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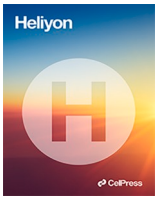

Research article

The association between infantile microcytic anemia and attention deficit hyperactivity disorder, a case-control study

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ABSTRACT

Background: Microcytic anemia due to iron deficiency is the most common type of anemia in children in Israel and many parts of the world, and has been shown to have negative consequences for the cognitive performance. We aimed to examine the association between microcytic anemia at age 9–18 months and ADHD during childhood.

Methods: This case-control study included healthy children aged 6–18 years at data collection (April 2020), insured by Clalit-Health-Services, and aged 9–18 months between June 2004 and December 2013, when a blood-count was performed. The study group included children diagnosed with ADHD based on the medical documentation of at least two consecutive stimulant prescriptions. A control group without any stimulant prescriptions was matched in a ratio of 1–3:1, by year of birth, sex and cultural background. Any microcytic anemia was defined as Hb < 10.5 g/dl and MCV 60–75 fl. Moderate microcytic anemia as Hb 7–9.9 g/dl. We performed a conditional-logistic-regression analysis, adjusted by socioeconomic status (SES) and year of birth. Sensitivity analysis examined this association stratified by sex, cultural background, SES and age at data collection quintiles.

Results: Any microcytic anemia prevalence was lower in the ADHD group (n = 19,467) as compared to the controls (n = 39,004) (3.4 % and 4.0 %, respectively), adjusted-OR = 0.86 (95% CI: 0.78, 0.98). The prevalence of moderate microcytic anemia was similar (0.9 % vs. 1.0 %). Lower any microcytic anemia prevalence in the ADHD group was found in boys, secular-traditional Jews, and in the 4th quintile of age (12.1–13.5 years).

Conclusions: We found a small inverse association between microcytic anemia at 9–18-months and ADHD during childhood, thus rejecting our hypothesis that microcytic anemia at infancy is associated with a higher prevalence of ADHD. Further studies are warranted, to examine the effects of ID and brain iron concentration on the development of ADHD in childhood.

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1. 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]. ADHD is one of the most common neurodevelopmental disorders diagnosed around the world, and more common among boys as compared to girls [3,5].

According to several meta-analyses, global estimates of ADHD among children under age 18 years range from 5 to 8% [3,6]. One meta-analysis reported no significant differences in prevalence between North America and Europe, Asia, Africa, South America, and Oceania.4 However, a later meta-analysis reported 4 % higher prevalence of ADHD among children in the Middle East compared with North America [5]. One meta-analysis found no increase in the prevalence of ADHD in children over the past three decades [4]. However, large studies from the U.S., Sweden and Israel indicate that ADHD is more likely to have been diagnosed in recent years, which reflects changes in administrative and clinical practices [6–9].

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 depression, anxiety, and behavioral disorders, and also for accidents, social impairment, and obesity [2,5,6]. Although the pathogenesis of ADHD is still unknown, the current literature supports that the majority of cases of ADHD are brought on by the combined impacts of numerous genetic and environmental factors, each of which has a comparatively small impact. ADHD is very seldom brought on by a single genetic or environmental risk factor [6]. Prematurity was also found as a risk factor for ADHD [10].

Iron is a critical component in a wide range of biological functions, particularly in early life [11]. Iron deficiency (ID) is the most common dietary deficit in the world, according to the World Health Organization [12]. 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 ID anemia (IDA) among 2.7 % [13–16]. In Israel, the prevalence of anemia in infants was estimated as 15.5 % in 2003 and declined to 3.4 % in 2014 [17].

The most common initial diagnostic test used to evaluate for anemia is a complete blood count, which differentiate microcytic, normocytic, and macrocytic anemia based on the mean corpuscular volume [18]. Microcytic anemia due to ID is the most common type of anemia in children in Israel [19] and many parts of the world, and happens at the late stage of iron deficiency [18]. Ferritin is a good reflection of total iron storage and declines at an early stage of iron deficiency. Serum ferritin measurement is a sensitive and a very common test for diagnosing ID even before IDA occurs. Further testing may also be necessary if suspected iron deficiency anemia does not respond to treatment [18].

During childhood, especially in infancy, ID with or without anemia has a negative impact on children's cognition, behavior, and motor connections [20]. Even in the absence of anemia, mild to moderate ID has been shown to have negative functional consequences for the cognitive performance, behavior, and physical growth of newborns, children, and adolescents [20]. A meta-analysis that included 17 observational studies found that ferritin levels, which were measured in children aged 6.7–13.3 years, were lower in those who diagnosed with ADHD than in a healthy control group [21]. A sub-analysis based on seven studies showed that the severity of ADHD was considerably higher in children who were diagnosed with ID at ages 1.5–11.5 years as compared to a matched control group of children with no ID [21]. 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 [18]. Several small interventional studies suggest that iron supplementation may improve ADHD symptoms in children aged 5–11 years with ID [22,23]. More high-quality studies are needed to validate the effects of iron supplementation on ADHD symptoms in children and adolescents. Despite good mechanistic evidence for the role of iron in brain development, evidence for the impact of iron deficiency or iron supplementation on early development is still inconsistent [24].

In this study, we aimed to examine the association between microcytic anemia, which dominantly represents IDA at age 9–18 months and the diagnosis of ADHD later in life. Due to a lack of information in our database, ferritin and iron values were not considered; however, congenital anemia and anemia-related diseases were ruled out, indicating that the main reason for anemia in our cohort was ID. Our hypothesis was that a higher proportion of children diagnosed with ADHD had microcytic anemia at age 9–18 months than did children not diagnosed with ADHD.

2. Materials and methods

2.1. Case-control selection

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.

The study population included all the children insured by CHS, aged 6–18 years at data collection (April 2020), when data on ADHD diagnosis was collected. We have additionally collected historical data from the electronic medical records for each of the participants at age 9–18 months (between June 16, 2004 and December 30, 2013) which included blood count indices [hemoglobin (Hb), mean cell volume (MCV) levels, white blood cells and thrombocyte count]. In Israel, the assessment of anemia between 9 and 18 months is a routine in all infants, as it is included in the pediatric medical quality measurements and the prevalence of performance is high (above 87 % in the CHS) [19]. 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 [9,25–30]. In Israel, the diagnosis of ADHD and the first recommendation for medication is expected to be given by a neurologist, a psychiatrist or by a qualified pediatrician recognized by the Ministry of Health upon completion of a course on ADHD diagnosis based on updated DSM criteria and a formal diagnostic questionnaire for parents and teachers [9,27,31].

A control group of healthy individuals without any stimulant prescriptions on record for the entire follow-up was matched in a ratio of 1–3:1, by year of birth (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), abnormal leukocytes and thrombocytes values, a malignant disease or a known hematology, an organ transplantation, chronic kidney disease, and other chronic diseases.

A total of 20,258 children in the ADHD group and 39,958 in the control group fulfilled the study inclusion 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 6 g/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).

2.2. Exposure and measured confounders

The primary independent variable was any microcytic anemia diagnosis at age 9–18 months (Hb < 10.5 g/dl, MCV 60–75 fl) according to the CHS medical quality measurements [19]. Anemia was also classified according to the WHO definition for children 6–59 months of age (no anemia Hb > 11.5 g/dl, mild 10–10.9 g/dl, moderate 7–9.9 g/dl, severe <7 g/dl) [32].

Potential confounders included sex, cultural background (Arab, orthodox Jew, and secular-traditional Jew) and age at the time of the case diagnosis (first stimulant prescription). These potential confounders were controlled by matching. Additional potential confounders included age at data collection (birth year) and residential socioeconomic status (SES), as defined according to the Israeli Central Bureau of Statistics, and categorized as low, medium, or high [33].

2.3. Statistical analysis

The statistical analysis was performed using SPSS version 27 (IBM Corp 2020). Sociodemographic parameters and blood count indices are presented as counts and percentages, median and interquartile range (IQR) or mean and standard deviation (SD), according to the variable distribution. 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).

Conditional logistic regression analysis according to the matching between the ADHD and the controls was performed to evaluate the association between microcytic anemia at 9–18 months and ADHD. The conditional logistic regression was further adjusted to SES, (as this variable was found to be statistically different between the ADHD and the control group).

Sensitivity analysis was performed by stratifying the study cohort by sex, SES, cultural background, and age at data collection quintiles.

The data was complete for all variables, with the exception of SES, which was unavailable for 367 (0.6 %) participants. As almost all the exposure and outcome variables had no missing data, no imputation was performed.

3. Results

A total of 19,467 in the ADHD group and 39,004 in the control group were included in the analysis. 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

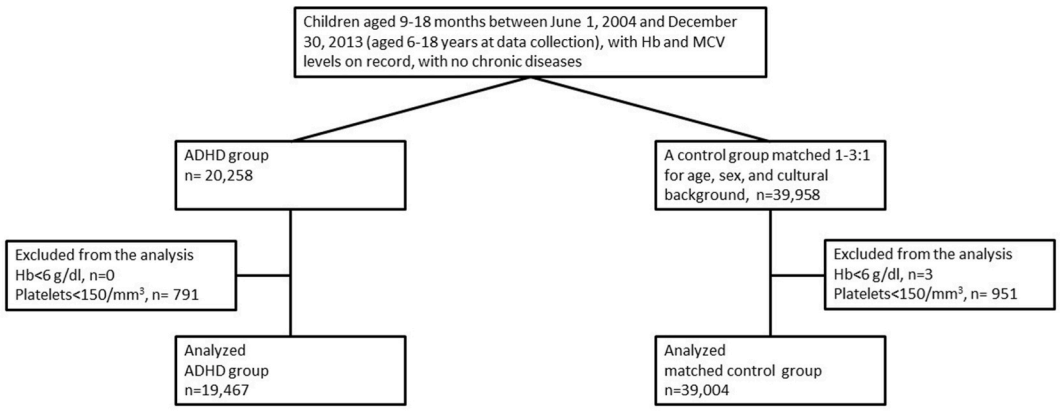

Fig. 1. Flow chart of the study population. Hb, hemoglobin; MCV, mean cell volume; ADHD, attention deficit hyperactivity disorder.

median age at data collection was 11 years (IQR 9, 13), the median age at microcytic anemia assessment was 12 months (IQR 11, 14). The median age at first stimulant prescription was 8 years (IQR 7, 9). The majority, 67.6 %, were males, and 84 % were secular or traditional Jews. The magnitude of differences between the groups in the distribution of socioeconomic status (SES) categories was relatively small, but significantly differed between groups ($P < 0.001$), as the ADHD group had a lower prevalence of low SES and high SES, and a higher prevalence of medium SES, as compared to the control group.

Any microcytic anemia prevalence (defined as Hb < 10.5 g/dl, MCV 60–75 fl according to the CHS medical quality measurements [19]) was lower by 0.6 % in the ADHD group as compared to the controls (3.4 % and 4.0 %, respectively), OR = 0.86 (95%CI: 0.78, 0.94), adjusted OR = 0.91 (95%CI 0.84–0.98) (Table 2).

The prevalence of mild microcytic anemia (Hb 10–10.9 g/dl, WHO definition for children 6–59 months of age),[30] was lower in the ADHD group (10.7 %) as compared to the control group (11.6 %), crude OR 0.91 (95%CI 0.86, 0.96) and adjusted OR 0.94 (95%CI 0.90,0.98). The prevalence of moderate microcytic anemia (Hb 7–9.9 g/dl) 30 was similar in the ADHD group (0.9 %) and the control group (1.0 %), crude OR = 0.86 (95%CI 0.72, 1.03) adjusted OR = 0.91; 95%CI: 0.79, 1.06). Only one participant had severe anemia (Hb = 6.2 g/dl) and was excluded from this analysis (Table 2).

The mean Hb levels at age 9–18 months was 0.04 higher (95 % CI 0.03, 0.06) in the ADHD group as compared to the control group (11.97 ± 0.88 and 11.92 ± 0.89 g/dl, respectively, $P < 0.001$). No between-group differences were found in MCV and in mean cell hemoglobin (MCH) levels at age 9–18 months (Table 3).

In the stratified analysis (Table 4), the prevalence of any microcytic anemia in 9–18-month-old children was highest among those with low (n = 4.5 %) compared to medium (3.4 %) or high SES (3.5 %). Any microcytic anemia prevalence was higher among orthodox-Jews (6.1 %) (a population characterized by large numbers of children and relatively low SES) than Arabs (4.5 %) and secular-traditional Jews (3.5 %). The prevalence of any microcytic anemia was lower in the first quintile of age at data collection (most recent years of birth) (3.2 %) than in the higher quintile (3.8 %, 3.9 % and 3.9 %, in the 2nd, 3rd and 4th quintiles, respectively) and the highest in the 5th quintile (most early years of birth) (4.2 %).

Differences in any microcytic anemia prevalence between the ADHD and the control groups were found in boys (3.4 % vs. 4.1 %, respectively, OR = 0.83, 95%CI: 0.74,0.93); in secular-traditional Jews (3.2 % vs. 3.6 %, respectively, OR = 0.85, 95%CI: 0.77,0.95); and in the 4th age at data collection quintile (12.1–13.5 years) (3.2 % vs. 4.2 %, respectively, OR = 0.69, 95%CI: 0.51, 0.94). When the stratification was done according to SES, no differences in any microcytic anemia prevalence were found between the ADHD and the control group (Table 4).

4. Discussion

In the current study, we evaluated the association between microcytic anemia (which mostly represents 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 a small inverse association between any microcytic anemia at age 9–18-months and ADHD development during childhood, thus rejecting our hypothesis that microcytic anemia at infancy is associated with a higher prevalence of ADHD.

Any microcytic anemia prevalence in our cohort was 3.8 %, which is comparable to the country's microcytic anemia prevalence. The prevalence of any microcytic anemia in our sample was reduced along the years, as the prevalence was 3.2 % in the first quintile of age at data collection (children born between 2010 and 2013), and the highest (4.2 %) in the in the fifth quintile (children born between 2006 and 2004). This observation is in line with an earlier report that following an intervention program aimed at reducing the prevalence of infantile anemia, which was initiated in 2005 by the CHS in Israel, the prevalence of infantile anemia according to the same definition, was reduced from 7.8 % in 2005 to 3.4 % in 2014 and to 2.7 % in 2019 [19]. 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.

The prevalence of any microcytic anemia in 9–18-month-old children was higher among those with low compared to medium or

Table 1
Sociodemographic characteristics of the ADHD and the control groups.

		ADHD Group n = 19,467	Control Group n = 39,004	P Value
Sex *n* (%)	Male	13,169 (67.6 %)	26,356 (67.6 %)	0.86
	Female	6298 (32.4 %)	12,648 (32.4 %)	
Cultural background *n* (%)	Arab	1520 (7.8 %)	3057 (7.8 %)	
	Orthodox Jewish	1631 (8.4 %)	3321 (8.5 %)	0.83
	Secular and Traditional Jewish	16,316 (83.8 %)	32,626 (83.7 %)	<0.001
Socioeconomic Status *n* (%)	Low	5923 (30.6 %)	12,091 (31.2 %)	
	Medium	9142 (47.2 %)	17,647 (45.5 %)	
	High	4296 (22.2 %)	9005 (23.2 %)	
	Missing data	106 (0.5 %)	261 (0.7 %)	
Age at Anemia assessment (months), Median (IQR)		12 (11, 14)	12 (11, 14)	0.48
Age (years), Median (IQR) at first stimulant prescription at data collection		8 (7, 9)	11 (9, 13)	0.91
		11 (9, 13)		

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.

Table 2
Microcytic anemia prevalence at age 9–18 months in the ADHD and the control groups.

	ADHD Group n = 19,467	Control Group n = 39,004	Crude OR (95 % CI)	Adjusted OR[c] (95 % CI)
Any microcytic anemia[a] n (%)	667 (3.4 %)	1541(4.0 %)	0.86 (0.78, 0.94)	0.91 (0.84, 0.98)
Microcytic anemia categories[b] *n* (%)				
Mild	2080 (10.7 %)	4541 (11.6 %)	0.91 (0.86, 0.96)	0.94 (0.90, 0.98)
Moderate	177 (0.9 %)	406 (1.0 %)	0.86 (0.72, 1.03)	0.91 (0.79, 1.06)

Only one participant had severe anemia (Hb = 6.2 g/dl), and he was excluded from this analysis.
ADHD, attention deficit hyperactivity disorder; OR, odds ratio.
[a] Any microcytic anemia was defined as Hb < 10.5 g/dl, MCV 60–75 fl, according to the CHS medical quality measurements.[22].
[b] Anemia categories were defined according to the WHO definition for children 6–59 months of age (no anemia Hb > 115 g/dl, mild 10–10.9 g/dl, moderate 7–9.9 g/dl, severe <7 g/dl).[30].
[c] Conditional logistic regression. OR adjusted by socio-economic status.

Table 3
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	P Value
Hb (g/dl)			
Median (IQR)	11.9 (11.4, 12.5)	11.9 (11.3, 12.5)	
Mean ± SD	11.97 ± 0.88	11.92 ± 0.89	<0.001
MCV (g/dl)			
Median (IQR)	76.6 (73.7, 79.5)	76.6 (73.8, 79.4)	
Mean ± SD	76.72 ± 3.77	76.71 ± 3.77	0.69
MCH (g/dl)			
Median (IQR)	25.9 (24.9, 26.9)	25.9 (24.9, 26.9)	
Mean ± SD	25.90 ± 1.47	25.92 ± 1.49	0.14

P values represent Mann Whitney *U* Test for numerical variables with a skewed distribution.
ADHD, attention deficit hyperactivity disorder; Hb, hemoglobin; IQR, interquartile range; MCV, mean cell volume; MCH, mean cell hemoglobin.

Table 4
Microcytic anemia prevalence at ages 9–18 months in the ADHD and the control groups, stratified by sex, socioeconomic status, cultural background, and age at data collection quintiles.

			ADHD Group	Control Group	OR (95 % CI)
Sex	Male	*n*	13,169	26,356	0.83 (0.74, 0.93)
		Microcytic anemia *n* (%)	452 (3.4 %)	1072 (4.1 %)	
	Female	*n*	6298	12,648	0.92 (0.78, 1.08)
		Microcytic anemia *n* (%)	215 (3.4 %)	469 (3.7 %)	
Cultural background	Arab	*n*	1520	3057	0.83 (0.65, 1.20)
		Microcytic anemia *n* (%)	63 (4.1 %)	141 (4.6 %)	
	Orthodox Jew	*n*	1631	3321	0.88 (0.53, 1.47)
		Microcytic anemia *n* (%)	89 (5.5 %)	211 (6.4 %)	
	Secular and Traditional Jew	*n*	16,316	32,626	0.85 (0.77, 0.95)
		Microcytic anemia *n* (%)	515 (3.2 %)	1189 (3.6 %)	
Socio-Economic Status	Low	*n*	5923	12,091	0.87 (0.69, 1.09)
		Microcytic anemia *n* (%)	234 (4.0 %)	573 (4.7 %)	
	Medium	*n*	9142	17,647	0.99 (0.83, 1.20)
		Microcytic anemia *n* (%)	296 (3.2 %)	624 (3.5 %)	
	High	*n*	4296	9005	0.79 (0.57, 1.09)
		Microcytic anemia *n* (%)	133 (3.1 %)	332 (3.7 %)	
age at data collection quintiles	6–9.0 years	n	3432	7726	0.98 (0.76, 1.27)
		Microcytic anemia *n* (%)	109 (3.2 %)	247 (3.2 %)	
	9.1–10.4 years	*n*	3987	8323	0.89 (0.67, 1.18)
		Microcytic anemia *n* (%)	130 (3.3 %)	332 (4.0 %)	
	10.5–12.0 years	*n*	4097	7849	0.80 (0.59, 1.07)
		Microcytic anemia *n* (%)	129 (3.1 %)	333 (4.2 %)	
	12.1–13.5 years	*n*	3685	7657	0.69 (0.51, 0.94)
		Microcytic anemia n (%)	118 (3.2 %)	322 (4.2 %)	
	13.6–16 years	*n*	4266	7449	1.11 (0.90, 1.37)
		Microcytic anemia n (%)	181 (4.2 %)	307 (4.1 %)	

ADHD, attention deficit hyperactivity disorder.
Conditional logistic regression.

high socioeconomic status, higher among orthodox Jews (a population characterized by large numbers of children and relatively low SES) than among Arabs (who had medium prevalence of microcytic anemia) and secular-traditional Jews (who had the lowest prevalence of microcytic anemia). These findings are consistent with the literature and indicate that lower socioeconomic groups have a greater prevalence of anemia [6,24,34]. A possible explanation is that parents from low SES 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.

Contrary to our hypothesis, we observed a small difference in any microcytic anemia prevalence, which was 0.6 % lower in the ADHD group (3.4 %) than in the control group (4.0 %). The prevalence of moderate microcytic anemia (7–9.9 g/dl) was similar (0.9 % in the ADHD group vs. 1.0 % in the controls). It possible that in a national setting, where severe anemia is rare, microcytic anemia does not explain differences in ADHD. According to these results, microcytic anemia does not seem to be a risk factor in the etiology of ADHD in developed countries with a national policy of reducing the prevalence of infantile anemia. Inconsistence results in the association between ID and ADHD were shown in the recent review by McWilliams et al., while among 30 observational studies, 22 showed an association between ADHD and ID and eight did not, and among six RCTs, only two studies demonstrated a benefit of iron supplementation on both inattention and hyperactivity [35]. There are several reasons for discrepant results between the ADHD association studies, including our results. The main reasons include inconsistency in the use of instruments employed for the diagnosis of ADHD, inconsistencies in the choice of ID markers and the time of evaluation. In our study we evaluated microcytic anemia at infancy, while most of the association studies evaluated iron deficiency at later childhood, at the same time of ADHD evaluation [35,36], and hence, cannot prove causality.

A possible explanation for our finding is that brain iron, rather than systemic iron levels may be more strongly associated with the pathophysiology of ADHD in children [35]. A recent systemic review by Degremont et al. [36] which included 20 case-control studies, showed inconsistency in results in systemic iron status in children with ADHD (in 10 of 18 studies higher serum ferritin concentration was found in patients with ADHD compared with healthy controls, and in only 2 of 10 studies lower serum iron concentration was found in children with ADHD compared with healthy controls, while 1 study found an inverse association). However, in 3 of 3 studies in which brain iron concentration was assessed, a lower thalamic iron concentration was found in children with ADHD as compared to in healthy controls. The authors concluded that the evidence, though limited, suggests that brain iron, specifically in the thalamus, rather than systemic iron levels, may be more associated with the pathophysiology of ADHD in children [36]. Additional factors, such as 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 also be involved in the development of ADHD [2,6].

In the stratified analyses, differences in any microcytic anemia prevalence between the ADHD and the control groups were small (the maximal difference in any microcytic anemia prevalence was 1 %), and found only among boys, among secular-traditional Jews, and in the 4th quintile of age at data collection (12.1–13.5 years). When the stratification was done according to SES, no differences in any microcytic anemia prevalence were found. The differences in any microcytic anemia prevalence between the ADHD and the control groups 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. The lower any microcytic anemia prevalence in the ADHD compared to the control group among those within the 4th quintile of age at data collection, cannot be attributed to a larger sample size and to a greater statistical power. The differences in the association between any microcytic anemia and ADHD among the different age at diagnosis quintiles suggests that the year of birth might be a partial confounder in this association. The results of the stratification according to SES suggest that SES might also be a partial confounder in the association between any microcytic anemia and ADHD, as the associations weakened in each of the SES strata as compared to the association in the entire sample. A confounder is a factor that is associated with the exposure that independently affects the risk of developing the outcome [37]. Our data indeed showed associations between the exposure (any microcytic anemia) and both age at data collection and SES, as microcytic anemia prevalences were different among the different strata. As the control group in our study was matched to the ADHD group on a fixed ratio, we cannot examine whether ADHD prevalence was affected by the year of data collection or SES. However, an earlier study in Israel, which was based on a database of the second largest health maintenance organization in Israel, (Maccabi Healthcare Services), and included children aged 5–17 years between the years 2005–2014, with a physician-recorded ADHD diagnosis and/or two purchases of ADHD medication, showed that both the year of birth and SES were associated with the prevalence of ADHD [9]. This study reported that the prevalence of ADHD diagnoses rose twofold from 6.8 % to 14.4 % between 2005 and 2014 and ADHD medication usage by children and adolescents was 3.57 % in 2005 and 8.51 % by 2014 [9]. Furthermore, ADHD was diagnosed more commonly in the average and high average SES strata as compared to the lower SES strata. The authors suggest a possible explanation for this observation, that parents in the higher SES are more concerned with their child's academic achievement, and hence, more aware of ADHD symptoms and seek evaluation and treatment [9].

Another plausible explanation for our findings, may relate to differences in parents' awareness of their children's health. Parents with higher awareness may be both more compliant with the recommendation of iron supplementation in infants 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 prevalence of diagnosed/treated ADHD and a lower prevalence of IDA. Unfortunately, we cannot explore these speculations in our sample, as parents' awareness of their children's health was not measured in our study.

A main strength of this study is the high reliability of the data, derived from the database of CHS. The exposure parameters (diagnosis of microcytic anemia) were recorded from a database of medical records, and not based on a persons' memory. Hence, a recall 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 [9,27,31].

There are several methodological limitations to this study. First, we diagnosed microcytic anemia based on Hb and MCV values. Due to a lack of information in our database, ferritin and iron values were not considered. This may raise the possibility of selection bias, mainly the inclusion of carriers of the thalassemia trait, as most carriers of this trait, which manifests clinically as microcytic anemia, are relatively healthy. In Israel, the mean carrier frequency for β Thalassemia is about 2.4 %; and in villages with a primarily Arab population, the frequency rises to up to 9 % [38]. β thalassemia prevention in Israel is based on screening young couples early in pregnancy for carrier detection and subsequent prenatal diagnosis [38]. In our study, congenital anemia and anemia-related diseases, including thalassemia, were ruled out, indicating that the main reason for anemia was indeed ID. It is important to mention that we extracted data from the medical records of Clalit-Health-Services on the participants from birth until the age of 6 years or older (up to 18 years, depending on the age at data collection), a period long enough in the child's life to diagnose anemia-related diseases like thalassemia. Moreover, iron deficiency in ADHD, may be a functional brain iron deficiency, which not necessarily reflected in peripheral iron levels and IDA [36]. Second, the timing of IDA is an important factor in neurocognitive development [39]. In our study, microcytic anemia 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 may lead to misclassification of the outcome for the two groups, as some children who meet the criteria for ADHD diagnosis may choose not to receive pharmaceutical treatment. This misclassification is not necessarily random, if the likelihood for compliance with the recommendation of iron supplementation in infants (which reduce the prevalence of IDA) is related to medical care later in life. Nonetheless, other studies have classified people as having ADHD according to medical treatment [9,25–30]. A fourth limitation is that our data was lacking several possible confounders, which may influence both the development of infantile IDA and ADHD. These unmeasured confounders include maternal smoking during pregnancy and passive smoking later in childhood, birthweight, maternal diet during pregnancy, the infant's diet (i.e., breastfeeding, formula, complementary feeding), maternal and child exposure to toxins (such as blood lead levels) [6,40]. However, in our study design and analysis we dealt with several major possible confounders. This was done by excluding preterm infants, children diagnosed with anemia-related diseases and other chronic diseases and by matching the case and the control groups by age at ADHD diagnosis, sex and cultural background and by adjusting the analysis to SES and age at data collection.

5. Conclusions

We found a small inverse association between microcytic anemia (which mostly represents IDA) at age 9–18 months and ADHD during childhood, opposed to our hypothesis. We cannot fully explain this association, but our analysis suggests that the year of birth and SES might be partial confounders in this association. We also speculate that this association might be related to differences in parents' awareness of their children's health, which might be another confounder. Further studies are warranted, to examine the effects of ID and brain iron concentration in different brain regions from the early developmental stages of the brain (during pregnancy and the first weeks after birth) to adolescence, on the development of ADHD in childhood.

Data availability statement

The authors do not have permission to share data according to the ethics committee rules.

Ethics and consent statement

This study was reviewed and approved by Clalit-Health-Services institutional review board, ethical approval number COM2-0130-17, dated December 7th, 2017.

The database did not include any patient identifiers. Subject consent was waived due to the retrospective design, based on data from the medical records.

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CRediT authorship contribution statement

Michal Yackobovitch-Gavan: Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Daniel Ben-Hefer:** Software, Methodology, Investigation, Formal analysis, Conceptualization. **Ilan Feldhamer:** Methodology, Data curation. **Joseph Meyerovitch:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders (DSM-5®), American Psychiatric Pub, 2013.
[2] Attention-Deficit/Hyperactivity Disorder, nimh.nih.gov, 2024, pp. 1–5. https://www.nimh.nih.gov/health/topics/attention-deficit-hyperactivity-disorder-adhd. (Accessed 22 June 2024).
[3] E.G. Willcutt, The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review, Neurotherapeutics 9 (2012) 490–499, https://doi.org/10.1007/s13311-012-0135-8.
[4] G.V. Polanczyk, E.G. Willcutt, G.A. Salum, C. Kieling, L.A. Rohde, ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis, Int. J. Epidemiol. 43 (2) (2014) 434–442, 0.1093/ije/dyt261.
[5] R. Thomas, S. Sanders, J.A. Doust, E. Beller, P. Glasziou, Prevalence of attention-deficit/Hyperactivity disorder: a systematic review and meta-analysis, Pediatrics 135 (2015) e994–e1001, https://doi.org/10.1542/peds.2014-3482.
[6] S.V. Faraone, T. Banaschewski, D. Coghill, et al., The world federation of ADHD international consensus statement: 208 evidence-based conclusions about the disorder, Neurosci. Biobehav. Rev. 128 (2021) 789–818, https://doi.org/10.1016/j.neubiorev.2021.01.022.
[7] G. Xu, L. Strathearn, B. Liu, B. Yang, W. Bao, Twenty-year trends in diagnosed attention-deficit/hyperactivity disorder among US children and adolescents, 1997-2016. JAMA. Netw, Open 1 (4) (2018) e181471, https://doi.org/10.1001/jamanetworkopen.2018.1471.
[8] M. Rydell, S. Lundström, C. Gillberg, P. Lichtenstein, H. Larsson, Has the attention deficit hyperactivity disorder phenotype become more common in children between 2004 and 2014? Trends over 10 years from a Swedish general population sample, J. Child. Psychol. Psychiatry. 59 (8) (2018) 863–871, https://doi.org/10.1111/jcpp.12882.
[9] M. Davidovitch, G. Koren, N. Fund, M. Shrem, A. Porath, Challenges in defining the prevalences of ADHD diagnosis and treatment: trends over the last decade, BMC Pediatr. 17 (1) (2017) 218, https://doi.org/10.1186/s12887-017-971-0.
[10] J. Allotey, J. Zamora, F. Cheong-See, et al., Cognitive, motor, behavioural and academic performances of children born preterm: a meta-analysis and systematic review involving 64 061 children, BJOG 125 (1) (2018) 16–25, https://doi.org/10.1111/1471-0528.14832.
[11] J.L. Beard, Why iron deficiency is important in infant development, J. Nutr. 138 (2008) 2534–2536, https://doi.org/10.1093/jn/138.12.2534.
[12] M.H. Chen, T.P. Su, Y.S. Chen, et al., Association between psychiatric disorders and iron deficiency anemia among children and adolescents: a nationwide population-based study, BMC Psychiatr. 13 (2013) 161, https://doi.org/10.1186/1471-244X-13-161.
[13] M. McDonagh, I. Blazina, T. Dana, A. Cantor, C. Bougatsos, 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], Agency for Healthcare Research and Quality (US), Rockville (MD), 2015 Mar, 13-05187-EF-1.
[14] B. Ha, D.L. O'Sullivan, C.A. Diamond, et al., Improving prevalence of screening for anemia in infancy, Clin. Pediatr. 57 (9) (2018) 1064–1068, https://doi.org/10.1177/0009922817744608.
[15] P.M. Gupta, C.G. Perrine, Z. Mei, K.S. Scanlon, Iron, anemia, and iron deficiency anemia among young children in the United States, Nutrients 8 (6) (2016) 330, https://doi.org/10.3390/nu8060330.
[16] K. Rajendran, J.W. Trampush, D. Rindskopf, D.J. Marks, S. O'Neill, J.M. Halperin, Association between variation in neuropsychological development and trajectory of ADHD severity in early childhood, Am. J. Psychiatr. 170 (10) (2013) 1205–1211, https://doi.org/10.1176/appi.ajp.2012.12101360.
[17] J. Meyerovitch, M. Sherf, F. Antebi, et al., The incidence of anemia in an Israeli population: a population analysis for anemia in 34512 Israeli infants aged 9 to 18 months, Pediatrics 188 (2006) e1060, https://doi.org/10.1542/peds.2006-0024.
[18] M. Wang, Iron deficiency and other types of anemia in infants and children, Am. Fam. Physician 93 (2016) 270–278.
[19] J. Meyerovitch, D. Carmi, S. Aviner, et al., 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 Pol. Res. 11 (2022) 2, https://doi.org/10.1186/s13584-021-00510-9.
[20] Y. Wang, L. Huang, L. Zhang, Y. Qu, D. Mu, Iron status in attention-deficit/hyperactivity disorder: a systematic review and meta-analysis, PLoS One 12 (2017) e0169145, 0.1371/journal.pone.0169145.
[21] P. Tseng, Y. Cheng, C. Yen, et al., Peripheral iron levels in children with attention-deficit hyperactivity disorder: a systematic review and meta-analysis, Sci. Rep. 8 (1) (2018) 788, https://doi.org/10.1038/s41598-017-19096-x.
[22] Y. Sever, A. Ashkenazi, S. Tyano, A. Weizman, Iron treatment in children with attention deficit hyperactivity disorder. A preliminary report, Neuropsychobiology 35 (4) (1997) 178–180, https://doi.org/10.1159/000119341.
[23] E. Konofal, M. Lecendreux, J. Deron, et al., Effects of iron supplementation on attention deficit hyperactivity disorder in children, Pediatr. Neurol. 38 (1) (2008) 20–26, https://doi.org/10.1016/j.pediatrneurol.2007.
[24] S. McCann, M. Perapoch Amadó, S.E. Moore, The role of iron in brain development: a systematic review, Nutrients 12 (2020) 2001.
[25] P. Hodgkins, R. Sasané, W.M. Meijer, Pharmacologic treatment of attention-deficit/hyperactivity disorder in children: incidence, prevalence, and treatment patterns in The Netherlands, Clin. Therapeut. 33 (2) (2011) 188–203, https://doi.org/10.1016/j.clinthera.2011.03.001.
[26] J. Norum, A.I. Olsen, F.I. Nohr, A. Heyd, A. Totth, Medical treatment of children and youths with attention-deficit/hyperactivity disorder (ADHD): a Norwegian Prescription Registry Based Study, Global J. Health Sci. 6 (4) (2014) 155–162, https://doi.org/10.5539/gjhs.v6n4p155.
[27] L. Jaber, S. Rigler, A. Shuper, G. Diamond, Changing epidemiology of methylphenidate prescriptions in the community: a multifactorial model, J. Atten. Disord. 21 (4) (2017) 1143–1150, https://doi.org/10.1177/1087054714528044.
[28] Z. Wang, A.Y.L. Chan, D. Coghill, et al., Association between prenatal exposure to antipsychotics and attention-deficit/hyperactivity disorder, autism spectrum disorder, preterm birth, and small for gestational age, JAMA Intern. Med. 181 (10) (2021) 1332–1340, https://doi.org/10.1001/jamainternmed.2021.4571.
[29] M. Yackobovitch-Gavan, A. Mimouni-Bloch, U. Gabbay, et al., 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 (2021) 296–304, https://doi.org/10.1016/j.jpeds.2021.07.018.
[30] W. Yuchi, M. Brauer, A. Czekajlo, et al., Neighborhood environmental exposures and incidence of attention deficit/hyperactivity disorder: a population-based cohort study, Environ. Int. 161 (2022) 107120, https://doi.org/10.1016/j.envint.2022.107120.
[31] Israeli Ministry of Health, Attention deficit hyperactivity disorder – ADHD. https://www.health.gov.il/English/Topics/KidsAndMatures/child_development/Pages/ADHD.aspx. (Accessed 25 June 2023).
[32] WHO, Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System, World Health Organization, Geneva, 2011. WHO/NMH/NHD/MNM/11.1).
[33] J. Meyerovitch, M. Zlotnik, M. Yackobovitch-Gavan, M. Phillip, S. Shalitin, Real-life glycemic control in children with type 2 diabetes: a population-based study, J. Pediatr. 188 (2017) 173–180, https://doi.org/10.1016/j.jpeds.2017.05.074.
[34] S. Syed, O.Y. Addo, V. De la Cruz-Góngora, F.A.S. Ashour, T.R. Ziegler, P.S. Suchdev, Determinants of anemia among school-aged children in Mexico, the United States and Colombia, Nutrients 8 (2016) 387, https://doi.org/10.3390/nu8070387.
[35] S. McWilliams, I. Singh, W. Leung, S. Stockler, O.S. Ipsiroglu, Iron deficiency and common neurodevelopmental disorders-A scoping review, PLoS One 17 (9) (2022 Sep 29) e0273819.
[36] A. Degremont, R. Jain, E. Philippou, G.O. Latunde-Dada, Brain iron concentrations in the pathophysiology of children with attention deficit/hyperactivity disorder: a systematic review, Nutr. Rev. 79 (2021) 615–626, https://doi.org/10.1093/nutrit/nuaa065.
[37] B. Mann, E. Wood, Confounding in observational studies explained, Open Epidemiol. J. 5 (2012) 18–20.
[38] A. Koren, L. Profeta, L. Zalman, et al., Prevention of β thalassemia in northern Israel - a cost-benefit analysis, Mediterr J Hematol Infect Dis. 6 (1) (2014) e2014012, https://doi.org/10.4084/MJHID.2014.012.
[39] J. Beard, Iron deficiency alters brain development and functioning, J. Nutr. 133 (5S) (2003) 1468S–1472S, https://doi.org/10.1093/jn/133.5.1468S.
[40] S.R. Pasricha, J. Tye-Din, M.U. Muckenthaler, D.W. Swinkels, Iron deficiency, Lancet 397 (10270) (2021) 233–248, https://doi.org/10.1016/S0140-6736(20)32594-0.