasian populations, as females had lower values in femoral and tibial mediolateral and anteroposterior dimensions.[22,23] Other studies have included statistical shape modeling (SSM), which is a geometric model used to capture and quantify shape variations of an anatomical structure within a particular population.[24] Schneider et al. applied SSM to MRI scans to study the knee bone morphology and cartilage thickness distribution of young and healthy subjects (28.4 ± 4.1 years old). They observed that male sex and tall height correlated with larger bones and thicker cartilage. Females, on the other hand, had generally smaller bones and lower aspect ratios, steeper mediolateral tibial tilt, and more pronounced patellar ridge. They concluded that sex and height strongly influenced knee joint morphology, while body mass and age did not.[25]

Shape of the pelvis and its consequences to human gait

Understanding the consequences of sexual dimorphism in the hip and pelvis can provide information about gait and its consequences to the knee. The female pelvis is wider to allow for a safe child delivery regardless of race. Based on ideas from several researchers about the evolution and sexual dimorphism of the human pelvis, in 1960 Sherwood Washburn created the term “obstetrical dilemma”.[26] This concept hypothesized that *a wider pelvis in women compromised an effective bipedal locomotion*. Specifically, women would have less effective hip abductor muscles, requiring more force to stabilize the pelvis during walking and running. This hypothesis has been both questioned and supported since then. Warrener et al. challenged it by showing that a wider hip does not predict hip abductor mechanics, and that men and women are equally efficient at running and walking.[27] Although these authors still detected a significantly lower anatomical effective mechanical advantage in women, they concluded that this sexual dimorphism did not result from the differences in pelvic width, but from shorter hip abductor moment arms in women. However, Haeusler et al. reanalyzed Warrener’s data revealing that when regression lines are fitted separately to male and female data, a wider distance between the hip joints appears to be associated with higher locomotion costs only in females.[28]

It has been proposed that the hip joint stress for women is higher compared to men.[29] After 50 years old, non-OA women have greater external hip adduction and internal rotation along with increased hip extension moments compared to men, even after normalizing for body size and walking speeds. The walking style or kinematics seems to be the main determinant in the observed differences in joint kinetics.[29] The predominance of hip adduction in healthy females has been observed in both pre- and postmenopausal age.[29,30] Indeed, Abd-Eltawab et al. proposed that training exercises aiming to decrease hip adduction and strengthen abductor muscles could decrease the occurrence of patellofemoral pain syndrome and iliotibial band injuries.[30] Furthermore, the human pelvis changes throughout the reproductive life span. Huseynov et al. revealed that before puberty, the male and female pelvis follow similar developmental trajectories, with only moderate sexual dimorphism. However, on the onset of puberty, these trajectories divert significantly until around 40 years of age. After that, the female pelvis goes back to a male-like developmental trajectory, significantly reducing the obstetric dimensions.[31] These changes seem clearly associated to female sex hormones preparing the body for reproduction and childbirth. The variability in the female pelvis adds a confounding factor in studies addressing sex differences in gait and muscle mechanics, making it necessary to consider whether the females included on the studies are in reproductive period, have gone through childbirth (perhaps even the number of deliveries), or if they passed the reproductive state. Remarkably, although the developmental trajectory of the female pelvis becomes more similar to the male trajectory after 40 years old,[31] Boyer et al. still found sexual dimorphism on the gait of older individuals (50–79 years old),[29] indicating that other factors not limited to the shape of the pelvis are involved in a sex-specific gait.

Sex differences in articular cartilage, meniscus, and ACL

Articular cartilage

Sex differences in cartilage thickness and volume have been observed across several stages of life, even starting as early as childhood. Jones et al. measured knee cartilage thickness in 92 Tasmanian children (9– 18 years old) and observed that boys had 16–31% more cartilage volume compared to girls, most marked at the medial tibial site, even after adjusting for age, body mass index, bone area, and physical activity.[32] This last factor is very important, as physical

activity was a significant explanatory factor for cartilage volume at all sites, however, it did not explain the observed sex differences. Therefore, although boys may be more active than girls, on average, physical activity is not sufficient to explain sex-related differences in cartilage volume. A study of 200 healthy Taiwanese children (5–13 years old) found that for all the joints studied (knee, ankle, wrist, metacarpophalangeal, and proximal interphalangeal joints), cartilage was thicker in boys compared to girls.[17] Of note, these results are across both weight and non-weight bearing joints. Similar results were observed in 394 healthy Danish children, 7–16 years old, where boys had thicker cartilage than girls on the same joints mentioned above.[15] Remarkably, these sex differences remain constant throughout puberty[32] and no significant changes in cartilage volume were observed between pre- and post-menarchical girls,[32] which questions the role of sex hormones in the observed dimorphism. Indeed, in prepubescent children as young as 4–9 years old, boys still have a thicker cartilage at the medial epicondyle compared to girls.[33]

The relationship between bone, muscle, and cartilage is also important. For example, the medial and lateral cartilage volumes have been found to be significantly associated with total bone mineral density (BMD) and bone mass content in 25–60 years old in both sexes, although stronger associations were detected in men.[34] In addition, there is a positive association between serum testosterone and medial cartilage in healthy men.[35] Testosterone increases muscle strength in males,[36,37] while estrogen increases bone density and muscle strength in females,[38,39] although conflicting evidence on the effect of estrogen in muscle also exist.[40] Ruff et al. studied 20 healthy kids from near birth to adolescence, measuring growth in bone strength, body size, and muscle size. Results indicate that growth in stature had little effect on changes in bone strength and that growth velocity in femoral strength was weakly but significantly correlated with the growth velocity in thigh muscle.[41] In general, biological sex had only a minor effect prior to adolescence on the femoral strength. However, sex differences in muscle strength and aerobic work capacity have been detected in children as young as 5–6 years old.[42]

Sex differences were also observed in young adults, as women consistently display smaller cartilage volumes than men in several areas of the knee.[13,14,18,43–45] In addition, a positive correlation between joint space and body size was detected only in men.[13] The cartilage covered area of the subchondral bone is larger in men, and this parameter correlates with weight and height.[14] Similarly, Schneider et al. observed that male sex and tall height correlated with larger bones and thicker cartilage.[25] In general, men are taller than age-matched women. However, more importantly, even after adjusting for height and weight, women still have lower cartilage volumes than men.

In older populations, the maximal and mean cartilage thickness in patella and tibial sites are still higher in males compared to females,[12,46,47] as well as the thickness of subchondral mineralized tissue zone in patella.[48] Akin to children, the sex differences observed were not mediated by physical activity,[46] although the amount of physical activity is inversely associated to total and medial tibial cartilage volumes in males.[35]

Cartilage thickness loss occurs in healthy individuals as well as people with knee OA. In children, cartilage thickness of the knee declines faster in girls than in boys.[17] In adults, women have a higher rate of cartilage volume loss in the medial and lateral tibial sites with and without OA.[47,49] This difference is more pronounced after 50 years of age.[49] While there is an association between cartilage volume loss with age in women, there is no such association in the case of men.[49] Indeed, women, but not men, have a rapid loss around the time of the menopause.[46] Interestingly, sex differences in cartilage volume loss were not seen in a short 1-year follow up study in OA patients,[50] contrasting with longer 2–3 years follow up studies,[47,49] which suggests that detection of significant volume loss might take a few years.

Meniscus

An MRI study of 186 individuals (4 months to 17 years old) revealed females have lower tibial and sagittal width in the lateral and medial meniscus in both normal and discoid menisci.[51] This is consistent with the lower tibial and femoral bone dimensions in females.[21–23] Discoid meniscus, most commonly discoid lateral meniscus (DLM), is a condition where the meniscus is abnormally thick and more disc-shaped compared to the crescent shape of healthy menisci. This overgrowth of tissue is more prone to tears and alters the contact of the femoral condyle and tibial plateau which causes aberrant mechanical loading.[52] Women have over 2-fold higher risk of DLM, and experience more tears than men in DLM cases,[52] although no differences have been detected after DLM repair.[53] Also, females exhibit lower anterior horn height, and coronal width in the medial meniscus.[51,54]

ACL

The ACL is a multifascicular structure that attaches to the femur and the tibia and consists of two bundles. ACL bundles are composed of collagen fibrils and at least one is consistently taut and functional across all knee positions.[55] Sex differences in the anatomical structure of the ACL have been briefly mentioned in recent literature related to the ultrastructural characteristics of the ACL, including size distribution of the collagen fibrils, number of fibrils per unit area (concentration), and percent area occupied by collagen (area fraction).[56–58] Specifically, Hashemi et al. reported that female ACLs exhibited reduced fibril concentration and area fraction compared to males; however, the latter was significantly influenced by age, height, and body mass.[58] Additionally, while average fibril diameter did not differ by sex, the distribution of these data was qualitatively determined to be more concentrated about the mean (leptokurtic) in males and generally more variable (stochastically larger) in females.[58] This difference may be explained by the association found between fibril concentration and both ACL stiffness and modulus of elasticity in female ACLs, while male ACLs exhibited an association between fibril area fraction and both failure load and strength of the ACL.[58] Wang et al. reported findings from a morphometry study that indicated recreationally active, young adult males had greater ACL volume and width compared to females.[59] However, sex differences in ACL width resolved once femoral notch width and body mass index were considered.[59] Similarly, Anderson et al. found that regardless of body mass, ACL size was significantly greater in young male athletes compared to female athletes, including axial width, sagittal width, and cross-sectional area.[60] Supporting this finding, Morales-Avalos et al. reported greater ACL area (femoral footprint area) in males compared to females, while no differences were found in ACL diameters, attachment location measures, or insertion area measures.[61] Therefore, an objective measure of ACL volume may be most indicative of sex differences and thus help to highlight sex-related disparities in ACL injury risk.

Physical activity, youth sports, and injuries

Cartilage

Cartilage deforms after physical activity in response to mechanical load, and these deformations are more apparent in the younger compared to older population.[62] A study in young healthy adults indicated that females experience greater deformations and hence changes in cartilage volume in the lateral tibia compared to males after 15 minutes of treadmill running at a moderate speed.[45]

Although serum levels of the cartilage oligomeric matrix protein (COMP) are associated with magnitude, duration, frequency, and type of mechanical loading,[63] no significant association between serum levels of COMP and acute cartilage deformation was observed after physical activity, such as walking or a drop-landing routine of exercise.[64] However, for females only, greater concentrations of COMP at rest were significantly associated with smaller medial and lateral cartilage cross sectional area.[64] Differences in COMP levels in serum in patients with knee OA have been detected not only based on biological sex—men having higher serum levels of COMP than women[64,65]—but also on race, as African American women have higher serum levels of COMP than Caucasian women even in non-OA population.[65]

The effect of physical activity in subjects with knee OA was assessed in a 4-year follow up study, where patients (61.6 ± 8.9 years old) with radiographic knee OA and a Kellgren and Lawrence (K-L) grade ≥2 showed a loss of 0.20 mm in cartilage thickness in the medial femorotibial compartment. This loss was observed independent of the type of physical activity. However, women with low physical activity had a greater cartilage loss than women with moderate levels of physical activity, a difference that was not observed in men.[66]

Meniscus

Females have delayed maximal recovery and worse knee function after meniscectomy,[67,68] experience higher rates of youth and sports related injuries with higher rates of surgery with appropriately matched controls,[69,70] and are at a higher risk of developing OA compared to age-matched men.[71,72] Data suggest that women experience worse meniscal injuries, delayed and inferior healing compared to men,[73,74] and longer times to significant pain relief after partial meniscectomies.[73,75] In pediatric and adolescent population, Rhode et al. observed that males had higher repair rates and females presented with more medial tears and more white-white zone tears.[76] Women also demonstrate a higher overall risk for meniscal tear when controlled for sports.[69] Stanley et al. indicated some sport-specific sex differences, but no overall difference in the incidence of injury, with women only being more prone to tears in ice hockey, but males having higher risks in other sports.[77] Mercurio et al. reported that male sex was associated as a risk factor for meniscal tears, but also noted males were more likely to have direct knee trauma and increased body mass index in their dataset.[78] Longo et al. observed higher rates of OA progression in men with meniscal tears versus women, and found than men were at higher risk after bucket handle tears, whereas women were at higher risk after longitudinal tears.[79] Surgically, women are up to 100% more likely to have a lateral meniscectomy compared to men, which is associated with a higher risk of symptomatic OA.[72] Often, these repairs do not last as women are 2.2× more likely to require repeat surgery, with the risk increasing 1.3× higher with each year of increasing age.[70] While there are contradictions, when controlled for sport and/or injury, women experience higher incidence of meniscal injury, with worse outcomes from surgical repair and are more likely to present with abnormally shaped menisci.

Roos et al. suggested that removal of the meniscus, but not sex, was found to be a significant predictor of developing OA later in life. However, as previously established women are at a much higher risk for meniscal damage, and meniscal allograft transplant indicating their higher prevalence for this pre-requisite.[80] Quantitative polymerase chain reaction analysis of menisci from osteoarthritic knees revealed no major OA genes were identified as significantly different between the sexes, besides expression of CCL3L1, an inflammatory cytokine.[81] Ding et al. observed that female sex was a significant predictor for body tears of the meniscus, but not for anterior or posterior horn tears.[71] Englund et al. studied the degree of meniscal tears in OA populations and saw that while males had a higher overall rate of tears, meniscal destruction was higher in women, particularly with higher age.[82] This group also demonstrated that women are more than 60% more likely to have radiographic OA following meniscectomy, and importantly are 2× more likely to have a lateral meniscectomy compared to age-matched men.[72] Women have also been found to functionally perform worse following meniscus injuries, with longer time to pain relief, worse outcome scores, and overall worse knee movement.[72,74,75] Lange et al. studied post-menopausal women with OA and found meniscal tears were present in 73% of individuals with knee OA; however, no sex-based comparison was made.[83] Investigational and demographic data on postmenopausal women suggest worse outcomes in meniscal injury, higher prevalence of abnormal menisci, and high presence of meniscal damage in OA patients and highlight that sex-specific differences in the meniscus lead to worse outcomes with OA with progression of age.[72,82–84]

ACL

As youth athletes are encouraged to participate in sports at an early age, specialize in a single sport, and compete year-round, a drastic increase in the frequency and severity of sport-related injuries has been observed.[85–88] This is especially concerning as it is well known that reduced participation in physical activities can lead to a multitude of long-term health-related problems.[89,90] Health professionals have also voiced similar concern that physical activity levels of affected adolescent athletes will diminish over the course of the athlete's lifetime.[91,92] Additionally, early childhood ACL injuries specifically can lead to long-term risks such as meniscus injuries, early onset knee OA, and the possible need for total knee replacement in adulthood.[11,93–95] In the United States, approximately sixty million children between the ages of 6 and 18 participate in organized sports,[96,97] and the number of ACL injuries has nearly doubled annually in active adolescents over the past two decades.[98,99] It has been recently reported that over 350,000 children and adolescents suffer an ACL tear per year[98] with at least 30% suffering a consecutive ACL injury to either the reconstructed ipsilateral limb or the contralateral limb.[100,101] Evidence reported on secondary ACL injury demonstrates that contralateral limb injuries occur more frequently than ipsilateral re-injuries,[102] however, sex and maturation status appear to play a role in both initial injury and reinjury rates.[103]

At pre-pubertal stages, recent studies report that males have twice the rate of injuries as the females.[104] However, once puberty begins, female athletes are four to six times more likely to suffer an ACL injury in sport.[105–109] Following puberty, musculoskeletal injury risk becomes more elevated for female athletes, similar to the increased ACL injury risk experienced during puberty.[110,111] Simultaneously, males post-puberty (17–19 years old) once again become more likely to sustain an ACL injury compared to females.[104] Alternatively, for secondary knee injuries, Brodeur et al. found that male patients had a higher incidence of an ipsilateral reinjury whereas female patients were more prone to contralateral secondary injuries in a cohort of 20,170 recovered patients post-ACL reconstruction.[103] However, other studies have conflicting findings that have shown sex is not a predictor of a secondary injury to either the ipsilateral or contralateral knee.[112–114]

Regarding movement patterns and biomechanical risk factors between sexes, literature is conflicting. While a cornerstone study by Swartz et al. did not report any sex differences in kinematics during a drop vertical jump task,[115] more recent studies indicate otherwise. Specifically, several studies find that females have decreased dynamic knee stability and neuromuscular control as they progress through adolescence compared to males.[110,111,116] Holden et al.

reported that adolescent female athletes demonstrated more high-risk landing biomechanics compared to their male counterparts given they exhibited less knee flexion upon landing and a more valgus position (medial collapse) of the knee joint.[117] This greater reliance on knee extensor muscles during eccentric contraction, resulting in reduced knee flexion and thus insufficient power absorption, is a characteristic of 'quadriceps dominance theory' described in detail by Pappas et al. as a potential explanation for the increased ACL injury risk observed in female athletes.[118,119] Similarly, Holden et al. further emphasized that female adolescent athletes are at higher risk for injury given increased 'dynamic knee valgus' during landing tasks,[120] which has been defined as a combination of movements across all three planes of motion, including femoral adduction and internal rotation, anterior tibial translation, external tibial rotation, ankle eversion, and knee valgus.[121–123] Motion analysis studies also report sex differences in muscle activation patterns during a landing and cutting task, including increased quadriceps dependence and reduced hamstring engagement exhibited by female athletes, which are also associated with increased risk of ACL injury.[110,119,124]

Chia et al. observed that transition into adolescence was associated with decreased hip and knee flexion and increased medial loading on the knee (increased valgus moments) in female athletes during a run-cut maneuver.[116] As female athletes age, the combination of abnormal bony alignment (genu valgum) and poor neuromuscular control may increase the knee's reliance on passive structures, referred to as ligament dominance.[110,116,119] Thus, Myer et al. recommended initiating integrative neuromuscular training programs during early adolescence (pre-puberty)[125] as recent evidence has shown that neuromuscular training, specific for female athletes, successfully decreases the incidence of ACL injuries.[126,127] However, additional research is needed to better understand how maturation status influences the impact of neuromuscular training in adolescent female athletes.

A possible molecular explanation for the differences in ACL injuries between males and females is the action of relaxin. This peptide hormone is mostly responsible for connective tissue remodeling and pelvic joint laxity during late pregnancy and parturition.[128] It is present in female serum and in male sperm.[129] Relaxin receptors have been detected in female ACL (human) and appears to be regulated by the action of estrogen[130] but its role in knee joint laxity in female athletes is still controversial as some studies suggest that it is not related to joint laxity,[131] while others indicate its association to a higher risk of ACL tears.[132]

A summary of the most important findings in sex differences in the knee is depicted in Table I.

Metabolism

Leptin and metabolism

Leptin is a protein released by the adipose tissue that signals the hypothalamus to suppress appetite. During the years prior to the onset of puberty, the levels of leptin increase progressively in both males and females.[133] Higher levels of leptin are observed in females in this period, possibly related to their earlier onset in puberty.[133] *In vitro* experiments have shown that 5α-dihydrotestosterone reduces the secreted levels of leptin while 17-β estradiol (E2) increases them.[134] Up to 50% of the increase in leptin in boys occurs before the rise in the concentration of testosterone and levels are stable until adult age. Leptin maybe a link between adipose tissue and puberty since their values correlate with the degree of adiposity at puberty.[133] However, levels of leptin do not always correlate with body fat content in adulthood.[135] Elbers et al. observed that sex differences in serum levels of leptin were reversed in a transgender population after going through gender-affirming medical intervention. They registered serum levels of leptin in 17 male to female (M-F, 18–37 years old) and 15 female to male (F-M, 16–34 years old) transgender people before gender-affirming intervention and 12 months post intervention. For M-F transgender subjects, leptin levels increased significantly, while the opposite was true for F-M transgender subjects, and these changes were independent of the body fat content.[135] Given that testosterone can still be converted to E2 in F-M transgender people, but an antiandrogen was administered to M-F transgender subjects, the authors concluded that the lack of testosterone rather than the increase in E2 might be the cause of the rise in leptin levels. Supporting this finding, higher serum levels of leptin in women compared to men were found at post-menopausal age when E2 levels are low (~ 0–30 pg/ml).[136] Ding et al. found that in subjects aged 52–78 years old, serum levels of leptin were negatively associated with total cartilage volume. Females had lower cartilage volumes than males, and higher serum levels of leptin. Interestingly, the observed sexual dimorphism in total cartilage volume in this older population decreased substantially after adjustment for leptin, however, it was not eliminated.[136]

Metabolic signatures

The metabolome includes a variety of small molecules such as amino acids, peptides, fatty acids, sugars, organic acids, aldehydes and other small molecules derived from biochemical reactions. There are key differences between metabolomic profiles of healthy men and women. Costanzo et al. highlighted sex-related differences in the plasma, serum, and urine metabolomes of healthy patients.[137] The plasma metabolome showed higher levels of phenylalanine, glutamate, glutamine, kynurenine, methionine, proline, and tyrosine in men than in women. Also, the branched-chain amino acids (BCAAs—valine, leucine, and isoleucine) were more abundant in men than women. This may result from dietary differences (e.g., higher protein) and different muscle metabolism between men and women.[138] In the adult serum metabolome, there were higher levels of methionine, asparagine, proline, tyrosine, glutamate, citrulline, and BCAAs in men than in women, whereas tryptophan was significantly lower in men.[139] Similarly, serine and glycine were more abundant in adult women, whereas glutamine, ornithine, and arginine were higher in men.[140] Sex differences in the urine metabolome showed greater heterogeneity for amino acids, acylcarnitine, organic acids and carbohydrates than plasma and serum. In adults, proline, leucine, l-carnosine, and 2,6-diaminopimelic acid were increased in males, while higher levels of glycine and other non-canonical amino acids (acetylphenylalanine, 2-aminoadipic acid, *N*-acetylaspartic acid, nicotinuric acid, aminosalicyluric acid) were detected in females. Levels of α-ketoglutarate and 4-hydroxybutyric acid were 2.3-fold and 4.4-fold higher in males compared to females, respectively.[141–143]

Similarly, there are differences in other classes of metabolites. The majority of carbohydrates found in the urine of female participants, were D-fructose, xylose, maltose, lyxose, galactonic acid, pentose, acetaminophen glucuronide, gluconic acid, glucuronic acid, threonic acid, erythronic acid and glyceric acid, whereas only uridine diphosphate-glucuronic acid was detectable in the male urine.[142] A common theme from the plasma, serum and urine metabolomes is increased creatinine in males and increased creatine in females. These are often associated with diet, nutritional state, and energy metabolism. Creatine synthesized by the liver *de novo* and dietary creatine are transported through the blood to the creatine-requiring tissues, such as muscle that absorb up to 94% of the total creatine which is then transformed into creatinine at a steady state (~2% of the total creatine per day), and later being excreted into the urine through glomerular filtration. Therefore, higher creatinine levels found in the urine samples of males is related to the higher muscle

Tissue/parameter	Childhood (~0–11 y.o.)	Adolescence (~12–18 y.o.)	Early adulthood (~19–49 y.o.)	Late adulthood (~50+)
Bone dimensions	Growth in stature had little effect on changes in bone strength.[41]	Growth in stature had little effect on changes in bone strength.[41]	Females have lower values for transepicondylar width, and lateral and medial posterior condylar offset.[21] Reduced femoral and tibial mediolateral and anteroposterior dimensions.[22,23] Male sex and tall height correlated with larger bones. Females had lower aspect ratios and steeper mediolateral tibial tilt and more pronounced patellar ridge.[25]	
Gait	Pelvis trajectory similar between sexes.[31]	Pelvis trajectories divert significantly.[31] Females have a reduced hip and knee flexion and increased medial loading of the knee during a run-cut maneuver.[121] Females have increased high-risk landing biomechanics, exhibited less knee flexion upon landing and have a more valgus position of the knee.[122] Females have a greater reliance on knee extensor muscles during eccentric contraction resulting in reduced knee flexion and insufficient power absorption.[123,124]	Females have less effective hip abductor muscles.[26] A wider distance between hip joints may be associated with higher locomotion cost only in females.[28] Predominance of hip adduction in females.[29,30]	Pelvis trajectories in females go back to male-like.[31] Females have greater external hip adduction and internal rotation along with increased hip extension moments.[29,30]
Cartilage volume and thickness	Cartilage loss is faster in females.[17] Males have thicker cartilage in several joints.[17,32,33]	Cartilage loss is faster in females.[17] Males have thicker cartilage in several joints.[15,17,32]	Cartilage loss is faster in females.[47,49] Male sex and tall height correlated with thicker cartilage.[25] Females have reduced knee cartilage volumes.[13,14,18,43–45] Males have higher cartilage thickness in patella and tibial sites.[12,46,47] Females have greater cartilage deformation in the lateral tibia after 15 min of treadmill running.[45] Higher COMP concentrations at rest were associated with smaller medial and lateral cartilage cross sectional area.[69]	Cartilage loss is faster in females.[46,49] Females with low physical activity had a greater cartilage loss compared to females with moderate physical activity. This was not seen for men.[71]
Meniscus	Females have lower tibial and sagittal width in the lateral and medial meniscus.[51] Females have over 2-fold higher risk of DLM.[52] Males have higher repair rates while females present more medial tears and more white-white zone tears.[76] Females have increased OA risk after longitudinal tears.[79] Males have increased OA risk after bucket handle tears.[79]	Females have lower tibial and sagittal width in the lateral and medial meniscus.[51] Females have over 2-fold higher risk of DLM.[52] No sex differences detected after DLM repair.[53] Females have lower anterior horn height and coronal width in the medial meniscus.[51,54] Females have increased rates of meniscal injuries related to sports.[69,70] Females have higher risk for repeated surgery for meniscal repair.[70] Males have higher repair rates while females present more medial tears and more white-white zone tears.[76] Male sex was a risk factor for meniscal tears.[78] Females have increased OA risk after longitudinal tears.[79] Males have increased OA risk after bucket handle tears.[79]	Females have over 2-fold higher risk of DLM.[52] Females have delayed maximal recovery and worse knee function after meniscectomy.[67,68] No sex differences in expression of OA-related genes, only in expression of the inflammatory cytokine CCL3L1.[81]	Females have over 2-fold higher risk of DLM.[52] Females have delayed maximal recovery and worse knee function after meniscectomy.[67,68] Females have worse meniscal injuries and delayed healing.[74] Females experience longer times to pain relief after partial meniscectomy[73,75] No sex differences in expression of OA-related genes, only in expression of the inflammatory cytokine CCL3L1.[81] Females are more likely to have lateral meniscectomy compared to age-matched men.[72] Females have worse outcomes following meniscal injuries.[72,74,75,82–84]
ACL	Males have twice the rate of injuries.[109]	ACL size is higher in young male athletes.[60] Female athletes are 4-6-fold more likely to suffer ACL injuries.[110–114] Females have a reduced dynamic knee stability and neuromuscular control.[115,116,121] Females have increased quadriceps dependence and reduced hamstring engagement associated with increased ACL risk.[115,124,129]	Females have reduced fibril concentration and area fraction influenced by age, height, and body mass.[58] Association between fibril concentration and ACL stiffness and modulus in females.[58] Association between fibril area fraction and failure load and strength in males.[58] Males are more likely to sustain ACL injury[109]	

Table I

Summary of findings on sex differences related to knee anatomy, gait, and injury, across the lifespan. For this review, early adulthood and late adulthood refer to pre- and post- the onset of menopause in women. Some studies cover multiple age ranges.

mass in males.[144,145] These analyses of the baseline metabolomes in healthy cohorts provide comparison data to understand and investigate the multidimensional pathophysiology of OA.

Metabolic signatures in OA

In the Multicenter Osteoarthritis observational cohort study, a sex-specific comparison of knee OA progressors vs non-progressors indicated that higher phenylalanine plasma levels were strongly associated with knee OA progression in women but not men.[146] Metabolomic profiling on a female cohort found that the serum BCAA to histidine ratios were significantly associated with knee OA.[147] The BCAAs valine, isoleucine, and leucine are essential amino acids that constitute approximately one-third of the skeletal muscle in the human body and play an important role in protein synthesis. An increased level of free BCAA may suggest an increased rate of protein breakdown. BCAAs also increase the production of cytokines including interleukin 1 and 2, tumor necrosis factor and interferon which can lead to increased collagen degradation in the joint.[147]

A study by Xu et al.[148] used Differential Correlation Metabolic networks for describing metabolites with significant correlation variations between plasma and synovial fluid samples from advanced knee OA patients. In the female group, glycerophospholipids were associated with positive differential correlations while the negative differential correlations were identified as acylcarnitines. In contrast for the male network, sphingolipids were the main metabolites that contributed to the differential correlation between the plasma and synovial fluid.

Moreover, there are decreased levels of Vitamin D metabolites ($25(OH)D_3$, $25(OH)D_3 + 25(OH)D_2 + 24,25(OH)_2D_3$, and $24,25(OH)_2D_3 + 25(OH)D_2$ in the synovial fluid of female knee OA patients compared to male OA patients. Vitamin D metabolites play an important role in skeletal development and maintain cartilage and bone homeostasis.[149] Importantly, $24,25(OH)_2D_3$ is associated with calcium homeostasis and terminal differentiation of chondrocytes and osteoblasts.

In a cross-sectional analysis of human synovial fluid following different injury types (ligament, meniscus, and combined ligament meniscus injuries), Welhaven et al. observed differences in metabolomic profiles across males and females.[150] Metabolic phenotypes were mainly associated with amino acid metabolism, lipid-related oxidative pathways and inflammation-associated pathways. Phenylalanine was significantly increased in males compared to females, and Alpha-Chaconine, Cyclotricuspidoside C, and Lucidenic acid N were found to be in greater abundance in males with meniscus injuries compared to females with the same injury. Dysregulated amino acid pathways included metabolism of asparagine, arginine, and proline. Dysregulated lipid pathways included the carnitine shuttle, linoleate metabolism, saturated fatty acids β-oxidation, and dimethyl-branched-chain fatty acid mitochondrial β-oxidation. This differential oxidation of fatty acids between males and females can be attributed to hormonal differences.[151] Cervonyl carnitine was elevated in all female participants compared to males. Elevated carnitine levels in females may indicate different metabolic pathways utilized (e.g., AMPK activation via estrogen) for energy requirements.

Carnitines are involved in β-oxidation by transporting medium and long chain fatty acids into the inner mitochondrial membrane, help in maintaining cell membrane stability through supporting acetylation of membrane phospholipids, and are associated with anti-oxidative effects.[152]

What can we learn from transgender individuals?

Transgender populations represent a unique opportunity to study the interactions between sex hormones and chromosomal health in the musculoskeletal system. Unfortunately, this remains an understudied area and the currently available data indicates contrasting results. In general, a lower BMD was detected in transgender women (individuals assigned as male at birth but that identify as women) compared to cisgender men[153] and even prior to gender-affirming hormone therapy (GAHT). This is probably less dependent on sex hormones and more dependent on behavioral differences including physical activity.[154,155] In the case of transgender males, no significant differences have been observed in BMD compared to cisgender women. However, when transgender men received an aromatase inhibitor together with their testosterone therapy, their BMD at the lumbar spine was lower compared to individuals receiving testosterone alone suggesting the required action of estrogen.[156] Likely due to testosterone treatment, transgender men experience a reduction in fat mass and an increase in lean body mass, while the opposite was observed in transgender women.[157] Other studies have not detected differences in BMD in transgender women from baseline to after 24 months of hormonal therapy despite substantial muscle loss.[158]

Regarding the ACL, it appears that female sex hormones impact ACL laxity in trans women, but it has been also suggested that rather than being specific to a particular sex hormone, the overall changes in the hormonal balance are to blame.[159] Miro et al. observed that transgender women on GAHT had higher cumulative incidences of all-cause knee injuries compared to cisgender women.[160] However, the specific relationship between GAHT and ACL mechanics has gone unanswered.[159–161]

Taken together, differences in the transgender population can be partly attributed to hormonal therapy but other important factors in musculoskeletal health such as levels of physical activity, muscle mass, fat tissue, vitamin D, and inclusion of aromatase in GAHT should be considered in future studies.

Pain in OA

Women consistently report greater knee pain than men at equivalent levels of radiographic knee OA.[162] It is thought that women with symptomatic knee OA may have an enhanced central sensitivity compared to men, via an unknown mechanism.[163] One of the possible candidates for this sex difference is Interleukin-6 (IL-6) given its role in inflammation and pain.[164] A study in male and female patients scheduled to have a knee arthroplasty due to OA measured systemic IL-6 levels before and after a laboratory-evoked pain test. Patients were asked to undergo a quantitative sensory testing while blood was collected up to 2 hours later. Females, but not males, presented a rapid increase in IL-6 levels.[165] Another study observed that after undergoing knee arthroplasty, females reported higher postoperative pain scores 2 weeks later, although these differences were leveled after 6 weeks. Together with this, they detected a negative correlation of IL-6 levels and pain in males and a slightly positive relation in females, although no sex differences were detected in overall IL-6 concentrations.[166]

Another candidate for sex differences in pain is innate immunity. Several clinical and pre-clinical studies suggest that the innate immune system is key for pain generation in OA,[167] and sex differences in the immune system are known. These are influences by chromosomal sex, sex hormones, and environmental factors.[168] Women are more susceptible to autoimmune diseases compared to males and this difference seems to be marked by the X-chromosome inactivation via Xist.[169] Using small animal models, researchers recently observed that Xist promotes a female-biased autoimmunity,[170] and moreover, it accelerates neuropathic pain progression.[171] Interestingly, inhibition of Xist-related neuroinflammation downregulates the production of IL-6,[171] opening new windows in the need for research on sex differences in OA-related pain.

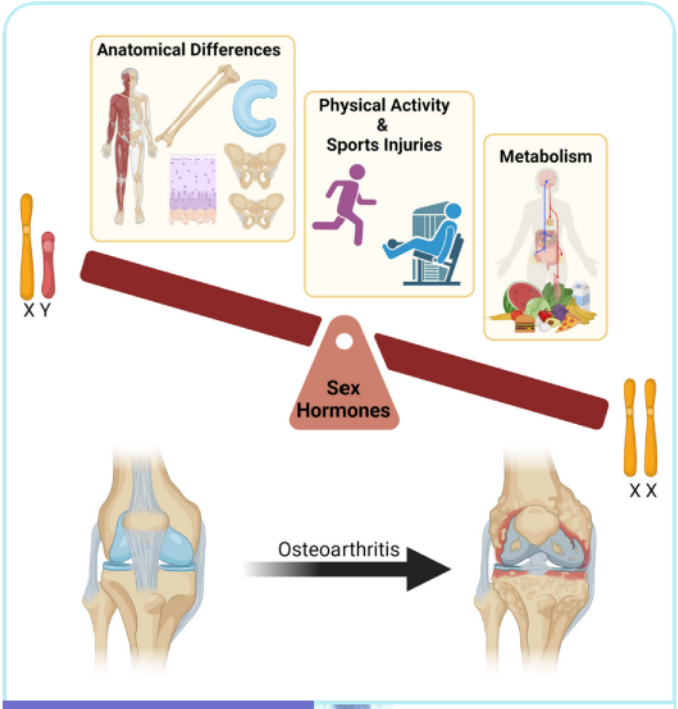


Fig. 1 Osteoarthritis and Cartilage

Contribution of biological sex (XX vs XY) and sex hormones to the development of OA. Subtle but significant geometrical sexual dimorphisms in bone, meniscus, ACL, and articular cartilage have been found throughout the life span, starting as early as childhood. These factors, together with sex-specific metabolism, gait, and the body's reaction to physical activity, could be key to understanding the unbalanced development of knee OA between the sexes. Sex hormones appear to be the largest contributing factor to the risk of knee OA, but understanding their differential effect on XX versus XY is crucial to develop targeted, preventive approaches. We propose that considering sex disparities in knee joint health starting from childhood can help reveal the biological components behind women being more prone to knee OA later in life. This is especially important in times when children are exposed to large ranges in activity from competitive sports at a very young age to frequent inactivity and high incidences of obesity. Created with BioRender.com.

Conclusions

There are several factors in knee joint health that display sexual dimorphism. Among them are gait, bone shape, cartilage volume, meniscus shape, ACL size, metabolism, and sex hormones. These factors may have a key role in the risks of injury during youth sports and pose a potential risk for the development of knee OA later in life. Most importantly, although many of the observed sex differences are enhanced by sex hormones, some of them appear sooner than pubescence or are simply not explained solely by the action of sex hormones (Fig. 1). An example is leptin: estrogen upregulates the production of leptin,[134] however, after menopause when the estrogen is low, leptin levels in females are still higher than in males. Higher levels of serum leptin seem to correlate with smaller cartilage volumes even post the menopause transition.[136]

In addition, there is an urgent need for studies focusing on the biological drivers of these dimorphisms, as the roles of sex hormones in musculoskeletal health and disease are still under discussion. Whether the modulation of basic cellular functions has any sex-specific component is unknown. For example, differences in the abundance of amino acids detected with metabolomic analysis are intriguing. Amino acids such as glutamine and leucine—which are enriched in males[137,140]—promote the synergistic activation of the mammalian target of rapamycin complex 1 affecting the autophagy-lysosome pathway in animal models.[172] The mammalian target of rapamycin pathway also cross-talks with phosphoinositide 3-kinase-RAC-alpha serine/threonine kinase and PKC to regulate cell proliferation. PKC can be activated by estrogen in a non-genomic way in vitro experiments[173,174] which appears to happen only in female cells.[174] Whether these proteins and/or pathways are differentially regulated in males and females is yet to be discovered. Unfortunately, only a very few studies using animal models for OA have properly considered sex as a biological variable. This was recently reviewed for the case of large animal models[175] and is critical when planning studies dedicated to unveiling male-female differences in OA.

Furthermore, there are social components such as cultural, behavioral, and occupational differences where the concept of gender could be as relevant as biological sex. For example (depending on culture and income), work-related physical activities with a higher risk for injuries such as construction, landscaping, or manipulating heavy machinery for mostly the male gender, while using high heels, housekeeping, and caregiving for children and others in the household for mostly the female gender. Although a pertinent discussion is outside of the scope of this review, we believe that studies specifically comparing the relationship between what was previously defined as gender roles in the society with the risk of OA are needed, recognizing that gender roles have changed over generations.

We propose that considering and investigating sex disparities in knee joint health starting from childhood can help reveal the biological components behind women being more prone to knee OA later in life (Fig. 1). This is especially important in present times, as children are exposed to competitive sports at a very young age, or the complete opposite, to inactivity and high indices of obesity. Neuromuscular training programs for girls and young athletes are promising to reduce the incidence of ACL injuries. Expanding this approach to develop sex-specific exercise routines within physical education including exercises for lower extremity strengthening and trunk stabilization as previously described[125] could be a feasible option. Moreover, elucidating the effect of sex hormones in the musculoskeletal cells and tissue from males and females, can help understand their effect in the transgender population after going through gender-affirming intervention, so they are also incorporated when designing, planning, and promoting proper and equitable access to preventive care for OA.

Role of the funding source

Dr. Hernandez was supported by the American Orthopaedic Society for Sports Medicine AOSSM, grant number OARG 1018987. Dr. Robinson was supported by NIH NIGMS 1R35GM143081. Dr. June was supported by NSF CMMI 1554708 and NIH NIAMS R01AR073964. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results. The content is solely the responsibility of the authors and does not necessarily represent the official views of the American Orthopaedic Society for Sports Medicine.

Competing interests

R.J. owns stocks in Beartooth Biotech and OpenBioWorks; P.B. owns stocks in OpenBioWorks. These companies had no involvement in this study.

CRediT authorship contribution statement

Conceptualization and design of the work, P.H. and M.C.; acquisition, P.H., J.B., P.B., S.U., J.R., R.J., M.C.; drafting the manuscript, P.H., J.B., P.B., S.U., J.R., R.J., M.C.; review and editing, P.H., S.U., J.B., J.R., R.J., M.C.; all authors have read and agreed to the published version of the manuscript. P.H. is accountable for all aspects of the work.

References

1. Grimstad F, Kremen J, Streed Jr. CG, Dalke KB. The health care of adults with differences in sex development or intersex traits is changing: time to prepare clinicians and health systems. LGBT Health 2021;8:439–43.
2. National Academies of Sciences, Engineering, and Medicine. Measuring sex, gender identity, and sexual orientation. In: Becker T, Chin M, Bates N, editors. Measuring Sex, Gender Identity, and Sexual Orientation. Washington (DC): The National Academies Press; 2022.
3. Long H, Liu Q, Yin H, Wang K, Diao N, Zhang Y, *et al*. Prevalence trends of site-specific osteoarthritis from 1990 to 2019: findings from the global burden of disease study 2019. Arthritis Rheumatol 2022;74:1172–83.
4. Boyan BD, Tosi L, Coutts R, Enoka R, Hart DA, Nicolella DP, *et al*. Sex differences in osteoarthritis of the knee. J Am Acad Orthop Surg 2012;20:668–9.
5. Nevitt MC, Felson DT. Sex hormones and the risk of osteoarthritis in women: epidemiological evidence. Ann Rheum Dis 1996;55:673–6.
6. Srikanth VK, Fryer JL, Zhai G, Winzenberg TM, Hosmer D, Jones G. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. Osteoarthr Cartil 2005;13:769–81.
7. Eaton CB, Schaefer LF, Duryea J, Driban JB, Lo GH, Roberts MB, *et al*. Prevalence, incidence, and progression of radiographic and symptomatic hand osteoarthritis: the osteoarthritis initiative. Arthritis Rheumatol 2022;74:992–1000.
8. Mountcastle SB, Posner M, Kragh JF, Taylor DC. Gender differences in anterior cruciate ligament injury vary with activity - epidemiology of anterior cruciate ligament injuries in a young, athletic population. Am J Sports Med 2007;35:1635–42.
9. Montalvo AM, Schneider DK, Webster KE, Yut L, Galloway MT, Heidt RS, *et al*. Anterior cruciate ligament injury risk in sport: a systematic review and meta-analysis of injury incidence by sex and sport classification. J Athl Train 2019;54:472–82.
10. Wang LJ, Zeng N, Yan ZP, Li JT, Ni GX. Post-traumatic osteoarthritis following ACL injury. Arthritis Res Ther 2020;22:57.
11. Friel NA, Chu CR. The role of ACL injury in the development of posttraumatic knee osteoarthritis. Clin Sports Med 2013;32:1–12.
12. Cicuttini F, Forbes A, Morris K, Darling S, Bailey M, Stuckey S. Gender differences in knee cartilage volume as measured by magnetic resonance imaging. Osteoarthr Cartil 1999;7:265–71.
13. Duren DL, Sherwood RJ, Chumlea WC, Siervogel RM, Towne B. Radiographic joint space of the knee in healthy young adults. Hum Biol 2006;78:353–64.
14. Otterness IG, Eckstein F. Women have thinner cartilage and smaller joint surfaces than men after adjustment for body height and weight. Osteoarthr Cartil 2007;15:666–72.
15. Spannow AH, Pfeiffer-Jensen M, Andersen NT, Herlin T, Stenbog E. Ultrasonographic measurements of joint cartilage thickness in healthy children: age- and sex-related standard reference values. J Rheumatol 2010;37:2595–601.
16. Bedewi MA, Elsifey AA, Naguib MF, Saleh AK, Nwihadh NB, Abd-Elghany AA, *et al*. Sonographic assessment of femoral cartilage thickness in healthy adults. J Int Med Res 2020;48. 300060520948754.
17. Gau CC, Yao TC, Gan ST, Lin SJ, Yeh KW, Chen LC, *et al*. Age, gender, height and weight in relation to joint cartilage thickness among school-aged children from ultrasonographic measurement. Pediatr Rheumatol Online J 2021;19:71.
18. Baboli R, Sharafi A, Chang G, Regatte RR. Isotropic morphometry and multicomponent T(1) ρ mapping of human knee articular cartilage in vivo at 3T. J Magn Reson Imaging 2018;48:1707–16.
19. Kim TK, Phillips M, Bhandari M, Watson J, Malhotra R. What differences in morphologic features of the knee exist among patients of various races? A systematic review. Clin Orthop Relat Res 2017;475:170–82.
20. Kim DI, Kwak DS, Han SH. Sex determination using discriminant analysis of the medial and lateral condyles of the femur in Koreans. Forensic Sci Int 2013;233:121–5.
21. Han H, Oh S, Chang CB, Kang SB. Anthropometric difference of the knee on MRI according to gender and age groups. Surg Radiol Anat 2016;38:203–11.
22. Cheng FB, Ji XF, Lai Y, Feng JC, Zheng WX, Sun YF, *et al*. Three dimensional morphometry of the knee to design the total knee arthroplasty for Chinese population. Knee 2009;16:341–7.
23. Terzidis I, Totlis T, Papathanasiou E, Sideridis A, Vlasis K, Natsis K. Gender and side-to-side differences of femoral condyles morphology: osteometric data from 360 Caucasian dried femori. Anat Res Int 2012;2012, 679658.
24. Audenaert EA, Pattyn C, Steenackers G, De Roeck J, Vandermeulen D, Claes P. Statistical shape modeling of skeletal anatomy for sex discrimination: their training size, sexual dimorphism, and asymmetry. Front Bioeng Biotechnol 2019;7:302.
25. Schneider MT, Rooks N, Besier T. Cartilage thickness and bone shape variations as a function of sex, height, body mass, and age in young adult knees. Sci Rep 2022;12, 11707.
26. Washburn SL. Tools and human evolution. Sci Am 1960;203:63–75.
27. Warrener AG, Lewton KL, Pontzer H, Lieberman DE. A wider pelvis does not increase locomotor cost in humans, with implications for the evolution of childbirth. PLoS One 2015;10, e0118903.
28. Haeusler M, Grunstra NDS, Martin RD, Krenn VA, Fornai C, Webb NM. The obstetrical dilemma hypothesis: there's life in the old dog yet. Biol Rev Camb Philos Soc 2021;96:2031–57.
29. Boyer KA, Beaupre GS, Andriacchi TP. Gender differences exist in the hip joint moments of healthy older walkers. J Biomech 2008;41:3360–5.
30. Abd-Eltawab AE, Ameer MA, Eladl MA, El-Sherbiny M, Ebrahim HA, Elsherbini DMA. Sexual dimorphism impact on the ground reaction force acting on the mediolateral direction during level walking: hip abductor muscle biomechanics and its correlation to GRF moment arm. Front Bioeng Biotechnol 2022;10, 863194.
31. Huseynov A, Zollikofer CP, Coudyzer W, Gascho D, Kellenberger C, Hinzpeter R, *et al*. Developmental evidence for obstetric adaptation of the human female pelvis. Proc Natl Acad Sci U S A 2016;113:5227–32.
32. Jones G, Glisson M, Hynes K, Cicuttini F. Sex and site differences in cartilage development: a possible explanation for variations in knee osteoarthritis in later life. Arthritis Rheum 2000;43:2543–9.
33. Chauvin NA, Ho-Fung V, Jaramillo D, Edgar JC, Weiss PF. Ultrasound of the joints and entheses in healthy children. Pediatr Radiol 2015;45:1344–54.
34. Berry PA, Wluka AE, Davies-Tuck ML, Wang Y, Strauss BJ, Dixon JB, *et al*. Sex differences in the relationship between bone mineral density and tibial cartilage volume. Rheumatology (Oxford) 2011;50:563–8.
35. Cicuttini FM, Wluka A, Bailey M, O'Sullivan R, Poon C, Yeung S, *et al*. Factors affecting knee cartilage volume in healthy men. Rheumatology (Oxford) 2003;42:258–62.

36. Griggs RC, Kingston W, Jozefowicz RF, Herr BE, Forbes G, Halliday D. Effect of testosterone on muscle mass and muscle protein synthesis. J Appl Physiol (1985) 1989;66:498–503.
37. Vingren JL, Kraemer WJ, Ratamess NA, Anderson JM, Volek JS, Maresh CM. Testosterone physiology in resistance exercise and training: the up-stream regulatory elements. Sports Med 2010;40:1037–53.
38. Chidi-Ogbolu N, Baar K. Effect of estrogen on musculoskeletal performance and injury risk. Front Physiol 2018;9:1834.
39. Collins BC, Laakkonen EK, Lowe DA. Aging of the musculoskeletal system: how the loss of estrogen impacts muscle strength. Bone 2019;123:137–44.
40. Elliott-Sale KJ. The relationship between oestrogen and muscle strength: a current perspective. Rev Bras Educ Fís Esporte 2014;28:339–49.
41. Ruff C. Growth in bone strength, body size, and muscle size in a juvenile longitudinal sample. Bone 2003;33:317–29.
42. Yoshizawa S, Ishizaki T, Honda H. Physical fitness of children aged 5 and 6 years. J Hum Ergol (Tokyo) 1977;6:41–51.
43. Faber SC, Eckstein F, Lukasz S, Mühlbauer R, Hohe J, Englmeier KH, *et al*. Gender differences in knee joint cartilage thickness, volume and articular surface areas: assessment with quantitative three-dimensional MR imaging. Skeletal Radiol 2001;30:144–50.
44. Eckstein F, Siedek V, Glaser C, Al-Ali D, Englmeier KH, Reiser M, *et al*. Correlation and sex differences between ankle and knee cartilage morphology determined by quantitative magnetic resonance imaging. Ann Rheum Dis 2004;63:1490–5.
45. Brenneman Wilson EC, Gatti AA, Maly MR. A new technique to evaluate the impact of running on knee cartilage deformation by region. Magma 2021;34:593–603.
46. Ding C, Cicuttini F, Scott F, Glisson M, Jones G. Sex differences in knee cartilage volume in adults: role of body and bone size, age and physical activity. Rheumatology (Oxford) 2003;42:1317–23.
47. Hanna FS, Teichtahl AJ, Wluka AE, Wang Y, Urquhart DM, English DR, *et al*. Women have increased rates of cartilage loss and progression of cartilage defects at the knee than men: a gender study of adults without clinical knee osteoarthritis. Menopause 2009;16:666–70.
48. Eckstein F, Milz S, Anetzberger H, Putz R. Thickness of the subchondral mineralised tissue zone (SMZ) in normal male and female and pathological human patellae. J Anat 1998;192(Pt 1):81–90.
49. Ding C, Cicuttini F, Blizzard L, Scott F, Jones G. A longitudinal study of the effect of sex and age on rate of change in knee cartilage volume in adults. Rheumatology (Oxford) 2007;46:273–9.
50. Eckstein F, Maschek S, Wirth W, Hudelmaier M, Hitzl W, Wyman B, *et al*. One year change of knee cartilage morphology in the first release of participants from the Osteoarthritis Initiative progression subcohort: association with sex, body mass index, symptoms and radiographic osteoarthritis status. Ann Rheum Dis 2009;68:674–9.
51. Beck J, Wood A, Bennet A, Jackson N. Magnetic resonance image (MRI) measurements of lateral discoid meniscus (LDM) in pediatric patients match adult lateral discoid meniscus definitions. Orthop J Sports Med 2022;10:23259671215232596004 9.
52. Chen G, Zhang Z, Li J. Symptomatic discoid lateral meniscus: a clinical and arthroscopic study in a Chinese population. BMC Musculoskelet Disord 2016;17:329.
53. Su L, Bennett A, Combs K, Torrez TW, Pham DC, Jackson NJ, *et al*. Arthroscopic treatment of symptomatic discoid lateral meniscus and nondiscoid meniscus in adolescent patients. Am J Sports Med 2022;50:3805–11.
54. Bedoya MA, Barrera CA, Chauvin NA, Delgado J, Jaramillo D, Ho-Fung VM. Normal meniscal dimensions at different patient ages—MRI evaluation. Skelet Radiol 2019;48:595–603.
55. Arnoczky SP. Anatomy of the anterior cruciate ligament. Clin Orthop Relat Res 1983;172:19–25.
56. Baek GH, Carlin GJ, Vogrin TM, Woo SL, Harner CD. Quantitative analysis of collagen fibrils of human cruciate and meniscofemoral ligaments. Clin Orthop Relat Res (1976-2007) 1998;357:205–11.
57. Strocchi R, De Pasquale V, Facchini A, Raspanti M, Zaffagnini S, Marcacci M. Age-related changes in human anterior cruciate ligament (ACL) collagen fibrils. Ital J Anat Embryol 1996;101:213–20.
58. Hashemi J, Chandrashekar N, Mansouri H, Slauterbeck JR, Hardy DM. The human anterior cruciate ligament: sex differences in ultrastructure and correlation with biomechanical properties. J Orthop Res 2008;26:945–50.
59. Wang H-M, Shultz SJ, Ross SE, Henson RA, Perrin DH, Kraft RA, *et al*. Sex comparisons of in vivo anterior cruciate ligament morphometry. J Athl Train 2019;54:513–8.
60. Anderson AF, Dome DC, Gautam S, Awh MH, Rennirt GW. Correlation of anthropometric measurements, strength, anterior cruciate ligament size, and intercondylar notch characteristics to sex differences in anterior cruciate ligament tear rates. Am J Sports Med 2001;29:58–66.
61. Morales-Avalos R, Perelli S, Vilchez-Cavazos F, Castillo-Escobedo T, Peña-Martínez VM, Elizondo-Omaña R, *et al*. The morphology of the femoral footprint of the anterior cruciate ligament changes with aging from a large semicircular shape to a small flat ribbon-like shape. Knee Surg Sports Traumatol Arthrosc 2022;30:3402–13.
62. Eckstein F, Reiser M, Englmeier KH, Putz R. In vivo morphometry and functional analysis of human articular cartilage with quantitative magnetic resonance imaging–from image to data, from data to theory. Anat Embryol (Berl) 2001;203:147–73.
63. Dreiner M, Willwacher S, Kramer A, Kummel J, Frett T, Zaucke F, *et al*. Short-term response of serum cartilage oligomeric matrix protein to different types of impact loading under normal and artificial gravity. Front Physiol 2020;11:1032.
64. Harkey MS, Blackburn JT, Hackney AC, Lewek MD, Schmitz RJ, Pietrosimone B. Sex-specific associations between cartilage structure and metabolism at rest and acutely following walking and drop-landing. Cartilage 2021;13:1772s–81s.
65. Jordan JM, Luta G, Stabler T, Renner JB, Dragomir AD, Vilim V, *et al*. Ethnic and sex differences in serum levels of cartilage oligomeric matrix protein: the Johnston County Osteoarthritis Project. Arthritis Rheum 2003;48:675–81.
66. Bricca A, Wirth W, Juhl CB, Kemnitz J, Hunter DJ, Kwoh CK, *et al*. Moderate physical activity and prevention of cartilage loss in people with knee osteoarthritis: data from the osteoarthritis initiative. Arthritis Care Res (Hoboken) 2019;71:218–26.
67. Haviv B, Bronak S, Kosashvili Y, Thein R. Gender effect on the outcome of partial medial meniscectomy. Orthopedics 2015;38:e925–8.
68. Rosenberger PH, Dhabhar FS, Epel E, Jokl P, Ickovics JR. Sex differences in factors influencing recovery from arthroscopic knee surgery. Clin Orthop Relat Res 2010;468:3399–405.
69. Mitchell J, Graham W, Best TM, Collins C, Currie DW, Comstock RD, *et al*. Epidemiology of meniscal injuries in US high school athletes between 2007 and 2013. Knee Surg Sports Traumatol Arthrosc 2016;24:715–22.
70. Patel NM, Mundluru S, Beck N, Ganley TJ. Which factors increase the risk of re-operation after meniscus surgery in the skeletally immature? Orthop J Sports Med 2018;6:23259671185232590064.
71. Ding C, Martel-Pelletier J, Pelletier J-P, Abram F, Raynauld J-P, Cicuttini F, *et al*. Meniscal tear as an osteoarthritis risk factor in a largely non-osteoarthritic cohort: a cross-sectional study. J Rheumatol 2007;34:776–84.

72. Englund M, Lohmander LS. Risk factors for symptomatic knee osteoarthritis fifteen to twenty-two years after meniscectomy. Arthritis Rheum 2004;50:2811–9.
73. Fabricant PD, Rosenberger PH, Jokl P, Ickovics JR. Predictors of short-term recovery differ from those of long-term outcome after arthroscopic partial meniscectomy. Arthroscopy 2008;24:769–78.
74. Roos EM, Östenberg A, Roos H, Ekdahl C, Lohmander LS. Long-term outcome of meniscectomy: symptoms, function, and performance tests in patients with or without radiographic osteoarthritis compared to matched controls. Osteoarthr Cartil 2001;9:316–24.
75. Haviv B, Bronak S, Kosashvili Y, Thein R. Which patients are less likely to improve during the first year after arthroscopic partial meniscectomy? A multivariate analysis of 201 patients with prospective follow-up. Knee Surgery Sports Traumatol Arthrosc 2016;24:1427–31.
76. Rohde MS, Shea KG, Dawson T, Heyworth BE, Milewski MD, Edmonds EW, *et al*. Age, sex, and BMI differences related to repairable meniscal tears in pediatric and adolescent patients. Am J Sports Med 2023;51:389–97.
77. Stanley LE, Kerr ZY, Dompier TP, Padua DA. Sex differences in the incidence of anterior cruciate ligament, medial collateral ligament, and meniscal injuries in collegiate and high school sports: 2009-2010 through 2013-2014. Am J Sports Med 2016;44:1565–72.
78. Mercurio AM, Coene RP, Cook DL, Feldman L, Milewski MD. Influence of sex, race/ethnicity, and socioeconomic factors on meniscal treatment with pediatric and adolescent ACL reconstruction. Am J Sports Med 2022;50:2909–16.
79. Longo UG, Papalia R, Mazzola A, Ruzzini L, De Salvatore S, Piergentili I, *et al*. Epidemiology of pediatric meniscectomy: a nationwide study in Italy from 2001 to 2016. J Clin Med 2022;11:6259.
80. Roos H, Laurén M, Adalberth T, Roos EM, Jonsson K, Lohmander LS. Knee osteoarthritis after meniscectomy: prevalence of radiographic changes after twenty-one years, compared with matched controls. Arthritis Rheum 1998;41:687–93.
81. Brophy RH, Farooq Rai M, Zhang Z, Torgomyan A, Sandell LJ. Molecular analysis of age and sex-related gene expression in meniscal tears with and without a concomitant anterior cruciate ligament tear. J Bone Joint Surg 2012;94:385–93.
82. Englund M, Guermazi A, Gale D, Hunter DJ, Aliabadi P, Clancy M, *et al*. Incidental meniscal findings on knee MRI in middle-aged and elderly persons. N Engl J Med 2008;359:1108–15.
83. Lange AK, Fiatarone Singh MA, Smith RM, Foroughi N, Baker MK, Shnier R, *et al*. Degenerative meniscus tears and mobility impairment in women with knee osteoarthritis. Osteoarthr Cartil 2007;15:701–8.
84. Ding C, Martel-Pelletier J, Pelletier JP, Abram F, Raynauld JP, Cicuttini F, *et al*. Meniscal tear as an osteoarthritis risk factor in a largely non-osteoarthritic cohort: a cross-sectional study. J Rheumatol 2007;34:776–84.
85. Brenner JS. Council on Sports Medicine and Fitness. Sports specialization and intensive training in young athletes. Pediatrics 2016;138:e20162148.
86. Fabricant PD, Lakomkin N, Cruz AI, Spitzer E, Lawrence JTR, Marx RG. Early ACL reconstruction in children leads to less meniscal and articular cartilage damage when compared with conservative or delayed treatment. J ISAKOS 2016;1:10–5.
87. Fabricant PD, Lakomkin N, Sugimoto D, Tepolt FA, Stracciolini A, Kocher MS. Youth sports specialization and musculoskeletal injury: a systematic review of the literature. Phys Sportsmed 2016;44:257–62.
88. Jayanthi NA, LaBella CR, Fischer D, Pasulka J, Dugas LR. Sports-specialized intensive training and the risk of injury in young athletes: a clinical case-control study. Am J Sports Med 2015;43:794–801.
89. Biddle SJ, Asare M. Physical activity and mental health in children and adolescents: a review of reviews. Br J Sports Med 2011;45:886–95.
90. Janssen I, Leblanc AG. Systematic review of the health benefits of physical activity and fitness in school-aged children and youth. Int J Behav Nutr Phys Act 2010;7:40.
91. Adirim TA, Cheng TL. Overview of injuries in the young athlete. Sports Med 2003;33:75–81.
92. Dodwell ER, Lamont LE, Green DW, Pan TJ, Marx RG, Lyman S. 20 years of pediatric anterior cruciate ligament reconstruction in New York State. Am J Sports Med 2014;42:675–80.
93. Kilcoyne KG, Dickens JF, Haniuk E, Cameron KL, Owens BD. Epidemiology of meniscal injury associated with ACL tears in young athletes. Orthopedics 2012;35:208–12.
94. Suter LG, Smith SR, Katz JN, Englund M, Hunter DJ, Frobell R, *et al*. Projecting lifetime risk of symptomatic knee osteoarthritis and total knee replacement in individuals sustaining a complete anterior cruciate ligament tear in early adulthood. Arthritis Care Res (Hoboken) 2017;69:201–8.
95. Whittaker JL, Woodhouse LJ, Nettel-Aguirre A, Emery CA. Outcomes associated with early post-traumatic osteoarthritis and other negative health consequences 3-10 years following knee joint injury in youth sport. Osteoarthr Cartil 2015;23:1122–9.
96. Matzkin E, Garvey K. Youth sports specialization: does practice make perfect? NASN Sch Nurse 2019;34:100–3.
97. Popkin CA, Bayomy AF, Ahmad CS. Early sport specialization. J Am Acad Orthop Surg 2019;27:e995–1000.
98. Beck NA, Lawrence JTR, Nordin JD, DeFor TA, Tompkins M. ACL tears in school-aged children and adolescents over 20 years. Pediatrics 2017;139:e20161877.
99. Mall NA, Chalmers PN, Moric M, Tanaka MJ, Cole BJ, Bach Jr. BR, *et al*. Incidence and trends of anterior cruciate ligament reconstruction in the United States. Am J Sports Med 2014;42:2363–70.
100. King E, Richter C, Daniels KAJ, Franklyn-Miller A, Falvey E, Myer GD, *et al*. Biomechanical but not strength or performance measures differentiate male athletes who experience ACL reinjury on return to level 1 sports. Am J Sports Med 2021;49:918–27.
101. Paterno MV, Rauh MJ, Schmitt LC, Ford KR, Hewett TE. Incidence of second ACL injuries 2 years after primary ACL reconstruction and return to sport. Am J Sports Med 2014;42:1567–73.
102. Nester JR, Torino D, Sylvestre D, Young A, Ney SM, Fernandez MM, *et al*. Risk of reoperation after primary anterior cruciate ligament reconstruction in children and adolescents. J Orthop Surg (Hong Kong) 2022;30. 10225536221122340.
103. Brodeur PG, Licht AH, Modest JM, Testa EJ, Gil JA, Cruz Jr. AI. Epidemiology and revision rates of pediatric ACL reconstruction in New York State. Am J Sports Med 2022;50:1222–8.
104. Bloom DA, Wolfert AJ, Michalowitz A, Jazrawi LM, Carter CW. ACL injuries aren't just for girls: the role of age in predicting pediatric ACL injury. Sports Health 2020;12:559–63.
105. Bram JT, Magee LC, Mehta NN, Patel NM, Ganley TJ. Anterior cruciate ligament injury incidence in adolescent athletes: a systematic review and meta-analysis. Am J Sports Med 2021;49:1962–72.
106. Arendt E, Dick R. Knee injury patterns among men and women in collegiate basketball and soccer. NCAA data and review of literature. Am J Sports Med 1995;23:694–701.
107. Hewett TE, Myer GD, Ford KR. Anterior cruciate ligament injuries in female athletes: part 1, mechanisms and risk factors. Am J Sports Med 2006;34:299–311.

108. Lal S, Hoch AZ. Factors that affect the young female athlete. Phys Med Rehabil Clin N Am 2007;18:361–83. (vii).
109. Renstrom P, Ljungqvist A, Arendt E, Beynnon B, Fukubayashi T, Garrett W, *et al*. Non-contact ACL injuries in female athletes: an International Olympic Committee current concepts statement. Br J Sports Med 2008;42:394–412.
110. Hewett TE, Myer GD, Ford KR. Decrease in neuromuscular control about the knee with maturation in female athletes. J Bone Joint Surg Am 2004;86:1601–8.
111. Hewett TE, Myer GD, Kiefer AW, Ford KR. Longitudinal increases in knee abduction moments in females during adolescent growth. Med Sci Sports Exerc 2015;47:2579–85.
112. Andernord D, Desai N, Bjornsson H, Ylander M, Karlsson J, Samuelsson K. Patient predictors of early revision surgery after anterior cruciate ligament reconstruction: a cohort study of 16,930 patients with 2-year follow-up. Am J Sports Med 2015;43:121–7.
113. Kaeding CC, Pedroza AD, Reinke EK, Huston LJ, Consortium M, Spindler KP. Risk factors and predictors of subsequent ACL injury in either knee after ACL reconstruction: prospective analysis of 2488 primary ACL reconstructions from the MOON cohort. Am J Sports Med 2015;43:1583–90.
114. Persson A, Fjeldsgaard K, Gjertsen JE, Kjellsen AB, Engebretsen L, Hole RM, *et al*. Increased risk of revision with hamstring tendon grafts compared with patellar tendon grafts after anterior cruciate ligament reconstruction: a study of 12,643 patients from the Norwegian Cruciate Ligament Registry, 2004-2012. Am J Sports Med 2014;42:285–91.
115. Swartz EE, Decoster LC, Russell PJ, Croce RV. Effects of developmental stage and sex on lower extremity kinematics and vertical ground reaction forces during landing. J Athl Train 2005;40:9–14.
116. Chia L, Myer GD, Hewett TE, McKay MJ, Sullivan J, Ford KR, *et al*. When puberty strikes: longitudinal changes in cutting kinematics in 172 high-school female athletes. J Sci Med Sport 2021;24:1290–5.
117. Holden S, Boreham C, Doherty C, Wang D, Delahunt E. Clinical assessment of countermovement jump landing kinematics in early adolescence: sex differences and normative values. Clin Biomech (Bristol, Avon) 2015;30:469–74.
118. Hewett TE, Ford KR, Hoogenboom BJ, Myer GD. Understanding and preventing acl injuries: current biomechanical and epidemiologic considerations - update 2010. N Am J Sports Phys Ther 2010;5:234–51.
119. Pappas E, Shiyko MP, Ford KR, Myer GD, Hewett TE. Biomechanical deficit profiles associated with ACL injury risk in female athletes. Med Sci Sports Exerc 2016;48:107–13.
120. Holden S, Boreham C, Delahunt E. Sex differences in landing biomechanics and postural stability during adolescence: a systematic review with meta-analyses. Sports Med 2016;46:241–53.
121. Ford KR, Nguyen AD, Dischiavi SL, Hegedus EJ, Zuk EF, Taylor JB. An evidence-based review of hip-focused neuromuscular exercise interventions to address dynamic lower extremity valgus. Open Access J Sports Med 2015;6:291–303.
122. Hewett TE, Myer GD, Ford KR, Heidt Jr. RS, Colosimo AJ, McLean SG, *et al*. Biomechanical measures of neuromuscular control and valgus loading of the knee predict anterior cruciate ligament injury risk in female athletes: a prospective study. Am J Sports Med 2005;33:492–501.
123. Wilczynski B, Zorena K, Slezak D. Dynamic knee valgus in single-leg movement tasks. potentially modifiable factors and exercise training options. A literature review. Int J Environ Res Public Health 2020;17:8208–25.
124. Otsuki R, Del Bel MJ, Benoit DL. Sex differences in muscle activation patterns associated with anterior cruciate ligament injury during landing and cutting tasks: a systematic review. J Electromyogr Kinesiol 2021;60, 102583.
125. Myer GD, Chu DA, Brent JL, Hewett TE. Trunk and hip control neuromuscular training for the prevention of knee joint injury. Clin Sports Med 2008;27:425–48. ix.
126. Sugimoto D, Mattacola CG, Bush HM, Thomas SM, Foss KD, Myer GD, *et al*. Preventive neuromuscular training for young female athletes: comparison of coach and athlete compliance rates. J Athl Train 2017;52:58–64.
127. Zebis MK, Andersen LL, Brandt M, Myklebust G, Bencke J, Lauridsen HB, *et al*. Effects of evidence-based prevention training on neuromuscular and biomechanical risk factors for ACL injury in adolescent female athletes: a randomised controlled trial. Br J Sports Med 2016;50:552–7.
128. Bryant-Greenwood GD, Yamamoto SY. Control of peripartal collagenolysis in the human chorion-decidua. Am J Obstet Gynecol 1995;172:63–70.
129. Weiss G. Relaxin in the male. Biol Reprod 1989;40:197–200.
130. Dragoo JL, Lee RS, Benhaim P, Finerman GA, Hame SL. Relaxin receptors in the human female anterior cruciate ligament. Am J Sports Med 2003;31:577–84.
131. Eich GF, Babyn P, Giedion A. Pediatric pelvis: radiographic appearance in various congenital disorders. RadioGraphics 1992;12:467–84.
132. Dragoo JL, Castillo TN, Braun HJ, Ridley BA, Kennedy AC, Golish SR. Prospective correlation between serum relaxin concentration and anterior cruciate ligament tears among elite collegiate female athletes. Am J Sports Med 2011;39:2175–80.
133. Ballabriga A. Morphological and physiological changes during growth: an update. Eur J Clin Nutr 2000;54(Suppl 1):S1–6.
134. Jenks MZ, Fairfield HE, Johnson EC, Morrison RF, Muday GK. Sex steroid hormones regulate leptin transcript accumulation and protein secretion in 3T3-L1 cells. Sci Rep 2017;7:8232.
135. Elbers JM, Asscheman H, Seidell JC, Frolich M, Meinders AE, Gooren LJ. Reversal of the sex difference in serum leptin levels upon cross-sex hormone administration in transsexuals. J Clin Endocrinol Metab 1997;82:3267–70.
136. Ding C, Parameswaran V, Cicuttini F, Burgess J, Zhai G, Quinn S, *et al*. Association between leptin, body composition, sex and knee cartilage morphology in older adults: the Tasmanian older adult cohort (TASOAC) study. Ann Rheum Dis 2008;67:1256–61.
137. Costanzo M, Caterino M, Sotgiu G, Ruoppolo M, Franconi F, Campesi I. Sex differences in the human metabolome. Biol Sex Differ 2022;13:30.
138. Rist MJ, Roth A, Frommherz L, Weinert CH, Kruger R, Merz B, *et al*. Metabolite patterns predicting sex and age in participants of the Karlsruhe Metabolomics and Nutrition (KarMeN) study. PLoS One 2017;12, e0183228.
139. Ruoppolo M, Campesi I, Scolamiero E, Pecce R, Caterino M, Cherchi S, *et al*. Serum metabolomic profiles suggest influence of sex and oral contraceptive use. Am J Transl Res 2014;6:614–24.
140. Mittelstrass K, Ried JS, Yu Z, Krumsiek J, Gieger C, Prehn C, *et al*. Discovery of sexual dimorphisms in metabolic and genetic biomarkers. PLoS Genet 2011;7, e1002215.
141. Slupsky CM, Rankin KN, Wagner J, Fu H, Chang D, Weljie AM, *et al*. Investigations of the effects of gender, diurnal variation, and age in human urinary metabolomic profiles. Anal Chem 2007;79:6995–7004.
142. Fan S, Yeon A, Shahid M, Anger JT, Eilber KS, Fiehn O, *et al*. Sex-associated differences in baseline urinary metabolites of healthy adults. Sci Rep 2018;8, 11883.
143. Thevenot EA, Roux A, Xu Y, Ezan E, Junot C. Analysis of the human adult urinary metabolome variations with age, body mass index, and gender by implementing a comprehensive workflow for univariate and OPLS statistical analyses. J Proteome Res 2015;14:3322–35.

144. Brosnan ME, Brosnan JT. The role of dietary creatine. Amino Acids 2016;48:1785–91.
145. Wyss M, Kaddurah-Daouk R. Creatine and creatinine metabolism. Physiol Rev 2000;80:1107–213.
146. Zhai G, Sun X, Randell EW, Liu M, Wang N, Tolstykh I, *et al*. Phenylalanine is a novel marker for radiographic knee osteoarthritis progression: the MOST study. J Rheumatol 2021;48:123–8.
147. Zhai G, Wang-Sattler R, Hart DJ, Arden NK, Hakim AJ, Illig T, *et al*. Serum branched-chain amino acid to histidine ratio: a novel metabolomic biomarker of knee osteoarthritis. Ann Rheum Dis 2010;69:1227–31.
148. Xu B, Su H, Wang R, Wang Y, Zhang W. Metabolic networks of plasma and joint fluid base on differential correlation. PLoS One 2021;16, e0247191.
149. Idelevich A, Kerschnitzki M, Shahar R, Monsonego-Ornan E. 1,25(OH)2D3 alters growth plate maturation and bone architecture in young rats with normal renal function. PLoS One 2011;6, e20772.
150. **Welhaven HD, Welfley AH, Pershad P, Satalich J, O'Connell R, Bothner B, *et al*. Metabolomic phenotypes reflect patient sex and injury status: a cross-sectional analysis of human synovial fluid. bioRxiv 2023;2023.2002.2003.527040.** https://doi.org/10.1101/2023.02.03.527040.
151. Varlamov O, Bethea CL, Roberts Jr. CT. Sex-specific differences in lipid and glucose metabolism. Front Endocrinol (Lausanne) 2014;5:241.
152. Agarwal A, Sengupta P, Durairajanayagam D. Role of L-carnitine in female infertility. Reprod Biol Endocrinol 2018;16:5.
153. Chrisostomo KR, Skare TL, Chrisostomo HR, Barbosa EJL, Nisihara R. Transwomen and bone mineral density: a cross-sectional study in Brazilian population. Br J Radiol 2020;93:20190935.
154. Davidge-Pitts C, Clarke BL. Transgender bone health. Maturitas 2019;127:35–42.
155. Van Caenegem E, T'Sjoen G. Bone in trans persons. Curr Opin Endocrinol Diabetes Obes 2015;22:459–66.
156. Meriggiola MC, Armillotta F, Costantino A, Altieri P, Saad F, Kalhorn T, *et al*. Effects of testosterone undecanoate administered alone or in combination with letrozole or dutasteride in female to male transsexuals. J Sex Med 2008;5:2442–53.
157. Ford K, Huggins E, Sheean P. Characterising body composition and bone health in transgender individuals receiving gender-affirming hormone therapy. J Hum Nutr Diet 2022;35:1105–14.
158. Van Caenegem E, Wierckx K, Taes Y, Schreiner T, Vandewalle S, Toye K, *et al*. Preservation of volumetric bone density and geometry in trans women during cross-sex hormonal therapy: a prospective observational study. Osteoporos Int 2015;26:35–47.
159. McGovern MM, Lowenstein NA, Matzkin EG. Sports medicine considerations when caring for the transgender athlete. Arthrosc Sports Med Rehabil 2023;5, 100736.
160. Miro EW, Taylor E, Curtin A, Newman MG, Ose D, Knox J. Cumulative incidence of all-cause knee injury, concussion, and stress fracture among transgender patients on gender-affirming hormone therapy: an exploratory retrospective cohort study. Int J Environ Res Public Health 2023;20:7060–71.
161. Dubon ME, Abbott K, Carl RL. Care of the transgender athlete. Curr Sports Med Rep 2018;17:410–8.
162. Glass N, Segal NA, Sluka KA, Torner JC, Nevitt MC, Felson DT, *et al*. Examining sex differences in knee pain: the multicenter osteoarthritis study. Osteoarthr Cartil 2014;22:1100–6.
163. Bartley EJ, King CD, Sibille KT, Cruz-Almeida Y, Riley 3rd JL, Glover TL, *et al*. Enhanced pain sensitivity among individuals with symptomatic knee osteoarthritis: potential sex differences in central sensitization. Arthritis Care Res (Hoboken) 2016;68:472–80.
164. De Jongh RF, Vissers KC, Meert TF, Booij L, De Deyne CS, Heylen RJ. The role of interleukin-6 in nociception and pain. Anesth Analg 2003;96:1096–103.
165. Mun CJ, Letzen JE, Nance S, Smith MT, Khanuja HS, Sterling RS, *et al*. Sex differences in interleukin-6 responses over time following laboratory pain testing among patients with knee osteoarthritis. J Pain 2020;21:731–41.
166. Perruccio AV, Badley EM, Power JD, Canizares M, Kapoor M, Rockel J, *et al*. Sex differences in the relationship between individual systemic markers of inflammation and pain in knee osteoarthritis. Osteoarthr Cartil Open 2019;1, 100004.
167. Valdrighi N, Vago JP, Blom AB, van de Loo FAJ, Blaney Davidson EN. Innate immunity at the core of sex differences in osteoarthritic pain? Front Pharmacol 2022;13, 881500.
168. Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol 2016;16:626–38.
169. **Forsyth KS, Jiwrajka N, Lovell CD, Toothacre NE, Anguera MC. The conneXion between sex and immune responses. Nat Rev Immunol 2024.** https://doi.org/10.1038/s41577-024-00996-9
170. Dou DR, Zhao Y, Belk JA, Zhao Y, Casey KM, Chen DC, *et al*. Xist ribonucleoproteins promote female sex-biased autoimmunity. Cell 2024;187:733–749.e716.
171. Yan XT, Lu JM, Wang Y, Cheng XL, He XH, Zheng WZ, *et al*. XIST accelerates neuropathic pain progression through regulation of miR-150 and ZEB1 in CCI rat models. J Cell Physiol 2018;233:6098–106.
172. Yoshimura R, Nomura S. Co-ingestion of glutamine and leucine synergistically promotes mTORC1 activation. Sci Rep 2022;12, 15870.
173. **Wang N, Lu Y, Rothrauff BB, Zheng A, Lamb A, Yan Y, *et al*. Mechanotransduction pathways in articular chondrocytes and the emerging role of estrogen receptor-α. Bone Research 2023;11.** https://doi.org/10.1038/s41413-023-00248-x
174. Elbaradie KB, Wang Y, Boyan BD, Schwartz Z. Sex-specific response of rat costochondral cartilage growth plate chondrocytes to 17β-estradiol involves differential regulation of plasma membrane associated estrogen receptors. Biochim Biophys Acta 2013;1833:1165–72.
175. Stewart HL, Gilbert D, Stefanovski D, Garman Z, Albro MB, Bais M, *et al*. A missed opportunity: a scoping review of the effect of sex and age on osteoarthritis using large animal models. Osteoarthritis Cartilage 2024;32:501–13.