The neonatal risk factors associated with attention-deficit/ hyperactivity disorder: An umbrella review

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Running title: Risk factors associated with ADHD

Declarations

Statements of ethical Approval-Not applicable

Consent to Participate-Not applicable

Consent for Publication-Not applicable

Disclosure Statement- There is nothing to declare.

Data availability Statement-Not Applicable.

Data deposition- Not Applicable.

Author contribution- F.M and E. J performed the systematic search. S.B, E.J designed the study. S.F wrote the manuscript. E.A discussed the statistical outcomes. All authors had significant contribution for discussing the results.

Funding details- This work was funded by Hamadan University of Medical Sciences, Hamadan, Iran IR.UMSHA.REC.1401.406/No. 140105183629).
The neonatal risk factors associated with attention-deficit/ hyperactivity disorder: An umbrella review

Abstract

Background- Attention-deficit/ hyperactivity disorder (ADHD) is one of the increasing neurodevelopmental disorders.

Purpose- In this study, by compiling the evidence from available meta-analyses, an umbrella systematic review was performed for neonatal risk factors associated with ADHD.

Methods- Databases including PubMed, Scopus and Web of sciences were searched for retrieving eligible studies. Only systematic reviews were included in the study. Using a random-effect model, 95% prediction intervals were reported for each risk factor. Three studies were included in the review.

Results- The results showed that risk factors such as congenital heart disease (CHD), incomplete breastfeeding, low birth weight, and Apgar score < 7 at 5 minutes were significant risk factors for ADHD symptoms. However, the quality of included systematic reviews was low to moderate and the level of credibility for evidence was at most suggestive to weak.

Conclusion- This umbrella review proposed that congenital anomalies, short duration or incomplete breastfeeding, low birth weight, and low Apgar score were all important factors for the manifestation of ADHD symptoms. However, the inclusion of more high-quality studies is needed for a conclusion.
Keywords—ADHD, neonatal, risk factors, umbrella review

Key messages

- **Question:** The risk factors for ADHD such as breastfeeding, congenital heart disease, and low birth weight are not well understood in neonates.

- **Findings:** The umbrella review obtained effect size of congenital heart disease (OR 3.04), low birth weight (OR 2.25), never breastfeed (OR 1.55), and Apgar score (OR 1.30) on ADHD.

- **Meaning:** The results showed that congenital heart disease, low birth weight, breastfeeding and Apgar score factors were all significant for ADHD.
Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the common neurodevelopmental disorders characterized by a deficit in attention, hyperactivity, and impulsiveness\(^1\). The prevalence of ADHD among primary school children was reported to be 11.32\%\(^2\). Even though genetic factors are the most important triggering factor for ADHD, environmental risk factors may contribute to 10-40 percent of such a disorder\(^3\). The environmental factor may interact with genetic factors to trigger the symptoms of ADHD\(^4,5\). Since most ADHD symptoms manifest in the early life stages, neonatal risk factors have gained special attention regarding the development of ADHD.

Previous studies investigated several risk factors including low birth weight, incomplete breastfeeding, and congenital anomalies\(^6-9\). Incomplete breastfeeding implies both cases of the absence of breastfeeding or low-duration breastfeeding conditions. Jenabi et al. (2021) performed a systematic review for investigating the association between congenital heart disease (CHD) and the risk of ADHD and autism spectrum disorders\(^8\). The eligible sources were found by a systematic search from major databases including Web of Science, PubMed, and Scopus and the association was found according to odds ratio and hazard ratio. By adjusting some confounding factors and using a random-effect model, they showed that there was a significant relationship between ADHD and CHD (6 studies, odds ratio=3.04, 95\% CI: 1.58 4.49, \(I^2=88.1\%\)). Franz et al. (2018) using observational studies retrieved from Embase, Medline, PsychINFO, and Cochrane databases investigated the effect of low birth weight on ADHD symptoms. Very low birth weight
(VLBW) and extremely low birth weight (ELBW) were defined by weight smaller than 1500gr and 1000gr, respectively. They showed a significant association between low birth weight and ADHD (8 studies, odds ratio=2.25, 95%CI: 1.56 3.26). Furthermore, they showed that for VLBW cases, the association was more significant (4 studies, odds ratio=4.05, 95% CI: 2.38 6.87)\(^7\). In another study, Tseng et al. (2019) investigated the causal relationship between ADHD symptoms and breastfeeding by retrieving relevant studies from PubMed, Embase, ClinicalKey, ScienceDirect, ProQuest, Cochrane Library, and ClinicalTrials.gov databases. The cumulative study using a random-effect model was performed according to Hedge’s g and odds ratio measures for 656 ADHD children and 369 control samples. They reported a significant association between the duration of breastfeeding and ADHD symptoms (8 studies, odds ratio=1.90, 95%CI: 1.45 2.48, P<0.001)\(^9\). Bitsko et al. searched databases including PubMed, Web of science, and Embase for relevant studies regarding ADHD and pregnancy-related risk factors \(^6\). The obtained results according to the odds ratio showed a positive association between ADHD and postnatal factors such as Apgar score, neonatal illness, and no breastfeeding (odds ratio range: 1.1-1.6). Even though there are several studies regarding ADHD risk factors, there is a lack of a comprehensive review for compiling the available evidence from existing reviews. The main purpose of the current study was to combine the obtained results of several eligible systematic reviews and meta-analyses regarding the neonatal risk factors for ADHD in an umbrella review framework.

\textbf{Materials and methods}

This umbrella systematic review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.
Search strategy

The major databases including PubMed, Web of sciences, and Scopus were used for searching the available eligible studies until April 2022. Only systematic reviews were considered without any constraints on the date of publication or the language. The keywords included: (influencing factors OR related factors OR risk factors) AND (neonate OR neonatal) AND (attention deficit hyperactivity disorder OR ADHD) AND (systematic review OR meta-analysis). The reference lists of eligible studies, systematic reviews, and meta-analyses, were checked carefully for retrieving missed documents. The search procedure, as well as, screening the studies, and assessing the quality of eligible studies were performed by two independent authors (E.J and F.M).

Study selection, inclusion, and exclusion criteria

The process of retrieving eligible studies was performed by two independent reviewers (E.J and F.M). A PICO (P: Participant, I: intervention, C: comparison, and O: outcome) model was used for the current umbrella review. The population was neonatal samples, the intervention was any risk factor, the comparison was performed according to the odds ratio and the outcome was the effect of the risk factor on the manifestation of ADHD symptoms. As inclusion criteria, all systematic reviews and meta-analyses related to the risk factors for ADHD were included. Studies with any type of risk factors, including low birth weight, CHD, and breastfeeding were considered. As exclusion criteria, non-systematic review studies (including observational studies, letters to the
editor, experimental studies, and clinical trials) were excluded. Furthermore, systematic reviews without meta-analysis were excluded.

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132 **Data extraction**

133 An electronic form for extracting data from retrieved sources was used. Information regarding the first author’s name, publication year, study design, number of included studies, the number of ADHD samples, effect size, and neonatal risk factors for ADHD was extracted. Furthermore, according to the level of credibility of evidence, each meta-analysis was allocated to one class. When there was an overlap between two meta-analyses, the one with more included studies was considered. Data extraction was performed by two independent authors (E.J and F.M) and any disagreement was resolved through discussion.

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140 **Level of credibility of evidence**

141 For each meta-analysis, the credibility of evidence was estimated. In this regard, the studies were classified into five classes: class I (convincing), Class II (highly suggestive), Class III (suggestive), Class IV (weak), and Class V (not significant). Criteria for assigning each meta-analysis to one of the classes were p-value of random effect model, p-value for the largest study, the total number of ADHD cases, heterogeneity ($I^2$), small study effect, excess significance bias, prediction interval, and 10% predictability ceiling. The prediction interval indicates the interval for the possible real effect of the risk factor. The credibility ceiling method is a kind of sensitivity analysis to account for the effect of confounding factors and biases (the lack of randomization, measurement errors, or incorrect grouping) in a meta-analysis $^{10}$. The excess significance bias is calculated according
to the number of expected studies and the observed number of studies with nominally significant results. The significant level for statistical analyses was adjusted to 0.05.

Quality assessment

The quality of studies was assessed using the assessment of multiple systematic reviews instrument i.e. AMSTAR which was suited for both randomized and non-randomized designs. This is an 11-item tool in which each item should be answered by "yes", "no", "can't answer" or "not applicable". The total score for each study was determined by the number of 'yes' answers. For a total score of 0-3, the quality of meta-analysis was considered low, for scores 4-7, the quality was medium and for scores between 8 and 11, meta-analysis was considered a high-quality study.

Results

Twenty-eight articles were retrieved from searching three main databases until April 12, 2022. Three meta-analysis studies were identified (Figure 1) which included six meta-analyses with 148,455 children with ADHD and 29,927,763 control participants. Studies with design of cohort and case-control were included in the present umbrella review (47 original; 22 cohort studies and 25 case-control studies).

We identified six risk factors including CHD, VLBW, ELBW, Apgar score < 7 at 5 minutes, never breastfeeding, and neonatal intensive care unit (NICU) admission. CHD is related to structural problems with a baby’s heart and affects the normal functions of the heart. In the current study, all kinds of CHD including mild to severe cases were considered. VLBW is considered for infants with a birth weight
lower than 1500 gr, while ELBW is defined for a birth weight lower than 1000 gr. In the present umbrella review, out of six included meta-analyses, four studies had at least 1000 cases, four presented heterogeneity ($P^2 < 50\%$), one had small study effects, and none of the studies had excess significance bias (Table 2). According to the findings of sensitivity analyses, three studies were relatively sensitive to unmeasured confounding factors (a bias factor of less than 1.75 in each of the meta-analyses). The other three studies (CHD, VLBW, ELBW) were relatively robust to unmeasured confounding (a bias factor of more than 1.90 in each of the meta-analyses).

The risk factor of NICU admission (OR 1.50 95% CI: 1.18, 1.92) was graded as suggestive evidence (class III). The five risk factors of CHD (OR 3.04 95% CI: 1.58, 4.49), VLBW (OR 2.25 95% CI: 1.56, 3.26), ELBW (OR 4.05 95% CI: 2.38, 6.87), never breastfeed (OR 1.55 95% CI: 1.15, 2.10) and Apgar score < 7 at 5 minutes (OR 1.30 95% CI: 1.09, 1.54) were graded as weak evidence (class IV) (Table 1). The quality of included meta-analyses was reported based on the AMSTAR checklist (see Table 3). According to the AMSTAR checklist, among three included meta-analyses, one of them was low-quality and the others were medium-quality studies.

Discussion

The evidence level for NICU admission and never breastfed was classified as suggestive (class III), although most of the criteria were met except for the p-value (statistical significance; $p < 0.000001$). Since the classification criteria are objective and standard, they are criticized due to arbitrary cut-offs and are prone to misclassification bias $^{13}$. On the other hand, the produced evidence from meta-analyses is highly dependent on the methodology and reporting of the primary and individual studies $^{14}$. Prediction intervals including the null value were observed for CHD and
Apgar score < 7 at 5 minutes. Moreover, IntHout et al. \(^{15}\) argued that assumptions for estimating
prediction interval can be difficult to establish and these interval may be imprecise in the presence
of substantial between-study heterogeneity. Thus, all-or-nothing thinking may be misleading when
judging the certainty of evidence from an umbrella review and two risk factors of NICU admission
and never breastfed can be considered as the higher level of evidence.

The sensitivity analysis showed that the observed associations for NICU admission, never
breastfed, and Apgar score <7 at 5 minutes were biased by unmeasured or uncontrolled
confounding factors, indicating the observed associations do not imply causation. In other words,
the investigators of the individual studies had controlled for only some confounders but not for all
of the known or unknown confounders and these unmeasured confounders might be associated
with NICU admission, never breastfed, and Apgar score <7 at 5 minutes as well as were associated
with ADHD. In this regard, for example in the primary individual studies that aimed to evaluate
the association between two aforementioned factors, estimating the minimum strength of
association that an unmeasured confounder would need to have with both the NICU admission and
ADHD can help to understand the true effect of NICU admission on ADHD \(^{16}\).

The heterogeneity for CHD and Apgar score < 7 at 5 minutes were 88.1\% and 90.55\%, respectively,
indicating large between-study heterogeneity. It may be due to the fact that groups of ADHD
patients were different across the individual studies in the meta-analyses evaluating the effect of
these two risk factors and the estimated overall effect may not generalizable to all of the included
studies. On the other hand, weak (class IV) evidence level for CHD and Apgar score < 7 at 5
minutes may be due to the observed great heterogeneity \(^{17}\).

The limitations of this umbrella review that should be acknowledged are as follow; according to
the AMSTAR checklist, the quality of meta-analyses was low to medium. The quality less than
acceptable level was a result of missing information in item 1 (lack of published protocol before conducting meta-analyses), item 5 (lack of reporting inclusion and exclusion criteria in meta-analyses), items 7 and 8 (failure to check the quality of individual studies) and item 9 (weaknesses in the methodology of combining findings of individual studies). All of these potential biases can lead to misleading when interpreting the results from meta-analyses. This review did not cover other important risk factors such as prenatal risk factors. Previous works showed that a combination of prenatal and perinatal risk factors and their interaction plays a pivotal role in the causal pathway of childhood ADHD. Moreover, we acknowledge our review may prone to a degree of selection bias because we only searched three databases (PubMed, Web of sciences, and Scopus) and we had only three meta-analysis studies including six meta-analyses.

In this umbrella review, the current knowledge regarding the risk factors for ADHD in neonatal period was investigated. The results indicated the significant effect of risk factors such as never breastfeeding, VLBW, ELBW, CHD, and NICU admission. The possible reasons for such results may be explained as follows.

**Congenital heart anomalies**

Studies in human and animal samples showed that stresses during early life stages may trigger chronic disease in the future. Furthermore, studies indicated that people with CHD at born had a higher risk of developing neurological deficits. Due to congenital heart defects, the blood flow and consequently the oxygen received to the brain reduces. This hypoxemia condition might significantly affect the brain developmental stages. Hypoxemia also affects highly oxygen-sensitive areas of the brain such as the striate body of the brain and prefrontal cortex which contain
important networks for executive attention control \(^{21}\). However, it is important to take into account the possible common genetics of ADHD and heart diseases. Patients with 22q11 syndrome show both cardiovascular abnormalities and several psychiatric disorders including ADHD (40% overlap) \(^{22}\).

### Low birth weight

ELBW increases the risk for ADHD to 13.8% \(^{23}\). Previous studies suggested that ADHD severity was related to poor neurophysiological functioning. The birth weight is an important factor in primary neurophysiological functions and in this way, low birth weight condition affects indirectly ADHD severity and symptoms \(^{24}\). For ELBW cases executive function abilities is degraded compared with normal children \(^{25}\). Lower birth weight due to the insufficient supply to the fetus disturbs hypothalamic-pituitary-adrenal (HPA) axis and increases fetal exposure to glucocorticoid levels. This can affect developmental pathways and trigger psychiatric disorders such as ADHD \(^{26, 27}\).

### Breastfeeding

Previous studies emphasized the positive role of longer breastfeeding on cognitive development \(^{28}\). Such a beneficial effect might be due to the transfer of long-chain polyunsaturated fatty acids to the child through breast milk \(^{29}\) which enhances the cognitive functions to a large extent \(^{28}\). The physical or social interactions between mother and child during breastfeeding and the effects of mother's milk on microbiota are other possible factors that may be responsible for the protective effect of breastfeeding against ADHD symptoms \(^{4}\).
Implications for Practice

In this study using an umbrella systematic review framework, the effect of neonatal risk factors on ADHD was investigated. These risk factors were congenital heart diseases, breastfeeding, low birth weight, and Apgar score < 7 at 5 minutes. The results proposed that such factors were all effective for ADHD manifestation. The small-sample size of the study and the inclusion of low-quality studies were the main obstacles to conclusion and further studies are needed for obtaining a clinically applicable outcome. However, these findings implied that in case of children with CHD, incomplete breastfeeding, low birth weight, or low Apgar score, the symptoms of ADHD should be screened with special attention by the experts and the child's family.

Declarations

Statements of ethical approval- Not applicable
Consent to participate- Not applicable
Consent for publication- Not applicable
Disclosure statement- There is nothing to declare.
Data availability statement- Not Applicable.
Data deposition- Not Applicable.
References


Appendix

Table S1: Search strategy

1. Influencing factors or related factors or risk factors
2. Neonate or neonatal
3. Attention deficit hyperactivity disorder OR ADHD
4. Systematic review or Meta-analysis or Meta-analysis or synthesis
5. #1 and #2 and #3 and #4

Table S2: Excluded references with reasons

No meta-analysis (n=2)

There were in a larger meta-analysis (n=2)

No inclusion criteria (n= 2)
Table 1: The risk factors for neonatal attention-deficit/hyperactivity disorder in the present umbrella review

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Source (year)</th>
<th>Number of population</th>
<th>Number of included studies</th>
<th>Study design</th>
<th>Effect metrics</th>
<th>Random effect summary estimate</th>
<th>Credibility of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital heart disease (CHD)</td>
<td>Jenabi (2022)</td>
<td>21,551,625</td>
<td>5</td>
<td>Case-control, Cohort</td>
<td>Odds ratio</td>
<td>3.04 (1.58, 4.49)</td>
<td>Class IV</td>
</tr>
<tr>
<td>Neonatal intensive care unit (NICU) admission</td>
<td>Bitsko (2022)</td>
<td>166,891</td>
<td>11</td>
<td>Case-control, Cohort</td>
<td>Odds ratio</td>
<td>1.50 (1.18, 1.92)</td>
<td>Class III</td>
</tr>
<tr>
<td>Very Low birth weight (VLBW)</td>
<td>Franz (2018)</td>
<td>5,410</td>
<td>8</td>
<td>Case-control, Cohort</td>
<td>Odds ratio</td>
<td>2.25 (1.56, 3.26)</td>
<td>Class IV</td>
</tr>
<tr>
<td>Never breastfed</td>
<td>Bitsko (2022)</td>
<td>13,229</td>
<td>9</td>
<td>Case-control, Cohort</td>
<td>Odds ratio</td>
<td>1.55 (1.15, 2.10)</td>
<td>Class IV</td>
</tr>
<tr>
<td>Extremely low birth weight (ELBW)</td>
<td>Franz (2018)</td>
<td>1,345</td>
<td>4</td>
<td>Case-control, Cohort</td>
<td>Odds ratio</td>
<td>4.05 (2.38, 6.87)</td>
<td>Class IV</td>
</tr>
<tr>
<td>Apgar score &lt; 7 at 5 min</td>
<td>Bitsko (2022)</td>
<td>8,189,263</td>
<td>15</td>
<td>Case-control, Cohort</td>
<td>Odds ratio</td>
<td>1.30 (1.09, 1.54)</td>
<td>Class IV</td>
</tr>
</tbody>
</table>

Class III: Suggestive; class IV: Weak
Table 2: The credibility of the evidence for neonatal factors associated with attention-deficit/hyperactivity disorder

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Number of cases</th>
<th>Summary associations (p-value) per random-effects calculations</th>
<th>Small-study effects (p-value for Egger)</th>
<th>Excess of significance bias (p-value)</th>
<th>Prediction intervals</th>
<th>Largest study nominally significant (p-value)</th>
<th>Heterogeneity (I²%)</th>
<th>Sensitivity analysis</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital heart disease (CHD)</td>
<td>2,827</td>
<td>0.0071</td>
<td>0.39</td>
<td>0.07</td>
<td>0.68-6.76</td>
<td>&lt;.0001</td>
<td>88.10</td>
<td>T=1.87, G=3.14</td>
<td>Class IV</td>
</tr>
<tr>
<td>Neonatal intensive care unit (NICU) admission</td>
<td>9,417</td>
<td>&lt;.0001</td>
<td>0.77</td>
<td>0.58</td>
<td>1.60-1.83</td>
<td>&lt;.0001</td>
<td>0.00</td>
<td>T=1.47, G=2.30</td>
<td>Class III</td>
</tr>
<tr>
<td>Very Low birth weight (VLBW)</td>
<td>939</td>
<td>0.0003</td>
<td>0.72</td>
<td>0.99</td>
<td>1.37-2.80</td>
<td>&lt;.0001</td>
<td>0.00</td>
<td>T=1.83, G=3.06</td>
<td>Class IV</td>
</tr>
<tr>
<td>Never breastfed</td>
<td>3,151</td>
<td>0.0004</td>
<td>0.23</td>
<td>0.23</td>
<td>1.14-1.59</td>
<td>&lt;.0001</td>
<td>0.00</td>
<td>T=1.33, G=1.99</td>
<td>Class IV</td>
</tr>
<tr>
<td>Extremely low birth weight (ELBW)</td>
<td>234</td>
<td>&lt;.0001</td>
<td>0.12</td>
<td>0.99</td>
<td>1.62-3.21</td>
<td>.004</td>
<td>34.00</td>
<td>T=2.65, G=4.74</td>
<td>Class IV</td>
</tr>
<tr>
<td>Apgar score &lt; 7 at 5 min</td>
<td>131,887</td>
<td>0.0002</td>
<td>0.07</td>
<td>0.27</td>
<td>0.91-1.95</td>
<td>&lt;.0001</td>
<td>90.55</td>
<td>T=1.30, G=1.93</td>
<td>Class IV</td>
</tr>
</tbody>
</table>

Class III: Suggestive; class IV: Weak
### Table 3: Quality of studies based on AMSTAR items

<table>
<thead>
<tr>
<th>Study</th>
<th>Item 1</th>
<th>Item 2</th>
<th>Item 3</th>
<th>Item 4</th>
<th>Item 5</th>
<th>Item 6</th>
<th>Item 7</th>
<th>Item 8</th>
<th>Item 9</th>
<th>Item 10</th>
<th>Item 11</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jenabi (2022)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>C</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>C</td>
<td>4/11</td>
</tr>
<tr>
<td>Bitsko (2022)</td>
<td>No</td>
<td>No</td>
<td>C</td>
<td>C</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>C</td>
<td>3/11</td>
</tr>
<tr>
<td>Franz (2018)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>C</td>
<td>5/11</td>
</tr>
</tbody>
</table>

Yes, No, Can’t answer(C), or Not applicable (NA). 1-Was an ‘a priori’ design provided? 2-Was there duplicate study selection and data extraction? 3-Was a comprehensive literature search performed? 4-Was the status of publication (i.e. grey literature) used as an inclusion criterion? 5-Was a list of studies (included and excluded) provided? 6-Were the characteristics of the included studies provided? 7-Was the scientific quality of the included studies assessed and documented? 8-Was the scientific quality of the included studies used appropriately in formulating conclusions? 9-Were the methods used to combine the findings of studies appropriate? 10-Was the likelihood of publication bias assessed? 11-The conflict of interest stated?
Figure 1: The included meta-analyses in the present umbrella review
Figure captions

**Figure 1:** The included meta-analyses in the present umbrella review