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What is the Prevalence of ADHD in Children who were Diagnosed with Neonatal Abstinence Syndrome? A Retrospective Chart Review.

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Running Head: NAS and ADHD

What is the Prevalence of ADHD in Children who were Diagnosed with Neonatal Abstinence Syndrome?

A Retrospective Chart Review.

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By

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Abstract

Background: Neonatal abstinence syndrome (NAS) is the set of signs and symptoms present in a newborn whose mother was addicted to drugs while pregnant. NAS can occur due to sudden withdrawal from several drugs, including opioids, benzodiazepines, methamphetamines, and caffeine. It can cause many different issues in the newborn, including diarrhea, tremors, fever, and seizures. While these specific signs and symptoms are self-limited, research is showing that these children grow in to childhood and adolescence with increased risk of Attention-Deficit/Hyperactivity Disorder (ADHD), autism, motor dysregulation, and other cognitive and behavioral sequelae.

Purpose: The purpose of this project was to establish a correlation between a diagnosis of NAS in infancy and a diagnosis of ADHD later in adolescence. This was a retrospective chart review of a large academic health science center's electronic health record system that identified children who had a diagnosis of NAS in infancy and then later received a diagnosis of ADHD. The goal of this chart review was to identify the prevalence of ADHD among children who were born addicted to drugs. If this data shows a correlation between the two conditions, it will provide the support to intervene early and to improve outcomes for mothers, infants and families.

Methods: The University of Kentucky Center for Clinical and Transitional Science (CCTS) group extracted data from Sunrise Clinical Manager and Ambulatory Electronic Health Records to identify the samples needed for the study. The primary sample criterion was patients being treated at the University of Kentucky Neonatal Intensive Care Unit for NAS at any time from August 1st, 2008 until August 1st, 2018. ICD 9 and ICD 10 billing codes were then used to search this sample population for children with a diagnosis of ADHD, medication prescription for Guanfacine, Adderall, Ritalin (methylphenidate), and Focalin (dexmethylphenidate), and zip code (first 3 digits). These data points were extracted to see which children with NAS developed ADHD, and where these patients lived.

Results: 1432 patients were identified from the electronic health records as having NAS during the requested time range. Of these patients, 22 (1.5%) had a subsequent diagnosis of ADHD, and 31 (2.1%) had subsequent pharmacologic treatment with one or more of the ADHD medications. Only 157 (10.9%) of the patients live in Fayette County, and 329 (22.9%) live in a neighboring county. Nine hundred and forty six (66%) of the patients live further than two counties away from Fayette County.

Conclusion: Current research shows a 30-60% correlation between NAS and subsequent development of ADHD, which is much higher than the data present in this study. Many patients with NAS that are treated at the University of Kentucky NICU are transferred from outside hospitals and live far away from Lexington, in areas where traveling to the University for primary care may not be feasible. If the patient doesn't return to a University of Kentucky outpatient clinic then they were not captured in the ADHD data, regardless if they suffered from the condition or not. Many of the patients with NAS (up to 88.9% of them) live in Eastern Kentucky and may not be included in the ADHD portion of the data. As a result, patient education programs on the short-term and long-term effects of NAS, including the risk of ADHD and other developmental disorders, and early intervention services for children and families may be more effective in the counties where the patient and families reside.

Dedication

My DNP project is dedicated to my friends and family. I am thankful for the love and support from my wife, mother, and grandmother. None of this would have been possible without your continued support and encouragement. My children, Abigail, Esther, Elliott, Andi, and Archer have been my primary motivators for returning to school and completing this nearly 10-year long journey, and I hope they will always be proud of my hard work and accomplishments.

This is also dedicated to my friends and fellow UK College of Nursing DNP students. I am proud to have worked alongside you and I am thankful that we have reached the end of this journey together. I will always value our friendship, no matter where life takes us after graduation.

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Introduction

Neonatal abstinence syndrome (NAS) is the set of signs and symptoms present in a newborn whose mother was suffering from substance use disorder while pregnant. NAS can occur due to maternal use of legal, illegal, prescribed, and non-prescribed drugs during pregnancy. Some commonly abused drugs include heroin, codeine, methamphetamines, methadone, antidepressants, benzodiazepines, and caffeine. The syndrome is becoming a major health problem in many areas of the United States, especially in rural and poorer states like Kentucky (Kentucky Department for Public Health, 2015). According to the CDC, the incidence of NAS quadrupled from 1999-2013, and Kentucky was one of the most strongly affected states in the nation (Duncan, 2016). Records indicate that the number of NAS newborns discharged from Kentucky hospitals has increased 23-fold since 2000; going from 46 in 2001 to 1060 in 2014 (Kentucky Department for Public Health, 2015). In one study quoted by Kocherlakota (2014), maternal opioid use in the United States increased from 1.2 mothers per 1,000 in 2000 to 5.6 mothers per 1,000 in 2009. In that time, NAS cases nearly tripled, from 1.2 to 3.4 per 1,000 births (Kocherlakota, 2014).

These babies can develop mild to severe withdrawal symptoms in the immediate post-natal period which can lead to hospitalization in the NICU. Research on the long-term effects of NAS is limited. However, recent studies have shown that children can develop neurocognitive delays even after successful detoxification in the NICU, as evidenced by heightened NICU Neurobehavioral Scale, ADHD Rating Scale, and Bayley Infant Record Behavior scores (Logan, Brown, & Hayes, 2014).

One of the neurocognitive issues that is common in individuals who suffered from NAS as infants is attention-deficit/hyperactivity disorder (ADHD). ADHD is a pediatric neurodevelopmental disorder that is marked by inattention, hyperactivity, and impulsivity (National Institute of Mental Health, 2019). Risk factors for ADHD include genetics; exposure to environmental toxins during

pregnancy or during childhood; low birth weight; and smoking, alcohol, or drug use during pregnancy (NIMH, 2019). Signs and symptoms of ADHD can begin as early as age 3, and can persist in to adolescence and early adulthood. Diagnosis of ADHD involves the identification of signs/symptoms involved with chronic inattention, hyperactivity, and impulsivity that interferes with school and activities of daily living. Some of these signs and symptoms include (NIMH, 2019):

- Inattention: overlooking or missing details; having problems sustaining interest and attention in play, conversation, and reading; not being able to listen when spoken directly to; having problems with organization; losing things easily; being easily distracted; and being forgetful with daily activities.
- Hyperactivity/Impulsivity: being fidgety while sitting; leaving their seat in situations where sitting is required; being unable to be quiet in situations that require it; nonstop talking; having trouble waiting their turn; blurting out answers and finishing other people's sentences; and interrupting/intruding on other people's games and activities.

As NAS rates soar, research is underway to find out how drug exposure affects the brain long-term. According to Kocherlakota (2014), animal experiments are underway to find a connection between maternal opioid use and fetal brain growth. While this connection has yet to be proven or disproven, studies are showing that these fetuses have altered maturation of neurons and smaller neuroanatomic volumes, perhaps demonstrating the link between NAS and smaller head circumference (Kocherlakota, 2014). Kocherlakota (2014) also discusses the need for follow-up care in pediatric specialties related to altered CNS function, such as neurology (related to delayed motor development and microcephaly), ophthalmology (related to nystagmus, strabismus, and other visual defects), and psychiatry (related to hyperactivity, impulsivity, and ADHD).

Many researchers have discussed the correlation between NAS and cognitive delay in childhood. For example, Lall (2008) found that cocaine exposure was linked to higher rates of cerebral palsy, low IQ scores, increased delinquent behavior, and poor language development. In addition, Klinger et al. (2011) found that children with NAS have smaller head circumferences at birth, and commonly test lower on the Denver Developmental Screen Test 2 (DDSTII) at age 6. Also, Logan, Brown, and Hayes (2014) found that opioid-exposed infants scored lower on the Bayley Scaled of Infant Development (BSID) at ages 18 and 36 months. Researchers haven't figured out exactly why these correlations occur and what pathophysiologic changes precede them. However, it is important for healthcare providers to know that NAS is linked to cognitive issues later in life, and that they should initiate therapy and preventative measures early and often.

Nygaard, Slinning, Moe, and Walhovd (2016) found that children at ages 4 ½ and 8 ½, who were treated for NAS were more likely to show ADHD symptoms (per the ADHD Rating Scale) than children who were not exposed. In Kentucky, teachers are beginning to notice these signs and symptoms earlier and more often in Kindergarten-aged children. A Director of Advocacy for the Kentucky School Board Association notes that educators in the state are "seeing the first generation of children enter our schools in Kentucky, in Kindergarten and first grade that were born with NAS resulting from the current opioid crisis". These children have significant developmental delays that directly correlate with NAS rates (Acquisito and Spears, 2019). This trend is resulting in more children with behavioral issues and more children needing special education services in the school system (Acquisito and Spears, 2019).

Drug abuse is becoming a major health problem, and as a result NAS rates are rapidly increasing. In 2014, Kentucky NICUs saw a 7% increase in NAS visits (Duncan, 2016), and it is becoming a major problem in poorer/rural states where opioid addiction is at an all-time high. Researchers are learning more about the sequelae of NAS in older children, and pediatric primary care providers have a responsibility to treat these conditions as early as possible to prevent developmental delays in children

as they age. ADHD is one of the conditions commonly found in children with a history of NAS (Richards-Gustafson, 2017), and after synthesizing the evidence, it is clear that there is a correlation between the two. This correlation can provide the basis for evidence-based education programs aimed at preventing and treating children and families that have experienced NAS.

Research Barriers

Research on the correlation between NAS and ADHD is limited, in large part because many factors may contribute to developmental and cognitive delays in childhood. According to Acquisito and Spears, "certain developmental delays and disabilities are a consequence of the opioid crisis, but we don't know which piece" (Acquisito and Spears, 2019, pg. 4). Other socioeconomic factors that may contribute to developmental and cognitive delays include parents' financial instability, unsafe housing, abuse, incarceration, and being in the care of foster or adoptive parents.

The University of Kentucky Neonatal Intensive Care Unit (NICU) is one of the only NICU's in Kentucky that treats NAS. In general, any baby suffering from NAS who is delivered at a hospital in Eastern/Appalachia Kentucky will be transferred to the University of Kentucky hospital for a higher level of care. The University of Kentucky hospital provides higher acuity care than most Eastern Kentucky hospitals, but this transfer may create socioeconomic strains on the family, which can be especially difficult given the conditions that many of the people in that region face already. The number of babies born with NAS in Eastern/Appalachian Kentucky as high as 65 cases per 1,000 live births; nearly 3 times higher than the Kentucky rate of 22 cases per 1,000 live births (Acquisito & Spears, 2019). This places a significant strain on the parents of children with NAS in this area, as well as on the University of Kentucky NICU staff. Many of these families are inconvenienced by their child receiving care in a hospital that may be hours away from home. These families may not return to the hospital for follow-up care, and that may exacerbate efforts for follow-up care of these children. Research suggests that patients

will not travel further than 20-30 miles for routine primary care (Yen, 2013), so it can be assumed that many of the patients treated for NAS at UK Healthcare will be lost to outside hospitals and clinics for follow-up care.

Purpose

The purpose of this project was to determine if there was a correlation between NAS and ADHD at a large university hospital. The literature makes it clear that children with NAS often suffer from long-term cognitive and developmental complications. Unfortunately, the same research shows that the causes and correlations are not easily identifiable. This DNP project was a retrospective chart review aimed at identifying a correlation between NAS and ADHD. Electronic health records at a large university hospital were searched for key words and ICD codes to identify children who were treated at the hospital for NAS, and of those children, which ones went on to have a diagnosis of ADHD. The goal of this search is to provide tangible evidence of a correlation between NAS and ADHD. These data can be the foundation for evidence-based education programs aimed at helping children and families with NAS.

Methods

The data were extracted from the electronic health record with the help of the Center for Clinical and Transitional Science (CCTS) group. De-identified data that met the inclusion and exclusion criteria were extracted. ICD 9 and ICD 10 codes were used as the basis for the inclusion criteria search. The following codes were used in the data search:

- ICD-9 diagnosis codes:
    - 779.5 – drug withdrawal syndrome in the newborn

  - 314.01 – attention deficit disorder without mention of hyperactivity
  - 314.01 – attention deficit disorder with hyperactivity
- ICD-10 diagnosis codes:
  - P96.1 – neonatal withdrawal symptoms from maternal use of drugs of addiction
  - F90.0 – attention-deficit hyperactivity disorder, predominantly inattentive type
  - F90.2 – attention-deficit hyperactivity disorder, combined type
  - F90.9 – attention-deficit hyperactivity disorder, unspecified type

The primary inclusion criterion, which provided the total sample population of the study, was a diagnosis of NAS within the date range of August 1st 2008 to August 1st 2018. From this population, the following secondary inclusion criteria were extracted: diagnosis of ADHD, medication prescription for Guanfacine, Adderall, Ritalin (methylphenidate), Focalin (dexmethylphenidate), and zip code. Institutional Review Board (IRB) approval for this project was obtained on October 8th, 2019.

Setting and Sample

This retrospective chart review was conducted by the University of Kentucky Center for Clinical and Translation Science (CCTS) and was exported from Sunrise Clinical Manager and Ambulatory Electronic Health Record, both of which are electronic health database systems utilized by the University. It involved a search for every child that was treated for Neonatal Abstinence Syndrome (NAS) in the University of Kentucky NICU for a 10-year period beginning August 1st, 2008 and ending August 1st, 2018. Acquisito and Spears (2019) estimate that the opioid crisis in Kentucky began around 2009, which is why this 10-year period was used for the chart review. In total, 1432 NAS babies were isolated from the CCTS database search. This was the sample that was used to search for the necessary inclusion criteria.

Theoretical Framework

NAS can be considered a tertiary result of maternal drug use: the mother develops an addiction to a drug, the mother uses the drug before and/or during pregnancy, and as a result the child is born addicted to the drug. If proper primary and secondary preventions are implemented, NAS can be prevented (Hamdan, 2017). Drug cessation, proper prenatal care, and proper treatment for pregnant women with substance use disorders can eliminate or quell the signs and symptoms of NAS. Addiction is a multifaceted condition, and Neuman's Systems Model can provide a framework for treating this problem. Neuman's model focuses on a person's reaction to stress, and uses a multidimensional and holistic approach in treating it (Fulbrook, 1991). The major concepts of the model include the person, the environment, health, and nursing, and Neuman emphasizes that primary, secondary, and tertiary care may all be required in the treatment of a given condition (Fulbrook, 1991). Care of the mother who has been addicted to opioids, care of the baby with NAS, and prevention of complications later in life involve all of these factors.

Results

Of the 1432 children in the sample population, 832 (58.1%) infants were male and 600 (41.9%) were female. Many different races were represented, but the majority of them were Caucasian (1331, 92.9%). The most surprising statistic to come from the data search was that only 22 (1.5%) children had a diagnosis of ADHD. In addition, 31 (2.1%) children were prescribed an ADHD medication. These were children seen at UK Health Care clinics who did not have an ADHD diagnosis through UK Health Care, but were prescribed an ADHD medication there. These children were likely diagnosed with ADHD at an outside facility but were seen at UK Health Care for an unrelated issue. The preceding statistics show that at most, 53 (3.6%) children in the NAS population sample developed an ADHD diagnosis. This data is clearly

inconsistent with current evidence-based research. At this point, zip codes were added to the inclusion criteria to examine where these patients with NAS live. The University of Kentucky NICU is one of the primary NAS treatment centers in the state, and many families may have to travel a long way from home while their babies are being treated. Many of these children may not ever return to the University of Kentucky for primary care treatment, which is why county of residence played a role in the interpretation of the data. Interestingly, the zip code data shows that most of the children in the population sample live in areas outside of Lexington:

- 157 (10.9%) children were from Lexington

- 329 (22.9%) children resided in a county that is within 2 counties of Fayette County KY

- 42 (2.9%) children live in counties west of Fayette County KY

- 295 (20.6%) children live in counties that are north or south of Fayette County KY and its surrounding counties

- Between 514 and 823 (36-58.8%) children live in counties east of Fayette County.

Discussion

More than 61.9% of the children in this study live further than one county away from Fayette County. This was a large portion of the sample size. Current evidence-based research estimates the rate of ADHD among babies with NAS to be anywhere from 30-40%, much higher than the 3.6% estimated in this study. Children are being discharged from the University of Kentucky Hospital to homes that are several counties away, and they never return to this hospital or primary care clinics within the university healthcare system, and were not be captured in this study.

Implications for Practice

As the opioid crisis gets worse, the number of NAS cases in the United States increases. NAS is not a new diagnosis; however, studies on the long-term effects of NAS are limited. The goal of this project was to see if a link between NAS and ADHD exists in hopes of expanding the literature. These data could be beneficial to providers in many areas, including general pediatrics, behavioral and developmental pediatrics, and OB-GYN. A few ways that this research could help providers within the university setting include:

- General Pediatrics: Identify children who may be at risk for ADHD due to a verified history of NAS. Pediatric providers could begin teaching the parent about the early signs and symptoms of ADHD in kids who may be at risk. Programs, such as the Incredible Years Parenting Program, which is an evidence-based parenting program, could be beneficial in helping families and be delivered in primary care offices where these families reside.
- OB-GYN: If the OB-GYN knows that the mother has a history of drug use, and if they suspect that they will deliver a baby with NAS, the OB-GYN could begin patient education on the signs/symptoms of withdrawal and other helpful evidence-based interventions.
- Family practitioners and drug counselors: This project highlights the importance of providing evidence-based treatments to support mothers to stop using drugs. A campaign aimed at women during childbearing years may help to decrease drug use and prevent NAS.

Current evidence-based research is showing improved NAS outcomes from effective antidrug education during pregnancy and before conception. Education aimed at getting mothers to stop taking drugs during pregnancy would have a direct and positive impact on babies. NAS can be reduced or even eliminated with effective primary care either early in pregnancy or pre-conception (Ko et al., 2017).

Nearly 86% of pregnancies involving mothers with opioid addiction are unintentional, so NAS education must occur quickly and as soon as the mother begins seeking prenatal care (Ko et al., 2017).

Data from this project shows that a large percentage of children with NAS live in eastern Kentucky. Therefore, providing services and interventions in this area may improve outcomes for these children. Infants with NAS who are raised by their biological families tend to score lower on the Bayley Scales of Infant Developmental-Mental Developmental Index (Shearer et al., 2018). In addition, infants with NAS who live in homes with lower socioeconomic status were much more likely to score lower on multiple developmental tests than those in homes with average to high socioeconomic status (Shearer et al., 2018). Intellectual outcomes were similar to developmental outcomes: infants with NAS were much more likely to suffer from intellectual disabilities at one year, 18 months, and three years, and 7th graders with NAS tend to score less than or at a 5th grade level on standardized tests (Shearer et al., 2018). Babies with NAS are more likely to be born with smaller head circumferences and have abnormal MRI scans, as evidenced by decreased volumes of basal ganglia and cerebellar white matter, at ages 10-14 (Shearer et al., 2018). Babies with NAS may have cognitive and developmental delays. These issues are compounded when they occur in rural, poor areas like Eastern and Appalachian Kentucky.

Eastern Kentucky is one of the poorest economic regions in the country. Of all the counties that lie east of I-75, 36 of them are considered 'distressed' by a survey conducted by the Appalachian Regional Commission of the U.S. Census Bureau (see Appendix C). The area is among the poorest and most rural in the nation, and median household income is well below the national average in nearly every county. These socioeconomic factors, when combined with higher rates of opioid use, compound the effects of NAS on children growing up in these areas. As many as 25% of children with opioid exposure may not receive necessary healthcare within the first 2 years of life (Shearer et al., 2018). Further, children with NAS who grow up with mothers who suffer from substance use disorder are much more likely to develop mental health disorders as adults, and this correlation can predict future drug use

by up to 50% (Shearer et al., 2018). Considering these facts, as well as the facts present throughout this study, Eastern Kentucky is an area that may benefit from NAS education. Through the University of Kentucky's Area Health Education Centers (AHEC), delegates from the university work to train, support, and recruit effective healthcare providers in all areas of the state. Nearly 60% of babies with NAS seen at the University of Kentucky NICU reside in counties within the Northeast and Southeast AHEC's (see Appendix A). Healthcare professionals in these areas should be trained about NAS, its signs and symptoms, and how to properly treat and wean mothers with substance use disorder who are pregnant or thinking about becoming pregnant. This education should include the importance of weaning off drugs as soon as they know they are pregnant, the use of Subutex programs, and the short and long-term consequences of NAS (if they choose to continue using drugs).

Limitations

The major limitation of this study is that children who were not seen for follow-up ADHD treatment were not included in the results. If a child was treated for NAS at UK Healthcare, but never returned to UK for follow-up care or received their ADHD diagnosis at an outside clinic, the ICD 9 and ICD 10 codes for their diagnoses were not captured in the follow-up data. If it had been somehow possible to track these children at their respective healthcare facilities, ADHD rates for this study may have been more consistent with nation-wide studies that show a much higher incidence.

Conclusion

Neonatal abstinence syndrome isn't a new health problem, but it is becoming more common due to the worsening opioid crisis in the United States. The long-term effects of the condition are not well studied, but data suggests that children are developing chronic developmental, behavioral, and cognitive problems. These conditions have origins that may be hard to pinpoint, because there may be

many contributing factors: socioeconomic status, wealth, living conditions, marital status, and access to quality healthcare are just a few factors that may initiate or exacerbate cognitive and developmental changes to the brain. Data, as well as first-hand accounts from teachers, parents, and healthcare providers in high risk areas are seeing an increase in children with developmental delays, behavioral problems, and the need for special education services. While it isn't possible to label NAS as the only or major cause, it is certainly possible to assume that it is a major causative factor.

NAS is the result of drug use during pregnancy, and it can be completely avoided in parents who do not use these substances, or in those who cease using these substances once they become pregnant. The major goal of patient education is to enlighten people and promote change, and NAS is a condition that can be prevented with proper prenatal and pre-pregnancy patient education. This education should focus on the short and long-term consequences of the condition, ranging from the gastrointestinal and neurologic withdrawal symptoms present at birth to the potential developmental and cognitive deficiencies noted in school aged and adolescent children. Eliminating NAS would have a profound impact on patient outcomes, especially in poor and disadvantaged areas, as well as promote cost savings in a variety of healthcare areas. Kentucky is one of the poorest and most rural states in the country, and likewise opioid use and NAS rates are very high in many areas of the state. As a leader of healthcare in Kentucky, and as one of the only NAS treatment centers in the state, the University of Kentucky, through outreach programs, can impact the community where NAS rates are prevalent and improve outcomes for children and families living within the state.

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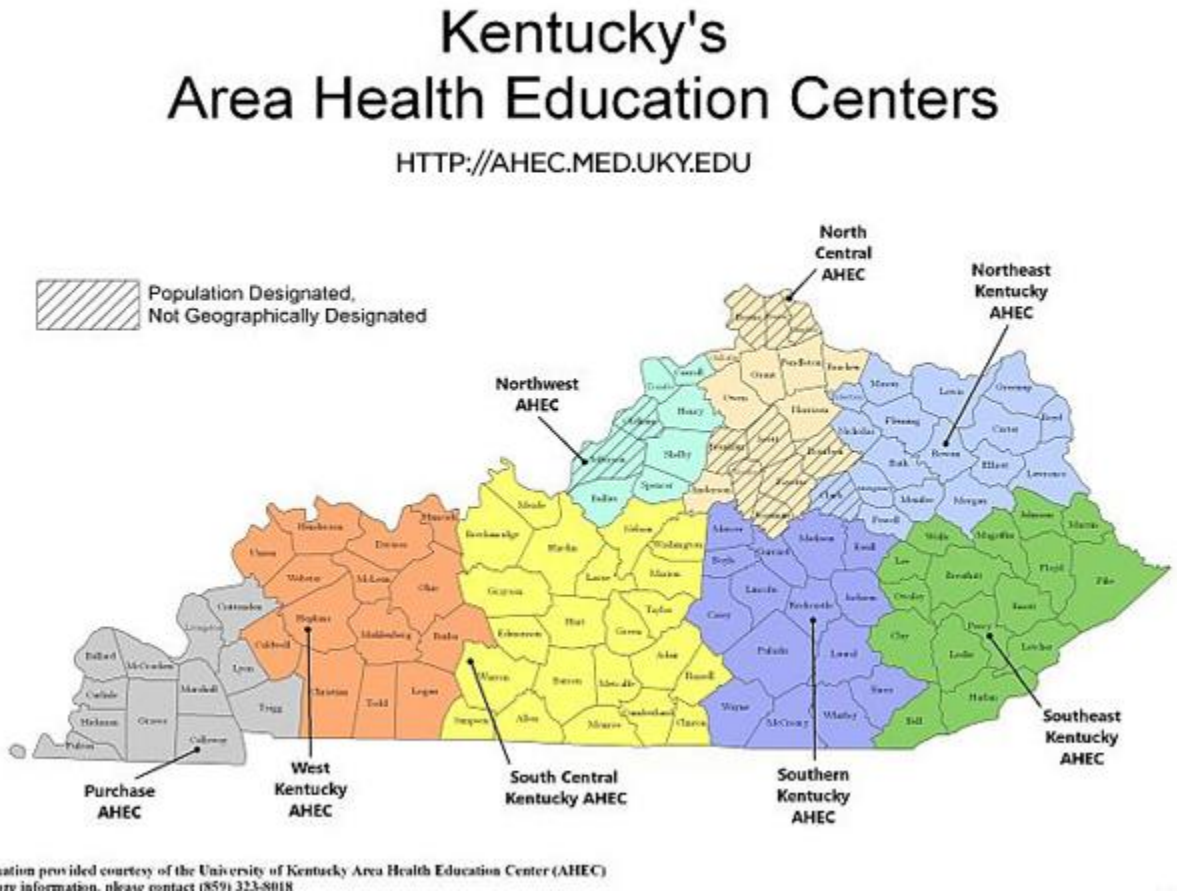
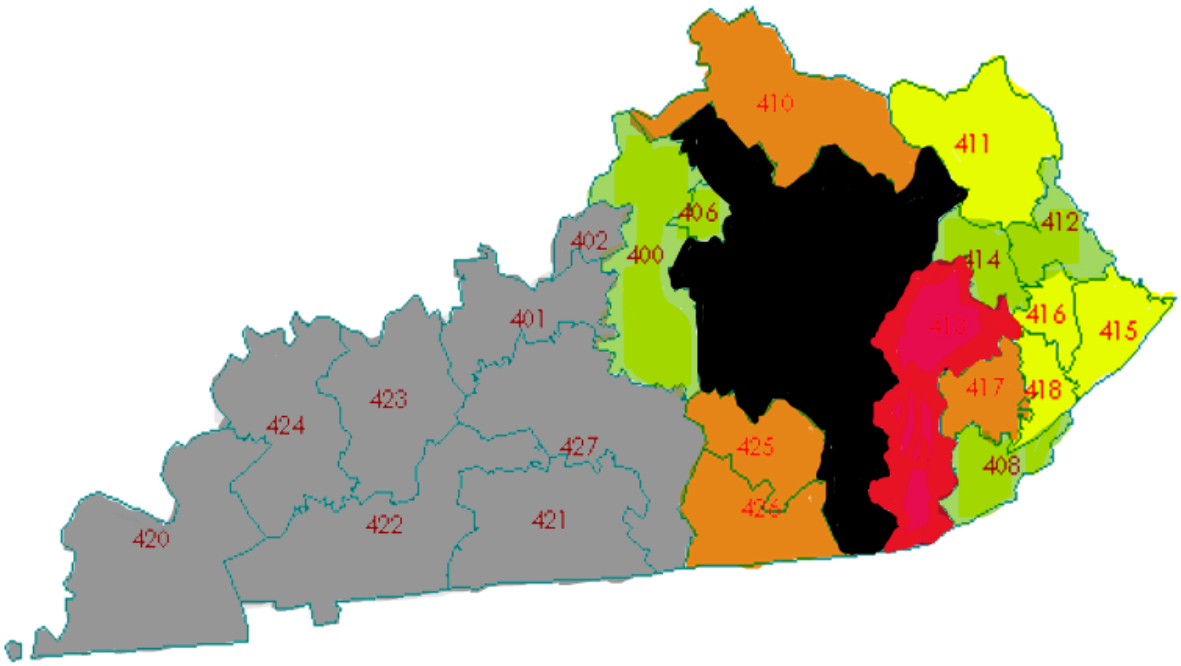
Appendix A

Map of Kentucky Area Health Education Centers



Appendix B

Distribution of University of Kentucky Babies with NAS in Kentucky Zip Codes



< 10 Children = GRAY

11-20 Children = GREEN

21-40 Children = YELLOW

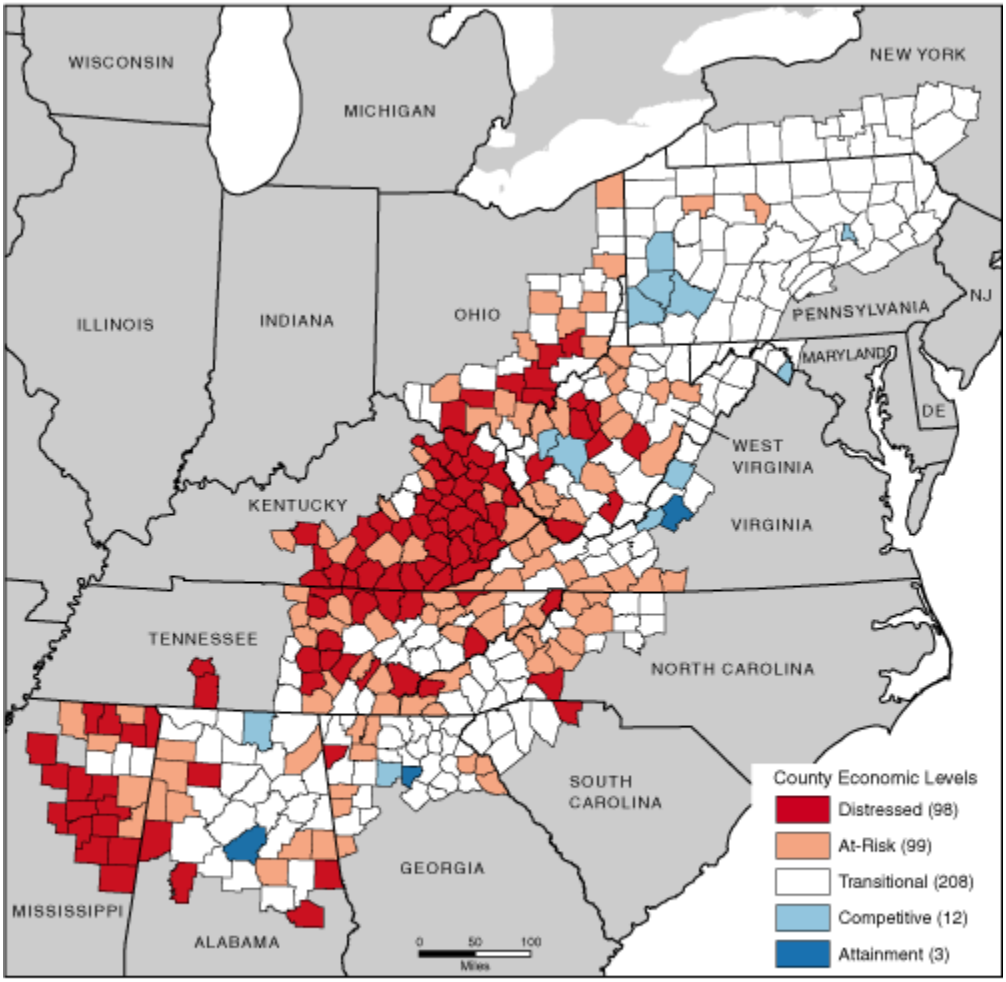
41-60 Children = ORANGE

61-100 Children = RED

> 100 Children = BLACK

Appendix C

Appalachian County Economic Levels

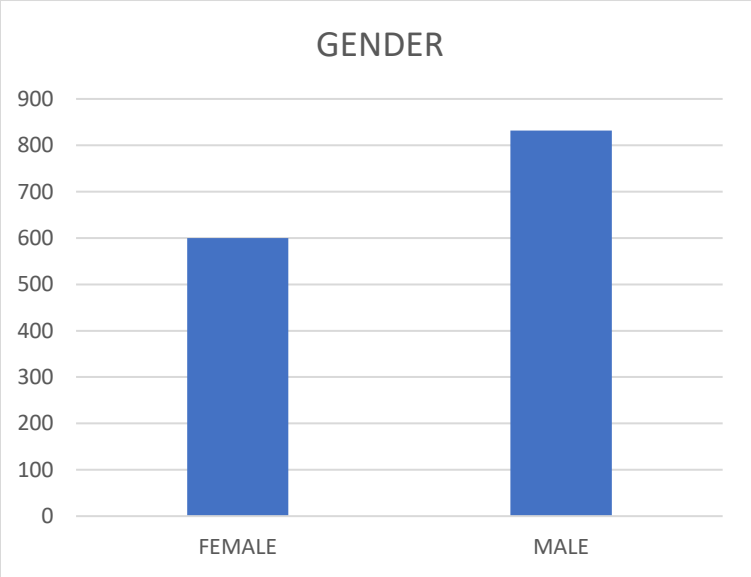


Created by the Appalachian Regional Commission, March 2012
Data Sources:
Unemployment data: U.S. Bureau of Labor Statistics, LAUS, 2008–2010
Income data: U.S. Bureau of Economic Analysis, REIS, 2009
Poverty data: U.S. Census Bureau, American Community Survey, 2006–2010

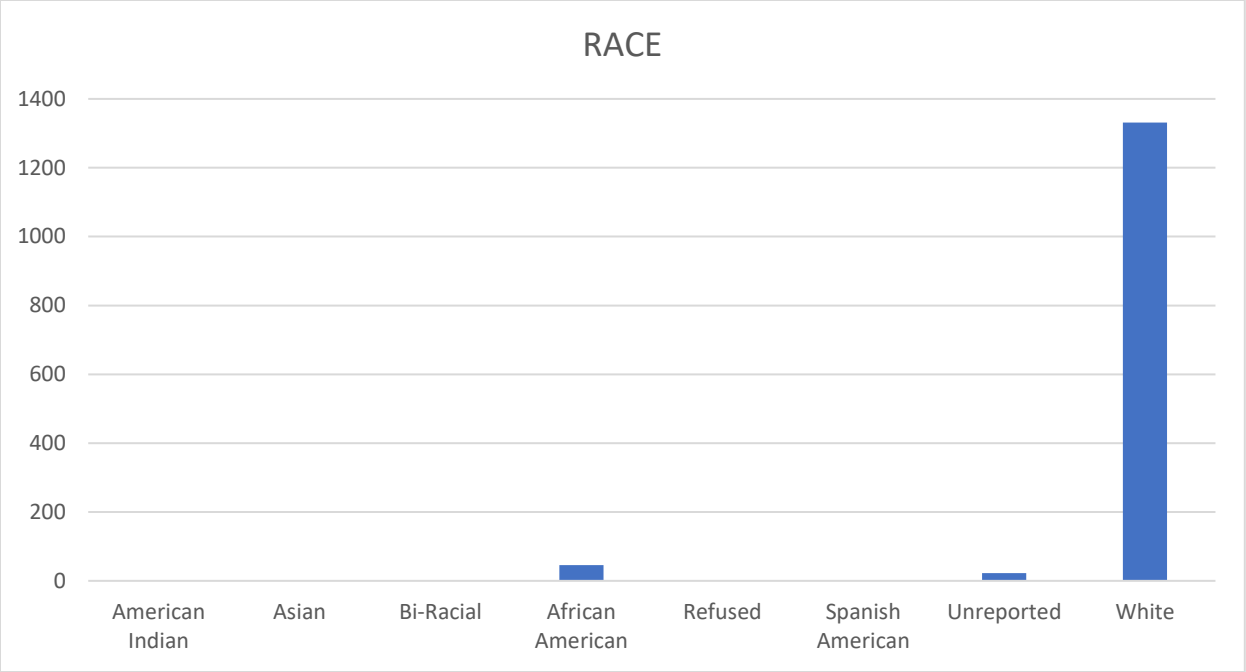
Effective October 1, 2012
through September 30, 2013

Appendix D

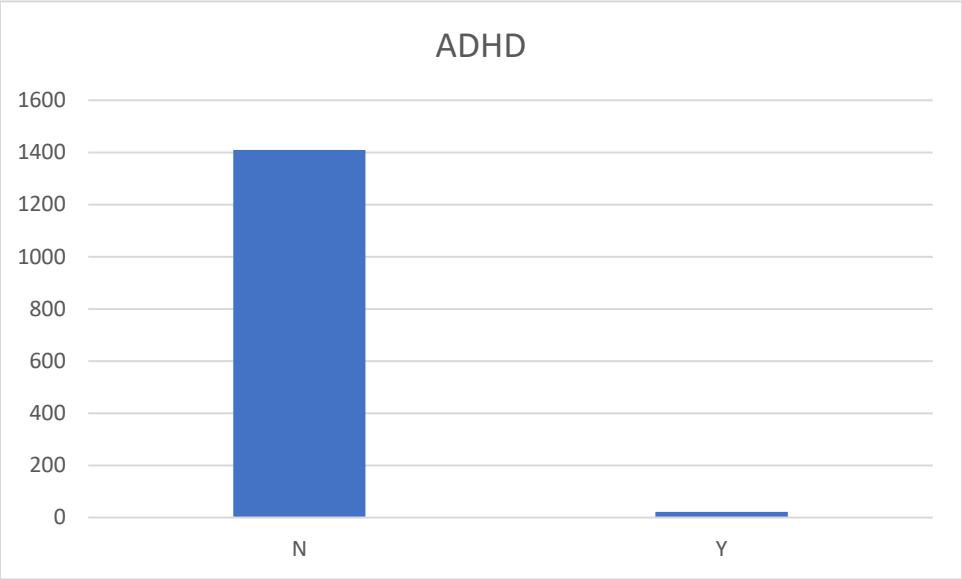
Data Tables from CCTS Chart Extract



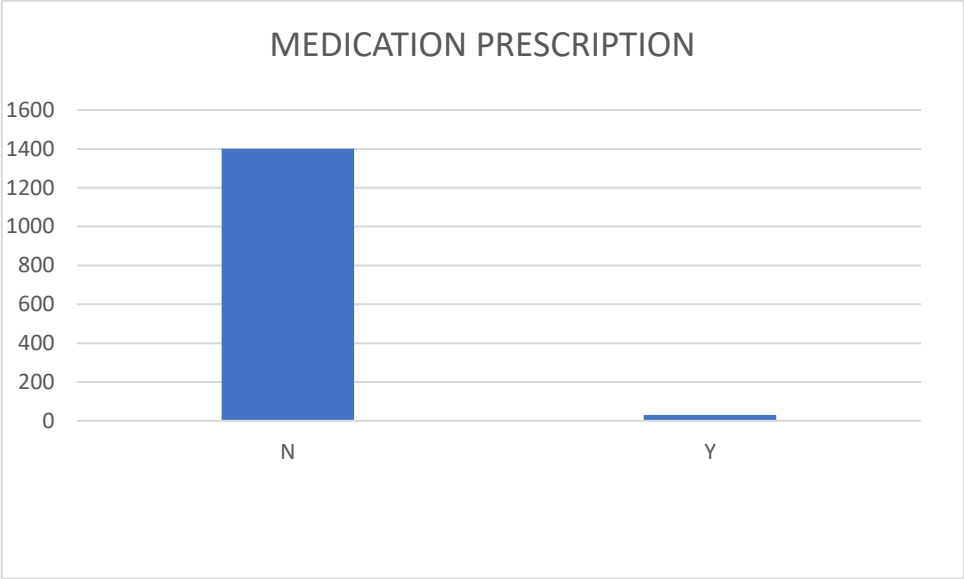
GENDER	COUNT
FEMALE	600
MALE	832



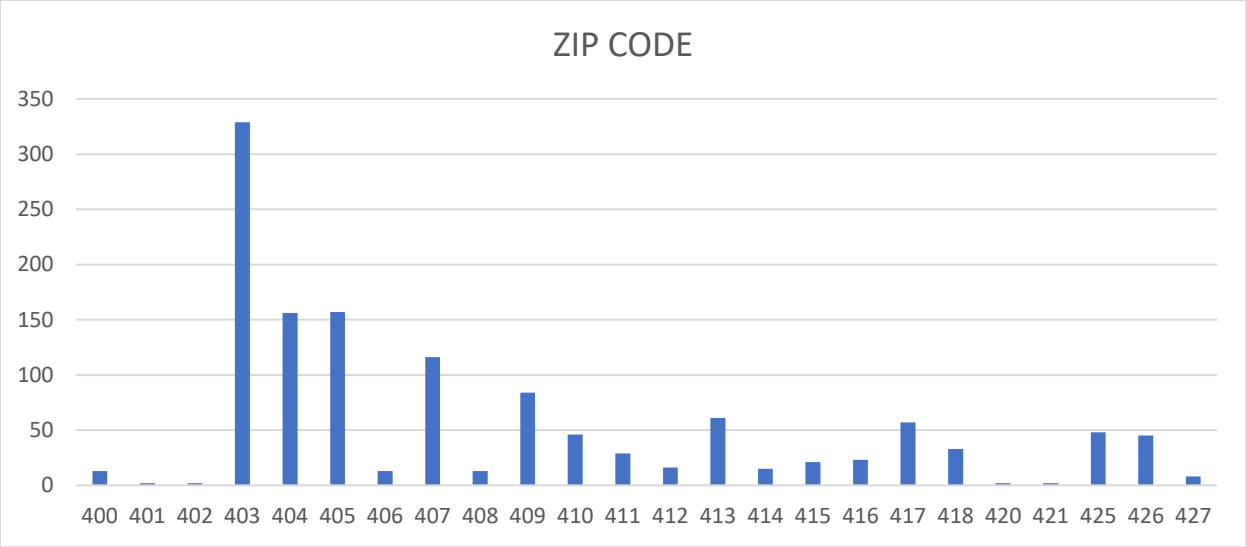
RACE	COUNT
AMERICAN INDIAN	2
ASIAN	1
BI-RACIAL	2
AFRICAN AMERICAN	46
REFUSE	1
SPANISH AMRICAN	1
UNREPORT	22
WHITE	1331



ADHD	COUNT
N	1410
Y	22



MEDICATION PRESCRIPTION	COUNT
N	1401
Y	31



ZIP CODE	COUNT
400 (Shelby, Nelson, Trimble, Oldham, Jefferson, Marion, Washington, Henry, Spencer)	13
401 (Bullitt, Breckinridge, Hardin, Meade, Nelson, Grayson, Jefferson)	2
402 (Jefferson)	2
403 (Mercer, Nicholas, Powell, Rowan, Menifee, Scott, Marion, Estill, Bourbon, Owen, Bath, Montgomery, Jessamine, Anderson, Woodford, Clark)	329
404 (Madison, Jackson, Rockcastle, Garrard, Estill, Lincoln, Boyle)	156
405 (Fayette)	157
406 (Franklin)	13
407 (Laurel, Whitley, Knox)	116
408 (Harlan, Letcher, Leslie, Bell)	13
409 (Knox, Clay, Bell, Whitley, Harlan)	84
410 (Harrison, Bracken, Boone, Owen, Campbell, Gallatin, Fleming, Mason, Robertson, Grant, Carroll, Kenton, Fleming, Pendleton)	46
411 (Carter, Greenup, Boyd, Elliott, Lewis, Lawrence)	29
412 (Johnson, Martin, Floyd, Lawrence)	16
413 (Morgan, Wolfe, Lee, Owsley, Breathitt, Perry, Lee)	61
414 (Morgan, Magoffin)	15
415 (Pike, Letcher)	21
416 (Floyd, Magoffin, Knott)	23
417 (Perry, Leslie, Knott)	57
418 (Perry, Letcher, Knott)	33
420 (McCracken, Carlisle, Marshall, Hickman, Crittenden, Lyon, Fulton, Calloway, Graves, Livingston, Ballard)	2
421 (Warren, Allen, Barren, Simpson, Edmonson, Metcalfe, Monroe)	2
425 (Casey, Pulaski)	48
426 (Clinton, Russell, McCreary, Wayne)	45
427 (Hardin, LaRue, Hart, Adair, Grayson, Cumberland, Taylor, Green)	8

Appendix E

APA Citation	Purpose Statement	Study Design	Sample	Key Findings
Sandtorv, L.B., Fevang, S.K.E., Nilsen, S.A., Boe, T., Gjestad, R., Haugland, S., and Elgen. I.B. (2018). Symptoms Associated With Attention Deficit/Hyperactivity Disorder and Autism Spectrum Disorders in School-Aged Children Prenatally Exposed to Substances	To evaluate the mental health symptoms associated with prenatal substance abuse	Cross-sectional	57 children, ages 6-14, from a large hospital in Norway, who were exposed to illicit drugs in-utero	37% of the children presented with high risk symptoms of ADHD based on the SNAP-IV
Nygaard, E., Slinning, K., Moe, V., and Walhovd, K.B. (2016). Behavior and Attention Problems in Eight-Year-Old Children with Prenatal Opiate and Poly-Substance Exposure: A Longitudinal Study	To investigate whether behavior and attention problems are more prominent in children who were exposed to drugs prenatally.	Longitudinal	136 infants (78 who were exposed in utero and 58 who were not exposed) were recruited from a large hospital in Norway. Their development was followed until age 8 ½. The ADHD rating scale was used at age 4 ½ and at age 8 ½.	25% of the at-risk children had scores that were indicative of ADHD, and an additional 17% had scores suggesting ADHD-related problems.
Simes, E., Oltedal, L., Bartsch, H., Eide, G.E., Elgin, I.B., and Aukland, S.M. (2017). Brain morphology in school-aged children with prenatal opioid exposure: A structural MRI study. *Early Human Development*. 106: 33-39.	To investigate the association between prenatal opioid exposure and brain morphology in school-aged children.	A cross-sectional study of prenatally opioid-exposed children	A sample of 16 children, aged 10-14 with prenatal exposure to opioids	Volumes of the basal ganglia, thalamus, and white matter were reduced in the opioid-exposed group.

APA Citation	Purpose Statement	Study Design	Sample	Key Findings
Klinger, G., Frankenthal, D., Merlob, P., Diamond, G., Sirota, L., Levinson-Castiel, R., Linder, N., Stahl, B., and Inbar, D. (2011). Long-term outcome following selective serotonin reuptake inhibitor induced neonatal abstinence syndrome	To assess the neurodevelopment outcomes of children exposed to SSRI's in utero that developed a neonatal abstinence syndrome	Prospective cohort design	30 children with NAS and 52 children without NAS were recruited from a large Israeli hospital.	27% of the children with NAS had lingual abnormalities and 47% of the children with NAS had social abnormalities (based on the Denver Developmental test)
Yeoh, S.L., Eastwood, J., and Wright, I.M. (2019). Cognitive and motor outcomes of children with prenatal opioid exposure.	Key Question: is prenatal opioid exposure associated with differences in childhood cognitive and motor development?	Systemic review and meta-analysis of cohort studies involving children with prenatal opioid exposure	Meta-analysis of 26 studies, which included 1455 children exposed to prenatal opioids	Up to 6.3% of children with prenatal opioid exposure will have an IQ score 2 standard deviations below normal, compared to 2.3% of normal children. Thus, these children are 3 times more likely to have a severe intellectual disability based on DSM-5 criteria
Nygaard, E., Slinning, K., Moe, V., and Walhovd, B. (2015). Cognitive function of youths born to mothers with opioid and poly-substance abuse problems during pregnancy	To evaluate the outcomes of children exposed to drugs prenatally	Longitudinal study	45 children born to mothers who were poly-substance users and 48 children who were born without prenatal exposure. Participants were administered 10 neuropsychologic tests between ages 17-21	36% of the children in the at risk group were diagnosed with ADHD at some point in childhood. 13% of people in the risk group developed substance abuse or addictions in their teens