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Trajectory research in children on the autism spectrum: A scoping review protocol

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Abstract

Introduction. Longitudinal trajectory methods, featuring outcome assessments at three or more timepoints, are increasingly being used as appropriate approaches to understand developmental pathways of people on the autism spectrum across the lifespan. Understanding the scope of this rapidly expanding body of research can help inform future trajectory studies and identify areas for potential meta-analysis as well as key evidence gaps. The objective of this scoping review is to identify and summarize the scope of research that uses a longitudinal trajectory study design to examine development in children diagnosed with autism. Specifically, we will identify outcome domains and age intervals that have been well-characterized, areas where further research is needed, and the historical use of various longitudinal trajectory analytic approaches.

Methods and analysis. We outline the methods for the proposed scoping review according to the framework outlined by Arksey and O'Malley, with subsequent clarifications and enhancements by other authors. Using a search strategy developed by a medical librarian, we will search six databases for relevant publications. Titles and abstracts will be screened in duplicate, followed by full-text screening. Data extraction fields developed predominantly *a priori* from a set of guiding sub-questions will be used to chart relevant data. The findings will include quantitative aggregate summaries, narrative summaries, and appraisal of trajectory studies according to our methodological sub-questions. We will consult Autistic self-advocate and parent-caregiver stakeholders to facilitate interpretation of the findings.

Ethics and dissemination. Research ethics approval is not required for this scoping review. The results will be presented to researcher, care professional, policy-maker, and

stakeholder audiences at local and international conferences, other dissemination activities, and published in a peer-reviewed journal.

Keywords

Autism, longitudinal research, trajectory studies, scoping review, child development

Word count

3636 words

Article Summary

'Strengths and limitations of this study'

- This scoping review of will be the first to establish which outcome domains and age intervals have been characterized by longitudinal trajectory research examining development in children diagnosed with autism, and which warrant further study.
- An innovative aspect of this scoping review is its use of pre-specified sub-questions to guide development of the extraction (charting) form.
- We will summarize information corresponding to methodological sub-questions that may provide a useful basis for future critical appraisal of trajectory studies in this area.
- This review is limited in its scope because it excludes trajectory studies whose focus is on adulthood, and a separate review is therefore warranted to report on trajectories of outcome domains that may only be relevant at later life stages.

Background

Autism (autism spectrum disorder) is a neurodevelopmental condition recently estimated to affect 1 in 54 children [1], the prevalence of which is not likely to be substantively affected by geography, race, or socioeconomic factors [2]. The diagnosis is defined by variation in social communication and interaction, and restricted, repetitive patterns of behaviour, interests, or activities [3]. Autism is also increasingly being understood to be characterized by different strengths [4]. It has long been recognized that the characteristics used to define autism vary developmentally over the life-course, and that there is a need for rigorous longitudinal research to understand changes in relevant outcomes over time, identify prognostic factors, and understand what may improve developmental pathways of relevant outcome domains [5].

Trajectory methodology, defined here as featuring longitudinal analysis of assessments at three or more time points, has emerged as more appropriate for understanding development in autism compared to traditional cohort studies characterized by assessments at only two timepoints. In an early review of longitudinal research in autism that included studies with traditional cohort and cross-sectional designs, Selzer and colleagues [6] highlighted the key limitations of research featuring assessments at only two timepoints, noting it "makes it impossible to characterize the shape of the developmental function, the timing of changes, or the possibility that there are different subtypes of individuals on the autism spectrum characterized by different trajectories to the same outcome." Recognizing these limitations, researchers in the field of autism have increasingly turned to trajectory methods, which feature assessments at three or more time points. Some large-scale longitudinal autism cohort research groups have published serial reports on the development of their child cohorts, increasing the number of assessments as they age over time (for example, [7, 8]). Such research has expanded our understanding of

autism in important ways, including by defining important variation in the developmental trajectories of children on the autism spectrum—variation that exists both between trajectory groups or clusters, and between children within those clusters (for example see, [9-11]). Consequently, other approaches, which simply report or graph average measures across individuals at each timepoint, have limited use for studying development in people on the autism spectrum, because they ignore and obscure the correlated nature of within-case data over time.

Given the expansion of published trajectory studies in autism, there is a need to understand its scope to provide a broad picture of aspects such as the variety of outcome domains (i.e., measurable outcomes, which potentially vary over development) that have been studied over time, the age intervals over which outcome domains have been followed, and trends in the statistical analytic approaches that have been used. Two broad types of analytic approaches have been used to study autism trajectories: multi-level modeling (MLM), a variable-centred approach that estimates the average intercept and slope of the outcome domain of interest for pre-defined cohort groups (e.g., autistic, non-autistic); and growth mixture modeling (GMM), a person-centred approach that estimates distinct trajectories of latent groups formed on the basis of similar trajectories of individual participants within a cohort population.

Previous reviews. The early reviews on longitudinal studies in autism (published 2004–2013) of which we are aware neglected to report a systematic search strategy, and have at least some focus on adults on the autism spectrum [5, 6, 12]. Three subsequent reviews of longitudinal autism research (published 2014 onwards), which did report a systematic search strategy, included studies following up to adulthood. Magiati and colleagues [13] included 25 studies and summarized findings from multiple outcome domains including cognitive ability, language, adaptive functioning, autism severity, and social functioning; a focus of this review was

childhood predictors of later outcomes, and a mix of studies using trajectory and traditional two-timepoint cohort designs were included but not separated from each other in the review. Bieleninik and colleagues [14] conducted a systematic review and meta-analysis that included 35 prospective cohort studies and 5 randomized controlled trials, and evaluated two outcome domains: diagnostic stability, and autism symptom severity; trajectory studies were not distinguished from two-timepoint follow-up studies. Howlin and Magiati [15] reviewed all adult outcome-focused research (43 studies), of which five were trajectory studies described individually in a separate section. A search for existing published (PubMed) or registered (PROSPERO) protocols did not reveal other scoping reviews of trajectory studies in autism research.

Our planned scoping study will be the first we are aware of to review research that uses a longitudinal trajectory study design to study change in outcome domains over time in children on the autism spectrum (to age 18). Notably, it will exclude studies whose focus is on adulthood (i.e., where at least half of age timepoints assessed are above 18 years), because the set of outcome domains that are relevant after the transition to adulthood differs sufficiently from childhood, in our view, to warrant a separate review. Namely, some domains relevant to early development (e.g., language) are generally less relevant in adulthood, while numerous adult-relevant domains are inapplicable to early childhood (e.g., employment status, romantic relationships). The planned review will address the breadth of outcome domains relevant to children on the autism spectrum including clinical (developmental, behavioral, functional), educational (e.g., academic achievement), and social. We will, however, exclude studies of trajectories of neuroanatomical or physiological development, which have been previously reviewed [16, 17].

Objectives

The primary objective of this scoping review is to identify and summarize the scope of research that uses a longitudinal trajectory study design (with three or more timepoints) to study the progression of different outcome domains—including the shape, timing and sub-groups—in children on the autism spectrum (to age 18). A secondary objective is to summarize methodological trends in terms of analytic approaches used in trajectory studies of child development in autism research. Findings from this review will provide a useful understanding of 1) how and where trajectory research has already been used, and the areas where future trajectory research can produce needed knowledge about autism (gaps), 2) specific outcome domains or research questions for which sufficient data exist to conduct more focused quantitative systematic reviews or meta-analyses, and 3) the general utility and value of trajectory study methodology for providing actionable knowledge to support positive development of children on the autism spectrum.

Methods and Analysis

The scoping review methodology was judged to be appropriate for this review topic given its breadth, objectives, and the lack of known recent reviews on similar topics [18]. We outline the methods here according to the scoping review framework put forth by Arksey and O'Malley [19], informed by subsequent clarifications and enhancements [20, 21], reporting relevant elements outlined in the corresponding PRISMA Extension for Scoping Reviews (PRISMA-ScR) [22].

Stage 1: identifying the research question

The primary objective and corresponding research question for this review was informed by the experience of review group members with trajectory studies of children on the autism spectrum (e.g., [7, 23, 24]) and by an examination of existing reviews on the topic which identified three narrative reviews in children [6, 16, 17] and five additional reviews of trajectories to adulthood [5, 12-15]. In addition to helping confirm the appropriateness and need for our focus on children, the examination of existing reviews helped us understand the potential scope of the literature and, later, to iteratively exclude two research categories we felt represented distinct topics of interest warranting separate reviews: 1) studies of trajectories of neuroanatomical or physiological development, and 2) descriptive case studies or case series of individual trajectories. The two primary research questions for this review that we used to inform study identification and selection are as follows:

- How has research that employs a longitudinal trajectory study design (i.e., featuring three or more timepoints and an aggregative statistical analysis that accounts for the correlated nature of within-case data over time) been used to produce knowledge about the change—including shape, timing and sub-groups—in child developmental, behavioral, functional, social, or outcome domains in children on the autism spectrum (to age 18)?
- What are some of the key methodological characteristics of this research?

The first question above identifies the key domains of our search strategy and screening criteria, namely the population (diagnosis and age), methodology, and outcome domains measured (i.e., non-anatomical). Under the umbrella of the primary research questions, lead

investigators on this review (SG, ED, SJG) also developed a set of sub-questions (Table 1) that were used to plan the data extraction and reporting of results, described below.

Table 1. Sub-questions to guide data extraction

Questions about scope of the research
1. What outcome domains have been studied in trajectory studies?
2. What outcome measures have been used to follow the different outcome domains over time?
3. What ages have been characterized for each outcome domain?
4. For studies using person-centred (GMM) approaches, how many trajectory groups (or clusters) have been defined for different outcome domains followed in different trajectory studies?
5. What and where are the different autism cohort research groups that have reported trajectory study findings?
6. To what extent have each of the different autism cohort research groups contributed to the trajectory study literature, and what are the general characteristics of their research (narrative summary)?
7. To what extent have the proposed implications (utility) of trajectory study findings been reported clearly?
8. How much impact (in terms of citation metrics) have different sources or types of trajectory research had?

Questions about methodological aspects of research
1. What terms (text words) have been used to describe multi-level modeling (MLM) and growth mixture modeling (GMM) trajectory studies of child development in autism?
2. How has the historical prevalence of MLM- and GMM-type trajectory approaches for studying development of children on the autism spectrum evolved by year?
3. How do select study characteristics (e.g., sample size, comparison to non-autism groups) vary between MLM- and GMM-type studies?
4. How reliable is the ascertainment of autism diagnosis in trajectory studies?
5. To what extent was representative sampling used across trajectory studies?
6. What other methodological aspects of trajectory research in autism could be used as a basis for identifying sources of risk of bias or for quality reporting standards?

Stage 2: identifying relevant studies

Our search was informed by the domains of the primary research question described above, and developed with the help of a medical librarian (LB), starting with Medline (OVID) because the subject heading definitions of this database are well developed (Table 2).

Table 2. MEDLINE search strategy.

1	exp Autism Spectrum Disorder/
2	Child Development Disorders, Pervasive/

3	Asperger*.mp.
4	ASD.mp.
5	autis*.mp.
6	or/1-5
7	exp Child/
8	child*.mp.
9	Adolescent/
10	Infant/
11	Infant, Newborn/
12	infan*.mp.
13	newborn*.mp.
14	Child, Preschool/
15	Child Development/
16	adolescen*.mp.
17	Pediatrics/
18	youth.mp.
19	teen*.mp.
20	p?ediatric*.mp.

21	or/7-20
22	trajector*.mp.
23	Longitudinal Studies/
24	Follow-Up Studies/
25	Prospective Studies/
26	longitudinal*.mp.
27	follow-up stud*.mp.
28	prospective*.mp.
29	followup stud*.mp.
30	Cohort Studies/
31	(cohort* stud* or cohort analys?s).mp.
32	panel stud*.mp.
33	or/22-32
34	6 and 21 and 33

The MEDLINE search was translated into the five other databases to be searched: EMBASE, CINAHL, PSYCInfo, ERIC, Cochrane Database of Systematic Reviews. Search results will be imported into EndNote reference management software (Clarivate Analytics), where duplicates will be removed and citations managed in the subsequent screening stages. We will not search the grey literature or conference proceedings, because we are interested in

mapping successfully peer-reviewed published literature that is likely to influence the field. For similar reasons, we will exclude doctoral theses or dissertations retrieved by the searches. Searches will not be restricted by language or year of publication.

Stage 3: study selection

After removal of duplicates from our EndNote database, we will select articles for inclusion in the review through a two-step screening process: title and abstract, and full-text screening. In both steps, all records will be screened in duplicate (by two reviewers), and disagreements will be resolved through consensus in regular meetings. Reviewer decisions will be recorded in EndNote, with mutual consensus required before an include or exclude decision is reached. For the first step, title and abstract screening, screening decisions will err on the side of inclusivity (sensitivity), so that records for which insufficient information is available in the title or abstract will be included, and passed on, to the second screening step. Based on preliminary work, in this step we expect to partially filter records based on indicators of diagnosis (autism), age, and methodology (trajectory design), and definitively exclude records based on their identity as case studies or series, trajectories of neuroanatomy or physiology, or non-published status (e.g., dissertations or theses).

In the second step, the full text of articles will be retrieved (in PDF) and read to confirm eligibility. Based on preliminary work, one of the predominant decisions in this step will be to determine if studies qualify as true trajectory study methodology both in terms of the data collection criterion (three timepoints or more) and two analysis criteria (analysis accounts for the correlated nature of within-case data over time; and analysis does not simply average measures across individuals at each timepoint yielding only cross-sectional estimates). Given the potential number and complexity of analytic techniques, a statistician will be involved as a second

reviewer for full-text screening decisions involving analysis-related criteria where necessary. Reasons for exclusions at the full-text screening step will be recorded in EndNote. A PRISMA flow-chart will be used to report the results of the searches and both screening steps.

Stage 4: charting the data

The fields that we will extract data on (Table 3) have been developed as much as possible, a priori, from the sub-questions listed in Table 1. These fields are captured in an initial extraction form designed in Word, with the input of lead investigators (SG, ED, SJG) and the extraction team, to streamline the extraction process (e.g., containing in-line instructions, and other needed reference information). This form was piloted by the four-person extraction team (SJG, MCH, AJM, ENA) who each independently applied it to one paper for training and reliability purposes. The form was judged easy to use by all, there was little disagreement, and misunderstandings were discussed and corrected. We anticipate it will be possible to develop a relatively stable form for addressing the pre-specified sub-questions. Nevertheless, we expect some unanticipated but important extraction fields will become apparent in the course of reviewing the included literature, which may require the iterative adaptation of the extraction form. Consequently, we have included a field in the extraction form to record ideas or suggestions for adaptation or revision that may iteratively arise when reviewing a specific article.

Information regarding methodological quality of individual studies will be extracted to address two of our sub-questions. Some extraction fields pertaining to trajectory methodology will be developed iteratively as there are no existing methodological quality criteria that we are aware of for this study design, and it is not possible to anticipate all aspects of quality in advance of reviewing this literature. Additionally, quality indicators already accepted in the field of

epidemiological autism research will be extracted, namely those pertaining to research-level diagnostic ascertainment standards.

Given the inevitability that there will be multiple publications by the same study group on the same cohort as it is reported on over multiple age timepoints, it may be possible to find helpful information pertaining to a given study in other publications by the same cohort research group. In addition to keeping careful records of which publications are linked in this way (as an extraction and reporting field of interest), we will assign papers belonging to the same cohort group to the same extractor so they can be aware of, and cross-reference as needed, the shared context of linked papers while extracting.

While articles will be extracted individually, we will have regular extraction meetings to discuss challenging articles, ideas for revising the extraction form, and other issues. Additionally, extractors will be able to consult with each other regarding areas of uncertainty related to specific publications. Finally, completed extraction forms will be verified by the review coordinator (SJG) before transferring their data to the analysis database, maintained in Excel, which will allow for aggregative summary and cross-tabulation of the extracted data. Fields in the Excel form will be programmed with data validation settings to minimize errors in data entry.

Table 3. Information fields for extraction from each included publication

Category	**Information extraction field**
Article characteristics	• Year of publication • Article impact • Country(ies) of origin of cohort

	• Purpose of trajectory study (narrative) • Applicability of findings (narrative) • Clarity of applicability of findings
Cohort research group	• Autism Cohort Research Group: Title • Autism Cohort Research Group: Lead author
Sample	• Sample setting (community-based, clinical, etc.) • Type of sampling of autism participants (non-representative, representative) • Sample size, overall • Sample size, autism only
Diagnostic ascertainment	• Autism diagnosis methods reported? • Use of Autism Diagnostic Observation Schedule • Use of Autism Diagnostic Interview-Revised • Clinical judgment used
Analysis	• Prospective • MLM-type • MLM terms used • GMM-type • GMM terms used

	• Clarity of ages of assessment
Outcome domain (repeated for each domain)	• Outcome domain name • Measure used • Age interval start • Age interval end • Number of timepoints assessed • Ages of timepoints assessed • Rationale for ages assessed (narrative) • Clinical schedule used • Number of trajectory groups (clusters) defined

Stage 5: collating, summarising and reporting the results

Along with presenting standard publication retrieval in a PRISMA flow chart, we plan to report on the number of unique studies that were captured by each successive database, from MEDLINE, to Embase, PsycINFO, CINAHL, ERIC, and Cochrane Reviews.

We expect a high number of included studies (>60), which may affect the level of aggregation we employ to summarize data presentations. We plan to present a summary table displaying key characteristics of the extracted literature, organized hierarchically by country, major cohort research group (where applicable), and individual publication (as hierarchically indented rows); and include citations for each of the characteristics presented in columns—

including sample sizes, outcome domains followed, age interval followed, number of time points, analytic approach, and citation impact. We also plan to use graphs to visually represent data on historical trends in the use of MLM versus GMM analytic approaches over time, and on the density of age timepoint assessments for each outcome domain. In addition, we will present data that may provide a useful basis for future critical appraisal of trajectory studies according to our methodological sub-questions regarding autism diagnosis ascertainment, and trajectory review method reporting criteria. A table will display a proposed set of text words that can be used to search for each type of trajectory analysis approach (MLM and GMM) in future.

A section of the review will provide narrative summaries to address the sub-question regarding the impact and extent to which the major autism cohort research groups have contributed to the trajectory study literature including general characteristics of their research. Narrative will also be used to provide interpretive commentary on other sub-question–related aspects, including suitability of the outcome measures that have been used to follow the different outcome domains over time (including their patient-centeredness, per stakeholder consultation described below), the number of trajectory groups (clusters) that have been defined for different outcome domains, the extent to which the implications (or utility) of trajectory study findings have been reported clearly, and the merit of future research to target gaps in the ages or outcome domains not previously assessed.

Patient and Public Involvement

Corresponding to Stage 6 of the Arksey–O'Malley scoping review framework (*optional consultation exercise*), we have engaged two stakeholders in this review—an adult Autistic self-advocate and a parent of a child on the autism spectrum—to provide feedback at key points. For purposes of this protocol, they have provided early feedback on aspects of the planned extraction

related to outcome domains. This feedback informed plans for interpreting the relevance and importance of different outcomes in the final report, but it did not alter our decision to extract and report on all outcomes assessed by the studies to be included in this review. We did not involve patient stakeholders in development of the research question, or design of this study. While they will not be involved in data collection or analysis, we will re-engage these individuals once the review is complete to provide interpretations of the findings from their perspectives as members of the stakeholder community. Their interpretations will be used to inform the discussion of findings. We will also involve these individuals in presentations of the results described in the next section, according to their interest.

Ethics and Dissemination

The research ethics boards at our institutions do not need to be engaged to provide ethics approval for consulting with stakeholders about this research project since it does not involve their providing study data. We will follow best practices for patient engagement in research.

This review will represent a source of valuable knowledge and guidance to researchers who are currently engaged in, or planning to conduct, longitudinal research on child development in autistic samples. It will also be of interest to clinicians, policy makers, and other professionals responsible for care or services for children on the autism spectrum, allowing them to quickly identify the trajectory literature on clinically-relevant outcome domains. It will also be of interest to families of children on the autism spectrum, who are known for their desire for access to research findings, by providing an overview of the kind of research that is often conducted to find answers about "what to expect" during the development of children on the autism spectrum. Finally, it will be useful to other reviewers seeking to identify one or more outcome domains for which there is sufficient published trajectory research data to conduct a

systematic review or meta-analysis. To reach these audiences, we plan to disseminate findings at major international autism research conferences, local autism conferences attended by families, and to publish the completed review in open access format in a peer-reviewed autism research journal. Other dissemination activities include plans to develop a webinar for parent and professional audiences, and lay research summaries for publication on provincial and national autism organization web sites.

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Author contributions

SJG, SG, and ED led the design and conceptualization. EDB, LB, and SJG developed the search strategy. AJM, EN-C, MCH, CMK, and PS were involved in design and conceptualization of the extraction form. SJG drafted the protocol. SG, ED, AJM, EN-C, MCH, CMK, and PS provided feedback and helped revise drafts of this manuscript for important intellectual content and clarity.

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Competing interests

None declared.

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

Based on the PRISMA-P guidelines.

Instructions to authors

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

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	na
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	na
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	2
Contribution	#3b	Describe contributions of protocol authors and identify the	21

		guarantor of the review	
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	na
Support			
Sources	#5a	Indicate sources of financial or other support for the review	21
Sponsor	#5b	Provide name for the review funder and / or sponsor	Na
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	Na
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	5-7
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8-9
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	11-14
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	13
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	11-13
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	13-14
Study records -	#11b	State the process that will be used for selecting studies (such as	14-15

selection process		two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	15-16
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	16-17
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	16-17
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	15-16
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	18-19
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)	18-19
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Na
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	18-19
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Na
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	na

BMJ Open

Trajectory research in children on the autism spectrum: A scoping review protocol

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Trajectory research in children on the autism spectrum: A scoping review protocol

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Abstract

Introduction. Longitudinal trajectory methods, featuring outcome assessments at three or more timepoints, are increasingly being used as appropriate approaches to understand developmental pathways of people on the autism spectrum across the lifespan. Understanding the scope of this rapidly expanding body of research can help inform future trajectory studies and identify areas for potential meta-analysis as well as key evidence gaps. We present the protocol for a scoping review whose objective is to identify and summarize the scope of research that uses a longitudinal trajectory study design to examine development in children diagnosed with autism. Specifically, we will identify outcome domains and age intervals that have been well-characterized, areas where further research is needed, and the historical use of various longitudinal trajectory analytic approaches.

Methods and analysis. We outline the methods for the proposed scoping review according to the framework outlined by Arksey and O'Malley, with subsequent clarifications and enhancements by other authors. Using a search strategy developed by a medical librarian, we will search six databases for relevant publications. Titles and abstracts will be screened in duplicate, followed by full-text screening. Data extraction fields developed predominantly *a priori* from a set of guiding sub-questions will be used to chart relevant data. The findings will include quantitative aggregate summaries, narrative summaries, and appraisal of trajectory studies according to our methodological sub-questions. We will consult Autistic self-advocate and parent-caregiver stakeholders to facilitate interpretation of the findings.

Ethics and dissemination. Research ethics approval is not required for this scoping review. The results will be presented to researcher, care professional, policy-maker, and

stakeholder audiences at local and international conferences, other dissemination activities, and published in a peer-reviewed journal.

Keywords

Autism, longitudinal research, trajectory studies, scoping review, child development

Word count

3636 words

Article Summary

'Strengths and limitations of this study'

- The scoping review whose protocol is presented will be the first to establish which outcome domains and age intervals have been characterized by longitudinal trajectory research examining development in children diagnosed with autism, and which warrant further study.
- An innovative aspect of this scoping review will be its use of pre-specified sub-questions to guide development of the extraction (charting) form.
- We will summarize information corresponding to methodological sub-questions that may provide a useful basis for future critical appraisal of trajectory studies in this area.
- This review is limited in its scope because it excludes trajectory studies whose focus is on adulthood, and a separate review is therefore warranted to report on trajectories of outcome domains that may only be relevant at later life stages.

Background

Autism (autism spectrum disorder) is a neurodevelopmental condition recently estimated to affect 1 in 54 children [1], the prevalence of which is not likely to be substantively affected by geography, race, or socioeconomic factors [2]. The diagnosis is defined by variation in social communication and interaction, and restricted, repetitive patterns of behaviour, interests, or activities [3]. Autism is also increasingly being understood to be characterized by different strengths [4]. It has long been recognized that the characteristics used to define autism vary developmentally over the life-course, and that there is a need for rigorous longitudinal research to understand changes in relevant outcomes over time, identify prognostic factors, and understand what may improve developmental pathways of relevant outcome domains [5].

Trajectory methodology, defined here as featuring longitudinal analysis of assessments at three or more time points, has emerged as more appropriate for understanding development in autism compared to traditional cohort studies characterized by assessments at only two timepoints. In an early review of longitudinal research in autism that included studies with traditional cohort and cross-sectional designs, Selzer and colleagues [6] highlighted the key limitations of research featuring assessments at only two timepoints, noting it "makes it impossible to characterize the shape of the developmental function, the timing of changes, or the possibility that there are different subtypes of individuals on the autism spectrum characterized by different trajectories to the same outcome." Recognizing these limitations, researchers in the field of autism have increasingly turned to trajectory methods, which feature assessments at three or more time points. Some large-scale longitudinal autism cohort research groups have published serial reports on the development of their child cohorts, increasing the number of assessments as they age over time (for example, [7, 8]). Such research has expanded our understanding of

autism in important ways, including by defining important variation in the developmental trajectories of children on the autism spectrum—variation that exists both between trajectory groups or clusters, and between children within those clusters (for example see, [9-11]). Consequently, other approaches, which simply report or graph average measures across individuals at each timepoint, have limited use for studying development in people on the autism spectrum, because they ignore and obscure the correlated nature of within-case data over time.

Given the expansion of published trajectory studies in autism, there is a need to understand its scope to provide a broad picture of aspects such as the variety of outcome domains (i.e., measurable outcomes, which potentially vary over development) that have been studied over time, the age intervals over which outcome domains have been followed, and trends in the statistical analytic approaches that have been used. Two broad types of analytic approaches have been used to study autism trajectories: multi-level modeling (MLM), a variable-centred approach that estimates the average intercept and slope of the outcome domain of interest for pre-defined cohort groups (e.g., autistic, non-autistic); and growth mixture modeling (GMM), a person-centred approach that estimates distinct trajectories of latent groups formed on the basis of similar trajectories of individual participants within a cohort population.

Previous reviews. The early reviews on longitudinal studies in autism (published 2004–2013) of which we are aware neglected to report a systematic search strategy, and have at least some focus on adults on the autism spectrum [5, 6, 12]. Three subsequent reviews of longitudinal autism research (published 2014 onwards), which did report a systematic search strategy, included studies following up to adulthood. Magiati and colleagues [13] included 25 studies and summarized findings from multiple outcome domains including cognitive ability, language, adaptive functioning, autism severity, and social functioning; a focus of this review was

childhood predictors of later outcomes, and a mix of studies using trajectory and traditional two-timepoint cohort designs were included but not separated from each other in the review. Bieleninik and colleagues [14] conducted a systematic review and meta-analysis that included 35 prospective cohort studies and 5 randomized controlled trials, and evaluated two outcome domains: diagnostic stability, and autism symptom severity; trajectory studies were not distinguished from two-timepoint follow-up studies. Howlin and Magiati [15] reviewed all adult outcome-focused research (43 studies), of which five were trajectory studies described individually in a separate section. A search for existing published (PubMed) or registered (PROSPERO) protocols did not reveal other scoping reviews of trajectory studies in autism research.

Our planned scoping study will be the first we are aware of to review research that uses a longitudinal trajectory study design to study change in outcome domains over time in children on the autism spectrum (to age 18). Notably, it will exclude studies whose focus is on adulthood (i.e., where at least half of age timepoints assessed are above 18 years), because the set of outcome domains that are relevant after the transition to adulthood differs sufficiently from childhood, in our view, to warrant a separate review. Namely, some domains relevant to early development (e.g., language) are generally less relevant in adulthood, while numerous adult-relevant domains are inapplicable to early childhood (e.g., employment status, romantic relationships). The planned review will address the breadth of outcome domains relevant to children on the autism spectrum including clinical (developmental, behavioral, functional), educational (e.g., academic achievement), and social. We will, however, exclude studies of trajectories of neuroanatomical or physiological development, which have been previously reviewed [16, 17].

Objectives

The primary objective of this scoping review is to identify and summarize the scope of research that uses a longitudinal trajectory study design (with three or more timepoints) to study the progression of different outcome domains—including the shape, timing and sub-groups—in children on the autism spectrum (to age 18). A secondary objective is to summarize methodological trends in terms of analytic approaches used in trajectory studies of child development in autism research. Findings from this review will provide a useful understanding of 1) how and where trajectory research has already been used, and the areas where future trajectory research can produce needed knowledge about autism (gaps), 2) specific outcome domains or research questions for which sufficient data exist to conduct more focused quantitative systematic reviews or meta-analyses, and 3) the general utility and value of trajectory study methodology for providing actionable knowledge to support positive development of children on the autism spectrum.

Methods and Analysis

The scoping review methodology was judged to be appropriate for this review topic given its breadth, objectives, and the lack of known recent reviews on similar topics [18]. We outline the methods here according to the scoping review framework put forth by Arksey and O'Malley [19], informed by subsequent clarifications and enhancements [20, 21], reporting relevant elements outlined in the corresponding PRISMA Extension for Scoping Reviews (PRISMA-ScR) [22].

Stage 1: identifying the research question

The primary objective and corresponding research question for this review was informed by the experience of review group members with trajectory studies of children on the autism spectrum (e.g., [7, 23, 24]) and by an examination of existing reviews on the topic which identified three narrative reviews in children [6, 16, 17] and five additional reviews of trajectories to adulthood [5, 12-15]. In addition to helping confirm the appropriateness and need for our focus on children, the examination of existing reviews helped us understand the potential scope of the literature and, later, to iteratively exclude two research categories we felt represented distinct topics of interest warranting separate reviews: 1) studies of trajectories of neuroanatomical or physiological development, and 2) descriptive case studies or case series of individual trajectories. The two primary research questions for this review that we used to inform study identification and selection are as follows:

- How has research that employs a longitudinal trajectory study design (i.e., featuring three or more timepoints and an aggregative statistical analysis that accounts for the correlated nature of within-case data over time) been used to produce knowledge about the change—including shape, timing and sub-groups—in child developmental, behavioral, functional, social, or outcome domains in children on the autism spectrum (to age 18)?
- What are some of the key methodological characteristics of this research?

The first question above identifies the key domains of our search strategy and screening criteria, namely the population (diagnosis and age), methodology, and outcome domains measured (i.e., non-anatomical). Under the umbrella of the primary research questions, lead

investigators on this review (SG, ED, SJG) also developed a set of sub-questions (Table 1) that were used to plan the data extraction and reporting of results, described below.

Table 1. Sub-questions to guide data extraction

Questions about scope of the research
1. What outcome domains have been studied in trajectory studies?
2. What outcome measures have been used to follow the different outcome domains over time?
3. What ages have been characterized for each outcome domain?
4. For studies using person-centred (GMM) approaches, how many trajectory groups (or clusters) have been defined for different outcome domains followed in different trajectory studies?
5. What and where are the different autism cohort research groups that have reported trajectory study findings?
6. To what extent have each of the different autism cohort research groups contributed to the trajectory study literature, and what are the general characteristics of their research (narrative summary)?
7. To what extent have the proposed implications (utility) of trajectory study findings been reported clearly?
8. How much impact (in terms of citation metrics) have different sources or types of trajectory research had?

Questions about methodological aspects of research
1. What terms (text words) have been used to describe multi-level modeling (MLM) and growth mixture modeling (GMM) trajectory studies of child development in autism?
2. How has the historical prevalence of MLM- and GMM-type trajectory approaches for studying development of children on the autism spectrum evolved by year?
3. How do select study characteristics (e.g., sample size, comparison to non-autism groups) vary between MLM- and GMM-type studies?
4. How reliable is the ascertainment of autism diagnosis in trajectory studies?
5. To what extent was representative sampling used across trajectory studies?
6. What other methodological aspects of trajectory research in autism could be used as a basis for identifying sources of risk of bias or for quality reporting standards?

Stage 2: identifying relevant studies

Our search was informed by the domains of the primary research question described above, and developed with the help of a medical librarian (LB), starting with Medline (OVID) because the subject heading definitions of this database are well developed (Table 2).

Table 2. MEDLINE search strategy.

1	exp Autism Spectrum Disorder/
2	Child Development Disorders, Pervasive/

3	Asperger*.mp.
4	ASD.mp.
5	autis*.mp.
6	or/1-5
7	exp Child/
8	child*.mp.
9	Adolescent/
10	Infant/
11	Infant, Newborn/
12	infan*.mp.
13	newborn*.mp.
14	Child, Preschool/
15	Child Development/
16	adolescen*.mp.
17	Pediatrics/
18	youth.mp.
19	teen*.mp.
20	p?ediatric*.mp.

21	or/7-20
22	trajector*.mp.
23	Longitudinal Studies/
24	Follow-Up Studies/
25	Prospective Studies/
26	longitudinal*.mp.
27	follow-up stud*.mp.
28	prospective*.mp.
29	followup stud*.mp.
30	Cohort Studies/
31	(cohort* stud* or cohort analys?s).mp.
32	panel stud*.mp.
33	or/22-32
34	6 and 21 and 33

The MEDLINE search was translated into the five other databases to be searched: EMBASE, CINAHL, PSYCInfo, ERIC, Cochrane Database of Systematic Reviews. Search results will be imported into EndNote reference management software (Clarivate Analytics), where duplicates will be removed and citations managed in the subsequent screening stages. We will not search the grey literature or conference proceedings, because we are interested in

mapping successfully peer-reviewed published literature that is likely to influence the field. For similar reasons, we will exclude doctoral theses or dissertations retrieved by the searches. Searches will not be restricted by language or year of publication. We will include articles published from database inception to the year 2020, based on a search completed May 24 of 2021. The expected study completion date is December 2021.

Stage 3: study selection

After removal of duplicates from our EndNote database, we will select articles for inclusion in the review through a two-step screening process: title and abstract, and full-text screening. In both steps, all records will be screened in duplicate (by two reviewers), and disagreements will be resolved through consensus in regular meetings. Reviewer decisions will be recorded in EndNote, with mutual consensus required before an include or exclude decision is reached. For the first step, title and abstract screening, screening decisions will err on the side of inclusivity (sensitivity), so that records for which insufficient information is available in the title or abstract will be included, and passed on, to the second screening step. Based on preliminary work, in this step we expect to partially filter records based on indicators of diagnosis (autism), age, and methodology (trajectory design), and definitively exclude records based on their identity as case studies or series, trajectories of neuroanatomy or physiology, or non-published status (e.g., dissertations or theses).

In the second step, the full text of articles will be retrieved (in PDF) and read to confirm eligibility. Based on preliminary work, one of the predominant decisions in this step will be to determine if studies qualify as true trajectory study methodology both in terms of the data collection criterion (three timepoints or more) and two analysis criteria (analysis accounts for the correlated nature of within-case data over time; and analysis does not simply average measures

across individuals at each timepoint yielding only cross-sectional estimates). Given the potential number and complexity of analytic techniques, a statistician will be involved as a second reviewer for full-text screening decisions involving analysis-related criteria where necessary. Reasons for exclusions at the full-text screening step will be recorded in EndNote. A PRISMA flow-chart will be used to report the results of the searches and both screening steps.

Stage 4: charting the data

The fields that we will extract data on (Table 3) have been developed as much as possible, a priori, from the sub-questions listed in Table 1. These fields are captured in an initial extraction form designed in Word, with the input of lead investigators (SG, ED, SJG) and the extraction team, to streamline the extraction process (e.g., containing in-line instructions, and other needed reference information). This form was piloted by the four-person extraction team (SJG, MCH, AJM, ENA) who each independently applied it to one paper for training and reliability purposes. The form was judged easy to use by all, there was little disagreement, and misunderstandings were discussed and corrected. We anticipate it will be possible to develop a relatively stable form for addressing the pre-specified sub-questions. Nevertheless, we expect some unanticipated but important extraction fields will become apparent in the course of reviewing the included literature, which may require the iterative adaptation of the extraction form. Consequently, we have included a field in the extraction form to record ideas or suggestions for adaptation or revision that may iteratively arise when reviewing a specific article.

Information regarding methodological quality of individual studies will be extracted to address two of our sub-questions. Some extraction fields pertaining to trajectory methodology will be developed iteratively as there are no existing methodological quality criteria that we are aware of for this study design, and it is not possible to anticipate all aspects of quality in advance

of reviewing this literature. Additionally, quality indicators already accepted in the field of epidemiological autism research will be extracted, namely those pertaining to research-level diagnostic ascertainment standards.

Given the inevitability that there will be multiple publications by the same study group on the same cohort as it is reported on over multiple age timepoints, it may be possible to find helpful information pertaining to a given study in other publications by the same cohort research group. In addition to keeping careful records of which publications are linked in this way (as an extraction and reporting field of interest), we will assign papers belonging to the same cohort group to the same extractor so they can be aware of, and cross-reference as needed, the shared context of linked papers while extracting.

While articles will be extracted individually, we will have regular extraction meetings to discuss challenging articles, ideas for revising the extraction form, and other issues. Additionally, extractors will be able to consult with each other regarding areas of uncertainty related to specific publications. Finally, completed extraction forms will be verified by the review coordinator (SJG) before transferring their data to the analysis database, maintained in Excel, which will allow for aggregative summary and cross-tabulation of the extracted data. Fields in the Excel form will be programmed with data validation settings to minimize errors in data entry.

Table 3. Information fields for extraction from each included publication

Category	**Information extraction field**
Article characteristics	• Year of publication • Article impact

	• Country(ies) of origin of cohort • Purpose of trajectory study (narrative) • Applicability of findings (narrative) • Clarity of applicability of findings
Cohort research group	• Autism Cohort Research Group: Title • Autism Cohort Research Group: Lead author
Sample	• Sample setting (community-based, clinical, etc.) • Type of sampling of autism participants (non-representative, representative) • Sample size, overall • Sample size, autism only
Diagnostic ascertainment	• Autism diagnosis methods reported? • Use of Autism Diagnostic Observation Schedule • Use of Autism Diagnostic Interview-Revised • Clinical judgment used
Analysis	• Prospective • MLM-type • MLM terms used • GMM-type

	• GMM terms used • Clarity of ages of assessment
Outcome domain (repeated for each domain)	• Outcome domain name • Measure used • Age interval start • Age interval end • Number of timepoints assessed • Ages of timepoints assessed • Rationale for ages assessed (narrative) • Clinical schedule used • Number of trajectory groups (clusters) defined

Stage 5: collating, summarising and reporting the results

Along with presenting standard publication retrieval in a PRISMA flow chart, we plan to report on the number of unique studies that were captured by each successive database, from MEDLINE, to Embase, PsycINFO, CINAHL, ERIC, and Cochrane Reviews.

We expect a high number of included studies (>60), which may affect the level of aggregation we employ to summarize data presentations. We plan to present a summary table displaying key characteristics of the extracted literature, organized hierarchically by country, major cohort research group (where applicable), and individual publication (as hierarchically

indented rows); and include citations for each of the characteristics presented in columns—including sample sizes, outcome domains followed, age interval followed, number of time points, analytic approach, and citation impact. We also plan to use graphs to visually represent data on historical trends in the use of MLM versus GMM analytic approaches over time, and on the density of age timepoint assessments for each outcome domain. In addition, we will present data that may provide a useful basis for future critical appraisal of trajectory studies according to our methodological sub-questions regarding autism diagnosis ascertainment, and trajectory review method reporting criteria. A table will display a proposed set of text words that can be used to search for each type of trajectory analysis approach (MLM and GMM) in future.

A section of the review will provide narrative summaries to address the sub-question regarding the impact and extent to which the major autism cohort research groups have contributed to the trajectory study literature including general characteristics of their research. Narrative will also be used to provide interpretive commentary on other sub-question–related aspects, including suitability of the outcome measures that have been used to follow the different outcome domains over time (including their patient-centeredness, per stakeholder consultation described below), the number of trajectory groups (clusters) that have been defined for different outcome domains, the extent to which the implications (or utility) of trajectory study findings have been reported clearly, and the merit of future research to target gaps in the ages or outcome domains not previously assessed.

Patient and Public Involvement

Corresponding to Stage 6 of the Arksey–O'Malley scoping review framework (*optional consultation exercise*), we have engaged two stakeholders in this review—an adult Autistic self-advocate and a parent of a child on the autism spectrum—to provide feedback at key points. For

purposes of this protocol, they have provided early feedback on aspects of the planned extraction related to outcome domains. This feedback informed plans for interpreting the relevance and importance of different outcomes in the final report, but it did not alter our decision to extract and report on all outcomes assessed by the studies to be included in this review. We did not involve patient stakeholders in development of the research question, or design of this study. While they will not be involved in data collection or analysis, we will re-engage these individuals once the review is complete to provide interpretations of the findings from their perspectives as members of the stakeholder community. Their interpretations will be used to inform the discussion of findings. We will also involve these individuals in presentations of the results described in the next section, according to their interest.

Ethics and Dissemination

The research ethics boards at our institutions do not need to be engaged to provide ethics approval for consulting with stakeholders about this research project since it does not involve their providing study data. We will follow best practices for patient engagement in research.

This review will represent a source of valuable knowledge and guidance to researchers who are currently engaged in, or planning to conduct, longitudinal research on child development in autistic samples. It will also be of interest to clinicians, policy makers, and other professionals responsible for care or services for children on the autism spectrum, allowing them to quickly identify the trajectory literature on clinically-relevant outcome domains. It will also be of interest to families of children on the autism spectrum, who are known for their desire for access to research findings, by providing an overview of the kind of research that is often conducted to find answers about "what to expect" during the development of children on the autism spectrum. Finally, it will be useful to other reviewers seeking to identify one or more

outcome domains for which there is sufficient published trajectory research data to conduct a systematic review or meta-analysis. To reach these audiences, we plan to disseminate findings at major international autism research conferences, local autism conferences attended by families, and to publish the completed review in open access format in a peer-reviewed autism research journal. Other dissemination activities include plans to develop a webinar for parent and professional audiences, and lay research summaries for publication on provincial and national autism organization web sites.

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Author contributions

SJG, SG, and ED led the design and conceptualization. EDB, LB, and SJG developed the search strategy. AJM, EN-C, MCH, CMK, and PS were involved in design and conceptualization of the extraction form. SJG drafted the protocol. SG, ED, AJM, EN-C, MCH, CMK, and PS provided feedback and helped revise drafts of this manuscript for important intellectual content and clarity.

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Competing interests

None declared.

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

Based on the PRISMA-P guidelines.

Instructions to authors

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

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	na
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	na
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	2
Contribution	#3b	Describe contributions of protocol authors and identify the	21

		guarantor of the review	
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	na
Support			
Sources	#5a	Indicate sources of financial or other support for the review	21
Sponsor	#5b	Provide name for the review funder and / or sponsor	Na
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	Na
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	5-7
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8-9
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	11-14
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	13
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	11-13
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	13-14
Study records -	#11b	State the process that will be used for selecting studies (such as	14-15

selection process		two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	15-16
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	16-17
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	16-17
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	15-16
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	18-19
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)	18-19
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Na
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	18-19
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Na
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	na