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Magnesium status and attention deficit hyperactivity disorder (ADHD): A meta-analysis

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ABSTRACT

Current research suggests conflicting evidence surrounding the association between serum magnesium levels and the diagnosis of attention deficit hyperactivity disorder (ADHD). This systematic review and meta-analysis aims to explore, summarize and quantify the published literature addressing this topic. We conducted an exhaustive literature search on Scopus and PubMed for all the relevant observational studies published up to August 2018. A meta-analysis using a random-effects model was used to summarize the overall association between serum magnesium level and ADHD from the available data. We identified seven studies which reported the mean and standard deviation (SD) of magnesium concentration in both ADHD and control groups. The random-effects meta-analysis showed that subjects with ADHD had 0.105 mmol/l (95% CI: -0.188, -0.022; $P < 0.013$) lower serum magnesium levels compared with to their healthy controls. Moreover, we observed striking and statistically significant heterogeneity among the included studies ($I^2 = 96.2\%$, $P = 0.0103$). The evidence from this meta-analysis supports the theory that an inverse relationship between serum magnesium deficiency and ADHD exists. High heterogeneity amongst the included studies suggests that there is a residual need for observational and community-based studies to further investigate this issue.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is increasingly recognized as a growing diagnosis among children, adolescents, and adults (Akinbami et al., 2011; Barbaresi et al., 2007). The prevalence of ADHD is between 5% and 10% in children, whilst, it is estimated to be around 4% amongst adults (Biederman, 2005). ADHD is categorized as a neurobehavioral disorder, defined by decreased attention, hyperactivity, and impulsivity (Yang et al., 2018). This condition often lowers the overall quality of life of affected individuals by posing a significant strain on an individual's social life, personal relationships, and school or work performance (Kooij, 2012). Established evidence has shown that various medical and psychosocial therapies can be useful in the treatment of ADHD and its related disorders (Shaw et al., 2012; Reale et al., 2017; Maia et al., 2017). Nevertheless, experts remain uncertain regarding the underlying pathophysiology of ADHD (Eaves et al., 1997). Certain evidence proposes genetic and environmental etiologies- such as an imbalance of essential dietary nutrients – being a contributor to the development of ADHD (Reading, 2012). Magnesium is one of the essential trace minerals and it plays an

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important role in over 300 metabolic reactions including: protein synthesis, nucleic acid production, and cellular energy generation (Ford and Mokdad, 2003). Magnesium deficiency is linked with disturbances in cognitive capability which can lead to symptoms such as: fatigue, lack of concentration, nervousness, mood swings and aggression (Huss et al., 2010). Considering that the aforementioned symptoms commonly manifest in ADHD, it is not surprising that most evidence from clinical trials states that patients with ADHD have lower serum magnesium levels compared to healthy subjects (Firouzkouhi Moghaddam et al., 2016; El Baza et al., 2016; Doyle et al., 2015; Mousain-Bosc et al., 2006; Mousain-Bosc et al., 2004; Starobrat-Hermelin and Kozielec, 1997; Weiss et al., 1985). Nevertheless, a minority of clinical studies report that ADHD patients have equal or higher serum magnesium levels than their healthy counterparts (Irmisch et al., 2011; Antalis et al., 2006b). Therefore, we aim to employ a meta-analytical approach to summarize and explore the available evidence from observational studies and clarify the association between magnesium deficiency and ADHD.

2. Methods

The present meta-analysis was performed following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000).

2.1. Search strategy

We performed a systematic review in PubMed and Scopus for all published observational studies conducted up to August 2018. We only included studies that assessed serum magnesium level in both ADHD patients and healthy counterparts. In addition, the reference lists of related articles were manually reviewed to avoid the potential omission of relevant articles. We used the following search strategy including both Medical Subject Headings (MeSH) and other related keywords in the search process (Fig. 1):

I) PubMed = (("Magnesium"[Mesh]) OR "Magnesium"[tiab])) AND (("minimal brain dysfunction"[tiab]) OR "minimal brain disorder"[tiab]) OR "overactive child syndrome"[tiab]) OR "adhd"[tiab]) OR "ADHD"[tiab]) OR "addh"[tiab]) OR "ADD"[tiab]) OR "attention deficit"[tiab]) OR "hyperactiv"[tiab]) OR "hyperkinetic"[tiab]) OR "Attention Deficit Disorder with Hyperactivity"[Mesh]) OR "Attention Deficit Disorder with Hyperactivity"[tiab]).

II) Scopus = (TITLE-ABS-KEY (Magnesium)) AND ((TITLE-ABS-KEY ("minimal brain dysfunction") OR TITLE-ABS-KEY ("minimal brain disorder") OR TITLE-ABS-KEY ("overactive child syndrome") OR TITLE-ABS-KEY (adhd) OR TITLE-ABS-KEY (adhd) OR TITLE-ABS-KEY (addh) OR TITLE-ABS-KEY (add) OR TITLE-ABS-KEY ("attention deficit") OR TITLE-ABS-KEY (hyperactiv) OR TITLE-ABS-KEY (hyperkinetic) OR TITLE-ABS-KEY ("Attention Deficit Disorder with Hyperactivity") OR TITLE-ABS-KEY ("Attention Deficit Disorder with Hyperactivity"))).

We downloaded the articles retrieved from the literature search into EndNote (version X8) to merge all the citations, to remove the duplicates and to ease the screening process (Fig. 1).

2.2. Eligibility criteria

All original observational case-control studies that explored the association between magnesium levels and ADHD were included in this meta-analysis. We excluded studies that were not published in the English language or that included children with other neurological disorders. We also excluded literature reviews, case reports, animal studies or republished data.

2.3. Study selection

Two independent authors (HK-V and SMM) participated in the full study selection process. The first part included reviewing the titles and abstracts of the retrieved articles and used a hierarchical method to assess the study design, population and outcome. Articles that did not meet the eligibility criteria based on the initial screening process were excluded. The second screening process involved the analysis of the full-text of the remaining studies. Studies not meeting the inclusion criteria were eliminated and any disagreements were resolved amongst the two reviewers. If discrepancies continued a third author was involved to resolve these.

2.4. Data extraction and quality assessment

Reviewers extracted the following information individually and in duplicate: the first author's last name, the publication year, the study location, the participants' age, the participants' gender, the sample size and the serum magnesium levels in both the case and the control group. The data extraction was performed by two independent reviewers and any lack of consensus was resolved via discussion. If any additional information was required from the studies, the main authors were contacted via email. To assess the quality of the case-control we used the Newcastle-Ottawa Scale (NOS) (Wells et al., 2012).

2.5. Statistical analysis

The overall relationship between serum magnesium level and the diagnosis of ADHD was estimated by comparing the mean and standard deviation (SD) of magnesium levels in ADHD versus the control groups. The random effects model was used to conduct the meta-analyses and calculate the pooled effect size of the mean serum magnesium levels in ADHD patients (DerSimonian and Laird, 1986). Cochran's Q test and the I^2 statistic were used to test the heterogeneity between the included studies (Higgins and Thompson, 2002). Subgroup analyses were performed in order to establish possible sources of heterogeneity. Sensitivity analyses were carried out using the metaninf test to assess the impact of each individual study on the overall result. To investigate the presence of publication bias we performed Begg's funnel plots and Egger's linear regression tests (Egger et al., 1997). Furthermore, the meta-trim and fill tests were conducted to impute missing studies (Palmer et al., 2008). All analyses were carried out using Stata (version 14) and with the use of the "metan" command. *P* values of less than 0.05 were considered statistically significant.

3. Results

3.1. Search results and study characteristics

The database searches of PubMed and Scopus retrieved 1485 titles and abstracts and after removing the duplicates a total of 1346 articles remained. During the title and abstract review, 1309 articles were removed as per the predefined exclusion criteria. In the second screening process, we examined the full text of the remaining 37 studies, after which, 7 articles remained. The latter 30 articles were excluded, due to the following reasons: 13 articles did not report the outcomes of interest (Leviton et al., 2018; Doyle et al., 2015; Black et al., 2015; Palli et al., 2012; Caylak, 2012; Biederman et al., 2012; Classi et al., 2011; Huss et al., 2010; Pohl et al., 2009; Huskamp et al., 2005; Arnold et al., 2005; Schmidt et al., 1994b), 6 papers were review articles (Lange et al., 2017; Greenblatt and Delane, 2017; Gröber et al., 2015; Villagomez and Ramtekkar, 2014; Bisht and Kukreti, 2014; Liebscher et al., 2011), 7 were clinical trials (Firouzkouhi Moghaddam et al., 2016; El Baza et al., 2016; Doyle et al., 2015; Mousain-Bosc et al., 2006; Mousain-Bosc et al., 2004; Starobrat-Hermelin and Kozielec, 1997; Weiss et al., 1985), 3 articles reported the same data

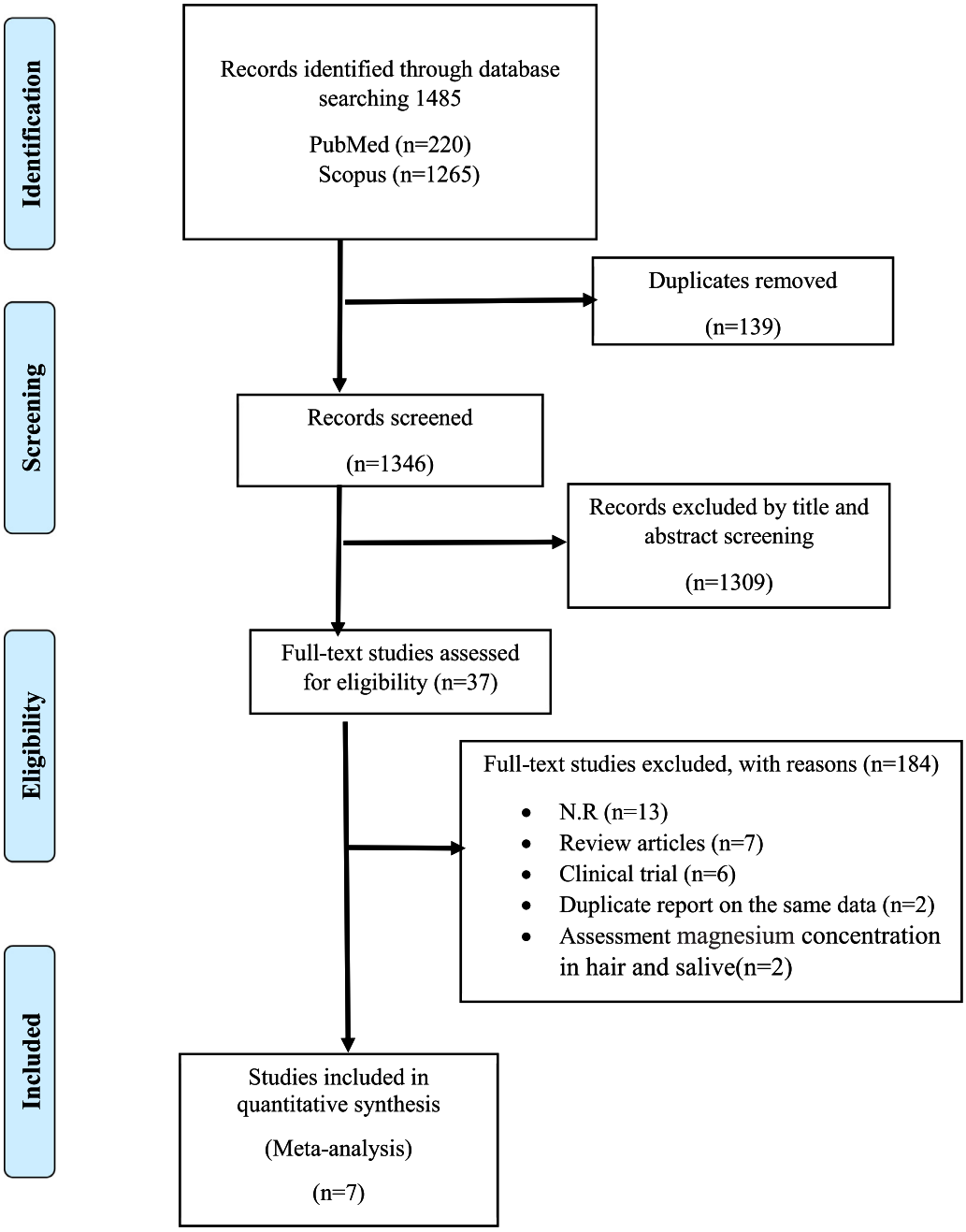

Fig. 1. Flow diagram for study identified and included into the meta-analysis.

(Kamal et al., 2014; Bener et al., 2014; Bener and Kamal, 2013) (out of which we included the study that had a bigger sample size (Bener and Kamal, 2013)), and two studies reported magnesium concentrations measured in saliva and hair (Tippairote et al., 2017; Archana et al., 2012). Therefore, 7 observational studies that reported serum magnesium levels in ADHD patients and control subjects proved eligible. Characteristics of the included studies are summarized in the Table 1. The studies were conducted in several different countries: two were conducted in Egypt (Elbaz et al., 2017; Mahmoud et al., 2011), one in the USA (Antalis et al., 2006b), one in the UK (Bener and Kamal, 2013), one in Germany (Irmisch et al., 2011), one in China (Yang et al., 2018), and one in Russia (Nogovitsina and Levitina, 2005). The articles were published between 2006 and 2018. The sample size of the eligible studies ranged from 24 to 1331 children and adolescents. The age of the participants ranged between 6 and 24 years with the mean age in five studies being under the age of 10 (Yang et al., 2018; El Baza et al., 2016; Mahmoud et al., 2011; Irmisch et al., 2011; Nogovitsina and Levitina, 2005) and in two studies, above (Bener and Kamal, 2013; Antalis et al., 2006b). All included studies, were coincidentally, case-control studies. Of the 7 included studies, one solely included males (Irmisch et al., 2011) while the others included individuals of both genders (Elbaz et al., 2017; Bener and Kamal, 2013; Mahmoud et al., 2011; Antalis et al., 2006b; Nogovitsina and Levitina, 2005; Yang et al., 2018). The quality of the studies as classified by the NOS scale ranged from 5 to 8 (supplementary Table 1).

3.2. Meta-analysis of mean serum magnesium levels

The seven included studies reported the mean and SD of serum magnesium levels in both ADHD and control subjects (Elbaz et al., 2017; Bener and Kamal, 2013; Mahmoud et al., 2011; Irmisch et al., 2011; Antalis et al., 2006b; Nogovitsina and Levitina, 2005; Yang et al.,

Table 1
Characteristics of included studies.

Authors (year)	Country	gender	Study design	Age(year)	Sample size	Serum magnesium concentration, mmol/L	Newcastle-Ottawa score
Antalis et al. (2006)	USA	Both	Case-control	Cases: 24.17 Controls: 23.27	Cases: 12 Controls: 12	Cases: 0.78 ± 0.12 Controls: 0.63 ± 0.08	8
Bener et al. (2014)	UK	Both	Case-control	Cases: 16.6 Controls: 23.5	Cases: 1331 Controls: 1331	Cases: 0.79 ± 0.12 Controls: 0.88 ± 0.10	8
Irmisch et al. (2011)	Germany	Boy	Case-control	Cases: 8.2 Controls: 7.9	Cases: 9 Controls: 11	Cases: 0.86 ± 0.068 Controls: 0.815 ± 0.71	5
Yang et al. (2018)	Chinese	Both	Case-control	Cases: 8.8 Controls: 8.9	Cases: 419 Controls: 395	Cases: 1.62 ± 0.22 Controls: 1.65 ± 0.22	8
Nogovitsinaet al. (2007)	Russia	Both	Case-control	6–11	Cases: 51 Controls: 15	Cases: 0.55 ± 0.04 Controls: 0.82 ± 0.08	5
Mahmoud et al. (2011)	Egypt	Both	Case-control	Cases: 8.3 Controls: 8.6	Cases: 58 Controls: 25	Cases: 0.85 ± 0.4 Controls: 1.1 ± 0.45	7
Elbaz et al. (2016)	Egypt	Both	Case-control	Cases: 7.74 Controls: 7.40	Cases: 20 Controls: 20	Cases: 0.81 ± 0.24 Controls: 1.28 ± 0.24	6

2018). The random effects meta-analysis revealed that subjects with ADHD had a lower serum magnesium concentration of 0.105 mmol/l (95% CI: −0.188, −0.022; P < 0.013) compared with their healthy counterparts (Fig. 2). However, the statistical tests also demonstrated that there was significant heterogeneity among the studies (I^2 = 96.2%, P = 0.0103). Heterogeneity in meta-analysis refers to the variation amongst the obtained results and can be due to clinical diversity or methodological diversity amongst the selected studies. In order to identify these possible sources of heterogeneity we conducted a subgroup analysis according to participants' ages, the study location, and their quality NOS score. The subgroup analyses did not suggest that any of the explored variables represented a significant source of heterogeneity. However, the location based subgroup analysis revealed that the study conducted in Egypt had lower heterogeneity, but this was not statistically significant (I^2 = 63.2%, P = 0.099). Moreover, the analysis highlighted that this study reported the lowest serum magnesium levels in subjects with ADHD compared to their healthy counterparts (−0.384 mmol/l, 95% CI, −0.512, −0.257; P < 0.001) (Table 2). Sensitivity analysis confirmed the robustness of the results as removing some of the studies would not make a significant impact on the overall conclusions (Fig. 3). Visual inspection of the funnel plot did not suggest the presence of publication bias in the meta-analysis (Begg's test, P = 0.881; Egger's test, P = 0.930) (Fig. 4). The trim and fill sensitivity analysis did not reveal the presence of any unpublished study.

4. Discussion

This meta-analysis is the first to investigate the relationship between serum magnesium levels and ADHD. The findings of this review support previously published evidence stating that serum magnesium levels are lower in ADHD patients compared with their healthy controls.

An up to date literature review yielded that low levels of magnesium have been associated with numerous central nervous system disorders, such as Alzheimer's disease, migraine headaches, and ADHD (Villagomez and Ramtekkar, 2014; Gröber et al., 2015). In a recent narrative review, Villagomez and Ramtekkar (2014) summarized the results from published studies that assessed the association between zinc, ferritin, magnesium, and vitamin D status with ADHD emphasizing their potential clinical relevance and possible inclusion in clinical practice. However, to the best of our knowledge, no meta-analysis with the aim of quantifying these associations has yet been conducted.

Our findings are in line with previous studies conducted in this field. Bener and Kamal (2013) revealed that there is a relationship between magnesium deficiency and the diagnosis of ADHD in 2662 young children. Similarly another research group confirmed that saliva magnesium levels were lower in children with ADHD compared to healthy controls (Archana et al., 2012).

However, these results are in disagreement with those reported by Irmisch et al. (2011) who concluded that children with ADHD have higher magnesium levels compared to their healthy counterparts. Similar results regarding high serum magnesium levels in ADHD patients were reported by Antalis et al. (2006b). In their case-control study, individuals diagnosed with ADHD had higher serum magnesium levels compared to their healthy controls. However, the difference in magnesium levels between the two groups were not confirmed by checking magnesium levels in their red blood cells (intracellular magnesium), suggesting increased magnesium blood concentrations could have been due to therapeutic stimulant medications, as previously demonstrated (Schmidt et al., 1994a). Likewise, Tippairote reported hair magnesium levels in ADHD patients to be higher than in the control group, but without reaching significance (Tippairote et al., 2017). Discrepancies amongst these results could be explained by the differences in the study populations, by the different methods of magnesium level measurement or by the different ADHD mediations taken by enrolled individuals. Other existing evidence reporting magnesium levels obtained from sources other than serum (such as aforementioned red blood cells,

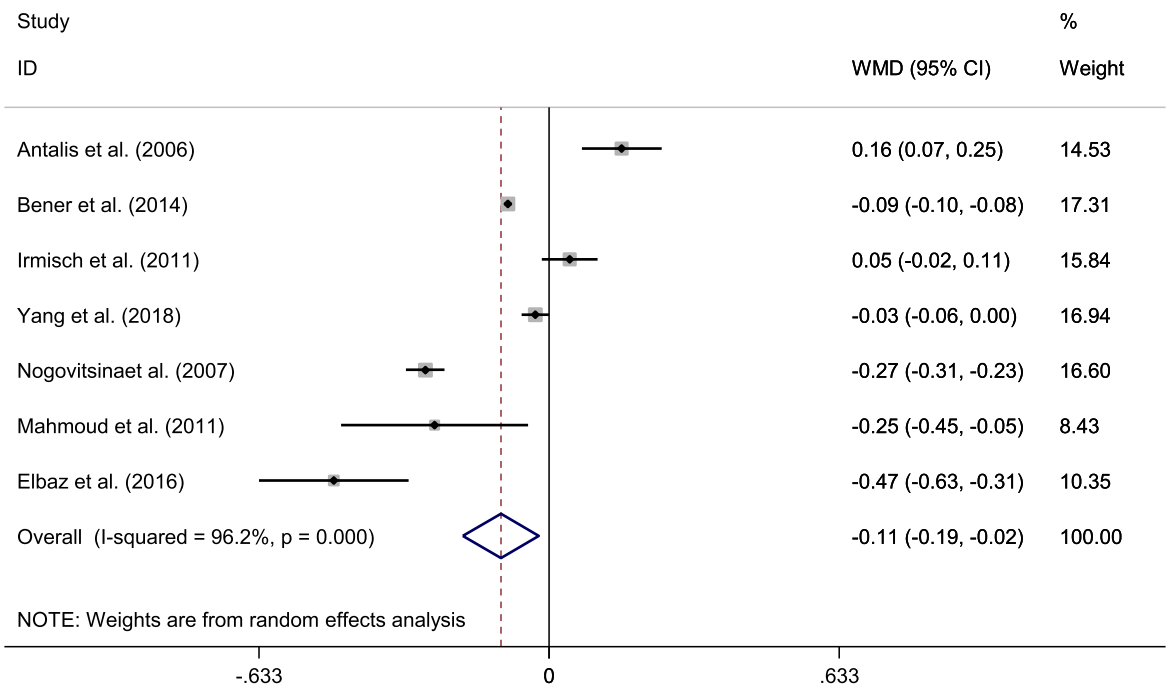

Fig. 2. Forest plot show the WMD in serum magnesium concentrations between participants with ADHD and healthy control participants. The analysis reveals that children and adolescents with ADHD have 0.11 mmol/l lower magnesium concentrations on average.

Table 2
Subgroup analyses.

	No.	ES (95% CI)	p-*Significance test(s) of ES*	p-heterogeneity intergroup	I^2 (%)	p-heterogeneity between group
Mean age						0.341
<10	5	−0.099 (95% CI, −0.122, −0.077)	0.001	0.000	96.9	
≥10	2	−0.088 (95% CI, −0.096, −0.079)	0.001	0.000	96.8	
Continent location study						
European and American	3	−0.085 (95% CI, −0.094, −0.077)	0.001	0.000	95.9	0.000
Chinese and Russia	2	−0.112 (95% CI, −0.137, −0.088)	0.001	0.000	98.8	
Egypt	2	−0.384 (95% CI, −0.512, −0.257)	0.001	0.099	63.2	
Quality scale						
≥7	4	−0.084 (95% CI, −0.092,−0.076)	0.000	0.000	93.5	0.000
≤6	3	−0.182 (95% CI, −0.216,−0.148)	0.000	0.000	97.6	

saliva or hair) was not included in the meta-analysis as this would not result in accurate results.

Interventional clinical trials have also suggested that magnesium supplementation may provide moderate benefits to ADHD patients. For example, one large observational cohort study involving 810 children who received polyunsaturated fatty acids (PUFA) in combination with magnesium and zinc, showed improved attention, hyperactivity and impulsivity after 12 weeks of therapy (Huss et al., 2010) . Another trial, concluded that supplementation with 200 mg of magnesium daily led to a significant improvement in hyperactivity, impulsivity and inattention amongst magnesium deficient children (El Baza et al., 2016). Similar findings are reported by other studies as well (Mousain-Bosc et al., 2006; Starobrat-Hermelin and Kozielec, 1997). As indicated by Durá-Travé et al. an underlying behavioral explanation of this phenomenon could be related to the lack of appetite that is common among individuals with this disorder (Durá-Travé and Gallinas-Victoriano, 2014). In fact, ADHD medical treatment is known to result in appetite suppression in some patients, which thus, results in decreased nutrient intake, including that of magnesium (Berlin et al., 2011; Kiddie et al., 2010).

To explain magnesium's involvement in ADHD's pathogenesis several other possible molecular explanations have been proposed. Firstly, magnesium is an essential trace mineral in the body and plays an important role in biochemical and physiological neuronal processes where it can induce excitotoxicity (the apoptosis of the nerve cells) by controlling the glutamate N-methyl-aspartate pathway (Lau and Tymianski, 2010). Secondly, several recent studies have documented that magnesium plays a critical role in conversion of essential fatty acids to omega-6 and omega-3 LC-PUFA, important co-factors in the desaturase enzymes implicated in hyperactive behavior (Antalis et al., 2006a).

This review has several limitations, mostly due to the small number of studies identified as eligible for inclusion. Firstly, due to a lack of studies that involved participants of only one gender we were unable to draw a conclusion on whether gender is an important confounder in the observed associations. We believe that this concept warrants further investigation because there is previous evidence suggesting that magnesium deficiency is more prevalent in male compared to female ADHD patients (El Baza et al., 2016). Furthermore, we were only able to perform the subgroup analyses according to age, location of the study and the quality NOS score, as these were the only parameters available from all included studies. Other parameters, such as ADHD diagnostic criteria or patient ethnicity, may have altered our results. However, most of our included studies used different diagnostic methods and enrolled participants of different ethnicities, therefore, we were unable to include these components in the meta-analysis. Finally, although, there are further published studies that investigated magnesium levels in ADHD, we were not able to include them because they used cellular

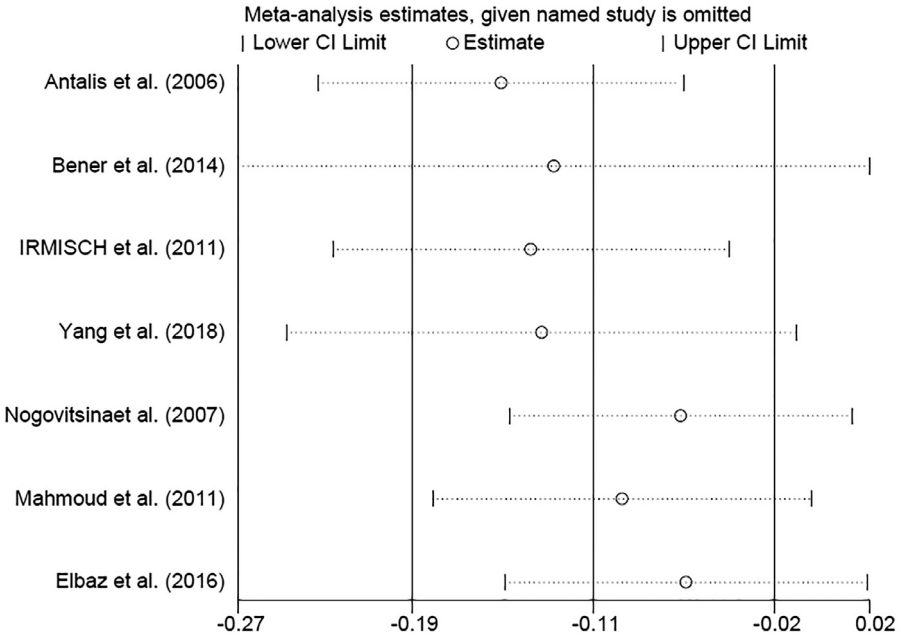

Fig. 3. Leave-one-out sensitivity analysis.

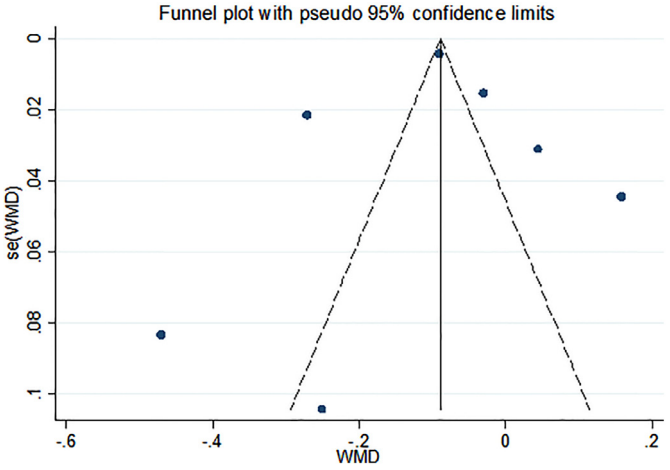

Fig. 4. Funnel plot of the weighted mean difference (WMD) versus the s.e. of the weighted mean difference (WMD).

magnesium measurements (e.g. from muscle, bone or nuclear magnetic resonance studies). Previous evidence states that these measurements tend not to accurately reflect systemic magnesium levels (Arnaud, 2008), therefore, merging these results with our studies which used serum levels may not portray accurate conclusions. In summary, these limitations can be a potential guide for designing future observational studies exploring the relationship of magnesium deficiency in ADHD patients.

In conclusion, our meta-analysis reports that children and adolescents with ADHD have significantly lower serum magnesium levels compared to their healthy counterparts.

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Conflicts of interest

All authors declared no conflicts of interest.

Declarations of interest

None

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.02.043.

References

Akinbami, L.J., Liu, X., Pastor, P.N., Reuben, C.A., 2011. Attention deficit hyperactivity disorder among children aged 5-17 years in the United States, 1998-2009. In: NCHS Data Brief. Number 70. Centers for Disease Control and Prevention.

Antalis, C.J., Stevens, L.J., Campbell, M., Pazdro, R., Ericson, K., Burgess, J.R., 2006a. Omega-3 fatty acid status in attention-deficit/hyperactivity disorder. Prostaglandins Leukot. Essent. Fatty Acids 75 (4–5), 299–308.

Antalis, C.J., Stevens, L.J., Campbell, M., Pazdro, R., Ericson, K., Burgess, J.R., 2006b. Omega-3 fatty acid status in attention-deficit/hyperactivity disorder. Prostaglandins Leukot. Essent. Fatty Acids 75 (4–5), 299–308.

Archana, E., Pai, P., Prabhu, B.K., Shenoy, R.P., Prabhu, K., Rao, A., 2012. Altered biochemical parameters in saliva of pediatric attention deficit hyperactivity disorder. Neurochem. Res. 37 (2), 330–334.

Arnaud, M.J., 2008. Update on the assessment of magnesium status. Br. J. Nutr. 99 (S3), S24–S36.

Arnold, L.E., Bozzolo, H., Hollway, J., Cook, A., Disilvestro, R.A., Bozzolo, D.R., Crowl, L., Ramadan, Y., Williams, C., 2005. Serum zinc correlates with parent- and teacher-rated inattention in children with attention-deficit/hyperactivity disorder. J. Child Adolesc. Psychopharmacol. 15 (4), 628–636.

Barbaresi, W.J., Katusic, S.K., Colligan, R.C., Weaver, A.L., Jacobsen, S.J., 2007. Long-term school outcomes for children with attention-deficit/hyperactivity disorder: a population-based perspective. J. Development. Behav. Pediat. 28 (4), 265–273.

Bener, A., Kamal, M., 2013. Predict attention deficit hyperactivity disorder? Evidence -based medicine. Glob. J. Health Sci. 6 (2), 47–57.

Bener, A., Kamal, M., Bener, H., Bhugra, D., 2014. Higher prevalence of iron deficiency as strong predictor of attention deficit hyperactivity disorder in children. Ann. Med. Health Sci. Res. 4 (Suppl 3), S291–S297.

Berlin, K.S., Lobato, D.J., Pinkos, B., Cerezo, C.S., Leleiko, N.S., 2011. Patterns of medical and developmental comorbidities among children presenting with feeding problems: a latent class analysis. J. Development. Behav. Pediat. 32 (1), 41–47.

Biederman, J., 2005. Attention-deficit/hyperactivity disorder: a selective overview. Biol. Psychiatry 57 (11), 1215–1220.

Biederman, J., Fried, R., Petty, C.R., Henin, A., Wozniak, J., Corkum, L., Claudat, K., Faraone, S.V., 2012. Examining the association between stimulant treatment and cognitive outcomes across the life cycle of adults with attention-deficit/hyperactivity disorder: a controlled cross-sectional study. J. Nerv. Ment. Dis. 200 (1), 69–75.

Bisht, A.T., Kukreti, V.T., 2014. Role of micronutrients on children with attention deficit hyperactivity disorder: a contentious issue. Ind. J. Publ. Health Res. Develop. 5 (4), 90–94.

Black, L.J., Allen, K.L., Jacoby, P., Trapp, G.S., Gallagher, C.M., Byrne, S.M., Oddy, W.H., 2015. Low dietary intake of magnesium is associated with increased externalising behaviours in adolescents. Public Health Nutr. 18 (10), 1824–1830.
Caylak, E., 2012. Biochemical and genetic analyses of childhood attention deficit/hyperactivity disorder. Am. J. Med. Genet. Part B: Neuropsychiat. Genet. 159 (B(6)), 613–627.
Classi, P.M., Le, T.K., Ward, S., Johnston, J., 2011. Patient characteristics, comorbidities, and medication use for children with ADHD with and without a co-occurring reading disorder: a retrospective cohort study. Child Adolesc. Psychiatry Mental Health 5.
Dersimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. Control. Clin. Trials 7 (3), 177–188.
Doyle, L.W., Anderson, P.J., Haslam, R., Lee, K.J., Crowther, C., 2015. School-age outcomes of very preterm infants after antenatal treatment with magnesium sulfate vs placebo. Obstet. Gynecol. Surv. 70 (1), 13–15.
Durá-Travé, T., Gallinas-Victoriano, F., 2014. Caloric and nutrient intake in children with attention deficit hyperactivity disorder treated with extended-release methylphenidate: analysis of a cross-sectional nutrition survey. JRSM Open 5 (2), 2042533313517690.
Eaves, L.J., Silberg, J.L., Meyer, J.M., Maes, H.H., Simonoff, E., Pickles, A., Rutter, M., Reynolds, C.A., Heath, A.C., Truett, K.R., 1997. Genetics and developmental psychopathology: 2. the main effects of genes and environment on behavioral problems in the Virginia twin study of adolescent behavioral development. J. Child Psychol. Psychiatry 38 (8), 965–980.
Egger, M., Smith, G.D., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ 315 (7109), 629–634.
El Baza, F., Alshahawi, H.A., Zahra, S., Abdelhakim, R.A., 2016. Magnesium supplementation in children with attention deficit hyperactivity disorder. Egypt. J. Med. Human Genet. 17 (1), 63–70.
Elbaz, F., Zahra, S., Hanafy, H., 2017. Magnesium, zinc and copper estimation in children with attention deficit hyperactivity disorder (ADHD). Egypt. J. Med. Human Genet. 18 (2), 153–163.
Firouzkouhi Moghaddam, M., Rakhshani, T., Khosravi, M., 2016. Effectiveness of methylphenidate supplemented by zinc,calcium,and magnesium for treatment of ADHD patients in the city of Zahedan. Shiraz E. Med. J. 17 (9).
Ford, E.S., Mokdad, A.H., 2003. Dietary magnesium intake in a national sample of US adults. J. Nutr. 133 (9), 2879–2882.
Greenblatt, J.M., Delane, D.D., 2017. Micronutrient deficiencies in ADHD: a global research consensus. J. Orthomol. Med. 32 (6).
Gröber, U., Schmidt, J., Kisters, K., 2015. Magnesium in prevention and therapy. Nutrients 7 (9), 8199–8226.
Higgins, J.P., Thompson, S.G., 2002. Quantifying heterogeneity in a meta-analysis. Stat. Med. 21 (11), 1539–1558.
Huskamp, H.A., Deverka, P.A., Epstein, A.M., Epstein, R.S., Mcguigan, K.A., Muriel, A.C., Frank, R.G., 2005. Impact of 3-tier formularies on drug treatment of attention-deficit/hyperactivity disorder in children. Arch. Gen. Psychiatry 62 (4), 435–441.
Huss, M., Völp, A., Stauss-Grabo, M., 2010. Supplementation of polyunsaturated fatty acids, magnesium and zinc in children seeking medical advice for attention-deficit/hyperactivity problems - An observational cohort study. Lipids Health Dis. 9.
Irmisch, G., Thome, J., Reis, O., Häßler, F., Weirich, S., 2011. Modified magnesium and lipoproteins in children with attention deficite hyperactivity disorder (ADHD). World J. Biolog. Psychiatry 12 (SUPPL. 1), 63–65.
Kamal, M., Bener, A., Ehlayel, M.S., 2014. Is high prevalence of vitamin D deficiency a correlate for attention deficit hyperactivity disorder? Atten. Defic. Hyperact. Disord. 6 (2), 73–78.
Kiddie, J.Y., Weiss, M.D., Kitts, D.D., Levy-Milne, R., Wasdell, M.B., 2010. Nutritional status of children with attention deficit hyperactivity disorder: a pilot study. Int. J. Pediat. 2010.
Kooij, J.S., 2012. Adult ADHD: Diagnostic Assessment and Treatment. Springer Science & Business Media.
Lange, K.W., Hauser, J., Lange, K.M., Makulska-Gertruda, E., Nakamura, Y., Reissmann, A., Sakaue, Y., Takano, T., Takeuchi, Y., 2017. The role of nutritional supplements in the treatment of ADHD: what the evidence says. Curr. Psychiatry Rep. 19 (2), 8.
Lau, A., Tymianski, M., 2010. Glutamate receptors, neurotoxicity and neurodegeneration. Pflügers Archiv-Eur. J. Physiol. 460 (2), 525–542.
Leviton, A., Hooper, S.R., Hunter, S.J., Scott, M.N., Allred, E.N., Joseph, R.M., O'shea, T.M., Kuban, K., Ware, J., Coster, T., Henson, B., Wilson, R., Mcghee, K., Lee, P., Asgarian, A., Sadhwani, A., Perrin, E., Neger, E., Mattern, K., Walkowiak, J., Barron, S., Frazier, J., Venuti, L., Powers, B., Foley, A., Dessureau, B., Wood, M., Damon-Minow, J., Ehrenkranz, R., Benjamin, J., Romano, E., Tsatsanis, K., Chawarska, K., Kim, S., Dieterich, S., Bearrs, K., O'shea, T.M., Peters, N., Brown, P., Ansusinha, E., Waldrep, E., Friedman, J., Hounshell, G., Allred, D., Engelke, S.C., Darden-Saad, N., Stainback, G., Warner, D., Wereszczak, J., Bernhardt, J., Mckeeman, J., Meyer, E., Pastyrnak, S., Burdo-Hartman, W., Rathbun, J., Nota, S., Crumb, T., Lenski, M., Weiland, D., Lloyd, M., Hunter, S., Msall, M., Ramoskaite, R., Wiggins, S., Washington, K., Martin, R., Prendergast, B., Scott, M., Klarr, J., Kring, B., Deridder, J., Vogt, K., Investigators, E.S., 2018. Antecedents of screening positive for attention deficit hyperactivity disorder in ten-year-old children born extremely preterm. Pediatr. Neurol. 81, 25–30.
Liebscher, D.H., Baerlocher, K., Classen, H.G., Liebscher, U.C., Ratzmann, G.W., Vierling, W., Weigert, A., Kisters, K., 2011. Magnesium deficiency and therapy in ADHD. Recommend. German Soc. Magnes. Res. Nieren- und Hochdruckkrankheiten 40 (3), 123–128.
Mahmoud, M.M., El-Mazary, A.a.M., Maher, R.M., Saber, M.M., 2011. Zinc, ferritin, magnesium and copper in a group of Egyptian children with attention deficit hyperactivity disorder. Ital. J. Pediat. 37 (1).
Maia, C.R.M., Cortese, S., Caye, A., Deakin, T.K., Polanczyk, G.V., Polanczyk, C.A., Rohde, L.a.P., 2017. Long-term efficacy of methylphenidate immediate-release for the treatment of childhood ADHD: a systematic review and meta-analysis. J. Atten. Disord. 21 (1), 3–13.
Mousain-Bosc, M., Roche, M., Polge, A., Pradal-Prat, D., Rapin, J., Bali, J.P., 2006. Improvement of neurobehavioral disorders in children supplemented with magnesium-vitamin B6. I. Attention deficit hyperactivity disorders. Magnes. Res. 19 (1), 46–52.
Mousain-Bosc, M., Roche, M., Rapin, J., Bali, J.P., 2004. Magnesium VitB6 intake reduces central nervous system hyperexcitability in children. J. Am. Coll. Nutr. 23 (5), 545s–548s.
Nogovitsina, O.P., Levitina, E.V., 2005. Diagnostic value of examination of the magnesium homeostasis in children with attention deficit hyperactive syndrome. Klinicheskaya Laboratornaya Diagnostika 5, 17–19.
Palli, S.R., Kamble, P.S., Chen, H., Aparasu, R.R., 2012. Persistence of stimulants in children and adolescents with attention-deficit/hyperactivity disorder. J. Child Adolesc. Psychopharmacol. 22 (2), 139–148.
Palmer, T.M., Peters, J.L., Sutton, A.J., Moreno, S.G., 2008. Contour-enhanced funnel plots for meta-analysis. Stata. J. 8 (2), 242.
Pohl, G.M., Van Brunt, D.L., Ye, W., Stoops, W.W., Johnston, J.A., 2009. A retrospective claims analysis of combination therapy in the treatment of adult attention-deficit/hyperactivity disorder (ADHD). BMC Health Serv. Res. 9.
Reading, R., 2012. What causes attention deficit hyperactivity disorder? Child Care Health Develop. 38 (2) 300-300.
Reale, L., Bartoli, B., Cartabia, M., Zanetti, M., Costantino, M.A., Canevini, M.P., Termine, C., Bonati, M., Group, L.A., 2017. Comorbidity prevalence and treatment outcome in children and adolescents with ADHD. Eur. Child Adoles. Psychiatry 26 (12), 1443–1457.
Schmidt, M.E., Kruesi, M.J., Elia, J., Borcherding, B.G., Elin, R.J., Hosseini, J., Mcfarlin, K.E., Hamburger, S., 1994a. Effect of dextroamphetamine and methylphenidate on calcium and magnesium concentration in hyperactive boys. Psychiatry Res. 54 (2), 199–210.
Schmidt, M.E., Kruesi, M.J.P., Elia, J., Borcherding, B.G., Elin, R.J., Hosseini, J.M., Mcfarlin, K.E., Hamburger, S., 1994b. Effect of dextroamphetamine and methylphenidate on calcium and magnesium concentration in hyperactive boys. Psychiatry Res. 54 (2), 199–210.
Shaw, M., Hodgkins, P., Caci, H., Young, S., Kahle, J., Woods, A.G., Arnold, L.E., 2012. A systematic review and analysis of long-term outcomes in attention deficit hyperactivity disorder: effects of treatment and non-treatment. BMC Med. 10 (1), 99.
Starobrat-Hermelin, B., Kozielec, T., 1997. The effects of magnesium physiological supplementation on hyperactivity in children with attention deficit hyperactivity disorder (ADHD). Positive response to magnesium oral loading test. Magnes. Res. 10 (2), 149–156.
Stroup, D.F., Berlin, J.A., Morton, S.C., Olkin, I., Williamson, G.D., Rennie, D., Moher, D., Becker, B.J., Sipe, T.A., Thacker, S.B., 2000. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA 283 (15), 2008–2012.
Tippairote, T., Temviriyanukul, P., Benjapong, W., Trachootham, D., 2017. Hair zinc and severity of symptoms are increased in children with attention deficit and hyperactivity disorder: a hair multi-element profile study. Biol. Trace Elem. Res. 179 (2), 185–194.
Villagomez, A., Ramtekkar, U., 2014a. Iron, magnesium, vitamin D, and zinc deficiencies in children presenting with symptoms of attention-deficit/hyperactivity disorder. Children (Basel) 1 (3), 261–279.
Weiss, R.D., Pope Jr., H.G., Mirin, S.M., 1985. Treatment of chronic cocaine abuse and attention deficit disorder, residual type, with magnesium pemoline. Drug Alcohol Depend. 15 (1–2), 69–72.
Wells, G., Shea, B., O'connell, D., Petersen, J., Welch, V., Losos, M., Tugwell, P., 2012. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
Yang, R., Zhang, Y., Gao, W., Lin, N., Li, R., Zhao, Z., 2018. Blood levels of trace elements in children with attention-deficit hyperactivity disorder: results from a case-control study. Biol. Trace Elem. Res. 1–7.