Title

Perinatal Risk Factors and Autism in Los Angeles County: The Role of Air Pollution, Maternal Race/Ethnicity and Nativity

Author

Becerra, Tracy Ann

Publication Date

2013

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Perinatal Risk Factors and Autism in Los Angeles County: The Role of Air Pollution, Maternal Race/Ethnicity and Nativity

A dissertation submitted in partial satisfaction of the

requirements for the degree

Doctor of Philosophy in Epidemiology

by

Tracy Ann Becerra

2013

ABSTRACT OF THE DISSERTATION

Perinatal Risk Factors and Autism in Los Angeles County:

The Role of Air Pollution, Maternal Race/Ethnicity and Nativity

by

Tracy Ann Becerra

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2013

Professor Beate Ritz, Chair

Background: Autistic Disorder (AD) is a serious developmental condition with a wide range of symptoms and the prevalence has risen dramatically over the past two decades. The pathogenic mechanisms of autism have yet to be determined or are not well understood. Epidemiologic investigations support a prenatal or early postnatal origin of autism and it is likely that multiple genes interacting with one or more environmental factors cause some cases. However, high-quality population-based research addressing etiology is limited. There may be phenotypic differences in the presentation of autism in minority groups that may indicate etiologic heterogeneity, but it is unknown whether maternal race/ethnicity and nativity are risk factors for childhood autism in the U.S. Few studies to date have examined the impact of air pollution on brain development in general during pregnancy, although epidemiologic studies have associated air pollution exposure during the prenatal period to a variety of adverse birth outcomes. Few studies to date have examined the impact of air pollution on brain development in general during pregnancy, although epidemiologic studies have associated air pollution exposure during the prenatal period to a variety of adverse birth outcomes. Our first aim was to investigate the

association between traffic related air pollution exposures during pregnancy and autism using: 1) ambient criteria air pollutant measurements, and 2) land-use regression (LUR) to model traffic related air pollution exposures, using a matched case-control design. The second and third aim was to determine whether the risk of autism and autistic phenotypes, i.e., comorbid mental retardation, expressive language, and emotional/behavioral deficits, differ by maternal race/ethnicity and nativity. Using U.S.-born white mothers as reference, we examined autism relative risks in Hispanics and black mothers born in or outside of the U.S of which mothers born in Mexico or Central/South America were specified. In addition, we examined the association between autism and maternal Asian race/ethnicity in women born in the U.S., China, Japan, Korea, Philippines, or Vietnam.

Methods: Children of mothers who gave birth in Los Angeles who were diagnosed with a primary AD diagnosis at ages 3-5 years during 1998-2009 were identified through the California Department of Developmental Services and linked to 1995-2006 California birth certificates. For 7,603 children with autism, in the first study we selected 10 controls per case matched by sex, birth year, and minimum gestational age, birth addresses were mapped and linked to the nearest air monitoring station and a LUR model. For the second study, 6,485 children with AD were selected from a cohort of 1,461,610 births from white, Hispanic, and black mothers; and for the final study 2,532 children with AD were selected from a cohort of 401,091 births from Asian and U.S.-born white mothers. We further identified a subgroup of children with AD and a secondary diagnosis of mental retardation (AD-MR). To appropriately investigate language and behavior heterogeneity, we restricted assessments to 5-year olds. We identified from DDS evaluation records two subgroups with either “impaired” or “less impaired” expressive language; and two subgroups with “severe” or “less severe” emotional outburst behavior.

Summary of findings: Per interquartile range (IQR) increase, we estimated a 12-15% relative increase in odds of autism for O_3 (11.54ppb) and $PM_{2.5}$ (4.68 $\mu g/m^3$) when mutually adjusting for both pollutants. Furthermore, we estimated 3-9% relative increases in odds per IQR increase for LUR-based NO (9.4ppb) and NO_2 (5.4ppb) exposure estimates. LUR-based associations were strongest for children of mothers with less than a high school education. We found increases in risk for AD and AD-MR for children of foreign-born (FB) black mothers and Hispanic mothers from Central/South America, as well as of mothers who immigrated from the Philippines and Vietnam compared to U.S.-born whites. We estimated a 52% and 53% relative increase in risk of having a child with AD-MR for both U.S.-born African American/black and Hispanic mothers, respectively. Compared to children with autism of U.S.-born white mothers, most other maternal subgroups, except for foreign-born Chinese or Japanese mothers, had children with a higher risk of impaired expressive language. Severity of emotional outbursts was higher in children of foreign-born black and Centra/South American mothers, as well as in U.S.-born Hispanics. However, severe emotional outbursts seem to co-occur with impaired language.

The dissertation of Tracy Ann Becerra is approved.

Jorn Olsen

Onyebuchi A. Arah

Shafali Spurling Jeste

Michael A. Rodriguez

Beate Ritz, Committee Chair

University of California, Los Angeles

2013

DEDICATION

To the children, families, and staff at Pediatric Therapy Network in Torrance, California, who gave me the invaluable understanding of what it takes to care for a child with autism. Your hardships and hope motivated me throughout this long journey and I hope to have contributed something meaningful.

As a Hispanic woman of immigrant parents this very unique path I've taken couldn't have been done without the support of the Hispanic Scholarship Fund and the Bill and Melinda Gates Foundation, Gates Millennium Scholars Program. Your dedication to minority students has changed my life.

I thank my family and friends for being my "cheerleaders." Your presence, understanding, and patience, has made this worthwhile. To Eric Culqui, you have been there at every step, thank you for listening and validating this journey; I couldn't have finished without you.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AD: Autistic Disorder

ASD: Autism Spectrum Disorders

CDER: Client Development Evaluation Report

CDC: Centers for Disease Control and Prevention

CI: Confidence interval

CO: carbon monoxide

DDS: Department of Developmental Services

DSM: Diagnostic and Statistical Manual

FB: Foreign-born

GIS: Geographic Information Systems

IQR: Inter-quartile range

LA: Los Angeles

LUR: land use-based regression

NO: nitric oxide

NO_2: nitrogen dioxide

NO_x: nitrogen oxides

O_3: ozone

OR: odds ratio

$PM_{2.5}$: particulate matter <2.5 μm in aerodynamic diameter

PM_{10}: particulate matter <10 μm in aerodynamic diameter

PPM: parts per million

PPB: parts per billion

RR: risk ratio

SES: socioeconomic status

UFP: ultrafine particles; particles <0.1μm in aerodynamic diameter

ACKNOWLEDGEMENTS

Chapter 4 is a version of "Ambient Air Pollution and Autism in Los Angeles County, California" that was published in Environmental Health Perspectives:

Becerra TA, Wilhelm M, Olsen J, Cockburn M, Ritz B. Ambient Air Pollution and Autism in Los Angeles County, California. *Environ Health Perspect*. 2012. doi:10.1289/ehp.1205827.

Acknowledgement of co-authors:

Michelle Wilhelm, who generated LUR air pollution estimates and provided important content knowledge on the manuscript.

Jorn Olsen, who provided topic expertise and critical feedback on the final manuscript.

Myles Cockburn, who geocoded all birth certificate addresses and provided critical feedback on the manuscript.

Beate Ritz, principal investigator

Part of this research was sponsored by the University of California Los Angeles (UCLA) Graduate Division, and the California Center for Population Research, UCLA, supported by infrastructure grant R24HD041022 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

VITA

2001-2005	B.S., Occupational Therapy University of Southern California Los Angeles, California
2006-Present	Occupational Therapist Pediatric Therapy Network Torrance, California
2006-2008	Masters of Public Health, Epidemiology University of California, Los Angeles Los Angeles, California
2008	Special Reader (Teaching Assistant) University of California, Los Angeles Department of Epidemiology Los Angeles, California
2009-2010	Researcher, Climate Survey University of California, Los Angeles School of Public Health Los Angeles, California
2010-2011	Graduate Student Researcher University of California, Los Angeles Department of Epidemiology Los Angeles, California
2010-Present	Health & Disabilities Manager Early Head Start, Pediatric Therapy Network Torrance, California

PUBLICATIONS & PRESENTATIONS

Becerra TA, Wilhelm M, Olsen J, Cockburn M, Ritz B. Ambient Air Pollution and Autism in Los Angeles County, California. Environ Health Perspect. 2013; 121(3):380–386.

Becerra TA. Understanding The Sensory Needs of Young Children. Oral presentation at the California Head Start Annual Conference (CHSA 2013), San Diego, California, February 2013.

Crivici F, Anderson C, Edelman D, Georges M, Macken J, Mason-Marti P, Agurcia-Parker C, Becerra TA. Utilizing community partnerships to implement and evaluate a culturally competent

prenatal education curriculum. Oral presentation at the 140th American Public Health Association Annual Meeting (APHA 2012), San Francisco, California, October 2012.

Becerra TA, Ritz B. Effect modification of birth weight outcomes and gestational weight gain by pre-pregnancy body mass index in a diverse population. Oral presentation at the 138th American Public Health Association Annual Meeting (APHA 2010), Denver, Colorado, November 2010.

Becerra TA, Ritz B. Combined effects of pre-gestational body mass index and gestational weight gain on birth weight outcomes in a diverse population. Poster presentation at the 43rd annual meeting of the Society for Epidemiologic Research (SER 2010), Seattle, Washington, June 2010.

Chapter 1: Introduction

The patterns of illness and disease among children have significantly changed over the past two centuries in the United States. Chronic health conditions, such as asthma, type 2 diabetes, obesity, and autism are the most common disorders experienced by children today. Over 20 years ago, the incidence of autism in the state of California was 6.2 cases per 10,000 births (in 1990). By 2001 this number rose to almost seven-times that, now reported at 42.5 cases per 10,000 births (1), and the debate about how much of the increase is from a true rise of incident cases versus changes in diagnostic criteria continues to be discussed (2).

Background of Autistic Disorder

Autistic Disorder is a serious developmental condition with a wide range of symptoms expressed by individuals with the diagnosis. It is the most severe among common and increasingly diagnosed developmental disorders that are referred to as Autism Spectrum Disorders (ASD). ASD is a term commonly used to describe overlapping neurodevelopmental deficits and impairments, though not formally defined as a group of disorders in the DSM-IV, will be a formal diagnosis in the DSM-5 (3).

Autistic Disorder was one of five Pervasive Developmental Disorders (PDD) officially described in the DSM-IV; three are considered an ASD: 1) Autistic Disorder, 2) Asperger's Disorder, 3) Pervasive Developmental Disorder, Not Otherwise Specified, 4) Rett's Disorder, and 5) Childhood Disintegrative Disorder. Autistic Disorder is characterized by impairments in social interaction, abnormalities in verbal and nonverbal communication, and restricted stereotyped behaviors (4). Many of those afflicted with autism also differ in their way of learning, paying attention, or reacting to sensations.

Autism impairments are characteristic of early insults to the brain, such that neuronal connections and subsequently higher-level brain processes are impaired. Difficulty registering meaningful sensory input is often one of the most disabling and commonly observed aspects in children with autism. Children often have heightened sensitivities not only to the sensory qualities inherent in everyday experiences and environments (eg. visual and auditory stimuli) but also to basic variations in place and time e.g. limited ability to tolerate change (5). Similarly, children may also have some lowered sensitivities and are unable to register sensory inputs and act meaningfully in response.

Children diagnosed with Autistic Disorder express symptoms at different ages but are usually identified and diagnosed by the age of three. Males are four times as likely as females to be diagnosed with autism (6). It is presumed that autism is present from birth and some individuals are thought to manifest abnormal development from this time. However, others experience what appears to be regressive development between 18 and 24 months of age, after a period of normal development (7). The Medical Investigation of Neurodevelopmental Disorders Institute (M.I.N.D. Institute) described recognizable developmental differences between typical infants and those at high risk of ASD as early as 12 months (8). The divergence in development between these two groups was expressed by a lack of shared eye-contact, smiling and communicative babbling that emerged gradually and only became apparent during the latter part of the first year of life. Regardless of the different developmental trajectories, individuals will live with most of the symptoms of their disorder for the remainder of their lives.

The prevalence of autism has reportedly risen for the past 20 years, partly due to changes in case definition and improved case recognition. In California, Hertz-Picciotto et al suggested that the rise in autism could also be explained by younger age at diagnosis and inclusion of

milder cases, but that this would still not fully explain the observed rise in numbers (1). Early reports (1966-1991) estimated the average prevalence of autism alone at 4 cases per 10,000 births (9). Croen et al reported an increase in the prevalence of autism in California from 5.8 in 1987 to 14.9 per 10,000 births in 1994; the trend was independent of maternal age, education, race, ethnicity, and parity (10). More recently in the United States, the Centers for Disease Control reported that 1 in 88 8-year-old children fall into the broader spectrum of autism (ASD) (8 years was chosen as a reasonable index age at which to monitor peak prevalence) (11).

Pathogenesis of Autism

The pathogenic mechanisms of autism have yet to be determined. Early speculations were that autism resulted from bad parent-child interactions (12). However, it is now known that abnormal brain development underlies the pathogenesis of autism (13–16). Autopsy studies show that autistic individuals display structural differences in their brain. Imaging and electrophysiologic research has revealed differences in information processing in children with autism compared with those experiencing typical development (17–21). Today, we suspect that both genes and the environment play a role, and that autism is a complex disorder with many contributing causes.

Risk Factors for Autism

The factors contributing to autism are not well understood. Evidence for genetic causes is strong and recent research projects that in at least 37% of autism cases genetic factors are main contributors (22). In California, concordance rates of 77% for identical twin pairs and 31% for fraternal twin pairs have been reported for ASD, and these numbers are comparable to those reported in other populations (22). Previous twin and family studies provided evidence for a strong genetic component to the etiology of autism, and strong familial aggregation of autism has

also been demonstrated (22–25). The sibling recurrence risk, i.e., the probability of developing autism given a person's sibling is autistic, was estimated at 2-14%, a 10- to 20- fold increase over the general population's prevalence (26). Family histories of general social deficits, language abnormalities, and psychiatric disorders have also been linked to autism in case-control and clinic-based studies (23)(27,28). A novel human gene autism susceptibility candidate 2 (AUTS2) was found by Sultana et al to be associated with ASD and was later described to express itself at increasingly higher levels throughout brain development (29,30). By in situ hybridization in mice, AUTS2 expression was found to encode a nuclear protein expressed in developing brain regions, like the developing cortex, thalamus, and cerebellum implicated in autism neuropathology (30). However, the functional role of AUTS2 for neuronal development is still unknown. Another genetic study found autism and its severity to be associated with polymorphisms in the monoamine oxidase A (*MAOA*) gene in both child and mothers, and proposed that this genetic variance is associated with neurophysiological, neuroanatomical, and behavioral changes in humans (31). Specifically, they found a difference between low activity and high activity MAOA alleles, such that boys with the low activity 3-repeat allele had more severe sensory behaviors, such as arousal regulation problems, aggression, and worse social communication skills than boys with the high activity allele; while maternal MAOA genotype modified the presence of aggression, fears, and ritualistic behaviors in autistic children (31). Overall, only 10-20 percent of autism has been explained by more recent advancements in autism genetics (32,33).

A few environmental factors have also been associated with autism and it is likely that some autism cases are caused by multiple genes interacting with one or more environmental factors (28)(34). Prenatal exposure to thalidomide, a drug used in the late 1950's to help

pregnant women with morning sickness, and valproic acid an anticonvulsant medication used in the U.S. have been implicated as teratogens also causing autism (35–39). Also, within a cohort of 250 children with congenital rubella, 7% were later diagnosed with autism (40). A case-control study using both maternal reports and medical records of illnesses during pregnancy reported relative risks of 3.3 for rubella and 4.1 for influenza and subsequent diagnoses of autism in the offspring (41). Maternal infections are likely to alter fetal brain development and some authors suggested that influenza and prolonged episodes of fever may increase autism risk (42–47). However, some of these factors have played a smaller role during the past decade in the United States due to the wide use of vaccinations and efforts to eliminate the use of these drugs during pregnancy. Neuroimmunomodulatory factors may also play a role in the etiology of autism, and the viral nature of influenza, rubella, or immune insults in general during pregnancy may point to immunotoxicity (48–51). Neuroinflammation may be a potential mediator between autoimmune disorders and autism as one study found that the number of autoimmune disorders were greater in families with autism compared to controls – type 1 diabetes, adult rheumatoid arthritis, hypothyroidism, and systemic lupus erythematosus (52).

Epidemiologic investigations support a prenatal or early postnatal origin of autism. One study observed cerebellar abnormalities consistent with abnormalities in cell migration between the third and fifth month of gestation (14). Pathological changes in the cerebellum in autism are thought to correspond to events prior to the 30–32nd week of gestation. Another study found a higher incidence of prenatal stressors at 21–32 weeks gestation, with a peak at 25–28 weeks to be related to the occurrence of autism (53). The timing of stressors was found to be consistent with the embryological age suggested by neuroanatomical findings in the cerebellum of autistic individuals.

These studies aim to contribute to a body of literature on autism with regard to potential environmental risk factors not previously addressed. Our first aim was to investigate the association between traffic related air pollution exposures during pregnancy and autism using: 1) ambient criteria air pollutant measurements, and 2) land-use regression (LUR) to model traffic related air pollution exposures, using a matched case-control design. The second and third aim was to determine whether the risk of autism and autistic phenotypes, i.e., comorbid mental retardation, expressive language, and emotional/behavioral deficits, differ by maternal race/ethnicity and nativity. Using U.S.-born white mothers as reference, the second aim examined autism relative risks in Hispanics and black mothers born in or outside of the U.S, and the third aim was to examine the association between autism and maternal Asian race/ethnicity in women born in the U.S., China, Japan, Korea, Philippines, or Vietnam.

References

1. Hertz-Picciotto I, Delwiche L. The rise in autism and the role of age at diagnosis. Epidemiol Camb Mass. 2009 Jan;20(1):84–90.
2. Hertz-Picciotto I. Commentary: Diagnostic change and the increased prevalence of autism. Int J Epidemiol. 2009 Oct;38(5):1239–1241; author reply 1243–1244.
3. Vivanti G, Hudry K, Trembath D, Barbaro J, Richdale A, Dissanayake C. Towards the DSM-5 criteria for autism: Clinical, cultural, and research implications. Aust Psychol. 2013 Aug;48(4):258–61.
4. American Psychiatric Association. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. 4th ed. Washington, DC: American Psychiatric Association; 2000.
5. Smith Roley S, Blanche EI, Schaaf RC. Understanding the Nature of Sensory Integration with Diverse Populations. Austin: Pro Ed; 2001.
6. Gillberg C, Wing L. Autism: not an extremely rare disorder. Acta Psychiatr Scand. 1999;99(6):399–406.
7. Lainhart JE, Ozonoff S, Coon H, Krasny L, Dinh E, Nice J, et al. Autism, regression, and the broader autism phenotype. Am J Med Genet. 2002 Dec 1;113(3):231–7.
8. Ozonoff S, Young GS, Steinfeld MB, Hill MM, Cook I, Hutman T, et al. How early do parent concerns predict later autism diagnosis? J Dev Behav Pediatr JDBP. 2009 Oct;30(5):367–75.
9. Fombonne E. Epidemiological Surveys of Autism and Other Pervasive Developmental Disorders: An Update. J Autism Dev Disord. 2003;33(4):365–82.

10. Croen LA, Grether JK, Hoogstrate J, Selvin S. The changing prevalence of autism in California. J Autism Dev Disord. 2002 Jun;32(3):207–15.
11. Prevalence of autism spectrum disorders--Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008. Morb Mortal Wkly Rep Surveill Summ Wash DC 2002. 2012 Mar 30;61(3):1–19.
12. Chess S. The Empty Fortress: Infantile Autism and the Birth of the Self. JAMA J Am Med Assoc. 1967 Mar 20;199(12):949.
13. Bauman ML, Kemper TL. The neuropathology of the autism spectrum disorders: what have we learned? Novartis Found Symp. 2003;251:112–122; discussion 122–128, 281–297.
14. Courchesne E, Yeung-Courchesne R, Press G, Hesselink J, Jernigan T. Hypoplasia of cerebellar vermal lobules VI and VII in autism. N Engl J Med. 1988 May 26;318(21):1349–54.
15. Piven J, Berthier ML, Starkstein SE, Nehme E, Pearlson G, Folstein S. Magnetic resonance imaging evidence for a defect of cerebral cortical development in autism. Am J Psychiatry. 1990 Jun;147(6):734–9.
16. Rodier PM, Ingram JL, Tisdale B, Croog VJ. Linking etiologies in humans and animal models: Studies of autism. Reprod Toxicol. 1997 Mar;11(2-3):417–22.
17. Dawson G, Carver L, Meltzoff AN, Panagiotides H, McPartland J, Webb SJ. Neural Correlates of Face and Object Recognition in Young Children with Autism Spectrum Disorder, Developmental Delay, and Typical Development. Child Dev. 2002 May 1;73(3):700–17.

18. Maziade M, Merette C, Cayer M, Roy M-A, Szatmari P, Cote R, et al. Prolongation of Brainstem Auditory-Evoked Responses in Autistic Probands and Their Unaffected Relatives. Arch Gen Psychiatry. 2000 Nov 1;57(11):1077–83.

19. McPartland J, Dawson G, Webb SJ, Panagiotides H, Carver LJ. Event-related brain potentials reveal anomalies in temporal processing of faces in autism spectrum disorder. J Child Psychol Psychiatry. 2004 Oct;45(7):1235–45.

20. Dunn M, Rapin I. Update on the language disorders of individuals on the autistic spectrum. Brain Dev. 25(3):166–72.

21. Rosenhall U, Nordin V, Brantberg K, Gillberg C. Autism and Auditory Brain Stem Responses. Ear Hear. 2003 Jun;24(3):206–14.

22. Hallmayer J, Cleveland S, Torres A, Phillips J, Cohen B, Torigoe T, et al. Genetic Heritability and Shared Environmental Factors Among Twin Pairs With Autism. Arch Gen Psychiatry. 2011 Jul 4;68(11):1095–102.

23. Folstein S, Rutter M. Autism: familial aggregation and genetic implications. J Autism Dev Disord. 1988;8(1):3 – 30.

24. Folstein S, Rutter M. Infantile Autism: A Genetic Study of 21 Twin Pairs. J Child Psychol Psychiatry. 1977;18(4):297–321.

25. Jorde LB, Mason-Brothers A, Waldmann R, Ritvo ER, Freeman BJ, Pingree C, et al. The UCLA–university of Utah epidemiologic survey of autism: Genealogical analysis of familial aggregation. Am J Med Genet. 1990 May 1;36(1):85–8.

26. Ritvo ER, Jorde LB, Mason-Brothers A, Freeman BJ, Pingree C, Jones MB, et al. The UCLA-University of Utah epidemiologic survey of autism: recurrence risk estimates and genetic counseling. Am J Psychiatry. 1989 Aug;146(8):1032–6.

27. Piven J, Palmer P. Psychiatric Disorder and the Broad Autism Phenotype: Evidence From a Family Study of Multiple-Incidence Autism Families. Am J Psychiatry. 1999 Apr 1;156(4):557–63.

28. Cederlund M, Gillberg C. One hundred males with Asperger syndrome: a clinical study of background and associated factors. Dev Med Child Neurol. 2004 Oct 1;46(10):652–60.

29. Sultana R, Yu C-E, Yu J, Munson J, Chen D, Hua W, et al. Identification of a novel gene on chromosome 7q11.2 interrupted by a translocation breakpoint in a pair of autistic twins. Genomics. 2002 Aug;80(2):129–34.

30. Bedogni F, Hodge RD, Nelson BR, Frederick EA, Shiba N, Daza RA, et al. Autism susceptibility candidate 2 (Auts2) encodes a nuclear protein expressed in developing brain regions implicated in autism neuropathology. Gene Expr Patterns GEP. 2010 Jan;10(1):9–15.

31. Cohen IL, Liu X, Lewis MES, Chudley A, Forster-Gibson C, Gonzalez M, et al. Autism severity is associated with child and maternal MAOA genotypes. Clin Genet. 2010 May 22;79(4):355–62.

32. Geschwind DH. Advances in autism. Annu Rev Med. 2009;60:367–80.

33. Geschwind DH. Genetics of autism spectrum disorders. Trends Cogn Sci. 2011 Sep;15(9):409–16.

34. Glasson EJ, Bower C, Petterson B, de Klerk N, Chaney G, Hallmayer JF. Perinatal factors and the development of autism: a population study. Arch Gen Psychiatry. 2004 Jun;61(6):618–27.

35. Rodier PM, Hyman SL. Early environmental factors in autism. Ment Retard-Dev Disabil Res Rev. 1998;4:121–8.

36. Kim KC, Kim P, Go HS, Choi CS, Yang S-I, Cheong JH, et al. The critical period of valproate exposure to induce autistic symptoms in Sprague-Dawley rats. Toxicol Lett. 2011 Mar 5;201(2):137–42.

37. Christianson AL, Chesler N, Kromberg JG. Fetal valproate syndrome: clinical and neurodevelopmental features in two sibling pairs. Dev Med Child Neurol. 1994;36(4):361 – 369.

38. Meador KJ LD. RIsks of in utero exposure to valproate. JAMA. 2013 Apr 24;309(16):1730–1.

39. Roullet FI, Lai JKY, Foster JA. In utero exposure to valproic acid and autism--a current review of clinical and animal studies. Neurotoxicol Teratol. 2013 Apr;36:47–56.

40. Chess S, Fernandez P, Korn S. Behavioral consequences of congenital rubella. J Pediatr. 1978 Oct;93(4):699–703.

41. Deykin EY, Macmahon B. Viral exposure and autism. Am J Epidemiol. 1979 Jun 1;109(6):628 –638.

42. Patterson PH. Maternal infection: window on neuroimmune interactions in fetal brain development and mental illness. Curr Opin Neurobiol. 2002 Feb 1;12(1):115–8.

43. Patterson PH. Immune involvement in schizophrenia and autism: Etiology, pathology and animal models. Behav Brain Res. 2009 Dec 7;204(2):313–21.

44. Shi L, Tu N, Patterson PH. Maternal influenza infection is likely to alter fetal brain development indirectly: the virus is not detected in the fetus. Int J Dev Neurosci. 2005 Apr;23(2–3):299–305.

45. Zerbo O, Iosif A-M, Walker C, Ozonoff S, Hansen RL, Hertz-Picciotto I. Is Maternal Influenza or Fever During Pregnancy Associated with Autism or Developmental Delays?

Results from the CHARGE (CHildhood Autism Risks from Genetics and Environment) Study. J Autism Dev Disord. 2013 Jan 1;43(1):25–33.

46. Atladóttir HÓ, Henriksen TB, Schendel DE, Parner ET. Autism after infection, febrile episodes, and antibiotic use during pregnancy: an exploratory study. Pediatrics. 2012 Dec;130(6):e1447–1454.

47. Gardener H, Spiegelman D, Buka SL. Prenatal risk factors for autism: comprehensive meta-analysis. Br J Psychiatry. 2009 Jul 1;195(1):7–14.

48. Dietert RR, Dietert JM. Potential for early-life immune insult including developmental immunotoxicity in autism and autism spectrum disorders: focus on critical windows of immune vulnerability. J Toxicol Environ Health B Crit Rev. 2008 Oct;11(8):660–80.

49. Hagberg H, Gressens P, Mallard C. Inflammation during fetal and neonatal life: implications for neurologic and neuropsychiatric disease in children and adults. Ann Neurol. 2012 Apr;71(4):444–57.

50. Silva SC, Correia C, Fesel C, Barreto M, Coutinho AM, Marques C, et al. Autoantibody repertoires to brain tissue in autism nuclear families. J Neuroimmunol. 2004 Jul;152(1-2):176–82.

51. Vargas DL, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA. Neuroglial activation and neuroinflammation in the brain of patients with autism. Ann Neurol. 2005 Jan;57(1):67–81.

52. Comi AM, Zimmerman AW, Frye VH, Law PA, Peeden JN. Familial clustering of autoimmune disorders and evaluation of medical risk factors in autism. J Child Neurol. 1999 Jun;14(6):388–94.

53. Beversdorf DQ, Manning SE, Hillier A, Anderson SL, Nordgren RE, Walters SE, et al. Timing of Prenatal Stressors and Autism. J Autism Dev Disord. 2005;35(4):471–8.

Chapter 2*:* Review of the Literature

Prenatal Air Pollution Exposure & Autism

The causes of autism remain unknown, but both genetic and environmental factors are likely to contribute to its etiology. While only 10-20% of autism is attributed to known genetic factors, contributions of environmental factors are possible and may be disproportionately prevalent in minority populations (1–3). The National Academy of Sciences suggested that 3% of brain developmental disorders may be attributed to a toxic environmental exposure, and another 25% may result from an environmental insult occurring in conjunction with a genetic predisposition (4). However, research to identify possible environmental factors that may be interacting with genetic predispositions is sparse.

Few studies to date have examined the impact of air pollution on brain development in general during pregnancy, although epidemiologic studies have associated air pollution exposure during the prenatal period to a variety of adverse birth outcomes (5–8). Several research studies on air pollution and birth outcomes in Los Angeles reported positive associations between average carbon monoxide (CO) concentrations and term low birth weight (LBW) and between CO and PM_{10} concentrations six weeks prior to birth and prematurity (5,6). Since then, traffic-related air pollution in Los Angeles has consistently been found to be associated to term low birth weight and preterm birth using several sources and methods of measurement, i.e. air toxic and criteria air pollutant monitoring data, land use regression (LUR) model, and distance-weighted traffic density (9–15).

Exposure to air pollution during pregnancy has also been found to be associated with neuropsychological effects later in childhood (16–21). A small study that employed personal air sampling in pregnant women in New York suggested that high prenatal exposures to

environmental PAHs (constituents of particulate air pollution) might adversely affect children's cognitive development by the age of 3 (18). Other studies have implicated environmental causes of autism in California, through season of conception (22), residential proximity to a freeway during pregnancy (23), and geographic clustering of autism cases (24).

The human nervous system begins to develop within the first few weeks after conception, and the onset of brain histogenesis occurs prenatally providing the cellular structure and framework of basic connectivity necessary for establishing and modifying later-developing circuitry (25). Pregnancy represents a sensitive period when toxins may disrupt these processes of cell proliferation, organ development, and fetal metabolism (26). Disrupting basic histogenic processes in utero, such as the migration of neurons and axon pathfinding that establish proper patterns of basic connectivity, is an obvious junction of interactions between genes and environmental factors that may influence the development of autism (27). Disrupting this developmental hierarchy, first at the level of disconnection, targets certain higher-order association systems, such as those involved in joint attention (27).

The biological mechanisms by which air pollution may cause autism are largely unknown, although the immune system has been implicated as possibly playing a role (28). Children with autism have been found to have pro-inflammatory cytokines higher than in typically developing children, and inflammatory responses are known to be cytotoxic (29). Consider experimental research conducted with lead, commonly present in ambient air, which identified prenatal lead exposure effects on T-cell maturation and macrophage function in rodent studies (30). Here they found differential susceptibility based on gender, such that late gestational exposures gave rise to male-specific effects of lead on thymic weight, delayed type hypersensitivity, numbers of monocytes, and IL-10 and IL-12 production. The induction of

neuropathology by immunotoxicity prenatally is important to consider in the effect of the environment on neurodevelopment.

Few studies have previously examined associations between air pollution related exposures during the prenatal period and later development of autism, and none used ambient air monitoring data or land use regression models to estimate risk in a large population (23,31–33). In one study, autism was associated with ambient air concentrations of chlorinated solvents and heavy metals near birth residences (33). This study relied on estimated hazardous air pollutant concentrations compiled by the U.S. Environmental Protection Agency and suggested that mercury, cadmium, nickel, trichloroethylene, and vinyl chloride might be potentially toxic to the developing brain. Another study of autism reported elevated odds ratios for methylene chloride, quinoline, and styrene exposures in ambient air but near-null effect estimates for ambient air metals and other pollutants (31). A third and fourth study reported that children born to mothers living within 309 meters of a freeway during pregnancy were more likely to be diagnosed with autism than children whose mothers lived >1,419 meters from a freeway; and children with autism were more likely to live at residences with the highest quartile of exposure to traffic-related air pollution during gestation (23,32). These two small studies were the first to suggest that traffic-related exposures might increase the risk of autism.

Childhood Autism Related to Maternal Race/Ethnicity and Nativity

Early studies on race/ethnicity and autism in the United States (U.S.) were almost nonexistent since mass immigration of different ethnic groups occurred for this generation only in the latter part of the 20th century. Country-specific studies in addition to reporting low incidences of autism, some could not identify a single case in many Latin American countries, mainland China, and Japan. However, 14 children in Hong Kong and 9 children in Africa were

found autistic (34–36). In Europe in the 1960's and 70's, prevalence of autistic disorder (AD) was estimated at 4.1-4.8 per 10,000 2-14 year old children (35). In the 1970's U.S., 0.7 per 10,000 was the estimated prevalence of AD in 3-12 year olds. Yet nothing was written about autism, or clinicians had never seen a truly autistic child in Hispanic, blacks, or Puerto Ricans (37).

The U.S. race/ethnicity make-up diversified after the signage of the immigration bill by president Lyndon B. Johnson (38). Early immigrants were mostly highly-skilled workers and their families from Europe (mostly Germany and Italy) and Canada, and some from the Philippines (39,40). Unlike most of the foreign-born from Asia, those from Vietnam came to the U.S. as refugees between 1975 and 1985 during and after the Vietnam war (41), and only one-third arrived during the 1990s (42). Similarly, mass emigration from Central America increased beginning in the late 1970s through the early 1980s in response to the repression and violence associated with the onset of civil war (43,44). Starting in 1980, the largest foreign-born group in the U.S. was Mexicans, and this group continues to grow in size (40). Following, Chinese migrated between the early 1980's to the early 1990's after communist China opened its economy and travel to the outside world (45). After political, economic, and demographic transitions, new Japanese and Korean immigrants followed (46). African immigrants in the U.S. grew 40-fold since 1960 though most of the growth took place in the 1990's of highly educated people mostly from Nigeria, Egypt, and Ethiopia, and refugees from Somalia, Sudan, and Liberia (47).

Current information about autism incidence and prevalence in developing countries like Vietnam, the Philippines, and Africa is very limited which makes it difficult to determine whether autism risk is a migratory phenomenon (48). In Mexico, estimates of autism prevalence

also do not exist (49). The only information on AD for South East Asian countries was in Indonesia in 1992 where the estimated prevalence was 11.7 per 10,000 4-7 year olds (35). More recently, however, autism is reportedly on the rise in Vietnam, probably explained by previous under identification of children (50). The prevalence of AD in Asian countries was lowest in China with 10.9 per 10,000 2-6 year olds (2005), followed by 37.5 per 10,000 5-year olds in Japan (2005), and 94 per 10,000 7-12 year old children in South Korea in 2011 (35).

In 2008, the U.S. Autism and Developmental Disabilities Monitoring Network (ADDM) reported that ASD prevalence in eight year-olds varied by race/ethnicity, such that non-Hispanic white children had significantly greater prevalence (12.0 per 1,000) than non-Hispanic black children (10.2 per 1,000) and Hispanic children (7.9 per 1,000) (51,52). Another study using a sample from the National Survey of Children's Health suggested that the rate of ASD between non-Hispanic white children and Hispanic children may not be different after all, such that after taking parental nativity into account, U.S.-born Hispanic parents may have similar risks (53).

Studies of autism that consider parental race/ethnicity and nativity are limited in the United States. However, autism has previously been associated with maternal immigration status in Europe (54–56). Immigrant black and Asian mothers in the UK and Sweden have been reported to be at increased risk of having a child with autism with comorbid intellectual disability (57–59). In the UK, immigrant mothers were generally from Africa, Asia, or the Caribbean; and in Sweden, women were specifically from Sub-Saharan Africa, Northern Africa, Southern Asia, or Latin America (mostly Chile)/Caribbean (54,59). Unlike these European studies, a California study did not find associations between immigration and autism, due to the possible lower risks among offspring of foreign-born Mexican women, who make up the majority of the foreign-born in California (4.3 million)(60).

With the rise in autism emerged a concern with differential diagnosis of children (a difference in diagnosis rates between children of color or lower socioeconomic status (SES) compared to white or affluent populations), possibly due to disparities in parental education and access to resources. Autism with a comorbid diagnosis of mental retardation and severely impaired language abilities has been found to be associated with lower SES, black, and Hispanic race/ethnicity possibly indicating an ascertainment or a diagnostic bias of identifying more severe cases in these populations (61–63). Lack of familiarity with institutions and how to navigate them could also be more of a barrier for immigrant families, such that cultural differences can affect the referral, diagnosis, or treatment of autism in these populations (64–67).

To our knowledge, this is the first U.S. study addressing autism risk with respect to maternal nativity and race/ethnicity. L.A. County has a unique composition of racial/ethnic and foreign-born populations, and our large dataset allowed us to assess autism risk variations in offspring of mothers who migrated from different world regions and were of different racial/ethnic origins. By identifying differences, we highlight the importance of investigating autism risks and phenotypes in diverse populations and with respect to maternal nativity.

References

1. Geschwind DH. Genetics of autism spectrum disorders. Trends Cogn Sci. 2011 Sep;15(9):409–16.
2. Woods R, LaSalle JM. Epigenetic Epidemiology of Autism and Other Neurodevelopmental Disorders. In: Michels KB, editor. Epigenetic Epidemiol [Internet]. Springer Netherlands; 2012 [cited 2013 May 7]. p. 321–42. Available from: http://link.springer.com/chapter/10.1007/978-94-007-2495-2_17
3. Miyake K, Hirasawa T, Koide T, Kubota T. Epigenetics in Autism and Other Neurodevelopmental Diseases. MSc SIABs, editor. Neurodegener Dis. 2012;724:91–8.
4. Miodovnik A. Environmental Neurotoxicants and Developing Brain. Mt Sinai J Med J Transl Pers Med. 2011 Jan;78(1):58–77.
5. Ritz B, Yu F, Chapa G, Fruin S. Effect of Air Pollution on Preterm Birth Among Children Born in Southern California Between 1989 and 1993. Epidemiology. 2000;11(5):502–11.
6. Ritz B, Yu F. The effect of ambient carbon monoxide on low birth weight among children born in southern California between 1989 and 1993. Environ Health Perspect. 1999 Jan;107(1):17–25.
7. Srám RJ, Binková B, Dejmek J, Bobak M. Ambient air pollution and pregnancy outcomes: a review of the literature. Environ Health Perspect. 2005 Apr;113(4):375–82.
8. Williams L, Spence A, Tideman SC. Implications of the observed effects of air pollution on birth weight. Soc Biol. 1977;24(1):1–9.
9. Ghosh JKC, Wilhelm M, Su J, Goldberg D, Cockburn M, Jerrett M, et al. Assessing the Influence of Traffic-Related Air Pollution on Risk of Term Low Birth Weight on the

Basis of Land-Use-Based Regression Models and Measures of Air Toxics. Am J Epidemiol. 2012 May 13;175(12):1262–74.

10. Ponce NA, Hoggatt KJ, Wilhelm M, Ritz B. Preterm Birth: The Interaction of Traffic-related Air Pollution with Economic Hardship in Los Angeles Neighborhoods. Am J Epidemiol. 2005 Jul 15;162(2):140 –148.
11. Ritz B, Yu F, Fruin S, Chapa G, Shaw GM, Harris JA. Ambient Air Pollution and Risk of Birth Defects in Southern California. Am J Epidemiol. 2002 Jan 1;155(1):17 –25.
12. Ritz B, Wilhelm M, Hoggatt KJ, Ghosh JKC. Ambient air pollution and preterm birth in the environment and pregnancy outcomes study at the University of California, Los Angeles. Am J Epidemiol. 2007 Nov 1;166(9):1045–52.
13. Wilhelm M, Ghosh JK, Su J, Cockburn M, Jerrett M, Ritz B. Traffic-Related Air Toxics and Term Low Birth Weight in Los Angeles County, California. Environ Health Perspect. 2011 Aug 11;120(1):132–8.
14. Wilhelm M, Ritz B. Residential proximity to traffic and adverse birth outcomes in Los Angeles county, California, 1994-1996. Environ Health Perspect. 2003 Feb;111(2):207–16.
15. Wilhelm M, Ritz B. Local variations in CO and particulate air pollution and adverse birth outcomes in Los Angeles County, California, USA. Environ Health Perspect. 2005 Sep;113(9):1212–21.
16. Calderón-Garcidueñas L, Mora-Tiscareño A, Ontiveros E, Gómez-Garza G, Barragán-Mejía G, Broadway J, et al. Air pollution, cognitive deficits and brain abnormalities: a pilot study with children and dogs. Brain Cogn. 2008 Nov;68(2):117–27.

17. Edwards SC, Jedrychowski W, Butscher M, Camann D, Kieltyka A, Mroz E, et al. Prenatal exposure to airborne polycyclic aromatic hydrocarbons and children's intelligence at 5 years of age in a prospective cohort study in Poland. Environ Health Perspect. 2010 Sep;118(9):1326–31.

18. Perera FP, Rauh V, Whyatt RM, Tsai W-Y, Tang D, Diaz D, et al. Effect of prenatal exposure to airborne polycyclic aromatic hydrocarbons on neurodevelopment in the first 3 years of life among inner-city children. Environ Health Perspect. 2006 Aug;114(8):1287–92.

19. Suglia SF, Gryparis A, Wright RO, Schwartz J, Wright RJ. Association of black carbon with cognition among children in a prospective birth cohort study. Am J Epidemiol. 2008 Feb 1;167(3):280–6.

20. Tang D, Li T, Liu JJ, Zhou Z, Yuan T, Chen Y, et al. Effects of prenatal exposure to coal-burning pollutants on children's development in China. Environ Health Perspect. 2008 May;116(5):674–9.

21. Wang S, Zhang J, Zeng X, Zeng Y, Wang S, Chen S. Association of traffic-related air pollution with children's neurobehavioral functions in Quanzhou, China. Environ Health Perspect. 2009 Oct;117(10):1612–8.

22. Zerbo O, Iosif A-M, Delwiche L, Walker C, Hertz-Picciotto I. Month of Conception and Risk of Autism. Epidemiol Camb Mass. 2011 May 3;22(4):469–75.

23. Volk HE, Hertz-Picciotto I, Delwiche L, Lurmann F, McConnell R. Residential Proximity to Freeways and Autism in the CHARGE study. Environ Health Perspect. 2010 Dec 13;119(6):873–7.

24. Van Meter KC, Christiansen LE, Delwiche LD, Azari R, Carpenter TE, Hertz-Picciotto I. Geographic distribution of autism in California: a retrospective birth cohort analysis. Autism Res Off J Int Soc Autism Res. 2010 Feb;3(1):19–29.

25. Levitt P. Structural and functional maturation of the developing primate brain. J Pediatr. 2003 Oct;143(4 Suppl):S35–45.

26. Selevan SG, Kimmel CA, Mendola P. Identifying critical windows of exposure for children's health. Environ Health Perspect. 2000 Jun;108 Suppl 3:451–5.

27. Geschwind DH, Levitt P. Autism spectrum disorders: developmental disconnection syndromes. Curr Opin Neurobiol. 2007 Feb;17(1):103–11.

28. Hertz-Picciotto I, Park H-Y, Dostal M, Kocan A, Trnovec T, Sram R. Prenatal exposures to persistent and non-persistent organic compounds and effects on immune system development. Basic Clin Pharmacol Toxicol. 2008 Feb;102(2):146–54.

29. Molloy CA, Morrow AL, Meinzen-Derr J, Schleifer K, Dienger K, Manning-Courtney P, et al. Elevated cytokine levels in children with autism spectrum disorder. J Neuroimmunol. 2006 Mar;172(1-2):198–205.

30. Bunn TL, Parsons PJ, Kao E, Dietert RR. Exposure to lead during critical windows of embryonic development: differential immunotoxic outcome based on stage of exposure and gender. Toxicol Sci Off J Soc Toxicol. 2001 Nov;64(1):57–66.

31. Kalkbrenner AE, Daniels JL, Chen J-C, Poole C, Emch M, Morrissey J. Perinatal Exposure to Hazardous Air Pollutants and Autism Spectrum Disorders at Age 8. Epidemiol Camb Mass. 2010 Jun 17;21(5):631–41.

32. Volk HE, Lurmann F, Penfold B, Hertz-Picciotto I, McConnell R. Traffic-related air pollution, particulate matter, and autism. JAMA Psychiatry Chic Ill. 2013 Jan;70(1):71–7.

33. Windham GC, Zhang L, Gunier R, Croen LA, Grether JK. Autism Spectrum Disorders in Relation to Distribution of Hazardous Air Pollutants in the San Francisco Bay Area. Environ Health Perspect. 2006 Sep;114(9):1438–44.

34. Ney DP, Lieh-Mak F, Cheng R, Collins W. Chinese autistic children. Soc Psychiatry. 1979 Sep 1;14(3):147–50.

35. Elsabbagh M, Divan G, Koh Y-J, Kim YS, Kauchali S, Marcín C, et al. Global Prevalence of Autism and Other Pervasive Developmental Disorders. Autism Res. 2012;5(3):160–79.

36. Lotter V. Childhood Autism in Africa. J Child Psychol Psychiatry. 1978;19(3):231–44.

37. Sanua VD. Autism, childhood schizophrenia and culture: A critical review of the literature. Transcult Psychiatry. 1981;18(3):165–81.

38. Johnson LB. President Lyndon B. Johnson's Remarks at the Signing of the Immigration Bill, Liberty Island, New York October 3, 1965 [Internet]. Liberty Island, New York; 1965 [cited 2013 Apr 21]. Available from: http://www.lbjlib.utexas.edu/johnson/archives.hom/speeches.hom/651003.asp

39. San Juan Jr E. Filipino immigrants in the United States. Philipp Stud Hist Ethnogr Viewpoints. 2000;48(1):121–5.

40. Terrazas A. Mexican Immigrants in the United States [Internet]. Migr. Inf. Source. 2010 [cited 2013 May 15]. Available from: http://www.migrationinformation.org/usfocus/display.cfm?ID=767

41. Gordon LW. 7: Southeast Asian Refugee Migration to the United States. Cent Migr Stud Spec Issues. 1987;5(3):153–73.

42. Terrazas A, Batog C. Vietnamese Immigrants in the United States [Internet]. Migr. Inf. Source. 2010 [cited 2013 Apr 21]. Available from: http://www.migrationinformation.org/USfocus/display.cfm?ID=799

43. Gammage S. El Salvador: Despite End to Civil War, Emigration Continues [Internet]. Migr. Inf. Source. 2007 [cited 2013 Apr 24]. Available from: http://www.migrationinformation.org/Profiles/display.cfm?ID=636

44. Smith J. Guatemala: Economic Migrants Replace Political Refugees [Internet]. Migr. Inf. Source. 2006 [cited 2013 Apr 24]. Available from: http://www.migrationinformation.org/Profiles/display.cfm?ID=392

45. Skeldon R. Migration from China. J Int Aff. 1996;49(2):434, 22p, 2 charts.

46. Bloom DE, Williamson JG. Demographic Transitions and Economic Miracles in Emerging Asia. World Bank Econ Rev. 1998 Sep 1;12(3):419–55.

47. Terrazas A. African Immigrants in the United States [Internet]. Migr. Inf. Source. 2009 [cited 2013 Apr 23]. Available from: http://www.migrationinformation.org/usfocus/display.cfm?ID=719

48. Bakare MO, Munir KM. Autism spectrum disorders (ASD) in Africa: a perspective. Afr J Psychiatry. 2011;14(3):208–10.

49. Tuman JP, Roth-Johnson D, Lee Baker D, Vecchio J. Autism and Special Education Policy in Mexico. Glob Heal Gov [Internet]. 2008 Spring [cited 2013 May 15];II(1). Available from: http://ghgj.org/Tuman_Autism.pdf

50. Yi Y. Children with autism on the rise in Vietnam - Xinhua | English.news.cn [Internet]. 2013 [cited 2013 Apr 21]. Available from: http://news.xinhuanet.com/english/health/2013-03/14/c_132234027.htm

51. Prevalence of autism spectrum disorders - Autism and Developmental Disabilities Monitoring Network, United States, 2006. MMWR Surveill Summ Morb Mortal Wkly Rep Surveill Summ CDC. 2009 Dec 18;58(10):1–20.

52. Prevalence of autism spectrum disorders--Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008. Morb Mortal Wkly Rep Surveill Summ Wash DC 2002. 2012 Mar 30;61(3):1–19.

53. Schieve LA, Boulet SL, Blumberg SJ, Kogan MD, Yeargin-Allsopp M, Boyle CA, et al. Association between parental nativity and autism spectrum disorder among US-born non-Hispanic white and Hispanic children, 2007 National Survey of Children's Health. Disabil Health J. 2012 Jan;5(1):18–25.

54. Magnusson C, Rai D, Goodman A, Lundberg M, Idring S, Svensson A, et al. Migration and autism-spectrum disorder: population-based study. Br J Psychiatry [Internet]. 2012 Feb 23 [cited 2012 Dec 18]; Available from: http://bjp.rcpsych.org/content/early/2012/02/11/bjp.bp.111.095125

55. Maimburg RD, Vaeth M. Perinatal risk factors and infantile autism. Acta Psychiatr Scand. 2006 Oct;114(4):257–64.

56. Van der Ven E, Termorshuizen F, Laan W, Breetvelt EJ, van Os J, Selten JP. An incidence study of diagnosed autism-spectrum disorders among immigrants to the Netherlands. Acta Psychiatr Scand. 2012 Dec 9;

57. Barnevik–Olsson M, Gillberg C, Fernell E. Prevalence of autism in children born to Somali parents living in Sweden: a brief report. Dev Med Child Neurol. 2008;50(8):598–601.

58. Dealberto M-J. Prevalence of autism according to maternal immigrant status and ethnic origin. Acta Psychiatr Scand. 2011 May;123(5):339–48.

59. Keen DV, Reid FD, Arnone D. Autism, ethnicity and maternal immigration. Br J Psychiatry. 2010 Apr 1;196(4):274–81.

60. Johnson H, Cuellar Mejia, Marisol. Immigrants in California [Internet]. Public Policy Institute of California; 2013 May. Available from: http://www.ppic.org/main/publication_show.asp?i=258

61. Bhasin TK, Schendel D. Sociodemographic Risk Factors for Autism in a US Metropolitan Area. J Autism Dev Disord. 2007 Apr 1;37(4):667–77.

62. Chaidez V, Hansen RL, Hertz-Picciotto I. Autism spectrum disorders in Hispanics and non-Hispanics. Autism Int J Res Pr. 2012 Jul;16(4):381–97.

63. Liptak GS, Benzoni LB, Mruzek DW, Nolan KW, Thingvoll MA, Wade CM, et al. Disparities in Diagnosis and Access to Health Services for Children with Autism: Data from the National Survey of Children's Health. J Dev Behav Pediatr. 2008 Jun;29(3):152–60.

64. Begeer S, Bouk SE, Boussaid W, Terwogt MM, Koot HM. Underdiagnosis and Referral Bias of Autism in Ethnic Minorities. J Autism Dev Disord. 2009 Jan 1;39(1):142–8.

65. Mandell DS, Ittenbach RF, Levy SE, Pinto-Martin JA. Disparities in Diagnoses Received Prior to a Diagnosis of Autism Spectrum Disorder. J Autism Dev Disord. 2006 Dec;37(9):1795–802.

66. Mandell DS, Listerud J, Levy SE, Pinto-Martin JA. Race Differences in the Age at Diagnosis Among Medicaid-Eligible Children With Autism. J Am Acad Child Adolesc Psychiatry. 2002 Dec;41(12):1447–53.

67. Mandell DS, Wiggins LD, Carpenter LA, Daniels J, DiGuiseppi C, Durkin MS, et al. Racial/Ethnic Disparities in the Identification of Children With Autism Spectrum Disorders. Am J Public Heal. 2009 Mar 1;99(3):493–8.

Chapter 3: Study Design & Methods

Study Design and Population

This is a population-based study focused on children born in Los Angeles (1995 to 2006) to mothers who resided in Los Angeles County during pregnancy. We selected cases from existing data of children diagnosed with Autistic Disorder (AD) between the ages 3 to 5 years (36 to 71 months) at a Los Angeles regional center during 1998 – 2009, readily available from the California Department of Developmental Services (DDS)(Figure 3-1 demonstrates catchment period).

Case Ascertainment and Definition

Regional Center System

Children with autism are identified through regional center (RC) staff, contracted by the California Department of Developmental Services (DDS), who determine eligibility and coordinate services in their respective service areas - there are seven regional centers in Los Angeles County (Figure 3-2). To be a consumer of the regional center, an eligible diagnosis of mental retardation, autism, cerebral palsy, epilepsy, or another developmental delay is required. During our study period, eligibility in the DDS system did not depend on citizenship or financial status and it was available to everyone irrespective of socioeconomic status or racial/ethnic identification. Referrals to the regional centers are usually from pediatricians, other clinical providers, and schools, but parents may also refer themselves and their children. Table 3-1 gives an example of the overall consumer capacity of the regional centers in Los Angeles, with North Los Angeles being the largest (1).

Diagnosis

The diagnosis of AD has changed with the revisions of the Diagnostic and Statistical Manual of Mental Disorders (DSM). Since 1994 (DSM-IV) and during our study period, a diagnosis was made when there was evidence of abnormal social interactions and communication or when stereotyped patterns of behavior exist. At least 6 of a list of 12 symptoms must be present for an individual to qualify for a diagnosis of AD, with at least two symptoms from the social interaction category and one each from the communication and stereotyped patterns of behavior areas (see Appendix A).

There is no uniform method of evaluating a possible case of AD or of an Autism Spectrum Disorder (ASD). Although California continues to work to improve consistency in diagnosis and reporting, there currently is no mechanism in place that rigorously evaluates inter-rater reliability or diagnostic consistency across regional centers (2). DDS has however partnered with the University of California Medical Schools to provide training to community practitioners, and regular meetings are held at which regional center specialty groups of psychologists, physicians, and clinical directors discuss diagnostic criteria.

In 2002, DDS, in collaboration with regional centers and numerous experts in the field, published, *Autism Spectrum Disorders: Best Practice Guidelines for Screening, Diagnosis and Assessment* for the purpose of establishing best practices for the diagnosis of autism (3). Accordingly, a comprehensive diagnostic evaluation for ASD should encompass a thorough assessment of multiple domains, including six specific components:

1. Review of relevant background information
2. Parent/Caregiver interview
3. Comprehensive medical evaluation
4. Direct Observation

5. Cognitive Assessment
6. Measures of Adaptive Functioning

Client Development Evaluation Report (CDER) - Case Definition

The Client Development Evaluation Report (CDER) is the instrument that the Department of Developmental Service (DDS) utilizes to collect data on client diagnostic characteristics, and to measure and evaluate the functioning levels of persons with developmental disabilities on an ongoing basis (4). The CDER is not a diagnostic instrument but is used to document eligibility and diagnosis results from professional evaluators that reference the Diagnostic and Statistical Manual of Mental Disorders (DSM).

Prior to 2008, the earlier CDER instrument dated from March 1986 recorded autism as one of three different codes: Code 1, Code 2 or Code 9. Code 1 corresponded to the DSM IV-R (APA, 1994) classification of Autistic Disorder (DSM IV-R code 299.00). Code 2 corresponded to the earlier DSM III (APA, 1980) – "autism, residual." Code 9 was used in cases when a diagnosis of autism is "suspected" but not yet formally determined, e.g., for very young children whose diagnostic status has not yet been clarified . Most of the cases in our analysis were diagnosed with this earlier CDER instrument, dated from March 1986 – i.e. children diagnosed between the years 1998 – 2008 with Autistic Disorder (see Appendix B for CDER DS 3753 (3/86)).

The CDER was revised in January 2008, but the diagnosis of AD (Code 1) did not change from one CDER to another (see Appendix C for a summary of the diagnostic changes). Autism is now recognized for services as either having AD (Code 1) or not (DSM-IV-R), and a new item was included to indicate whether the client instead has another pervasive developmental disorder such as Asperger Disorder (Code 3), or Pervasive Developmental

Disorder – Not Otherwise Specified (PDD- NOS) (Code 4). Diagnosis is coded using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), Sixth Edition, issued for use beginning October 1, 2008 for the federal fiscal year 2009 and on. These changes only impacted children diagnosed in 2009, but only for children who would have otherwise been given a code 2 or 9 in the 1986 CDER, which were not included in our case definition of AD, Code 1.

For purposes of this study we only include cases with Autistic Disorder (Code 1) and exclude others under "autism, residual" (Code 2), "autism, suspected" (Code 9), Asperger Disorder (Code 3), and PDD-NOS (Code 4). An individual diagnosed as having a Pervasive Developmental Disorder, Not Otherwise Specified (PDD-NOS) is recognized to have some behaviors seen in autism but does not meet the full DSM-IV TR criteria for having Autistic Disorder. Although information about PDD-NOS can be found in the updated CDER, it is not a categorically eligible condition for services - this non-eligibility criterion also applies to the diagnosis of Asperger Disorder.

CDER Reliability

In 1982, the California Department of Developmental Services, in conjunction with the Association of Regional Center Agencies and the Neuropsychiatric Institute at the University of California, Los Angeles, conducted a study of the interrater reliability of the CDER. Based on a sample of 360 active clients statewide of all ages and levels of disability, independent ratings of clients' levels of functioning from two interviewers deemed appropriate were collected. Based on these ratings of the same client, the interrater reliability ranged between 0.8 and 0.9 for almost all sixty-six CDER evaluation items indicating that that the CDER is a highly reliable client assessment instrument (4).

CDER Validity

The validity of the CDER was tested by the Department in 1983 in cooperation with the Mental Retardation Research Center at Lanterman State Hospital and the Neuropsychiatric Institute at UCLA. The study evaluated the validity of the CDER by comparing it with two nationally recognized instruments -- the Corman-Escalona Object Permanence test and the Behavior Development Survey (BDS). The study yielded positive correlations ranging from 0.5 to 0.9 between CDER and BDS indicating that the CDER is a valid measure of cognition, adaptive, and maladaptive behaviors (4).

CDER Considerations

The DDS counts of persons with autism likely underestimate the actual California population with autism since it has been estimated that 75 to 80 percent of the total population of persons in California with autism are enrolled in the developmental service system (5).

DDS does not collect CDER information for children ages 0-2, thus we are only including children with autism 36 months of age and older.

Diagnostic Stability

The CDER was developed in response to the Lanterman Developmental Disabilities Services Act of 1977, and it must be completed at least annually for each client. Thus, we used the latest diagnosis available because it is considered the most reliable. Although many trained professionals are able to make a definitive diagnosis at a younger age, the stability of a diagnosis within the spectrum may fluctuate; as is often the case with children at the extreme ends of the spectrum. However, the diagnostic stability of autism, in general, is great i.e. once clinicians assign this classification they rarely change it (2). For instance, in a longitudinal study Lord et al reported a diagnostic consistency of 90 percent for ASD between ages 2 and 9 years (6).

Diagnostic Validity

Autism is a spectrum disorder that presents itself with a phenotype of varying symptoms and differs in degree of severity among those diagnosed. The non-uniform nature of this disorder poses a challenge to diagnostic validity of epidemiologic research especially when based on routine record systems that record disease. As mentioned before, there is no mechanism in place that consistently evaluates inter-rater reliability or diagnostic consistency across regional centers (2). Thus, there will be possible variations in the diagnosis and recording between regional centers.

Linkage

We linked the State of California Department of Developmental Services autism records for Los Angeles County (1998-2009 and birthday 1995-2006) (n=10,821) to their respective birth records (1995 to 2006) employing the National Program of Cancer Registries (NPCR) Registry Plus™ Link Plus Software (7). Based on child's first and last name, birthdate, and gender; mother's first and last name, birthdate; as well as father's last name and birthdate, we used probabilistic matching to estimate the probability/likelihood that two records are or are not for the same person. Probabilistic matching assigns a total score for a linkage between any two records as the sum of the scores generated from matching individual fields. The score assigned to a match of individual fields is based on the probability that a matching variable agrees given that a comparison pair is a match - similar to "sensitivity"; minus the probability that a matching variable agrees given that a comparison pair is not a match - similar to "specificity."

Of 22,806 linked records, only the highest scoring ones (score $\geq$ 25) were manually reviewed (n=9,120). The remaining 13,443 lower scoring linked records were reviewed using SAS 9.2 on the condition that the child's first name, last name, and birthday matched exactly. Of

all linkages between records, 8,492 links were accepted as correct. We also identified some record linkages for births registered outside of Los Angeles county for mothers who had resided in L.A. during their pregnancy, n = 108. The final sample included 8,600 correctly linked records, thus we had 79.5% success in linking ASD cases identified in LA County by DDS to their respective birth records. Of the 2,221 DDS records not linked to birth records, 35% were not born in LA County, 46% were missing birthplace information; only 19% recorded the child born in LA County. The most common reason for non-linkage was missing/incomplete linkage information on the birth or DDS record.

Additional Inclusion Criteria:

Ambient Air Pollution and Autism in Los Angeles County, California: From among linked cases, we further excluded children whose mother's residency was outside of LA County during her pregnancy (n=41), records with missing or implausible gestational ages (<21 or >46 weeks) or birth weights (<500g or >6800g) (n=508), and cases who did not have a primary diagnosis of Autistic Disorder (n=448), leaving a final sample of 7,603 children with autism successfully linked to a birth certificate who met all inclusion criteria. Further, residential locations at delivery reported on birth certificates were mapped using a custom geocoder and further exclusions were necessary if residential addresses were not geocodable, 9 cases (8).

Childhood Autism Related to Maternal Race/Ethnicity and Nativity: 1. Of the 8,600 subjects, 6,485 were eligible for inclusion because they had a primary diagnosis of AD, a plausible gestational age (21-46 weeks inclusive) and birth weight (500-6800g inclusive), available maternal place of birth recorded on the birth certificate, and a mother of non-Hispanic white, Hispanic, or black race/ethnicity. 2. Of the same 8,600 DDS records to birth records, 2,532 had a primary diagnosis of AD, a plausible gestational age (21-46 weeks inclusive) and

birth weight (500-6800g inclusive), and documented maternal place of birth and were of non-Hispanic white or Asian race/ethnicity.

Autism Phenotypes:

Childhood Autism Related to Maternal Race/Ethnicity and Nativity: We further identified a subgroup of children with AD and a secondary diagnosis of mental retardation (AD-MR) (ICD-9-CM code: 317-mild, 318.0-moderate, 318.1-severe, 318.2-profound, 319-MR unspecified) on the CDER. To appropriately investigate language and behavior heterogeneity, we restricted assessments to 5-year olds. We identified from DDS evaluation records two subgroups with either "impaired" or "less impaired" expressive language (AD-impaired expressive language: the child does not use words, says simple words, or says two-word sentences; AD-less impaired expressive language: the child uses sentences of 3 words or more or at least can engage in basic conversation); and two subgroups with "severe" or "less severe" emotional outburst behavior (AD-severe outbursts: the child has daily or weekly tantrums requiring restraint; AD-less severe outburst: child has no tantrums, weekly, or less than weekly tantrums without needing restraint).

Control Selection

Two different control selection procedures were completed for the three different studies. In the autism and air pollution study we used a matched case-control design. In the second and third studies, we used all births in LA County 1995-2006 to estimate risks of autism by maternal race/ethnicity and nativity.

Matched Case-Control:

We selected 10 controls for each case from our source population. Using birth certificates, each control was randomly selected without replacement and matched on birth year

and sex. In addition, each control's gestational age at birth had to be equal to or greater than the gestational age at birth of their matched case to ensure prenatal exposures could be estimated for comparable lengths of time. Children were eligible as controls if they had no documentation of autism, i.e. did not have a DDS record in LA County by 2009, had a plausible gestational age (21-46 weeks inclusive) and birth weight (500-6800g inclusive), and the mother resided in LA County at the time of birth.

Matching by birth year balanced the large increase in autism rates during the case ascertainment period, 1998 to 2009. The matched control set included 76,030 children born during 1995-2006. From among these, we further excluded 248 control children who died prior to 5 years of age (71 months) based on California death records, leaving 75,782 controls.

Residential locations at delivery reported on birth certificates were mapped using a custom geocoder and further exclusions were necessary if residential addresses were not geocodable, 147 controls (8).

Case-Cohort Design:

We selected from the entire cohort of children born between 1995-2006 to mothers who resided in LA County, California at the time of giving birth. Children were eligible for inclusion if they had a plausible gestational age (21-46 weeks inclusive) and birth weight (500-6800g inclusive), and if maternal race/ethnicity and nativity information was available on the birth certificate.

For the second analysis focusing on non-Hispanic white, Hispanic, and non-Hispanic black mothers, we excluded all other or unknown racial/ethnic groups and mothers with unknown place of birth; a total of 175,352 exclusions (94.6% Asian, 3.3% unknown

race/ethnicity, 1.5% Native American, 0.3% Hispanic, 0.2% white, 0.1% black, and .01% Eskimo/Aleut). The final cohort consisted of 1,461,610 births.

For the final analysis focusing on non-Hispanic white and Asian mothers, we excluded foreign-born white mothers, records with unknown place of birth or unknown/other race/ethnicity. There were a total of 1,235,871 exclusions (83.2% Hispanic, 10.8% black, 5.1% foreign born? white, 0.9% unknown/other race/ethnicity). The final cohort thus consisted of 401,091 children of non-Hispanic U.S.-born white and Asian mothers.

Autism Phenotype Control Selection: The selection of 5-year olds in the autism phenotype analysis for language and behavior subtypes required that we choose an appropriate control group. The source population for these 5-year olds was children in our cohort who had an equal opportunity to be 5-year olds with autism before and during 2009. This applied to most children except those born in 2005 and 2006 who could have only reached 3 or 4 years during our case ascertainment period. Thus, the cohort of children selected for these subanalyses were born between 1995 and 2004.

Human Subjects Research

In order to perform data linkages and geocoding of home locations, we needed to access personal identities and addresses stored in computerized databases through state birth records and DDS.

This research was approved by the University of California Los Angeles Office of Human Research Protection Program and the California Committee for the Protection of Subjects, and was exempted from informed consent requirements.

Exposure Assessment

Ambient Air Pollution and Autism in Los Angeles County, California:

Births and their corresponding pregnancy addresses were identified using electronic birth certificate data from the State of California and geocoded using geographic information systems (GIS). Two distinct exposure assessment methods were used.

Exposure Assessment: CARB monitoring stations

The California Air Resources Board (CARB) has maintained a network of air monitoring stations in California that measure criteria air pollutants, including 16 LA County sites (Figure 3-3) . Criteria pollutants measured for this study were carbon monoxide (CO), nitric oxide (NO), nitrogen dioxide (NO_2), ozone (O_3), particulate matter concentrations with an aerodynamic diameter $\leq$10 µm (PM_{10}), and $\leq$2.5 µm ($PM_{2.5}$). CARB has monitored the gaseous criteria pollutants CO, NO_2 and O_3 since its inception in 1968, PM_{10} since 1986, and $PM_{2.5}$ since 1999 (9,10).

Exposure estimates were created for several key pregnancy periods, including the 1st, 2nd, 3rd trimester, and the entire pregnancy period. Averages were created for hourly CO (6-9am), NO, NO_2, and O_3 (10am – 6pm), as well as 24-hour average PM_{10} (every 6 days) and $PM_{2.5}$ (every 3 days) using data from the closest air monitoring station to residential addresses at the time of birth. We first created daily 24-hour averages then averaged these daily averages over the pregnancy period of interest. Exclusion criteria when estimating pregnancy period specific monitor-based air pollution exposure metrics were used (see supplemental table 4-2). To prepare for analysis, the entire pregnancy inter-quartile exposure range for each pollutant was used to scale pregnancy-period air pollution averages to make them comparable across periods. Because $PM_{2.5}$ only began to be monitored in 1999, estimates for births before this year (1995-1998) were not computed.

Exposure Assessment: Land Use Regression (LUR) model

Almost all existing studies of air pollution during pregnancy used ambient air monitoring data to assess exposure, a method that is limited by its inability to capture fine spatial variations in primary exhaust pollutants. Measurement data indicated that concentrations of certain motor vehicle exhaust components such as CO, NO_x and ultrafine particles (UFP) (i.e., UFP emitted directly in vehicle exhaust and not formed through atmospheric reactions) and adsorbed species such as polycyclic aromatic hydrocarbons (PAHs) are most elevated near their roadway sources and exhibit considerable spatial variability over short distances. Thus, air-monitoring data may not well reflect this variability. Since personal measurements of UFP, PAHs, elemental or organic carbon (EC/OC), and other traffic exhaust pollutants are too costly and logistically difficult to obtain for large population-based epidemiologic studies, especially over time periods longer than 48 hours needed for pregnancy studies, a number of surrogate exposure measures have previously been employed but have not been validated with residential or personal air pollution measurements. (e.g., residential distance to roadways, traffic counts on roadways near homes, self-reported traffic density on street of residence).

A novel approach for assessing exposure to traffic exhaust pollutants, land use-based regression (LUR) modeling, has been applied in Europe (11–16), Canada (17,18), San Diego, California (19), and in LA County, California (20). This approach incorporated outdoor pollution measurements taken at many locations throughout an urban area, in addition to Geographic Information System (GIS) predictors of traffic exhaust concentrations (such as traffic counts, truck routes, and roadways). The results of LUR modeling were air pollution surfaces (i.e. maps) for the geographic region, from which estimates of longer-term air pollution exposure is extracted for individuals, typically based on their GIS-mapped address locations. These models have been shown to have good predictive capability. For example, in a recent

model developed in San Diego, California, 79% of the variation in NO_2 levels measured at 39 locations was predicted by various GIS traffic parameters (19). Our model in LA County based on over 200 measurement locations in two seasons and explained 81%, 86% and 85% of the variance in measured NO, NO_2 and NO_x concentrations, respectively (21).

LUR-modeled estimates of NO, NO_2, and NO_x were extracted from the LA County LUR model developed previously, based on physical measurements from 2006-2007, in locations across LA County (21). This model allowed us to evaluate the importance of spatial variability in exhaust toxin concentrations of NO_x, NO, and NO_2 not captured by existing fixed site monitoring stations. LUR estimates of air pollution represent long-term exposures and most closely approximate annual average concentrations.

In addition to using LUR annual average ("unseasonalized") estimates, we also created "seasonalized" LUR estimates using measurement data from the government monitoring station closest to and linked to each woman's home location during pregnancy. Specifically, the LUR estimates were adjusted (multiplied) to generate pregnancy-month specific LUR values as follows (using NOx as an example):

*First month seasonalized NOx average = LUR NOx * (first month average NOx/2006 annual average NOx)*

The "seasonalized" pregnancy month LUR estimates were then averaged over each pregnancy period.

Childhood Autism Related to Maternal Race/Ethnicity and Nativity:

1) We examined maternal race/ethnicity and nativity based on mother's reported Hispanic origin (yes/no) and race information provided on the birth certificate to create three groups: non-Hispanic white, Hispanic, and non-Hispanic black, by maternal nativity (U.S.-born

or foreign-born). Mother's country of origin information on California birth certificates was only specified for some foreign-born Hispanic groups but not for foreign-born blacks. We separately examined the two subgroups that represented the largest foreign-born groups in the 12-year study period with origin or country of birth documented: Central/South America and Mexico. For this analysis, we excluded 175,352 children with other or unknown racial/ethnic group (99.4% of exclusions) and mothers with unknown nativity (0.6%). The final cohort here consisted of 1,461,610 births.

2) For the final analysis we identified U.S.-born whites, U.S-born or foreign-born Asians. Separate investigation of specific U.S.-born Asian subgroups was not possible because of small numbers. However, we identified five subgroups of foreign-born Asian mothers who represented the largest immigrant groups in the 12-year period for whom nativity was available on the birth certificate: China, Japan, Korea, Philippines, and Vietnam. For this analysis, we excluded 1,235,871 children with other or unknown race/ethnicity. The final cohort consisted of children of 236,347 U.S.-born white, 21,678 U.S.-born Asian, and 143,066 foreign-born Asian mothers.

Analysis

For the matched case-control study of autism and air pollution, individual pollutants were examined separately for each different pregnancy period. We examined associations using standard methods of analysis developed for case-control studies and employed stratified analyses and conditional logistic regression models (for matched data) to obtain point and interval estimates of odds ratios, representing valid estimates of rate ratios, given that we are using a population-based case and control ascertainment strategy and given that the disease is rare. We additionally analyzed the criteria air pollutants and LUR estimates using two-pollutant models,

excluding pairs of pollutants that covary strongly within the pregnancy period. We calculate estimates that are unadjusted and adjusted for at least the following possible confounders available on birth certificates: maternal age, race/ethnicity, education, parity, payment source of delivery (a proxy for socioeconomic status), and other demographic and pregnancy characteristics. Confounders were selected based on *a priori* hypotheses and using a directed acyclic graph (DAG) (see Figure 3-4). We conducted other stratified analyses to explore differences in effect estimates across maternal education groups.

For the case-cohort analyses of maternal race/ethnicity and nativity in relation to autism, we estimated risk of autism in offspring in subgroups according to maternal race/ethnicity and nativity. Using unconditional logistic regression and U.S.-born white mothers as the reference group, we estimated crude and adjusted relative risks (RRs) and 95% confidence intervals for the following outcomes: AD, AD with a comorbid diagnosis of mental retardation, and two categories of impairment/severity in expressive language or emotional outburst behavior, in Hispanic, black, and Asian populations. Confounders were selected based on *a priori* hypotheses and using a directed acyclic graph (DAG) (Figure 3-5).

Methodological Issues

Possible Selection Bias:

Survival bias: Both our case and control selection procedures may be susceptible to survival bias. Survival bias occurs when exposure affects case and control selection differently. The exposures of interest (traffic-related air pollution, maternal race/ethnicity and nativity) or correlated perinatal conditions may cause fetal or infant mortality and this would lead to selection bias if potential autism cases were more likely to have died than control children. If exposed cases had a higher mortality rate early in life compared to exposed controls, then our

analysis would be biased toward the null. Although exposure to traffic-related air pollution and infant death has been implicated (22), with stronger effects among infants with suboptimal perinatal conditions, we are unsure if this affected our case and control survival differently. Similarly, in our analysis of maternal race/ethnicity and nativity, it is known that infants of black mothers have a higher mortality rate than other race/ethnicity groups (23), so if cases born to black mothers had a higher mortality rate compared to black controls, then our analysis would also be biased toward the null.

Further, we do not know whether cases, compared to controls, were similarly or more likely to have moved outside the Los Angeles area prior to the age of 3 years, when they would have been referred to a regional center in our catchment area if symptoms of autism occurred. If mothers of cases and controls had survival rates and moving patterns non-differentially with regard to exposure during pregnancy, our analyses would not be biased. Although it is plausible to assume that traffic-related air pollution and suboptimal perinatal conditions related to race/ethnicity and nativity may cause infant death or that it affects moving patterns after birth, we can only cautiously assume that this occurred non-differentially between cases and controls.

Much like survival bias, selection bias can also arise through differential detection/diagnosis of autism. If psychologists had reason to believe that exposure to traffic-related air pollution affects autism or a variable highly correlated with prenatal air pollution such as socioeconomic status, then this affects the probability of identifying an autism case and this study would be subject to detection bias. It is likely that diagnosis rates are higher among high socioeconomic groups versus lower SES groups such as people of color or certain foreign-born populations. However, high SES populations might have lower exposures to traffic-related air pollution, which would bias our results towards the null.

Challenges to modeling air pollution exposures in pregnancy

There are challenges in estimating air pollution exposure in population-based studies, especially when medium- or longer-term exposures are of interest, as is in the case of pregnancy. Here, we discuss some of the main challenges related to exposure modeling.

Temporal and spatial variation

Air pollution varies both spatially and temporally. Spatial variation is dependent on the location of sources of air pollution (e.g. freeways, industrial sources), the specific pollutant (e.g. NO_2 vs O_3), as well as wind direction, and geographical features (e.g. valleys). Temporal variation is due to a variety of meteorological factors, including temperature, sunlight, humidity, and wind speed and direction. In Los Angeles, the predominant temporal patterns are high levels of ozone in the summer months, when sunlight causes NO_2 to react with oxygen in the air and form ozone; whereas in the winter months, there are higher levels of NO_x because of the lack of sunlight to break down these gases.

Networks of government air monitoring stations provide detailed data on temporal variation of air pollutants, but have somewhat limited spatial coverage. There are only 16 California Air Resources Board (CARB) air-monitoring stations for the whole Los Angeles County metropolitan areas, and exposures based on monitoring station data are unlikely to reflect more local exposures for people living further away from a station.

A method that helps characterize finer spatial variations in air pollution, regardless of distance from a monitoring station, is land use-based regression (LUR) modeling. In this modeling approach, outdoor pollution measurements taken at locations throughout an urban area are related to Geographic Information System (GIS) predictors of air pollution sources such as traffic exhaust concentrations, e.g. using traffic density, roadways, and population density (18).

Such a regression model can be used to predict local exposures from specific sources near residential locations.

Pollution exposure mix, multiple pollutants and correlated data

In Los Angeles County, traffic is a major source of air pollution. Because air pollution is a mixture of gases, particles, and air toxics, which are often correlated due to common sources, it is difficult to identify any one causal agent within the mix of pollutants. Multipollutant models can be used to disentangle effects of different air pollutants and it is recommended they be used in epidemiologic studies of air pollution (24).

Critical time windows during pregnancy

We examined several possible critical time windows to assess the possible impact of prenatal air pollution exposures on autism development, assuming that the neurological impact resulting in autism is initiated during pregnancy. In this reproductive developmental study we are dealing with short critical time windows of exposure susceptibility. But because the critical time window of exposure is unknown, using too broad a time window, especially if the exposure highly varies during this time period, can lead to misclassification of exposure, i.e. for those exposed in one and not other trimesters, considerable exposure misclassification can occur if we would assume that exposures are homogenous throughout pregnancy. Assessing exposures during a variety of time windows including the entire pregnancy period and each trimester will provide a comprehensive look at the potential effects of air pollution exposures during pregnancy and autism.

Maternal race/ethnicity and nativity

Latinos and Asian Americans make up a large proportion of the U.S. population. There are considerable differences among the health of U.S. racial and ethnic groups, with African

Americans having the worst health profile, and Asian Americans having the fewest health problems (25). Research on race/ethnicity and health is controversial as many argue that it is an invalid biological concept and thus should not be used as a scientific concept (25). Nevertheless, it has become clear that race/ethnicity has become a profoundly important determinant of health status and health care equity in the U.S.

Methodological issues arise when we try to describe what race/ethnicity represents or the causes of autism differences. So we emphasize that the purpose of our use of race/ethnicity is only to describe variation in autism risk. In turn, we hypothesize that differences were likely correlated to distinctions in other factors, such as nutrition, stress, or environmental exposures. Further, because racial differentials are associated with differences in education level, income, etc., an issue arose when we tried to adjust by these variables. Race/ethnicity could not be confounded by these social variables because they are mediators and race is an antecedent to these factors (26). So we report results before and after adjustment by socioeconomic (SES) variables, i.e. education level and source of health insurance payment, in order to demonstrate the impact of adjustment on SES.

Power & Sample Size

For our matched case-control design, we expected to have 80% statistical power (alpha of 0.05) to estimate a 20% or greater increase in risk with 8,000 cases and 10 controls each, at an exposure prevalence of 25% in population controls and the correlation coefficient for exposure between matched cases and controls is 0.9. To reach 90% statistical power, if the true odds ratio for disease in exposed subjects relative to unexposed subjects is 1.25, we needed to study 7,128 cases with 10 matched controls per case to be able to reject the null hypothesis that this odds ratio equals 1; at type I error probability of 0.05 when testing of the null hypothesis.

Role in the project

My interest in autism generated collaboration with my dissertation chair, Beate Ritz, to investigate a possible association between autism and traffic-related air pollution. Under her supervision, my role was to generate a proposal for IRB, pilot grant, and to request data from the California Department of Developmental Services. I managed the case dataset, and linked autism cases to birth certificate records in Los Angeles County by using an existing dataset my chair possessed. Geocoding of home addresses and assessment of air pollution using the Land Use Regression (LUR) model was completed previously. My chair suggested the design of the first study on air pollution and I completed the data analysis with her guidance. I designed and analyzed the second and third study on maternal race/ethnicity and nativity with increased independence, with critical revisions from Ondine von Ehrenstein and Beate Ritz.

Table 3-1. The seven Los Angeles County Regional Centers: Monthly caseload report for all consumers through December 2009

Regional Center	Active status clients
Eastern LA	7,650
Harbor	8,525
Lanterman	6,439
North LA	14,071
South-Central	8,844
Westside	6,110
San Gabriel/Pomona	9,454

All consumers: eligible diagnosis of mental retardation, autism, cerebral palsy, epilepsy, other developmental delays

Study catchment periods

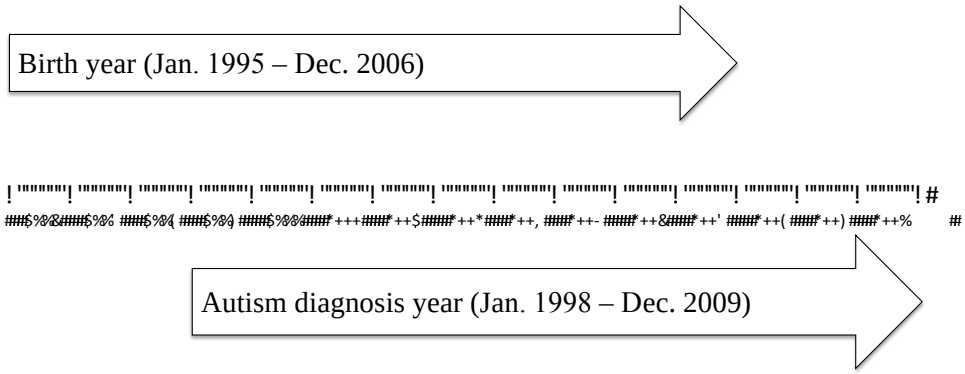

Figure 3-1. Study catchment periods

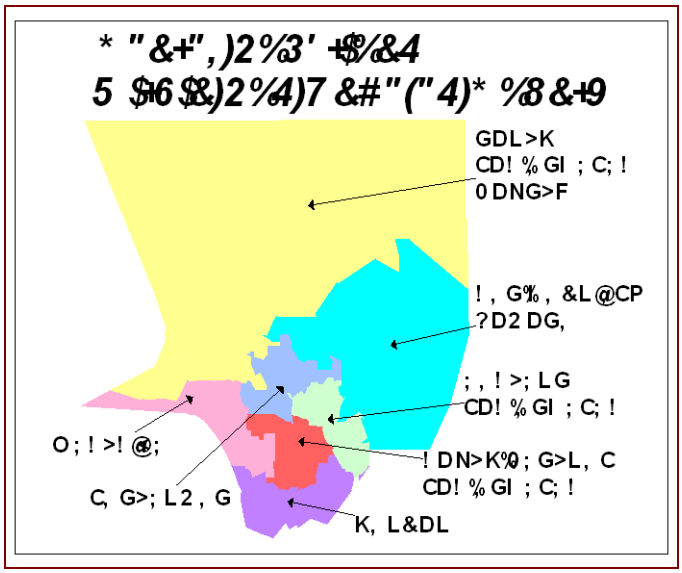

Figure 3-2. Map of the seven regional centers in Los Angeles County.

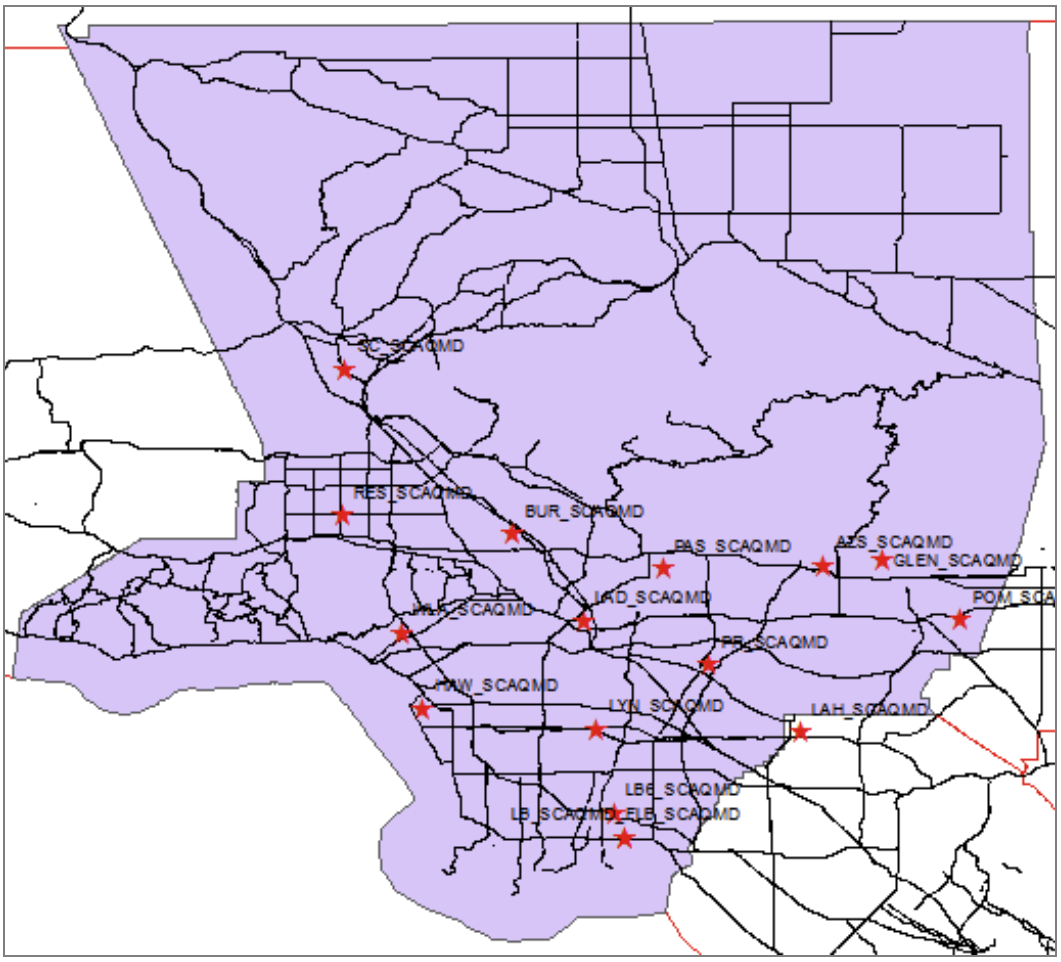

Figure 3-3 . Map of California Air Resources Board monitoring stations in Los Angeles County

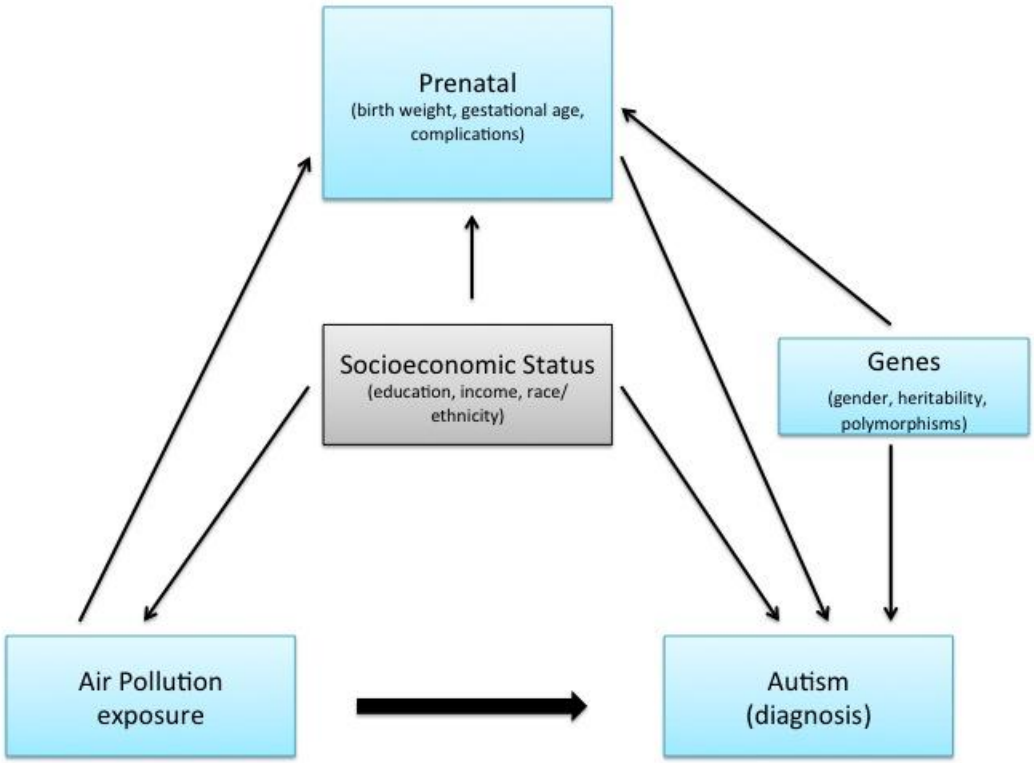

Figure 3-4. Proposed directed acyclic graph for investigating air pollution exposure and autism, displaying key associations of interest and potential confounders. Parental age and parity also considered potential confounders not shown here.

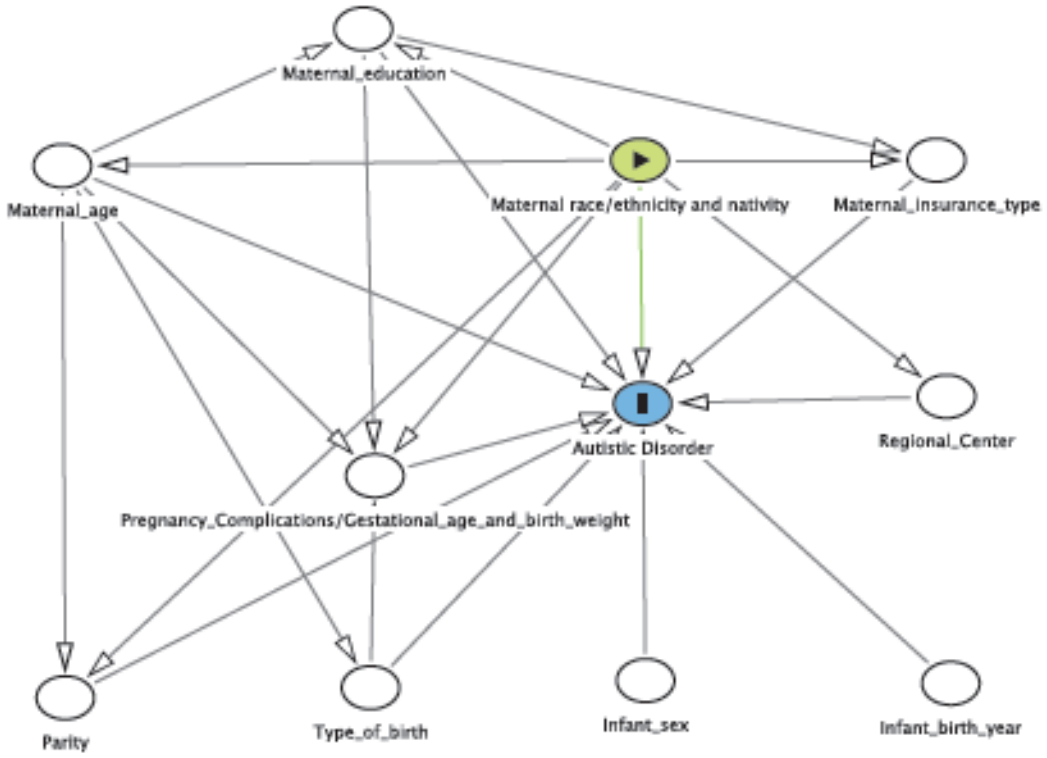

Figure 3-5. Proposed directed acyclic graph for investigating maternal race/ethnicity/nativity and autism, displaying key associations of interest and potential confounders and mediators.

References

1. State of California Department of Developmental Services. 2009 Monthly Caseload Reports: December 2009 [Internet]. 2009 Dec. Available from: http://www.dds.ca.gov/FactsStats/Caseload_2009.cfm
2. California Department of Develomental Services. Autism Spectrum Disorders: Changes in the California Caseload, an update: June 1987 – June 2007 [Internet]. 2007. Available from: http://www.dds.ca.gov/Autism/Home.cfm
3. California Department of Developmental Services. Autism Spectrum Disorders: Best Practice Guidelines for Screening, Diagnosis and Assessment [Internet]. 2002. Available from: http://www.dds.ca.gov/Autism/docs/ASD_Best_Practice2002.pdf
4. State of California Health & Welfare Agency: Department of Developmental Services. CDER Manual [Internet]. 1986 Jul. Available from: http://www.dds.ca.gov/FactsStats/Diagnostic_Main.cfm
5. Croen LA, Grether JK, Hoogstrate J, Selvin S. The changing prevalence of autism in California. J Autism Dev Disord. 2002 Jun;32(3):207–15.
6. Lord C, Risi S, DiLavore PS, Shulman C, Thurm A, Pickles A. Autism From 2 to 9 Years of Age. Arch Gen Psychiatry. 2006 Jun 1;63(6):694–701.
7. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion. Registry Plus, a suite of publicly available software programs for collecting and processing cancer registry data. [Internet]. 2010 [cited 2010 Nov 15]. Available from: http://www.cdc.gov/cancer/npcr/

8. Goldberg DW, Wilson JP, Knoblock CA, Ritz B, Cockburn MG. An effective and efficient approach for manually improving geocoded data. Int J Heal Geogr. 2008;7:60.
9. California Environmental Protection Agency. Gaseous Criteria Pollutant Monitoring [Internet]. Air Resour. Board. 2010 [cited 2013 Jun 14]. Available from: http://www.arb.ca.gov/aaqm/am_tables/criteria.htm
10. California Environmental Protection Agency. Particulate Matter Pollutant Monitoring [Internet]. Air Re. 2013 [cited 2013 Jun 14]. Available from: http://www.arb.ca.gov/aaqm/partic.htm
11. Brauer M, Hoek G, Van Vliet P, Meliefste K, Fischer PH, Wijga A, et al. Air Pollution from Traffic and the Development of Respiratory Infections and Asthmatic and Allergic Symptoms in Children. Am J Respir Crit Care Med. 2002 Oct 15;166(8):1092–8.
12. Gehring U, Cyrys J, Sedlmeir G, Brunekreef B, Bellander T, Fischer P, et al. Traffic-related air pollution and respiratory health during the first 2 yrs of life. Eur Respir J Off J Eur Soc Clin Respir Physiol. 2002 Apr;19(4):690–8.
13. Aguilera I, Guxens M, Garcia-Esteban R, Corbella T, Nieuwenhuijsen MJ, Foradada CM, et al. Association between GIS-based exposure to urban air pollution during pregnancy and birth weight in the INMA Sabadell Cohort. Environ Health Perspect. 2009 Aug;117(8):1322–7.
14. Ballester F, Estarlich M, Iñiguez C, Llop S, Ramón R, Esplugues A, et al. Air pollution exposure during pregnancy and reduced birth size: a prospective birth cohort study in Valencia, Spain. Environ Heal Glob Access Sci Source. 2010;9:6.
15. Slama R, Morgenstern V, Cyrys J, Zutavern A, Herbarth O, Wichmann H-E, et al. Traffic-related atmospheric pollutants levels during pregnancy and offspring's term birth weight:

a study relying on a land-use regression exposure model. Environ Health Perspect. 2007 Sep;115(9):1283–92.

16. Llop S, Ballester F, Estarlich M, Esplugues A, Rebagliato M, Iñiguez C. Preterm birth and exposure to air pollutants during pregnancy. Environ Res. 2010 Nov;110(8):778–85.
17. Gilbert NL, Goldberg MS, Beckerman B, Brook JR, Jerrett M. Assessing spatial variability of ambient nitrogen dioxide in Montréal, Canada, with a land-use regression model. J Air Waste Manag Assoc 1995. 2005 Aug;55(8):1059–63.
18. Sahsuvaroglu T, Arain A, Kanaroglou P, Finkelstein N, Newbold B, Jerrett M, et al. A land use regression model for predicting ambient concentrations of nitrogen dioxide in Hamilton, Ontario, Canada. J Air Waste Manag Assoc 1995. 2006 Aug;56(8):1059–69.
19. Ross Z, English PB, Scalf R, Gunier R, Smorodinsky S, Wall S, et al. Nitrogen dioxide prediction in Southern California using land use regression modeling: potential for environmental health analyses. J Expo Sci Environ Epidemiol. 2006 Mar;16(2):106–14.
20. Wilhelm M, Ghosh JK, Su J, Cockburn M, Jerrett M, Ritz B. Traffic-Related Air Toxics and Term Low Birth Weight in Los Angeles County, California. Environ Health Perspect. 2011 Aug 11;120(1):132–8.
21. Su JG, Jerrett M, Beckerman B, Wilhelm M, Ghosh JK, Ritz B. Predicting traffic-related air pollution in Los Angeles using a distance decay regression selection strategy. Environ Res. 2009 Aug;109(6):657–70.
22. Ritz B, Wilhelm M, Zhao Y. Air Pollution and Infant Death in Southern California, 1989–2000. Pediatrics. 2006 Aug;118(2):493 –502.
23. Gonzales J. Black infant mortality: An international perspective [Internet]. Cent. Heal. Report. 2013 [cited 2013 Jun 17]. Available from:

http://centerforhealthreporting.org/blog/black-infant-mortality-international-perspective1105

24. Dominici F, Peng RD, Barr CD, Bell ML. Protecting Human Health From Air Pollution. Epidemiology. 2010 Mar;21(2):187–94.

25. LaVeist TA. Why We Should Study Race, Ethnicity, and Health. Race Ethn Heal. 1st ed. San Francisco, CA: Jossey-Bass; 2002. p. 1–7.

26. Cooper R. A Note on the Biological Concept of Race and Its Applicatio in Epidemiologic Research. Race Ethn Heal. 1st ed. San Francisco, CA: Jossey-Bass; 2002. p. 99–114.

Chapter 4: Ambient Air Pollution and Autism Risk in Los Angeles County, California

Introduction

Autistic Disorder is a serious developmental condition characterized by impairments in social interaction, abnormalities in verbal and nonverbal communication, and restricted stereotyped behaviors thought to be due to insults to the developing fetal and/or infant brain (American Psychiatric Association 2000; Geschwind and Levitt 2007). The prevalence of autism has risen for the past 20 years, partly due to changes in case definition and improved case recognition. Hertz-Picciotto and Delwiche (2009) suggested the observed rise in incidence in California between 1990-2001 may partially but not fully be explained by younger age at diagnosis (12% increase) and inclusion of milder cases (56% increase). While evidence for genetic contributions is considered quite strong, twin concordance research recently suggested environmental causes are also important (Hallmayer et al. 2011), and it is quite conceivable that multiple genes interact with environmental factors (Cederlund and Gillberg 2004; Glasson et al. 2004).

Few studies to date have examined the impact of air pollution on brain development in general during pregnancy, although air pollution exposure during the prenatal period has been associated with a variety of adverse birth outcomes in epidemiologic studies (Ritz et al. 2000; Ritz and Yu 1999; Srám et al. 2005; Williams et al. 1977), and neuropsychological effects later in childhood (Calderón-Garcidueñas et al. 2008; Edwards et al. 2010; Perera et al. 2006; Perera et al. 2012; Suglia et al. 2008; Tang et al. 2008; Wang et al. 2009). The biological mechanisms by which air pollution may cause autism are largely unknown, although the immune system has been implicated as possibly playing a role (Hertz-Picciotto et al. 2008). Only three studies to date have examined associations between autism and air pollution exposures during the prenatal period (Kalkbrenner et al. 2010; Volk et al. 2010; Windham et al. 2006). In one study, autism

was associated with ambient air concentrations of chlorinated solvents and heavy metals near birth residences (Windham et al. 2006). Another study of autism reported elevated odds ratios for methylene chloride, quinoline, and styrene exposures in ambient air but near-null effect estimates for ambient air metals and other pollutants (Kalkbrenner et al. 2010). A third study reported that children born to mothers living within 309 meters of a freeway during pregnancy were more likely to be diagnosed with autism than children whose mothers lived >1,419 meters from a freeway (Volk et al. 2010).

We derived air pollution exposure measures using data from government air monitoring stations that provide information on spatial and temporal variations in criteria pollutants, and from a land use regression (LUR) model we developed for the Los Angeles (LA) air basin. The LUR model allowed us to greatly improve our spatial characterization of traffic-related air pollution. Because heterogeneity of the autism phenotype and its severity may be due to influences on different critical gestational windows of brain development (Geschwind and Levitt 2007), we also seasonalized these traffic measures to investigate vulnerable trimesters of development. Here we examine associations between measured and modeled exposures to prenatal air pollution and autism in children born to mothers in LA County, California since 1995.

Methods

In this population-based case-control study, our source population consisted of children born between 1995-2006 to mothers who resided in LA County, California at the time of giving birth.

Case ascertainment and definition

In LA, children with autism are identified through seven Regional Centers, contracted by the California Department of Developmental Services (DDS), whose staff determine eligibility and coordinate services in their respective service areas. Cases are children given a primary diagnosis of Autistic Disorder (AD), the most severe among the autism spectrum disorders (ASD) diagnoses, between the ages of 36 to 71 months at a Los Angeles Regional Center during 1998-2009. During our study period, eligibility for DDS services did not depend on citizenship or financial status, i.e. services were available to all children irrespective of socioeconomic, health insurance status, or racial/ethnic identification. Referrals to the regional centers are usually made by pediatricians, other clinical providers, and schools, but parents may also self-refer their children.

The diagnosis of AD was based on the Diagnostic and Statistical Manual of Mental Disorders (DSM IV-R) (American Psychiatric Association 2000) (code 299.00) reported on the Client Development Evaluation Report (CDER). Validation studies have established the reliability and validity of the CDER in California (California Department of Developmental Services 2007; State of California Health and Welfare Agency: Department of Developmental Services 1986).

Record Linkage

We attempted to link 10,821 DDS records of children with autism to their respective birth records using the National Program of Cancer Registries Registry Plus™ Link Plus Software (U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion 2010a). Based on child's first and last name, birthdate, and gender; mother's first and last name, and birthdate; and father's last name and birthdate, we probabilistically matched the two records and reviewed all

high scoring linkages (≥25), almost half of the linkages (9,120 out of 22,806), only accepting those manually confirmed to be likely matches (see CDC for record linkage concepts) (U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion 2010b). The remaining lower scoring linkages were reviewed using SAS 9.2 and accepted on the condition that the child's first and last name, and birthdate matched perfectly. We correctly linked 8,600 DDS records (79.5% of all cases) to birth records. Of the 2,221 DDS records not linked to CA birth records, 35% were not born in LA County, 46% were missing birthplace information, and only 19% recorded the child as born in Los Angeles County. The most common reason for non-linkage was missing/incomplete linkage information on either of the records.

From among linked cases, we further excluded children whose mother's residency was outside of LA County during her pregnancy (n=41), records with missing or implausible gestational ages (<21 or >46 weeks) or birth weights (<500g or >6800g) (n=508), and cases who did not have a primary diagnosis of Autistic Disorder (n=448), leaving a final sample of 7,603 children with autism successfully linked to a birth certificate who met all inclusion criteria.

Control selection

We selected 10 controls for each case from our source population. Using birth certificates, each control was randomly selected without replacement and matched on birth year and sex. In addition, each control's gestational age at birth had to be equal to or greater than the gestational age at birth of their matched case to ensure prenatal exposures could be estimated for comparable lengths of time. Children were eligible as controls if they had no documentation of autism, i.e. did not have a DDS record in LA County by 2009, had a plausible gestational age

(21-46 weeks inclusive) and birth weight (500-6800g inclusive), and the mother resided in LA County at the time of birth.

Matching by birth year balanced the large increase in autism rates during the case ascertainment period, 1998 to 2009. The matched control set included 76,030 children born during 1995-2006. From among these, we further excluded 248 control children who died prior to 5 years of age (71 months) based on California death records, leaving 75,782 controls.

Residential locations at delivery reported on birth certificates were mapped using a custom geocoder (Goldberg et al. 2008) and further exclusions were necessary if residential addresses were not geocodable (9 cases, 147 controls; see Supplemental Material, Table 4-5). The geocoded residential locations at birth were then linked to the nearest government air monitoring station in LA County and our LUR model.

This research was approved by the University of California Los Angeles Office of the Human Research Protection Program and the California Committee for the Protection of Human Subjects, and was exempted from informed consent requirements.

Exposure assessment

Using measurements for the criteria pollutants carbon monoxide (CO), nitrogen dioxide (NO_2), nitric oxide (NO), ozone (O_3), particulate matter concentrations with an aerodynamic diameter $\leq$10 μm (PM_{10}) and $\leq$2.5 μm ($PM_{2.5}$) from nearest monitoring stations, we estimated average exposures for the entire pregnancy and for three specific periods during pregnancy based on the birth date and gestational age reported on the birth certificate: first trimester (estimated first day of last menstrual period through day 92), second trimester (days 93-185), and third trimester (day 186 to date of birth). The length of each pregnancy averaging period for controls was the same as for their matched case, i.e., averaging periods for each autistic risk set were

truncated at the gestational age of the matched case at birth. Hourly measurements for CO, NO_2, NO, and O_3 (10am-6pm) were first averaged for each day if sufficient data were available (see Supplemental Material, Table 4-6 for details). Daily averages for the gaseous pollutants and 24-hour measurements of PM_{10} and $PM_{2.5}$ (collected every 6 and 3 days, respectively) were then averaged over the different pregnancy periods when data were sufficient to do so (see Supplemental Material, Table 4-6).

To classify prenatal exposures to traffic-related pollutants on a more spatially-resolved scale, we extracted NO and NO_2 concentration estimates at each residential location from the LUR model surfaces we developed for the LA Basin (Su et al. 2009). This LUR model was based on approximately two hundred measurements of outdoor air pollution taken during 2006-2007 in locations across LA County, in addition to predictors of traffic exhaust concentrations (such as traffic counts, truck routes, and roadways). The model explained 81% and 86% of the variance in measured NO and NO_2 concentrations, respectively (Su et al. 2009).

The LUR models most closely approximate annual average concentrations. Thus, in addition to using the LUR annual average ("unseasonalized") estimates, we also generated "seasonalized" estimates to incorporate yearly and monthly air pollution variations. Specifically, using ambient air monitoring data for NO and NO_2 at the closest monitoring station, the LUR estimates were adjusted to represent pregnancy-month specific LUR values by multiplying the LUR (unseasonalized) estimates for NO and NO_2 by the ratio of average ambient NO and NO_2 during each pregnancy month to annual average ambient NO and NO_2 (2006-2007). These seasonalized monthly LUR values were then averaged over each pregnancy period. We applied the same exclusion criteria for missing values as described above when generating the pregnancy month scaling factors using the government monitoring data.

Statistical Analysis

We calculated Pearson's correlation coefficients to examine relations between the various pollutant measures. Associations between air pollution exposure and odds of AD diagnosis were examined using one and two-pollutant models. We adjusted for LUR estimates of traffic related exposures in our monitor-based pollutant models and assessed particles and the gaseous pollutant ozone together in the same model. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) using conditional logistic regression to estimate increases in odds of AD per inter-quartile range (IQR) increase in pregnancy exposures, based on exposure distributions in the controls.

We adjusted for potential confounders for which data were available on birth certificates based on prior knowledge (see Table 4-1 for categories used in models): maternal age, maternal place of birth and race/ethnicity, and maternal education; type of birth (single, multiple), parity, insurance type (public, private, or other, a proxy for socioeconomic status), and gestational age at birth (weeks). In addition, we estimated pollutant effects without adjustment for gestational age to allow for the possibility that this factor might be an intermediate and thus on the causal pathway between air pollution and autism.

We expected maternal education to correlate with estimates of air pollution and autism (Ponce et al. 2005), therefore we also used unconditional logistic regression models to estimate associations stratified by maternal education (less than high school, high school, more than high school) controlling for the matching variables, birth year, sex, and gestational weeks at birth, in addition to the other covariates noted above.

Results

Both mothers and fathers of children with autism were older and more educated than parents of control children, and mothers were more often non-Hispanic white but less often Hispanic, especially foreign-born Hispanic (Table 4-1). A higher percentage of mothers of case children were primiparous and had multiple gestations. As expected, children with autism had a lower mean gestational age at birth and birth weight than control children. Of the children with autism not linked to a LA County birth record, parental characteristics were undetermined because of frequent missing information, i.e. 50–60% missing maternal and paternal age/birthday (results not shown). However, of these non-linked DDS records, 42% of families were Hispanic (results not shown), comparable to the 41.9% of Hispanic mothers of case children included in this study (Table 4-1).

Unseasonalized LUR-based exposure estimates for NO and NO_2 were negatively correlated with entire pregnancy ozone (r: -0.23 and -0.33, respectively) but positively correlated with entire pregnancy CO, NO, NO_2, and $PM_{2.5}$ (r: 0.22 to 0.43), and as expected, correlations between measured levels of pollutants and seasonalized LUR estimates were stronger than correlations with unseasonalized LUR estimates (r: 0.30 to 0.73) (Supplemental Material, Table 4-7). Even though all trimester specific measures correlated moderately with entire pregnancy averages ($r \geq 0.46$), second trimester exposure averages correlated most strongly with entire pregnancy averages ($r \geq 0.80$), and first and third trimester averages for the same pollutants were least correlated (r: 0.05 to 0.37) (results not shown).

We estimated 4-7% relative increases in odds of an Autistic Disorder diagnosis per IQR increase in unseasonalized LUR measures of NO and NO_2 in adjusted models (Table 4-2). These odds ratio estimates remained similar (1.03 to 1.09) in two-pollutant adjusted models (Table 4-3). Odds ratios for autism per IQR increase in monitor-based estimates of entire pregnancy

exposure to NO and NO_2 were slightly smaller than associations with IQR increases in LUR-based estimates (see Table 4-2). We also estimated increases in odds of AD diagnosis per IQR increase in entire pregnancy exposure to ozone [OR=1.06, CI=1.01, 1.12] and $PM_{2.5}$ [OR=1.07, CI=1.00, 1.15] (Table 4-2). In two-pollutant models these estimates increased [ozone OR=1.12, CI=1.06, 1.19; $PM_{2.5}$ OR=1.15, CI=1.06, 1.24] when we mutually adjusted for both pollutants (Table 4-3). In addition, without adjustment for gestational weeks at birth associations increased further or remained the same; i.e. for the two-pollutant models including ozone and $PM_{2.5}$ [ozone OR=1.14, CI=1.10, 1.19; $PM_{2.5}$ OR=1.15, CI=1.09, 1.22] or ozone and LUR-NO_2 [ozone OR=1.10, CI=1.06, 1.14; LUR-NO_2 OR= 1.10, CI=1.07, 1.13] (results not shown).

In general, effect estimates did not show consistent patterns across trimesters in one-pollutant models. For example, average second and third but not first trimester exposures to ozone were associated with AD [first trimester OR=1.00 (0.97, 1.03); second trimester OR=1.02 (1.00, 1.05); third trimester OR=1.04 (1.01, 1.06)] (Supplemental Material, Table 4-8).

Adjusting for maternal education changed air pollution effect estimates most strongly, likely because socioeconomic status is strongly associated both with air pollution exposure and autism diagnosis. We also investigated potential effect measure modification of the air pollution and autism association, i.e. examined whether air pollution effect estimates vary according to strata of maternal education possibly due to differences in vulnerability, in actual exposure, or exposure and outcome misclassification. Generally, LUR-based traffic-related pollutant estimates showed the strongest association with autism in children of the least educated mothers, compared to mothers in the highest educational stratum (Table 4-4).

Discussion

We estimated an approximately 3 to 9% relative increase in the odds of Autistic Disorder per inter-quartile range increase in entire pregnancy exposure to NO (9.40 ppb) and NO_2 (5.41 ppb) as estimated by our two-pollutant LUR models. Our LUR model was built upon neighborhood-level measures of NO_x and represents smaller-scale variability in exhaust pollutants, compared to estimates based on air monitoring station measurements (Zhou and Levy 2007). We also estimated a 5-15% relative increase in the odds of AD per inter-quartile range increase in entire pregnancy exposure to $PM_{2.5}$ (4.68 $\mu g/m^3$) (Table 4-3), a pollutant which concentrations are driven in part by fossil fuel combustion in motor vehicles. In addition, an 11.54 ppb increase in ozone exposures during pregnancy was associated with a 6-12% relative increase in the odds of having a child diagnosed with autism.

Few studies have previously examined associations between air pollution related exposures during the prenatal period and later development of autism, and none used ambient air monitoring data or land use regression models to estimate risk in a large population. A relatively small study (284 cases, 657 controls) in the San Francisco Bay, California used study-specific census tract pollution scores derived from annual average concentrations and found hazardous air pollutant (HAP) concentrations (i.e. mercury, cadmium, nickel, trichloroethylene, and vinyl chloride) near birth residences to be associated with autism (Windham et al. 2006). A study by Kalkbrenner et al. (2010) in North Carolina and West Virginia, with less exposure variability compared to California, reported near-null effect estimates for metals and several pollutants associated with AD in the San Francisco study. Both studies relied on the same HAP pollutant data source and the Centers for Disease Control and Prevention (CDC) autism surveillance system (Autism and Developmental Disabilities Monitoring Network) to identify cases. However, instead of sampling controls from birth certificates, using education records North

Carolina/West Virginia study investigators selected control children with speech and language impairment (383 cases, 2829 controls). A third study (304 autism cases and 259 typically developing controls) based in California (Childhood Autism Risks from Genetics and the Environment (CHARGE) study) reported relatively strong associations (OR: 1.86, 95% CI: 1.04, 3.45) between childhood autism and proximity (living within 309 meters) to a freeway during pregnancy (Hertz-Picciotto et al. 2006; Volk et al. 2010). Trimester-specific addresses were geocoded, and measures of distance to freeways and major roads were calculated using GIS software. This small study was the first to suggest that traffic-related exposures might increase the risk of autism. In our study, we observed weaker associations with monitor-based and modeled air pollution exposure estimates in a much larger study population.

Gestational toxicity may plausibly result from maternal exposure to NO_2, which has been shown to disturb early neuromotor development in animals, causing coordination deficits, and reduced activity and reactivity in rats (Tabacova et al. 1985); specifically, NO_2 exposure at low ($0.05 – 0.10$ mg/m^3) and high (1 and 10 mg/m^3) concentrations for 6 hours each day throughout gestation affected neuromotor development in offspring. The mean NO_2 level in our study (30.8ppb; Supplemental Material, Table 4-7) falls within the exposure range classified as "low" in this animal study ($0.05 – 0.10$ mg/m^3 or 26.6ppb – 53.2ppb). Beckerman et al. (2008) suggested that NO may be a proxy measure for ultrafine particle (UFP, $< 0.1\mu$m in aerodynamic diameter) exposures from traffic exhaust and reported strong correlations between one-week average concentrations of NO, NO_2, and NO_x and short-term (10 minute) measures of UFP ($r=0.8$-0.9) at varying distances from a major expressway in Toronto, Canada. Fine particles ($PM_{2.5}$) can cause oxidative stress, and in-vitro animal and human post-mortem brain studies showed they can trigger cellular toxicity and brain cell pathology (Lai et al., 2005; Li et al.,

2003, Peters et al 2006). Hertz-Picciotto et al. (2005) found maternal $PM_{2.5}$ exposures two weeks before birth associated with altered lymphocyte immunophenotypes and suggested this might mediate effects of air pollution on childhood morbidity. Developmental immune system disruption has been hypothesized to play a role in neurobehavioral disorders such as autism, considering the close connection between the development of the immune system and the central nervous system (Hertz-Picciotto et al. 2008).

To our knowledge, this is the first study to suggest associations between ozone and Autistic Disorder. Although ozone levels have dropped over the last decade, the LA region still often has the highest levels of ozone nationwide, violating federal health standards an average of 137 days a year (averages from 2007 through 2009) (Roosevelt 2011). In contrast with the traffic-related and particle associations that only became positive when we adjusted for maternal education, ozone effect estimates moved closer towards the null after adjustment for covariates, consistent with expectations, since traffic-related pollution is higher in lower SES neighborhoods while ozone levels are higher in suburban high SES areas, and autism is more likely to be diagnosed earlier in children of mothers with higher SES. Specifically, ozone and NO follow opposite distribution patterns across the LA basin. Ozone is formed by photochemical reactions in the presence of precursor pollutants from exhaust, and concentrations are low near freeways/roadways (due to presence of strong NO emission sources) and higher in suburban neighborhoods (Wilhelm et al. 2009). Controlled animal studies suggest ozone may cause adverse neurobehavioral effects after gestational exposure (Kavlock et al. 1980; Petruzzi et al. 1995; Sorace et al. 2001).

We relied on information recorded on California birth certificates to adjust for potential confounding by prenatal risk factors for autism reported in the literature (Gardener et. al. 2009,

2011), i.e. parental age at birth, parity, maternal place of birth, and multiple births. However, we were unable to control for potential confounding due to maternal physical and mental health history, or maternal active or passive smoking. Women giving birth in LA are predominantly Hispanic, and our survey of 2,543 women giving birth in LA County in 2003 found only 1% of foreign-born Hispanic, 5% of US born Hispanics and 7% of non-Hispanic whites are active smokers during pregnancy (Hoggatt et al. 2011). Also, a recent study found no association [prevalence ratio=0.88 (95% CI=0.72, 1.08)] for maternal smoking during pregnancy and Autistic Disorder (Kalkbrenner et al. 2012). Confounding by other SES-related factors potentially correlated with air pollution is also a concern. Families of lower SES are more likely exposed to air pollution, and less likely represented in the autism case group, possibly due to under ascertainment (Durkin et al. 2010; Grineski et al. 2007; Institute of Medicine 1999), which could have potentially biased our effect estimates toward the null. However, we estimated stronger associations among those with the lowest maternal education for LUR-based estimates of NO and NO_2. We adjusted for type of insurance (public vs. private pay), as well as other SES indicators important in the LA community (i.e. maternal place of birth and education) since we previously showed these factors were sufficient to adjust adequately for SES in LA County birth outcome and air pollution studies; i.e. effect estimates for air pollution and birth outcomes were very similar when we adjusted for maternal occupation, income, and education or simply for birth certificate derived SES measures (Hoggatt et al. 2011).

In addition to being a confounder, gestational age at birth may also be a mediator between air pollution and autism. In analyses not adjusting for gestational weeks at birth we estimated larger or similar effect sizes. However, not adjusting for gestational age at birth may also result in biased estimates because of our matching design. Specifically, since controls were

sampled from among children who at birth had reached at minimum the gestational age of the matched case, gestational age as a matching variable required that we analytically control for it. Thus the magnitude and direction of any potential bias from adjusting or not adjusting for gestational age at birth is not easily quantifiable.

A source of exposure measurement error is the reliance on address information reported on birth certificates, which does not account for women who worked far from home or residential mobility during pregnancy. Previous U.S.-based studies (1997–2004) indicate 15-30% of women move during pregnancy (Chen et al. 2010; Lupo et al. 2010). In our previous population-based survey of 2,543 women residing in 111 zipcodes in LA County and delivering in 2003, 22% reported moving during pregnancy (Ritz et al. 2007). Our survey also found pregnant women of lower SES less likely to be employed and more likely to spend time near their residence, suggesting exposure is less misclassified for lower compared to higher SES women.

Distance from a monitoring station likely introduced some non-differential misclassification of exposure, especially for pollutants such as CO and NO_2 that are more heterogeneously distributed. On average, the distance between home addresses and the nearest monitoring station was 6.7 miles in our study, and monitor-based estimates of CO, NO and NO_2 are questionable in their validity if air pollution measurements are more accurate representations of actual exposures for women living closer to a station (Ghosh et al. 2012; Wilhelm et al. 2011). Ambient station measures for $PM_{2.5}$ and ozone, however, are less likely to be misrepresenting actual exposures, as these pollutants are generally considered more homogeneously distributed over larger regions.

LUR derived NO and NO_2 are much more spatially resolved than monitor-based

estimates, and were previously associated with adverse pregnancy outcomes in the same LA population (Ghosh et al. 2012; Wilhelm et al. 2011). Our LUR model not only represents local traffic-related pollution well, it reduces possible confounding by spatial SES factors. For example, autism diagnoses have been reported to vary spatially in California due to SES (Van Meter et al. 2010), but measures of air pollution are not inherently influenced by these spatial factors related to SES (Wilhelm et al. 2009). For pollutants that are more homogeneous over larger regional areas like $PM_{2.5}$ and ozone, confounding due to SES is possible, nevertheless associations were stronger when we mutually adjusted for both pollutants.

A major strength of our study was the use of our novel LUR exposure measures for traffic-related pollution in addition to routine, government monitoring station data for criteria pollutants to help identify specific emissions of concern for autism. Furthermore, selection bias due to participation is unlikely to have occurred.

Conclusions

The observed association with the LUR model estimates and monitoring station-based ozone and $PM_{2.5}$ measures suggest a link between Autistic Disorder and traffic-related exposures during pregnancy. Ideally, future autism and air pollution studies should use neighborhood-level monitoring or modeling of air toxins such as PAHs and possibly speciated $PM_{2.5}$ to determine whether these results are reproducible with improved air pollution assessment.

Table 4-1. Demographic and prenatal characteristics by case (7,594) and control group (n=75,635)

Characteristics	Autistic Disorder Cases n (%)	Controls[a] n (%)
Gender		
Males	6291 (82.8)	62643 (82.8)
Females	1303 (17.2)	12992 (17.2)
Birth Year		
1995	277 (3.7)	2762 (3.7)
1996	319 (4.2)	3173 (4.2)
1997	382 (5.0)	3812 (5.0)
1998	487 (6.4)	4859 (6.4)
1999	455 (6.0)	4533 (6.0)
2000	594 (7.8)	5904 (7.8)
2001	732 (9.6)	7285 (9.6)
2002	885 (11.7)	8776 (11.6)
2003	1035 (13.6)	10336 (13.7)
2004	1034 (13.6)	10284 (13.6)
2005	874 (11.5)	8735 (11.6)
2006	520 (6.9)	5176 (6.8)
Gestational age (weeks)		
mean (sd)	39.0 (2.6)	39.4 (2.3)
Maternal Characteristics		
Maternal age at delivery		
≤18 y.o.	178 (2.3)	4997 (6.6)
19 - 25	1673 (22.0)	23906 (31.6)
26 -30	2034 (26.8)	20228 (26.7)
31 - 35	2159 (28.4)	16845 (22.3)
>35	1550 (20.4)	9654 (12.8)
Missing	0	5 (0.0)
Maternal birthplace		
U.S.-born	3544 (46.7)	32590 (43.1)
Foreign-born	4038 (53.2)	42930 (56.8)
Unknown	12 (0.1)	115 (0.1)
Maternal Race/Ethnicity		
Non-Hispanic white	2625 (34.6)	20616 (27.3)
Non-Hispanic African American	622 (8.2)	6028 (8.0)
Hispanic	3183 (41.9)	40118 (53.0)
Asian	1073 (14.1)	8123 (10.7)
Other/unknown	91 (1.2)	750 (1.0)

Table 4-1 (cont.) Demographic and prenatal characteristics by case (7,594) and control group (n=75,635)

Characteristics	Autistic Disorder Cases n (%)	Controls[a] n (%)
Maternal education		
<High school	1725 (22.7)	27232 (36.0)
High school	1861 (24.5)	20115 (26.6)
>High school	3926 (51.7)	27400 (36.2)
Unknown	82 (1.1)	888 (1.2)
Prenatal Characteristics		
Type of birth		
Single	7218 (95.0)	73880 (97.7)
Twin/Triplet+	376 (5.0)	1755 (2.3)
Insurance Type		
Public (Medi-Cal)	2971 (39.1)	39382 (52.1)
Private	4432 (58.4)	33746 (44.6)
Other	117 (1.5)	1925 (2.6)
Unknown	74 (1.0)	582 (0.8)
Parity		
One (index birth)	3280 (43.2)	29399 (38.9)
Two	2556 (33.7)	23495 (31.1)
Three	1134 (14.9)	13296 (17.6)
>Three	623 (8.2)	9417 (12.4)
Unknown	1 (0.0)	28 (0.0)
Birthweight (grams)		
mean (sd)	3321.0 (640.9)	3377.8 (543.3)
Paternal Characteristics		
Paternal age at delivery (yrs)		
≤18	53 (0.7)	1484 (2.0)
19-25	1017 (13.4)	16067 (21.2)
26-30	1545 (20.4)	17752 (23.5)
31-35	1999 (26.3)	17174 (22.7)
>35	2502 (32.9)	17286 (22.9)
Unknown	478 (6.3)	5872 (7.8)
Paternal education		
<High school	1508 (19.9)	23653 (31.3)
High school	1931 (25.4)	19725 (26.1)
>High school	3589 (47.3)	25145 (33.2)
Unknown	566 (7.4)	7112 (9.4)

[a] Controls are matched to cases by gender, birth year, and at minimum reached the gestational age of the case

Table 4-2. Associations between inter-quartile range increases in entire pregnancy average air pollution exposures and Autistic Disorder, conditional logistic regression analysis using matched controls[a]

Exposure Metric	IQR	Unadjusted	Adjusted[b]	
		Odds Ratio (OR)	N[c] (case/control)	OR (95%CI)
U-LUR-NO[d]	9.40ppb	0.87	7420/72231	1.04 (1.00, 1.08)
U-LUR-NO_2[d]	5.41ppb	0.91	7420/72231	1.07 (1.03, 1.12)
S-LUR-NO[e]	18.46ppb	0.84	6279/52144	1.02 (0.96, 1.08)
S-LUR-NO_2[e]	9.70ppb	0.87	6279/52144	1.05 (0.98, 1.12)
CO	0.55ppm	0.85	7421/72253	0.99 (0.94, 1.05)
NO	29.67ppb	0.85	7421/72253	1.01 (0.95, 1.07)
NO_2	10.47ppb	0.89	7421/72253	1.04 (0.98, 1.10)
Ozone (O_3)	11.54ppb	1.19	7421/72253	1.06 (1.01, 1.12)
PM_{10}	8.25μg/m^3	0.96	6795/63662	1.03 (0.96, 1.10)
$PM_{2.5}$	4.68μg/m^3	1.01	5840/55776	1.07 (1.00, 1.15)

[a] Controls matched to cases by birth year, sex, and at minimum reached the gestational age of the case

[b] Adjusted for: maternal age, education, race/ethnicity, maternal place of birth; type of birth, parity, insurance type, gestational weeks at birth (continuous)

[c] N reflects sample with complete data, i.e. strata with at least one case and one control

[d] U-LUR: unseasonalized land use regression

[e] S-LUR: seasonalized land use regression

Table 4-3. Associations between inter-quartile range increases in entire pregnancy average air pollution exposures and Autistic Disorder, conditional logistic regression analysis using matched controls[a], adjusted[b] two-pollutant models

					Pollutant1	Pollutant2
Pollutant1	IQR	Pollutant2	IQR	N[c] (case/control)	OR (95%CI)	OR (95%CI)
Ozone(O_3)	11.54ppb	U-LUR-NO	9.4ppb	7420/72231	1.08 (1.03, 1.14)	1.06 (1.02, 1.11)
Ozone(O_3)	11.54ppb	U-LUR-NO_2	5.4ppb	7420/72231	1.08 (1.03, 1.14)	1.09 (1.04, 1.13)
NO	29.67ppb	U-LUR-NO	9.4ppb	7420/72231	0.99 (0.93, 1.05)	1.04 (1.00, 1.09)
NO	29.67ppb	U-LUR-NO_2	5.4ppb	7420/72231	0.98 (0.92, 1.04)	1.08 (1.03, 1.13)
CO	0.55ppm	U-LUR-NO	9.4ppb	7420/72231	0.97 (0.92, 1.03)	1.05 (1.00, 1.09)
CO	0.55ppm	U-LUR-NO_2	5.4ppb	7420/72231	0.96 (0.91, 1.02)	1.08 (1.03, 1.13)
PM_{10}	8.25μg/m^3	U-LUR-NO	9.4ppb	6794/63642	1.02 (0.95, 1.10)	1.04 (1.00, 1.09)
PM_{10}	8.25μg/m^3	U-LUR-NO_2	5.4ppb	6794/63642	1.00 (0.93, 1.07)	1.08 (1.03, 1.13)
$PM_{2.5}$	4.68μg/m^3	U-LUR-NO	9.4ppb	5839/55757	1.06 (0.99, 1.14)	1.03 (0.98, 1.08)
$PM_{2.5}$	4.68μg/m^3	U-LUR-NO_2	5.4ppb	5839/55757	1.05 (0.97, 1.12)	1.07 (1.01, 1.12)
Ozone(O_3)	11.54ppb	PM_{10}	8.25μg/m^3	6795/63662	1.06 (1.01, 1.12)	1.04 (0.97, 1.11)
Ozone(O_3)	11.54ppb	$PM_{2.5}$	4.68μg/m^3	5840/55776	1.12 (1.06, 1.19)	1.15 (1.06, 1.24)

[a] Controls matched to cases by birth year, sex, and at minimum reached the gestational age of the case
[b] Adjusted for: maternal age, education, race/ethnicity, maternal place of birth; type of birth, parity, insurance type, gestational weeks at birth (continuous)
[c] N reflects sample with complete data, i.e. strata with at least one case and one control

Table 4-4. Associations between inter-quartile range increases in entire pregnancy average air pollution exposures and Autistic Disorder, unconditional logistic regression by maternal education

		Adjusted Odds Ratios By Maternal Education[a]					
		<High school		High school		>High school	
Pollutant	IQR	case/control	Adjusted OR	case/control	Adjusted OR	case/control	Adjusted OR
U-LUR-NO[b]	9.40ppb	1713/27051	1.11 (1.05, 1.18)	1842/19962	1.03 (0.97, 1.09)	3865/26987	0.99 (0.95, 1.03)
U-LUR-NO_2[b]	5.41ppb	1713/27051	1.17 (1.10, 1.25)	1842/19962	1.06 (1.00, 1.13)	3865/26987	1.03 (0.99, 1.07)
S-LUR-NO[c]	18.46ppb	1435/23270	1.03 (0.96, 1.10)	1513/16533	1.02 (0.95, 1.09)	3331/22872	1.01 (0.96, 1.07)
S-LUR-NO_2[c]	9.70ppb	1435/23270	1.04 (0.97, 1.27)	1513/16533	1.07 (0.99, 1.15)	3331/22872	1.07 (1.01, 1.12)
CO	0.55ppm	1714/27036	0.90 (0.85, 0.96)	1842/19949	1.03 (0.97, 1.09)	3865/26960	1.09 (1.04, 1.14)
NO	29.67ppb	1714/27036	0.96 (0.89, 1.03)	1842/19949	1.02 (0.95, 1.09)	3865/26960	1.04 (0.99, 1.10)
NO_2	10.47ppb	1714/27036	0.97 (0.90, 1.04)	1842/19949	1.08 (1.01, 1.16)	3865/26960	1.07 (1.02, 1.12)
Ozone	11.54ppb	1714/27036	1.09 (1.02, 1.16)	1842/19949	1.07 (1.01, 1.14)	3865/26960	1.04 (0.99, 1.09)
$PM_{2.5}$	8.25μg/m^3	1352/20540	1.04 (0.96, 1.12)	1415/15547	1.09 (1.01, 1.17)	3074/21970	1.06 (1.00, 1.12)
PM_{10}	4.68μg/m^3	1585/24775	0.97 (0.91, 1.04)	1670/18273	1.08 (1.01, 1.16)	3550/24707	1.02 (0.97, 1.07)

[a] Adjusted for: child's birth year, sex; maternal age, race/ethnicity, maternal place of birth; type of birth, parity, insurance type, gestational weeks at birth (continuous)

[b] U-LUR: Unseasonalized Land Use Regression

[c] S-LUR: Seasonalized Land Use Regression

Note: missing maternal education (case/control): U-LUR: 63/718; S-LUR: 50/605; monitor-based criteria: 63/715; PM_{10}: 57/659; $PM_{2.5}$: 51/596

Supplemental Material, Table 4-5. Results of birth certificate residential address geocoding.

Mapping level	Autistic Disorder cases (n=7,603) n (%)	Controls (n=75,782) n (%)
Parcel centroid	3578 (47.1)	34658 (45.7)
Uniform lot interpolation	1537 (20.2)	14865 (19.6)
Address range interpolation	2054 (27.0)	21375 (28.2)
Zip code tabulation area centroid, city centroid, or county subdivision centroid	425 (5.6)	4737 (6.2)
Not geocoded	9 (0.1)	147 (0.2)

Supplemental Material, Table 4-6. Exclusion criteria used when estimating pregnancy period specific monitor-based air pollution exposure metrics.		
Pollutant	Data Availability	Criteria
CO	hourly	*Criteria for hourly measurements:* At least 50% of hourly values available per 24-hr period and at least 50% of hourly values available from 6am-6pm. If sufficient data were available, a daily (24-hour) average was generated based on the hourly data.
		Criteria for pregnancy periods: We required at least 15 readings for each full month in a given period (trimester or entire pregnancy) as well as 15 readings during the last 30 days of the pregnancy period.
NO, NO_2,	hourly	*Criteria for hourly measurements:* At least 50% of hourly values available per 24-hr period and at least 50% of hourly values available from 8am-8pm.
		Criteria for pregnancy periods: We required at least 15 readings for each full month in a given period (trimester or entire pregnancy) as well as 15 readings during the last 30 days of the pregnancy period.
O_3 (10am-6pm)	hourly	*Criteria for hourly measurements:* At least 50% of hourly values available from 10am-6pm.
		Criteria for pregnancy periods: We required at least 15 readings for each full month in a given period (trimester or entire pregnancy) as well as 15 readings during the last 30 days of the pregnancy period.
PM_{10}	24-hour average, every 6 days	*We required 3 or more values to be available per each full pregnancy month and during the last 30 days of pregnancy.*
$PM_{2.5}$	24-hour average, every 3 days	*We required 5 or more values to be available per each full pregnancy month and during the last 30 days of pregnancy.*

Supplemental Material, Table 4-7. Pollutant distributions and Pearson's correlation coefficients for entire pregnancy averages in controls

					Pearson's Correlation Coefficients									
					U-LUR[b]		S-LUR[c]		Criteria Pollutants					
Pollutant[a]	n	Mean	IQR	SD	LUR - NO	LUR- NO_2	LUR - NO	LUR- NO_2	CO	NO	NO_2	O_3	PM_{10}	$PM_{2.5}$
U-LUR - NO[b]	75623	22.4	9.40	8.3	1.00									
U-LUR- NO_2[b]	75623	22.9	5.41	4.5	0.81	1.00								
S-LUR - NO[c]	64129	28.7	18.46	14.7	0.77	0.62	1.00							
S-LUR- NO_2[c]	64128	28.0	9.70	7.3	0.66	0.70	0.71	1.00						
CO	75565	1.0	0.55	0.5	0.27	0.26	0.56	0.53	1.00					
NO	75565	39.2	29.67	20.5	0.37	0.31	0.70	0.44	0.78	1.00				
NO_2	75565	30.8	10.47	7.6	0.35	0.43	0.58	0.73	0.77	0.73	1.00			
Ozone	75565	36.8	11.54	8.9	-0.33	-0.23	-0.57	-0.34	-0.55	-0.73	-0.50	1.00		
PM_{10}	69263	36.3	8.25	6.1	0.11	0.23	0.30	0.55	0.42	0.28	0.57	-0.17	1.00	
$PM_{2.5}$	59483	19.6	4.68	3.5	0.22	0.26	0.45	0.52	0.60	0.58	0.65	-0.47	0.58	1.00

[a] Pollutant values are expressed in the following units: CO ppm; NO, NO_2, ppb; PM, $\mu g/m^3$

[b] Unseasonalized Land Use Regression

[c] Seasonalized Land Use Regression

Supplemental Material, Table 4-8. Associations between trimester average air pollution exposure during pregnancy and Autistic Disorder, conditional logistic regression analysis using matched controls

Exposure Metric	IQR[b]	Adjusted[a]	
		N (case/control)	OR (95% CI)
S-LUR-NO, 1st trimester	18.5ppb	6281/52173	1.01 (0.98, 1.04)
S-LUR-NO, 2nd trimester	18.5ppb	6281/52173	1.01 (0.98, 1.04)
S-LUR-NO, 3rd trimester	18.5ppb	6246/51897	0.99 (0.96, 1.03)
S-LUR-NO_2, 1st trimester	9.7ppb	6281/52173	1.03 (0.98, 1.08)
S-LUR-NO_2, 2nd trimester	9.7ppb	6281/52173	1.03 (0.98, 1.08)
S-LUR-NO_2, 3rd trimester	9.7ppb	6246/51897	1.04 (0.98, 1.09)
CO, 1st trimester	0.55ppm	7421/72253	1.01 (0.98, 1.05)
CO, 2nd trimester	0.55ppm	7421/72253	0.99 (0.95, 1.02)
CO, 3rd trimester	0.55ppm	7383/71912	0.98 (0.94, 1.02)
NO, 1st trimester	29.67ppb	7421/72253	1.02 (0.99, 1.05)
NO, 2nd trimester	29.67ppb	7421/72253	1.00 (0.97, 1.03)
NO, 3rd trimester	29.67ppb	7383/71912	0.98 (0.95, 1.02)
NO_2, 1st trimester	10.47ppb	7421/72253	1.04 (0.99, 1.08)
NO_2, 2nd trimester	10.47ppb	7421/72253	1.01 (0.97, 1.06)
NO_2, 3rd trimester	10.47ppb	7383/71912	1.02 (0.97, 1.07)
Ozone (O_3), 1st tri	11.54ppb	7421/72253	1.00 (0.97, 1.03)
Ozone (O_3), 2nd tri	11.54ppb	7421/72253	1.02 (1.00 1.05)
Ozone (O_3), 3rd tri	11.54ppb	7383/71912	1.04 (1.01, 1.06)
PM_{10}, 1st trimester	8.25μg/m^3	6795/63662	1.00 (0.96, 1.05)
PM_{10}, 2nd trimester	8.25μg/m^3	6795/63662	1.01 (0.97, 1.06)
PM_{10}, 3rd trimester	8.25μg/m^3	6752/63259	1.02 (0.98, 1.06)
$PM_{2.5}$, 1st trimester	4.68μg/m^3	5840/55776	1.04 (0.99, 1.08)
$PM_{2.5}$, 2nd trimester	4.68μg/m^3	5840/55776	1.02 (0.98, 1.06)
$PM_{2.5}$, 3rd trimester	4.68μg/m^3	5811/55512	1.03 (0.99, 1.08)

[a] Adjusted for: maternal age, education, race/ethnicity, maternal place of birth; type of birth, parity, insurance type, gestational weeks at birth (continuous)
[b] Pollutant-specific entire-pregnancy IQR used as standard for trimester specific IQR

Supplemental Material, Table 4-9. Pollutant Distributions and Pearson's Correlation Coefficients for trimester-specific and entire pregnancy average criteria pollutants in controls

				Pearson Correlation Coefficients Corresponding Pollutant Metric			
Pollutant[a]	n	mean	sd	1st Tri	2nd Tri	3rd Tri	Entire
S-LUR - NO, 1st tri	64146	31.7	26.0	1.00			
S-LUR - NO, 2nd tri	64146	29.2	24.9	0.19	1.00		
S-LUR - NO, 3rd tri	63831	26.6	22.6	-0.30	0.26	1.00	
S-LUR - NO, Entire	64129	28.6	14.7	0.54	0.80	0.46	1.00
S-LUR- NO2, 1st tri	64146	29.4	9.1	1.00			
S-LUR- NO2, 2nd tri	64146	28.6	8.9	0.65	1.00		
S-LUR- NO2, 3rd tri	63830	27.5	8.4	0.37	0.64	1.00	
S-LUR- NO2, Entire	64128	28.0	7.3	0.82	0.91	0.78	1.00
CO, 1st Tri	75565	1.1	0.6	1.00			
CO, 2nd Tri	75565	1.0	0.6	0.50	1.00		
CO, 3rd Tri	75210	1.0	0.6	0.14	0.53	1.00	
CO, Entire	75565	1.0	0.5	0.74	0.88	0.69	1.00
NO, 1st Tri	75565	42.0	35.1	1.00			
NO, 2nd Tri	75565	39.3	34.1	0.19	1.00		
NO, 3rd Tri	75210	36.7	31.8	-0.31	0.26	1.00	
NO, Entire	75565	39.4	20.5	0.54	0.80	0.46	1.00
NO2, 1st Tri	75565	31.6	9.4	1.00			
NO2, 2nd Tri	75565	30.7	9.3	0.62	1.00		
NO2, 3rd Tri	75210	30.2	9.1	0.32	0.62	1.00	
NO2, Entire	75565	30.8	7.6	0.80	0.91	0.77	1.00
Ozone, 1st Tri	75565	35.8	14.9	1.00			
Ozone, 2nd Tri	75565	36.6	14.6	0.21	1.00		

Supplemental Material cont., Table 4-9. Pollutant Distributions and Pearson's Correlation Coefficients for trimester-specific and entire pregnancy average criteria pollutants in controls

				Pearson Correlation Coefficients			
				Corresponding Pollutant Metric			
Pollutant[a]	n	mean	sd	1st Tri	2nd Tri	3rd Tri	Entire
Ozone, 3rd Tri	75210	37.8	14.6	-0.36	0.30	1.00	
Ozone, Entire	75565	36.7	8.9	0.50	0.82	0.48	1.00
PM2.5, 1st Tri	59483	20.0	4.9	1.00			
PM2.5, 2nd Tri	59483	19.5	4.9	0.35	1.00		
PM2.5, 3rd Tri	59202	19.3	4.9	0.05	0.39	1.00	
PM2.5, Entire	59483	19.6	3.5	0.67	0.81	0.65	1.00
PM10, 1st Tri	69263	36.7	8.4	1.00			
PM10, 2nd Tri	69263	36.2	8.3	0.35	1.00		
PM10, 3rd Tri	68871	36.2	8.4	0.12	0.37	1.00	
PM10, Entire	69263	36.3	6.0	0.69	0.80	0.67	1.00

[a] Pollutant values are expressed in the following units: CO ppm; NO, NO2 ppb; PM $\mu g/m^3$

References

American Psychiatric Association. 2000. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (4th ed.). Washington, DC: American Psychiatric Association.

Beckerman B, Jerrett M, Brook JR, Verma DK, Arain MA, Finkelstein MM. 2008. Correlation of nitrogen dioxide with other traffic pollutants near a major expressway. Atmos Environ 42:275–290.

Calderón-Garcidueñas L, Mora-Tiscareño A, Ontiveros E, Gómez-Garza G, Barragán-Mejía G, Broadway J, et al. 2008. Air pollution, cognitive deficits and brain abnormalities: a pilot study with children and dogs. Brain Cogn 68(2):117–127.

California Department of Develomental Services. 2007. Autism spectrum disorders: Changes in the California caseload, an update: June 1987 – June 2007. Available: http://www.dds.ca.gov/Autism/Home.cfm [accessed 23 October 2011]

Cederlund M, Gillberg C. 2004. One hundred males with Asperger syndrome: a clinical study of background and associated factors. Dev Med Child Neurol 46(10):652–660.

Chen L, Bell EM, Caton AR, Druschel CM, Lin S. 2010. Residential mobility during pregnancy and the potential for ambient air pollution exposure misclassification. Environ Res 110(2):162–168.

Durkin MS, Maenner MJ, Meaney FJ, Levy SE, DiGuiseppi, C, Nicholas JS, et al. 2010. Socioeconomic inequality in the prevalence of autism spectrum disorder: Evidence from a U.S. cross-sectional study. *PLoS One*;doi:10.1371/journal.pone.0011551 [Online 12 July 2010].

Edwards SC, Jedrychowski W, Butscher M, Camann D, Kieltyka A, Mroz E, et al. 2010. Prenatal exposure to airborne polycyclic aromatic hydrocarbons and children's intelligence at 5 years of age in a prospective cohort study in Poland. Environ Health Perspect 118(9):1326–1331.

Gardener H, Spiegelman D, Buka SL. 2009. Prenatal risk factors for autism: comprehensive meta-analysis. Br J Psychiatry 195(1):7–14.

Gardener H, Spiegelman D, Buka SL. 2011. Perinatal and neonatal risk factors for autism: a comprehensive meta-analysis. Pediatrics 128(2):344–355.

Geschwind DH, Levitt P. 2007. Autism spectrum disorders: developmental disconnection syndromes. Curr Opin Neurobiol 17(1):103–111.

Ghosh JKC, Wilhelm M, Su J, Goldberg D, Cockburn M, Jerrett M, et al. 2012. Assessing the influence of traffic-related air pollution on risk of term low birth weight on the basis of land-use-based regression models and measures of air toxics. Am J Epidemiol; doi:10.1093/aje/kwr469 [Online 13 May 2012].

Glasson EJ, Bower C, Petterson B, de Klerk N, Chaney G, Hallmayer JF. 2004. Perinatal factors and the development of autism: a population study. Arch Gen Psychiatry 61(6):618–627.

Goldberg DW, Wilson JP, Knoblock CA, Ritz B, Cockburn MG. 2008. An effective and efficient approach for manually improving geocoded data. Int J Health Geogr 7:60.

Grineski S, Bolin B, Boone C. 2007. Criteria air pollution and marginalized populations: environmental inequity in metropolitan Phoenix, Arizona. Soc Sci Q 88(2);535–554.

Hallmayer J, Cleveland S, Torres A, Phillips J, Cohen B, Torigoe T, et al. 2011. Genetic heritability and shared environmental factors among twin pairs with autism. Arch Gen Psychiatry; doi:10.1001/archgenpsychiatry.2011.76 [Online 4 July 2011]

Hertz-Picciotto I, Croen LA, Hansen R, Jones CR, van de Water J, Pessah IN. 2006. The CHARGE study: an epidemiologic investigation of genetic and environmental factors contributing to autism. Environ Health Perspect 114(7):1119–1125.

Hertz-Picciotto I, Delwiche L. 2009. The rise in autism and the role of age at diagnosis. Epidemiology 20(1):84–90.

Hertz-Picciotto I, Herr CEW, Yap P-S, Dostál M, Shumway RH, Ashwood P, et al. 2005. Air pollution and lymphocyte phenotype proportions in cord blood. Environ Health Perspect 113(10):1391–1398.

Hertz-Picciotto I, Park H-Y, Dostal M, Kocan A, Trnovec T, Sram R. 2008. Prenatal exposures to persistent and non-persistent organic compounds and effects on immune system development. Basic Clin Pharmacol Toxicol 102(2):146–154.

Hoggatt K, Flores M, Solorio R, Wilhelm M, Ritz B. 2011. The "Latina Epidemiologic Paradox" revisited: The role of birthplace and acculturation in predicting infant low birth weight for Latinas in Los Angeles, CA. J Immigr Minor Health:1–10.

Institute of Medicine. 1999. Toward environmental justice: research, education, and health policy needs - Institute of Medicine. Available: http://www.iom.edu/Reports/1999/Toward-Environmental-Justice-Research-Education-and-Health-Policy-Needs.aspx [accessed 9 December 2012].

Kalkbrenner AE, Braun JM, Durkin MS, Maenner MJ, Cunniff C, Lee L-C, et al. 2012. Maternal smoking during pregnancy and the prevalence of autism spectrum disorders using data from the Autism and Developmental Disabilities Monitoring Network. Environ Health Perspect; doi:10.1289/ehp.1104556 [July 2012]

Kalkbrenner AE, Daniels JL, Chen J-C, Poole C, Emch M, Morrissey J. 2010. Perinatal exposure to hazardous air pollutants and autism spectrum disorders at age 8. Epidemiology 21(5):631-41.

Kavlock RJ, Meyer E, Grabowski CT. 1980. Studies on the developmental toxicity of ozone: Postnatal effects. Toxicol Lett 5(1):3–9.

Lai C-H, Liou S-H, Lin H-C, Shih T-S, Tsai P-J, Chen J-S, et al. 2005. Exposure to traffic exhausts and oxidative DNA damage. Occup Environ Med 62(4):216–222.

Li N, Sioutas C, Cho A, Schmitz D, Misra C, Sempf J, et al. 2003. Ultrafine particulate pollutants induce oxidative stress and mitochondrial damage. Environ Health Perspect 111(4):455–460.

Lupo PJ, Symanski E, Chan W, Mitchell LE, Waller DK, Canfield MA, et al. 2010. Differences in exposure assignment between conception and delivery: the impact of maternal mobility. Paediatr Perinat Epidemiol 24(2):200–208.

Perera FP, Rauh V, Whyatt RM, Tsai W-Y, Tang D, Diaz D, et al. 2006. Effect of prenatal exposure to airborne polycyclic aromatic hydrocarbons on neurodevelopment in the first 3 years of life among inner-city children. Environ Health Perspect 114(8):1287–1292.

Perera FP, Tang D, Wang S, Vishnevetsky J, Zhang B, Diaz D, et al. 2012. Prenatal polycyclic Aromatic Hydrocarbon (PAH) exposure and child behavior at 607 years. Environ Health Perspect 120(6):921- 926.

Peters A, Veronesi B, Calderón-Garcidueñas L, Gehr P, Chen LC, Geiser M, et al. 2006. Translocation and potential neurological effects of fine and ultrafine particles a critical update. Part Fibre Toxicol 3;13.

Petruzzi S, Fiore M, Dell'Omo G, Bignami G, Alleva E. 1995. Medium and long-term behavioral effects in mice of extended gestational exposure to ozone. Neurotoxicol Teratol 17(4):463–470.

Ponce NA, Hoggatt KJ, Wilhelm M, Ritz B. 2005. Preterm birth: The interaction of traffic-related air pollution with economic hardship in Los Angeles neighborhoods. Am J Epidemiol 162(2):140 –148.

Ritz B, Yu F. 1999. The effect of ambient carbon monoxide on low birth weight among children born in southern California between 1989 and 1993. Environ Health Perspect 107(1):17–25.

Ritz B, Wilhelm M, Hoggatt KJ, Ghosh JKC. 2007. Ambient air pollution and preterm birth in the environment and pregnancy outcomes study at the University of California, Los Angeles. Am J Epidemiol 166(9):1045–1052.

Ritz B, Yu F, Chapa G, Fruin S. 2000. Effect of air pollution on preterm birth among children born in southern California between 1989 and 1993. Epidemiology 11(5):502-511.

Roosevelt M. 2011, April 27. L.A., Bakersfield remain among U.S.'s most polluted cities, report says. Los Angeles Times. Available: http://articles.latimes.com/2011/apr/27/local/la-me-california-air-20110427 [accessed 8 December 2012]

Sorace A, Acetis LD, Alleva E, Santucci D. 2001. Prolonged exposure to low doses of ozone: short- and long-term changes in behavioral performance in mice. Environ Res 85(2):122–134.

Srám RJ, Binková B, Dejmek J, Bobak M. 2005. Ambient air pollution and pregnancy outcomes: a review of the literature. Environ Health Perspect 113(4):375–382.

State of California Health & Welfare Agency: Department of Developmental Services. 1986. CDER Manual. Available: http://www.dds.ca.gov/FactsStats/Diagnostic_Main.cfm

Su JG, Jerrett M, Beckerman B, Wilhelm M, Ghosh JKC, Ritz B. 2009. Predicting traffic-related air pollution in Los Angeles using a distance decay regression selection strategy. Environ Res 109(6):657–670.

Suglia SF, Gryparis A, Wright RO, Schwartz J, Wright RJ. 2008. Association of black carbon with cognition among children in a prospective birth cohort study. Am J Epidemiol 167(3):280–286.

Tabacova S, Nikiforov B, Balabaeva L. 1985. Postnatal effects of maternal exposure to nitrogen dioxide. Neurobehav Toxicol Teratol 7:785–789.

Tang D, Li T, Liu JJ, Zhou Z, Yuan T, Chen Y, et al. 2008. Effects of prenatal exposure to coal-burning pollutants on children's development in China. Environ Health Perspect 116(5):674–679.

U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion. 2010. Registry Plus, a suite of publicly available software programs for collecting and processing cancer registry data. Available: http://www.cdc.gov/cancer/npcr/ [accessed 8 December 2012].

U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion. 2010. Link Plus: Probabilistic Record Linkage Software from CDC. Available: www.cdc.gov/nceh/tracking/webinars/mar06/rawson.pdf [accessed 8 December 2012].

Van Meter KC, Christiansen LE., Delwiche LD., Azari R, Carpenter TE, Hertz-Picciotto I. 2010. Geographic distribution of autism in California: a retrospective birth cohort analysis. Autism Res 3(1):19–29.

Volk HE, Hertz-Picciotto I, Delwiche L, Lurmann F, McConnell R. 2010. Residential proximity to freeways and autism in the CHARGE study. Environ Health Perspect 119(6):873-877.

Wang S, Zhang J, Zeng X, Zeng Y, Wang S, Chen S. 2009. Association of traffic-related air pollution with children's neurobehavioral functions in Quanzhou, China. Environ Health Perspect 117(10):1612–1618.

Wilhelm M, Ghosh JK, Su J, Cockburn M, Jerrett M, Ritz B. 2011. Traffic-related air toxics and term low birth weight in Los Angeles county, California. Environ Health Perspect 120(1):132-138.

Wilhelm M, Qian L, Ritz B. 2009. Outdoor air pollution, family and neighborhood environment, and asthma in LA FANS children. Health Place 15(1):25-36.

Williams L, Spence A, Tideman SC. 1977. Implications of the observed effects of air pollution on birth weight. Soc Biol 24(1):1–9.

Windham GC, Zhang L, Gunier R, Croen LA, Grether JK. 2006. Autism spectrum disorders in relation to distribution of hazardous air pollutants in the San Francisco bay area. Environ Health Perspect 114(9):1438–1444.

Zhou Y, Levy JI. 2007. Factors influencing the spatial extent of mobile source air pollution impacts: a meta-analysis. BMC Public Health 7:89.

Chapter 5: Autism and Maternal Race/Ethnicity and Nativity in Hispanic and Black Populations in Los Angeles

Introduction

Approximately 1 in 88 children in the United States (U.S.) is being diagnosed with an autism spectrum disorder (ASD), a group of developmental disabilities characterized by atypical development in terms of socialization, communication, and behavior (1,2). Autism prevalence has been reported to be highest among white non-Hispanic children (hereon "white") and lower in Hispanic and African American/black children (hereon "black")(2–4). However, population-based data that considers maternal race/ethnicity and nativity in relation to childhood autism risk is sparse. It is important to consider the influence of nativity and related risk factors in the development and etiology of autism, given that 22% of young children (<6 years) born in the U.S. have immigrant parents (5).

European studies reported that having an immigrant mother is a risk factor for autism (6–10). However, due to great differences in migration patterns to and from countries and the variety of conditions related to migration, these findings might not be generalizable to U.S. immigrant populations. In the UK and Sweden, immigrant mothers were at increased risk of having a child with autism with comorbid intellectual disability (6,11,12). These mothers had migrated from Africa, the Caribbean, and Latin America (mostly Chile) (6,7). Unlike the European studies, U.S. studies found children of foreign-born mothers overall, and foreign-born Hispanics in particular to have a similar or lower risk for autism compared with children of U.S.-born or white mothers (4,13). The discrepancy between studies highlights the need for large-scale population-based examination of autism prevalence/incidence, including phenotypes, of specific immigrant groups in the U.S.

Children with autism often experience heightened sensitivities to sensory stimuli in

everyday life, are unable to regulate behavior or emotional responses, or are afflicted by severe language delays (1,14,15). In some cases, autism is associated with a diagnosis of mental retardation (MR), a comorbid condition generally defined as having intellectual [intelligence quotient (IQ)≤70] and adaptive functioning deficits (1). Previous research suggested lower IQ scores or a higher prevalence of intellectual disabilities and greater expressive language delays among Hispanic and black children with autism (3,16,17). This may indicate differences in diagnosis and treatment of these disorders across racial/ethnic groups (18), or alternatively suggest differences in etiology (16,19). While only 10-20% of ASD is attributed to known genetic factors (20), contributions of environmental factors such as maternal stress, nutritional deficiencies, toxic substances or infections should be considered and these risk factors may be disproportionately prevalent in minority populations (21,22).

Here we assess whether the incidence of autism and specific autistic phenotypes, i.e., comorbid MR, expressive language, and emotional/behavioral deficits, differs by maternal race/ethnicity and nativity. We focused our investigation on children born in Los Angeles (L.A.) County, California, a metropolitan county with large numbers of black (400,000 in 2010) and Hispanic (4.7 million in 2009) inhabitants, and a high proportion of immigrants (30% in 2011) (23–25).

Methods

Case ascertainment and definition

We included as cases children with a primary diagnosis of autistic disorder (AD) at ages 36 to 71 months diagnosed during 1998-2009, born between 1995-2006. In L.A. County, children with autism are diagnosed and recorded through seven regional centers contracted by the California Department of Developmental Services (DDS). Referrals to the regional centers

are usually made by pediatricians, other clinical providers, and schools, but parents may also self-refer their children. During our study period, DDS services were available to all children irrespective of socioeconomic status, type of health insurance, or immigration status.

The diagnosis of AD was based on the Diagnostic and Statistical Manual of Mental Disorders (DSM IV-R code 299.00) (1), as reported on the DDS Client Development Evaluation Report (CDER). Validation studies have established the reliability and validity of the CDER (26,27).

We further identified a subgroup of children with AD and a secondary diagnosis of mental retardation (AD-MR) (ICD-9-CM code: 317-mild, 318.0-moderate, 318.1-severe, 318.2-profound, 319-MR unspecified) on the CDER. To investigate language and behavior heterogeneity, we restricted assessments to 5-year olds which reduces differences related to age dependent development. We identified from DDS evaluation records two subgroups with either "impaired" or "less impaired" expressive language (AD-impaired expressive language: the child does not use words, says simple words, or says two-word sentences; AD-less impaired expressive language: the child uses sentences of 3 words or more or at least can engage in basic conversation); and two subgroups with "severe" or "less severe" emotional outburst behavior (AD-severe outbursts: the child has daily or weekly tantrums requiring restraint; AD-less severe outburst: child has no tantrums, weekly, or less than weekly tantrums without needing restraint).

Record Linkage

We attempted to link 10,821 DDS records of children with autism to their respective birth records using a probabilistic linkage program, as described previously (28,29). We linked 8,600 DDS records (79.5% of all cases) to birth records. Of the 2,221 DDS records not linked to birth records the most common reason for non-linkage was missing/incomplete information on the

birth or DDS record (29). Of the 8,600 subjects, 6,485 were eligible for inclusion because they had a primary diagnosis of AD, a plausible gestational age (21-46 weeks inclusive) and birth weight (500-6800g inclusive), maternal place of birth recorded on the birth certificate, and a mother of non-Hispanic white, Hispanic, or black race/ethnicity.

We examined maternal race/ethnicity and nativity based on mother's reported Hispanic origin (yes/no) and race information provided on the birth certificate to create three groups: non-Hispanic white, Hispanic, and non-Hispanic black, by maternal nativity (U.S.-born or foreign-born). Mother's country of origin information on California birth certificates was only specified for some foreign-born Hispanic groups but not for foreign-born blacks. We separately examined the two subgroups that represented the largest foreign-born groups in the 12-year study period with origin or country of birth documented: Central/South America and Mexico. For this analysis, we excluded 175,352 children with other or unknown racial/ethnic group (99.4% of exclusions) and mothers with unknown nativity (0.6%). The final cohort consisted of 1,461,610 births.

Statistical Analysis

Using unconditional logistic regression, we estimated risk of autism in offspring in subgroups according to maternal race/ethnicity and nativity using U.S.-born white mothers as the reference group. We estimated crude and adjusted relative risks (RRs) and 95% confidence intervals for the following outcomes: AD, AD-MR, AD-impaired expressive language, AD-less impaired expressive language, AD-severe outbursts, and AD-less severe outbursts.

We adjusted models for the following suspected risk factors for autism (30–34), which were taken from birth certificates: maternal age ($\leq$18, 19-25, 26-30, 31-35, >35) and education (<high school, high school, >high school); type of birth (single, twin+), parity (one, two, three,

>three), gestational age (<37weeks, ≥37 weeks), birth weight (<2500g, 2500-4500g, >4500g), trimester start of prenatal care (none, 1st trimester, 2nd trimester, 3rd trimester), pregnancy complications (any of the following: hypertension, renal, lung, or cardiac disease, asthma, pyelonephritis, diabetes, gestational diabetes, RH sensitivity, hemoglobinopathy, uterine bleeding, hydramnios, incomplete cervix, STDs, hepatitis B, rubella, other infections, tobacco use during pregnancy, and large fibroids), insurance type (Medi-Cal, private, other; we previously observed this to be a reasonable proxy for socioeconomic status), and regional center (35).

This research was approved by the University of California Los Angeles Human Research Protection Program and the California Committee for the Protection of Human Subjects.

Results

U.S.- and foreign-born white, and foreign-born black mothers were more likely to have multiple births, were older at the time of the child's birth, and had more years of education. Also, they had more pregnancy complications in addition to U.S.-born black mothers (Table 5-1). Only 53% of foreign-born blacks had private insurance compared to 82% of U.S.-born white mothers. The highest crude rates for autism were observed among children of foreign and U.S.-born white, and foreign-born black mothers.

The mean age of children entering the DDS system differed by as much as 5 months across race/ethnic and nativity based groups (Table 5-2). In general, black and Hispanic mothers' risk of AD in offspring varied by nativity, with 76% higher risk in foreign-born black mothers and 13-14% higher risk in U.S.-born Hispanics and blacks compared to U.S.-born whites. Children born to foreign-born Central/South American women were at 26% higher risk.

Autistic Disorder – Mental Retardation

We identified 690 children with AD-MR in total (Table 5-3). Children of black mothers, regardless of maternal nativity, in addition to children of U.S.-born Hispanic and foreign-born Central/South American women, were at higher risk of AD-MR compared to U.S.-born white mothers.

Autistic Disorder by Expressive Language Skills

We identified 2,107 5-year old children with AD for whom language abilities were documented as "impaired" and 1,506 with "less impaired" expressive language. Compared to children born to U.S.-born white women, all other race/ethnicity groups were at higher risk of having a child with AD-impaired expressive language regardless of nativity (Table 5-4). Compared to U.S.-born whites, most other children had similar risk of less impaired language, except children of foreign-born Mexican and of U.S.-born black mothers who were at lower risk.

Autistic Disorder by Severity of Emotional Outbursts

We identified 1,226 5-year old children with AD and "severe" emotional outburst behavior and 2,361 with "less severe" outbursts (Table 5-5). Children of U.S.-born Hispanic and foreign-born Central/South American mothers were at higher risk of AD with severe emotional outbursts compared to U.S.-born whites. Children of foreign-born black mothers were at increased risk for both severe and less severe emotional outburst behavior.

In children who exhibited both impaired expressive language and severe emotional outbursts, we observed the highest risks for children of U.S.-born Hispanic (RR=1.72, CI=1.32, 2.24), U.S.-born black (RR=1.44, CI=1.03, 2.01), foreign-born Central/South American (RR=1.81, CI=1.33, 2.48), and foreign-born black women (RR=2.46, CI=1.28, 4.74) compared to offspring of U.S.-born whites. Higher risks of language impairment in these racial/ethnic and

nativity based groups persisted when the child had less severe outburst behaviors for most children except those of U.S.-born Hispanics (Supplemental Table 5-6).

Discussion

In this population-based study conducted in L.A. County, foreign-born black mothers were at elevated risk of having a child with AD and AD-MR, consistent with findings of a higher autism risk among children born to mothers from Africa and the Caribbean living in the UK and Sweden (6,7). Our data for the first time show that children born to immigrant Central/South American, but not Mexican women (the largest Hispanic immigrant group in L.A. County), were at higher risk for AD and specifically for AD-MR compared to U.S.-born whites. Also, U.S.-born Hispanic women were at slightly higher risks of having a child with AD and AD-MR while U.S.-born black offspring were at similar risk of AD as U.S.-born whites but at increased risk of AD with comorbid mental retardation.

Variation of autism phenotype and severity by race/ethnicity and nativity may be due to differences in stress, diet, toxic exposures, or infections, which can affect fetal development during pregnancy (21,22). Thus, to understand the nativity differentials by race/ethnicity and country/region of origin, it may be pertinent to consider the experiences by members of different immigrant groups in their home country. The economic and security condition of their country of origin, period of and age at immigration, as well as factors prompting the migration such as economic or family reunification reasons, being a skilled worker, or a wartime refugee may provide clues about etiologic factors. Life event stress and psychiatric disorders, possibly related to experiences of refugees escaping wars and disasters, nutritional deficiencies and psychological stress from famine and trauma common in Central American and certain African immigrant groups (36–41) are considered risk factors for autism in offspring (42–48).

Alternative explanations are that having been born and raised in a foreign country may lead to less immunity against local pathogens, thus increasing susceptibility during pregnancy to infections more common in the U.S. Maternal severe infections are likely to alter fetal brain development and some authors suggested that influenza and prolonged episodes of fever may increase autism risk (30,49–55). Toxic stress during pregnancy such as chronic exposure to social and environmental hazards has been suggested as a strong determinant of child developmental outcomes and these may be particularly common in some Hispanic and black minorities (56). Folic acid and vitamin D deficiencies, which are implicated as possible factors in autism, are also common among black and Hispanic women (57–63).

Hispanics' autism risk varied by maternal nativity and region/country of origin. No associations between immigration status and autism have previously been reported in California (4), possibly due to the apparently lower risks among offspring of foreign-born Mexican women, who make up the majority of the foreign-born in California (53%) (23). Interestingly, our study found a higher risk of autism among offspring of U.S.-born Hispanics, supporting one previous report (13), and also among foreign-born Central/South Americans, to our knowledge not reported before. Women from certain Central American nations (Guatemala, El Salvador) migrated to L.A. County in the 1980's seeking asylum and may have a history of trauma from civil war, violence, and displacement, related to fleeing their countries (64–66). In contrast, the lower risks of autism in foreign-born Mexican women resembles the "Latino paradox" which notes that despite low income and education, Mexican immigrants have healthier birth outcomes with similar or lower rates of low birth weight than U.S.-born Hispanics and non-Hispanic white women (67–70); this phenomenon is not seen in Central/South American immigrants (71). Although there is little research as to how the Latino paradox extends through childhood, two

studies including children of Mexican immigrants found rates of maternal reported diagnoses of congenital anomalies, mental retardation, speech problems, and chronic medical conditions (including asthma) similar to non-Hispanic whites, despite variation in health care access (72,73).

To our knowledge, this is the first U.S. study addressing autism risk with respect to maternal nativity and race/ethnicity. L.A. County has a unique composition of racial/ethnic and foreign-born populations and our results are in part in line with previous findings from Europe with regard to black immigrant parents and autism risks in offspring (6,7,11,12,74,75). Although the countries/regions of origin among foreign-born black women were not identified in our study, they likely migrated from Africa or the Caribbean (76). Information about autism incidence or prevalence in low and lower-middle income countries is very limited, in particular for Africa (77), making it difficult to determine whether the observed autism risk is a migratory phenomenon due to the causes discussed above.

The relative risks of autism in children from U.S.-born black mothers differed from foreign-born blacks and thus should be considered separately in future studies, unlike what has been done in most previous U.S. studies (78,79). Children of U.S.-born black mothers had similar risks of AD as those of white mothers, but more often exhibited a AD phenotype with co-occurring MR. Previous studies found children born to women of black race to be at highest risk of a primary MR diagnosis (80), and for children with autism to be at higher risk of a comorbid intellectual disability, greater delay in language, and in addition less likely to be diagnosed with milder forms of autism than white children (16,18). Although higher comorbidity with intellectual disability has been associated with indicators of a poor intrauterine environment (81),

under-diagnosis of milder forms of autism at a young age in black children is a concern, such that more children are identified later when they reach school age (18,82).

Minority groups historically thought to be under-ascertained with regard to autism, i.e. Hispanics and blacks, showed equivalent or higher risks of AD compared with U.S.-born white mothers when maternal nativity and other well-known risk factors were considered. Specifically, children of foreign-born black, foreign-born Central/South American, and U.S.-born Hispanic mothers were at higher risk of AD with more severe emotional outbursts than children of U.S.-born whites. Ascertainment bias is possible, such that more severe behaviors would prompt identification, and that language and cultural barriers, i.e., low access to psychologists from minority groups, appropriately standardized and translated assessment instruments (83–86), could have caused differential misclassification of language and behavior skills. However, we also identified increased/similar risk of less impaired expressive language and less severe emotional outbursts in children from mothers in these three groups. This indicates that children with milder deficits in language and behavior are being identified in these groups, and suggests a true excess of more severe cases, which may explain their higher AD risks. While genetic studies have found more severe sensory behaviors, arousal regulation problems, aggression, and worse social communication skills in carriers of some monoamine oxidase A (MAOA) genotypes (87), a common genetic variant reported to differ by race/ethnicity (88), higher exposure to environmental risk factors and less possibilities to mitigate such exposures, may also be related to maternal nativity and explain the excess of more severe cases.

The large and diverse population in our study allowed us to assess autism risk variations in offspring of mothers who migrated from different regions of the world and were of different racial/ethnic origins. Though our sample size did not allow us to validate diagnoses, the

diagnostic stability of autism is considered good within the age group we studied (diagnostic consistency for ASD between ages 2 and 9 years is 90 percent) (26,89). Further, our study included children with a strict diagnosis of AD, more likely to hold under DSM-5 criteria (sensitivity: 0.76) than other ASD groups, i.e. Asperger's syndrome, pervasive developmental disorder, not otherwise specified (Sensitivity: 0.25-0.28) (90). Expressive language skills and social-emotional behavior assessment relied on caregiver report. Though the parent interview is considered as critical as direct observation of the child for diagnostically assessing language and behavior (91), it might be hampered by the parent's ability to understand and accurately report such observations.

Conclusion

Our results underscore the importance of investigating autism risks and phenotypes in Hispanic and black populations with respect to maternal nativity. We could not operationalize pathophysiological hypotheses for autistic phenotypes, though more severe autism cases appear to be present in children of Hispanic and black women, except among Mexican-born mothers. Systematic exploration of risk and protective factors related to living circumstances prior to and after migration is sorely needed. Exploring infections and immunologic profiles across immigrant subgroups, their exposures to stress and environmental factors, as well as the influence of acculturation and the adoption of the new culture's diet may be particularly important and informative in providing us with clues about AD etiology.

Table 5-1. Distribution of demographic and prenatal characteristics by maternal race/ethnicity and nativity

	U.S.-born White (236,347) n (%)	Foreign-born White (63,464) n (%)	U.S.-born Hispanic (316,565) n (%)	Foreign-born Hispanic (711,825) n (%)	U.S.-born Black (123,316) n (%)	Foreign-born Black (10,093) n (%)
Gestational Time						
Preterm (<37 weeks)	23438 (9.9)	5955 (9.4)	35606 (11.3)	77902 (10.9)	20004 (16.2)	1311 (13.0)
Term (≥37 weeks)	212909 (90.1)	57509 (90.6)	280959 (88.7)	633923 (89.1)	103312 (83.8)	8782 (87.0)
Birth weight						
Low (<2500g)	14678 (6.2)	3889 (6.1)	19874 (6.3)	39421 (5.5)	14697 (11.9)	945 (9.4)
Normal (≥2500g, <4500g)	217495 (92.0)	58875 (92.8)	292505 (92.4)	661925 (93.0)	107466 (87.2)	8971 (88.8)
Macrosomia (≥4500g)	4174 (1.8)	700 (1.1)	4185 (1.3)	10478 (1.5)	1153 (0.9)	177 (1.8)
Maternal Characteristics						
Maternal age at delivery (years)						
≤18	5746 (2.4)	412 (0.6)	49924 (15.8)	40706 (5.7)	11904 (9.7)	173 (1.7)
19 - 25	42116 (17.8)	11211 (17.7)	146597 (46.3)	247927 (34.8)	47504 (38.5)	1839 (18.2)
26 -30	58701 (24.8)	19023 (30.0)	67929 (21.5)	203818 (28.6)	29104 (23.6)	2985 (29.6)
31 - 35	75587 (32.0)	20136 (31.7)	36871 (11.6)	142819 (20.1)	21814 (17.7)	3254 (32.2)
>35	54190 (22.9)	12675 (20.0)	15229 (4.8)	76460 (10.7)	12975 (10.5)	1842 (18.3)
missing	7 (0.0)	7 (0.0)	15 (0.0)	95 (0.0)	15 (0.0)	0
Maternal education						
<high school	15925 (6.7)	4040 (6.4)	101315 (32.0)	450568 (63.3)	22855 (18.5)	895 (8.9)
high school	49673 (21.0)	14252 (22.5)	118393 (37.4)	164226 (23.1)	48991 (39.7)	2714 (26.9)
>high school	169129 (71.6)	44452 (70.0)	94867 (30.0)	89943 (12.6)	50092 (40.6)	6332 (62.7)
unknown	1620 (0.7)	720 (1.1)	1990 (0.6)	7088 (1.0)	1378 (1.1)	152 (1.5)
Prenatal Characteristics						
Type of birth						
Single	225931 (95.6)	60620 (95.5)	309723 (97.8)	697974 (98.0)	118967 (96.5)	9681 (95.9)
Multiple	10416 (4.4)	2844 (4.5)	6842 (2.2)	13851 (2.0)	4349 (3.5)	412 (4.1)
Start of prenatal care						
none	880 (0.4)	101 (0.2)	1667 (0.5)	2654 (0.4)	1027 (0.8)	42 (0.4)
1st trimester	219645 (92.9)	59215 (93.3)	270961 (85.6)	604493 (84.9)	103583 (84.0)	8718 (86.4)
2nd trimester	13438 (5.7)	3423 (5.4)	36859 (11.6)	82614 (11.6)	15711 (12.7)	1021 (10.1)
3rd trimester	1927 (0.8)	549 (0.9)	5182 (1.6)	15417 (2.2)	2196 (1.8)	245 (2.4)
unknown	457 (0.2)	176 (0.3)	1896 (0.6)	6647 (0.9)	799 (0.7)	67 (0.7)
Insurance Type						
Medi-Cal	35489 (15.0)	14881 (23.4)	156899 (49.6)	537710 (75.5)	62267 (50.5)	4379 (43.4)

Table 5-1 continued. Distribution of demographic and prenatal characteristics by maternal race/ethnicity and nativity

	U.S.-born White (236,347) n (%)	Foreign-born White (63,464) n (%)	U.S.-born Hispanic (316,565) n (%)	Foreign-born Hispanic (711,825) n (%)	U.S.-born Black (123,316) n (%)	Foreign-born Black (10,093) n (%)
Private	193373 (81.8)	46071 (72.6)	150422 (47.5)	156175 (21.9)	57155 (46.3)	5337 (52.9)
other	5648 (2.4)	2073 (3.3)	6317 (2.0)	14974 (2.1)	2323 (1.9)	274 (2.7)
unknown	1837 (0.8)	439 (0.7)	2927 (0.9)	2966 (0.4)	1571 (1.3)	103 (1.0)
Parity						
one (index birth)	105618 (44.7)	29945 (47.2)	139113 (43.9)	217039 (30.5)	47055 (38.2)	3912 (38.8)
two	79000 (33.4)	22532 (35.5)	94322 (29.8)	215713 (30.3)	34522 (28.0)	3137 (31.1)
three	33477 (14.2)	7816 (12.3)	50006 (15.8)	154580 (21.7)	20866 (16.9)	1803 (17.9)
>three	18205 (7.7)	3162 (5.0)	33043 (10.4)	124263 (17.5)	20773 (16.8)	1234 (12.2)
unknown	47 (0.0)	9 (0.0)	81 (0.0)	230 (0.0)	100 (0.1)	7 (0.1)
Previous miscarriage						
none	190094 (80.4)	53916 (85.0)	270885 (85.6)	616721 (86.6)	99507 (80.7)	8362 (82.8)
one	32676 (13.8)	6801 (10.7)	34606 (10.9)	74154 (10.4)	16446 (13.3)	1208 (12.0)
two	9075 (3.9)	1904 (3.0)	3031 (1.0)	16035 (2.3)	4749 (3.9)	350 (3.5)
≥three	4432 (1.9)	837 (1.3)	7960 (2.5)	4706 (0.7)	2481 (2.0)	170 (1.7)
unknown	70 (0.0)	6 (0.0)	83 (0.0)	209 (0.0)	133 (0.1)	3 (0.0)
Previous stillborn						
none	233773 (98.9)	62841 (99.0)	31288 (98.9)	702100 (98.6)	120307 (97.6)	9911 (98.2)
≥1	2506 (1.1)	616 (1.0)	3584 (1.1)	9478 (1.4)	2879 (2.3)	177 (1.8)
unknown	68 (0.0)	7 (0.0)	98 (0.0)	247 (0.0)	130 (0.1)	5 (0.0)
Pregnancy Complications						
All	29847 (12.6)	5483 (8.6)	28884 (9.1)	49230 (6.9)	16075 (13.0)	1209 (12.0)
Hypertension	5501 (2.3)	904 (1.4)	5801 (1.8)	8510 (1.2)	3263 (2.7)	279 (2.8)
Diabetes	4442 (1.9)	1306 (2.1)	6482 (2.1)	15077 (2.1)	2301 (1.9)	297 (2.9)
Infections	5294 (2.2)	763 (1.2)	5600 (1.8)	10266 (1.4)	4056 (3.3)	208 (2.1)
Smoking	5030 (2.1)	452 (0.7)	3101 (1.0)	2230 (0.3)	2154 (1.8)	86 (0.9)
Anemia	1067 (0.5)	243 (0.4)	1441 (0.5)	2052 (0.3)	1010 (0.8)	86 (0.9)
Paternal Characteristics						
Paternal age at delivery (years)						
≤18	1828 (0.8)	43 (0.1)	17654 (5.6)	9370 (1.3)	4046 (3.3)	50 (0.5)
19 - 25	25725 (10.9)	3259 (5.2)	118933 (37.6)	164345 (23.1)	29738 (24.1)	737 (7.3)
26 -30	46738 (19.8)	11186 (17.6)	76705 (24.2)	190796 (26.8)	23413 (19.0)	1329 (13.2)
31 - 35	69375 (29.3)	18938 (29.8)	46402 (14.6)	155697 (21.9)	20158 (16.4)	2134 (21.1)
>35	81970 (34.7)	28807 (45.4)	28387 (9.0)	136046 (19.1)	22510 (18.2)	4808 (47.6)
unknown	10711 (4.5)	1231 (1.9)	28484 (9.0)	55571 (7.8)	23451 (19.0)	1035 (10.3)
Paternal education						
<High school	11735 (5.0)	4377 (6.9)	89222 (28.2)	399336 (56.1)	11449 (9.3)	482 (4.8)

High school	51354 (21.7)	14069 (22.2)	117415 (37.1)	158501 (22.3)	50356 (40.8)	2292 (22.7)
>High school	160721 (68.0)	43089 (67.9)	75329 (23.8)	86170 (12.1)	37908 (30.7)	6180 (61.2)
unknown	12537 (5.3)	1929 (3.0)	34599 (10.9)	67818 (9.5)	23603 (19.1)	23603 (19.1)

Table 5-2. Maternal race/ethnicity and nativity in relation to children's diagnosis of autistic disorder in Los Angeles County

Maternal race/ethnicity and nativity	Mean age (years) at diagnosis (SD)	case/cohort	Avg. Crude Rate (per 10,000 births)	Crude Risk Ratio (RR) (95% CI)	Maternal Age Adjusted Risk Ratio (RR) (95% CI)	Adjusted Risk Ratio[a] (RR) (95% CI)	Additionally Adjusted Risk Ratio[b] (RR) (95% CI)	Additionally Adjusted by Regional Center (RR) (95% CI)
White								
U.S.-born	3.4 (0.9)	1477/236347	62.5	1.00	1.00	1.00	1.00	1.00
Foreign-born	3.3 (0.9)	420/63464	66.2	1.06 (0.95, 1.18)	1.06 (0.95, 1.19)	1.02 (0.91, 1.14)	1.05 (0.94, 1.17)	1.04 (0.93, 1.16)
Black								
U.S.-born	3.4 (0.9)	526/123316	42.6	0.68 (0.62, 0.75)	0.84 (0.76, 0.93)	1.00 (0.90, 1.10)	1.04 (0.94, 1.15)	1.14 (1.02, 1.26)
Foreign-born	3.2 (0.9)	92/10093	91.2	1.46 (1.18, 1.80)	1.49 (1.20, 1.84)	1.59 (1.28, 1.96)	1.65 (1.33, 2.05)	1.76 (1.41, 2.18)
Hispanic								
U.S.-born	3.5 (0.8)	1376/316565	43.5	0.70 (0.65, 0.75)	0.97 (0.90, 1.05)	1.08 (1.00, 1.17)	1.15 (1.06, 1.24)	1.13 (1.04, 1.22)
Foreign-born	3.5 (0.9)	2594/711825	36.4	0.58 (0.55, 0.62)	0.69 (0.64, 0.73)	0.85 (0.79, 0.91)	1.05 (0.97, 1.14)	1.06 (0.98, 1.15)
Mexico	3.5 (0.9)	1792/548977	32.6	0.52 (0.49, 0.56)	0.61 (0.57, 0.66)	0.76 (0.70, 0.82)	0.95 (0.86, 1.05)	0.95 (0.86, 1.05)
Ctrl/S. America	3.6 (0.9)	760/157147	48.4	0.77 (0.71, 0.84)	0.89 (0.81, 0.97)	1.08 (0.98, 1.19)	1.25 (1.13, 1.39)	1.26 (1.14, 1.40)

[a] Adjusted for maternal age, type of birth, parity, infant sex, year of birth, gestational age, birth weight, trimester start of prenatal care, and any pregnancy complication

[b] Additionally adjusted for maternal education and insurance type

Table 5-3. Maternal race/ethnicity and nativity in relation to children's diagnosis of autistic disorder with comorbid mental retardation in Los Angeles County

Maternal race/ethnicity and nativity	Mean age (years) at diagnosis (SD)	case/cohort	Avg. Crude Rate (per 10,000 births)	Crude Risk Ratio (RR) (95% CI)	Maternal Age Adjusted Risk Ratio (RR) (95% CI)	Adjusted Risk Ratio[a] (RR) (95% CI)	Additionally Adjusted Risk Ratio[b] (RR) (95% CI)	Additionally Adjusted by Regional Center (RR) (95% CI)
White								
U.S-born	3.2 (0.8)	122/236347	5.2	1.00	1.00	1.00	1.00	
Foreign-born	3.6 (1.1)	35/63464	5.5	1.07 (0.73, 1.56)	1.06 (0.73, 1.54)	1.06 (0.73, 1.55)	1.08 (0.74, 1.57)	1.20 (0.82, 1.75)
Black								
U.S.-born	3.6 (1.0)	78/123316	6.3	1.23 (0.92, 1.63)	1.38 (1.04, 1.84)	1.42 (1.06, 1.90)	1.47 (1.09, 1.97)	1.52 (1.11, 2.06)
Foreign-born	3.4 (0.9)	13/10093	12.9	2.49 (1.41, 4.42)	2.50 (1.41, 4.42)	2.56 (1.44, 4.53)	2.67 (1.50, 4.74)	2.63 (1.44, 4.78)
Hispanic								
U.S-born	3.6 (0.9)	161/316565	5.1	0.99 (0.78, 1.25)	1.20 (0.94, 1.53)	1.30 (1.02, 1.66)	1.35 (1.04, 1.73)	1.53 (1.18, 1.98)
Foreign-born	3.6 (0.9)	281/711825	3.9	0.76 (0.62, 0.95)	0.83 (0.67, 1.03)	0.91 (0.73, 1.14)	1.01 (0.79, 1.30)	1.16 (0.90, 1.50)
Mexico	3.6 (0.9)	190/548977	3.5	0.67 (0.53, 0.84)	0.71 (0.56, 0.89)	0.79 (0.62, 1.01)	0.94 (0.70, 1.26)	1.04 (0.77, 1.41)
Ctrl/S. America	3.7 (0.9)	86/157147	5.5	1.06 (0.80, 1.40)	1.11 (0.84, 1.46)	1.20 (0.90, 1.60)	1.42 (1.03, 1.96)	1.66 (1.20, 2.28)

[a] Adjusted for maternal age, type of birth, parity, infant sex, year of birth, gestational age, birth weight, trimester start of prenatal care, and any pregnancy complication

[b] Additionally adjusted for maternal education and insurance type

Table 5-4. Maternal race/ethnicity and nativity in relation to children's diagnosis of autistic disorder by expressive language skills at 5 years of age

	Impaired Expressive Language				Less Impaired Expressive Language			
Maternal race/ethnicity and nativity	case/cohort	Avg. Crude Rate (per 10,000 births)	Crude Risk Ratio (RR) (95% CI)	Adjusted Risk Ratio[a] (RR) (95% CI)	case/cohort	Avg. Crude Rate (per 10,000 births)	Crude Risk Ratio (RR) (95% CI)	Adjusted Risk Ratio[a] (RR) (95% CI)
White								
U.S-born	349/197992	17.6	1.00	1.00	509/197992	25.7	1.00	1.00
Foreign-born	109/51540	21.1	1.16 (0.94, 1.44)	1.24 (1.00, 1.54)	117/51540	22.7	0.88 (0.72, 1.08)	0.91 (0.74, 1.11)
Black								
U.S.-born	189/103643	18.2	1.04 (0.87, 1.24)	1.37 (1.13, 1.66)	106/103643	10.2	0.40 (0.32, 0.49)	0.84 (0.68, 1.05)
Foreign-born	38/8331	45.6	2.55 (1.83, 3.57)	2.76 (1.96, 3.89)	14/8331	16.8	0.65 (0.38, 1.11)	0.90 (0.53, 1.54)
Hispanic								
U.S.-born	429/250825	17.1	0.92 (0.80, 1.06)	1.28 (1.09, 1.49)	309/250825	12.3	0.48 (0.42, 0.55)	1.01 (0.86, 1.19)
Foreign-born	993/595680	16.7	0.95 (0.84, 1.07)	1.36 (1.17, 1.57)	451/595680	7.6	0.30 (0.26, 0.33)	0.83 (0.71, 0.97)
Mexico	700/460141	15.2	0.86 (076, 0.98)	1.12 (0.95, 1.33)	301/460141	6.5	0.25 (0.22, 0.29)	0.78 (0.64, 0.95)
Ctrl/S. America	275/130579	21.1	1.18 (1.01, 1.39)	1.57 (1.31, 1.89)	142/130579	10.9	0.42 (0.35, 0.51)	1.03 (0.84, 1.28)

[a] Adjusted for maternal age, type of birth, parity, infant sex, year of birth, gestational age, birth weight, trimester start of prenatal care, any pregnancy complication, maternal education, insurance type, and regional center

Language information is presented for cases 5 years of age at evaluation; Cohort is for 1995-2004 births, n=1,208,011

Table 5-5. Maternal race/ethnicity and nativity in relation to children's diagnosis of autistic disorder with severe or less severe emotional outburst behavior at 5 years of age

	Severe Emotional Outbursts				Less Severe Emotional Outbursts			
Maternal race/ethnicity and nativity	case/cohort	Avg. Crude Rate (per 10,000 births)	Crude Risk Ratio (RR) (95% CI)	Adjusted Risk Ratio[a] (RR) (95% CI)	case/cohort	Avg. Crude Rate (per 10,000 births)	Crude Risk Ratio (RR) (95% CI)	Adjusted Risk Ratio[a] (RR) (95% CI)
White								
U.S-born	272/197992	13.7	1.00	1.00	586/197992	29.6	1.00	1.00
Foreign-born	66/51540	12.8	0.93 (0.71, 1.22)	0.98 (0.74, 1.28)	154/51540	29.9	0.98 (0.82, 1.17)	1.04 (0.87, 1.24)
Black								
U.S.-born	84/103643	8.1	0.59 (0.46, 0.75)	0.93 (0.72, 1.20)	209/103643	20.2	0.68 (0.58, 0.80)	1.10 (0.93, 1.31)
Foreign-born	17/8331	20.4	1.49 (0.91, 2.43)	1.72 (1.03, 2.86)	34/8331	40.8	1.38 (0.96, 1.92)	1.63 (1.15, 2.31)
Hispanic								
U.S.-born	279/250825	11.1	0.81 (0.69, 0.96)	1.29 (1.07, 1.55)	453/250825	18.1	0.58 (0.51, 0.65)	0.99 (0.86, 1.13)
Foreign-born	508/595680	8.5	0.62 (0.54, 0.72)	1.10 (0.92, 1.32)	925/595680	15.5	0.52 (0.47, 0.58)	1.01 (0.89, 1.15)
Mexico	345/460141	7.5	0.55 (0.47, 0.64)	0.93 (0.75, 1.16)	649/460141	14.1	0.48 (0.43, 0.53)	0.89 (0.77, 1.04)
Ctrl/S. America	160/130579	12.2	0.89 (0.73, 1.08)	1.47 (1.17, 1.85)	253/130579	19.4	0.65 (0.56, 0.75)	1.12 (0.94, 1.32)

[a] Adjusted for maternal age, type of birth, parity, infant sex, year of birth, gestational age, birth weight, trimester start of prenatal care, any pregnancy complication, maternal education, insurance type, and regional center

Behavioral information is presented for cases 5 years of age at evaluation; Cohort is for 1995-2004 births, n=1,208,011

Supplemental Table 5-6. Maternal race/ethnicity and nativity in relation to children's diagnosis of autistic disorder with combined levels of impairment in expressive language and severity of emotional outbursts at 5 years of age

	Impaired Language & Severe Outbursts		Impaired Language & Less Severe Outbursts		Less Impaired Language & Severe Outbursts		Less Impaired Language & Less Severe Outbursts	
Maternal race/ethnicity and nativity	case/cohort	Adjusted Risk Ratio[a] (RR) (95% CI)	case/cohort	Adjusted Risk Ratio[a] (RR) (95% CI)	case/cohort	Adjusted Risk Ratio[a] (RR) (95% CI)	case/cohort	Adjusted Risk Ratio[a] (RR) (95% CI)
White								
U.S-born	109/197992	1.00	240/197992	1.00	163/197992	1.00	344/197992	1.00
Foreign-born	35/51540	1.29 (0.88, 1.89)	72/51540	1.20 (0.92, 1.56)	31/51540	0.77 (0.52, 1.13)	82/51540	0.93 (0.73, 1.18)
Hispanic								
U.S.-born	179/250825	1.72 (1.32, 2.24)	245/250825	1.05 (0.86, 1.28)	100/250825	1.01 (0.76, 1.34)	207/250825	1.01 (0.84, 1.23)
Foreign-born	357/595680	1.45 (1.12, 1.87)	627/595680	1.29 (1.08, 1.54)	151/595680	0.91 (0.69, 1.21)	298/595680	0.79 (0.65, 0.96)
Mexico	253/460141	1.20 (0.89, 1.60)	442/460141	1.07 (0.87, 1.32)	92/460141	0.76 (0.54, 1.08)	207/460141	0.79 (0.62, 1.01)
Ctrl/S. America	103/130579	1.81 (1.33, 2.48)	168/130579	1.41 (1.12, 1.77)	57/130579	1.32 (0.94, 1.87)	85/130579	0.91 (0.70, 1.20)
Black								
U.S.-born	61/103643	1.44 (1.03, 2.01)	126/103643	1.31 (1.04, 1.65)	23/103643	0.54 (0.34, 0.85)	82/103643	0.98 (0.76, 1.27)
Foreign-born	11/8331	2.46 (1.28, 4.74)	26/8331	2.76 (1.83, 4.16)	6/8331	1.24 (0.54, 2.82)	8/8331	0.75 (0.37, 1.52)

[a] Adjusted for maternal age, type of birth, parity, infant sex, year of birth, gestational age birth weight, trimester start of prenatal care, pregnancy complications, maternal education, insurance type, and regional center

Information is presented for cases 5 years of age at evaluation; Cohort is for 1995-2004 births, n=1,208,011

References

1. American Psychiatric Association. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. 4th ed. Washington, DC: American Psychiatric Association; 2000.
2. Prevalence of autism spectrum disorders--Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008. Morb Mortal Wkly Rep Surveill Summ Wash DC 2002. 2012 Mar 30;61(3):1–19.
3. Pedersen A, Pettygrove S, Meaney FJ, Mancilla K, Gotschall K, Kessler DB, et al. Prevalence of autism spectrum disorders in Hispanic and non-Hispanic white children. Pediatrics. 2012 Mar;129(3):e629–635.
4. Croen LA, Grether JK, Selvin S. Descriptive epidemiology of autism in a California population: who is at risk? J Autism Dev Disord. 2002 Jun;32(3):217–24.
5. Urban Institute. Children of Immigrants: Facts and Figures [Internet]. 2006 [cited 2013 May 8]. Available from: http://www.urban.org/publications/900955.html
6. Keen DV, Reid FD, Arnone D. Autism, ethnicity and maternal immigration. Br J Psychiatry. 2010 Apr 1;196(4):274–81.
7. Magnusson C, Rai D, Goodman A, Lundberg M, Idring S, Svensson A, et al. Migration and autism-spectrum disorder: population-based study. Br J Psychiatry [Internet]. 2012 Feb 23 [cited 2012 Dec 18]; Available from: http://bjp.rcpsych.org/content/early/2012/02/11/bjp.bp.111.095125
8. Van der Ven E, Termorshuizen F, Laan W, Breetvelt EJ, van Os J, Selten JP. An incidence study of diagnosed autism-spectrum disorders among immigrants to the Netherlands. Acta Psychiatr Scand. 2012 Dec 9;

9. Maimburg RD, Vaeth M. Perinatal risk factors and infantile autism. Acta Psychiatr Scand. 2006 Oct;114(4):257–64.

10. Lauritsen MB, Pedersen CB, Mortensen PB. Effects of familial risk factors and place of birth on the risk of autism: a nationwide register-based study. J Child Psychol Psychiatry. 2005;46(9):963–71.

11. Barnevik–Olsson M, Gillberg C, Fernell E. Prevalence of autism in children born to Somali parents living in Sweden: a brief report. Dev Med Child Neurol. 2008;50(8):598–601.

12. Dealberto M-J. Prevalence of autism according to maternal immigrant status and ethnic origin. Acta Psychiatr Scand. 2011 May;123(5):339–48.

13. Schieve LA, Boulet SL, Blumberg SJ, Kogan MD, Yeargin-Allsopp M, Boyle CA, et al. Association between parental nativity and autism spectrum disorder among US-born non-Hispanic white and Hispanic children, 2007 National Survey of Children's Health. Disabil Health J. 2012 Jan;5(1):18–25.

14. Smith Roley S, Blanche EI, Schaaf RC. Understanding the Nature of Sensory Integration with Diverse Populations. Austin: Pro Ed; 2001.

15. Dominick KC, Davis NO, Lainhart J, Tager-Flusberg H, Folstein S. Atypical behaviors in children with autism and children with a history of language impairment. Res Dev Disabil. 2007 Apr;28(2):145–62.

16. Cuccaro ML, Brinkley J, Abramson RK, Hall A, Wright HH, Hussman JP, et al. Autism in African American families: clinical-phenotypic findings. Am J Med Genet Part B Neuropsychiatr Genet Off Publ Int Soc Psychiatr Genet. 2007 Dec 5;144B(8):1022–6.

17. Chaidez V, Hansen RL, Hertz-Picciotto I. Autism spectrum disorders in Hispanics and non-Hispanics. Autism Int J Res Pr. 2012 Jul;16(4):381–97.

18. Jarquin VG, Wiggins LD, Schieve LA, Van Naarden-Braun K. Racial disparities in community identification of autism spectrum disorders over time; Metropolitan Atlanta, Georgia, 2000-2006. J Dev Behav Pediatr JDBP. 2011 Apr;32(3):179–87.
19. Szatmari P, White J, Merikangas KR. The use of genetic epidemiology to guide classification in child and adult psychopathology. Int Rev Psychiatry. 2007 Jan;19(5):483–96.
20. Geschwind DH. Genetics of autism spectrum disorders. Trends Cogn Sci. 2011 Sep;15(9):409–16.
21. Woods R, LaSalle JM. Epigenetic Epidemiology of Autism and Other Neurodevelopmental Disorders. In: Michels KB, editor. Epigenetic Epidemiol [Internet]. Springer Netherlands; 2012 [cited 2013 May 7]. p. 321–42. Available from: http://link.springer.com/chapter/10.1007/978-94-007-2495-2_17
22. Miyake K, Hirasawa T, Koide T, Kubota T. Epigenetics in Autism and Other Neurodevelopmental Diseases. MSc SIABs, editor. Neurodegener Dis. 2012;724:91–8.
23. Johnson H, Cuellar Mejia, Marisol. Immigrants in California [Internet]. Public Policy Institute of California; 2013 May. Available from: http://www.ppic.org/main/publication_show.asp?i=258
24. Rastogi S, Johnson TD, Hoeffel EM, Drewery MPJ. The Black Population: 2010 [Internet]. United States Census Bureau; 2011 Sep. Available from: http://www.census.gov/prod/cen2010/briefs/c2010br-06.pdf
25. U. S. Census Bureau. Hispanic Americans: Census Facts | Infoplease.com [Internet]. [cited 2013 May 8]. Available from: http://www.infoplease.com/spot/hhmcensus1.html

26. California Department of Develomental Services. Autism Spectrum Disorders: Changes in the California Caseload, an update: June 1987 – June 2007 [Internet]. 2007. Available from: http://www.dds.ca.gov/Autism/Home.cfm

27. State of California Health & Welfare Agency: Department of Developmental Services. CDER Manual [Internet]. 1986 Jul. Available from: http://www.dds.ca.gov/FactsStats/Diagnostic_Main.cfm

28. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion. Registry Plus, a suite of publicly available software programs for collecting and processing cancer registry data. [Internet]. 2010 [cited 2010 Nov 15]. Available from: http://www.cdc.gov/cancer/npcr/

29. Becerra TA, Wilhelm M, Olsen J, Cockburn M, Ritz B. Ambient Air Pollution and Autism in Los Angeles County, California. Environ Health Perspect. 2013; 121(3):380–386.

30. Gardener H, Spiegelman D, Buka SL. Prenatal risk factors for autism: comprehensive meta-analysis. Br J Psychiatry. 2009 Jul 1;195(1):7–14.

31. Gardener H, Spiegelman D, Buka SL. Perinatal and neonatal risk factors for autism: a comprehensive meta-analysis. Pediatrics. 2011 Aug;128(2):344–55.

32. Bhasin TK, Schendel D. Sociodemographic Risk Factors for Autism in a US Metropolitan Area. J Autism Dev Disord. 2006 Sep;37(4):667–77.

33. Zwaigenbaum L, Szatmari P, Jones MB, Bryson SE, Maclean JE, Mahoney WJ, et al. Pregnancy and Birth Complications in Autism and Liability to the Broader Autism Phenotype. J Am Acad Child Adolesc Psychiatry. 2002 May;41(5):572–9.

34. Gillberg C, Gillberg IC. Infantile autism: A total population study of reduced optimality in the pre-, peri-, and neonatal period. J Autism Dev Disord. 1983 Jun;13(2):153–66.

35. Ritz B, Wilhelm M, Hoggatt KJ, Ghosh JKC. Ambient air pollution and preterm birth in the environment and pregnancy outcomes study at the University of California, Los Angeles. Am J Epidemiol. 2007 Nov 1;166(9):1045–52.

36. Campagna AM, Settgast AM, Walker PF, DeFor TA, Campagna EJ, Plotnikoff GA. Effect of country of origin, age, and body mass index on prevalence of vitamin D deficiency in a US immigrant and refugee population. Mayo Clin Proc Mayo Clin. 2013 Jan;88(1):31–7.

37. Dharod JM, Croom JE, Sady CG. Food insecurity: its relationship to dietary intake and body weight among Somali refugee women in the United States. J Nutr Educ Behav. 2013 Feb;45(1):47–53.

38. Seal AJ, Creeke PI, Mirghani Z, Abdalla F, McBurney RP, Pratt LS, et al. Iron and vitamin A deficiency in long-term African refugees. J Nutr. 2005 Apr;135(4):808–13.

39. Pfortmueller CA, Graf F, Tabarra M, Lindner G, Zimmermann H, Exadaktylos AK. Acute health problems in African refugees: ten years' experience in a Swiss emergency department. Wien Klin Wochenschr. 2012 Sep;124(17-18):647–52.

40. Jaranson JM, Butcher J, Halcon L, Johnson DR, Robertson C, Savik K, et al. Somali and Oromo refugees: correlates of torture and trauma history. Am J Public Health. 2004 Apr;94(4):591–8.

41. Lindert J, Ehrenstein OS von, Priebe S, Mielck A, Brähler E. Depression and anxiety in labor migrants and refugees--a systematic review and meta-analysis. Soc Sci Med 1982. 2009 Jul;69(2):246–57.

42. Beversdorf DQ, Manning SE, Hillier A, Anderson SL, Nordgren RE, Walters SE, et al. Timing of Prenatal Stressors and Autism. J Autism Dev Disord. 2005;35(4):471–8.

43. Rai D, Golding J, Magnusson C, Steer C, Lewis G, Dalman C. Prenatal and early life exposure to stressful life events and risk of autism spectrum disorders: population-based studies in Sweden and England. PloS One. 2012;7(6):e38893.

44. Roberts AL, Lyall K, Rich-Edwards JW, Ascherio A, Weisskopf MG. Association of Maternal Exposure to Childhood Abuse With Elevated Risk for Autism in Offspring. JAMA Psychiatry Chic Ill. 2013 Mar 20;1–8.

45. Larsson HJ, Eaton WW, Madsen KM, Vestergaard M, Olesen AV, Agerbo E, et al. Risk Factors for Autism: Perinatal Factors, Parental Psychiatric History, and Socioeconomic Status. Am J Epidemiol. 2005 May 15;161(10):916–25.

46. Piven J, Palmer P. Psychiatric Disorder and the Broad Autism Phenotype: Evidence From a Family Study of Multiple-Incidence Autism Families. Am J Psychiatry. 1999 Apr 1;156(4):557–63.

47. Yirmiya N, Shaked M. Psychiatric disorders in parents of children with autism: a meta-analysis. J Child Psychol Psychiatry. 2005;46(1):69–83.

48. Daniels JL, Forssen U, Hultman CM, Cnattingius S, Savitz DA, Feychting M, et al. Parental psychiatric disorders associated with autism spectrum disorders in the offspring. Pediatrics. 2008 May;121(5):e1357–1362.

49. Zerbo O, Iosif A-M, Walker C, Ozonoff S, Hansen RL, Hertz-Picciotto I. Is Maternal Influenza or Fever During Pregnancy Associated with Autism or Developmental Delays? Results from the CHARGE (CHildhood Autism Risks from Genetics and Environment) Study. J Autism Dev Disord. 2013 Jan 1;43(1):25–33.

50. Atladóttir HÓ, Henriksen TB, Schendel DE, Parner ET. Autism after infection, febrile episodes, and antibiotic use during pregnancy: an exploratory study. Pediatrics. 2012 Dec;130(6):e1447–1454.

51. Chess S, Fernandez P, Korn S. Behavioral consequences of congenital rubella. J Pediatr. 1978 Oct;93(4):699–703.

52. Deykin EY, Macmahon B. Viral exposure and autism. Am J Epidemiol. 1979 Jun 1;109(6):628 –638.

53. Patterson PH. Maternal infection: window on neuroimmune interactions in fetal brain development and mental illness. Curr Opin Neurobiol. 2002 Feb 1;12(1):115–8.

54. Patterson PH. Immune involvement in schizophrenia and autism: Etiology, pathology and animal models. Behav Brain Res. 2009 Dec 7;204(2):313–21.

55. Shi L, Tu N, Patterson PH. Maternal influenza infection is likely to alter fetal brain development indirectly: the virus is not detected in the fetus. Int J Dev Neurosci. 2005 Apr;23(2–3):299–305.

56. Shonkoff JP, Garner AS, Siegel BS, Dobbins MI, Earls MF, Garner AS, et al. The Lifelong Effects of Early Childhood Adversity and Toxic Stress. Pediatrics. 2012 Jan 1;129(1):e232–e246.

57. Yetley EA. Assessing the vitamin D status of the US population. Am J Clin Nutr. 2008 Aug;88(2):558S–564S.

58. Grant WB, Peiris AN. Possible role of serum 25-hydroxyvitamin D in black-white health disparities in the United States. J Am Med Dir Assoc. 2010 Nov;11(9):617–28.

59. Schmidt RJ, Tancredi DJ, Ozonoff S, Hansen RL, Hartiala J, Allayee H, et al. Maternal periconceptional folic acid intake and risk of autism spectrum disorders and

developmental delay in the CHARGE (CHildhood Autism Risks from Genetics and Environment) case-control study. Am J Clin Nutr. 2012 Jul 1;96(1):80–9.

60. Surén P RC. Association between maternal use of folic acid supplements and risk of autism spectrum disorders in children. JAMA. 2013 Feb 13;309(6):570–7.
61. Cannell JJ. Autism and Vitamin D Medical Hypotheses. Med Hypotheses. 2008;70(4):750–9.
62. Kočovská E, Fernell E, Billstedt E, Minnis H, Gillberg C. Vitamin D and autism: Clinical review. Res Dev Disabil. 2012 Sep;33(5):1541–50.
63. Yang Q-H, Carter HK, Mulinare J, Berry RJ, Friedman JM, Erickson JD. Race-ethnicity differences in folic acid intake in women of childbearing age in the United States after folic acid fortification: findings from the National Health and Nutrition Examination Survey, 2001–2002. Am J Clin Nutr. 2007 May 1;85(5):1409–16.
64. Smith J. Guatemala: Economic Migrants Replace Political Refugees [Internet]. Migr. Inf. Source. 2006 [cited 2013 Apr 24]. Available from: http://www.migrationinformation.org/Profiles/display.cfm?ID=392
65. Terrazas A. Salvadoran Immigrants in the United States [Internet]. Migr. Inf. Source. 2010 [cited 2013 May 14]. Available from: http://www.migrationinformation.org/usfocus/display.cfm?ID=765
66. Gammage S. El Salvador: Despite End to Civil War, Emigration Continues [Internet]. Migr. Inf. Source. 2007 [cited 2013 Apr 24]. Available from: http://www.migrationinformation.org/Profiles/display.cfm?ID=636

67. Cervantes A, Keith L, Wyshak G. Adverse birth outcomes among native-born and immigrant women: replicating national evidence regarding mexicans at the local level. Matern Child Health J. 1999;3(2):99–109.

68. Acevedo-Garcia D, Soobader M-J, Berkman LF. Low birthweight among US Hispanic/Latino subgroups: the effect of maternal foreign-born status and education. Soc Sci Med 1982. 2007 Dec;65(12):2503–16.

69. Flores MES, Simonsen SE, Manuck TA, Dyer JM, Turok DK. The "Latina epidemiologic paradox": contrasting patterns of adverse birth outcomes in U.S.-born and foreign-born Latinas. Womens Heal Issues Off Publ Jacobs Inst Womens Heal. 2012 Sep;22(5):e501–507.

70. Romero CX, Duke JK, Dabelea D, Romero TE, Ogden LG. Does the epidemiologic paradox hold in the presence of risk factors for low birth weight infants among Mexican-born women in Colorado? J Health Care Poor Underserved. 2012 May;23(2):604–14.

71. Fuentes-Afflick E HN. Testing the epidemiologic paradox of low birth weight in latinos. Arch Pediatr Adolesc Med. 1999 Feb 1;153(2):147–53.

72. Padilla YC, Hamilton ER, Hummer RA. Beyond the Epidemiological Paradox: The Health of Mexican-American Children at Age Five. Soc Sci Q. 2009 Dec;90(5):1072–88.

73. Mendoza FS. The health of Latino children in the United States. Future Child Cent Future Child David Lucile Packard Found. 1994;4(3):43–72.

74. Gillberg C, Steffenburg S, B√∂rjesson B, Andersson L. Infantile autism in children of immigrant parents. A population-based study from G√∂teborg, Sweden. Br J Psychiatry. 1987 Jun 1;150(6):856–8.

75. Gillberg C, Schaumann H, Gillberg IC. Autism in immigrants: children born in Sweden to mothers born in Uganda. J Intellect Disabil Res JIDR. 1995 Apr;39 (Pt 2):141–4.

76. Lopez A. The Foreign-born in California: Place of Origin, Region of Residence, Race, Time of Entry, and Citizenship [Internet]. Stanford, CA: Center for Comparitive Studies in Race and Ethnicity, Stanford University; 2003. Report No.: 15. Available from: http://www.stanford.edu/dept/csre/reports/report_15.pdf

77. Bakare MO, Munir KM. Autism spectrum disorders (ASD) in Africa: a perspective. Afr J Psychiatry. 2011;14(3):208–10.

78. Liptak GS, Benzoni LB, Mruzek DW, Nolan KW, Thingvoll MA, Wade CM, et al. Disparities in Diagnosis and Access to Health Services for Children with Autism: Data from the National Survey of Children's Health. J Dev Behav Pediatr. 2008 Jun;29(3):152–60.

79. Mandell DS, Wiggins LD, Carpenter LA, Daniels J, DiGuiseppi C, Durkin MS, et al. Racial/Ethnic Disparities in the Identification of Children With Autism Spectrum Disorders. Am J Public Heal. 2009 Mar 1;99(3):493–8.

80. Croen LA, Grether JK, Selvin S. The Epidemiology of Mental Retardation of Unknown Cause. Pediatrics. 2001 Jun 1;107(6):e86–e86.

81. Langridge AT, Glasson EJ, Nassar N, Jacoby P, Pennell C, Hagan R, et al. Maternal conditions and perinatal characteristics associated with autism spectrum disorder and intellectual disability. PloS One. 2013;8(1):e50963.

82. Yeargin-Allsopp M, Rice C, Karapurkar T, Doernberg N, Boyle C, Murphy C. Prevalence of autism in a US metropolitan area. JAMA J Am Med Assoc. 2003 Jan 1;289(1):49–55.

83. Michalski D, Mulvey T, Kohout J. 2008 APA Survey of Psychology Health Service Providers [Internet]. Am. Psychol. Assoc. 2010 [cited 2013 May 22]. Available from: http://www.apa.org/workforce/publications/08-hsp/index.aspx

84. Lord C, Rutter M, Goode S, Heemsbergen J, Jordan H, Mawhood L, et al. Austism diagnostic observation schedule: A standardized observation of communicative and social behavior. J Autism Dev Disord. 1989 Jun 1;19(2):185–212.

85. Lord C, Risi S, Lambrecht L, Cook EH Jr, Leventhal BL, DiLavore PC, et al. The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. J Autism Dev Disord. 2000 Jun;30(3):205–23.

86. McInnes LA, Gonzalez PJ, Manghi ER, Esquivel M, Monge S, Delgado MF, et al. A genetic study of autism in Costa Rica: multiple variables affecting IQ scores observed in a preliminary sample of autistic cases. BMC Psychiatry. 2005 Mar 21;5:15.

87. Cohen IL, Liu X, Lewis MES, Chudley A, Forster-Gibson C, Gonzalez M, et al. Autism severity is associated with child and maternal MAOA genotypes. Clin Genet. 2010 May 22;79(4):355–62.

88. Williams RB, Marchuk DA, Gadde KM, Barefoot JC, Grichnik K, Helms MJ, et al. Serotonin-related gene polymorphisms and central nervous system serotonin function. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol. 2003 Mar;28(3):533–41.

89. Lord C, Risi S, DiLavore PS, Shulman C, Thurm A, Pickles A. Autism From 2 to 9 Years of Age. Arch Gen Psychiatry. 2006 Jun 1;63(6):694–701.

90. McPartland JC, Reichow B, Volkmar FR. Sensitivity and Specificity of Proposed DSM-5 Diagnostic Criteria for Autism Spectrum Disorder. J Am Acad Child Adolesc Psychiatry. 2012 Apr;51(4):368–83.

91. California Department of Developmental Services. Autism Spectrum Disorders: Best Practice Guidelines for Screening, Diagnosis and Assessment [Internet]. 2002. Available from: http://www.dds.ca.gov/Autism/docs/ASD_Best_Practice2002.pdf

Chapter 6: Autism Among Children in Asian Subgroups in Los Angeles

Introduction

In the United States (U.S.), 113 per 10,000 children aged 8 years is being diagnosed with an autism spectrum disorder (ASD), a group of developmental disabilities characterized by impairments in social skills, communication, and behavior (1,2). Prevalence estimates of ASD for Asian/Pacific Islander (Asian/P.I.) children is reported to range widely from 22 to 190 per 10,000, and population-based data that considers the diverse origins of Asians is sparse. In California, 37% of immigrants are of Asian descent and are the second largest immigrant group. Most Asians arrive from Eastern and Southeastern Asia, with the Philippines and China as the leading countries of origin (3). Worldwide, the prevalence of autistic disorder (AD) is reported lowest in China (2005: 10.9 per 10,000 2-6 year olds), followed by Japan (2005: 37.5 per 10,000 5 year olds), and South Korea (2011: 94 per 10,000 7-12 year olds) with no estimates for Filipino and Vietnamese populations (4).

One California study found that children of Asian women were not at higher risk of autism compared to white women (5). However this study did not stratify by country of origin, and to our knowledge, no studies in the U.S. have examined autism risk across different Asian groups and considered maternal nativity. European studies have observed that immigrant mothers from Iran and India, living in the UK and in Sweden, had increased risk of having a child with autism relative to European-born mothers, and specifically of low-functioning autism (6,7). Due to the differing economic and political circumstances in Asian countries, the various Asian subgroups differ by demographics, socioeconomic status and immigration history to the U.S., which may suggest variation in autism prevalence.

Children with autism often have more difficulty regulating behavior or emotional responses, are afflicted with severe language delays, and in addition may be diagnosed with mental retardation, a comorbid condition defined as having intellectual [intelligence quotient (IQ)<70] and adaptive functioning deficits (2,8). Phenotypic heterogeneity in autism in relation to maternal race/ethnicity and nativity is suggested by previous research that found lower IQ scores or a higher prevalence of intellectual disabilities and greater expressive language delays among Hispanic and black children with autism (9–11). It is not clear, however, whether this pattern generalizes in Asians, particularly in specific Asian subgroups. Variation in diagnosis and treatment is possible, but it also raises the question about exposures experienced by parents from certain race/ethnicity and nativity groups that may contribute to autism (10,12,13).

We relied on a diverse population of children in Los Angeles County, California to determine whether the incidence of autism and specific autistic phenotypes, i.e., comorbid mental retardation, expressive language, and emotional/behavioral deficits, differs by nativity in Asian mothers born in the U.S., China, Japan, Korea, Philippines, or Vietnam.

Methods

We studied children born to mothers who resided in LA County, California between 1995 and 2006 whose birth certificate provided maternal race/ethnicity and nativity information such that a mother self-identified as non-Hispanic white or Asian. We excluded all mothers that reported any Hispanic ethnicity, regardless of their race, and all mothers of other or unknown race (n=1,235,871). For inclusion, a plausible gestational age (21-46 weeks inclusive) and birth weight (500-6800g inclusive) must be available in birth certificate records. Among these, we identified children with a primary AD diagnosis at 36 to 71 months of age during 1998-2009 at one of seven regional centers contracted by the California Department of Developmental

Services (DDS). Out of 10,821 DDS records of children with autism we were able to link 8,600 (79.5% of all cases) to their respective birth records using a probabilistic linkage program, as described previously (14). The main reason for non-linkage of 2,221 DDS records was missing/incomplete information on the birth or DDS record. In total, 2,532 had a primary diagnosis of AD who also met the inclusion criteria.

Based on mother's self-reported race, ethnicity, and place of birth on the birth certificate, we created two groups: U.S.-born non-Hispanic white (from hereon "white"), non-Hispanic Asian/P.I. (hereon "Asian"). We further divided Asian mothers as U.S-born or foreign-born. Although birth certificates collect Asian ethnic ancestry from U.S.-born mothers, separate investigation of specific U.S.-born Asian subgroups was not possible due to small numbers across groups. However, the highest proportions were of Filipino (23.1%), Japanese (20.0%), Pacific Islander (15.4%), and Chinese (12.7%) descent. We examined the five subgroups of foreign-born Asian mothers who represented the largest immigrant groups in the 12-year period for whom country of origin was available on the birth certificate: China, Japan, Korea, Philippines, and Vietnam. The final cohort consisted of children of 236,347 U.S.-born white, 21,678 U.S.-born Asian, and 143,066 foreign-born Asian mothers.

In Los Angeles, referrals to the regional centers are assigned according to residential address and are usually made by pediatricians, other clinical providers, and schools, but parents may also self-refer their children. During the study period, DDS services were available to all children irrespective of socioeconomic status, type of health insurance, or immigration status. The diagnosis of AD was based on the Diagnostic and Statistical Manual of Mental Disorders (DSM IV-R code 299.00) as reported on the Client Development Evaluation Report (CDER) (American Psychiatric Association 2000). Validation studies have established the reliability and

validity of the CDER in California (California Department of Developmental Services 2007; State of California Health and Welfare Agency: Department of Developmental Services 1986).

We also identified a subgroup of children with AD and a comorbid diagnosis of mental retardation (AD-MR) (ICD-9-CM code: 317-mild, 318.0-moderate, 318.1-severe, 318.2-profound, 319-MR unspecified). To investigate language and behavior heterogeneity, we restricted assessments to 5-year olds, which reduces differences related to age dependent development. Using DDS evaluation records, we grouped children with AD with either "impaired" or "less impaired" expressive language (AD-impaired expressive language: the child does not use words, says simple words, or says two-word sentences; AD-less impaired expressive language: the child uses sentences of 3 words or more or at least can engage in basic conversation). We also categorized children as having "severe" or "less severe" outbursts (AD-severe outbursts: the child has daily or weekly tantrums requiring restraint; AD-less severe outburst: child has no tantrums, weekly, or less than weekly tantrums without needing restraint). Also, we grouped children with varying combinations of expressive language and behavior deficits to gauge the overall risk of more severe autistic types.

We used unconditional logistic regression to estimate risk of autism in offspring of U.S.-born or foreign-born Asian subgroups using U.S.-born white mothers as the reference group. We estimated crude and adjusted relative risks (RRs) and 95% confidence intervals for the following outcomes: AD, AD-MR, AD-impaired expressive language, AD-less impaired expressive language, AD-severe outbursts, and AD-less severe outbursts.

To examine the influence of other autism risk factors likely to vary between race/ethnic groups and by nativity we present several adjusted models (15–19). Models were first adjusted by maternal age (<18, 19-25, 26-30, 31-35, >35). Second, they were additionally adjusted by

child's sex (male, female), birth year (1995-2006), type of birth (single, twin+), parity (one, two, three, >three), gestational age (<37weeks, >37 weeks), birth weight (<2500g, 2500-4500g, >4500g), which trimester prenatal care began (no prenatal care, 1st trimester, 2nd trimester, 3rd trimester), and pregnancy complications (any of the following: hypertension, renal, lung, or cardiac disease, asthma, pyelonephritis, diabetes, gestational diabetes, RH sensitivity, hemoglobinopathy, uterine bleeding, hydramnios, incomplete cervix, STDs, hepatitis B, rubella, other infections, tobacco use during pregnancy, and large fibroids). Third, models were additionally adjusted for maternal education (<high school, high school, >high school) and insurance type [Medi-Cal, private insurance, other (which included self-pay and other governmental programs such as CHAMPUS)]; previously observed to be a reasonable proxy for socioeconomic status (20). Finally, to consider possible diagnostic variability we controlled for regional center, which is assigned to children according to their residential address of which can also be related to the general geographic areas where certain racial/ethnic and immigration groups settle.

This research was approved by the University of California Los Angeles Office of the Human Research Protection Program and the California Committee for the Protection of Human Subjects.

Results

U.S.-born Asian and foreign-born mothers from the Philippines had the highest proportions of preterm births (Table 6-1). Filipino women also had the highest prevalence of pregnancy complications, particularly from diabetes, while other foreign-born Asians had fewer pregnancy complications in comparison to U.S.-born whites. Vietnamese women reported fewer years of formal education and were more likely to have had prenatal care paid by Medi-Cal.

The mean age of children entering the DDS system varied by 6 months across groups, with the children identified the earliest more likely to be from U.S.-born Asian mothers (Table 6-2). Overall, U.S- and foreign-born Asian mothers' risks of having a child with autism was the same as that of U.S.-born whites. However, when considering Asian immigrants and their different countries of origin, children of mothers born in the Philippines and Vietnam were at 25% and 43% higher risk, respectively, while children of mothers born in China and Japan were at ~30% reduced risk compared to whites. Further investigation of Filipino and Chinese U.S.-born Asian mothers demonstrated consistent, yet less stable, relative risks for autism in offspring comparable to their foreign-born counterparts (not shown). However, a similar risk in U.S.-born Japanese compared to U.S.-born whites was found (not shown).

Autistic Disorder – Mental Retardation

We identified a total of 238 children with AD-MR. The mean age of children identified with both AD and MR varied by 10 months across groups, with children of foreign-born Korean's identified the earliest and of the Philippines the latest (Table 6-3). In aggregate, foreign-born Asian women were at increased risk of having a child with AD-MR compared to U.S.-born white women, an increase driven by children born to women who immigrated from the Philippines and Vietnam.

Autistic Disorder by Expressive Language Skills

We identified a total of 739 5-year old children with impaired expressive language documented with their AD diagnosis and 733 with less impaired expressive language (Table 6-4). Compared to children born to U.S.-born white women, offspring of all subgroups of Asian mothers were at higher risk of having an AD phenotype with impaired expressive language, though Chinese and Japanese offspring estimates had wider confidence intervals. Though most

groups of children from foreign-born Asian mothers were less likely to be identified with less impaired expressive language, children of U.S.-born Asian and foreign-born Vietnamese mothers had similar risks to offspring of U.S.-born whites.

Autistic Disorder by Severity of Emotional Outbursts

We identified a total of 442 5-year old children who had AD with severe emotional outbursts, and 1,026 with AD-less severe outbursts (Table 6-5). Children of most maternal Asian subgroups were at similar risk of AD with both severe and less severe outbursts than U.S.-born whites. However, Vietnamese and Filipino offspring had a higher risk of AD with less severe outbursts.

The risk for having a child with both impaired expressive language and severe emotional outbursts was highest for immigrant Korean (RR=1.82, CI=1.05, 3.16), Filipino (RR=1.88, CI=1.24, 2.71), and Vietnamese (RR=2.05, CI=1.26, 3.33) mothers compared to U.S.-born whites (Supplemental Table 6-6).

Discussion

We observed that mothers who immigrated from the Philippines or Vietnam were at increased risk not only of having a child with AD, but also of having a child with lower functioning due to comorbid mental retardation. Although one previous U.S. study observed children of Asian mothers were at increased risk of having a primary MR diagnosis compared to whites, that study did not examine families by country of origin (21). Our findings support those of European studies, which observed a higher risk of autism in offspring among Asian immigrant parents (6,7). In Sweden, mothers from Iran and India, had higher odds ratios for having a child with low-functioning autism compared to Swedish-born mothers. Although their Asian immigrant population composition was different than ours, they also found a greater risk among

parents who migrated from regions with a low human development index (HDI), a composite indicator of development derived using indicators of life expectancy, education and income (7). Our study corroborates that children whose Asian parents migrated from the Philippines and Vietnam, countries with lower HDIs (http://hdr.undp.org/en/data/trends), were at higher risk.

To understand the different autism risks among Asian subgroups in the U.S., it may be important to consider the experiences and historical context under which members of different Asian groups entered the U.S. Chinese immigrant women who gave birth during the period of study likely migrated between the early 1980's and early 1990's after China opened its economy and allowed travel (22). After political, economic, and demographic transitions starting in the late 1980's, Japanese and Korean people also began to migrate for economic opportunities (23). A possible explanation for the relatively low autism risk in offspring of Chinese and Japanese mothers may lie in the social and economic advantages they have in the U.S., given their longer history of settlement groups in the U.S. in comparison to other Asian groups which could have given them a quality of life and health advantage (24). Koreans, though historically a newer immigrant group, may have cultural norms and values that promote their overall health that may also be protective of adverse childhood conditions such as autism (25).

Vietnamese immigrants mostly came to the U.S. between 1975 and 1985 as refugees of the Vietnam War (26). A high prevalence of psychiatric disorders, i.e. posttraumatic stress disorder, generalized anxiety disorder, and depression, have been identified among refugees from war and are considered risk factors for low-functioning autism in offspring (27–34). Thus effects from war-related trauma among Vietnamese refugees may have played a role in autism among their U.S.-born offspring. Information about autism prevalence in low or low-middle income countries like Vietnam and the Philippines is very limited, though autism is reportedly on

the rise in Vietnam (4,35). This makes it difficult to assess whether the observed autism risk is a migratory phenomenon due to either selective migration of people predisposed to having a child with autism or an increase in risk due to migration circumstances.

Women from the Philippines likely immigrated to the U.S. as the children of skilled workers who came to the U.S. post-1965 under new immigration policies (36). The higher autism risks were consistent between offspring of U.S.- and foreign-born Filipino mothers (data not shown) thus making it likely that shared cultural norms may play a bigger role than immigration-related factors in this group. Though, due to small sample size, it is unknown whether severity of autism would persist in the U.S.-born Filipino population.

Another possible explanation for the observed association between country of origin in Asia and risk for AD might be the role of culture-specific nutrition since diets low in preconception intake of folic acid recently may play a role in childhood autism (37,38). A population-based, prospective Norwegian Cohort Study reported autism prevalence of 0.10% among children born to mothers who took folic acid supplements around the time of conception compared with 0.21% in those who did not take folic acid (38). A California study reported similar results for folic acid intake in the first month of pregnancy and autism risk (37). Although differences may be explained by variation in diet across cultures, it is more plausible that women born in low-income countries may have diets with micronutrient deficiencies during pregnancy. In the Philippines, Vietnam, and Cambodia, a high prevalence of anemia and micronutrient deficiencies (median intake of 38.4% of the recommended nutrient intake for iron, zinc, vitamin A and folic acid) was observed among women of reproductive age, necessitating the implementation of preventive iron-folic acid supplementation programs (39,40). In

comparison, in China, folic acid deficiency in pregnant women is less common in the southern regions where the majority of U.S. immigrants from China originate (22,41).

Regardless of country of origin, offspring of Asian women were at higher risk of AD with impaired expressive language. However, ascertainment bias or differential misclassification may occur due to language barriers between foreign-born non-English speaking parents and evaluation personnel. Though more recent efforts are being made to increase the diversity of languages by key service providers, it is likely that many were monolingual English speakers during the period under investigation. Underutilization of formal health services has been reported in Asian populations, particularly among the Chinese (42,43). However, there is sufficient evidence that among children of Vietnamese mothers their higher risk of severe autism indicates true higher risks than U.S.-born white mothers as they also displayed similar risk of less impaired expressive language, higher risk of both severe and less severe emotional outburst behavior.

An important strength of our study was our ability to observe autism risk heterogeneity in offspring of specific Asian subgroups of mothers through a large and diverse dataset. Though our sample size did not allow us to validate diagnoses, the diagnostic stability of autism is good, i.e. diagnostic consistency for ASD between ages 2 and 9 years is 90 percent (44,45). Although expressive language skills and social-emotional behavior also relied on caregiver report, and we report on the most up-to-date information for 5-year olds, the parent interview is as critical as direct child observation and diagnostic evaluations (46). However, it is possible that social cultural norms vary with regard to language and behaviors that may have contributed to under ascertainment of milder cases among Asian groups. Our study looked at a young group of children (3 to 5 years) with a strict diagnosis of AD, and not the larger spectrum. Thus these

families may have been more proactive overall in getting services early and their children's condition less likely to go unnoticed, which may not be representative of children identified at later ages.

Although our results provide us with clues for understanding autism differences with respect to the largest Asian origin population groups in the US, a limitation of this study is that we could not operationalize many pathophysiological factors limited by our use of vital statistics data. Despite this, the present research highlights the importance for future investigations of autism in Asian populations, which have not been adequately recognized in the literature. Studies should focus on dietary risk and protective factors in specific Asian subgroups, psychiatric disorders in refugee parents, in addition to systematic investigation of Asian immigrants who continue to arrive in the U.S. by tracking their adoption of the new culture will provide further direction in autism etiology.

Table 6-1. Distribution of demographic and prenatal characteristics by maternal Asian subgroups

	USB White (236,347) n (%)	USB Asian/PI (21,678) n (%)	China (29,666) n (%)	Japan (5,815) n (%)	Korea (22,206) n (%)	Phillipines (35,306) n (%)	Vietnam (19,287) n (%)
Sex of child							
Males	121381 (51.4)	11236 (51.8)	15510 (52.3)	2966 (51.0)	11563 (52.1)	18289 (51.8)	10084 (52.3)
Females	114966 (48.6)	10442 (48.2)	14155 (47.7)	2849 (48.9)	10643 (47.9)	17017 (48.2)	9203 (47.7)
Gestational Time							
Preterm (<37 weeks)	23438 (9.9)	2505 (11.6)	2282 (7.7)	412 (7.1)	1525 (6.9)	4225 (12.0)	2069 (10.7)
Term (≥37 weeks)	212909 (90.1)	19173 (88.4)	27384 (92.3)	5403 (92.9)	103312 (83.8)	8782 (87.0)	17218 (89.3)
Birthweight							
LBW (<2500g)	14678 (6.2)	1765 (8.1)	1609 (5.4)	419 (7.2)	1042 (4.7)	2782 (7.9)	1247 (6.5)
NBW (≥2500g, <4500g)	217495 (92.0)	19718 (91.0)	27866 (93.9)	5383 (92.6)	21004 (94.6)	32299 (91.5)	17946 (93.0)
Macrosomia (≥4500g)	4174 (1.8)	195 (0.9)	191 (0.6)	13 (0.2)	160 (0.7)	225 (0.6)	94 (0.5)
Maternal Characteristics							
Maternal age at delivery (years)							
≤18	5746 (2.4)	1146 (5.3)	35 (0.1)	7 (0.1)	36 (0.2)	458 (1.3)	95 (0.5)
19 - 25	42116 (17.8)	5107 (23.6)	1838 (6.2)	350 (6.0)	1348 (6.1)	6057 (17.2)	2470 (12.8)
26 -30	58701 (24.8)	5083 (23.4)	8370 (28.2)	1550 (26.7)	8464 (38.1)	10036 (28.4)	6575 (34.1)
31 - 35	75587 (32.0)	6388 (29.5)	12376 (41.7)	2399 (41.3)	8953 (40.3)	11146 (31.6)	6779 (35.2)
>35	54190 (22.9)	3954 (18.2)	7047 (23.8)	1509 (26.0)	3405 (15.3)	7608 (21.5)	3368 (17.5)
missing	7 (0.0)	0	0	0	0	1 (0.0)	0
Maternal education							
<highschool	15925 (6.7)	1620 (7.5)	2329 (7.9)	97 (1.7)	268 (1.2)	1327 (3.8)	5693 (29.5)
highschool	49673 (21.0)	3802 (17.5)	4996 (16.8)	3237 (14.6)	3237 (14.6)	4448 (12.6)	4397 (22.8)
>highschool	169129 (71.6)	16097 (74.3)	22076 (74.4)	18528 (83.4)	18528 (83.4)	29342 (83.1)	9009 (46.7)
unknown	1620 (0.7)	159 (0.7)	265 (0.9)	173 (0.8)	173 (0.8)	189 (0.5)	188 (1.0)
Prenatal Characteristics							
Type of birth							
Single	225931 (95.6)	20902 (96.4)	28887 (97.4)	5639 (97.0)	21660 (97.5)	34618 (98.0)	18860 (97.8)
Multiple	10416 (4.4)	776 (3.6)	779 (2.6)	176 (3.0)	546 (2.5)	688 (2.0)	427 (2.2)
Start of prenatal care							
none	880 (0.4)	106 (0.5)	18 ((0.1)	5 (0.1)	23 (0.1)	103 (0.3)	30 (0.2)
1st trimester	219645 (92.9)	19347 (89.2)	27338 (92.2)	5401 (92.9)	20692 (93.2)	31230 (88.5)	17942 (93.0)
2nd trimester	13438 (5.7)	1832 (8.5)	1677 (5.6)	335 (5.8)	1129 (5.1)	3401 (9.6)	1060 (5.5)
3rd trimester	1927 (0.8)	344 (1.6)	420 (1.4)	54 (0.9)	299 (1.3)	501 (1.4)	144 (0.7)

Table 6-1 continued. Distribution of demographic and prenatal characteristics by maternal Asian subgroups

	USB White (236,347) n (%)	USB Asian/PI (21,678) n (%)	China (29,666) n (%)	Japan (5,815) n (%)	Korea (22,206) n (%)	Phillipines (35,306) n (%)	Vietnam (19,287) n (%)
unknown	457 (0.2)	49 (0.2)	213 (0.7)	20 (0.3)	63 (0.3)	71 (0.2)	111 (0.6)
Insurance Type							
Public (Medi-Cal)	35489 (15.0)	4036 (18.6)	5771 (19.4)	655 (11.2)	6369 (28.7)	8662 (24.5)	6170 (32.0)
Private	193373 (81.8)	16958 (78.2)	17755 (59.9)	4569 (78.6)	12880 (58.0)	25266 (71.6)	12258 (63.5)
other	5648 (2.4)	441 (2.0)	5688 (19.2)	558 (9.6)	2848 (12.8)	1010 (2.9)	538 (2.8)
unknown	1837 (0.8)	243 (1.2)	452 (1.5)	33 (0.6)	109 (0.5)	368 (1.0)	321 (1.7)
Parity							
one (index birth)	105618 (44.7)	11105 (51.2)	15165 (51.1)	3213 (55.2)	11185 (50.4)	15539 (44.0)	8937 (46.3)
two	79000 (33.4)	6853 (31.6)	11418 (38.5)	1944 (33.4)	8318 (37.5)	11983 (33.9)	6870 (35.6)
three	33477 (14.2)	2510 (11.6)	2595 (8.8)	511 (8.8)	2322 (10.5)	5521 (15.7)	2408 (12.5)
>three	18205 (7.7)	1208 (5.6)	483 (1.6)	147 (2.5)	379 (1.7)	2260 (6.4)	1071 (5.6)
unknown	47 (0.0)	2 (0.0)	5 (0.0)	0	2 (0.0)	3 (0.0)	1 (0.0)
Previous miscarriage							
none	190094 (80.4)	18255 (84.2)	26063 (87.8)	4970 (85.5)	18717 (84.3)	30447 (86.2)	17005 (88.2)
one	32676 (13.8)	2628 (12.1)	2603 (8.8)	654 (11.3)	2507 (11.3)	3742 (10.6)	1788 (9.3)
two	9075 (3.9)	566 (2.6)	725 (2.4)	141 (2.4)	731 (3.3)	841 (2.4)	379 (2.0)
≥three	4432 (1.9)	27 (1.1)	270 (0.9)	48 (0.8)	248 (1.1)	261 (0.8)	115 (0.6)
unknown	70 (0.0)	2 (0.0)	5 (0.0)	2 (0.0)	3 (0.0)	5 (0.0)	0
Previous stillborn							
none	233773 (98.9)	21478 (99.1)	29460 (99.3)	5776 (99.3)	21979 (99.0)	9911 (98.2)	34917 (98.9)
≥1	2506 (1.1)	197 (0.9)	201 (0.7)	37 (0.6)	223 (1.0)	177 (1.8)	384 (1.1)
unknown	68 (0.0)	3 (0.0)	5 (0.0)	2 (0.0)	4 (0.0)	5 (0.0)	5 (0.0)
Pregnancy Complications							
All	29847 (12.6)	2322 (10.7)	1527 (5.1)	401 (6.9)	829 (3.7)	4127 (11.7)	1231 (6.4)
Hypertension	5501 (2.3)	470 (2.2)	172 (0.6)	56 (1.0)	151 (0.7)	898 (2.5)	146 (0.8)
Diabetes	4442 (1.9)	537 (2.5)	669 (2.3)	71 (1.2)	261 (1.2)	1647 (4.7)	496 (2.6)
Infections	5294 (2.2)	445 (2.1)	344 (1.2)	70 (1.2)	175 (0.8)	594 (1.7)	328 (1.7)
Smoking	5030 (2.1)	196 (0.9)	46 (0.2)	24 (0.4)	41 (0.2)	253 (0.7)	52 (0.3)
Anemia	1067 (0.5)	79 (0.4)	43 (0.1)	11 (0.2)	23 (0.1)	110 (0.3)	31 (0.2)
Paternal Characteristics							
Paternal age at delivery (years)							
≤18	1828 (0.8)	458 (2.1)	10 (0.0)	4 (0.1)	10 (0.0)	180 (0.5)	12 (0.1)
19 - 25	25725 (10.9)	3726 (17.2)	498 (1.7)	181 (3.1)	424 (1.9)	4151 (11.8)	665 (3.4)
26 -30	46738 (19.8)	4336 (20.0)	4159 (14.0)	997 (17.2)	4788 (21.6)	7787 (22.1)	3316 (17.2)
31 - 35	69375 (29.3)	6092 (28.1)	10305 (34.8)	2078 (35.7)	9632 (43.4)	9821 (27.8)	6569 (34.1)

Table 6-1 continued. Distribution of demographic and prenatal characteristics by maternal Asian subgroups

	USB White (236,347) n (%)	USB Asian/PI (21,678) n (%)	China (29,666) n (%)	Japan (5,815) n (%)	Korea (22,206) n (%)	Phillipines (35,306) n (%)	Vietnam (19,287) n (%)
>35	81970 (34.7)	6082 (28.1)	14148 (47.7)	2508 (43.1)	7219 (32.5)	12224 (34.6)	7291 (37.8)
unknown	10711 (4.5)	984 (4.5)	546 (1.8)	47 (0.8)	133 (0.6)	1143 (3.2)	1434 (7.4)
Paternal education level							
<highschool	11735 (5.0)	1190 (5.5)	1923 (6.5)	114 (2.0)	183 (0.8)	1315 (3.7)	3109 (16.1)
highschool	51354 (21.7)	4268 (19.7)	4009 (13.5)	829 (14.3)	2433 (11.0)	5662 (16.0)	4866 (25.2)
>highschool	160721 (68.0)	15032 (69.3)	22855 (77.0)	4769 (82.0)	19268 (86.8)	26878 (76.1)	9584 (49.7)
unknown	12537 (5.3)	1188 (5.5)	879 (3.0)	103 (1.8)	322 (1.4)	1451 (4.1)	1728 (9.0)
Paternal race/ethnicity							
Concordant	211575 (89.5)	11860 (54.7)	26627 (89.8)	3854 (66.3)	20396 (91.9)	26240 (74.3)	16527 (85.7)
Discordant	15597 (6.6)	8943 (41.3)	2530 (8.5)	1921 (33.0)	1692 (7.6)	8038 (22.8)	1473 (7.6)
unknown	9175 (3.9)	875 (4.0)	509 (1.7)	40 ((0.7)	118 (0.5)	1028 (2.9)	1287 (6.7)

USB: U.S.-born
FB: Foreign-born

Note: not all foreign-born Asians are presented in this table

Table 6-2. Associations Between Maternal Nativity among Asians and Autistic Disorder in Los Angeles County

Maternal race/ethnicity and nativity	Mean age (years) at diagnosis (SD)	case/cohort	Avg. Crude Rate (per 10,000 births)	Crude Risk Ratio (RR) (95% CI)	Maternal Age Adjusted Risk Ratio (RR) (95% CI)	Adjusted Risk Ratio[a] (RR) (95% CI)	Adjusted Risk Ratio[b] (RR) (95% CI)	Additionally Adjusted by Regional Center (RR) (95% CI)
White								
U.S.-born	3.4 (0.9)	1477/236347	62.5	1.00	1.00	1.00	1.00	1.00
Asian/P.I								
U.S.-born	3.1 (0.8)	138/21678	63.7	1.02 (0.85, 1.21)	1.08 (0.91, 1.29)	1.03 (0.86, 1.22)	1.02 (0.85, 1.21)	1.04 (0.87, 1.24)
Foreign-born	3.5 (0.9)	917/143066	64.1	1.03 (0.94, 1.11)	1.01 (0.93, 1.10)	0.98 (0.90, 1.06)	1.04 (0.95, 1.13)	1.02 (0.93, 1.11)
China	3.5 (0.9)	145/29666	48.9	0.78 (0.66, 0.93)	0.74 (0.62, 0.87)	0.66 (0.56, 0.79)	0.74 (0.62, 0.89)	0.69 (0.57, 0.83)
Japan	3.2 (0.7)	29/5815	49.9	0.82 (0.57, 1.18)	0.76 (0.53, 1.09)	0.71 (0.49, 1.02)	0.72 (0.50, 1.04)	0.70 (0.48, 1.03)
Korea	3.4 (0.9)	136/22206	61.2	0.98 (0.82, 1.16)	0.98 (0.82, 1.18)	0.92 (0.77, 1.10)	0.95 (0.80, 1.14)	0.97 (0.81, 1.17)
Philippines	3.5 (1.0)	266/35306	75.3	1.21 (1.06, 1.37)	1.21 (1.06, 1.37)	1.23 (1.08, 1.40)	1.23 (1.08, 1.41)	1.25 (1.09, 1.43)
Vietnam	3.6 (0.9)	179/19287	92.8	1.48 (1.27, 1.74)	1.49 (1.27, 1.74)	1.45 (1.24, 1.70)	1.58 (1.35, 1.86)	1.43 (1.21, 1.68)

[a] Adjusted for maternal age, type of birth, parity, infant sex, year of birth, gestational age, birth weight, trimester start of prenatal care, and pregnancy complications

[b] Additionally adjusted for maternal education and insurance type

Table 6-3. Associations Between Maternal Nativity Among Asians and Autistic Disorder With Comorbid Mental Retardation in Los Angeles County

Maternal race/ethnicity and nativity	Mean age (years) at diagnosis (SD)	case/cohort	Avg. Crude Rate (per 10,000 births)	Crude Risk Ratio (RR) (95% CI)	Maternal Age Adjusted Risk Ratio (RR) (95% CI)	Adjusted Risk Ratio[a] (RR) (95% CI)	Adjusted Risk Ratio[b] (RR) (95% CI)	Additionally Adjusted by Regional Center (RR) (95% CI)
White								
U.S-born	3.2 (0.8)	122/236347	5.2	1.00	1.00	1.00	1.00	1.00
Asian/P.I.								
U.S.-born	3.6 (1.1)	14/21678	6.5	1.25 (0.72, 2.18)	1.30 (0.75, 2.26)	1.31 (0.75, 2.27)	1.30 (0.75, 2.27)	1.48 (0.85, 2.58)
Foreign-born	3.6 (0.9)	102/143066	7.1	1.38 (1.06, 1.80)	1.35 (1.04, 1.76)	1.36 (1.04, 1.77)	1.41 (1.08, 1.84)	1.66 (1.26, 2.18)
China	3.6 (1.0)	19/29666	6.4	1.24 (0.76, 2.01)	1.19 (0.74, 1.94)	1.19 (0.73, 1.93)	1.25 (0.76, 2.05)	1.40 (0.84, 2.35)
Japan	3.7 (0.3)	2/5815	3.4	0.67 (0.16, 2.69)	na	na	na	na
Korea	3.0 (0.5)	6/22206	2.7	0.52 (0.23, 1.19)	na	na	na	na
Philippines	3.8 (1.0)	35/35306	9.9	1.92 (1.32, 2.80)	1.90 (1.31, 2.77)	1.92 (1.31, 2.80)	1.98 (1.36, 2.90)	2.27 (1.54, 3.34)
Vietnam	3.6 (0.9)	20/19287	10.4	2.01 (1.25, 3.22)	1.96 (1.22, 3.15)	1.96 (1.22, 3.16)	2.07 (1.28, 3.35)	2.45 (1.50, 4.01)

[a] Adjusted for maternal age, type of birth, parity, infant sex, year of birth, gestational age, birth weight,, trimester start of prenatal care, and pregnancy complications

[b] Additionally adjusted for maternal education, and insurance type

Table 6-4. Associations Between Maternal Nativity among Asians and Autistic Disorder By Expressive Language Ability at 5 Years of Age (n=330,831)

	Impaired Expressive Language				Less Impaired Expressive Language			
Maternal race/ethnicity and nativity	case/cohort	Avg. Crude Rate (per 10,000 births)	Crude Risk Ratio (RR) (95% CI)	Adjusted Risk Ratio[a] (RR) (95% CI)	case/cohort	Avg. Crude Rate (per 10,000 births)	Crude Risk Ratio (RR) (95% CI)	Adjusted Risk Ratio[a] (RR) (95% CI)
White								
U.S-born	349/197992	17.6	1.00	1.00	509/197992	25.7	1.00	1.00
Asian/P.I.								
U.S.-born	42/16886	24.9	1.31 (0.95, 1.81)	1.34 (0.97, 1.86)	42/16886	24.9	0.97 (0.71, 1.33)	1.01 (0.74, 1.39)
Foreign-born	348/115953	30.0	1.65 (1.42, 1.91)	1.58 (1.35, 1.84)	182/115953	15.7	0.61 (0.51, 0.72)	0.66 (0.55, 0.79)
China	56/23536	23.8	1.28 (0.96, 1.70)	1.06 (0.78, 1.42)	38/23536	16.1	0.63 (0.45, 0.87)	0.61 (0.43, 0.87)
Japan	13/4646	28.0	1.51 (0.87, 2.63)	1.34 (0.75, 2.40)	5/4646	10.8	0.42 (0.17, 1.01)	na
Korea	54/17766	30.4	1.65 (1.24, 2.19)	1.82 (1.34, 2.43)	20/17766	11.3	0.44 (0.28, 0.68)	0.52 (0.33, 0.81)
Philippines	94/28901	32.5	1.80 (1.43, 2.26)	1.86 (1.48, 2.34)	55/28901	19.0	0.74 (0.56, 0.98)	0.82 (0.62, 1.10)
Vietnam	73/16070	45.4	2.56 (1.99, 3.30)	2.06 (1.58, 2.70)	34/16070	21.1	0.82 (0.58, 1.16)	0.96 (0.67, 1.37)

[a] Adjusted for maternal age, type of birth, parity, infant sex, year of birth, gestational age, birth weight,, trimester start of prenatal care, pregnancy complications, maternal education, insurance type, regional center

Table 6-5. Associations Between Maternal Nativity among Asians and Autistic Disorder By Severity of Emotional Outburst Behavior at 5 Years of Age (n=330,831)

	Severe Emotional Outbursts				Less Severe Emotional Outbursts			
Maternal race/ethnicity and nativity	case/cohort	Avg. Crude Rate (per 10,000 births)	Crude Risk Ratio (RR) (95% CI)	Adjusted Risk Ratio[a] (RR) (95% CI)	case/cohort	Avg. Crude Rate (per 10,000 births)	Crude Risk Ratio (RR) (95% CI)	Adjusted Risk Ratio[a] (RR) (95% CI)
White								
U.S-born	272/197992	13.7	1.00	1.00	586/197992	29.6	1.00	1.00
Asian/P.I.								
U.S.-born	26/16886	15.4	1.12 (0.75, 1.68)	1.18 (0.79, 1.77)	57/16886	33.8	1.14 (0.87, 1.50)	1.11 (0.84, 1.46)
Foreign-born	144/115953	12.4	0.90 (0.74, 1.11)	0.97 (0.78, 1.19)	383/115953	33.0	1.12 (0.98, 1.27)	1.07 (0.93, 1.22)
China	25/23536	10.6	0.77 (0.51, 1.16)	0.71 (0.46, 1.11)	68/23536	28.9	0.98 (0.76, 1.25)	0.79 (0.61, 1.03)
Japan	3/4646	6.5	0.47 (0.15, 1.47)	na	15/4646	32.3	1.09 (0.65, 1.82)	0.84 (0.48, 1.45)
Korea	22/17766	12.4	0.90 (0.58, 1.39)	1.13 (0.73, 1.76)	51/17766	28.7	0.97 (0.73, 1.29)	0.99 (0.74, 1.33)
Philippines	40/28901	13.8	1.01 (0.72, 1.40)	1.11 (0.79, 1.55)	108/28901	37.4	1.26 (1.03, 1.55)	1.29 (1.05, 1.59)
Vietnam	29/16070	18.0	1.31 (0.89, 1.93)	1.22 (0.81, 1.84)	78/16070	48.5	1.64 (1.29, 2.08)	1.53 (1.19, 1.96)

[a] Adjusted for maternal age, type of birth, parity, infant sex, year of birth, gestational age, birth weight,, trimester start of prenatal care, pregnancy complications, maternal education, insurance type, and regional center

Supplemental Table 6-6. Associations Between Maternal Nativity among Asians and Autistic Disorder With Combined Levels of Impairment in Expressive Language and Severity of Emotional outbursts at 5 Years of Age (n=330,831)

Maternal race/ethnicity and nativity	Impaired Language & Severe Outbursts		Impaired Language & Less Severe Outbursts		Less Impaired Language & Severe Outbursts		Less Impaired Language & Less Severe Outbursts	
	case/cohort	Adjusted Risk Ratioa (RR) (95% CI)	case/cohort	Adjusted Risk Ratioa (RR) (95% CI)	case/cohort	Adjusted Risk Ratioa (RR) (95% CI)	case/cohort	Adjusted Risk Ratioa (RR) (95% CI)
White								
U.S-born	109/197992	1.00	240/197992	1.00	163/197992	1.00	344/197992	1.00
Asian/P.I.								
U.S.-born	15/16886	1.67 (0.97, 2.87)	27/16886	1.20 (0.80, 1.81)	11/16886	0.86 (0.46, 1.58)	30/16886	1.06 (0.73, 1.54)
Foreign-born	105/115953	1.65 (1.25, 2.18)	240/115953	1.51 (1.26, 1.82)	39/115953	0.48 (0.33, 0.69)	143/115953	0.74 (0.61, 0.91)
China	18/23536	1.23 (0.72, 2.10)	37/23536	0.94 (0.65, 1.36)	7/23536	0.34 (0.15, 0.79)	31/23536	0.73 (0.49, 1.07)
Japan	2/4646	na	11/4646	1.60 (0.85, 3.02)	1/4646	na	4/4646	na
Korea	15/17766	1.82 (1.05, 3.16)	38/17766	1.72 (1.21, 2.45)	7/17766	0.66 (0.30, 1.42)	13/17766	0.47 (0.27, 0.82)
Philippines	28/28901	1.88 (1.24, 2.87)	65/28901	1.81 (1.37, 2.39)	12/28901	0.58 (0.32, 1.06)	43/28901	0.94 (0.68, 1.30)
Vietnam	23/16070	2.05 (1.26, 3.33)	50/16070	2.05 (1.48, 2.83)	6/16070	0.55 (0.24, 1.27)	28/16070	1.14 (0.76, 1.72)

[a] Adjusted for maternal age, type of birth, parity, infant sex, year of birth, gestational age, birth weight,, trimester start of prenatal care, pregnancy complications, maternal education, insurance type, and regional center

References

1. Prevalence of autism spectrum disorders--Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008. Morb Mortal Wkly Rep Surveill Summ Wash DC 2002. 2012 Mar 30;61(3):1–19.
2. American Psychiatric Association. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. 4th ed. Washington, DC: American Psychiatric Association; 2000.
3. Johnson H, Cuellar Mejia, Marisol. Immigrants in California [Internet]. Public Policy Institute of California; 2013 May. Available from: http://www.ppic.org/main/publication_show.asp?i=258
4. Elsabbagh M, Divan G, Koh Y-J, Kim YS, Kauchali S, Marcín C, et al. Global Prevalence of Autism and Other Pervasive Developmental Disorders. Autism Res. 2012;5(3):160–79.
5. Croen LA, Grether JK, Selvin S. Descriptive epidemiology of autism in a California population: who is at risk? J Autism Dev Disord. 2002 Jun;32(3):217–24.
6. Keen DV, Reid FD, Arnone D. Autism, ethnicity and maternal immigration. Br J Psychiatry. 2010 Apr 1;196(4):274–81.
7. Magnusson C, Rai D, Goodman A, Lundberg M, Idring S, Svensson A, et al. Migration and autism-spectrum disorder: population-based study. Br J Psychiatry [Internet]. 2012 Feb 23 [cited 2012 Dec 18]; Available from: http://bjp.rcpsych.org/content/early/2012/02/11/bjp.bp.111.095125
8. Smith Roley S, Blanche EI, Schaaf RC. Understanding the Nature of Sensory Integration with Diverse Populations. Austin: Pro Ed; 2001.

9. Pedersen A, Pettygrove S, Meaney FJ, Mancilla K, Gotschall K, Kessler DB, et al. Prevalence of autism spectrum disorders in Hispanic and non-Hispanic white children. Pediatrics. 2012 Mar;129(3):e629–635.

10. Cuccaro ML, Brinkley J, Abramson RK, Hall A, Wright HH, Hussman JP, et al. Autism in African American families: clinical-phenotypic findings. Am J Med Genet Part B Neuropsychiatr Genet Off Publ Int Soc Psychiatr Genet. 2007 Dec 5;144B(8):1022–6.

11. Chaidez V, Hansen RL, Hertz-Picciotto I. Autism spectrum disorders in Hispanics and non-Hispanics. Autism Int J Res Pr. 2012 Jul;16(4):381–97.

12. Jarquin VG, Wiggins LD, Schieve LA, Van Naarden-Braun K. Racial disparities in community identification of autism spectrum disorders over time; Metropolitan Atlanta, Georgia, 2000-2006. J Dev Behav Pediatr JDBP. 2011 Apr;32(3):179–87.

13. Szatmari P, White J, Merikangas KR. The use of genetic epidemiology to guide classification in child and adult psychopathology. Int Rev Psychiatry. 2007 Jan;19(5):483–96.

14. Becerra TA, Wilhelm M, Olsen J, Cockburn M, Ritz B. Ambient Air Pollution and Autism in Los Angeles County, California. Environ Health Perspect. 2012 Dec 18;

15. Gardener H, Spiegelman D, Buka SL. Prenatal risk factors for autism: comprehensive meta-analysis. Br J Psychiatry. 2009 Jul 1;195(1):7–14.

16. Gardener H, Spiegelman D, Buka SL. Perinatal and neonatal risk factors for autism: a comprehensive meta-analysis. Pediatrics. 2011 Aug;128(2):344–55.

17. Bhasin TK, Schendel D. Sociodemographic Risk Factors for Autism in a US Metropolitan Area. J Autism Dev Disord. 2006 Sep;37(4):667–77.

18. Gillberg C, Gillberg IC. Infantile autism: A total population study of reduced optimality in the pre-, peri-, and neonatal period. J Autism Dev Disord. 1983 Jun;13(2):153–66.

19. Zwaigenbaum L, Szatmari P, Jones MB, Bryson SE, Maclean JE, Mahoney WJ, et al. Pregnancy and Birth Complications in Autism and Liability to the Broader Autism Phenotype. J Am Acad Child Adolesc Psychiatry. 2002 May;41(5):572–9.

20. Ritz B, Wilhelm M, Hoggatt KJ, Ghosh JKC. Ambient air pollution and preterm birth in the environment and pregnancy outcomes study at the University of California, Los Angeles. Am J Epidemiol. 2007 Nov 1;166(9):1045–52.

21. Croen LA, Grether JK, Selvin S. The Epidemiology of Mental Retardation of Unknown Cause. Pediatrics. 2001 Jun 1;107(6):e86–e86.

22. Skeldon R. Migration from China. J Int Aff. 1996;49(2):434, 22p, 2 charts.

23. Bloom DE, Williamson JG. Demographic Transitions and Economic Miracles in Emerging Asia. World Bank Econ Rev. 1998 Sep 1;12(3):419–55.

24. Frisbie WP, Cho Y, Hummer RA. Immigration and the Health of Asian and Pacific Islander Adults in the United States. Am J Epidemiol. 2001 Feb 15;153(4):372–80.

25. LaVeist TA. Why We Should Study Race, Ethnicity, and Health. Race Ethn Heal. 1st ed. San Francisco, CA: Jossey-Bass; 2002. p. 1–7.

26. Gordon LW. 7: Southeast Asian Refugee Migration to the United States. Cent Migr Stud Spec Issues. 1987;5(3):153–73.

27. Hinton WL, Chen YC, Du N, Tran CG, Lu FG, Miranda J, et al. DSM-III-R disorders in Vietnamese refugees. Prevalence and correlates. J Nerv Ment Dis. 1993 Feb;181(2):113–22.

28. Hinton WL, Tiet Q, Tran CG, Chesney M. Predictors of depression among refugees from Vietnam: a longitudinal study of new arrivals. J Nerv Ment Dis. 1997 Jan;185(1):39–45.

29. Ta K, Westermeyer J, Neider J. Physical disorders among Southeast Asian refugee outpatients with psychiatric disorders. Psychiatr Serv Wash DC. 1996 Sep;47(9):975–9.

30. Wagner J, Burke G, Kuoch T, Scully M, Armeli S, Rajan TV. Trauma, Healthcare Access, and Health Outcomes Among Southeast Asian Refugees in Connecticut. J Immigr Minor Health. 2012 Sep 14;1–8.

31. Larsson HJ, Eaton WW, Madsen KM, Vestergaard M, Olesen AV, Agerbo E, et al. Risk Factors for Autism: Perinatal Factors, Parental Psychiatric History, and Socioeconomic Status. Am J Epidemiol. 2005 May 15;161(10):916–25.

32. Lauritsen MB, Pedersen CB, Mortensen PB. Effects of familial risk factors and place of birth on the risk of autism: a nationwide register-based study. J Child Psychol Psychiatry. 2005;46(9):963–71.

33. Piven J, Palmer P. Psychiatric Disorder and the Broad Autism Phenotype: Evidence From a Family Study of Multiple-Incidence Autism Families. Am J Psychiatry. 1999 Apr 1;156(4):557–63.

34. Yirmiya N, Shaked M. Psychiatric disorders in parents of children with autism: a meta-analysis. J Child Psychol Psychiatry. 2005;46(1):69–83.

35. Yi Y. Children with autism on the rise in Vietnam - Xinhua | English.news.cn [Internet]. 2013 [cited 2013 Apr 21]. Available from: http://news.xinhuanet.com/english/health/2013-03/14/c_132234027.htm

36. San Juan Jr E. Filipino immigrants in the United States. Philipp Stud Hist Ethnogr Viewpoints. 2000;48(1):121–5.

37. Schmidt RJ, Tancredi DJ, Ozonoff S, Hansen RL, Hartiala J, Allayee H, et al. Maternal periconceptional folic acid intake and risk of autism spectrum disorders and developmental delay in the CHARGE (CHildhood Autism Risks from Genetics and Environment) case-control study. Am J Clin Nutr. 2012 Jul 1;96(1):80–9.

38. Surén P RC. Association between maternal use of folic acid supplements and risk of autism spectrum disorders in children. JAMA. 2013 Feb 13;309(6):570–7.

39. Cavalli-Sforza T. Effectiveness of weekly iron-folic acid supplementation to prevent and control anemia among women of reproductive age in three Asian countries: development of the master protocol and implementation plan. Nutr Rev. 2005 Dec;63(12 Pt 2):S77–80.

40. Smitasiri S, Solon FS. Implementing preventive iron-folic acid supplementation among women of reproductive age in some Western Pacific countries: possibilities and challenges. Nutr Rev. 2005 Dec;63(12 Pt 2):S81–86.

41. Ren A, Zhang L, Hao L, Li Z, Tian Y, Li Z. Comparison of blood folate levels among pregnant Chinese women in areas with high and low prevalence of neural tube defects. Public Health Nutr. 2007 Aug;10(8):762–8.

42. Chung I. Changes in the Sociocultural Reality of Chinese Immigrants: Challenges and Opportunities in Help-Seeking Behaviour. Int J Soc Psychiatry. 2010 Jul 1;56(4):436–47.

43. Yamashiro G, Matsuoka JK. Help-Seeking among Asian and Pacific Americans: A Multiperspective Analysis. Soc Work. 1997 Mar 1;42(2):176–86.

44. Lord C, Risi S, DiLavore PS, Shulman C, Thurm A, Pickles A. Autism From 2 to 9 Years of Age. Arch Gen Psychiatry. 2006 Jun 1;63(6):694–701.

45. California Department of Develomental Services. Autism Spectrum Disorders: Changes in the California Caseload, an update: June 1987 – June 2007 [Internet]. 2007. Available from: http://www.dds.ca.gov/Autism/Home.cfm

46. California Department of Developmental Services. Autism Spectrum Disorders: Best Practice Guidelines for Screening, Diagnosis and Assessment [Internet]. 2002. Available from: http://www.dds.ca.gov/Autism/docs/ASD_Best_Practice2002.pdf

Chapter 7: Summary and Public Health Relevance

Strengths and Limitations

This study was a large population-based case-control study, an efficient design with regard to time and cost for studying autism. Given the low incidence of autistic disorder and time to disease diagnosis (3-13 years), a cohort study would have been less efficient in comparison. However, because differential diagnosis of autism is an issue, especially in low versus high socioeconomic groups, potential ascertainment bias is a limitation in our study. Thus, another limitation of this study was our inability to validate diagnosis of autistic disorder and our dependence on government-based birth and autism data that can sometimes be flawed with measurement error without continuous quality control. Also, we were unable to identify children who moved outside of LA County after birth limiting associations with autism to children who were both born and diagnosed within the county.

A strength of this study was the variability in the independent variables under study, such that Los Angeles County is an ethnically diverse geographic area highly dependent on cars and freeways that allowed us to explore heterogeneity in air pollution, maternal race/ethnicity and nativity and associations with autism. The design of the first study matching controls to cases based on child's sex and birth year, including length of gestation, assured appropriate comparison of air pollution exposure between cases and controls. Since personal measurements are too costly and logistically difficult to obtain for large population-based epidemiologic studies, especially over time periods longer than 48 hours needed for pregnancy studies, the land-use regression analysis was a good spatially refined method to estimate traffic-related air pollution with good predictive value. However, because air pollution is a mixture of gases, particles, and air toxics, which are often correlated due to common sources, we could not

definitively say that any one pollutant within the mix caused autism. Similarly, we could not operationalize pathophysiological hypotheses for autistic phenotypes in the second and third study as we focused on maternal race/ethnicity and nativity as the independent variables.

Public Health Relevance

This research identified risk factors for autism in Los Angeles County and allowed us to give attention to an ethnically diverse population. The literature demonstrates little evidence regarding heterogeneity in autism risk by maternal race/ethnicity and nativity, and by indicators of environmental disparities such as exposure to air pollution. By better understanding risk factors for autism, or considering that some populations fair worse with regard to risk, we hope to stimulate further research attention on vulnerable populations like those with higher exposure to traffic-related air pollution and populations of color.

Targeting prevention and intervention policies in racial/ethnic minorities can help toward the reduction of autism disparities. First, by continuing to improve early screening programs by safe guarding community-based programs that promote favorable developmental outcomes in low socioeconomic neighborhoods can offset the educational disadvantages experienced by families and assure the early intervention and identification of autism in children. Secondly, by eliminating harmful sources of exposures in environmentally disadvantaged neighborhoods can help reduce the overall incidence of autism. Place-based interventions are one good way to improve the outcome of autism, and First 5 Los Angeles, a non-profit agency funded by cigarette taxes in the state of California, is one example of targeting programs in the most vulnerable communities in Los Angeles County. By addressing gaps in services as well as guiding initiatives focused on healthy births, black infant health, and family development they are targeting intervention during pregnancy and infancy in the Los Angeles community. The LA

County ‘211’ hotline also serves as a safety net for families not enrolled in high-quality early childhood programs for the screening of early developmental milestones. Early Head Start, a federally funded health and education program for high-risk women and children, in collaboration with the Medi-Cal (Medicaid) program, i.e. Early and Periodic Screening, Diagnosis and Treatment (EPSDT), also structures child developmental screenings throughout their first few years of life. The regional centers in turn serve as the primary receivers of referrals, and coordinators of lifelong services and supports for people with developmental disabilities including autism. However, recent transitions for health insurance to have the primary responsibility of evaluation and treatment should be carefully monitored, as it may pose a challenge for new systems to maintain the progress that many community- and government-based organizations have reached with regard to childhood developmental delays. Thus, these programs and others like it should be protected as they may continue to be the best resource in improving autism outcomes in vulnerable communities.

A significant gap in autism research has been the recruitment and evaluation of genetic risk for ASD in underserved groups. The Autism Genetic Resource Exchange (AGRE), a non-profit DNA repository and family registry program of Autism Speaks has mostly observed participation from a primarily white population, and in some instances limited the participation of other groups through biased exclusion practices (1,2). However, the National Institutes of Health Autism Centers for Excellence program recently funded research to expand representation of human diversity in autism genetics and aim to fill this gap in African American populations (3). Though this is a good step in the right direction, more research is needed in other minority populations that include immigrant families. Preceding recruitment however should be focused on building community capacity, such that parent education and childhood

intervention programs need to be in place in order for families from underrepresented groups to feel supported and in turn participate in research (4).

Future Research

Future research of autism in the U.S. is warranted specifically in environmentally disadvantaged, Hispanic, black, Asian minority, and immigrant populations. Systematic exploration of risk and protective factors related to living conditions in U.S. communities, as well as circumstances prior to migration in certain immigrant groups is needed. Perhaps exploring exposures to stress, psychiatric disorders, environmental factors, dietary risk and protective factors, infections and immunologic profiles across race/ethnicity, immigrant and refugee parent subgroups may be particularly important in providing us with clues about autism etiology in vulnerable populations.

References

1. Geschwind DH, Sowinski J, Lord C, Iversen P, Shestack J, Jones P, et al. The autism genetic resource exchange: a resource for the study of autism and related neuropsychiatric conditions. Am J Hum Genet. 2001 Aug;69(2):463–6.
2. Hilton CL, Fitzgerald RT, Jackson KM, Maxim RA, Bosworth CC, Shattuck PT, et al. Brief report: Under-representation of African americans in autism genetic research: a rationale for inclusion of subjects representing diverse family structures. J Autism Dev Disord. 2010 May;40(5):633–9.
3. Wheeler M. Autism in black and white: NIH grant helps scientist study disorder in African Americans. UCLA Newsroom [Internet]. Los Angeles; 2013 Apr 8; Available from: http://newsroom.ucla.edu/portal/ucla/nih-grant-awarded-for-autism-research-244929.aspx
4. Wheeler B. A Model for Inclusion of Minorities in Genetic Research NIH Partners in Research Grant [Internet]. USC Univ. Cent. Excel. Dev. Disabil. [cited 2013 Jun 17]. Available from: http://www.uscucedd.org/index.php?option=com_content&view=article&id=263&Itemid=278

Appendices

Appendix A

Diagnostic and Statistical Manual of Mental Disorders: DSM IV

(I) A total of six (or more) items from (A), (B), and (C), with at least two from (A), and one each from (B) and (C)

(A) qualitative impairment in social interaction, as manifested by at least two of the following:

1. marked impairments in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body posture, and gestures to regulate social interaction
2. failure to develop peer relationships appropriate to developmental level
3. a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people, (e.g., by a lack of showing, bringing, or pointing out objects of interest to other people)
4. lack of social or emotional reciprocity (note: in the description, it gives the following as examples: not actively participating in simple social play or games, preferring solitary activities, or involving others in activities only as tools or "mechanical" aids)

(B) qualitative impairments in communication as manifested by at least one of the following:

1. delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
2. in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
3. stereotyped and repetitive use of language or idiosyncratic language
4. lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level

(C) restricted repetitive and stereotyped patterns of behavior, interests and activities, as manifested by at least two of the following:

1. encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
2. apparently inflexible adherence to specific, nonfunctional routines or rituals
3. stereotyped and repetitive motor mannerisms (e.g hand or finger flapping or twisting, or complex whole-body movements)
4. persistent preoccupation with parts of objects

(II) Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years:

(A) social interaction
(B) language as used in social communication
(C) symbolic or imaginative play

(III) The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder

---

Source: American Psychiatric Association. (2000). *American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (4th ed.). Washington, DC: American Psychiatric Association.

Appendix B:

State of California--Health and Human Services Agency — Department of Developmental Services

CLIENT DEVELOPMENT EVALUATION REPORT

DS 3753 (3/86) (Electronic Version)

AUTISM (See Manual pg. VI.7.1)

23. | | **Autism**

0 None
1 Autism, full syndrome
2 Autism, residual state
9 Autism suspected, not diagnosed

Contributing Factors
(ICD-9-CM Code)

24a. | | | |.| | |

24b. | | | |.| | |

25. | | | | | **Date of Determination**
M M Y Y

26. | | **Condition Impact**

EPILEPSY / SEIZURE DISORDER (See Manual pg. VI.8.1)

If the client has only one type of seizure, record it in 27a and also complete 27b and 27c for that type. If the client has more than one type of seizure, record the other types in 28a and 29a and complete b and c items for these other types.

Type of Seizure

27a. | | **28a.** | | **29a.** | |

0 Does not have seizure disorder
1 Partial, with elementary symptomatology
2 Partial, with complex symptomatology
3 Partial, secondarily generalized
4 Generalized, Absences (Petit Mal)
5 Generalized, Bilateral massive epileptic myoclonic
6 Generalized, Infantile spasms
7 Generalized, Tonic-Clonic (Grand Mal)
8 Generalized, Atonic / Akinetic
9 Other / Undetermined

Seizure Frequency

27b. | | **28b.** | | **29b.** | |

1 History of seizures, none in two years
2 History of seizures, none in one year
3 One to six per year
4 Seven to 11 per year
5 One per month (approximate)
6 One per week (approximate)
7 One per day (approximate)
8 More than one per day
9 Frequency undetermined

27c. | | **Condition Impact** **28c.** | | **Condition Impact** **29c.** | | **Condition Impact**

Etiology
(ICD-9-CM Code)

30a. | | | |.| | |

30b. | | | |.| | |

31. | | **Client takes anticonvulsant medication**
1 = Yes 2 = No

32. | | **Status Epilepticus**
Has the client had Status Epilepticus in the past year?
1 = Yes 2 = No 3 = Not known

Appendix C:

Autism:

ORIGINAL	REVISED
Item 23: Autism 0 = None 1 = Autism, full syndrome 2 = Autism, residual state 9 = Autism suspected, not diagnosed	*Item 23a: Presence of Autistic Disorder* 0 = None (No Diagnosis) 1 = Autistic Disorder *Item 23b: Presence of Other Pervasive Developmental Disorder* 0 = None (No Diagnosis) 3 = Asperger Disorder 4 = Pervasive Developmental Disorder NOS
Item 26: Condition Impact 0 = None 1 = Mild 2 = Moderate 3 = Severe 9 = Impact undetermined	*Item 26: Condition Impact* 0 = None 1 = Mild 2 = Moderate 3 = Severe