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# BMJ Open

## Atopic dermatitis and neurodevelopmental disorders: protocol for a systematic scoping review.

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## Abstract

### Introduction

Children with atopic dermatitis (AD) are more at risk for the neurodevelopmental disorders Attention-Deficit/Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD) with parallel increases in prevalence. Children afflicted with these conditions appear to share similar problems in sensory modulation but investigational studies on the underlying etiology are scarce. This scoping review aims to find knowledge gaps, collate hypotheses and to summarize available evidence on the shared pathophysiology of AD, ADHD, and ASD in children.

### Methods and analysis

Our study will follow the methodological manual published by the Joanna Briggs Methodology for Scoping Reviews and will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR). The following electronic databases will be searched for studies focused on children with AD and ADHD and/or ASD: Medline ALL via Ovid, Embase, Web of Science Core Collection and the Cochrane Central Register of Controlled Trials via Wiley.

### Ethics and dissemination

This review does not require ethics approval as it will not be conducted with human participants. We will only use published data. Our dissemination strategy includes peer review publication and conference reports.

## Article Summary

### Strengths and limitations of this study

- This scoping review marks the pioneering attempt to explore the relation between Attention Deficit (AD), and Attention-Deficit/Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD) in children.
- To ensure methodological rigor, we will collaborate with health sciences librarians to construct an established methodology and execute a systematic search, encompassing a wide spectrum of publication types.
- The identification and synthesis of data will be limited to published articles found on the MEDLINE, Embase, Web of Science, and Cochrane databases and snowball references.
- Relevant articles in the grey literature or written in another language than English may be missed.

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## Introduction

### Background

Atopic dermatitis (AD) is a common chronic inflammatory skin disorder characterized by pruritus and recurrent eczematous skin lesions affecting up to 20% of children in high-income countries<sup>1</sup>. Besides other atopic diseases such as allergic rhinitis, food allergies, and asthma, children with AD are also more at risk for non-allergic comorbidities including infectious and systemic diseases, as well as neurodevelopmental disorders such as attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD)<sup>2-4</sup>. Current studies on pediatric AD focus on the clinical treatment of the disease but there are still gaps in knowledge regarding aforementioned neurodevelopmental comorbidities. Complex pathomechanisms, involving both genetic and environmental factors, combined with global increases in prevalence of AD, ADHD, and ASD in the past decades has led to many hypotheses on the underlying etiological associations between the diseases<sup>5-9</sup>.

ADHD is one of the most common neurodevelopmental disorders in children, characterized by symptoms of inattention, restlessness, and sensory processing problems, also known as sensory modulation disorder (SMD), which is the inability to effectively regulate and organize a graded and adaptive response to sensory stimuli<sup>10-12</sup>. Similar to ADHD, children with AD also exhibit altered sensory modulation, expressed in sensory hyper-reactivity compared to regular children<sup>13</sup>. Epidemiologically, individuals with AD are more at risk for ADHD with an estimated OR = 1.32 (95% CI 1.20–1.45) for all ages to OR = 1.56 (95% CI, 1.38–1.77) in children and adolescents<sup>14,15</sup>.

ASD is a heterogeneous neurodevelopmental disorder, encompassing former diagnoses such as autistic disorder, Asperger syndrome, and pervasive developmental disorder not otherwise specified<sup>16</sup>. Traits displayed by diagnosed individuals include persistent difficulties with social communication and interaction, and the presence of restricted and repetitive patterns of behavior from an early developmental period<sup>16,17</sup>. Comparable to both AD and ADHD, children with ASD have also been found to have more sensory hyper-reactivity symptoms<sup>18</sup>. The risk for developing ASD in individuals with AD has been estimated to be OR = 1.49 (95% CI 1.20-1.83) in all ages to OR = 2.57 (95% CI 1.47-4.51) in children and adolescents<sup>15,19</sup>. Moreover, children with ASD with AD may have more pronounced ASD symptoms overall and on the social domain outcomes, relative to children with ASD without AD<sup>20</sup>.

Due to the parallel rises in the global prevalences of AD, ADHD, and ASD, an increasing interest among many research groups emerges for the potential influence of atopic diseases on the skin-brain axis within the field of neurodevelopment<sup>15,20</sup>. A positive association between pediatric AD and the neurodevelopmental disorders ADHD and ASD has consistently been found in epidemiologic studies<sup>15</sup>, but studies on the underlying pathophysiological mechanisms are scarce, leaving an ambiguous underlying interplay between dermatological, neurodevelopmental, and behavioral elements.

## Objectives

The main goal for this proposed scoping review is to provide an extensive overview on pediatric AD and its association with ADHD and ASD, and to highlight knowledge gaps regarding this matter. Extracted data will be mapped according to the following research questions:

1. What are risk factors of both ADHD and ASD in AD?
2. What are current hypotheses on the pathogenesis of ADHD and ASD in AD?
3. What are gaps in the current evidence for the relation between AD, ADHD, and ASD?

## Methods and analysis

### Scoping review

Scoping reviews allow for the exploration of broad research questions with the goal of mapping key concepts, theories, and knowledge gaps based on available evidence in current literature. The aim of this study is to provide a comprehensive overview of etiological theories on pediatric AD and its association with its associated neurodevelopmental comorbidities ADHD and ASD, and to discover knowledge gaps in current literature. This scoping review will follow the methodological manual published by the Joanna Briggs Methodology for Scoping Reviews and will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR)<sup>21,22</sup>.

### Inclusion criteria

### Participants

Children and adolescents < 18 years old must have been diagnosed with AD by a health care provider. Additionally, subjects either must have a diagnosis or documented signs or symptoms of ADHD and/or ASD, as identified through validated psychological measuring instruments by a health care provider, parent, teacher, or as self-reported. Studies solely focusing on sleeping problems, cognitive functioning, or school performance were excluded. Peer-reviewed primary and secondary studies in children and adolescents under the age of 18 that were published in English between January 1, 1946 and August 23, 2023, will be eligible for inclusion. Translational research and theoretical studies on AD and ADHD and/or ASD are eligible. Studies with a mix of both children and adults will be excluded, unless separate data for children is provided. Exclusion criteria are non-peer-reviewed publications such as textbooks, commentaries, dissertations, and conference abstracts.

### Search strategy

The search strategy will be developed by an information specialist (CN). The following databases will be searched from inception until August 2023: Medline ALL in Ovid, Embase, Web of Science Core Collection, and the Cochrane Central Register of Controlled Trials via Wiley.

An exemplary search string for Medline:

(exp \*"Eczema"/ OR exp \*"Dermatitis, Atopic"/ OR \*"Pruritus"/ OR (eczema\* OR ((atopic\*) ADJ3 (dermatit\* OR neurodermat\*)) OR eczematous\* OR prurit\* OR itch\*).ti.) **AND** ("Attention Deficit Disorder with Hyperactivity"/ OR (((attention\*) ADJ3 (deficit\*) ADJ3 (disorder\*))) OR ((attenti\* OR concentrat\*) ADJ3 (defici\*))) OR ADHD).ti.) **AND** (exp "Child"/ OR exp "Infant"/ OR "Adolescent"/ OR exp "Pediatrics"/ OR (adolescent\* OR teenager\* OR child\* OR toddler\* OR boy OR boys OR girl OR girls OR infant OR infants OR baby OR babies OR newborn\* OR pediatric\* OR paediatric\*).ab,ti,kf.)

For the full search strategy, see Supplement S1. The search will be supplemented by forward and backward citation searches of all included papers.

## Study selection

After removal of duplicates from the initial search, two reviewers (NTN and AR) will independently screen all articles on title and abstract for potential eligibility using Rayyan Software<sup>23</sup>. Potentially eligible articles that answer any of the research questions will be read in full. References from included articles will be manually screened for additional eligible articles. Any differences and discussions will be resolved by a third author (RS) and justified in a group meeting with all the authors. The study selection process will adhere to recommendations in the PRISMA-ScR checklist<sup>21</sup>.

## Data extraction

Data from the final articles that will be included in this scoping review will be independently added into an electronic standardized template by two researchers (NTN and AR). This form will include at least the following: author, year of publication, title, design, study aim, country, characteristics of study population, outcomes for AD, ADHD, and ASD. Any discrepancies or uncertainties during the data extraction process will be discussed and resolved by the entire study team.

## Presentation of results

The search results and study selection process will be presented in a flow chart following the PRISMA statement<sup>24</sup>. Extracted data from included studies will be mapped to each of the relevant research questions in a tabular format and graphically if needed. A narrative summary will accompany the tabulated or charted results and will describe how the results relate to the review objectives and questions.

## Patient and public involvement

No patients were involved in developing this protocol. No involvement from patients, nor from the general public will be pursued for this scoping review.

## Ethical considerations

Due to the nature of this study, there are no ethical or safety considerations to be made.

## Acknowledgements

We thank information specialist Christa Niehot for her help with designing the search strategy.

## Funding statement

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## Conflict of interest

All authors have no conflicts of interest.

## Author statement

N.T.N. and A.R. conceived the study and were in charge of overall direction, planning and writing this protocol. N.T.N., A.R., A.B.R., T.N. and R.S. will contribute to the analysis of the results and to the writing of the final manuscript.

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## S1. Appendix. Full Search Strategy.

### ADHD

Database searched	Platform	Years of coverage	Records	Records after duplicates removed
Medline ALL	Ovid	1946 - Present	44	44
Embase	Embase.com	1971 - Present	115	81
Web of Science Core Collection*	Web of Knowledge	1975 - Present	95	39
Cochrane Central Register of Controlled Trials	Wiley	1992 - Present	3	1
<b>Total</b>			<b>257</b>	<b>165</b>

\*Science Citation Index Expanded (1975-present) ; Social Sciences Citation Index (1975-present) ; Arts & Humanities Citation Index (1975-present) ; Conference Proceedings Citation Index- Science (1990-present) ; Conference Proceedings Citation Index- Social Science & Humanities (1990-present) ; Emerging Sources Citation Index (2005-present)

No other database limits were used than those specified in the search strategies

Medline

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(exp *"Eczema"/ OR exp *"Dermatitis, Atopic"/ OR *"Pruritus"/ OR (eczema* OR ((atopic*) ADJ3 (dermatit* OR neurodermat*)) OR eczematous* OR prurit* OR itch*).ti.) AND ("Attention Deficit Disorder with Hyperactivity"/ OR (((attention*) ADJ3 (deficit*) ADJ3 (disorder*))) OR ((attenti* OR concentrat*) ADJ3 (defici*)) OR ADHD).ti.) AND (exp "Child"/ OR exp "Infant"/ OR "Adolescent"/ OR exp "Pediatrics"/ OR (adolescent* OR teenager* OR child* OR toddler* OR boy OR boys OR girl OR girls OR infant OR infants OR baby OR babies OR newborn* OR pediatric* OR paediatric*).ab,ti,kf.)
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Embase

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('eczema'/exp/mj OR 'atopic dermatitis'/exp/mj OR 'pruritus'/exp/mj OR (eczema* OR ((atopic*) NEAR/3 (dermatit* OR neurodermat*)) OR eczematous* OR prurit* OR itch*):ti) AND ('attention deficit hyperactivity disorder'/exp OR (((attention*) NEAR/3 (deficit*) NEAR/3 (disorder*))) OR ((attenti* OR concentrat*) NEAR/3 (defici*)) OR ADHD):ab,ti,kw) AND ('juvenile'/exp OR 'pediatrics'/exp OR (adolescent* OR teenager* OR child* OR toddler* OR boy OR boys OR girl OR girls OR infant OR infants OR baby OR babies OR newborn* OR pediatric* OR paediatric*):ab,ti,kw)
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Web of Science

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TI=(eczema* OR ((atopic*) NEAR/2 (dermatit* OR neurodermat*)) OR eczematous* OR prurit* OR itch*) AND TS=((attention*) NEAR/2 (deficit*) NEAR/2 (disorder*)) OR ((attenti* OR concentrat*) NEAR/2 (defici*)) OR ADHD) AND TS=(adolescent* OR teenager* OR child* OR toddler* OR boy OR boys OR girl OR girls OR infant OR infants OR baby OR babies OR newborn* OR pediatric* OR paediatric*)
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Cochrane CENTRAL

((eczema\* OR ((atopic\*) NEAR/3 (dermatit\* OR neurodermat\*)) OR eczematous\* OR prurit\* OR itch\*):ti) **AND** (((attention\*) NEAR/3 (deficit\*) NEAR/3 (disorder\*)) OR ((attenti\* OR concentrat\*) NEAR/3 (defici\*)) OR ADHD):ab,ti,kw) **AND** ((adolescent\* OR teenager\* OR child\* OR toddler\* OR boy OR boys OR girl OR girls OR infant OR infants OR baby OR babies OR newborn\* OR pediatric\* OR paediatric\*):ab,ti,kw)

## ASD

Database searched	Platform	Years of coverage	Records	Records after duplicates removed
Medline ALL	Ovid	1946 - Present	26	26
Embase	Embase.com	1971 - Present	44	26
Web of Science Core Collection*	Web of Knowledge	1975 - Present	34	16
Cochrane Central Register of Controlled Trials	Wiley	1992 - Present	1	1
<b>Total</b>			<b>105</b>	<b>69</b>

\*Science Citation Index Expanded (1975-present) ; Social Sciences Citation Index (1975-present) ; Arts & Humanities Citation Index (1975-present) ; Conference Proceedings Citation Index- Science (1990-present) ; Conference Proceedings Citation Index- Social Science & Humanities (1990-present) ; Emerging Sources Citation Index (2005-present)

No other database limits were used than those specified in the search strategies

Medline

(exp \*"Eczema"/ OR exp \*"Dermatitis, Atopic"/ OR \*"Pruritus"/ OR (eczema\* OR ((atopic\*) ADJ3 (dermatit\* OR neurodermat\*)) OR eczematous\* OR prurit\* OR itch\*):ti.) **AND** (exp "Autism Spectrum Disorder"/ OR (autis\* OR ((development\* OR neurocognitiv\* OR neuro-cognitiv\*) ADJ2 (disorder\*))) OR Asperger\*).ab,ti,kf.) **AND** (exp "Child"/ OR exp "Infant"/ OR "Adolescent"/ OR exp "Pediatrics"/ OR (adolescent\* OR teenager\* OR child\* OR toddler\* OR boy OR boys OR girl OR girls OR infant OR infants OR baby OR babies OR newborn\* OR pediatric\* OR paediatric\*).ab,ti,kf.)

Embase

('eczema'/exp/mj OR 'atopic dermatitis'/exp/mj OR 'pruritus'/exp/mj OR (eczema\* OR ((atopic\*) NEAR/3 (dermatit\* OR neurodermat\*)) OR eczematous\* OR prurit\* OR itch\*):ti) **AND** ('autism'/exp OR (autis\* OR ((development\* OR neurocognitiv\* OR neuro-cognitiv\*) NEAR/2 (disorder\*))) OR Asperger\*):ab,ti,kw) **AND** ('juvenile'/exp OR 'pediatrics'/exp OR (adolescent\* OR teenager\* OR child\* OR toddler\* OR boy OR boys OR girl OR girls OR infant OR infants OR baby OR babies OR newborn\* OR pediatric\* OR paediatric\*):ab,ti,kw)

Web of Science

TI=(eczema\* OR ((atopic\*) NEAR/2 (dermatit\* OR neurodermat\*)) OR eczematous\* OR prurit\* OR itch\*) **AND** TS=(autis\* OR ((development\* OR neurocognitiv\* OR neuro-cognitiv\*) NEAR/2 (disorder\*))) OR Asperger\*) **AND** TS=(adolescent\* OR teenager\* OR child\* OR toddler\* OR boy OR boys OR girl OR girls OR infant OR infants OR baby OR babies OR newborn\* OR pediatric\* OR paediatric\*)

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6 (disorder\*))) OR Asperger\*):ab,ti,kw) **AND** ((adolescent\* OR teenager\* OR child\* OR toddler\* OR boy  
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3 **Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for**  
4 **Scoping Reviews (PRISMA-ScR) Checklist**  
5

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
<b>TITLE</b>			
Title	1	Identify the report as a scoping review.	
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	
<b>METHODS</b>			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	



SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
<b>RESULTS</b>			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	
<b>DISCUSSION</b>			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	
Limitations	20	Discuss the limitations of the scoping review process.	
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	
<b>FUNDING</b>			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

\* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.



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# BMJ Open

## Shared symptomatology between atopic dermatitis, ADHD, and autism spectrum disorder symptoms a protocol for a systematic scoping review

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Keywords:	Eczema < DERMATOLOGY, Developmental neurology & neurodisability < PAEDIATRICS, Paediatric dermatology < DERMATOLOGY, Child & adolescent psychiatry < PSYCHIATRY

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5 **Shared symptomatology between**

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36 Keywords: Atopic dermatitis, Attention Deficit Disorder with Hyperactivity, Autism Spectrum

37 Disorder

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39 Word count: 1398

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42 **Abstract**

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44 Introduction

45 Children with atopic dermatitis (AD) are more at risk for the neurodevelopmental disorders

46 Attention-Deficit/Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD) with

47 parallel increases in prevalence. Children afflicted with these conditions appear to share

48 similar problems in sensory modulation but investigational studies on the underlying

49 etiology are scarce. This scoping review aims to find knowledge gaps, collate hypotheses and

50 to summarize available evidence on the shared pathophysiology of AD, ADHD, and ASD in

51 children.

52

53

54 Methods and analysis

55 Our study will follow the methodological manual published by the Joanna Briggs

56 Methodology for Scoping Reviews and will be reported in accordance with the Preferred

57 Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

58 (PRISMA-ScR). The following electronic databases will be searched for studies focused on

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60

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2  
3 35 children with AD and ADHD and/or ASD: Medline ALL via Ovid, Embase, Web of Science Core  
4 36 Collection and the Cochrane Central Register of Controlled Trials via Wiley.  
5  
6  
7 38 Ethics and dissemination  
8 39 This review does not require ethics approval as it will not be conducted with human  
9 participants. We will only use published data. Our dissemination strategy includes peer  
10 40 review publication and conference reports.  
11 41  
12 42  
13  
14 43 Article Summary

## 17 44 Strengths and limitations of this study

- 18 45 • This scoping review marks the pioneering attempt to explore the relation between  
19 46 Attention Deficit (AD), and Attention-Deficit/Hyperactivity Disorder (ADHD) and  
20 47 Autism Spectrum Disorder (ASD) in children.  
21 48 • To ensure methodological rigor, we will collaborate with health sciences librarians to  
22 49 construct an established methodology and execute a systematic search,  
23 50 encompassing a wide spectrum of publication types.  
24 51 • The identification and synthesis of data will be limited to published articles found on  
25 52 the MEDLINE, Embase, Web of Science, and Cochrane databases and snowball  
26 53 references.  
27 54 • Relevant articles in the grey literature or written in another language than English  
28 55 may be missed.

## Introduction

### Background

Atopic dermatitis (AD) is a common chronic inflammatory skin disorder characterized by pruritus and recurrent eczematous skin lesions affecting up to 20% of children in high-income countries<sup>1</sup>. Besides other atopic diseases such as allergic rhinitis, food allergies, and asthma, children with AD are also more at risk for non-allergic comorbidities including infectious and systemic diseases, as well as neurodevelopmental disorders such as attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD)<sup>2-4</sup>. Current studies on pediatric AD focus on the clinical treatment of the disease but there are still gaps in knowledge regarding aforementioned neurodevelopmental comorbidities. Complex pathomechanisms, involving both genetic and environmental factors, combined with global increases in prevalence of AD, ADHD, and ASD in the past decades has led to many hypotheses on the underlying etiological associations between these conditions<sup>5-9</sup>.

ADHD is one of the most common neurodevelopmental disorders in children, characterized by symptoms of inattention, hyperactivity, and impulsivity<sup>10</sup>. Children with ADHD often have sensory processing problems, which is the inability to effectively regulate and organize a graded and adaptive response to sensory stimuli<sup>11-13</sup>. Similar to ADHD, children with AD also exhibit symptoms of altered sensory processing, expressing sensory hypo- or hyper-reactivity compared to controls<sup>14,15</sup>. Epidemiologically, individuals with AD are more at risk for ADHD with an estimated OR = 1.32 (95% CI 1.20–1.45) for all ages to OR = 1.56 (95% CI, 1.38–1.77) in children and adolescents<sup>16,17</sup>.

ASD is a heterogeneous neurodevelopmental disorder, encompassing former diagnoses such as autistic disorder, Asperger syndrome, and pervasive developmental disorder not otherwise specified<sup>18</sup>. Traits displayed by diagnosed individuals include persistent difficulties with social communication and interaction, and the presence of restricted and repetitive patterns of behavior from an early developmental period<sup>18,19</sup>. Comparable to both AD and ADHD, children with ASD have also been found to have more sensory hypo- or hyper-reactivity symptoms<sup>20</sup>. The risk for developing ASD in individuals with AD has been estimated to be OR = 1.49 (95% CI 1.20-1.83) in all ages to OR = 2.57 (95% CI 1.47-4.51) in children and adolescents<sup>17,21</sup>. Moreover, children with ASD with AD may have more pronounced ASD symptoms overall and on the social domain outcomes, relative to children with ASD without AD<sup>22</sup>.

Due to the parallel rises in the global prevalences of AD, ADHD, and ASD, an increasing interest among many research groups emerges for the potential influence of atopic diseases on the skin-brain axis within the field of neurodevelopment<sup>17,22</sup>. A positive association between pediatric AD and the neurodevelopmental disorders ADHD and ASD has consistently been found in epidemiologic studies<sup>17</sup>, but studies on the underlying pathophysiological mechanisms are scarce, leaving an ambiguous underlying interplay between dermatological, neurodevelopmental, and behavioral elements.

## 100 Objectives

101 The main goal for this proposed scoping review is to provide an extensive overview on  
102 pediatric AD and its shared symptomatology with ADHD and ASD, and to highlight  
103 knowledge gaps regarding this matter. Extracted data will be mapped according to the  
104 following research questions:

- 105 1. What are mutual traits in AD, ADHD, ASD, and AD?
- 106 2. What are current hypotheses for the shared symptomatology of AD, ADHD, and ASD?
- 107 3. What are gaps in the current evidence for a potential underlying shared etiology of  
108 AD, ADHD, and ASD?

## 109 Methods and analysis

### 110 Scoping review

111 Scoping reviews allow for the exploration of broad research questions with the goal of  
112 discovering key concepts, theories, and knowledge gaps in an upcoming field. The aim of this  
113 study is to provide a comprehensive overview of etiological theories on pediatric AD and its  
114 relation with neurodevelopmental comorbidities ADHD and ASD, and to map, report, and  
115 discuss the concepts in current literature. Due to the broad research question and the  
116 exploratory nature of this study on an emerging field of interest with great heterogeneity in  
117 literature, we expect a scoping review to be more suitable than a systematic review<sup>23</sup>.  
118 This scoping review will follow the methodological manual published by the Joanna Briggs  
119 Methodology for Scoping Reviews and will be reported in accordance with the Preferred  
120 Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews  
121 (PRISMA-ScR)<sup>24,25</sup>.

### 123 Inclusion criteria

### 124 Participants

125 Children and adolescents < 18 years old must have been diagnosed with AD by a health care  
126 provider. Additionally, subjects either must have a diagnosis or documented signs or  
127 symptoms of ADHD and/or ASD, as identified through validated psychological measuring  
128 instruments by a health care provider, parent, teacher, or as self-reported. Studies solely  
129 focusing on sleeping problems, cognitive functioning, or school performance were excluded.  
130 Peer-reviewed primary and secondary studies in children and adolescents under the age of  
131 18 that were published in English between January 1, 1946 and April 1, 2024, will be eligible  
132 for inclusion. Translational research and theoretical studies on AD and ADHD and/or ASD are  
133 eligible. Studies with a mix of both children and adults will be excluded, unless separate data  
134 for children is provided. Exclusion criteria are non-peer-reviewed publications such as  
135 textbooks, commentaries, dissertations, and conference abstracts.

### 137 Search strategy

138 The search strategy will be developed by an information specialist (CN). The following  
139 databases will be searched from inception until April 2024: Medline ALL in Ovid, Embase,  
140 Web of Science Core Collection, and the Cochrane Central Register of Controlled Trials via  
141 Wiley.

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3 142  
4 143 An exemplary search string for Medline:  
5 (exp \*"Eczema"/ OR exp \*"Dermatitis, Atopic"/ OR \*"Pruritus"/ OR (eczema\* OR ((atopic\*) ADJ3  
6 (dermatit\* OR neurodermat\*)) OR eczematous\* OR prurit\* OR itch\*).ti.) **AND** ("Attention Deficit  
7 Disorder with Hyperactivity"/ OR (((attention\*) ADJ3 (deficit\*) ADJ3 (disorder\*)) OR ((attenti\* OR  
8 concentrat\*) ADJ3 (defici\*)) OR ADHD).ti.) **AND** (exp "Child"/ OR exp "Infant"/ OR "Adolescent"/ OR  
9 exp "Pediatrics"/ OR (adolescent\* OR teenager\* OR child\* OR toddler\* OR boy OR boys OR girl OR  
10 girls OR infant OR infants OR baby OR babies OR newborn\* OR pediatric\* OR paediatric\*).ab,ti,kf.)  
11 149  
12 150  
13 151 For the full search strategy, see Supplement 'S1 Search Strategy'. The search will be  
14 152 supplemented by forward and backward citation searches of all included papers.  
15 153  
16  
17  
18 154 **Study selection**  
19 After removal of duplicates from the initial search, two reviewers (NTN and AR) will  
20 independently screen all articles on title and abstract for potential eligibility using Rayyan  
21 Software<sup>26</sup>. Potentially eligible articles that answer any of the research questions will be read  
22 in full. References from included articles will be manually screened for additional eligible  
23 articles. Any differences and discussions will be resolved by a third author (RS) and justified  
24 in a group meeting with all the authors. The study selection process will adhere to  
25 recommendations in the PRISMA-ScR checklist<sup>24</sup>.  
26  
27  
28  
29  
30 163 **Data extraction**  
31 Data from the final articles that will be included in this scoping review will be independently  
32 added into an electronic standardized template by two researchers (NTN and AR). This form  
33 will include at least the following: author, year of publication, title, design, study aim,  
34 country and characteristics of study population such as age, sex, ethnicity, socioeconomic  
35 status, and use of ADHD medication. Measures of AD, ADHD, ASD diagnosis or symptoms  
36 (either clinically diagnosed, self-reported, retrospective or structured assessments and  
37 questionnaires) will be extracted. See Supplement 'S2 Data Extraction Template' for a  
38 template of the data extraction form. Any discrepancies or uncertainties during the data  
39 extraction process will be discussed and resolved by the entire study team.  
40  
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43  
44 174 **Presentation of results**  
45 The search results and study selection process will be presented in a flow chart following the  
46 PRISMA statement<sup>27</sup>. Extracted data from included studies will be mapped to each of the  
47 relevant research questions in a tabular format and graphically if needed. A narrative  
48 summary will accompany the tabulated or charted results and will describe how the results  
49 relate to the review objectives and questions.  
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53 180 **Patient and public involvement**  
54 No patients were involved in developing this protocol. No involvement from patients, nor  
55 from the general public will be pursued for this scoping review.  
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## 183 Ethical considerations

184 Due to the nature of this study, there are no ethical or safety considerations to be made.

## 185 Acknowledgements

186 We thank information specialist Christa Niehot for her help with designing the search  
187 strategy.

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190 or not-for-profit sectors.

## 191 Conflict of interest

192 All authors have no conflicts of interest.

## 194 Author statement

195 N.T.N. and A.R. conceived the study and were in charge of overall direction, planning and  
196 writing this protocol. N.T.N., A.R., A.B.R., T.N. and R.S. will contribute to the analysis of the  
197 results and to the writing of the final manuscript.

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30 248 young people on the autism spectrum. *Autism Research* 2022; **15**: 1840-54.  
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32 250 Spectrum Disorder: A Systematic Review and Meta-analysis. *Acta Derm Venereol*  
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48 266  
49 267

## S1. Appendix. Full Search Strategy.

ADHD

Database searched	Platform	Years of coverage	Records	Records after duplicates removed
Medline ALL	Ovid	1946 - Present	44	44
Embase	Embase.com	1971 - Present	115	81
Web of Science Core Collection*	Web of Knowledge	1975 - Present	95	39
Cochrane Central Register of Controlled Trials	Wiley	1992 - Present	3	1
<b>Total</b>			<b>257</b>	<b>165</b>

\*Science Citation Index Expanded (1975-present) ; Social Sciences Citation Index (1975-present) ; Arts & Humanities Citation Index (1975-present) ; Conference Proceedings Citation Index- Science (1990-present) ; Conference Proceedings Citation Index- Social Science & Humanities (1990-present) ; Emerging Sources Citation Index (2005-present)

No other database limits were used than those specified in the search strategies

Medline

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(exp *"Eczema"/ OR exp *"Dermatitis, Atopic"/ OR *"Pruritus"/ OR (eczema* OR ((atopic*) ADJ3 (dermatit* OR neurodermat*)) OR eczematous* OR prurit* OR itch*).ti.) AND ("Attention Deficit Disorder with Hyperactivity"/ OR (((attention*) ADJ3 (deficit*) ADJ3 (disorder*))) OR ((attenti* OR concentrat*) ADJ3 (defici*)) OR ADHD).ti.) AND (exp "Child"/ OR exp "Infant"/ OR "Adolescent"/ OR exp "Pediatrics"/ OR (adolescent* OR teenager* OR child* OR toddler* OR boy OR boys OR girl OR girls OR infant OR infants OR baby OR babies OR newborn* OR pediatric* OR paediatric*).ab,ti,kf.)
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Embase

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('eczema'/exp/mj OR 'atopic dermatitis'/exp/mj OR 'pruritus'/exp/mj OR (eczema* OR ((atopic* NEAR/3 (dermatit* OR neurodermat*)) OR eczematous* OR prurit* OR itch*):ti) AND ('attention deficit hyperactivity disorder'/exp OR (((attention*) NEAR/3 (deficit*) NEAR/3 (disorder*))) OR ((attenti* OR concentrat*) NEAR/3 (defici*)) OR ADHD):ab,ti,kw) AND ('juvenile'/exp OR 'pediatrics'/exp OR (adolescent* OR teenager* OR child* OR toddler* OR boy OR boys OR girl OR girls OR infant OR infants OR baby OR babies OR newborn* OR pediatric* OR paediatric*):ab,ti,kw)
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Web of Science

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TI=(eczema* OR ((atopic*) NEAR/2 (dermatit* OR neurodermat*)) OR eczematous* OR prurit* OR itch*) AND TS=((attention*) NEAR/2 (deficit*) NEAR/2 (disorder*)) OR ((attenti* OR concentrat*) NEAR/2 (defici*)) OR ADHD) AND TS=(adolescent* OR teenager* OR child* OR toddler* OR boy OR boys OR girl OR girls OR infant OR infants OR baby OR babies OR newborn* OR pediatric* OR paediatric*)
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Cochrane CENTRAL

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((eczema* OR ((atopic*) NEAR/3 (dermatit* OR neurodermat*))) OR eczematous* OR prurit* OR itch*):ti) AND (((attention*) NEAR/3 (deficit*) NEAR/3 (disorder*))) OR ((attenti* OR concentrat*)
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38 NEAR/3 (defici\*) OR ADHD):ab,ti,kw) **AND** ((adolescent\* OR teenager\* OR child\* OR toddler\* OR  
 39 boy OR boys OR girl OR girls OR infant OR infants OR baby OR babies OR newborn\* OR pediatric\* OR  
 40 paediatric\*):ab,ti,kw)

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42 ASD

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Database searched	Platform	Years of coverage	Records	Records after duplicates removed
Medline ALL	Ovid	1946 - Present	26	26
Embase	Embase.com	1971 - Present	44	26
Web of Science Core Collection*	Web of Knowledge	1975 - Present	34	16
Cochrane Central Register of Controlled Trials	Wiley	1992 - Present	1	1
<b>Total</b>			<b>105</b>	<b>69</b>

24

44  
 45 \*Science Citation Index Expanded (1975-present) ; Social Sciences Citation Index (1975-present) ; Arts  
 46 & Humanities Citation Index (1975-present) ; Conference Proceedings Citation Index- Science (1990-  
 47 present) ; Conference Proceedings Citation Index- Social Science & Humanities (1990-present) ;  
 48 Emerging Sources Citation Index (2005-present)

49

50 No other database limits were used than those specified in the search strategies

51 Medline

52 (exp \*"Eczema"/ OR exp \*"Dermatitis, Atopic"/ OR \*"Pruritus"/ OR (eczema\* OR ((atopic\*) ADJ3  
 53 (dermatit\* OR neurodermat\*)) OR eczematous\* OR prurit\* OR itch\*).ti.) **AND** (exp "Autism Spectrum  
 54 Disorder"/ OR (autis\* OR ((development\* OR neurocognitiv\* OR neuro-cognitiv\*) ADJ2 (disorder\*)))  
 55 OR Asperger\*).ab,ti,kf.) **AND** (exp "Child"/ OR exp "Infant"/ OR "Adolescent"/ OR exp "Pediatrics"/  
 56 OR (adolescent\* OR teenager\* OR child\* OR toddler\* OR boy OR boys OR girl OR girls OR infant OR  
 57 infants OR baby OR babies OR newborn\* OR pediatric\* OR paediatric\*).ab,ti,kf.)

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59 Embase

60 ('eczema'/exp/mj OR 'atopic dermatitis'/exp/mj OR 'pruritus'/exp/mj OR (eczema\* OR ((atopic\*)  
 61 NEAR/3 (dermatit\* OR neurodermat\*)) OR eczematous\* OR prurit\* OR itch\*):ti) **AND** ('autism'/exp  
 62 OR (autis\* OR ((development\* OR neurocognitiv\* OR neuro-cognitiv\*) NEAR/2 (disorder\*))) OR  
 63 Asperger\*):ab,ti,kw) **AND** ('juvenile'/exp OR 'pediatrics'/exp OR (adolescent\* OR teenager\* OR child\*  
 64 OR toddler\* OR boy OR boys OR girl OR girls OR infant OR infants OR baby OR babies OR newborn\*  
 65 OR pediatric\* OR paediatric\*):ab,ti,kw)

66

67 Web of Science

68 TI=(eczema\* OR ((atopic\*) NEAR/2 (dermatit\* OR neurodermat\*)) OR eczematous\* OR prurit\* OR  
 69 itch\*) **AND** TS=(autis\* OR ((development\* OR neurocognitiv\* OR neuro-cognitiv\*) NEAR/2  
 70 (disorder\*))) OR Asperger\*) **AND** TS=(adolescent\* OR teenager\* OR child\* OR toddler\* OR boy OR  
 71 boys OR girl OR girls OR infant OR infants OR baby OR babies OR newborn\* OR pediatric\* OR  
 72 paediatric\*)

73

74 Cochrane CENTRAL

75 ((eczema\* OR ((atopic\*) NEAR/3 (dermatit\* OR neurodermat\*)) OR eczematous\* OR prurit\* OR  
 76 itch\*):ti) **AND** ((autis\* OR ((development\* OR neurocognitiv\* OR neuro NEXT/1 cognitiv\*) NEAR/2

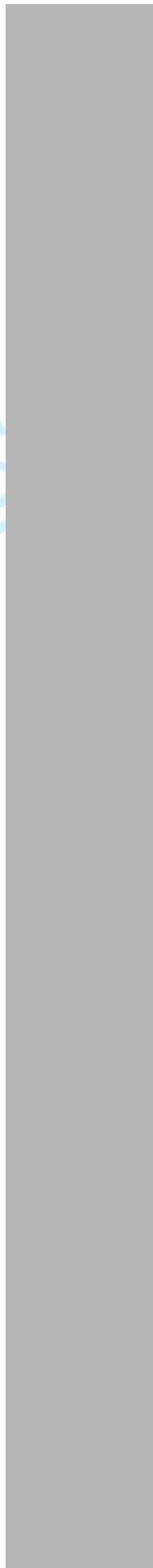
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3 77 (disorder\*):ab,ti,kw) **AND** ((adolescent\* OR teenager\* OR child\* OR toddler\* OR boy  
4 78 OR boys OR girl OR girls OR infant OR infants OR baby OR babies OR newborn\* OR pediatric\* OR  
5 79 paediatric\*):ab,ti,kw)  
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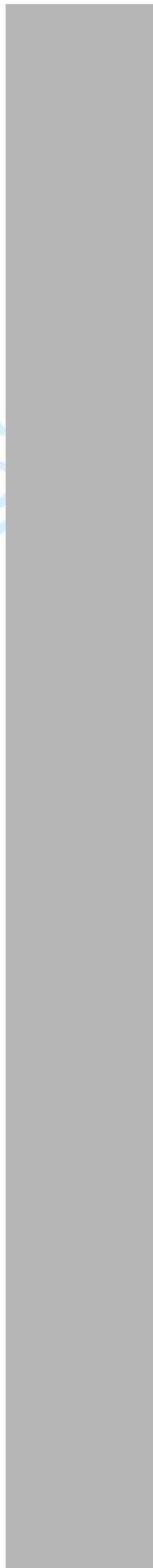


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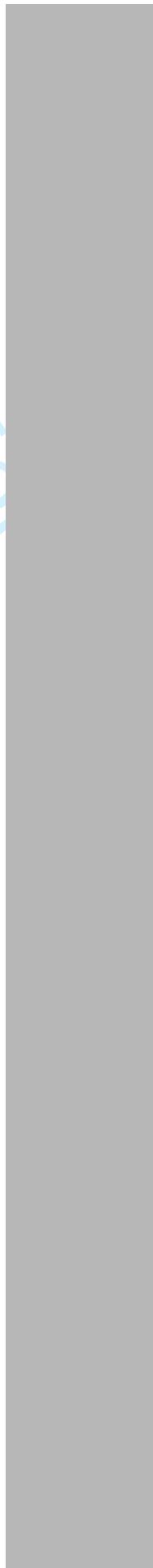


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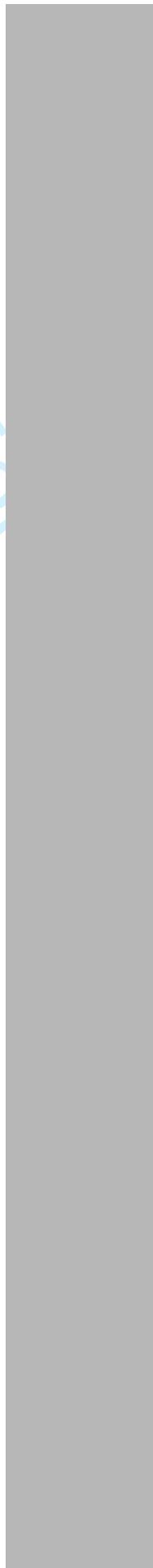


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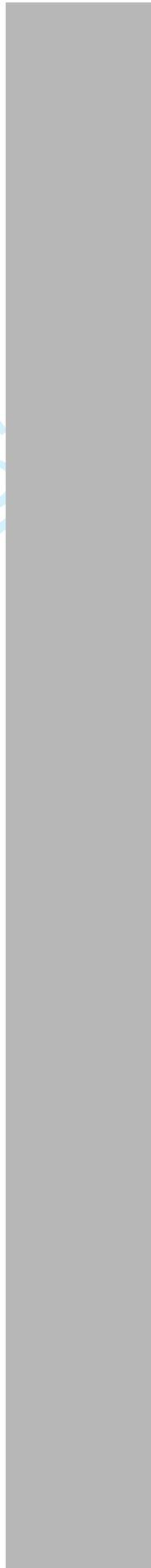


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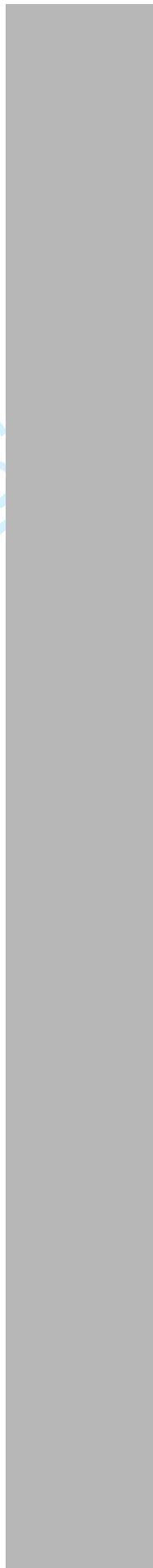


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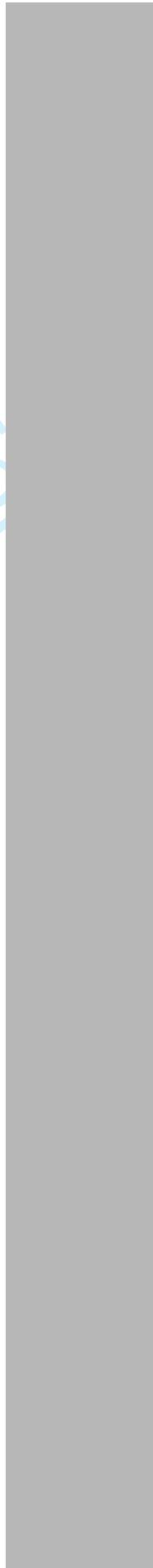


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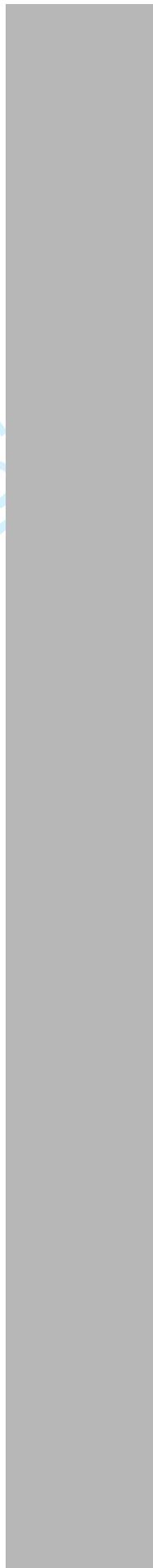


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**Patients with AD**    **Patients with ADHD**    **Patients with AD/ADHD**    **Patients with ASD**    **Patients with AD/ASD**    **AD diagnosis**

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ADHD diagnosis	ASD diagnosis	AD traits	ADHD traits	ASD traits	Data Source	Population Age
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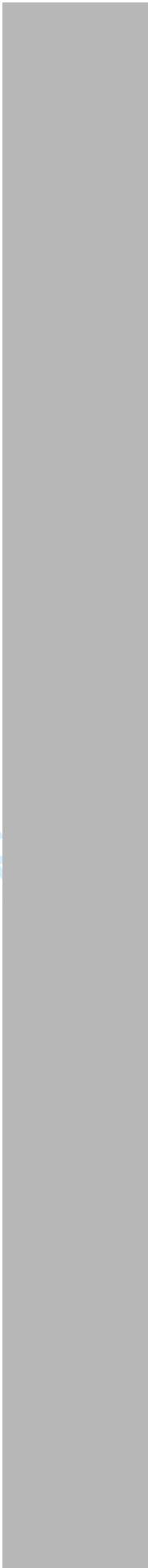
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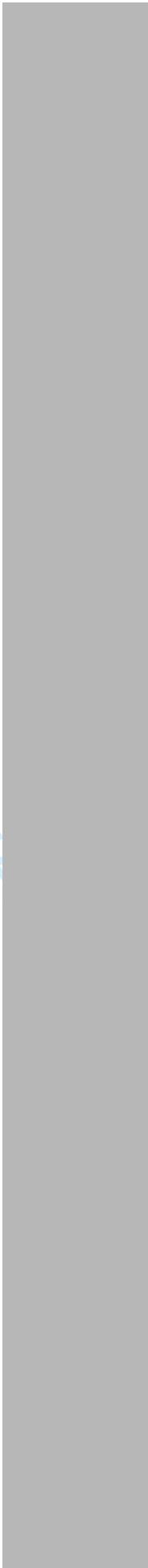
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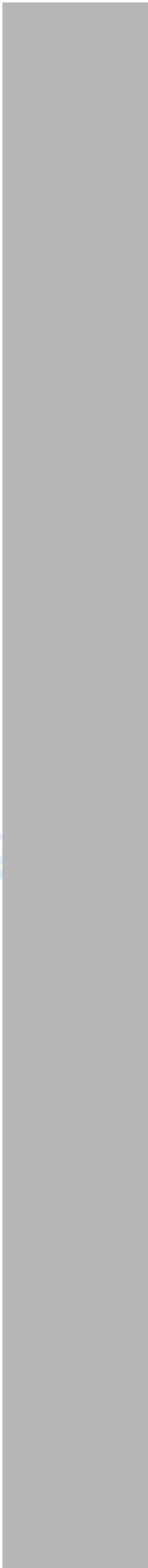
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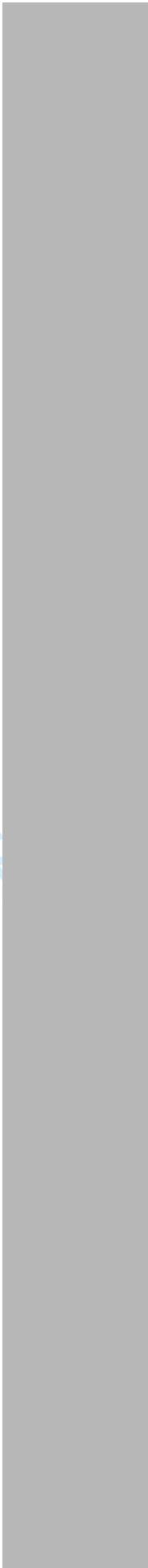
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**Potentially relevant references**

**Question 1:  
Mutual traits**

I: Trait

I: Outcome

I: Effects

**Question 2:  
Hypotheses on shared symptomatology**

I: Hypothesis

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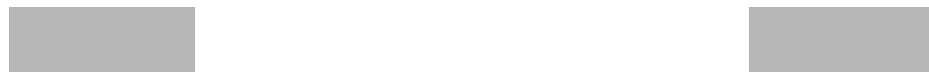
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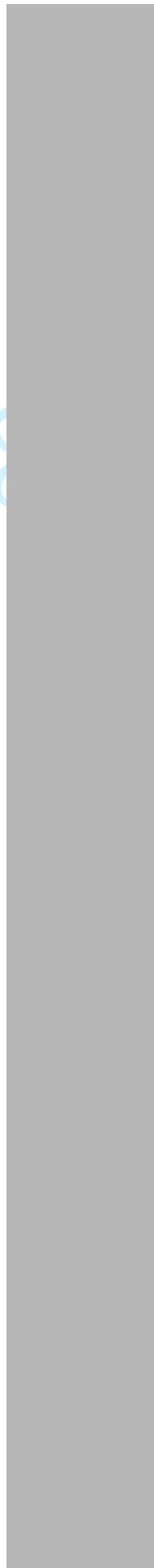
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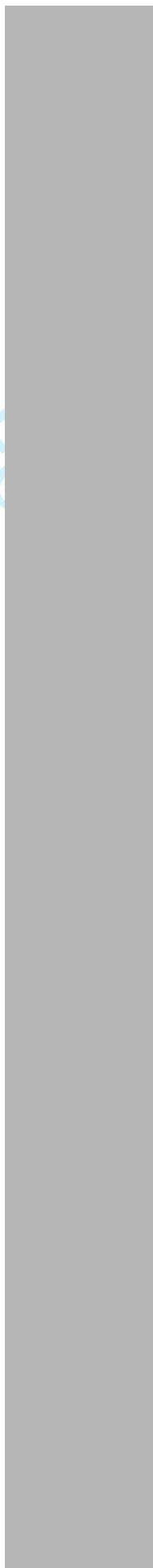
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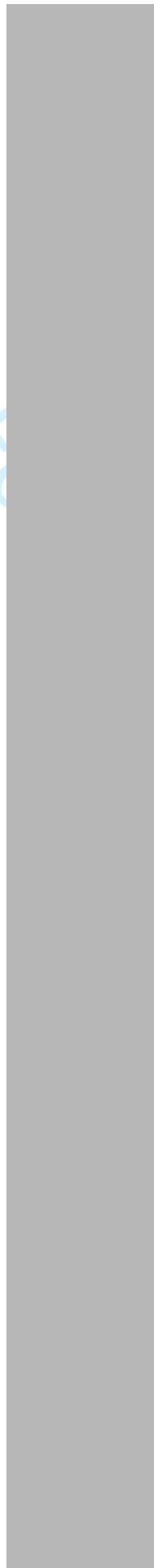
**Question 3:  
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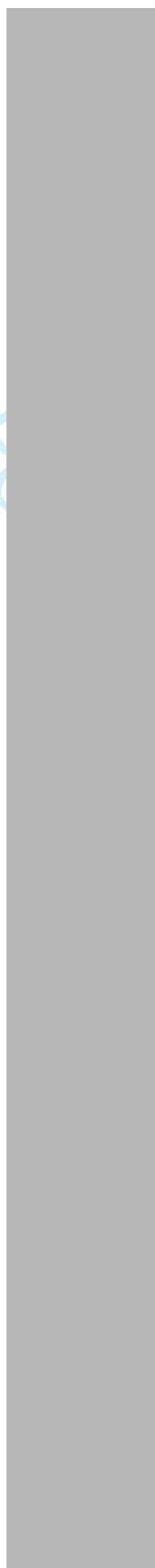
I: Outcome    I: Effect

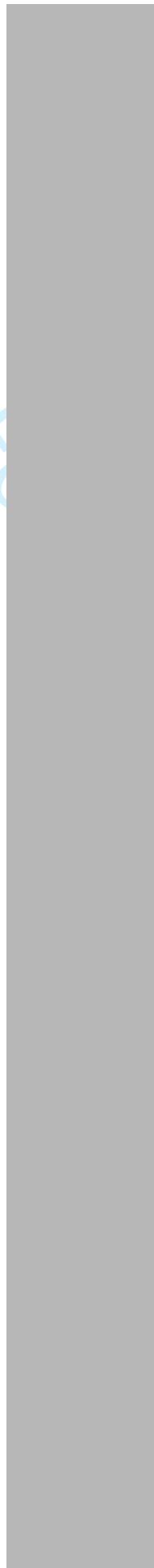
I: Hypothesis    I: Outcome    I: Effect

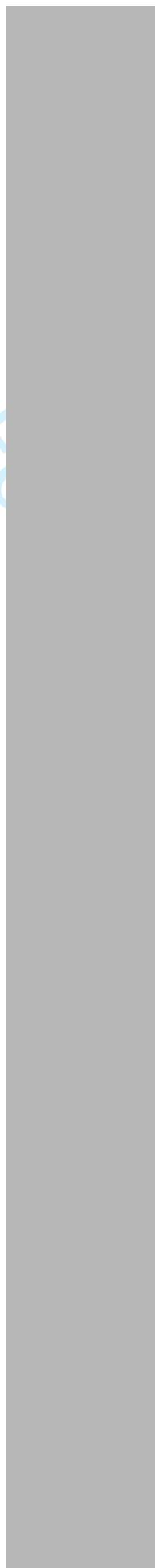


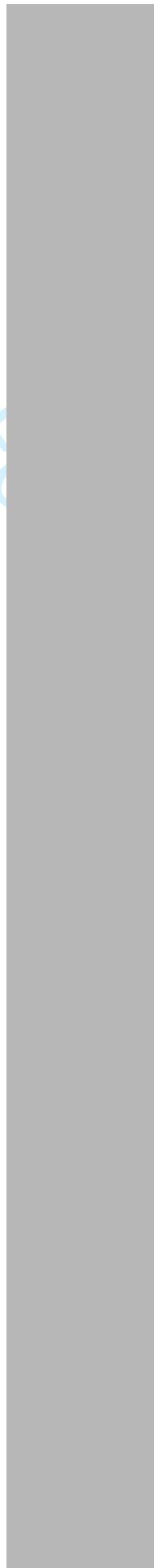


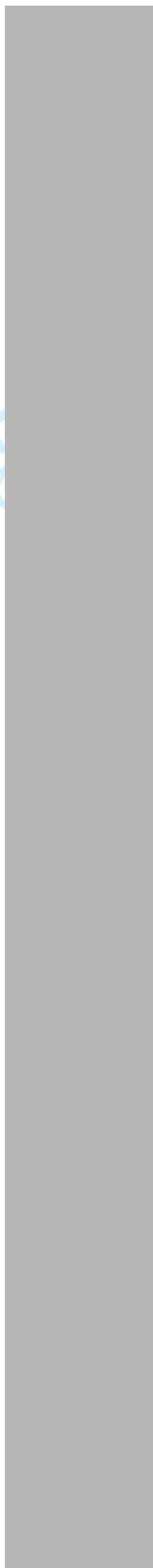


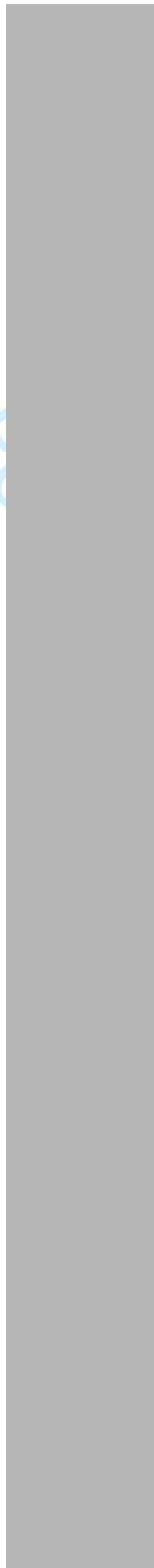




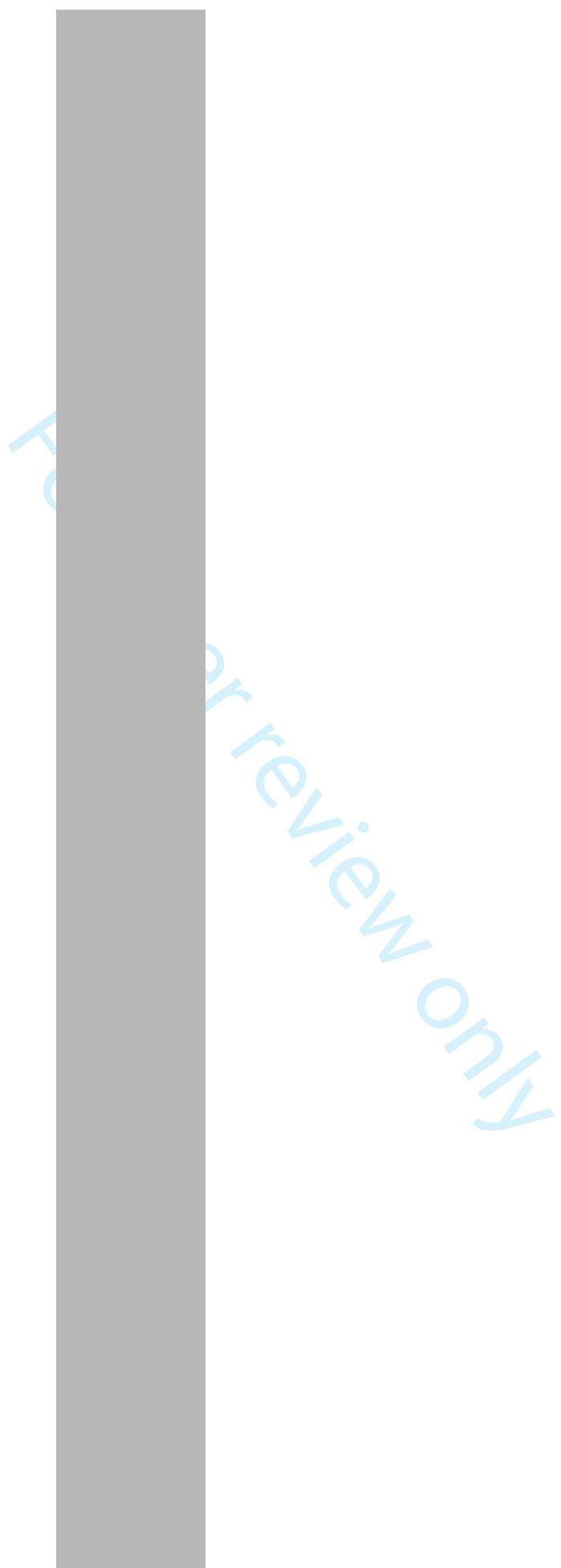


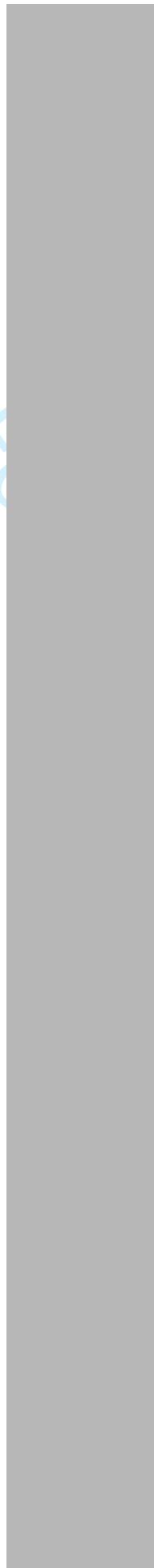


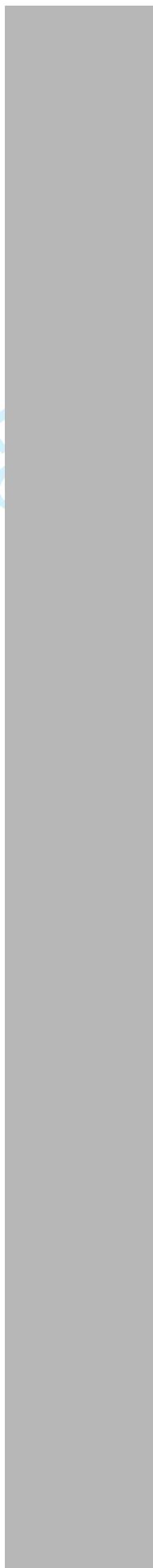


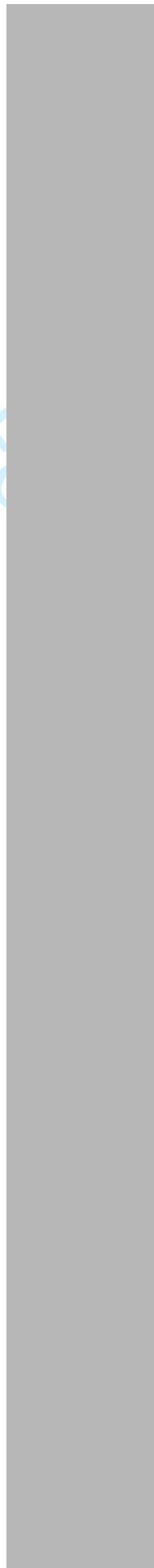


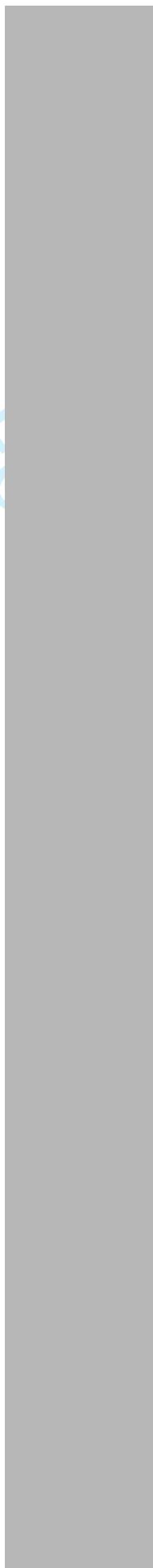
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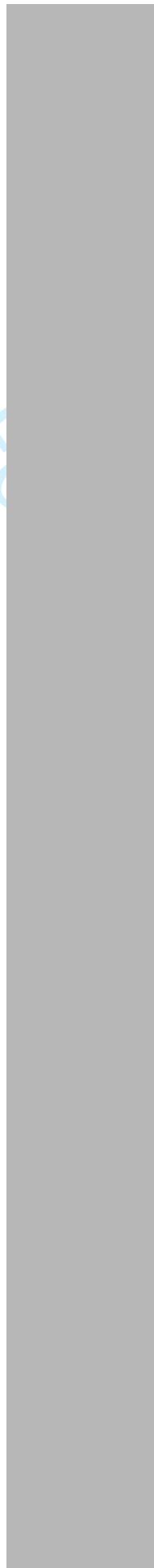


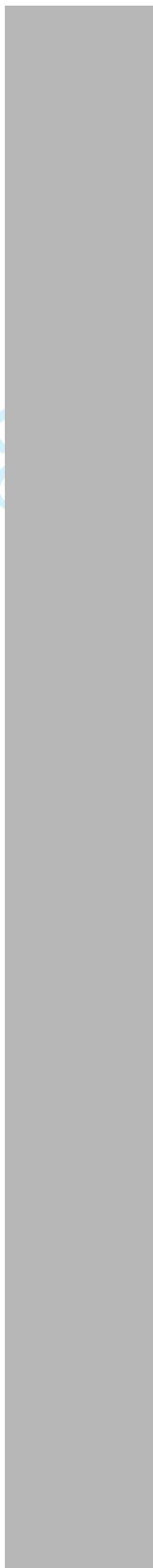














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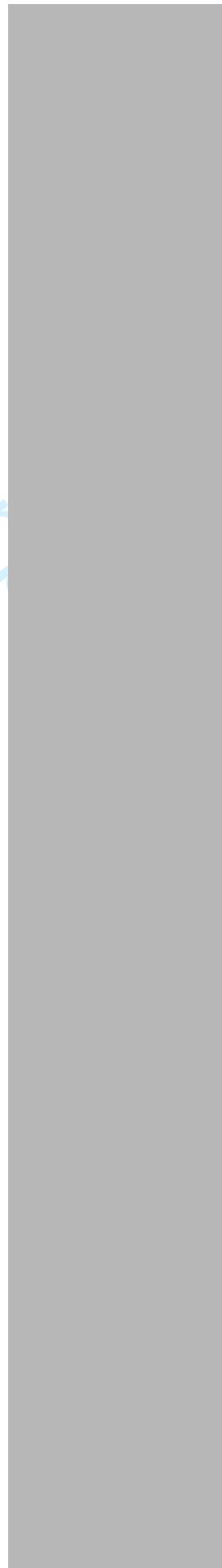
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**Limitations****Other remarks**

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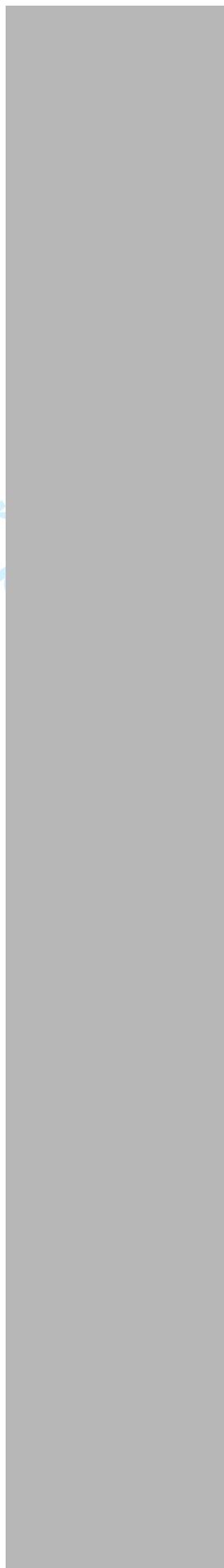
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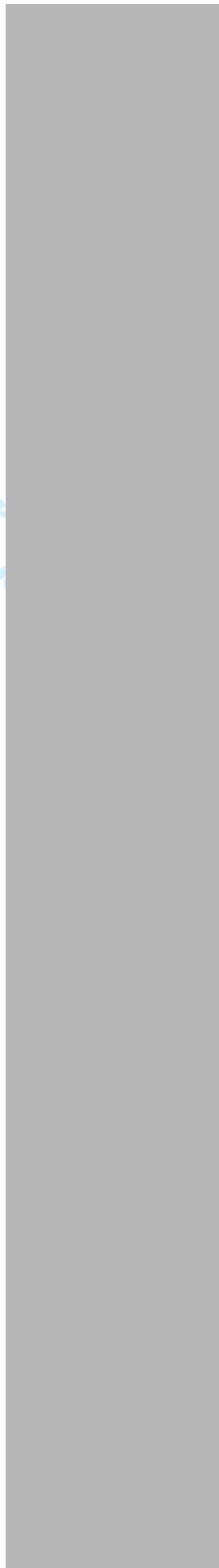
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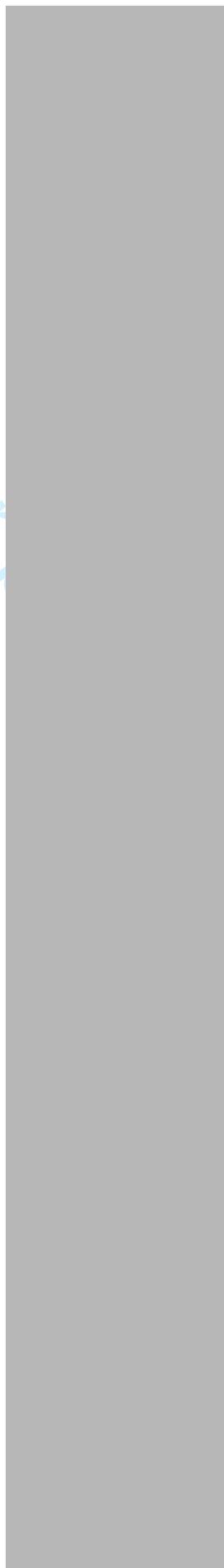
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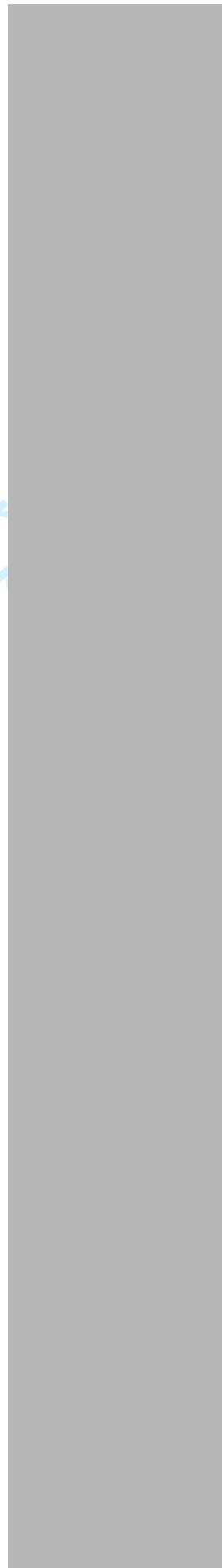
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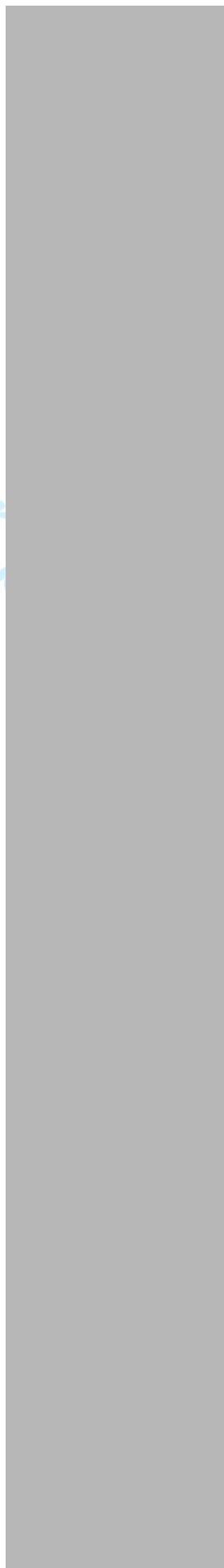
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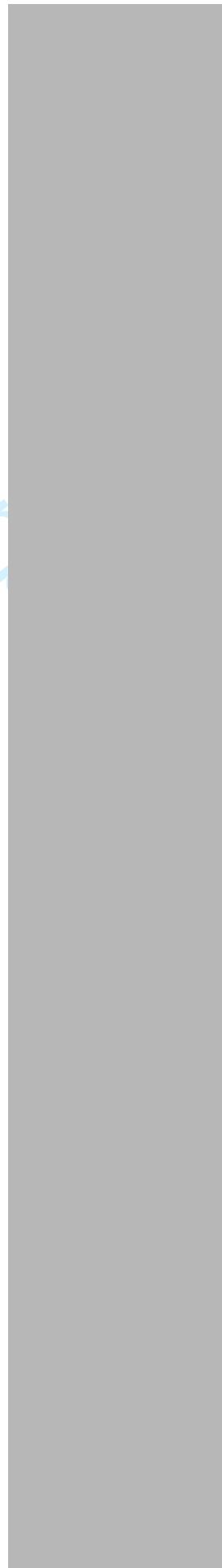
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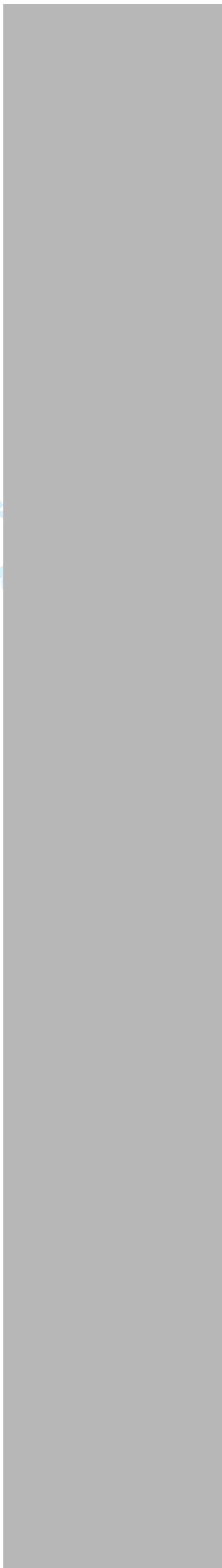


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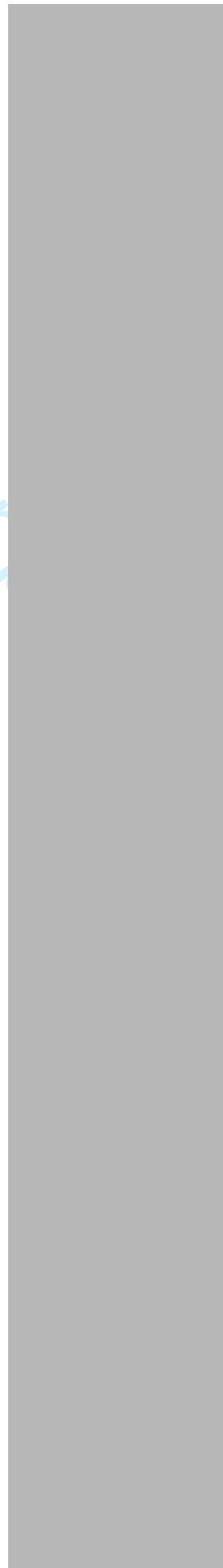


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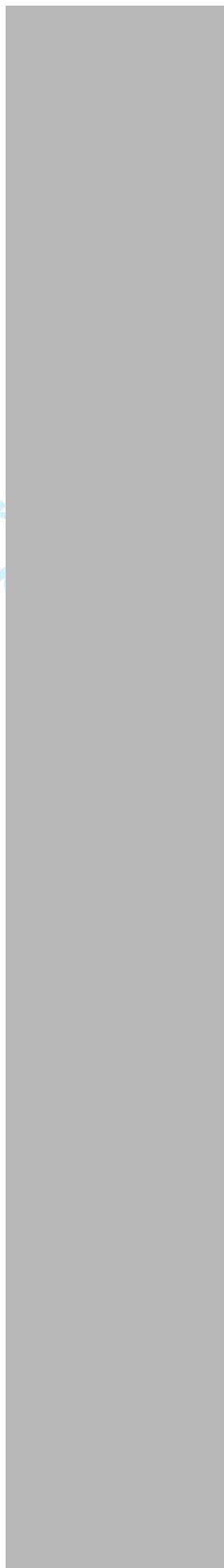


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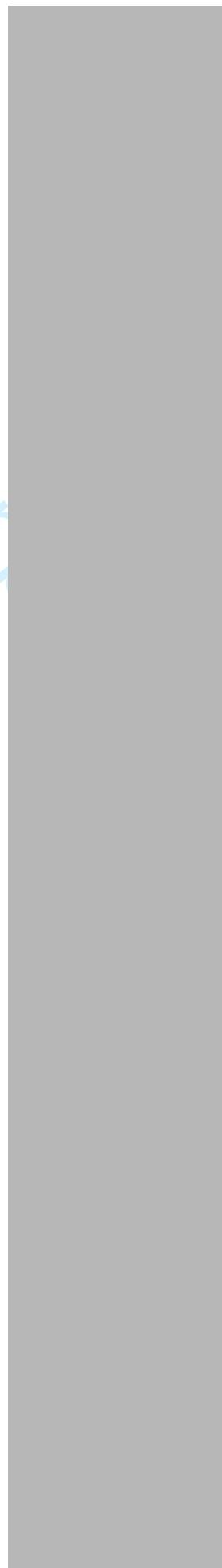


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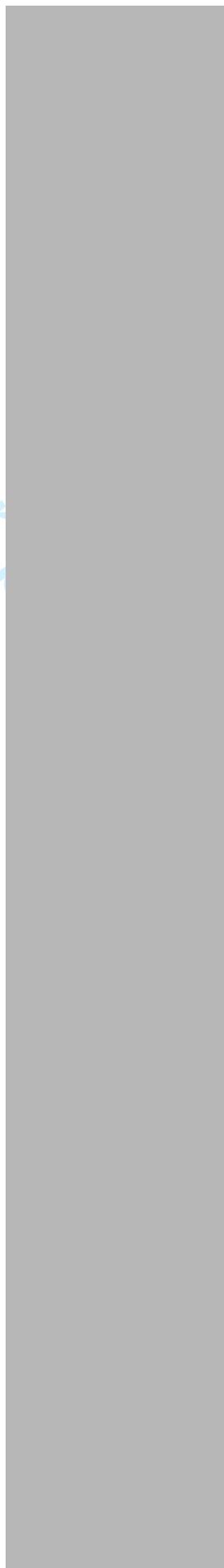
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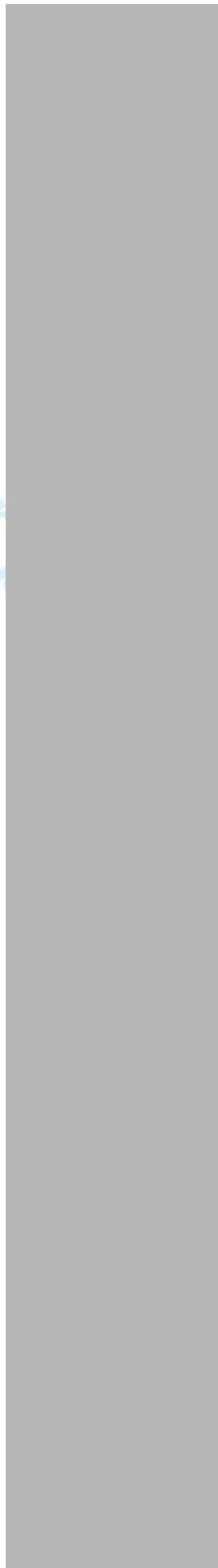
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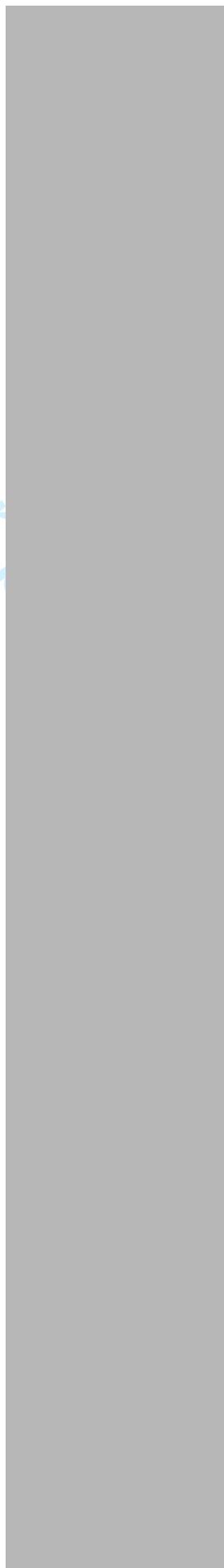
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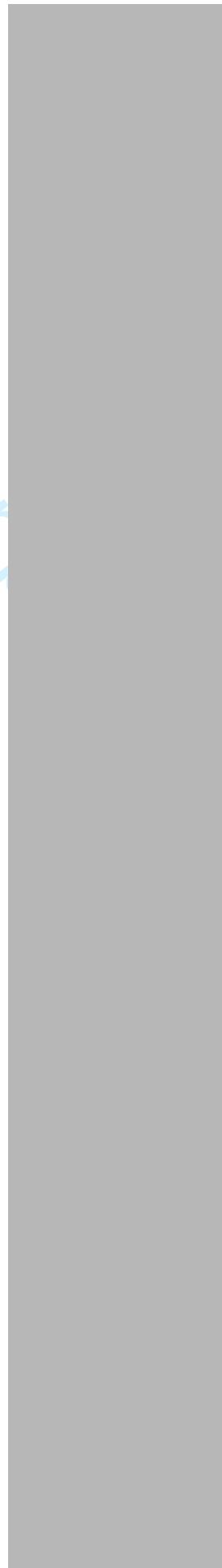
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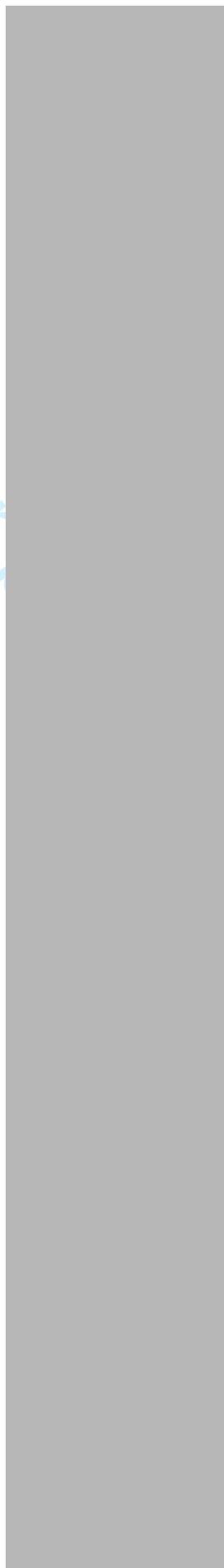
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**3 Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for**  
**4 Scoping Reviews (PRISMA-ScR) Checklist**  
 5

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
<b>TITLE</b>			
Title	1	Identify the report as a scoping review.	
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	
<b>METHODS</b>			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	



SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
<b>RESULTS</b>			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	
<b>DISCUSSION</b>			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	
Limitations	20	Discuss the limitations of the scoping review process.	
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	
<b>FUNDING</b>			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

\* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.



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## Shared symptomatology between atopic dermatitis, ADHD, and autism spectrum disorder: a protocol for a systematic scoping review

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# Shared symptomatology between atopic dermatitis, ADHD, and autism spectrum disorder: a protocol for a systematic scoping review

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Keywords: Atopic dermatitis, Attention Deficit Disorder with Hyperactivity, Autism Spectrum Disorder

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Word count: 1720

## Abstract

### Introduction

Children with atopic dermatitis (AD) are more at risk for the neurodevelopmental disorders Attention-Deficit/Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD) with parallel increases in global prevalences. Children afflicted with these conditions appear to share similar problems in sensory modulation but investigational studies on the underlying etiology are scarce. This scoping review aims to find knowledge gaps, collate hypotheses and to summarize available evidence on the shared pathophysiology of AD, ADHD, and ASD in children.

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3     37 Methods and analysis  
4     38 Our study will follow the methodological manual published by the Joanna Briggs  
5     39 Methodology for Scoping Reviews and will be reported in accordance with the Preferred  
6     40 Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews  
7     41 (PRISMA-ScR). The following electronic databases will be searched for studies focused on  
8     42 children with AD and symptoms of ADHD and/or ASD: Medline ALL via Ovid, Embase, Web of  
9     43 Science Core Collection and the Cochrane Central Register of Controlled Trials via Wiley.  
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## Article Summary

### Strengths and limitations of this study

- This scoping review marks the pioneering attempt to explore the relation between Atopic Dermatitis (AD), and symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD) in children.
- To ensure methodological rigor, we will collaborate with health sciences librarians to construct an established methodology and execute a systematic search, encompassing a wide spectrum of publication types.
- The identification and synthesis of data will be limited to published articles found on the MEDLINE, Embase, Web of Science, and Cochrane databases and snowball references.
- Relevant articles in the grey literature or written in another language than English may be missed.

## Introduction

### Background

Atopic dermatitis (AD) is a common chronic inflammatory skin disorder characterized by pruritus and recurrent eczematous skin lesions affecting up to 20% of children in high-income countries<sup>1</sup>. Besides other atopic diseases such as allergic rhinitis, food allergies, and asthma, children with AD are also more at risk for non-allergic comorbidities including infectious and systemic diseases, as well as neurodevelopmental disorders such as attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD)<sup>2-4</sup>. Current studies on pediatric AD focus on the clinical treatment of the disease but there are still gaps in knowledge regarding aforementioned neurodevelopmental comorbidities. Complex pathomechanisms, involving both genetic and environmental factors, combined with global increases in prevalence of AD, ADHD, and ASD in the past decades has led to many hypotheses on the underlying etiological associations between these conditions<sup>5-9</sup>.

ADHD is one of the most common neurodevelopmental disorders in children, characterized by symptoms of inattention, hyperactivity, and impulsivity<sup>10</sup>. Children with ADHD often have sensory processing problems, which is the inability to effectively regulate and organize a graded and adaptive response to sensory stimuli<sup>11-13</sup>. Similar to ADHD, children with AD also exhibit symptoms of altered sensory processing, expressing sensory hypo- or hyper-reactivity compared to controls<sup>14,15</sup>. Epidemiologically, individuals with AD are more at risk for ADHD with an estimated OR = 1.32 (95% CI 1.20–1.45) for all ages to OR = 1.56 (95% CI, 1.38–1.77) in children and adolescents<sup>16,17</sup>.

ASD is a heterogeneous neurodevelopmental disorder, encompassing former diagnoses such as autistic disorder, Asperger syndrome, and pervasive developmental disorder not otherwise specified<sup>18</sup>. Traits displayed by diagnosed individuals include persistent difficulties with social communication and interaction, and the presence of restricted and repetitive patterns of behavior from an early developmental period<sup>18,19</sup>. Comparable to both AD and ADHD, children with ASD have also been found to have more sensory hypo- or hyper-reactivity symptoms<sup>20</sup>. The risk for developing ASD in individuals with AD has been estimated to be OR = 1.49 (95% CI 1.20-1.83) in all ages to OR = 2.57 (95% CI 1.47-4.51) in children and adolescents<sup>17,21</sup>. Moreover, children with ASD with AD may have more pronounced ASD symptoms overall and on the social domain outcomes, relative to children with ASD without AD<sup>22</sup>.

Due to the parallel rises in the global prevalences of AD, ADHD, and ASD, an increasing interest among many research groups emerges for the potential influence of atopic diseases on the skin-brain axis within the field of neurodevelopment<sup>17,22</sup>. A positive association between pediatric AD and the neurodevelopmental disorders ADHD and ASD has consistently been found in epidemiologic studies<sup>17</sup>, but studies on the underlying pathophysiological mechanisms are scarce, leaving an ambiguous underlying interplay between dermatological, neurodevelopmental, and behavioral elements.

## 107 Objectives

108 The main goal for this proposed scoping review is to provide an extensive overview on the  
109 shared symptomatology between pediatric AD, and ADHD and ASD, and to highlight  
110 knowledge gaps regarding this matter. Extracted data will be mapped according to the  
111 following research questions:

- 112 1. What are mutual traits in AD, and ADHD and ASD?
- 113 2. What are current hypotheses for the shared symptomatology of AD, ADHD, and ASD?
- 114 3. What are gaps in the current evidence for a potential underlying shared etiology of  
115 AD, ADHD, and ASD?

## 116 Methods and analysis

### 117 Scoping review

118 Scoping reviews allow for the exploration of broad research questions with the goal of  
119 discovering key concepts, theories, and knowledge gaps in an upcoming field. The aim of this  
120 study is to provide a comprehensive overview of etiological theories on overlapping traits  
121 between pediatric AD and neurodevelopmental comorbidities ADHD and ASD, and to map,  
122 report, and discuss the concepts in current literature. Due to the broad research question  
123 and the exploratory nature of this study on an emerging field of interest with great  
124 heterogeneity in literature, we expect a scoping review to be more suitable than a  
125 systematic review<sup>23</sup>.

126 This scoping review will follow the methodological manual published by the Joanna Briggs  
127 Methodology for Scoping Reviews and will be reported in accordance with the Preferred  
128 Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews  
129 (PRISMA-ScR)<sup>24,25</sup>.

### 131 Inclusion criteria

### 132 Participants

133 Children and adolescents < 18 years old must have been diagnosed with AD by a health care  
134 provider. Additionally, subjects either must have a diagnosis or documented signs or  
135 symptoms of ADHD and/or ASD, as identified through validated psychological measuring  
136 instruments by a health care provider, parent, teacher, or as self-reported. Studies solely  
137 focusing on sleeping problems, cognitive functioning, or school performance were excluded.  
138 Peer-reviewed primary and secondary studies in children and adolescents under the age of  
139 18 that were published in English between January 1, 1946 and June 1, 2024, will be eligible  
140 for inclusion. Translational research and theoretical studies on AD and ADHD and/or ASD are  
141 eligible. Studies with a mix of both children and adults will be excluded, unless separate data  
142 for children is provided. Exclusion criteria are non-peer-reviewed publications such as  
143 textbooks, commentaries, dissertations, and conference abstracts.

### 145 Search strategy

146 The search strategy will be developed by an information specialist (CN). The following  
147 databases will be searched from inception until August 2023: Medline ALL in Ovid, Embase,

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3 148 Web of Science Core Collection, and the Cochrane Central Register of Controlled Trials via  
4 149 Wiley.  
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6 150  
7 151 An exemplary search string for Medline:  
8 152 (exp \*"Eczema"/ OR exp \*"Dermatitis, Atopic"/ OR \*"Pruritus"/ OR (eczema\* OR ((atopic\*) ADJ3  
9 (dermatit\* OR neurodermat\*)) OR eczematous\* OR prurit\* OR itch\*).ti.) **AND** ("Attention Deficit  
10 Disorder with Hyperactivity"/ OR (((attention\*) ADJ3 (deficit\*) ADJ3 (disorder\*))) OR ((attenti\* OR  
11 concentrat\*) ADJ3 (defici\*)) OR ADHD).ti.) **AND** (exp "Child"/ OR exp "Infant"/ OR "Adolescent"/ OR  
12 exp "Pediatrics"/ OR (adolescent\* OR teenager\* OR child\* OR toddler\* OR boy OR boys OR girl OR  
13 156 girls OR infant OR infants OR baby OR babies OR newborn\* OR pediatric\* OR paediatric\*).ab,ti,kf.)  
14 157  
15 158  
16 159 For the full search strategy, see Supplement S1. The search will be supplemented by forward  
17 160 and backward citation searches of all included papers.  
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## 20 162 Study selection

21  
22 163 After removal of duplicates from the initial search, two reviewers (NTN and AR) will  
23 164 independently screen all articles on title and abstract for potential eligibility using Rayyan  
24 165 Software<sup>26</sup>. Potentially eligible articles that answer any of the research questions will be read  
25 166 in full. References from included articles will be manually screened for additional eligible  
26 167 articles. Any differences and discussions will be resolved by a third author (RS) and justified  
27 168 in a group meeting with all the authors. The study selection process will adhere to  
28 169 recommendations in the PRISMA-ScR checklist<sup>24</sup>.  
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## 32 171 Data extraction

33  
34 172 Data from the final articles that will be included in this scoping review will be independently  
35 173 added into an electronic standardized template by two researchers (NTN and AR), see also  
36 174 Supplement S2. This form will include at least the following: author, year of publication, title,  
37 175 design, study aim, country and characteristics of study population such as age, sex, ethnicity,  
38 176 socioeconomic status, and use of ADHD medication. Measures of AD, ADHD, ASD diagnosis  
39 177 or symptoms (either clinically diagnosed, self-reported, retrospective or structured  
40 178 assessments and questionnaires) will be extracted. Any discrepancies or uncertainties during  
41 179 the data extraction process will be discussed and resolved by the entire study team.  
42  
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## 45 181 Presentation of results

46  
47 182 The search results and study selection process will be presented in a flow chart following the  
48 183 PRISMA statement<sup>27</sup>. Extracted data from included studies will be mapped to each of the  
49 184 relevant research questions in a tabular format and graphically if needed. A narrative  
50 185 summary will accompany the tabulated or charted results and will describe how the results  
51 186 relate to the review objectives and questions. This study will be conducted from June 2024  
52 187 and is expected to finalize in October 2024.  
53  
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## 55 188 Patient and public involvement

56  
57 189 No patients were involved in developing this protocol. No involvement from patients, nor  
58 190 from the general public will be pursued for this scoping review.  
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## 191 Ethical considerations

192 Due to the nature of this study, there are no ethical or safety considerations to be made.  
193 Approval by a local ethics committee is therefore not needed. Findings will be disseminated  
194 widely through a peer-reviewed publication and conference reports.

## 195 Acknowledgements

196 We thank information specialist Christa Niehot for her help with designing the search  
197 strategy.

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200 or not-for-profit sectors.

## 201 Conflict of interest

202 All authors have no conflicts of interest.

## 204 Author statement

205 N.T.N., A.R., and R.S. conceived the study and N.T.N and A.R. were in charge of overall  
206 direction, planning and writing this protocol. N.T.N., A.R., A.B.R., T.N. and R.S. will contribute  
207 to the analysis of the results and to the writing of the final manuscript.

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For peer review only

## 1      S1. Appendix. Full Search Strategy.

2      ADHD

10 <b>Database searched</b>	11 <b>Platform</b>	12 <b>Years of coverage</b>	13 <b>Records</b>	14 <b>Records after duplicates removed</b>
15      Medline ALL	16      Ovid	17      1946 - Present	18      44	19      44
20      Embase	21      Embase.com	22      1971 - Present	23      115	24      81
25      Web of Science Core Collection*	26      Web of Knowledge	27      1975 - Present	28      95	29      39
30      Cochrane Central Register of Controlled Trials	31      Wiley	32      1992 - Present	33      3	34      1
<b>Total</b>			<b>257</b>	<b>165</b>

\*Science Citation Index Expanded (1975-present) ; Social Sciences Citation Index (1975-present) ; Arts & Humanities Citation Index (1975-present) ; Conference Proceedings Citation Index- Science (1990-present) ; Conference Proceedings Citation Index- Social Science & Humanities (1990-present) ; Emerging Sources Citation Index (2005-present)

No other database limits were used than those specified in the search strategies

Medline

(exp \*"Eczema"/ OR exp \*"Dermatitis, Atopic"/ OR \*"Pruritus"/ OR (eczema\* OR ((atopic\*) ADJ3 (dermatit\* OR neurodermat\*)) OR eczematous\* OR prurit\* OR itch\*).ti.) **AND** ("Attention Deficit Disorder with Hyperactivity"/ OR (((attention\*) ADJ3 (deficit\*) ADJ3 (disorder\*))) OR ((attenti\* OR concentrat\*) ADJ3 (defici\*)) OR ADHD).ti.) **AND** (exp "Child"/ OR exp "Infant"/ OR "Adolescent"/ OR exp "Pediatrics"/ OR (adolescent\* OR teenager\* OR child\* OR toddler\* OR boy OR boys OR girl OR girls OR infant OR infants OR baby OR babies OR newborn\* OR pediatric\* OR paediatric\*).ab,ti,kf.)

Embase

('eczema'/exp/mj OR 'atopic dermatitis'/exp/mj OR 'pruritus'/exp/mj OR (eczema\* OR ((atopic\* NEAR/3 (dermatit\* OR neurodermat\*)) OR eczematous\* OR prurit\* OR itch\*):ti) **AND** ('attention deficit hyperactivity disorder'/exp OR (((attention\*) NEAR/3 (deficit\*) NEAR/3 (disorder\*))) OR ((attenti\* OR concentrat\*) NEAR/3 (defici\*)) OR ADHD):ab,ti,kw) **AND** ('juvenile'/exp OR 'pediatrics'/exp OR (adolescent\* OR teenager\* OR child\* OR toddler\* OR boy OR boys OR girl OR girls OR infant OR infants OR baby OR babies OR newborn\* OR pediatric\* OR paediatric\*):ab,ti,kw)

Web of Science

TI=(eczema\* OR ((atopic\*) NEAR/2 (dermatit\* OR neurodermat\*))) OR eczematous\* OR prurit\* OR itch\* **AND** TS=((attention\*) NEAR/2 (deficit\*) NEAR/2 (disorder\*)) OR ((attenti\* OR concentrat\*) NEAR/2 (defici\*)) OR ADHD) **AND** TS=(adolescent\* OR teenager\* OR child\* OR toddler\* OR boy OR boys OR girl OR girls OR infant OR infants OR baby OR babies OR newborn\* OR pediatric\* OR paediatric\*)

Cochrane CENTRAL

((eczema\* OR ((atopic\*) NEAR/3 (dermatit\* OR neurodermat\*))) OR eczematous\* OR prurit\* OR itch\*):ti) **AND** (((attention\*) NEAR/3 (deficit\*) NEAR/3 (disorder\*))) OR ((attenti\* OR concentrat\*)

38 NEAR/3 (defici\*) OR ADHD):ab,ti,kw) **AND** ((adolescent\* OR teenager\* OR child\* OR toddler\* OR  
 39 boy OR boys OR girl OR girls OR infant OR infants OR baby OR babies OR newborn\* OR pediatric\* OR  
 40 paediatric\*):ab,ti,kw)

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42 ASD

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Database searched	Platform	Years of coverage	Records	Records after duplicates removed
Medline ALL	Ovid	1946 - Present	26	26
Embase	Embase.com	1971 - Present	44	26
Web of Science Core Collection*	Web of Knowledge	1975 - Present	34	16
Cochrane Central Register of Controlled Trials	Wiley	1992 - Present	1	1
<b>Total</b>			<b>105</b>	<b>69</b>

\*Science Citation Index Expanded (1975-present) ; Social Sciences Citation Index (1975-present) ; Arts & Humanities Citation Index (1975-present) ; Conference Proceedings Citation Index- Science (1990-present) ; Conference Proceedings Citation Index- Social Science & Humanities (1990-present) ; Emerging Sources Citation Index (2005-present)

No other database limits were used than those specified in the search strategies

Medline

(exp \*"Eczema"/ OR exp \*"Dermatitis, Atopic"/ OR \*"Pruritus"/ OR (eczema\* OR ((atopic\*) ADJ3 (dermatit\* OR neurodermat\*)) OR eczematous\* OR prurit\* OR itch\*).ti.) **AND** (exp "Autism Spectrum Disorder"/ OR (autis\* OR ((development\* OR neurocognitiv\* OR neuro-cognitiv\*) ADJ2 (disorder\*))) OR Asperger\*).ab,ti,kf.) **AND** (exp "Child"/ OR exp "Infant"/ OR "Adolescent"/ OR exp "Pediatrics"/ OR (adolescent\* OR teenager\* OR child\* OR toddler\* OR boy OR boys OR girl OR girls OR infant OR infants OR baby OR babies OR newborn\* OR pediatric\* OR paediatric\*).ab,ti,kf.)

Embase

('eczema'/exp/mj OR 'atopic dermatitis'/exp/mj OR 'pruritus'/exp/mj OR (eczema\* OR ((atopic\*) NEAR/3 (dermatit\* OR neurodermat\*)) OR eczematous\* OR prurit\* OR itch\*):ti) **AND** ('autism'/exp OR (autis\* OR ((development\* OR neurocognitiv\* OR neuro-cognitiv\*) NEAR/2 (disorder\*))) OR Asperger\*):ab,ti,kw) **AND** ('juvenile'/exp OR 'pediatrics'/exp OR (adolescent\* OR teenager\* OR child\* OR toddler\* OR boy OR boys OR girl OR girls OR infant OR infants OR baby OR babies OR newborn\* OR pediatric\* OR paediatric\*):ab,ti,kw)

Web of Science

TI=(eczema\* OR ((atopic\*) NEAR/2 (dermatit\* OR neurodermat\*)) OR eczematous\* OR prurit\* OR itch\*) **AND** TS=(autis\* OR ((development\* OR neurocognitiv\* OR neuro-cognitiv\*) NEAR/2 (disorder\*))) OR Asperger\*) **AND** TS=(adolescent\* OR teenager\* OR child\* OR toddler\* OR boy OR boys OR girl OR girls OR infant OR infants OR baby OR babies OR newborn\* OR pediatric\* OR paediatric\*)

Cochrane CENTRAL

((eczema\* OR ((atopic\*) NEAR/3 (dermatit\* OR neurodermat\*)) OR eczematous\* OR prurit\* OR itch\*):ti) **AND** ((autis\* OR ((development\* OR neurocognitiv\* OR neuro NEXT/1 cognitiv\*) NEAR/2

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3     77 (disorder\*):ab,ti,kw) **AND** ((adolescent\* OR teenager\* OR child\* OR toddler\* OR boy  
4     78 OR boys OR girl OR girls OR infant OR infants OR baby OR babies OR newborn\* OR pediatric\* OR  
5     79 paediatric\*):ab,ti,kw)  
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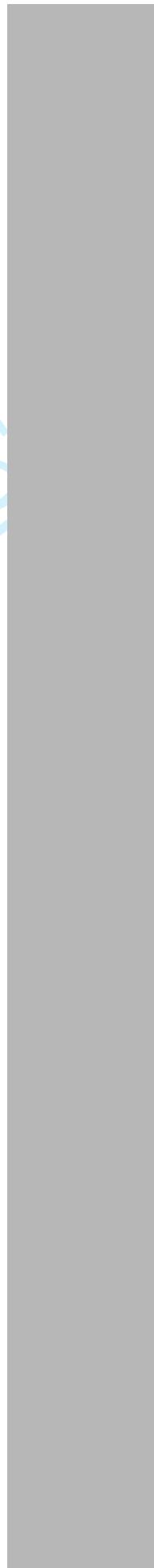
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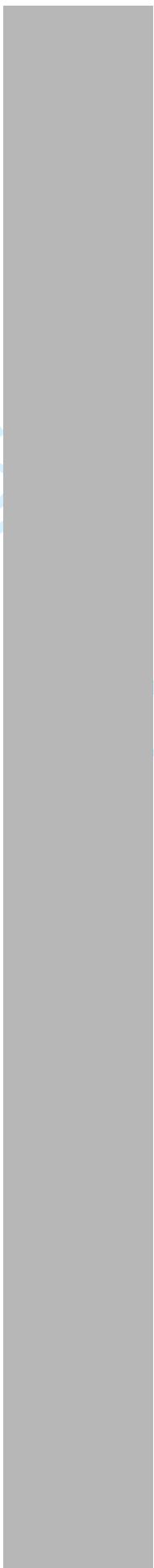
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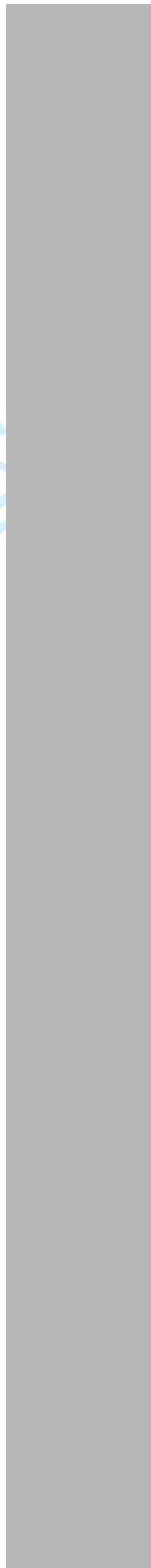
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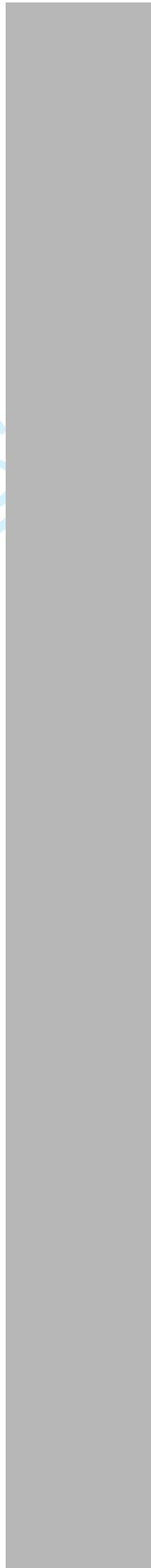
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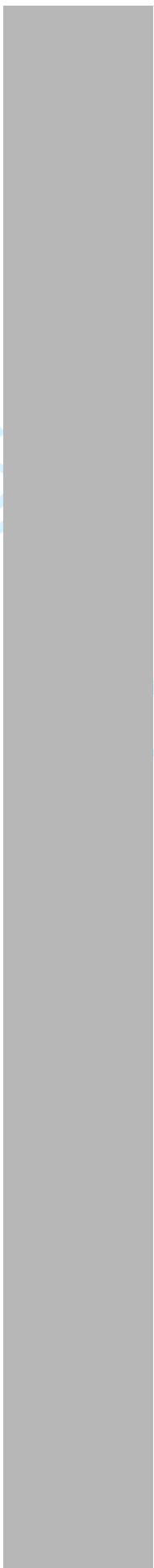
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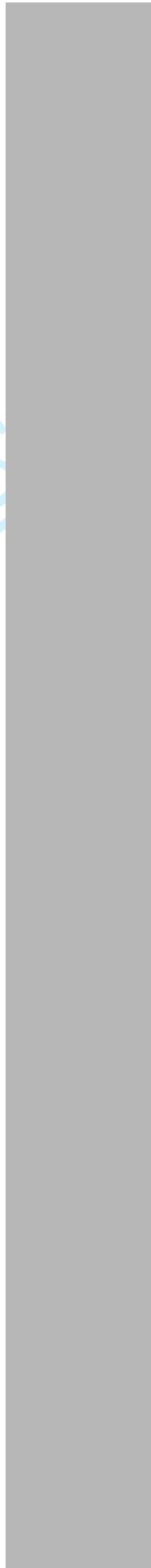
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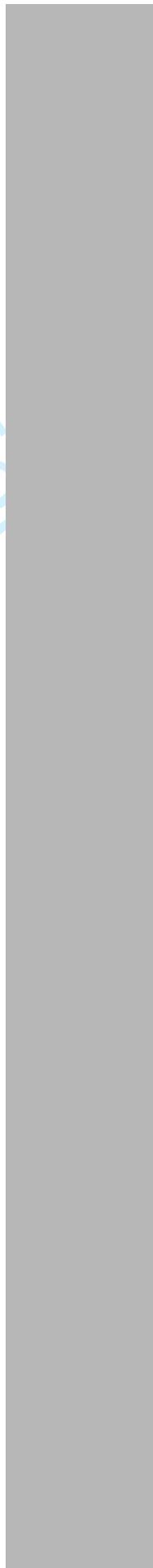


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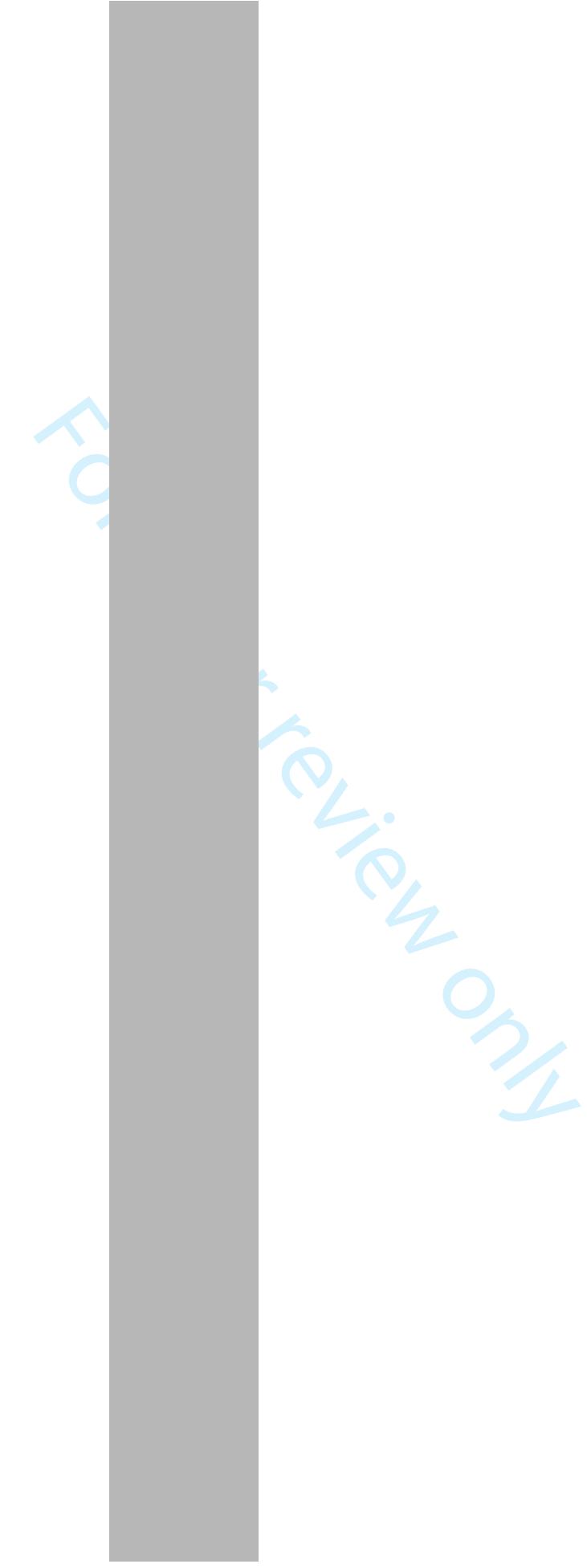
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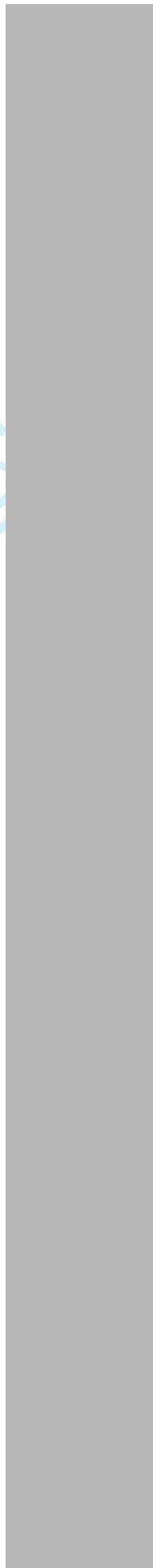


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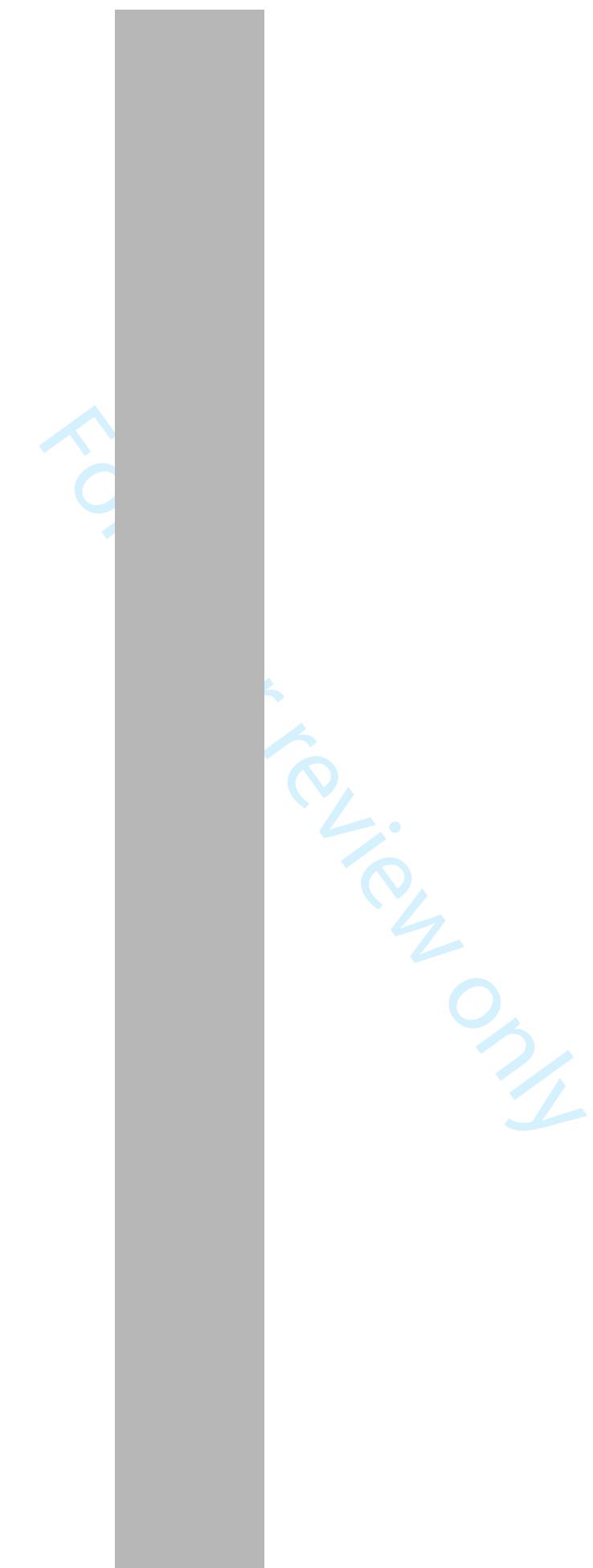
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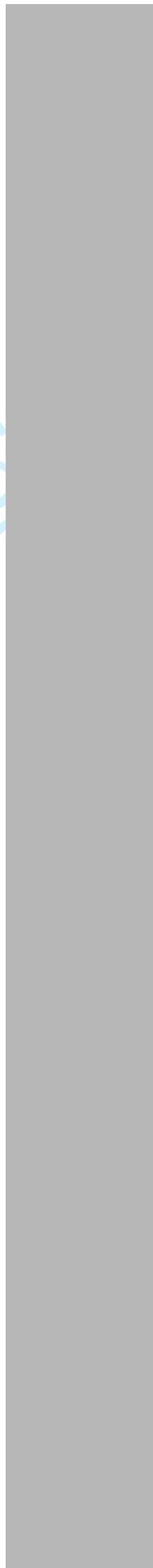
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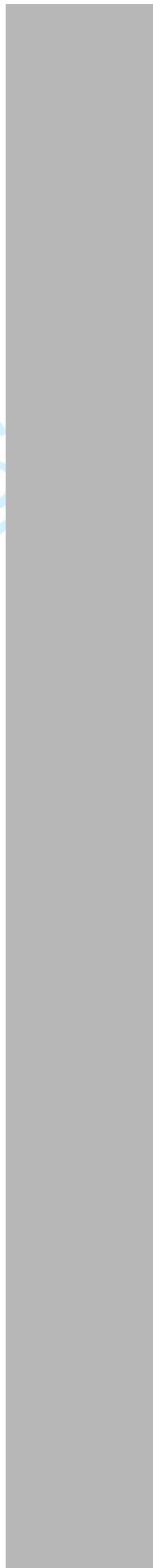
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ADHD diagnosis	ASD diagnosis	AD traits	ADHD traits	ASD traits	Data Source	Population Age
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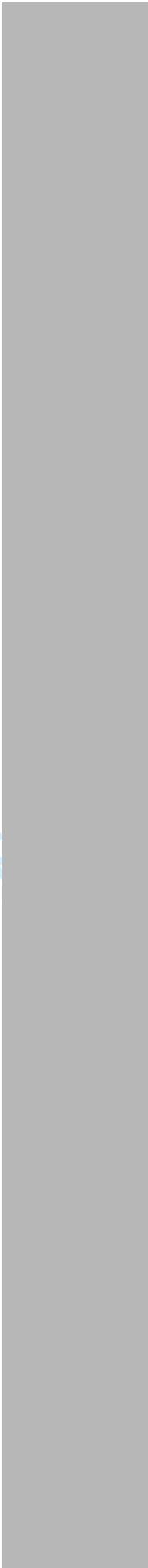
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Total population sex, male (%)	Patients with AD, male (%)	Country/Region	Socioeconomic status	Miscellaneous	Funding	Conflicts of Interest
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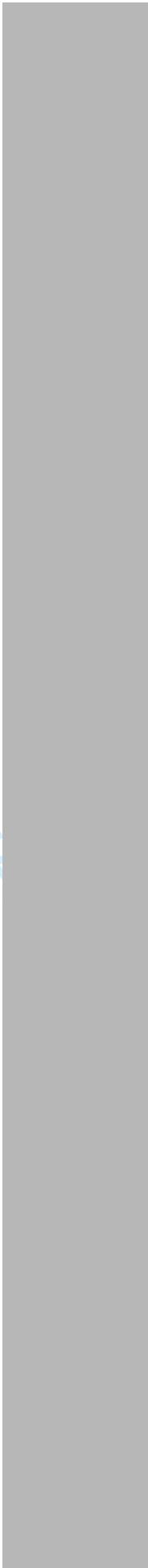
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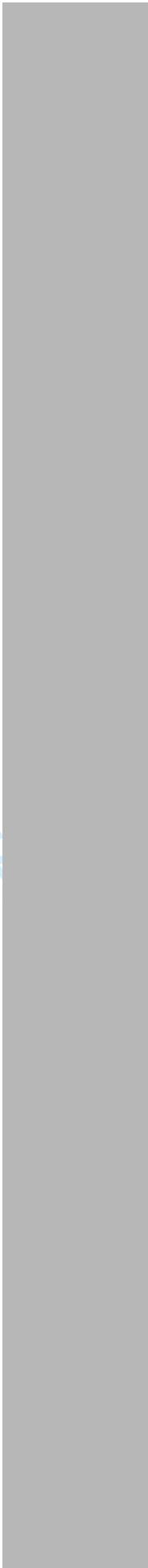
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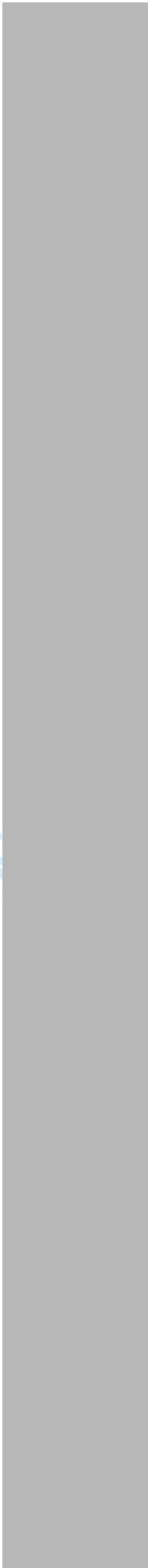
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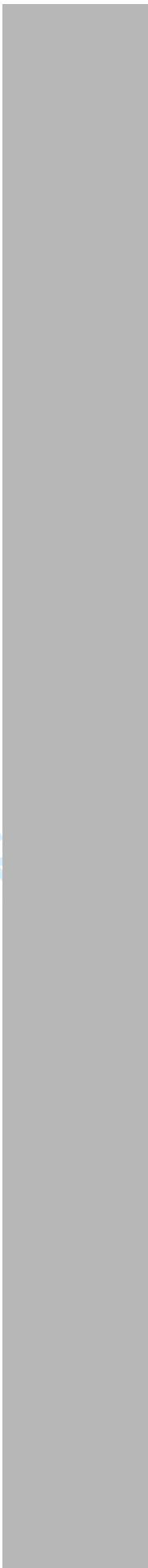
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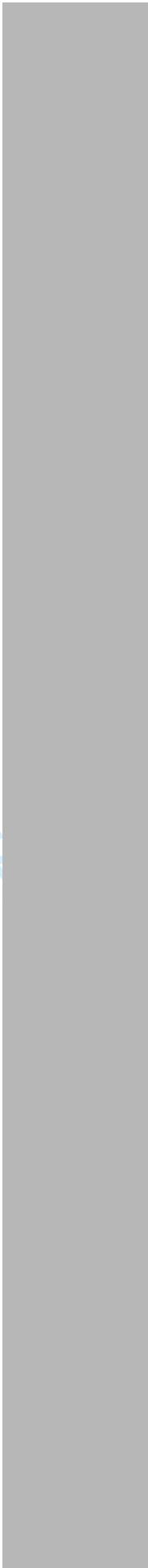
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Potentially relevant references	Question 1: Mutual traits	I: Trait	I: Outcome	I: Effects	Question 2: Hypotheses on shared symptomatology	I: Hypothesis

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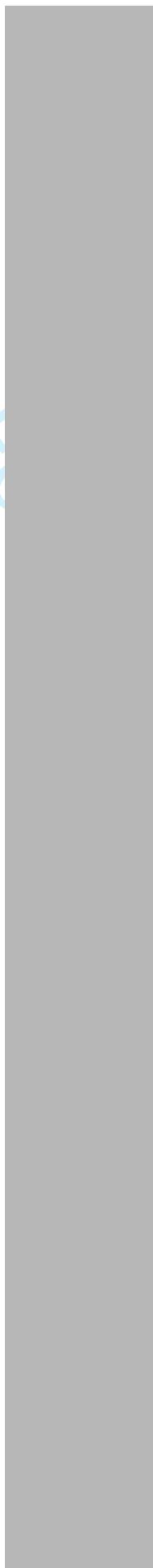
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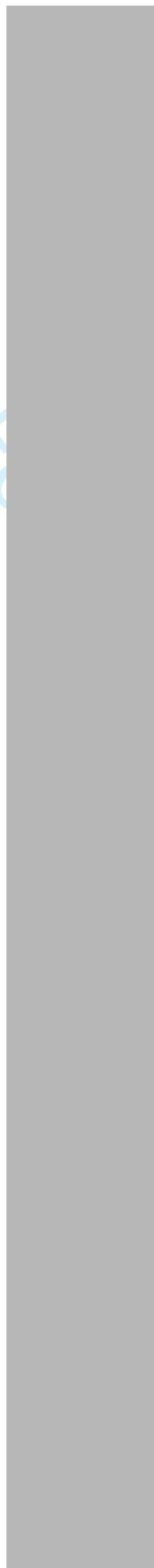
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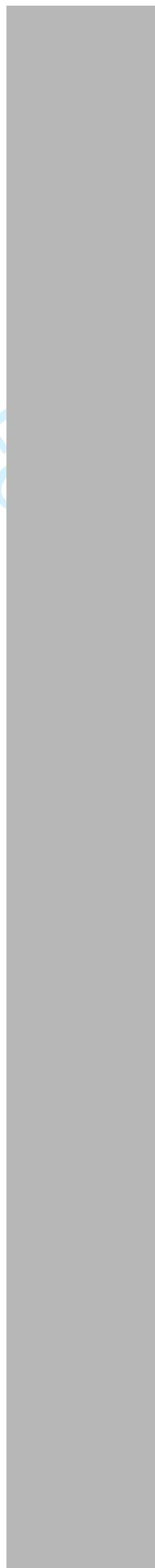
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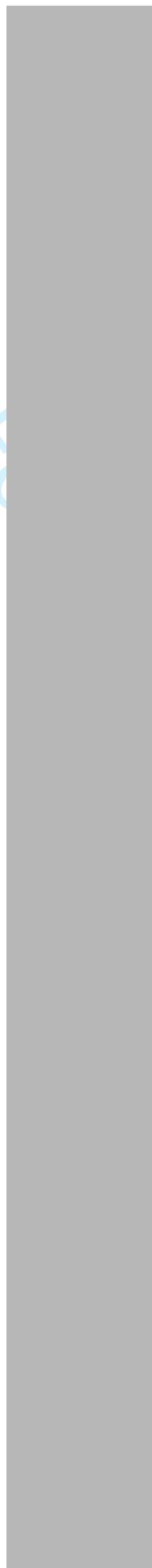
Question 3:  
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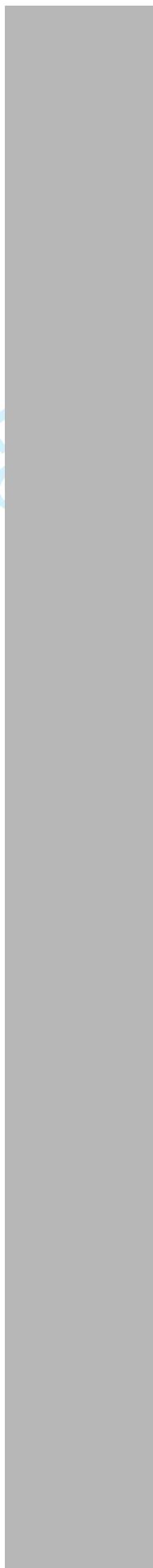
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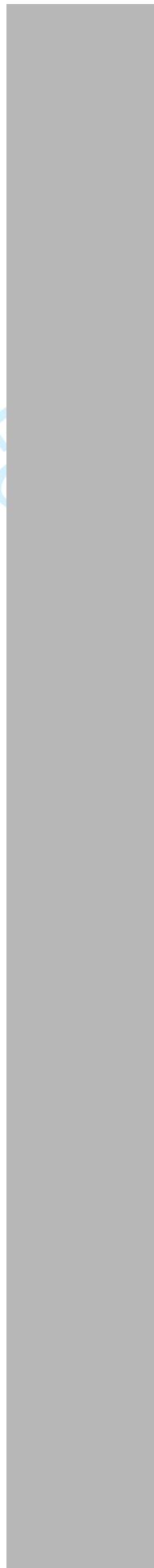


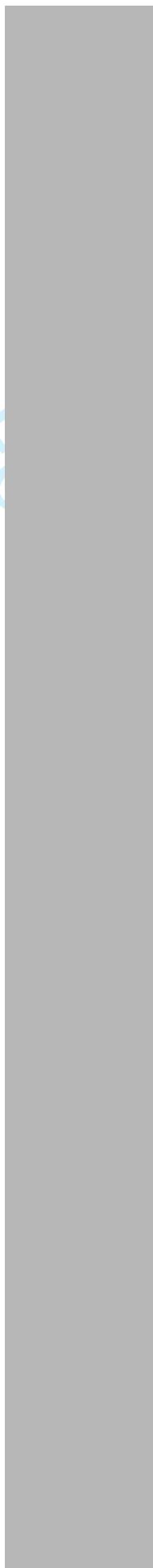


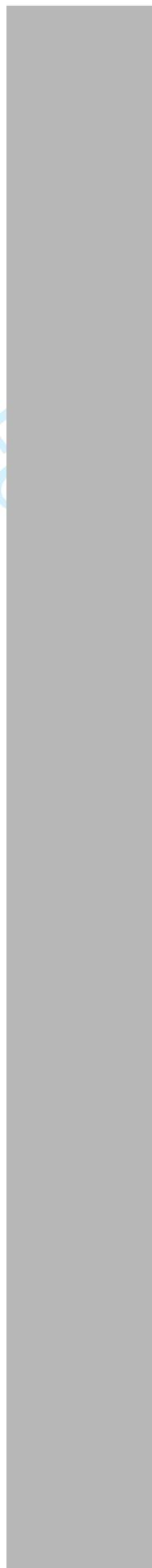


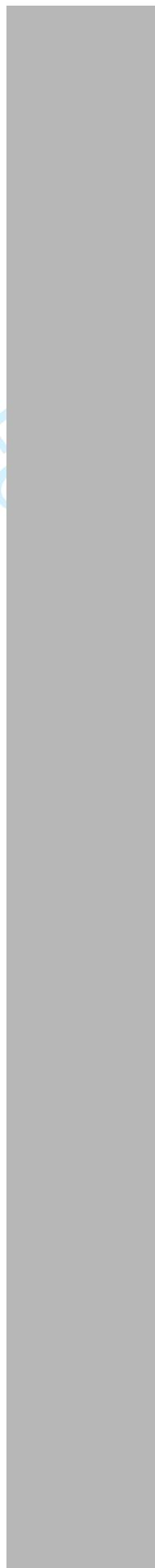


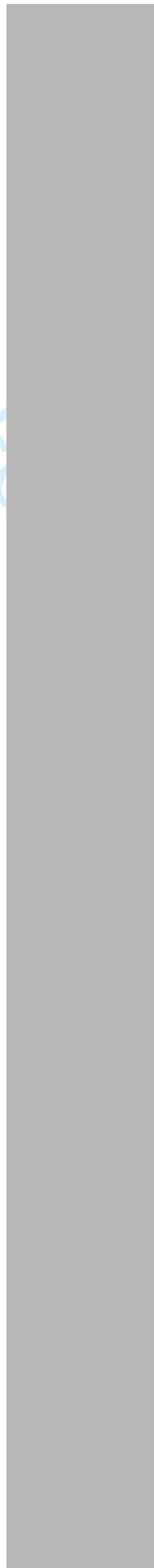


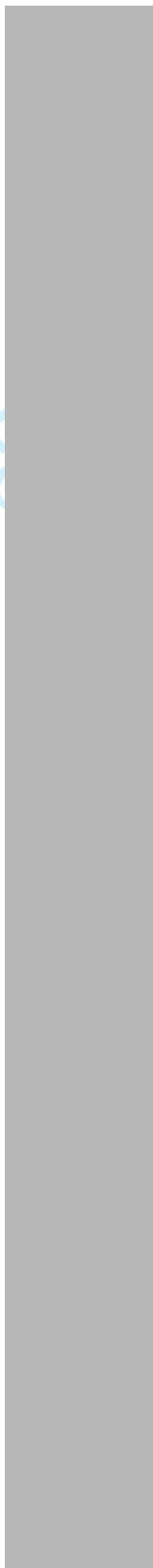


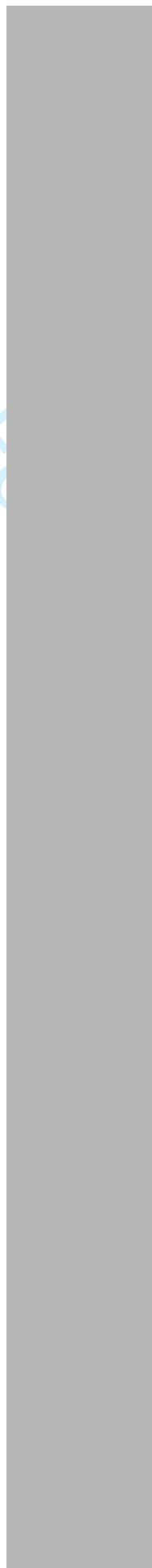


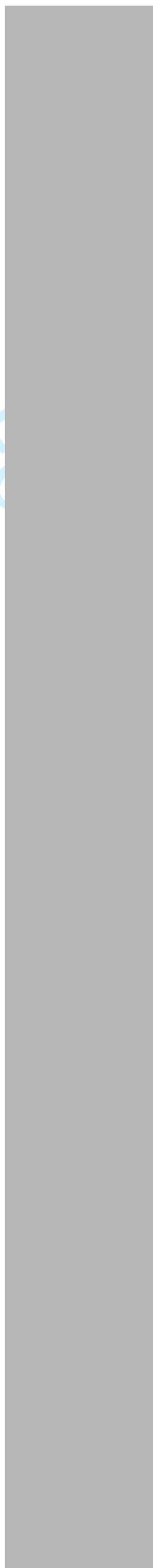


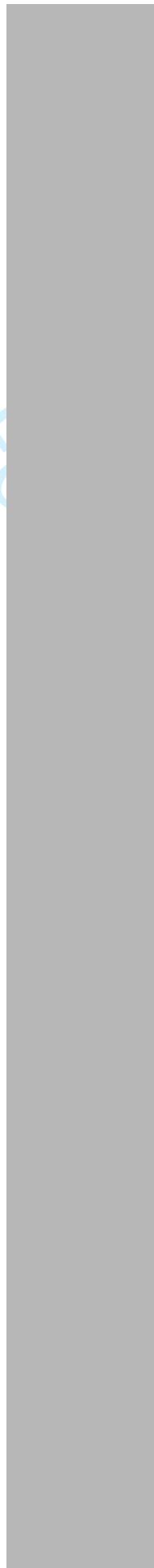


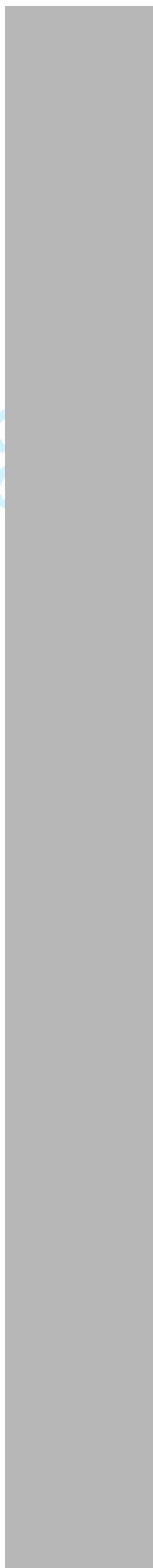


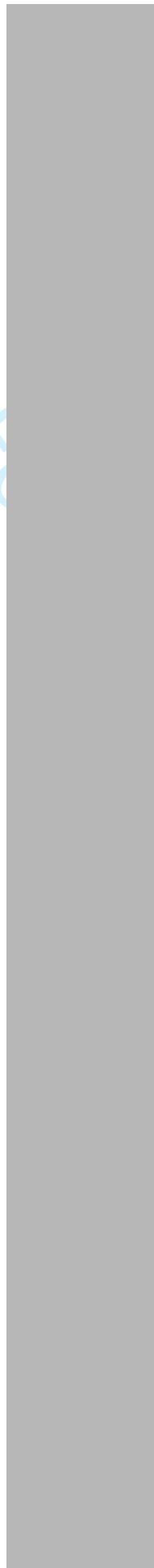












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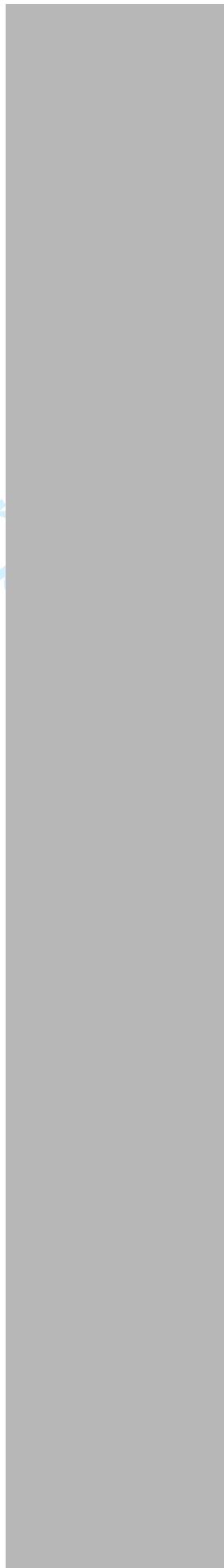
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**Limitations****Other remarks**

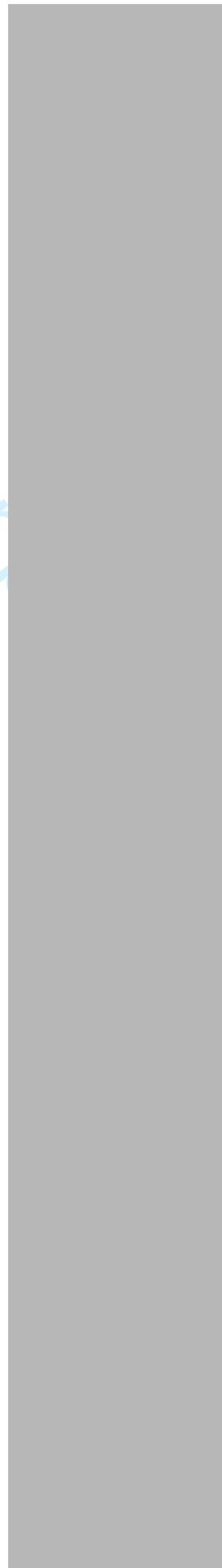
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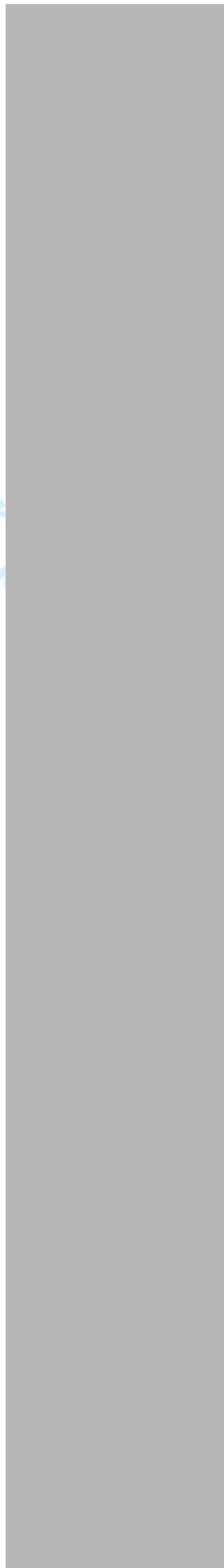
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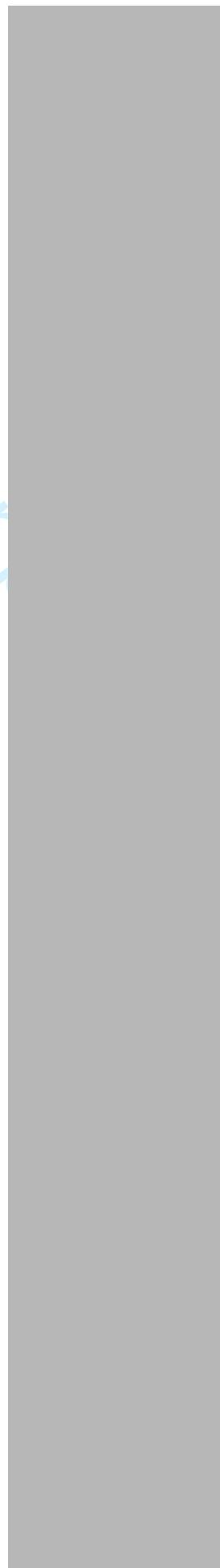
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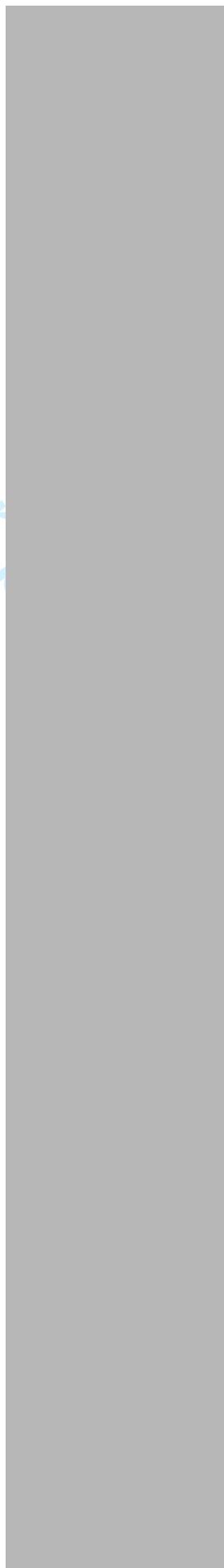
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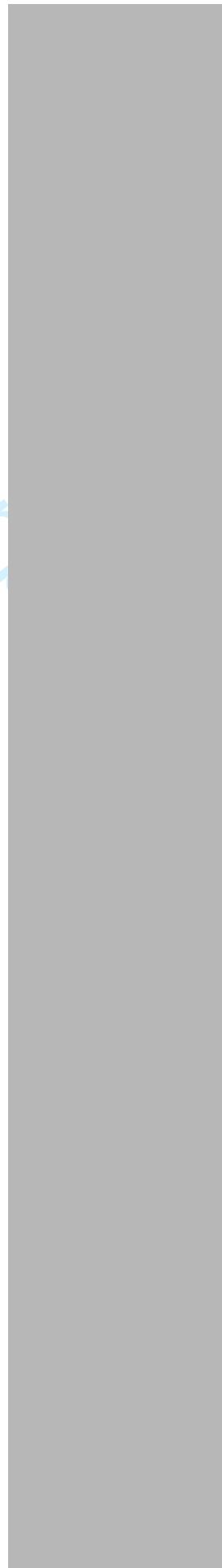
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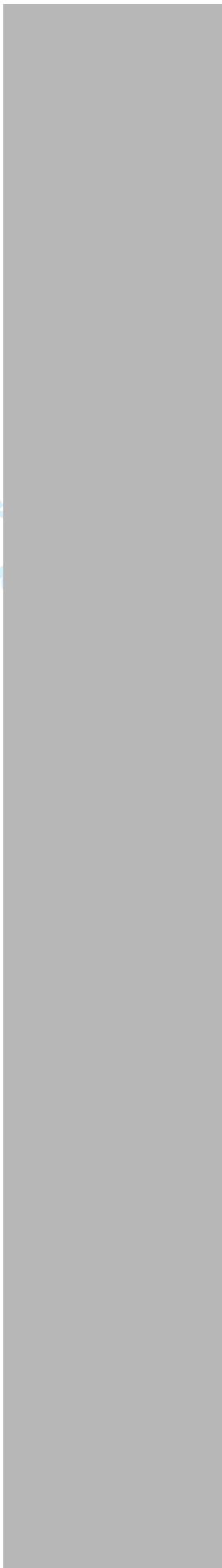
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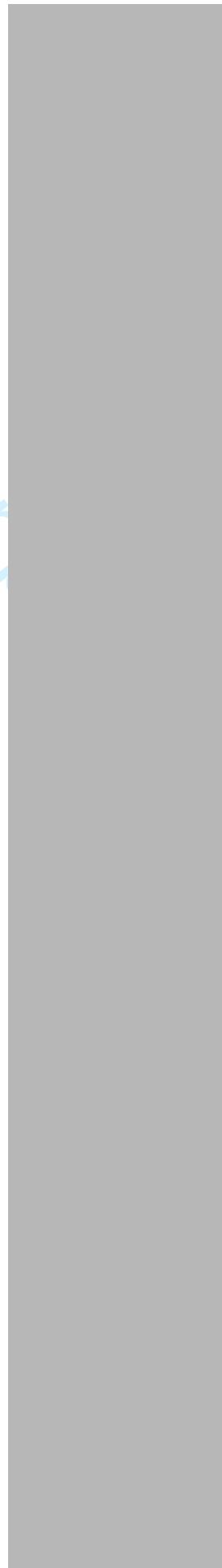
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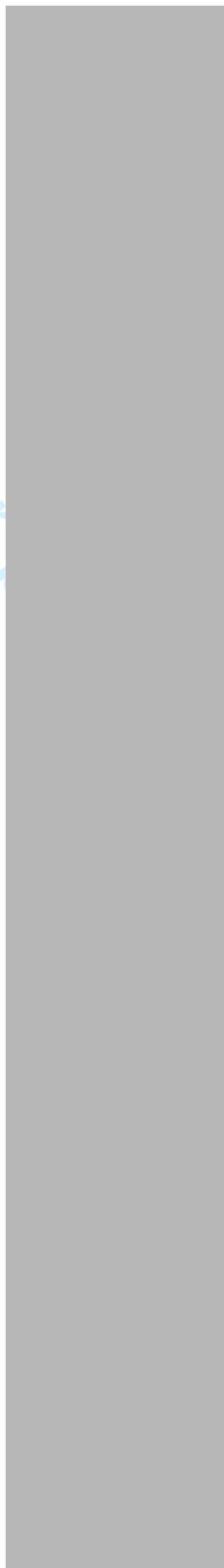
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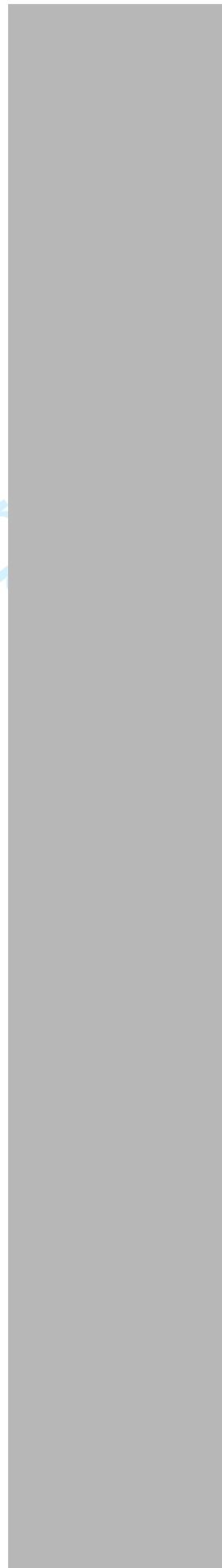
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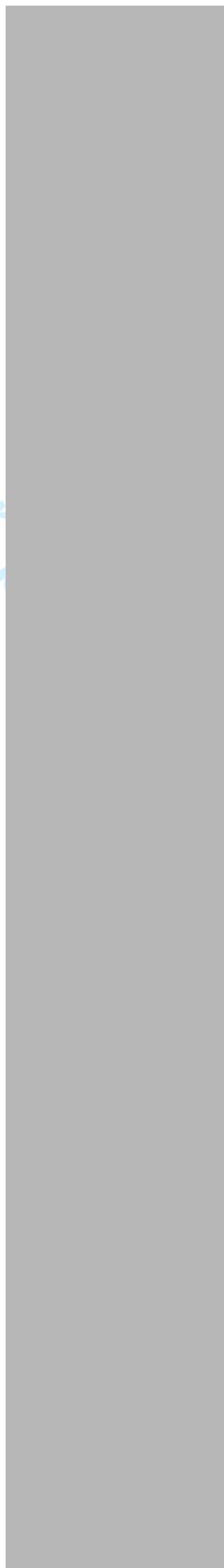
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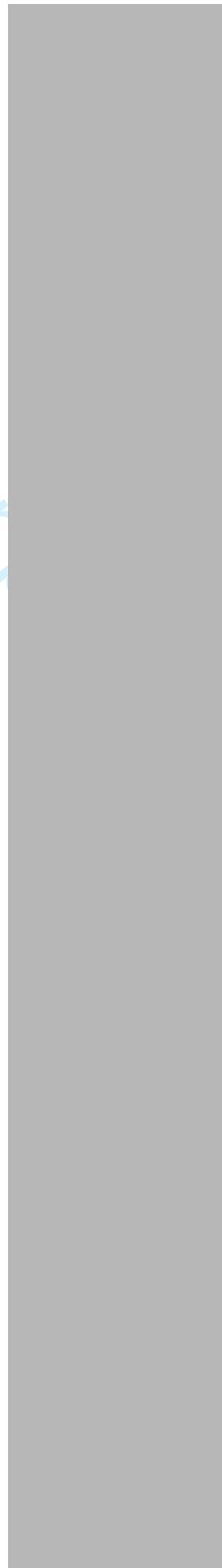
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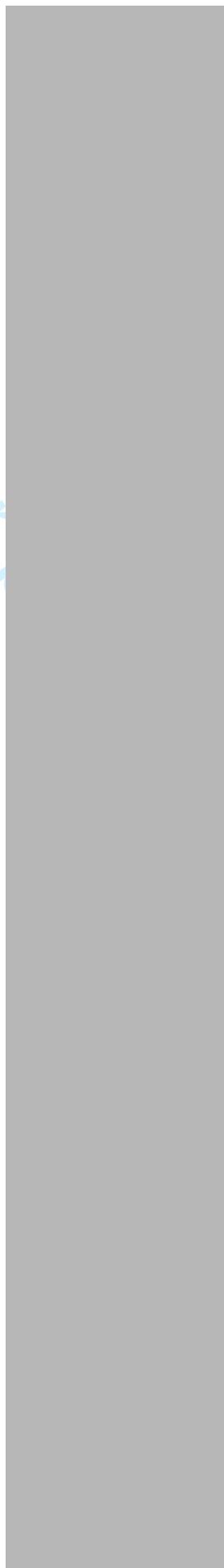
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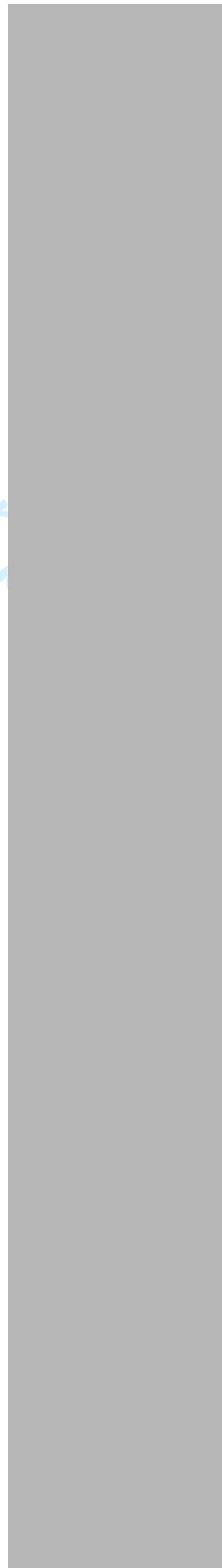
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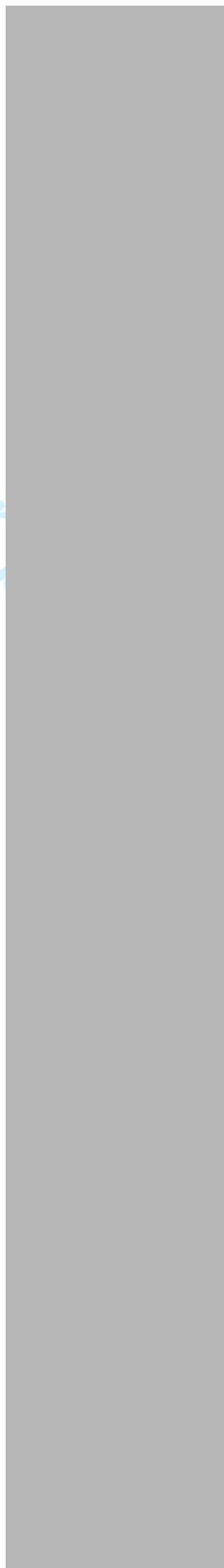
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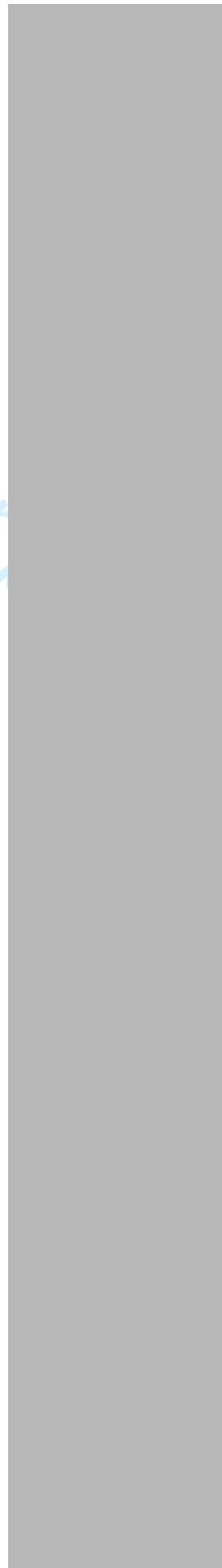
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3 **Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for**  
4 **Scoping Reviews (PRISMA-ScR) Checklist**  
5

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
<b>TITLE</b>			
Title	1	Identify the report as a scoping review.	
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	
<b>METHODS</b>			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	



SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
<b>RESULTS</b>			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	
<b>DISCUSSION</b>			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	
Limitations	20	Discuss the limitations of the scoping review process.	
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	
<b>FUNDING</b>			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

\* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.



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