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Review

Impact of Crohn's disease during pregnancy on children with attention deficit hyperactivity disorder: A review

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ABSTRACT

Background: Iron deficiency anemia (IDA) is a common complication of inflammatory bowel disease (IBD) in pregnant women. Although studies have shown that certain maternal autoimmune diseases are associated with attention deficit hyperactivity disorder (ADHD) in children, no studies have found a relationship specifically between and IDA in pregnant women with IBD and ADHD in their children. This review aims identify a relationship between maternal Crohn's disease (CD) with IDA and ADHD in children.

Materials and methods: A review of existing literature was conducted using PubMed to search for articles on pregnant women with CD and IDA and children with ADHD. The studies included nested case-control studies, cohort studies, cross-sectional studies, case-control studies, and literature reviews published from 2012 to 2021.

Results: Among 876 articles generated, 11 studies were chosen for this review. Inclusion criteria consisted of no animal studies, meta-analysis or systematic reviews followed by ADHD related topics and maternal CD and IDA. The findings show that ADHD in progeny may be attributed to maternal CD. Although no studies have shown that IDA in mothers with CD is related to ADHD in offspring, several studies have shown a positive correlation between maternal IDA and ADHD in offspring. Some studies suggest inflammation in IBD during pregnancy can inflame the central nervous system, leading to ADHD in offspring.

Conclusion: IDA is a prevalent complication in CD, and inadequate iron levels are associated with neurodevelopmental problems, such as ADHD. Iron therapy for pregnant mothers diagnosed with CD is suggested to prevent ADHD in offspring.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in childhood, affecting approximately 8.4% of US children between 2 and 17 years of age [1,2]. Symptoms of ADHD include losing items, disorganization, an inability to pay attention and concentrate, forgetting things quickly, and struggling to complete activities [2]. Evidence links the disorder's etiology to multiple factors, including genetics, environmental aspects and certain maternal autoimmune disorders such as psoriasis, rheumatoid arthritis, asthma and others [3,4].

Although studies have shown an association between certain maternal autoimmune diseases and ADHD in offspring, not much is known about how maternal inflammatory bowel diseases (IBDs), such as Crohn's disease (CD), affect neurodevelopment in progeny. It was recently estimated that approximately 1.5 million people have IBD, including ulcerative colitis, in the United States, causing considerable health and financial loss every year [5]. In most cases, the development of anemia is caused by iron deficiency, and results have shown that nearly 27% of people treated for CD have iron deficiency anemia (IDA) [4]. Furthermore, women with CD are at higher risk of anemia than men with CD possibly due to blood loss during menstruations [6].

Studies have suggested that inflammation from autoimmune disorders is the main trigger of the fetal neurodevelopment that leads to ADHD [3,4]. In CD, IDA is a common comorbid condition in the onset of the disease, but few studies have explored the relationship between CD in pregnant women with IDA, the most common complication, and the development of ADHD in children. The aim of this review is to assess whether IDA in pregnant women with CD is a risk factor for ADHD, and understanding this relationship could help prevent this outcome in children. We hypothesized that evidence exists that children of pregnant women with CD and IDA have higher risk of ADHD than children from mothers without CD and IDA.

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2. Methods

2.1. Search strategy

A computerized literature search was conducted on the PubMed database to locate relevant peer-reviewed studies to answer the research question. The search terms were combined using Boolean operators to narrow and broaden the search strings to identify relevant results. The Boolean operators used were "and" and "or." Articles containing any of the search terms were considered.

2.2. Search terms

The following search terms were used: Crohn's disease, Crohn's disease and epidemiology, maternal Crohn's disease, Crohn's disease and iron deficiency anemia, Crohn's disease and ADHD, ADHD and iron deficiency anemia, iron homeostasis, iron homeostasis and Crohn's disease, maternal iron deficiency and ADHD or hyperactivity. We revised the search terms to narrow down the search to produce more specific results. The modified search strings were as follows:

a. Crohn's disease or irritable bowel diseases in pregnant women and ADHD or hyperactivity in children.
b. Relationship between maternal Crohn's disease or irritable bowel diseases and ADHD in children.
c. Crohn's disease and iron deficiency or anemia or iron homeostasis in pregnant women.

The first search using the above search strings generated 876 articles with abstracts or titles with multiple critical terms related to the research topic (Fig. A1). By applying additional restrictions, we avoided producing more than 600 irrelevant abstracts or article titles, and 276 relevant articles were generated. Of the articles meeting the selection criteria, we chose only those from 2012 to 2021 were chosen, resulting in 11 articles. In this review, we included all relevant articles published within the past ten years. We considered studies about ADHD, CD, or IBD that focused on pregnant women or children to be relevant to this review not including animal studies, systematic reviews or meta-analysis. The results included several types of studies, nested case-control studies, cohort studies, cross-sectional studies, cases control studies, and literature reviews.

2.3. Data analysis

To synthesize the collected data, we designed an evidence table for the 11 articles (Appendix 1). In summarizing and comparing the evidence, we recorded the type of study, number of participants, age range, gender, aim, and outcome. In addition, we located studies considering gender differences in ADHD linked to maternal CD, and we analyzed these sources according to whether the initial study sample included male or female children.

3. Results

This review attempted to answer the question, "Is there a relationship between IDA in maternal CD and ADHD?" The search resulted in 11 studies (Appendix 1). These studies include 2 literature reviews [7,8], 4 cohort studies, 3 cross-sectional studies, 1 case-control study, and 1 nested case-control study.

3.1. Case-control studies

We found one case-control study [9] assessing the link between iron deficiency and ADHD in children (n = 630) from 5 to 18 years of age in Qatar. The findings indicated that mean ferritin levels were significantly lower in children with ADHD than in the control group (36.26 ± 5.93, 38.19 ± 5.61, respectively; $p \leq .01$). Ferritin levels in children without ADHD were within the normal range. The researchers suggested that iron deficiency is linked to cognitive impairment, instability in psychomotor aspects in children, and difficulties in learning because of impairment within the central dopaminergic pathway. In summary, the study found that iron deficiency was strongly associated with ADHD symptoms, and these findings revealed the need for careful examination and possibly early intervention of iron supplementation in affected children to reduce the risk of ADHD.

3.2. Cohort studies

We identified four cohort studies. One investigated the relationship between IBD and pregnancy outcomes [10]. Pregnant women (n = 85,000) were monitored from the first trimester until birth. The findings showed that CD is associated with multiple adverse pregnancy outcomes, such as low Apgar scores (<7) in newborns (n = 629). Although not part of this review, previous results also showed that low Apgar scores are associated with ADHD during development [11,12]. Babies born to women with IBD who did not use corticosteroids were more likely to have congenital disorders, such as choanal atresia and spina bifida, than babies born to women with IBD who used corticosteroids [10]. Although CD in pregnant mothers is associated with preterm delivery, low birth weight, pregnancy loss, preeclampsia, and placental problems, the authors did not assess the risk of ADHD in newborns during development [10].

Another cohort study [4] from Denmark examined if an association exists between maternal autoimmune disorders and the risk of ADHD in children (n = 23,645). The authors found that mothers with type 1 diabetes, psoriasis, autoimmune hepatitis, or ankylosing spondylitis were more likely to have children with ADHD compared healthy mothers ($p < .05$). However, these results were not significant for pregnant mothers with CD ($p = .30$). The authors suggested that the etiology of ADHD in children is multifactorial and affected by genetic and environmental factors. Another cohort study [13] examined pregnant mothers (n = 299,786) with anemia (using hemoglobin levels at 10, 25, and 37 weeks) within 30 weeks of gestation. They found that the children (n = 532,232), aged from 6 to 29 years, had a higher risk of ADHD (9.3%) compared to those from mothers not diagnosed with anemia (7.2%) (OR, 1.37; 95% CI, 1.14–1.64). Early screening of anemia and nutritional counseling in pregnant women is suggested to help prevent the outcome of ADHD in their offspring. The last cohort study showed that non-anemic infants who received iron-fortified formula (12.7 mg Fe/L) from 6 to 12 months of age demonstrated better math and verbal skills when assessed at 5, 10, and 16 years of age compared to infants who received low-iron formula (2.3 mg Fe/L) showing poorer skills indirectly through their ADHD behavior [14]. The authors suggested that early-life iron deficiency can be an early predictor of ADHD symptoms through verbal and math skills. Hence, early prevention and treatment of iron deficiency may be useful.

3.3. Cross-sectional studies

The first study [15] researched the correlation between ferritin levels in boys (n = 613) and girls (n = 100) aged from 7 to 15 years and hyperactivity ratings by teachers and parents. Using a multiple regression analysis for the Conners' Parent Rating Scale (CPRS), the researchers found that hyperactivity symptoms were strongly associated ($p = .002$) with low ferritin, which was measured every morning for 15 days. Similarly, investigators in India showed that, in children from 11 to 15 years of age, maternal IDA was strongly associated with ADHD symptoms according to the CPRS for teachers and parents [16]. The results showed that 22% of the children with ADHD had anemia compared to 7% without ADHD. The authors suggested using iron as a prophylactic treatment to reduce the risk of this condition. The last study [17] examined the relationship between ADHD and autoimmune diseases on

2,500,188 participants in Norway. Because sex was considered an essential factor in the investigation, male (3.2%) and female (1.9%) participants with ADHD were identified and investigated independently using logistic regression. Females with CD were more likely to have ADHD compared to males with CD, with adjusted odds ratio at 1.44 (95% CI, 1.16–1.79). The study's findings indicate that a relationship exists between ADHD and autoimmune disorders, although the results for male participants were negative.

3.4. Nested case-control studies

One nested case-control study [3] investigated whether maternal autoimmune condition during pregnancy is a risk factor for ADHD in children. The study applied a case-control design on population groups, and the results indicated a significant relationship between ADHD in offspring and maternal autoimmune conditions, such as asthma, type 1 diabetes, hypothyroidism, rheumatoid arthritis, and multiple sclerosis using logistic regression models with adjusted odds ratio at 95% CI ($p < .01$) compared to mothers of control subjects. This relationship did not vary according to the child's sex. Although IBD was not addressed in this study, future studies should evaluate its impact on ADHD.

3.5. Reviews

Both reviews [7,8] mentioned that the pervasiveness of iron deficiency has a major impact on people with IBD. The inflammation caused by IBD impairs iron absorption, leading to the accumulation of hepcidin, a hormone produced in the liver that inhibits ferroprotein activity. People with IBD are likely to develop anemia from the loss of significant amounts of iron caused by bleeding. IBD patients must be examined for iron deficiency every time they are anemic and have serum iron levels below 100 μg/L.

4. Discussion

The results of this review support our hypothesis that IDA in maternal CD is a risk factor for ADHD in children. Hegvick et al. [17] concluded that one of the standard autoimmune contributors to ADHD among children is IBD, specifically in female children. In contrast, although Nielsen et al. [4] found that certain autoimmune disorders in mothers, such as asthma, psoriasis, and others, were linked to ADHD in their offspring, they found no significant difference for CD. However, the authors did not mention whether the mothers with CD were taking medication or had internal bleeding during the onset of the condition.

The results of this review demonstrate that iron plays a contributory function in the pathophysiology of ADHD [9,13–16]. Brain development can become impaired because of ID, which, in turn, can increase the risk of ADHD in children. Individuals with CD are likely to develop anemia because of malabsorption or bleeding caused by the disease [7,8]. Pregnant mothers diagnosed with CD may have low iron levels, which may have a negative and possibly irreversible impact on fetal brain development.

Our results support previous findings, which indicate that children diagnosed with ADHD also have lower serum ferritin compared to their counterparts. Many results have also shown that maternal iron deficiency is linked to iron deficiency in their offspring [18–24]. According to Wiegersma et al. [13], a direct correlation exists between ADHD in children and maternal anemia. The researchers suggested that adequate iron levels are needed for optimal brain development because iron plays a role in the neurotransmitter homeostatic process.

4.1. Pathophysiology of anemia in Crohn's disease

Several factors can trigger iron deficiency anemia in IBD, such as increased iron loss from mucosal bleeding caused by gastrointestinal inflammation [7]. A decrease in iron absorption can also cause iron deficiency anemia in short bowel syndrome, decreased appetite during IBD outbreaks, and inflammation-driven blockage of intestinal iron acquisition and macrophage iron reutilization. Moreover, inflammatory cytokines, such as those in IBD, can directly inhibit iron absorption and stimulate the uptake and retention of iron in macrophages. This process can result in anemia in the long term and is reflected by low ferritin levels [26]. Inflammatory cytokines also seem to reduce the circulating half-life of erythrocytes. Other factors may also contribute to anemia, such as vitamin deficiencies (vitamin B12 and folic acid) as a result of intestinal inflammation or bowel resection [27]. Certain drugs for treating IBD, such as proton pump inhibitors, sulfasalazine, methotrexate, and thiopurines, can also worsen the progression of anemia [28].

In general, healthy adults store approximately 1–3 g of iron balanced between its physiological loss, and 15%–35% comes from diet intake [25]. However, only 2%–20% is absorbed. The rest of the iron formation is acquired by recycling iron from degraded erythrocytes. Furthermore, about 75% of iron is needed for erythropoiesis. About 1–2 mg of iron is lost daily, mainly via feces, menstruation, and cellular desquamation from both skin and intestinal epithelium.

4.2. Pathophysiology of iron deficiency in ADHD

Several studies have suggested that iron deficiency is a risk factor in the pathology of ADHD because iron acts as a coenzyme of tyrosine hydroxylase, which is critical for forming dopamine [15,29]. Furthermore, dopamine is a crucial neurotransmitter required for the pathophysiology of ADHD [15]. Patients with ADHD seem to have decreased dopamine transporter activity, causing dopamine dysfunction, which results in increased extracellular dopamine and reduced dopamine receptors in the striatum. Some studies found that children with post-natal iron deficiency had symptoms associated with ADHD because of iron deficiency that harmed dopaminergic neurotransmission [29].

4.3. Crohn's disease and ADHD

Today, there is little knowledge about the association between ADHD and CD. Recent studies on this relationship show that the prevalence of ADHD is higher in females with CD than males with CD [17]. This influence might result from a sex-specific genetic process that affects the X chromosome more than the Y chromosome.

Studies have shown that any state of inflammation state, such as that in an autoimmune disease, can affect fetal brain development. This process might happen during pregnancy in active CD cases with internal bleeding. This process would increase the possibility of the child acquiring ADHD from the mother because of ID. Nonetheless, there is still no research on the impact of CD in pregnant mothers with iron deficiency on their children's acquisition of ADHD during development. More longitudinal studies should be conducted to test this hypothesis to help prevent this condition.

4.4. Strengths and limitations

To our knowledge, this is the first review to investigate whether IDA in maternal CD is a risk factor for the pathophysiology of ADHD in children. Another strength is that we did not limit our search by year, population number, or country of origin. However, a primary limitation is that an insufficient number of articles related to ADHD and maternal CD were found. Although many studies have shown a link between IDA and ADHD, the mechanisms are not fully understood. Bleeding loss and iron-deficient diets should be better explored during IBD active states in pregnant mothers to better understand the risk of ADHD in children. In addition, data regarding IDA and ADHD from the postnatal period are more available than data from the prenatal period. Hence, future studies are recommended to explore this relationship in the gestational period to better understand the etiology of ADHD in children and prevent its

outcome.

5. Conclusion

This review provides evidence that iron deficiency anemia in mothers with CD is a potential risk factor for the onset of ADHD in children. Future research should explore whether pregnant women with CD should receive iron supplements to reduce the risk of ADHD in their children. In addition, screening for and treating anemia in pregnant women with CD might be an effective strategy to prevent this condition.

Provenance and peer review

Not commissioned, externally peer reviewed.

Conflicts of interest

No conflict of interest.

Sources of funding

No funding sources.

Ethical approval

This article is a review, hence no ethical approval is required for this type of study.

Consent

Not applicable.

Author contribution

NS contributed to the concept and design, analysis and interpretation of data, literature search, data extraction and wrote the paper. DP guided and supervised in different stages and contributed to the interpretation of data, revising the manuscript for important intellectual content and approval of the final manuscript. NS and DP were involved in drafting and revising the manuscript and approved the final version.

Registration of research studies

Name of the registry: Not applicable
Unique Identifying number or registration ID: Not applicable
Hyperlink to your specific registration (must be publicly accessible and will be checked): Not applicable

Guarantor

Dr. Dipendra Pandeya.

Appendix 1. List of articles with characteristics and outcomes

Authors	Year of publication	Type of study	Study population	Aim	Outcome
Oner, P., Oner, O., Azik, F. M., Cop, E., & Munir, K. M.	2012	Cross-sectional study	Males (n = 613) and females (n = 100) aged from 7 to 15 years with ADHD and recruited from ADHD clinics in Turkey	To find an association between iron studies and parents with teachers reports and cognitive measures (Conners rating scale-CRS) among those children and adolescents.	Children with lower ferritin levels had higher CRS hyperactivity score levels reported from parents than the control group. Parents may also not have interpretedhyperactivity appropriately with ferritin levels. Although this type of study could not find a causality effect between iron levels and ADHD, researchers suggested to further analyze this case may be by using other types of study design.
Goldberg, N.D.	2013	Literature review	Several articles related to IDA and IBD in adult women and men	To increase awareness of IDA and to diagnose and treat IDA in people with IBD.	IDA is a very common complication in people living with IBD. Inflammation and blood loss in IBD reduces iron levels in the body leading to IDA. Causes need to be treated early in order to reduce the impact of IDA and help for a better quality of life in people with IBD. Recommendations are also given to gastroenterologists in order to treat this matter.
Bener, A., Kamal, M., Bener, H., & Bhugra, D.	2014	Case control	Children (n = 630) aged from 5 to 18 years with ADHD in School and Health care center in Qatar	To determine if there is an association between iron deficiency and ADHD in children including its impact on ADHD development.	Children living with ADHD had decreased serum iron, ferritin, and vitamin D levels compared to their counterpart group after being adjusted for age and gender. Further longitudinal studies need to assess external factors that may have an impact on iron levels in children.
Boyd, H., Basit, S., Harpsøe, M., Wohlfahrt, J. and Jess, T.	2015	Cohort	Pregnant (n = 85000) women with IBD and their newborns in Denmark	To assess the outcomes of women with IBD during pregnancy.	Maternal Crohn's disease results in preterm delivery, low birth weight, pregnancy loss, preeclampsia, and placental problems. However, these observations were viewed when using corticosteroids during pregnancy due to IBD. Children were not followed during childhood to assess the risk of ADHD.
Nielsen, O. H., Ainsworth, M., Coskun, M., & Weiss, G.	2015	Cohort	Children (n = 23645) with ADHD in Denmark	To see if there is an association with ADHD in children and parental autoimmune diseases	Results showed that autoimmune diseases in mothers such as diabetes type 1 and others were linked with ADHD in children. Mothers with Crohn's disease did not show a

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Authors	Year of publication	Type of study	Study population	Aim	Outcome
					significant impact on the risk of ADHD in children. ADHD is multifactorial and influenced by genetic and environmental factors.
Instanes J., Halmoy A, Engeland A., Haavik J., Furu K., Klungsoyr K.	2017	Nested case-control	Mothers having an autoimmune disease and their offspring (n = 47944) with ADHD during development in Norway	To assess if maternal autoimmune disorders during pregnancy are associated with the occurrence of ADHD in children.	Results indicated that maternal autoimmune diseases such as multiple sclerosis increase the risk of developing ADHD in children by 80%. Other diseases such diabetes type 1, rheumatoid arthritis and asthma also showed an impact on ADHD in children. Authors suggested that inflammatory mechanism during pregnancy could possibly explain the occurrence of ADHD in offspring. These results also correlate with Crohn's disease during pregnancy due to its inflammatory mechanism, although results are not shown in this study. Furthermore, those results help better understand the etiology of ADHD in children.
Hegvik, T. A., Instanes, J. T., Haavik, J., Klungsøyr, K., & Engeland, A.	2018	Cross-sectional	Young adult females and males (n = 2,500,118), aged around 25 years, with ADHD from mothers with autoimmune disease living in Norway	To see the association between ADHD in children and autoimmune diseases such as Crohn's disease in mothers with respect to gender.	Ratio is 3:1 in males to females for the occurrence of ADHD. However, this study showed that females with Crohn's disease had higher prevalence of ADHD, but no significant difference was seen in males with ADHD. Authors suggest that these differences among genders can possibly be explained by glial cells mechanisms in CNS, genetic variations on X chromosomes, lifestyle exposure such as smoking or stress occurring in females compared to males.
Islam, K., Seth, S., Saha, S., Roy, A., Das, R., & Datta, A. K.	2018	Cross-sectional	Children (n = 119) diagnosed with ADHD, aged from 8 to 14 years, in the pediatric and psychiatric outpatient clinic in Burdwan Medical College located in India	To find out if there is an association between iron deficiency and ADHD	ADHD was negatively correlated with all hematological values of iron levels, such as hemoglobin, serum ferritin, MCV and MCH. Iron prophylaxis is suggested to help prevent the occurrence of ADHD, since higher levels of iron studies may help protect against this condition.
Kilby, K., Mathias, H., Boisvenue, L., Heisler, C., & Jones, J. L.	2019	Literature review	Articles focusing on adults with IBD and micronutrients deficiencies	To assess the common micronutrients deficiencies associated with IBD with respect to the absorption and outcomes followed by recommendations during screening.	Adults with Crohn's disease have shown several nutritional deficiencies such as reduced levels of iron, cobalamin, folic acid, vitamin K, selenium, calcium, vitamin D and vitamin A. Iron deficiency is explained by iron loss due to mucosal bleeding and inflammatory changes between hepcidin and iron absorption. Since iron deficiency reoccurs quickly in IBD, authors suggest a maintained iron therapy (oral or IV) in order to help adjust iron levels.
Wiegersma, A. M., Dalman, C., Lee, B. K., Karlsson, H., & Gardner, R. M.	2019	Cohort	Mothers (n = 299,768) with IDA during pregnancy and their offspring (n = 532,232) during childhood and adulthood with ADHD in Sweden	To assess the relationship between anemia during pregnancy and the risk of having an offspring with ADHD, autism and intellectual deficiency.	An increased association was observed with maternal IDA within 30 weeks of gestation and ADHD in their offspring males, including autism spectrum disorder and intellectual disability, compared to mothers diagnosed with IDA later during pregnancy. Authors suggest an early screen of IDA in order to help reduce the development of ADHD in their progeny during development.
East, P. L., Doom, J. R., Blanco, E., Burrows, R., Lozoff, B., & Gahagan, S.	2021	Cohort study	Children (n = 959) diagnosed with ADHD, aged from 5 to 16 years, and assessing their hemoglobin levels after randomly receiving an iron fortified formula or none fortified at 6 and 12 months postnatal in Chile	To assess if iron rich formula during infancy helps prevent the occurrence of ADHD during childhood with better verbal and math skills.	Children who received an iron fortified formula during infancy showed better verbal and math skills indirectly through ADHD behavior compared their counterpart group. Fortified iron formulas may help prevent the occurrence of ADHD later during development.

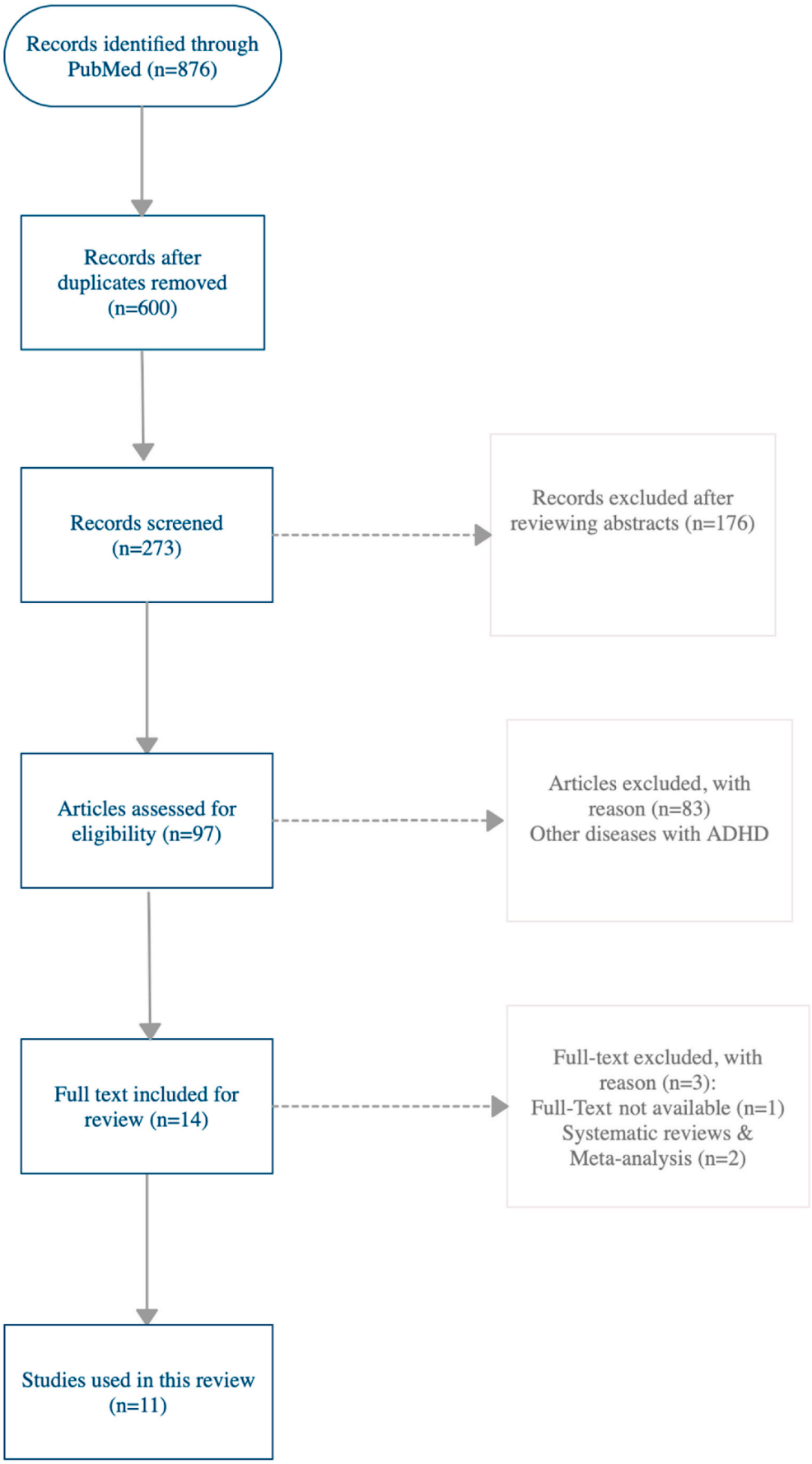

Fig. A1. Method for articles selected in flowchart diagram.

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