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# Pre-conception folic acid intake and attention deficit and hyperactivity disorder in children

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## ABSTRACT

**Objectives:** Attention Deficit Hyperactivity Disorder (ADHD) is a common disorder in children. It is thought to occur due to the interaction of many genetic and environmental factors during early development. Many studies have been conducted to investigate the etiology of ADHD. Some have investigated neurobiology, and others have investigated malnutrition and trace element deficiency. To investigate the effect of folic acid intake during the pre-conception period in terms of ADHD development.

**Methods:** Five hundred and ninety-eight participants, 246 children with ADHD, and 352 healthy controls were enrolled. A questionnaire was completed, including socio-demographic information and the use of folic acid and other supplements such as a multivitamin, iron, and omega 3 during pregnancy. Data were examined to determine associations with ADHD. Mann-Whitney U tests for continuous variables, Pearson's chi-square, and Fisher's exact tests for categorical variables were used to compare groups.

**Results:** The use of folic acid during pre-pregnancy among mothers who had a child with ADHD was 13% and this was 31% in the control group ($p < 0.001$). There was no statistically significant difference between the groups' use of folic acid in pregnancy ($p = 0.617$). Other situations related to ADHD were advanced maternal age ($p < 0.001$ for both groups), abnormal double screening test results in pregnancy (27% vs. 5%, $p < 0.001$) and omega 3 use in pregnancy ($p < 0.001$).

**Conclusions:** The use of folic acid before and during pregnancy is important for neurological development. However, there is little data on use before pregnancy in the literature. This study shows that folic acid taken before pregnancy may prevent ADHD in childhood. The present study recommends folic acid usage in planned pregnancy to prevent ADHD in the child.

**Keywords:** Pre-pregnancy, folic acid, attention deficit hyperactivity disorder, children

The use of folic acid before and during pregnancy is known to be important for neurological development. Folic acid supplementation during the pre-conception period and first trimester of pregnancy reduces the incidence of neural tube defects (NTDs). Studies show that the supplementation of 0.4 mg folic acid during the periconceptional period prevents 50-70% of NTDs [1].

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Just as it prevents the development of NTDs, lack of folate has been found to be associated with the development of many neurodevelopmental disorders [2]. For example, aggression [3], impaired cognitive functions [4] and reduced memory function [5] have found to be associated with folate/homocysteine levels.

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in children, with a prevalence estimated from 5% to 7% across cultures. There may be accompanying comorbid diseases and problems affecting life. Individuals with this disorder have lower self-esteem, social functioning, academic and economic achievement [6]. Medical problems include smoking, obesity, nonadherence, and comorbid medical illnesses [7]. Though the etiology is not fully identified, it is thought to be multifactorial [6]. The majority view is that environmental and genetic factors like toxins, pregnancy/birth problems, brain damage, and immune system problems, play a role together. Exposure of the baby to trauma during pregnancy and birth (e.g., asphyxia, infection, toxic-metabolic-mechanic trauma) may cause minimal brain damage or functional disorders in the baby's brain [8]. This functional disorder might cause ADHD accompanied by neurological soft signs [9]. Lower folate status in early pregnancy was associated with impaired fetal brain development and affects hyperactivity/inattention and peer problems in childhood [10]. To our knowledge, there is no study or contribution relating to the association of prepregnancy folate usage and ADHD development in the literature. The present study aimed to investigate the effect of folic acid intake during the pre-conception period in terms of possible relation with ADHD development.

## METHODS

A case-control study was carried out. The study included 251 children with ADHD and their parents, and 450 healthy children and their parents. Exclusion criteria were as follows: (1) Premature babies; (2) Those with known neurological disease like mental motor retardation and epilepsy in mother and child and known accompanying chronic disease (cardiovascular, endocrinological, psychiatric); (3) Those who used substances such as alcohol; (4) Having a child with any neurologic disease such as neural tube defect; and (5) Mother and children who did not wish to be included in the study.

As a result, the sample included 246 children who were diagnosed as ADHD by the Child and Adolescent Psychiatry out-patient clinic and 352 healthy children who were chosen from the pediatric policlinic as control group. In AD/HD group, diagnosis was based on criteria from the Diagnostic and Statistical Manual of Mental Disorders (Fourth edition, Washington, DC: American Psychiatric Association, 1994) by Child and Adolescent Psychiatry doctors.

Parents and children provided written informed consent for participation and the necessary legal approvals and University Ethical Committee approval were obtained. Demographic characteristics (age, educational level, socioeconomic situation), obstetric history (preeclampsia, vaginal bleeding during pregnancy, gestational diabetes mellitus), and the use of folic acid during the pre and periconceptional period were questioned. Folic acid supplement use was categorized in three groups: (i) starting preconception, (ii) starting within the first 10 weeks of pregnancy or (iii) no use. Other supplemental treatments such as multivitamin and omega 3 intake during pregnancy, were also questioned. Socioeconomic status was self-reported and defined into three terms as good, moderate, or poor.

### Ethical Approval

Ethical approval for the study was obtained from the ethics committee of Şevket Yılmaz Training and Research Hospital on 04.03.2015 with the decision number 2015/05-03.

### Statistical Analysis

The data was examined by the Shapiro Wilk test whether or not it presents normal distribution. The results were presented as median (minimum-maximum) or frequency and percentage. Mann Whitney U tests were used for nonnormally distributed data. Categorical variables were compared using Pearson's chi-square test and Fisher's exact test between groups. $p < 0.05$ was considered as significance levels. Statistical analyses were performed with IBM SPSS ver.23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.).

## RESULTS

Five hundred and ninety-eight participants, 246 children with ADHD and 352 healthy controls, were enrolled in the study. Characteristics of the groups are given in Table 1.

The use of preconception folic acid appeared to be statistically significantly low in the ADHD group compared to the control group. This situation is shown in Fig 1. Folic acid use during pregnancy was not related to ADHD (Fig 2). Similarly, using multivitamins and iron during pregnancy was not related to ADHD ($p$ = 0.223 and $p$ = 0.228; respectively). In pregnancy, the omega 3 use was 11% in the ADHD group, while this rate was 31% in the control group ($p < 0.001$).

T he groups were statistically similar in terms of socioeconomic status ($p = 0.036$). In both groups, though the number of mothers smoking preconception and during pregnancy was low, there was no difference between the groups ($p = 0.806$). There was a statistically significant difference between the groups in terms of maternal age. In the ADHD group the mean maternal age was 35, while in the control group the mean maternal age was 32 ($p < 0.001$). Similarly, in the ADHD group the age of fathers appeared to be older (mean age of 38 vs. 36 years, $p < 0.001$).

There was no difference between the groups in terms of situations like gestational diabetes mellitus experienced during pregnancy by the mother (n=15 vs. n = 49), preeclampsia (n = 13 vs. n = 32), and progesterone requirements due to vaginal bleeding (n = 44 vs. n = 49). The number of abnormal double-screening tests in the first trimester was higher in the ADHD group, and this was significant statistically (27% vs. 5%, $p < 0.001$). This was linked to advanced maternal age.

## DISCUSSION

This study showed that the use of folic acid before pregnancy might be effective at preventing the development of ADHD. Maternal nutrition affects fetal brain development [11]. Some micronutrients have been shown to be linked with the maladjusted behavior of the offspring later in life [12]. Folic acid affects neural stem cell proliferation and differentiation, decreases apoptosis, and alters DNA biosynthesis [13].

**Table 1. Characteristics of the groups**

| | | ADHD group (n = 246) | Non-ADHD group (n = 352) | *p* value |
|---|---|---|---|---|
| **Age (year)** | | 10 (6.25-15.75) | 9,13 (6-15) | **< 0.001*** |
| **Gender** | Female | 60 (24.3%) | 121 (34.3%) | 0.09** |
| | Male | 186 (75.7%) | 231 (65.7%) | |
| **Delivery Type** | NVD | 118 (47.9%) | 179 (50.8%) | 0.518** |
| | C/S | 127 (52.1%) | 173 (49.2%) | |
| **Birth weight (gram)** | | 3290 (2550-4300) | 3250 (2500-4500) | 0.635* |
| **Birth order** | | 2 (1-5) | 2 (1-7) | 0.958* |
| **Maternal age (year)** | | 35 (20-52) | 32 (20-49) | < 0.001* |
| **Paternal age (year)** | | 38 (23-60) | 36 (22-56) | **< 0.001*** |
| **Maternal education** | < 8years | 109 (44.3%) | 159 (45.1%) | 0.835** |
| | > 8years | 137 (45.7%) | 193 (54.9%) | |
| **Paternal education** | < 8years | 186 (75.6%) | 124 (35.2%) | 0.946** |
| | > 8years | 160 (24.4%) | 228 (64.8%) | |

Data are given median (minimum-maximum) or frequency (n) with percentage (%). NVD = Normal Vaginal Delivery, C/S = Cesarian section

*Mann-Whitney U test, **Pearson chi-Square test

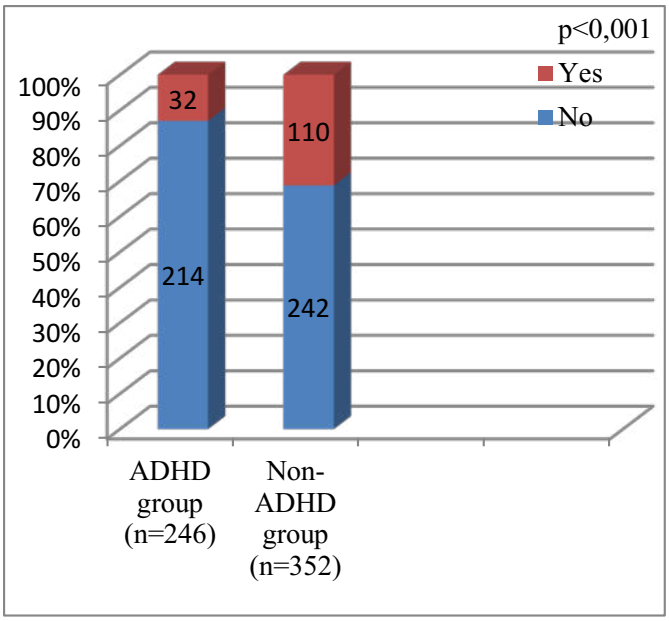


**Fig. 1. Cumulative bar graph of folic acid intake during pre-pregnancy period (ADHD = Attention Deficit Hyperactivity Disorder) (Statistically significant difference was found between ADHD and Non-ADHD groups using Pearson chi-square test).**

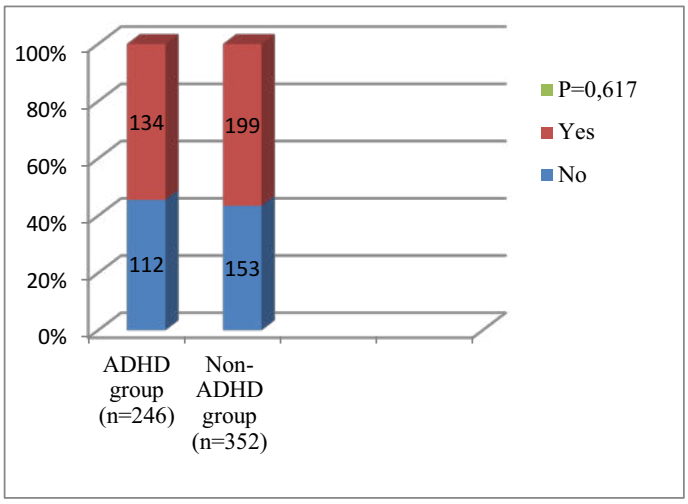


**Fig. 2. Cumulative bar graph of folic acid intake during pregnancy (ADHD = Attention Deficit Hyperactivity Disorder) (Statistically significant difference was not found between ADHD and Non-ADHD groups using Pearson chi-square test).**

Folate deficiency during gestation can impair cellular growth and replication in the fetus [14] and has been demonstrated to cause a net reduction of cells in the fetal brain [15], a loss of progenitor cells in the brain, as well as reduced brain weight [16] in mice. Such brain structure alterations may be long-lasting and contribute to behavioral difficulties later in life [17]. For example, abnormal folate transport into the fetal central nervous system has been found to be related to cerebral folate deficiency associated developmental delays, cognitive impairment and reduced memory function [4], while higher plasma folate showed a correlation with better cognitive performance [18]. A strong association was reported between neural tube defect (NTD) and folate-related gene polymorphisms [19]. The risk of NTD recurrence in subsequent pregnancy is 2-3% [20]. In these patients, though of multifactorial origin, in light of our study, we believe the use of folate before pregnancy should be recommended before planned pregnancy and for women with risks of having an ADHD child. A study questioned maternal use of folate before pregnancy and assessed the correlation with autism in women with blood folate levels examined in the first trimester. In conclusion, similar to our study, they identified a correlation not with pregnancy folate levels but with pre-conception folate use. However, it should be taken into account that the patient and control groups were not the same age in our study [21]. That may indicate that maternal folate's potential effect on offspring's brain development might occur earlier.

Fatty acids, in particular omega-3 fatty acids, have a substantial impact on human brain development and function and have been found to affect behavior and cognition [22]. It is unclear whether a deficit in intake or metabolism of long chain polyunsaturated fatty acids (LC-PUFA) may play a major role in the pathogenesis of ADHD. Increasing evidence indicates that LC-PUFA imbalance or deficiencies may be associated with ADHD through involvement in the dopaminergic corico-striatal metabolism. In studies, the omega 3 levels in children with ADHD were shown to be lower [23]. Moreover dietary supplementation with ω-3 PUFAs was found to improve ADHD symptoms [24]. In our study, we questioned the omega 3 situation and use it in children with ADHD; however we found the omega 3 use during pregnancy by mothers with ADHD children was clearly low. On the other hand, the mothers' fish consumption was not questioned, which may be considered one of the limitations of the present study. Due to the antioxidant properties of omega 3 affects the neuroinflammatory process, and as it is thought to play a role in ADHD development, dietary supplementation is recommended during pregnancy [25].

Both young and old mothers are considered to belong to an obstetric risk group, according to clinical experience and research [26]. Lower maternal age has been addressed as a risk factor for ADHD in children [27]. Contrary to this, in our study we identified a correlation between advanced maternal age and ADHD. Additionally, the age of fathers in the ADHD group was older. Studies have reported associations between paternal age and ADHD, with conflicting results [28].

## Limitations

There are some limitations of our study. The study represents one region in Turkey. Another limitation is that the study is not prospective. If the study was prospective and folic acid levels in the blood of both mother and child were examined, and a correlation was found, this would be a more valuable study. Other limitations are the lack of comparison in terms of gender and ADHD subtypes and the age difference between the patient and control groups. However, this study notes the preconception use of folic acid and is useful in attracting attention to this topic for families and health care professionals.

## CONCLUSION

Folic acid is important for the growing fetus and deficiency may lead to irreversible or treatment-requiring situations. This study showed that folic acid use before pregnancy might prevent childhood ADHD. In conclusion, according to our study, using preconceptional folic acid supplement seems to reduce the risk of ADHD and neural tube NTDs.

*Authors' Contribution*

Study Conception: MEU, NK; Study Design: NK, HA, MEU; Supervision: N/A; Funding: N/A; Materials: N/A; Data Collection and/or Processing: MEU, ESG; Statistical Analysis and/or Data Interpretation: HA, FB, HŞ; Literature Review: HŞ, FB; Manuscript Preparation: MEU, NK, HŞ and Critical Review: HA, FB, ESG.

*Conflict of interest*

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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