# Combined hormonal contraceptive use is not protective against musculoskeletal conditions or injuries: a systematic review with data from 5 million females

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## ABSTRACT

**Objective** Assess the association between combined hormonal contraceptives (CHC) use and musculoskeletal tissue pathophysiology, injuries or conditions.

**Design** Systematic review with semiquantitative analyses and certainty of evidence assessment, guided by the Grading of Recommendations Assessment, Development and Evaluation approach.

**Data Sources** MEDLINE, EMBASE, CENTRAL, SPORTDiscus, CINAHL searched from inception to April 2022.

**Eligibility** Intervention and cohort studies that assessed the association between new or ongoing use of CHC and an outcome of musculoskeletal tissue pathophysiology, injury or condition in postpubertal premenopausal females.

**Results** Across 50 included studies, we assessed the effect of CHC use on 30 unique musculoskeletal outcomes (75% bone related). Serious risk of bias was judged present in 82% of studies, with 52% adequately adjusting for confounding. Meta-analyses were not possible due to poor outcome reporting, and heterogeneity in estimate statistics and comparison conditions. Based on semiquantitative synthesis, there is low certainty evidence that CHC use was associated with elevated future fracture risk (risk ratio 1.02–1.20) and total knee arthroplasty (risk ratio 1.00–1.36). There is very low certainty evidence of unclear relationships between CHC use and a wide range of bone turnover and bone health outcomes. Evidence about the effect of CHC use on musculoskeletal tissues beyond bone, and the influence of CHC use in adolescence versus adulthood, is limited.

**Conclusion** Given a paucity of high certainty evidence that CHC use is protective against musculoskeletal pathophysiology, injury or conditions, it is premature and inappropriate to advocate, or prescribe CHC for these purposes.

**PROSPERO registration number** This review was registered on PROSPERO CRD42021224582 on 8 January 2021.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Fifty per cent of young females start combined hormonal contraceptive (CHC) use for non-contraceptive reasons.
⇒ Adolescent CHC use may interfer with gain to peak bone mass and may delay the development of ovulatory menstrual cycles.
⇒ Some proponents of CHC suggest they may be protective against musculoskeletal injuries including anterior cruciate ligament tears.

### WHAT THIS STUDY ADDS

⇒ There is low certainty evidence that CHC use is associated with higher future fracture risk by up to 1.20 times, and total knee arthroplasty risk by up to 1.36 times.
⇒ There is a paucity of high certainty evidence about the effects of CHC use on non-bone-related musculoskeletal injuries or conditions (ie, cartilage, ligament, muscle, tendon) or the influence of CHC use in adolescence versus adulthood.
⇒ Currently, there is insufficient high-quality evidence to make recommendations about the protective or negative effects of CHC use on musculoskeletal health.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Health care providers should use this information and consider patient's individual needs/priorities when prescribing CHC for non-contraceptive purposes.
⇒ It is premature to prescribe or pressure adolescent females to use CHCs to prevent musculoskeletal injuries or conditions.
⇒ Future research should test the cause-effect relationship between new CHC use and musculoskeletal injuries or conditions while accounting for confounding and other sources of bias that can distort findings (ie, self-selection).

## BACKGROUND

In 2019, the Global Burden of Disease study estimated that 1.7 billion people, or 22% of the world's population, were affected by musculoskeletal (MSK) conditions.[1] MSK conditions reduce physical function, impair quality of life and are a significant cause of physical disability,[2] compromising mental health and increasing the risk of other chronic health conditions and opioid use.[3]

The lifelong burden of MSK conditions is greater in women than men. Women are more likely to

report MSK pain than men,[4] and they experience higher rates of chronic MSK conditions such as osteoarthritis.[5] Girls and women also have a greater risk of sport and recreation-related MSK injury.[6] For example, women are up to 2–5 times more likely to experience a knee ligament injury than men playing the same sport.[7] Once they have an MSK condition, women also account for greater expenditures related to pharmaceuticals, treatment of comorbidities and caregiving compared with men.[8] This disparity is multifactorial and associated with both biological (eg, anatomical predispositions, movement characteristics, tissue morphology) and sociocultural (eg, family roles, access to healthcare, type, and level of physical activity participation, exercise preference, and life events) factors.[9 10]

One biological factor that is alleged to contribute to the increased incidence of MSK conditions in females is their menstrual status.[11–17] This has led some to suggest that combined hormonal contraceptives (CHC) could be used to 'control' or 'stabilise' the menstrual cycle as a means to reduce the burden of MSK conditions. Unfortunately, much of the research informing non-contraceptive uses of CHC is based on hypothesis generating (ie, case series, cross-sectional, case–control or syntheses of these) not hypothesis testing studies (ie, cohort, intervention or syntheses of these).[12 14 17] In contrast, CHC use negatively impacts the ovulatory cycle,[18] peak bone mass[19] and is associated with reductions in bone mineral density (BMD), a precursor to osteoporosis and associated comorbidities.[19 20] The negative association between CHC use and bone health or other MSK tissue pathophysiology is rarely mentioned when encouraging CHC use to reduce injury risk.[12 14 21] Further, the long-term consequence of prolonged CHC use on MSK tissues and health is unknown.[22]

Given that ~50% of young females start CHC use for non-contraceptive reasons (ie, to control menstrual cycle irregularity (17%–18%), menstrual cramping (14%–26%), acne (10%–12%) and other reason including injury prevention (10%),[20] it is essential these decisions are evidence guided. The objective of this systematic review was to assess the association between CHC use and MSK tissue (ie, tendon, ligament, muscle, cartilage and bone) pathophysiology, injury and conditions based on a critical appraisal of existing studies. Given that adolescence is a key period in the life cycle for MSK tissue accrual,[23] and the effects of CHC may be unique to age groups,[19] a secondary objective was to consider adolescent (≤18 years of age) or adult (>18 years) CHC use.

## METHODS

### Framework

The Cochrane Handbook[24] guided the conduct, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[25] and PRISMA-Search extension guided reporting of this review.[26]

### Data sources and search

Relevant studies were identified by searching five databases (Medline-Ovid, EMBASE-Ovid, CENTRAL-Ovid, SPORTDiscus-EBSCOhost, CINAHL-EBSCOhost). Search strategies consisted of medical subject headings and text words related to CHC, the concept of MSK tissues, injuries or conditions with limitations for human participants, and the English language. The Medline search strategy was developed in consultation with a health sciences librarian and adapted for other databases. The search strategy for Medline-Ovid is available in online supplemental file 1. Searches were run on 28 December 2020, and updated on 27 April 2022. Searches were documented and reference lists of identified systematic reviews and included studies were handsearched to identify additional relevant records. Records were transferred to a reference management software (RefWorks, ProQuest, USA).

### Eligibility

We included studies that reported primary data from humans that assessed the association between CHC use by postpubertal, premenopausal females with normal menstrual status (ie, not amenorrhoea or oligomenorrhoea), and MSK tissue (ie, bone, joint, ligament, muscle, tendon and associated connective tissues) pathophysiology, injuries or conditions. CHC use was operationalised as new or ongoing use of a pharmacologic dose of synthetic ethinyl estradiol (EE) in combination with progestin in pill, patch or vaginal ring forms. Studies including participants with mixed menstrual status were included if data were sufficiently disaggregated (eg, normal menses vs oligomenorrhoea). Pathophysiology was defined as disordered physiological processes, and a condition as a disease or lesion that negatively affects the structure or function of a tissue. We included all defined outcomes of MSK injury regardless of onset type (ie, acute or chronic) or time loss. Analyses reporting data from the same parent study were included if they assessed different CHC exposures (ie, preparation or dose), MSK outcomes or presented data at different time points. We excluded studies with participants who had a condition (eg, anorexia nervosa) or were undergoing treatment that could affect reproductive hormone levels (eg, Turner syndrome) that assessed an outcome of MSK performance only (eg, muscle strength, exercise-induced muscle damage, $VO_2$ max, electromyography activity and functional performance), and contraceptive preparations that included oestrogen only, progestin-only or were implanted or intrauterine devices (IUD), as these devices are either non-hormonal (IUD) or progestin-only (implant, IUD).

### Study selection

After manual identification and removal of duplicates in Refworks (LW), records were imported into a screening and data extraction platform (Covidence, Veritas Health Innovation). Authors (LW, JML, KS, SG, AS and JLW) independently screened titles and corresponding abstracts in duplicate to determine potentially relevant records, followed by full-text review to determine final record selection. A third author resolved any disagreements at all stages if the two primary reviewers could not reach a consensus. All decisions and reasons for inclusion and exclusion were recorded in Covidence.

### Data extraction

Authors (LW, JML, KS, SG, AS and JLW) independently performed data extraction, in duplicate using a structured data extraction form (Covidence). Data extraction included: study information (first author, publication date, title, location, design, population description, sample size, participants per group, funding sources and conflicts of interest); participant characteristics (sample description, and age at enrolment and subsequent follow-up); CHC details (dosage and chemical compound, method of delivery and length of prestudy and within-study use); follow-up duration (start and end date); MSK outcomes (ie, outcome and measurement method) and results (unadjusted and adjusted group level values and between-group comparisons as available).

### Study quality and risk of bias

Authors (LW, JML, KS, SG, AS, JLW) independently assessed study quality and risk of bias across included studies in duplicate

using the Downs and Black Quality Assessment Tool (DBQAT).[27] This tool assigns an individual score calculated out of 32 total points for each study (11 points for reporting, 3 points for external validity, 7 points for bias, 6 points for confounding and 5 for power: see online supplemental file.[27] Disagreements were resolved through consensus or third author when needed. The potential for selection, attrition and measurement bias, and bias due to confounding and statistical analysis were rated as 'not serious' (≥12/13 points), 'serious' (11/13 points) or 'very serious' (≤10/13 points) using questions 14–26 to facilitate semiquantitative synthesis (see Semiquantitative synthesis below).[27]

## Data syntheses

Data synthesis involved three steps. First, we identified and categorised unique MSK tissue (ie, bone, joint, ligament, muscle, tendon and associated connective tissues) pathophysiology, injuries or conditions assessed across the included studies. Second, within each MSK outcome category, studies were grouped based on similar statistics of effect (eg, ORs, HRs, mean difference), follow-up times and age. If no statistic of effect was reported, it was calculated (Cohen's d for continuous outcomes, ORs for dichotomous outcomes) when the necessary raw data were available. Finally, quantitative (meta-analysis) or semiquantitative synthesis was conducted. Meta-analyses were planned a priori for MSK outcomes where there were two or more studies with similar statistics of effect, with the remaining outcomes (those with insufficient data for meta-analyses) to undergo semiquantitative analyses.[28]

### Quantitative synthesis

If possible, meta-analyses (random effects models with inverse variance weighting using restricted maximum likelihood estimation) were performed to estimate an overall mean difference (same unit continuous outcomes), standardised mean difference (different scale continuous outcomes), or OR (dichotomous outcomes), and a rating of overall certainty of the evidence was assigned as 'high' or downgraded to 'moderate', 'low' or 'very low' using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.[29]

### Semiquantitative synthesis

When meta-analyses were not possible, semiquantitative syntheses[28] were performed. This involved rating the certainty and confidence of evidence for CHC effect on each MSK outcome using a modified GRADE approach with adaptations to assess non-pooled data across five domains including study design (randomised controlled trials (RCTs) were assigned higher certainty than observational studies); risk of bias (DBQAT questions 14–26 rating); inconsistency (inconsistency in sample, methods and heterogeneity statistic results); indirectness (generalisability of findings to the target population and research question) and imprecision (95% CI width).[24] All domain ratings were considered when assigning an overall judgement of high, moderate, low or very low certainty of evidence[28] and a corresponding statement of the direction (considering consistency reported across studies) and magnitude of the treatment effect of CHC on each respective outcome. A similar approach has been used in a previous review paper by our group.[30]

## Protocol deviations

During study selection and data synthesis, we made post hoc changes to our study protocol. Specifically, we narrowed our selection criteria to hypothesis testing study designs, (ie, cohort and intervention studies including RCTs and quasi-experimental), which are less prone to bias (eg, survivor bias or reverse causality) and provide more robust evidence to inform clinical recommendations (ie, prescription of CHC to prevent MSK conditions).[31–33] We also increased the minimum number of studies with a similar effect statistic needed for meta-analyses and semiquantitative analyses to outcomes with three or more studies. This decision was based on best practice guidance,[24] to reduce the probability of ambiguous and unclear conclusions.

### Equity and diversity statement

Due to the nature of our research question, we only included studies with female participants but did not restrict on gender, geographical region, or socioeconomic or education level. The study team included diverse perspectives including those of women and men, clinicians (physiotherapists) and clinician scientists with a diversity of career stages (PhD candidates through to professor), persons of colour and members of the two-spirit, lesbian, gay, bisexual, transgender, queer and/or questioning, intersex, asexual and additional sexual orientations and gender identities (2SLGBTQIA+) community. We acknowledge that we lack perspectives of persons from middle-income to low-income geographical regions.

### Patient and public Involvement

There was no patient or public involvement in this study.

# RESULTS

Of 5438 potential records identified from database searches, 50 were included (figure 1)[34–83] incorporating data from 5 695 908 participants from 48 unique cohorts.[34 35 38–66 69–83]

## Study characteristics

Included studies are summarised in online supplemental file 1. Three were RCTs (6%),[35 43 74] 14 were quasi-experimental (28%),[46 47 49 50 52 56 62 64–66 76 77 79 83] 25 were prospective cohort studies (50%)[38–42 44 45 48 51 53–55 57 60 61 63 69–72 75 78 80–82] and 8 were retrospective cohort studies (16%).[34 36 37 58 59 67 68 73]

Six studies (12%)[39 40 64 66 71 76] assessed participants who took CHC under the age of 18 (adolescent) exclusively and 44 studies (88%)[34–38 41–63 65 67–70 72–75 77–83] assessed participants across various age ranges without stratification by age groups. The length of CHC interventions across studies ranged from 28 days51[61] to 14.5 years.[59] Prior CHC exposure across participants in the CHC intervention groups ranged from no prior use[43 46 47 49 52 57 59 64–66 71 74 77–80 83] to >97 months.[36 37] Comparison conditions included a variety of 'non-CHC users', including participants with no lifetime CHC use[80] to no CHC use 2–6 months before enrolment.[82 83] Follow-up ranged from 25 days[51] to 26 years,[36 37] with 12 studies (24%)[40 46 47 49 50 62 64–66 71 77 82] concluding at 1 year.

## MSK outcomes

Thirty unique MSK outcomes spanning five tissue types (ie, bone, tendon, joint, ligament and muscle) were identified (table 1). Seventeen outcomes (57%) were assessed in three or more studies. Of these, 14 outcomes (82%) were bone related, with lumbar spine BMD (n=23 studies, 46%)[35 39 42 46–50 52 58 62–66 71 73–75 77–79] and femoral neck BMD (n=14 studies, 28%)[35 40 42 48 50 52 58 62–64 66 71 75 78] being the most common.

## Study quality and risk of bias

The results of the study quality and risk of bias assessment are summarised in online supplemental file 1. The median DBQAT score was 15 (8-24). Only 9 studies[34 39 42 53 71–73 78 80] (18%) were judged to be at 'not serious' risk of bias, while 26 (52%)[39 40 42 43 45 53 55 57–60 63 64 67 68 71–76 78–82] were judged to

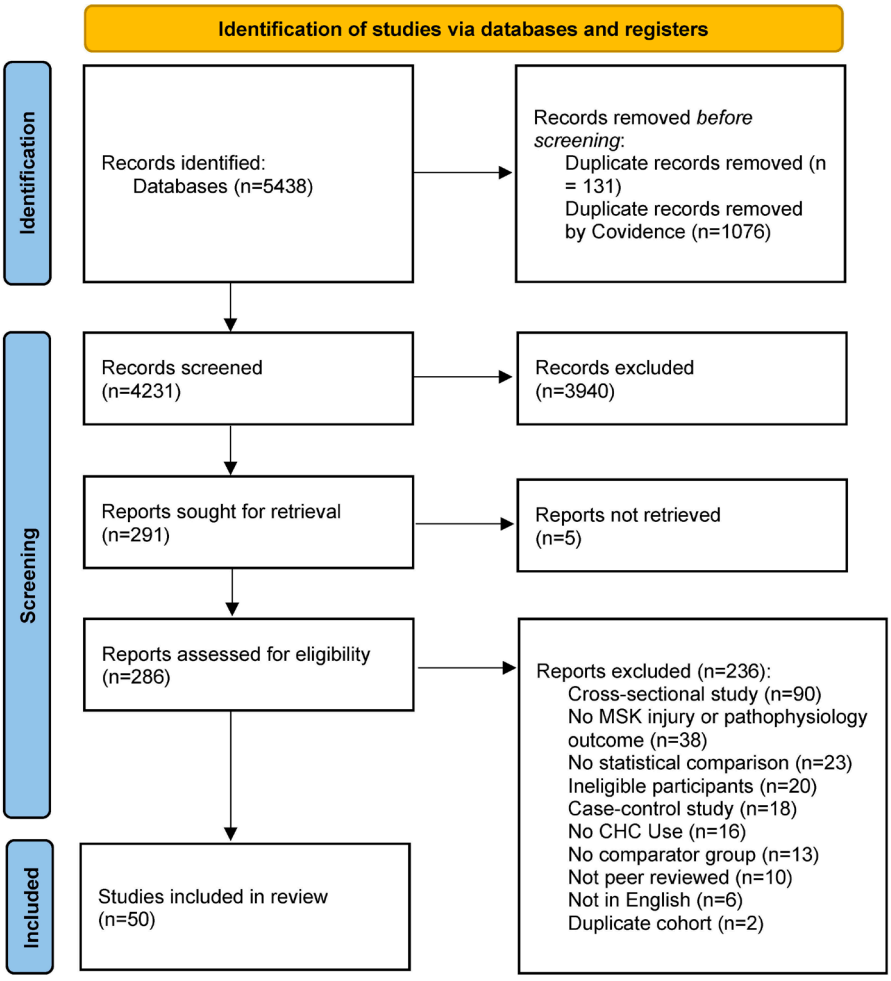


**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses[25] flow chart. CHC, combined hormonal contraceptive MSK, musculoskeletal.

adequately adjust for confounding. Concerns for data dredging were judged in 20 studies (40%),[35–37 43 45 48 55–60 62–66 69 74 81] and for selection biases in 7 studies (14%).[35 41 50 51 60 62 63]

## Effect of CHC use on MSK outcomes

All estimates of CHC effect are summarised in online supplemental file 1. Twenty-one studies (42%)[35 38 40 42 44–46 49 51 52 56 61 63 65 66 69–71 73 82 83] provided a comparison of group means, 7 (14%)[39 43 50 63 67 74 75] provided a comparison of pre-post change scores, 13 (26%)[39 42 48 62–64 66 69 70 77–80] comparison of percent pre–post change, 1 (2%)[68] an OR, 2 (4%)[57 72] rate ratios, 3 (6%)[36 37 53] risk ratios, 6 (12%)[34 55 59 60 74 81] HRs and 2 (4%)[41 47] only reported a p value.

### Meta-analyses

Despite 17 outcomes being assessed in three or more studies (table 1), meta-analyses were not possible due to poor outcome reporting (ie, missing group means and/or SD), differences in estimate statistics and significant heterogeneity in comparison condition.

### Semiquantitative analyses

The results of the semiquantitative analyses of outcomes assessed in three or more studies are summarised in table 2, with additional detail in online supplemental file 1. Due to limited stratification of data in the source studies, it was not possible to consider adolescent versus adult use. Modified GRADE ratings were consistently downgraded for risk of bias (81.3% with very serious limitations), indirectness (56.3%) and imprecision (87.5%). The evidence for two outcomes (total knee arthroplasty and any fracture) was rated low certainty, while the evidence for all other outcomes was rated very low certainty. There is low certainty evidence that CHC use may be associated with increased future fracture risk by up to 1.20 times (risk ratios range from 1.02 to 1.20),[34 37 72 81] and total knee arthroplasty by up to 1.36 times (risk ratios range from 1.00 to 1.36; see online supplemental file).[53 55 60]

## The effect of adolescent CHC use

Six studies exclusively assessed females ≤18 years old across nine outcomes.[40 64 66 71 76 80] Four studies assessed the effect of CHC use on lumbar spine and femoral neck BMD,[40 64 66 71] each, while one study assessed the other seven outcomes each (ie, whole body BMD, radius BMD, deoxypyridinoline, bone alkaline phosphatase, lumbar spine bone mineral content (BMC), whole body BMC, lean body mass). Semiquantitative synthesis indicate there is very low certainty evidence of an unclear association between CHC use and lumbar spine and femoral neck BMD.

## DISCUSSION

Semiquantitative analyses reveal low certainty evidence that CHC use may be associated with higher future fracture risk (up to 1.2 times), and total knee arthroplasty risk (up to 1.36 times). Beyond

**Table 1** Musculoskeletal outcome by number of studies

| Outcome tissue (type) | Outcome | No of studies |
|---|---|---|
| Bone (density) | Lumbar BMD | 23[35 39 40 42 46–50 52 58 62–66 71 73–75 77–79] |
| Bone (density) | Femur BMD | 14[35 40 42 48 50 52 58 62–64 66 71 75 78] |
| Bone (density) | Whole Body BMD | 8[39 42 45 58 64 73 77 82] |
| Bone (turnover; resorption) | D-PYD | 6[40 46 47 49 65 67] |
| Bone (content) | Lumbar BMC | 5[35 58 62 64 77] |
| Bone (content) | Whole Body BMC | 5[35 58 64 74 77] |
| Bone (turnover; resorption) | CTX | 5[41 45 51 61 82] |
| Muscle/bone/ligament/tendon (mass) | LBM | 5[43 70 73 76 82] |
| Bone (density) | Total Hip BMD | 4[39 73–75] |
| Bone (density) | Radius BMD | 4[35 48 62 80] |
| Bone (turnover; formation) | BAP | 4[40 41 45 51] |
| Bone (turnover; formation) | P1NP | 4[45 51 61 83] |
| Bone (turnover; formation) | BGP | 4[46 47 49 65] |
| Bone (turnover; resorption) | PYD | 4[46 47 49 65] |
| Bone (injury) | Any fracture | 4[34 37 72 81] |
| Muscle (structure) | Quadriceps morphology* | 4[38 44 69 70] |
| Joint (condition) | TKA | 3[53 55 60] |
| Bone (density) | Trochanter BMD | 2[35 63] |
| Bone (density) | Calcaneus BMD | 2[67 68] |
| Bone (density) | Ward's Triangle BMD | 2[35 63] |
| Bone (density) | Tibia BMD | 2[45 62] |
| Bone (content) | Femur BMC | 2[58 64] |
| Bone (content) | Radius BMC | 2[35 63] |
| Bone (injury) | Stress fracture | 2[57 74] |
| Joint (condition) | THA | 2[53 60] |
| Ligament (injury) | ACL Injury | 2[54 59] |
| Bone (density) | Subtotal BMD | 1[77] |
| Bone (content) | Subtotal BMC | 1[77] |
| Bone (turnover; resorption) | IGF-1 | 1[83] |
| Tendon (structure) | Tendon morphology† | 1[70] |
| Joint (injury) | Back disorder‡ | 1[36] |
| Joint (motion) | Anterior tibial translation | 1[56] |

*Muscle fibre cross-sectional area, whole muscle cross-sectional area, fibre type, myonuclei content, muscle thickness.
†Tendon cross-sectional area, collagen concentration, collagen cross-linking.
‡Tendon cross-sectional area, collagen concentration, collagen cross-linking.
ACL, anterior cruciate ligament; BAP, bone alkaline phosphatase; BGP, osteocalcin; BMC, bone mineral content; BMD, bone mineral density; CTX, C-terminal peptide; D-PYD, deoxypyridinoline; IGF-1, insulin-like growth factor 1; LBM, lean body mass; P1NP, procollagen type 1 terminal peptide; THA, total hip arthroplasty; TKA, total knee arthroplasty.

this, there is very low certainty evidence of unclear relationships between CHC use and a wide range of bone turnover and bone health outcomes, and a paucity of evidence about the effect of CHC use on other MSK tissue (ie, tendon, ligament, muscle, cartilage) physiology, injury or conditions. Despite the importance of the adolescence period for MSK tissue accrual,[23] and evidence that the effect of CHC use may be unique to life stage,[19] stratification by adolescent or adult CHC use was not possible.

Our results build on the findings of past reviews that report on the short-term associations between CHC use and specific MSK injuries[12] or BMD.[19] By assessing the effect of CHC use on a broader spectrum of MSK tissue pathophysiology, injuries and associated conditions without restriction by follow-up length, our review has been able to consider MSK conditions which are more prevalent in women that typically appear later in life (eg, osteoarthritis, frailty fracture).[5 37] This more inclusive approach, combined with an assessment of the certainty of the evidence, provides a comprehensive overview of the MSK considerations of CHC use across the lifespan that can be used by females and their healthcare providers to inform decisions about CHC prescription.

Across 50 studies and 32 unique outcomes included in this review, the majority were related to bone structure or bone physiology. Despite this large evidence base, there is still a lot that is unclear. Although there is evidence that past CHC use is associated with higher future fracture risk at any site, this was judged to be low certainty evidence suggesting that the estimate of effect is likely to change with future research. Similarly, there is only very low certainty evidence of unclear or absent relationships between CHC use and most other bone-related outcomes. Outside of bone-related outcomes, we identified an elevated risk for total knee arthroplasty (a common end-stage treatment for knee osteoarthritis) in past CHC users.

An important finding from this review is the paucity of evidence assessing CHC use and tendon, ligament, or muscle-related outcomes (eg, tendinopathy, ligament ruptures or sprains, muscle strains), which is foundational information needed before encouraging CHC use for injury prevention. This is in direct contrast to previous reviews that suggest CHC use may decrease the risk of ACL laxity and ACL tears,[12 14 21] which, in turn, could reduce the prevalence of one of the most burdensome MSK conditions—knee osteoarthritis.[30 84] There are important methodological differences between the current and past reviews that may explain the discrepancy in findings. Specifically, conclusions of past reviews are based on selective interpretation of case series and case–control studies,[12 14] and either did not rate evidence certainty (ie, GRADE) or did not follow best practice to summarises the totality of the evidence for each outcome, and indicate how likely the findings are to change with future research.[24 28]

Although these case-series and case–control study designs are important for generating hypotheses, they are without strict controls that make them prone to bias (error that consistently increases or decreases the effect of an intervention) and confounding (distortion of the effect of an intervention by a third factor) which require cautious interpretation of their results.[32] To highlight this, Herzog *et al*[59] conducted a population cohort study with nearly 3 million females and a nested case–control analyses (see figure 2). The cohort study demonstrated no difference in ACL tear risk (adjusted HR 0.95; 95% CI 0.89 to 1.01) between new CHC users and non-CHC (ie, IUD) users, while the case–control analyses identified that participants who used CHC at any time in the past 5 years had lower odds of an ACL tear (adjusted OR 0.90; 95% CI 0.85 to 0.94).[59] The discrepancy demonstrates that case–control analyses may be influenced by bias, including selection bias (selected based on outcome vs exposure) or comparator bias (active contraceptive seeking control vs non-contraceptive seeking control) and/or confounding. This skillful illustration of the limitations of hypothesis generating study designs to understand associations supports our decision to limit our inclusion to cohorts and intervention study designs.

A secondary aim of this review was to consider the differential effects of CHC use on MSK outcomes stratified by adolescent (≤18 years of age) or adult (>18 years) use. This aim was based on the fact that adolescence is a critical period for the developing MSK system,[19 85] and a previous review that demonstrated adolescent CHC use may have a detrimental effect on BMD accrual.[19] While speculative, our finding of an elevated risk of

**Table 2** Semiquantitative synthesis with modified GRADE rating

| Outcome | Studies (n) | Participants (n) | Follow-up (years) | Study design | Study limitations | Inconsistency | Indirectness | Imprecision | Modified GRADE rating | Direction and magnitude (without stratifying for age) |
|---|---|---|---|---|---|---|---|---|---|---|
| Lumbar BMD[35 39 40 42 46–50 52 58 62–66 71 73–75 77–79] | 23 | 4484 | 1–20 | +++ | XX | ✓ | X | X | + | CHC use may not be associated with lumbar BMD |
| Femoral Neck BMD[35 40 42 48 50 52 58 62–64 66 71 75 78] | 14 | 3314 | 1–20 | ++++ | XX | ✓ | X | X | + | CHC use may not be associated with femoral neck BMD |
| Whole Body BMD[39 42 45 58 64 73 77 82] | 8 | 1914 | 0.8–20 | +++ | XX | X | X | X | + | Association between CHC use and whole body BMD is unclear |
| D-PYD[40 46 47 49 65 67] | 6 | 668 | 1–2 | +++ | XX | X | ✓ | X | + | Association between CHC use and DPD is unclear |
| CTX[41 45 51 61 82] | 5 | 180 | 0.08–1 | +++ | XX | ✓ | X | X | + | Association between CHC use and CTX is unclear |
| LBM[43 70 73 76 82] | 5 | 713 | 0.18–2.2 | ++++ | XX | X | X | X | + | Association between CHC use and LBM is unclear |
| Lumbar BMC[35 58 62 64 77] | 5 | 1230 | 1–20 | +++ | XX | X | X | X | + | Association between CHC use and lumbar BMC is unclear |
| Whole body BMC[35 58 64 74 77] | 5 | 1321 | 1–20 | ++++ | XX | X | ✓ | X | + | Association between CHC use and whole body BMC is unclear |
| Any fracture[34 37 72 81] | 4 | 1 663 062 | 2.5–26 | +++ | X | ✓ | ✓ | ✓ | ++ | CHC use may ↑ fracture risk by 1.20 times (RR 95% CI 1.08 to 1.34) |
| P1NP[45 51 61 83] | 4 | 119 | 0.08–0.8 | +++ | XX | ✓ | X | X | + | Association between CHC use and P1NP is unclear |
| PYD[46 47 49 65] | 4 | 233 | 1 | ++ | XX | ✓ | ✓ | X | + | Association between CHC use and PYD is unclear |
| BAP[40 41 45 51] | 4 | 397 | 0.08–1 | +++ | XX | X | X | X | + | Association between CHC use and BAP is unclear |
| BGP[46 47 49 65] | 4 | 233 | 1 | ++ | XX | X | ✓ | X | + | Association between CHC use and BPG is unclear |
| Radius BMD[35 48 62 80] | 4 | 655 | 1–5 | ++++ | XX | ✓ | ✓ | X | + | Association between CHC use and radius BMD is unclear |
| Total Hip BMD[39 73–75] | 4 | 933 | 2–7 | ++++ | X | X | X | X | + | CHC use may not be associated with Total Hip BMD |
| TKA[53 55 60] | 3 | 1 345 078 | 6–15 | +++ | X | ✓ | ✓ | ✓ | ++ | CHC use may ↑ TKR risk by 1.36 times (RR 95% CI 1.00 to 1.86) |

✓, no limitation; +++, moderate-quality evidence; +, very low quality evidence; ++, low-quality evidence; ++++, high-quality evidence; BAP, bone alkaline phosphatase; BGP, Osteocalcin; BMC, bone mineral content; BMD, bone mineral density; CHC, combined hormonal contraceptive; CTX, C-terminal peptide; D-PYD, deoxypyridinoline; GRADE, Grading of Recommendations Assessment, Development and Evaluation; LBM, lean body mass; P1NP, procollagen type 1 terminal peptide; RR, risk ratio; TKA, total knee arthroplasty; X, serious limitation; XX, very serious limitation.

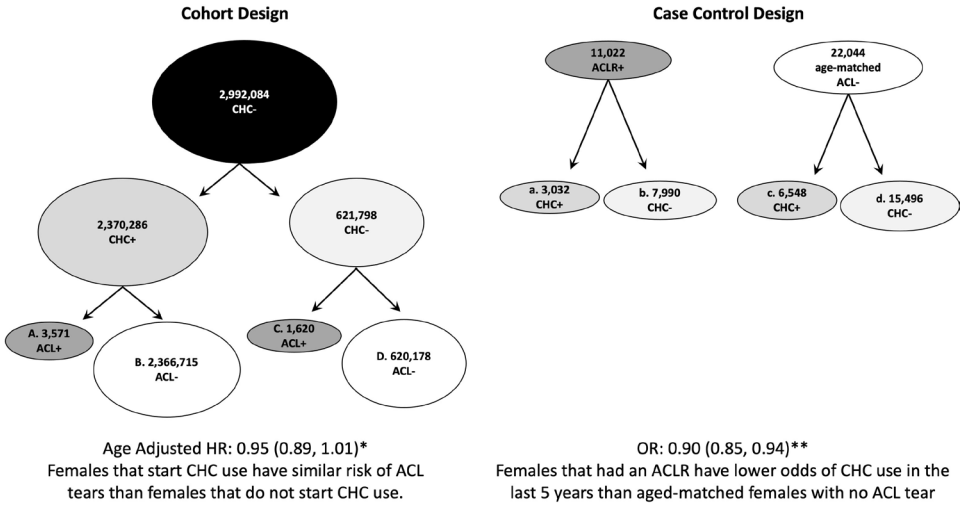


**Figure 2** Comparison of cohort versus case–control design by Herzog *et al*[59] ACL (anterior cruciate ligament), ACL+ (ACL tear), ACL– (no ACL tear), ACLR (ACL reconstruction), ACLR+ (had an ACL reconstruction), CHC (combined hormonal contraceptive), CHC+ (CHC use), CHC– (no CHC use), HR, OR. *HR: The risk of an ACL tear among females who initiated CHC use relative to the risk of anterior cruciate ligament tear among women who did not initiate combined hormonal contraceptives adjusted for age. HR=(A/(A+B))/(C/(C+D)). **OR: The odds of using CHC over the previous 5 years among females who had an ACLR relative to the odds of taking CHC over the same period among age-matched females who did not have an ACL tear. OR=(a/b)/(c/d).

future fracture in CHC users could be related to poor BMD accrual in adolescence. Unfortunately, 88% of studies included in this review had participants that spanned adolescence through adulthood and did not provide stratified results which interfered with our ability to fully explore the difference in the effect of CHC between these two life stages. Across the two outcomes (lumbar spine and femoral neck BMD) where semiquantitative analyses were possible, there was very low quality evidence of an unclear association with CHC use.

## Clinical implications

Currently, there is insufficient evidence to recommend CHC use to protect MSK health including the prevention of ACL tears. In contrast, CHC use could increase the risk of future fractures and total knee arthroplasty. Females and their healthcare providers can use this information to inform decisions about CHC prescriptions.

## Recommendations for future research

Given the paucity of high certainty evidence about the effect of CHC use on MSK outcomes, in particular non-bone-related outcomes, there are many opportunities to contribute to the field through rigorously designed prospective cohort studies or RCTs. Future studies should follow established reporting guidelines for cohort and RCTs (Strengthening the Reporting of Observational Studies in Epidemiology), Consolidated Standards of Reporting Trials (CONSORT)).[86 87] This includes reporting results in their native units, avoiding selective reporting of p values, and reporting data only in figures. Investigators are also encouraged to clearly define the non-user comparator group and any washout period used to facilitate study pooling. For bone-related outcomes, we encourage investigators to disaggregate their results by life stage (eg, adolescent vs adult) and consider the influence of menstrual status (eg, normal menses, amenorrhoea or oligomenorrhoea) to facilitate better understanding of the relationship between CHC use and BMD.[19]

## Strengths and limitations

We followed best practices for systematic reviews including a priori protocol registration, a comprehensive search strategy developed in collaboration with a librarian scientist, and grading risk of bias plus the certainty of evidence. These efforts facilitated an extensive synthesis and analysis across many relevant outcomes. Post hoc protocol changes allowed us to focus on rigorous study designs that can directly inform treatment decisions (ie, RCTs and cohort studies) while avoiding the inherent biases of cross-sectional studies (eg, reverse-causality bias) or case–control studies (eg, incidence-prevalence bias). The decision against pooling data across different estimate statistics (ie, per cent change and mean change) and life stages reduced the ambiguity of our conclusions. We chose not to contact individual authors for missing data which may have prevented us from performing further meta-analyses. This decision was made based on the broad scope of the review, many source studies being published more than 5 years previously, and past experiences where efforts infrequently result in helpful clarification.[88]

Despite our extensive search strategy, it is important to acknowledge the possibility of omitting a relevant study. Although approximately two-thirds of the studies included in this review were conducted in North America or Europe, the remaining one-third represents data from Africa, Asia and South America suggesting that our findings may be considered applicable beyond white communities in high-income countries. A few of the included studies reported data about the education level or other determinants of health, it is not possible to comment on the generalisability of our findings in this respect. The semiquantitative GRADE approach relies on the judgement of the research team and the ratings may reflect implicit biases. This likely resulted in more downgrading of evidence-certainty ratings to avoid overstating findings without supporting quantitative estimates. We chose to only synthesise outcomes with three or more studies of similar outcomes based on our previous experience using this approach and the high likelihood that the ratings based on two studies would be downgraded due to uncertainty. Despite this, we have included the full findings of all studies in online supplemental file 1. The decision to synthesise studies with different comparison conditions (eg, never vs new user) can increase heterogeneity and lead to evidence-certainty downgrading. The decision to restrict study inclusion to

designs (ie, only intervention or cohort studies) that are hypothesis testing, led to case–control studies being omitted from our review and is one potential reason why our findings may differ from past reviews. Finally, the decision to not restrict study follow-up length enhances the generalisability of these findings, but also creates variability that could lead to evidence downgrading.

## CONCLUSION

There is insufficient evidence to support the use of CHC to prevent MSK injuries in females, including ACL tears. Low certainty evidence suggests that past CHC use may be associated with a slightly elevated risk of future fracture and total knee arthroplasty. Very low certainty evidence indicates that the association between CHC use and BMD, BMC, and other biomarkers of bone physiology is unclear or absent.

Given a paucity of high certainty evidence that CHC use is protective against MSK pathophysiology, injury or conditions, it is premature and inappropriate to advocate or prescribe CHC for these purposes.

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