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Is There an Association Between Cigarette Smoking in Pregnancy and Attention Deficit Hyperactivity Disorder?

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IS THERE AN ASSOCIATION BETWEEN CIGARETTE SMOKING IN PREGNANCY AND ATTENTION DEFICIT HYPERACTIVITY DISORDER?

By

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ABSTRACT

IS THERE AN ASSOCIATION BETWEEN CIGARETTE SMOKING IN PREGNANCY AND ATTENTION DEFICIT HYPERACTIVITY DISORDER?

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This study investigated the relationship between cigarette smoking during pregnancy and attention deficit and hyperactivity disorder. Subjects were 1st through 6th grade children with DSM-IV ADHD (N=94), and normal comparison subjects (N=46), and their biological relatives. Information on smoking during pregnancy was obtained from mothers in a standardized manner by questionnaire. The data was analyzed using univariate methods (i.e. chi-square and t-tests). All analysis was two-tailed with results being statistically significant if the p-value was less than or equal to 0.05. No significant difference was found between ADHD probands and normal subjects in rates of maternal cigarette smoking in pregnancy. ADHD probands had stronger parental, and overall, histories of ADHD (20% versus 6.5%) ($X = 0.275$, $df = 1$, $p = 0.0473$) and (47% versus 26%) ($X = 2.2$, $df = 1$, $p = 0.03$), respectively. These findings suggest that cigarette smoking during pregnancy and ADHD. The results support a familial etiology for ADHD.

To my other half: I could not have done this without you.

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Chapter 1: Introduction

This study explores the relationship between attention deficit hyperactivity disorder in children and maternal cigarette smoking during pregnancy. Because of the relatively high prevalence of both smoking in pregnancy and ADHD, such an association would provide an opportunity to intervene to improve the health of both mothers and children.

An association between cigarette smoking in pregnancy and ADHD has been explored in several earlier studies. This study attempts to look at this relationship within a context of better controlling of potential confounders. The context of the relationship is first discussed by describing what is currently known about the epidemiology of both smoking during pregnancy and ADHD. A detailed literature review lays the groundwork for this study.

The isolation of attention deficit and hyperactivity as a distinct disorder can be seen as early as the turn of the century. In 1902, a group of children were described as having an 'abnormal' incapacity for sustained attention' and deficits in 'volitional inhibition'.[1] In 1937 amphetamines were found to decrease behavioral difficulties and hyperactivity. In the 1950s, the term 'minimal brain damage' was given to describe children with inattention and hyperactive symptoms although there was no evidence of brain damage in most cases.[2]

The present day definition of ADHD evolved in the 1960s and is characterized by a symptomatic difficulty with attention, impulsivity, and hyperactivity beginning in early childhood.[3] The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) requires symptoms of ADHD to be pervasive, present before the age of seven, persistent

for more than six months, out of keeping with developmental level, maladaptive, and significantly impairing social, academic, or occupational functioning.[4 5]

Textbooks of fifty years ago made very little reference to ADHD, then known as hyperkinesis. An exception was in Hendersen and Gillespie, where ADHD was characterized as one of the "very rare" psychoses of childhood.[6] However, by the 1970's estimates placed the prevalence at five to ten percent among North American school children. [7 8] With approximately five million hyperactive children in the United States, ADHD was described as "the single most common behavioral disorder seen by child psychiatrists".[9] A recent summary of nine epidemiological studies suggested a prevalence of 4-12% (median 5.8%) in the general population of 6-12 year-olds with rates in primary care settings being close to those in the general population. [10]

Boys are five to nine times more likely to be diagnosed with ADHD than girls. However, girls with ADHD are less likely to show behavioral problems and may therefore be under-diagnosed. [11] Girls with ADHD are more likely than boys to have depression, low self-esteem, and cognitive impairment.[12]

There is a coinciding increasing prevalence of ADHD with an increased cigarette-smoking rate in women.[13] Cigarette smoking among women was rare in the early 20th century but by 1980 tobacco use among women was comparable to men.[14] A large proportion of this increase occurred in the late 1960s and early 1970s due to a marked sale and advertising drive to entice women to smoke.[15] Smoking prevalence has since declined from 33.9% in 1965 to 22.0% in 1998 with peak female smoking rates occurring from 1974 to 1990. [14]

Chapter 2: Literature Review

Twenty years of research has documented a relationship between cigarette smoking and neurologic aspects of behavior. Only in the last five years has the relationship of cigarette smoking in pregnancy and ADHD been addressed.

There is no consensus regarding the etiology of ADHD but most investigators endorse a neural foundation to the disorder.[17] On the basis of animal studies, researchers have hypothesized that catecholaminergic pathways play an important role in the etiology of ADHD [18] with the dopamine system being identified as the culprit because of the successful therapies with stimulant medication.[19] Nicotine receptors regulate dopaminergic activity and animal studies in mice and rats have shown a positive association between chronic exposure to nicotine and hyperactive offspring.[20-24] Chronic exposure to nicotine results in a tolerance to the drug and an increase in brain nicotinic receptors. It is not understood how an increase in nicotinic receptors relates to hyperactivity. [21-27]

Studies in humans have helped to elucidate the effect of smoking on the fetus. Nicotine freely crosses the placenta and the fetus is exposed to higher nicotine concentrations than the smoking mother. [28] Also, previous literature has found a relationship between cigarette smoking in pregnancy and behavioral and cognitive impairment in children. [13, 29-36] And since ADHD is a behavioral and cognitive impairment, the findings were extended to ADHD.

The National Child Development Study, a longitudinal study of 17,000 children born in Britain, found that at age seven and eleven years physical and mental retardation was associated with smoking in pregnancy with deficits increasing with the number of

cigarettes smoked after the fourth month of pregnancy. Children of mothers who smoked ten or more cigarettes a day were between three and five months delayed in reading, mathematics, and general ability when compared with off-spring of non-smoking mothers. [35]

The Ottawa Prenatal Prospective Study assessed whether maternal smoking is associated with children's vigilance performance on computer controlled continuous performance tasks. Approximately 700 women were interviewed up to three times during pregnancy. Maternal nicotine scores were determined by multiplying the number of cigarettes smoked per day by the nicotine content of the brand used. For the vigilance test, children had to be four to seven years old and were divided into "smoking" and "non-smoking" groups with smoking being defined as nicotine use during pregnancy greater than 1 mg/day. Significant relationships were seen between maternal cigarette use and errors of auditory commission and overall activity level. Statistical significance was approached ($p = 0.06$) for visual commission errors but not for errors of omission in either modality. Commission errors are thought to be related to both impulsivity and poor attention while errors of omission are thought to reflect lapses in attention. [37]

Denson, et al [13] looked at the relationship between hyperkinesis and maternal smoking. Twenty consecutive cases of hyperkinesis, diagnosed by accepted criteria, and evaluated for an unequivocal improvement on methylphenidate were entered into the study. Retarded children and adopted children whose mothers could not supply the requested information were excluded. Each child was then matched on age, sex, and social class with a non-hyperkinetic dyslexic child and a normal control.

Mothers of cases reported smoking an average 14.3 cigarettes daily, which is more than twice the amount reported by controls ($p < 0.05$). The fathers and stepfathers of the hyperkinetic children also smoked more heavily than the controls but this was not statistically significant. [13]

Milberger et al examined the gene-environment interaction of pregnancy, delivery, and infancy complications (PDICs) in the etiology of ADHD. They compared two groups of index children: 140 ADHD probands and 120 normal controls. Cases were recruited from psychiatric and pediatric referrals with controls being active outpatients at the pediatric medical clinics. Children were Caucasian, non-Hispanic, males between the ages of six and seventeen. Those children with any major sensorimotor handicaps, psychosis, autism, an IQ less than 80, or from low socioeconomic class were excluded. A positive relationship between ADHD and PDICs was formed. Specific complications associated with ADHD were those that reflected chronic exposure, such as maternal bleeding, smoking, family problems, and illicit drug use. Maternal smoking itself was present in 31 (22%) of cases and 10 (8%) of controls (OR = 3.15; $p = 0.002$). [38]

A subsequent study by Milberger et al focused on whether smoking in pregnancy was related to ADHD in their offspring. The methodology was the same as the previous study except that adopted probands were excluded. Maternal smoking during pregnancy was ascertained by using the Diagnostic Interview for Children and Adolescents – Parent Version module on pregnancy, delivery, and infancy complications. This includes a question assessing whether the mother smoked as much as a pack per day for at least three months during pregnancy. Twenty-two percent of ADHD children had a maternal history of smoking during pregnancy, compared with eight percent of normal subjects.

After controlling for socioeconomic status, parental IQ, and parental ADHD status, the odds ratio remained significant at 2.7 ($p = 0.04$). Whether the relationship would remain significant after controlling for low birth weight, alcohol use during pregnancy, and depression remains to be seen. [39]

This finding was further evaluated by looking at whether the association between ADHD and maternal smoking during pregnancy existed in high-risk siblings of participants in the previous study. High-risk was defined as having a sibling with ADHD. When high-risk siblings with ADHD were compared to those without ADHD, fifteen (47%) of the high-risk siblings with ADHD had a history of maternal smoking during pregnancy compared with 33 (24%) of the siblings without ADHD (OR = 4.4; $p = 0.02$). Of note is that there was also an association between ADHD and a greater history of maternal ADHD (37% vs. 10%). It remains to be seen whether this association would stand up in the control group. [40]

Milberger, et al were the only studies that specifically address the question of whether ADHD is associated with cigarette smoking in pregnancy, so further information is needed to see if the association is consistent across populations. The association was strong with an odds ratio of 2.7 ($p = 0.02$) [39] with an increase of strength in a high-risk population (OR = 4.4; $p = 0.02$). [40]

Unfortunately, Milberger et al's work has some methodological limitations. All information collected on the exposure is based on maternal recall. Children in the study were between six and seventeen years old. The minimum amount of time that the mother has to remember the exposure is six years. In addition to the usual recall bias potential present, mothers of psychiatrically ill children try harder to remember their smoking

status than mothers of normal children. Maternal recall continues to be the best method available pending a prohibitively expensive twenty-year follow-up study utilizing cotinine urine testing.

In addition to recall bias, one must consider that it may be possible that mothers may under-report their usage of cigarettes in pregnancy because of all the other possible negative effects of smoking in pregnancy and the social stigma associated with smoking during pregnancy. Misclassification bias may also have been at issue since smokers were categorized as those that smoked at least a pack a day for at least three months during pregnancy and any smoking less than that amount would place them in the non-smoking group leading to an underestimate of the true value.

Other potential confounding variables were not controlled for in their model. The study controlled for socioeconomic status, parental IQ, and parental ADHD status but not for low birth weight. Maternal smoking has been linked to low birth weight [41] [42], and low birth weight is associated with ADHD. [43] In Milberger's study, none of the children of smoking mothers had low birth weights suggesting that low birth weight is not involved in the causal pathway of maternal cigarette smoking and ADHD. Alternately, a selection bias in the study may have prevented children with low birth weight from being enrolled. For example, those of low socioeconomic status were excluded from the study. If people of low socioeconomic status have different rates of ADHD and/or rates of cigarette smoking, then the relationship between ADHD and maternal cigarette smoking might be inaccurate.

Alcohol use may be more common in individuals, who smoke, and heavy smoking during pregnancy may indicate a strong nicotine dependency, and alcohol use is

associated with hyperactivity, inattention, and lower IQ in the offspring. [44] [45] Therefore, alcohol use during pregnancy should also be included in the analysis. Finally, the relationship between smoking and depression should also be accounted for in studies of ADHD and maternal smoking. [44] [46]

The Ottawa Prenatal Prospective Study raised the possibility of a dose-response relationship between cigarette smoking in pregnancy and ADHD. This study compared children with active versus active smoking exposure's vigilance performance task. Women were also asked if they were regularly exposed to a smoke-filled environment and were questioned about their husband's smoking habits. The "active" smoking group was defined as children of mothers who smoked any quantity of cigarettes any time during their pregnancy. The "passive" smoking group consisted of children of non-smoking women who were passively exposed to cigarette smoking during their pregnancy. The non-smoking group included children of mothers who were neither active nor passive smokers during their pregnancy.

The Ottawa Prenatal Prospective Study indicated that the effects of passive smoking are similar to the effects of active smoking, but smaller in magnitude. After controlling for potential confounders, including examiner, maternal education, maternal age, and SES, children of non-smoking mothers were found to perform better than the two smoking groups on tests of language and speech skills, intelligence, visual/special abilities and on the mother's rating of behavior. The performance of children of passive smokers was found to be between that of the active smoking group and the non-smoking group. The research concluded that there is a continuum of long-term smoking effects

and that children of passive smokers are also at risk of negative developmental outcomes.[36]

A comprehensive review of the literature strengthens the hypothesis that a cigarette smoking in pregnancy is associated with ADHD in the child. These studies lay the groundwork for choosing a design and method that provides better control of the confounding variables.

Chapter 3: Methodology

Children from 1st through 6th grade were recruited from four sources: a local pediatric clinic specializing in ADHD referrals, a local support group for parents of children with ADHD, invitation letters sent to parents of children in the local school districts, and newspaper ads placed in local papers.

Children were categorized as possible ADHD-combined type (C) or ADHD-inattentive (I) if they either (A) passed prescreen cut-offs on both parent and teacher versions of common ADHD rating instruments (Child Behavior Checklist or Teacher Report Form; Behavior Assessment Scale for Children, Connors Rating Scale, or a DSM-IV symptoms checklist SNAP-IV of the ADHD Rating Scale), or (B) were diagnosed as ADHD (any type) by a physician or psychologist in the community who utilized teacher and parent ratings to arrive at their diagnosis. Children were categorized as possible controls if they were below cut offs on all of these parent and teacher scales and had never been diagnosed with ADHD in the community.

Possible cases were then assessed using a parent structured diagnostic interview (the DISC-IV) supplemented by an "or" algorithm following the DSM-IV field trials validity data. Prior versions of the DISC have exhibited acceptable reliability and validity. Minimal changes were made to the newest version of the DISC, so it is assumed that the DISC-IV has acceptable reliability and validity also. If the children met age of onset, duration, impairment, and cross-situational criteria, then diagnostic assignment was determined by summing parent-reported symptoms on the DISC-IV and teacher reported symptoms on the DSM-IV symptom checklist.

Control children were negative for ADHD (all types) based on the above criteria, with four or fewer symptoms in either domain by the "or" algorithm. Cases with five symptoms of inattention or over activity were excluded from all groups based on the field trial data indicating that these borderline cases might have ADHD-C or ADHD-I.

Each child was assessed for Reading Disorder (RD). RD was assigned if (a) absolute levels of average reading and spelling were less or equal to a standard score of 85, and (b) Full Scale IQ minus reading/spelling average was at least 15 points. Full Scale IQ was estimated with a reliable and valid 5-test short form of the Weschler Intelligence Scale for Children, 3rd edition (WISC-III): Vocabulary, Block Design, Information, Object Assembly, and Picture Completion. Reading and spelling were assessed with the Wechsler Individual Achievement Test.

Children were excluded from all groups if they had mental retardation, autistic disorder, Tourette syndrome, current major depressive episode, bipolar disorder, or physical or neurological handicap ascertained by parent report. All children were native English speakers, had normal hearing or corrected vision, and had a valid Full Scale IQ > 75. Children on stimulants were requested to be free of medications when tested. Including methylphenidate, dextroamphetamine and the mixed salts amphetamines. [47]

Maternal smoking during pregnancy was ascertained from a family background form that asking whether the mother smoked during pregnancy and how much she smoked. The form also collected information on alcohol use during pregnancy, birth weight, occupation, and family history of ADHD. Socioeconomic status was calculated using the Duncan Socioeconomic Index. [48] Diagnostic assessments of parents were based

on direct interviews, which used the DSM-IV, with each parent. If direct diagnosis was not available, information from the family background form was used.

All assessments were made by raters who were blind to proband diagnosis (ADHD or control). All parents signed a written consent form for participation in the study. Carefully trained raters who had been trained to high levels of interrater reliability conducted interviews.

The data was first analyzed using univariate methods (i.e., chi-square and t-tests). Logistic regression models were developed to simultaneously control for two or more potentially confounding variables. These included gender, ethnicity, age, IQ, socioeconomic status, birth weight, alcohol use during pregnancy, and parental ADHD status. All analysis was two-tailed. Results were considered statistically significant if the p value was less than or equal to 0.05.

Chapter 4: Results

A total of n=168 children participated: 114 ADHD and 54 controls. Children were on average 117.6 months old (9.8 yrs) at first visit, male (66.1%), and Caucasian (75.6%) with an average IQ of 105.2 and a socioeconomic status equivalent to middle class (40.3) (Table 1).

Exposure values were missing for 28 participants (20 ADHD and 8 controls) and had to be dropped from the analysis. No significant differences were found between participants kept and those dropped in age, IQ, socioeconomic status, gender, and ethnicity (Table 2).

When compared with normal subjects, ADHD probands came from families with a higher rate of parental ADHD (20% versus 6.5%) ($X = 0.28$, $df = 1$, $p = 0.047$) and a stronger family history of ADHD (47% versus 26%) ($X = 2.2$, $df = 1$, $p = 0.03$). No significant differences were found between ADHD probands and controls for age, gender, ethnicity, IQ, socioeconomic status, birth weight, smoking in pregnancy, or alcohol use in pregnancy (Table 3).

Even if all the dropped participants were assumed to be exposed, or unexposed, there was no significant difference found between cases and controls ($p=0.237$ & $p=0.286$ respectively).

TABLE 1: Characteristics of Subjects

Characteristics	Before (N=168)
Age, months (SD)	117.6 (14.2)
Gender, # male (%)	111.0 (66.1)
Ethnicity, # white (%)	127.0 (75.6)
IQ (SD)	105.2 (13.6)
SES (SD)	40.3 (15.9)

TABLE 2: Missing Data

Characteristics	Kept (N=140)	Dropped (N=28)	p-value
Age, months (SD)	118.1 (14.2)	115.0 (14.1)	0.295
Gender, # male (%)	97.0 (69.3)	14.0 (50.0)	0.086
Ethnicity, # white (%)	107.0 (76.4)	20.0 (71.4)	0.749
IQ (SD)	105.5 (13.3)	103.3 (15.4)	0.914
SES (SD)	39.5 (15.5)	45.6 (17.7)	0.805

TABLE 3: ADHD Correlates

Variable (referent)	OR (95% CI)
Smoking during pregnancy (No)	1.80 (0.67-4.85)
Alcohol use during pregnancy (No)	1.68 (0.52-5.49)
ADHD in family (No)	2.49 (1.15-5.40)
ADHD in dad (No)	2.30 (0.62-8.52)
ADHD in mom (No)	3.62 (0.43-30.33)
ADHD in dad and/or mom (No)	3.63 (1.02-12.98)
Gender (female)	1.77 (0.84-3.75)
Ethnicity (non-white)	0.82 (0.36-1.85)
Age in months (continuous)	0.99 (0.97-1.02)
IQ of child (continuous)	0.98 (0.95-1.00)
SES (continuous)	1.00 (0.98-1.03)
Birth weight (continuous)	0.99 (0.81-1.22)

TABLE 4: Characteristics of ADHD versus Controls

Characteristics	ADHD (N=94)	Controls (N=46)	p=value
Age, months (SD)	117.61 (14.75)	119.11 (13.22)	0.545
Gender, # male (%)	69 (73.40)	28 (60.87)	0.212
Ethnicity, # white (%)	73 (77.66)	34 (73.91)	0.754
IQ (SD)	104.11 (13.29)	108.41 (12.9)	0.070
SES (SD)	39.82 (15.72)	38.81 (15.18)	0.716
Birth weight (SD)	7.85 (1.06)	7.87 (2.65)	0.961
Dad ADHD, # (%)	13 (13.83)	3 (6.52)	0.352
Mom ADHD, # (%)	7 (7.45)	1 (2.17)	0.404
Family history, # (%)	44 (46.81)	12 (26.09)	0.028
Smoking in pregnancy, # (%)	20 (21.28)	6 (13.04)	0.360
Alcohol use in pregnancy, # (%)	13 (13.83)	4 (8.70)	0.568

Chapter 5: Discussion

This study did not find an association between smoking by mothers in pregnancy and ADHD in their children but due to missing data, the power would only have been able to detect a difference of 15%. We did find a strong and significant positive association between a parental history and family history of attention deficit disorder and ADHD in the child. Previous literature suggests a genetic contribution to the disorder.

If ADHD does have an underlying genetic etiology, then the risk of ADHD should increase as the degree of the familial relationship increases. Information on the second- and third- degree relatives was not determined by diagnostic criteria, but a questionnaire that assessed ADHD status by second-hand knowledge was administered. Assessing the second- and third- degree relatives with diagnostic criteria might allow a dose-response relationship to be seen, but such a study would require significant resources.

In addition to being underpowered, a difference may not have been detectable because the cases and controls in the study may have been too similiar. Recruitment was based on subjects volunteering to be in the study. This may bias the sample because a parent is more likely to bring their child in to the study because of behavior problems as they seek a diagnosis for their child. The controls will then be children that have behavior problems but their symptoms are not severe enough to be diagnosed as ADHD.

This study is a secondary data analysis. The research question of this study is different from the original proposed study and had an impact on what data was collected and how. Data was taken in its existing format and there was no say in how the data was collected. As a consequence the sample size was small and subjects were dropped

because of the exposure variable was missing. Power was therefore lowered and the ability of this study to detect a difference between cases and controls may have been compromised.

Previous studies that found associations between cigarette smoking and pregnancy used a chronic variable (i.e. at least three months in duration) as their measure of exposure. And data suggests that chronic exposures during pregnancy, particularly those producing hypoxia, are most associated with neuropsychiatric impairment. This study used any amount of smoking as the exposure. Perhaps a smaller amount of smoking reduces the "dose" or the probability of the dose occurring during a presumed critical period in gestation.[39]

Alternately, perhaps no relationship between cigarette smoking in pregnancy and ADHD exists. The coinciding prevalence curves of cigarette smoking in women and ADHD may be artificial and reflect increased knowledge and recognition of ADHD during the same time in which cigarette smoking increased. ADHD was only defined as a disorder in the 1960s and the present prevalence rates are based on individual studies, not surveillance methods.

Adults with ADHD are more likely to be users of tobacco and other addictive substances than non-ADHD adults. A study in the Journal of Learning Disabilities prospectively studied tobacco smoking and substance dependencies in ADHD and non-ADHD participants. They found that by age 17, 46% of all participants with ADHD reported smoking cigarettes daily compared to 24% of the age-matched controls, with lifetime tobacco dependency rates being 35% and 10% respectively.[16]

We hypothesize an association between attention deficit hyperactivity disorder and cigarette smoking in pregnancy, but the type of relationship remains questionable. One possible scenario is that mothers of children with ADHD smoke in pregnancy more than non-ADHD mothers because they themselves have ADHD and therefore cigarette smoking in pregnancy is a confounder between the familial patterns of ADHD. The second scenario is that ADHD mothers are more likely to smoke and that smoking in pregnancy predisposes a child to ADHD. This scenario makes cigarette smoking a mediator. Finally, a third scenario is that whether a mother smokes in pregnancy, or not, affects the risk of a child getting ADHD familially. This would make cigarette smoking an effect modifier. These scenarios cannot be explored in this study because of the small numbers of mothers with ADHD. A study with a much larger sample size may be able to explore these scenarios.

The results of this study do not indicate a relationship between cigarette smoking during pregnancy and attention deficit and hyperactivity disorder. The limitations of the study, primarily inadequate sample size, might have prevented a significant difference from being detected, so more work needs to be done in this area to evaluate this relationship. If such a relationship was found, interventions could be aimed at improving the health of both mothers and children.

BIBLIOGRAPHY

[1] Still GF. *Some Abnormal Psychiatric Conditions in Children.* Lancet 1902; I: 1008-12, 1077-82, 1163-8.

[2] Bradley C. *The Behavior of Children Receiving Benzedrine.* Am J Psychiatry 1937; 152: 1652-8.

[3] Reid R. *Assessment of ADHD with Culturally Different Groups: the use of behavioral rating scales.* School Psychol Rev 1995; 24: 637-60.

[4] World Health Organization. *The ICD-10 Classification of Mental and Behavioral Disorders. Diagnostic Criteria for Research.* Geneva: WHO, 1993.

[5] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders. [Fourth Edition.]* Washington, USA: APA, 1994.

[6] Henderson, D.K. & Gillespie, R.D. *A Textbook of Psychiatry for Students and Practitioners; 6th Edition.* London, Oxford University Press, p 647, 1944.

[7] Huessy H.R. *Study of the Prevalence and Therapy of the Choreatiform Syndrome of Hyperkinesis in Rural Vermont.* Acta Paedopsychiatr 1967; 34: 130-5.

[8] Laufer M.W. *In: Comprehensive Textbook of Psychiatry.* Edited by A.M. Freedman and H.I. Kaplan. Baltimore, Williams, and Wilkins, p 1444, 1967.

[9] Wender P.H. *The Hyperactive Child.* New York, Crown Publishers, p 3, 31, 1973.

[10] Brown R.T. et al. *Prevalence and Assessment of Attention-Deficit/Hyperactivity Disorder in Primary Care Settings.* American Academy of Pediatrics 2001; 107(3): e43.

[11] Gaub B. & Carlson CL. *Gender Differences in ADHD: a meta-analysis and critical review.* J Am Acad Child Psychiatry 1997; 4: 343-8.

[12] Biederman J. *Attention Deficit and Hyperactivity Disorder (ADHD).* Ann Clin Psychology 1991; 3: 9-22.

[13] Denson R., Nanson J.L., & McWatters M.A. *Hyperkinesis and Maternal Smoking.* Can Psychiatr Assoc J 1975; 20: 183-7.

[14] *Pattern of Tobacco Use Among Women and Girls- fact sheet.* In: Women and Smoking: A report of the Surgeon General 2001. www.cdc.gov/tobacco/sgr/sgr_forwomen/factsheet_tobaccouse.htm

[15] Women and Smoking. In: American Lung Association Fact Sheet 2001. www.lungusa.org/tobacco/women_factsheet99.html.

[17] Barkley RA: *Attention Deficit Hyperactivity Disorder: A handbook for diagnosis and treatment.* New York, Guilford Press, 1990.

[18] Zametkin AJ, Rapaport JL: *Neurobiology of Attention Deficit Disorder with Hyperactivity: where have we come in 50 years?* J Am Acad Child Adolesc Psychiatry 1987; 26: 676-86.

[19] McCracken JT: *Neuropsychiatric Practice and Opinion: a two-part model of stimulant action on attention deficit hyperactivity disorder in children.* J Neuropsychiatry 1991; 3: 201-16.

[20] Richardson G. & Day N. *Detrimental Effects of Prenatal Cocaine Exposure: illusion or reality?* J Am Acad Child Adoles Psychiatry 1994; 33: 28-34.

[21] Hagino N. & Lee J. *Effect of Maternal Nicotine on the Development of Sites for [3H] Nicotine Binding in the Fetal Brain.* Int J Dev NeuroSci 1985; 3: 567-71.

[22] Van De Kamp J & Collins A. *Prenatal Nicotine Alters Nicotinic Receptors Development in the Mouse Brain.* Pharmacol Biochem Behav 1994; 47: 889-900.

[23] Johns JM, Louis TM, Becker RF, & Means LW. *Behavioral Effects of Prenatal Exposure to Nicotine in Guinea Pigs.* Neurobehav Toxicol Teratol 1982; 4: 365-9.

[24] Fung YK & Lau YS. *Effects of Prenatal Nicotine Exposure on Rat Striatal Dopaminergic and Nicotinic Systems.* Pharmacol Biochem Behav 1989; 33: 1-6.

[25] Marks MJ et al. *Nicotine Binding and Nicotinic Receptor Subunit RNA After Chronic Nicotine Treatment.* J Neurosci 1992; 12: 2765-84.

[26] Marks MJ, Grady SR, & Collins SR. *Downregulation of Nicotinic Receptors After Chronic Nicotine Infusion.* J Pharmacol Exp Ther 1993; 266: 1268-76.

[27] Slotkin TA, Lappi SE, & Seidler FJ. *Impact of Fetal Nicotine Exposure on Development of Rat Brain Regions: critical sensitive period or effects of withdrawal?* Brain Res Bull 1993; 31: 319-28.

[28] Luck W, Nau H, Hansen R, & Steldinger R. *Extent of Nicotine and Cotinine Transfer to the Human Fetus, Placenta, and Amniotic Fluid of Smoking Mothers.* Dev Pharmacol Ther 1985; 8: 384-95.

[29] Weitzman M, Gortmaker S, & Sobol A. *Maternal Smoking and Behavior Problems of Children.* Pediatrics 1992; 90: 342-9.

[30] Saxton D. *The Behavior of Infants Whose Mothers Smoke in Pregnancy.* Early Human Dev 1978; 2: 363-9.

[31] Naeye RL, & Peters EC. *Mental Development of Children Whose Mothers Smoked During Pregnancy.* Obstet Gynecol 1984; 64: 601-7.

[32] Sexton M, Fox N, & Hebel J. *Prenatal Exposure to Tobacco, II: effects on cognitive function at age three.* Int J Epidemiol 1990; 19: 72-7.

[33] Rantakallio P. *A Follow-up Study up to the Age of 14 of Children Whose Mothers Smoked During Pregnancy.* Acta Paediatr Scand 1983; 72: 747-53.
[34] Fogelman KR & Manor O. *Smoking in Pregnancy and Development into Early Adulthood.* BMJ 1988; 297: 1233-6.

[35] Butler NR & Goldstein H. *Smoking in Pregnancy and Subsequent Child Development.* BMJ 1973; 4: 573-5.

[36] Makin J, Fried PA, & Watkinson B. *A Comparison of Active and Passive Smoking During Pregnancy: long-term effects.* Neurotoxical Teratol 1991; 13: 5-12.

[37] Kristjansson EA, Fried PA, & Watkinson B. *Maternal Smoking During Pregnancy Affects Children's Vigilance Performance.* Drug and Alcohol Dependence 1989; 24: 11-9.

[38] Milberger S. et al. *Pregnancy, Delivery, and Infancy Complications and Attention Deficit Hyperactivity Disorder: Issues of Gene-Environment Interaction.* Biol Psychiatry 1997; 41: 65-75.

[39] Milberger et al. *Is Maternal Smoking During Pregnancy a Risk Factor for Attention Deficit Hyperactivity Disorder in Children?* Am J Psychiatry 1996; 153(9): 1138-42.

[40] Milberger S, Biederman J, Faraone SV, & Jones J. *Further Evidence of an Association Between Maternal Smoking During Pregnancy and Attention Deficit Hyperactivity Disorder: findings from a high-risk sample of siblings.* J Clin Child Psychology 1998; 27(3): 352-8.
[41] Kline J, Stein Z, & Susser MW. *Conception to Birth: Epidemiology of Prenatal Development.* New York, Oxford University Press, 1989.

[42] Landesman-Dwyer S. & Emanuel I. *Smoking During Pregnancy.* Teratology 1979; 19: 119-25.

[43] Breslau N. et al. *A Gradient Relationship Between Low Birth Weight and IQ at age 6 Years.* Arch Pediatr Adolesc Med 1994; 148: 377-83.

[44] Chabrol H. & Peresson G. *ADHD and Maternal Smoking During Pregnancy.* Am J Psychiatry 1997; 154(8): 1177-8.

[45] Aronson M, Kyllerman M, Sabel KG, Sandin B, & Olegard R. *Children of Alcoholic Mothers: developmental, perceptual, and behavioral characteristics as compared to matched controls.* Acta Paediatr Scand 1985; 74: 27-35.

[46] Cogill SR, Caplan HL, Alexandra H, Robson KM, & Kumar R. *Impact of Maternal Postnatal Depression on Cognitive Development of Young Children.* BMJ 1986; 292: 1165-7.

[47] Nigg JT, Blaskey LG, Huang-Pollok CL, & Rappley MD. Neuropsychological Executive Functions and ADHD DSM-IV Subtypes. In Press: Journal of the American Academy of Child and Adolescent Psychiatry.

[48] Mueller CW & Parcel TL. Supplement to "Measures of Socioeconomic Status: Alternatives and Recommendations". Child Development 1981; 52: 13-30.