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Search process

Appendix A. Search strategy

Primary search steps:

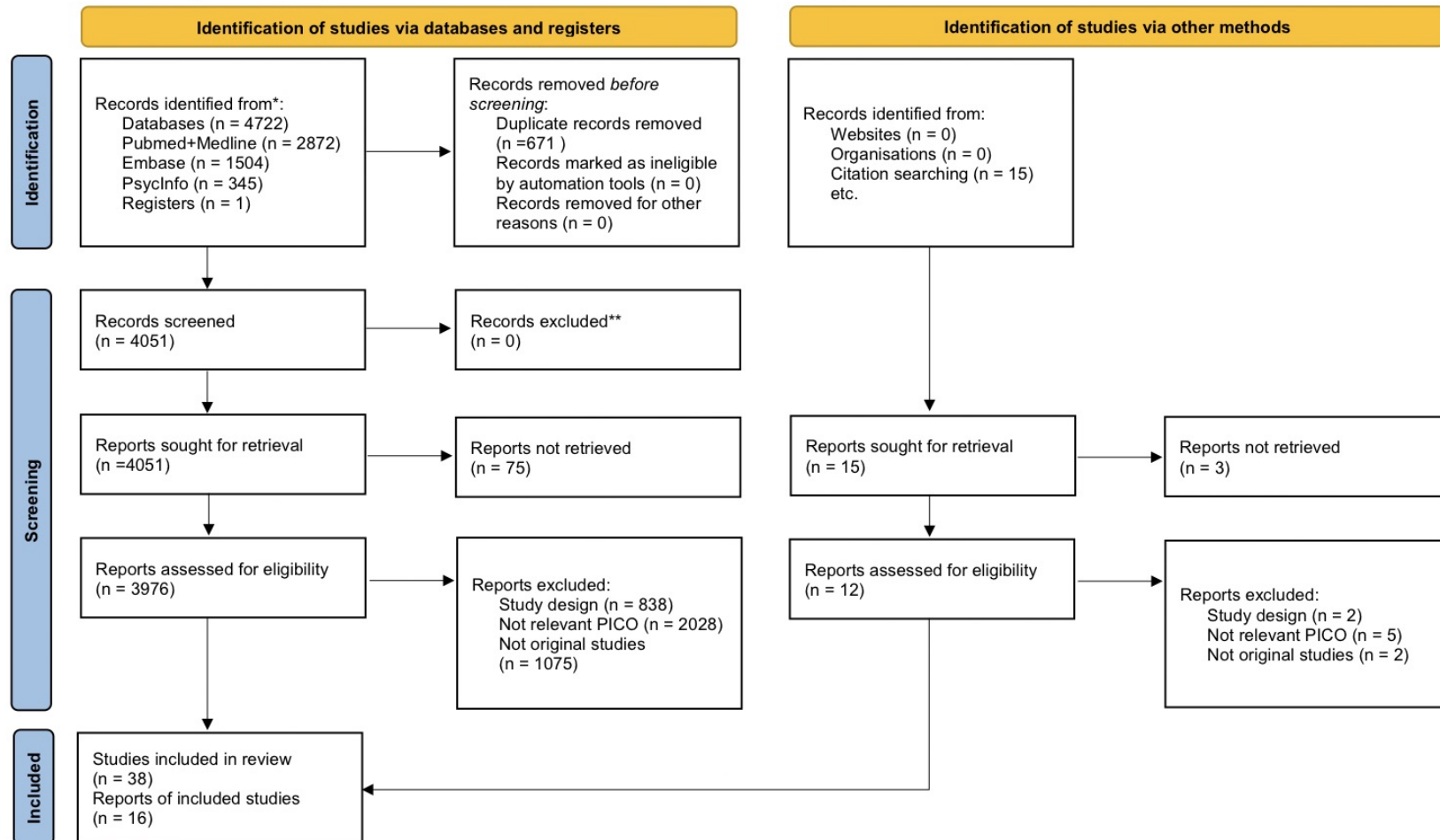
- #1. Atopic dermatitis
- #2. Atopic eczema
- #3. Allergic rhinitis
- #4. Asthma
- #5. #1, #2, #3, OR #4
- #6. ADHD
- #7. Attention-deficit/hyperactivity disorder
- #8. Hyperactivity
- #9. Inattention
- #10. Attention deficit
- #11. Impulsivity
- #12. Behavior problem
- #13. (Mental illness) OR (Mental disorder)
- #14. #6, #7, #8, #9, #10, #11, #12, #13
- #15. Preschool children
- #16. Preschooler
- #17. Children
- #18. Adolescent
- #19. Toddler
- #20. #14, #15, #16, #17, #18 OR #19
- #21. #5 AND #14 AND #20

Final syntax in PubMed (an example):

```
((Atopic dermatitis) OR (Atopic eczema) OR (Allergic rhinitis) OR (Asthma)) AND ((ADHD) OR (Attention-deficit/hyperactivity disorder) OR (Hyperactivity) OR (Inattention) OR (Attention deficit) OR (Impulsivity) OR (Behavior problem) OR ((Mental illness) OR (Mental disorder))) AND ((Preschool children) OR (Preschooler) OR (Children) OR (Adolescent) OR (Toddler))
```

Appendix B. PRISMA flowchart

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/register).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: <http://www.prisma-statement.org/>

Figure

Figure S1. Linear regression model of the Egger's test for the meta-analysis of the severity of hyperactivity/impulsivity in childhood and the presence of atopic diseases

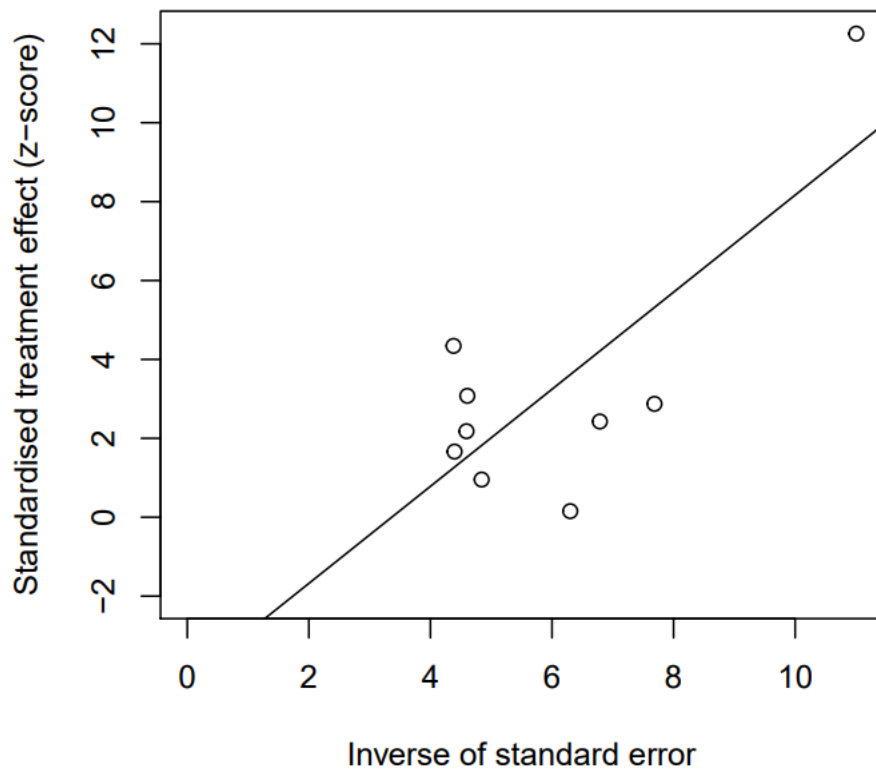


Figure S2. Linear regression model of the Egger's test for the meta-analysis of the severity of attention deficit in childhood and the presence of atopic diseases

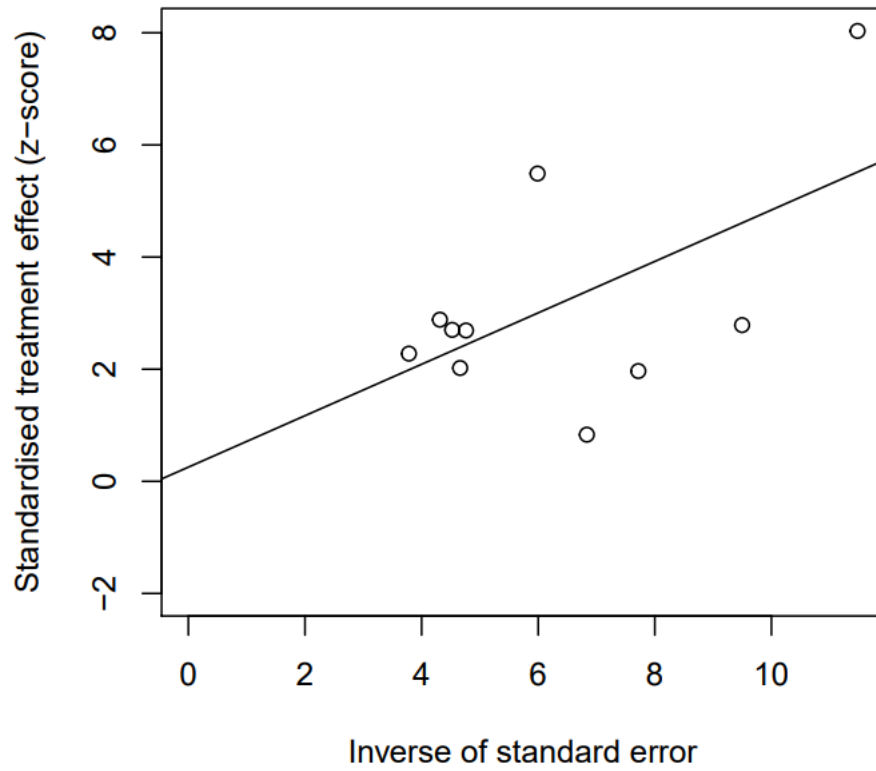


Figure S3. Mechanism underlying the interaction between atopic diseases and ADHD

1. Czarnowicki et al., 2015¹ 2. Czarnowicki et al., 2020² 3. Looman et al., 2020³ 4. Tumes et al., 2017⁴ 5. Park et al., 2018⁵ 6. Xing et al., 2016⁶ 7. Banks 2015⁷ 8. Buske-Kirschbaum et al., 2013⁸ 9. Kim et al., 2018⁹ 10. Levy et al., 2008¹⁰ 11. Puiu et al., 2018¹¹ 12. Buske-Kirschbaum et al., 2002¹² 13. Chamlin et al., 2004¹³ 14. Lin et al., 2017¹⁴ 15. McCrory et al., 2010¹⁵ 16. Nicolaidis et al., 2015¹⁶ 17. Quinlan et al., 2017¹⁷ 18. Buske-Kirschbaum et al., 2019¹⁸ 19. Lau et al., 2012¹⁹ 20. Tsai 2006²⁰ 21. Wamboldt et al., 2000²¹ 22. Cowell et al., 2019²² 23. Van den Bergh et al., 2017²³

Abbreviation: ADHD, Attention-deficit/hyperactivity disorder; BBB, blood–brain barrier; PFC, prefrontal cortex; ACC, anterior cingulate cortex; HPA axis, hypothalamic–pituitary–adrenal axis; SAM, sympathomedullary pathway

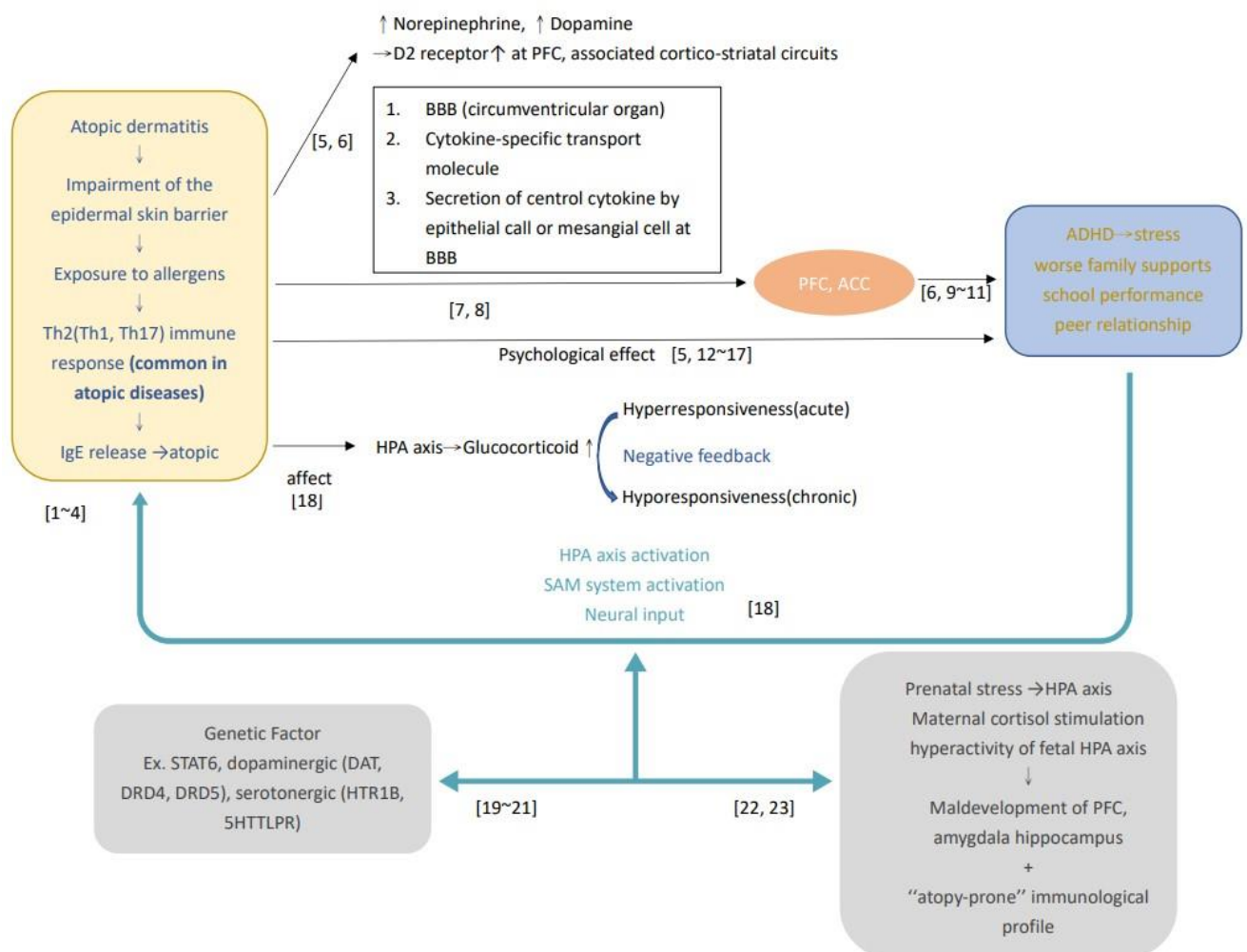
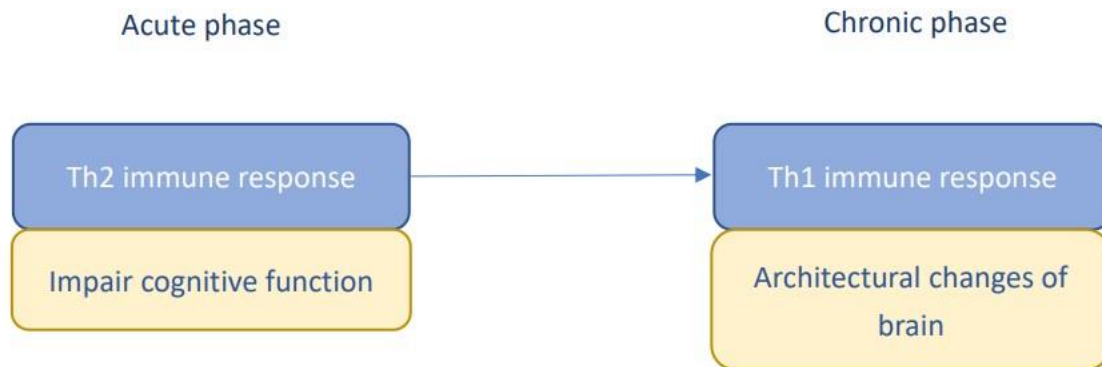


Figure S4. Comparison of immune responses and related effects between acute and chronic phases of atopic diseases



Table

Table S1. Detailed information of studies included in the qualitative analysis

	Study
Outcome type	<p>OR/ Hazard ratios: (Goodwin et al., 2013, Lin et al., 2016, Strom et al., 2016)²⁴⁻²⁶; Fuhrmann et al., 2020²⁷; Huang et al., 2020²⁸; Jackson-Cowan et al., 2020²⁹; Sollander et al., 2020³⁰; Wan et al., 2020³¹; Chai et al., 2021³²; Hou et al., 2021³³; Vittrup et al., 2021³⁴</p> <p>Continuous data for HI, IN, or total ADHD symptoms: (Yuksel et al., 2008, Camfferman et al., 2010, Chang et al., 2013, Kim et al., 2014, Lee et al., 2014, Yang et al., 2014, Catal et al., 2016, Hammer-Helmich et al., 2016, Yang et al., 2016, Feng et al., 2017, Kuniyoshi et al., 2018, Schmitt et al., 2018, L et al., 2019, Feng et al., 2020, Guo et al., 2020, Kuo et al., 2020)³⁵⁻⁵⁰; Minatoya et al., 2020⁵¹, Montalbano et al., 2020⁵²; Berzosa-Grande et al., 2021⁵³; Galéra et al., 2021⁵⁴; Özyurt et al., 2021⁵⁵; Rajhans et al., 2021⁵⁶; Yüksel et al., 2021⁵⁷</p> <p>Prevalence/percentage: (Abd El-Hamid et al., 2018, Tajdini et al., 2019, Zhou et al., 2019)⁵⁸⁻⁶⁰</p> <p>Other: Keller et al., 2021⁶¹</p>
Exposed	<p>Atopy in patients with ADHD: (Kim et al., 2014, Abd El-Hamid et al., 2018)^{49,58}; Yüksel et al., 2021⁵⁷</p> <p>Pure atopy and healthy controls: (Yuksel et al., 2008, Yang et al., 2014, Schmitt et al., 2018, Feng et al., 2020)^{38,42,45,46}</p> <p>Atopy and nonatopic groups: (Camfferman et al., 2010, Chang et al., 2013, Goodwin et al., 2013, Lee et al., 2014, Catal et al., 2016, Hammer-Helmich et al., 2016, Lin et al., 2016, Strom et al., 2016, Kuniyoshi et al., 2018, L et al., 2019, Zhou et al., 2019, Guo et al., 2020, Fuhrmann et al., 2020²⁷, Kuo et al., 2020)^{24-26,35,36,39,40,43,44,47,48,50,60}; Huang et al., 2020²⁸; Jackson-Cowan et al., 2020²⁹; Minatoya et al., 2020⁵¹; Sollander et al., 2020³⁰; Wan et al., 2020³¹; Berzosa-Grande et al., 2021⁵³; Galéra et al., 2021⁵⁴; Hou et al., 2021³³</p> <p>Atopy patients and healthy controls: (Yang et al., 2016, Feng et al., 2017, Tajdini et al., 2019)^{37,41,59}; Chai et al., 2021³²; Keller et al., 2021⁶¹; Özyurt et al., 2021⁵⁵; Rajhans et al., 2021⁵⁶</p> <p>ADHD (symptoms) in patients with atopy: Montalbano et al., 2020⁵²; Vittrup et al., 2021³⁴</p>
Other variables	<p>Description for potential confounding factors</p> <p>Age and sex: (Yang et al., 2014, Yang et al., 2016, Feng et al., 2017, Feng et al., 2020)^{37,38,41,42}; Fuhrmann et al., 2020²⁷; Jackson-Cowan et al., 2020²⁹; Sollander et al., 2020³⁰; Minatoya et al., 2020⁵¹; Montalbano et al., 2020⁵²; Wan et al., 2020³¹; Berzosa-Grande et al.,</p>

2021⁵³; Galéra et al., 2021⁵⁴; Hou et al., 2021³³; Özyurt et al., 2021⁵⁵; Rajhans et al., 2021⁵⁶; Vittrup et al., 2021³⁴; Yüksel et al., 2021⁵⁷

Birth Hx: Feng et al., 2020⁴²; Galéra et al., 2021⁵⁴; Yüksel et al., 2021⁵⁷

Parents' stress or mental health: (Goodwin et al., 2013, Lee et al., 2014, Schmitt et al., 2018)^{24,36,45}; Kuo et al., 2020⁴⁴; Montalbano et al., 2020⁵²; Berzosa-Grande et al., 2021⁵³; Galéra et al., 2021⁵⁴

Primary caregiver's education: (Goodwin et al., 2013, Feng et al., 2020)^{24,42}; Sollander et al., 2020³⁰; Wan et al., 2020³¹; Galéra et al., 2021⁵⁴; Hou et al., 2021³³; Özyurt et al., 2021⁵⁵

Family income: Jackson-Cowan et al., 2020²⁹; Wan et al., 2020³¹; Galéra et al., 2021⁵⁴; Hou et al., 2021³³; Vittrup et al., 2021³⁴

Environment (tobacco): (Goodwin et al., 2013, Feng et al., 2017, Tajdini et al., 2019)^{24,41,59}

Sleep disturbance: (Camfferman et al., 2010, Lin et al., 2016, Strom et al., 2016, Schmitt et al., 2018, Feng et al., 2020)^{25,26,40,42,45}

Other physical conditions: Strom et al., 2016²⁶; Wan et al., 2020³¹; Galéra et al., 2021⁵⁴; Hou et al., 2021³³; Vittrup et al., 2021³⁴; Yüksel et al., 2021⁵⁷

Mental health: Jackson-Cowan et al., 2020²⁹; Galéra et al., 2021⁵⁴

Assessment for atopic diseases

Eosinophils in peripheral blood: (Chang et al., 2013)⁴⁷

IgE and allergens: (Guo et al., 2020)⁴⁸

Symptoms: (Yang et al., 2014, Yang et al., 2016, Feng et al., 2017, Schmitt et al., 2018, Feng et al., 2020)^{37,38,41,42,45}; Rajhans et al., 2021⁵⁶

Persistent atopic diseases: (Yang et al., 2014, Yang et al., 2016, Feng et al., 2017)^{37,38,41}

Severity of atopic diseases: (Yang et al., 2014, Yang et al., 2016, Tajdini et al., 2019, Zhou et al., 2019, Feng et al., 2020)^{37,38,42,59,60}; Minatoya et al., 2020⁵¹; Montalbano et al., 2020⁵²; Berzosa-Grande et al., 2021⁵³

Atopic disease onset: (Schmitt et al., 2018, Tajdini et al., 2019, Zhou et al., 2019, Feng et al., 2020)^{42,45,59,60}; Fuhrmann et al., 2020²⁷; Rajhans et al., 2021⁵⁶

Duration: (Zhou et al., 2019, Feng et al., 2020)^{42,60}; Rajhans et al., 2021⁵⁶

Positive allergens: Feng et al., 2017⁴¹; Berzosa-Grande et al., 2021⁵³

Treatments: (Schmitt et al., 2018, Tajdini et al., 2019, Zhou et al., 2019, Feng et al., 2020)^{42,45,59,60}

Family history of atopic diseases: (Yang et al., 2014, Yang et al., 2016, Tajdini et al., 2019, Zhou et al., 2019)^{37,38,59,60}; Minatoya et al., 2020⁵¹

Multiple atopic diseases: (Yang et al., 2014, Yang et al., 2016, Feng et al., 2017, Schmitt et al., 2018, Tajdini et al., 2019)^{37,38,41,45,59}; Jackson-Cowan et al., 2020²⁹; Sollander et al., 2020³⁰; Berzosa-Grande et al., 2021⁵³; Vittrup et al., 2021³⁴

Other assessment for ADHD

Percentage of abnormal scores: (Hammer-Helmich et al., 2016, Feng et al., 2020)^{35,42}

	<p>Quality of life: (Feng et al., 2017, Schmitt et al., 2018, Feng et al., 2020)^{41,42,45}</p> <p>CPT/CAT: (Kim et al., 2014, Yang et al., 2014, Yang et al., 2016)^{37,38,49}</p>
Subgroup	<p>Treatments: (Chang et al., 2013, Kim et al., 2014, Yang et al., 2016)^{37,47,49}, Fuhrmann et al., 2020²⁷</p> <p>Age: (Strom et al., 2016, Kuniyoshi et al., 2018)^{26,43}; Berzosa-Grande et al., 2021⁵³; Hou et al., 2021³³</p> <p>Sex: Jackson-Cowan et al., 2020²⁹</p> <p>Severity of atopic diseases: (Chang et al., 2013, Goodwin et al., 2013, Strom et al., 2016, Kuniyoshi et al., 2018)^{24,26,43,47}; Montalbano et al., 2020⁵²</p> <p>Pure atopy (without ADHD), total atopy, pure ADHD (without atopy): Yang et al., 2014³⁸; Galéra et al., 2021⁵⁴</p> <p>Primary caregiver's education: Hammer-Helmich et al., 2016³⁵, Sollander et al., 2020³⁰</p> <p>Multiple atopic diseases: Hammer-Heimich et al., 2016³⁵; Kuo et al., 2020⁴⁴, Strom et al., 2016²⁶, Sollander et al., 2020³⁰</p> <p>Atopy with or without ADHD symptoms: Feng et al., 2020⁴²</p> <p>ADHD type: (Lin et al., 2016, Zhou et al., 2019)^{25,60}</p> <p>Comorbidity of ADHD: (Yang et al., 2014, Yang et al., 2016)^{37,38}</p>

Abbreviations: OR, odds ratio; ADHD, attention-deficit/hyperactivity disorder; CPT/CAT, (Continuous Performance Test/Comprehensive Attention Test)

Table S2. Detailed information on the risk of bias assessment

Risk of bias assessment

The quality of included studies was determined using the Joanna Briggs Institute's critical appraisal checklist for systematic reviews⁶². We used this checklist to evaluate case-control and cross-sectional study designs. The checklist for cross-sectional studies consisted of 10 questions assessing the following factors: (1) use of clearly defined inclusion criteria, (2) detailed description of study objects and settings, (3) exposure measurement, (4) inclusion of objective and standard criteria for the measurement of the condition (5) strategies adopted to identify confounding factors (questions 5 and 6 were related to this factor), (6) strategies adopted to deal with confounding factors (7) outcome measurement, and (8) use of appropriate statistical analysis methods. Each question had the following response options: yes, no, unclear, and not applicable. The overall appraisal of whether to include, exclude, or seek further information on studies according to the results of questions mentioned above.

Risk of bias

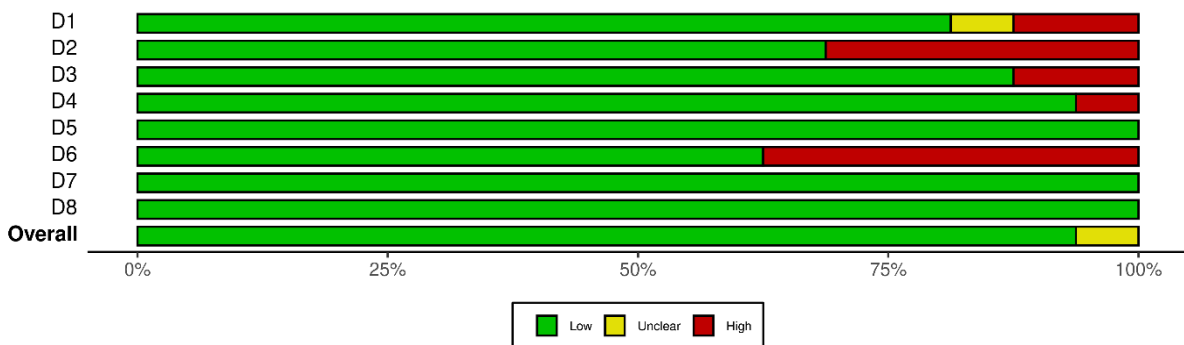
Table mentioned below lists the results of the overall risk of bias⁶³. The complete form used to examine the risk of bias is shown below. The studies were all cross-sectional studies. In these studies, the risk of bias was mainly related to not providing a detailed description of study participants, and the settings and strategies adopted to identify and manage confounding factors. One study⁴⁴ was determined was given the note "seek further information" because it did not provide detailed information regarding the inclusion of both study participants and settings and strategies adopted to identify and manage confounding factors. None of the studies had an overall appraisal category of "exclusion." Most studies provided detailed information regarding strategies adopted to identify and manage confounding factors.

Study	Risk of bias								Overall
	D1	D2	D3	D4	D5	D6	D7	D8	
Yuksel et al., 2008	+	X	+	+	+	X	+	+	+
Camfferman et al., 2010	+	+	+	+	+	+	+	+	+
Lee et al., 2014	+	X	+	+	+	+	+	+	+
Yang et al., 2014	+	X	+	+	+	+	+	+	+
Catal et al., 2016	+	+	+	+	+	X	+	+	+
Yang et al., 2016	+	+	+	+	+	+	+	+	+
Hammer-Heimich et al., 2016	+	+	X	+	+	+	+	+	+
Feng et al., 2017	+	+	+	+	+	+	+	+	+
Schmitt et al., 2017	+	+	+	+	+	+	+	+	+
Kuniyoshi et al., 2018	-	+	+	X	+	+	+	+	+
Kuo et al., 2020	X	X	+	+	+	X	+	+	-
Feng et al., 2020	+	+	+	+	+	+	+	+	+
Minatoya et al., 2020	X	+	+	+	+	+	+	+	+
Berzosa-Grande et al., 2021	+	+	X	+	+	X	+	+	+
Özyurt et al., 2021	+	+	+	+	+	X	+	+	+
Rajhans et al., 2021	+	X	+	+	+	X	+	+	+

Judgement
 X No
 - Unclear
 + Yes
 NA

Overall
 - Seek further info
 + included

D1: Were the criteria for inclusion in the sample clearly defined?
 D2: Were the study subjects and the setting described in detail?
 D3: Was the exposure measured in a valid and reliable way?
 D4: Were objective, standard criteria used for measurement of the condition?
 D5: Were confounding factors identified?
 D6: Were strategies to deal with confounding factors stated?
 D7: Were the outcomes measured in a valid and reliable way?
 D8: Was appropriate statistical analysis used?



Appendix C. References to articles solely

included in qualitative synthesis

- Abd El-Hamid, Z. B., M. M. Refaat, H. H. El-Shahawy, A. M. Eissa, M. M. El-Sheikh, A. S. Abdel-Rehim, S. A. Elgaaly, M. H. Abd El-Moneam, N. A. Mohamed and O. M. Abdel Latif , 2018. Impact of allergy on children with attention deficit hyperactivity disorder. *Eur Ann Allergy Clin Immunol* 50(6), 262-267. <https://doi.org/10.23822/EurAnnACI.1764-1489.72>
- Berzosa-Grande, M. P., González-Fraile, E., Sánchez-López, R., Soria-Oliver, M. & Rueda-Esteban, S. The relationship between allergic diseases and internalising and externalising behaviours in Spanish children: A cross-sectional study. *Allergol Immunopathol (Madr)* 49, 65-72, [https://doi.org/10.15586/aei.v49i3.78\(2021\)](https://doi.org/10.15586/aei.v49i3.78(2021)).
- Chai, P. H., Chang, S. & Cawthorpe, D. The temporal hyper-morbidity of asthma and attention deficit disorder: Implications for interpretation based on comparison of prospective and cross-sectional population samples. *Psychiatry Investigation* 18, 166-171, [https://doi.org/10.30773/pi.2020.0349\(2021\)](https://doi.org/10.30773/pi.2020.0349(2021)).
- Chang, H. Y., J. H. Seo, H. Y. Kim, J. W. Kwon, B. J. Kim, H. B. Kim, S. Y. Lee, G. C. Jang, D. J. Song, W. K. Kim, J. Y. Shim, H. J. Kim, J. W. Park, S. H. Cho, J. S. Lee, Y. J. Shin and S. J. Hong, 2013. Allergic diseases in preschoolers are associated with psychological and behavioural problems. *Allergy Asthma Immunol Res* 5(5), 315-321. <https://doi.org/10.4168/aaair.2013.5.5.315>
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- Galéra, C. et al. Medical conditions and Attention-Deficit/Hyperactivity Disorder symptoms from early childhood to adolescence. *Molecular Psychiatry*, [https://doi.org/10.1038/s41380-021-01357-x\(2021\)](https://doi.org/10.1038/s41380-021-01357-x(2021))
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- Guo, M. M. H., L. J. Wang, T. Y. Hsu, K. D. Yang and H. C. Kuo, 2020. Peanut sensitivity and allergic rhinitis in young children are associated with attention-deficit hyperactivity disorder symptoms in adolescence. *Neuropsychiatric Disease and Treatment* 16, 1349-1357. <https://doi.org/10.2147/NDT.S232299>

Hou, A. & Silverberg, J. I. Predictors and age-dependent pattern of psychologic problems in childhood atopic dermatitis. *Pediatric Dermatology* 38, 606-612, [https://doi.org/10.1111/pde.14588\(2021\)](https://doi.org/10.1111/pde.14588(2021)).

Huang, A. H., Y. S. Roh, N. Sutaria, J. Choi, K. A. Williams, J. K. Canner, A. L. Grossberg and S. G. Kwatra, 2021. Real-world comorbidities of atopic dermatitis in the pediatric ambulatory population in the United States. *J Am Acad Dermatol*. <https://doi.org/10.1016/j.jaad.2021.03.016>

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L, L. K., A. Cices, A. B. Fishbein and A. S. Paller, 2019. Neurocognitive function in moderate-severe pediatric atopic dermatitis: A case-control study. *Pediatr Dermatol* 36(1), 110-114. <https://doi.org/10.1111/pde.13710>

Minatoya, M., Suyama, S. & Kishi, R. [Relationship between atopic dermatitis and children's mental and behavioral health: The Hokkaido Study]. *Nihon Koshu Eisei Zasshi* 67, 745-751, [https://doi.org/10.11236/jph.67.10_745\(2020\)](https://doi.org/10.11236/jph.67.10_745(2020)).

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Edvinsson Sollander, S., H. Fabian, A. Sarkadi, R. Salari, E. Fält, A. Dahlberg, I. Feldman and N. Durbeej, 2020. Asthma and allergies correlate with mental health problems in preschool children. *Acta Paediatr*. <https://doi.org/10.1111/apa.15709>

Strom, M. A., A. B. Fishbein, A. S. Paller and J. I. Silverberg, 2016. Association between atopic dermatitis and attention deficit hyperactivity disorder in U.S. children and adults. *Br J Dermatol* 175(5), 920-929. <https://doi.org/10.1111/bjd.14697>

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Wan, J., Takeshita, J., Shin, D. B. & Gelfand, J. M. Mental health impairment among children with atopic dermatitis: A United States population-based cross-sectional study of the 2013-

2017 National Health Interview Survey. *Journal of the American Academy of Dermatology* **82**, 1368-1375, <https://doi.org/10.1016/j.jaad.2019.10.019>(2020).

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Appendix D. References to articles solely included in meta-analysis

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<https://doi.org/10.1016/j.aller.2015.04.006>

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Appendix E. Reference to articles included in supplementary materials

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