The association between iron deficiency anemia at infancy and attention deficit hyperactivity disorder

Michal Yackobovitch-Gavan (michalyg2000@gmail.com)
Tel Aviv University
Daniel Ben-Hefer
Tel Aviv University
Joseph Meyerovitch
Tel Aviv University

Research Article

Keywords: Iron deficiency anemia, ADHD, Childhood, Case-control study, Hemoglobin

Posted Date: April 25th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1567781/v1

Abstract

Purpose: To examine the association between iron deficiency anemia (IDA) at age 9-18 months and attention deficit/ hyperactivity disorder (ADHD) during childhood.

Methods: This case-control study included all the children insured by Clalit Health Services, aged 9-18 months between June 1, 2004 and December 30, 2013 (aged 6-18 years at data collection) with documented hemoglobin (Hb) and mean cell volume levels (MCV). The analysis comprised 19,467 children diagnosed with ADHD based on medical documentation of at least two consecutive stimulant prescriptions. The control group comprised 39,004 children without a record of receiving any prescriptions for ADHD. IDA was defined as Hb<10.5gr/dl and 60fl<MCV<75fl. Moderate anemia was defined as Hb<10gr/dl. The prevalence of IDA was compared by Pearson Chi-Square test and by logistic regression, adjusted to age, sex, cultural background and socioeconomic status.

Results: IDA prevalence was 0.6% lower in the ADHD than the control group: *n*=667 (3.4%) vs. *n*=1,541 (4.0%) (P=0.002), adjusted OR=0.863 (95%CI: 0.816–0.910). The prevalence of moderate ID anemia (Hb<10gr/dl) was similar in the ADHD and the control groups (0.9% vs. 1.0%, P=0.149) (adjusted OR=0.877; 95%CI: 0.725–1.047). Hb at age 9-18 months was clinically similar in the ADHD and control groups (11.965±0.880 and 11.921±0.889 gr/dl, respectively); however, this difference was statistically significant (P<0.001), apparently due to the large sample size.

Conclusions: IDA in infants 9-18 months old was not found to be associated with an increased risk of ADHD during childhood. Other etiological factors for ADHD, such as genetics and environmental factors should be further studied.

What Is Known

- Iron deficiency is the most common dietary deficit in the world.
- During childhood, iron deficiency with or without anemia has a negative impact on children's cognition, behavior, and motor performances.
- Low ferritin levels were reported as a common symptom among children with ADHD.

What is New

- Analyses using the Clalit Health Services database (Israel's largest health service provider), that used univariant and multivariant logistic regression, adjusted to age, sex, cultural background, and socioeconomic status, did not find an association between IDA at age 9–18-months and ADHD during childhood.

Introduction

Attention deficit hyperactivity disorder (ADHD) is a brain, neurodevelopmental disorder characterized by a persistent and inappropriate pattern of inattention, and hyperactivity or impulsivity, which interfere with function or development [1, 2, 3]. ADHD is one of the most common neurodevelopmental disorders diagnosed in Israel and around the world. Global estimates of ADHD among children under age 18 years range from 8 to 12%; the prevalence is higher among boys [4, 5]. Children and adolescents with ADHD have difficulties in school, while studying, and in interpersonal relationships. These lead to social, developmental, and educational setbacks, and substantial financial burden on the education and health systems. ADHD is a lifelong risk factor for comorbidities, such as psychiatric diseases including depression, anxiety, and behavioral disorders, and also accidents, social impairment, and obesity [2, 6]. Although the pathogenesis of ADHD is still unknown, the current view is that it is caused by a complex web of interactions impacted by genetic, environmental, and social variables [7].

Iron is a critical component in a wide range of biological functions, particularly in early life. Although iron has an important role in brain development, the mechanisms by which it functions and the extent of its involvement in physiological mechanisms in the brain are yet unknown. Iron deficiency (ID) is the most common dietary deficit in the world, according to the World Health Organization [8]. In addition, ID is the most common cause for anemia worldwide. The US National Health and Nutrition Examination Survey of 2007–2010 reported anemia among 5.4% of children aged 1–2 years, and IDA among 2.7% [9–11]. In Israel, the rate of anemia in infants was estimated as 15.5% in 2003 and declined to 3.4% in 2014 [13]. During childhood, especially in infancy, ID with or without anemia has a negative impact on children's cognition, behavior, and motor connections [14]. Even in the absence of anemia, mild to moderate ID has been shown to have detrimental functional consequences for the cognitive performance, behavior, and physical growth of newborns, children, and adolescents.

A meta-analysis that included 17 observational studies found that ferritin levels were lower in children with ADHD than in a healthy control group [15]. In addition, a sub-analysis based on seven studies showed that the severity of ADHD was considerably higher in children with than without ID. Although the findings of that meta-analysis do not indicate a causal relationship, low ferritin levels were reported as a common symptom among children diagnosed with ADHD [16]. A number of small interventional studies suggest that iron supplementation may improve ADHD symptoms in children with ID [17, 18]. More high-quality studies are needed to validate the effects of iron supplementation on ADHD symptoms in children and adolescents.

In this study, we aimed to examine the association between IDA at age 9–18 months and the diagnosis of ADHD later in life. Our hypothesis was that a higher proportion of children diagnosed with ADHD had IDA at age 9–18 months than did children not diagnosed with ADHD.

Materials And Methods

We conducted a case-control study utilizing the database of Clalit Health Services (CHS), Israel's largest health service provider, insuring about 5 million people (over 50% of the Israeli population) under the

National Health Insurance Law. CHS provides nationwide primary and secondary community services and hospitalization, medical supplies, and approved medications. The study was approved by CHS institutional review board. The database did not include any patient identifiers. Subject consent was waived due to the retrospective design, based on data from the medical records.

The study population included all the children insured by CHS, aged 9–18 months between June 16, 2004 and December 30, 2013 (aged 6–18 years at data collection) with documented hemoglobin (Hb) and mean cell volume (MCV) levels. The study group included those diagnosed with ADHD or attention deficit disorder based on the medical documentation of at least two consecutive stimulant prescriptions (methylphenidate, dexmethylphenidate, amphetamine, dexamphetamine, lisdexamfetamine), as has been defined in other studies [19, 20]. A control group of healthy individuals without any stimulant prescriptions on record was matched in a ratio of 1–3:1, by age (maximal difference ± 6 months), sex, and cultural background (Arabs, Orthodox Jews, secular-traditional Jews). All those included in the ADHD and study groups were born at term (≥ 37 gestational weeks). Exclusion criteria were diagnoses of anemia-related diseases (thalassemia, spherocytosis, G6PD deficiency, sickle-cell disease), a malignant disease or a known hematology, an organ transplantation, chronic kidney disease, and other chronic diseases.

The primary independent variable was IDA diagnosis at age 9–18 months (Hb < 10.5gr/dl, 60fl < MCV < 75fl) [21]. Moderate IDA anemia was defined as (Hb < 10.5 gr/d, 60fl < MCV < 75fl). Potential confounders included sex (male or female), cultural background (Arab, orthodox Jew, and secular-traditional Jew) and residential socioeconomic status, as defined according to the Israeli Central Bureau of Statistics, and categorized as low, moderate, or high [22].

Statistical analysis

The sample size was calculated according to the assumption that the IDA rate in the general Israeli 9–18-month toddler population is 7% [23, 24], and 20% higher (8.4%) in the ADHD group. For a 5% significance level, an 80% power and a ratio of 1:2 (ADHD: control), a total of 12,981 individuals, 4,327 in the ADHD group and 8,654 in the control group, are required.

The statistical analysis was performed using SPSS version 26 (IBM Corp 2020). Sociodemographic parameters and outcome parameters were compared between the ADHD and the control groups using Pearson's chi-squared tests for categorical variables and Mann Whitney U tests for continuous variables (all had a skewed distribution). Logistic regression analysis was performed to evaluate the association between IDA at 9–18 months and ADHD, adjusted to potential confounders (sex, age, cultural background, and socioeconomic status).

IDA rates at ages 9–18 months, compared between the ADHD and the control groups, using Pearson chi square test, were also stratified by gender, socioeconomic status, and cultural background.

Due to the large sample size (about 4.5 times larger than the calculated sample size), a sensitivity analysis was performed to further examine the significance of the results attained for the entire cohort. The cohort was divided into four case-control matched random samples (such that the sample size of each of the four samples corresponds to the sample size calculated for a power of 80% and a significance level of 5%, in a ratio of 1:2). The ADHD and the control groups were compared according to each of these four random samples separately, using chi-squared and logistic regression to adjust for potential confounders.

Results

A total of 20,258 children in the ADHD group and 39,958 in the control group (age, sex, and cultural background matched) fulfilled the study inclusion and exclusion criteria. From the ADHD group, 791 children were excluded due to platelet levels lower than 150/mm^3. From the control group, 954 children were excluded: three due to Hb levels lower than 1gr/dl, and 951 due to platelet levels lower than 150/mm^3. A total of 19,467 in the ADHD group and 39,004 in the control group were included in the analysis (Fig. 1).

Sociodemographic characteristics of the ADHD group (n = 19,467) and the matched control group (n = 39,004) are presented in Table 1. For both groups, the median age was 8 years, the majority, 67.6%, were males, and the majority, 84%, were secular or traditional Jews. The magnitude of differences between the groups in the distribution of socioeconomic status categories was small. However, the between-group difference was statistically significant ($P < 0.001$), apparently due to the large sample size.

Table 1
Sociodemographic characteristics of the ADHD and the control groups

		ADHD Group n = 19,467	**Control Group** n = 39,004	**P**
Sex *n* (%)	Male	13,169 (67.6%)	26,356 (67.6%)	0.862
	Female	6,298 (32.4%)	12,648 (32.4%)	
Cultural background *n* (%)	Arab	1,520 (7.8%)	3,057 (7.8%)	0.831
	Orthodox Jewish	1,631 (8.4%)	3,323 (8.5%)	
	Secular and Traditional Jewish	16,316 (83.8%)	32,621 (83.6%)	
Socioeconomic Status *n* (%)	Low	5,923 (30.6%)	12,091 (31.2%)	< 0.001
	Medium	9,142 (47.2%)	17,647 (45.5%)	
	High	4,296 (22.2%)	9,005 (23.2%)	
Age, Median (IQR)		8 (7, 9)	8 (7, 9)	0.905

P values represent Pearson Chi-Square test for categorial variables or Mann Whitney U Test for numerical variables with a skewed distribution.

ADHD, attention deficit hyperactivity disorder; IQR, interquartile range

The difference, 0.6%, in IDA rates between the ADHD and control groups (3.4% and 4.0%, respectively) was small in magnitude; yet statistically significant (P = 0.002), apparently due to the large sample size. The difference remained statistically significant after controlling for potential confounders (age, sex, cultural background, and socioeconomic status) OR = 0.865 95%CI: 0.816–0.910 (P = 0.005) (Table 2). The rate of moderate ID anemia (60fl < MCV < 75fl, Hb $\leq$ 10/dl) was similar in the ADHD group (0.9%) and the control group (1.0%) OR = 0.877 95%CI: 0.725–1.047 (P = 0.149) (Table 2). The mean Hb levels at age 9–18 months were similar in magnitude in the ADHD and control groups (11.965 ± 0.880 and 11.921 ± 0.889 gr/dl, respectively); however, this difference was statistically significant (P < 0.001), apparently due to the large sample size. No between-group differences were found in MCV and in mean cell hemoglobin (MCH) levels at age 9–18 months.

Table 2
IDA rate, hemoglobin, MCV, MCH levels at age 9–18 months in the ADHD and the control groups

		ADHD Group **n = 19,467**	**Control Group** **n = 39,004**	**Crude P**	**OR** **(95% CI)**	**Adjusted P**
IDA rate *n* (%)		667 (3.4%)	1,541(4.0%)	0.002	0.865 (0.788–0.949)	0.005
Moderate anemia with ID rate *n* (%)		178 (0.9%)	406 (1.0%)	0.160	0.877 (0.735–1.047)	0.149
Blood count indices at age 8–19 months, Median (IQR) Mean ± SD	Hb (gr/dl)	11.9 (11.4, 12.5) 11.965 ± 0.880	11.9 (11.3, 12.5) 11.921 ± 0.890	< 0.001		
	MCV (gr/dl)	76.6 (73.7, 79.5) 76.721 ± 3.773	76.6 (73.8, 79.4) 76.706 ± 3.768	0.691		
	MCH (gr/dl)	25.9 (24.9, 26.9) 25.900 ± 1.468	25.9 (24.9, 26.9) 25.920 ± 1.489	0.144		

Crude P values represent Pearson Chi-Square test for categorial variables or Mann Whitney U Test for numerical variables with a skewed distribution.

Adjusted P values represent logistic regression analysis for the association between IDA at 9–18 months and ADHD, adjusted to potential confounders (sex, age, cultural background and socio-economic status).

ADHD, attention deficit hyperactivity disorder; OR, odds ratio; Hb, hemoglobin; IDA, iron deficient anemia; MCV, mean cell volume; MCH, mean cell hemoglobin; IQR, interquartile range; SD, standard deviation

Table 3compares between the ADHD and the control group, IDA rates at age 9–18 months, stratified by gender, socioeconomic status, and cultural background. The prevalence of IDA in 9-18-month-old children was highest among those with low (n = 4.5%) compared to medium (3.4%) or high socioeconomic status (3.5%) (P < 0.001). IDA prevalence was higher among orthodox Jews (6.1%) (a population characterized by large numbers of children and relatively low socioeconomic status) than Arabs (4.5%) and secular-traditional Jews (3.5%) (P < 0.001). Statistically significant differences in IDA rates between the ADHD and the control groups were found in boys (3.4% vs. 4.1%, P < 0.002) but not in girls, in low socioeconomic status (4.0% vs. 4.7%, respectively, P = 0.018) but not in medium and high socioeconomic status, and in secular-traditional Jews (3.2% vs. 3.6%, respectively, P = 0.006) but not in the other cultural background groups.

Table 3
IDA rates at ages 9–18 months in the entire cohort, and in the ADHD and the control groups, stratified by gender, socioeconomic status, and cultural background

			ALL	**ADHD Group**	**Control Group**	***P***
Gender	Male	*n*	39,525	13,169	26,356	0.002
		IDA *n* (%)	1,497 (3.8%)	452 (3.4%)	1,072 (4.1%)	
	Female	*n*	18,946	6,298	12,648	0.326
		IDA *n* (%)	684 (3.6%)	215 (3.4%)	469 (3.7%)	
Socio-Economic Status	Low	*n*	18,014	5,923	12,091	0.018
		IDA *n* (%)	807 (4.5%)	234 (4.0%)	573 (4.7%)	
	Medium	*n*	26,789	9,142	17,647	0.217
		IDA *n* (%)	920 (3.4%)	296 (3.2%)	624 (3.5%)	
	High	*n*	13,301	4,296	9,005	0.092
		IDA *n* (%)	465 (3.5%)	133 (3.1%)	332 (3.7%)	
Cultural background	Arab	*n*	4,577	1,520	3,057	0.518
		IDA *n* (%)	204 (4.5%)	63 (4.1%)	141 (4.6%)	
	Orthodox Jew	*n*	4,954	1,631	3,323	0.240
		IDA *n* (%)	300 (6.1%)	89 (5.5%)	211 (6.3%)	
	Secular and Traditional Jew	*n*	48,937	16,316	32,621	0.006
		IDA *n* (%)	1704 (3.5%)	515 (3.2%)	1,189 (3.6%)	
P values represent Pearson Chi-Square test						
ADHD, attention deficit hyperactivity disorder; IDA, iron deficient anemia						

In a sensitivity analysis, in which the study cohort was divided to four case-control random samples, statistically significant differences in IDA rates between the ADHD and the control groups were found only in two of four of the random samples (Table 4). This result was consistent also after controlling for potential confounders (age, sex, cultural background, and socioeconomic status).

Table-4: A sensitivity analysis performed by dividing the study cohort to four random samples, comparing IDA rates in ages 9-18 months between the ADHD and the control groups

		ADHD Group	Control Group	Crude P	OR (95% CI)	Adjusted P
1	*n*=14,618	*n*=4,881	*n*=9,737	0.031	0.819 (0.679-0.988)	0.037
	IDA *n* (%)	161 (3.3%)	393 (4.0%)			
2	*n*=14,618	*n*=4,856	*n*=9,762	0.018	0.801 (0.661-0.971)	0.024
	IDA *n* (%)	152 (3.1%)	383 (3.9%)			
3	*n*=14,620	*n*=4,877	*n*=9,743	0.470	0.933 (0.779-1.118)	0.453
	IDA *n* (%)	182 (3.7%)	389 (4.0%)			
4	*n*=14,615	*n*=4,853	*n*= 9,762	0.381	0.908 (0.755-1.092)	0.306
	IDA *n* (%)	172 (3.5%)	376 (3.9%)			

Crude P values represent Pearson Chi-Square tests.

Adjusted P values represent logistic regression analysis for the association between IDA at 9-18 months and ADHD, adjusted to potential confounders (sex, age, cultural background and socio-economic status).

ADHD, attention deficit hyperactivity disorder; IDA, iron deficient anemia

Discussion

In the current study, we evaluated the association between IDA at 9–18 months and ADHD during childhood in a large Israeli cohort (n = 58,471) of healthy children insured by CHS.

Our findings showed no association between IDA at age 9–18-months and ADHD development during childhood, thus rejecting our hypothesis.

The IDA rate in our cohort was 3.8%, which is comparable to the country's IDA rates. According to CHS data, IDA rates in the general pediatric population in the country between 2005 and 2013 were 5–8%, while the rate in 2014 was about 3.4% [25]. Our findings reflect a downward trend in the prevalence of IDA in Israel over time, which is likely due to increased awareness of iron supplementation in babies and IDA prevention amongst the general population in Israel. The prevalence of IDA in 9-18-month-old children was higher among those with low compared to medium or high socioeconomic status. IDA prevalence was higher among orthodox Jews (a population characterized by large numbers of children and relatively low socioeconomic status) than among Arabs (who had medium rates of IDA) and secular-traditional Jews (who had the lowest rates of IDA). These findings are consistent with the literature, and indicate that lower socioeconomic groups have a greater prevalence of anemia [26]. A possible explanation is that parents from low socioeconomic status are less aware and are less likely to treat IDA. Preventive public health actions such as parental guidance, medical and social follow-up to support a balanced and iron-rich diet for mother and baby, and daily treatment with iron drops for infants according to the Ministry of Health's protocol, may reduce the prevalence of IDA in these groups and improve public health in Israel.

Iron is a key component in brain development, particularly in infancy, and in brain function and dopaminergic activity regulation, all of which may be linked to the pathogenesis and symptoms of ADHD [15, 27, 28]. Animal models showed very clear irreversible abnormalities resulting from ID during pregnancy and infancy; however, in humans, the effects of ID in the first two years of life on cognitive and mental development in childhood are unclear [29].

Contrary to our hypothesis, we observed that IDA rate in the ADHD group (3.4%) was 0.6% lower than in the control group (4.0%), a difference that was small in magnitude yet statistically significant, due to the large sample size. Sensitivity analysis, in which the analysis was repeated in four random case-control matched samples, each with an adequate sample size to answer the primary outcome, showed higher rates of IDA, with statistical significance, in the ADHD group than in the control group only in two of four random samples. Comparing the rates of moderate ID anemia (Hb < 10gr/dl), significant between-group differences were not found (0.9% in the ADHD group vs. 1.0% in the control group). According to these results, ID is not a significant factor in the etiology of ADHD. Genetic factors, brain function and structure, acute or cumulative exposures to environmental toxins, prematurity, low birth weight, epilepsy, in utero brain damage, and severe head injury during life are among the factors that may be involved in the development of ADHD [30].

In the stratified analyses, significant differences in IDA rates between the ADHD and the control groups were found only among boys, among children of low socioeconomic status, and among secular-traditional Jews. All these statistically significant differences in IDA rates were small in magnitude (the maximal difference in IDA rate was 0.7%). The statistically significant findings among boys and among secular and traditional Jews, but not in the other stratified subgroups, may be attributed to the substantially larger proportion of boys compared to girls, and of secular-traditional Jews compared to the other cultural background subcategories. However, the significantly lower IDA rates in the ADHD compared to the control group, among those with low but not higher socioeconomic status, cannot be attributed only to large sample size. This is because the largest socioeconomic category was medium socioeconomic status, comprising about 46% of the sample. A plausible explanation for the results is a larger gap between parents with high compared to low awareness to their children's health in the low socioeconomic group. Parents with higher awareness are both more compliant with the recommendation of iron supplementation in babies and more aware of ADHD symptoms. They are more apt to seek evaluation and treatment, and hence their offspring may be expected to show a higher rate of diagnosed /treated ADHD and a lower rate of IDA. In contrast, parents with lower awareness may have less awareness to the importance of iron supplementation and may also be less aware of ADHD symptoms. Hence, their offspring may be expected to show lower rates of diagnosed /treated ADHD and higher rates of IDA. Similar differences in awareness may also help explain the results in the entire study cohort.

To the best of our knowledge, this is the first study that evaluated the association between IDA in childhood and the development of ADHD. This highlights the need for more research on the implications of IDA in childhood on cognitive and mental development later in life. A main strength of this study is the high reliability of the data, derived from the database of CHS. The exposure parameters (diagnosis of IDA) were recorded from a database of medical records, and not based on persons' memory. Hence, a memory bias, which is common in case-control studies, was avoided. Furthermore, the definition of ADHD for inclusion in the study group required a diagnosis of ADHD, and receipt of a prescription by a medical specialist.

There are several methodological limitations to this study. First, the IDA definition was based solely on Hb and MCV values (Hb < 10.5gr/dl, 60fl < MCV < 75fl). Due to a lack of information in our database, ferritin and iron values were not considered. However, congenital anemia was ruled out, indicating that the main reason for anemia was indeed IDA. Second, the timing of IDA is an important factor in neurocognitive development [31]. In our study, IDA was evaluated at age 9–18 months, and we have no information from earlier life to determine the initiation of IDA (i.e., mother's diet iron content during pregnancy or whether the child had significant iron deficiency from birth to the examination of IDA). A third limitation is the definition of ADHD, which was based on medical prescription. This results in a non-differential misclassification of the outcome for the two groups. Accordingly, some children who meet the criteria for ADHD diagnosis may choose not to receive pharmaceutical treatment. Nonetheless, other studies have classified people as having ADHD according to medical treatment [19, 20, 32].

This study did not find an association between IDA at age 9–18 months and ADHD development during childhood. Further studies are warranted, to examine the effects of ID in the early developmental stages of the brain (during pregnancy and in the first weeks after birth) and other environmental factors, on the development of ADHD in childhood.

Abbreviations

ADHD (attention deficit hyperactivity disorder), CHS (Clalit Health Services), ID (iron deficiency), IDA (iron deficiency anemia), MCV (mean cell volume), OR (odds ratio), SD (standard deviation).

Statements And Declarations

Funding: The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing interests: The authors have no relevant financial or non-financial interests to disclose.

Author Contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Michal Yackobovitch-Gavan, Daniel Ben-Hefer and Joseph Meyerovitch. The first draft of the manuscript was written by Michal Yackobovitch-Gavan and Daniel Ben-Hefer, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval: The study was approved by Clalit Health Services (CHS) institutional review board. The database did not include any patient identifiers. Subject consent was waived due to the retrospective design, based on data from the medical records.

Consent to participate: Not applicable.

Consent for publication: Not applicable.

References

1. American Psychiatric Association (2013). Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). American Psychiatric Pub.
2. Attention-Deficit/Hyperactivity Disorder. Nimh.nih.gov (2021). Available from: https://www.nimh.nih.gov/health/topics/attention-deficit-hyperactivity-disorder-adhd/index.shtml. Accessed 21 January 2022.
3. Attention Deficit Hyperactivity Disorder. Nhs.uk. (2021) Available from: https://www.nhs.uk/conditions/attention-deficit-hyperactivity-disorder-adhd/diagnosis/ Accessed 21 January 2022.
4. Luo Y, Weibman D, Halperin JM, Li X (2019). A Review of Heterogeneity in Attention Deficit/Hyperactivity Disorder (ADHD). Front Hum Neurosci 13:42. https://doi.org/10.3389/fnhum.2019.00042.
5. Thomas R, Sanders S, Doust JA, Beller E, Glasziou P (2015). Prevalence of attention-deficit/Hyperactivity disorder: A systematic review and meta-analysis. Pediatrics 135:e994-1001. https://doi.org/10.1542/peds.2014-3482.
6. Xu G, Strathearn L, Liu B, Yang B, Bao W (2018). Twenty-Year Trends in Diagnosed Attention-Deficit/Hyperactivity Disorder Among US Children and Adolescents, 1997–2016. JAMA Network Open 1:e181471. https://doi.org/10.1001/jamanetworkopen.2018.1471.
7. Greenblatt JM (2017). Micronutrient Deficiencies in ADHD: A Global Research Consensus. Orthomol Med 32(6).
8. Chen MH, Su TP, Chen YS, Hsu JW, Huang KL, Chang WH, Chen TJ, Bai YM (2013). Association between psychiatric disorders and iron deficiency anemia among children and adolescents: a

nationwide population-based study. BMC psychiatry 13:161. https://doi.org/10.1186/1471-244X-13-161.

9. McDonagh M, Blazina I, Dana T, Cantor A, Bougatsos C (2015). Routine Iron Supplementation and Screening for Iron Deficiency Anemia in Children Ages 6 to 24 Months: A Systematic Review to Update the U.S. Preventive Services Task Force Recommendation [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US). Report No.: 13-05187-EF-1.
10. Ha B, O'Sullivan DL, Diamond CA, Plumb AJ, Sleeth JS, Greer FR, Kling PJ (2018). Improving Rates of Screening for Anemia in Infancy. Clin Pediatr (Phila) 57:1064–1068. https://doi.org/10.1177/0009922817744608.
11. Gupta PM, Perrine CG, Mei Z, Scanlon KS (2016). Iron, Anemia, and Iron Deficiency Anemia among Young Children in the United States. Nutrients 8:330. https://doi.org/10.3390/nu8060330.
12. Rajendran K, Trampush JW, Rindskopf D, Marks DJ, O'Neill S, Halperin JM (2013). Association Between Variation in Neuropsychological Development and Trajectory of ADHD Severity in Early Childhood. Am J Psychiatry 170:1205–1211. https://doi.org/10.1176/appi.ajp.2012.12101360.
13. Meyerovitch J, Sherf M, Antebi F, Barhoum-Noufi M, Horev Z, Jaber L, Weiss D, Koren A (2006). The Incidence of Anemia in an Israeli Population: A Population Analysis for Anemia in 34512 Israeli Infants Aged 9 to 18 Months. Pediatrics 118:e1060. https://doi.org/10.1542/peds.2006-0024.
14. Wang Y, Huang L, Zhang L, Qu Y, Mu D (2017). Iron Status in Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-Analysis. PloS one 12:e0169145. https://doi.org/10.1371/journal.pone.0169145.
15. Tseng PT, Cheng YS, Yen CF, Chen YW, Stubbs B, Whiteley P, Carvalho AF, Li DJ, Chen TY, Yang WC, Tang CH, Chu CS, Yang WC, Liang HY, Wu CK, Lin PY (2018). Peripheral iron levels in children with attention-deficit hyperactivity disorder: a systematic review and meta-analysis. Sci Rep 8:788. https://doi.org/10.1038/s41598-017-19096-x.
16. Wang M (2016). Iron Deficiency and Other Types of Anemia in Infants and Children. Am Fam Physician 93:270–278.
17. Sever Y, Ashkenazi A, Tyano S, Weizman A (1997). Iron Treatment in Children with Attention Deficit Hyperactivity Disorder. Neuropsychobiology 35:178–180. https://doi.org/10.1159/000119341.
18. Konofal E (2008). Effects of Iron Supplementation on Attention Deficit Hyperactivity Disorder in Children. Pediatr Neurol 38:20–26. https://doi.org/10.1016/j.pediatrneurol.2007.08.014.
19. Hodgkins P, Sasané R, Meijer WM (2011). Pharmacologic Treatment of Attention-Deficit/Hyperactivity Disorder in Children: Incidence, Prevalence, and Treatment Patterns in The Netherlands. Clin Ther 33:188–203. https://doi.org/10.1016/j.clinthera.2011.03.001.
20. Norum J, Olsen AI, Nohr FI, Heyd A, Totth A (2014). Medical treatment of children and youths with attention-deficit/hyperactivity disorder (ADHD): a Norwegian Prescription Registry Based Study. Glob J Health Sci 6:155–162. https://doi.org/10.5539/gjhs.v6n4p155.
21. What is ADHD?. cdc.gov. 2021. Available from: https://www.cdc.gov/ncbddd/adhd/facts.html. Accessed 23 January 2022.

22. Meyerovitch J, Zlotnik M, Yackobovitch-Gavan M, Phillip M, Shalitin S (2017). Real-Life Glycemic Control in Children with Type 2 Diabetes: A Population-Based Study. J Pediatr 188:173–180. https://doi.org/10.1016/j.jpeds.2017.05.074.
23. Farbstein I, Mansbach-Kleinfeld I, Auerbach JG, Ponizovsky AM, Apter A (2014). The Israel Survey of Mental Health among Adolescents: prevalence of attention-deficit/hyperactivity disorder, comorbidity, methylphenidate use, and help-seeking patterns. Isr Med Assoc J 16:568–573.
24. Meyerovitch J, Aviner S, Sherf M, Comaneshter D, Fredkin,A, Lax Y (2015). Prevention of anemia in a large in pediatric population-using information technology. Society of Medical Quality, Tel Aviv.
25. Meyerovitch J, Carmi D, Aviner S, Sherf M, Comaneshter D, Laks Y, Key C, Gabbay U, Cohen AD (2022). Reducing infantile anemia: insight on patterns of process and outcome indicators by ethnicity and socioeconomic class during a 10-year intervention program and 5 years after. Isr J Health Policy Res 11:2. https://doi.org/0.1186/s13584-021-00510-9.
26. Syed S, Addo OY, De la Cruz-Góngora V, Ashour FAS, Ziegler TR, Suchdev PS (2016). Determinants of Anemia among School-Aged Children in Mexico, the United States and Colombia. Nutrients 8:387. https://doi.org/10.3390/nu8070387.
27. Cortese S, Azoulay R, Castellanos FX, Chalard F, Lecendreux M, Chechin D, Delorme R, Sebag G, Sbarbati A, Mouren MC, Bernardina BD, Konofal E (2012). Brain iron levels in attention-deficit/hyperactivity disorder: a pilot MRI study. World J Biol Psychiatry 13:223–231. https://doi.org/10.3109/15622975.2011.570376.
28. Beard JL (2008). Why iron deficiency is important in infant development. J Nutr 138:2534–2536. https://doi.org/10.1093/jn/138.12.2534.
29. McCann S, Perapoch Amadó M, Moore SE (2020). The Role of Iron in Brain Development: A Systematic Review. Nutrients 12:2001. https://doi.org/10.3390/nu12072001.
30. Attention deficit hyperactivity disorder (ADHD). nhs.uk. 2021. Available from: https://www.nhs.uk/conditions/attention-deficit-hyperactivity-disorder-adhd/ Accessed 21 January 2022.
31. Beard J (2003). Iron deficiency alters brain development and functioning. J Nutr 133(5 S):1468S-1472S. https://doi.org/10.1093/jn/133.5.1468S.
32. Yackobovitch-Gavan M, Mimouni-Bloch A, Gabbay U, Carmi D, Goldstein B, Keinan-Boker L, Bloch S, Meyerovitch J (2021). Sex-Specific Long-Term Height and Body Mass Index Trajectories of Children Diagnosed with Attention-Deficit/Hyperactivity Disorder and Treated with Stimulants. J Pediatr 238:296–304. https://doi.org/10.1016/j.jpeds.2021.07.018.

Figures

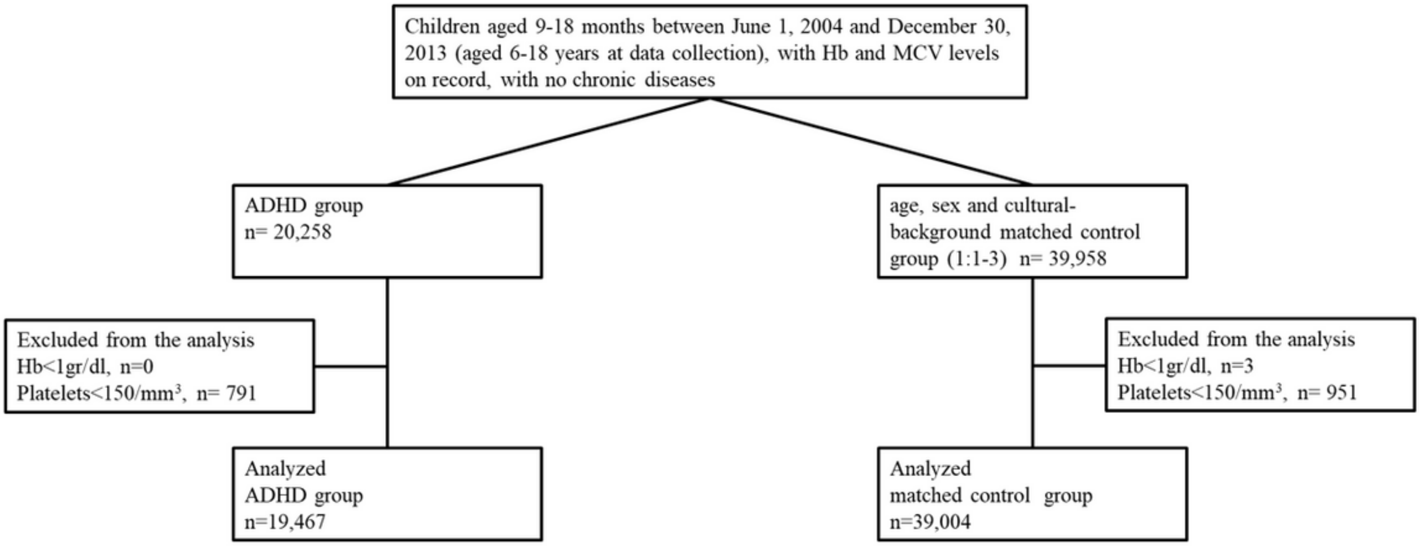

Figure 1

Flow chart of the study population.

Hb, hemoglobin; MCV, mean cell volume; ADHD, attention deficit hyperactivity disorder.