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In clinical and community-based samples, do insomnia and/or sleep disturbances compared to typical sleep predict child and youth depression? Protocol for a systematic review and meta-analysis

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Abstract

Introduction

Disturbed sleep represents a potentially important modifiable risk factor for the development of depression in children and youth. This protocol for a systematic review proposes to investigate whether insomnia and/or sleep disturbances predict child and youth depression in community and clinical-based samples.

Methods and analysis

The protocoll adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis protocols (PRISMA-P) guidelines. English-written, prospective, longitudinal observational studies that quantitatively estimated the prediction of depression by insomnia and/or sleep disturbances in individuals 5-24 years of age will be included. EMBASE, MEDLINE, PsychINFO, Scopus and Web of Science and grey literature will be searched from 1980 to the present. For the selection of studies, two reviewers will be involved. Data

extraction will be conducted by one author and checked independently by a second author using a pre-defined data extraction form. Risk of bias will be appraised using the Research Triangle Institute Item Bank (RTI-IB) tool. Heterogeneity will be measured using the I^2 statistic. Meta-analysis will be carried out if $I^2 \leq 75\%$ and if ≥ 3 results are available and if outcome measures can be pooled. The random-effect model will be used if $I^2 \geq 50$ is detected, otherwise the fixed-effect model. Results of the meta-analyses will be summarized by a forest plot. Analyses will be performed in subgroups stratified by key variables, e.g. risk of bias score, type of ascertainment, type of sleep disturbance, measurement of outcome, presence of baseline comorbidity, sample size, age group, gender. Subgroups will be defined depending on the amount and type of information retrieved.

A narrative synthesis will be conducted in place of the meta-analysis, should pooling of data not be possible. Quality of evidence will be rated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines.

Strengths and limitations of this study

- This is a protocol for a systematic review and meta-analysis of existing prospective, longitudinal evidence on insomnia and/or sleep disturbances predicting depression in children and youth.
- This protocol will adhere to the Preferred Reporting Items for Systematic review and Meta-Analysis protocols (PRISMA-P) guidelines
- This protocol is registered at PROSPERO, the international prospective register of systematic reviews
- Full-text screening and extraction will be performed by two reviewers. Any uncertainty regarding selection will be resolved by consensus and if necessary, by a third reviewer.
- With regards to limitations, the review will not include treatment studies and will include only English-written articles. We include individuals aged 5-24 years, therefore excluding studies on child and youth disturbed sleep predicting depression at later stages of life.

Ethics and dissemination As this is a protocol for systematic review and meta-analysis of published data, ethics review and approval are not required. The findings will be published in a peer-reviewed journal and disseminated at scientific conferences and to patient advocacy organizations.

Trial registration number: International Prospective Register for Systematic Reviews (PROSPERO) registration number CRD42019136729.

Introduction

Depression affects 2-4% of children and 11% of youth between 13 and 18 years of age, and peaks at 20 years of age[1] with disrupting effects on normative developmental trajectories. Prevalence is equal for both sexes prior to puberty, then it is higher in females.[2] Treatment shows limited efficacy,[3-5] suggesting that prevention may be a more effective resource to reduce the incidence of depression.

Targeting modifiable risk factors of illnesses is becoming a relevant therapeutic strategy for disease prevention.[6] Among modifiable risk factors predicting child and youth depression, insomnia is increasingly recognized as an important component of the complex and multi-factorial causal pathway of depression.[7]

Treating insomnia to specifically reduce the incidence and/or severity of depression has been the focus of controlled, high quality, randomized treatment studies in depressed or at risk for depression adult or elderly individuals.[8 9] In a recent meta-analysis, internet-based cognitive behavioural therapy (CBT) for insomnia had a significant, small effect on comorbid depression in individuals older than 18 years.[10]

Similar evidence in younger individuals is scarce, mostly consists of studies with small sample size/no follow-up, and it is limited to individuals older than 12 years of age [11-17].

In a randomized controlled trial, CBT for insomnia for six weekly sessions and a booster session after 2 months was significantly more effective in decreasing comorbid depression compared to waitlist in 12-19-year-old individuals with DSM-5 insomnia and no comorbid psychiatric disorders. The effect was large, was maintained after 12 months, and was fully mediated by the reduction of insomnia symptoms.[16]

In a longitudinal, randomised controlled trial study (SENSE, i.e.Sleep and Education: learning New Skills Early) the preventative effect on the incidence of depression in at risk for depression, 12-17-year-old adolescents with sleeping difficulties is investigated.[12] The interventions consist of seven weekly sessions of either a CBT/mindfulness-based sleep intervention or an active control intervention, followed by two booster sessions after three and six months post-intervention. One-hundred-twenty-three participants have completed the interventions,[13 14] however findings regarding the main outcomes of the study (preventative effects of depression) from the two-year follow-up are not available yet.

It is currently not known whether treating sleep problems in affected or unaffected, at risk for depression children (e.g. children with history of abuse, with high emotional dysregulation, offspring of depressed

parents) would lead to a lower incidence of depression than it would be if sleep problems were not treated.[18] To understand whether earlier prevention efforts could be more effective, a precise quantitative estimate of the prediction of depression by insomnia in the entire developmental population, including clinical and non-clinical individuals, is needed.

Insomnia consists of clinically significant long sleep-onset latency and/or awakening after sleep onset and/or early-morning awakening, accompanied by diurnal tiredness and functional impairment. Prevalence of insomnia is 19.5% in children, equally distributed among boys and girls; in youth, prevalence is 17.4%, and higher among girls.[19]

Six systematic reviews have summarized cohort studies on insomnia predicting depression.[20-25] Estimates of the meta-analytic odds ratios are consistent across studies ranging 2.10-2.83,[21 24] and across subgroups stratified by the most common confounders, e.g. sex (male: 1.46; females: 1.96), type of ascertainment (clinical: 2.05; non-clinical: 2.34), and age (elderly 1.87-1.92; adults: 2.50).[23]

However, only three of the six systematic reviews included subjects younger than 18 years,[21 22] and a meta-analytic estimate, i.e. odds ratio= 2.0, was provided by only one of the three reviews.[21] This estimate was based on studies up to 2010, and included only three studies.[26-28] Li et al. updated and used the same selection criteria of Baglioni et al.[21] and although fifteen new cohort studies were added, no new studies on children and youth were included. Finally, Pigeon et al.[22] summarized studies published from 2014 to 2017; four studies on children and youth were included, of which three supported insomnia predicting depression,[29-31] and one found no such association.[32] In sum, while it is well established that insomnia is a risk factor for depression in adults and the elderly,[20-24] an updated systematic review and meta-analysis on whether insomnia predicts child and youth depression is missing. The most recent review for children and youth is based on studies up to 2010 and all three systematic reviews of this age group excluded studies which did not control for baseline depression. This led to a greatly reduced number of studies. While the rationale of this choice is clear for studies of risk and prediction, it might not have been the ideal choice, due to the overall paucity of studies in the child and youth age-range compared to other age groups. Including studies that did not control for baseline depression would allow testing of whether there are significant differences in the meta-analytic estimates between studies controlling versus not-controlling for this variable. If no differences are found, studies not controlling for baseline depression could contribute to the pooled data with an overall increase of the precision for the estimate of the meta-analytic effects.

There is also some evidence available on whether sleep disturbances other than insomnia predicts child and youth depression.[33-42] This may include increased/short/disrupted sleep duration with/without diurnal

sleepiness, sleepwalking/talking, nightmares, bedwetting, breathing-related sleep disorders, and/or circadian disturbances. Furthermore, sleep disturbances more broadly defined may include challenges either generically defined with regards to duration and consistency over time, measured by self-reported questionnaires, interview or by EEG/actigraph-based measures, and scored by either single-item or cumulative scores. A recent meta-analysis summarized studies testing the association of broadly defined sleep disturbances on depression in 12-20-year-old already clinically depressed subjects. In all selected studies,[43-49] sleep was defined by EEG-based, objective measures. Estimates of the meta-analytic effects identified that EEG-based longer sleep onset latency, more wake after sleep onset and lower sleep efficiency were significant predictors of depression compared to typical sleep (effect sizes ranging .43-.58).[50]

Although findings from this review are of crucial importance for potential secondary prevention programs in depressed youth, it would be useful to have summarized data on the longitudinal association of broadly defined sleep disturbances with depression on the entire developmental population, including non-clinical individuals as well as a broader age range, which would allow to apply findings to primary prevention and/or early intervention programs.

Finallly, insomnia and/or sleep disturbances are often associated to comorbid psychiatric and medical conditions.[18] Most previous knowledge synthesis studies have excluded comorbidities, limiting the generalizability and transferability of findings. For this reason, in this systematic review studies focusing on both primary and comorbid insomnia and/or sleep disturbances will be included. To understand the extent to which insomnia and/or sleep disturbances have a distinct risk to depression across comorbid disorders, subgroup analyses will be performed.

Understanding whether insomnia and/or sleep disturbances significantly increase the risk of depression in children and youth could lead to variation in clinical practice and inform policy development. Preventive strategies could include treating sleep problems starting as early as childhood. This is particularly important in light of evidence on the differential effectiveness of a number of treatment for sleep problems (e.g. melatonin,[51 52] cognitive behavioural therapy,[53] physical exercise,[54] and bright light therapy[55]) and the fact that sleep problems in children are under-diagnosed[56] and rarely treated.[57]

The purpose of this protocol is to outline a methods for a systematic review and meta-analysis of data from prospective, longitudinal studies in clinical and community-based samples of children and youth investigating the role of insomnia and/or sleep disturbances compared to typical sleep as predictors of depression. “Do children and youth with insomnia and/or sleep disturbance have higher rates of later depression than children and youth without insomnia and/or sleep disturbance”?

Our study will add to the currently available knowledge synthesis in that:

1. It will provide an updated meta-analytic estimate of the effects of insomnia predicting child and youth depression, adding studies from 2010 onward compared to Baglioni et al.[21]
2. By including studies on 5-24-year-old subjects from both clinical and non-clinical populations, it will provide a more comprehensive and updated meta-analytic estimate compared to Lovato and Gradisar[50]
3. It will include studies whether controlling for baseline depression or not
4. It will include studies of both primary and comorbid insomnia and/or sleep disturbances

Furthermore, we aim to explore the sources of potential heterogeneity and examine the robustness of the primary hypothesis against key confounding variables. Specifically, our secondary aim is to address whether the prediction of child and youth depression by insomnia and/or sleep disturbances significantly differ between studies controlling versus not controlling for baseline depression, and more generally between studies stratified by key variables, e.g. risk of bias score, type of ascertainment, type of sleep disturbance, measurement of outcome, presence of baseline comorbidity, sample size, age group, gender. Subgroups will be defined depending on the amount and type of information retrieved.

Methods

For the protocol, we will follow the guidelines outlined in "Preferred Reporting Items for Systematic review and Meta-Analysis protocols (PRISMA-P)".[58] For the final report we will follow the guidelines set in "Meta-analysis Of Observational Studies in Epidemiology: a proposal for reporting" (MOOSE).[59]

Inclusion criteria

Study types

This study will include (1) English-written, (2) prospective, longitudinal observational studies that quantitatively estimated the prediction of depression by insomnia and/or sleep disturbances in children and youth. Only those studies reporting descriptive statistics, analyses of trajectories, effect sizes, odds ratios, β scores, frequency, hazard or relative risk will be selected. Grey literature including relevant dissertations/PhD theses and key conference publications will be included. Case series, case reports, systematic reviews, meta-analyses, as well as experimental, retrospective, cross-sectional, treatment, theoretical and position studies will be excluded.

Population type

Studies focusing on subjects aged 5-24 years belonging to either community or clinical based samples with any comorbid psychiatric/neurological/medical diagnosis will be included.

Exposure

Studies will be included if focusing on either one of the following two exposures:

1. Insomnia, defined as clinically significant difficulty in initiating or maintaining sleep or non-restorative sleep, as based on DSM III and later versions. Although the criterion of daytime impairment is required to define clinically significant insomnia, it has been shown that the meta-analytic odds ratio of insomnia predicting depression when this criterion is taken into account[24] is of comparable magnitude relative to the ones obtained when this criterion is not considered (Baglioni et al. 2011; Li et al. 2016).[21] Therefore, to allow for inclusion of the highest number of studies, daytime impairment will be free to vary.
2. Sleep disturbances, defined as increased/short/disrupted sleep duration with or without daytime fatigue/sleepiness, nightmares/terror attacks, circadian disturbances, and/or night walking/talking. Sleep disturbances can be generically defined with regards to duration and consistency over time, and can be based on subjective and/or EEG/actigraph-based, objective measures. Measures can be based on single or multiple items, or a cumulative score of various items. Narcolepsy, breathing-related sleep disorders, central sleep apnea, non-rapid/rapid eye movement sleep disorder, restless legs syndrome, substance/medication-induced sleep disorder, and enuresis nocturna primaria may also be included.

Exposures' assessment can be administered by a clinician, a researcher, or based on self-report, parent-report, and/or teacher-report questionnaires.

Outcome

Studies will be included if they focus on either one of the following outcomes: major depressive disorder, depressive disorder not otherwise specified, dysthymic disorder, and/or dimensional construct of depression, internalizing disorders or anxious depression. Studies focusing on anxiety without a measure of depression will not be included. Outcome is measured by standardized and validated tools administered by a clinician, a researcher, and/or based on self-report, parent-report, and/or teacher-report questionnaires.

To be included, both exposure and outcome have to be measured at mean age ≥ 5 years and ≤ 24. To address the research question on the role of insomnia and/or sleep disturbances as predictor of depression, only studies reporting on the exposure measured at least one month before the outcome will be included. When multiple assessments are conducted on the same cohort, each pair where both exposures and outcomes are measured at mean age ≤ 24 and ≥ 5 years and exposures are measured before the outcome will be considered.

Confounders

Studies will be included regardless of whether they contain estimates adjusted for common confounding factors, such as sex, socio-economic status, demographics, type of comorbidity at baseline. Studies that do not control for common confounding factors will be highlighted for potentially confounded results.

Identification of eligible studies and data extraction

Search strategy

The following databases will be searched: EMBASE, MEDLINE, PsychINFO, Scopus and Web of Science. A draft of the Medline search strategy will be developed using a combination of MeSH and keywords terms relating to sleep disorders, depression/depressive disorder and children/adolescents/young adults with the help of a research librarian. The search will be limited to the years 1980 (to focus on current diagnostic terminology from the DSM III) to the present and will also be limited to observational studies using the search filter developed by the Scottish Intercollegiate Guidelines Network (SIGN). The draft Medline search will also be piloted to ensure the sensitivity and efficacy of the final search strategy and will also be reviewed by all of the participating authors. The finalized Medline search will be adapted for each bibliographic database individually.

The grey literature will be screened for relevant material, including use of the search checklist Grey Matters: "A Practical Search Tool for Evidence-Based Medicine" from the Canadian Agency for Drugs and Technologies in Health (CADTH), and by also searching other sources to identify relevant dissertations/PhD theses and conference publications, i.e. Proquest Dissertations and Theses, ProceedingsFirst, PapersFirst, Conference Abstracts from Embase, Google Scholar Search. The references of selected articles will also be hand-searched for eligible studies and all the searches will be re-run just before the final analyses to identify additional relevant studies. Experts in the field will be contacted to locate potentially eligible studies and/or unpublished data.

Selection of studies

Search results will be exported into Covidence, merged and checked for duplicates. For the selection of studies two students will be involved, with minimum an undergraduate level of education in a health-related field and previous experience with the systematic review methodology. They will be given the systematic review protocol and 5-hour training on the content of the systematic review and basic knowledge of the procedure. For the selection of studies based on title&abstract screening, eligible studies will be selected by two reviewers until at least 80% of agreement is achieved with the remainder being selected by one reviewer. For the selection of studies based on full-text screening, reviewers will perform the selection in duplicate. Any uncertainty regarding selection will be resolved by consensus and if necessary, it will be reviewed by a third reviewer. The PRISMA search flow chart will be used to report the number of studies included and excluded at each step in the process, along with the rationale for the exclusion.

Data extraction

Data extraction will be conducted by one author and checked independently by a second author using a pre-defined data extraction form. Extracted variables will pertain to the following domains: general study information, study characteristics, participant characteristics, exposures and outcome measures, interval between baseline and follow-up, sample size, how missing data are handled, covariates that were adjusted in the analyses, outcome data, including effect sizes, odds ratio, relative risk or hazard ratio with respective 95% confidence interval. Information on the sources of funding for each study will be retrieved. Discrepancies between the two authors will be resolved by discussion. When relevant data are missing, corresponding authors will be contacted to obtain the information.

Risk of bias assessment

Risk of bias of included studies' results will be appraised using the Research Triangle Institute Item Bank (RTI-IB) tool. The RTI-B is a practical, quality-scoring tool for observational studies with a focus on bias and precision.[60] It has a high inter-rater reliability (75%) and consists of 29 items tapping 12 domains (1) background, (2) sample definition and selection, (3) interventions/exposure, (4) outcomes, (5) creation of treatment groups, (6) blinding, (7) soundness of information, (8) follow-up, (9) analysis comparability, (10) analysis outcome, (11) interpretation, and (12) presentation and reporting. Possible response categories to

each item are 'yes', 'no', 'partially', 'cannot determine', and 'not applicable'. The quality appraisal will be performed by two authors independently with discrepancies being resolved by discussion. Results will be reported narratively and summarized in a descriptive table. Items will be subdivided into six categories: selection bias/confounding, performance bias, attrition bias, detection bias, reporting bias, and information bias. Items are scored as high, low, or unclear risk of bias. If at least one item in a category is scored as high, the risk of bias within this category is scored as moderate risk. If at least 50% of the items in a category are scored as high, the risk of the category is scored as high. Each study will receive a summary score that corresponds to the highest score obtained in any category.[60]

Data synthesis and analysis

Data will be synthesized by a table reporting study type, participant characteristics, exposure and outcome measures, and a second table on the risk of bias assessment. The data will be categorised into each type of exposure, i.e. insomnia and sleep disturbances. Heterogeneity of pooled estimates for each exposure category will be measured using the I^2 statistic, which represents the percentage of variation attributable to between-study heterogeneity. I^2 values of 25%, 50%, and 75% will be considered as low, medium, and high heterogeneity, respectively. Meta-analysis of studies will be carried out if $I^2 \leq 75\%$ and if ≥ 3 results for each exposure category are available.[61] A narrative synthesis will be conducted in place of the meta-analysis, should this latter cannot be performed. For the meta-analysis, the random-effect model will be used if $I^2 \geq 50$ is detected, which is robust against both the between-study and within-study variability, otherwise the fixed-effect model will be used. Results of the meta-analyses will be summarized by a forest plot.

Meta-analyses will be performed in subgroups stratified by key variables if there are ≥ 3 studies. Such variables include risk of bias score, type of ascertainment, type of sleep disturbance, measurement of outcome, presence of baseline comorbidity, sample size, age group, gender. Subgroups will be defined depending on the amount and type of information retrieved.

To assess sensitivity of the pooled estimate to each included study, we will apply the leave-one-out method, which consists of repeating the analysis removing one study at a time.[62] Potential publication bias and other source of bias will be further assessed by visual inspection of the symmetry of funnel plots.

Quality of evidence will be rated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines taking into account risk of bias, applying the RTI-IB tool; heterogeneity; directness, evaluating the relevance of the sample, the outcomes and the exposure; precision, examining the 95% confidence interval; and publication bias of the included studies. We will assess inter-rater

agreement between investigators for study inclusion, data extraction, and methodological quality assessment using Kappa Cohen's coefficient.

Discussion

This systematic review and meta-analysis will synthesize and quantify the existing evidence on insomnia and/or sleep disturbances predicting depression in children and youth. While this link is well established and quantified in adult and elderly populations,[20-24] a comprehensive and updated summary is missing in children and youth.

Understanding the magnitude of the risk of sleep problems predicting later depression in children and youth will contribute significantly to the development of treatment and secondary prevention strategies of depression.[4 5 63] Sleep is often impaired in child and youth depression.[64] Treating sleep problems in childhood can become an adjunctive tool to treat more effectively childhood depression but also to change the risk trajectories of depression, reducing the incidence and severity of depressive episodes later in life. This study will also potentially inform strategies for primary prevention of depression in healthy children and youth. Sleep patterns physiologically change from birth to early adulthood as a consequence of a number of maturational changes in the brain, and as a result of an adjustment to the social environment.[65 66] The most evident change concerns the duration of sleep, which decreases from approximately 14 hours at 6 months of age to 8 hours at 16 years of age.[67 68] Another relevant maturational change concerns the sleep-onset time, which delays up to approximately 2 hours when transitioning to adolescence. This process is typical of puberty, and it is part of the phase delay of a host of circadian rhythms related to gonadal hormones' changes. The delay in sleep-onset time, called evening chronotype, manifests at a younger age in females than males, corresponding to the sex difference in the onset of puberty.[66 69] Evidence shows that over the last century child and youth sleep has consistently reduced beyond normative maturational changes.[70 71] It has been claimed that this "epidemic" shortage of sleep might be related to the concomitant occurrence of the evening chronotype and earlier morning wake-up time of youth compared to younger children.[72] Other studies claim that decreased sleep in children and youth may instead be due to the increase of electronic screen media use during late hours.[73] As a result, an increasing proportion of otherwise healthy children and youth is exposed to insufficient sleep. An open question is whether this newly occurring, sleep-deprived child and youth cohort is at risk of depression. Understanding if the same risk pathway identified in affected or at-risk individuals exists also in typically developing children and youth is essential to understand the size

and potential consequences of the secular trend toward insufficient sleep and to eventually plan effective programs of primary prevention to reduce the incidence of depression.

Ethics and dissemination: As this is a protocol for systematic review and meta-analysis of published data, ethics review and approval are not required. The findings will be published in a peer-reviewed journal and disseminated at scientific conferences.

Author contributions: CM, BA, MA and PS conceived the idea, planned and designed the study protocol. CM wrote the first draft. SB provided expertise to the search strategy. WW provided expertise to the data extraction and statistical analysis. JH provided critical insights. All authors have approved and contributed to the final written manuscript. CM guarantor of the review.

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Competing interests statement. None declared.

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Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination of our research

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Reporting checklist for protocol of a systematic review.

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.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

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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	2
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	12
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	12
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	12
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	3-5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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	6-7
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	8
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
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)	9
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	10

		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	10
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9-10
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	10
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	10-11
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)	10-11
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10-11
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10-11
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10-11
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

BMJ Open

Do insomnia and/or sleep disturbances predict the onset, relapse or worsening of depression in community and clinical samples of children and youth? Protocol for a systematic review and meta-analysis.

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Do insomnia and/or sleep disturbances predict the onset, relapse or worsening of depression in community and clinical samples of children and youth? Protocol for a systematic review and meta-analysis.

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Abstract

Introduction

Disturbed sleep represents a potentially important modifiable risk factor for the development of depression in children and youth. This protocol for a systematic review proposes to investigate whether insomnia and/or sleep disturbances predict child and youth depression in community and clinical-based samples.

Methods and analysis

The protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis protocols (PRISMA-P) guidelines. English-written, longitudinal studies that quantitatively estimated the prediction of depression by insomnia and/or sleep disturbances in individuals 5-24 years of age will be included. EMBASE, MEDLINE, PsychINFO, Scopus and Web of Science and grey literature will be searched from 1980 to the present. For the selection of studies, two reviewers will be involved. Data extraction will be conducted by one author and checked independently by a second author. Risk of bias will be appraised

using the Research Triangle Institute Item Bank (RTI-IB) tool. Heterogeneity will be measured using the I^2 statistic. Meta-analysis will be carried out if ≥ 3 results are available and if outcome measures can be pooled. The choice between a random-effect or fixed-effect model will be based both on the I^2 statistics and the participant-level characteristics of the combined studies. Results of the meta-analyses will be summarized by a forest plot. Analyses will be performed in subgroups stratified by key variables defined depending on the amount and type of information retrieved.

A narrative synthesis will be conducted in place of the meta-analysis, should pooling of data not be possible. Quality of evidence will be rated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines.

As this is a protocol for systematic review and meta-analysis of published data, ethics review and approval are not required. The findings will be published in a peer-reviewed journal and disseminated at scientific conferences and to patient advocacy organizations.

Strengths and limitations of this study

- This is a protocol for a systematic review and meta-analysis of existing prospective, longitudinal evidence on insomnia and/or sleep disturbances predicting depression in children and youth.
- This protocol will adhere to the Preferred Reporting Items for Systematic review and Meta-Analysis protocols (PRISMA-P) guidelines
- This protocol is registered at PROSPERO, the international prospective register of systematic reviews
- Full-text screening and extraction will be performed by two reviewers. Any uncertainty regarding selection will be resolved by consensus and if necessary, by a third reviewer.
- With regards to limitations, the review will not include treatment studies and will include only English-written articles. We include individuals aged 5-24 years, therefore excluding studies on child and youth disturbed sleep predicting depression at later stages of life.

Trial registration number: International Prospective Register for Systematic Reviews (PROSPERO) registration number CRD42019136729.

Introduction

A recent epidemiological study analyzing data from the 2016 National Survey of Children's Health reports prevalence estimates of depression of 1.7% and 6.1% in 6-11 and 12-17 years age-ranges, respectively.[1] The incidence of depression peaks at 20 years of age[2] with disrupting effects on normative developmental trajectories. Prevalence is equal for both sexes prior to puberty, then it is higher in females.[3] Treatment shows limited efficacy,[4-6] suggesting that prevention may be a more effective resource to reduce the incidence of depression.

Targeting modifiable risk factors of illnesses is becoming a relevant therapeutic strategy for disease prevention.[7] Among modifiable risk factors predicting child and youth depression, insomnia is increasingly recognized as an important component of the complex and multi-factorial causal pathway of depression.[8] Treating insomnia to specifically reduce the incidence and/or severity of depression has been the focus of controlled, high quality, randomized treatment studies in depressed or at risk for depression adult or elderly individuals.[9 10] In a recent meta-analysis, internet-based cognitive behavioural therapy (CBT) for insomnia had a significant, small effect on comorbid depression in individuals older than 18 years.[11]

Similar evidence in younger individuals is scarce, mostly consists of studies with small sample size/no follow-up, and it is limited to individuals older than 12 years of age [12-18].

In a randomized controlled trial, CBT for insomnia for six weekly sessions and a booster session after 2 months was significantly more effective in decreasing comorbid depression compared to waitlist in 12-19-year-old individuals with DSM-5 insomnia and no comorbid psychiatric disorders. The effect was large, was maintained after 12 months, and was fully mediated by the reduction of insomnia symptoms.[17]

In a longitudinal, randomised controlled trial study (SENSE, i.e.Sleep and Education: learning New Skills Early) the preventative effect on the incidence of depression in at risk for depression, 12-17-year-old adolescents with sleeping difficulties is investigated.[13] The interventions consist of seven weekly sessions of either a CBT/mindfulness-based sleep intervention or an active control intervention, followed by two booster sessions after three and six months post-intervention. One-hundred-twenty-three participants have completed the interventions,[14 15] however findings regarding the main outcomes of the study (preventative effects of depression) from the two-year follow-up are not available yet.

It is currently not known whether treating sleep problems in depressed or at risk for depression children (e.g. children with history of abuse, with high emotional dysregulation, offspring of depressed parents)

would lead to a reduction or lower incidence of depression, respectively, than it would be if sleep problems were not treated.[19] To understand whether earlier prevention efforts could be more effective, a precise quantitative estimate of the prediction of depression by insomnia in the entire developmental population, including depressed and non-depressed individuals, is needed.

Insomnia consists of clinically significant long sleep-onset latency and/or awakening after sleep onset and/or early-morning awakening, accompanied by diurnal tiredness and functional impairment. Prevalence of insomnia is 19.5% in children, equally distributed among boys and girls; in youth, prevalence is 17.4%, and higher among girls.[20]

Six systematic reviews have summarized cohort studies on insomnia predicting depression.[21-25] Pooled estimates are consistent across reviews ranging 2.10 (95% CI= 1.86-2.38)[26]-2.83 (95% CI= 1.55-5.17)[24], and across subgroups stratified by the most common confounders, e.g. sex [male: 1.46 (95% CI= 1.13-1.88)[25]; females: 1.96 (95% CI= 1.05-3.66)[25]], type of ascertainment [non-general population: 2.05 (95% CI= 1.53-2.74)[25]; general population: 2.34 (95% CI= 1.85-2.96)[25]], and age [individuals of age ≥ 60 years: 1.87 (95% CI= 1.47, 2.37)[25]-1.92 (95% CI: 1.61–2.30)[23]; individuals younger than 60 years of age: 2.50 (95% CI= 1.96, 3.20)[25]].

However, only three of the six systematic reviews included participants younger than 18 years,[22 25 26] and a pooled estimate, i.e. odds ratio= 2.0 (95% CI= 1.5-2.7), was provided by only one of the three reviews.[26] This estimate was based on three studies up to 2010 and included 7404 participants, whose age ranged between 6 and 16 years.[27-29] In all three studies, depression was defined according to DSM IV, and insomnia to DSM-IV-TR criteria. The test for heterogeneity for this group did not show a significant index (Q-value= 0.3; df(Q)=2; p=0.9; and I^2=0.0). Li et al.[25] updated and used the same selection criteria of Baglioni et al.[26] and although fifteen new cohort studies were added, no new studies on children and youth were included. Finally, Pigeon et al.[22] summarized studies published from 2014 to 2017; four studies on children and youth were included, of which three supported insomnia predicting depression,[30-32] and one found no such association.[33] All three systematic reviews of this age group excluded studies which did not control for baseline depression. This led to a greatly reduced number of studies. While the rationale of this choice is clear for studies of risk and prediction, it might not have been the ideal choice, due to the overall paucity of studies in the child and youth age-range compared to other age groups. Including studies that did not control for baseline depression would allow testing of whether there are significant differences in the meta-analytic estimates between studies controlling versus not-controlling for this variable. If no differences

are found, studies not controlling for baseline depression could contribute to the pooled data with an overall increase of the precision for the estimate of the meta-analytic effects.

There is also some evidence available on whether sleep disturbances other than insomnia predicts child and youth depression.[34-43] This may include increased/short/disrupted sleep duration with/without diurnal sleepiness, sleepwalking/talking, nightmares, bedwetting, breathing-related sleep disorders, and/or circadian disturbances. Furthermore, sleep disturbances more broadly defined may include challenges either generically defined with regards to duration and consistency over time, measured by self-reported questionnaires, interview or by EEG/actigraph-based measures, and scored by either single-item or cumulative scores. A recent meta-analysis summarized studies testing the association of broadly defined sleep disturbances on depression in 12-20-year-old already clinically depressed participants. In all selected studies,[44-50] sleep was defined by EEG-based, objective measures. Estimates of the meta-analytic effects identified that EEG-based longer sleep onset latency, more wake after sleep onset and lower sleep efficiency were significant predictors of depression compared to typical sleep (effect sizes ranging .43-.58).[51]

Although findings from this review are of crucial importance for potential secondary prevention programs in depressed youth, it would be useful to have summarized data on the longitudinal association of broadly defined sleep disturbances with depression on the entire developmental population, including non-clinical individuals as well as a broader age range, which would allow to apply findings to primary prevention and/or early intervention programs.

Finallly, insomnia and/or sleep disturbances are often associated to comorbid psychiatric and medical conditions.[19] Most previous knowledge synthesis studies have excluded comorbidities, limiting the generalizability and transferability of findings. For this reason, in this systematic review studies focusing on both primary and comorbid insomnia and/or sleep disturbances will be included. To understand the extent to which insomnia and/or sleep disturbances have a distinct risk to depression across comorbid disorders, subgroup analyses will be performed.

Understanding whether insomnia and/or sleep disturbances significantly increase the risk of depression in children and youth could lead to variation in clinical practice and inform policy development. Preventive strategies could include treating sleep problems starting as early as childhood. This is particularly important in light of evidence on the differential effectiveness of a number of treatment for sleep problems (e.g. melatonin,[52 53] cognitive behavioural therapy,[54] physical exercise,[55] and bright light therapy[56]) and the fact that sleep problems in children are under-diagnosed[57] and rarely treated.[58]

The purpose of this protocol is to outline methods for a systematic review and meta-analysis of data from prospective, longitudinal studies of children and youth ascertained from clinical or community-based samples investigating the role of insomnia and/or sleep disturbances compared to typical sleep as predictors of depression. "Do children and youth with insomnia and/or sleep disturbance have higher rates of later depression than children and youth without insomnia and/or sleep disturbance"?

We are interested in testing this relationship in the context of both the absence and presence of baseline depression, i.e. whether insomnia and/or sleep disturbance predict both new and relapse/worsening of depression, respectively.

Our study will add to the currently available knowledge synthesis in that:

1. It will provide an updated meta-analytic estimate of the effects of insomnia predicting child and youth depression, adding studies from 2010 onward compared to Baglioni et al.[26]
2. By including studies on 5-24-year-old participants from both clinical and non-clinical populations, it will provide a more comprehensive and updated meta-analytic estimate compared to Lovato and Gradisar[51]
3. It will include studies on participants with/without baseline depression and whether or not controlling for baseline depression
4. It will include studies of both primary and comorbid insomnia and/or sleep disturbances

As a secondary aim, we will test whether insomnia and/or sleep disturbance predict new onset and/or worsening/relapse of depression, by testing the pooled estimate in two subgroups of studies, respectively, those including participants with baseline depression or where baseline depression has been controlled for, and studies including participants without baseline depression or where baseline depression has not been controlled for.

Finally, we aim to explore the sources of potential heterogeneity and examine the robustness of the primary hypothesis against key confounding variables. Specifically, we will address whether the prediction of child and youth depression by insomnia and/or sleep disturbances significantly differ between studies stratified by key variables, e.g. risk of bias score, type of ascertainment, type of sleep disturbance, measurement of outcome, presence of baseline comorbidity, sample size, age group, gender. Subgroups will be defined depending on the amount and type of information retrieved.

Methods

For the protocol, we will follow the guidelines outlined in "Preferred Reporting Items for Systematic review and Meta-Analysis protocols (PRISMA-P)".[59] For the final report we will follow the guidelines set in "Meta-analysis Of Observational Studies in Epidemiology: a proposal for reporting" (MOOSE).[60]

Inclusion criteria

Study types

This study will include (1) English-written, (2) prospective, longitudinal observational studies that quantitatively estimated the prediction of depression by insomnia and/or sleep disturbances in children and youth. Only those studies reporting odds ratio, relative risk, hazard ratio, regression coefficients or correlation coefficients with their respective measurements of error and p-values will be selected. Grey literature including relevant dissertations/PhD theses and key conference publications will be included. Case series, case reports, systematic reviews, meta-analyses, as well as experimental, retrospective, cross-sectional, treatment, theoretical and position studies will be excluded.

Population type

Mean age to determine eligibility for inclusion of the study is between 5-24 years. This age range was chosen to cover the whole age range of risk for depression in childhood and youth, and to include the period of peak incidence for depression.[1 2] In our review, we identify three categories: 'childhood' between 5 and 9 years of age, 'adolescence' between 10 and 19 years of age, and 'young adulthood' between 20 and 24 years of age.[61] For simplicity, the term 'youth' refers to individuals whose age is between 10 and 24 years. Studies focusing on participants belonging to either community or clinical based samples with any comorbid psychiatric/neurological/medical diagnosis will be included.

Exposure

Studies will be included if focusing on either one of the following two exposures:

1. Insomnia, defined as clinically significant difficulty in initiating or maintaining sleep or non-restorative sleep, as based on DSM III and later versions. Although the criterion of daytime impairment is required to define clinically significant insomnia, it has been shown that pooled estimates of insomnia predicting depression when this criterion is taken into account[24] is of comparable magnitude relative to the ones obtained when this criterion is not considered (Baglioni et al. 2011;

Li et al. 2016).[26] Therefore, to allow for inclusion of the highest number of studies, daytime impairment will be free to vary.

2. Sleep disturbances, defined as patterns of quality and sleep duration which deviate from expected age-related norms, i.e. increased/short/fragmented sleep duration with or without daytime fatigue/sleepiness, nightmares/terror attacks, circadian disturbances, and/or night walking/talking. Sleep disturbances can be generically defined with regards to duration and consistency over time, and can be based on subjective and/or EEG/actigraph-based, objective measures. Measures can be based on single or multiple items, or a cumulative score of various items. To increase the generalizability of the results, narcolepsy, breathing-related sleep disorders, central sleep apnea, non-rapid/rapid eye movement sleep disorder, restless legs syndrome, substance/medication-induced sleep disorder, and enuresis nocturna primaria may also be included.

Exposures' assessment can be administered by a clinician, a researcher, or based on self-report, parent-report, and/or teacher-report questionnaires.

Outcome

Studies will be included if they focus on either one of the following outcomes: major depressive disorder, depressive disorder not otherwise specified, dysthymic disorder, and/or dimensional constructs of depression, i.e. defined by scores from single- or multiple-item questionnaires, internalizing disorders or anxious depression. Studies focusing on anxiety without a measure of depression will not be included. Studies including participants with bipolar disorders will be excluded given that sleep problems' prevalence differ significantly in bipolar versus unipolar disorders.[47 62] Outcome is measured by standardized and validated tools administered by a clinician, a researcher, and/or based on self-report, parent-report, and/or teacher-report questionnaires.

To be included, both exposure and outcome have to be measured at mean age ≥ 5 years and ≤ 24 and the time between the exposure and outcome is ≥ one month. To address the research question on the role of insomnia and/or sleep disturbances as predictor of depression, only studies reporting on the exposure measured at least one month before the outcome will be included. When multiple assessments are conducted on the same cohort, each pair where both exposures and outcomes are measured at mean age ≤ 24 and ≥ 5 years and exposures are measured before the outcome will be considered.

Confounders

Studies will be included regardless of whether they contain estimates adjusted for common confounding factors, such as sex, socio-economic status, demographics, type of comorbidity at baseline. Studies that do not control for common confounding factors will be highlighted for potentially confounded results.

Identification of eligible studies and data extraction

Search strategy

The following databases will be searched: EMBASE, MEDLINE, PsychINFO, Scopus and Web of Science. A draft of the Medline search strategy will be developed using a combination of MeSH and keywords terms relating to sleep disorders, depression/depressive disorder and children/adolescents/young adults with the help of a research librarian. The search will be limited to the years 1980 (to focus on current diagnostic terminology from the DSM III) to the present and will also be limited to observational studies using the search filter developed by the Scottish Intercollegiate Guidelines Network (SIGN). The draft Medline search will also be piloted to ensure the sensitivity and efficacy of the final search strategy and will also be reviewed by all of the participating authors (figure 1). The finalized Medline search will be adapted for each bibliographic database individually.

Grey literature, i.e. dissertations and conference proceeding/papers, will be included in the search in order to mitigate against publication bias.[63] Dissertations have been noted as providing a valuable methodology and clinical source of information.[64] Additionally, searching for relevant conference proceedings/papers is recommended in order to identify recent, but unpublished research.[65]

The grey literature will be screened for relevant material, including use of the search checklist Grey Matters: "A Practical Search Tool for Evidence-Based Medicine" from the Canadian Agency for Drugs and Technologies in Health (CADTH), and by also searching other sources to identify relevant dissertations/PhD theses and conference publications, i.e. Proquest Dissertations and Theses, ProceedingsFirst, PapersFirst, Conference Abstracts from Embase, Google Scholar Search. The references of selected articles will also be hand-searched for eligible studies and all the searches will be re-run just before the final analyses to identify additional relevant studies. Experts in the field will be contacted to locate potentially eligible studies and/or unpublished data.

Selection of studies

Search results will be exported into Covidence, merged and checked for duplicates. For the selection of studies two students will be involved, with minimum an undergraduate level of education in a health-related

field and previous experience with the systematic review methodology. They will be given the systematic review protocol and 5-hour training on the content of the systematic review and basic knowledge of the procedure. For the selection of studies based on title&abstract screening, eligible studies will be selected by two reviewers until a kappa score of 0.8 is achieved with the remainder being selected by one reviewer. Full text papers will be obtained for all references thought potentially eligible by a single reviewer based on title&abstract; all full text papers will be reviewed by two independent reviewers, with disagreements referred to a third, senior-author reviewer. The PRISMA search flow chart will be used to report the number of studies included and excluded at each step in the process, along with the rationale for the exclusion.

Data extraction

Data extraction will be conducted by one author and checked independently by a second author using a pre-defined data extraction form. Extracted variables will pertain to the following domains: general study information, study characteristics (i.e. year of publication, type of sample ascertainment, sample size), participant characteristics (i.e. age at baseline, age at follow up, number of follow up, interval between baseline and each follow-up, exposure and outcome definition and diagnostic tool, covariates that were adjusted in the analyses). Outcome data will include odds ratio, relative risk, hazard ratio, regression coefficients or correlation coefficients with their respective measurements of error and p-values. Information on the sources of funding for each study will be retrieved. Discrepancies between the two authors will be resolved by discussion with a third, senior-author reviewer. When relevant data are missing, corresponding authors will be contacted to obtain the information.

Risk of bias assessment

Risk of bias of included studies' results will be appraised using the Research Triangle Institute Item Bank (RTI-IB) tool. The RTI-B is a practical, quality-scoring tool for observational studies with a focus on bias and precision.[66] It has a high inter-rater reliability (75%) and consists of 29 items tapping 12 domains (1) background, (2) sample definition and selection, (3) interventions/exposure, (4) outcomes, (5) creation of treatment groups, (6) blinding, (7) soundness of information, (8) follow-up, (9) analysis comparability, (10) analysis outcome, (11) interpretation, and (12) presentation and reporting. Possible response categories to each item are 'yes', 'no', 'partially', 'cannot determine', and 'not applicable'. The quality appraisal will be performed by two authors independently with discrepancies being resolved by discussion with a third, senior-

author reviewer. Results will be reported narratively and summarized in a descriptive table. Items will be subdivided into six categories: selection bias/confounding, performance bias, attrition bias, detection bias, reporting bias, and information bias. Items are scored as high, low, or unclear risk of bias. If at least one item in a category is scored as high, the risk of bias within this category is scored as moderate risk. If at least 50% of the items in a category are scored as high, the risk of the category is scored as high. Each study will receive a summary score that corresponds to the highest score obtained in any category.[66]

Description of primary studies and data analysis

Data will be synthesized by a table reporting study type, participant characteristics, exposure and outcome measures, and a second table on the risk of bias assessment. Studies will be combined based on similarities across relevant characteristics, e.g. type of sample ascertainment, age at baseline, duration of follow-up, exposure and outcome definition and diagnostic tool, and meta-analysis will be performed if ≥ 3 studies are available. Heterogeneity of pooled estimates will be measured using the I^2 statistic, which represents the percentage of variation attributable to between-study heterogeneity. I^2 values of 25%, 50%, and 75% will be considered as low, medium, and high heterogeneity, respectively.[67] For the meta-analysis, the choice between a random-effect or fixed-effect model will be based both on the I^2 statistics and the participant-level characteristics of the combined studies. Results of the meta-analyses will be summarized by a forest plot. Meta-analysis and test of heterogeneity will be performed using STATA 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). A narrative synthesis will be conducted in place of the meta-analysis, should this latter cannot be performed.To test the robustness of the primary hypothesis against study-level characteristics, e.g. risk-of-bias score, sample size, year of publication, sensitivity analyses will be performed by excluding those studies with the characteristic that can potentially be a source of heterogeneity, e.g. excluding studies with a high risk-of-bias score. Likewise, a sensitivity analysis will be performed by removing studies focusing on medically based sleep disorders, i.e. narcolepsy, breathing-related sleep disorders, central sleep apnea, non-rapid/rapid eye movement sleep disorder, restless legs syndrome, substance/medication-induced sleep disorder, and enuresis nocturna primaria, to prevent the possibility that the pooled estimates could be impacted by factors related to the chronicity of these conditions.

Subgroup analyses will be performed related to relevant participant-level characteristics, e.g. baseline comorbidity, age at baseline, gender, duration of follow up, exposure and outcome definition and diagnostic tool, by calculating pooled estimates in subgroups of studies, e.g. studies of children versus adolescents

versus young adults, and/or taking different estimates from the same study related to the subgroups of interest, e.g. male versus female. Subgroups will be defined depending on the amount and type of information retrieved.

To assess sensitivity of the pooled estimate to each included study, we will apply the leave-one-out method, which consists of repeating the analysis removing one study at a time.[68] Potential publication bias and other source of bias will be further assessed by visual inspection of the symmetry of funnel plots. Quality of evidence will be rated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines taking into account risk of bias, applying the RTI-IB tool; heterogeneity; directness, evaluating the relevance of the sample, the outcomes and the exposure; precision, examining the 95% confidence interval; and publication bias of the included studies. We will assess inter-rater agreement between investigators for study inclusion, data extraction, and methodological quality assessment using Kappa Cohen's coefficient.

Discussion

This systematic review and meta-analysis will synthesize and quantify the existing evidence on insomnia and/or sleep disturbances predicting depression in children and youth.

Understanding the magnitude of the risk of sleep problems predicting later depression in children and youth will contribute significantly to the development of treatment and secondary prevention strategies of depression.[5 6 69] Sleep is often impaired in child and youth depression.[70] Treating sleep problems in childhood can become an adjunctive tool to treat more effectively childhood depression but also to change the risk trajectories of depression, reducing the incidence and severity of depressive episodes later in life. This study will also potentially inform strategies for primary prevention of depression in healthy children and youth. Sleep patterns physiologically change from birth to early adulthood as a consequence of a number of maturational changes in the brain, and as a result of an adjustment to the social environment.[71 72] The most evident change concerns the duration of sleep, which decreases from approximately 14 hours at 6 months of age to 8 hours at 16 years of age.[73 74] Another relevant maturational change concerns the sleep-onset time, which delays up to approximately 2 hours when transitioning to adolescence.[75] This process is typical of puberty, and it is part of the phase delay of a host of circadian rhythms related to gonadal hormones' changes.[75] The delay in sleep-onset time, called evening chronotype, manifests at a younger age in females than males, corresponding to the sex difference in the onset of puberty.[72 75] Evidence shows that over the last century child and youth sleep has consistently reduced beyond normative maturational

changes.[76 77] It has been claimed that this "epidemic" shortage of sleep might be related to the concomitant occurrence of the evening chronotype and earlier morning wake-up time of youth compared to younger children.[78] Other studies claim that decreased sleep in children and youth may instead be due to the increase of electronic screen media use during late hours.[79] As a result, an increasing proportion of otherwise healthy children and youth is exposed to insufficient sleep. An open question is whether this newly occurring, sleep-deprived child and youth cohort is at risk of depression. Understanding if the same risk pathway identified in affected or at-risk for depression individuals exists also in typically developing children and youth is essential to understand the size and potential consequences of the secular trend toward insufficient sleep and to eventually plan effective programs of primary prevention to reduce the incidence of depression.

Ethics and dissemination: As this is a protocol for systematic review and meta-analysis of published data, ethics review and approval are not required. The findings will be published in a peer-reviewed journal and disseminated at scientific conferences.

Author contributions: CM, BA, MA and PS conceived the idea, planned and designed the study protocol. CM wrote the first draft. SB provided expertise to the search strategy. WW provided expertise to the data extraction and statistical analysis. JH provided critical insights. All authors have approved and contributed to the final written manuscript. CM guarantor of the review.

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Figure 1: Database: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® <1946-Present>

Search Strategy:

1 exp Sleep Wake Disorders/

2 exp Sleep/

3 (apnea$ adj3 sleep$).mp.

4 (restless adj3 leg$ adj3 syndrome$).mp.

5 narcolep$.mp.

6 (night$ adj3 terror$).mp.

7 sleep$.mp.

8 dyssomni$.mp.

9 parasomni$.mp.

10 insomni$.mp.

11 exp Depressive Disorder/

12 exp Depression/

13 depress$.mp.

14 exp Child/

15 exp Adolescents/

16 exp Young Adult/

17 (child$ or juvenile$ or pubescen$ or prepubescen or pre-pubescen* or teen$ or preteen$ or tween$ or youth$ or adoles$ or young$ adult$ or emerg$ adult$).mp.*

18 exp Epidemiologic studies/

19 exp Case control studies/

20 exp Cohort studies/

21 case control.tw.

22 (cohort adj (study or studies)).tw.

23 cohort analy$.tw.

24 (follow up adj (study or studies)).tw.

25 (observational adj (study or studies)).tw.

26 longitudinal.tw.

27 *retrospective.tw.*

28 *cross sectional.tw.*

29 *cross-sectional studies/*

30 *or/1-10*

31 *or/11-13*

32 *or/14-17*

33 *or/18-29*

34 *30 and 31 and 32 and 33*

35 *limit 34 to yr="1980 -Current"*

Reporting checklist for protocol of a systematic review.

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.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		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	2
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	12
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	12
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	12
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	3-5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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	6-7
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	8
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
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)	9
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	10

		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	10
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9-10
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	10
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	10-11
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)	10-11
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10-11
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10-11
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10-11
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

BMJ Open

Do insomnia and/or sleep disturbances predict the onset, relapse or worsening of depression in community and clinical samples of children and youth? Protocol for a systematic review and meta-analysis.

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Do insomnia and/or sleep disturbances predict the onset, relapse or worsening of depression in community and clinical samples of children and youth? Protocol for a systematic review and meta-analysis.

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Abstract

Introduction

Disturbed sleep represents a potentially important modifiable risk factor for the development of depression in children and youth. This protocol for a systematic review proposes to investigate whether insomnia and/or sleep disturbances predict child and youth depression in community and clinical-based samples.

Methods and analysis

The protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis protocols (PRISMA-P) guidelines. English-written, longitudinal studies that quantitatively estimated the prediction of depression by insomnia and/or sleep disturbances in individuals 5-24 years of age will be included. EMBASE, MEDLINE, PsychINFO, Scopus and Web of Science and grey literature will be searched from 1980 to the present. For the selection of studies, two reviewers will be involved. Data extraction will be conducted by one author and checked independently by a second author. Risk of bias will be appraised

using the Research Triangle Institute Item Bank (RTI-IB) tool. Heterogeneity will be measured using the I^2 statistic. Meta-analysis will be carried out if ≥ 3 results are available and if outcome measures can be pooled. The choice between a random-effect or fixed-effect model will be based both on the I^2 statistics and the participant and study characteristics of the combined studies. Results of the meta-analyses will be summarized by a forest plot. Analyses will be performed in subgroups stratified by key variables defined depending on the amount and type of information retrieved.

A narrative synthesis will be conducted in place of the meta-analysis, should pooling of data not be possible. Quality of evidence will be rated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines.

As this is a protocol for systematic review and meta-analysis of published data, ethics review and approval are not required. The findings will be published in a peer-reviewed journal and disseminated at scientific conferences and to patient advocacy organizations.

Strengths and limitations of this study

- This is a protocol for a systematic review and meta-analysis of existing prospective, longitudinal evidence on insomnia and/or sleep disturbances predicting depression in children and youth.
- This protocol will adhere to the Preferred Reporting Items for Systematic review and Meta-Analysis protocols (PRISMA-P) guidelines
- This protocol is registered at PROSPERO, the international prospective register of systematic reviews
- Full-text screening and extraction will be performed by two reviewers. Any uncertainty regarding selection will be resolved by consensus and if necessary, by a third reviewer.
- With regards to limitations, the review will not include treatment studies and will include only English-written articles. We include individuals aged 5-24 years, therefore excluding studies on child and youth disturbed sleep predicting depression at later stages of life.

Trial registration number: International Prospective Register for Systematic Reviews (PROSPERO) registration number CRD42019136729.

Introduction

A recent epidemiological study analyzing data from the 2016 National Survey of Children's Health reports prevalence estimates of depression of 1.7% and 6.1% in 6-11 and 12-17 years age-ranges, respectively.[1] The incidence of depression peaks at 20 years of age[2] with disrupting effects on normative developmental trajectories. Prevalence is equal for both sexes prior to puberty, then it is higher in females.[3] Treatment shows limited efficacy,[4-6] suggesting that prevention may be a more effective resource to reduce the incidence of depression.

Targeting modifiable risk factors of illnesses is becoming a relevant therapeutic strategy for disease prevention.[7] Among modifiable risk factors predicting child and youth depression, insomnia is increasingly recognized as an important component of the complex and multi-factorial causal pathway of depression.[8] Treating insomnia to specifically reduce the incidence and/or severity of depression has been the focus of controlled, high quality, randomized treatment studies in depressed or at risk for depression adult or elderly individuals.[9 10] In a recent meta-analysis, internet-based cognitive behavioural therapy (CBT) for insomnia had a significant, small effect on comorbid depression in individuals older than 18 years.[11]

Similar evidence in younger individuals is scarce, mostly consists of studies with small sample size/no follow-up, and it is limited to individuals older than 12 years of age [12-18].

In a randomized controlled trial, CBT for insomnia for six weekly sessions and a booster session after 2 months was significantly more effective in decreasing comorbid depression compared to waitlist in 12-19-year-old individuals with DSM-5 insomnia and no comorbid psychiatric disorders. The effect was large, was maintained after 12 months, and was fully mediated by the reduction of insomnia symptoms.[17]

In a longitudinal, randomised controlled trial study (SENSE, i.e.Sleep and Education: learning New Skills Early) the preventative effect on the incidence of depression in at risk for depression, 12-17-year-old adolescents with sleeping difficulties is investigated.[13] The interventions consist of seven weekly sessions of either a CBT/mindfulness-based sleep intervention or an active control intervention, followed by two booster sessions after three and six months post-intervention. One-hundred-twenty-three participants have completed the interventions,[14 15] however findings regarding the main outcomes of the study (preventative effects of depression) from the two-year follow-up are not available yet.

It is currently not known whether treating sleep problems in depressed or at risk for depression children (e.g. children with history of abuse, with high emotional dysregulation, offspring of depressed parents)

would lead to a reduction or lower incidence of depression, respectively, than it would be if sleep problems were not treated.[19] To understand whether earlier prevention efforts could be more effective, a precise quantitative estimate of the prediction of depression by insomnia in the entire developmental population, including depressed and non-depressed individuals, is needed.

Insomnia consists of clinically significant long sleep-onset latency and/or awakening after sleep onset and/or early-morning awakening, accompanied by diurnal tiredness and functional impairment. Prevalence of insomnia is 19.5% in children, equally distributed among boys and girls; in youth, prevalence is 17.4%, and higher among girls.[20]

Six systematic reviews have summarized cohort studies on insomnia predicting depression.[21-25] Pooled estimates are consistent across reviews ranging 2.10 (95% CI= 1.86-2.38)[26]-2.83 (95% CI= 1.55-5.17)[24], and across subgroups stratified by the most common confounders, e.g. sex [male: 1.46 (95% CI= 1.13-1.88)[25]; females: 1.96 (95% CI= 1.05-3.66)[25]], type of ascertainment [sample drawn from a special population: 2.05 (95% CI= 1.53-2.74)[25]; sample representative of a community or population: 2.34 (95% CI= 1.85-2.96)[25]], and age [individuals of age ≥ 60 years: 1.87 (95% CI= 1.47, 2.37)[25]-1.92 (95% CI: 1.61–2.30)[23]; individuals younger than 60 years of age: 2.50 (95% CI= 1.96, 3.20)[25]].

However, only three of the six systematic reviews included participants younger than 18 years,[22 25 26] and a pooled estimate, i.e. odds ratio= 2.0 (95% CI= 1.5-2.7), was provided by only one of the three reviews.[26] This estimate was based on three studies up to 2010 and included 7404 participants, whose age ranged between 6 and 16 years.[27-29] In all three studies, depression was defined according to DSM IV, and insomnia to DSM-IV-TR criteria. The test for heterogeneity for this group did not show a significant index (Q-value= 0.3; df(Q)=2; p=0.9; and I^2=0.0). Li et al.[25] updated and used the same selection criteria of Baglioni et al.[26] and although fifteen new cohort studies were added, no new studies on children and youth were included. Finally, Pigeon et al.[22] summarized studies published from 2014 to 2017; four studies on children and youth were included, of which three supported insomnia predicting depression,[30-32] and one found no such association.[33] All three systematic reviews of this age group excluded studies which did not control for baseline depression. This led to a greatly reduced number of studies. While the rationale of this choice is clear for studies of risk and prediction, it might not have been the ideal choice, due to the overall paucity of studies in the child and youth age-range compared to other age groups. Including studies that did not control for baseline depression would allow testing of whether there are significant differences in the meta-analytic estimates between studies controlling versus not-controlling for this variable. If no differences

are found, studies not controlling for baseline depression could contribute to the pooled data with an overall increase of the precision for the estimate of the meta-analytic effects.

There is also some evidence available on whether sleep disturbances other than insomnia predicts child and youth depression.[34-43] This may include increased/short/disrupted sleep duration with/without diurnal sleepiness, sleepwalking/talking, nightmares, bedwetting, breathing-related sleep disorders, and/or circadian disturbances. Furthermore, sleep disturbances more broadly defined may include challenges either generically defined with regards to duration and consistency over time, measured by self-reported questionnaires, interview or by EEG/actigraph-based measures, and scored by either single-item or cumulative scores. A recent meta-analysis summarized studies testing the association of broadly defined sleep disturbances on depression in 12-20-year-old already clinically depressed participants. In all selected studies,[44-50] sleep was defined by EEG-based, objective measures. Estimates of the meta-analytic effects identified that EEG-based longer sleep onset latency, more wake after sleep onset and lower sleep efficiency were significant predictors of depression compared to typical sleep (effect sizes ranging .43-.58).[51]

Although findings from this review are of crucial importance for potential secondary prevention programs in depressed youth, it would be useful to have summarized data on the longitudinal association of broadly defined sleep disturbances with depression on the entire developmental population, including non-clinical individuals as well as a broader age range, which would allow to apply findings to primary prevention and/or early intervention programs.

Finallly, insomnia and/or sleep disturbances are often associated to comorbid psychiatric and medical conditions.[19] Most previous knowledge synthesis studies have excluded comorbidities, limiting the generalizability and transferability of findings. For this reason, in this systematic review studies focusing on both primary and comorbid insomnia and/or sleep disturbances will be included. To understand the extent to which insomnia and/or sleep disturbances have a distinct risk to depression across comorbid disorders, subgroup analyses will be performed.

Understanding whether insomnia and/or sleep disturbances significantly increase the risk of depression in children and youth could lead to variation in clinical practice and inform policy development. Preventive strategies could include treating sleep problems starting as early as childhood. This is particularly important in light of evidence on the differential effectiveness of a number of treatment for sleep problems (e.g. melatonin,[52 53] cognitive behavioural therapy,[54] physical exercise,[55] and bright light therapy[56]) and the fact that sleep problems in children are under-diagnosed[57] and rarely treated.[58]

The purpose of this protocol is to outline methods for a systematic review and meta-analysis of data from prospective, longitudinal studies of children and youth ascertained from clinical or community-based samples investigating the role of insomnia and/or sleep disturbances compared to typical sleep as predictors of depression. “Do children and youth with insomnia and/or sleep disturbance have higher rates of later depression than children and youth without insomnia and/or sleep disturbance”?

We are interested in testing this relationship in the context of both the absence and presence of baseline depression, i.e. whether insomnia and/or sleep disturbance predict both new and relapse/worsening of depression, respectively.

Our study will add to the currently available knowledge synthesis in that:

1. It will provide an updated meta-analytic estimate of the effects of insomnia predicting child and youth depression, adding studies from 2010 onward compared to Baglioni et al.[26]
2. By including studies on 5-24-year-old participants from both clinical and non-clinical populations, it will provide a more comprehensive and updated meta-analytic estimate compared to Lovato and Gradisar[51]
3. It will include studies on participants with/without baseline depression and whether or not controlling for baseline depression
4. It will include studies of both primary and comorbid insomnia and/or sleep disturbances

As a secondary aim, we will test whether insomnia and/or sleep disturbance predict new onset and/or worsening/relapse of depression, by testing the pooled estimate in two subgroups of studies, respectively, those including participants with baseline depression or where baseline depression has been controlled for, and studies including participants without baseline depression or where baseline depression has not been controlled for.

Finally, we aim to explore the sources of potential heterogeneity and examine the robustness of the primary hypothesis against key confounding variables. Specifically, we will address whether the prediction of child and youth depression by insomnia and/or sleep disturbances significantly differ between studies stratified by key variables, e.g. risk of bias score, type of ascertainment, type of sleep disturbance, measurement of outcome, presence of baseline comorbidity, sample size, age group, gender. Subgroups will be defined depending on the amount and type of information retrieved.

Methods

For the protocol, we will follow the guidelines outlined in "Preferred Reporting Items for Systematic review and Meta-Analysis protocols (PRISMA-P)".[59] For the final report we will follow the guidelines set in "Meta-analysis Of Observational Studies in Epidemiology: a proposal for reporting" (MOOSE).[60]

Patient and Public Involvement: no patient involved

Inclusion criteria

Study types

This study will include (1) English-written, (2) prospective, longitudinal observational studies that quantitatively estimated the prediction of depression by insomnia and/or sleep disturbances in children and youth. Only those studies reporting odds ratio, relative risk, hazard ratio, regression coefficients or correlation coefficients with their respective measurements of error and p-values will be selected. Grey literature including relevant dissertations/PhD theses and key conference publications will be included. Case series, case reports, systematic reviews, meta-analyses, as well as experimental, retrospective, cross-sectional, treatment, theoretical and position studies will be excluded.

Population type

Mean age to determine eligibility for inclusion of the study is between 5-24 years. This age range was chosen to cover the whole age range of risk for depression in childhood and youth, and to include the period of peak incidence for depression.[1 2] In our review, we identify three categories: 'childhood' between 5 and 9 years of age, 'adolescence' between 10 and 19 years of age, and 'young adulthood' between 20 and 24 years of age.[61] For simplicity, the term 'youth' refers to individuals whose age is between 10 and 24 years. Studies focusing on participants belonging to either community or clinical based samples with any comorbid psychiatric/neurological/medical diagnosis will be included.

Exposure

Studies will be included if focusing on either one of the following two exposures:

1. Insomnia, defined as clinically significant difficulty in initiating or maintaining sleep or non-restorative sleep, as based on DSM III and later versions. Although the criterion of daytime impairment is required to define clinically significant insomnia, it has been shown that pooled estimates of

insomnia predicting depression when this criterion is taken into account[24] is of comparable magnitude relative to the ones obtained when this criterion is not considered (Baglioni et al. 2011; Li et al. 2016).[26] Therefore, to allow for inclusion of the highest number of studies, daytime impairment will be free to vary.

2. Sleep disturbances, defined as patterns of quality and sleep duration which deviate from expected age-related norms, i.e. increased/short/fragmented sleep duration with or without daytime fatigue/sleepiness, nightmares/terror attacks, circadian disturbances, and/or night walking/talking. Sleep disturbances can be generically defined with regards to duration and consistency over time, and can be based on subjective and/or EEG/actigraph-based, objective measures. Measures can be based on single or multiple items, or a cumulative score of various items. To increase the generalizability of the results, narcolepsy, breathing-related sleep disorders, central sleep apnea, non-rapid/rapid eye movement sleep disorder, restless legs syndrome, substance/medication-induced sleep disorder, and enuresis nocturna primaria may also be included.

Exposures' assessment can be administered by a clinician, a researcher, or based on self-report, parent-report, and/or teacher-report questionnaires.

Outcome

Studies will be included if they focus on either one of the following outcomes: major depressive disorder, depressive disorder not otherwise specified, dysthymic disorder, and/or dimensional constructs of depression, i.e. defined by scores from single- or multiple-item questionnaires, internalizing disorders or anxious depression. Studies focusing on anxiety without a measure of depression will not be included. Studies including participants with bipolar disorders will be excluded given that sleep problems' prevalence differ significantly in bipolar versus unipolar disorders.[47 62] Outcome is measured by standardized and validated tools administered by a clinician, a researcher, and/or based on self-report, parent-report, and/or teacher-report questionnaires.

To be included, both exposure and outcome have to be measured at mean age ≥ 5 years and ≤ 24 and the time between the exposure and outcome is ≥ one month. To address the research question on the role of insomnia and/or sleep disturbances as predictor of depression, only studies reporting on the exposure measured at least one month before the outcome will be included. When multiple assessments are conducted on the same cohort, each pair where both exposures and outcomes are measured at mean age ≤ 24 and ≥ 5 years and exposures are measured before the outcome will be considered.

Confounders

Studies will be included regardless of whether they contain estimates adjusted for common confounding factors, such as sex, socio-economic status, demographics, type of comorbidity at baseline. Studies that do not control for common confounding factors will be highlighted for potentially confounded results.

Identification of eligible studies and data extraction

Search strategy

The following databases will be searched: EMBASE, MEDLINE, PsychINFO, Scopus and Web of Science. A draft of the Medline search strategy will be developed using a combination of MeSH and keywords terms relating to sleep disorders, depression/depressive disorder and children/adolescents/young adults with the help of a research librarian. The search will be limited to the years 1980 (to focus on current diagnostic terminology from the DSM III) to the present and will also be limited to observational studies using the search filter developed by the Scottish Intercollegiate Guidelines Network (SIGN). The draft Medline search will also be piloted to ensure the sensitivity and efficacy of the final search strategy and will also be reviewed by all of the participating authors (figure 1). The finalized Medline search will be adapted for each bibliographic database individually.

Grey literature, i.e. dissertations and conference proceeding/papers, will be included in the search in order to mitigate against publication bias.[63] Dissertations have been noted as providing a valuable methodology and clinical source of information.[64] Additionally, searching for relevant conference proceedings/papers is recommended in order to identify recent, but unpublished research.[65]

The grey literature will be screened for relevant material, including use of the search checklist Grey Matters: "A Practical Search Tool for Evidence-Based Medicine" from the Canadian Agency for Drugs and Technologies in Health (CADTH), and by also searching other sources to identify relevant dissertations/PhD theses and conference publications, i.e. Proquest Dissertations and Theses, ProceedingsFirst, PapersFirst, Conference Abstracts from Embase, Google Scholar Search. The references of selected articles will also be hand-searched for eligible studies and all the searches will be re-run just before the final analyses to identify additional relevant studies. Experts in the field will be contacted to locate potentially eligible studies and/or unpublished data.

Selection of studies

Search results will be exported into Covidence, merged and checked for duplicates. For the selection of studies two students will be involved, with minimum an undergraduate level of education in a health-related field and previous experience with the systematic review methodology. They will be given the systematic review protocol and 5-hour training on the content of the systematic review and basic knowledge of the procedure. For the selection of studies based on title&abstract screening, eligible studies will be selected by two reviewers until a kappa score of 0.8 is achieved with the remainder being selected by one reviewer. Full text papers will be obtained for all references thought potentially eligible by a single reviewer based on title&abstract; all full text papers will be reviewed by two independent reviewers, with disagreements referred to a third, senior-author reviewer. The PRISMA search flow chart will be used to report the number of studies included and excluded at each step in the process, along with the rationale for the exclusion.

Data extraction

Data extraction will be conducted by one author and checked independently by a second author using a pre-defined data extraction form. Extracted variables will pertain to the following domains: general study information, study characteristics (i.e. year of publication, type of sample ascertainment, sample size), participant characteristics (i.e. age at baseline, age at follow up, number of follow up, interval between baseline and each follow-up, exposure and outcome definition and diagnostic tool, covariates that were adjusted in the analyses). Outcome data will include odds ratio, relative risk, hazard ratio, regression coefficients or correlation coefficients with their respective measurements of error and p-values. Information on the sources of funding for each study will be retrieved. Discrepancies between the two authors will be resolved by discussion with a third, senior-author reviewer. When relevant data are missing, corresponding authors will be contacted to obtain the information.

Risk of bias assessment

Risk of bias of included studies' results will be appraised using the Research Triangle Institute Item Bank (RTI-IB) tool. The RTI-B is a practical, quality-scoring tool for observational studies with a focus on bias and precision.[66] It has a high inter-rater reliability (75%) and consists of 29 items tapping 12 domains (1) background, (2) sample definition and selection, (3) interventions/exposure, (4) outcomes, (5) creation of treatment groups, (6) blinding, (7) soundness of information, (8) follow-up, (9) analysis comparability, (10) analysis outcome, (11) interpretation, and (12) presentation and reporting. Possible response categories to

each item are 'yes', 'no', 'partially', 'cannot determine', and 'not applicable'. The quality appraisal will be performed by two authors independently with discrepancies being resolved by discussion with a third, senior-author reviewer. Results will be reported narratively and summarized in a descriptive table. Items will be subdivided into six categories: selection bias/confounding, performance bias, attrition bias, detection bias, reporting bias, and information bias. Items are scored as high, low, or unclear risk of bias. If at least one item in a category is scored as high, the risk of bias within this category is scored as moderate risk. If at least 50% of the items in a category are scored as high, the risk of the category is scored as high. Each study will receive a summary score that corresponds to the highest score obtained in any category.[66]

Description of primary studies and data analysis

Data will be synthesized by a table reporting study type, participant characteristics, exposure and outcome measures, and a second table on the risk of bias assessment. Studies will be combined based on similarities across relevant characteristics, e.g. type of sample ascertainment, age at baseline, duration of follow-up, exposure and outcome definition and diagnostic tool, and meta-analysis will be performed if ≥ 3 studies are available. Heterogeneity of pooled estimates will be measured using the I^2 statistic, which represents the percentage of variation attributable to between-study heterogeneity. I^2 values of 25%, 50%, and 75% will be considered as low, medium, and high heterogeneity, respectively.[67] For the meta-analysis, the choice between a random-effect or fixed-effect model will be based both on the I^2 statistics, and the participant and study characteristics of the combined studies. Results of the meta-analyses will be summarized by a forest plot. Meta-analysis and test of heterogeneity will be performed using STATA 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). A narrative synthesis will be conducted in place of the meta-analysis, should this latter cannot be performed. To test the robustness of the primary hypothesis against study-level characteristics, e.g. risk-of-bias score, sample size, year of publication, duration of follow up, exposure and outcome definition and diagnostic tool, sensitivity analyses will be performed by excluding those studies with the characteristic that can potentially be a source of heterogeneity, e.g. excluding studies with a high risk-of-bias score. Likewise, a sensitivity analysis will be performed by removing studies focusing on medically based sleep disorders, i.e. narcolepsy, breathing-related sleep disorders, central sleep apnea, non-rapid/rapid eye movement sleep disorder, restless legs syndrome, substance/medication-induced sleep disorder, and enuresis nocturna primaria, to prevent the possibility that the pooled estimates could be impacted by factors related to the chronicity of these conditions.

Subgroup analyses will be performed related to relevant participant-level characteristics, e.g. baseline comorbidity, age at baseline, gender, by calculating pooled estimates in subgroups of studies, e.g. studies of children versus adolescents versus young adults, and/or taking different estimates from the same study related to the subgroups of interest, e.g. male versus female. Subgroups will be defined depending on the amount and type of information retrieved.

To assess sensitivity of the pooled estimate to each included study, we will apply the leave-one-out method, which consists of repeating the analysis removing one study at a time.[68] Potential publication bias and other source of bias will be further assessed by visual inspection of the symmetry of funnel plots.

Quality of evidence will be rated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines taking into account risk of bias, applying the RTI-IB tool; heterogeneity; directness, evaluating the relevance of the sample, the outcomes and the exposure; precision, examining the 95% confidence interval; and publication bias of the included studies. We will assess inter-rater agreement between investigators for study inclusion, data extraction, and methodological quality assessment using Kappa Cohen's coefficient.

Discussion

This systematic review and meta-analysis will synthesize and quantify the existing evidence on insomnia and/or sleep disturbances predicting depression in children and youth.

Understanding the magnitude of the risk of sleep problems predicting later depression in children and youth will contribute significantly to the development of treatment and secondary prevention strategies of depression.[5 6 69] Sleep is often impaired in child and youth depression.[70] Treating sleep problems in childhood can become an adjunctive tool to treat more effectively childhood depression but also to change the risk trajectories of depression, reducing the incidence and severity of depressive episodes later in life. This study will also potentially inform strategies for primary prevention of depression in healthy children and youth. Sleep patterns physiologically change from birth to early adulthood as a consequence of a number of maturational changes in the brain, and as a result of an adjustment to the social environment.[71 72] The most evident change concerns the duration of sleep, which decreases from approximately 14 hours at 6 months of age to 8 hours at 16 years of age.[73 74] Another relevant maturational change concerns the sleep-onset time, which delays up to approximately 2 hours when transitioning to adolescence.[75] This process is typical of puberty, and it is part of the phase delay of a host of circadian rhythms related to gonadal hormones' changes.[75] The delay in sleep-onset time, called evening chronotype, manifests at a younger age in

females than males, corresponding to the sex difference in the onset of puberty.[72 75] Evidence shows that over the last century child and youth sleep has consistently reduced beyond normative maturational changes.[76 77] It has been claimed that this "epidemic" shortage of sleep might be related to the concomitant occurrence of the evening chronotype and earlier morning wake-up time of youth compared to younger children.[78] Other studies claim that decreased sleep in children and youth may instead be due to the increase of electronic screen media use during late hours.[79] As a result, an increasing proportion of otherwise healthy children and youth is exposed to insufficient sleep. An open question is whether this newly occurring, sleep-deprived child and youth cohort is at risk of depression. Understanding if the same risk pathway identified in affected or at-risk for depression individuals exists also in typically developing children and youth is essential to understand the size and potential consequences of the secular trend toward insufficient sleep and to eventually plan effective programs of primary prevention to reduce the incidence of depression.

Ethics and dissemination: As this is a protocol for systematic review and meta-analysis of published data, ethics review and approval are not required. The findings will be published in a peer-reviewed journal and disseminated at scientific conferences.

Author contributions: CM, BA, MA and PS conceived the idea, planned and designed the study protocol. CM wrote the first draft. SB provided expertise to the search strategy. WW provided expertise to the data extraction and statistical analysis. JH provided critical insights. All authors have approved and contributed to the final written manuscript. CM guarantor of the review.

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Competing interests statement. None declared.

Word Count: 4,130 words.

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination of our research

Figure 1: Database: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® <1946-Present>

Search Strategy

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1 exp Sleep Wake Disorders/
2 exp Sleep/
3 (apnea$ adj3 sleep$).mp.
4 (restless adj3 leg$ adj3 syndrome$).mp.
5 narcolep$.mp.
6 (night$ adj3 terror$).mp.
7 sleep$.mp.
8 dyssomni$.mp.
9 parasomni$.mp.
10 insomni$.mp.
11 exp Depressive Disorder/
12 exp Depression/
13 depress$.mp.
14 exp Child/
15 exp Adolescents/
16 exp Young Adult/
17 (child$ or juvenile$ or pubescen$ or prepubescen* or pre-pubescen* or teen$ or preteen$ or tween$ or youth$ or adoles$ or young$ adult$ or emerg$ adult$).mp.
18 exp Epidemiologic studies/
19 exp Case control studies/
20 exp Cohort studies/
21 case control.tw.
22 (cohort adj (study or studies)).tw.
23 cohort analy$.tw.
24 (follow up adj (study or studies)).tw.
25 (observational adj (study or studies)).tw.
26 longitudinal.tw.
27 retrospective.tw.
28 cross sectional.tw.
29 cross-sectional studies/
30 or/1-10
31 or/11-13
32 or/14-17
33 or/18-29
34 30 and 31 and 32 and 33
35 limit 34 to yr="1980 -Current"

Reporting checklist for protocol of a systematic review.

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.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		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	2
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	12
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	12
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	12
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	3-5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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	6-7
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	8
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
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)	9
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	10

		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	10
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9-10
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	10
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	10-11
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)	10-11
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10-11
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10-11
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10-11
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11