ISCHEMIC-HYPOXIC PERINATAL CONDITIONS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER

by

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ABSTRACT OF THE DISSERTATION

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Attention deficit hyperactivity disorder (ADHD) is a common psychiatric disorder in the nation affecting 8%-13% of all school-aged children. ADHD diagnoses have reached epidemic proportions in the U.S. with an estimated annual cost of $36 to $52.4 billion, in 2005 dollars.

The etiology of ADHD is largely unknown. Emerging evidence suggests that Ischemic-hypoxic conditions (IHC) have profound effects on fetal brain development that are not apparent in infants. Given that rates of ADHD are increasing and IHC increases the risk of fetal brain injury, we hypothesize that IHCs are important and independent risk factor for ADHD.

In this nested case-control study, we evaluated the risk of ADHD in a cohort of children aged 5-11 years, born at ≥28 weeks of gestation, and cared for at Kaiser Permanente Southern California (KPSC) between 1995-2010 (n =308,634; 4.3% had ADHD). Electronic clinical, laboratory, and pharmacy records were obtained for these children and their mothers. Cases were children with a clinical diagnosis of ADHD (ICD-9 codes 314.x) and positive for at least 2 ADHD prescriptions during the follow-up period. For each case, five controls were matched to cases on child age at diagnosis. IHC was defined based on ICD-9 codes.

Compared to control children, case children were more likely to be male and of white or black race/ethnicity. Mothers of case children were more likely to be older, have ≥12 years education, history of smoking and psychosocial disorders during pregnancy. In contrast to control children, case children were more likely (odds ratio [OR] 1.16, 95% confidence interval [CI] 1.11, 1.21) to experience IHC. Stratified analyses by gestational age revealed that case children than controls were more likely to experience IHC at 28-33 (OR 1.5, 95% CI 1.2, 2.0), 34-36 (OR 1.2, 95% CI 1.1, 1.5), and 37-42 (OR 1.1, 95% CI 1.0, 1.2) weeks of gestation. IHC was associated with increased odds of ADHD across all race/ethnicity groups.

These findings suggest that IHC is an independent risk factor for ADHD, especially in preterm birth. This suggests that events in pregnancy contribute to the etiology of this condition over and above the well-known familial/genetic influences.

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Introduction

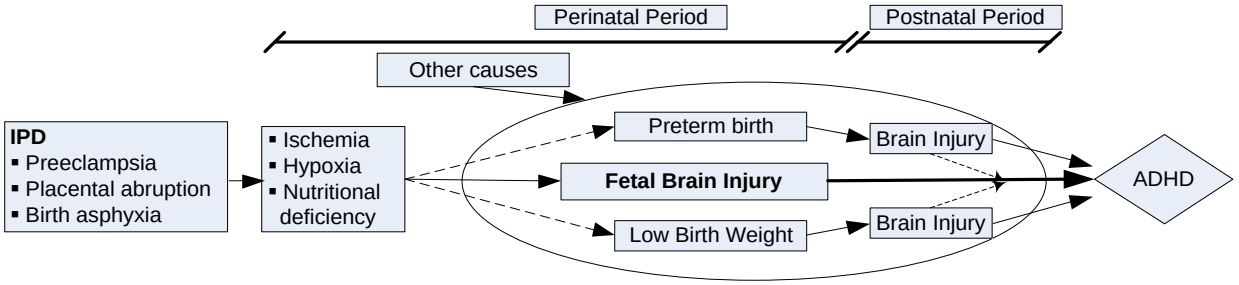
Burden of disease

In the United States, 8 to 13 percent of all children (5 million) aged 5 to 17 years suffered from ADHD in 2008.[1] It is one of the most common chronic conditions of childhood,[1] with the disorder persisting into adulthood for approximately half of the affected children.[2-5] Children with ADHD are more likely to have other mental and physical conditions requiring intensive medical care, mental health, social, and special education services, and are more likely to use psychotropic medications and to be at greater risk of substance use than unaffected children.[6-12] Emergency room visits, hospitalizations, and treatments attributable to ADHD account for a disproportionate amount of health care expenditures. Among children aged 5-18 years, the number of physician office visits related to ADHD increased by 148.9% over six years (from 947,208 children in 1990 to 2,357,833 children in 1995) period.[13] From 1995 through 1999, over 14 million children aged 5 to 18 years visited physicians' offices.[14] In 2006, there were a total of 7 million ambulatory care visits for ADHD.[15] Children with ADHD are more likely to experience learning problems, missed school days, troublesome relationships with peer and family members,[16-19] and higher parental stress and depression.[20] In 2000, Birnbaum et al[21] showed that compared with family members of children without ADHD, family members of children with ADHD incur $6.78 billion in increased health-related costs. The annual cost of illness related to ADHD in those aged ≤18 years is estimated to be between $36 and $52.4 billion, in 2005 dollars.[22] With the increasing prevalence of ADHD, costs are expected to rise proportionally. ***The high prevalence rate, its chronic nature and the rising ADHD-related health care costs emphasize its importance as a public health problem.***

Existing knowledge

Ischemic-hypoxic condition is the term for a number of pregnancy conditions that involve the placental. These conditions include preeclampsia (new-onset hypertension [blood pressure >140/90 mmHg] occurring at ≥ 20 weeks gestation and proteinuria [>0.3 g/24 h), placental abruption (premature separation of normally implanted placenta) and birth asphyxia.[23] In this study, the clinical diagnosis of perinatal asphyxia will be based on several criteria, the two main ones being evidence of cardiorespiratory and neurological depression (defined as an Apgar score remaining less than 7 at 5 minutes after birth) and evidence of acute hypoxic compromise with acidemia (defined as an arterial blood pH of less than 7 or base excess greater than 12 mmol/L).[23] Although the etiology and pathophysiology underpinnings of these conditions remain elusive, they pose significant risks to the unborn child through common pathophysiological mechanisms, namely, uteroplacental underperfusion, placental ischemia, and hypoxia.[24] Preeclampsia and abruption are implicated in approximately 54% of all pregnancies complicated by medically indicated preterm births.[25, 26] They are also known to be associated with increased risk for fetal brain injury, [27-30] and NICU admissions.[31] There is an increased risk for recurrence in subsequent pregnancies[32] and structural and functional brain injuries in the offspring is significant.[33-40]

The following diagram depicts the hypothesized pathways through which IHC leads to fetal brain injuries and, consequently, to childhood ADHD. Causal relationships are represented by solid arrows and intermediate variables are represented by broken arrows.



Other factors* include confounders (perinatal tobacco and alcohol exposure and psychosocial disorders) and modifiers (maternal [anemia, iodine deficiency, viral infection, and use of terbutaline and antidepressant] and child [hyperbilirubinemia, iron & zinc deficiency, history of recurrent otitis media, asthma, diabetes and traumatic brain injury])

Preterm birth, low birth weight, and antepartum antibiotic treatment lie on the causal pathway between IPD and ADHD

Oxygen and nutrients from the mother's blood enter fetal circulation via the placenta. During critical periods of fetal organ development, may compromise optimal supply of oxygen and nutrients needed for fetal organ development leading to increased risk of hypoxic-ischemic encephalopathy, including altered attention capacity, cognitive function and decreased school performance.[41, 42] Hypoxic injury during fetal development leads to significant structural and functional brain injuries in the offspring.[27, 33-40, 43, 44] Selective vulnerability of striatal neurons have been described in children born after a pregnancy complicated by asphyxia.[45] Lower concentrations of N-acetylaspartate and Creatine levels have also been shown in the central nervous system tissue of fetuses affected by hypoxic conditions indicating neuronal loss or damage.[43, 44] Evidence from imaging studies demonstrated that placental ischemic injury and resulting hypoxia alters brain development and causes structural changes such as a marked reduction in absolute gray matter volume and intraventricular volume, and periventricular leukomalacia.[27, 40, 46] Studies based on animal models and human subjects have also reported detrimental effect of chronic fetal hypoxia and protein restriction on brain weight and synapsal numbers.[38, 47, 48] Potential mechanisms through which fetal ischemia and hypoxemia increase the risk for fetal brain injury are through degenerative changes in the hippocampal pyramidal neurons, loss of dendritic branches and density of granular

neurons in the dentate gyrus leading to reduced overall hippocampal volume.[36, 49-51] These findings appear to be central to altered development and function of the fetal brain and increased risk of ADHD.

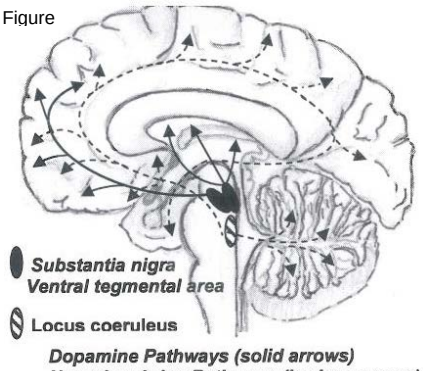
Although several epidemiological, animal model and imaging studies demonstrated an adverse impact of preeclampsia, placental abruption and birth asphyxia on fetal brain development, they have not examined how this conditions may lead to the development of ADHD.

Etiologies of ADHD

The etiology of ADHD is largely unknown; however, genetic and environmental factors are believed to contribute to the risk.[52-56] Although there is no single pathophysiologic profile of ADHD, brain scans of children with ADHD show structural and functional changes in the striate and prefrontal cortex, basal ganglia, corpus callosum, cerebellum,[57-61] and changes in blood flow and metabolic rates.[62, 63] Selective vulnerability of striatal neurons have also been reported in children born after a pregnancy complicated by asphyxia.[45]

Several studies have implicated abnormalities in the neurotransmitters, dopamine, norepinephrine, and serotonin,[64-67] which appear to play an important role in the child's ability to focus and pay attention to tasks (Figure). A Positron Emission Tomography study of children with ADHD revealed midbrain dopaminergic dysfunction.[68] Dopamine is vital in self-regulation of goal-directed behaviors, as well as learning and maintaining trained

Figure



or conditioned responses.[69-71] Norepinephrine plays a vital role in controlling alertness, attention and memory.[72] The serotonin system regulates sleep patterns, mood, and aggression.

Genetic factor

Monozygotic twins are more strongly concordant than dizygotic twins for ADHD.[73-78] Children of parents with ADHD are at increased risk of ADHD.[79] More boys than girls are diagnosed with ADHD.[80-83]

Preterm birth (PTB) and low birthweight births (LBW)

In 2008, the PTB rate in the U.S. was 12.3%.[84] Inflammatory processes are a major cause of PTB[85-93] and LBW.[94] While studies that examined the associations between PTB and neurobehavioral disorders[95-97] have laid an important foundation for future work, they have shortcomings. An increasing number of PTBs are due to maternal or fetal indications (e.g., intrauterine growth restriction, preeclampsia, placental abruption, nonreassuring antenatal fetal testing).[26, 98] Most studies that found an association between PTB and ADHD did not differentiate medically indicated PTB from spontaneous PTB, which is thought to have multiple pathways and mechanisms, including endocrine dysfunction or exaggerated inflammatory response/infection.[99] Therefore, studies aimed at elucidating the association between PTB and ADHD need to recognize and fully consider the two clinical subtypes of PTB.

The underlying mechanism through which PTB and LBW are associated with neurobehavioral disorders may be attributable to hypoxic-ischemic mediated fetal brain injury. The research we propose will attempt to directly assess the association between IHC and ADHD in an effort to better understand whether there is added risk of ADHD above that of just prematurity.

Psychosocial distress disorder during pregnancy

Recent evidence from human and animal studies suggests that antenatal psychosocial distress disorder has profound effects on morphological changes in the brain. It decreases attention span, delays neuromotor development, and affects learning, anxiety and social behavior.[100-103] Elevated levels of maternal norepinephrine results in compromised feto-placental blood flow, fetal oxygenation and cerebral ischemia.[104]

In utero tobacco and drug exposure

Recent studies have documented that in utero exposure to tobacco smoke and illicit drug increase risk of ADHD-related behaviors.[105-110] However, the potential for alcohol use during pregnancy to increase the risk of ADHD is equivocal. In a case-control study, Mick et al.,[109] reported that children with ADHD were 2.5-fold (95% CI 1.1-5.5) more likely to have been exposed to alcohol in utero than were children without ADHD. Findings from prospective cohort studies revealed no association between alcohol use during pregnancy and ADHD.[111, 112]

Infectious diseases during pregnancy

In their case-control study, Arpino et al.,[113] found that children born to women with measles, varicella, or rubella rashes during pregnancy were more likely to develop ADHD compared with children born to women without viral infection. Viral infection during winter months during the first trimester of a pregnancy or the birth of a child also pose increased risk of developing ADHD.[114]

Pre- and postnatal drug exposures

Maternal antibiotic use during pregnancy[115, 116] and exposure to Terbutaline,[117] a bronchodilator and widely used tocolytic agent, have been documented to be neurotoxic.

Use of the antidepressant bupropion during pregnancy may also pose risk for ADHD in offspring.[118] Long-term postnatal exposure to antibiotic drugs has also been found to be associated with ADHD.[119]

Postnatal factors

Environmental tobacco smoke and lead exposures are known to be associated with increased risk of ADHD or ADHD-related behaviors.[120-126] Furthermore, factors that may modify the effect of IHC on ADHD include a history of hyperbilirubinemia,[127] recurrent otitis media,[119] influenza virus infection[128] and traumatic brain injuries.[129-133] Recently, there has been interest in the comorbidity of childhood asthma with behavioral disorders including ADHD.[134-137] In a recent study, we showed chorioamnionitis at a preterm gestation to be independently associated with childhood asthma.[138] Therefore, these studies further support our hypothesis that IHC is a likely explanation for the etiological mechanisms underlying the development of ADHD.

Nutritional and metabolic

Antenatal anemia and iodine deficiency,[139, 140] low blood ferritin and zinc levels,[141-143] Type 1 diabetes before age 5,[144] and generalized resistance to thyroid hormone[140, 145] are found to be associated with increased risk of ADHD.

Knowledge gaps

Most epidemiological studies only explored the association between potential risk factors and ADHD in relation to events occurring during delivery and the postpartum period. We focus on the importance of IHC as potential contributors to the etiology of ADHD. Although previous studies have provided valuable data on the association between perinatal factor and ADHD in children, none have explored the association

between IHC and ADHD. Existing studies do tell us that 1) over half of all pregnancies complicated by PTB in the U.S. are medically indicated PTBs and 2) the risk of fetal brain injury among preterm infants with IHC is substantially higher compared to those without IHC. However, to our knowledge, there are no data regarding the long-term effect of IHC in childhood ADHD.

Unlike most epidemiological studies in this area, our large, population-based, racially, and socioeconomically diverse population will permit us to evaluate most of the factors that have previously been shown to be associated with childhood ADHD in addition to IHC. We will utilize the comprehensive electronic clinical, laboratory, and pharmacy records on all KPSC member children and their mothers (1995-2010). Thus, the diagnosis of ADHD will be based on clinical examination of subjects, which is less likely influenced by bias due to self-reporting. In addition, prescription medication use will be based on dispensing of medications, which more accurately reflects use than records of physician prescriptions.

Description of setting

Kaiser Permanente Southern California (KPSC) is a large integrated health care system that provides health services to ≥3.4 million members. Members are insured under employer sponsored or individually-purchased health plans, and state- or federally-sponsored programs such as Medicare. KPSC owns and operates 14 hospitals and over 200 other medical offices and pharmacies to deliver ambulatory care. A partnership of over 6,400 physicians representing the entire range of medical specialists provides the vast majority of care received by KPSC members. The KPSC membership is broadly representative of the racial/ethnic groups living in Southern California. Compared to the 2000 census data of Southern California region, KPSC membership for children aged between 5-17 years is similar in terms of sex and age. The rate was

slightly higher for non-Hispanic whites and blacks among members. For the past ten years, the annual number of maternal deliveries in all KPSC hospitals averaged 30,000 children.

KPSC members receive medical care almost solely in KPSC owned facilities. A tracking system is in place to assure appropriate follow-up for members receiving outside care and claims are paid upon review of documented diagnoses and services received. Among the members active on 01/01/06, outside claims for services received accounted for <3% of all utilization by children aged ≤12 years.

Oracle and SAS research data warehouse, based on information extracted from electronic medical records and legacy systems, is playing an important role in our daily research work. KPSC electronic research data warehouse contains members' current and historical medical, procedural, laboratory and pharmacy records.

Member Retention Rates

64% of all KPSC children 0-17 years of age remained in the health plan in 2010. The retention rates vary slightly by race/ethnicity with a 5-year retention rate of 63%, 61%, 71%, and 65% for Hispanics, non-Hispanic whites, Blacks, and Asian/Pacific Islanders, respectively.

Age (years)	**Count (n)**	**Membership (%) in 2010 of Children active member in 2005**				
		2006	**2007**	**2008**	**2009**	**2010**
Overall	778,907	91.4	84.0	77.6	71.5	64.5
0-2	99,613	89.9	82.6	76.8	71.8	66.5
3-6	151,506	91.0	84.4	79.1	74.1	68.8
7-12	271,325	92.0	86.0	80.9	76.3	71.1
13-17	256,463	92.5	83.1	73.6	63.8	51.5

The following three chapters are based on studies conducted to examine:

1) the accuracy of clinical diagnosis information extracted from the Perinatal Surveillance System and clinical utilization records,
2) the recent trends in the diagnosis of ADHD based on child race/ethnicity, age, gender, and median household income, and
3) the impact of in utero exposure to Ischemic-hypoxic conditions and ADHD.

Chapter 1: Accuracy of Reporting Maternal and Infant Perinatal Service System coding and Clinical Utilization Coding

Introduction

While several studies have used information from hospitalization and birth certificate records to evaluate maternal and child health programs[146] and study pregnancy outcomes such as placental abruption,[147] preeclampsia,[148] and uterine rupture,[149] the accuracy of this information has been challenged by researchers.[150-152] It is argued that medical and obstetrical information gathered for billing purposes by health providers, which are a frequent source of data for many epidemiological studies and service evaluations, may lead to bias due to poorly recorded information.[153, 154] This problem is further complicated by inconsistency in the way this important information is collected and reported across hospitals and states,[155] creating challenges for researchers in the field. Therefore, rigorous assessment of the reliability and accuracy of this clinical information is critical.

Many epidemiologic studies use birth certificate and/or hospital discharge records as a source of data.[147-149] Birth certificate records provide researchers important maternal and child information, such as maternal demographic characteristics, parity, and child sex, which have been described by many authors to be fairly accurate. However, the accuracy can be poor for other important items, such as behavioral information (e.g., smoking and drinking alcohol in pregnancy), medical and obstetrical diagnoses, procedures, and birth defects.[156-159]

Kaiser Permanente Southern California (KPSC) is a large integrated health care system with a patient population that is broadly representative of the racial/ethnic groups living in Southern California. It makes extensive use of its clinical record information for research, decision-making, and evaluation of the effectiveness of programs. The electronic medical record (EMR) system was fully implemented in all KPSC hospitals

circa 2008. Among other reasons, it was intended to provide improved information on maternal and child health issues. However, the accuracy of coding of perinatal outcomes collected from EMRs in this large health plan has not been validated. In light of the common use of clinical coding at KPSC, it is important to evaluate the quality of perinatal outcome data collected from medical records and vital records.

This study has a twofold purpose: (1) to evaluate the completeness and accuracy of reporting perinatal outcomes in health plan medical records and (2) to compare the quality of clinical information collected before and after the implementation of the EMR system.

Methods

Study Population

The study population includes 6,000 women who gave birth in KPSC-Los Angeles and KPSC-San Diego medical centers. These two medical centers were chosen because they represent the two largest medical centers of KPSC and the combination of these two medical centers provides racial/ethnic and age distribution of the general KPSC membership. We selected a stratified sample of 100 deliveries from each of the two medical centers in each of the two time periods (1/1/2003-12/31/2004 and 1/1/2008-12/31/2008). The selection of the two time periods allowed us to study the accuracy of the health plan medical records before and after the implementation of the electronic medical system. We refer to the two timeframes as the paper medical record system [PMR] period and the electronic medical record system [EMR] period. Within each medical center and period, study subjects were divided into groups based on gestational age and birthweight categories. Since the rate of preterm birth in KPSC setting is about 10%, in order to draw a valid conclusion, we need at least 10 cases per group. Women with low birth weight (<2,499 grams) babies and/or with preterm birth (<37 weeks of

gestation) were oversampled to ensure enough number of adverse events to be evaluated, especially for rare adverse outcomes. Chart abstraction was performed by trained Research Associates using a standardized abstraction instrument that contains information on medical and obstetrical diagnosis and procedures, ultrasounds, and laboratory reports.

Data sources

To compare the characteristics of study subjects with all pregnant women in KPSC and the state of California, abstractors were instructed to record each child's sex and the following maternal characteristics: age, race/ethnicity, education, prenatal care, smoking during pregnancy, and body-mass index. The Perinatal Service System (PSS) was used to extract information about KPSC births, demographic and behavioral characteristics as well as complication codes for pregnant women delivered in KPSC hospitals. Information on KPSC births is routinely entered into the PSS records to be sent to the California Department of Public Health for inclusion in the state vital statistics records. This was used to extract data about KPSC births, including demographic and behavioral characteristics as well as complication codes for pregnant women delivered in KPSC hospitals. In addition to the demographic and behavioral characteristics collected about mothers, birth information on infants delivered to all California residents in California hospitals between 2003 and 2004 was obtained from CDC Wonder,[160] a publicly available resource which includes information about California births. Data on maternal obstetric and medical outcomes were obtained from Inpatient and Outpatient Physician Encounters (clinical utilization) records. Chart abstractors printed or photocopied key portions of PSS and clinical utilization records to be reviewed and adjudicated by the study investigator (DG).

Definition of variables

Information on maternal and infant characteristics, including maternal age (<20, 20–29, 30–34, ≥35 years) and education (<12, 12, and ≥ 13 years of completed schooling), race/ethnicity (non-Hispanic white [White], non-Hispanic black [African American], Hispanic, Asian/Pacific Islander, and other racial ethnic groups), prenatal care (early or first trimester and none or late initiation), smoking during pregnancy (yes/no), child's sex (male/female), birthweight (<2500, 2500-3499, 3500-3999, and ≥4000 grams) and gestational age (<37, 37-40, and ≥41 weeks) at the time of delivery were taken from the infants' PSS. Gestational age was based on a combination of last menstrual period and clinical estimates of gestational age from medical records.

The maternal and infant clinical utilization records includes International Classification of Diseases, Ninth Revision; Clinical Modification (ICD-9-CM) codes from which we derived maternal medical and obstetrical history and procedures. The ICD-9-CM system is a widely used international coding system with standard classifications that are updated periodically.[161] Items examined, from complete chart review, in this validation study include: placental abruption, placenta previa, preeclampsia, premature rupture of membranes, chorioamnionitis, oligohydramnios, polyhydramnios, gestational fever, intrauterine growth restriction, fetal distress, fetal malpresentation, incompetent cervix, cephalopelvic disproportion, prolapsed cord, perineal laceration, Cesarean delivery, chronic hypertension, pregestational hypertension, and respiratory conditions and group B streptococcal (GBS) infection during pregnancy. The definitions of variables as well as ICD-9-CM diagnostic and procedural codes are listed in Appendix 1.

Statistical Analysis

First, we assessed the distributions of maternal and child characteristics of the study population and compared these with distributions for all women in KPSC and the

state of California who gave birth during 2003-2004 study period. Using chart-reviewed medical records as the criterion standard, we estimated true positive fraction (TPF) and false positive fraction (FPF) for medical and perinatal diagnoses and procedural codes in the (i) PSS records, (ii) the clinical utilization records, and (iii) either PSS or clinical utilization record. To examine the level of agreement with the criterion standard diagnosis, we used the kappa statistics (κ), which estimates the extent of observed agreement between two data sources after accounting for the role of chance.[162, 163] Using the chart review for the criterion of truth we calculated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for clinical codes obtained from PSS and clinical utilization records, as well as 95% confidence intervals (CI) for each measure. Sensitivity was calculated as the percentage of true-positive (by chart review) who were correctly coded. Similarly, specificity was calculated as the percentage of true negatives who were correctly coded. PPV was calculated as the percentage of true positives among all positives identified by chart review. NPV was calculated as the percentage of true negatives among all negatives identified by chart review. To account for our stratified sampling approach, PPV and NPV estimates were weighted to incorporate sampling fractions. This approach provides a more accurate estimate of predictive values for an unselected population. We also examined the accuracy of clinical coding separately for both study periods. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, SC, USA.). The study was approved by the KPSC Institutional Review Board.

Results

Table 1 includes distributions of selected infant and maternal demographic, medical, and obstetrical characteristics of study subjects, for all of KPSC, and for the state of California. In 2003 and 2004 combined, there were 59,492 and more than 1

million births to state residents in KPSC hospitals and in all California hospitals, respectively. Study subjects were more likely to be of advanced maternal age (≥35 years) and African-American. Women in KPSC and in the sample were more educated and more likely to initiate prenatal care in the first trimester than women delivered in other hospitals. As a result of our sampling approach, we also observed a higher prevalence of premature delivery with low birthweight. The very low rate of smoking in reviewed charts suggests that this exposure was not reliably captured in the birth hospital record.

Table 1 Characteristics of women and their infants delivered in 2003-04 in all KPSC hospitals and the State of California

	Sample(n=400)[‡]		KPSC hospitals	[†]California State
Characteristics	Chart reviewed	Row (%) in reviewed charts	Births N=59,492 (%)	Births N=1,053,318 (%)
Maternal age (years)				
<20	18	4.5	3,540 (5.9)	99,090 (9.4)
20-29	151	37.8	27,611 (46.4)	518,635 (49.2)
30-34	119	29.8	17,066 (28.7)	259,988 (24.7)
≥35	112	28.0	11,275 (19.0)	175,605 (16.7)
Race/ethnicity				
White	95	23.8	15,451 (26.0)	315,584 (29.9)
African-American	48	12.2	5,636 (9.5)	58,990 (5.6)
Hispanic	190	47.5	30,561 (51.4)	522,834 (49.6)
Asian/Pacific Islander	49	12.3	7,101 (11.9)	132,566 (12.5)
Other	8	2.0	685 (1.2)	10,381 (1.0)
Unknown	10	2.5	58 (0.1)	12,963 (1.2)
Education (years)				
<12	28	7.0	7,319 (12.3)	291,076 (27.6)
12	84	21.0	17,468 (29.4)	291,964 (27.7)
≥13	195	48.8	31,532 (53.0)	442,880 (42.5)
Missing	93	23.3	3,173 (5.3)	27,398 (2.6)
Prenatal care				
1st trimester	371	92.8	52,673 (88.5)	814,600 (77.3)
No or late care	27	6.8	6,254 (10.5)	133,690 (12.7)
Missing	2	0.5	565 (1.0)	17,902 (1.7)
Smoking during pregnancy	5	1.3	3,555 (6.0)	--

Child's sex				
Female	223	51.0	28,777 (48.4)	514,180 (48.8)
Male	214	49.0	30,709 (51.6)	539,138 (51.2)
Birthweight (gram)				
< 2500	321	73.7	4,311 (7.3)	54,219 (5.2)
2500-3499	85	19.5	31,120 (52.3)	583,565 (55.4)
3500-3999	23	5.3	17,682 (29.7)	312,797 (29.7)
≥4000	8	2.0	6,379 (10.7)	102,626 (9.7)
Missing	0	0.0	9 (0.0)	111 (0.0)
Gestational age (weeks)				
<37	310	77.5	5,852 (9.8)	89,890 (8.5)
37-40	84	21.0	47,691 (80.2)	720,451 (68.4)
≥41	6	1.5	5,949 (10.0)	170,860 (16.2)
Missing	0	0.0	0 (0.0)	71,986 (6.8)

[†]Data came from the Natality information of CDC webpage: http://wonder.cdc.gov/natality.html (accessed on January 24, 2012)
[‡]Sample is based on data from 2003-04 and 2008

Table 2 shows the frequencies of identified medical and obstetrical conditions in reviewed medical records, PSS, and clinical utilization, and the degree of agreement between these data sources and medical chart. As compared to PSS, perinatal risk factors and adverse outcomes were more frequently noted in chart review and from clinical utilization records.

The agreement between PSS records and medical charts ranged from slight for intrauterine growth restriction (k = 0.11 [95% CI 0.05, 0.28) to fair for gestational anemia, chorioamnionitis, and Oligo-/Polyhydramnios. Moderate agreements were observed for for fetal distress, cephalopelvic disproportion, chronic hypertension, group B streptococcal infection, and a substantially higher kappa estimates for the remaining medical and perinatal conditions. On the other hand, the agreement between the various

medical and obstetrical diagnostic coding in clinical utilization records and medical charts ranged from moderate (k = 0.46 [95% CI 0.23, 0.69]) to almost perfect (k = 0.98 [95% CI 0.95, 1.00]).

PSS and clinical utilization records were combined by counting a condition as present if it was coded in either source. The combination identified more conditions than either approach alone. The agreement between the combined PSS and clinical utilization records and medical chart ranged from moderate (k = 0.49 [95% CI 0.27, 0.70]) for respiratory conditions to a perfect agreement for cord prolapse (k = 1.00 [95% CI 1.00, 1.00]). In general, kappa values were very similar for the combined data and for clinical utilization records alone.

Table 2 Frequencies and agreements of medical and obstetrical conditions with medical chart based on data sources

Conditions	Perinatal Service System (PSS)				Clinical utilization				PSS or Clinical utilization			
	Chart	Codes Positive		Agreement with medical chart	Chart	Codes positive		Agreement with medical chart	Chart	Codes Positive		Agreement with medical chart
	No	TP (n)	FP (n)	K† (95% CI)	No	TP (n)	FP (n)	K† (95% CI)	No	TP (n)	FP (n)	K† (95% CI)
Perinatal conditions												
Placental abruption	31	18	1	0.70 (0.56, 0.85)	31	30	0	0.98 (0.95, 1.00)	31	31	1	0.98 (0.95, 1.00)
Placenta previa*	6	3	0	0.66 (0.30, 1.00)	14	14	4	0.87 (0.74, 1.00)	6	6	3	0.79 (0.57, 1.00)
Preeclampsia	81	48	2	0.68 (0.59, 0.78)	81	76	8	0.90 (0.85, 0.95)	81	80	10	0.92 (0.87, 0.97)
Gestational anemia*	31	7	0	0.33 (0.14, 0.52)	102	93	4	0.91 (0.87, 0.96)	31	30	1	0.96 (0.91, 1.00)
Premature rupture of membranes	82	50	12	0.63 (0.53, 0.73)	82	68	3	0.86 (0.80, 0.93)	82	77	15	0.85 (0.79, 0.92)
Chorioamnionitis	31	6	3	0.28 (0.09, 0.46)	31	30	1	0.97 (0.92, 1.00)	31	31	4	0.93 (0.87, 1.00)
Gestational fever*	13	7	0	0.69 (0.45, 0.92)	16	7	6	0.46 (0.23, 0.69)	13	12	3	0.85 (0.70, 0.99)
Oligohydramnios/Polyhydramnios*	18	4	0	0.34 (0.09, 0.59)	40	34	5	0.85 (0.76, 0.94)	18	17	1	0.94 (0.86, 1.00)
Intrauterine growth restriction	25	2	3	0.11 (0.05, 0.28)	25	20	5	0.79 (0.66, 0.92)	25	21	8	0.76 (0.63, 0.89)
Fetal distress*	45	19	0	0.53 (0.38, 0.68)	91	83	11	0.87 (0.81, 0.93)	45	42	4	0.90 (0.83, 0.97)
Breech/Other Malpresentation	92	62	5	0.73 (0.64, 0.81)	92	85	7	0.90 (0.85, 0.95)	92	89	12	0.90 (0.85, 0.95)
Incompetent cervix*	16	10	0	0.76 (0.57, 0.94)	26	19	12	0.64 (0.49, 0.79)	16	15	4	0.84 (0.71, 0.98)
Cephalopelvic disproportion*	6	3	3	0.49 (0.13, 0.84)	8	5	3	0.62 (0.34, 0.90)	6	5	5	0.61 (0.33, 0.90)
Cord prolapse	3	2	0	0.80 (0.41, 1.00)	3	2	0	0.80 (0.41, 1.00)	3	3	0	1.00 (1.00, 1.00)

Perineal laceration	--	N/A	N/A	--	80	80	6	0.95 (0.92, 0.99)	80	80	6	0.95 (0.92, 0.99)
Mode of delivery												
Cesarean section	55	52	3	0.94 (0.89, 0.99)	55	52	4	0.93 (0.87, 0.98)	55	53	5	0.93 (0.88, 0.98)
VBAC	8	5	3	0.62 (0.34, 0.90)	8	6	4	0.66 (0.40, 0.92)	8	6	4	0.66 (0.40, 0.92)
Medical conditions												
Chronic hypertension	47	21	1	0.58 (0.44, 0.72)	47	46	13	0.85 (0.77, 0.93)	47	46	14	0.84 (0.76, 0.92)
Prepregnancy diabetes	--	N/A	N/A	--	18	11	8	0.58 (0.38, 0.77)	18	11	8	0.58 (0.38, 0.77)
Respiratory conditions*	16	0	0	--	43	22	18	0.48 (0.34, 0.62)	16	9	9	0.49 (0.27, 0.70)
Group B streptococcal infection	57	26	12	0.49 (0.36, 0.62)	57	40	11	0.70 (0.60, 0.81)	57	47	17	0.74 (0.64, 0.83)

TP, true positive; FP, false positive, †K, kappa statistic; CI, confidence interval; VBAC, vaginal birth after cesarean delivery
*Only available up to 2005 in PSS records; therefore, the combination (PSS or Clinical utilization codes) has been studied against the chart cases where both sources were available

Table 3 shows the sensitivity and specificity for selected medical and obstetrical conditions of PSS and clinical utilization coding. Careful review of the full medical record by one of the authors (DG) was used as the criterion of truth. We observed low sensitivity of PSS records in capturing the following medical and obstetrical conditions: placental abruption (58%), placenta previa (50%), preeclampsia (59%), gestational anemia (23%), premature rupture of membranes (61%), chorioamnionitis (19%), gestational fever (54%), oligo-/polyhyramnios (22%), intrauterine growth restriction (8%), breech and other forms of malpresentation of the fetus (67%), fetal distress (42%), vaginal birth after cesarean delivery (VBAC, 63%), chronic hypertension (45%), respiratory conditions (0%), and Group B Streptococcus (GBS) infection (46%). However, the sensitivity of both PSS and clinical utilization records was low for respiratory conditions (51%). Observed specificities were mostly very high in both sources. When PSS and clinical utilization records were combined, sensitivity was substantially improved over that provided by the clinical records for only a few outcomes: PROM, gestational fever, incompetent cervix and CPD. It is notable that there was very little loss of specificity associated with this sensitivity improvement. Sensitivity and specificity based on combined PSS and clinical utilization records were much higher than either source alone.

Table 3 Sensitivity and Specificity for perinatal and medical conditions based on data sources among study sample

	Perinatal Service System (PSS) codes		Clinical utilization codes		PSS or Clinical utilization codes	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Perinatal conditions						
Placental abruption	0.58 (0.41, 0.75)	1.00 (1.00, 1.00)	0.97 (0.91, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Placenta previa*	0.50 (0.10, 0.90)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.99 (0.98, 1.00)	1.00 (1.00, 1.00)	0.98 (0.96, 1.00)
Preeclampsia	0.59 (0.48, 0.70)	0.99 (0.98, 1.00)	0.94 (0.89, 0.99)	0.97 (0.95, 0.99)	0.97 (0.95, 1.00)	0.97 (0.95, 0.99)
Gestational anemia*	0.23 (0.08, 0.38)	1.00 (1.00, 1.00)	0.91 (0.85, 0.97)	0.99 (0.98, 1.00)	0.97 (0.91, 1.00)	0.99 (0.97, 1.00)
PROM	0.61 (0.50, 0.72)	0.96 (0.94, 0.98)	0.83 (0.75, 0.91)	0.99 (0.98, 1.00)	0.94 (0.89, 0.99)	0.95 (0.93, 0.97)
Chorioamnionitis	0.19 (0.05, 0.33)	0.99 (0.98, 1.00)	0.97 (0.91, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.99 (0.98, 1.00)
Gestational fever*	0.54 (0.27, 0.81)	1.00 (1.00, 1.00)	0.44 (0.20, 0.68)	0.98 (0.97, 0.99)	0.92 (0.77, 1.00)	0.98 (0.96, 1.00)
Oligo-/Polyhydramnios*	0.22 (0.03, 0.41)	1.00 (1.00, 1.00)	0.85 (0.74, 0.96)	0.99 (0.98, 1.00)	0.94 (0.83, 1.00)	0.99 (0.98, 1.00)
IUGR	0.08 (0.00, 0.19)	0.99 (0.98, 1.00)	0.80 (0.64, 0.96)	0.99 (0.98, 1.00)	0.84 (0.70, 0.98)	0.98 (0.97, 0.99)
Fetal distress*	0.42 (0.28, 0.56)	1.00 (1.00, 1.00)	0.91 (0.85, 0.97)	0.96 (0.94, 0.98)	0.93 (0.86, 1.00)	0.97 (0.94, 1.00)
Fetal Malpresentation	0.67 (0.57, 0.77)	0.98 (0.96, 1.00)	0.92 (0.86, 0.98)	0.98 (0.96, 1.00)	0.97 (0.94, 1.00)	0.96 (0.94, 0.98)
Incompetent cervix*	0.63 (0.39, 0.87)	1.00 (1.00, 1.00)	0.73 (0.56, 0.90)	0.97 (0.95, 0.99)	0.94 (0.82, 1.00)	0.98 (0.96, 1.00)
CPD*	0.50 (0.10, 0.90)	0.98 (0.96, 1.00)	0.63 (0.30, 0.96)	0.99 (0.98, 1.00)	0.83 (0.53, 1.00)	0.97 (0.95, 0.99)
Cord prolapse	0.67 (0.14, 1.00)	1.00 (1.00, 1.00)	0.67 (0.14, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)

Perineal laceration	N/A	N/A	1.00 (1.00, 1.00)	0.98 (0.96, 1.00)	N/A	N/A
Mode of delivery						
Cesarean	0.95 (0.89, 1.00)	0.99 (0.98, 1.00)	0.95 (0.89, 1.00)	0.99 (0.98, 1.00)	0.96 (0.91, 1.01)	0.99 (0.98, 1.00)
VBAC	0.63 (0.30, 0.96)	0.99 (0.98, 1.00)	0.75 (0.45, 1.00)	0.99 (0.98, 1.00)	0.75 (0.45, 1.00)	0.99 (0.98, 1.00)
Medical conditions						
Chronic hypertension	0.45 (0.31, 0.59)	1.00 (1.00, 1.00)	0.98 (0.94, 1.00)	0.96 (0.94, 0.98)	0.98 (0.94, 1.00)	0.96 (0.94, 0.98)
Pregestational diabetes	N/A	N/A	0.61 (0.38, 0.84)	0.98 (0.97, 0.99)	N/A	N/A
Respiratory conditions*	0.00 (0.00, 0.00)	1.00 (1.00, 1.00)	0.51 (0.36, 0.66)	0.95 (0.93, 0.97)	0.56 (0.32, 0.80)	0.95 (0.92, 0.98)
GBS infection	0.46 (0.33, 0.59)	0.97 (0.95, 0.99)	0.70 (0.58, 0.82)	0.97 (0.95, 0.99)	0.82 (0.72, 0.92)	0.95 (0.93, 0.97)

CI, confidence interval; PROM, premature rupture of membranes; IUGR, intrauterine growth restriction; CPD, cephalopelvic disproportion; VBAC, vaginal birth after cesarean delivery; GBS, Group B streptococcal

*Only available up to 2005 in PSS records; therefore, the combination (PSS or Clinical utilization codes) has been studied against the chart cases where both sources were available

Table 4 shows the PPVs and NPVs for studied medical and obstetrical conditions for PSS and clinical utilization records again using reviewed medical records as the criterion standard. Predictive values have been adjusted to reflect the prevalence of preterm birth and low birth weight in the general population (as compared to the high prevalence in our sample). Despite the low sensitivity of the PSS for many diagnoses, its PPV was reasonable for most. However, we observed low PPV with PSS records for following medical and obstetrical conditions: premature rupture of membranes (41%), intrauterine growth restriction (17%), and VBAC (64%). The PPV for cephalopelvic disproportion was equally poor with both PSS and clinical utilization records. In comparison to PSS, the PPVs in clinical utilization records were much lower for placenta previa (98% vs. 79%), preeclampsia (99% vs. 65%), fetal distress (100% vs. 69%), incompetent cervix (100% vs. 43%), and chronic hypertension (98% vs. 69%).

Table 4. Positive predictive values (PPV) and Negative predictive values (NPV) of perinatal and medical conditions based on data sources among study sample

	Perinatal Service System (PSS) codes		Clinical utilization codes		PSS or Clinical utilization codes	
	PPV (95% CI)	NPV (95% CI)	PPV (95% CI)	NPV (95% CI)	PPV (95% CI)	NPV (95% CI)
Perinatal conditions						
Placental abruption	0.91 (0.49, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.95 (0.70, 1.00)	1.00 (1.00, 1.00)
Placenta previa*	0.98 (0.44, 1.00)	1.00 (1.00, 1.00)	0.79 (0.23, 1.00)	1.00 (1.00, 1.00)	0.67 (0.36, 0.98)	1.00 (1.00, 1.00)
Preeclampsia	0.99 (0.94, 1.00)	0.99 (0.98, 1.00)	0.65 (0.47, 0.83)	1.00 (1.00, 1.00)	0.66 (0.49, 0.83)	1.00 (1.00, 1.00)
Gestational anemia*	1.00 (1.00, 1.00)	0.80 (0.74, 0.86)	0.93 (0.89, 0.97)	0.96 (0.94, 0.98)	0.97 (0.91, 1.00)	0.99 (0.97, 1.00)
PROM	0.41 (0.24, 0.58)	0.99 (0.98, 1.00)	0.98 (0.91, 1.00)	1.00 (1.00, 1.00)	0.47(0.31, 0.63)	1.00 (1.00, 1.00)
Chorioamnionitis	0.85 (0.16, 1.00)	1.00 (1.00, 1.00)	0.97 (0.73, 1.00)	1.00 (1.00, 1.00)	0.92 (0.58, 1.00)	1.00 (1.00, 1.00)
Gestational fever*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.95 (0.82, 1.00)	0.98 (0.97, 0.99)	0.80 (0.60, 1.00)	0.99 (0.98, 1.00)
Oligo-/Polyhydramnios*	1.00 (1.00, 1.00)	0.99 (0.98, 1.00)	0.98 (0.93, 1.00)	1.00 (1.00, 1.00)	0.94 (0.83, 1.00)	0.99 (0.98, 1.00)
IUGR	0.17 (0.00, 1.00)	0.97 (0.95, 0.99)	0.95 (0.82, 1.00)	1.00 (1.00, 1.00)	0.92 (0.77, 1.00)	1.00 (1.00, 1.00)
Fetal distress*	1.00 (1.00, 1.00)	0.85 (0.80, 0.90)	0.69 (0.59, 0.79)	0.97 (0.95, 0.99)	0.91 (0.83, 0.99)	0.98 (0.96, 1.00)
Fetal Malpresentation	0.97 (0.90, 1.00)	0.97 (0.95, 0.99)	0.95 (0.88, 1.00)	1.00 (1.00, 1.00)	0.94 (0.86, 1.00)	1.00 (1.00, 1.00)
Incompetent cervix*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.43 (0.13, 0.99)	1.00 (1.00, 1.00)	0.79 (0.61, 0.97)	0.99 (0.98, 1.00)
CPD*	0.13 (0.07, 0.33)	1.00 (1.00, 1.00)	0.51 (0.28, 0.74)	1.00 (1.00, 1.00)	0.50 (0.19, 0.81)	0.99 (0.98, 1.00)

Cord prolapse	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Perineal laceration	N/A	N/A	0.94 (0.90, 0.98)	1.00 (1.00, 1.00)	0.94 (0.90, 0.98)	1.00 (1.00, 1.00)
Mode of delivery						
Cesarean	0.88 (0.81, 0.95)	1.00 (1.00, 1.00)	0.99 (0.97, 1.00)	1.00 (1.00, 1.00)	0.88 (0.81, 0.95)	1.00 (1.00, 1.00)
VBAC	0.64 (0.31, 1.00)	0.98 (0.97, 0.99)	0.96 (0.84, 1.00)	1.00 (1.00, 1.00)	0.96 (0.84, 1.00)	1.00 (1.00, 1.00)
Medical conditions						
Chronic hypertension	0.98 (0.80, 1.00)	0.95 (0.93, 0.97)	0.69 (0.53, 0.85)	1.00 (1.00, 1.00)	0.69 (0.53, 0.85)	1.00 (1.00, 1.00)
Pregestational diabetes	N/A	N/A	0.93 (0.78, 1.00)	0.97 (0.95, 0.99)	0.93 (0.78, 1.00)	0.97 (0.95, 0.99)
Respiratory conditions*	N/A	0.90 (0.96, 0.94)	0.60 (0.46, 0.74)	0.97 (0.95, 0.99)	0.50 (0.27, 0.73)	0.96 (0.93, 0.99)
GBS infection	0.71 (0.60, 0.82)	0.94 (0.91, 0.97)	0.68 (0.56, 0.80)	0.92 (0.89, 0.95)	0.74 (0.64, 0.84)	0.97 (0.95, 0.99)

PROM, premature rupture of membranes; IUGR, intrauterine growth restriction; CPD, cephalopelvic disproportion; GBS, VBAC, vaginal birth after cesarean delivery; Group B streptococcal

*Only available up to 2005 in PSS records; therefore, the combination (PSS or Clinical utilization codes) has been studied against the chart cases where both sources were available

PPV and NPV estimates were weighted to incorporate sampling fraction

We also examined the impact of EMR implementation on the accuracy of PSS and clinical utilization records. Our analysis revealed that the overall sensitivity, and specificity of these records improved slightly after EMR implementation (Table 5).

Table 5 Sensitivity and Specificity of clinical utilization codes for medical and obstetrical conditions before and after implementation of the EMR in 2006

	Paper chart period (2003-04)		Electronic Medical Record period (2008)	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Perinatal conditions				
Placental abruption	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.97 (0.71, 1.00)	1.00 (1.00, 1.00)
Placenta previa	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Preeclampsia	0.95 (0.84, 1.00)	1.00 (1.00, 1.00)	0.95 (0.77, 1.00)	0.95 (0.92, 0.98)
Gestational anemia	0.80 (0.69, 0.91)	0.94 (0.90, 0.98)	0.99 (0.97, 1.00)	1.00 (1.00, 1.00)
PROM	0.98 (0.90, 1.00)	1.00 (1.00, 1.00)	0.72 (0.31, 1.00)	1.00 (1.00, 1.00)
Chorioamnionitis	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.65 (0.35, 1.00)	1.00 (1.00, 1.00)
Gestational fever	0.04 (0.08, 0.16)	1.00 (1.00, 1.00)	0.99 (0.93, 1.00)	1.00 (1.00, 1.00)
Oligo-/Polyhydramnios	0.98 (0.90, 1.00)	1.00 (1.00, 1.00)	0.99 (0.95, 1.00)	1.00 (1.00, 1.00)
IUGR	0.83 (0.17, 1.00)	1.00 (1.00, 1.00)	0.95 (0.82, 1.00)	1.00 (1.00, 1.00)
Fetal distress	0.70 (0.54, 0.86)	0.89 (0.84, 0.94)	0.99 (0.96, 1.00)	0.94 (0.90, 0.98)
Fetal Malpresentation	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.95 (0.74, 1.00)	0.99 (0.98, 1.00)
Incompetent cervix	0.67 (0.32, 1.00)	1.00 (1.00, 1.00)	0.92 (0.30, 1.00)	0.99 (0.98, 1.00)
CPD	0.35 (0.00, 1.00)	0.95 (0.92, 0.98)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Cord prolapse	0.00 (0.00, 0.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Perineal laceration	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.91 (0.85, 0.97)
Mode of delivery				
Cesarean	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
VBAC	0.98 (0.89, 1.00)	1.00 (1.00, 1.00)	0.23 (0.00, 1.00)	1.00 (1.00, 1.00)
Medical conditions				
Chronic hypertension	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.99 (0.93, 1.00)	0.95 (0.92, 0.98)
Pregestational diabetes	0.49 (0.27, 0.71)	1.00 (1.00, 1.00)	0.74 (0.27, 1.00)	1.00 (1.00, 1.00)
Respiratory conditions	0.95 (0.85, 1.00)	0.90 (0.86, 0.94)	0.49 (0.28, 0.70)	0.99 (0.98, 1.00)
GBS infection	0.53 (0.38, 0.68)	1.00 (1.00, 1.00)	0.68 (0.51, 0.85)	0.89 (0.84, 0.94)

PROM, premature rupture of membranes; IUGR, intrauterine growth restriction; CPD, cephalopelvic disproportion; VBAC, vaginal birth after cesarean delivery; GBS, Group B streptococcal
Sensitivity and specificity of clinical utilization codes are assessed against findings on chart review

Discussion

In this validation study of multiple obstetrical and medical conditions, we observed higher levels of sensitivity, specificity, PPV, and NPV for clinical diagnoses and procedural coding in clinical utilization records than PSS. However, the sensitivity of gestational fever was higher for PSS than clinical utilization records. Relative to clinical utilization records, we found that PSS are not a valid source for most studied perinatal outcomes. Sensitivity was low for PSS records in capturing nearly all medical and obstetrical conditions. These findings suggest that epidemiologists should not rely exclusively on PSS to investigate adverse perinatal outcomes. With the exception of respiratory conditions during pregnancy, the combination of PSS and clinical utilization records yields higher levels of sensitivity and specificity than either of the individual data sources. Furthermore, the combined data showed marginal improvement in PPV and NPV for most conditions.

The findings of this study support continued skepticism regarding the accuracy of birth certificate records. These records vary considerably by medical and obstetrical condition, posing methodologic challenges for perinatal studies.[5, 13-15] Our findings confirm that sensitivity can be improved by using clinical diagnoses and procedural coding from clinical utilization records to identify perinatal outcomes, extending the findings of Romano et al.[154]

The quality of birth certificate and hospital discharge records has been well studied. These data are typically created for non-research purposes[164] and methods of data collection vary greatly by institution.[155] Editorials published in the *Obstetrics & Gynecology*[164] and *American Journal of Epidemiology*[165] reflect the concerns of several researchers regarding data quality in perinatal epidemiological studies. Therefore, it is important to assess the accuracy of clinical utilization and PSS records in an integrated health maintenance organization such as KPSC. Additionally, it is important to examine

the impact of EMR implementation on the quality of clinical coding in clinical utilization records.

Between the years of 2004 and 2008, KPSC fully transitioned from hard copy to electronic medical records for both inpatient and outpatient services. The highly sophisticated EMR system at KPSC is an integrated health information management and care delivery system designed to enhance the quality of patient care. It provides access to comprehensive patient information, latest research regarding relevant best medical practices, and also helps to coordinate patient care. While switching from paper to electronic medical records confers many advantages, the impact of this transition upon PSS and clinical diagnoses is not well understood. To assess the accuracy of clinical utilization records, we examined key medical and obstetrical conditions both before and after EMR implementation. For most conditions, we observed a slight improvement in the accuracy of clinical coding in clinical utilization records following implementation, suggesting that electronic medical records may positively impact data quality.

This large, population-based study, examined key medical and obstetrical conditions which have been shown to adversely affect pregnancy, including: respiratory conditions, Group B streptococcal infection, and incompetent cervix. The socio-economically diverse patient population at KPSC, which is broadly representative of Southern California, makes our findings widely generalizable. The validation of clinical utilization records from time periods both prior to and subsequent to EMR implementation further enhances the strength of this study.

Objective assessments of data quality require masking of medical record abstractors. One potential limitation of this study is that medical record abstractors were not blinded to the source of the data. We do not know if this may have influenced our

findings. However, a previous study that examined agreement showed no difference in the level of agreement between masked and unmasked medical records abstractors.[166]

Conclusions

The findings of this study suggest that PSS records have serious accuracy and validity problems in identifying perinatal outcomes. Therefore, researchers should be aware of its potential limitations. It further suggests that the accuracy of perinatal data can be improved by using a combination of both PSS and clinical utilization records. In general, we found the overall accuracy of reporting maternal and fetal clinical diagnoses and procedural coding improved slightly after the implementation of electronic medical records.

Chapter 2: Recent trends in Childhood Attention Deficit Hyperactivity Disorder

Introduction

Over the last decade, attention deficit hyperactivity disorder (ADHD) diagnosis has reached epidemic proportion in the United States.[167] It is one of the most common chronic childhood psychiatric disorders, affecting between 8 and 13 percent of all school-aged children,[2, 167-170] and persisting into adulthood for nearly half.[3, 5] The condition is characterized by hyperactivity, inattention/distractibility, and impulsivity.[2, 171] There are three major subtypes of the disease: predominantly inattentive type, predominantly hyperactive-impulsive type, and combined type.[172]

Children with ADHD are more likely than unaffected children to experience learning problems, miss school, become injured, and to experience troublesome relationships with family members and peers.[16, 17, 19] They also are at a higher risk for mental and physical conditions.[13] Between 1995 and 1999, more than 14 million children in the United States aged 5-18 years, visited physicians for ADHD.[14] By 2005, in children younger than 18 years of age, the burden of the disease and the annual cost attributable to ADHD was estimated between $36 and $52.4 billion.[22] In 2006, there were approximately 7 million ADHD-related ambulatory care visits.[15] Costs are likely to continue growing proportional to increasing ADHD prevalence.

While the etiology of ADHD is not fully understood, emerging evidence suggests that both genetic and environmental factors play important roles in the underlying pathogenesis of the condition.[173-175] Potential risk factors include, family history of ADHD,[79] maternal borderline personality disorders,[176] perinatal and environmental tobacco smoke, [120, 123, 177] toxins and lead exposure,[123, 126] maternal use of antidepressant medications during pregnancy,[178] male sex,[179, 180] low birthweight,[181] prematurity,[96] and artificial food additives.[182]

As a result of small and non-representative samples, existing studies have frequently been limited in their applicability to the general population. Furthermore, studies have relied on parent and teacher reported cases, which overestimate true prevalence.[183-185] Accurate estimates of disease burden in a large study population will provide information for determining healthcare resource allocation with respect to ADHD prevention programs. Additionally, research on the influence of child race/ethnicity on ADHD trends is sparse and identifying potential disparities in ADHD prevalence is an important step in eliminating health inequalities. KPSC systems have detailed medical records and treatment information for hundreds of thousands of children in the health plan. Using these integrated patient's medical records, we will investigate recent trends in ADHD by child race/ethnicity, age, gender, and median household income.

Methods

Data Source and Subject Selection

For this analysis, demographic and clinical information from 2001-2010 were obtained from KPSC medical records. These records include information about membership, inpatient and outpatient physician encounters, and pharmacy utilization. KPSC membership records come from a comprehensive Oracle database integrated with the electronic medical record system, retired Membership information, and perinatal services. The KPSC membership records contain information from 1988 to the present about race/ethnicity, gender, and date of birth. Information on supplemental drug benefits, Medicaid status, and changes to membership and demographics are also available.

Child ADHD was identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes from hospitalization and outpatient physician encounters across all KPSC hospitals and medical offices. Data for

medications specific to ADHD were extracted from pharmacy records. The study cohort is comprised of member children aged 5-11 years who received care at KPSC between 2001 and 2010, regardless of membership status at the time of delivery. Children with diagnoses of Autism Spectrum Disorder (n = 15,400) were excluded from the final study cohort (n = 842,830).

Potential confounders and mediators for children included race/ethnicity (categorized as non-Hispanic white [White], non-Hispanic black [Black], Hispanic, Asian/Pacific Islander, and Other/Multiple [Other] racial ethnic groups), gender (male/female), age (5-7, 8-9, and 10-11 years), and socioeconomic status. Socioeconomic status was defined according to median family household income based on census tract of residence (< $29,999, $30,000-$49,000, $50,000-$69,999, $70,000-$89,999, and ≥ $90,000). Child race/ethnicity was determined using maternal and paternal race/ethnicity. The Other/Multiple (Other) race/ethnicity category includes non-Hispanic children with multiple recorded races.

Primary diagnosis of ADHD was determined using ICD-9-CM diagnosis code 314.x from child hospitalization, outpatient office visit, and emergency room visit in all KPSC hospitals. The following criteria were used to diagnose and code ADHD within KPSC: 1) a child behavior checklist must be filled out by parents, care providers, and teachers to describe child behavioral and emotional problems and 2) a clinical interview must be performed by a qualified mental health professional. In a preliminary study conducted for this project, 96% of children with ADHD were found to have been diagnosed by doctors specializing in the diagnosis and treatment of ADHD. To further increase the specificity of the case definition, we used data for receipt of drugs specific to ADHD. These drugs included: amphetamine aspartate, amphetamine sulfate, dextroamphetamine aspartate, dextroamphetamine sulfate, and methylphenidate hydrochloride.

Statistical analysis

Eligible subjects for our analysis of ADHD trends were children aged 5-11 years who were members of the health plan and were cared for in KPSC between 01/01/2001 and 12/31/2010. First, we compared the distribution of child age, gender, race/ethnicity, and median household income by ADHD status using χ^2 tests. Second, the annual rates of ADHD per 100 children were estimated using Poisson regression from GENMOD. For this, the yearly count of ADHD was the outcome variable and year of diagnosis was the independent variable, adjusting for potential confounding factors (Table 1). Dummy variables were constructed for the various categories of potential confounders. Predicted probabilities from the adjusted model were used to estimate the mean of the predicted probabilities. Third, increases of relative risk from 2001 to 2010 were quantified using regression analysis. The population-based nature of our study and the low rates of ADHD allows odds ratios to be reasonably good approximations of relative risks.

We further stratify the analyses by child age and gender. We examined temporal trends in the diagnosis of ADHD by comparing rates in the earliest (2001) versus most recent (2010) years. The significance of differences in ADHD trend rates was tested using linear regression analysis.

Utilization records with missing values on race are more likely to have come from non-english speaking children (Asian/Pacific Islander and Black racial groups). As compared to whites, these children are less likely to utilize mental health services.[186, 187] The large amount of missing race/ethnicity data observed in our cohort (Table 1) may have greatly affected estimates for Asian/Pacific Islanders and black racial/ethnic groups. To investigate the impact of missing data, we performed two sensitivity analyses. For the first, children with missing race/ethnicity data were classified as black. A similar analysis was conducted in which these same children were assigned a racial/ethnic status of Asian/Pacific Islander. All statistical analyses were performed

using SAS (Version 9.2; SAS Institute Inc., Cary, SC, USA). This study was approved by the KPSC Institutional Review Board.

Results

Among children in the study who were cared for in KPSC between 2001 and 2010, 4.9% (39,200/842,830) had a diagnosis of ADHD. Over the same period, the number of children with prevalent ADHD increased from 6,869 cases in 2001 to 8,006 cases in 2010. As of 2010, the rate of ADHD was at an all-time high of 3.1 percent. Both the race/ethnicity and gender-specific mean ages at ADHD diagnosis remained relatively stable throughout the study period, ranging from 8.4 to 9.5 years.

Table 1 includes distributions of child characteristics based on ADHD status. White and black children were more likely to be diagnosed with ADHD. By contrast, Hispanics and Asian/Pacific Islanders were less likely to be diagnosed with ADHD. Children between 8-9 years of age and those from high-income families (≥ $70,000 UD) were more likely to be diagnosed with ADHD, as were boys in general.

Table 1 Distribution of child characteristics based on ADHD[†] status

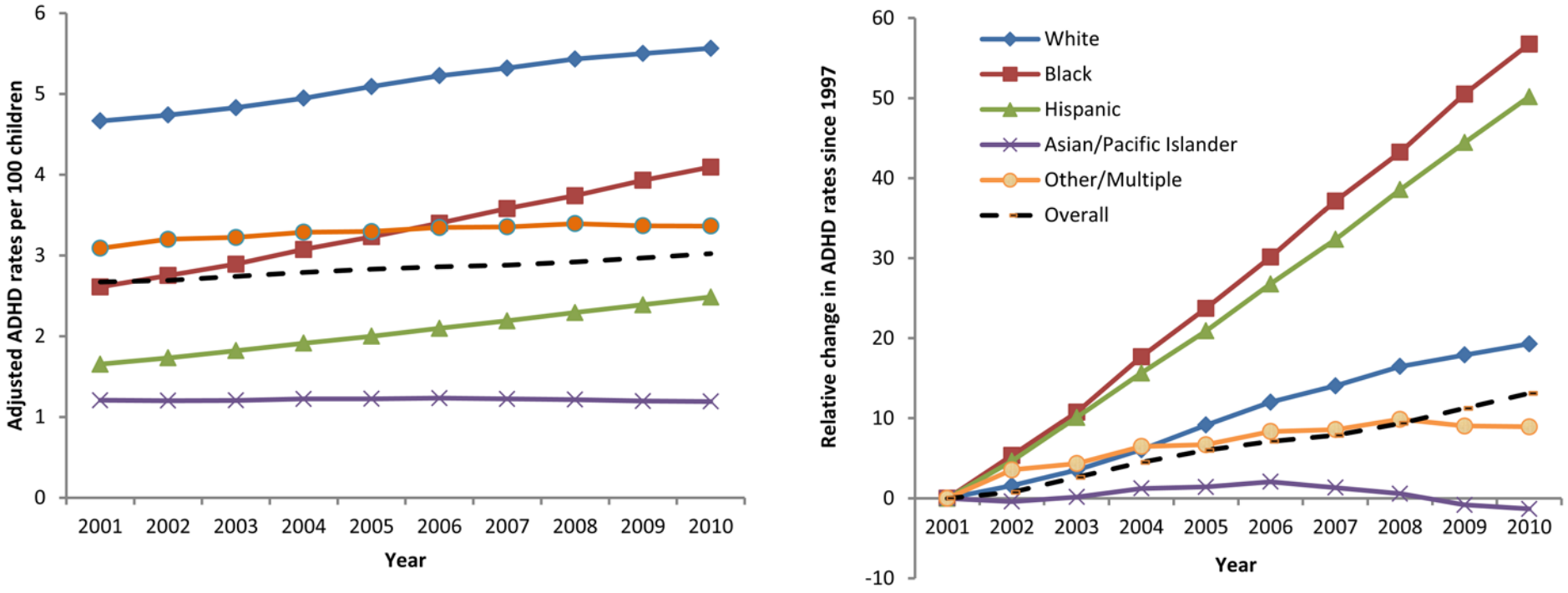
Characteristics	No ADHD n= 803,630 (%)	ADHD n= 39,200 (%)
Child age (years)*		
5-7	23.9	16.4
8-9	17.2	26.6
10-11	59.0	57.0
Child gender*		
Female	50.2	25.4
Male	49.9	74.6
Child race*		
Non-Hispanic White	18.3	34.3
Non-Hispanic Black	8.1	10.2
Hispanics	40.8	31.8
Asian/Pacific Islanders	5.6	2.6
Others[†]	2.1	2.5
Unknown	25.2	18.6
Household income[‡]		
< $30,000	5.7	4.0
$30,000-$49,999	27.6	22.3
$50,000-$69,999	29.1	28.1
$70,000-$89,999	19.8	22.8
≥ $90,000	17.5	22.3

*Differences between ADHD and No-ADHD by child characteristics were statistically significant ($p < .001$)

[†]ADHD, Attention Deficit Hyperactivity Disorder; [‡]Median household income based on census tract information; [†]Other race and ethnicity, includes non-Hispanic children with multiple recorded race

Figure 1 shows race/ethnicity-specific adjusted rates of ADHD and their relative increases between 2001 and 2010. During the study period, we observed markedly higher rates of ADHD diagnoses among whites (4.5%) and a relatively lower rate among Asian/Pacific Islanders (1.1%). Between 2001 and 2010, blacks (70%) show the highest relative increase in ADHD rates, followed by Hispanics (60%), and whites (30%) (p - value for linear trend <.001). Rates for Asian/Pacific Islanders essentially remained unchanged over time.

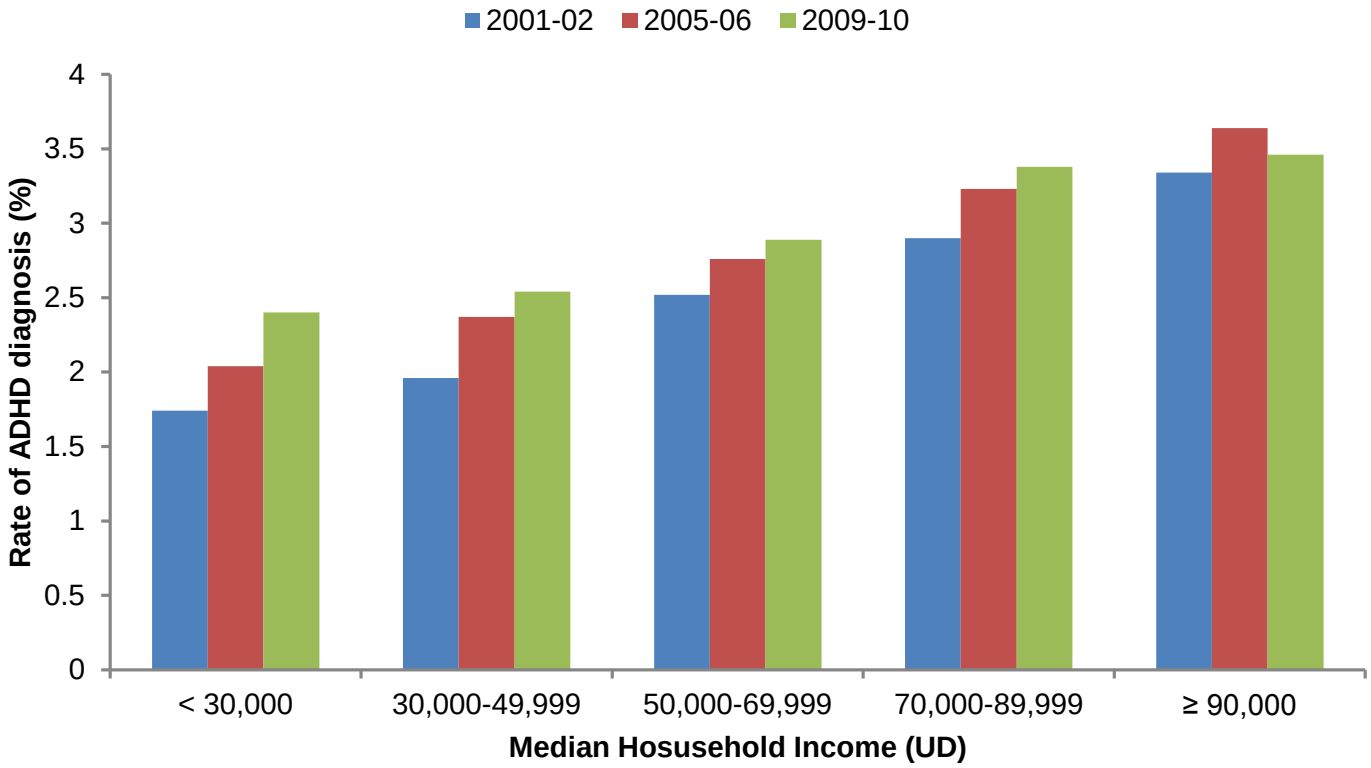
Figure 1 Race/ethnicity specific rates (A) and percent changes in ADHD relative to 2001 (B): Kaiser Permanente Southern California (2001-2010)



†Adjustments were made for child age, gender, and median household income

Figure 2 shows biannual median household income rates of ADHD diagnosis with adjustment for race/ethnicity, age, and gender. We observed a markedly higher rate of ADHD diagnosis among children living in high-income household (p-value for linear trend <.001).

Figure 2 Median household income specific adjusted rate of ADHD diagnosis during three time periods: Kaiser Permanente Southern California (2001-2010)



†Adjustments were made for child race/ethnicity, age, and gender

Table 2 and 3 show adjusted ADHD rates and relative changes from the earliest to the most recent years. Also included are significance levels for temporal trends derived using Poisson regression analysis. After controlling for child age and household income (Table 2), we observed increases in ADHD diagnosis rates over the study period for white, Hispanic, and black race/ethnicity and gender categories. ADHD increased among whites from 4.7% in 2001 to 5.6% in 2010 (RR 1.3, 95% CI 1.2, 1.4), blacks from 2.6% in 2001 to 4.1% in 2010 (RR 1.7, 95% CI 1.5, 1.9), Hispanics from 1.7% in 2001 to 2.5% in 2010 (RR 1.6, 95% CI 1.5, 1.7). Rates for Asian/Pacific Islander race/ethnicity group remained unchanged over time. In all racial/ethnic categories, rates for males across the study period were substantially higher than those for females. However, between 2001 and 2010 we noted a marked increase in rates of ADHD diagnosis among females of black racial groups (RR 1.9, 95% CI 1.5, 2.3).

Table 3 shows race/ethnicity and age-specific ADHD rates with adjustment for gender and median family household income. During the study period, ADHD rates increased consistently for all race/ethnicity and age categories. Although white children had substantially higher ADHD rates than non-white children in every age group, the increase was especially pronounced among blacks in the age groups of 5-7 (RR 1.8, 95% CI 1.4, 2.2) and 8-9 (RR 1.8, 95% CI 1.5, 2.1). The same was true for Hispanics in the age groups of 8-9 (RR 1.7, 95% CI 1.5, 1.8) and 10-11 (RR 1.7, 95% CI 1.6, 1.9) years.

Table 2. Rates and relative increases in ADHD diagnosis among KPSC member children by race/ethnicity and gender, 2001-2010

	Child race/ethnicity and gender specific adjusted rates per 100 children														
	White			Hispanic			Black			Asian/Pacific Islander			Others		
Year	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total
2001	2.49	6.74	4.66	0.73	2.56	1.65	1.19	3.99	2.61	0.47	1.90	1.21	1.64	4.61	3.09
2002	2.56	6.81	4.74	0.76	2.68	1.73	1.28	4.17	2.75	0.48	1.88	1.20	1.65	4.75	3.20
2003	2.63	6.92	4.83	0.80	2.82	1.82	1.37	4.37	2.89	0.49	1.88	1.21	1.66	4.78	3.22
2004	2.72	7.06	4.95	0.84	2.95	1.91	1.47	4.59	3.07	0.51	1.88	1.22	1.67	4.84	3.29
2005	2.81	7.24	5.09	0.88	3.08	2.00	1.58	4.80	3.23	0.52	1.87	1.22	1.64	4.89	3.30
2006	2.91	7.40	5.22	0.91	3.23	2.10	1.68	5.02	3.40	0.53	1.88	1.23	1.68	4.95	3.35
2007	2.99	7.52	5.32	0.96	3.70	2.19	1.79	5.26	3.58	0.54	1.85	1.22	1.70	4.96	3.35
2008	3.08	7.64	5.43	1.00	3.52	2.29	1.92	5.48	3.74	0.55	1.83	1.21	1.72	4.98	3.39
2009	3.15	7.68	5.50	1.04	3.67	2.39	2.05	5.71	3.93	0.56	1.79	1.20	1.72	4.98	3.37
2010	3.21	7.74	5.56	1.08	3.82	2.48	2.18	5.93	4.09	0.57	1.78	1.19	1.74	5.00	3.36
Relative Risk 2001 vs 2010 (95% CI)	1.3 (1.2, 1.5)	1.2 (1.1, 1.3)	1.3 (1.2, 1.4)	1.7 (1.5, 1.9)	1.6 (1.5, 1.7)	1.6 (1.5, 1.7)	1.9 (1.5, 2.3)	1.6 (1.5, 1.8)	1.7 (1.5, 1.9)	1.1 (0.7, 1.8)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	1.4 (0.9, 2.2)	1.3 (1.0, 1.7)	1.1 (1.0, 1.2)
P-value for linear trend from 2001 to 2010	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	.608	.723	0.928	.107	.030	.010

[†]Adjustments were made for child age and median household income

Table 3. Rates and relative increases in ADHD diagnosis among KPSC member children by race/ethnicity and age, 2001-2010

	Child race/ethnicity and age (yr) specific adjusted rates per 100 children														
	White			Hispanic			Black			Asian/Pacific Islander			Others		
Year	5-7 yr	8-9 yr	10-11 yr	5-7 yr	8-9 yr	10-11 yr	5-7 yr	8-9 yr	10-11 yr	5-7 yr	8-9 yr	10-11 yr	5-7 yr	8-9 yr	10-11 yr
2001	2.64	5.69	6.10	1.04	2.13	2.09	1.54	3.23	3.31	0.80	1.63	1.41	1.91	3.62	3.90
2002	2.69	5.80	6.25	1.07	2.25	2.18	1.66	3.38	3.44	0.78	1.60	1.45	1.89	3.83	3.99
2003	2.71	5.95	6.44	1.10	2.36	2.31	1.77	3.56	3.60	0.77	1.57	1.53	1.87	3.98	4.03
2004	2.76	6.07	6.61	1.15	2.46	2.45	1.89	3.79	3.76	0.75	1.54	1.58	1.88	4.00	4.24
2005	2.78	6.23	6.85	1.19	2.55	2.57	2.02	3.96	3.95	0.73	1.52	1.62	1.87	3.93	4.45
2006	2.83	6.38	7.04	1.23	2.67	2.70	2.15	4.16	4.17	0.70	1.53	1.66	1.85	4.04	4.45
2007	2.87	6.46	7.26	1.27	2.79	2.81	2.28	4.43	4.34	0.69	1.48	1.72	1.92	4.06	4.45
2008	2.92	6.62	7.47	1.31	2.90	2.97	2.45	4.59	4.50	0.68	1.43	1.79	1.95	4.04	4.56
2009	2.98	6.76	7.66	1.36	3.04	3.11	2.63	4.76	4.75	0.67	1.40	1.82	1.93	4.15	4.56
2010	3.03	6.92	7.89	1.41	3.17	3.26	2.79	5.02	4.91	0.66	1.38	1.85	1.93	4.26	4.53
Relative Risk 2001 vs 2010 (95% CI)	1.2 (1.2, 1.3)	1.3 (1.2, 1.5)	1.4 (1.3, 1.5)	1.4 (1.3, 1.6)	1.7 (1.5, 1.8)	1.7 (1.6, 1.9)	1.8 (1.4, 2.2)	1.8 (1.5, 2.1)	1.6 (1.4, 1.9)	0.8 (0.6, 1.4)	0.9 (0.6, 1.2)	1.3 (0.9, 1.7)	1.0 (0.9, 2.7)	1.3 (1.1, 2.2)	1.3 (0.9, 1.8)
P-value for linear trend from 2001 to 2010	.004	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	.073	.025	.154

[†]Adjustments were made for child gender and median household income

It is important to note that the degree of missing racial/ethnic data is substantial for blacks and Asian/Pacific Islanders (Table 1) and may have biased our findings. To investigate this potential bias, we performed a sensitivity analysis, separately assigning race/ethnicity values of black and Asian/Pacific Islander to children with missing data. Results were comparable to those in which children with missing race/ethnicity had been excluded from analysis (data not shown).

Discussion

Within the ethnically diverse patient population at KPSC, we observed increasing trends in ADHD diagnosis across the study period. Our study demonstrated wide variation in ADHD diagnosis by child race/ethnicity, age, sex, and median household income. White, black, and Hispanic children were more likely to be diagnosed with ADHD than Asian/Pacific Islanders and children of "Other" race/ethnicities. Furthermore, children living in high-income households were at increased risk of diagnosis with ADHD.

Confirming findings from previous studies, we observed a female-to-male ratio of approximately 3:1 in ADHD rates.[179, 180] Our new findings highlight disproportionately higher relative increases in ADHD diagnosis rates among girls of black racial/ethnic groups in recent (2010) years. This suggests narrowing of gaps between genders from previous years. Mean age at ADHD diagnosis for girls of Hispanic race/ethnicity has increased over the study period by approximately one year, from 8.4 to 9.3 years ($p < 0.01$). This finding is partially explained by increases in ADHD diagnosis rates among Hispanics aged 8-11 years, suggesting delayed diagnosis.

While the reasons for increasing ADHD rates are not well understood, there are several potential contributing factors. Variability in ADHD surveillance methods between institutions may partially explain increases in ADHD rates. This may also account for

discrepancies in prevalence estimates seen in the literature. Because the signs and symptoms for ADHD can often resemble normal behaviors, diagnosing the disorder can be challenging. Prevalence estimates are further complicated by comorbid conditions, including learning disabilities, conduct disorders, and anxiety disorders. Furthermore, higher awareness of ADHD among parents and physicians, as well as increased utilization of screening and other preventive services, may contribute to diagnosis rate increases. The higher rates of ADHD in affluent white families likely represents an effort by these highly educated parents to seek help for their children who may not be fulfilling their expectations with regard to school work. The increasing number of girls with ADHD is an interesting finding and could represent an effort by parents to get more help for their daughters. Rates of ADHD in this study, while lower than some previous estimates, are similar to those reported.[168, 188] Lower rates of ADHD in our study may be explained by our use of more stringent case selection criteria.

Diagnoses of ADHD were based on DSM-IV criteria, requiring subjects to be: symptomatic for at least 6 months, impaired from symptoms in at least two settings (e.g., home and school), and significantly impacted by a clinical impairment.[172] DSM-IV criteria was not strictly followed in many of the previous epidemiological studies examining ADHD. After surveying 3,900 pediatricians and other primary care physicians, Wasserman et al.,[189] reported that only 38% of clinicians used DSM-IV criteria for diagnosing ADHD. This finding highlights the important role of qualified mental health professionals in the diagnosis of childhood ADHD. KPSC employs stringent criteria based on DSM-IV that must be met prior to diagnosis of ADHD. These include: 1) a child behavior checklist must be filled out by parents, care providers, and teachers to describe the child behavioral and emotional problems and 2) a clinical interview must be performed by a qualified mental health professional. These criteria lead to greater validity in the ADHD diagnoses made at KPSC relative to those based on parent/teacher

reports or diagnoses of health professionals. A preliminary analysis of diagnosing physician specialty was conducted among children at KPSC who were diagnosed with ADHD between the years of 2007 and 2008. We found that 96% of these children had been diagnosed by physicians who specialize in the disorder.

Strength and limitations: The large study cohort used in this study was based on a racially and socioeconomically diverse member base that is reasonably generalizable to the population. Furthermore, several potential confounding factors were considered during analysis. We were able to demonstrate heterogeneity in recent ADHD diagnosis trends based on child race/ethnicity, age, sex, and median household income. One serious limitation of most other epidemiological ADHD studies to date has been misclassification of the disorder due to reliance on parent/teacher reports. According to data from the National Children's Health Survey, there was a 21.8% increase in the prevalence of parent-reported childhood ADHD between 2003 and 2007.[185] Teacher-report has also been found to overestimate ADHD rates (23%).[183] This is primarily due to the lack of stringent diagnosis criteria, such as duration of symptoms, age at onset, and demonstrated dysfunction in multiple settings (criterion C of DSM-IV). Unlike many previous studies, case identification in our study required a combination of: (i) diagnosis on at least two occasions by specialized physicians or (ii) diagnosis on one occasion and at least two refills of medications specific to ADHD. We believe this approach increases the specificity of case identification. Previous studies assessing mental health services utilization in the state of California reported that black and Asian/Pacific Islander children are less likely to receive the service.[186, 187] The large amount of missing race/ethnicity data in our study (Table 1) is a significant limitation, which warrants some caution when interpreting the findings. However, in a sensitivity analysis after including data on those

children with missing values for race to black and Asian/Pacific Islander race/ethnicity data yielded similar estimates.

Conclusions

The findings of this study suggest increasing trends in the clinical diagnosis of ADHD among children in the health plan. We also observed disproportionately high ADHD diagnosis rates among white children and dramatic increases among girls of black racial/ethnic.

Chapter 3: The Impact of in Utero Exposure to Ischemic-Hypoxic Conditions on Childhood Attention Deficit Hyperactivity Disorder

Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a highly prevalent chronic childhood disease which persists into adulthood for approximately half of affected children.[1-5] In the United States, 8 to 13 percent of all children aged 5 to 17 years suffered from ADHD in 2008.[1, 2, 168] The disorder is characterized by hyperactivity, inattention/distractibility, and impulsivity. Additionally, children with ADHD are more likely to develop other mental and physical conditions, often requiring intensive medical care and special social and educational services.[8, 9, 12] Nationally, the annual cost of illness related to ADHD in children aged ≤18 years is estimated to be between $36 and $52.4 billion, in 2005 dollars. The high prevalence and chronic nature of ADHD combined with its rising health care costs[22] highlight its importance as a public health priority.

Previous studies indicate that genetic,[75, 77] environmental,[175, 190] and pre- and postnatal[95, 191-193] factors are associated with altered neurodevelopment; however, we are still far from fully understanding the pathoetiology of ADHD. Emerging evidence suggests that ischemic-hypoxic conditions (IHC) in pregnancy resulting from acute (placental abruption, birth asphyxia) and chronic (preeclampsia) perinatal events, have adverse consequences on fetal brain development that are not apparent at birth.[100, 101, 138, 194-196] Although previous studies have provided important background data about in utero exposure to IHC on risk of fetal brain injury,[27, 33-44] its impact on the development of ADHD is not known.

Given the increased risk for fetal brain injury confirmed by IHC and its substantial contribution to medically indicated preterm births, we hypothesize that IHC is an important and independent risk factor for childhood ADHD. Preeclampsia and fetal

asphyxia may be modifiable risk factors for ADHD; therefore, the clinical application of this new knowledge has direct implications in identifying newborns at risk and could be useful in disease surveillance and early diagnosis when treatment is more effective.

Methods

Data Source

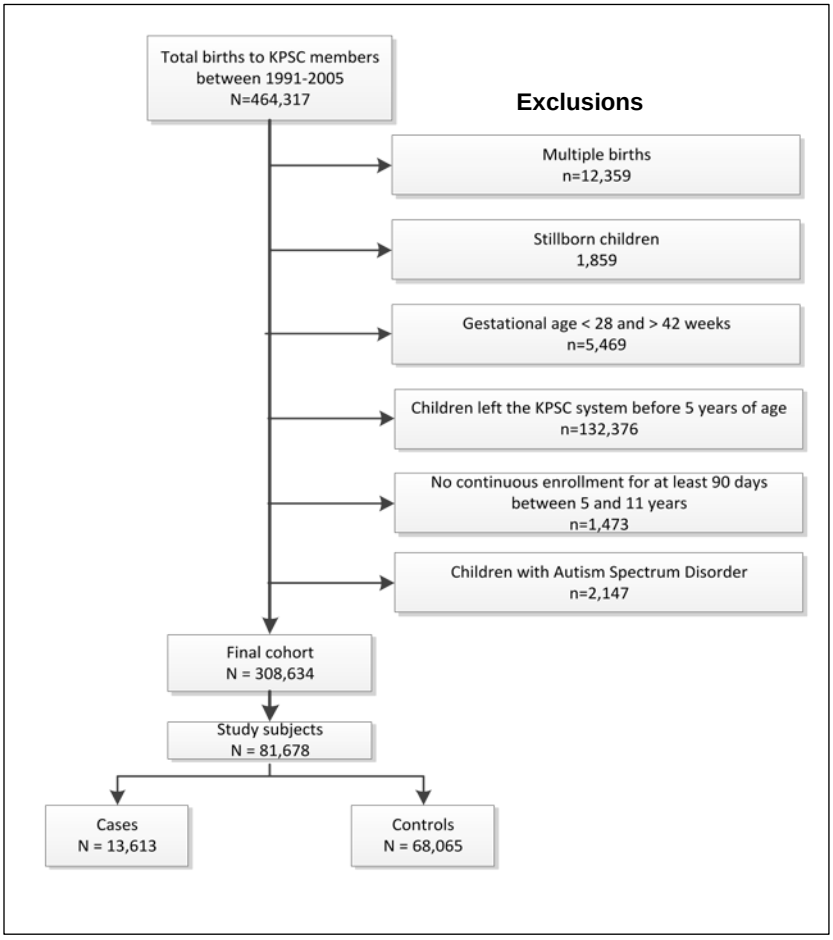
This study utilizes population-based data from children born at Kaiser Permanente Southern California (KPSC) health system between the years 1991 and 2005 (n=464,317). For each study subject, we compiled data from the Perinatal Service System (PSS), Hospital Inpatient, Outpatient Physician Encounters, Laboratory and Pharmacy records. Information extracted from PSS records includes maternal sociodemographic and behavioral characteristics, perinatal complications, and child race/ethnicity, age, and gender. Hospital inpatient and outpatient physician encounter records include maternal obstetrical complications and procedures as well as child medical history. Laboratory records were used to extract data on fetal asphyxia (cord blood pH and base excess values). Pharmacy records were used to extract data on medication specific to ADHD.

Subject Selection

This study employs a case-control approach within an established cohort of children. To be included in the cohort, children must have been born to KPSC-members, be a singleton birth between 28 and 42 weeks of gestation in KPSC hospitals between 01/01/1991 and 12/31/2005, and were KPSC health plan members at least three months between 5-11 years of age, during the years 1995-2010. Because small lapses are not uncommon due to administrative procedures, gaps in enrollment of up to 31 days were permitted. Births at <28 weeks of gestation were excluded because of high morbidity and

mortality among such infants. The eligible study cohort is described in Figure 1. Excluding children with a clinical diagnosis of autism yielded a total of 308,634 children.

Fig. 1. Flow diagram of study cohort composition.



Gestational age, expressed in completed weeks, was based on the clinical estimates of gestational ages contained in electronic medical records. Potential confounders included child sex (male/female), median family household income based on census tract of residence (< $29,999, $30,000-$49,000, $50,000-$69,999, $70,000-$89,999, and ≥ $90,000), maternal age (< 20, 20–29, 30–34, ≥35 years) and education (<12, 12, and ≥ 13 years of completed schooling), prenatal care (early or first trimester

and none or late initiation), smoking during pregnancy (yes/no), and maternal psychosocial disorders during pregnancy (yes/no). Child race/ethnicity was based on maternal and paternal race/ethnicity from the PSS records and categorized as non-Hispanic white (White), non-Hispanic black (African American), Hispanic, Asian/Pacific Islander, and other/mixed racial ethnic groups. Children of “unknown” or missing race/ethnicity were excluded from all race/ethnicity-specific analyses due to their small number (<3.3%).

Definition of the exposure (IHC) required presence of at least one of the following acute or chronic perinatal conditions: placental abruption [premature separation of a normally implanted placenta; International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 6412.x, and 762.1], preeclampsia [hypertensive disorder detected for the first time after 20 weeks' gestation combined with proteinuria and/or edema; ICD-9-CM codes 642.x], and perinatal risk factors for birth asphyxia [ICD-9-CM codes 768.x] included malpresentation of the fetus [ICD-9-CM codes 652.x, 669.x, 763.0, and 72.x], dystocia [ICD-9-CM codes 653.x, 660.x, 661.x, 662.x, and 658.x], cord complication [ICD-9-CM codes 762.4, 663.x, and 73.92], apgar score <7 at 5 minute, acute respiratory distress syndrome [ICD-9-CM codes 769.x and 770.x]).[23, 24, 197-201] We validated the accuracy of the ICD-9-CM coding by abstracting a random sample of 400 maternal medical records. Children with low birthweight or earlier gestational age were oversampled to insure adequate number of these risk factors to be reviewed. Because we applied a stratified sampling approach, the accuracy measures were estimated using weighted analyses to incorporate the sampling fraction. This approach provides a more accurate estimate of the prevalence of the rare outcomes. Abstracted records were compared with diagnosis codes collected electronically. After adjusting for sampling fractions, the estimated sensitivity, specificity, positive, and negative predictive values for placental abruption, IUGR, fetal distress, and preeclampsia were (97%, 100%, 100%,

100%), (80%, 99%, 95%, 100%), (91%, 96%, 69%, 97%), and (94%, 97%, 65%, 100%), respectively. These findings highlight the validity of the ICD-9-CM diagnosis codes used for ascertainment of the exposure variables.

To be eligible as a case, the child must meet the following criteria: (i) positive for clinical-diagnosed ADHD (ICD-9 codes 314.x) on at least two occasions or positive for diagnosis on one occasion and at least 2 refills of medications specific to ADHD (including amphetamine aspartate, amphetamine sulfate, dextroamphetamine aspartate, dextroamphetamine sulfate, methylphenidate hydrochloride) during the follow-up period. This approach increases the specificity of case ascertainment. Prescription medication use was based on records of medications dispended. For the clinical diagnosis of ADHD to be made the following criteria must be met. 1) The Child Behavior Checklist must be filled out by parents, care providers, and teachers to describe the child's behavioral and emotional problems and 2) a clinical interview must be performed by a qualified mental health professional. In a preliminary study conducted for this project, 96% of children with ADHD were primarily diagnosed by doctors who specialized in the diagnosis and treatment of ADHD. Incidence density (risk set) sampling was used to sample the cases and the comparison group (controls). For each case, five controls without ADHD at the time of case identification were selected randomly from all those matching on age at outcome. These controls were at-risk of subsequently developing the outcome. Approximately 1,000 (1.5%) of selected controls developed the outcome over the course of the study. Subjects were eligible for participation in the control sample for more than one case.

Statistical analysis

We performed a nested case-control analysis to examine the association between IHC and ADHD diagnosis. Statistical analysis was performed in four steps: 1)

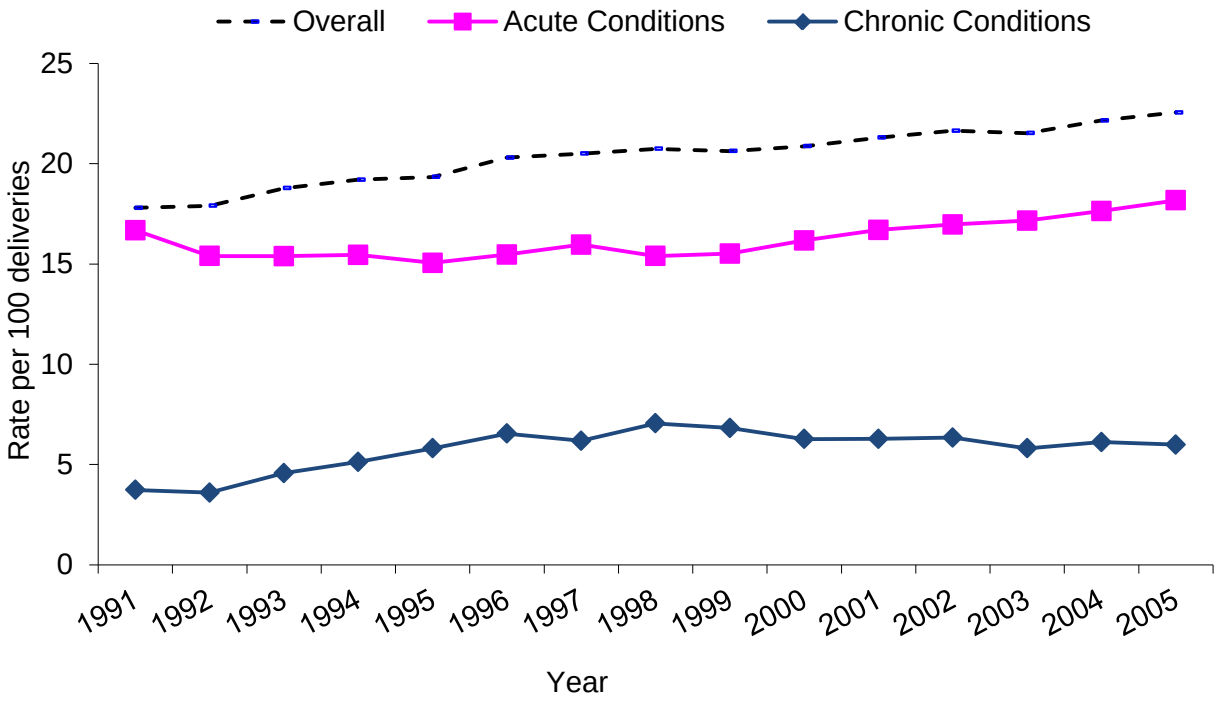
we examined the distributions of maternal and child characteristics by case status, 2) a conditional logistic regression model was fitted to examine the association between IHC and childhood ADHD before and after controlling for potential confounding variables (maternal age, education, prenatal care, household income, smoking and psychosocial disorder during pregnancy, gestational age at birth, and child's sex and race/ethnicity). Confounders were entered in the model using dummy variables (0, 1) with break points shown in Table 1. We assessed for changing frequency of ADHD diagnosis by the year of diagnosis, 3) we repeated the analysis using conditional logistic regression approach in matched cases and controls (1:5 ratio) by gestational age and by child race/ethnicity groups in an attempt to characterize risks in the various categories. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to quantify associations. Potential confounding variables were chosen a priori or if they resulted in shifts of at least 10% between the unadjusted and adjusted ORs. To estimate the impact of IHC on risk of ADHD in the population, we calculated the population attributable fraction (PAF) by employing the following formula: PAF = pdi [(ORi – 1)/ORi], where ORi is the adjusted odds ratio for the exposure category and pdi represents the proportion of cases in the population from the ith exposure category. This formula has specifically been designed to be used with an adjusted effect estimate.[202] All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, SC, USA.). This study was approved by the KPSC Institutional Review Board.

Results

Cases comprised 13,613 children born at KPSC and diagnosed with ADHD between the age of 5 and 11 years were selected. These were individually matched to 68,065 controls (Figure 1). During the study period, the incidence rate of ADHD at KPSC was 4.3 per 100 children. Mean child age at time of first diagnosis was approximately 8

years (SD = 1.7). The overall rate of IHC diagnoses per 100 singleton birth increased from 17.8% in 1991 to 22.6% in 2007-08 (p-value for trends <.001, Figure 2).

Figure 2. Temporal Trends in Ischemic-Hypoxic Conditions by Subtypes



Characteristics of mothers and children in both the case and control groups are shown in Table 1. In contrast with control mothers, case mothers were more likely to be older, have ≥12 years education, high household income, history of smoking, and psychosocial disorders during pregnancy. Case children were more likely to be male and of White or African American and less likely to be Hispanics or Asian/Pacific Islanders.

Table 1 Distribution of maternal and infant characteristics based on ADHD† status

Characteristics	No ADHD n= 68,065 (%)	ADHD n= 13,613 (%)
Maternal age (years)*		
<20	7.5	6.9
20-29	48.5	46.3
30-34	26.6	27.1
≥35	17.4	19.8
Maternal education (years)*		
<12	16.5	10.2
12	31.3	32.4
≥13	45.8	51.7
Household income‡		
< $29,999	6.2	4.5
$30,000-$49,999	27.4	21.9
$50,000-$69,999	29.0	27.5
$70,000-$89,999	19.4	22.6
≥ $90,000	18.0	23.5
Parity		
Parity 0	39.8	44.8
Parity 1	32.9	32.3
Parity 3	17.3	15.4
Parity ≥ 3	10.0	7.5
Gestational age at birth (weeks)		
28-33	1.4	2.0
34-36	5.4	6.5
37-42	93.2	91.5
Smoking during pregnancy*	9.4	10.9
Late initiation of prenatal care*	18.3	13.8
Maternal psychosocial Disorder*	2.5	4.1
Child race*		
Non-Hispanic White	22.1	31.9
Non-Hispanic Black	9.9	11.5
Hispanics	36.5	26.1
Asian/Pacific Islanders	7.1	2.7
Others/Mixed	20.8	24.8
Child's sex*		

Female	49.5	25.7
Male	50.5	74.3

[†]ADHD, Attention Deficit Hyperactivity Disorder; [‡]Median household income based on census tract information

*Differences between ADHD and No-ADHD by maternal and infant characteristics were statistically significant (p <.001)

The proportion of cases exposed to IHC in utero was significantly higher (23.4%) than controls (19.9%). Case children were significantly more likely (adj. OR 1.16, 95% CI 1.11, 1.21) than controls to be exposed to IHC (Table 2). Although we observed a significant association between each component of IHC (placental abruption and birth asphyxia and preeclampsia) and childhood ADHD in un-adjusted analysis, the association between placental abruption and ADHD was attenuated and became insignificant (adj. OR 1.18, 95% CI 0.97, 1.44) after accounting for effect of maternal age, education, smoking status during pregnancy, parity, perinatal care, household income, psychosocial disorder during pregnancy, child race/ethnicity, and gender. Further adjustment for gestational age did not substantially change this result (data not shown). The adjusted association of birth asphyxia with ADHD (OR 1.13, 95% CI 1.07, 1.19) was even weaker than for placental abruption but with the larger number affected, achieved statistical significance. In contrast to these acute conditions, preeclampsia (OR 1.34, 95% CI 1.24, 1.44) had a stronger association with ADHD and remained significant. The estimated maternal age, education, smoking during pregnancy, parity, prenatal care, household income, psychosocial disorder during pregnancy, child race/ethnicity, and gender- adjusted PAF for IHC and ADHD was 3%. The estimated proportion of ADHD attributable to preeclampsia was 2%.

Table 2. Associations between Ischemic Hypoxic Conditions and Attention Deficit Hyperactivity Disorder

Conditions	ADHD-Cases (n = 13,613), No. (%)	Controls (n = 68,065), No. (%)	Unadjusted OR (95% CI)	Adjusted[†] OR (95% CI)	PAF[‡] (%)
No-Ischemic Hypoxic Conditions	10,428 (76.6)	54,537 (80.1)	1.00 (Ref.)	1.00 (Ref.)	
Ischemic Hypoxic Conditions	3,185 (23.4)	13,528 (19.9)	1.23 (1.18, 1.29)	1.16 (1.11, 1.21)	3.0
Acute conditions					
Placental abruption	135 (1.1)	564 (0.9)	1.25 (1.04, 1.51)	1.18 (0.97, 1.44)	0.1
Birth asphyxia	2,339 (18.1)	10,119 (15.5)	1.21 (1.15, 1.27)	1.13 (1.07, 1.19)	2.0
Chronic condition					
Preeclampsia	1,031 (9.0)	3,865 (6.6)	1.40 (1.30, 1.50)	1.34 (1.24, 1.44)	2.0

[‡]PAF, population attributable fraction; [†]Odds ratios (OR) were adjusted for maternal age, education, smoking during pregnancy, parity, prenatal care, household income, psychosocial disorder during pregnancy, child race/ethnicity, and gender

Table 3 shows rates of IHC for cases and controls and its association with ADHD based on gestational age at birth and IHC subtypes. Among children 28-33 weeks, case children than controls were more likely (OR 1.5, 95% CI 1.2-2.2) to be exposed to IHC. This association decreased in other gestational age categories. Among 34-36 weeks, the magnitude of association decreased to 1.2 (95% CI 1.1-1.5) and among 37-42 weeks, the magnitude of association decreased to 1.1-fold (95% CI 1.0, 1.2). Children exposed to placental abruption experienced significantly increased risk of ADHD (adj. OR 1.7, 95% CI 1.1, 2.6) at age 5-11 only if the abruption occurred before 34 weeks. Birth asphyxia and preeclampsia were also most strongly associated with ADHD before 34 weeks but preeclampsia persisted as a risk factor throughout gestation. The findings remained largely unchanged after adjustment for gestational age.

Table 3

Associations between Ischemic Hypoxic Conditions and Attention Deficit Hyperactivity Disorder by Gestational Age

	Gestational age specific rates and odds ratios (95% confidence intervals) for ADHD								
	28-33 weeks			34-36 weeks			37-42 weeks		
Conditions	Cases n = 275, No. (%)	Controls n = 1375, No. (%)	†Adjusted OR (95% CI)	Cases n= 881, No. (%)	Controls n= 4405, No. (%)	†Adjusted OR (95% CI)	Cases n= 12457, No. (%)	Controls n= 62285, No. (%)	†Adjusted OR (95% CI)
No-IHC	104 (37.8)	663 (48.2)	1.0 (Ref.)	582 (66.1)	2,992 (67.9)	1.0 (Ref.)	9,604 (77.1)	49822 (80.0)	1.0 (Ref.)
IHC	171 (62.2)	712 (51.8)	1.5 (1.2, 2.0)	299 (33.9)	1,413 (32.1)	1.2 (1.1, 1.5)	2,853 (22.9)	12,463 (20.0)	1.1 (1.0, 1.2)
Acute conditions									
P. abruption	40 (17.8)	144 (12.5)	1.7 (1.1, 2.6)	30 (4.1)	144 (3.8)	1.0 (0.7, 1.5)	65 (0.6)	393 (0.7)	0.9 (0.7, 1.1)
Birth asphyxia	81 (36.0)	394 (30.2)	1.4 (1.1, 2.0)	127 (17.2)	709 (18.4)	0.9 (0.7, 1.1)	2,129 (18.1)	9,325 (15.7)	1.1 (1.1, 1.2)
Chronic condition									
Preeclampsia	88 (45.8)	350 (34.6)	1.7 (1.2, 2.3)	185 (24.1)	776 (20.6)	1.2 (1.1, 1.5)	941 (8.9)	3,721 (7.0)	1.3 (1.1, 1.3)

IHC, ischemic hypoxic conditions

†Odds ratios (OR) derived from unconditional logistic regression models adjusted for maternal age, education, smoking during pregnancy, perinatal care, parity, household income, psychosocial disorder during pregnancy, child race/ethnicity, and gender

Race/ethnicity-specific rate of ADHD is shown in Table 4. The rate of ADHD among children of NHW, NHB, Hispanic, Asian/Pacific Islander, and Other race/ethnicity groups with a history of IHC were noted to be 25.4, 27.4, 22.2, 27.4, and 24.0 per 100 births, respectively. Children with a history of acute and chronic IHC were also much more likely to be diagnosed with ADHD than children without such a history.

Table 4 Rates of Ischemic-Hypoxic Conditions by Attention Deficit Hyperactivity Disorder status and child race/ethnicity

Conditions	NHW		NHB		Hispanic		Asian/PI		Others	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
	n = 4348, No. (%)	n = 21740, No. (%)	n = 1563, No. (%)	n = 7815, No. (%)	n = 3559, No. (%)	n = 17795, No. (%)	n = 373, No. (%)	n = 1865, No. (%)	n = 3373, No. (%)	n = 16865, No. (%)
No-IHC	3243 (74.6)	17139 (78.8)	1135 (72.6)	5974 (76.4)	2769 (77.8)	14356 (80.7)	271 (72.6)	1444 (77.4)	2565 (76.0)	13266 (78.7)
IHC	1105 (25.4)	4601 (21.2)	428 (27.4)	1841 (23.6)	790 (22.2)	3439 (19.3)	102 (27.4)	421 (22.6)	808 (24.0)	3599 (21.3)
Acute conditions										
P. abruption	36 (0.9)	185 (0.9)	17 (1.2)	69 (1.0)	37 (1.1)	129 (0.8)	8 (2.2)	17 (1.0)	33 (1.0)	140 (0.9)
Birth asphyxia	784 (19.3)	3342 (16.2)	283 (19.7)	1253 (17.2)	542 (16.2)	2391 (14.2)	78 (21.9)	332 (18.5)	588 (18.5)	2592 (16.2)
Chronic condition										
Preeclampsia	390 (10.7)	1442 (7.8)	189 (14.3)	709 (10.6)	291 (9.5)	1187 (7.6)	28 (9.4)	105 (6.8)	282 (9.9)	1188 (8.2)

NHW, Non-Hispanic white; NHB, Non-Hispanic Black; Asian/PI, Asian/Pacific Islander; Others, Other/Mixed racial ethnic groups; IHC, ischemic hypoxic conditions

After adjustment for maternal age, education, prenatal care, smoking during pregnancy, parity, median household income, psychosocial disorder during pregnancy, child's sex and year of diagnosis, a history of exposure to IHC in utero was associated with significantly increased odds of ADHD across all race/ethnic groups (Table 5). The association between chronic condition and ADHD was similar across race/ethnicity. These findings were not affected by adjustment for gestational age.

Table 5 Associations between Ischemic-Hypoxic Conditions and Attention Deficit Hyperactivity Disorder by child race/ethnicity

Conditions	Adjusted odds ratios† (95% confidence intervals) for ADHD				
	NHW	NHB	Hispanics	Asian/PI	Others
No-IHC	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
IHC	1.2 (1.1, 1.3)	1.2 (1.1, 1.4)	1.2 (1.1, 1.3)	1.3 (1.0, 1.7)	1.1 (1.0, 1.2)
Acute conditions					
Placental abruption	0.9 (0.7, 1.4)	1.4 (0.8, 2.4)	1.5 (1.0, 2.2)	3.2 (1.3, 8.0)	1.2 (0.8, 1.8)
Birth asphyxia	1.2 (1.1, 1.3)	1.1 (1.0, 1.3)	1.1 (1.0, 1.2)	1.3 (1.0, 1.7)	1.1 (1.0, 1.3)
Chronic condition					
Preeclampsia	1.4 (1.2, 1.6)	1.4 (1.2, 1.7)	1.3 (1.1, 1.4)	1.4 (0.9, 2.2)	1.2 (1.1, 1.4)

NHW, Non-Hispanic white; NHB, Non-Hispanic Black; Asian/PI, Asian/Pacific Islander; Others, Other/Mixed racial ethnic groups; IHC, ischemic hypoxic conditions

†Odds ratios were adjusted for maternal age, education, smoking during pregnancy, perinatal care, parity, household income, psychosocial disorder during pregnancy, child's sex, and year of diagnosis

Cesarean delivery also was strongly associated with IHC in a univariate analysis, but was not an independent risk factor in the final model (data not shown). Previous studies have reported central nervous system change in hyperbilirubinemia.[203] In an attempt to clarify whether the observed associations between IHCs and ADHD are modified by child's neonatal jaundice status, we repeated the analysis after stratifying the data by neonatal jaundice categories. Impact of neonatal jaundice status on the results was negligible (data not shown).

Discussion

In this nested case-control study we found that, cases than controls were significantly more likely to be exposed to IHC in utero. This association was independent of maternal sociodemographic and behavioral characteristics, psychosocial disorder status, and child gender and race/ethnicity. Much of the hypoxia-associated increase in ADHD risk can be explained by exposure to preeclampsia. Children exposed to preeclampsia had a significantly higher risk (34%) of ADHD compared to unexposed children. Further analysis by gestational age revealed that preeclampsia remained a significant predictor of ADHD regardless of the gestational age at delivery, but birth asphyxia and placental abruption conferred slight or absent risk for ADHD after 33 weeks. The estimated proportion of ADHD attributable to IHC is small (PAF= 3%) because of modest association between IHC and ADHD. Therefore, effort to reduce IHC would not have a substantial impact on ADHD rates.

The etiology of ADHD remains largely unknown. However, there is strong evidence for genetic influences on risk of ADHD from twin and family studies.[75, 77] Monozygotic twins are more strongly concordant than dizygotic twin for ADHD. Children of parents with ADHD are at increased risk of ADHD.[75] Furthermore, recent evidence from human and animal studies suggested that antenatal psychosocial disorder,[100, 101] pre-and

postnatal tobacco exposure,[121] viral infection during pregnancy[114], pre-and postnatal drug exposures[119, 178], and postnatal factors such as environmental lead exposure[123-125] and Type 1 diabetes before the age 5[144] are associated with increased risk of ADHD.

Although the etiology and pathophysiologic underpinnings of the ischemic-hypoxic conditions remain elusive, they pose significant risks to the unborn child through common pathophysiologic mechanisms, namely, uteroplacental underperfusion, placental ischemia, and hypoxia. Therefore, during critical periods of fetal organ development, IHC may result in suboptimal oxygen and nutrient transport from the mother's blood to fetal circulation via the placenta, which results in compromised oxygen delivery to tissues and cerebrovascular complications. In particular, it has long been known that hypoxic injury during fetal development leads to significant structural and functional brain injuries in the offspring.[27, 33-44] Selective vulnerability of striatal neurons have been described in children born after a pregnancy complicated by asphyxia.[45] Lower concentrations of N-acetylaspartate and creatine levels have also been found in the central nervous system tissue of fetuses affected by hypoxic conditions indicating neuronal loss or damage.[43, 44] Furthermore, evidence from imaging studies demonstrated that placental ischemic injury and resulting hypoxia alters brain development and causes structural changes such as a marked reduction in absolute gray matter volume, intraventricular volume, and periventricular leukomalacia.[27, 40, 46] Studies based on animal models and human subjects have also reported detrimental effect of chronic fetal hypoxia and protein restriction on brain weight and synapsal numbers.[38, 47, 48] Potential mechanisms through which fetal ischemia and hypoxemia increase the risk for fetal brain injury are through degenerative changes in the hippocampal pyramidal neurons, loss of dendritic branches and density of granular neurons in the dentate gyrus leading to reduced overall hippocampal volume.[36, 49-51]

Although the above mentioned epidemiological, animal model and imaging studies demonstrated an adverse impact of IHC on fetal brain development, it is not known whether this condition may lead to development of ADHD. Therefore, to date, there remains a knowledge gap in identifying potential perinatal risk factors. Our data suggest that the adverse effect of hypoxia on prenatal brain development may lead to functional problems, including ADHD.

Strength and limitations: The strengths of the present study include a large sample size, ability to control for potential confounding factors and presentation of disparities in the associations among race/ethnicity groups. KPSC has detailed electronic medical records on hundreds of thousands of children in our health plan. This integrated electronic medical record system provides access to comprehensive patient and treatment information. Thus, the pitfalls of incomplete, missing, or unreadable charts that confound epidemiological health studies are minimized although there is some movement of subjects in and out of KPSC.

Unlike many epidemiological studies that have relied on parent- and teacher-reported information about ADHD, we used the combination of (i) cases primarily diagnosed by doctors who specialized in the diagnosis and treatment of ADHD and (ii) use of prescriptions specific to ADHD during the follow-up period. Similar to a previous report,[204] this approach helped increase the specificity of case ascertainment. Moreover, KPSC has stringent criteria (based on DSM-IV) that must be met for the diagnosis of ADHD. These include (i) every child has a standardized form, “The Child Behavior Checklist”, that parents, care providers, and teachers fill out to describe the child's behavioral and emotional problems and (ii) a clinical interview by a qualified child mental health professional. The stringent criteria used in the KPSC health plan in diagnosis ADHD has more validity than diagnosis made by parent and teacher reports or by other

health professionals. Furthermore, the electronic database used in this study allowed us to identify and exclude children with autism. Moreover, in the database used for this study, among 100 randomly selected ADHD cases, all children were routinely screened for developmental and emotional status. Only 3% of the children with the diagnosis of ADHD also had an autism spectrum disorder.

Other elements that add to the strength of the study include the validation of the accuracy of hospital-based ICD-9-CM diagnosis codes for IHCs against the electronic medical records of 400 randomly selected patients and excellent ascertainment of exposure (birth asphyxia) diagnosis. The nested case-control study approach allowed us to limit the number of laboratory records required to ascertain birth asphyxia parameters (cord blood pH and base excess) and neonatal bilirubin levels.

Our study is not without limitations. We used the birth certificate records to extract data on behavioral characteristics such as maternal smoking during pregnancy with their known underreporting of these factors. The positive predictive value for a diagnosis of preeclampsia in our validity study was 68% suggesting some misclassification of this risk variable. Another potential limitation is the possibility of our results being affected by residual confounding due to unmeasured factors such as in utero exposure to illicit drug, lead and other environmental agents. Lead exposure during pregnancy and after birth has been linked with ADHD.[123-125] While findings of this study certainly add to our understanding about the perinatal circumstances in which childhood ADHD is more likely to occur, this should not be considered evidence of causation. Furthermore, surveillance bias due to ADHD diagnosis is also possible in our analyses. This non-random type of information bias occurs when subjects differentially undergo follow-up of disease status, often leading to an outcome diagnosed much more frequently in those closely monitored group.

Conclusions

The findings of this study suggest that IHCs are independently associated with an increased risk of childhood ADHD even after accounting for gestational age and other potential risk factors. This suggests that events in pregnancy contribute to the etiology of this condition over and above the well-known familial/genetic influences.

Summary remarks

The purpose of this study is to examine the association between IHC and ADHD among children who were delivered in KPSC hospitals. To accomplish our objectives, we conducted three interrelated studies. We first conducted a validation study assessing the accuracy of coding a number of clinical diagnosis and procedural conditions that are known to increase risk of adverse perinatal outcomes. The findings of our validation study suggest that many perinatal adverse outcomes are not reliably coded in the PSS records. While the sensitivities were generally low, the specificities and predictive values were acceptable for some, but not all conditions. Researchers should be aware of these limitations. Our findings further suggest the accuracy of perinatal data can be improved by using a combination of both PSS and clinical utilization records.

Our second study assessed trends in childhood ADHD between 2001 and 2010. Results were stratified by child's race/ethnicity, gender, age, and median family household income. This study helped describe temporal trends in clinically diagnosed ADHD among children in the health plan. Our findings revealed a steady increase in the rates of ADHD diagnoses among white, black, and Hispanic children over the past decade but relatively lower and unchanging rates among Asian/Pacific Islanders. Males of all race/ethnicities had substantially higher rates than females across the study period. The findings also highlight the disproportionately higher relative increase in ADHD diagnosis among black girls from 2001 to 2010, suggesting a narrowing of gender gaps from previous years.

The information obtained from the validation study on the accuracy of perinatal diagnostic coding and findings on the recent trends in ADHD diagnosis among member children were quite valuable for examining the effect of in utero exposure to ischemic-hypoxic conditions (IHC) resulting from acute (placental abruption, birth asphyxia) and chronic (preeclampsia) perinatal events on the development of ADHD in children aged 5-

11 years (1991-2005). In this nested case-control study, we found case children were more likely to have been exposed to IHC in utero than controls. Associations between IHC and ADHD were independent of maternal sociodemographic and behavioral characteristics, psychosocial disorder status, and child gender and race/ethnicity. Much of the hypoxia-associated increase in ADHD risk was explained by exposure to preeclampsia. Further analysis by gestational age revealed preeclampsia to be a significant predictor of ADHD despite declining odds ratios associated with increasing gestatinal age at time of delivery. Birth asphyxia and placental abruption conferred minimal to no risk for ADHD after 33 weeks. Associations between preeclampsia and ADHD were similar across all racial/ethnic groups.

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Appendix 1 Definitions and ICD-9-CM* diagnostic and procedural codes of medical and obstetrical conditions

	Definition (ICD-9-CM diagnostic and procedural codes)
Obstetrical conditions	
Placental abruption	Premature separation of the normally implanted placenta (641.2x and 762.1)
Placenta previa	Placenta that is abnormally placed and partially/totally covers the cervix (641.0-641.13, and 762.0)
Preeclampsia	Hypertensive disorder 1st detected after 20 weeks' gestation combined with proteinuria and/or edema (642.x)
Gestational anemia	Anemia during pregnancy (280.9, 281.x, 283.9, 285.x, and V78.0)
Premature rupture of membranes	Rupture of membranes before the onset of labor (658.1x and 761.1)
Chorioamnionitis	Inflammation at the maternal-fetal interface (658.4x and 762.7x)
Gestational fever	High maternal fever during gestation (659.2x, 659.3x, 670.xx, 672.x, 672.xx, and 780.60)
Oligohydramnios	Deficiency in the amount of amniotic fluid (658.0-658.03, and 761.2)
Polyhydramnios	Excessive accumulation of the amniotic fluid (657.0-657.03, and 761.3)
Intrauterine growth restriction	Less than 10 percentile of predicted fetal weight for gestational age (656.50-656.53, 764.x, and 768.x)
Fetal distress	Persistent late decelerations or other heart rate patterns consistent with fetal hypoxia (656.3, 663.0, 655.x, 656.x, 659.x, 763.x, and 768.x)
Breech/other malpresentation	Fetal presentation other than a vertex presentation (652.x, 660.x, 669.x, 763.0, and 72.5x)
Incompetent cervix	Abnormal weakness of the cervix (761.0, 654.5x, 654.63, 67.5x, and 69.96)
Cephalopelvic disproportion	Maternal pelvis that is small in proportion to the baby's head or body (653.x and 660.x)

Prolapsed Cord	Umbilical cord that descends into the vagina prematurely (762.4, 663.x, and 73.92)
Perineal laceration	A tear in the vaginal tissue (664.x)
Mode of delivery	
Cesarean	An incision through the abdominal wall and uterus, performed to deliver a fetus (674.1x, 669.7x, and 763.4)
Previous cesarean	An prior surgical incision through the abdominal wall and uterus, performed to deliver a fetus (654.2x)
Medical conditions	
Chronic hypertension	A blood pressure of ≥ 140 mm Hg systolic or 90 mm Hg diastolic pressure before pregnancy or before 20 weeks of pregnancy (401.0x, 402.0x, 402.1x,402.9x, 403.0x, 403.1x, 403.9x, 404.0x, 404.1x, 404.9x, 405.0x, 405.1x, 405.9x, 642.0x, 642.1x, 642.2x, 642.7x, 760.0, 997.91, and 94.26)
Pregestational diabetes	Diabetes that existed prior to pregnancy (250.0x, 250.1x, 250.2x, 250.3x, 250.6x, 250.7x, 250.8x, 250.9x, 357.2, and 648.0x)
Respiratory conditions	Respiratory disorders in pregnancy (493.0x,493.1x,493.2x,493.9x, 491.0x, 491.2x, 491.8,491.9,'492.0,492.8, 769.x, and 770.8x)
Group B streptococcal infection	(041.02, and V02.51)

CURRICULUM VITAE

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2001-2004 Primary Care Research (Health Service Research)
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2001 - 2003 Masters in Public Health (MPH) degree in Epidemiology/Biostatistics
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1984 – 1990 Doctor of Medicine (MD)
Leipzig University, Leipzig, Germany

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Academic appointments

2007 - present *Research Scientist*
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2007 - present *Clinical Assistant Professor of Obstetrics and Gynecology*
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1993 – 1997 *Research assistant*
Evaluating the relative effectiveness of different dialysis modalities in diabetic patients with ESRD
Department of Epidemiology and Biostatistics
McGill University, Montreal, Canada

Hospital appointments

1998-2201 *Recreational Therapist*
Las Vegas Healthcare and Rehabilitation Center
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1995 – 1996 *Externship in Respiratory, MICU, and General Medicine*
Montreal General Hospital, McGill University
Montreal, Quebec, Canada

1990 – 1993 *Assistant physician*
Curia Propositi Generalis Societatis Jesu
Rome, Italy

Licensure

1990 License to Practice Medicine
Certificate of State Approval, Germany

Certification

1991 – 1992 Certificate in French Language
Organisatio Internationale Pour Les Immigration, Rome, Italy

1984 – 1986 Certificate in German Language
Harder Institute, Leipzig, Germany

Professional Affiliations

2009 – Society for Maternal-Fetal Medicine
2004 –2007 New Jersey Maternal-Fetal Medicine Society
2003 – American Public Health Association
2003 – 2007 New Jersey Public Health Association
2002 – Society for Pediatric and Perinatal Epidemiologic Research (SPER)
2001 – New York Academy of Sciences and the Science Alliance
1988-1990 German Medical Student Association
1983-1985 German Red Cross Society

Editorial positions (Reviewer)

2010 – Human Reproduction

2010 –	Clinical Gastroenterology and Hepatology
2010 –	European Journal of Obstetrics & Gynecology and Reproductive Biology
2009 –	BioMed Central
2009 –	American Journal of Obstetrics & Gynecology
2009 –	Journal of Maternal-Fetal & Neonatal Medicine
2008 –	Journal of Obstetrics and Gynecology Research
2008 –	Journal of Public Health
2008 –	Journal of Adolescent Health
2007 –	Archives of Gynecology and Obstetrics
2007 –	Journal of Pediatrics and Perinatal Epidemiology
2007 –	American Journal of Perinatology
2006 –	Journal of the National Medical Association
2006 –	CHEST
2005 –	Journal of Epidemiology and Community Health
2005 –	American Journal of Epidemiology
2004 –	Annals of Allergy, Asthma and Immunology
2003 –	Annals of Family Medicine

Teaching responsibilities

03/2004	Division of Epidemiology, UMDNJ-School of Public Health Case-control and cross-sectional study designs Epidemiology course (PHCO 0502)
2004 - 2005	Supervising students in preparing scientific project (Fieldwork II) UMDNJ-School of Public Health, NJ Kahyun Yoon-Flannery (2005) Kidanemariam Meshesha (2004)

Peer reviewed publications

Andrade SE, Scott PE, Davis RL, Li D, **Getahun D**, Cheetham CT, Raebel MA, Toh S, Dublin S, PawloskilO PA, Hammad TA, Beaton SJ, Smith DH, Dashevskl I, Haffenreffer K, Cooper WO. Validity of Health Plan and Birth Certificate Data for Pregnancy Research. AJE 2012 (in press)

Smith N, Iyer R, Langer-Gould A, **Getahun D**, Strickland D, Jacobsen SJ, Chen W, Derose S and Koebnick C. Health Plan Administrative Records versus Birth Certificate Records: Quality of Race and Ethnicity Information in children. *BMC 2010: 23;10:316.*

Koebnick C, **Getahun D**, Smith N, Porter AH, Der-Sarkissian JK, Jacobsen SJ. Extreme childhood obesity is associated with increased risk for gastroesophageal reflux disease in a large population-based study. *Int J Pediatr Obes. 2010 Jul 9. [Epub ahead of print]*

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Ananth CV, Peltier MR, De Marco C, **Getahun D**, Smulian JC, Rozen RR, New Jersey-Placental Abruption Study investigators. Associations between 2 polymorphisms in the Methylenetetrahydrofolate Reductase gene and placental abruption. *American Journal of Obstetrics and Gynecology, 2007;197(4):385;1-7*

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Getahun D, Amre D, Ananth CV, Demissie K, Rhoads GG. Temporal changes in rates of stillbirths, neonatal and infant mortality among triplet gestations in the United States. *American Journal of Obstetrics & Gynecology. 2006;195:1506-11*

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Getahun D, Amre D, Rhoads GG, Demissie K. Maternal and obstetric risk factors for sudden infant death syndrome in the United States. *Obstetrics and Gynecology 2004;103:646-52.*

Getahun D, Demissie K, Lu SE, Rhoads GG. Sudden Infant Death Syndrome (SIDS) in twin births: United States, 1995-1998. *Journal of Perinatology 2004; 24: 544-551.*

Non peer reviewed publications

Getahun D, Demissie K, Lu Shou-En, Rhoads GG. SIDS among twins: A confounded relationship. (Letter) *Journal of Perinatology 2005; 25: 294.*

Getahun D, Oyelese Y, Salihu HM, Ananth CV. C-Section increases later risk of placenta previa. *Obstet Gynecol News. May 1, 2006;41(9):10.*

Doctoral theses

Medical Doctor Thesis
Getahun D. Mesothelioma in patients autopsied in the Institute of Pathological Anatomy from 1958 to 1987, University of Leipzig, Germany 1989

Invited presentations

Getahun D, Fassett MJ, Dublin S, Wing D, Caughey AB, Chiu VY, and Jacobsen SJ. Is the recent trend in elective induction of labor modified by race/ethnicity and gestational age at delivery? 32nd Annual Meeting of the Society for Maternal-Fetal Medicine (*SMFM), 206(1), p. 284, Dallas, Texas, February 9, 2012*

Caughey AB, Nicholson J, Dublin S, **Getahun D**, Cheng YW. Elective induction of labor and outcomes by gestational age. 32nd Annual Meeting of the Society for Maternal-Fetal Medicine (*SMFM), 206(1), p. 276, Dallas, Texas, February 9, 2012*

Getahun D, Fassett MJ, Dublin S, Wing DA, Caughey AB, Gezmu T, and Jacobsen SJ. Racial and Ethnic Differences in Trends in Induction of Labor. *Poster presentation at the 59th Annual Scientific Meeting of the Society for Gynecologic Investigation (SGI), 19(3), p. 239A, San Diego, California, March 23, 2012*

Getahun D, Fassett MJ, Wing DA, Jacobsen SJ. Race/ethnicity Difference in the Associations between Preeclampsia and Acute Renal Failure. *Poster presentation at the 59th Annual Scientific Meeting of the Society for Gynecologic Investigation (SGI), 19(3), p. 320A, San Diego, California, March 23, 2012*

Getahun D, Fassett MJ, Wing DA, Jacobsen SJ. Associations between Perinatal Hemorrhage and Acute Renal Failure: Race/ethnicity Disparity. *Poster presentation at the 59th Annual Scientific Meeting of the Society for Gynecologic Investigation (SGI), 19(3), p. 239A, San Diego, California, March 23, 2012*

Fassett MJ, **Getahun D**. Association between asthma during pregnancy and adverse perinatal outcome based on maternal prepregnancy BMI and race/ethnicity. *Poster presentation at the 59th Annual Scientific Meeting of the Society for Gynecologic Investigation (SGI), 19(3), p. 367A, San Diego, California, March 24, 2012*

Getahun D, Fassett MJ, Jacobsen SJ. Race/ethnicity difference in the association between perinatal conditions and acute renal failure. *Poster presentation at the 24th Annual Meeting of the Society for Pediatric and Perinatal Epidemiologic Research (SPER), Montreal, Canada, June 20-21, 2011*

Fassett MJ, Lurvey LD, and **Getahun D.** The impact of a perinatal patient safety initiative on measures of perinatal quality in a large health maintenance organization.

Fassett MJ, Wing D, and **Getahun D**. Temporal trends in chorioamnionitis by maternal race/ethnicity and gestational age: 1991-2008. 31st Annual Meeting of the Society for Maternal-Fetal Medicine (*SMFM), 204(1), p. s251, San Francisco, California, February 11, 2011*

Getahun D, Fassett MJ, Wing D, and Jacobsen SJ. Recurrence of chorioamnionitis in subsequent pregnancies: race/ethnicity disparities. 31st Annual Meeting of the Society for Maternal-Fetal Medicine (*SMFM), 204(1), p. s250, San Francisco, California, February 11, 2011*

Getahun D and SJ Jacobsen. Trends in Inflammatory Bowel Disease among Pregnant Women: 1995-2009. P92; *Poster presentation at the Annual Meeting of the American College of Epidemiology (ACE), p. 92; San Francisco, California, September 11-14, 2010*.

Getahun D, Fassett MJ, Koebnick C, Wing DA, and Jacobsen SJ. Association between prepregnancy BMI and Gastroesophagial Reflux Disease: Racial/Ethnic Disparities. 58th Annual Scientific Meeting of the Society for Gynecologic Investigation (*SGI), F-013, p. 177A, Miami Beach, Florida, March 18, 2011*

Getahun D, Fassett MJ, Wing DA, Strickland, D, and Jacobsen SJ. Association between prepregnancy BMI and Clinically-Diagnosed Respiratory Conditions: Race/Ethnicity Disparities. 58th Annual Scientific Meeting of the Society for Gynecologic Investigation (*SGI), F-014, p. 177A, Miami Beach, Florida, March 18, 2011*

Wing DA, Fassett MJ, and **Getahun D**. Acute Pyelonephritis in Pregnancy: A 15-Year Retrospective Analysis. 58th Annual Scientific Meeting of the Society for Gynecologic Investigation (*SGI), F-037, p. 184A, Miami Beach, Florida, March 18, 2011*

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