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Do Oral Contraceptives Affect Sleep among Women of Reproductive Age? A Systematic Review Protocol

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ABSTRACT

Introduction Oral contraceptives (OC) are one of the most popular contraceptives worldwide. Research evidence indicates that the hormones used in OC may affect sleep in humans. However, it remains unclear whether OC use is associated with poor quality of sleep and sleep disorders among women. This systematic review aims to elucidate the relationship between OC use and sleep in women of reproductive age (15-49 years).

Methods This review will analyze data from randomised controlled trials and non-randomised comparative studies investigating the association between OC (second generation or further) and sleep-related outcomes. Review papers addressing the same research question among the same population will be included. A literature search will be performed using the MEDLINE, EMBASE and Cochrane CENTRAL databases.

Risk of bias will be assessed using The Cochrane Collaboration's revised tool for assessing risk of bias for randomised trials (RoB 2.0), The Cochrane Risk of Bias in Non-randomised studies – of Interventions (ROBINS-1 tool), and Risk of Bias in Systematic Reviews (ROBIS) tool. Two reviewers will independently assess eligibility of studies and risk of bias and extract the data. A third author will solve discrepancies. All extracted data will be presented in summary tables and in a narrative synthesis. For sleep measures investigated by three or more studies with low heterogeneity, we will conduct random-effects meta-analysis to estimate the magnitude of the overall effect of OC. The GRADE approach will be used to summarize the quality of evidence.

Ethics and dissemination Ethics approval is not required as we analyze data from previously reported studies.

PROSPERO registration number Pending.

Article Summary

Strengths and limitations of this study:

- This review on the association between oral contraceptive use and sleep is based on a robust, librarian consulted search strategy.
- All papers are screened by two independent reviewers to mitigate bias.
- The quality of all eligible papers will be assessed with the appropriate methodological tool.
- Papers in languages other than English are not included, leading to potential for language bias.

Keywords: Birth control; Oral contraceptives; Reproductive medicine; Sleep; Systematic review

Word Count: 3051

INTRODUCTION

Worldwide, there are around 1.9 billion women of reproductive age. One hundred and fifty-one million women use oral contraceptives (OC), with usage varying by region.[1] OC are used more widely in Europe and North America, especially in developed countries, than in developing countries. [1] In 2019, 17.2% women of reproductive age in high-income countries, 6.7% in middle-income countries, and 3.8% in low-income countries used OC pills. [1] The prevalence of OC usage worldwide has remained stable in the last 25 years, however, the overall number of users increased since the world population has increased.[1]

The invention of OC is a medical innovation and OC have evolved dramatically in the past decades.[2] The first-generation OC pill, Enovid, contained high doses of norethynodrel (i.e., progestin, 10 mg) and mestranol (i.e., estrogen, 150µg) and was introduced in 1960. To lower the risk of thromboembolic complications associated with the use of OC pills, the second-generation of OC was developed in the 1970s by lowering the dose of the progestin component from 10 mg to 1 mg, and the estrogen component from 150µg to 35µg. Development of new progestins, mainly levonorgestrel, gave way to the second generation of OC, which contained a lower dosage of progesterone.[3] The second-generation OC was shown to be associated with an increased risk of myocardial infarction, stroke, acne and weight gain, which were correlated with the androgenicity of the progestin. [4] Subsequently, the third generation of OC was developed in the 1990s to address side effects that arise due to the androgenicity of second generation progestins, such as acne and weight gain. [4] Fourth generation OC are more selective and bind specifically to the progesterone receptor, further reducing side effects such as edema and improving skin appearance. [5]

Progesterone, the primary component in OC, is an agonist of gamma-aminobutyric acid (GABA) receptors through a metabolite allopregnanolone. [6] GABA is a crucial molecule in sleep

promotion – most sleep-promoting neurons are sensitive to GABA.[7] Common sleep medications, such as benzodiazepines have been shown to positively modulate GABA signalling.[7] The potency of progestin is similar to that of benzodiazepines and has similar agonistic effects. Changes in electroencephalogram (EEG) activity seen with progesterone administration are similar to those evoked by benzodiazepines.[6] Studies in rat models have shown that administration of exogenous progesterone leads to dose-dependent decreased sleep latency and wakefulness.[6] The mechanism behind the effect of estrogen on sleep is not well elucidated but rat studies have shown that administration of estrogen promotes sleep during the sleep period and reduces sleep during the wakefulness period.[8] The overall effect on sleep is likely caused by a combination of both estrogen and progesterone, although the magnitude of their contribution to sleep changes is unknown.[9]

High quality sleep is as essential as regular exercise and eating a balanced diet for maintenance of optimal health and well-being. Severe sleeping problems, such as insomnia, are important matters from both a public health and individual perspective. Insomnia is associated with depression, anxiety, substance abuse, cognitive impairment, metabolic disorders (e.g., diabetes, dyslipidemia, and obesity) and cardiovascular diseases.[10-12] Women are more likely than men to have sleep problems including insomnia, restless leg syndrome, and sleep apnea since changing hormones during the menstrual cycle, pregnancy, and menopause can affect how well a woman sleeps.[13-15] During ovulation, there is a surge of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) which leads to a decrease in estrogen concentration and an increase in progesterone.[16] During the luteal phase, progesterone concentrations increase and estrogen levels are high.[16] Start from the mid-luteal phase, steroidal hormone levels decrease and women are awakened during sleep more often compared with the follicular phase.[17] OC are taken each day for 21 days, providing a constant, exogenous source of estrogen and progesterone, preventing the

release of FSH and LH and thus the production of a follicle or ovulation.[17] Therefore, OC use may affect women's sleep-wake cycle and cause physiological change that lead to sleep disturbance.

Unlike other commonly prescribed drugs, OC pills are taken by healthy women for long periods of time. Safety trials have focused largely on breast cancer and venous thromboembolism (VTE) risk. [18-19] Despite decreases in estrogen concentration with later OC generations, its use has been shown to be associated with an increased risk of developing breast cancer and venous thromboembolism.[4] A 2017 cohort study found OC intake was associated with a reduced risk of colorectal, endometrial and ovarian cancers and increased risk of cervical and breast cancer.[20] Another meta-analysis found a positive association between OC usage and risk of hypertension. [21] Studies in women have varied findings on the association between OC use and sleep quality and duration. Differences in methodology, including the formulation of contraceptives taken, stratification of formulations, measurements of sleep, or the phase of the menstrual cycle of naturally cycling women used as comparison may explain the different findings between studies. For instance, a study published in 2020 by Guida *et al* found significantly increased sleep duration for users of oral progestins and gestodene, compared with naturally cycling women (women not currently using any hormonal contraceptive), as well as increased sleep latency in the oral levonorgestrel group. [22] However, a polysomnography study published in 2012 by Hachul *et al* found decreased sleep latency in women using OC and no difference in overall sleep quality. [23] A randomised control trial by Lundin *et al* found no significant sleep related results, while a cross sectional analysis by Bezerra *et al* found that hormonal contraceptive users had worse sleep quality compared with their naturally cycling counterparts. [24-25]

Given the high prevalence of hormonal contraceptive use among women of reproductive age and the relationship between OC use and sleep varying in both magnitude and direction in the

current literature, there is an urgent need to provide women with accurate, evidence based information to inform their use of hormonal contraception.[22-25] Hence, the objective of this systematic review is to compile and elucidate the association between OC use and sleep (including the quality of sleep, sleep disorders, and duration of sleep). Findings from this review will provide insights to women choosing between different methods and formulations, while also inform the development of new progestins for future generations of OC. The systematic review protocol was registered at the website of the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number pending.

METHOD

Our protocol follows the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols 2015 (PRISMA-P 2015) guidelines.[26]

Literature search

We developed a comprehensive search strategy with input from a research librarian at McMaster University. The systematic search for existing relevant systematic review and original studies is conducted in the Ovid MEDLINE and Embase (Excerpta Medica dataBASE) electronic databases, and the Cochrane Library (including Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials). Search terms covered all words related to birth control, ingredients of oral contraceptives, and sleep. We limited the search to studies or systematic reviews published from 1970 to present to ensure that we include all published studies or reviewers on second and further generation OC. For sleep outcome measures, we searched sleep terms in the full text besides the title and abstract in case sleep is investigated as a secondary outcome and

therefore not reported in the abstract. The comprehensive search strategies for each database are presented in Table 1.

Study Selection and Screening

Systematic screening of the studies will be first conducted at the title and abstract level, and then at the full-text level to determine if a study meets eligibility criteria by two independent reviewers. Any potential conflicts between the reviewers will be resolved through discussion. If discrepancies in judgment remain after discussion, a third-party reviewer will be consulted to resolve the conflict and provide a final decision.

Eligibility criteria

(1) Study Characteristics

Existing systematic reviews will be included if they (i) address the same research question with similar inclusion and exclusion criteria as ours; and (ii) have a low risk of bias in study eligibility criteria, identification and selection of studies, data collection and study appraisal, and synthesis and findings assessed using the Risk of Bias in Systematic Reviews (ROBIS) tool.[27]

For original studies, we will include (i) randomised controlled trials and non-randomised comparative studies that take into account the effect of potential confounders (e.g., age, race, and socioeconomic status)[28-30] using methods such as multivariable analysis, propensity-score matching, or showing no statistically significant differences in baseline characteristics between participants in comparison groups; (ii) studies on human participants; (iii) studies investigate second generation or more recent OC; and (iv) studies investigate the association between OC use and sleep-related outcomes, either as the primary or secondary objective.

(2) Participants

Participants or subgroups of participants are female, between 15 and 49 years old.

(3) Exposure

Participants or subgroups of participants take second generation or more recent OC, regardless of its brand, dose, frequency, and duration, to avoid pregnancy, as long as it contains hormonal ingredients.

(4) Comparator

Included studies must have comparison groups of women who are using (i) non-hormonal contraceptives; (ii) naturally cycling (i.e., not use any contraceptive methods); (iii) same agent as the exposure but in different dose, frequency, and duration; and (iv) second generation or more recent OC but different from the exposure.

(5) Outcomes

We are interested in any sleep-related outcomes and a variety of sleep measurements for sleep quality, sleep duration, and sleep disorder will be included in this systematic review. The sleep measurements can be questionnaires based on Likert Scale items listed below but not limited to these tools:

(i) The Pittsburgh Sleep Quality Index (PSQI).[31] It measures seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction over the last four weeks. The PSQI is a subjective measure of sleep. Subjects self-rate each of the seven domains of sleep from 0 to 3, where 3 represents the negative extreme on the Likert Scale. A subject with a global sum of 5 or greater is considered as a poor sleeper. Studies reported sleep quality in any of the above seven domains during and after taking OC will be included in the review.

(ii) The Epworth Sleepiness Scale (ESS) is a self-administered test used to assess daytime sleepiness.[32] It consists of 8 questions with different scenarios and a scale from 0-3 where subjects would indicate how likely they are to fall asleep in that situation. The scores are summed for a total score between 0 and 24. [32] Studies reporting sleepiness with any of the 8 questions during and after taking OC will be included in the review.

(iii) The Athens Insomnia Scale (AIS), which is also a self-administered psychometric instrument designed for quantifying sleep difficulty.[33] The AIS consists of eight items: sleep induction (i.e., time to fall asleep after turning-off the lights), night awakenings, final awakening earlier than desired, total sleep duration, overall quality of sleep, sense of well-being during the day, functioning (physical and mental) during the day, and sleepiness during the day. Each item is rated from 0 to 3 with higher scores indicating more impaired sleep. The total score ranges from 0 to 24 and a total score of 6 or more is considered as insomnia. Studies reported any or all of the above eight insomnia-related items during and after taking OC will be included in the review.

(iv) The Insomnia Severity Index (ISI), a self-administered questionnaire used to assess insomnia. [34] The ISI consists has a one month recall period and assesses 7 domains: severity of sleep onset, sleep maintenance, difficultly waking up in the morning, sleep dissatisfaction, interference of sleep with daytime functioning, noticeability of sleep problems by others, and distress caused by sleep difficulties. Each domain is rated on a scale from 0 to 4 with higher scores indicating more problematic sleep. The score is summed forming a total score between 0 and 28, with a score of 8 and above indicative of insomnia. [34] Studies reporting any domains from the ISI during and after taking OC will be included in the review.

We will also include continuous measures of sleep quality and disorder. These measures include: (i) total amount of sleep obtained, either during nocturnal sleep episode or across the 24-hour period; (ii) sleep latency, i.e., how long it takes the participant to fall asleep; (iii) how many times do the participant wake up; (iv) how many minutes is the participant awake during the night; (v) sleep efficiency, i.e., what percentage of time spent in bed is the participant actually asleep. The total sleep time is equal to the total amount of time spent in bed (in minutes) minus the time it takes to fall asleep plus the time spent awake throughout the night. The percentage is calculated as the total sleep time divided by total time in bed.

Exclusion criteria

The following studies will be excluded from this systematic review: (1) studies only recruited patients with specific conditions (such as all patients with hypertension); (2) studies investigating the first-generation OC since it is not available in the market anymore due to severe side effects; (3) studies investigating emergency contraception; and (4) studies in languages other than English. We will exclude emergency contraception from this review as the hormonal effect of the contraception is significantly different from long-acting contraception. The half-life of estradiol is around 12 hours, which is not significant when considering long-term effect on sleep.[35]

Data abstraction

A standard form will be developed to extract data from the included studies. From each article, the author, study design, study population, publication year, journal, participant demographics, OC used, intervention details, comparison groups, sleep outcomes, and the association between OC use and sleep will be extracted. Additionally, any mean values, standard deviation and confidence intervals, and all information needed for appraisal of internal validity

will be extracted. This will be done in a standardized data extraction form by two reviewers independently. When consensus is not reached, a third researcher will be consulted to reach the final decision. Data will be presented in narrative form and summary tables.

Risk of bias assessment

For randomised controlled trials, the risk of bias in each included study for each outcome will be evaluated independently by two reviewers, using the Cochrane Collaboration Risk of Bias in randomised trials (RoB 2.0 tool).[36] Studies will be assessed from 5 domains: bias from randomisation, bias from deviates from intended interventions, bias due to missing data, bias in outcome measurement and bias in the selection of the reported result. [36] An overall rating of low bias, some concerns about bias or high bias will be given depending on the result of assessment. The Cochrane Risk of Bias in Non-randomised studies – of Interventions (ROBINS-1 tool) will be used to assess the risk of bias for each outcome in non-randomised comparative studies. [37] Risk of Bias in Systematic Reviews (ROBIS) tool will be used to assess the risk of bias for the eligible systematic reviews.[38]

Grading the strength of evidence

The certainty of the evidence per outcome for each comparison will be assessed from five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach and be classified into four levels of evidence (high, moderate, low or very low).[39]

Data synthesis

All data extracted will be presented in both narrative form and in summary tables. If data is missing, the study authors will be contacted to try to obtain the data. For sleep measures investigated by three or more studies, heterogeneity will be assessed using Q statistic with a p

value < 0.1 indicating for significant heterogeneity. The I^2 statistic will also be calculated with 25%, 50% and 75% representing low, medium, and high heterogeneity, respectively.[40] The heterogeneity in OC effects may be caused by differences in study populations (such as age of patients), different OC or doses received, length of follow-up, and other factors. If heterogeneity level is low or medium, we will conduct random-effects meta-analyses to estimate the magnitude of the overall effect of OC, with 95% confidence interval depicting the uncertainty around the estimate. Subgroup analyses (e.g., by age) and sensitivity analyses (e.g., by progesterone dose) will be conducted as if sufficient data are available.

DISCUSSION

Strengths and limitations

This systematic review will be the first to provide quantitative estimates of the association between OC use and sleep outcomes in healthy women. Our systematic review methodology includes explicit eligibility criteria created in consultation with research librarians, and the usage of tested, standardized abstraction forms. We will calibrate our review methods throughout the review process for optimal consistency among reviewers. The GRADE approach will be applied to aggregate data, the PRISMA-P reporting checklist is followed to draft this systematic review protocol, and the PRISMA reporting checklist will be followed to draft this systematic review later. The κ statistic will be reported to identify issues with reproducibility. Our review will encompass a wide range of OC formulations and sleep outcome measurements. We anticipate limitations with regard to publication bias and recall bias as the majority of studies employ self-administered tools to assess sleep quality and duration.

Study implications

Sleep quality is a crucial outcome that affect overall life quality in women of reproductive age and may indicate risk of developing comorbid conditions. The relationship between OC use and sleep quality, duration and disorder have been reported inconsistently in the current literature. OC have been more and more widely accepted by women. However, no study has attempted to provide systematic evidence on the association between OC use and sleep. Our systematic review will elucidate the association between OC use and sleep quality. Moreover, it will contribute evidence that will support the improvement of guidelines for taking OC in healthy women and promote awareness of safety for taking OC.

It is challenging to design, conduct, and analyze original studies investigating the association between OC use and sleep quality. For instance, a wide variety of OC are utilized in women and they may change to other brands of OC tablets or birth control methods. In addition, most studies use subjective sleep measures, which may involve recall the information in the past. Through appraisal of published studies, our systematic review will inform the improvement in the design and implementation of future research in this field.

Conflict of Interest Disclosures: All the authors have declared no financial conflicts of interest.

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Author Contributions: JM, MC, CW, and XY conceptualized the idea of the study. JM, XY and MC drafted the manuscript. CW, LT, CM, NZ, QW critically appraised the methodology. All authors contributed to and approve of the final version of the manuscript.

Table 1: Search Strategies for OVID Medline, Embase and Cochrane Central

Database(s): OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp contraceptive agents/ or exp hormonal contraception/
2	exp contraception/ or fertility control.mp. or fertilization inhibition.mp. or inhibition of fertilization.mp.
3	exp birth control/
4	exp family planning services/
5	desogestrel/ or norpregnenes/ or progesterone congeners/
6	exp ethinylestradiol/ or ethinyl estradiol.mp. or ethinylestradiol.mp.
7	dienogest.mp.
8	exp progestin/ or progestin$.mp. or progestogen.mp.
9	lynestrenol/
10	norethindrone/
11	levonorgestrel/
12	(etynodiol diacetate or ethynodiol diacetate).mp.
13	norgestrel/
14	mestranol.mp. or exp mestranol/
15	exp estradiol/ or estradiol.mp. or oetradiol.mp.
16	(desogestrel or norpregnene$ or progestins).mp.
17	(progesterone congeners adj2 synthetic).mp.
18	drospirenone.mp.
19	lynestrenol.mp.
20	norethindrone.mp.
21	norgestrel.mp.
22	etonogestrel.mp.
23	gestodene.mp.
24	(levonorgestrel or D-norgestrel).mp.
25	norgestimate.mp.
26	dienogest.mp.
27	contracept*.mp.
28	birth control.mp.
29	family planning.mp.
30	or/1-29
31	exp sleep/

32	exp sleep-wake transition disorders/ or exp sleep deprivation/ or exp sleep wake disorders/ or exp dyssomnias/
33	(fragmented sleep or insufficient sleep syndrome$).mp.
34	exp sleep latency/ or exp sleep hygiene/
35	exp sleep arousal disorder/
36	exp sleep disorder/
37	sleep.mp.
38	(insomnia$ or hypersomnia$).mp. or "disorders of excessive somnolence"/
39	exp restless legs syndrome/ or restless legs syndrome.mp.
40	or/31-39
41	(comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case reports or historical article).pt.
42	animal/ not human/
43	or/41-42
44	(30 and 40) not 43
45	limit 44 to yr="1970-current"

Database: Embase 1974 to 2020 August 17

#	Searches
1	exp contraceptive agents/ or hormonal contraception/
2	exp contraception/ or fertility control.mp. or fertilization inhibition.mp. or inhibition of fertilization.mp.
3	exp birth control/
4	exp family planning services/
5	desogestrel/ or norpregnenes/ or progesterone congeners/
6	exp ethinylestradiol/ or ethinyl estradiol.mp. or ethinylestradiol.mp.
7	dienogest.mp.
8	exp progestin/ or progestin$.mp. or progestogen.mp.
9	lynestrenol/
10	norethindrone/
11	norgestrel/
12	levonorgestrel/
13	(etynodiol diacetate or ethynodiol diacetate).mp.
14	mestranol.mp. or exp mestranol/
15	exp estradiol/ or estradiol.mp. or oetradiol.mp.
16	(desogestrel or norpregnene$ or progestins).mp.
17	(progesterone congeners adj2 synthetic).mp.

18	drospirenone.mp.
19	lynestrenol.mp.
20	norethindrone.mp.
21	norgestrel.mp.
22	etonogestrel.mp.
23	gestodene.mp.
24	(levonorgestrel or D-norgestrel).mp.
25	norgestimate.mp.
26	dienogest.mp.
27	contracept*.mp.
28	Birth Control.mp.
29	Family planning.mp.
30	or/1-29
31	exp sleep/
32	exp Sleep-Wake Transition Disorders/ or exp Sleep Deprivation/ or exp Sleep Wake Disorders/ or exp dyssomnias/
33	(fragmented sleep or insufficient sleep syndrome$).mp.
34	exp sleep latency/ or exp sleep hygiene/
35	exp sleep arousal disorder/
36	sleep*.mp.
37	(insomnia$ or hypersomnia$).mp. or "disorders of excessive somnolence"/
38	exp restless legs syndrome/ or restless legs syndrome.mp.
39	exp sleep disorder/
40	or/31-39
41	(editorial or note or letter erratum or short survey or abstract).pt. or abstract report/ or letter/ or case study/
42	animal/ not human/
43	or/41-42
44	exp female/ or female$.mp. or women.mp. or woman.mp.
45	(30 and 40 and 44) not 43
46	limit 45 to yr="1970-current"

Database: Cochrane Central

#	Searches
1	MeSH descriptor: [Contraceptive Agents] explode all trees
2	MeSH descriptor: [Hormonal Contraception] explode all trees

3	MeSH descriptor: [Contraception] explode all trees
4	Fertility Control
5	Fertilization inhibition
6	inhibition of fertilization
7	MeSH descriptor: [Family Planning Services] explode all trees
8	MeSH descriptor: [Desogestrel] this term only
9	MeSH descriptor: [Norpregnenes] this term only
10	MeSH descriptor: [Progesterone Congeners] this term only
11	MeSH descriptor: [Ethinyl Estradiol] explode all trees
12	ethinyl estradiol
13	ethinylestradiol
14	dienogest
15	MeSH descriptor: [Progestins] explode all trees
16	progestin$
17	progestogen
18	MeSH descriptor: [Lynestrenol] this term only
19	MeSH descriptor: [Norethindrone] this term only
20	MeSH descriptor: [Norgestrel] this term only
21	MeSH descriptor: [Levonorgestrel] this term only
22	(Etynodiol diacetate) OR (Ethyndiol diacetate)
23	mestranol
24	MeSH descriptor: [Mestranol] explode all trees
25	MeSH descriptor: [Estradiol] explode all trees
26	estradiol
27	oetradiol
28	(desogestrel or norpregnene$ or progestins)
29	progesterone congeners adj2 synthetic
30	drospirenone
31	lynestrenol
32	norethindrone
33	norgestrel
34	etonogestrel
35	gestodene
36	levonorgestrel or d-norgestrel
37	norgestimate
38	dienogest
39	contracept*
40	birth control
41	family planning
42	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
43	MeSH descriptor: [Sleep] explode all trees

44	MeSH descriptor: [Sleep-Wake Transition Disorders] explode all trees
45	MeSH descriptor: [Sleep Deprivation] explode all trees
46	MeSH descriptor: [Sleep Wake Disorders] explode all trees
47	MeSH descriptor: [Dyssomnias] explode all trees
48	fragmented sleep or insufficient sleep syndrome$
49	MeSH descriptor: [Sleep Hygiene] explode all trees
50	MeSH descriptor: [Sleep Latency] explode all trees
51	MeSH descriptor: [Sleep Arousal Disorders] explode all trees
52	sleep*
53	insomnia$ or hypersomnia$
54	disorders of excessive somnolence
55	MeSH descriptor: [Restless Legs Syndrome] explode all trees
56	restless legs syndrome
57	43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56
58	(comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case reports or historical article).pt.
59	MeSH descriptor: [Animals] explode all trees
60	MeSH descriptor: [Humans] explode all trees
61	58 and 59 not 60
62	(42 and 57) not 61
63	limit 62 to yr="1970-current"

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Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a-not an update
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2-PROSPERO pending
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	1
Amendments			

	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	14
Sponsor	#5b	Provide name for the review funder and / or sponsor	n/a
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	n/a
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	4-7
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-11
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	15-19
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8

Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	11
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9-11
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	12
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	12
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	12-13
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	13
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	12-13
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	12
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	12

Notes:

- 1b: n/a-not an update
- 2: 2-PROSPERO pending The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution License CC-BY 4.0. This checklist was completed on 07. October 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

The Relationship between Hormonal Contraceptives and Insomnia among Women of Reproductive Age: A Systematic Review Protocol

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The Relationship between Hormonal Contraceptives and Insomnia among Women of Reproductive Age: A Systematic Review Protocol

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ABSTRACT

Introduction The exact etiology of sleep disruptions is unknown but hormonal fluctuations during the menstrual cycle, pregnancy, and menopause have been shown to potentially affect how well a woman sleeps. The aim of this systematic review is to investigate whether oral contraceptives (OC) and other hormonal contraceptives are associated with a decreased quality of sleep and increased sleep duration in women of reproductive age.

Methods This review will analyze data from randomized controlled trials or non-randomized comparative studies investigating the association between hormonal contraceptives, especially OC (second generation or further), and sleep-related outcomes among women of reproductive age, including sleep quality and sleep disorders. Reviews addressing the same research question with similar inclusion/exclusion criteria will be included. A literature search will be performed using the MEDLINE, EMBASE and Cochrane CENTRAL databases. Risk of methodological bias will be assessed using The Cochrane Collaboration's revised tool for assessing risk of bias in randomised trials (RoB 2.0). Two reviewers will independently assess eligibility of studies, risk of bias and extract the data. A third author will solve discrepancies. All extracted data will be presented in summary tables and narrative form. For sleep measures investigated by two or more studies with low heterogeneity, we will conduct random-effects meta-analysis to estimate the magnitude of the overall effect of hormonal contraceptives. As long as studies included in the systematic review form a connected network, a network meta-analysis will be conducted to estimate the comparative effect of different contraceptives. The GRADE approach will be used to summarise the quality of evidence.

Keywords: hormonal contraceptive, oral contraceptive, contraception, sleep quality, sleep duration

Ethics and dissemination: Ethics approval is not required as we analyze data from previously reported studies.

PROSPERO registration number: CRD42020199958.

Article Summary

Strengths and Limitations of this study:

- This review on the association of oral contraceptive use and sleep is based on a robust, librarian consulted search strategy.
- All papers are assessed by two independent reviewers to mitigate bias.
- The quality of all papers will be assessed with the appropriate tool.
- Papers in languages other than English are not included, leading to potential for language bias.

Word Count: 3531

INTRODUCTION

The invention of oral contraceptives (OC) is a medical innovation which has evolved dramatically in the past decades.[1] The first-generation OC pill, Enovid, contained high doses of norethynodrel (i.e., progestin, 10 mg) and mestranol (i.e., estrogen, 150µg) and was introduced in 1960. To lower the risk of thromboembolic complications associated with the use of OC pills, the second-generation of OC was developed in the 1970s by lowering the dose of the progestin component from 10 mg to 1 mg, and the estrogen component from 150µg to 35µg. Development of new progestins, mainly levonorgestrel, gave way to the second generation of OCs, which contained a lower dosage of progesterone.[2] The second-generation OCs was shown to be associated with an increased risk of myocardial infarction, stroke, acne and weight gain, which were correlated with the androgenicity of the progestin. [3] Subsequently, the third generation of OCs was developed in the 1990s to address side effects that arise due to the androgenicity of second generation progestins, such as acne and weight gain. [3] Fourth generation OCs are more selective and bind specifically to the progesterone receptor, further reducing side effects such as edema and improving skin appearance.[4] Presently, combined OCs containing both progesterone and estrogen, and progesterone only pills are used.

Worldwide, there are around 1.9 billion women of reproductive age. Hormonal contraceptives, OC, vaginal ring, contraceptive skin patches, implants, injections, and hormonal intrauterine contraceptive devices (IUDs), are widely used around the world in women of reproductive age.[5] One hundred and fifty-one million women use OCs with usage varying by region.[5] OC are used more widely in developed countries, especially Europe and North America, than in developing countries. [5] In 2019, 17.2% women of reproductive age in high-income countries, 6.7% in middle-income countries, and 3.8% in low-income countries used OC pills. [5]

The prevalence of OC usage worldwide has remained stable in the last 25 years, however, the overall number of users increased since the world population has increased.[5] Other hormonal contraceptives have been widely adopted as well and used by over 97 million women in the world.[5] These hormonal contraceptives have different dosage, formulation, mechanism of action, and applicable groups compared to OCs.[6] Unlike oral contraceptives which are taken consistently and provide a stable dosage of the estrogen and progestin components, other hormonal contraceptives have the potential to provide lower dose of progestin and estrogen. It has been shown that hormonal IUDs release levonorgestrel directly into the uterus, only a small amount is absorbed into the rest of the body, i.e. its effects are mostly paracrine rather then systemic. [7]An investigation of Nexplanon, an implant contraceptive lasting 3 years, found progestin absorption at 60 mg/day after 3 months and 30mg/day after 6 months.[8]

Progesterone, the primary component in OCs and other hormonal contraceptives, is an agonist of gamma-aminobutyric acid (GABA) receptors through a metabolite allopregnanolone. [9] GABA is a crucial molecule in sleep promotion – most sleep-promoting neurons are sensitive to GABA. [10] Common sleep medications, such as benzodiazepines have been shown to positively modulate GABA signalling. [10] The potency of progestin is similar to that of benzodiazepines and has similar agonistic effects. Changes in electroencephalogram (EEG) activity seen with progesterone administration are similar to those evoked by benzodiazepines. [9] Studies in rat models have shown that administration of exogenous progesterone leads to dose-dependent decreased sleep latency and wakefulness. [9] The mechanism behind the effect of estrogen on sleep is not well elucidated but rat studies have shown that administration of estrogen promotes sleep during the sleep period and reduces sleep during the wakefulness period.[11] The overall effect on sleep is likely

caused by a combination of both estrogen and progesterone, although the magnitude of their contribution to sleep changes is unknown.[12]

High quality sleep is as essential as regular exercise and eating a balanced diet for maintenance of optimal health and well-being. Severe sleeping problems, such as insomnia, are important matters from both a public health perspective and an individual level. Insomnia is associated with depression, anxiety, substance abuse, cognitive impairment, metabolic disorders (e.g., diabetes, dyslipidemia, and obesity) and cardiovascular diseases.[13-15] Women are more likely than men to have sleep problems including insomnia and restless leg syndrome. The exact etiology of these sleep disruptions is unknown but hormonal fluctuations during the menstrual cycle, pregnancy, and menopause have been shown to potentially affect how well a woman sleeps.[16-18] During ovulation, there is a surge of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) which leads to a decrease in estrogen concentration and an increase in progesterone.[19] During the luteal phase, progesterone concentrations increase and estrogen levels are high up to the mid-phase. Starting from the mid-luteal phase, both estrogen and progesterone levels decrease.[19] Sleep disturbances are most commonly reported at the end of the luteal phase and early follicular phase.[20] OCs are taken each day for 21 days, providing a constant, exogenous source of estrogen and progesterone, preventing the release of FSH and LH and thus the production of a follicle or ovulation.[21] Therefore, OC use may affect women's sleep-wake cycle and cause physiological changes that lead to sleep disturbance.

Unlike other commonly prescribed drugs, OC pills and other contraceptives are taken by healthy women for long periods of time. Safety trials have focussed largely on breast cancer and venous thromboembolism (VTE) risk. [22-23] Despite decreases in estrogen concentration with later OC generations, its use has been shown to be associated with an increased risk of developing breast

cancer and venous thromboembolism.[3] A 2017 cohort study found OC intake was associated with a reduced risk of colorectal, endometrial and ovarian cancers and increased risk of cervical and breast cancer.[24] Another meta-analysis found a positive association between OC usage and risk of hypertension. [25] Studies in women have varied findings on the association between OC use and sleep quality and duration. Differences in methodology, including the formulation of contraceptives taken, stratification of formulations, measurements of sleep, or the phase of the menstrual cycle of naturally cycling women used as comparison may explain the different findings between studies. For instance, a pilot study published in 2020 by Guida *et al* found significantly increased sleep duration for users of oral progestins, oral gestodene and 13.5 mg levonorgestrel intrauterine systems, compared with naturally cycling women (women not currently using any hormonal contraceptive), and decreased sleep latency and better sleep quality for users of depot-administered contraceptives. [26] However, a polysomnography study published in 2012 by Hachul *et al* found decreased sleep latency in women using OC and no difference in overall sleep quality. [27] A randomized control trial by Lundin *et al* found no significant sleep related results, while a cross sectional analysis by Bezerra *et al* found that hormonal contraceptive users had worse sleep quality compared with their naturally cycling counterparts. [28-29]

Given the high prevalence of hormonal contraceptive use among women of reproductive age and the relationship between hormonal contraceptive use and sleep varying in both magnitude and direction in the current literature, there is an urgent need to provide women with accurate, evidence based information to inform their use of hormonal contraception.[26-29] Hence, the objective of this systematic review is to compile and elucidate the association between hormonal contraceptive, especially OC, use and sleep (including the quality of sleep, sleep disorders, and duration of sleep). Our hypothesis is that OCs and other hormonal contraceptives are associated

with a decreased quality of sleep and increased sleep duration in women of reproductive age. Findings from this review will provide insights to women choosing between different methods and formulations, while also inform the development of new progestins for future generations of OCs. The systematic review protocol was registered at the website of the International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42020199958).

METHODS

Our protocol follows the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols 2015 (PRISMA-P 2015) guidelines.[30]

Patient and Public Involvement

No patients were involved in this protocol.

Literature search

We developed a comprehensive search strategy with input from a research librarian at McMaster University. The systematic search for existing relevant systematic review and original studies is conducted in the Ovid MEDLINE and Embase (Excerpta Medica dataBASE) electronic databases, and the Cochrane Library (including Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials). Search terms covered all words related to birth control, ingredients of oral contraceptives, hormonal contraceptives, menstrual cycle, and sleep. We limited the search to studies or systematic reviews published from 1970 to present to ensure that we include all published studies or reviewers on second and further generation OCs. For sleep outcome measures, we searched sleep terms in the full text besides the title and abstract in case sleep is investigated as a secondary outcome and therefore not reported in the abstract. The

comprehensive search strategies for each database are presented in Table 1. The reference lists of all included studies will be checked to identify additional potentially eligible studies.

Study Selection and Screening

Systematic screening of the studies will be first conducted at the title and abstract level, and then at the full-text level to determine if a study meets eligibility criteria by two independent reviewers. Any potential conflicts between the reviewers will be resolved through discussion. If discrepancies in judgment remain after discussion, a third-party reviewer will be consulted to resolve the conflict and provide a final decision.

Eligibility criteria

(1) Study Characteristics

Existing systematic reviews will be included if they (i) address the same research question with similar inclusion and exclusion criteria as ours; and (ii) have a low risk of bias in study eligibility criteria, identification and selection of studies, data collection and study appraisal, and synthesis and findings assessed using the Risk of Bias in Systematic Reviews (ROBIS) tool.[31]

For original studies, we will include (i) randomized controlled trials and non-randomized comparative studies that take into account the effect of potential confounders (e.g., age, race, and socioeconomic status)[32-34] using methods such as multivariable analysis, propensity-score matching, or showing no statistically significant differences in baseline characteristics between participants in comparison groups; (ii) studies on human participants; (iii) studies investigate second generation or more recent OCs; and (iv) studies investigate the association between OC use and sleep-related outcomes, either as the primary or secondary objective.

(2) Participants

Participants or subgroups of participants are females between 15 and 49 years old.

(3) Exposure

Participants or subgroups of participants take second generation or more recent OC or other hormonal contraceptives containing both progesterone and estrogen or progesterone only, regardless of its brand, dose, and frequency, to avoid pregnancy, as long as their hormonal contraceptive use pattern is sustained for at least three months.

(4) Comparator

Included studies must have comparison groups of women who are using (i) non-hormonal contraceptives; (ii) naturally cycling (i.e., not use any contraceptive methods); (iii) same agent as the exposure but in different dose, frequency, and duration; and (iv) second generation or more recent OC or other contraceptives but different from the exposure. Since recent usage or cessation of hormonal contraceptive use may cause hormonal oscillations, we will only include studies with participants keeping their contraceptive use pattern (either using or not using hormonal contraceptives) for at least three months.

(5) Outcomes

We are interested in any sleep-related outcomes and a variety of sleep measurements for sleep quality, sleep duration, and sleep disorder will be included in this systematic review. The sleep measurements can be questionnaires based on Likert Scale items listed below but not limited to these tools:

(i) The Pittsburgh Sleep Quality Index (PSQI).[35] It measures seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction over the last four weeks. The PSQI is a subjective measure of sleep. Subjects self-rate each of the seven domains of sleep from 0 to 3, where 3 represents the negative extreme on the Likert

Scale. A subject with a global sum of 5 or greater is considered as a poor sleeper. Studies reported sleep quality in any of the above seven domains during and after taking OCs will be included in the review.

(ii) The Epworth Sleepiness Scale (ESS) is a self-administered test used to assess daytime sleepiness.[36] It consists of 8 questions with different scenarios and a scale from 0-3 where subjects would indicate how likely they are to fall asleep in that situation. The scores are summed for a total score between 0 and 24. [36] Studies reporting sleepiness with any of the 8 questions during and after taking OCs will be included in the review.

(iii) The Athens Insomnia Scale (AIS), which is also a self-administered psychometric instrument designed for quantifying sleep difficulty.[37] The AIS consists of eight items: sleep induction (i.e., time to fall asleep after turning-off the lights), night awakenings, final awakening earlier than desired, total sleep duration, overall quality of sleep, sense of well-being during the day, functioning (physical and mental) during the day, and sleepiness during the day. Each item is rated from 0 to 3 with higher scores indicating more impaired sleep. The total score ranges from 0 to 24 and a total score of 6 or more is considered as insomnia. Studies reported any or all of the above eight insomnia-related items during and after taking OCs will be included in the review.

(iv) The Insomnia Severity Index (ISI), a self-administered questionnaire used to assess insomnia. [38] The ISI consists has a one month recall period and assesses 7 domains: severity of sleep onset, sleep maintenance, difficultly waking up in the morning, sleep dissatisfaction, interference of sleep with daytime functioning, noticeability of sleep problems by others, and distress caused by sleep difficulties. Each domain is rated on a scale from 0 to 4 with higher scores indicating more problematic sleep. The score is

summed forming a total score between 0 and 28, with a score of 8 and above indicative of insomnia. [38] Studies reporting any domains from the ISI during and after taking OCs will be included in the review.

We will also include continuous measures of sleep quality and disorder. These measures include: (i) total amount of sleep obtained, either during nocturnal sleep episode or across the 24-hour period; (ii) sleep latency, i.e., how long it takes the participant to fall asleep; (iii) how many times the participant wakes up; (iv) how many minutes the participant is awake during the night; (v) sleep efficiency, i.e., what percentage of time spent in bed is the participant actually asleep. The total sleep time is equal to the total amount of time spent in bed (in minutes) minus the sum of time it takes to fall asleep and the time spent awake throughout the night. The percentage is calculated as the total sleep time divided by total time in bed. Given we will only include studies with participants keeping their contraceptive use pattern for at least three months, the sleep outcomes from the eligible studies will be summarized after participants keeping their contraceptive use pattern for at least three months as well.

Exclusion criteria

The following studies will be excluded from this systematic review: (1) studies only recruited patients with specific comorbidities or conditions, such as hormonal disorder, acne, perimenopause, postmenopause, dysmenorrhea, depression etc,, since these conditions may be associated with sleep problems and will not allow us to elucidate the association between hormonal contraceptives and sleep; (2) studies investigating the first-generation OC since it is not available in the market anymore due to severe side effects; (3) studies investigating emergency contraception; and (4) studies in languages other than English. We will exclude emergency

contraception from this review as the hormonal effect of the contraception is significantly different from long-acting contraception. The half-life of oral leovnoregestrel is around 24-32 hours, which is not significant when considering long-term effect on sleep.[39]

Data abstraction

A standard form will be developed to extract data from the included studies. From each article, the author, study design, study population, publication year, journal, participant demographics, OC used, intervention details, comparison groups, sleep outcomes, and the association between OC use and sleep will be extracted. Additionally, any mean values, standard deviation and confidence intervals, and all information needed for appraisal of internal validity will be extracted. This will be done in a standardized data extraction form by two reviewers independently. When consensus is not reached, a third researcher will be consulted to reach the final decision. Data will be presented in narrative form and summary tables.

Risk of bias assessment

For randomized controlled trials, the risk of bias in each included study for each outcome will be evaluated independently by two reviewers, using the Cochrane Collaboration Risk of Bias in randomized trials (RoB 2.0 tool).[40] Studies will be assessed from 5 domains: bias from randomisation, bias from deviates from intended interventions, bias due to missing data, bias in outcome measurement and bias in the selection of the reported result. [40] An overall rating of low bias, some concerns about bias or high bias will be given depending on the result of assessment. The Cochrane Risk of Bias in Non-randomized studies – of Interventions (ROBINS-1 tool) will be used to assess the risk of bias for each outcome in non-randomized comparative studies. [41]Risk

of Bias in Systematic Reviews (ROBIS) tool will be used to assess the risk of bias for the eligible systematic reviews.[42]

Grading the strength of evidence

The certainty of the evidence per outcome for each comparison will be assessed from five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach and be classified into four levels of evidence (high, moderate, low or very low).[43]

Data synthesis

All data extracted will be presented in both narrative form and in summary tables. If data is missing, the study authors will be contacted to try to obtain the data. For sleep measures investigated by two or more studies, if there are no clinical heterogeneity (e.g., different age or intervention) and methodological heterogeneity (e.g., different measurement tools), statistical heterogeneity will be assessed using Q statistic with a p value < 0.1 indicating for significant heterogeneity. The I^2 statistic will also be calculated with 25%, 50% and 75% representing low, medium, and high heterogeneity, respectively.[44] The heterogeneity in OC effects may be caused by differences in study populations (such as age of patients), different OC or doses received, length of follow-up, and other factors. If heterogeneity level is low or medium, we will conduct random-effects meta-analyses to estimate the magnitude of the overall effect of OC, with 95% confidence interval depicting the uncertainty around the estimate. Subgroup analyses (e.g., by age) and sensitivity analyses (e.g., by progesterone dose) will be conducted as if sufficient data are available. As long as studies included in the systematic review form a connected network, a network meta-analysis using both direct and indirect evidence will be conducted to estimate the comparative harm of different contraceptives.[45-46] Results from the network meta-analysis will

allow us to summarize and interpret a wider picture of the evidence for the putative effect of hormonal contraceptives on sleep.

DISCUSSION

Strengths and limitations

This systematic review will be the first to provide quantitative estimates of the association between hormonal contraceptives, especially OC, use and sleep outcomes in healthy women. Our systematic review methodology includes explicit eligibility criteria created in consultation with research librarians, and the usage of tested, standardized abstraction forms. We will calibrate our review methods throughout the review process for optimal consistency among reviewers. The GRADE approach will be applied to aggregate data, the PRISMA-P reporting checklist is followed to draft this systematic review protocol, and the PRISMA reporting checklist will be followed to draft this systematic review later. The κ statistic will be reported to identify issues with reproducibility. Our review will encompass a wide range of hormonal contraceptive formulations and sleep outcome measurements. We anticipate limitations with regard to publication bias and recall bias as the majority of studies employ self-administered tools to assess sleep quality and duration.

Study implications

Sleep quality is a crucial outcome that affect overall life quality in women of reproductive age and may indicate risk of developing comorbid conditions. The relationship between hormonal contraceptive use and sleep quality, duration and disorder have been reported inconsistently in the current literature. Hormonal contraceptives have been more and more widely accepted by women. However, no study has attempted to provide systematic evidence on the association between hormonal contraceptive use and sleep. Our systematic review will elucidate the association

between hormonal contraceptive use and sleep quality. Moreover, it will contribute evidence that will support the improvement of guidelines for taking hormonal contraceptive in healthy women and promote awareness of safety for taking hormonal contraceptive, especially OCs.

It is challenging to design, conduct, and analyze original studies investigating the association between OC use and sleep quality. For instance, a wide variety of OC are utilized in women and they may change to other brands of OC tablets or birth control methods. In addition, most studies use subjective sleep measures, which may involve recall the information in the past. Through appraisal of published studies, our systematic review will inform the improvement in the design and implementation of future research in this field.

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Contributors: JM, MC, XY, CW conceptualized and designed the protocol, drafted the initial manuscript and reviewed the manuscript. MC, XY, JM, QW, HK, and HR defined the concepts and search items, data extraction process as well as methodological appraisal of the study. MC, JM, QW, and XY planned the data extraction and statistical analysis. LT, CM, and NZ provided critical insights. All authors approved the final manuscript.

Table 1: Search Strategies for OVID Medline, Embase and Cochrane Central

Database(s): OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp contraceptive agents/ or exp hormonal contraception/
2	exp contraception/ or fertility control.mp. or (fertiliz* adj3 inhibit*).mp.
3	exp birth control/
4	exp family planning services/
5	desogestrel/ or nor pregnenes/ or progesterone congeners/
6	exp ethinylestradiol/ or ethinyl estradiol.mp. or ethinylestradiol.mp.
7	dienogest.mp.
8	exp progestin/ or progestin$.mp. or progestogen.mp.
9	lynestrenol/
10	norethindrone/
11	levonorgestrel/
12	(etynodiol diacetate or ethynodiol diacetate).mp.
13	norgestrel/
14	mestranol.mp. or exp mestranol/
15	exp estradiol/ or estradiol.mp. or oetradiol.mp.
16	(desogestrel or norpregnene$ or progestins).mp.
17	(progesterone congeners adj2 synthetic).mp.
18	drospirenone.mp.
19	lynestrenol.mp.
20	norethindrone.mp.
21	norgestrel.mp.
22	etonogestrel.mp.
23	gestodene.mp.
24	(levonorgestrel or D-norgestrel).mp.
25	norgestimate.mp.
26	dienogest.mp.
27	contracept*.mp.
28	birth control.mp.
29	family planning.mp.
30	Intrauterine device.mp. or “intra uterine device”.mp.
31	exp Contraceptive Devices, Female/
32	Intrauterine system.mp.
33	Intrauterine contraceptive device.mp.
34	iud*.mp. or iucd*.mp.
35	exp Medroxyprogesterone/ or Depotmedroxyprogesterone.mp. or depo-medroxyprogesterone.mp. or medroxyprogesterone.mp.
36	Depo-provera.mp. or depo provera.mp.

37	(vaginal or hormon* or contraceptive) adj2 (ring or patch or injection).mp.
38	DPMA.mp.
39	or/1-38
40	exp sleep/
41	exp sleep-wake transition disorders/ or exp sleep deprivation/ or exp sleep wake disorders/ or exp dyssomnias/
42	(fragmented sleep or insufficient sleep syndrome$).mp.
43	exp sleep latency/ or exp sleep hygiene/
44	exp sleep arousal disorder/
45	exp sleep disorder/
46	Sleep*.af.
47	(insomnia$ or hypersomnia$).mp. or "disorders of excessive somnolence"/
48	exp restless legs syndrome/ or restless legs syndrome.mp.
49	or/40-48 → all sleep terms
50	(comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case reports or historical article).pt.
51	animal/ not human/
52	or/50=51 or/two above
53	(39 and 49) not 52
54	limit 53 to yr="1970-current"

Database: Embase 1974 to 2020 August 17

#	Searches
1	exp contraceptive agents/ or hormonal contraception/
2	exp contraception/ or fertility control.mp. or fertilization inhibition.mp. or inhibition of fertilization.mp.
3	exp birth control/
4	exp family planning services/
5	desogestrel/ or norpregnenes/ or progesterone congeners/
6	exp ethinylestradiol/ or ethinyl estradiol.mp. or ethinylestradiol.mp.
7	dienogest.mp.
8	exp progestin/ or progestin$.mp. or progestogen.mp.
9	lynestrenol/
10	norethindrone/
11	norgestrel/
12	levonorgestrel/
13	(etynodiol diacetate or ethynodiol diacetate).mp.
14	mestranol.mp. or exp mestranol/
15	exp estradiol/ or estradiol.mp. or oetradiol.mp.
16	(desogestrel or norpregnene$ or progestins).mp.

17	(progesterone congeners adj2 synthetic).mp.
18	drospirenone.mp.
19	lynestrenol.mp.
20	norethindrone.mp.
21	norgestrel.mp.
22	etonogestrel.mp.
23	gestodene.mp.
24	(levonorgestrel or D-norgestrel).mp.
25	norgestimate.mp.
26	dienogest.mp.
27	contracept*.mp.
28	Birth Control.mp.
29	Family planning.mp.
30	Intrauterine device.mp. or “intra uterine device”.mp.
31	exp Contraceptive Devices, Female/
32	Intrauterine system.mp.
33	Intrauterine contraceptive device.mp.
34	iud*.mp. or iucd*.mp.
35	exp Medroxyprogesterone/ or Depotmedroxyprogesterone.mp. or depo-medroxyprogesterone.mp. or medroxyprogesterone.mp.
36	Depo-provera.mp. or depo provera.mp.
37	(vaginal or hormon* or contraceptive) adj2 (ring or patch or injection).mp.
38	DPMA.mp.
39	or/1-38
40	exp sleep/
41	exp Sleep-Wake Transition Disorders/ or exp Sleep Deprivation/ or exp Sleep Wake Disorders/ or exp dyssomnias/
42	(fragmented sleep or insufficient sleep syndrome$).mp.
43	exp sleep latency/ or exp sleep hygiene/
44	exp sleep arousal disorder/
45	sleep*.af.
46	(insomnia$ or hypersomnia$).mp. or "disorders of excessive somnolence"/
47	exp restless legs syndrome/ or restless legs syndrome.mp.
48	exp sleep disorder/
49	or/40-48
50	(editorial or note or letter erratum or short survey or abstract).pt. or abstract report/ or letter/ or case study/
51	animal/ not human/
52	or/50-51
53	exp female/ or female$.mp. or women.mp. or woman.mp.
54	(39 and 49 and 53) not 52

55	limit 54 to yr="1970-current"

Database: Cochrane Central

#	Searches
1	MeSH descriptor: [Contraceptive Agents] explode all trees
2	MeSH descriptor: [Hormonal Contraception] explode all trees
3	MeSH descriptor: [Contraception] explode all trees
4	Fertility Control
5	Fertilization inhibition
6	inhibition of fertilization
7	MeSH descriptor: [Family Planning Services] explode all trees
8	MeSH descriptor: [Desogestrel] this term only
9	MeSH descriptor: [Norpregnenes] this term only
10	MeSH descriptor: [Progesterone Congeners] this term only
11	MeSH descriptor: [Ethinyl Estradiol] explode all trees
12	ethinyl estradiol
13	ethinylestradiol
14	dienogest
15	MeSH descriptor: [Progestins] explode all trees
16	progestin$
17	progestogen
18	MeSH descriptor: [Lynestrenol] this term only
19	MeSH descriptor: [Norethindrone] this term only
20	MeSH descriptor: [Norgestrel] this term only
21	MeSH descriptor: [Levonorgestrel] this term only
22	Etynodiol diacetate
23	mestranol
24	MeSH descriptor: [Mestranol] explode all trees
25	MeSH descriptor: [Estradiol] explode all trees
26	estradiol
27	oetradiol
28	(desogestrel or norpregnene$ or progestins)
29	progesterone congeners adj2 synthetic
30	drospirenone
31	lynestrenol
32	norethindrone
33	norgestrel
34	etonogestrel
35	gestodene
36	levonorgestrel
37	norgestimate
38	dienogest
39	contracept*

40	birth control
41	family planning
42	MeSH descriptor: [Intrauterine device] this term only
43	Intrauterine device
44	Intrauterine system
45	Intrauterine contraceptive device
46	Iud
47	d-norgestrel
48	iucd
49	Depotmedroxyprogesterone
50	depo-medroxyprogesterone
51	medroxyprogesterone
52	Depo-provera
53	depo provera
54	DPMA
55	Vaginal ring/
56	Ethyndiol diacetate
57	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56
58	MeSH descriptor: [Sleep] explode all trees
59	MeSH descriptor: [Sleep-Wake Transition Disorders] explode all trees
60	MeSH descriptor: [Sleep Deprivation] explode all trees
61	MeSH descriptor: [Sleep Wake Disorders] explode all trees
62	MeSH descriptor: [Dyssomnias] explode all trees
63	fragmented sleep or insufficient sleep syndrome$
64	MeSH descriptor: [Sleep Hygiene] explode all trees
65	MeSH descriptor: [Sleep Latency] explode all trees
66	MeSH descriptor: [Sleep Arousal Disorders] explode all trees
67	sleep*
68	insomnia$ or hypersomnia$
69	disorders of excessive somnolence
70	MeSH descriptor: [Restless Legs Syndrome] explode all trees
71	restless legs syndrome
72	58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71
73	(comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case reports or historical article).pt.
74	MeSH descriptor: [Animals] explode all trees
75	MeSH descriptor: [Humans] explode all trees
76	73 and 74 not 75
77	(57 and 72) not 76
78	limit 77 to yr="1970-current"

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Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	16

Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	16
Sponsor	#5b	Provide name for the review funder and / or sponsor	n/a
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	n/a
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	4-8
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7-8
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-12
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	17-24
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	12-13
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8-9
Study records - data	#11c	Describe planned method of extracting data from reports (such as	8-9

collection process		piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	13
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	13
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	13
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	14
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	14-15
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	14
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	14
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	14

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The Relationship between Hormonal Contraceptives and Sleep among Women of Reproductive Age: A Systematic Review Protocol

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The Relationship between Hormonal Contraceptives and Sleep among Women of Reproductive Age: A Systematic Review Protocol

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ABSTRACT

Introduction The exact etiology of sleep disruptions is unknown but hormonal fluctuations during the menstrual cycle, pregnancy, and menopause have been shown to potentially affect how well a woman sleeps. The aim of this systematic review is to investigate whether hormonal contraceptives are associated with a decreased quality of sleep and increased sleep duration in women of reproductive age.

Methods This review will analyze data from randomized controlled trials or non-randomized comparative studies investigating the association between hormonal contraceptives and sleep-related outcomes among women of reproductive age, including sleep quality and sleep disorders. Reviews addressing the same research question with similar inclusion/exclusion criteria will be included. A literature search will be performed using the MEDLINE, EMBASE and Cochrane CENTRAL databases. The Cochrane Collaboration's Risk of Bias for Randomised Trials (RoB 2.0) and The Cochrane Risk of Bias for Non-randomized studies – of Interventions (ROBINS-1 tool) will be used to assess risk of bias for each outcome in eligible studies. Two reviewers will independently assess eligibility of studies, risk of bias and extract the data. A third author will solve discrepancies. All extracted data will be presented in summary tables and narrative form. For sleep measures investigated by two or more studies with low heterogeneity, we will conduct random-effects meta-analysis to estimate the magnitude of the overall effect of hormonal contraceptives. If studies included in this systematic review form a connected network, a network meta-analysis will be conducted to estimate the comparative effect of different contraceptives. The GRADE approach will be used to summarise the quality of evidence. Our protocol follows the

Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols 2015 (PRISMA-P 2015) guidelines.

Keywords: hormonal contraceptive, oral contraceptive, contraception, sleep quality, sleep duration

Ethics and dissemination: Ethics approval is not required as we analyze data from previously reported studies.

PROSPERO registration number: CRD42020199958.

Article Summary

Strengths and Limitations of this study:

- This systematic review on the association between hormonal contraceptive use and sleep is based on a robust, librarian consulted search strategy.
- The literature review, data extraction, and risk of bias assessment are performed by two independent reviewers to mitigate bias.
- The risk of bias of each outcome from included papers will be assessed with the appropriate tool.
- Papers in languages other than English are not included, leading to potential for language bias.

Word Count: 3633

INTRODUCTION

Worldwide, there are around 1.9 billion women of reproductive age. Hormonal contraceptives including oral contraceptives (OC), vaginal ring, contraceptive skin patches, implants, injections, and hormonal intrauterine contraceptive devices (IUDs), are widely used around the world in women of reproductive age to avoid unintentional pregnancy.[1] Of the 842 million women using modern forms of contraception, 43% are using hormonal contraceptives. The overall number of users of hormonal contraceptives is increasing annually.[1] One hundred and fifty-one million women use OCs with usage varying by region.[1] Other hormonal contraceptives such as implants, vaginal rings, and intrauterine devices have been widely adopted as well and used by over 256 million women in the world.[1] These hormonal contraceptives have different dosage, formulation, mechanism of action, and applicable groups compared to OCs.[2] Unlike OCs which are taken consistently and provide a stable dosage of the estrogen and progestin components, other hormonal contraceptives have the potential to provide lower dose of progestin and estrogen. It has been shown that hormonal IUDs release levonorgestrel directly into the uterus, only a small amount is absorbed into the rest of the body, thus its effects are mostly paracrine rather than systemic.[3]

Progesterone, a primary component in hormonal contraceptives, is an agonist of gamma-aminobutyric acid (GABA) receptors through a metabolite, allopregnanolone. [4] GABA is a crucial molecule in sleep promotion – most sleep-promoting neurons are sensitive to GABA. [5] Common sleep medications, such as benzodiazepines have been shown to positively modulate GABA signalling.[5] The potency of progestin is comparable to that of benzodiazepines and has similar agonistic effects. Changes in electroencephalogram activity seen with progesterone administration

are similar to those evoked by benzodiazepines.[4] Studies in rat models have shown that administration of exogenous progesterone leads to dose-dependent decreased sleep latency and wakefulness.[4] The mechanism behind the effect of estrogen on sleep is not well elucidated but rat studies have shown that administration of estrogen promotes sleep during the sleep period and reduces sleep during the wakefulness period.[6] The overall effect on sleep is likely caused by a combination of both estrogen and progesterone, although the magnitude of their contribution to sleep changes is unknown.[7]

High quality sleep is as essential as regular exercise and eating a balanced diet for maintenance of optimal health and well-being. Severe sleeping problems, such as insomnia, are important matters from both a public health perspective and an individual level. Insomnia is associated with depression, anxiety, substance abuse, cognitive impairment, metabolic disorders (e.g., diabetes, dyslipidemia, and obesity) and cardiovascular diseases.[8-10] Women are more likely than men to have sleep problems including insomnia and restless leg syndrome. The exact etiology of these sleep disruptions is unknown but hormonal fluctuations during the menstrual cycle, pregnancy, and menopause have been shown to potentially affect how well a woman sleeps.[11-13] During ovulation, there is a surge of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) which leads to a decrease in estrogen concentration and an increase in progesterone.[14] During the luteal phase, progesterone concentrations increase and estrogen levels are high up to the mid-phase. Starting from the mid-luteal phase, both estrogen and progesterone levels decrease.[14] Sleep disturbances are most commonly reported at the end of the luteal phase and early follicular phase.[15] OCs are taken each day for 21 days, providing a constant, exogenous source of estrogen and progesterone, preventing the release of FSH and LH and thus the production of a

follicle or ovulation.[16] Therefore, hormonal contraceptives may affect women's sleep-wake cycle and cause physiological changes that lead to sleep disturbance.

Unlike other commonly prescribed drugs, hormonal contraceptives are used by healthy women for long periods of time. Safety trials of hormonal contraceptives have focussed largely on breast cancer and venous thromboembolism risk. [17-19] Despite decreases in estrogen concentration with later OC generations, its use has been shown to be associated with an increased risk of developing breast cancer and venous thromboembolism.[20] A 2017 cohort study found OC intake was associated with a reduced risk of colorectal, endometrial and ovarian cancers and increased risk of cervical and breast cancer.[21] Studies in women have varied findings on the association between hormonal contraceptive use and sleep quality and duration. Differences in methodology, including the formulation of contraceptives taken, stratification of formulations, measurements of sleep, or the phase of the menstrual cycle of naturally cycling women used as comparison may explain the different findings between studies. For instance, a pilot study published in 2020 by Guida *et al* found significantly increased sleep duration for users of oral progestins, oral gestodene and 13.5 mg levonorgestrel intrauterine systems, compared with naturally cycling women (women not currently using any hormonal contraceptive), and decreased sleep latency and better sleep quality for users of depot-administered contraceptives.[22] However, a polysomnography study published in 2012 by Hachul *et al* found decreased sleep latency in women using OC and no difference in overall sleep quality.[23] A randomized control trial by Lundin *et al* found no significant sleep related results, while a cross sectional analysis by Bezerra *et al* found that hormonal contraceptive users had worse sleep quality compared with their naturally cycling counterparts. [24-25]

Given the high prevalence of hormonal contraceptive use among women of reproductive age and the relationship between hormonal contraceptive use and sleep varying in both magnitude and direction in the current literature, there is an urgent need to provide women with accurate, evidence-based information to inform their use of hormonal contraception.[22-25] Hence, the objective of this systematic review is to compile and elucidate the association between hormonal contraceptive use and sleep (including the quality of sleep, sleep disorders, and duration of sleep). Our hypothesis is hormonal contraceptives are associated with a decreased quality of sleep and increased sleep duration in women of reproductive age. Findings from this review will provide insights to women choosing between different methods and formulations, while also inform the development of new progestins for future generations of hormonal contraceptives. The systematic review protocol was registered at the website of the International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42020199958).

METHODS

Our protocol follows the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols 2015 (PRISMA-P 2015) guidelines.[26]

Patient and Public Involvement

No patients were involved in this protocol.

Literature search

We developed a comprehensive search strategy with input from a research librarian at McMaster University. The systematic search for existing relevant systematic review and original studies will be conducted in the Ovid MEDLINE and Embase (Excerpta Medica dataBASE) electronic databases, and the Cochrane Library (including Cochrane Database of Systematic

Reviews and Cochrane Central Register of Controlled Trials). Search terms will cover all words related to birth control, ingredients of oral contraceptives, hormonal contraceptives, menstrual cycle, and sleep. We will limit the search to studies or systematic reviews published from 1970 to present to ensure that we include all published studies or reviewes on hormonal contraceptives, excluding first generation oral contraceptives which had been discontinued after 1970s. For sleep outcome measures, we will search sleep terms in multi-purpose fields besides the title and abstract in case sleep is investigated as a secondary outcome and therefore not reported in the abstract. The comprehensive search strategies for each database are presented in Table 1. The reference lists of all included studies will be checked to identify additional potentially eligible studies.

Study Selection and Screening

Systematic screening of the studies will be first conducted at the title and abstract level, and then at the full-text level to determine if a study meets eligibility criteria by two independent reviewers. Any potential conflicts between the reviewers will be resolved through discussion. If discrepancies in judgment remain after discussion, a third-party reviewer will be consulted to resolve the conflict and provide a final decision.

Eligibility criteria

(1) Study Characteristics

Existing systematic reviews will be included if they (i) address the same research question with similar inclusion and exclusion criteria as ours; and (ii) have a low risk of bias in study eligibility criteria, identification and selection of studies, data collection and study appraisal, and synthesis and findings assessed using the Risk of Bias in Systematic Reviews (ROBIS) tool.[27]

For original studies, we will include (i) randomized controlled trials, and non-randomized comparative studies that take into account the effect of potential confounders (e.g., age, race, and

socioeconomic status)[28-30] using methods such as multivariable analysis, propensity-score matching, or showing no statistically significant differences in baseline characteristics between participants in comparison groups; (ii) studies on human participants; and (iii) studies which investigate the association between hormonal contraceptive use and sleep-related outcomes, either as the primary or secondary objective.

(2) Participants

Participants or subgroups of participants are females between 15 and 49 years old.

(3) Exposure

Participants who take second generation or more recent OC or other hormonal contraceptives containing both progesterone and estrogen or progesterone only, regardless of its brand, dose, and frequency, to avoid pregnancy, as long as their hormonal contraceptive use pattern is sustained for at least three months by the time sleep outcomes are assessed. The first three months of hormonal contraception use or discontinuation of hormonal contraception are excluded to account for altered menstruation that occurs following discontinuation of hormonal contraception and significant mood changes seen with initiation of hormonal contraception.[31-32]

(4) Comparator

Included studies must have comparison groups of women who are using (i) non-hormonal contraceptives; (ii) naturally cycling (i.e., not use any contraceptive methods) or placebo; (iii) same agent as the exposure but in different dose, frequency, and duration; and (iv) second generation or more recent OC or other hormonal contraceptives different from the exposure. Since recent usage or cessation of hormonal contraceptive use may cause hormonal oscillations, we will only include studies with participants keeping their contraceptive use pattern (either using different hormonal

contraceptives from the exposure or placebo, or not using any hormonal contraceptive) for at least three months by the time sleep outcomes are assessed.

(5) Outcomes

We are interested in any sleep-related outcomes assessed at any time points after keeping their contraceptive use pattern for at least three months. A variety of sleep measurements for sleep quality, sleep duration, and sleep disorder will be included in this systematic review. The sleep measurements can be questionnaires based on Likert Scale items listed below but not limited to these tools:

(i) The Pittsburgh Sleep Quality Index (PSQI). [33] It measures seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction over the last four weeks. The PSQI is a subjective measure of sleep. Subjects self-rate each of the seven domains of sleep from 0 to 3, where 3 represents the negative extreme on the Likert Scale. A subject with a global sum of 5 or greater is considered as a poor sleeper. Studies reported sleep quality in any of the above seven domains during and after taking hormonal contraceptives will be included in the review.

(ii) The Epworth Sleepiness Scale (ESS) is a self-administered test used to assess daytime sleepiness.[34] It consists of 8 questions with different scenarios and a scale from 0-3 where subjects would indicate how likely they are to fall asleep in that situation. The scores are summed for a total score between 0 and 24. [34] Studies reporting sleepiness with any of the 8 questions during and after taking hormonal contraceptives will be included in the review.

(iii) The Athens Insomnia Scale (AIS), which is also a self-administered psychometric instrument designed for quantifying sleep difficulty.[35] The AIS consists of eight items: sleep induction (i.e., time to fall asleep after turning-off the lights), night awakenings, final awakening earlier than desired, total sleep duration, overall quality of sleep, sense of well-being during the day, functioning (physical and mental) during the day, and sleepiness during the day. Each item is rated from 0 to 3 with higher scores indicating more impaired sleep. The total score ranges from 0 to 24 and a total score of 6 or more is considered as insomnia. Studies which report any or all of the above eight insomnia-related items during and after taking hormonal contraceptives will be included in the review.

(iv) The Insomnia Severity Index (ISI), a self-administered questionnaire used to assess insomnia.[36] The ISI consists has a one month recall period and assesses 7 domains: severity of sleep onset, sleep maintenance, difficultly waking up in the morning, sleep dissatisfaction, interference of sleep with daytime functioning, noticeability of sleep problems by others, and distress caused by sleep difficulties. Each domain is rated on a scale from 0 to 4 with higher scores indicating more problematic sleep. The score is summed forming a total score between 0 and 28, with a score of 8 and above indicative of insomnia.[36] Studies reporting any domains from the ISI during and after taking hormonal contraceptives will be included in the review.

We will also include continuous measures of sleep quality and disorder. These measures include: (i) total amount of sleep obtained, either during nocturnal sleep episode or across the 24-hour period; (ii) sleep latency, i.e., how long it takes the participant to fall asleep; (iii) how many times the participant wakes up; (iv) how many minutes the participant is awake during the night;

(v) sleep efficiency, i.e., what percentage of time spent in bed the participant is actually asleep. The total sleep time is equal to the total amount of time spent in bed (in minutes) minus the sum of time it takes to fall asleep, and the time spent awake throughout the night. The percentage is calculated as the total sleep time divided by total time in bed. Given we will only include studies with participants keeping their contraceptive use pattern for at least three months, the sleep outcomes from the eligible studies will be summarized after participants keeping their contraceptive use pattern for at least three months as well.

Exclusion criteria

The following studies will be excluded from this systematic review: (1) studies only recruited patients with specific comorbidities or conditions, such as hormonal disorder, acne, perimenopause, postmenopause, dysmenorrhea, depression etc,, since these conditions may be associated with sleep problems and will not allow us to elucidate the association between hormonal contraceptives and sleep; (2) studies investigating the first-generation OC since it is not available in the market anymore due to severe side effects; (3) studies investigating emergency contraception; and (4) studies in languages other than English. We will exclude emergency contraception from this review as the hormonal effect of the emergency contraception is significantly different from long-acting contraception. The half-life of oral leovnoregestrel is around 24-32 hours, which is not significant when considering long-term effect on sleep.[37]

Data abstraction

A standard form will be developed to extract data from the included studies. From each article, the author, study design, study population, publication year, journal, participant

demographics, hormonal contraceptive used, intervention details, comparison groups, sleep outcomes, and the association between hormonal contraceptive use and sleep will be extracted. Additionally, any mean values, standard deviation and confidence intervals, and all information needed for appraisal of internal validity will be extracted. This will be done in a standardized data extraction form by two reviewers independently. When consensus is not reached, a third researcher will be consulted to reach the final decision. Data will be presented in narrative form and summary tables.

Risk of bias assessment

For randomized controlled trials, the risk of bias in each included study for each outcome will be evaluated independently by two reviewers, using the Cochrane Collaboration Risk of Bias in randomized trials (RoB 2.0 tool).[38] Studies will be assessed from 5 domains: bias from randomisation, bias from deviates from intended interventions, bias due to missing data, bias in outcome measurement and bias in the selection of the reported result.[38] An overall rating of low bias, some concerns about bias, or high bias will be given depending on the result of assessment. The Cochrane Risk of Bias in Non-randomized studies – of Interventions (ROBINS-1 tool) will be used to assess the risk of bias for each outcome in non-randomized comparative studies.[39] Studies will be assessed from 7 domains: bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement outcomes, and bias in selection of the reported result. Risk of Bias in Systematic Reviews (ROBIS) tool will be used to assess the risk of bias for the eligible systematic reviews.[40] Reviews will be assessed from four domains: study eligibility criteria, identification and selection of studies, data collection and study appraisal, and

synthesis and findings. We will also assess the overall risk of bias in the interpretation of review findings and whether this considered limitations identified in any of the above 4 domains.

Grading the strength of evidence

The certainty of the evidence per outcome for each comparison will be assessed from five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach and be classified into four levels of evidence (high, moderate, low or very low).[41]

Data synthesis

All data extracted will be presented in both narrative form and in summary tables. If data are missing, the study authors will be contacted to attempt to obtain the data. For sleep measures investigated by two or more studies, if there is no clinical heterogeneity (e.g., different age or intervention) and methodological heterogeneity (e.g., different measurement tools), statistical heterogeneity will be assessed using forest plot visually, the chi-square test of homogeneity (p value < 0.05), and quantified using the Higgins' I^2 statistic with 25%, 50% and 75% representing low, medium, and high heterogeneity, respectively.[42] The presence of publication bias will be evaluated using a funnel plot and the Duval and Tweedie's trim and fill method.[43]

We will use frequentist approach to estimate the overall effect of hormonal contraceptives on sleep. For binary outcome measures, we will express the results of each study as a risk ratio (RR) and its 95% confidence interval (CI). We will perform meta-analyses of pooling the RRs with 95% CIs of studies using a random-effects model, because of anticipated heterogeneity of hormonal contraceptives, study designs, and participants. For continuous outcome measures, standardized mean differences (SMDs) will be used for the final assessment from individual studies due to the likely variability in the measuring scales. The SMD will be categorized as small,

medium, and large based on the thresholds 0.2, 0.5 and 0.8, respectively, as suggested by Cohen's.[44] The 95% CI will be used to represent the deviation from the point estimate for both the individual studies and the pooled estimate. Random-effects meta-analysis will be used to obtain the pooled estimates. If sleep outcomes are measured at multiple time points in a study, the measure done at the similar time point as the other studies will be used in the primary meta-analysis. The outcome measured at other time points will be considered in the subgroup analysis by duration of hormonal contraceptives.

We will run subgroup analyses by hormonal method of contraception (implant, IUD, injections, pills, vaginal rings, or skin patches), agent (progesterone and estrogen combined or progesterone only), dose, and duration of contraceptives. We will run sensitivity analyses to assess whether our conclusions will be robust if excluding studies with high risk of bias and non-randomized comparative studies. As long as studies included in the systematic review form a connected network, a network meta-analysis using both direct and indirect evidence will be conducted to estimate the comparative harm of different contraceptives.[45-46] Results from the network meta-analysis will allow us to summarize and interpret a wider picture of the evidence for the putative effect of hormonal contraceptives on sleep. We will conduct data analysis using the Cochrane Collaboration Review Manager statistical software (Version 5.4.1) (http://ims.cochrane.org/RevMan).

DISCUSSION

Strengths and limitations

This systematic review will be the first to provide quantitative estimates of the association between hormonal contraceptive use and sleep outcomes in healthy women. Our systematic review methodology includes explicit eligibility criteria created in consultation with research librarians,

and the usage of tested, standardized abstraction forms. We will calibrate our review methods throughout the review process for optimal consistency among reviewers. The GRADE approach will be applied to aggregate data, the PRISMA-P reporting checklist is followed to draft this systematic review protocol, and the PRISMA reporting checklist will be followed to draft this systematic review later. The κ statistic will be reported to identify issues with reproducibility. Our review will encompass a wide range of hormonal contraceptive formulations and sleep outcome measurements. We anticipate limitations with regard to publication bias and recall bias as the majority of studies employ self-administered tools to assess sleep quality and duration.

Study implications

Sleep quality is a crucial outcome that affect overall life quality in women of reproductive age and may indicate risk of developing comorbid conditions. The relationship between hormonal contraceptive use and sleep quality, duration and disorder have been reported inconsistently in the current literature. Hormonal contraceptives have been more and more widely accepted by women. However, no study has attempted to provide systematic evidence on the association between hormonal contraceptive use and sleep. Our systematic review will elucidate the association between hormonal contraceptive use and sleep quality. Moreover, it will contribute evidence that will support the improvement of guidelines for taking hormonal contraceptive in healthy women and promote awareness of safety for taking hormonal contraceptive.

It is challenging to design, conduct, and analyze original studies investigating the association between hormonal contraceptive use and sleep quality. For instance, a wide variety of hormonal contraceptives are utilized by women who may change to other brands of contraceptive or birth control methods. In addition, most studies use subjective sleep measures, which may involve recall the information in the past. Through appraisal of published studies, our systematic

review will inform the improvement in the design and implementation of future research in this field.

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Author Contributions: JM, MC, XY, CW conceptualized and designed the protocol, drafted the initial manuscript and reviewed the manuscript. MC, XY, JM, QW, HK, and HR defined the concepts and search items, data extraction process as well as methodological appraisal of the study. MC, JM, QW, and XY planned the data extraction and statistical analysis. LT, CM, and NZ provided critical insights. All authors approved the final manuscript.

Table 1: Search Strategies for OVID Medline, Embase and Cochrane Central

Database(s): OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp contraceptive agents/ or exp hormonal contraception/
2	exp contraception/ or fertility control.mp. or (fertiliz* adj3 inhibit*).mp.
3	exp birth control/
4	exp family planning services/
5	desogestrel/ or nor pregnenes/ or progesterone congeners/
6	exp ethinylestradiol/ or ethinyl estradiol.mp. or ethinylestradiol.mp.
7	dienogest.mp.
8	exp progestin/ or progestin$.mp. or progestogen.mp.
9	lynestrenol/
10	norethindrone/
11	levonorgestrel/
12	(etynodiol diacetate or ethynodiol diacetate).mp.
13	norgestrel/
14	mestranol.mp. or exp mestranol/
15	exp estradiol/ or estradiol.mp. or oetradiol.mp.
16	(desogestrel or norpregnene$ or progestins).mp.
17	(progesterone congeners adj2 synthetic).mp.
18	drospirenone.mp.
19	lynestrenol.mp.
20	norethindrone.mp.
21	norgestrel.mp.
22	etonogestrel.mp.
23	gestodene.mp.
24	(levonorgestrel or D-norgestrel).mp.
25	norgestimate.mp.
26	dienogest.mp.
27	contracept*.mp.
28	birth control.mp.
29	family planning.mp.
30	Intrauterine device.mp. or “intra uterine device”.mp.
31	exp Contraceptive Devices, Female/
32	Intrauterine system.mp.
33	Intrauterine contraceptive device.mp.
34	iud*.mp. or iucd*.mp.
35	exp Medroxyprogesterone/ or Depotmedroxyprogesterone.mp. or depo-medroxyprogesterone.mp. or medroxyprogesterone.mp.
36	Depo-provera.mp. or depo provera.mp.

37	(vaginal or hormon* or contraceptive) adj2 (ring or patch or injection).mp.
38	DPMA.mp.
39	or/1-38
40	exp sleep/
41	exp sleep-wake transition disorders/ or exp sleep deprivation/ or exp sleep wake disorders/ or exp dyssomnias/
42	(fragmented sleep or insufficient sleep syndrome$).mp.
43	exp sleep latency/ or exp sleep hygiene/
44	exp sleep arousal disorder/
45	exp sleep disorder/
46	Sleep*.af.
47	(insomnia$ or hypersomnia$).mp. or "disorders of excessive somnolence"/
48	exp restless legs syndrome/ or restless legs syndrome.mp.
49	or/40-48 → all sleep terms
50	(comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case reports or historical article).pt.
51	animal/ not human/
52	or/50-51
53	(39 and 49) not 52
54	limit 53 to yr="1970-current"

Database: Embase 1974 to 2020 August 17

#	Searches
1	exp contraceptive agents/ or hormonal contraception/
2	exp contraception/ or fertility control.mp. or fertilization inhibition.mp. or inhibition of fertilization.mp.
3	exp birth control/
4	exp family planning services/
5	desogestrel/ or norpregnenes/ or progesterone congeners/
6	exp ethinylestradiol/ or ethinyl estradiol.mp. or ethinylestradiol.mp.
7	dienogest.mp.
8	exp progestin/ or progestin$.mp. or progestogen.mp.
9	lynestrenol/
10	norethindrone/
11	norgestrel/
12	levonorgestrel/
13	(etynodiol diacetate or ethynodiol diacetate).mp.
14	mestranol.mp. or exp mestranol/
15	exp estradiol/ or estradiol.mp. or oetradiol.mp.
16	(desogestrel or norpregnene$ or progestins).mp.

17	(progesterone congeners adj2 synthetic).mp.
18	drospirenone.mp.
19	lynestrenol.mp.
20	norethindrone.mp.
21	norgestrel.mp.
22	etonogestrel.mp.
23	gestodene.mp.
24	(levonorgestrel or D-norgestrel).mp.
25	norgestimate.mp.
26	dienogest.mp.
27	contracept*.mp.
28	Birth Control.mp.
29	Family planning.mp.
30	Intrauterine device.mp. or “intra uterine device”.mp.
31	exp Contraceptive Devices, Female/
32	Intrauterine system.mp.
33	Intrauterine contraceptive device.mp.
34	iud*.mp. or iucd*.mp.
35	exp Medroxyprogesterone/ or Depotmedroxyprogesterone.mp. or depo-medroxyprogesterone.mp. or medroxyprogesterone.mp.
36	Depo-provera.mp. or depo provera.mp.
37	(vaginal or hormon* or contraceptive) adj2 (ring or patch or injection).mp.
38	DPMA.mp.
39	or/1-38
40	exp sleep/
41	exp Sleep-Wake Transition Disorders/ or exp Sleep Deprivation/ or exp Sleep Wake Disorders/ or exp dyssomnias/
42	(fragmented sleep or insufficient sleep syndrome$).mp.
43	exp sleep latency/ or exp sleep hygiene/
44	exp sleep arousal disorder/
45	sleep*.af.
46	(insomnia$ or hypersomnia$).mp. or "disorders of excessive somnolence"/
47	exp restless legs syndrome/ or restless legs syndrome.mp.
48	exp sleep disorder/
49	or/40-48
50	(editorial or note or letter erratum or short survey or abstract).pt. or abstract report/ or letter/ or case study/
51	animal/ not human/
52	or/50-51
53	exp female/ or female$.mp. or women.mp. or woman.mp.
54	(39 and 49 and 53) not 52

55	limit 54 to yr="1970-current"

Database: Cochrane Central

#	Searches
1	MeSH descriptor: [Contraceptive Agents] explode all trees
2	MeSH descriptor: [Hormonal Contraception] explode all trees
3	MeSH descriptor: [Contraception] explode all trees
4	Fertility Control
5	Fertilization inhibition
6	inhibition of fertilization
7	MeSH descriptor: [Family Planning Services] explode all trees
8	MeSH descriptor: [Desogestrel] this term only
9	MeSH descriptor: [Norpregnenes] this term only
10	MeSH descriptor: [Progesterone Congeners] this term only
11	MeSH descriptor: [Ethinyl Estradiol] explode all trees
12	ethinyl estradiol
13	ethinylestradiol
14	dienogest
15	MeSH descriptor: [Progestins] explode all trees
16	progestin$
17	progestogen
18	MeSH descriptor: [Lynestrenol] this term only
19	MeSH descriptor: [Norethindrone] this term only
20	MeSH descriptor: [Norgestrel] this term only
21	MeSH descriptor: [Levonorgestrel] this term only
22	Etynodiol diacetate
23	mestranol
24	MeSH descriptor: [Mestranol] explode all trees
25	MeSH descriptor: [Estradiol] explode all trees
26	estradiol
27	oetradiol
28	(desogestrel or norpregnene$ or progestins)
29	progesterone congeners adj2 synthetic
30	drospirenone
31	lynestrenol
32	norethindrone
33	norgestrel
34	etonogestrel
35	gestodene
36	levonorgestrel
37	norgestimate
38	dienogest
39	contracept*

40	birth control
41	family planning
42	MeSH descriptor: [Intrauterine device] this term only
43	Intrauterine device
44	Intrauterine system
45	Intrauterine contraceptive device
46	Iud
47	d-norgestrel
48	iucd
49	Depotmedroxyprogesterone
50	depo-medroxyprogesterone
51	medroxyprogesterone
52	Depo-provera
53	depo provera
54	DPMA
55	Vaginal ring/
56	Ethyndiol diacetate
57	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56
58	MeSH descriptor: [Sleep] explode all trees
59	MeSH descriptor: [Sleep-Wake Transition Disorders] explode all trees
60	MeSH descriptor: [Sleep Deprivation] explode all trees
61	MeSH descriptor: [Sleep Wake Disorders] explode all trees
62	MeSH descriptor: [Dyssomnias] explode all trees
63	fragmented sleep or insufficient sleep syndrome$
64	MeSH descriptor: [Sleep Hygiene] explode all trees
65	MeSH descriptor: [Sleep Latency] explode all trees
66	MeSH descriptor: [Sleep Arousal Disorders] explode all trees
67	sleep*
68	insomnia$ or hypersomnia$
69	disorders of excessive somnolence
70	MeSH descriptor: [Restless Legs Syndrome] explode all trees
71	restless legs syndrome
72	58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71
73	(comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case reports or historical article).pt.
74	MeSH descriptor: [Animals] explode all trees
75	MeSH descriptor: [Humans] explode all trees
76	73 and 74 not 75
77	(57 and 72) not 76
78	limit 77 to yr="1970-current"

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Reporting checklist for protocol of a systematic review and meta analysis.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	17

Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	17
Sponsor	#5b	Provide name for the review funder and / or sponsor	n/a
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	17
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	5-7
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-12
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7-8
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	18-23
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	12-13
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	12-13
Study records - data	#11c	Describe planned method of extracting data from reports (such as	12-13

collection process		piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	12-13
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	12-13
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	13
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	14-15
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	14-15
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14-15
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	14-15
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	14
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	14

BMJ Open

The Relationship between Hormonal Contraceptives and Sleep among Women of Reproductive Age: A Systematic Review Protocol

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The Relationship between Hormonal Contraceptives and Sleep among Women of Reproductive Age: A Systematic Review Protocol

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ABSTRACT

Introduction The etiology of sleep disruptions is unknown but hormonal fluctuations during the menstrual cycle, pregnancy, and menopause have been shown to potentially affect how well a woman sleeps. The aim of this systematic review is to investigate whether hormonal contraceptives are associated with a decreased quality of sleep and increased sleep duration in women of reproductive age.

Methods This review will analyze data from randomized controlled trials or non-randomized comparative studies investigating the association between hormonal contraceptives and sleep outcomes among women of reproductive age. Reviews addressing the same research question with similar eligibility criteria will be included. A literature search will be performed using the MEDLINE, EMBASE and Cochrane CENTRAL databases from inception to March 7, 2021. The Cochrane Collaboration's Risk of Bias for Randomised Trials (RoB 2.0) and The Cochrane Risk of Bias for Non-randomized studies – of Interventions (ROBINS-1 tool) will be used to assess risk of bias for each outcome in eligible studies. Two reviewers will independently assess eligibility of studies, risk of bias and extract the data. All extracted data will be presented in tables and narrative form. For sleep measures investigated by two or more studies with low heterogeneity, we will conduct random-effects meta-analysis to estimate the magnitude of the overall effect of hormonal contraceptives. If studies included in this systematic review form a connected network, a network meta-analysis will be conducted to estimate the comparative effect of different contraceptives. The GRADE approach will be used to summarise the quality of evidence. Our protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols 2015 (PRISMA-P 2015) guidelines.

Ethics and dissemination: Ethics approval is not required as data is sourced from previously reported studies. The findings of this review will be published in a peer-reviewed journal and presented at relevant conferences.

Keywords: hormonal contraceptive, oral contraceptive, contraception, sleep quality, sleep duration
PROSPERO registration number: CRD42020199958.

Article Summary

Strengths and Limitations of this study:

- This systematic review on the association between hormonal contraceptive use and sleep is based on a robust, librarian consulted search strategy.
- The literature review, data extraction, and risk of bias assessment are performed by two independent reviewers to mitigate bias.
- The risk of bias of each outcome from included papers will be assessed with the appropriate tool.
- Papers in languages other than English are not included, leading to potential for language bias.

Word Count: 3703

INTRODUCTION

Worldwide, there are around 1.9 billion women of reproductive age. Hormonal contraceptives including oral contraceptives (OC), vaginal ring, contraceptive skin patches, implants, injections, and hormonal intrauterine contraceptive devices (IUDs), are widely used around the world in women of reproductive age to avoid unintentional pregnancy.[1] Of the 842 million women using modern forms of contraception, 43% are using hormonal contraceptives. The overall number of users of hormonal contraceptives is increasing annually. [1] One hundred and fifty-one million women use OCs with usage varying by region.[1] Other hormonal contraceptives such as implants, vaginal rings, and intrauterine devices have been widely adopted as well and used by over 256 million women in the world.[1] These hormonal contraceptives have different dosage, formulation, mechanism of action, and applicable groups compared to OCs.[2] Unlike OCs which are taken consistently and provide a stable dosage of the estrogen and progestin components, other hormonal contraceptives have the potential to provide lower dose of progestin and estrogen. It has been shown that hormonal IUDs release levonorgestrel directly into the uterus, only a small amount is absorbed into the rest of the body, thus its effects are mostly paracrine rather than systemic.[3]

Progesterone, a primary component in hormonal contraceptives, is an agonist of gamma-aminobutyric acid (GABA) receptors through a metabolite, allopregnanolone. [4] GABA is a crucial molecule in sleep promotion – most sleep-promoting neurons are sensitive to GABA. [5] Common sleep medications, such as benzodiazepines have been shown to positively modulate GABA signalling.[5] The potency of progestin is comparable to that of benzodiazepines and has similar agonistic effects. Changes in electroencephalogram activity seen with progesterone administration

are similar to those evoked by benzodiazepines.[4] Studies in rat models have shown that administration of exogenous progesterone leads to dose-dependent decreased sleep latency and wakefulness.[4] The mechanism behind the effect of estrogen on sleep is not well elucidated but rat studies have shown that administration of estrogen promotes sleep during the sleep period and reduces sleep during the wakefulness period.[6] The overall effect on sleep is likely caused by a combination of both estrogen and progesterone, although the magnitude of their contribution to sleep changes is unknown.[7]

High quality sleep is as essential as regular exercise and eating a balanced diet for maintenance of optimal health and well-being. Severe sleeping problems, such as insomnia, are important matters from both a public health perspective and an individual level. Insomnia is associated with depression, anxiety, substance abuse, cognitive impairment, metabolic disorders (e.g., diabetes, dyslipidemia, and obesity) and cardiovascular diseases.[8-10] Women are more likely than men to have sleep problems including insomnia and restless leg syndrome. The exact etiology of these sleep disruptions is unknown but hormonal fluctuations during the menstrual cycle, pregnancy, and menopause have been shown to potentially affect how well a woman sleeps.[11-13] During ovulation, there is a surge of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) which leads to a decrease in estrogen concentration and an increase in progesterone.[14] During the luteal phase, progesterone concentrations increase and estrogen levels are high up to the mid-phase. Starting from the mid-luteal phase, both estrogen and progesterone levels decrease.[14] Sleep disturbances are most commonly reported at the end of the luteal phase and early follicular phase.[15] OCs are taken each day for 21 days, providing a constant, exogenous source of estrogen and progesterone, preventing the release of FSH and LH and thus the production of a

follicle or ovulation.[16] Therefore, hormonal contraceptives may affect women's sleep-wake cycle and cause physiological changes that lead to sleep disturbance.

Unlike other commonly prescribed drugs, hormonal contraceptives are used by healthy women for long periods of time. Safety trials of hormonal contraceptives have focussed largely on breast cancer and venous thromboembolism risk. [17-19] Despite decreases in estrogen concentration with later OC generations, its use has been shown to be associated with an increased risk of developing breast cancer and venous thromboembolism.[20] A 2017 cohort study found OC intake was associated with a reduced risk of colorectal, endometrial and ovarian cancers and increased risk of cervical and breast cancer.[21] Studies in women have varied findings on the association between hormonal contraceptive use and sleep quality and duration. Differences in methodology, including the formulation of contraceptives taken, stratification of formulations, measurements of sleep, or the phase of the menstrual cycle of naturally cycling women used as comparison may explain the different findings between studies. For instance, a pilot study published in 2020 by Guida *et al* found significantly increased sleep duration for users of oral progestins, oral gestodene and 13.5 mg levonorgestrel intrauterine systems, compared with naturally cycling women (women not currently using any hormonal contraceptive), and decreased sleep latency and better sleep quality for users of depot-administered contraceptives.[22] However, a polysomnography study published in 2012 by Hachul *et al* found decreased sleep latency in women using OC and no difference in overall sleep quality.[23] A randomized control trial by Lundin *et al* found no significant sleep related results, while a cross sectional analysis by Bezerra *et al* found that hormonal contraceptive users had worse sleep quality compared with their naturally cycling counterparts. [24-25]

Given the high prevalence of hormonal contraceptive use among women of reproductive age and the relationship between hormonal contraceptive use and sleep varying in both magnitude and direction in the current literature, there is an urgent need to provide women with accurate, evidence-based information to inform their use of hormonal contraception.[22-25] Hence, the objective of this systematic review is to compile and elucidate the association between hormonal contraceptive use and sleep (including the quality of sleep, sleep disorders, and duration of sleep). Our hypothesis is hormonal contraceptives are associated with a decreased quality of sleep and increased sleep duration in women of reproductive age. Findings from this review will provide insights to women choosing between different methods and formulations, while also inform the development of new progestins for future generations of hormonal contraceptives. The systematic review protocol was registered at the website of the International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42020199958).

METHODS

Our protocol follows the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols 2015 (PRISMA-P 2015) guidelines.[26]

Literature search

We developed a comprehensive search strategy with input from a research librarian at McMaster University (tables 1-3). The systematic search for existing relevant systematic review and original studies will be conducted in the Ovid MEDLINE and Embase (Excerpta Medica dataBASE) electronic databases, and the Cochrane Library (including Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials), from inception to March 7, 2020. Search terms will cover all words related to birth control, ingredients of oral

contraceptives, hormonal contraceptives, menstrual cycle, and sleep. We will limit the search to studies or systematic reviews published from 1970 to present to ensure that we include all published studies or reviews on hormonal contraceptives, excluding first generation oral contraceptives which had been discontinued after 1970s. For sleep outcome measures, we will search sleep terms in multi-purpose fields besides the title and abstract in case sleep is investigated as a secondary outcome and therefore not reported in the abstract. The comprehensive search strategies for each database are presented in Tables 1-3. The reference lists of all included studies will be checked to identify additional potentially eligible studies.

Study Selection and Screening

Systematic screening of the studies will be first conducted at the title and abstract level, and then at the full-text level to determine if a study meets eligibility criteria by two independent reviewers. Any potential conflicts between the reviewers will be resolved through discussion. If discrepancies in judgment remain after discussion, a third-party reviewer will be consulted to resolve the conflict and provide a final decision.

Eligibility criteria

(1) Study Characteristics

Existing systematic reviews will be included if they (i) address the same research question with similar inclusion and exclusion criteria as ours; and (ii) have a low risk of bias in study eligibility criteria, identification and selection of studies, data collection and study appraisal, and synthesis and findings assessed using the Risk of Bias in Systematic Reviews (ROBIS) tool.[27]

For original studies, we will include (i) randomized controlled trials, and non-randomized comparative studies that take into account the effect of potential confounders (e.g., age, race, and socioeconomic status)[28-30] using methods such as multivariable analysis, propensity-score

matching, or showing no statistically significant differences in baseline characteristics between participants in comparison groups; (ii) studies on human participants; and (iii) studies which investigate the association between hormonal contraceptive use and sleep-related outcomes, either as the primary or secondary objective.

(2) Participants

Participants or subgroups of participants are females between 15 and 49 years old.

(3) Exposure

Participants who take second generation or more recent OC or other hormonal contraceptives containing both progesterone and estrogen or progesterone only, regardless of its brand, dose, and frequency, to avoid pregnancy, as long as their hormonal contraceptive use pattern is sustained for at least three months by the time sleep outcomes are assessed. The first three months of hormonal contraception use or discontinuation of hormonal contraception are excluded to account for altered menstruation that occurs following discontinuation of hormonal contraception and significant mood changes seen with initiation of hormonal contraception.[31-32]

(4) Comparator

Included studies must have comparison groups of women who are using (i) non-hormonal contraceptives; (ii) naturally cycling (i.e., not use any contraceptive methods) or placebo; (iii) same agent as the exposure but in different dose, frequency, and duration; and (iv) second generation or more recent OC or other hormonal contraceptives different from the exposure. Since recent usage or cessation of hormonal contraceptive use may cause hormonal oscillations, we will only include studies with participants keeping their contraceptive use pattern (either using different hormonal contraceptives from the exposure or placebo, or not using any hormonal contraceptive) for at least three months by the time sleep outcomes are assessed.

(5) Outcomes

We are interested in any sleep-related outcomes assessed at any time points after keeping their contraceptive use pattern for at least three months. A variety of sleep measurements for sleep quality, sleep duration, and sleep disorder will be included in this systematic review. The sleep measurements can be questionnaires based on Likert Scale items listed below but not limited to these tools:

(i) The Pittsburgh Sleep Quality Index (PSQI). [33] It measures seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction over the last four weeks. The PSQI is a subjective measure of sleep. Subjects self-rate each of the seven domains of sleep from 0 to 3, where 3 represents the negative extreme on the Likert Scale. A subject with a global sum of 5 or greater is considered as a poor sleeper. Studies reported sleep quality in any of the above seven domains during and after taking hormonal contraceptives will be included in the review.

(ii) The Epworth Sleepiness Scale (ESS) is a self-administered test used to assess daytime sleepiness.[34] It consists of 8 questions with different scenarios and a scale from 0-3 where subjects would indicate how likely they are to fall asleep in that situation. The scores are summed for a total score between 0 and 24. [34] Studies reporting sleepiness with any of the 8 questions during and after taking hormonal contraceptives will be included in the review.

(iii) The Athens Insomnia Scale (AIS), which is also a self-administered psychometric instrument designed for quantifying sleep difficulty.[35] The AIS consists of eight items: sleep induction (i.e., time to fall asleep after turning-off the lights), night awakenings,

final awakening earlier than desired, total sleep duration, overall quality of sleep, sense of well-being during the day, functioning (physical and mental) during the day, and sleepiness during the day. Each item is rated from 0 to 3 with higher scores indicating more impaired sleep. The total score ranges from 0 to 24 and a total score of 6 or more is considered as insomnia. Studies which report any or all of the above eight insomnia-related items during and after taking hormonal contraceptives will be included in the review.

(iv) The Insomnia Severity Index (ISI), a self-administered questionnaire used to assess insomnia.[36] The ISI consists has a one month recall period and assesses 7 domains: severity of sleep onset, sleep maintenance, difficultly waking up in the morning, sleep dissatisfaction, interference of sleep with daytime functioning, noticeability of sleep problems by others, and distress caused by sleep difficulties. Each domain is rated on a scale from 0 to 4 with higher scores indicating more problematic sleep. The score is summed forming a total score between 0 and 28, with a score of 8 and above indicative of insomnia.[36] Studies reporting any domains from the ISI during and after taking hormonal contraceptives will be included in the review.

We will also include continuous measures of sleep quality and disorder. These measures include: (i) total amount of sleep obtained, either during nocturnal sleep episode or across the 24-hour period; (ii) sleep latency, i.e., how long it takes the participant to fall asleep; (iii) how many times the participant wakes up; (iv) how many minutes the participant is awake during the night; (v) sleep efficiency, i.e., what percentage of time spent in bed the participant is actually asleep. The total sleep time is equal to the total amount of time spent in bed (in minutes) minus the sum of time it takes to fall asleep, and the time spent awake throughout the night. The percentage is

calculated as the total sleep time divided by total time in bed. Given we will only include studies with participants keeping their contraceptive use pattern for at least three months, the sleep outcomes from the eligible studies will be summarized after participants keeping their contraceptive use pattern for at least three months as well.

Exclusion criteria

The following studies will be excluded from this systematic review: (1) studies only recruited patients with specific comorbidities or conditions, such as hormonal disorder, acne, perimenopause, postmenopause, dysmenorrhea, depression etc,, since these conditions may be associated with sleep problems and will not allow us to elucidate the association between hormonal contraceptives and sleep; (2) studies investigating the first-generation OC since it is not available in the market anymore due to severe side effects; (3) studies investigating emergency contraception; and (4) studies in languages other than English. We will exclude emergency contraception from this review as the hormonal effect of the emergency contraception is significantly different from long-acting contraception. The half-life of oral leovnoregestrel is around 24-32 hours, which is not significant when considering long-term effect on sleep.[37]

Data abstraction

A standard form will be developed to extract data from the included studies. From each article, the author, study design, study population, publication year, journal, participant demographics, hormonal contraceptive used, intervention details, comparison groups, sleep outcomes, and the association between hormonal contraceptive use and sleep will be extracted. Additionally, any mean values, standard deviation and confidence intervals, and all information

needed for appraisal of internal validity will be extracted. This will be done in a standardized data extraction form by two reviewers independently. When consensus is not reached, a third researcher will be consulted to reach the final decision. Data will be presented in narrative form and summary tables.

Risk of bias assessment

For randomized controlled trials, the risk of bias in each included study for each outcome will be evaluated independently by two reviewers, using the Cochrane Collaboration Risk of Bias in randomized trials (RoB 2.0 tool).[38] Studies will be assessed from 5 domains: bias from randomisation, bias from deviates from intended interventions, bias due to missing data, bias in outcome measurement and bias in the selection of the reported result.[38] An overall rating of low bias, some concerns about bias, or high bias will be given depending on the result of assessment. The Cochrane Risk of Bias in Non-randomized studies – of Interventions (ROBINS-1 tool) will be used to assess the risk of bias for each outcome in non-randomized comparative studies.[39] Studies will be assessed from 7 domains: bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement outcomes, and bias in selection of the reported result. Risk of Bias in Systematic Reviews (ROBIS) tool will be used to assess the risk of bias for the eligible systematic reviews.[40] Reviews will be assessed from four domains: study eligibility criteria, identification and selection of studies, data collection and study appraisal, and synthesis and findings. We will also assess the overall risk of bias in the interpretation of review findings and whether this considered limitations identified in any of the above 4 domains.

Grading the strength of evidence

The certainty of the evidence per outcome for each comparison will be assessed from five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach and be classified into four levels of evidence (high, moderate, low or very low).[41]

Data synthesis

All data extracted will be presented in both narrative form and in summary tables. If data are missing, the study authors will be contacted to attempt to obtain the data. For sleep measures investigated by two or more studies, if there is no clinical heterogeneity (e.g., different age or intervention) and methodological heterogeneity (e.g., different measurement tools), statistical heterogeneity will be assessed using forest plot visually, the chi-square test of homogeneity (p value < 0.05), and quantified using the Higgins' I^2 statistic with 25%, 50% and 75% representing low, medium, and high heterogeneity, respectively.[42] The presence of publication bias will be evaluated using a funnel plot and the Duval and Tweedie's trim and fill method.[43]

We will use frequentist approach to estimate the overall effect of hormonal contraceptives on sleep. For binary outcome measures, we will express the results of each study as a risk ratio (RR) and its 95% confidence interval (CI). We will perform meta-analyses of pooling the RRs with 95% CIs of studies using a random-effects model, because of anticipated heterogeneity of hormonal contraceptives, study designs, and participants. For continuous outcome measures, standardized mean differences (SMDs) will be used for the final assessment from individual studies due to the likely variability in the measuring scales. The SMD will be categorized as small, medium, and large based on the thresholds 0.2, 0.5 and 0.8, respectively, as suggested by Cohen's.[44] The 95% CI will be used to represent the deviation from the point estimate for both the individual studies and the pooled estimate. Random-effects meta-analysis will be used to obtain

the pooled estimates. If sleep outcomes are measured at multiple time points in a study, the measure done at the similar time point as the other studies will be used in the primary meta-analysis. The outcome measured at other time points will be considered in the subgroup analysis by duration of hormonal contraceptives.

We will run subgroup analyses by hormonal method of contraception (implant, IUD, injections, pills, vaginal rings, or skin patches), agent (progesterone and estrogen combined or progesterone only), dose, and duration of contraceptives. We will run sensitivity analyses to assess whether our conclusions will be robust if excluding studies with high risk of bias and non-randomized comparative studies. As long as studies included in the systematic review form a connected network, a network meta-analysis using both direct and indirect evidence will be conducted to estimate the comparative harm of different contraceptives.[45-46] Results from the network meta-analysis will allow us to summarize and interpret a wider picture of the evidence for the putative effect of hormonal contraceptives on sleep. We will conduct data analysis using the Cochrane Collaboration Review Manager statistical software (Version 5.4.1) (http://ims.cochrane.org/RevMan).

Patient and Public Involvement

There is no patient or public involvement in this study.

Ethics and Dissemination

Ethical approval is not required for this protocol nor the subsequent review, as this review only consists of an analysis of previously published works. The findings of this review will be published in a peer-reviewed journal and disseminated in conferences related to this topic. All amendments to this protocol will be documented in the publication of the review.

DISCUSSION

Strengths and limitations

This systematic review will be the first to provide quantitative estimates of the association between hormonal contraceptive use and sleep outcomes in healthy women. Our systematic review methodology includes explicit eligibility criteria created in consultation with research librarians, and the usage of tested, standardized abstraction forms. We will calibrate our review methods throughout the review process for optimal consistency among reviewers. The GRADE approach will be applied to aggregate data, the PRISMA-P reporting checklist is followed to draft this systematic review protocol, and the PRISMA reporting checklist will be followed to draft this systematic review later. The κ statistic will be reported to identify issues with reproducibility. Our review will encompass a wide range of hormonal contraceptive formulations and sleep outcome measurements. We anticipate limitations with regard to publication bias and recall bias as the majority of studies employ self-administered tools to assess sleep quality and duration.

Study implications

Sleep quality is a crucial outcome that affect overall life quality in women of reproductive age and may indicate risk of developing comorbid conditions. The relationship between hormonal contraceptive use and sleep quality, duration and disorder have been reported inconsistently in the current literature. Hormonal contraceptives have been more and more widely accepted by women. However, no study has attempted to provide systematic evidence on the association between hormonal contraceptive use and sleep. Our systematic review will elucidate the association between hormonal contraceptive use and sleep quality. Moreover, it will contribute evidence that

will support the improvement of guidelines for taking hormonal contraceptive in healthy women and promote awareness of safety for taking hormonal contraceptive.

It is challenging to design, conduct, and analyze original studies investigating the association between hormonal contraceptive use and sleep quality. For instance, a wide variety of hormonal contraceptives are utilized by women who may change to other brands of contraceptive or birth control methods. In addition, most studies use subjective sleep measures, which may involve recall the information in the past. Through appraisal of published studies, our systematic review will inform the improvement in the design and implementation of future research in this field.

Conflict of Interest Disclosures: All the authors have declared no financial conflicts of interest.

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Author Contributions: JM, MC, XY, CW conceptualized and designed the protocol, drafted the initial manuscript and reviewed the manuscript. MC, XY, JM, QW, HK, and HR defined the concepts and search items, data extraction process as well as methodological appraisal of the study. MC, JM, QW, and XY planned the data extraction and statistical analysis. LT, CM, and NZ provided critical insights. All authors approved the final manuscript.

Table 1: Search Strategy for OVID Medline

Database(s): OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to March 7, 2021.

#	Searches
1	exp contraceptive agents/ or exp hormonal contraception/ or exp contraception/ or fertility control.mp. or (fertiliz* adj3 inhibit*).mp. or exp birth control/ or exp family planning services/ or desogestrel/ or nor pregnenes/ or progesterone congeners/ or exp ethinylestradiol/ or ethinyl estradiol.mp. or ethinylestradiol.mp. or dienogest.mp. or exp progestin/ or progestin$.mp. or progestogen.mp. or lynestrenol/ or norethindrone/ or levonorgestrel/ or etynodiol diacetate.mp. or ethynodiol diacetate.mp. or norgestrel or mestranol.mp. or exp mestranol/ or exp estradiol/ or estradiol.mp. or oetradiol.mp. or desogestrel.mp. or norpregnene$ or progestins).mp. or drospirenone.mp. or lynestrenol.mp. or norethindrone.mp. or norgestrel.mp. or Etonogestrel.mp. or gestodene.mp. or levonorgestrel.mp. or d-norgestrel.mp. or norgestimate.mp. or dienogest.mp. or contracept*.mp. or birth control.mp. or family planning.mp. or intrauterine device.mp. or "intra uterine device".mp. exp contraceptive devices, Female/ intrauterine system.mp. or intrauterine contraceptive device.mp. or iud*.mp. or iucd*.mp. or exp Medroxyprogesterone/ or Depotmedroxyprogesterone.mp. or depo-medroxyprogesterone.mp. or medroxyprogesterone.mp. or Depo-provera.mp. or depo provera.mp. or (vaginal or hormon* or contraceptive) adj2 (ring or patch or injection).mp. or DPMA.mp.
2	Exp sleep/ or exp sleep-wake transition disorders/ or exp sleep deprivation/ or exp sleep wake disorders/ or exp dyssomnias/ or fragmented sleep.mp. or insufficient sleep syndrome$.mp. or exp sleep latency/ or exp sleep hygiene/ or exp sleep arousal disorder/ or exp sleep disorder/ or sleep*.af. or insomnia$.mp. or hypersomnia$.mp. or "disorders of excessive somnolence" or exp restless legs syndrome/ or restless legs syndrome.mp
3	(comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case reports or historical article).pt.
4	Animal/ not human/
5	3 or 4
6	1 and 2 not 5
7	Limit 6 to yr="1970-current"

Table 2: Search Strategy for OVID Embase

Database: Embase 1974 to March 7, 2021.

#	Searches
1	exp contraceptive agents/ or exp hormonal contraception/ or exp contraception/ or fertility control.mp. or (fertiliz* adj3 inhibit*).mp. or exp birth control/ or exp family planning services/ or desogestrel/ or nor pregnenes/ or progesterone congeners/ or exp ethinylestradiol/ or ethinyl estradiol.mp. or ethinylestradiol.mp. or dienogest.mp. or exp progestin/ or progestin$.mp. or progestogen.mp. or lynestrenol/ or norethindrone/ or levonorgestrel/ or etynodiol diacetate.mp. or ethynodiol diacetate.mp. or norgestrel or mestranol.mp. or exp mestranol/ or exp estradiol/ or estradiol.mp. or oetradiol.mp. or desogestrel.mp. or norpregnene$ or progestins).mp. or drospirenone.mp. or lynestrenol.mp. or norethindrone.mp. or norgestrel.mp. or Etonogestrel.mp. or gestodene.mp. or levonorgestrel.mp. or d-norgestrel.mp. or norgestimate.mp. or dienogest.mp. or contracept*.mp. or birth control.mp. or family planning.mp. or intrauterine device.mp. or “intra uterine device”.mp. exp contraceptive devices, Female/ intrauterine system.mp. or intrauterine contraceptive device.mp. or iud*.mp. or iucd*.mp. or exp Medroxyprogesterone/ or Depotmedroxyprogesterone.mp. or depo-medroxyprogesterone.mp. or medroxyprogesterone.mp. or Depo-provera.mp. or depo provera.mp. or (vaginal or hormon* or contraceptive) adj2 (ring or patch or injection).mp. or DPMA.mp.
2	Exp sleep/ or exp sleep-wake transition disorders/ or exp sleep deprivation/ or exp sleep wake disorders/ or exp dyssomnias/ or fragmented sleep.mp. or insufficient sleep syndrome$.mp. or exp sleep latency/ or exp sleep hygiene/ or exp sleep arousal disorder/ or exp sleep disorder/ or sleep*.af. or insomnia$.mp. or hypersomnia$.mp. or “disorders of excessive somnolence” or exp restless legs syndrome/ or restless legs syndrome.mp
3	(editorial or note or letter erratum or short survey or abstract).pt. or abstract report/ or letter/ or case study/
4	animal/ not human/
5	or/3-4
6	exp female/ or female$.mp. or women.mp. or woman.mp.
7	(1 and 2 and 6) not 5
8	limit 7 to yr="1970-current"

Table 3: Search Strategy for Cochrane Central

Database: Cochrane Central from inception to March 7, 2021.

#	Searches
	MeSH descriptor: [Contraceptive Agents] explode all trees or MeSH descriptor: [Hormonal Contraception] explode all trees or MeSH descriptor: [Contraception] explode all trees or fertility control or fertilization inhibition or inhibition of fertilization or MeSH descriptor: [Family Planning Services] explode all trees or MeSH descriptor: [Desogestrel] this term only or MeSH descriptor: [Norpregnenes] this term only or MeSH descriptor: [Progesterone Congeners] this term only or MeSH descriptor: [Ethinyl Estradiol] explode all trees or ethinyl estradiol or ethinylestradiol or dienogest or MeSH descriptor: [Progestins] explode all trees or progestin$ or progestogen or MeSH descriptor: [Lynestrenol] this term only or MeSH descriptor: [Norethindrone] this term only or MeSH descriptor: [Norgestrel] this term only or MeSH descriptor: [Levonorgestrel] this term only or Etynodiol diacetate or mestranol or MeSH descriptor: [Mestranol] explode all trees or MeSH descriptor: [Estradiol] explode all trees or estradiol or oetradiol or desogestrel or norpregnenes$ or progestins or progesterone congeners adj2 synthetic or drospirenone or lynestrenol or norethindrone or norgestrel or Etonogestrel or gestogene or levonorgestrel or norgestimate or dienogest or contracept* or birth control or family planning or MeSH descriptor: [Intrauterine device] this term only or intrauterine device or intrauterine system or intrauterine contraceptive device or iud or d-norgestrel or iucd or depotmedroxyprogesterone or depo-medroxyprogesterone or medroxyprogesterone or depo-provera or depo provera or DPMA or Vaginal ring/ or ethyndiol diacetate
2	MeSH descriptor: [Sleep] explode all trees or MeSH descriptor: [Sleep-Wake Transition Disorders] explode all trees or MeSH descriptor: [Sleep Deprivation] explode all trees or MeSH descriptor: [Sleep Wake Disorders] explode all trees or MeSH descriptor: [Dyssomnias] explode all trees or MeSH descriptor: [Dyssomnias] explode all trees or ragmented sleep or insufficient sleep syndrome$ or MeSH descriptor: [Sleep Hygiene] explode all trees or MeSH descriptor: [Sleep Latency] explode all trees or MeSH descriptor: [Sleep Arousal Disorders] explode all trees or sleep* or insomnia$ or hypersomnia$ or disorders of excessive somnolence or MeSH descriptor: [Restless Legs Syndrome] explode all trees or restless legs syndrome
3	(comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case reports or historical article).pt.
4	MeSH descriptor: [Animals] explode all trees
5	MeSH descriptor: [Humans] explode all trees
6	3 and 4 not 5
7	(1 and 2) not 6
8	limit 7 to yr="1970-current"

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	17

Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	17
Sponsor	#5b	Provide name for the review funder and / or sponsor	n/a
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	17
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	5-7
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-12
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7-8
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	18-23
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	12-13
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	12-13
Study records - data	#11c	Describe planned method of extracting data from reports (such as	12-13

collection process		piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	12-13
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	12-13
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	13
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	14-15
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	14-15
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14-15
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	14-15
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	14
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	14