

The Relationship Between Blood Lipid and Attention-Deficit/Hyperactivity Disorder (ADHD) in an Obese Population of Chinese Children: An Obesity-Stratified Cross-Sectional Study

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Background: Although obesity has been related to attention-deficit/hyperactivity disorder (ADHD), few studies have examined the relationship between blood lipid levels and ADHD in children. We aimed to evaluate whether increased blood lipid levels are associated with the prevalence of ADHD in children.

Methods: A total of 1179 children were studied in the cross-sectional analysis. Multivariate logistic regression and linear regression analyses were performed to evaluate the association of blood lipid levels with the prevalence of ADHD in children.

Results: In 1179 children, the average age was 10.4 years, and the percentage of boys was 50.3%. 97 (8.2%) of the children were diagnosed with ADHD. The logistic regression analysis demonstrated that elevated levels of total cholesterol (OR=2.001, 95% CI 1.247–3.541, P -trend=0.024), triglycerides (OR=1.776, 95% CI 1.448–2.187, P -trend=0.003) and LDL (low density lipoprotein; OR=2.016, 95% CI 1.335–3.966, P -trend<0.001) and reduced levels of HDL (high density lipoprotein; OR=0.577, 95% CI 0.298–0.948, P -trend=0.023) were associated with the prevalence of ADHD after adjustments were made for age, sex, body mass index (BMI), residence type, maternal smoking during pregnancy, breastfeeding and breastfeeding length, maternal and paternal educational levels, and marital status of parents in Model 3. The stratified analysis using “obese” as a covariate showed that elevated levels of total cholesterol, triglycerides and LDL and reduced levels of HDL were independently associated with an increased risk of ADHD in obese children.

Conclusion: Increased blood lipid levels were associated with ADHD in obese children.

Keywords: blood lipids, ADHD, obese, cross-sectional analysis

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of most common neurodevelopmental disorders in childhood and has been found to be closely associated with an increased risk of metabolic syndrome, such as obesity and diabetes mellitus.^{1–4} The prevalence of ADHD was suggested to increase by more than 30% during 2006–2008,⁵ and in recent years, the rate of childhood obesity has been significantly rising due to overnutrition.⁶ Existing studies have shown a high rate of obesity in children with ADHD or a high prevalence of ADHD in obese children.⁷ Despite mixed findings in some studies, meta-analyses have demonstrated a close association of ADHD with obesity, independent of potential confounding factors such as mental health conditions.⁷

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Metabolic syndrome is an increasing public health concern due to its associations with complications, including hyperlipidemia, hypertension, diabetes, cardiovascular disease (CVD) and cancer.^{8–10} Recently, a meta-analysis examined the association between obesity and ADHD after controlling for confounding factors such as age, sex and others among children.⁷ A significant association of ADHD with obesity was found in the meta-analysis, which included more than 700,000 children and adults.⁷ Metabolic syndrome, which is associated with obesity, includes a series of metabolic abnormalities, including hypertriglyceridemia, low levels of high-density lipoprotein cholesterol (HDL), high levels of low-density lipoprotein cholesterol (LDL), hypertension and insulin resistance.^{11,12} The incidence of metabolic syndrome has been significantly rising in the past few decades. Recent data have demonstrated that approximately 1/4 of American adults have metabolic syndrome, which accounts for much of the risk for premature cardiovascular death.^{13,14} Importantly, the median prevalence of metabolic syndrome in the whole population was 3%, with a prevalence of 29% among obese children.^{15,16}

Studies in the literature have investigated this association between blood lipid levels and ADHD.^{17–19} However, studies investigating the association between blood lipid levels and ADHD in Chinese children are limited. We aimed to investigate whether the relationship between blood lipid levels and ADHD is independent of other confounding factors. We also investigated whether this independent association can be modified by obesity.

Materials and Methods

Study Sample

For the purpose of this study, 1179 children who were registered Clinical Data Repository from January 2010 to December 2020 were included in our analysis. In the study, all children with ADHD were included if they had at least one registered diagnosis of ADHD. The diagnostic criteria for ADHD include the following:¹⁹ 1) the onset of ADHD is at or before the age of 7; 2) the symptoms of ADHD must manifest in two or more environments, such as school, workplace or home; 3) there is clear clinical impairment in social, academic or occupational functions; and 4) generalized developmental disorder, schizophrenia, emotional disorder or other mental disorders should be excluded. All included children met these 4 criteria. Additionally, the details of blood collection, storage and testing for blood lipid levels, including total cholesterol and triglycerides, LDL and HDL, are available elsewhere.¹⁸ Blind-duplicate coefficients of

variation ranged from 5% to 10%. According to the Declaration of Helsinki guidelines, the Ethics Committee of the Huai ‘an Maternal and Child Health Hospital approved this study, and all patients gave written informed consent.

Covariates

Sociodemographic characteristics and lifestyle factors, including age, sex, BMI, residence type, maternal smoking during pregnancy, breastfeeding and breastfeeding length, maternal and paternal educational levels, marital status of parents, nutritional status and physical activity. Residence type was defined as “urban” or “rural”. Breastfeeding was classified as “never breastfed” or “ever breastfed”. Maternal smoking during pregnancy was classified as “never smoked during pregnancy”, or “ever smoked during pregnancy”. Maternal and paternal educational levels were defined as “more than primary school” or “primary school and lower”. The marital status of parents was classified as “separated/divorced” or “other”. Nutritional status was dichotomized as “adequate” or “inadequate”. Physical activity was also dichotomized as “appropriate” or “inappropriate”. Additionally, since the growth patterns of boys and girls differ, evaluating the body mass index (BMI) of children is more complicated than and different from evaluating adults. Therefore, the WHO guidelines were used to diagnose obesity in children, with obesity defined as a BMI \geq 85th percentile and a triceps skinfold thickness and a subscapular skinfold thickness \geq 90th percentile.

Statistical Analysis

Data were analyzed by using SPSS 25.0. All measurement data in our study were normally distributed or had approximate normal distributions and are expressed as the mean \pm standard deviation (M \pm SD). Categorical variables are shown as n (%). All individuals in this study were divided into two groups according to whether they were obese (BMI \geq 24 kg/m²). Then, corrected logistic regression analysis was used to examine the associations between blood lipid levels (total cholesterol, triglycerides, LDL and HDL) and the risk of ADHD in children, with quartile 1 as the reference category. Blood lipid levels were categorized by quartiles (quartile 4: \geq 75th percentile, quartile 3: 50th–75th percentile, quartile 2: 25th–50th percentile, quartile 1: $<$ 25th percentile). Quartile 1 was defined as a reference group. Confounding factors were corrected as follows: Model 1: adjusted for age and sex; Model 2: adjusted for age, BMI, sex, residence type, maternal smoking during pregnancy, breastfeeding and breastfeeding

length; Model 3: adjusted for age, sex, BMI, residence type, maternal smoking during pregnancy, breastfeeding and breastfeeding length, maternal and paternal educational levels, marital status of parents and physical activity. Then, to further observe whether obesity can modify the relationship between blood lipids and ADHD in children, interaction analysis was performed.

To further assess the predictive value of blood lipid levels for detecting ADHD among children, sensitivity analysis was performed by adding “physical activity” as a covariate in the logistic regression model. $P \leq 0.05$ was considered to be statistically significant in all analyses.

Results

Baseline Characteristics of the Study Cohort

Of 1179 children in this cross-sectional analysis (Table 1), 593 (50.3%) were boys. The mean of age was 10.4 (10.4±3.6) years. A total of 793 (67.4%) individuals lived in urban areas, and had BMIs from 18.6±3.4. The number of individuals with maternal smoking during pregnancy was 20 (1.7%), and the number of breastfed individuals was 998 (84.6%) with a breastfeeding length of 6.2 ±3.1 months. Among these children, maternal and paternal educational levels with more than a primary school education were 95.4% and 98.6%, respectively.

The Association Between Blood Lipid Levels and the Risk of ADHD in Children Analyzed by Logistic Regression

We evaluated the association of blood lipid levels (total cholesterol, triglycerides, LDL and HDL) with the risk of ADHD among children by multivariate logistic regression analysis, as shown in Table 2. Model 1 indicated that elevated levels of total cholesterol [2.248 (1.380–4.226), P -trend=0.009], triglycerides [1.885 (1.501–3.099), P -trend<0.001] and LDL [2.326 (1.527–4.772), P -trend<0.001] were associated with a higher risk of ADHD after adjustment for age and sex. After adjusting for age, BMI, sex, residence type, maternal smoking during pregnancy, breastfeeding and breastfeeding length, the results in Model 2 were similar to those of Model 1. This association remained statistically significant and changed little when maternal and paternal educational levels, marital status of parents and physical activity were added to Model 2 (Model 3). Importantly, our results also showed that a higher HDL [0.455 (0.090–0.812), P -trend=0.008] was associated with a reduced risk of ADHD in Model 1 when age and sex

Table 1 The Characteristics of Study Population (N=1179)

Variables	M±SD or n (%)
Age (Years)	10.4±3.6
Gender (male), n (%)	593 (50.3)
Height (cm)	141.5±16.7
Weight (kg)	39.2±9.3
BMI (kg/m ²)	18.6±3.4
Residence	
Urban, n (%)	793 (67.4)
Rural, n (%)	386 (32.7)
Maternal smoking pregnancy, n (%)	20 (1.7)
Breastfeeding, n (%)	998 (84.6)
Breastfeeding length (months)	6.2 ±3.1
Maternal educational level, n (%)	
More than primary school, n (%)	1125 (95.4)
Primary school and lower, n (%)	54 (4.6)
Paternal educational level, n (%)	
More than primary school, n (%)	1162 (98.6)
Primary school and lower, n (%)	17 (1.4)
Marital status of parents	
Separated/divorced, n (%)	178 (15.1)
Others, n (%)	1001 (84.9)
Nutritional status	
Adequate, n (%)	1160 (98.4)
Inadequate, n (%)	19 (1.6)
Physical activity (kcal/d)	1195.4 ±717.4
ADHD, n (%)	97 (8.2)
Serum lipid level	
Triglycerides (mmol/L)	1.95±1.25
LDL (mmol/L)	2.13±0.84
HDL (mmol/L)	1.43±0.15
Total cholesterol (mmol/L)	4.04±1.21

Note: M ±SD for normally distributed data and n (%) for categorical variables.

Abbreviations: BMI, body mass index; ADHD, attention-deficit/hyperactivity disorder; LDL, low density lipoprotein; HDL, high density lipoprotein.

were adjusted. Interestingly, the association disappeared in Model 2 and Model 3, when the remaining confounding factors were adjusted for.

Stratified Analysis of the Association Between Blood Lipid Levels and the Risk of ADHD in Children

All included children were classified into two groups according to obesity status (obese group and nonobese group). We found that elevated levels of total cholesterol (OR=2.234, 95%

Table 2 Logistic Regression Analysis of the Relationship Between the Lipid Levels and Risk of ADHD in Children

Variables	Model 1	Model 2	Model 3
Total cholesterol			
Quartile 1	1.000 (ref.)	1.000 (ref.)	1.000 (ref.)
Quartile 2	1.625 (1.147–2.821)	1.570 (1.114–2.368)	1.484 (1.053–2.220)
Quartile 3	1.856 (1.247–3.155)	1.722 (1.162–2.872)	1.619 (1.116–2.877)
Quartile 4	2.248 (1.380–4.226)	2.105 (1.311–3.988)	2.001 (1.247–3.541)
P-trend	0.009	0.011	0.024
Triglycerides			
Quartile 1	1.000 (ref.)	1.000 (ref.)	1.000 (ref.)
Quartile 2	1.447 (1.312–1.915)	1.414 (1.303–1.879)	1.397 (1.256–1.833)
Quartile 3	1.634 (1.437–2.371)	1.497 (1.325–2.166)	1.459 (1.307–2.072)
Quartile 4	1.885 (1.501–3.099)	1.801 (1.467–2.302)	1.776 (1.448–2.187)
P-trend	<0.001	0.001	0.003
LDL			
Quartile 1	1.000 (ref.)	1.000 (ref.)	1.000 (ref.)
Quartile 2	1.624 (1.246–2.41)	1.490 (1.114–2.368)	1.484 (1.053–2.290)
Quartile 3	1.803 (1.211–3.164)	1.713 (1.157–2.972)	1.706 (1.137–2.811)
Quartile 4	2.326 (1.527–4.772)	2.147 (1.356–4.280)	2.016 (1.335–3.966)
P-trend	<0.001	<0.001	<0.001
HDL			
Quartile 1	1.000 (ref.)	1.000 (ref.)	1.000 (ref.)
Quartile 2	0.766 (0.291–1.008)	0.810 (0.299–1.013)	0.831 (0.383–1.131)
Quartile 3	0.637 (0.148–0.946)	0.751 (0.238–0.964)	0.766 (0.370–0.979)
Quartile 4	0.455 (0.090–0.812)	0.534 (0.158–0.866)	0.577 (0.298–0.948)
P-trend	0.008	0.017	0.023

Notes: Model 1: Adjusted for age and gender. Model 2: Adjusted for age, BMI, gender, residence, maternal smoking pregnancy, breastfeeding and breastfeeding length. Model 3: Adjusted for age, gender, BMI, residence, maternal smoking pregnancy, breastfeeding, breastfeeding length, maternal educational level, paternal educational level, marital status of parents and physical activity. ADHD, attention-deficit/hyperactivity disorder; LDL, low density lipoprotein; HDL, high density lipoprotein; BMI, body mass index.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; LDL, low density lipoprotein; HDL, high density lipoprotein; BMI, body mass index.

CI 1.112–5.103, $P < 0.001$), triglycerides (OR=1.585, 95% CI 1.037–2.572, $P = 0.010$) and LDL (OR=2.568, 95% CI 1.358–4.267, $P < 0.010$) were still independently associated with an increased risk of ADHD in obese children after adjustments for age, sex, BMI, residence type, maternal smoking during pregnancy, breastfeeding and breastfeeding length, maternal and paternal educational levels, and marital status of parents were made (Table 3). Importantly, the associations of these indices, including levels of total cholesterol (OR=1.232, 95% CI 1.008–2.336, $P = 0.205$), triglycerides (OR=1.458, 95% CI 1.016–2.752, $P = 0.176$) and LDL (OR=1.649, 95% CI 1.204–3.135, $P = 0.071$), with ADHD were not significant in nonobese children. Similarly, HDL levels were still related to a lower risk of ADHD in obese children (OR=0.446, 95% CI 0.125–0.802 $P = 0.008$) but not in nonobese children (OR=0.679, 95% CI 0.133–1.089, $P = 0.059$). The P values for interactions in the stratified analysis were 0.003 (total cholesterol), 0.003 (triglycerides), 0.005 (LDL) and 0.014 (HDL).

Importantly, to further assess the predictive value of blood lipid levels for detecting ADHD among children, sensitivity analysis was performed by adding “physical activity” as a covariate in the logistic regression model. After adjusting for age, sex, BMI, residence type, maternal smoking during pregnancy, breastfeeding and breastfeeding length, maternal and paternal educational levels, marital status of parents and physical activity, our results were consistent with those in Tables 3 and 4. The P values for interactions in the stratified analysis were 0.004 (total cholesterol), 0.002 (triglycerides), 0.007 (LDL) and 0.018 (HDL), as shown in Table 4.

Discussion

We found that elevated levels of blood lipids were related to an increased risk of ADHD in children when adjusting for potential confounding factors. This independent relationship can be significantly modified by obesity.

Table 3 Logistic Regression Analysis for the Relationship Between the Lipid Levels and Risk of ADHD in Children by Stratified Analysis Using “Obese”

Variables	Obese			Non-Obese		
	OR	95% CI	P value	HR	95% CI	P value
Serum cholesterol (per 1-SD increase)	2.234	1.112–5.103	<0.001	1.232	1.008–2.336	0.205
P value for interaction	0.003					
Serum triglycerides (per 1-SD increase)	1.585	1.037–2.572	0.010	1.458	1.016–2.752	0.176
P value for interaction	0.003					
Serum LDL (per 1-SD increase)	2.568	1.358–4.267	<0.001	1.649	1.204–3.135	0.071
P value for interaction	0.005					
Serum HDL (per 1-SD increase)	0.446	0.125–0.802	0.008	0.679	0.133–1.089	0.059
P value for interaction	0.014					

Notes: Adjusted for age, gender, BMI, residence, maternal smoking pregnancy, breastfeeding, breastfeeding length, maternal educational level, paternal educational level and marital status of parents.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; LDL, low density lipoprotein; HDL, high density lipoprotein; BMI, body mass index.

ADHD has a high prevalence of approximately 5% in school children worldwide.⁷ The average annual costs for ADHD have significantly risen in the past few years.²⁰ Although many existing studies have suggested a significant association of obesity with ADHD,^{21–23} others did not confirm this finding.^{24,25} The uncertain association between obesity and ADHD seems to be paradoxical because obese children

are usually described as being lazy.¹⁴ The effect of potential confounding factors, such as obesity, psychiatric comorbidities and low socioeconomic status, for explaining the association between levels of blood lipids and ADHD is still not entirely certain, especially among children.^{21–23,26}

One study suggested that no significant difference in triglycerides and HDL levels was found between a small

Table 4 Sensitivity Analysis for the Relationship Between the Lipid Levels and Risk of ADHD in Children by Using “Physical Activity”

Variables	Obese			Non-Obese		
	HR	95% CI	P value	HR	95% CI	P value
Serum cholesterol (per 1-SD increase)	2.223	1.109–5.102	<0.001	1.231	1.007–2.325	0.212
P value for interaction	0.004					
Serum triglycerides (per 1-SD increase)	1.573	1.029–2.561	0.011	1.436	1.004–2.654	0.178
P value for interaction	0.002					
Serum LDL (per 1-SD increase)	2.589	1.363–4.293	<0.001	1.627	1.164–3.129	0.082
P value for interaction	0.007					
Serum HDL (per 1-SD increase)	0.454	0.127–0.871	0.009	0.693	0.138–1.090	0.062
P value for interaction	0.018					

Notes: Adjusted for age, gender, BMI, residence, maternal smoking pregnancy, breastfeeding, breastfeeding length, maternal educational level, paternal educational level, marital status of parents and physical activity.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; LDL, low density lipoprotein; HDL, high density lipoprotein; BMI, body mass index.

sample of adults with ADHD who did not undergo treatment and adults without ADHD,²⁷ but individuals with ADHD had LDL levels above 160 mg/dl. Another study, based on the population-based German Health Interview and Examination Survey for children and adolescents, reported that 9.7% (666) of individuals were diagnosed with ADHD or suspected ADHD, and compared serum total cholesterol, triglycerides, LDL and HDL levels between children with ADHD and children without ADHD.²⁸ The results from the children's data showed that differences in total cholesterol and LDL levels, rather than triglycerides and HDL levels, were found between individuals with ADHD and individuals without ADHD. A weakly inverse association was found between LDL levels and ADHD symptoms. The above results are partly consistent with our findings that total cholesterol, triglycerides and LDL levels were associated with a higher risk of ADHD. Nigg et al found no relationship between the lipid profile and ADHD.²⁹ Pinho et al found an inverse relationship between LDL levels and ADHD.³⁰ In our study, a significant association existed only in obese children. These four indices of blood lipid levels had no association with ADHD risk among nonobese children. The heterogeneity of these study results might be at least partly explained by the different study designs used and hypotheses investigated, different confounding factors adjusted for, the populations of different ages selected and varying serum measurement methods and instruments. For instance, blood lipid levels under different physiological conditions and different questionnaires assessing confounding variables can account for some of these variations.

Our study has three main contributions to the literature. First, our study data are from the cross-sectional analysis with a large sample size.^{18,19} The analysis of the results suggested that elevated levels of blood lipids were closely related to ADHD among nonobese children, which expands national sample research on the association. Second, our results demonstrated that obesity is an important modifying variable that affects the association between blood lipid levels and ADHD. We found that the relationship between blood lipid levels and ADHD can be significantly affected, which seems to explain the heterogeneity of previous studies on the association between ADHD and obesity. Additionally, we conducted a robust and accurate calibration analysis to exclude the effects of other potential confounding factors, such as

sociodemographic characteristics and lifestyle factors, environmental factors, and nutritional status, which have been associated with ADHD and blood lipid levels.

Of course, a limitation of our study is the cross-sectional study design in which the causal relationship between serum lipid levels and ADHD is uncertain. Future research is necessary to identify the prognostic value of levels of blood lipids for predicting ADHD in children. Moreover, blood lipid levels were measured only once in each individual. Under different times, environments and physiological states, blood lipid levels will change and eventually affect the stability and reliability of the results.

In conclusion, the cross-sectional analysis revealed that blood lipid levels were related to an increased risk of ADHD among obese children but not in nonobese children. This study may provide further evidence that obesity is an important factor in the development of ADHD in children.

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Disclosure

The authors declare no conflicts of interest and have nothing to disclose.

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