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Effect of menstrual cycle phase, menstrual irregularities and hormonal contraceptive use on anterior knee laxity and non-contact anterior cruciate ligament injury occurrence in women: a protocol for a systematic review and meta-analysis

Elisa Nédélec,[1] Elvis Foli,[2] Sandra J Shultz,[2] Paul A Swinton,[3] Eimear Dolan,[4] Kevin Enright,[5] Jessica Piasecki,[1] Joseph J Matthews,[1] Craig Sale,[1] Kirsty Jayne Elliott-Sale [1]

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For numbered affiliations see end of article.

Correspondence to
Prof Kirsty Jayne Elliott-Sale; kirsty.elliottsale@ntu.ac.uk

ABSTRACT

Exercising women report three to six times more ACL tears than men, which happen, in the majority of cases, with a non-contact mechanism. This sex disparity has, in part, been attributed to the differences in reproductive hormone profiles between men and women. Many studies have shown that anterior knee (AK) laxity and the rate of non-contact ACL injuries vary across the menstrual cycle, but these data are inconsistent. Similarly, several studies have investigated the potential protective effect of hormonal contraceptives on non-contact ACL injuries, but their conclusions are also variable. The purpose of this systematic review and meta-analysis is to, identify, evaluate and summarise the effects of endogenous and exogenous ovarian hormones on AK laxity (primary outcome) and the occurrence of non-contact ACL injuries (secondary outcome) in women. We will perform a systematic search for all observational studies conducted on this topic. Studies will be retrieved by searching electronic databases, clinical trial registers, author's personal files and cross-referencing selected studies. Risk of bias will be assessed using the Newcastle Ottawa Quality Assessment Scale for Cohort and Case–Control Studies. Certainty in the cumulative evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation approach. The meta-analyses will use a Bayesian approach to address specific research questions in a more intuitive and probabilistic manner. This review is registered on the international database of prospectively registered systematic reviews (PROSPERO; CRD42021252365).

Key messages

What is already known

- Female athletes and exercisers report three to six times more anterior cruciate ligament (ACL) injuries than men. Most of them happen with a non-contact mechanism.
- The differences in reproductive hormone profiles between men and women have been identified as a risk factor for non-contact ACL injuries.
- Despite many studies on variations of anterior knee (AK) laxity and the rate of non-contact ACL injuries amongst normally menstruating participants and hormonal contraceptive users, the inconsistency of the literature makes it difficult to evaluate the effects of endogenous and exogenous ovarian hormones on AK laxity and the occurrence of non-contact ACL injuries.

What this study could add

- By including both anterior knee (AK) laxity and the occurrence of non-contact ACL injuries in naturally menstruating women, women with menstrual irregularities and hormonal contraceptive users, we will provide a detailed summary and interpretation of the current state of the art of this topic, following a theoretical biological pathway from mechanism to outcome.
- This study will be the most comprehensive review to date of AK laxity and the occurrence of non-contact ACL injuries, due to the diversity of included participants.
- The findings of this review will make the available evidence more accessible to practitioners and will therefore have practical implications for exercising women.

BACKGROUND

The participation of girls and women in sport has increased worldwide, both in recreational and professional practice.[1 2] This growth in and development of women's sport has resulted in a growing number of reports regarding the nature and rate of injuries sustained by sportswomen.[3] Depending on the age-group, the

sport and the level of practice, women report different rates of musculoskeletal, sports-related injuries than their male counterparts.[4] As one of the most prominent musculoskeletal injuries, exercising women report three to six times more ACL tears than men,[5] which occur, in the majority of cases, via a non-contact mechanism.[6] Most non-contact ACL injuries happen during fast-paced multidirectional activities (eg, snow skiing, netball, football, rugby, gymnastics).[7] The sex disparity for non-contact ACL injuries starts at the adolescent growth spurt and peaks during adolescence.[8] This sex difference has been attributed to several factors that also emerge at this time, namely: anatomical (eg, laxity, body composition), physiological (especially hormonal), biomechanical, neuromuscular recruitment patterns[9] and gendered factors present in the developmental environment.[10] The potential impact of hormones on the mechanisms underpinning non-contact ACL injuries deserves greater attention given the numerous differences in the concentration of reproductive hormones between sexes and the time course of reproductive endocrinology, especially in women.

Ovarian hormone profiles vary between and within women and are not stable over a women's lifespan (eg, they change across phases of the menstrual cycle, as a result of hormonal contraceptive use, during pregnancy and following menopause). Ovarian hormones influence the structure of all soft tissues (ie, muscles, tendons, and ligaments) by determining their collagen metabolism (Liu *et al*[11]: data from rabbits; Yu *et al*[12] and Konopka *et al*[13]: data from human ACL cells), and structural integrity (Konopka *et al*[13]: data from human ACL cells; Lee *et al*[14]: data from engineered ligaments). Alterations of the ACL structure, caused by fluctuations in ovarian hormone levels, may increase the risk for potential ligament failure (Lee *et al*[14]: data from engineered ligaments; Yu *et al*[12]: data from human ACL cells). Indeed, it has been suggested that women's ACLs and musculoskeletal systems react to changes in the reproductive hormone milieu, thus changing their properties at certain points of the lifespan corresponding to different hormonal profiles.[15]

In the last two decades, many studies have shown that anterior knee (AK) laxity[16] and the rate of non-contact ACL injuries[17] change during different phases of the menstrual cycle in eumenorrheic women, although the findings from studies in this area are inconsistent. Several studies have also been conducted on the potential protective effect of hormonal contraceptives, especially oral contraceptive pills (OCPs), on non-contact ACL injuries, due to their users having a consistently downregulated endogenous ovarian hormone profile, although these data are also inconsistent.[18] These inconsistencies in findings (ie, menstrual cycle phase and OCP use) might be due to poor methodological quality, especially with regards to the definition and confirmation of menstrual cycle phases and the heterogeneity of hormonal contraceptives used in these studies (for a comprehensive overview of methodological issues see Elliott-Sale *et al*[19]).

A systematic review and meta-analysis published in 2017[18] concluded that the quality of evidence (ie, data published up to August 2016), on the effect of the menstrual cycle and hormonal contraceptives on the laxity of the ACL and the occurrence of non-contact injuries to the ACL, was 'very low', due to numerous methodological shortcomings affecting the eligibility of the participants. Our systematic review and meta-analysis will expand the review by Herzberg *et al*[18] by: (i) including studies published up to and since August 2016, (ii) performing a meta-analysis on the injury data and not just the laxity data, (iii) employing different inclusion/exclusion criteria and (iv) including women with menstrual irregularities. In addition, our review will adopt a different statistical method (ie, a Bayesian approach) to allow for a more intuitive and probabilistic synthesis and interpretation of existing data. Therefore, the purpose of this systematic review is to identify, evaluate and summarise the effects of endogenous and exogenous ovarian hormones on knee joint laxity and occurrence of non-contact injuries of the ACL in women. We hypothesise that: (i) AK laxity will differ in response to the fluctuations in endogenous ovarian hormones that occur at different phases of the menstrual cycle, leading to an increased occurrence of non-contact ACL injury, (ii) AK laxity and the occurrence of non-contact ACL injury would be greater in non-hormonal contraceptive users.

METHODS

The protocol for this aetiology systematic review and meta-analysis follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols[20] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for Searching (PRISMA-S)[21] and is registered with the International Prospective Register of Systematic Reviews (PROSPERO) registration number CRD42021252365.

Eligibility criteria

Studies will be selected according to the PECOS (ie, participants, exposures, comparator, outcomes, study designs) criteria (table 1). There will be no restrictions on the time frame or setting of the studies. Studies reported in English, French, Spanish, Portuguese and German languages will be considered. A list of possibly relevant titles in other languages will be provided as an appendix if relevant.

Information sources

Search strategies will be developed using text words related to the population, exposures and outcomes. Five electronic databases will be searched from their inception onwards: PubMed Central (includes MEDLINE), SPORTDiscus (via EBSCOhost interface), Scopus, the Cochrane Central Register of Controlled Trials and ProQuest Central: Health and Medical Collection; Nursing and Allied Health; Research Library: Health

Table 1 Overview of PECOS eligibility criteria

Participants	Human female athletes (defined as one who takes part in an individual or organised team sport wherein: (i) they compete regularly against others; (ii) excellence and achievement are emphasised and (iii) systematic intensive training is required[32]) and female exercisers (defined as one who engages in physical activity with the will to: (i) augment their fitness level; (ii) improve their health; (iii) ameliorate their physique and (iv) acquire or improve skills[33]) of reproductive age (ie, postmenarche and premenopausal) will be included. Specifically, eumenorrheic, naturally menstruating women, women with menstrual irregularities (eg, oligomenorrhoea, polymenorrhoea, amenorrhoea, anovulatory and luteal phase deficient cycles) and hormonal contraceptive users (eg, combined and progestogen-only OCPs, injections, implants, patches, intra-uterine systems) will be included; with pregnant and perimenopausal women excluded. Participants must not be using any form of medication known to affect ovarian hormone profiles (with the exception of hormonal contraceptives) or the musculoskeletal system.
Exposures	Of interest will be habitual exposures affecting the endogenous ovarian hormone status of the participants; that is, menstrual cycle and associated disturbances and hormonal contraceptives.
Comparators	Where relevant, hormonal contraceptive users will be compared with non-hormonal contraceptive users.
Outcomes	Outcomes relating to the physical assessment of AK *laxity* (primary outcomes) and the occurrence of non-contact ACL *injuries* (secondary outcomes). The primary outcomes are focused on micro changes (ie, physiological changes to the AK laxity that potentially occur due to changes in ovarian hormone concentrations) and the secondary outcomes are focused on macro changes (ie, number of non-contact ACL injuries that may potentially occur due to micro changes). *AK laxity* refers to the degree of tightness/looseness of the AK in a sagittal plan; in the knee, ligaments are present to connect and stabilise the various bones that are present by keeping the knee joint flexible enough to move but also firm enough to provide support. It is measured using (i) clinical examination (eg, Lachman test—manual test to assess the AK laxity; subjective measure) and (ii) equipment designed to evaluate the AK laxity by quantifying the anterior displacement of the anterior tibial tubercle relative to the femur when a predefined anteriorly directed force is applied, from the upper calf (eg, arthrometers; objective measure). Within this systematic review and meta-analysis, we will exclusively focus on studies reporting primary *non-contact ACL injuries* (defined as sudden-onset injuries resulting from a non-contact mechanism showing no evidence of direct or indirect physical disruption or perturbation of the player's movement pattern by an external source.[34]
Study designs	Observational studies will be considered for inclusion if they meet the following inclusion criteria: (i) published, in full, in a peer-reviewed journal; (ii) have the objective of assessing changes in AK laxity in response to phases of the menstrual cycle, menstrual irregularities and/or hormonal contraceptive use and (iii) report the incidence of ACL injuries aligned with phases of the menstrual cycle, menstrual irregularities and/or hormonal contraceptive usage. Cohort studies and case–control studies will be included when reporting primary outcomes (ie, the physical assessment of AK laxity). Cross-sectional studies, cohort studies and case–control studies will be included when reporting secondary outcomes (ie, the occurrence of non-contact ACL injuries). Case studies, review articles, protocol papers, editorials, conference abstracts and commentaries will be excluded.

AK, anterior knee; OCPs, Oral contraceptive pills.

and Medicine. The electronic database search will be supplemented by searching for trial protocols through three registers: Clinical Trials (www.clinicaltrials.gov), EU Clinical Trials Register (www.clinicaltrialsregister.eu) and International Standard Randomised Controlled Trial Number (ISRCTN) (www.isrctn.com). To ensure literature saturation, the reference lists of included studies or relevant reviews identified, which may have been identified through the initial search strategy, will also be hand searched. All authors will search their personal files to make sure that all relevant material has been identified.

Search strategy

The PubMed Central search strategy will be developed with input from all authors using the Peer Review of Electronic Search Strategies standard.[22] In addition, the search strategy will be peer-reviewed by a research librarian who has expertise in systematic review searching and is not otherwise associated with the project. A draft search strategy for PubMed Central is included in online supplemental file 1. Once the PubMed Central search strategy is finalised, the search strategy will be adapted to the syntax and subject headings of the other databases. The search will be updated toward the end of the review, prior to publication, to retrieve any articles published during the interim period.

Study record

All search results will be uploaded and stored in a systematic review management platform (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia), which will be accessible to all reviewers. Covidence will automatically remove duplicates by checking the following fields: titles, year, volume, authorship. Two reviewers will independently check the duplicates removed by Covidence and verify their accuracy.

Titles and abstracts will be independently screened by two reviewers, guided by the inclusion and exclusion criteria. Disagreements will be resolved with a consensus-based discussion, and, when in doubt, articles will be carried forward to full-text review. The full text of eligible papers, based on the titles and abstracts, will be downloaded and independently screened. If the reviewers are not in agreement, a third reviewer will be consulted and will provide recommendations. The reviewers will use the annotation facility on the decision dashboard to explain their decision and inform further discussions. If a study is reported in more than one publication, the multiple

reports will be collated. When in doubt regarding the eligibility criteria of a study, the reviewers will contact the authors; with a maximum of three attempts, two emails and one phone call (if possible), over a 4-week period. Any ongoing trials, which have not yet been reported, will be recorded, so that they can be added to the ongoing studies table. A PRISMA flowchart detailing the search and selection process will be included (see online supplemental file 1 for a draft template); as well as a list of all full-text studies excluded, detailing the specific reason for exclusion.

A data extraction template will be created based on those used in similar meta-analyses.[23] Data will be extracted by two reviewers. To ensure consistency across reviewers, calibration exercises will be conducted before starting the data collection process (ie, the data extraction form will be pilot-tested by each reviewer on five randomly selected studies). When outcome data are not reported in a usable format (ie, in a figure instead of a numerical format) specialist software will be used to extract the data from the figure (eg, WebPlotDigitizer Version 4.4).

In order to avoid double-counting data, records will be scrupulously compared, for example, juxtaposing author names, treatment comparisons, sample sizes and/or outcomes. If the same study data are reported in more than one publication, all publications will be treated as one dataset rather than multiple datasets. When we extract data, we will prioritise the following criteria: greatest number of participants, longest follow-up and primary reports where the primary outcome assessed is most relevant to our research questions. If the data differ across publications, it will be noted, investigated, and the authors contacted for more information; with a maximum of three attempts, two emails and one phone call, over a 4-week period.

Disagreements will be recorded and resolved with a consensus-based discussion between the two reviewers. Any disagreement that cannot be resolved will be referred to a third reviewer who will provide a recommendation. Study authors will be contacted if there are any doubts about the extracted data, with a maximum of three attempts, two emails and one phone call, over a 4-week period. If any disagreement cannot be resolved (ie, either through discussion between the reviewers or with the authors) the disagreement will be reported in the review.

Data items

Reviewers will extract data on the following: (i) study characteristics (ie, design, location, sources of funding, study aim), (ii) participant characteristics (ie, eligibility criteria, age, height, body mass, body mass index, training status, etc), (iii) exposure and comparison characteristics (ie, type, dosage, and duration of hormonal contraceptive use, menstrual cycle phase, type of menstrual irregularity, methods of determining participants' ovarian hormonal status, etc), (iv) outcome characteristics for AK (ie, method of assessment, assessment characteristics, etc) and occurrence of ACL injuries (ie, method(s) used to confirm the injury, profile of the injury (injury mechanism, context of the injury, primary or recurrent injury, isolated ACL injury or other collateral structures injured), etc).

Outcomes and prioritisation

The primary outcomes are the physical assessment of AK laxity and the secondary outcomes are the occurrence of non-contact ACL injuries.

Risk of bias assessment

Risk of bias will be initially evaluated at the individual study level, using the Newcastle Ottawa Quality Assessment Scale for Cohort or Case–Control Studies.[24] The Newcastle Ottawa Quality Assessment Scale is a domain-based risk of bias tool that comprises eight items within three categories to assess the key bias domains: (i) selection; (ii) comparability and (iii) outcome/exposure. We have developed coding systems, that are very similar to formerly published work in our research area,[25] according to our outcomes (ie, anterior knee laxity and ACL injury occurrence) and ensured that the assessment is specific to each outcome. We have opted for using the Newcastle Ottawa Quality Assessment Scale without the star-rating system, as the PRISMA explanation and elaboration[26] states that presenting assessments for each domain in the tool is preferable to reporting an overall 'quality score' because it enables users to understand the specific domains that are at risk of bias in each study. Accordingly, we will separate the key bias domains covered by the Newcastle Ottawa Quality Assessment Scale when assessing bias and we will present the results in a table.

Certainty in cumulative evidence

Certainty will be assessed by two independent reviewers using a strategy based on the recommendations of the Grading of Recommendations Assessment Development and Evaluation working group.[27] Any differences between reviewers will be resolved by discussion and, if needed, in consultation with a third reviewer. Certainty in cumulative evidence will be based on consideration of five domains, namely risk of bias (assessed using the NOS as described above), indirectness, inconsistency, imprecision or evidence of publication bias. Directness will be ascertained based on the methods used to identify and confirm menstrual cycle phase, along with injury confirmation. This information is considered essential, given that if unconfirmed, any result observed cannot be directly attributed to the phase under investigation. This will be evaluated based on the response to two questions:

(Q1) Was the ovarian hormone profile confirmed?

If the authors provide a definition for the sampled population and report using blood samples to confirm ovarian hormone status, the a priori rating will be maintained, if not the study will be downgraded a level (eg, a

Table 2 Significance of the four certainty of evidence categories[35]

High	Confident that the true effect lies close to that of the estimate of the effect
Moderate	Moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low	Little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect

study that is classified as 'high' quality, would be downgraded to 'moderate' quality).

(Q2) Was the injury medically diagnosed either as part of the study or prior to the study?

These questions are based on methodological conclusions made in previous studies.[18 23]

Consistency will be ascertained using the meta-analysis results and will be based on visual inspection of effect size and variance estimates across the different levels (eg, within study variation, between study variation and between outcome variation). Precision will be judged based on the number of outcomes available (with outcomes based on <3 data points downgraded) and on interpretation of width of the credible intervals (CrIs). Small-study effects (ie, publication bias) will be visually inspected with funnel plots and quantified with a multi-level extension of Egger's regression-intercept test.[28] Collectively, these procedures will result in a final level of certainty for each outcome (table 2): namely of 'high', 'moderate', 'low' or 'very low'. This certainty appraisal strategy will not be used to exclude any study.

Data synthesis

Data will be presented in summary tables, which will describe the study characteristics and outcomes. A Bayesian framework was chosen over a frequentist approach as it provides a more flexible modelling approach that will enable results to be interpreted intuitively through reporting of subjective probabilities rather than null hypothesis tests or frequentist CIs.[29] For the primary outcomes comprising assessment of menstrual cycle phase, menstrual irregularities and hormonal contraceptive use on AK laxity, both repeated measures data and independent group data will be used to create standardised mean difference effect sizes. Standard distributional assumptions will be used to estimate within study sampling error.[30] For repeated measures data where a correlation value is required, a standard value of 0.7 will be used to generate an informative prior with variance included to account for correlations ranging from 0.5 to 0.9. For the secondary outcome comprising the occurrence of ACL injuries, count data will be used to calculate ORs and within study sampling error. All meta-analyses will comprise a three-level hierarchical model to account for random variation across studies and covariance between multiple outcomes reported from the same study. Inferences from all analyses will be performed on posterior samples generated by Hamiltonian Markov Chain Monte Carlo with Bayesian 95% CrIs. Interpretations will be based on visual inspection of the posterior sample, the median pooled effect size value ($ES_{0.5}$: 0.5-quantile) and 95% CrIs for location parameters and 75% CrIs for variance parameters. Heterogeneity will be quantified using the posterior distribution of the between study variance parameter. Where possible, meta-regressions will be used to explore sources of variance including the type of hormonal contraceptive (eg, OCPs, implants, injections, etc). Meta-regression will be performed when there is sufficient data including a minimum of four data points per category level or 10 data points for continuous variables.[31] Sensitivity analyses will also be conducted to assess the influence of research quality (inclusion of 'moderate' and 'high' quality studies only) on overall conclusions and effect size magnitudes. Results of meta-analyses will be presented in tables and visually through forest and funnel plots. Where quantitative pooling is not possible due to insufficient data, narrative synthesis will be conducted.

DISCUSSION

This systematic review and meta-analysis will synthetise evidence to evaluate the effects of various levels of endogenous and exogenous ovarian hormones on AK laxity and the occurrence of non-contact ACL injuries in women. By including both AK laxity and the occurrence of non-contact ACL injuries in naturally menstruating women, women with menstrual irregularities and hormonal contraceptive users, we will provide an up-to-date, detailed summary and interpretation of the current state of the art of this topic. Furthermore, this meta-analysis will examine the strength of the outcomes and indicate methodological considerations for future research. The findings of this review will have practical implications for female athletes (elite to recreational) and for those working with active women.

Author affiliations
[1]Musculoskeletal Physiology Research Group, Sport, Health and Performance Enhancement (SHAPE) Research Centre, School of Science and Technology, Nottingham Trent University, Nottingham, UK
[2]Department of Kinesiology, University of North Carolina at Greensboro, Greensboro, North Carolina, USA
[3]School of Health Sciences, Robert Gordon University, Aberdeen, UK
[4]Applied Physiology and Nutrition Research Group, Escola de Educação Física e Esporte, Faculdade de Medicina FMUSP, Universidade de São Paulo, Sao Paulo, Brazil
[5]Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK

Twitter Kirsty Jayne Elliott-Sale @ElliottSale

Contributors KES is the guarantor and takes responsibility for the contents of this protocol. All authors contributed to the concept and design of the study. EN, EF, ED and JJM developed and will perform the search and selection strategy, the risk of bias assessment, and data extraction. PAS will provide statistical expertise. SJS, KE, JP and CS will provide supervision and content expertise. EN and KES will draft the manuscript. All authors will read, edit and approve the final manuscript.

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Competing interests EN, EF, SJS, PAS, ED, KE, JP, JJM, and CS declare that they have no competing interests. KES is the recipient of a GnRB arthrometer from Bergstrom Nutrition.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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ORCID iD

Kirsty Jayne Elliott-Sale http://orcid.org/0000-0003-1122-5099

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