



# Mendelian randomization found no causal relationship between omega-6 fatty acids and attention deficit hyperactivity disorder (ADHD)

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**Background:** Attention deficit hyperactivity disorder (ADHD) is usually known as a hyperkinetic syndrome. It is also one of the primary reasons for academic struggle in children, and the most prevalent behavioral disorder especially in young people. Arachidonic acid (ARA), which is found in high concentrations in the brain, is formed in large part from gamma-linolenic acid (GLE). Mendelian randomization (MR) is an advanced method for overcoming the drawbacks of observational studies and using human genetics to guide prevention strategies for ADHD. This study aims to examine the therapeutic effect between omega-6 fatty acids and ADHD by means of a two-sample MR design.

**Methods:** To investigate evidence of a therapeutic effect between omega-6 fatty acids and the onset of ADHD. A two-sample MR method was used to assess data on single nucleotide polymorphisms (SNPs) related to omega-6 fatty acids that were downloaded from the genome-wide association study (GWAS) database. The instrument variables (IVs) were the SNPs. The findings were validated using data from the ADHD GWAS, which included 20,138 cases and 35,191 controls. The sample population was European, and the sample size was 13,506. A clumping procedure was performed to retain the SNPs that were related to omega-6 fatty acids at a genome-wide significance level of  $P < 5 \times 10^{-8}$ . SNPs were in linkage disequilibrium with the index SNPs ( $r^2$  threshold  $\leq 0.001$ ) or within a 10,000 kb distance.

**Results:** According to the inverse variance weighted (IVW) analysis, the odd ratio of the 5-SNP IVs was 0.94 per Standard deviation of omega-6 fatty acids, with a 95% confidence interval of 0.81–1.03 and a P value of 0.17. Analyses using the weighted median mode, MR-Egger, simple mode, and weighted mode revealed comparable findings.

**Conclusions:** Despite observational studies repeatedly reporting an association between reduced omega-6 fatty acids and the onset of ADHD, MR analyses in our study find no evidence of a therapeutic effect between omega-6 fatty acids and the onset of ADHD. Hence this suggests that excess omega-6 fatty acids may be a risk factor for ADHD.

**Keywords:** Omega-6 fatty acids; attention deficit hyperactivity disorder (ADHD); genome-wide association study (GWAS); Mendelian randomization (MR); inverse variance weighted analysis

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## Introduction

Long-chain polyunsaturated fatty acids (LCPUFA), such as omega-3 and omega-6, are important building blocks of cell membranes. Diet, which in Western nations is thought to have an omega-3:omega-6 ratio of 15–20:1, is the main source of these LCPUFA in humans (1). While over 5% of children and adolescents are diagnosed with attention deficit hyperactivity disorder (ADHD), making it one of the most prevalent mental health issues in pediatrics and adolescence. It is characterized by persistent attention deficit, hyperactivity, and impulsivity (2). ADHD is more prevalent in boys than in girls. Its specific cause is unknown. However, new research indicates that various gene and non-inherited factors play a significant role in ADHD (3). Compared to children without signs of ADHD, children with symptoms had greater omega-6 ratios, which may be related to dietary habits, changed gut flora, or abnormal LCPUFA metabolism (4).

Children with ADHD have underlying psychiatric problems such as bipolar disorder, schizophrenia, impulsive behaviour, and functional impairment (5). Although ADHD affects children aged 6–17 years. Most children with ADHD have not been fully cured, with estimates ranging from 60% to 80%. These symptoms will last till adulthood; many recent studies highlighted that adults with ADHD are at high risk of psychiatric disorders, including anxiety, depression, and suicidality (6). Human infants require omega-6 and omega-3 polyunsaturated fatty acids (PUFA) for neurodevelopment as well as to maintain neural integrity and function (7).

Although the pathogenesis of ADHD is not fully understood, current research suggests that catecholamines, particularly noradrenaline and dopamine, play an important role in treatment. Common pharmaceutical treatments for ADHD include methylphenidate and atomoxetine, which are essential in reducing symptoms (8). Recent randomized controlled trials (RCTs) suggest that omega-6 fatty acid supplementation may play a crucial role in improving cognitive function and behaviour in patients with neurological disorders (9,10). The omega-6 fatty acid gamma-linolenic acid (GLE) plays a crucial role in the formation of the brain-abundant arachidonic acid (ARA) (11,12). Along with omega-6 fatty acids, brain lipids with the cell membrane serve as a signalling medium, which is considered to play a crucial role in the prevention of anxiety disorders (13). However, some meta-analyses indicate that children and adults with ADHD have elevated ratios of blood omega-6 to omega-3, indicating a disruption in fatty acid metabolism (14). Although research on drug treatment is still in its early stages, some parents will select behaviour therapy for their children with ADHD; studies have shown that omega-3/6 supplementation reduces behavioural and learning difficulties in children with ADHD (15-19). Mendelian randomization (MR) is a method used to assess the association between exposure and result; in this study, genetic differences, or single nucleotide polymorphisms (SNPs), serve as instrument variables (IVs). The purpose of this study is to design a two-sample MR to explore the relationship between omega-6 fatty acids and ADHD. This manuscript is written following the STROBE-MR reporting checklist (available at <https://amj.amegroups.com/>

### Highlight box

#### Key findings

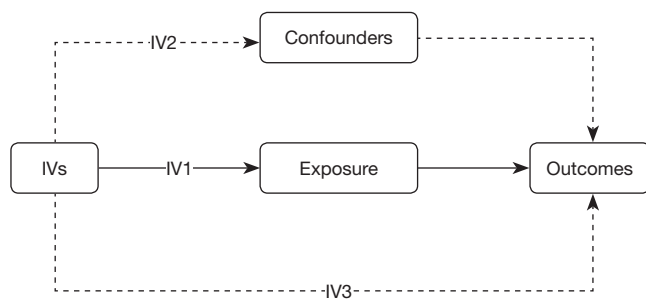
- Using two-sample Mendelian randomization (MR) method, this study finds no potential treatment impact of omega-6 on Attention deficit hyperactivity disorder (ADHD).

#### What is known and what is new?

- Studies have indicated that increasing one's intake of foods rich in omega-3, omega-6, and omega-9 fatty acids improves one's mental and physical well-being.
- The results were confirmed by using data from the ADHD GWAS, which comprised 20,138 cases and 35,191 controls for comparison. ADHD GWAS data, which included 20,138 cases and 35,191 controls, was used to corroborate the findings.
- By removing SNPs with incompatible alleles and palindromic SNPs with intermediate allele frequencies, the SNPs in the exposure and outcome datasets were harmonized (minor allele frequency threshold =0.01), resulting in a final set of 8 SNPs used for MR analysis (accounting for 4.6% of omega-6 fatty acids variance,  $R^2=0.046$ ). Thus, there is no evidence from our study that omega-6 fatty acids contribute to treatment of ADHD.

#### What is the implication, and what should change now?

- Due to a lack of supporting data, the use of omega-6 fatty acids in the treatment of ADHD is not currently recommended.



**Figure 1** Diagram of MR analysis. MR, Mendelian randomization; IVs, instrumental variables.

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## Methods

### Study design

MR analyses is a method commonly used in epidemiology to estimate the causal relationship between exposure and disease based on natural experiments assigned to high and low levels of exposure depending on individual genetic variation. The MR base platform was used to download data on SNPs related to omega-6 fatty acids, which were then analysed with R software (version 4.0.5). The MR base platform (<http://www.mrbase.org>) is a computer program and online medium for MR database and analysis developed by the integrative epidemiology unit of the University of Bristol's Medical Research Council (MRC) (20). The exposed cohort was drawn from the genome-wide association study (GWAS) cohort reported by Kettunen *et al.* in 2016 (21). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

### Sample population, size, and procedure

The sample population was European, and the sample size was 13,506. A clumping procedure was performed to retain the SNPs that were related to omega-6 fatty acids at a genome-wide significance level of  $P < 5 \times 10^{-8}$ . SNPs were in linkage disequilibrium with the index SNPs ( $r^2$  threshold  $\leq 0.001$ ) or within a 10,000 kb distance.

Furthermore, the outcome cohort was a GWAS meta-analysis of 12 cohorts that identified the first genome-wide significant ADHD loci and included 20,138 cases and 35,191 controls (22). Most people in the sample were European (approximately 95%). Patients with ADHD were

found in the national Psychiatric Central Research Register and diagnosed by psychiatrists in a psychiatric hospital using the ICD10 code.

MR is only a reliable method of making causal inferences if three conditions are met. The SNPs utilized in the IV relate to the exposure; there are no known or unknown confounders of the result, and the SNPs affect the outcome only through the pathway of interest (Figure 1).

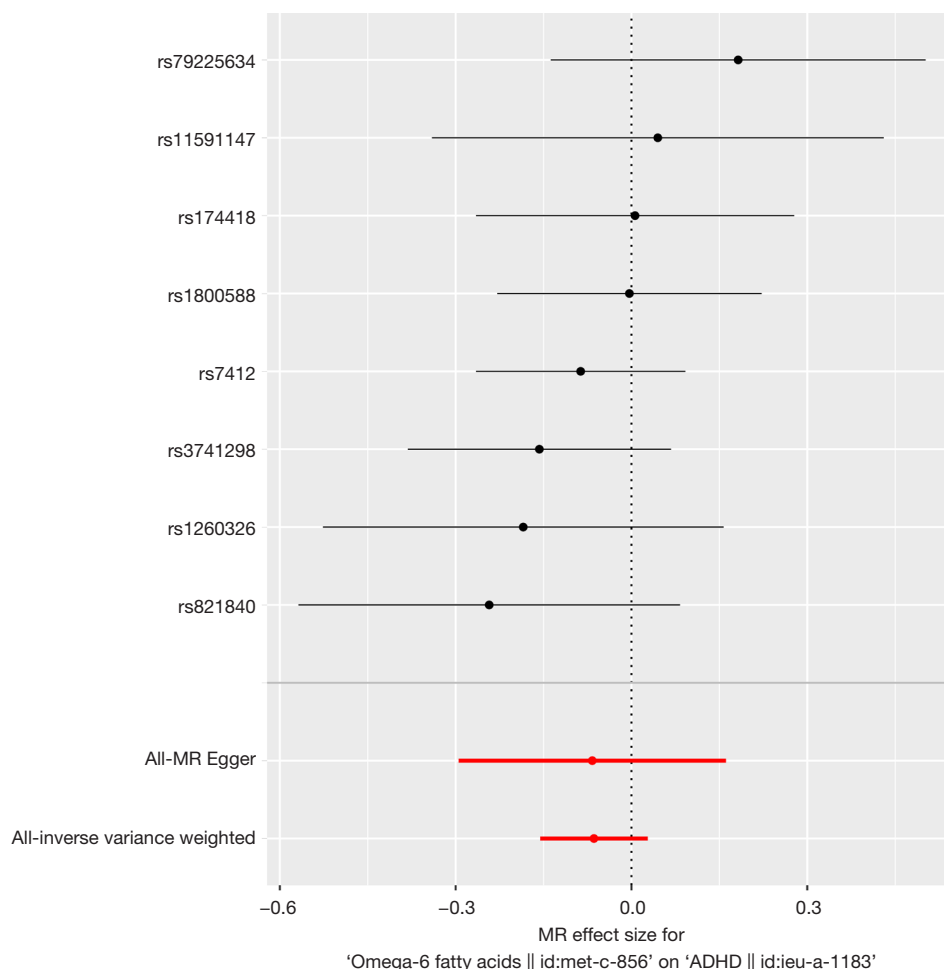
### Assumption of two-sample MR

MR necessitates that genetic instruments are related with a modifiable exposure of interest (assumption 1), and any relationship between the instruments and outcome is mediated by the exposure (assumption 2). The instrumental variable only affects the outcome through its effect on risk factors (assumption 3) (23). SNPs that violate these assumptions are called invalid instrumental variable and considering it in MR analyses may lead to a deviation in the results. In the absence of reliable information on the ratio and direction of functional pathways and various genetic variations, additional MR methods, including the weighted median of MR-Egger, were used to check the consistency of the estimated direction of the effect (24).

Inverse variance weighted (IVW) meta-analysis was used to combine MR estimates for each probable direction of influence, which is essentially a weighted regression of SNP-outcome effects on SNP-exposure effects with a zero intercept (25). Outcomes may be biased if instrument SNPs exhibit horizontal pleiotropy or they influence outcomes through causal pathways other than exposure (26). We compared IVW findings with that of other MR methods, whose estimates are known to be less affected by horizontal pleiotropy. Two orthogonal methods were used (weighted median estimator, which is consistent even when up to 50% of the information comes from invalid IVs (24). and MR-Egger, which provides a valid test of directional (unbalanced) pleiotropy, and an accurate test of the causal null hypothesis) to perform additional sensitivity analyses since the IVW method requires that all IVs meet all the MR assumptions.

### Statistical analysis

We evaluated the weak instrument bias by F statistics which was calculated using the following formula, where  $k$  is the number of SNPs and  $n$  is the sample size,  $R^2$  refers to the variance explained by SNPs in omega-6 fatty acids (25).



**Figure 2** Forest plot of the two-sample MR analysis. MR, Mendelian randomization; ADHD, attention deficit hyperactivity disorder.

$$F = \frac{n-k-1}{k} \times \frac{R^2}{1-R^2} \quad [1]$$

Further tests for horizontal pleiotropy were performed using the MR-Egger intercept test of deviation from the null to assess the robustness and significance of the results. Also, leave-1-SNP-out analyses were performed to check whether SNPs influence the overall estimates.

## Results

The SNPs were harmonized (minor allele frequency threshold =0.01) between the exposure and outcome data sets by removing SNPs with incompatible alleles as well as palindromic SNPs with intermediate allele frequencies, resulting in a final set of 8 SNPs used for MR analysis (accounting for 4.6% of omega-6 fatty acids variance,

$R^2=0.046$ ).

There is no significant relationship between omega-6 fatty acids and ADHD. The odds ratio (OR) of the 8-SNP IVs based the IVW analysis was 0.94 per standard deviation (SD) of omega-6 fatty acids, 95% CI, 0.86–1.02,  $P=0.17$  (Figure 2). Other analyses revealed comparable findings (MR Egger:  $P=0.59$ , 0.94 per SD of omega-6 fatty acids, 95% CI, 0.75–1.18; weighted median:  $P=0.27$ , 0.94 per SD of omega-6 fatty acids, 95% CI, 0.83–1.05; weighted model:  $P=0.39$ , 0.93 per SD of omega-6 fatty acids, 95% CI, 0.79–1.09) (Table 1).

The F statistics were 81, greater than 10, demonstrating the insignificant, weak instrument bias. Based on Cochran's Q, there was no significant heterogeneity in Wald ratios for individual SNPs in the IV ( $P=0.602$  for IVW;  $P=0.485$  for MR-Egger). The MR-Egger intercept test (Intercept =0.00038,  $P=0.979$ ) revealed no strong directional

horizontal pleiotropy (Figure 3).

Furthermore, funnel plot and leave-one-out sensitivity analysis using the IVW method revealed no single SNPs influenced the estimate results (Figures 4,5).

### Discussion

This study reveals no potential treatment impact of omega-6 on ADHD incidence. The negative outcome of this study

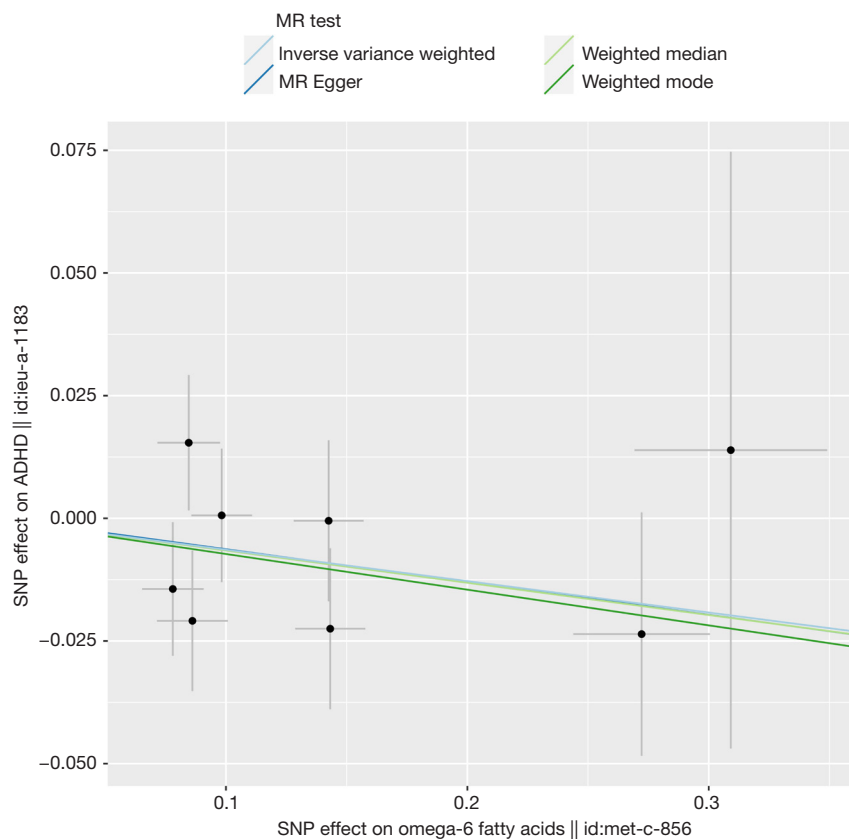
contradicts the findings of several prior investigations. ADHD is one of the most common neurodevelopment disorders, affecting between 5% and 12% of children (27). Although the fundamental cause of ADHD is unknown and numerous factors contribute to its progression, genetic and environmental factors may increase the chance of developing the condition. Recently, the connection between nutritional supplements and ADHD has been analyzed (28). Omega-6 fatty acid GLE play an essential role in the production of ARA which is present in brain in plenty amount Omega-6 fatty acid supplements may play a key role to improve cognitive function and behaviour in brain disorder.

Growing evidence and reports have shown that omega-3 and omega-6 PUFAs might be a potential treatment option for children with ADHD compared to typical medication, including methylphenidate hydrochloride and atomoxetine. Numerous cohort studies and meta-analyses published in the last decades have estimated pharmacological, non-pharmacological, and combined treatment efficacy and

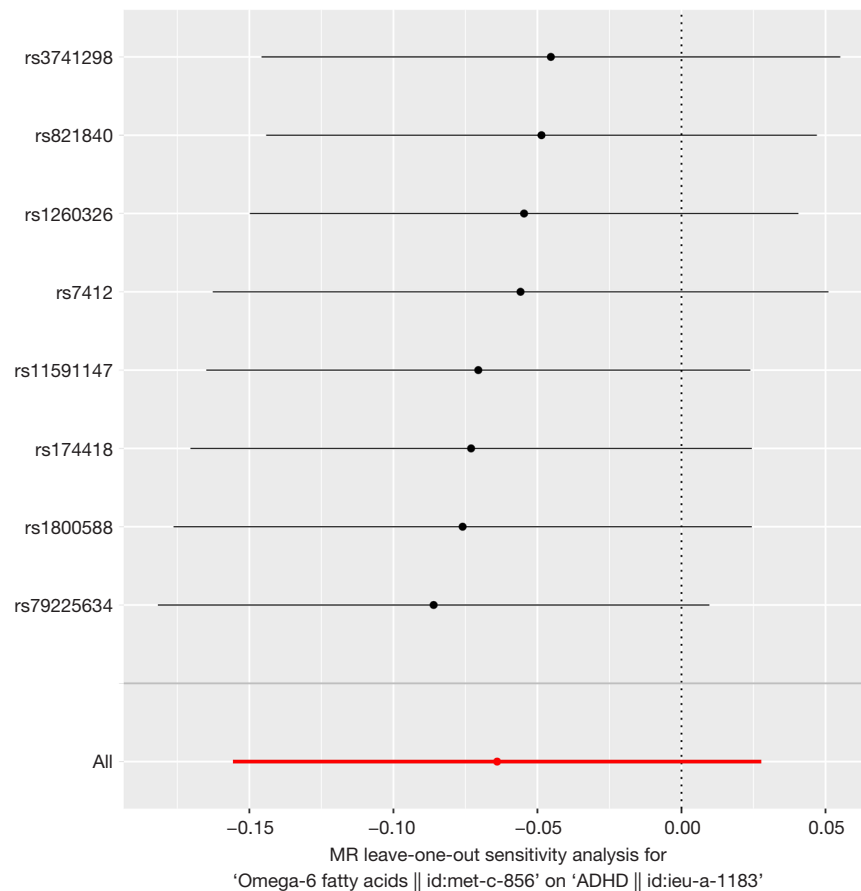
**Table 1** Causal effect of omega-6 fatty acids on ADHD

Method	OR	95% CI	P value
MR Egger	0.94	0.75–1.18	0.59
Weighted median	0.94	0.83–1.05	0.27
Inverse variance weighted	0.94	0.86–1.02	0.17
Weighted mode	0.93	0.79–1.09	0.39

ADHD, attention deficit hyperactivity disorder; MR, Mendelian randomization; OR, odds ratio; CI, confidence interval.



**Figure 3** Scatter plot of the two-sample MR analysis. MR, Mendelian randomization; SNP, single nucleotide polymorphism; ADHD, attention deficit hyperactivity disorder.



**Figure 4** Result of “leave-one-out” sensitivity analysis. MR, Mendelian randomization; ADHD, attention deficit hyperactivity disorder.

safety for managing ADHD (29–38). Increasing symptoms of ADHD at age 7 were associated with an increase in omega-6 to omega-3 LCPUFA in cord plasma. This shows that supplementing a mother’s diet with omega-6 fatty acids can lessen her child’s risk of developing ADHD (1).

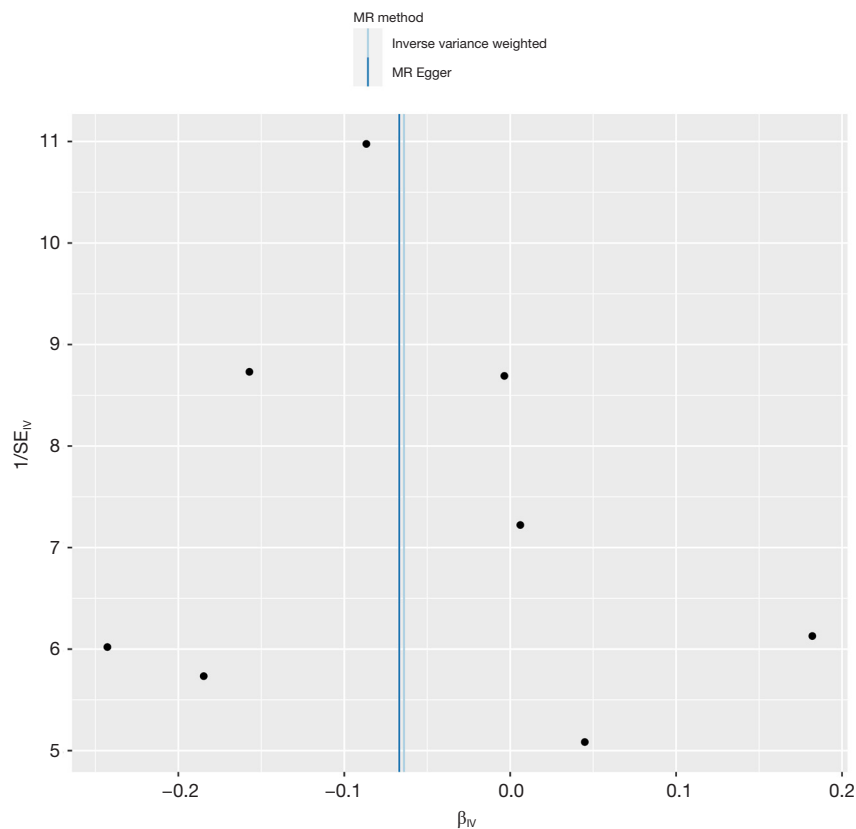
The evidence supporting the benefits of DHA and EPA on fetal and infant brain development is increasing, and pregnant women are increasingly being encouraged to consume them (39). A comprehensive review of RCTs was designed based on these findings. Muhammad Abdullah *et al.* examined the effects of omega-3&6 based on the mean difference in Conners’ rating scale and seven trials. They conclude that there is insufficient evidence to determine if omega-3&6 supplementation is useful in lowering the symptoms of ADHD in children and adolescents (40). Renata Ramalho *et al.* analyzed nine studies, including five RCTs and four cohort studies, and identified three studies with negative results (41). In an intriguing study comparing the efficacy and safety of omega-3/6 fatty acids,

methylphenidate, and combination treatment in children with ADHD, the effects of monotherapy methylphenidate were comparable to the effects of a combination of omega-3/6 fatty acids. Still, the methylphenidate (MPH) + omega combination demonstrated some unexpected benefits over methylphenidate (10). However, there is still no unified recommendation guideline or strong evidence for daily supplementary dose (42).

#### *Limitations of this study*

Likewise, our research has certain limitations. First, the MR analysis is predicated on three tight assumptions. However, we minimize their effect by employing several models and sensitivity analysis, we had limited power to detect causal effects for some traits. Second, MR methods depend on the source GWAS sample sizes and trait heritability. These factors had a particular impact on the GWAS summary data sets for attention, and intra-individual response time





**Figure 5** Funnel plot of the two sample MR analysis. MR, Mendelian randomization; SE, standard error; IV, instrument variable.

variability, as all GWAS were based on modestly sized samples. Many cognitive traits associated with ADHD, such as reward processing, visuospatial working memory, and sustained attention performance, still lack the publicly available GWAS data needed for MR. Thirdly, despite applying several methods to test for pleiotropy and finding limited evidence for any directional pleiotropy, we cannot entirely rule out possible bias due to residual horizontal pleiotropy. Fourth, only Europeans are allowed to participate; the outcome is not stable following a sensitivity analysis in which SNPs are eliminated one by one.

## Conclusions

Even though we did not find evidence that omega-6 had a therapeutic effect on ADHD, our results may provide light on why those with the disorder also tend to experience several co-occurring issues as they grow older age. They may hold promise as a fresh starting point for research into developing preventative medicines for ADHD and the potentially damaging effects of the disorder.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE-MR reporting checklist. Available at <https://amj.amegroups.com/article/view/10.21037/amj-22-74/rc>

*Peer Review File:* Available at <https://amj.amegroups.com/article/view/10.21037/amj-22-74/prf>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://amj.amegroups.com/article/view/10.21037/amj-22-74/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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