# Comparison of effects of chronic versus acute pregnancy, delivery, and infancy complications on symptom severity in children with Attention-Deficit/Hyperactivity Disorder

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**ABSTRACT**

**Background & Objectives:** Evidence from previous studies has consistently shown an association between pregnancy, delivery, and infancy complications (PDICs) and attention- deficit/hyperactivity disorder (ADHD). The objective of this study was to test the hypothesis that children with ADHD exposed to chronic complications (with and without acute complication) show more severe symptoms compared to either unexposed children or children exposed to only acute complications and to investigate the impact of individual PDICs on symptom severity in children with ADHD.

**Methods:** A total of 545 children, aged 6 to 12 years, who met DSM-IV diagnostic criteria for ADHD, participated in a double blind, placebo-controlled, randomized 2-week crossover trial of methylphenidate (MPH). The Child Behavior Checklist (CBCL) and the Conners' Global Index for Parents and teachers (CGI-P, CGI-T) were used to evaluate symptom severity in children with ADHD. The Kinney Medical Gynecological Questionnaire was used in interviews with mothers to report complications during pregnancy, as well as labour, delivery, and neonatal period (first 8 weeks) of these children and their siblings. This questionnaire was scored by using McNeil-Sjostrom scale for obstetrical complications. All complications with severity level of four and above were divided into two major groups: chronic and acute.

**Results:** One- way ANOVA with post hoc analysis showed that children with ADHD who were exposed to both acute and chronic PDICs scored higher only on CBCL externalizing behavior ($F(3,480) = 2.76$, $P = 0.04$) compared to those who were not exposed to either acute or chronic PDICS. There was no significant difference between

the groups exposed to at least one acute or chronic PDICs and the control group as well as within groups exposed to at least one acute or chronic PDICs.

Independent sample t test also showed that a few only individual acute or chronic complications such as smoking more than 10 cigarettes per day, bleeding, total first minute APGAR below 7, and acute miscellaneous complications contributed to more externalizing behavior in children with ADHD. Linear regression analysis indicated that only cigarette smoking with score 4 and above (10 or more cigarettes per day) and total first minute APGAR below 7 had an effect on CBCL-externalizing T score.

**Conclusion:** Our results show that a combination of acute and chronic complications have an effect on CBCL- externalizing T score compared to the control group. It could also be concluded that neither chronic nor acute PDICs alone result in more severe ADHD symptoms in terms of externalizing behaviour. This may be due to, in part, the child who was exposed to chronic complication being more susceptible or having lower threshold of injury to acute insult during delivery. Amongst chronic and acute PDICs, smoking during pregnancy and total first minute APGAR below 7 had a significant effect on symptom severity in children with ADHD.

**RÉSUMÉ**

**Contexte & objectif** :Des études empiriques, ont toujours démontré l'existence des liens entre la grossesse, l'accouchement, des complications de la petite enfance (GACPE) et le trouble déficitaire de l'attention avec ou sans l'hyperactivité (TDAH).

L'objectif de notre étude vise à valider l'hypothèse selon laquelle, d'une part, les enfants atteints au trouble déficitaire de l'attention avec hyperactivité (TDAH), exposés à des complications chroniques démontrent un comportement prononcé et distinctif par rapport aux enfants non exposés ou exposés à des complications aigües et, d'autre part, examiner l'impact de (PDICs) sur la sévérité des symptômes chez les enfants atteints au TDAH. Méthodes : un total de 545 enfants âgés de six à douze ans, qui ont rencontré les critères de Diagnostique du DSM-IV pour le TDAH, ont participé à un test de double aveugle, contrôlée contre placebo, examen de croisé aléatoire de 2 semaines du méthylphénidate (MPH). La liste de contrôle relatif au comportement de l'enfant (CBCL) et l'indice Global des « Conners » pour les Parents et enseignants (CGI-P, CGI-T) ont été utilisés pour évaluer la gravité des symptômes chez les enfants atteints de TDAH.

Le questionnaire médical gynécologique de « Kinney » a été utilisé dans les entrevues avec les mères afin d'élucider leurs complications de grossesse durant ; le travail, l'accouchement et la période néonatale (les huit premières semaines) de leurs frères et sœurs. Ce questionnaire a été conçu à l'aide de l'échelon de McNeil-Sjostrom relatif à la complication obstétricale. Les échelons de niveau 4 et plus, ont été catégorisés en deux grands groupes : chroniques et aigus.

**Résultats** : One-way ANOVA avec analyse post hoc a démontré que les enfants atteints de TDAH qui ont été exposés à des GACPE aiguës et chroniques ont fait l'objet d'un code élevé sur le CBCL extériorisation de comportement (F (3 480) = 2,76, P= 0.04) comparativement à ceux qui n'étaient pas exposés à des GACPE soit aiguës ou chroniques. Il n'y avait aucune différence significative entre les groupes exposés au moins à une des GACPE aiguës ou chroniques et au groupe de contrôle, ainsi qu'au sein des groupes exposés à au moins une des GACPE aiguës ou chroniques.

Le Test de l'échantillon t indépendant a également démontré que quelques complications individuelles aiguës ou chroniques comme le fait de fumer plus de dix cigarettes par jour, des saignements, un total de l'APGAR à une minute moins que 7 et quelques complications aiguës ont contribué à une plus grande extériorisation du comportement chez les enfants atteints du TDAH. L'analyse de régression linéaire a indiqué que seul l'usage de la cigarette avec un score de 4 ou plus (dix cigarettes ou plus par jour) et le total de APGAR à une minute inférieure à 7 a eu un effet sur le CBCL-extériorisation T score.

**Conclusion**: nos résultats démontrent qu'une combinaison de complications aiguës et chroniques a un effet sur le CBCL - score extériorisation de T par rapport au groupe témoin. On pourrait également conclure que seules les GACPE aiguës ou chroniques ne causeront pas des scores élevés sur le CBCL. Cela peut être dû au fait qu'un enfant qui est exposé à des complications chroniques peut être plus susceptible ou avoir un seuil plus bas pour des insultes à l'accouchement. Parmi les GACPE chroniques et aiguës, fumer pendant la grossesse et avoir un APGAR à une minute inférieure à 7 a eu un effet important sur la gravité des symptômes chez les enfants atteints de TDAH.

## LITERATURE REVIEW

### 1 Overview of the Conceptual History of Attention Deficit Hyperactivity Disorder

The current concept of Attention Deficit Hyperactivity Disorder (ADHD) has been defined by Diagnostic and Statistical Manual of Mental Disorders (DSM) since 1952. Previous studies of behavior of inattentive and hyperactive children and progressing knowledge of brain structure and functions have changed the concept of neuropathlogical deficits causing the disorder over the time. However, symptoms such as inattention, hyperactivity, and impulsivity in children have been described by many authors since last 200 years. Interestingly, some but not all of historical descriptions of hyperactivity are consistent with modern diagnostic criteria for ADHD (Lange et al., 2010). A similar disorder to ADHD was firstly described by Sir Alexander Crichton in 1798. Crichton in his short description of the first alteration of attention "*the incapacity of attending with a necessary degree of constancy to any one object"* described the second symptom of criterion of A1, *Inattention: the "difficulty sustaining attention in tasks or play activities*" in DSM-IV-TR for ADHD (Lange et al., 2010). Although Crichton observed difficulties at school in children with this disorder, he believed that they grow out of this disorder during puberty (Crichton.,1798 Reprinted:2008). This notion was popular until the 1990s (Barkley et al., 2002). In the 19$^{th}$ century, ADHD was described as a disorder in children, predominantly in boys, who had (present) unruly behavior and hyperactivity. A German physician Heinrich Hoffman wrote two stories; Fidgety Philip; and Johnny Look-in-the Air; in which he described the traits of two boys. Some authors believe that these two stories are early descriptions of ADHD (Greydanus., 2007; Thome, & Jacobs., 2004). Contrarily, some other authors believe that one cannot conclude whether or not Hoffman tried to describe two cases of ADHD (Seidler., 2004, cited by Lange et al., 2010). In

1902, Sir George Frederic Still, a British pediatrician who was involved with childhood diseases, introduced the concept of `defect of moral control`. He described the ADHD cases with a defect of moral control but without a ``general impairment of intelligence`` (Still.,1902, cited by Lange et al., 2010). He observed male to female ration of 3:1 in child and adolescence ADHD (Palmer & Finger., 2001) and this gender difference is still. Interestingly, Still also observed "a quite abnormal incapacity for sustained attention" in both school and home settings, indicating it as the main symptom of ADHD, similar to the current DSM-V (Still.,1902, cited by Lange et al., 2010). Despite this description of ADHD, most of the symptoms observed by Still such as cruelty to animals, aggression, a complete lack of affection, and lawlessness do not refer to ADHD, but rather describe deviant behavior in children (Still.,1902, cited by Lange et al., 2010). Conner believes that ADHD description by Still referred to the full range externalizing behavior disorders including conduct disorder, oppositional defiant disorder, learning disabilities, or antisocial personality disorder (Conner., 2000). Regardless of whether or not Still's description refers to ADHD cases, it was still highly influential to the further conceptualization of ADHD.

**2- Overview of the Conceptual History of ADHD Etiology**

As mentioned earlier, in 1902, Sir George Fredric Still depicted children with defect of moral control but without a ``general impairment of intelligence`` is considered as historical description of ADHD. Furthermore, he divided the cases into two groups "children with morbid defect of moral control associated with physical illness" including cerebral tumor, meningitis, epilepsy, head injury and typhoid fever, and children with " defect of morality as a morbid manifestation, without general impairment of intelligence

and physical illness" (Still., 1902, cited by Lange et al., 2010). Still also mentioned that some of the latter group had "history of severe cerebral disturbance in early infancy." Demonstration of association between brain damage and deviant behaviors in children by Still was important regarding later concepts of brain damage, minimal cerebral dysfunction, and hyperactivity as a historical precursor to ADHD (Lange et al, 2010). Following Still's lecture in 1902, the growing notion that brain damage was a cause of hyperactive behavior was also supported by an assumption of Tredgold in 1908, and epidemic encephalitis from 1917 to 1928. Tredgold suggested a correlation between an earlier brain damage such as birth defect or prenatal anoxia and subsequent behavioral problems or learning disabilities (Tredgold., 1908 cited by Lange et al., 2010). Additionally, many of the children who survived epidemic encephalitis lethargic known as Von Economo's disease, subsequently demonstrated behavioral problems such as remarkable change in personality, emotional instability, cognitive deficits, learning difficulties, hyperactivity, and distractibility (Conners., 2000). Indeed, some of post-encephalic children included a few distinctive symptoms of ADHD (Lange et al., 2010). Children with these same symptoms, but without the history of overt encephalitis were diagnosed with *minimum brain damage* or *dysfunction* (Clements., 1966). The idea of a causal connection between brain damage and behavioral disorder was further supported by researchers in 1930s and 1940s (Ross & Ross., 1976). History of head injury and birth trauma were found to be associated with behavioral disorders and mental retardation, respectively (Kessler., 1998). In 1930s, several animal studies showed similar behaviors between hyperactive children and monkeys with a frontal lobe ablation (Barkley., 2006). Taking these observations in consideration, the notion of a physiological explanation of

behavior disorders became plausible and led to a concept of brain damage and the idea that hyperactivity in children may be connected to damage to their brain. Moreover, it was assumed that minimal damage to the brain, even when it could not be demonstrated neurologically, causes hyperactivity in children (Barkley., 2006). Laufer and his colleagues in 2010 observed that the children with hyperactivity have a lower threshold for clinical response in EEG to administration of metrazol than children without hyperactivity ( Denhoff et al., 1957 cited by Lange et al., 2010). Regarding their results, a functional disturbance rather than a brain damage as an etiology of hyperactivity was suggested (Conner., 2000). Accordingly, the Oxford International Study Group of Child Neurology replaced the term ``minimal brain damage`` to ``minimal brain dysfunction` (Ross & Ross., 1976 cited by Lange et al.,2010). With regard to the concept of minimal brain dysfunction, the role of neurological factors including prenatal or perinatal ``cerebral hypoxemic lesion`` were more highlighted compared to the role of environmental and social factors, such as parents and family (Barkley., 2006). In the 20th century, hyperkinetic syndrome and hyperactive reaction of children were other names for ADHD (Dodson., 2005). This disorder was classified as ADD and ADHD by The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders (DSM*) in 1980 (Lin-Dyken & Wolraich., 1992).

**3 Definition of ADHD**

Attention deficit hyperactivity disorder (ADHD) is often identified in school age children because it causes disruption in classroom and difficulties in schoolwork. ADHD is a complex, heterogeneous in its clinical expression (Sagvolden & Sergeant., 1998), and multifaceted neurodevelopmental condition that can affect adult as well (American

Psychiatric Association., 2000). Children diagnosed with ADHD demonstrate characteristic pattern of inappropriate level of hyperactivity, impulsivity, and/or inattention (Stefanatos & Baron., 2007). However, there has been a significant debate about ADHD. Some critics have considered ADHD as a diagnosis extensively used to distinguish difficult children who are not actually ill but whose behavior is at extreme end of the normal range. Moreover, definition of ADHD as either disease per se or a group of symptoms representing a final common behavioral pathway for a whole series of emotional, psychological, and/or learning problems was questioned by Furman (Furman., 2005). In summary, the main symptoms of ADHD such as hyperactivity, inattention, and impulsivity are not exclusive to ADHD. There is an extensive overlap of these ADHD symptoms with other comorbid mental health conditions and learning difficulties. Some adverse outcomes of ADHD include: academic failure, peer and family conflict, poor self-image, antisocial behavior, and low occupational performance (Fergusson et al., 1997; Leslie & Wolraich., 2007).

## 4 Epidemiology of ADHD

Attention Deficit Hyperactivity Disorder (ADHD) is the most common early-onset mental health disorder, affecting approximately 5% of school-age children worldwide (Polanczyk et al., 2007). A prevalence rate is estimated between 2 to 9% in North America (Biederman & Faraone., 2005). Epidemiologically, it is 3- times more in males than females (American Psychiatric Association., 2000) and 50% of ADHD children maintain the symptoms of ADHD into adulthood (Okie., 2006). An incidence of 3 to 5% is found in adults over age 20 (Greydanus et al., 2007; Kessler et al., 2006). In 2006, 3.5 million individuals between ages 3 and 19, and 1.5 million individuals between ages 20

and 64 were prescribed psychostimulant medication in United States (Greydanus et al., 2007). (Figure 1&2)

**Figure 1**: Life time prevalence of ADHD in population aged 13 to 18 years old (Merikangas et al., 2010)

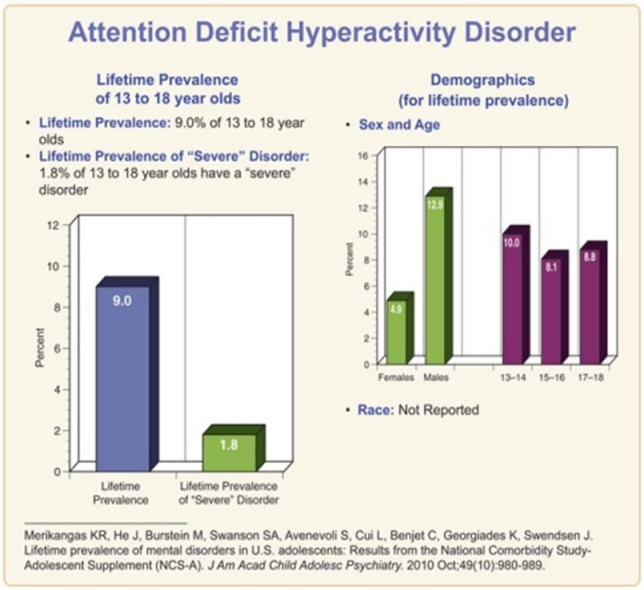
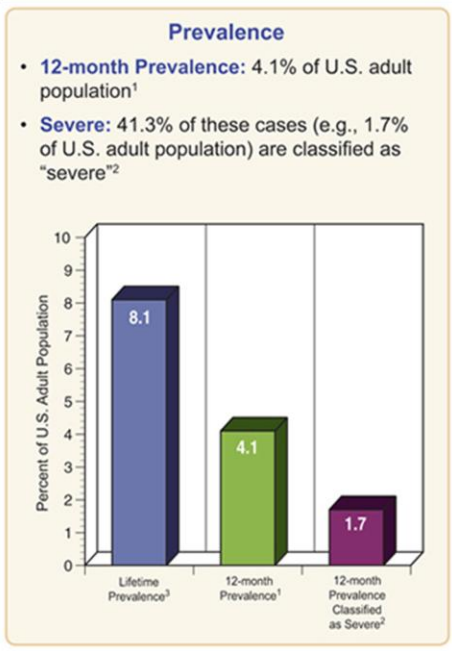


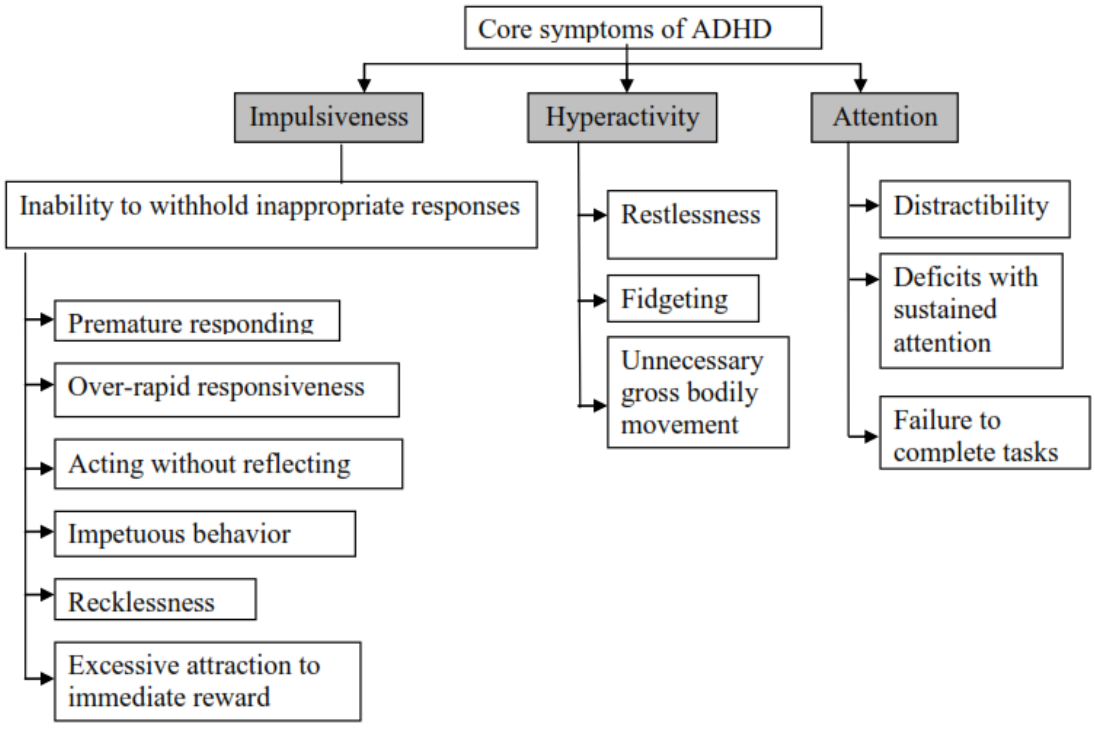

**Figure 2**: 12 month prevalence of ADHD among adult population



## 5 Clinical Features of ADHD

As it was mentioned earlier, ADHD is heterogeneous in its clinical expression. Children with ADHD present poor sustained attention, impulsiveness, and hyperactivity (Sagvolden & Sergeant., 1998). Clinically, ADHD is found to be around six times more common in males than females. Epidemiology, boys present higher level of disruptive behavior, whereas girls exhibit higher level of inattentive symptoms. This difference in clinical expression may result in gender bias in sex ratio (Stefanatos & Baron., 2007; Ramtekkar et al., 2010) (Figure 3)

**Figure 3:** Description of the three core symptoms of ADHD (Sagvolden & Sergeant, 1998)



## 6 ADHD Diagnosis

According to Diagnostic Statistic Manual fourth edition (DSM-IV) text revision definition, essential features of ADHD include:

A. Persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequently displayed and is more severe than is typically observed in individuals at comparable level of development

B. B. Some hyperactive-impulsive or inattentive symptoms must have been present before seven years of age.

C. Some impairment from the symptoms must be present in at least two settings.

D. There must be a clear evidence of interference with developmentally appropriate social, academic, or occupational functioning.

E. The disturbance does not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorders and is not better accounted for by another mental disorder.

C. Clinically, "attention deficit hyperactivity disorder" individuals as per DSM-IV were divided into three distinct subtypes: the *predominantly inattentive type (PIA)*; the *predominantly hyperactive/impulsive type (PHI);* and *combined type (C).* According to DSM-IV criteria for ADHD diagnosis, the child suspected to have ADHD should exhibit at least six symptoms from either or both of nine-item inattention and hyperactivity lists in DSM-IV- Text Revision manual (Table:1). To diagnose *ADHD* subtypes, at least six symptoms of the list should be presented on either the inattention (*PIA*) and/or the hyperactivity/impulssivity (*PHI*) or on both (*C*) by the child (Americam Psychiatric Association., 2000).

**Table 1:** DSM-IV-TR criteria for ADHD (American Psychiatric Association, 2000; Stefanatos & Baron, 2007)

A. Either (1) or (2)

(1) Six (or more) of the following symptoms of inattention have persisted for at least six months to a degree that these become maladaptive and inconsistent with developmental level:

*Inattention*

-Often fails to give close attention to details or makes careless mistakes in school work, work, or other activities.

-Often has difficulty sustaining attention in tasks or play activities.

-Often does not seem to listen when spoken to directly.

-Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not to do to oppositional behavior or failure to understand instructions).

-Often have difficulty organizing tasks and activities.

-Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework).

-Often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools).

-Often easily distracted by extraneous stimuli.

-Often forgetful in daily activities.

- Six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least six months to

a degree that it is maladaptive and inconsistent with developmental level:

(2)

*Hyperactivity*

-Often fidgets with hands or feet or squirms in seat.

-Often leaves seat in classroom or in other situations when remaining seated is expected.

-Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, they are limited to subjective feelings of restlessness).

-Often has difficulty playing or engaging in leisure activities quietly.

- Often "on the go" or often acts as if “driven by a motor."

-Often talks excessively.

*Impulsivity*

-Often blurts out answers before questions have been completed.

-Often has difficulty waiting for turn.

-Often interrupts or intrudes on others (e.g., butts into conversations or games).

- *Symptom total*

Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before the age of seven years.

Some impairment from both symptoms are present in two or more settings (e.g., at school or work, and at home).

Clear evidence of clinically significant impairment in social, academic, or occupational functioning .

Note. Adapted from (American Psychiatric Association, 2000; Stefanatos & Baron, 2007

**7 Highlights of Changes From DSM-IV- Text Revision To DSM-V**

The defintion of attention- deficit/hyperactivity disorder ( ADHD) has been updated in the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The fifth edition more accurately describes the experience of affected adult with ADHD. Based on 20 years of research, This revision demonestrates that ADHD, although is a disorder diagnosed in children, but can continue through adulthood for some not all people.

The diagnositic critera for attention- deficit/hyperactivity disorder (ADHD) in DSM-V is almost the same as it was in DSM-IV.

Two symptom domains including inattention and hyperactivity/impulsivity, of which at least six items are required for diagnosis are still valid. However, several changes have been made in DSM-V:

1) Compared to 7 years as the age of onset in DSM-IV, several inattentive or hyperactive-impulsive symptoms must be present prior to age 12. This change is supported by several reports published since 1994 showing no clinical diffrences between children diagnosed by 7 years of age versus later in terms of course, severity, outcome, and treatment respose

2) The three types in DSM-IV which refered to as `` subtypes`` are now refered to as " presentation". Additionally, presentations can change during the patients` lifetime

3) There is no exclusion criteria for people with autism spectrum disorder in DSM-V because symptoms of both disorders may co-occur. However, ADHD symptoms should not be present during the course of schizophrenia or other psychiatric disorders and must not be better explained by another mental disorder, such as depressive or bipolar

disorder, anxiety disorder, dissociative disorder, personality disorder, or substance intoxication or withdrawal

4) Since DSM-V adapts its criteria for adult, the cut off for ADHD of six symptoms required for younger persons, both for inattention and hyperactivity in DSM-IV was changed to five sympotoms in DSM-V

5) ADHD that is placed in a DSM-IV chapter that includes all usual diagnoses firstly made in infancy, childhood, or adolscence is now placed in a neurodevelpmental disorder chapter in DSM-V. This change emphesizes brain develpmental correlates with ADHD. The DSM-V compared to DSM-IV may be superior in term of illustrating children, older adolscences, and adult behaviour with ADHD at each stage of patients`lives by adding the examples to the criterion items.

**8 Etiology of ADHD**

ADHD is a complex neurobehavioural disorder. Although several studies have been conducted, a comprehensive understanding of etiology of ADHD has not yet been obtained. Growing evidance has shown that multiple risk factors interact to increase vulnerability of ADHD (Doyle et al., 2005). Genetic studies have shown that there is a strong genetic component to the disorder with heritability estimates of 80% (Shastry, 2004). Based on Family (Samuel et al., 1999), twin (Nadder et al., 1998), and adoption studies (Cadoret & Stewart., 1991) genetics appears to be a significant contributing factor in predisposing the development of ADHD. It has been believed that multiple genes that modulate response to the environmental risk factors which is known as genexenvironment interaction (GXE) contribute to an increased risk of ADHD

(Biederman & Faraone, 2005; Swanson et al., 2007). Additionally, many enviromental risk factors are also thought to be involved in the emergence of the disorder (Langley et al., 2005). It is thought that early trauma on the brain during critical period of development may cause structural-functional abnormalities that will be manifestated as disorders later in life a phenomena referred as sleeper effect (McGrath et al., 2000). Given this notion of enviromental risk factors, those complications during pregnancy and birth that expose the fetus very early in life and during critical period of brain development are more commonly seen as risk factors in ADHD childern when compared with control group (Kotimaa et al., 2003; Milberger et al., 1997) (Table 2).

**Table 2 :** Partially Adjusted OR and 95% CI of Maternal, Pregnancy, and Labor Risk and Protective Factors Associated With ADHD (Silva et al., 2014)

| Risk and Protective Factors | Male | | | Female | | |
|---|---|---|---|---|---|---|
| | Cases, N = 10 065 | Controls, N = 23 156 | OR (95% CI) | Cases, N = 2926 | Controls, N = 6915 | OR (95% CI) |
| **Maternal Factors** | | | | | | |
| Maternal age, y | | | | | | |
| ≤20 | 687 | 1026 | 1.57 (1.40–1.76) | 198 | 325 | 1.57 (1.28–1.93) |
| 20–24 | 2302 | 4765 | 1.17 (1.09–1.25) | 703 | 1407 | 1.26 (1.12–1.43) |
| 25–29 | 3432 | 8454 | 1 | 1001 | 2578 | 1 |
| 30–34 | 2538 | 6426 | 1.00 (0.94–1.07) | 727 | 1852 | 1.00 (0.89–1.13) |
| 35–39 | 975 | 2143 | 1.17 (1.06–1.28) | 256 | 659 | 1.01 (0.85–1.21) |
| 40+ | 131 | 339 | 0.98 (0.79–1.22) | 41 | 94 | 1.04 (0.70–1.55) |
| Marital status, single | 1288 | 2057 | 1.50 (1.39–1.63) | 407 | 664 | 1.55 (1.35–1.78) |
| First pregnancy | 2978 | 6711 | 1.02 (0.97–1.08) | 837 | 1996 | 1.00 (0.90–1.10) |
| Smoking in pregnancy[b] | 369 | 510 | 2.06 (1.74–2.44) | 78 | 113 | 1.73 (1.21–2.48) |
| **Pregnancy Factors** | | | | | | |
| Threatened abortion | 629 | 1275 | 1.15 (1.04–1.27) | 183 | 348 | 1.28 (1.06–1.55) Threatened |
| Threatened preterm[b] | 70 | 67 | 2.46 (1.73–3.51) | 12 | 14 | 2.09 (0.90–4.85) |
| Maternal UTI | 483 | 820 | 1.37 (1.21–1.55) | 144 | 227 | 1.51 (1.21–1.90) |
| Preeclampsia | 891 | 1587 | 1.32 (1.21–1.44) | 262 | 443 | 1.44 (1.22–1.70) |
| Premature rupture of membrane | 427 | 925 | 1.04 (0.92–1.18) | 104 | 246 | 1.02 (0.80–1.30) |
| **Onset of labor** | | | | | | |
| Spontaneous | 5621 | 14182 | 1 | 1594 | 4245 | 1 |
| Induced | 3099 | 6202 | 1.25 (1.18–1.32) | 932 | 1833 | 1.33 (1.20–1.48) |
| No labor | 1345 | 2772 | 1.17 (1.08–1.26) | 400 | 837 | 1.15 (1.01–1.31) |
| **Oxytocin use** | | | | | | |
| Oxytocin augmentation[b] | 99 | 249 | 0.93 (0.72–1.21) | 21 | 81 | 0.58 (0.34–0.98) |
| Oxytocin induction[b] | 261 | 503 | 1.18 (0.99–1.41) | 63 | 133 | 1.07 (0.74–1.55) |
| **Complications of labor** | | | | | | |
| Precipitate delivery | 487 | 1163 | 0.94 (0.84–1.06) | 166 | 363 | 1.10 (0.90–1.34) |
| Fetal distress | 1488 | 3161 | 1.09 (1.02–1.17) | 394 | 848 | 1.11 (0.97–1.27) |
| Cord prolapse | 30 | 59 | 1.13 (0.71–1.81) | 12 | 16 | 2.50 (1.08–5.77) |
| Cord tight around neck | 695 | 1610 | 0.99 (0.90–1.08) | 193 | 420 | 1.11 (0.93–1.33) |
| **Presentation** | | | | | | |
| Vertex | 9512 | 22065 | 1 | 2769 | 6536 | 1 |
| Breech | 471 | 952 | 1.17 (1.04–1.31) | 133 | 337 | 0.98 (0.79–1.21) |
| Other | 79 | 127 | 1.29 (0.97–1.73) | 23 | 40 | 1.47 (0.87–2.46) |
| **Mode of delivery** | | | | | | |
| Spontaneous vaginal | 5921 | 14 021 | 1 | 1800 | 4337 | 1 |
| Vacuum | 1071 | 2546 | 1.01 (0.93–1.10) | 283 | 648 | 1.09 (0.93–1.27) |
| Forceps | 1025 | 2249 | 1.08 (0.99–1.17) | 263 | 665 | 1.01 (0.86–1.19) |
| Elective caesarean | 1144 | 2428 | 1.15 (1.06–1.25) | 347 | 726 | 1.17 (1.01–1.36) |
| Emergency caesarean | 1063 | 2294 | 1.10 (1.01–1.19) | 265 | 596 | 1.03 (0.88–1.22) |

[a] **Partially adjusted by year of birth and SEIFA.**

[b] **Restricted data set: data available from 1997–2002.**

**Source: Pediatrics 2014;133;e14 (Silva et al, 2014)**

Previous studies showed that enviromental risk factors such as maternal stress, alcohol consumption, and smoking and drug abuse during pregnancy have all been implicated in the pathogenesis of ADHD (Grizenko et al., 2012; Linnet et al., 2003; Thakur et al., 2012; Kotimaa et al., 2003; Knopik et al., 2006; Milberger et al., 1997). Compared to non-ADHD children, mothers of ADHD children more likely experienced moderate or severe stress during pregnancy (Grizenko et al., 2008). Additionally, a strong association was found between behavioural/emotional problems later in life in children whose mothers experienced high level of anxiety late in pregnancy (O'Connor et al., 2003). Environmental adversity indexed by lower social class and maternal lifestyle have been investigated as risk factors for ADHD in offsprings (Langley et al., 2007). One such maternal lifestly factors is maternal smoking during pregnancy (MSDP), which has been exclusively studied and recognized as one of the most significant prenatal risk factor in ADHD (Linnet et al., 2003; Mick et al., 2002; Milberger et al., 1996). The association which was found between prenatal tobacco exposure and slower reaction time and variability reaction time on continous performance test (CPT) support the role of tabacco exposure in ADHD pathology (Motlagh et al., 2011). However, causal association between the tobacco exposure and neurodevelopmental disorder, such as ADHD, is not yet clearly undrestood. Recent studies suggest that the tobacco exposure early in life may be a trigger for several genetic and enviromental factors implicating in pathogenesis of ADHD (Obel et al., 2011). A meta- analytic review showed an association of prematurity with an increased risk of incidence of ADHD and other mental health problems. For example, premature birth was suggested to be associated with reduced congnitive test scores at school age (Bhutta et al., 2002; McGrath et al., 2000). Post-term born children

also showed almost two and a half times more risk for attention deficit hyperactivity disorder, therefore it is suggested that there is a relationship between gestational age and behavioural problems (El Marroun et al., 2012). In another large study, low birth weight was also identified as a contributing factor to attention problems and ADHD (Linnet et al., 2006; Nigg & Breslau, 2007). The association of low birth weight with ADHD may represent a causal risk factor and may not be challenged by genetic factors (Groen-Blokhuis et al., 2011). Additionally, a very recent study demonstrated that pregnancy, delivery, and labour complications such as maternal urinary tract infection, induced and experiencing threatened preterm labor and preeclampsia increased the risk of ADHD (Silva et al., 2014). Specifically, those complications that chronically exposed the fetus during pregnancy such as maternal bleeding, smoking, illicit drug use, and eclampsia are believed to significantly contribute to the risk of ADHD (Milberger et al., 1997). Furthermore, both maternal gestational diabetes and low socioeconomic status (SES) were showed to be associated with an approximately 2-fold increased risk for ADHD at 6 years of age. However, the risk of gestational diabetes appeared to be greater among lower SES families than higher SES families. Interestingly, children exposed to either gestational diabetes or low social economic status did not show a notable increased risk for ADHD (Nomura et al., 2012).

APGAR score as an indicator of the health of newborn immediately after birth has increasingly drawn many researcher's attention in the field of mental health problems.

Many studies showed that APGAR score below 7 at 5 minute is also significantly associated with increased risk of ADHD (Halmøy et al., 2012; Li et al., 2011; Gustafsson & Källén, 2011). Conclusively, compared to children with APGAR score of 9 or 10 at 5

minute, the risk for ADHD was 75% and 63% higher in children with APGAR score of 1 to 4 and 5 to 6 at 5 minute, respectively (Li et al., 2011). A recent study reported an elevated risk of ADHD following an administration of perinatal oxytocin ( Kurth & Haussmann., 2011). In summary, many studies suggest that the potent genetic risk for ADHD can be moderated or mediated by environmental influences such as prenatal, perinatal, and postnatal factors (Plomp et al., 2009; Getahun et al., 2013). Environmental risk factors could also mediate the outcome of ADHD and its sympotoms (Nigg et al., 2010). However, the importance of prenatal and perinatal complications as risk factors for ADHD has been an area of controversy. Many studies have shown different results from not eleveted to an highly elevated risk for ADHD due to these risk factors.

**9 Overview of Pathophysiology of ADHD**

The abnormalities in frontal neural circuit, as shown by many neurophysiological and imaging studies, seem to be resposible for the most recognized defects of executive and attention function implicated in this disorder (Sagvolden & Sergeant., 1998) ( Rubia et al., 2001; Oades et al., 2005). Moreover, neuroimaging studies using resting-state fMRI showed decreased activation of the DA pathway (PFC- striatal circuit) in ADHD (Rubia et al., 1999; Durston., 2003).

Interestingly, structural brain imaging studies have shown an overall size reduction in various brain regions in ADHD individuals. Of these brain regions, caudate nucleus, globus pallidus, anterior brain regions, and rostrum and splenium of the corpus callosum have been shown to be smaller in ADHD individuals (Swanson et al., 2007). As far as the biological factors are concerned, it is believed that in ADHD there is a dysfunction of

three main pathways including dopamine (DA), norepinephrine (NE), and serotonin (5-HT) (Aman et al., 1998; Durston., 2003; Sagvolden & Sergeant., 1998). Dopamine and norepinephrine stem from substantia nigra and locus coeruleus, respectively, and project extensively to the brain. It has been shown that projections to the prefrontal cortex (PFC) and the anterior cortex (AC) are predominantly involved in ADHD (Arnsten., 2006).

**10 Pathogenesis of ADHD: Significance of Ischemic-Hypoxic Conditions**

As mentioned, etiology of ADHD is heterogeneous, includes genetic and environmental risk factors. Among the latter, prenatal, perinatal, and neonatal events are significant. It is believed that fetal circulatory insufficiency with abnormal autoregulation and systemic hypotension make the waterwashed brain region such as striatum vulnerable to hypoxemia. For example, repeated ischemic-hypoxic injuries in prematurity can be attributed to the higher incidence of ADHD in these children ( Lou et al., 1996). Additionally, recent studies have investigated the effects of ischemic-hypoxic conditions on increased risk of ADHD. Emerging evidence suggest that ischemic-hypoxic conditions in pregnancy pose adverse consequences on the brain development that may not be present at birth and even early in life ( Li et al., 2011; Duncan et al., 2004). Recent study showed that ischemic-hypoxic conditions such as asphexia, respiratory distress syndrome, and preeclampsia independently play a role in increased risk of ADHD. Although ischemic-hypoxemic conditions appeared to be significant risk for ADHD, but pathophysiology of these events are not yet clear. It is believed that ischemic-hypoxic conditions pose their risk through pathogenetic mechanism including uteroplacental underperfusion, placental ischemia, and hypoxia. Therefore, during critical period of the

brain development, these hypoxic events result in compromised oxygen and nutrient delivery to the brain (Getahun et al., 2013). Conclusively, suboptimal oxygen and nutrient transport from mother to fetus can lead to prominent structural and functional brain injuries to offsprings ( Duncan et al., 2004). The striatum has a specific vulnerability to hypoxic events, and since striatum disturbances are very often seen in ADHD, role of ischemic-hypoxic injuries can be explained in a logical manner ( Lou et al., 1996).

**11 ADHD Pathogenesis: Pre- and Post-natal Exposure to Nicotine**

Prenatal and postnatal effects of maternal smoking have been extensively investigated. Cigarette smoking may cause a hypoxemic-ischemic event on fetus through interfering with normal placental function, and reducing the uterine blood flow (Suzuki et al., 1980). Episodic fetal hypoxemia along with carbon monoxide and other ingrerdients in tar can affect the fetal brain development (Ernst et al., 2001). Direct action of nicotine on fetal brain has also been reported. It can cause regional abnormality in cell proliferation and differentiation (Slotkin., 1987). The study of nicotine effect on neurotransmitter systems demonstrated hypoactivity of the dopaminergic and noradrenergic systems to exogenous stimulant after prenatal exposure to nicotine (Slotkin., 1987).

**12 Treatment of ADHD**

Methylphenidate (MPH) is a stimulant and one of the most common medication used for the management of ADHD symptoms. MPH is a potent dopamine and norepinephrine agonist and stimulates activity of DA and NE which are involved in the pathophysiology

of ADHD ( (Stroh et al., 2007). Behavioural intervention such as parent training, behavioural management, and social skills training have been shown to be effective in treatment of ADHD (Stroh et al., 2007; Hoza et al., 2006). Previous findings suggest that in clinical setting, ADHD patients with more severe symptoms have better response to MPH treatment. Furthermore, presence of comorbid disorders do not affect the treatment response to MPH in these ADHD patients (Victor et al., 2014; Garcia et al., 2009)

# CHAPTER II

# INTRODUCTION

## 1 Study Rational

Although, the involvement of genes in ADHD is clear in the litrature, but enviromental factors also play a significant role in increased risk of ADHD (Nigg et al., 2010). Genetic factor may affect conditional exposure to enviromental risk. Early life enviromental risk factors theoretically could act as causal factors for neuropsychiatric disorders, because they are believed to be harmful at critical times in the brain developmental process (Marsh et al., 2008). Several studies in this review have demonstrated an association between early environmental risk factors and development of ADHD later in life. Certain early environmental risk factors such as smoking (Kotimaa et al., 2003), alcohol use and psychological distress in pregnancy (Linnet et al., 2003), eclamsia, prolonged labour and bleeding (Milberger et al., 1997), preterm birth (Lindstrom et al., 2011), and low birth weight (Linnet et al., 2006) have been highlighted by previous studies. However, these studies did not explore the distinction between *chronic* exposure, such as smoking, and gestational diabetes and *acute,* traumatic events, such as delivery and labour complications regarding their possible influence on ADHD symptom diamension. Assumably, chronic exposure to environmental risk factors may indicate a larger cumulative "dose" or a higher possibility of a "dose" occurring during gestation or neonatal period for extended period. Moreover, cigarette smoking as a consistently related risk factor for ADHD and cognitive impairment appeared to result in some pregnancy, delivery, and neonatal complications including intrauterine growth restrication (Feng et al., 2014), birth weight below the10th percentile, placental

abruption, and premature rupture of membrane (Spiegler et al., 2013), as well as hyperbilirubinemia (Sochaczewska et al., 2010). Elevated risk of ADHD in maternal smoking can partly be attributed to biological sequelae of chronic prenatal exposure to nicotine. To date and to our knowledge, previous studies investigated the effect of prenatal nicotine exposure on risk of ADHD and its severity, but did not investigate the effect of maternal smoking on other pregnancy, delivery, and infancy complications.

## 2 Objective

The aim of this study is to determine:

1. To compare the severity of ADHD symptoms in children with ADHD stratified according to the level and duration of exposure to PDICs.
2. If specific complications among the chronic, and acute exposure are relevent to more severe ADHD and different phenotypes

## 3 Hypotheses

1. Given the importance of critical exposure to risk factors early in life, it can be proposed that duration of exposure may also be important for its effect on ADHD symptom dimensions. Therefore;We also hypthesized that chronic complications either alone or with actue complications could result in more severe symptom in children with ADHD.
2. Given the impostance of some specific pregnancy, delivery, and neonatal complications for the increased risk of ADHD, it can also be speculated that some of these complications categorized as either chronic or acute may comparably

affect ADHD symptom dimension. It is also hypothesized that complications related to more obvious ischemic-hypoxic events could affect symptom severity in children with ADHD.

# CHAPTER III

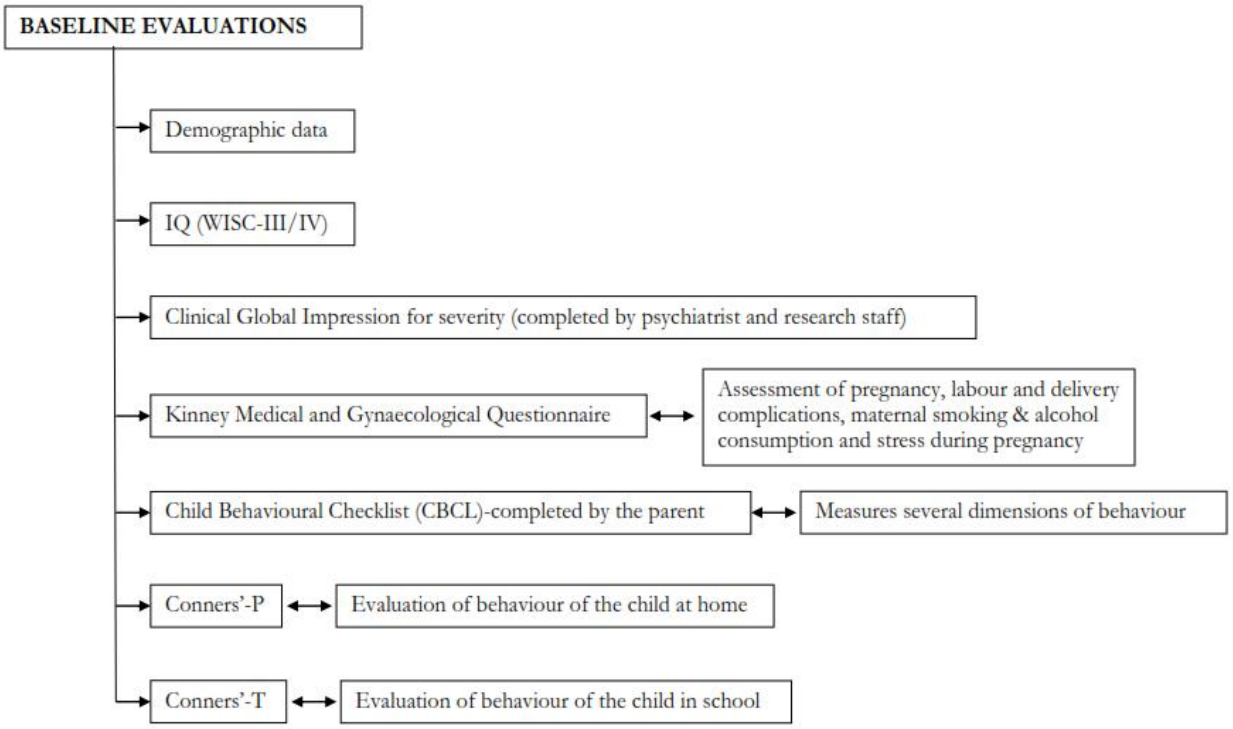
# Methods

### 1 Subject and Baseline Evaluations

ADHD subjects were recruited from Disruptive Behavior Disorder Program and the Child Psychiatry Outpatient Clinic at the Douglas Mental Health University Institute in Montreal, Canada. Children with ADHD were referred by schools, community social workers, family physicians, and pediatricians. The family and children agreed to participate in a double-blind, placebo-controlled, randomized 2-week crossover trial of methylphenidate (MPH). Participants in this study were between 6 to 12 years, and met DSM-IV diagnostic criteria for ADHD. A best diagnosis of ADHD according to DSM-IV criteria was made by the research child psychiatrists using clinical examination of the child and an interview with at least one parent being present. Diagnosis was corroborated by a structural interview with parents using Diagnostic Interview Schedule for Children-version IV (DISC-IV, parent report) (National Institute of Mental Health., 1998), evaluation of behaviour in school by the teacher using the Conners 'Global Index-teacher version ( CGI-T), and at home by parents using Conners' Global Index-Parents version (CGI-P). DISC-IV was also used to diagnose the presence of co-morbid disorders such as conduct disorder, oppositional defiant disorder, anxiety disorder, and mood disorder. At least one Conner's-Parents or Teachers sub-score must be 65 or more. Parents were also asked to complete Child Behavioral Checklist which assessed behavioral and emotional problems in participating children. Mothers were the primary source of information in most cases. All baseline evaluations were completed during the

week before the clinical trial and when the children were not taking any medication (drug wash out period) ADHD children with IQ less than 70 as measured by Wechsler Intelligence Scale, psychosis or developmental disorder such as autism, or a history of Tourette's syndrome were excluded from this study. Research Ethics board of Douglas Institute approved the study protocol. Parents were explained the study and they provided written consent. Children were explained the study and they gave their assent verbally to participate.

**Figure 4:** Baseline evaluations



## 3 Materials

### *3.1- Kinney Medical Gynecological Questionnaire*

*Kinney Medical Gynecological Questionnaire* (Kinney et al., 1998) was used in interviews with the mothers to evaluate complications during pregnancy, as well as labour, delivery, and neonatal period (first 8 weeks) of the children affected with ADHD and their siblings. This questionnaire was scored by using McNeil- Sjostrom scale for obstetrical complications (Mc Neil & Sjostrom., 1995). This scale takes into account the severity of complications during the first, second and third trimesters of pregnancy, as well as labour, delivery and the neonatal period. The scale ranges from 0 to 6 with respect to severity level that may be potentially harmful to the central nervous system of fetus:

Level 1: Not harmful or relevant

Level 2: Not likely harmful/relevant

Level 3: Possibly but not clearly harmful or relevant

Level 4: Clearly potentially harmful or relevant

Level 5: Clearly potentially greatly harmful or relevant

Level 6: Great harm to the offspring

To obtain more quantitative data, a questionnaire has been added to the Kinney Medical and Gynaecological Questionnaire. The questionnaire consists of three sections: 1) Fagerström Test (Fagerstrom., 1978), a validated questionnaire for nicotine dependency 2) AUDIT-C, an effective brief screening test for problem drinking and 3) selected questions from the Statistics Canada: Canadian Community Health Survey Cycle 3.1

### *3.2- Conners' Global Index for parents and teachers*

Overall behaviour of the child is assessed by parent(s) and teacher(s) using the Conners Global Index (Conner's-P and Conner's T, respectively) (Conners & Barkley., 1985). Conners'-P and Conners'-T are subsets of the original Conners' Rating Scales, which is widely used for assessing behavioral and emotional problems in children. Conners'-P and Conners'-T consist of 10 items. Each item describes a behavior rated on a 4-point Likert scale from 0 (not at all true) to 3 (very true). 'Emotional liability' (EL) and 'Restless-impulsive behavior' (RIB) are two major components of behavioral and emotional problems. These scales are also extensively used to evaluate ADHD symptoms in children between 3 and 17 years of age. Established normalized data are available for age, gender, and observer. The raw total and factor scores are transformed into normalized T-scores, a total score of 65 or higher are considered to be clinically significant.

### *3.3- Child behavior checklist*

Child behaviour checklist (CBCL) is a Comprehensive child behaviour rating scale (113-item Questionnaire) (Achenbach TM, 1991), which has been widely used in clinical and research settings. It assesses emotional and behavioural problems in children. Two main components of CBCL are externalizing and internalizing. CBCL- Internalizing includes mood disturbances such as anxiety, depression, and social withdrawal. CBCL-Externalizing reflects externalizing behaviour such as violation of social norms and conflict with others. CBCL-total, internalizing, and externalizing CBCL are reported as T-scores which were normalized score based on age and gender. A *t* test score of 70 and more is considered problematic. Table: 2

### *3.4-Intelligence Quotient*

The Wechsler Interview Scale for children-third edition (WISC-III) is used to assess the IQ (full scale, verbal, and performance IQ) of the child. (Table 3)

**Table 3:** Behavioral/neuropsychological assessments conducted in the Pharmaco-Behavioural Genetic Study

| Description of assessment/test | T/Standard score; average | Higher is better/worse? |
|---|---|---|
| IQ: WISC-III/IV | Standard score (average=100) | Better |
| CGI-severity, CGI-improvement, CGI-side effects | Not standardized | Worse |
| Child Behavioural Checklist (CBCL) | T score (average=50; 50-64 = normal 65-69=borderline;>70=problematic) | Worse |
| Conners'–Parents (Conners'-P) and Teachers (Conners'-T) | T score (average =50; >65=problematic) | Worse |

### *3.5- Demographics*

Parents were asked to answer the questions about their children's age, gender, and race/ ethnicity. Parental information comprised education level, mother's age at birth, and socioeconomic status.

## 4 Study Design and Procedure

In this study detailed assessment of complications occurring during pregnancy, as well as labor and delivery, and neonatal period were obtained using Kinney Medical Gynecological Questionnaire (described in detail in Methods section). Based on McNeil-Sjostrom scale, we considered only complications with severity level of four and above. The information of obstetrical complications was augmented by hospital records

wherever possible (over 90% responses). We divided all obstetrical complications with severity level of four and above into two major groups; chronic and acute. Chronic complications affected the central nervous system of fetus or infant to harmful events for more than 24 hours. Complications for duration less than 24 hours were classified as acute. Chronic complications mostly occurred during pregnancy and acute complications during labour and delivery. Complications found to be prevalent in our study are shown in table 2. Regarding adverse effects of smoking, alcohol consumption, and drug abuse (heroin, cocaine, marijuana, etc) on fetal central nervous system, these risk factors were considered as chronic pregnancy complications. Ten cigarettes per day and more than 32g or 7-9 cl ethyl alcohol per day result in severity level of four and above. Regarding alcohol consumption and smoking during pregnancy, the mother's report is supported with child's father or someone else who could was present during pregnancy. See Appendix I for description of complications (Appendix I).

**Table 4:** Most Prevalent Chronic and Acute Complications during Pregnancy, Delivery, and Infancy with Severity of Four and above Items.

| The time of occurrence | Chronic Complications | Acute Complications |
|---|---|---|
| **Pregnancy** | Smoking, Drug abuse (Heroin, Cocaine, Marijuana, etc), Alcohol consumption, Gestational diabetes, Bleeding, abdominal Trauma, Infection mostly urinary tract and respiratory infections, Anemia plus Iron therapy, Hypertension, Preeclampsia, systemic lupus erythematous, steroid therapy , medication such as Valporic acid, Dilantin, Phenothiazin, Hydrochlorothiazide, oral contraceptive, cardiac disease, epilepsy, oligohydraminous, Rh immunization, ulcerative colitis, Gonorrhea infection, factor V(leidn) deficiency, breech presentation . | Non- repetitive abdominal trauma and preeclampsia late in pregnancy |
| **Labour & Delivery** | | Non-vaginal delivery(emergency and elective caesarean section, vacuum & forceps), meconium stain, prolonged or precipitous labour, fetal distress, premature rupture of membrane, intrapartum bleeding, Epidural plus hypotension, induction with prostaglandins |
| **Infancy** | Post term, preterm, very preterm, low birth weight, Macrosomia, cardiac malformation, pyloric stenosis, Neonatal intensive care unit (NICU), pulmonary stenosis, neonatal meningitis, and jaundice requiring phototherapy. | APGAR first minute below 7, neonatal cyanosis, respiratory distress, cord around neck, neonatal hypoglycemia, neonatal hypothermia, Apnea, neonatal cardiac arrest, neonatal arrhythmia. |

Behaviour of children was evaluated Monday through Friday by teachers and on weekends by parents each week. Parents were asked to complete CGI-P. Behaviour of the child was also evaluated by teacher at school using CGI-T. In this study, CBCL total, CBCL externalizing and internalizing, and CGI-T and CGI-P at the baseline are considered to measure the severity of symptoms.

**5 Statistical Analysis**

Study subjects were stratified into four groups: affected children who were exposed to either chronic or acute or both acute and chronic complications (risk factors), anytime during pregnancy, labour, delivery, or neonatal period and children who were exposed to none of the complications (risk factors). Since there were more than 60 chronic and acute complications (risk factors) of interest, we reduced the number of independent variables to be studied. Consequently, those individual complications (risk factors) that did not have considerable frequency (less than 20) among our subjects were added together to create a "miscellaneous chronic and acute complications (risk factors)". ANOVA (analysis of variance) for continuous variables and Chi-square test for categorical variables were used to compare demographic characteristics between affected children exposed to at least one of the either chronic or acute or both complications (risk factors) and children exposed to none of the risk factors (control group). As the first step, frequency of individual chronic, acute, and miscellaneous chronic and acute complications (risk factors) were determined. Subsequently, A Pearson's chi-square test was used to analyze correlation between chronic and acute group of complications and between individual complications. Univariate ANOVA test was used to evaluate continuous variables to compare neurobehavioral characteristics of children with ADHD

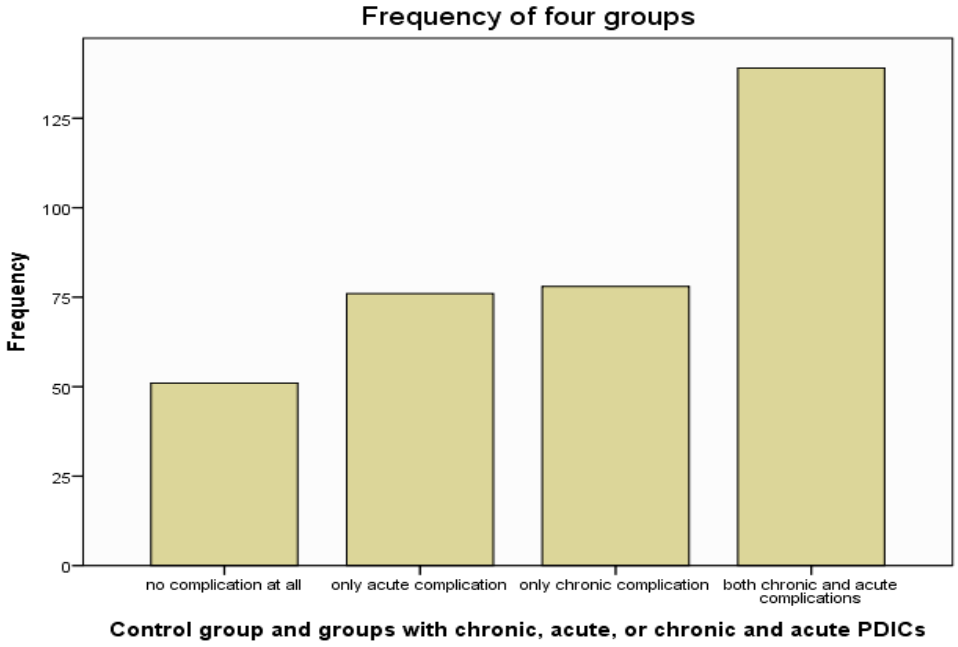
stratified according to the exposure to complications (risk factors). Our outcome variables included CGI-P, CGI-T, CBCL total t-score, and CBCL externalizing and internalizing t-score. Post-hoc Tukey's Honestly Significant Difference test was used when required. Furthermore, we conducted independent sample t-test analysis separately for each complication to determine which individual complication contributes to severity of ADHD. Afterward, a linear regression analysis was also conducted for those complications showing more contribution to severity of ADHD in independent sample t-test. The only outcome variable showing difference between the groups in ANOVA analysis were then entered in independent sample t-test and linear regression analysis. Main effects and any interactions were considered statistically significant when $p < 0.05$. Analyses were performed using SPSS version 20.

**CHAPTER IV**

## Results

Among the five hundred and forty two subjects (542) in this study, 24.9%, 21.9%, and 37.0% of mothers of Children with ADHD at least had either acute or chronic, or both acute and chronic exposure to complications during pregnancy, delivery, and infancy of their children, respectively. 16.9% of mothers with children with ADHD did not sustain any PDICs {pregnancy, delivery, and infancy complications} (Graph1).

**Graph 1:** Frequency of ADHD children exposed to neither of chronic or acute PDICs, compared to only acute PDICs, to only chronic PDICs, and both acute and chronic PDICs




Demographic characteristics of Children with ADHD in our study were stratified by exposure to at least either acute or chronic or both acute and chronic PDICs (table: 5) Group of Children with ADHD exposed to both chronic and acute PDICs came from a lower family income group ($X^2$=19.9, *df* =3, *P*< .001).

**Table 5:** Demographic Characteristics of Attention Deficit/Hyperactive Children Whose Mothers Had at Least Either One Chronic or Acute or both Chronic and Acute PDICs

| | **Control group (N=79)** | **at least one chronic complication (N=120)** | **at least one acute complication (N=107)** | **Both chronic and acute complication (N=179)** | **Test statistic & *P* value** |
|---|---|---|---|---|---|
| **Gender(%Male)** | 77.2 | 83.6 | 80.4 | 79.6 | $X^2$=1.38, *df*=3 *p*=0.70 |
| **Age(Mean/SD)** | 9.1/1.9 | 8.8/1.8 | 9.1/1.7 | 9.0/1.8 | *F*(1.488)=0.70 *P*= 0.40 |
| **Mother's age at child's birth(Mean/SD)** | 27.9/5.4 | 27.5/5.9 | 28.7/5.3 | 27.6/5.6 | *F*(1,443)=0.22 *P*=0.63 |
| **Mother`s years of education(Mean/SD)** | 13.6/2.9 | 12.6/2.7 | 14.0/3.4 | 12.9/3.1 | *F*(1.453)=0.56 *P*=0.45 |
| **Annual family income(% less than $30,000)** | 22.1 | 44.5 | 29.3 | 48.8 | *X2*=19.91, *df*=3 ***P*=0.00** |
| **Ethnicity(%white)** | 88.6 | 91.6 | 89.6 | 87.2 | $X^2$=1.5, *df*=3 *P*=0.68 |

Significance was set at $p = .05$; significant differences are indicated in bold

Four groups of children in our study were compared with respect to CBCL-total T score, CBCL- total externalizing, and internalizing T score, CGI-P, and CGI-T scores. CBCL and Conners indicate severity of psychology and severity of ADHD symptoms, respectively. A one- way repeated measure ANOVA with Tukey's post Hoc analysis showed that children with ADHD who were exposed to both acute and chronic PDICs scored higher only on CBCL externalizing ($F$ (3,480) =2.76, $P$<.05) compared to those who were not exposed to either acute or chronic PDICS. There was no significant difference between the groups exposed to at least one acute or chronic PDICs and the

control group as well as within groups exposed to at least one acute or chronic PDICs .(Table 6).

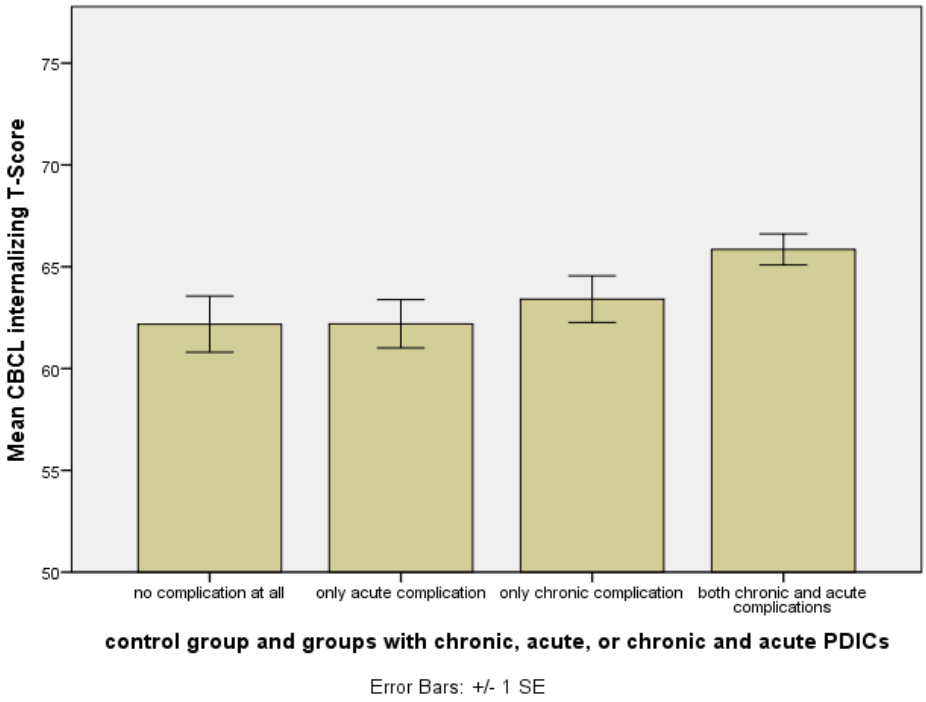
**Table 6:** Behavioral Features of Attention-Deficit/Hyperactivity Disorder Children With and Without Exposure to Acute, Chronic, or Both Acute and Chronic PDICs.

| **Qualitative exposure** | **Control group N=79** | **at least one chronic complication N=120** | **at least one acute complication N=107** | **Both chronic and acute complications N=179** | **Statistical Test & P value** |
|---|---|---|---|---|---|
| **CBCL total-*t* score** | 66.9 ± 7.9 | 68,5 ±9,5 | 68,0 ±9,0 | 69.8 ± 7.4 | *F* (3,480)=2.42 *P*=0.06 |
| **CBCL internalizing - *t* score** | 62.72 ± 9.4 | 63,5 ±10,1 | 63,4 ±10,8 | 65.3 ± 9.6 | *F* (3, 480)=1.65 *P*=0.17 |
| **CBCL externalizing - t score** | 65.1 ± 9.5 | 67,7 ±12,0 | 67,7 ±10,1 | 69.0 ± 8.4 | *F* (3, 480)=2.76 ***P*=0.04*** |
| **Conners total parent baseline** | 7.32 ± 10.5 | 72,2 ±11,6 | 72,6 ±11,2 | 73.3 ± 10.6 | *F* (3, 441)=1.3 *P*=0.27 |
| **Conners total teacher baseline** | 69.4 ± 13.2 | 68,1 ±12,7 | 67,4 ±11,4 | 71.0 ± 12.2 | *F* (3, 449)=2.1 *P=0.09* |

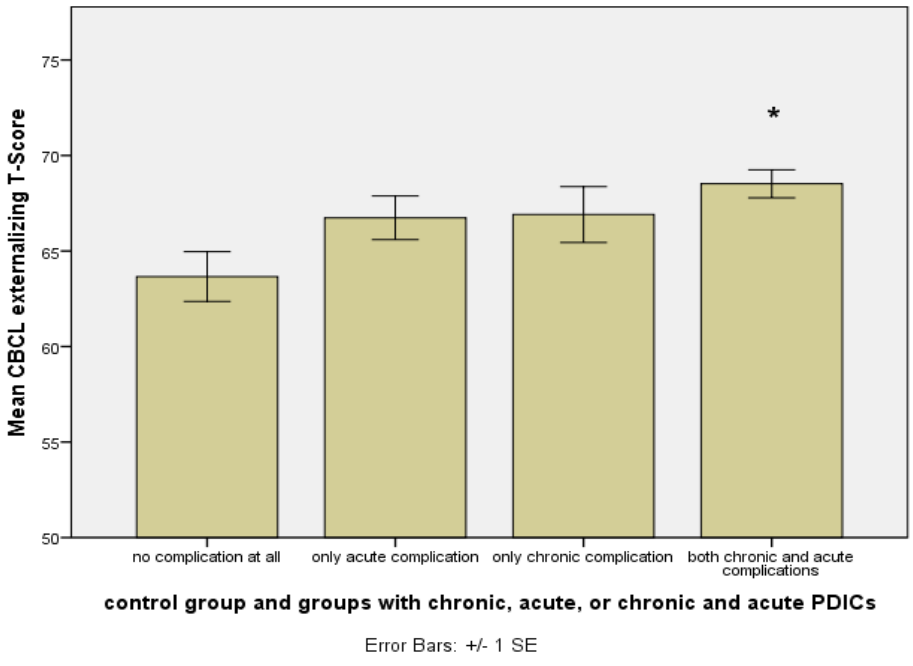
Significance was set at $p = .05$; significant differences are indicated in bold

The differences between four groups with respect to CBCL- total externalizing and internalizing T score, CGI-P, and CGI-T scores are shown in graphs: 2, 3, 4, and 5, respectively.

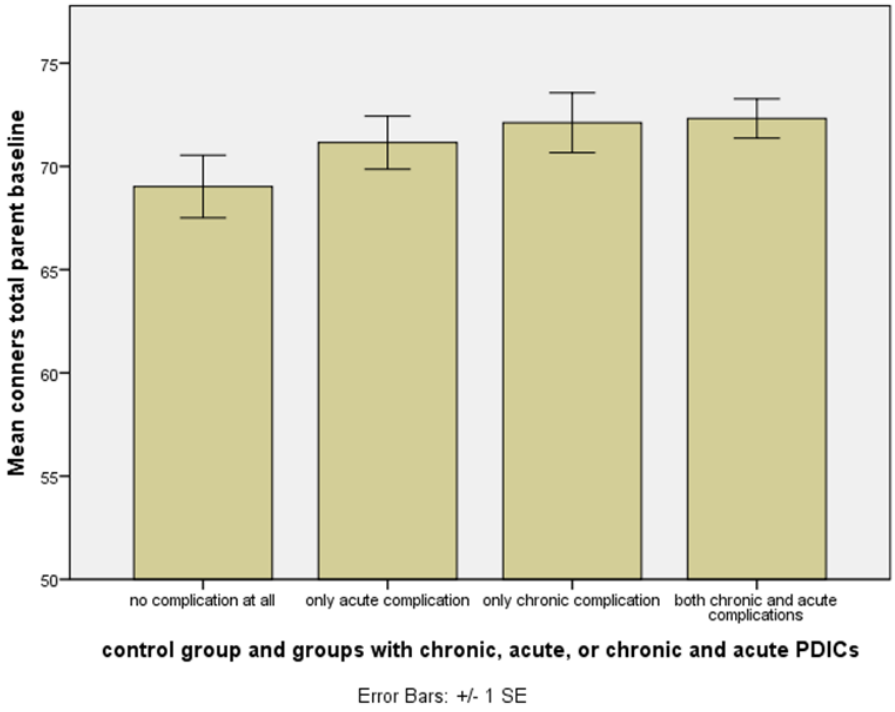
**Graph 2:** CBCL internalizing t score for ADHD children exposed to neither of chronic or acute PDICs, compared to only acute PDICs, to only chronic PDICs, and both acute and chronic PDICs



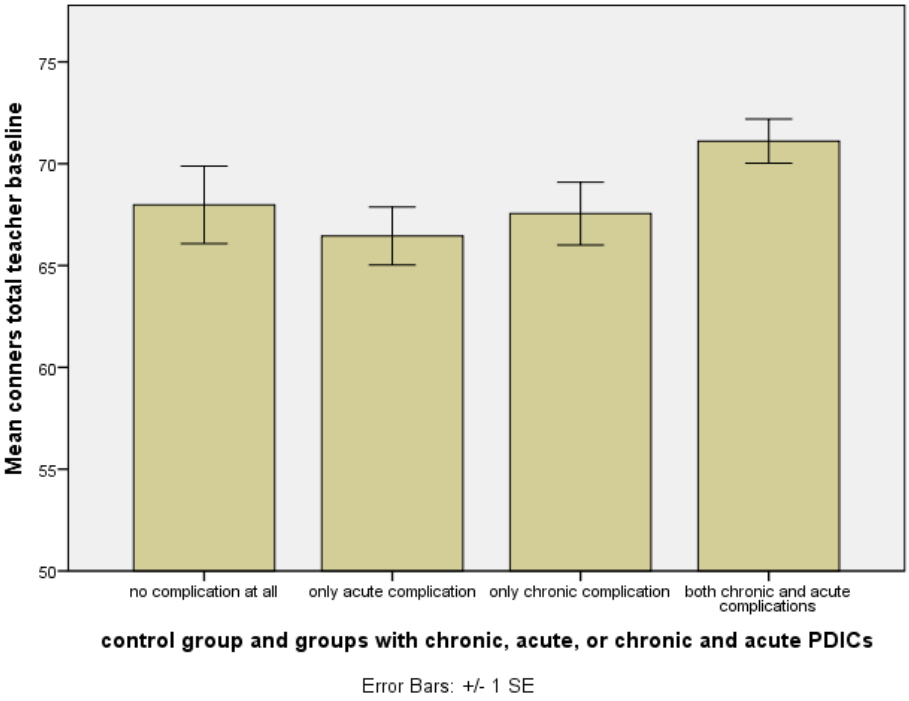

**Graph 3:** CBCL externalizing t score for ADHD children exposed to neither of chronic or acute PDICs, compared to only acute PDICs, to only chronic PDICs, and both acute and chronic PDICs.



**Graphs 4**: Conners total parents baseline score for ADHD children exposed to neither of chronic or acute PDICs, compared to only acute PDICs, to only chronic PDICs, and both acute and chronic PDICs
* =significant




**Graphs 5:** Conners total teacher baseline score for ADHD children exposed to neither of chronic or acute PDICs, compared to only acute PDICs, to only chronic PDICs, and both acute and chronic PDICs
* =significant



As shown in table 7, independent sample t test show that a few individual acute or chronic complications such as smoking more than 10 cigarettes per day, bleeding, total first minute APGAR below 7, and acute miscellaneous complications contributed to more externalizing behavior in children with ADHD.

**Table 7:** T test for all complication with respect to CBCL-externalizing t score

| Variables | | N | Mean | *df* | *T* | *P* |
|---|---|---|---|---|---|---|
| **Duration of labor based on mother & medical report** | Prolonged or precipitous labor | 67 | 67,87 | 505 | 0.07 | 0.24 |
| | Normal duration | 440 | 67,77 | | | |
| **Maturity based on mother & medical report** | Post or pre- term | 89 | 67,67 | 516 | 0.05 | 0.86 |
| | Term | 429 | 67,74 | | | |
| **Maternal Smoking** | More than 10 cigarette per day | 139 | 71,50 | 526 | 5.01 | **0.01*** |
| | No smoking or less that 10 cigarette per day | 398 | 66,55 | | | |
| **Bleeding either during pregnancy, during and after labor with score 4 and above based on mother & medical report** | Bleeding | 34 | 70,82 | 502 | 1.81 | **0.00*** |
| | No bleeding | 470 | 67,63 | | | |
| **Rupture of membrane based on mother report** | Premature rupture of membrane =>24 hours before contraction | 23 | 67,88 | 496 | 0.02 | 0.33 |
| | No premature rupture of membrane | 475 | 67.83 | | | |
| **Phototherapy for physiologic jaundice based on mother report** | Phototherapy | 65 | 66,37 | 503 | 1.29 | 0.45 |
| | No phototherapy | 440 | 66,08 | | | |
| **Result of monitoring based on mother & medical report** | Fetal distress | 87 | 68,51 | 508 | 0.74 | 0.47 |
| | No fetal distress | 423 | 67,62 | | | |
| **Gestational Diabetes based on mother & medical report** | Gestational diabetes | 52 | 70,15 | 520 | 1.84 | 0.22 |
| | No gestational diabetes | 470 | 67,46 | | | |
| **Type of delivery based on mother & medical report** | Non vaginal delivery | 144 | 68,1 | 510 | 0.67 | 0.58 |
| | Vaginal delivery | 368 | 67,60 | | | |
| **Meconium stain mother & medical report** | Meconium stain | 52 | 69,10 | 512 | 1.00 | 0.26 |
| | No meconium stain | 462 | 67,61 | | | |
| **Total first minute APGAR based on mother & medical report** | Total first minute APGAR below 7 | 63 | 70,51 | 326 | 3.03 | **0.00*** |
| | Normal APGAR | 265 | 66,29 | | | |
| **Rh immunization** | Rh immunization | 29 | 68,69 | 526 | 0.51 | 0.91 |
| | No RH immunization | 499 | 67,71 | | | |
| **Miscellaneous acute PDICs** | At least one miscellaneous acute PDICs | 77 | 68,69 | 501 | 1.06 | **0.00*** |
| | No miscellaneous acute PDICs | 426 | 67,68 | | | |
| **Miscellaneous chronic PDICs** | At least one miscellaneous chronic PDICs | 113 | 66,15 | 503 | 0.98 | 0.77 |
| | No miscellaneous chronic PDICs | 392 | 68,15 | | | |

Significance was set at $p = .05$; significant differences are indicated in bold

Neither acute nor chronic complications were significantly correlated with each other. Acute miscellaneous complications showed a weak correlation to total first minute APGAR below 7 which could probably be due to the fact that we included acute hypoxemic events such as neonatal respiratory distress, and cyanosis in this group. Chi-square result needed?

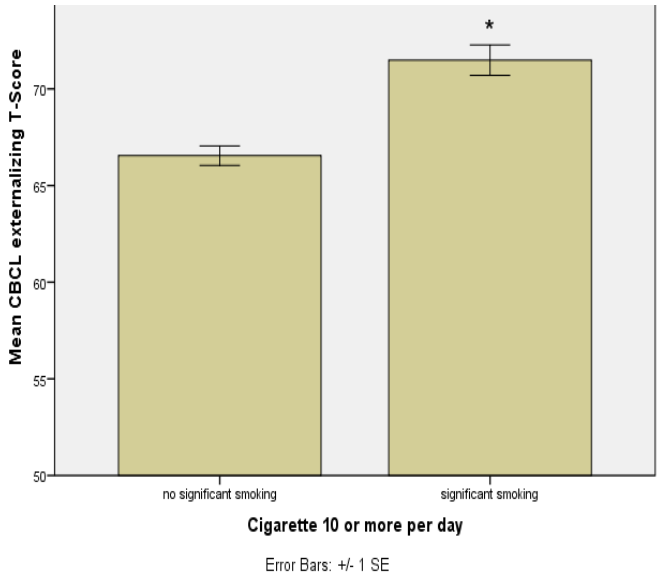
Linear regression analysis was used to individually evaluate the effect of each complication on CBCL- externalizing T score. Only cigarette smoking with score 4 and above (10 or more cigarettes per day), total first minute APGAR below 7, and annual income less than 30,000$ revealed an effect on CBCL-externalizing T score (Table: 8 and graphs: 6 & 7). As shown in this study, combination of acute and chronic complications had an effect on CBCL- externalizing T score when compare to control group.

**Table 8:** linear regression of symptom severity in children with attention deficit/hyperactivity disorder by Apgar score, income, and maternal smoking

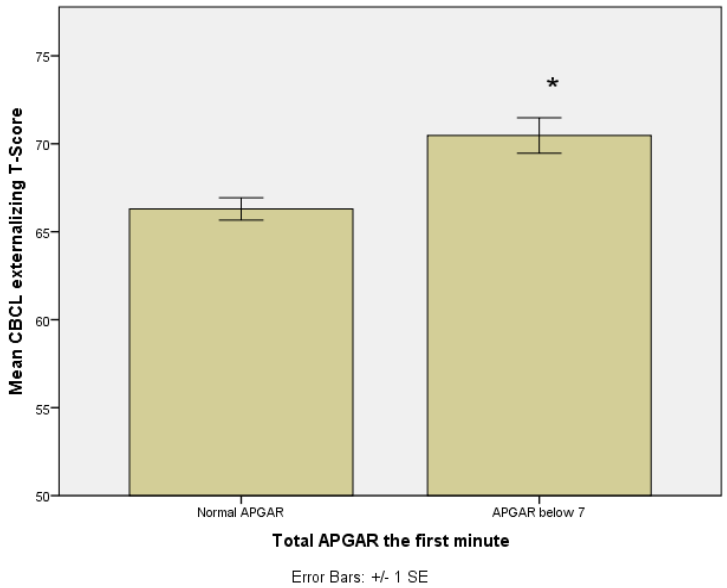
| | | B | (SE) | *P* value |
|---|---|---|---|---|
| **CBCL externalizing T-score** | First minute total APGAR below 7 | 3.48 | 1.4 | **0.01*** |
| | Income | 5.11 | 1.2 | **0.00*** |
| | Maternal smoking | 3.02 | 1.4 | **0.04*** |

Significance was set at $p = .05$; significant differences are indicated in bold

**Graph 6:** CBCL externalizing t score for ADHD children exposed to smoking with 10 cigarette or more per day compare to non exposed ADHD children. * =significant




**Graph 7:** CBCL externalizing t score for ADHD children exposed to first minute APGAR below 7 compare to non exposed ADHD children. * =significant



# CHAPTER V

## Discussion

### 1 Part A

The main goal of the present study was to investigate whether duration of exposure to PDICs that may reflect a larger cumulative "dose" or higher probability of a "dose" occurring mostly during gestational period could affect the symptom dimension of ADHD in exposed children. We compared the effects of chronic, acute or both chronic and acute complications with a control group and within groups on symptom severity in children with ADHD.

Regarding possible effect of exposure duration on the brain development early in life, we hypothesized that children with ADHD, who were exposed to chronic or both chronic and acute PDICs may represent a more homogenous subgroup with a distinguished phenotypic signature compared to children with ADHD who were not exposed to any complications or only to acute complications.

To this end, we investigated the effect of chronic and acute complication as categorical variables, on a few behavioral outcome measures in children with ADHD to provide a comparative profile of children exposed to chronic versus either acute or both chronic and acute, and comparison to non-exposed children. For this comparison, we meticulously controlled for potential socioeconomic status, ethnicity, mother's age at child birth, mother's years of education, and gender of child, and age.

Given the importance of duration of exposure to PDICs in development of ADHD (Marllard et al., 1998) demonstrated that the prolonged period of placental insufficiency inducing chronic fetal hypoxemia can affect neurodevelpmental process such as

myelination and growth of the cerebellum late in gestation. This chronic prenatal damage can also result in neuronal disconnectivity and subsequent brain dysfunction after birth (Mallard ., 1998). Moreover, since a reduction in cerebral white matter which is very often observed in ADHD individuals was shown to be associated to repeated hypoxemia. This chronic hypoxemic exposure during development may contribute to an increased risk of ADHD-like hyperactivity and cognitive deficit as well (Castellanos et al., 2002).

To the best of our knowledge, previous studies have not examined the significance of duration of exposure by comparing chronic versus acute PDICs with respect to sympotom severity in children with ADHD. In our sample of 525 children with ADHD, we observed that the chronic complications along with acute complications can cause more severe symptoms.Particularly , the ADHD children exposed to both chronic and acute complicatons had higher score for extenalizing behaviour as measured by CBCL.

We examined several chronic and acute complications in this study, and could conclude that neither chronic nor acute PDICs alone could result in more severe ADHD in terms of externalizing behaviour. A previous study demonestrated that chronic materno-fetal infection makes the brain even more vulnerable to mild hypoxic exposure by producing pro-inflammatory cytokines (Kendall & Peebles., 2005). In this study, it is possible that chronic exposure could have reduced the threshold at which acute complications with very short duration can severly affect the child's brain. Having both chronic and acutr complications would increase the severity of symptomatology.

As it was mentioned earlier, previous invistigations suggested APGAR below 7 as a risk factor for the development of ADHD in children (Li et al., 2011). However, in their

studies, exposure to any chronic complications mostly occuring during pregnancy was not considered, which may make the brain more sensetive to adverse effect of APGAR below 7, and subsequently development of ADHD later in life.

**1 Part B**

In addition to comparing the effect of complications on the symptom dimension of ADHD in children with respect to the duration of exposure, we further investigated the effect of individual complication regardless of their chronic and acute state on ADHD symptoms severity measured by externalizing CBCL.

As it was mentioned earlier, previous investigations have clearly identified a strong association between an elevated risk of being diagnosed with ADHD and exposure to early life environmental risk factors such as pregnancy, delivery, and neonatal risk factors. For early life environmental risk factors, evidence from animal and human studies have showed that prenatal tobacco exposure (Linnet et al, 2003), prenatal and postnatal drug exposure (Figueroa., 2010), lead exposure (Froehlich et al., 2009), and pregestational and gestational diabetes (Ornoy et al., 2001) are associated with increased risk of ADHD in children. Although, pathophysiology of early life environmental risk factors is not yet clearly understood, but most of these risk factors appeared to be associated with hypoxic injury during fetal development. It has been shown that significant functional and structural brain injury particularly in striatal region can be caused by a pregnancy, delivery, and neonatal period complications due to asphyxia (Krägeloh-Mann et al., 1999). Earlier studies showed that the prolonged period of placental insufficiency inducing chronic fetal hypoxemia can affect neurodevelpmental process such as myelination and growth of the cerebellum late in gestation (Mallard et al.,

1998). Of those complications, both fetal hyperglycemia and fetal hyperinsulinemia can independently result in fetal hypoxemia by increasing fetal oxygen consumption and inflammatory response in placentas (Teramo et al., 2013; Li et al., 2013). One study that examined possible factors in the development of cerebral palsy showed that the chronic infection during pregnancy can cause hypoxemia through different inflammatory processes and also reduce threshold at which hypoxemia becomes neurotoxic. Regarding those investigation, it could be concluded that the hypoxemic events by itself and those complications resulting in hypoxemia are more likely associated with the increseaed risk of ADHD in children. Thakur et al (2012) showed that the children with ADHD exposed to tobacco presented more severe ADHD symptoms and higher level of co-morbidities. Howevere, to our knowledge, the association between individual PDICs and different phenotypic signatures among ADHD children has not yet been studied.

Our study reinforce the importance of hypoxemic injuries as shown by smoking more than 10 cigarettes per day (chronic complication) and APGAR below 7 at first minute (acute complication), are associated with higher score in externalizing CBCL. Although, based on previous reports gestational diabetes, hyperinsulinemia and chronic materno-fetal infection could result in increased risk of ADHD due to compromised oxygen delivery or increased oxygen consumption. We demonstrate that the effects of maternal smoking and APGAR below 7 at first minute are prominently related to insufficient fetal oxygenation in a chronic and acute fashion respectively and are the most significant among all examined complications for ADHD severity. Since this study showed no correlation between smoking and APGAR below 7 at first minute, these could independently affect symptom dimension of ADHD. Moreover, no correlation between

smoking and other PDICs was found in our study therefore, possible causal effects between smoking and more externalizing problems in ADHD could be postulated.

Compared to previous studies with similar experimental design, this study has the following strengths. First, to our knowledge, this is the largest and the most comprehensive study comparing neuropsychological profiles of children with ADHD stratified according to their exposure to chronic, acute, and both chronic and acute PDICs. Second, using Kenney Medical Gynecological Questionnaire allowed us to examine and rate most of the PDICs in this study as well as the number of complications considered in this study is unique. Third, our sample size was among the largest sample size in terms of ADHD studies reported so far. Finally, all neurobehavioral assessments were carried out while children were not taking any medication.

Some limitations should also be considered when interpreting results of this study. Since, it is a retrospective study; one major limitation is our reliance on maternal recall to evaluate complications during pregnancy, delivery, and infancy as well. To minimize recall bias in this study, Kinney Medical and Gynecological Questionnaire were corroborated with medical and hospital obstetrical records whenever available. Furthermore, mothers are more likely to underreport the number of cigarettes smoked during pregnancy. Although, smoking behavior of mothers during pregnancy was usually corroborated with a close family member and the medical notes on the pregnancy if available, this may reduce our accuracy to detect smoking during pregnancy with score 4 and above. Another limitation is the lack of information on familial psychopathology, particularly history of ADHD in the mothers. Given that ADHD has a strong genetic component, and the same gene may contribute to increased risk of smoking behavior.

Therefore, it could be concluded that the mothers with ADHD may be more vulnerable to smoking during pregnancy and may have children with more severe ADHD. In this study, we could not include a quantitative measure of each complication during pregnancy, delivery, and infancy with the average number of scores assigned for each complication based on the severity level.

**3 Research implications**

The data presented above raises a number of important research questions:

- Do chronic complications particularly chronic hypoxemia events such as smoking make the brain more vulnerable to acute hypoxemia events such as low APGAR resulting in more severe ADHD?
- Does prevention of complications resulting in chronic hypoxemia such as smoking confer neuroprotection?

**4 Conclusions**

It is clear that brain injury occurring early in life encompasses a number of maturation-dependent pathology with multifactorial etiologies. These results suggest that the exposure of both chronic and acute PDICs together is associated with more severe form of ADHD manifested by higher score in CBCL-total externalizing. Of chronic and acute PDICs, smoking during pregnancy and total APGAR below 7 at one minute resulting in hypoxemia in the fetus had more significant effect on dimension of ADHD symptoms. In addition, it is possible that the chronic exposure to hypoxemia makes the brain more vulnerable to acute hypoxemia event such as low APGAR.

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APPENDIX

**Chronic Complications during Pregnancy with severity level of four and above**

1. **Diabetes Related- Condition**:

   A) **Hyperglycemia**: normal Fasting Blood Glucose level (Below 6.7 mmol per liter) but pathological glucose tolerance test (7.8-11.1 mmol per liter)*

   B) **Pregnancy Diabetes**: Over 6.7 mmol per liter fasting and over 11.1 mmol per liter on glucose tolerance test*

   C) **Pregnancy Diabetes:** NOS*

   D) **Preexistent Type 1 Diabetes,** well controlled during pregnancy or NOS*

   E) **Preexistent Type 1 Diabetes,** not well controlled ****

2. **Maternal Smoking**

   A) **10-20** Cigarettes per day*

   B) **Over 20** Cigarettes per day**

**Chronic Complications during Infancy with severity level of four and above:**

1. **Gestional Age at Birth**

A) **Preterm**, Less than end 37$^{th}$ week (34-37 wk)*

B) Less than end 35$^{th}$ week (34-35 wk)**

C) **Very Preterm**, Less than end 33 $^{th}$ week or earlier ***

D) **Postterm,** More than 42 $^{th}$ week *

**Acute Complications during Labour and Delivery with severity level of four and above:**

1. **Premature Rupture of Membrane**

A) Rupture of Membrane more than 24 hours before deliver

2. **Prolonged or precipitous Labour Based on Duration of Total Labour Including Phase I and II and parity**

A) **Prolonged**, Duration for nullipara is over 16 h and for primapara over 10 h*

B) **Very Prolonged,** Duration for nullipara is over 23h and for primapara over 16h**

C) **Definitely Precipitous,** Duration for the nullipara and for the primapara is one hour or less*

3. **Operation Delivery or Intervention**

A) **C-Section**- elective*

B) **C-Section-** emergency**

C) **C-Section**- NOS*

D) **Vacuum extraction-** mid (head at spinal plane or below), extraction duration less than 15 minute*

E) **Vacuum extraction-** mid (head at spinal plane or below), extraction duration more than 15 minute**

F) **Forceps**- low (cervix completely dilated, head fully rotated and above pelvic floor)*

G) **Forceps**- mid (head at spinal plane or below)**

H) **Forceps-** high (head above spinal plane)***

I) **Forceps**- NOS*

J) **Instrumental Delivery**- NOS*

K) **Operative Delivery**- NOS*

**4. Meconium**

A) Meconium in amniotic fluid in **Non-breech** presentation with normal **FHR****

B) Meconium in amniotic fluid in **Non-breech** presentation and NOS regarding **FHR** normality****

C) Meconium in amniotic fluid and NOS regarding **breech** presentation and **FHR** normality*

**5. Pathological Cardiotocographic patterns**

A) **Tachycardia** (more than 160 beats per min) with silent pattern*

B) **Late deceleration** ( onset more than 30s after onset uterine contractions)*

C) **Combined deceleration** including early and late*

D) **Variable deceleration** with silent pattern and pattern change*

E) **Prolonged deceleration** ( fewer than 80 beats for more than 2 min ,or fewer than 100 beats for more than 3 min)*

F) **Abnormal Cardiotographic** NOS*

**<u>Acute Complication during Infancy with severity level of four and above</u>**

**1. Abnormal APGAR**

A) APGAR score 0-3 at 1 min**

B) APGAR score 4-7 at 1 min*

C) APGAR score 0-3 at 5 and or 10 min***

D) APGAR score 4-7 at 5 and or 10 min**

E) Low APGAR score NOS**

*Severity Level 4, ** Severity Level 5, *** Severity Level 6

Severity level 4, 5, and 6 are potentially clearly, potentially clearly greatly, and very greatly harmful to fetus brain, respectively.

Severity Level 4 and above is considered in this project.