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Risk of Child ADHD and Low Birth Weight: A Systematic Review Study

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Abstract

Background: Attention deficit hyperactivity disorder (ADHD) and its possible causes still attract controversy. Genes, pre and perinatal risks, psychosocial factors and environmental toxins have all been considered as potential risk factors. The objective of this study was to evaluate an association between low birth weight (LBW) and attention-deficit hyperactivity disorder (ADHD).

Method: This systematic review was conducted through medical database, ISI Web of Knowledge, PubMed, Scopus, Medline, Embase, Google Scholar, and Cochrane for peer-reviewed, cross sectional, cohort studies assessing the correlation between child ADHD with Low birth weight (LBW) from 2005 to 2019 without language restriction. Keywords were selected based on the Mesh terms.

Results: From all 126 articles which were totally found, only 19 studies with 15 to 22 scores from STROBE checklist remained in the study for final assessment. Five studies assessed the relationship between VLBW and ADHD, one study the relationship between ELBW and ADHD, and another one between VLBW/ ELBW and ADHD. Significant correlations had been reported between LBW and ADHD in 7 studies, between VLBW and ADHD in 5 studies, and between ELBW and ADHD in 1 study. Nevertheless, some researchers had reported no significant correlation between LBW and ADHD in 5 studies and between VLBW and ADHD in 1 study.

Conclusion: Birth weight seems to have a decisive role in the development of attention deficit hyperactivity disorder in children. Specific prevention and management interventions are required to reduce the incidence of ADHD.

Key Words: Attention deficit hyperactivity disorder, Child, Low birth weight.

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1- INTRODUCTION

Children's health affects the health of society and future generations (1). Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by difficulty in paying attention, or having excessive activity and acting without regards to consequences, which are not appropriate for the person's age and occur repeatedly (2). Prevalence of ADHD in children and adolescents is estimated, respectively, as 3/4 and 5/3 percent worldwide (3-4). This disorder probability lasts into adulthood and its prevalence is about 2/5 percent among adults (5). compared with children who are normally developed, these patients show lower self-confidence, academic failure, social harm, antisocial behavior, addiction and also face with many conflicts of non-cash offences and accidents, which cost a lot of money for communities (6-7).

Factors influencing in ADHD creation are maternal factors, such as psychological (stress and anxiety), maternal disorders (diabetes), smoking, alcohol consumption during pregnancy and low social economical level; along with neonatal factors, such as preterm labor, low birth weight rate, asphyxia and low infant weight (8-10). According to some studies, this disorder has been reported mostly in boys weighing less than 2500 grams, but there is still no consensus on this issue (11-15). On the other hand, preterm delivery and the damages it causes to the nervous system increase its incidence among school age children (1-11-14-16). Numerous studies in different parts of the world have noted the relationship between being underweight and ADHD, so that Low Birth Weight has become known as one of the strongest risk factors of ADHD (14-17-18). Sengupta et al., show that social and environmental factors can affect the relationship between LBW and ADHD as an interfering variable (19). Yet in different studies, conflicting results have been reported regarding the correlation between LBW and ADHD (18-19). Pettersson et al. (2015), did not find any relationship (20), however, Groen-Blokhuis et al. (2015), observed a connection between these two variables (21). A number of researches have suggested the influence of genetic and multifactorial agents on the incidence of ADHD (20-22-23-24).

According to some studies, the formation of abnormal neural pathways and the abnormal release of neurotransmitters in neural pathways can cause ADHD in childhood (25-26). One of the genetic risk factors is having the parents who have ADHD, which is, per se, related to the increase in LBW and incidence of ADHD. However, the role of genetic factors is still unknown because of the limitations in measurement and control methods (27).

More than 30 million low birth weight babies are born each year worldwide and More than 50% of them are born in South Asia (28). Some studies conducted in Iran, reported the prevalence of LBW to be between 3-10% (29-30). Given the medical advances in prenatal and postnatal care over the past few decades, survival of most premature infants with low or even very low weight has become possible (31-32). More than Eighty-five percent of under 38-week premature or very low birth weight babies survive, but half of them suffer from disorders such as growth retardation and delay in the development of motor and cognitive skills (32-33). Shariati et al. (2017), showed that in Intra Uterine Growth Retarded fetus, degrees of damage happen to nerve cells and neurons during pregnancy and childbirth because of ischemia- hypoxia. This leads to an increase in dopamine production in the brain. It can increase the incidence of ADHD in these children. This retrospective study also has mentioned that LBW[1], VLBW[2] (under 1500 grams),

ELBW (under 1000 grams), and IUGR are correlated with ADHD (33). Other studies have shown an association between IUGR, the developmental disorders of the nervous system and ADHD (32-34). Due to the increased survival of children born with low birth weight, ADHD is more diagnosed in school time (11-35). Therefore, early detection of this disorder in childhood and its control can prevent many of the harms of schooling and social interactions. Despite the fact that the relationship between LBW and ADHD is still controversial, no systematic review has been conducted for analyzing the relationship between low birth weight factor and ADHD symptoms in children (36) The present systematic review was, thus, conducted to investigate the relationship between low birth weight and the incidence of ADHD.

2- METHODS

Studies reviewed in this paper were cross sectional and cohort studies assessing the relationship between child ADHD and Low birth weight (LBW). The articles, published since the beginning of 2005 till May 2019, were evaluated without any language restriction.

We included studies with children, less than 8 years of age, for whom one of the following conditions was diagnosed: low birth weight (LBW), very preterm (VP), extremely preterm (EP), very low birth weight (VLBW), and extremely low birth weight (ELBW) or extremely low birth weight (ELBW). In addition, ADHD identification must have been confirmed based on the DSM-III; DSM-III-R; DSM-IV; or DSM-5 criteria, Third Edition. Furthermore, Clinical evaluations must have been accomplished with CBCL[2] validated instrument. This scale was included because this is a part of the 2 best-known instruments for assessing psychopathology in children, and its accuracy has been tested for ADHD symptomatology (19).

The bibliographic search included the Web of Science, Scopus, Medline, Embase, Google Scholar, and Cochrane databases. To find related articles in databases, the keywords were selected based on the Mesh terms , which included ADHD, Attention deficit hyperactivity disorder, Inattention disorder, Attention problem, Birth weight, Low birth weight, Very low birth weight, Extremely low birth weight, Small for gestational age, Poor fetal growth, LBW, VLBW, ELBW, and SGA, which were combined by “OR” and “AND” Boolean operators. The search strategy for each database can be found in Supplemental **Table 1**.

PRISMA systematic study reporting system was used in all stages of study research. All articles were reviewed by two independent researchers. In addition, papers presented at national seminars and congresses, and dissertations related to the study issue were reviewed, and if the abstracts only were available, for getting access to the full article file, we e-mailed to their corresponding authors.

The 2-stage article selection process started with title and abstract reviewing done by 2 independent reviewers (S.H.A., M.A). They read the titles and abstracts and included studies which conformed to the inclusion and exclusion criteria. Any differences were resolved between the reviewers. An independent reviewer (E.Z) worked as referee if concord could not be gained. The process terminated with full text screening: 3 independent reviewers (S.H.A., M.A and E.Z) read the full text of the studies elected in step 1 to determine if the inclusion criteria were met. At this point, any differences were solved between the reviewers. A third reviewer (S.H.A.) worked as referee if agreement was not achieved.

Data were selected and twice controlled by 2 reviewers (S.H.A. and E.Z), with a third reviewer (M.A.) working as referee. When the selected article was confirmed with all reviewers, the inclusion criteria were used: (1) child age less than 8 years old, (2) enough sample size, (3) cross sectional and cohort study, (4) studies having quality

[2] . Child Behavior Checklist

scores of 19-22 with STROBE check list (37).

We gathered the following data from each of the selected studies: first author and year of publication; year of data collection; study design; presence of multiple births; mean age (weeks) and mean weight (grams) at birth; sex; mean age or age range at ADHD assessment; Source of information (self-report, parents or teachers); the name of the ADHD rating scale.

LBW was defined as birth weight 2000-2500g, VP and VLBW were defined as gestational age <32 weeks and birth weight 2000-1500 g, and EP and ELBW were defined as gestational age<28 weeks and birth weight 1000-1500 g.(20).

The primary outcome was defined as ADHD. The diagnosis could have been established through structured diagnostic interviews with parents or child subjects. The ADHD rating scales were filled out by child, parents, and/ or teachers.

All studies candidated for data extraction were separately evaluated for bias. Two researchers (S.H.A. and E.Z.) individually rated the studies according to the guidelines for strengthening the Reporting of Observational studies in Epidemiology (STROBE), which provide a readily available checklist to ensure a clear presentation of what was planned and conducted in an observational study. This checklist has 22 items. Item (1) is related to the title of the article, items (2 and 3) are related to introduction, items (4-12) to method, items (17-13) to results, items (21-18) to discussion and conclusion and finally, item (22) is about other information. Articles with a minimum score of 15 and a maximum score of 22 are considered to have the necessary quality to evaluate and enter to the study (37). Consequently, 5 articles were excluded from the study, based on STROBE guidelines; four of these articles considered the Difference of ADHD incidence in male and female children with LBW (1, 19, 22, and 32), and one article assessed ADHD incidences among male and female children with VLBW (43).

2-1. Ethical Considerations

The Midwifery and Reproductive Health research center funded this research project. This study was the result of a research project carried out at the Center for Midwifery and Reproductive Health of Shahid Beheshti University. This study was approved by the ethics committee with code of ethics IR. SBMU. PHARMACY. REC. 1399. 116.

3- RESULT

Of 126 references identified in the literature search, 107 articles were excluded due to the following reasons: 56 articles were published in two separate journals or in two different languages, 5 articles' authors didn't answer to E-mail for sending the full-texts, 13 articles considered ADHD in adolescence, in 2 articles the mothers used anti-depressants during pregnancy, 5 articles were meta-analysis, 2 articles were systematic review, 1 article was a poster presentation, 12 articles considered ADHD in adults, 5 articles did not achieved the quality scores based on the STROBE guide lines, and 4 articles evaluated ADHD in children more than 8 years old (Fig. 1). At last 19 studies with 15 to 22 scores from STROBE checklist remained in the study for final assessment (Table 2). All of these articles were published from 2006 to 2017. Among them, 1 study was cross-sectional, 1study was case-control and 17 were cohort studies. All studies used the Child Behavior Assessment Checklist (CBCL) to assess ADHD in children.

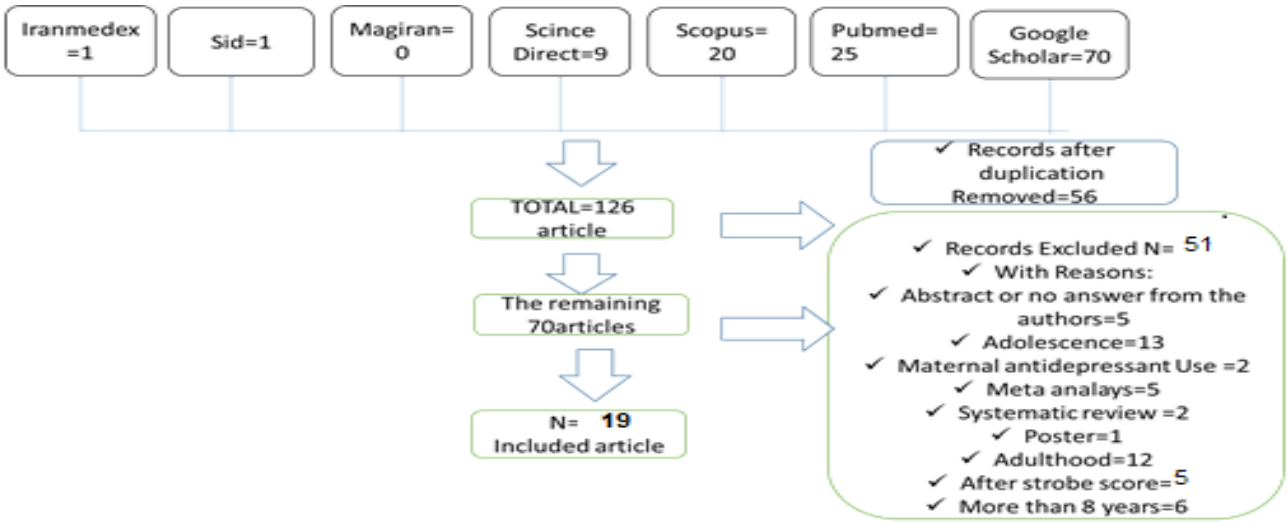
Table-1: Keywords in PubMed Database

LBW	((low birth weight)[tiab] OR (LBW)[tiab])[Mesh Terms] OR (birth weight)[tiab] OR (BW)[tiab] OR (very low birth weight)[tiab][Mesh Terms] OR (VLBW)[tiab] OR (extremely low birth weight)[tiab] [Mesh Terms] OR (ELBW)[tiab] OR (small for gestational age)[Mesh Terms] OR (SGA) [Mesh Terms] OR (poor fetal growth)[tiab] OR (intra uterine growth restriction)[tiab] OR (IUGR)[tiab] OR (growth restriction in uterus)[Mesh Terms] OR (intra uterine growth retardation)[tiab] OR (birth weight under 2500 g)[tiab] OR (birth weight<2500g)[Mesh Terms] OR (birth weight under 1500g))[Mesh Terms] OR (birth weight under 1500g)[tiab] OR (birth weight <1500g)[tiab] OR (birth weight under 1000g)[Mesh Terms] OR (birth weight under1000g)[tiab] OR (birth weight<1000g)[tiab]
ADHD	(Attention deficit hyperactivity disorder)[Mesh Terms] OR (Attention deficit hyperactivity disorder)[tiab] OR (ADHD)[tiab] OR (attention problem in child)[tiab] OR (child attention problem)[tiab] OR (Inattention disorder)[tiab] OR (child Inattention disorder)[tiab] OR (Inattention disorder in child)[tiab] OR (child hyperactivity)[tiab] OR (hyperactivity in child)[tiab] OR (child Attention deficit hyperactivity disorder)[tiab] OR (Attention deficit hyperactivity disorder in child)[tiab] OR (hyperactivity disorder)[tiab] OR (child hyperactivity disorder)[tiab] OR (attention deficit)[tiab] OR (attention deficit disorder)[tiab] OR (child attention deficit)[tiab] OR (attention deficit in child)[tiab] OR (attention deficit disorder in child)[tiab] OR (child attention deficit disorder)[tiab]

Twelve studies considered relation between LBW and ADHD among children (1,11,12,15,19,20,22,32,33,38,44,45), Five studies evaluated the relationship between VLBW and ADHD (21,39,41-43), one study assessed the relationship between ELBW and ADHD(46) and one study evaluated VLBW/ ELBW and ADHD(40). The participants' mean age were 5 years old. The mean of gestational age in LBW was 34w± 2d, in VLBW was 30w±2d and in ELBW was 26w±6d. Participants' mean normal weight at birth was 3170 gr, females mean normal weight at birth were 2980 gr, males mean normal weight at birth were 3150 gr, in LBW mean weight was 2340 gr, in females LBW mean weight was 2130 gr, in males LBW mean weight was 2070 gr, in VLBW mean weight was 1680 gr, in females VLBW mean weight was 1674 gr, in males VLBW mean weight was 1634 gr, and in ELBW mean weight was 1033 gr. Patients age ranges in 7 studies were between 6-8 years (1,22,32,40,41,43,46), in 7 studies between 4-6 years (15,19,20,33,38,39,42) and in 5 study between 2-4 years (11,12,21,44,45). 5 studies had considered the gender variable in their analyses (1, 19, 22, 32, 43). The age and birth weight ranged from 28weeks ±6 days (46) to 39 weeks ±6 days (38) and from 1033(46) to 3500 gr respectively (44). 7 studies had found significant relationships between LBW and ADHD (1, 15, 22, 32, 38, 44, 45), 5 studies between VLBW and ADHD (11, 39, 40, 42, 43) and 1 study between ELBW and ADHD (46). In 5 studies, the researchers had reported no significant relationship between LBW and ADHD (12, 19, 20, 21, 33) and in 1 study between VLBW and ADHD (41). 3 studies had found significant relationships between sex and ADHD (1, 22, 43), while 2 studies had reports regarding no significant relationships between these variables (19,

32). The range of CBCL scores among children with normal weight at birth was 51-60, among children with LBW, 63-66, among children with VLBW 67-70 and among those with ELBW was 71. The mean average of CBCL score among children with normal weight at birth was 55.5, among children with LBW 65.7, and among children with VLBW was 67.5. The range of CBCL score among females with normal weight at birth 54-59, among females with LBW 58-65, and among females with VLBW was 67. The range of CBCL score among males with normal weight at birth 58-59, among males with LBW 59-66, and among males with VLBW was 70. The mean average of CBCL score among females with normal weight at birth 56.6, and among females with LBW was 62.25. The mean average of CBCL score among males with normal weight at birth 58.6, and among females with VLBW was 63.75.

Fig. 1: Study selection flowchart



4- DISCUSSION

In this systematic review, we evaluated the risk of LBW/VLBW and ELBW individuals in developing ADHD. The 13 evaluated studies including a total of 6604 subjects, overall, suggested that LBW/ VLBW and ELBW individuals are more likely to be related with ADHD than term-born controls. VLBW was more strongly correlated with ADHD than was LBW; and respectively ELBW showed a stronger correlation than did LBW and VLBW. But in a study by Van der Meere et al., no significant relationship was reported between VLBW and ADHD (41). The reason for the difference in the results of this study with other studies can be due to the small sample size (N=90) and method of that study (case-control). Furthermore, 13 large-effect studies on ADHD symptoms demonstrated that inattention, hyperactivity, and impulsivity symptoms are correlated to LBW and VLBW newborns. Furthermore, 3 studies demonstrated the predominance of ADHD in male subjects in both LBW and VLBW groups (1, 22, 43), while 2 studies reported no difference between females and males in ADHD (19, 32). However, it is generally claimed that ADHD is typically associated with a high prevalence among male subjects in the general population (43). A number of studies have indicated that preterm-born individuals with ADHD have phenotypic specificities that differ

from their non-premature ADHD peers. These include a dominance of inattention symptoms, less psychiatric comorbidity, higher diagnostic consistency from childhood to adulthood, more perinatal clinical or neurologic complications, and major inabilities. Moreover, the predominance of male subjects, which is typically seen in non-premature ADHD, was also not observed in preterm subjects (19). It is important to consider that our findings confirming the existence of a strong risk of LBW and VLBW subjects in expanding ADHD are like those found in other behavioral and psychiatric disorders. In a previous systematic review and meta-analysis, Burnett et al. demonstrated that a prevalence of any psychiatric diagnosis in preterm or LBW subjects was 3.66 times higher (95% CI 2.57 to 5.21) than NBW controls (9). The causes of higher vulnerabilities of preterm or LBW subjects to ADHD and behavioral and psychiatric difficulties stay unclear. However several hypotheses have been recommended. These include pre- and post-natal difficulties, such as the environmental issues, as well as parental and biological problems such as hypothalamic-pituitary-adrenal axis dysregulations and perinatal systemic inflammation, which could cause functional and structural brain dysfunction such as ADHD and other psychiatric and developmental disorders (3, 4, 9).

Certain limitations should be taken into consideration when explaining our findings. First, a number of studies were excluded due to their data expression formats (such as different classification for prematurity or birth weight levels). Second, many articles were excluded during the eligibility phase for not using validated diagnostic instruments or the CBCL. Third, although excluding gray literature from our review, the OPEN consortium (48) indicated in a recent systematic review that the exclusion of these studies has an insignificant impact on effect sizes. Fourth, Among the 19 included studies, only the one by Van der Meere et.al. (41) followed a case-control design. In case- control studies, the variables could vary because of different determinant profiles (49). As for the strengths of our review, we performed a broad literature search of cohort, case-control, and cross sectional studies with no language restriction, allowing us to find a substantial number of articles. Most importantly, our strict inclusion criteria allowed only studies with a well-defined ADHD diagnosis and LBW, VLBW and ELBW in the systematic reviews.

5- CONCLUSION

In conclusion, our findings demonstrate strong evidence that LBW and VLBW subjects have a raised risk of ADHD, and there is an even stronger risk among the ELBW group. In terms of clinical usage, we recommend that premature, LBW, VLBW and ELBW infants need specific pediatric, psychiatric, and neonatology prevention and management interventions to reduce the ADHD bar. In addition researchers in this field should elucidate specific reason determinatives related with prematurity, LBW, VLBW and ELBW that could conducted to the extension of ADHD.

6- CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

Table-2: Summary of the evaluated studies (2005-2019)

Row	Author, Year	Mean Age at Birth, wk	ADHD Scale Mean (SD)	Age at Evaluation, (years)	Type of study	weight at Birth(gran) Mean(SD)	Sample	Relation between birth weight& ADHD	Relation between ADHD & sex	STROBE
1	Anderson Et al (2011)	ELBW=28W±6 NBW=38W±6	ELBW=71±8.34 NBW =60±8.13	6-8	Cohort	ELBW=1033 ±164 NBW=3100±253	ELBW= 283 199 = NBW	P<0/0001	-	21
2	Ochiai Etal (2015)	Male(VLBW)=30w0d Female(VLBW)=29w ±5d Male(NBW)=38w±2d Female(NBW)=38w± 5d	Male (VLBW)=70.98± 7.1 Female(VLBW)=67.78±5.2 Male(NBW)=59.12±2.6 Female(NBW)=57.32±1.2	6-8	Cohort	Male(VLBW) =1634 ±110 Female(VLBW)=1 674±115 Male(NBW)=3160 ±123 Female(NBW)=29 50±110	Male (VLBW)=45 Female(VLBW) =32 Male(NBW)= 34 Female(NBW)= 35	P<0.001	P<0.001	18
3	Huang Et al (2012)	LBW=34w±3d NBW = 39±6d	LBW =64.73±6.8 NBW = 57.60±1.8	4-6	Cohort	LBW= 2000±150 NBW = 3100±220	LBW = 844 NBW =870	p=0.006	-	19
4	Shariat Et al (2017)	LBW =33w±6d NBW= 38±6d	LBW =60.13±8.12 NBW=59.94±7.53	4-6	Cohort	LBW = 2000±108 NBW= 2980±170	LBW =124 NBW=105	P=0. 3	-	22
5	Groen-Blokhuis Et al (2011)	Male(LBW) 33w±2d Female(LBW)= 33w ±3d Male(NBW)=36w± 6d Female(NBW)= 37± 2d	Male(LBW) = 65.2 ±8.3 Female(LBW)= 63.1 ±3·9 Male(NBW) = 59.6 ±9.3 Female(NBW)= 55.7 ±9·9	6-8	Cohort	Male(LBW)= 2130±40 Female(LBW)= 2070±83 Male(NBW)=3050 ±103 Female(NBW)=29 50± 109	Male(LBW)=32 0 Female(LBW)= 350 Male(NBW)= 340 Female(NBW)= 350	P<0.001	P<0.001	22
6	Sucksdorff Et al (2015)	LBW=35w±1d NBW= 38±3d	LBW=66.73±8.42 NBW=55.24±7.53	3-4	Cohort	LBW= 2100±98 NBW= 3100±70	LBW=321 NBW=355	P=0.01		21

Row	Author, Year	Mean Age at Birth, wk	ADHD Scale Mean (SD)	Age at Evaluation, (years)	Type of study	weight at Birth(gran) Mean(SD)	Sample	Relation between birth weight& ADHD	Relation between ADHD & sex	STROBE
7	Verkerk Etal (2014)	VLBW=30w±4d NBW=39w± 2d	VLBW =67.3 ±6.8 NBW=59.9 ±2.7	5-6	Cohort	VLBW = 1890±70 NBW= 3150±65	VLBW=51 NBW=41	P=0.005	-	22
8	Sengupta Etal (2006)	NBW(Male)=38±3 LBW(Male)=35w±4d NBW(Female)=38w± 5d LBW(Female)=35w± 5d	NBW(Male)=58.41±1.3 LBW(Male)=59.34±3.9 NBW(Female)=58.32± 1.5 LBW(Female)=58.11± 0.5	5-6	Cohort	NBW(Male)=3260 ±110 LBW(Male)=2010 ±20 NBW(Female)=30 90± 220 LBW(Female)=20 80±90	Male(LBW)=75 Female(LBW)= 69 Male(NBW)= 76 Female(NBW)= 78	P= 0. 2	P= 0. 1	21
9	Pirdehghan Et al (2015)	NBW(Male)=39±1 LBW(Male)=34±5 NBW(Female)=39± 3 LBW(Female)=35± 1	NBW(Male)=58±0.3 LBW(Male)=66.2±4.2 NBW(Female)=54.1± 1.1 LBW(Female)=63.2± 1.3	6-8	Cohort	NBW(Male)=3150 ±180 LBW(Male)=2010 ±20 NBW(Female)=28 70± 150 LBW(Female)=21 80±90	Male(LBW)=63 Female(LBW)= 65 Male(NBW)= 72 Female(NBW)= 71	p=0.04	P=0.02	21
10	Kallankari Et al (2015)	LBW =34w±2d NBW =38w±4d	LBW=65.2±8.7 NBW= 57. 1±1.2	4	Cohort	LBW = 2090±100 NBW= 3080±150	LBW =143 NBW=136	P=0.001		21
11	Pettersson Et al (2015)	LBW =33w±3d NBW =37w±6d	LBW =59.4±5.5 NBW= 58.3±2.2	4	Cohort	LBW=2147±104 NBW=3150±80	LBW=143 NBW=146	P=0.1	-	22
12	Strang-karlsson. Et al (2008)	NBW=37w±2d LBW=33w±1d	NBW=58.7±2.7 LBW=60.8±3.6	1.5-3	Cohort	NBW=3100±50 LBW=2120±80	NBW=310 LBW=320	P=0.8		17

Row	Author, Year	Mean Age at Birth, wk	ADHD Scale Mean (SD)	Age at Evaluation, (years)	Type of study	weight at Birth(gran) Mean(SD)	Sample	Relation between birth weight& ADHD	Relation between ADHD & sex	STROBE
13	Pyhälä Et al (2009)	NBW(Male)=38±3 LBW(Male)=35±4 NBW(Female)=38± 5 LBW(Female)=35± 5	NBW(Male)=59±1.3 LBW(Male)=65.6±4 NBW(Female)=59.5± 0.5 LBW(Female)=65.8± 3.5	6	Cohort	NBW(Male)=3150 ±130 LBW(Male)=2140 ±80 NBW(Female)=30 50± 150 LBW(Female)=21 80±110	Male=400 Female=423	P=0.01	P=0. 4	22
14	Shum Et al (2008)	VLBW=31w±3d ELBW=26w±1d	VLBW=67.8±3.6 ELBW =69.9±3.2	6-8	Cohort	VLBW= 1780±87 ELBW=1130±60	VLBW= 167 ELBW=154	P<0.001	-	21
15	Ribeiro Et al (2011)	NBW= 37w±6d LBW= 34w±3d	NBW= 57±1.7 LBW= 65±3.1	1.5-3	Cohort	NBW=3500±74 LBW= 2000± 120	NBW=181 LBW=174	P<0.001		20
16	van der Meere Et al (2009)	NBW= 38±4 VLBW=30±3	NBW=59±0.7 VLBW= 58±2.8	8	Case-control	NBW= 3340±140 VLBW=1560±110	NBW=59 VLBW=31	P=0.1	-	20
17	Davis Et al (2007)	NBW= 39±1 VLBW= 30±2	NBW=58±0.5 VLBW=68.9±7.5	4-5	Cohort	NBW=3170±140 VLBW=1710±90	NBW=44 VLBW=56	P=0.03		22
18	Hultman Et al (2007)	NBW=39±4 LBW=33±3	NBW=51±1.1 LBW=64.1±2.5	3-4	Cohort	NBW=3230±210 LBW=2160±130	NBW=98 VLBW=87	P<0.001	-	20
19	Harris Et al (2013)	NBW=38±2 LBW=35±6	NBW=51±1.1 LBW=53.1±2.5	3-4	Cohort	NBW=3260±170 LBW=2340±115	NBW=343 LBW=297	P=0. 4	-	19

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