PARENTAL EXPOSURE TO OCCUPATIONAL ASTHMAGENS
AND RISK OF AUTISM SPECTRUM DISORDER

by

Alison B Singer

A dissertation submitted to Johns Hopkins University in conformity with the requirements for the
degree of Doctor of Philosophy

Baltimore, Maryland

April, 2015

© 2015 Alison Singer
All Rights Reserved
ABSTRACT

Background: Autism spectrum disorder (ASD) is a diverse neurodevelopment disorder manifested by repetitive or stereotypic behaviors, and interaction and communication impairments. The etiology is not well understood, but both genetic and environmental factors are suspected to influence ASD. There is evidence linking both environmental exposures and maternal immune activity during pregnancy to ASD, yet few studies have examined occupational agents that can trigger immune responses in relation to ASD. Asthmagens are agents that are capable of triggering or exacerbating asthma. The aim of this dissertation was to examine the association between prenatal parental exposure to asthmagens in the workplace and ASD in two population-based case-control studies.

Methods: Our first case-control study included 437 ASD cases, 660 general population (POP) controls and 628 children with non-ASD developmental delays (DD) with employed mothers from a United States ASD case-control study, the Study to Explore Early Development (SEED). Maternal jobs were coded according to the International Standard Classification of Occupations 1988 (ISCO-88). The second study sample included 6,830 cases and 29,670 controls in maternal analyses, and 7,799 cases and 32,335 controls in paternal analyses, selected from the Danish Registers. We linked children in the study population to maternal and paternal Danish International Standard Classification (DISCO-88) job codes. In both studies, we estimated occupational asthmagen exposure by linking job codes to an asthma-specific job-exposure matrix (JEM). Since exposure misclassification is a concern in our analyses, we also illustrate an application of a Bayesian correction for exposure misclassification, as a dissertation chapter.

Results: In the SEED study, we saw no evidence of a marginal association between maternal occupational asthmagen exposure and ASD. We observed an inverse association between maternal and paternal occupational asthmagen exposures and ASD in the Danish study. We attribute this inverse association to possible unmeasured confounding or selection bias. After correcting for exposure misclassification, our results were consistent with no detectable
association between occupational asthmagen exposure and ASD, but also demonstrated the potential importance of accounting for exposure misclassification.

**Conclusions:** Overall, our results are consistent with the conclusion that there is no measurable association between occupational asthmagen exposure and ASD.

**Thesis Readers:**

M. Daniele Fallin, PhD (Advisor)

Ana Navas-Acien, MD, PhD

Christine Ladd-Acosta, PhD

Judith Bass, PhD

Igor Burstyn, PhD
ACKNOWLEDGMENTS

I have been extremely fortunate to work with a number of amazing people both at Johns Hopkins and elsewhere. This dissertation would not have been possible without them.

First, I thank my advisor, Dani Fallin, for her support and guidance. She has facilitated amazing collaborative opportunities for me and has helped me navigate through difficult moments in my graduate school experience. She has taught me how to be a better epidemiologist, writer, and communicator. I appreciate her taking me on as a student, despite the fact that I do not study genetic epidemiology. She has always served as a voice of encouragement and has been a great mentor, both personally and professionally.

I must thank Igor Burstyn of Drexel University for co-mentoring me from a distance over the past few years. He played a crucial role in developing this dissertation work, and guided me through both the occupational exposure assessment and the Bayesian analyses. His input as a co-author on all three manuscripts (and feedback on the background and conclusion) has been extremely helpful. I thank him for answering my frequent questions.

This work would also not have been possible without Diana Schendel at Aarhus University in Denmark. Diana is a co-author on Chapters 2 and 3, and played a critical role in making the Denmark project a reality. I thank her for all she did to make me feel at home during my trip to Denmark and for her guidance on the project. I also thank Preben Bo Mortensen of the National Center for Register-based Research at Aarhus University for his support and input on the Danish study. I thank the National Center for Register-based Research for generously funding my travel to Denmark. Much gratitude to others in Denmark, in particular, Hanne Birgitte Hede Jørgensen, Malene Thygesen, and Morten Overgaard, for their help with my project. A thank you Vivi Schlünssen as well for answering questions about asthmagen exposures in Denmark.

I was very fortunate to work with a great group of co-authors on my SEED project, including Julie Daniels at the University of North Carolina, Gayle Windham at the California Department of Public Health, Lisa Croen at Kaiser Permanente, and Brian Lee at Drexel
University (in addition to Dani, Igor and Diana). They all provided valuable advice. Thank you as well to other SEED investigators and analysts for assistance with some of the SEED variables. I also thank current and former staff members at the Wendy Klag Center for Autism and Developmental Disabilities, especially Jamie Dahm, Michelle Landrum, and Carmen Berry. Jamie, Michelle, and Carmen provided valuable information on the SEED and EARLI studies.

I thank my thesis committee, Ana Navas-Acien, Li-Ching Lee, and Patrick Breysee for their helpful feedback on my project. They are all amazing people – even when I just run into them in the kitchen or hallway, I am always greeted with words of encouragement. A thank you as well to other faculty members who have served on my various exams: Genevieve Matanoski, Alison Abraham, Peter Lees, Terri Beaty, Bill Eaton, Christine Ladd-Acosta, and Judith Bass. Other faculty that deserve acknowledgement for help along the way include: Elizabeth Stuart, Craig Newschaffer, Rebecca Landa, Elizabeth Matsui, and Joanne Katz.

Many thanks to the other members of the Fallin lab group, especially to my office mates for their friendship and support through the ups and downs of my dissertation. A thank you to many staff members in the Department of Epidemiology, including Fran Burman for answering my many questions and Matt Miller for his help with funding. I was very fortunate to receive an Autism Speaks Dennis Weatherstone Fellowship Award (#8576) and I thank Autism Speaks immensely for this funding support. I was also the recipient of a Wendy Klag Center Award and the Charlotte Ferencz Award and received funding support from the Department of Epidemiology.

My friends and classmates have been an absolutely critical support network. We still managed to have fun despite the stress of graduate school. Finally, I thank my amazing family, particularly my mother, father, and Fred, for always encouraging me to pursue my passions. Words cannot express my thanks and appreciation for all my family has done for me.
## TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>ii</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>iv</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>vi</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>viii</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>x</td>
</tr>
<tr>
<td>Chapter 1. Background</td>
<td>1</td>
</tr>
<tr>
<td>1.1. Overview</td>
<td>2</td>
</tr>
<tr>
<td>1.2. Organization</td>
<td>3</td>
</tr>
<tr>
<td>1.3. Background on autism spectrum disorder</td>
<td>4</td>
</tr>
<tr>
<td>1.4. Impacts of autism spectrum disorder and project significance</td>
<td>5</td>
</tr>
<tr>
<td>1.5. Etiology of autism spectrum disorder</td>
<td>6</td>
</tr>
<tr>
<td>1.5.a. Overview</td>
<td>6</td>
</tr>
<tr>
<td>1.5.b. Heritability</td>
<td>7</td>
</tr>
<tr>
<td>1.5.c. Genetic risk factors</td>
<td>7</td>
</tr>
<tr>
<td>1.5.d. Environmental risk factors</td>
<td>9</td>
</tr>
<tr>
<td>1.6. Methodological concerns in occupational epidemiology</td>
<td>19</td>
</tr>
<tr>
<td>1.6.a. Occupational exposure assessment</td>
<td>19</td>
</tr>
<tr>
<td>1.6.b. Misclassification of occupational exposures</td>
<td>20</td>
</tr>
<tr>
<td>1.7. Introduction to occupational asthmagens and biological mechanism</td>
<td>21</td>
</tr>
<tr>
<td>1.8. Specific Aims</td>
<td>26</td>
</tr>
<tr>
<td>1.9. References</td>
<td>27</td>
</tr>
<tr>
<td>Chapter 2. Maternal exposure to occupational asthmagens and the risk of</td>
<td>49</td>
</tr>
<tr>
<td>autism spectrum disorder in the Study to Explore Early Development</td>
<td></td>
</tr>
<tr>
<td>2.1. Abstract</td>
<td>50</td>
</tr>
<tr>
<td>2.2. Introduction</td>
<td>51</td>
</tr>
<tr>
<td>2.3. Methods</td>
<td>53</td>
</tr>
<tr>
<td>2.3.a. Study population</td>
<td>53</td>
</tr>
<tr>
<td>2.3.b. Occupational exposure assessment</td>
<td>53</td>
</tr>
<tr>
<td>2.3.c. Covariates</td>
<td>55</td>
</tr>
<tr>
<td>2.3.d. Outcome assessment</td>
<td>56</td>
</tr>
<tr>
<td>2.3.e. Statistical analysis</td>
<td>57</td>
</tr>
<tr>
<td>2.4. Results</td>
<td>59</td>
</tr>
<tr>
<td>2.5. Discussion</td>
<td>61</td>
</tr>
<tr>
<td>2.6. References</td>
<td>67</td>
</tr>
</tbody>
</table>
Chapter 3. Parental exposures to occupational asthmagens and risk of autism spectrum disorders in a Danish population-based case-control study ..............................................................76
  3.1. Abstract ............................................................................................................................ 77
  3.2. Introduction .................................................................................................................... 78
  3.3. Methods .......................................................................................................................... 79
  3.3.a. Study design ................................................................................................................. 79
  3.3.b. Selection of eligible participants .................................................................................. 80
  3.3.c. Case and control selection ................................................................----------------------- 80
  3.3.d. Employment status definition ..................................................................................... 81
  3.3.e. Occupational asthmagen exposure assessment ............................................................ 82
  3.3.f. Creation of other covariates ....................................................................................... 83
  3.3.g. Statistical analysis ...................................................................................................... 83
  3.4. Results .............................................................................................................................. 85
  3.5. Discussion ....................................................................................................................... 88
  3.6. References ....................................................................................................................... 95

Chapter 4. The importance of exposure misclassification: Using Bayesian correction methods to assess maternal occupational asthmagen exposures and risk of autism spectrum disorder ..................................................................................105
  4.1. Abstract .......................................................................................................................... 106
  4.2. Introduction .................................................................................................................... 108
  4.3. Methods .......................................................................................................................... 111
  4.3.a. Motivating epidemiological studies .......................................................................... 111
  4.3.b. Occupational exposure assessment .......................................................................... 112
  4.3.c. Statistical analysis to accommodate misclassification of exposure ......................... 113
  4.4. Results ............................................................................................................................. 120
  4.5. Discussion ....................................................................................................................... 121
  4.6. References ....................................................................................................................... 125

Chapter 5. General Discussion and Concluding Remarks ....................................................132
  5.1. Summary of results ...................................................................................................... 133
  5.2. Strengths and weaknesses: comparing SEED and Danish case-control studies ..... 136
  5.3. Challenges in ASD epidemiology research ................................................................. 138
  5.4. Future directions ........................................................................................................... 139
  5.5. Public health significance ............................................................................................. 141
  5.6. References ....................................................................................................................... 143

Appendix I: Supplemental tables from Chapter 2 ............................................................145
Appendix II: Supplemental tables from Chapter 3 ..........................................................150
Appendix III: Code and model diagnostics from Chapter 4 .............................................155
Curriculum vitae ..................................................................................................................191
LIST OF TABLES

Table 1-1: Exposure axis of the asthma-specific job exposure matrix………………………….46

Table 1-2: Occupational asthmagen categories with examples of specific agents and jobs with exposures…………………………………………………………………………………………47

Table 2-1: Frequency of maternal occupational asthmagen exposure by covariates for all children in analytic sample in the SEED study, part 1………………………………………………….…71

Table 2-2: Frequency of maternal occupational asthmagen exposure by covariates for all children in analytic sample in the SEED study, part 2………………………………………………….…72

Table 2-3: Crude and adjusted odds ratios and 95% confidence intervals for maternal occupational asthmagen exposure comparing ASD to population controls and DD to population controls in the SEED study…………………………………………………………………………………………73

Table 2-4: Adjusted odds ratios (aOR) and 95% confidence intervals for models with interaction terms in the SEED study………………………………………………………………………………………..74

Table 2-5: Logistic regression models for the association between maternal occupational asthmagen exposure and ASD with intellectual disability (ID) and ASD without intellectual disability compared to population controls (POP) in the SEED study…………………………………………………………………………………………75

Table 3-1: Parent and child characteristics by maternal occupational asthmagen exposure and paternal occupational asthmagen exposure in the Danish case-control study………………..…100

Table 3-2: Independent and joint effects of parental occupational asthmagen exposure and parental asthma diagnosis by a specialist prior to child’s birth in the Danish case-control study…………………………………………………………………………………………101

Table 4-1: Prior distributions for SEED maternal occupational asthmagen exposure misclassification correction…………………………………………………………………………………………128

Table 4-2: Posterior distributions, median (95% Credible Interval), for SEED maternal occupational asthmagen exposure misclassification correction………………………………………129

Table 4-3: Prior distributions for Denmark contingency table exposure misclassification correction; differential exposure misclassification is assumed and modeled……………………………130

Table 4-4: Posterior distributions, median (95% Credible Interval), for Denmark contingency table maternal occupational asthmagen exposure misclassification correction………………..…131

Table I-1: Maternal employment during the pregnancy by participant characteristics among mothers starting the occupational section of the caregiver interview with a child in the ASD case, DD, or POP group in the SEED study, part 1…………………………………………………………………………………………146

Table I-2: Maternal employment during the pregnancy by participant characteristics among mothers starting the occupational section of the caregiver interview with a child in the ASD case, DD, or POP group in the SEED study, part 2…………………………………………………………………………………………147
Table I-3: Occupational asthmagen exposure by participant characteristics in population controls (POP) and ASD cases (ASD) in the SEED study, part 1………………………………………………148

Table I-4: Occupational asthmagen exposure by participant characteristics in population controls (POP) and ASD cases (ASD) in the SEED study, part 2…………………………………………..149

Table II-1: Associations between maternal occupational exposure to asthmagens during pregnancy and risk of ASD in a sample from the Danish population……………………..151

Table II-2: Associations between paternal occupational exposure to asthmagens during pregnancy and risk of ASD in a sample from the Danish population…………………………….152
LIST OF FIGURES

Figure 1-1: Two hypothesized biological mechanisms linking parental occupational asthmagen exposure and autism spectrum disorder (ASD)………………………………………………………………48

Figure 3-1: Adjusted odds ratios and 95% confidence intervals for parental occupational asthmagen exposure and ASD in the Danish case-control study………………………………………102

Figure 3-2: Sensitivity to unobserved confounder for the association between maternal occupational asthmagen exposure and ASD for fixed prevalence of unmeasured confounder among unexposed of 0.30………………………………………………………………………………104

Figure II-1: Inclusion criteria for the Danish case-control study…………………………153

Figure II-2: Selection of cases and controls for the Danish case-control study……………154
Chapter 1. Background Chapter
1.1. Overview

Autism spectrum disorder (ASD) is a phenotypically diverse disorder marked by impairments in social interaction and communication, and repetitive or stereotypic behaviors. One in 68 eight-year old children in the communities surveyed by the CDC’s Autism and Developmental Disabilities Monitoring (ADDM) Network in 2010 are estimated to have an ASD (CDC 2014). The prevalence of ASD is about four to five times higher in boys than girls (CDC 2014). The understanding of the etiology of ASD is very limited. Converging evidence suggests, however, that both environmental and genetic factors contribute to ASD risk. One potential hypothesis is that activation of maternal immune activity during pregnancy could be linked to ASD in the children. As such, we examined the association between parental occupational exposure to agents capable of triggering an asthmatic immune response (asthmagens) and ASD in the children in two populations. We estimated exposure to occupational asthmagens using an asthma-specific job exposure matrix (JEM) (Kennedy, Le Moual et al. 2000). We used a Bayesian approach to account for exposure misclassification by the JEM.
1.2. Organization

The current chapter lays out background and motivation for the project. It starts with a discussion of the clinical aspects of ASD and the importance of studying the etiology of this disorder. The existing literature examining the etiology of ASD is then reviewed, with a particular emphasis on environmental risk factors. We highlight some important methodological concerns addressed in this work, including occupational exposure assessment and correction for exposure misclassification. Next, we introduce occupational asthmagens and propose a biological mechanism that could link parental occupational asthmagen exposure to ASD in the children. Finally, we describe the aims of the study.

The first manuscript (Chapter 2) presents an analysis of the association between maternal occupational exposures to asthmagens during pregnancy and ASD in the Study to Explore Early Development (SEED), a population-based case-control study in the United States. In the second manuscript (Chapter 3), we examine the association between parental occupational asthmagen exposures and ASD in children in a population-based case-control study using data from the Danish registers. The third manuscript (Chapter 4) illustrates how to apply Bayesian methods for correction of misclassification error using the SEED study and Denmark case-control study as examples. In the conclusion chapter (Chapter 5), study results are reviewed, the public health significance is discussed, and ideas for future directions are introduced.
1.3. **Background on autism spectrum disorder**

ASD is a diverse condition characterized by impairments in social interactions and communication, and stereotypic or repetitive behaviors. Despite the fact that ASD is defined as one disorder in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association 2013), ASD can be highly variable in terms of both clinical presentation and co-morbidities. ASD symptoms typically emerge prior to age of 3 years. Though symptomatology can change overtime, ASD is a lifelong condition. ASD used to be diagnosed as three separate disorders: autistic disorder, Asperger’s syndrome, and pervasive developmental disorder not otherwise specified (PDD-NOS) in previous versions of the DSM (American Psychiatric Association 2000), and thus diagnostic codes and epidemiologic literature often refer to these separate diagnoses.

According to the DSM-5, ASD is diagnosed based on impairments in (A) social communication or interaction and (B) repetitive or stereotypic behavior. In terms of problems with social communication or interaction, an individual must (1) display impairments in reciprocating conversations with other people, (2) demonstrate difficulties developing and preserving relationships, and (3) show problems with non-verbal communication (American Psychiatric Association 2013, Hyman 2013). Examples of impaired social interaction could include difficulty in sharing emotions, abnormal eye contact, difficulty using or understanding gestures, and difficulty maintaining relationships with other people. In addition, the diagnosis also requires two of the following four restricted repetitive behavior patterns (1) stereotypic or repetitive motor patterns, (2) struggle with change or ritualized behavioral patterns, (3) fixated interests that are extreme in terms of intensity and focus, and (4) extreme sensitivity or indifference to the sensory environment. These symptoms must start in early childhood, though the complete development of the behaviors may not fully manifest until later in life (American Psychiatric Association 2013). Intellectual disability (Matson and Shoemaker 2009), anxiety (Gillott, Furniss et al. 2001, van Steensel, Bogels et al. 2011), depression (Lainhart and Folstein...
1994), seizures (Bolton, Carcani-Rathwell et al. 2011), gastrointestinal problems (McElhanon, McCracken et al. 2014), immune system abnormalities (Noriega and Savelkoul 2014), sleep disorders (Cohen, Conduit et al. 2014), and feeding problems (Sharp, Berry et al. 2013) are some conditions that are commonly comorbid with ASD (Newschaffer, Croen et al. 2007). In addition, ASD has been linked to lower life expectancy compared to people in the general population (Bilder, Botts et al. 2013).

There are no known biological markers of ASD and consequently ASD is diagnosed by behavioral observation and assessment. A number of different strategies have been used to identify ASD cases or behaviors related to ASD in epidemiology. The gold standard for diagnosing ASD in a research setting is a combination of the Autism Diagnostic Observation Schedule (ADOS) (Lord, Rutter et al. 2012) and the Autism Diagnostic Interview-Revised (ADI-R) (Rutter, Le Couteur et al. 2003). The combined use of the ADOS and the ADI-R has a correct classification percentage of 0.80 for ASD compared to diagnosis by a clinical team including multiple clinical assessments and clinical judgment (Falkmer, Anderson et al. 2013). The ADOS has also been used to develop an autism severity score. These scales are costly to administer, so an alternative approach is to identify ASD cases from medical databases using International Classification of Disease (ICD) and Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnosis codes. Finally, information from other behavioral assessments can be administered to measure behavioral phenotypes related to ASD.

1.4. Impacts of autism spectrum disorder and project significance

ASD significantly impacts an individual’s ability to function in society. Young adults with ASD are less likely to have worked in paid jobs than young adults with mental retardation, learning disabilities, emotional disturbances, and speech and language impairments (Shattuck, Narendorf et al. 2012, Roux, Shattuck et al. 2013). ASD also results in family stress as caregivers attempt to navigate treatment and educational options (Karst and Van Hecke 2012). There is
evidence that mothers of children with ASD spend increased time coordinating care than typically developing children (Kogan, Strickland et al. 2008). Parents of children with ASD are more likely to report parental stress and depression (Bromley, Hare et al. 2004, Davis and Carter 2008, Karst and Van Hecke 2012). ASD has been implicated in altering maternal employment decisions, resulting in lower maternal employment (Kogan, Strickland et al. 2008, Montes and Halterman 2008, Cidav, Marcus et al. 2012) and loss of family income (Montes and Halterman 2008, Cidav, Marcus et al. 2012). The financial impact of ASD is compounded by evidence that children with ASD have higher healthcare expenditures than other children (Peacock, Amendah et al. 2012). The costs for non-medical behavioral intervention treatment are also very high, estimated to range from $40,000-60,000 per year for pre-school age children (Amendah, Gross et al. 2011). Lifetime costs for supporting a person with an ASD and co-occurring intellectual disability is estimated to be $2.4 million in the United States (Buescher, Cidav et al. 2014). It has been estimated that ASD without an intellectual disability costs $1.4 million over the lifespan in the US (Buescher, Cidav et al. 2014). Despite the emotional and financial burdens of this disorder, little is known about the etiology of the disorder and there are currently no mechanisms in place for primary prevention. Further study of the biological mechanisms and risk factors underlying ASD may lead to earlier detection, improved interventions, and potentially prevention.

1.5. Etiology of autism spectrum disorder

1.5.a. Overview

Evidence suggests that both genetic and environmental factors influence risk of acquiring ASD. The following section will review the literature on heritability of ASD and the historical case reports that suggest that chemical exposures may be implicated in etiology of ASD. Then, there is a brief overview of the genetic epidemiology of ASD, followed by discussions of the plausibility of an environmental etiology for ASD, plausible windows of susceptibility to ASD, and a review of the current literature regarding environmental risk factors for ASD.
Environmental risk factors are defined very broadly so as to include parental characteristics, chemicals, and biological toxicants.

1.5.b. Heritability

Early twin studies indicated that ASD is highly heritable (Folstein and Rutter 1977, Steffenburg, Gillberg et al. 1989). As a result, many studies have investigated possible genetic etiologies of ASD (Ronald and Hoekstra 2011). Some recent studies have replicated these high genetic heritability results (Taniai, Nishiyama et al. 2008, Rosenberg, Law et al. 2009). For example, Taniai et al. (2008) estimated a genetic heritability for ASD of 73% for males and 87% for females. However, other recent twin studies, either in less selected study populations or with better case ascertainment, revealed that environment could have a greater impact on ASD etiology than previously appreciated (Hallmayer, Cleveland et al. 2011, Sandin, Lichtenstein et al. 2014). For example, Hallmayer et al. (2011) calculated a proband-wise concordance for ASD of 77% for monozygotic male twins and proband-wise concordance of 31% for dizygotic male twins in California. The authors estimated that shared environment was responsible for a large portion of the variance in liability for ASD (Hallmayer, Cleveland et al. 2011). For broader spectrum ASD, Hallmayer et al. (2011) estimated a genetic heritability of 38% and a shared environment component of 58%. A Swedish registry based study estimated a genetic heritability of 50% with non-shared environmental factors explaining another 50% of the variance (Sandin, Lichtenstein et al. 2014).

1.5.c. Genetic risk factors

Overview of types of genetic variants linked to ASD

Given twin studies suggesting a strong ASD concordance in twins and historical evidence of genetic abnormalities in some individuals with ASD, the study of genetic risk factors for ASD has expanded rapidly in recent years. Genetic variants linked to ASD can be categorized two
groups: inherited and de novo. Inherited variants are passed on from the parent to the child whereas de novo variants are the result of genetic changes in the child. Current lines of evidence suggest that 10-20% of ASD cases have an identifiable genetic etiology (Abrahams and Geschwind 2008). However, it has become increasingly clear that ASD is genetically heterogeneous with common genetic variants explaining only a small portion of ASD risk.

**Inherited genetics**

Three genome-wide association studies (GWAS) have been published, attempting to identify common variants impacting autism risk (Wang, Zhang et al. 2009, Weiss, Arking et al. 2009, Anney, Klei et al. 2010). These studies identified associations between ASD and single nucleotide polymorphisms (SNPs) on chromosomes 5p14.1 (Wang, Zhang et al. 2009), 5p15.2 (Weiss, Arking et al. 2009), and 20p12.1 (Anney, Klei et al. 2010). Unfortunately, the findings were not replicated across the studies. These genome-wide association platforms have also been utilized to identify common copy number variations (CNVs) associated with ASD. For example, Glessner et al. (2009) used this approach to identify a number of common CNVs in genes such as NLGN1.

Rare CNVs and rare single nucleotide variants (SNVs) have been implicated in increasing risk of ASD. A number of rare known Mendelian or genetic syndromes, such as Fragile X syndrome, Tuberous sclerosis, and Timothy syndrome, show a high co-occurrence with ASD (Devlin and Scherer 2012). For example, mutations in the Fragile-X mental retardation gene (FMR1) have been linked to ASD. Other rare chromosomal rearrangements and abnormalities, such as a duplication of the 15q11-15q13 region of the chromosomes, have also been linked to ASD (Cook, Lindgren et al. 1997). Candidate gene approaches and CNV identification have implicated many rare genetic mutations as potentially affecting ASD. Examples include NLGN3 and NLGN4 (Jamain, Quach et al. 2003), genes that code for neuroligins, which are cell adhesion molecules found on the synapse, and SHANK2 (Pinto,
Pagnamenta et al. 2010) and SHANK3 (Durand, Betancur et al. 2007, Marshall, Noor et al. 2008), scaffolding proteins in the post-synaptic density that bind to neuroligins. Greater overall burden of rare inherited and de novo CNVs have been identified in ASD cases as compared to controls, with an even stronger burden in areas previously associated with either intellectual disability or ASD (Pinto, Pagnamenta et al. 2010).

De novo genetic variants

Studies have identified numerous de novo CNVs in ASD cases, such as micro-deletions in 16p11.2 (Kumar, KaraMohamed et al. 2008, Marshall, Noor et al. 2008) and duplications of 7q11.23 (Sanders, Ercan-Sencicek et al. 2011). In a study comparing ASD cases to unaffected siblings, cases had a 3.5 time higher odds of at least one de novo CNV than the unaffected siblings (Sanders, Ercan-Sencicek et al. 2011). The odds ratio for having a CNV that overlapped with one or more gene was on average 5.6 comparing affected to unaffected siblings (Sanders, Ercan-Sencicek et al. 2011). Iossifov et al. (2012) only found a statistically significant elevation in SNVs that impact gene function, such as nonsense, splice, and frame-shift mutations, in children with ASD compared to unaffected siblings. So far, evidence points to a largely paternal origin for de novo mutations with results also showing a correlation between de novo mutations and advancing paternal age (Iossifov, Ronemus et al. 2012, O’Roak, Vives et al. 2012).

1.5.d. Environmental risk factors

Introduction and historical evidence of environmental risk factors

Environmental risk factors have generally been implicated in affecting neurodevelopment (Landrigan 2010, Bellinger 2013). Case reports and small clinical studies have also suggested that maternal exposures during pregnancy, such as valproic acid (Christianson, Chesler et al. 1994, Williams and Hersh 1997, Moore, Turnpenny et al. 2000, Williams, King et al. 2001), thalidomide (Stromland, Nordin et al. 1994, Rodier, Ingram et al. 1997, Rodier and Hyman

9
1998), misoprostol (Bandim, Ventura et al. 2003), rubella (Chess 1971, Chess 1977, Chess, Fernandez et al. 1978, Deykin and MacMahon 1979), cytomegalovirus (Markowitz 1983, Stubbs, Ash et al. 1984), measles or mumps (Deykin and MacMahon 1979), and herpes (Ritvo, Mason-Brothers et al. 1990), could be linked to ASD in the children. These studies in combination with recent twin studies suggesting the environmental liability of ASD provide proof of principle that non-genetic factors affect risk of ASD. Consequently, there are a growing number epidemiologic studies examining broadly defined environmental factors in relation to ASD.

Windows of susceptibility

Converging lines of evidence suggests that the prenatal period is a critical window of susceptibility to ASD. First, neuroanatomical differences in some ASD brains implicate the prenatal period. Bauman and Kemper (2005) discuss that some studies examining autistic brains from children have shown decreased numbers of Purkinje cells without reduction in the number of cells in the inferior olive. They argue that the insult changing the Purkinje cells must occur prior to 28-30 weeks gestation, the time at which the connection between the olivary neurons and Purkinje cells is established (Bauman and Kemper 2005). Brain stem abnormalities have been identified in some cases of ASD, which suggests that the disorder is initiated prior to neural tube closure (Rodier, Ingram et al. 1996, Bailey, Luthert et al. 1998, Rodier 2002). Furthermore, some of the teratogens associated with ASD in some of the early proof of principal studies, such as thalidomide, have critical periods during the early prenatal period (Miller 1991, Stromland, Nordin et al. 1994). Within the first year of life, some children with ASD present with behavioral differences (Zwaigenbaum, Bryson et al. 2005) and accelerated brain growth (Courchesne, Carper et al. 2003, Mraz, Green et al. 2007, Webb, Nalty et al. 2007) suggesting that the susceptibility window for these children must be in the pre-natal period or very early in post-natal life. Finally, chemical exposures during the prenatal period have been linked to other brain imaging
abnormalities (Sowell, Leow et al. 2010) and neurodevelopmental outcomes (Rice and Barone 2000, Bellinger 2013).

**Parental age**


**Parental socioeconomic status, race, and ethnicity**

Studies in the United States find higher prevalence of ASD in children from census blocks with higher socioeconomic status and higher percent of adults with a bachelor’s degree (Maenner, Arneson et al. 2009, Durkin, Maenner et al. 2010). However, the socioeconomic variables in these studies are not measured at the individual level. Studies also point to higher prevalence of ASD among white non-Hispanic children than either black non-Hispanic children
or black children (Windham, Anderson et al. 2011, CDC 2012, CDC 2014). Some evidence suggests, however, that these differences may be related to ascertainment bias, where more advantaged families may have greater access to care and interventions for developmental disabilities. Fountain et al. (2011) conducted an analysis that found an association between later diagnosis age and both lower parental education and non-white race. Similarly, Burstyn et al. (2010) observed a later median age of ASD diagnosis in children born to Aboriginal mothers compared to other children diagnosed with ASD in Alberta, Canada. Studies conducted in countries with universal health care systems link ASD with lower parental income (Larsson, Eaton et al. 2005, Rai, Lewis et al. 2012) and parental employment in manual occupations (Rai, Lewis et al. 2012).

**Obstetric complications and pregnancy-related factors**

A variety of poor birth outcomes and obstetric complications have been associated with ASD, including low birth weight, small for gestational age, low Apgar score, abnormal presentation, and maternal hemorrhage (Gardener, Spiegelman et al. 2011). No one suboptimal birth outcome or complication appears to drive these observed associations, which suggests that these factors may co-occur with ASD because of a common cause. Studies have also linked ASD with short intervals between pregnancies (Cheslack-Postava, Liu et al. 2011, Gunnes, Suren et al. 2013, Cheslack-Postava, Suominen et al. 2014) and long intervals between pregnancies (Cheslack-Postava, Suominen et al. 2014). Cheslack-Postava et al. (2011) posit that reduced nutrient availability following a previous pregnancy could explain the association with short inter-pregnancy interval. This idea coincides with recent literature linking ASD with prenatal vitamin use (Schmidt, Hansen et al. 2011, Schmidt, Tancredi et al. 2012) and folic acid intake (Schmidt, Tancredi et al. 2012, Suren, Roth et al. 2013) in the preconception and early pregnancy period, and iron intake from three months preconception through to the end of breastfeeding (Schmidt, Tancredi et al. 2014).
Parental medical conditions

ASD has been linked to parental medical conditions, such as parental history of mental health conditions (Larsson, Eaton et al. 2005, Lauritsen, Pedersen et al. 2005, Daniels, Forssen et al. 2008, Jokiranta, Brown et al. 2013, Rai, Lee et al. 2013), maternal metabolic conditions (type 2 diabetes, gestational diabetes, hypertension, or obesity) during pregnancy (Krakowiak, Walker et al. 2012), and maternal allergic or autoimmune conditions (Comi, Zimmerman et al. 1999, Sweeten, Bowyer et al. 2003, Keil, Daniels et al. 2010), including rheumatoid arthritis (Atladottir, Pedersen et al. 2009), celiac disease (Atladottir, Pedersen et al. 2009), psoriasis (Croen, Grether et al. 2005), ulcerative colitis (Mouridsen, Rich et al. 2007) and asthma and allergy during pregnancy (Croen, Grether et al. 2005). However, the maternal immune conditions have not been consistently reported as associated with ASD across different studies (Micali, Chakrabarti et al. 2004, Croen, Grether et al. 2005, Mouridsen, Rich et al. 2007, Lyall, Ashwood et al. 2014).

There is some evidence potentially linking ASD and maternal thyroid function, with single studies finding associations with severe maternal hypothyroxinemia (Roman, Ghassabian et al. 2013), maternal thyroid stimulating hormone levels (Yau, Lutsky et al. 2015), and maternal thyroid peroxidase antibody positivity (Brown, Surcel et al. 2015). Krakowiak et al. (2012) also reported an association between maternal metabolic conditions and other developmental delays, which suggests that an impact resulting from these conditions may not be specific for ASD.

Parental medical conditions could reflect shared genetic causes for disorders, altered in utero environment that may impact development, or increased following of families with parents with certain medical conditions.

Maternal pharmacologic exposures

Maternal use of valproate, an anticonvulsant drug, during pregnancy has been associated with risk of ASD (Christensen, Gronborg et al. 2013). Studies have also seen some suggestions
of an association between ASD and use of β-2 adrenergic receptor drugs in pregnancy, which are used to treat asthma but can also be utilized as a tocolytic during pregnancy (Connors, Crowell et al. 2005, Croen, Connors et al. 2011). Epidemiologic studies recently found higher risk of ASD among children whose mothers took antidepressant drugs during the pregnancy (Croen, Grether et al. 2011, Rai, Lee et al. 2013, Sorensen, Gronborg et al. 2013, Gidaya, Lee et al. 2014), with a number of these studies finding associations specifically between ASD and maternal use of selective serotonin reuptake inhibitors (Croen, Grether et al. 2011, Gidaya, Lee et al. 2014). With all of these studies there is concern of confounding by indication, where the underlying condition drives the association as opposed to the actual pharmaceutical exposure. For example, Sorensen et al. (2013) did not find an association between antidepressant use and ASD after restricting to mothers with an affective disorder diagnosis.

Other epidemiologic evidence implicating the maternal immune system

As previously discussed, ASD have been linked with various types of congenital infections in case reports and with maternal allergic and autoimmune conditions in epidemiologic studies. As described above, children with autism often have immune conditions (Noriega and Savelkoul 2014). Maternal cytokine production has been linked to altered brain development and behavior in animal models (Meyer, Feldon et al. 2009). However, the epidemiologic studies investigating maternal infections during pregnancy and ASD have largely produced conflicting results. A meta-analysis of 11 studies did not find an overall association between infections during pregnancy and autism (Gardener, Spiegelman et al. 2009). However, when Gardner et al. (2009) included only the four studies that controlled for confounders or utilized sibling controls, they observed an association between prenatal maternal infections and ASD. Since this meta-analysis was published, three studies found little suggestion of an association between ASD and risk of infection at any point in the pregnancy, but some suggestion of trimester specific associations (Buchmayer, Johansson et al. 2009, Atladottir, Thorsen et al. 2010, Atladottir,
Henriksen et al. 2012). However, Lee et al. (2014) found evidence for increased odds of ASD in children whose mothers where hospitalized for infection during the pregnancy. Studies examining the association between influenza or fever and autism have also produced mixed results (Deykin and MacMahon 1979, Atladottir, Henriksen et al. 2012, Zerbo, Iosif et al. 2012). These studies may have inconsistent results because of important deviations in study methodology, including different definitions for the case group and different methods for collecting information on exposure.

Environmental toxicants

A recent meta-analysis concluded that there was no evidence to indicate a link between smoking and ASD (Rosen, Lee et al. 2014). While exposure to prenatal alcohol and fetal alcohol syndrome can result in autistic-like symptoms (Nanson 1992, Harris, MacKay et al. 1995, Fombonne 2002), there is a lack of published epidemiologic literature examining the association between prenatal alcohol exposure and ASD.

There are numerous papers linking air pollutants to ASD, though the particular compounds that are found to be associated are not necessarily consistent across studies. An elevated risk of ASD has been linked to residential proximity to a freeway at the time of birth (Volk, Hertz-Picciotto et al. 2011) and to traffic-related air pollution during gestation (Volk, Lurmann et al. 2013). Recent studies have found associations between pregnancy exposures to air pollutants, such as ozone (Becerra, Wilhelm et al. 2013), particulate matter ≤2.5 μm (Becerra, Wilhelm et al. 2013, Volk, Lurmann et al. 2013, Raz, Roberts et al. 2014), particulate matter ≤10 μm (Volk, Lurmann et al. 2013, Kalkbrenner, Windham et al. 2014), nitrogen dioxide (Volk, Lurmann et al. 2013), heavy metals (Windham, Zhang et al. 2006, Roberts, Lyall et al. 2013), chlorinated solvents (Windham, Zhang et al. 2006, Kalkbrenner, Daniels et al. 2010, von Ehrenstein, Aralis et al. 2014), aromatic solvents (von Ehrenstein, Aralis et al. 2014), and diesel
particulate matter (Windham, Zhang et al. 2006, Roberts, Lyall et al. 2013), and ASD in the children. Variability in associations across studies may be the results of different case definitions and divergent methods for handling confounding and multiple testing. A limitation of these studies is that exposure estimates are largely based on air monitoring stations or modeled using information from toxicant emission databases. Individual exposure estimates are based on residential proximity to air pollutant sources or monitors around the time of pregnancy, so there could be discrepancies between the true and measured exposure.

A few studies also suggest links between exposure to pesticides and ASD. Organochlorine pesticide exposure during the time of nervous system development, as measured by maternal residence near agricultural pesticide application, has been associated with ASD (Roberts, English et al. 2007). Chlorpyrifos levels in cord blood (Rauh, Garfinkel et al. 2006) and organophosphate pesticide metabolites (Eskenazi, Marks et al. 2007) were associated with pervasive developmental disorder (PDD).

Thus far, few published studies have examined biomarkers of other environmental exposures and ASD. One study measured both maternal serum mercury and mercury from neonatal blood spots, and found no association between these mercury measures and ASD in the children (Yau, Green et al. 2014). Two studies, one measuring persistent organic pollutants (DDT, DDE, PCBs, hexachlorobenzene, BDE-47) (Cheslack-Postava, Rantakokko et al. 2013) and another measuring perfluoroalkyl substances (PFAS) (Liew, Ritz et al. 2014), did not find associations between these pollutants in maternal serum and ASD as assessed by linkage to national register data.

A few studies looked at the association between biomarkers of endocrine disruptors and severity of autistic traits and social impairments as indicated by scores on the Social Responsiveness Scale (SRS) (Constantino and Gruber 2005). One study found an association between low molecular weight phthalates with higher SRS scores (e.g. greater social impairments), but no association between high molecular weight phthalates or Bisphenol-A and
SRS scores (Miodovnik, Engel et al. 2011). Another study measured numerous endocrine disruptors in maternal blood or urine from pregnancy, including phthalate metabolites, polychlorinated biphenyls, organochlorine pesticides, flame retardants, and perfluoroalkyl chemicals, but did not find much evidence of consistent associations between endocrine disruptors and autism severity scores in the children, though the sample size of 175 was small (Braun, Kalkbrenner et al. 2014).

Gene-environment interactions

Three epidemiology studies have been published examining interactions between genes and modifiable exposures in relation to ASD, all using candidate gene approaches to identify polymorphisms to test for interactions (Schmidt, Hansen et al. 2011, Schmidt, Tancredi et al. 2012, Volk, Kerin et al. 2014). Schmidt et al. (2011) reported interactions between prenatal vitamin use in the periconception period (three months prior to pregnancy and the first month of pregnancy) and two maternal (MTHFR 677 and CBS rs234715) and one child (COMT 472) genetic polymorphism in genes related to one-carbon metabolism, finding greater than expected risk for people with certain genotypes and without prenatal vitamins use during the periconception period (Schmidt, Hansen et al. 2011). Mean maternal folic acid intake during the first month of the pregnancy was inversely associated with ASD, but this association was driven by mothers and/or children with C>T genotype at MTHFR 677 (Schmidt, Tancredi et al. 2012).

Volk et al. (2014) did not find associations between ASD and the MET CC genotype, but did report associations between traffic related air pollution, measured by PM$_{2.5}$, PM$_{10}$, and nitrogen dioxide. The synergistic effect of both the MET CC genotype and traffic related air pollution was higher than expected based on the independent effects (Volk, Kerin et al. 2014). The studies only included 200-300 ASD cases in the interaction models, so they have limited power to detect interactions and may be vulnerable to false positives.
Parental occupation

Two recent studies examined the impact of parental occupational exposures on ASD with some utilization of occupational histories to estimate workplace exposures. McCanlies et al. (2012) reported a link between parental report of asphalt and solvent exposure and ASD in the children. When occupational exposure was estimated through industrial hygienist assessment, the authors found that parents of ASD cases were more likely to be exposed to lacquer, varnish, and xylene than parents of controls (McCanlies, Fekedulegn et al. 2012). Another study found high odds of occupational exposures in general in ASD cases compared to controls using expert assessment to estimate occupational exposures based on occupation and industry information from birth certificates (Windham, Sumner et al. 2013). Particular occupational exposures associated with ASD included exhaust or combustion products, and disinfectants (Windham, Sumner et al. 2013). Major limitations of these studies included relatively small sample sizes, concerns with exposure assessment techniques, and lack of accounting for exposure misclassification.

A few studies explored the hypothesis that family members of persons with ASD may have milder forms of autistic characteristics that impacts job selection. Fathers of children with autism or Asperger syndrome were more likely to engage in engineering, accounting, science or medical jobs than fathers of children from a community sample or of children with other disabilities (Baron-Cohen, Wheelwright et al. 1997, Jarrold and Routh 1998, Wheelwright and Baron-Cohen 2001). These publications had many methodological weaknesses, including not accounting for any confounding by socioeconomic factors, lack of diagnostic confirmation, and concern regarding selection bias. In a more recent study adjusting for some demographic covariates, maternal highly technical jobs were associated with ASD in offspring (Windham, Fessel et al. 2009). Another study found increased odds of ASD among fathers in healthcare or accounting or financial analysis jobs compared to non-technical white-collar jobs (Dickerson, Pearson et al. 2014). Thus, while it is possible that parental jobs may differ for children with
ASD compared to children in the general population, the studies published thus far are inconsistent and suffer from methodological weaknesses.

1.6. Methodological concerns in occupational epidemiology

1.6.a. Occupational exposure assessment

Occupational epidemiology may potentially offer some advantages in elucidating risk factors for ASD because the intensity of occupational exposure is generally greater than environmental exposures. Nevertheless, assessment of occupational exposure is challenging. In the literature described above examining occupational exposures in relation to ASD, the researchers used industrial hygiene assessment to estimate occupational exposures. The gold standard exposure assessment technique in occupational epidemiology is personal quantitative measurement of individual employees, but since this is typically unavailable, industrial hygienists have developed methods to qualitatively estimate workplace exposures. One technique is to ask participants to self-report exposures. Measured and self-reported exposures can be highly correlated, but this correlation is highly variable (Teschke, Olshan et al. 2002). Problems with self-report of occupational exposures include that participants are more likely to report agents they can sense and may differentially rate exposure intensity (Teschke, Olshan et al. 2002). Self-reported exposures may also be influenced by recall bias if exposure questionnaires are implemented after case ascertainment (Teschke, Olshan et al. 2002).

Exposures to hazardous materials can also be estimated from job histories. Job histories are generally more reliable than self-reported exposure histories, but are subject to bias for longer periods of recall, shorter job durations, and complicated job histories (Teschke, Olshan et al. 2002). Two approaches are generally utilized to estimate exposures from job histories: expert assessment and job exposure matrices (JEMs). In expert assessment, experts (traditionally industrial hygienists or other trained professionals familiar with workplace exposures), attempt to infer exposure history from information provided from subjects or job histories. Quality of the
expert assessment greatly depends on the experience of the expert (Teschke, Olshan et al. 2002). Another problematic aspect of expert assessment is that the expert may not be familiar with the specific working conditions of the subject (Teschke, Olshan et al. 2002).

Job-exposure matrices have also been developed to link occupations with estimated workplace exposures. At its simplest, a JEM lists occupational categories on one axis and a series of exposures along another axis. Depending on the JEM, the inside cells of the JEM indicate the presence, intensity, and/or probability of each exposure for each job. “Generic” JEMs attempt to estimate exposure to a large number of agents across various jobs in industries. These JEMs can perform somewhat poorly because of variability across jobs and time periods (Teschke, Olshan et al. 2002).

The two previous studies examining occupational exposures in relation to ASD assessed exposure either by parental report (McCanlies, Fekedulegn et al. 2012) and/or expert assessment (McCanlies, Fekedulegn et al. 2012, Windham, Sumner et al. 2013). In this work, we used a JEM that was specifically designed to assess for agents that trigger asthma and combines the matrix approach with some aspects of expert assessment (Le Moual, Kennedy, Le Moual et al. 2000) (Table 1-1). The JEM has been designed by experts in the field of occupational asthma and provides a standardized approach to assessing occupational asthagen exposures. Importantly, we also have some partial knowledge of the sensitivity and specificity of the JEM that we can use to account for exposure misclassification.

1.6.b. Misclassification of occupational exposures

Exposure misclassification is a concern in epidemiologic studies and can result in biased results. Incorrect classification of a binary exposure can bias results both towards and away from the null, so understanding and attempting to account for these discrepancies is important to interpretation of epidemiologic results. While JEMs can be useful tools in estimating exposure, they are far from perfect classifiers (Teschke, Olshan et al. 2002). However, one advantage of
using a JEM over expert assessment is that we may have some understanding of the extent of exposure misclassification. One can implement algebraic “corrections” to account for exposure misclassification, but this requires selection of a specific value for sensitivity and specificity. In the case of the asthma JEM we have a rough idea of the sensitivity and specificity, but do not know the exact values of these probabilities. Marshall (1989) illustrate that estimates can be sensitive to small differences between the guessed and actual misclassification probabilities. In our analysis, we attempt to account for exposure misclassification by the JEM using a Bayesian approach that enables us to assume distributions for the JEM sensitivity and specificity (Gustafson, Le et al. 2001).

1.7. Introduction to occupational asthmagens and biological mechanism

Given the evidence supporting the involvement of the maternal immune system and possible environmental exposures in the etiology of ASD as well as the prenatal window of susceptibility, we sought to examine the association between parental occupational exposures agents that can trigger or exacerbate an asthmatic response (asthmagens) during pregnancy, and ASD in the children. Occupational asthagen exposure has been estimated to account for 10-25% of adult onset asthma (Kogevinas, Zock et al. 2007). Numerous occupational exposures are associated with occupational asthma. In Table 1-2, we present some categories of occupational asthmagens adapted from the asthma-specific JEM (Kennedy, Le Moual et al. 2000) with examples of particular compounds within these categories and some examples of jobs that may be exposed (Bernstein 1999, Kennedy, Le Moual et al. 2000, Quirce and Barranco 2010). Asthmagen exposures occur in a broad array of jobs including nurses, nursing aids, cleaners, carpenters, crop and animal producers, bakers, and hairdressers/beauticians (Kennedy, Le Moual et al. 2000).

Occupational asthmagens are broadly grouped into two different categories based on the size of the particles: high molecular weight (HMW) and low molecular weight (LMW). HMW
allergens generally trigger asthma through an immunoglobulin-E (IgE) mediated mechanism while LMW agents can initiate asthma through either an IgE mechanism or non-IgE cellular mediated process.

Though none of the previous ASD air pollutant and occupational epidemiology specifically focused on asthmagen exposures, some looked at agents that happen to trigger or exacerbate asthma (Windham, Zhang et al. 2006, Kalkbrenner, Daniels et al. 2010, McCanlies, Fekedulegn et al. 2012, Roberts, Lyall et al. 2013, Windham, Sumner et al. 2013, von Ehrenstein, Aralis et al. 2014). Air pollutant asthmagens include certain metals (cadmium, chromium, cobalt, manganese, nickel), aldehydes, styrene and ethylene oxide (Leikauf 2002). Two studies reported associations between air pollutant metal exposures and ASD (Windham, Zhang et al. 2006, Roberts, Lyall et al. 2013) while two other studies reported no association (Kalkbrenner, Daniels et al. 2010, von Ehrenstein, Aralis et al. 2014). Von Ehrenstein et al. (2014) linked ASD with air pollutant exposure to acetaldehyde and formaldehydes. McCanlies et al. (2012) did not find an association between parental occupational exposure to metals or disinfectants and ASD, but Windham et al. (2013) reported an association between maternal disinfectant exposures and ASD.

We hypothesized that there could be two different biological mechanisms that link occupational asthmagen exposures to ASD (Figure 1-1). First, maternal exposure to occupational asthmagens may result in an immune response that elevates production of maternal cytokines that in turn may impact neurodevelopment. Second, maternal occupational asthmagen exposure may cause active maternal asthma or asthmatic symptoms that may result in reduced fetal oxygenation and influence the developing nervous system. The mother may be exposed to an occupational asthmagen in her workplace or to an occupational asthmagen that the father takes home from his workplace (Krakowiak, Szulc et al. 1999, Krop, Doekes et al. 2007, Tagiyeva, Anua et al. 2012). We describe the two hypotheses in greater detail below.

In the first hypothesized mechanism, we propose that maternal immune activity in the mother, represented by increased production of inflammatory cytokines, alters neurodevelopment
of the child. This hypothesis has been proposed in the literature, and is supported by animal studies revealing that immune activity during pregnancy can impact offspring brain development and behavior (Meyer, Feldon et al. 2009, Hsiao 2013). Allergens may generate a maternal inflammatory response by either an IgE-mediated or cell mediated immune response. Antigen-promoting cells, called dendritic cells, that are located in the airway epithelium can take up allergens. The dendritic cell is activated upon binding to the allergen and migrates to lymph nodes where naïve T-cells are presented with the allergen. Allergic individuals will skew towards a TH2 phenotype, which is marked by expression of TH2 cytokines, such as IL-4 and IL-13. Production of these TH2 cytokines leads to the production of allergen specific IgE antibodies by B-lymphocytes (Paul 2008). IgE antibodies can bind to receptors on mast cells. When an individual is subsequently exposed to the same allergen, the binding of the allergen to the IgE on the mast cell triggers the release of prostaglandins, histamines, and various cytokines, such as interleukin (IL)-4, IL-5, IL-6, IL-13, granulocyte-macrophage colony-stimulating factor (GM-CSF), and tumor necrosis factor α (TNF α) (Amin 2012). As mentioned above, some responses to asthmagens do not appear to be mediated through an adaptive immunity pathway mediated by IgE. In these cases, cells in the airway epithelium can produce certain cytokines in response to allergens that can recruit mast cells, eosinophils, basophils, and cells from the adaptive immune system to release TH2 cytokines (Kim, DeKruyff et al. 2010).

This maternal immune activity may trigger altered neurological or immunological changes that may impact the developing fetus. Certain maternal cytokines, such as IL-6, may cross the placenta while others may indirectly trigger cytokine responses in the placenta or fetus (Zaretsky, Alexander et al. 2004, Meyer, Feldon et al. 2009, Parker-Athill and Tan 2010, Burd, Balakrishnan et al. 2012). Cytokines can bind to receptors on neurons, microglia, and astrocytes, and influence growth and development of neurons, neuronal path-finding, neural migration, and synapse formation (Dantzer, O'Connor et al. 2008, Parker-Athill and Tan 2010, Buehler 2011).
Pro-inflammatory cytokines, such as IL-6, can initiate transcription of genes implicated in neural stem cell proliferation and maintenance (Parker-Athill and Tan 2010). Under this first proposed mechanism potentially linking maternal occupational asthagen exposure to ASD risk in the children through immune activity, the biological mechanism is not at all mediated through actual asthma symptoms. Individuals can immunologically respond to asthagens without presenting overt asthma symptoms (Rom 2007).

In the second hypothesized mechanism, we posit that active asthma during pregnancy, following exposure to occupational asthagens, could lead to altered neurodevelopment as a result of reduced fetal oxygenation. Asthma is characterized by airway narrowing, airway hyper-responsiveness, and airway inflammation (Bernstein 1999). Uncontrolled or acute asthma may lead to maternal hypoxia, which in turn can result in reduced oxygen availability to the fetus (Rocklin 2011). Abnormalities in the vascular function of the placenta have also been noted in asthmatic women (Clifton, Giles et al. 2001). This could also suggest that the placental transfer of nutrients to the fetus could also be altered in asthmatic compared to non-asthmatic pregnant women (Rocklin 2011).

There is some evidence suggesting a link between fetal hypoxia and ASD. A meta-analysis found elevated risk of low birth weight, small for gestational age and preterm birth in pregnant women with asthma (Murphy, Namazy et al. 2011), factors that have also been found to be associated with ASD (Gardener, Spiegelman et al. 2011). Gardner et al. (2011) also suggest that fetal hypoxia may play a role in ASD given that many of the risk factors associated with ASD in the meta-analysis, including growth retardation, low Apgar score, respiratory distress, fetal distress, and Cesarean section delivery, may be downstream outcomes of hypoxia. Only one study examined association between direct measure of fetal hypoxia, measured by pH testing, and reported an association with ASD in males only (Burstyn, Wang et al. 2011). Additionally, fetal hypoxia has been linked to brain abnormalities in schizophrenic patients and non-schizophrenic
relatives, which suggests that fetal hypoxia can impact neurodevelopment among people with certain genetic predispositions (Cannon, van Erp et al. 2002).
1.8. Specific Aims

The overall goal of this work was to examine the association between prenatal parental exposure to occupational asthmagens and risk of ASD in the children. We evaluated this hypothesis using data from two different study samples. The first study sample consists of children enrolled in the Study to Explore Early Development (SEED) (Chapter 2). This population-based case control study contains three study groups: an ASD case group, a general population control group, and a group with non-ASD developmental delays. In the second study, we established a population-based case-control study of ASD cases and controls selected from children born in Denmark from 1993-2007 using data from the Danish Registers (Chapter 3). These study samples will be further explained and compared in subsequent chapters. Briefly, some strengths of the SEED study include detailed information on employment history, standardized ascertainment of ASD cases, and two comparison groups. The strengths of the Danish study include large sample size and little concern of selection bias given that the study population was selected from national Danish Registers. The final goal of this research was to illustrate correcting for exposure misclassification in these analyses using a Bayesian approach (Gustafson, Le et al. 2001, Luta, Ford et al. 2013) (Chapter 4).
1.9. References


chemicals and reciprocal social, repetitive, and stereotypic behaviors in 4- and 5-year-old children: the HOME study. " Environmental health perspectives 122(5): 513-520.


Table 1-1: Exposure axis of the asthma-specific job exposure matrix.

<table>
<thead>
<tr>
<th>Asthmagen Category</th>
<th>Subgroups</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td>High Molecular Weight (HMW)</td>
<td>Animal antigens</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fish/shellfish antigens</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flour associated antigens</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Latex antigens</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other plant associated antigens</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mite and insect antigens</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biological enzymes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bioaerosol antigens</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug antigens</td>
</tr>
<tr>
<td></td>
<td>Low Molecular Weight (LMW)</td>
<td>Highly reactive chemicals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Isocyanates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cleaning/disinfectant products</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wood dusts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metal and metal fume antigens</td>
</tr>
<tr>
<td></td>
<td>Mixed Environment</td>
<td>Metal-working fluids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Textile production</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Agricultural antigens</td>
</tr>
<tr>
<td></td>
<td>Irritants</td>
<td>Irritants</td>
</tr>
<tr>
<td>Low Risk</td>
<td>Exposure to asthmagens but not</td>
<td>Combustion particles/fumes</td>
</tr>
<tr>
<td></td>
<td>enough exposure for OA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Respiratory hazards not</td>
<td>Environmental tobacco smoke</td>
</tr>
<tr>
<td></td>
<td>associated with OA</td>
<td>Possible exposure to irritant gases and fumes</td>
</tr>
<tr>
<td>Non-exposed</td>
<td>Low risk for exposure OA or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>respiratory disease</td>
<td></td>
</tr>
<tr>
<td>Re-evaluation</td>
<td>Confidence</td>
<td>Exposures are uncertain even after checking</td>
</tr>
<tr>
<td></td>
<td>Verification</td>
<td>Check exposures: check an exposure group code</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Check job code: ISCO job code needs to be checked</td>
</tr>
<tr>
<td></td>
<td>Comments</td>
<td>Instructions for coding and exposure assignment during re-evaluation</td>
</tr>
</tbody>
</table>

Adapted from Kennedy et al 2000 and information available on the asthma-specific JEM website (http://cesp.vjf.inserm.fr/asthmajem/matrixtable.htm)
Table 1-2: Occupational asthmagen categories with examples of specific agents and jobs with exposures.

<table>
<thead>
<tr>
<th>Categories of asthmagens</th>
<th>Example Agents</th>
<th>Exposed occupations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal antigens</td>
<td>Laboratory animal</td>
<td>Laboratory workers</td>
</tr>
<tr>
<td></td>
<td>Cow dander</td>
<td>Agricultural workers</td>
</tr>
<tr>
<td></td>
<td>Egg protein</td>
<td>Egg producers</td>
</tr>
<tr>
<td>Fish/shellfish antigens</td>
<td>Crab</td>
<td>Crab processors</td>
</tr>
<tr>
<td></td>
<td>Prawn</td>
<td>Prawn processors</td>
</tr>
<tr>
<td></td>
<td>Hoya</td>
<td>Oyster farm</td>
</tr>
<tr>
<td></td>
<td>Salmon</td>
<td>Processing plant</td>
</tr>
<tr>
<td>Flour associated antigens</td>
<td>Wheat, rye and soya flour</td>
<td>Bakers, millers</td>
</tr>
<tr>
<td>Latex antigens</td>
<td>Natural rubber latex</td>
<td>Hospital workers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glove manufacture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Doll manufacture</td>
</tr>
<tr>
<td>Other plant associated antigens</td>
<td>Coffee bean</td>
<td>Food processor</td>
</tr>
<tr>
<td>Mite and insect antigens</td>
<td>Grain mite</td>
<td>Farmers</td>
</tr>
<tr>
<td></td>
<td>Fruit fly</td>
<td>Laboratory workers</td>
</tr>
<tr>
<td></td>
<td>Larva of silkworm</td>
<td>Silk farming</td>
</tr>
<tr>
<td>Biological enzymes</td>
<td>B. subtilis</td>
<td>Detergent industry</td>
</tr>
<tr>
<td></td>
<td>Papain</td>
<td>Pharmaceutical</td>
</tr>
<tr>
<td></td>
<td>Fungal amylase</td>
<td>Bakers</td>
</tr>
<tr>
<td>Bioaerosol antigens</td>
<td>Mold</td>
<td>Technician</td>
</tr>
<tr>
<td></td>
<td>Plasmopara viticolo</td>
<td>Agricultural</td>
</tr>
<tr>
<td>Drug antigens</td>
<td>Pharmaceuticals</td>
<td>Nursing/health personnel</td>
</tr>
<tr>
<td>Highly reactive chemicals</td>
<td>Reactive dyes</td>
<td>Textile industry</td>
</tr>
<tr>
<td></td>
<td>Anhydrides</td>
<td>Plastics, resin production</td>
</tr>
<tr>
<td></td>
<td>Amines</td>
<td>Chemist</td>
</tr>
<tr>
<td></td>
<td>Biocides</td>
<td>Endoscopy staff</td>
</tr>
<tr>
<td>Isocyanates</td>
<td>Toluene diisocyanate</td>
<td>Polyurethane, plastics</td>
</tr>
<tr>
<td></td>
<td>Combinations of diisocyanates</td>
<td></td>
</tr>
<tr>
<td>Cleaning/disinfectant products</td>
<td>Disinfectants</td>
<td>Cleaning</td>
</tr>
<tr>
<td></td>
<td>Aldehydes</td>
<td>Medical facilities</td>
</tr>
<tr>
<td></td>
<td>Quaternary ammonium</td>
<td>Cleaning</td>
</tr>
<tr>
<td>Wood dusts</td>
<td>Western red cedar</td>
<td>Carpenterly, sawmill</td>
</tr>
<tr>
<td>Metal and metal fume antigens</td>
<td>Platinum</td>
<td>Platinum refinery</td>
</tr>
<tr>
<td></td>
<td>Nickel</td>
<td>Metal plating</td>
</tr>
<tr>
<td></td>
<td>Cobalt</td>
<td>Diamond polisher</td>
</tr>
<tr>
<td>Irritants</td>
<td>Irritant gases or fumes</td>
<td>Firefighters</td>
</tr>
</tbody>
</table>

This is not a comprehensive list but serves to illustrate important examples. This list of categories is based on some of the categories from the asthma specific job exposure matrix created by Kennedy et al. 2000 and the list of example agents and exposed occupations from Bernstein 1999. This table is meant to illustrate the type of occupational agents that can trigger asthma and some examples of exposed occupations, but do not necessarily represent how Kennedy et al decided to categorize specific jobs in the asthma specific job exposure matrix.
According to the first proposed mechanism, maternal occupational asthmagen exposure triggers a maternal immune response that results in altered cytokine levels in the fetal central nervous system resulting in altered neural cell differentiation and organization leading to ASD. In the second proposed mechanism, one symptom of active maternal asthma is airway narrowing which can result in reduced fetal oxygen and affect neurodevelopment.
Chapter 2. Maternal exposure to occupational asthmagens and risk of autism spectrum disorder in the Study to Explore Early Development
2.1. Abstract

Background: Maternal immune activity and environmental exposures during the pregnancy period have both been linked to autism spectrum disorder (ASD). Yet, few studies have examined occupational exposures that are known to trigger immune response in relation to ASD. We examined the association between maternal occupational exposure to asthmagens, agents that can trigger an asthmatic immune response, and risk of ASD in the children.

Methods: Our analytic sample consisted of 437 ASD cases, 660 general population (POP) controls and 628 children with non-ASD developmental delays (DD) from the Study to Explore Early Development (SEED) study, whose mothers were employed during the pregnancy. We coded maternal jobs according to the International Standard Classification of Occupations 1988 (ISCO-88). Maternal occupational asthmagen exposure was assessed by linking the ISCO-88 codes to an asthma-specific job-exposure matrix.

Results: The odds ratio for maternal occupational asthmagen exposure comparing ASD to POP controls was 1.32 (95% CI: 0.90 - 1.94) and comparing DD to POP controls was 0.76 (95% CI: 0.54 - 1.08), adjusting for sociodemographic factors, smoking, and certain maternal health conditions.

Conclusion: Maternal workplace asthmagen exposure was not marginally associated with ASD. This conclusion does not preclude the involvement of the maternal immune system in ASD or detectable effect in a larger study.
2.2. Introduction

There is some evidence linking maternal asthma and allergy (Croen, Grether et al. 2005) and maternal immune conditions in general (Comi et al. 1999; Keil et al. 2010; Sweeten et al. 2003) to increased risk of autism spectrum disorder (ASD). However, results across studies are inconsistent (Micali, Chakrabarti et al. 2004, Croen, Grether et al. 2005, Mouridsen, Rich et al. 2007, Lyall, Ashwood et al. 2014) and the mechanism by which maternal immune conditions are related to ASD is unclear. Epidemiologic studies also implicate environmental and occupational exposures, including those capable of causing asthma and immune reactions in risk of ASD (Windham, Zhang et al. 2006, Roberts, English et al. 2007, Kalkbrenner, Daniels et al. 2010, Volk, Hertz-Picciotto et al. 2011, McCance, Fekedulegn et al. 2012, Becerra, Wilhelm et al. 2013, Roberts, Lyall et al. 2013, Volk, Lurmann et al. 2013, Windham, Sumner et al. 2013, Raz, Roberts et al. 2014, von Ehrenstein, Aralis et al. 2014).

Asthmagens are agents that are known to trigger or exacerbate an asthmatic response. Occupational exposure to asthmagens occur in a wide variety of job groups, including nurses, nursing aids, cleaners, carpenters, crop and animal producers, bakers, hairdressers, and beauticians. Some asthmagens cause asthma through immunologic pathways whereas others act as irritants that result in airway damage. It is suspected that both of these mechanisms ultimately lead to inflammatory responses. We hypothesized that two possible mechanisms might link occupational asthmagen exposure to ASD in the children: (1) mediated through production of maternal cytokines involved in asthmatic/allergic response and (2) mediated through reduced fetal oxygenation.

Some air pollutants, including certain metals (cadmium, chromium, cobalt, manganese, nickel), aldehydes, styrene, and ethylene oxide, are asthmagens (Leikauf 2002). Air pollutant exposures to acetaldehyde, formaldehyde, styrene, and metals have been linked to ASD, though the associations have not been consistently reported across studies (Windham, Zhang et al. 2006, Kalkbrenner, Daniels et al. 2010, Roberts, Lyall et al. 2013, von Ehrenstein, Aralis et al. 2014).
A limitation of these studies is that exposure assessment is not based on personal exposures but is estimated based on census tract level modeled air pollutant concentrations (Windham, Zhang et al. 2006, Kalkbrenner, Daniels et al. 2010, Roberts, Lyall et al. 2013) or measured pollutant exposures from air monitors closest to address at birth (von Ehrenstein, Aralis et al. 2014). Occupational exposures are generally thought to be of greater intensity than environmental exposures and can be estimated on an individual level. Two recent epidemiologic studies examined occupational exposures in relation to ASD, though neither focused specifically on asthmagen exposures (McCanlies, Fekedulegn et al. 2012, Windham, Sumner et al. 2013). Consequently, there are few studies examining exposure to toxicant agents that can trigger maternal immune response in relation to ASD, despite compelling mechanistic evidence that make such an association plausible (see Chapter 1).

We sought to examine whether or not maternal exposure to occupational asthmagens during the pregnancy influences risk of ASD in the children in a population-based case-control study, the Study to Explore Early Development (SEED). Croen et al. (in preparation) find some evidence of an association between asthma and ASD, but no evidence of a link between allergy and ASD. Since the effect of asthmagen exposure may differ depending on whether or not the mother has a history of asthma or allergy, we examined the association between occupational asthmagens and ASD among mothers with and without these conditions. Furthermore, because the prevalence of ASD and poor birth outcomes is higher in boys than girls (Newschaffer, Croen et al. 2007, Melamed, Yogeve et al. 2010), we also examined child sex by occupational asthmagen exposure interactions. Although our work does not evaluate mechanisms by which occupational asthmagens may cause ASD (immune-mediated or hypoxic), assessment of overall the association would contribute to understanding of modifiable risk factors in ASD.
2.3. Methods

2.3.a. Study population

The Study to Explore Early Development is a multi-site case-control study with population-based ascertainment. The study was designed to examine phenotypes and co-morbidities related to ASD as well as genetic and environmental risk factors. The study consists of three study groups: cases who meet the study criteria for ASD, typically developing children (POP), and children with non-ASD developmental delays (DD). The SEED has study catchment areas in six different states: California, Colorado, Georgia, Maryland, North Carolina, and Pennsylvania. Eligible children were born in one of the catchment areas between September 1, 2003 and August 31, 2006. Children were required to reside in the catchment area at the time of initial contact and had to live with a knowledgeable caregiver who could communicate in English (or in English or Spanish in California or Colorado.) At the completion of the developmental clinical assessments, the children were between 30 and 68 months of age (Schendel, Diguiseppi et al. 2012).

Children with possible ASD and DDs were ascertained through multiple sources providing services for children with developmental disorders including hospitals, individual providers, clinics, and education and intervention programs. Parents with a child with an ASD or DD diagnosis could also have contacted the study directly to enroll. General population controls (POP) were ascertained through random sampling of vital records in the catchment areas (Schendel, Diguiseppi et al. 2012). Institutional review boards at each study site and at the Centers for Disease Control and Prevention (CDC) approved the SEED study.

2.3.b. Occupational exposure assessment

Information on maternal occupational history was collected during a caregiver interview (CGI) administered as a computer assisted telephone interview shortly after enrollment in the study. Mothers were asked to report jobs held for one month or more in which she worked at
least ten hours per week from three months prior to the start of the index pregnancy until the child was born or she stopped breastfeeding. For each job meeting these criteria, mothers reported job title, employer, location, start and stop of work as month and year, hours per week, type of business, and main duties.

Maternal jobs were coded according to the International Labor Organization’s International Standard Classification of Occupations 1988 (ISCO-88) (International Labor Organization 1991) based on job title, task and industry information. Job coding was completed by ABS. A second investigator (IB) reviewed the ISCO codes and job texts for 370 of the 2708 jobs coded. Of the 370 jobs reviewed by IB, 109 jobs were manually flagged for secondary review and an additional 261 (10% of the remaining jobs) were randomly flagged for review. All discrepancies were resolved by reaching consensus and applied to correct the rest of the coding.

We used an asthma-specific job-exposure matrix (JEM) (Kennedy, Le Moual et al. 2000) to estimate maternal occupational exposure to asthmagens during the pregnancy. The asthma-specific JEM uses ISCO job codes to estimate occupational asthmagen exposure, classifying each job as “yes” or “no” as to whether or not the job has a high probability of exposure to an occupational asthmagen. The JEM was designed to favor specificity over sensitivity in exposure classification: when in doubt, a job was assessed as unexposed. The exposure axis of the JEM consists of the following four subgroups of asthmagens with smaller classes of agents nested within: (1) high molecular weight agents (animals, fish, flour, plants, mites, enzymes, latex, bioaerosols, pharmaceuticals), (2) low molecular weight agents (highly reactive chemicals, isocyanates, cleaning/disinfecting products, antigenetic wood dusts, and metals, (3) mixed environments (metal working fluids, textile, agricultural antigens), and (4) irritants. We completed a two-step expert review process recommended by the authors of the JEM in which flagged job codes and string text job descriptions are reviewed against comments in the JEM. This two-step review process consists of (a) reviewing selected ISCO job codes for possible recoding and (b) reviewing selected jobs for possible exposure recoding. These steps were first
completed by one investigator (ABS) and then reviewed by a second investigator (IB). All job coding and asthmagen exposure assessment was completed without knowledge of case or control status.

In order to determine whether or not a job overlapped with the pregnancy, we estimated the approximate start of the pregnancy by subtracting the mean gestational age for all children enrolled in SEED (265 days) from the child’s date of birth. We assumed that jobs started on the first day of the month and ended on the last day of the month.

2.3.c. Covariates

Information on potential confounders was obtained through a combination of interviews, questionnaires, and birth certificates. Self-reported maternal race, maternal ethnicity (Hispanic or non-Hispanic), highest year of completed maternal education, total current household income, and parity were collected during the CGI. Mothers were also asked whether or not she smoked cigarettes during the pregnancy and if so, how many cigarettes per day were smoked during each month of the pregnancy. For this analysis, we defined an active smoker as a mother who either smoked at least one cigarette per day for at least one month of the pregnancy, or a mother who smoked less than one cigarette per day for at least three months of the pregnancy. Gestational age was obtained from birth certificates.

The maternal medical history questionnaire and the family autoimmune disease survey, two questionnaires mailed to study participants, were used in concert with the CGI to create variables related to maternal medical conditions. Mothers were defined as having a history of psychiatric conditions (attention deficit hyperactivity disorder, anxiety disorder, Asperger’s syndrome, autism, bipolar disorder, childhood disintegrative disorder, depression, obsessive compulsive disorder, personality disorder, pervasive developmental disorder, schizophrenia, self-injuring behavior, and suicide attempt) if she either reported treatment/medication usage during the pregnancy for a psychiatric condition during the CGI or reported a history of a condition on
the maternal medical history form. Maternal allergy prior to the birth of the child was based on self-reported information on conditions from the maternal medical history and medication for allergic conditions from the CGI, and maternal asthma prior to birth of the child was derived from responses to the autoimmune disease survey and report of medication use for asthma from the CGI.

2.3.d. Outcome assessment

Primary caregivers completed the Social Communications Questionnaire, a screener for autism spectrum disorder, during the study invitation phone call. If the SCQ score was above 11, the child had previously received an ASD diagnosis, or a clinician suspected an ASD during the clinic visit, the child was asked to complete a full ASD evaluation that included the Autism Diagnostic Observation Study (ADOS), the Autism Diagnostic Interview Revised (ADI-R), and the Mullen Scales of Early Learning (MSEL). For children completing the full ASD evaluation with both the ADOS and ADI-R, a clinician from the study also completed a version of the Ohio State University Autism Rating Scale (OARS) modified for SEED (Wiggins, Reynolds et al. 2014).

Relaxed ADI-R criteria were utilized to resolve discordant results from the ADOS and the ADI-R. These relaxed ADI-R criteria were: (a) the child met criteria on the social domain and within two points on the communication domain, (b) the child met criteria on the communication domain and within two points on the social domain, or (c) the child met the cutoff score on the social domain and at least two points were noted on the behavioral domain. For children with a mental age of 24 months or higher, a child was classified as having an ASD if s/he (a) met the revised ADOS diagnostic algorithms ASD cutoff score and the ADI-R autism cutoff score, or (b) met the revised ADOS diagnostic algorithms ASD cutoff score and met one of the three relaxed criteria of the ADI-R explained above. If children had a mental age of less than 24 months, the child met the ASD criteria if s/he (a) met the revised ADOS diagnostic algorithms
ASD cutoff score, met the ADI-R autism cutoff score, and was classified as having an ASD by best clinical judgment using the revised OARS, or (b) met the revised ADOS diagnostic algorithms ASD cutoff score, met one of the three relaxed ADI-R criteria, and was classified as having an ASD by best clinical judgment on the revised OARS. A child received an incomplete classification, if the full ASD developmental evaluation was requested but not completed, or if the child had a mental age of less than 24 months and the clinician did not classify the child as having an ASD by the OARS (Wiggins, Reynolds et al. 2014).

Children were classified as DD if they were ascertained through a clinical or educational setting but either did not meet the SCQ screening criteria for ASD or did not meet criteria of ASD through the full developmental assessment work-up.

POP children were those that were recruited through random sampling of vital records, and either did not screen positive for a possible ASD using the SCQ or did not meet ASD criteria through the developmental assessments (Wiggins, Reynolds et al. 2014).

We defined intellectual disability based on results from the Mullen Scales of Early Learning, where a child was classified as having an intellectual disability if s/he had a Mullen Early Learning Composite Standard Score of less than 70.

2.3.e. Statistical analysis

The analysis was restricted to children who were ever enrolled in the SEED study whose mothers answered at least a portion of the occupational section of the caregiver interview (n=2991). We excluded children with an incomplete classification (n=247), such that all children in the analysis were either in the ASD, DD or POP group. Only one child per family was included in the analytic population. Children of mothers who were unemployed during the pregnancy interval or where timing could not be determined were not considered in further analyses.
We compared frequencies of demographic, socioeconomic, and maternal health characteristics in mothers exposed to occupational asthmagens during pregnancy to mothers not exposed to occupational asthmagens during pregnancy. We used logistic regression to estimate odds ratios of occupational asthmagen exposure comparing ASD and DD cases to population controls. Logistic regression models were fit for exposure categories in which more than 50 mothers across the three study groups were exposed: any asthmagen, any high molecular weight asthmagen, high molecular weight latex antigen, any low molecular weight asthmagen, low molecular weight highly reactive chemicals, and low molecular weight cleaning and disinfectant products. We also fit multiple logistic regression models to estimate these associations, adjusting for parity (1, 2, 3 or greater), child’s sex, maternal race (white, black, Asian, Hispanic, multi-racial/other), maternal education (less than high school, high school, some college/trade, bachelor’s degree, advanced degree), current household income at time of questionnaire (<$30,000, $30,000-70,000, $70,000-110,000, >$110,000), maternal age at birth (continuous), maternal psychiatric condition history (yes, no), active smoking during pregnancy (yes, no), gestational age (<35 weeks, 35-<37 weeks, ≥37 weeks), maternal allergy prior to child’s delivery (yes, no), and maternal asthma prior to child’s delivery (yes, no).

We hypothesized that the association between occupational asthmagen exposure and ASD might differ depending on whether or not the mother had a history of asthma or allergy. As a result, we fit two additional logistic regression models, one including an interaction term between occupational asthmagen exposure and self-reported history of maternal asthma prior to the child’s birth and a second including an interaction between occupational asthmagen exposure and self-reported history of maternal allergy prior to the birth of the index child. Since other studies suggest that the effect of environmental exposures on neurodevelopment may differ by the child’s sex, we also fit a logistic regression model that included an interaction term between maternal occupational asthmagen exposure and child’s sex. We estimated the independent and
joint effects of occupational asthmagen exposure and either maternal asthma, maternal allergy, or child’s sex.

Since risk factors for ASD may differ by subtype of ASD, we also examined whether maternal occupational asthmagen exposure differed for ASD cases with and without intellectual disability compared to population controls using logistic regression. ASD children missing a Mullen Early Learning Composite score (n=6) were excluded from this analysis.

2.4. Results

Of the 2702 children enrolled in SEED with an ASD, DD, or POP classification and with some occupational interview data, 744 (27.5%) mothers did not report a job that overlapped with the pregnancy. For another 39 (1.4%) mothers, we were unable to determine if there was a job that overlapped with the pregnancy (e.g. the start or end date of the job was missing, or the job start date was after the job end date). Thus, we restricted our analysis to the remaining 1,919 (71.0%) children whose mothers reported a job that we were relatively certain overlapped with the pregnancy.

Among these, the average number of jobs per mom was 1.14, with 1,684 (87.8%) of these moms reporting only one job during the pregnancy. Mothers of population controls were more likely to report having a job that overlapped with the pregnancy compared to the mothers of the children with an ASD or DD (75.2% of POP mothers versus 69.2% of ASD mothers and 68.4% of DD mothers). Women with higher parity, lower education, lower income, younger age at the time of birth of the child, and of Asian or Hispanic race or ethnicity were less likely to be employed during the pregnancy (Table I-1 and Table I-2).

Among the 1,725 children with employed mothers and complete covariate information, we estimated that 243 (14.1%) mothers had an occupational exposure to an asthmagen during the pregnancy. The most common asthmagen exposed jobs during pregnancy were nursing and midwifery professionals, institution-based personal care workers, hairdressers/beauticians,
medical assistants, and veterinary assistants. Women with higher parity, lower levels of education, lower current household income and lower maternal age at the time of the index child’s birth were more likely to work in a job exposed to at least one occupational asthmagen (Table 2-1). White and Asian mothers were less likely to be exposed to occupational asthmagens than women who classified themselves as Black, Hispanic, or multiracial/other. The prevalence of occupational asthmagen exposure in mothers with a self-reported history of allergy was 12.4% compared to 15.3% in those without a self-reported history of allergy (Table 2-2).

Among women employed during pregnancy, we estimate 92 (13.9%) mothers of population controls, 75 (17.2%) mothers of ASD cases, and 76 (12.1%) mothers of DDs were exposed to any type of occupational asthmagen during the pregnancy period (Table 2-3). The most common asthmagen exposure groups were latex antigens, highly reactive agents, and cleaning and disinfectant products. We did not see an elevated odds of maternal occupational asthmagen exposure comparing ASD to POP controls (adjusted OR (aOR)= 1.32, 95% Confidence Interval: 0.90 - 1.94) or comparing DD to POP controls (aOR= 0.76, 95% CI: 0.54 - 1.08). The direction of the association was generally positive comparing ASD cases to POP controls, but in an inverse direction comparing DD cases to POP controls. The odds ratios generally followed a similar pattern for the subgroups of occupational asthmagens.

In models that included interaction terms between maternal allergy and maternal occupational asthmagen exposure, we found that the joint effect of occupational asthmagen exposure and maternal allergy on ASD risk was higher than would be expected based on the independent effects alone (Table 2-4). The association between occupational asthmagen exposure and ASD in the child was stronger among mothers with a history of allergy (aOR: 1.87, 95% CI: 1.01 – 3.48) as compared to women without a history of allergy (aOR: 1.06, 95% CI: 0.65 – 1.73). We did not see any evidence for an interaction between maternal occupational asthmagen exposure and maternal history of asthma. The association between occupational
asthmagen exposure and ASD was slightly stronger for female children relative to male children, though there were relatively few females in the study population.

The adjusted odds ratios and 95% confidence intervals for occupational asthmagen exposure comparing ASD cases without intellectual disability to population controls and ASD cases with intellectual disability to controls were 1.22 (0.70 – 2.14) and 1.39 (0.90 – 2.16), respectively (Table 2-5).

2.5. Discussion

We did not observe an overall association between maternal occupational exposure to any asthmagen and ASD. We note that even in the absence of an association between maternal occupational asthmagen exposure and ASD, there could still be a link between maternal asthma as a condition and ASD. Asthma and ASD could share common genetic underpinnings, or another health factor that is correlated with both asthma and ASD, such as treatment for asthma, may connect them. Thus, these results do not preclude involvement of the maternal immune system in ASD, but may suggest that the particular biological response triggered by asthmagens is not important in the etiology of ASD.

These results could reflect the influence of healthy worker effects. However, the potential for this explanation in these data is ambivalent. If occupational asthmagen exposures are truly causing asthma, we might expect to see an association between occupational asthmagen exposure and maternal self-reported asthma prior to delivery of the child. We do not see such an association, but this is not surprising in a study of this size given that occupational asthmagen exposure only accounts for only 10-25% of adult onset asthma (Kogevinas, Zock et al. 2007). It is also possible that women with allergies or asthma may avoid jobs with asthmagen exposure, part of a phenomenon known in the literature as the healthy worker effect (HWE). If maternal allergy or asthma is associated with ASD and women with asthma or allergy avoid jobs with asthmagen exposure, then we may underestimate the occupational asthmagen to ASD association.
We do see some indication of reduced likelihood of maternal occupational asthmagen exposure in women with a history of maternal allergy, but not asthma, prior to the child’s birth, but it is not clear if this is an artifact of small numbers, confounding, or suggests that some elements of the HWE could be at play. Though we do see a decreased likelihood of occupational asthmagen exposure in women with allergies, we are also unable to determine if the allergies actually preceded the employment. We also found that occupational asthmagen exposure was associated with lower socioeconomic status, which may suggest that women with asthmagen exposed jobs could have less job agency and may need to work in certain positions regardless of health conditions. Thus, the impact of HWE is difficult to predict on the basis of available data.

A few studies examined air pollutants that can induce or exacerbate asthma, such as metals, aldehydes, styrene and ethylene oxide, in relation to ASD. The results from these analyses are inconsistent with two studies reporting no association between asthmagenic metals and ASD (Kalkbrenner, Daniels et al. 2010, von Ehrenstein, Aralis et al. 2014), and two studies finding a positive associations between ASD and hazardous air pollutant metal exposures (Windham, Zhang et al. 2006, Roberts, Lyall et al. 2013). One study also linked ASD to air pollutant exposure to acetaldehyde and formaldehyde (von Ehrenstein, Aralis et al. 2014). We did not have a large enough sample size to look at most individual categories of occupational asthmagens but we did not see an association between occupational asthmagen exposures in general and ASD.

Two previous occupational studies examined certain categories of asthmagenic agents in relation to ASD. Windham et al (2013) reported an association between maternal occupational exposure to disinfectants and ASD, whereas McCanlies et al (2012) do not find links between parental occupational exposure to metals and disinfectants and ASD. However, Windham et al (2013) only had 9 cases and 6 controls that were exposed to disinfectants, so there is concern that results may be sensitive to these small sample sizes. In our study, we estimated that 17 ASD case mothers and 21 population controls mothers were exposed to cleaning and disinfectant products.
In addition, in the Windham et al (2013) study, occupation information of “usual” occupation and industry was obtained from birth certificates. In contrast, we were able to base our exposure assessment on occupational histories from detailed questionnaires.

Another important difference between our study and these earlier studies is that we used an asthma-specific JEM while the two earlier studies used expert assessment to assess exposure. While both approaches have limitations, expert assessment is hampered by the degree of detail in the occupational histories and the familiarity of the experts with particular occupational settings (Teschke, Olshan et al. 2002). We utilized a job-exposure matrix to estimate occupational asthmagen exposure that has been used to demonstrate associations between asthmagen exposures in the workplace and asthma (Le Moual, Kennedy et al. 2004, Kogevinas, Zock et al. 2007, Beach, Burstyn et al. 2012). Unfortunately, exposures assessed by a JEM could be misclassified for a variety of reasons, including the assumption that individuals with the same job codes have the same exposure. The JEM also assumes that individuals are either exposed or unexposed to an agent, but in reality there is a gradation in the intensity of exposure. An advantage of this particular asthma JEM is that it includes an expert review step in which exposure codes are reviewed based on suggestions from the JEM authors. Despite this advantage over more general JEMs, prior knowledge suggests that the sensitivity of the JEM may be in the range of 0.4 with specificity close to 1 (Liu, Gustafson et al. 2009, Beach, Burstyn et al. 2012). Given the low sensitivity of the JEM, it is important to consider that exposure misclassification may impact study inference. We describe Bayesian methods to correct for exposure misclassification in this data and illustrate the impact on the results in a subsequent chapter (Chapter 4).

Asthma is highly genetic in nature with some individuals showing genetic susceptibility to allergic responses to agents that do not induce responses in other individuals (London and Romieu 2009). Given differential susceptibility to asthmagenic agents, we looked to see if the association between asthmagens and ASD differed in those with and without a history of maternal
asthma or allergy. We found that the positive association between maternal occupational asthmagen exposure and ASD was largely driven by mothers with a history of maternal allergy prior to the child’s delivery. This could suggest a link between asthmagen exposure and ASD among allergic women, but we caution against over-interpreting these results given the small sample size and overlapping confidence intervals, especially since we do not see any suggestion of the asthmagen affect being any stronger in asthmatic compared to non-asthmatic mothers. Additionally, our maternal asthma and allergy variables represent a history of asthma or allergy, so this does not necessarily indicate that these conditions were active during pregnancy nor are we sure that asthma or allergic conditions preceded occupational asthmagen exposure. History of maternal asthma or allergy is not a proxy for genetic susceptibility to asthmagens. Without consideration of genetic background, it may be challenging to detect an association between maternal asthmagen exposure and ASD, if there is indeed heterogeneity in the association that is dependent on genetic vulnerability to asthmagens.

The point estimates for the odds ratios were in a different direction for ASD and DD when compared to POP, but this observation must be tempered by the fact that all confidence intervals included the null. Further, the children in the DD group have a wide array of different conditions, so it is difficult to interpret why the effect of maternal asthmagen exposures in this group may be different than among controls. An additional explanation for this different directionality includes residual confounding given that the SEED ASD, DD and POP differ by other factors (Diguiseppi, Daniels et al. submitted). Finally, some studies have suggested that parents of children with and without ASD may choose different jobs (Windham, Fessel et al. 2009, Dickerson, Pearson et al. 2014). If the factors that influence job choice are also associated with asthmagen exposure than this could also explain the different directions of the odds ratios.

Limitations of our study include that both occupational histories and health conditions were based on self-report, which may be subject to recall bias because women with a child with
an ASD or a developmental delay may recall health conditions or describe occupational tasks differently than mothers of typically developing children.

We also recognize that fathers could bring home asthmagen exposures from his workplace and expose other family members (Krakowiak, Szulc et al. 1999, Krop, Doekes et al. 2007, Tagiyeva, Anua et al. 2012), but we did not account for paternal take-home exposures in our analyses. We are able to consider fathers’ exposures in the analyses we present in Chapter 3.

Selection bias related to selection of controls into the SEED study is also a concern in our analysis. Mothers of POP controls were more highly educated, older, and less likely to have reported Black, Asian, or Hispanic maternal race than the populations in the SEED study catchment areas (Diguiseppi, Daniels et al. submitted). Given that occupational asthmagen exposure is related to these maternal characteristics, it is possible that the control group does not represent the occupational asthmagen exposure distribution in the source population. If the asthmagen exposure prevalence is different in the POP group compared to the underlying source population than comparisons between this group and the ASD case group may be biased.

A major strength of our study over many others examining environmental and occupational exposures in ASD is the extensive phenotyping carried out in SEED. Trained professionals with experience in ASD diagnosis for research participated in network-level standardizations to maintain reliability throughout the study. These experienced clinicians used information on the ADOS and ADI-R, the current gold standards in ASD research, as well as standardized clinical impression ratings. Compared to general clinical diagnosis based on DSM-IV criteria, the SEED research criteria had a sensitivity of 0.86 and a specificity of 0.74. Thus, there is a potential discrepancy between administratively obtained ASD outcomes and directly observed research outcomes. Many children meeting SEED criteria for an ASD did not have a previous diagnosis of ASD and some with a previous diagnosis did not meet SEED criteria (Wiggins, Reynolds et al. 2014). This implies that research relying on less detailed phenotyping may have outcome misclassification bias.
In conclusion, we did not find evidence for a measurable association between maternal occupational exposures to asthmagens and ASD in the children. However, our analyses do not rule out a possible role for environmental exposures and maternal conditions in impacting risk of autism spectrum disorder.
2.6. References


Table 2-1: Frequency of maternal occupational asthmagen exposure by covariates for all children in analytic sample in the SEED study, part 1. (660 POP, 437 ASD, 628 DD)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Entire analytic sample, (N (row %))</th>
<th>Unexposed (n=1482)</th>
<th>Exposed (n=243)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child’s Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>491 (31.64)</td>
<td>83 (14.46)</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>991 (68.36)</td>
<td>160 (13.90)</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>772 (51.07)</td>
<td>110 (12.47)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>484 (32.83)</td>
<td>83 (14.64)</td>
</tr>
<tr>
<td>3 or greater</td>
<td></td>
<td>226 (15.10)</td>
<td>50 (18.12)</td>
</tr>
<tr>
<td>Maternal Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td></td>
<td>1064 (71.31)</td>
<td>155 (12.72)</td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td>242 (16.03)</td>
<td>50 (17.12)</td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td>67 (4.53)</td>
<td>6 (8.22)</td>
</tr>
<tr>
<td>Hispanic</td>
<td></td>
<td>43 (2.90)</td>
<td>16 (27.12)</td>
</tr>
<tr>
<td>Multiracial or other</td>
<td></td>
<td>66 (4.45)</td>
<td>16 (19.51)</td>
</tr>
<tr>
<td>Maternal Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td></td>
<td>36 (2.41)</td>
<td>16 (30.77)</td>
</tr>
<tr>
<td>High school</td>
<td></td>
<td>99 (6.60)</td>
<td>20 (16.81)</td>
</tr>
<tr>
<td>Some college/ trade</td>
<td></td>
<td>370 (25.00)</td>
<td>95 (20.43)</td>
</tr>
<tr>
<td>Bachelor’s degree</td>
<td></td>
<td>524 (35.00)</td>
<td>68 (11.49)</td>
</tr>
<tr>
<td>Advanced degree</td>
<td></td>
<td>453 (30.00)</td>
<td>44 (8.85)</td>
</tr>
<tr>
<td>Current Household Income</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;$30,000</td>
<td></td>
<td>232 (15.56)</td>
<td>60 (20.55)</td>
</tr>
<tr>
<td>$30,000 – 70,000</td>
<td></td>
<td>386 (25.98)</td>
<td>69 (15.16)</td>
</tr>
<tr>
<td>$70,000 – 110,000</td>
<td></td>
<td>410 (27.63)</td>
<td>58 (12.39)</td>
</tr>
<tr>
<td>&gt;$110,000</td>
<td></td>
<td>454 (31.00)</td>
<td>56 (10.98)</td>
</tr>
<tr>
<td>Child’s Year of Birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td></td>
<td>93 (6.31)</td>
<td>14 (13.08)</td>
</tr>
<tr>
<td>2004</td>
<td></td>
<td>532 (35.79)</td>
<td>88 (14.19)</td>
</tr>
<tr>
<td>2005</td>
<td></td>
<td>661 (44.22)</td>
<td>109 (14.16)</td>
</tr>
<tr>
<td>2006</td>
<td></td>
<td>196 (13.16)</td>
<td>32 (14.04)</td>
</tr>
<tr>
<td>Maternal Age at Birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 years old</td>
<td></td>
<td>164 (10.88)</td>
<td>28 (14.58)</td>
</tr>
<tr>
<td>25-29 years old</td>
<td></td>
<td>327 (21.87)</td>
<td>75 (18.66)</td>
</tr>
<tr>
<td>30-34 years old</td>
<td></td>
<td>550 (36.54)</td>
<td>82 (12.97)</td>
</tr>
<tr>
<td>≥35 years old</td>
<td></td>
<td>441 (29.31)</td>
<td>58 (11.62)</td>
</tr>
</tbody>
</table>

POP = population controls, ASD = ASD cases, DD = non-ASD developmental delay
Table 2-2: Frequency of maternal occupational asthmagen exposure by covariates for all children in analytic sample in the SEED study, part 2. (660 POP, 437 ASD, 628 DD)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Entire analytic sample, (N (row %))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unexposed (n=1482)</td>
</tr>
<tr>
<td>Maternal Asthma Prior to Child’s Birth</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1096 176 (13.84)</td>
</tr>
<tr>
<td>Yes</td>
<td>386 67 (14.79)</td>
</tr>
<tr>
<td>Maternal Allergy Prior to Child’s Birth</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>840 152 (15.32)</td>
</tr>
<tr>
<td>Yes</td>
<td>642 91 (12.41)</td>
</tr>
<tr>
<td>Maternal Psychiatric Condition</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1025 180 (14.94)</td>
</tr>
<tr>
<td>Yes</td>
<td>457 63 (12.12)</td>
</tr>
<tr>
<td>Gestational Age</td>
<td></td>
</tr>
<tr>
<td>&lt;35 weeks</td>
<td>147 20 (11.98)</td>
</tr>
<tr>
<td>35-&lt;37 weeks</td>
<td>117 23 (16.43)</td>
</tr>
<tr>
<td>≥37 or greater weeks</td>
<td>1218 200 (14.1)</td>
</tr>
<tr>
<td>Maternal Smoking During Pregnancy</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1358 214 (13.61)</td>
</tr>
<tr>
<td>Yes</td>
<td>124 29 (18.95)</td>
</tr>
</tbody>
</table>

POP = population controls, ASD = ASD cases, DD = non-ASD developmental delay
Table 2-3: Crude and adjusted odds ratios and 95% confidence intervals for maternal occupational asthmagen exposure comparing ASD to population controls and DD to population controls in the SEED study. (660 POP, 437 ASD, 628 DD)

<table>
<thead>
<tr>
<th>Exposure</th>
<th>POP (N=660)</th>
<th>ASD (N=437)</th>
<th>DD (N=628)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Any Asthmagen</td>
<td>92</td>
<td>13.94</td>
<td>75</td>
</tr>
<tr>
<td>Any HMW</td>
<td>66</td>
<td>10.00</td>
<td>55</td>
</tr>
<tr>
<td>Latex</td>
<td>60</td>
<td>9.09</td>
<td>44</td>
</tr>
<tr>
<td>Any LMW</td>
<td>45</td>
<td>6.82</td>
<td>35</td>
</tr>
<tr>
<td>Reactive</td>
<td>33</td>
<td>5.00</td>
<td>29</td>
</tr>
<tr>
<td>Cleaning</td>
<td>21</td>
<td>3.18</td>
<td>17</td>
</tr>
</tbody>
</table>

POP = population controls, ASD = ASD cases, DD = non-ASD developmental delay, cOR = crude odds ratio, aOR = adjusted odds ratio
^ Analyses adjusted for parity, child’s sex, maternal race, maternal education, current household income, maternal age at birth, maternal psychiatric condition, active smoking during pregnancy, gestational age, maternal allergy prior to child’s birth, and maternal asthma prior to child’s birth.
Logistic regressions here are complete case for confounders included in adjusted model.
Table 2-4: Adjusted odds ratios (aOR) and 95% confidence intervals for models with interaction terms in the SEED study.
(660 POP, 437 ASD, 628 DD)

<table>
<thead>
<tr>
<th>Asthmagen</th>
<th>Maternal Allergy</th>
<th>POP</th>
<th>ASD</th>
<th>aOR^</th>
<th>95% CI</th>
<th>DD</th>
<th>%</th>
<th>aOR^</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>308</td>
<td>46.67</td>
<td>208</td>
<td>47.60</td>
<td>REF</td>
<td>324</td>
<td>51.59</td>
<td>REF</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>60</td>
<td>9.09</td>
<td>44</td>
<td>10.07</td>
<td>1.06</td>
<td>0.65 - 1.73</td>
<td>48</td>
<td>7.64</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>260</td>
<td>39.39</td>
<td>154</td>
<td>35.24</td>
<td>0.86</td>
<td>0.63 - 1.17</td>
<td>228</td>
<td>36.31</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>32</td>
<td>4.85</td>
<td>31</td>
<td>7.09</td>
<td>1.61</td>
<td>0.87 - 2.99</td>
<td>28</td>
<td>4.46</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Asthmagen</th>
<th>Maternal Asthma</th>
<th>POP</th>
<th>ASD</th>
<th>aOR^</th>
<th>95% CI</th>
<th>DD</th>
<th>%</th>
<th>aOR^</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>426</td>
<td>64.55</td>
<td>267</td>
<td>61.10</td>
<td>REF</td>
<td>403</td>
<td>64.17</td>
<td>REF</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>65</td>
<td>9.85</td>
<td>53</td>
<td>12.13</td>
<td>1.28</td>
<td>0.81 - 2.01</td>
<td>58</td>
<td>9.24</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>142</td>
<td>21.52</td>
<td>95</td>
<td>21.74</td>
<td>1.00</td>
<td>0.71 - 1.41</td>
<td>149</td>
<td>23.73</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>27</td>
<td>4.09</td>
<td>22</td>
<td>5.03</td>
<td>1.42</td>
<td>0.72 - 2.81</td>
<td>18</td>
<td>2.87</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Asthmagen</th>
<th>Child’s Sex</th>
<th>POP</th>
<th>ASD</th>
<th>aOR^</th>
<th>95% CI</th>
<th>DD</th>
<th>%</th>
<th>aOR^</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Male</td>
<td>310</td>
<td>46.97</td>
<td>316</td>
<td>72.31</td>
<td>REF</td>
<td>365</td>
<td>58.12</td>
<td>REF</td>
</tr>
<tr>
<td>Yes</td>
<td>Male</td>
<td>44</td>
<td>6.67</td>
<td>60</td>
<td>13.73</td>
<td>1.20</td>
<td>0.77 - 1.88</td>
<td>56</td>
<td>8.92</td>
</tr>
<tr>
<td>No</td>
<td>Female</td>
<td>258</td>
<td>39.09</td>
<td>46</td>
<td>10.53</td>
<td>0.17</td>
<td>0.11 - 0.24</td>
<td>187</td>
<td>29.78</td>
</tr>
<tr>
<td>Yes</td>
<td>Female</td>
<td>48</td>
<td>7.27</td>
<td>15</td>
<td>3.43</td>
<td>0.28</td>
<td>0.15 - 0.52</td>
<td>20</td>
<td>3.18</td>
</tr>
</tbody>
</table>

POP = population controls, ASD = ASD cases, DD = non-ASD developmental delay, cOR = crude odds ratio, aOR = adjusted odds ratio
^ Analyses adjusted for parity, child’s sex, maternal race, maternal education, current household income, maternal age at birth, maternal psychiatric condition, active smoking during pregnancy, gestational age, maternal allergy prior to child’s birth, and maternal asthma prior to child’s birth. Logistic regressions here are complete case for confounders included in adjusted model.
Table 2-5: Logistic regression models for the association between maternal occupational asthagen exposure and ASD with intellectual disability (ID) and ASD without intellectual disability compared to population controls (POP) in the SEED study. (660 POP, 431 ASD)

<table>
<thead>
<tr>
<th>Asthmagen</th>
<th>POP</th>
<th>ASD without ID</th>
<th>ASD with ID</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>cOR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>cOR (95% CI)</td>
</tr>
<tr>
<td>No</td>
<td>568</td>
<td>143</td>
<td>REF</td>
</tr>
<tr>
<td>Yes</td>
<td>92</td>
<td>24</td>
<td>1.04 (0.64 – 1.68)</td>
</tr>
</tbody>
</table>

cOR = crude odds ratio, aOR = adjusted odds ratio
^ Analyses adjusted for parity, child’s sex, maternal race, maternal education, current household income, maternal age at birth, maternal psychiatric condition, active smoking during pregnancy, gestational age, maternal allergy prior to child’s birth, and maternal asthma prior to child’s birth.
Logistic regressions here are complete case for confounders included in adjusted model.
6 ASD cases in other analyses do not have information on intellectual disability.
Chapter 3. Parental exposures to occupational asthmagens and risk of autism spectrum disorder in a Danish population-based case-control study
3.1. Abstract

Background: There are suggestions that environmental exposures and maternal immune conditions during the pregnancy may be associated with autism spectrum disorder (ASD). There are few studies actually looking at environmental exposures that can trigger immune response in relation to ASD. In Chapter 2, we examined the association between maternal occupational exposure to asthmagens, agents that trigger asthma, in relation to ASD in the children in the Study to Explore Early Development (SEED) and did not see evidence of a marginal association. However, the sample of size of SEED may have prevented us from detecting a modest effect and we did not incorporate paternal exposure into our SEED analysis.

Methods: We conducted a population-based case-control study in the Danish population using Danish register linkage. Our study population consisted of 11,869 ASD cases and 48,045 controls born between 1993 and 2007. Cases were identified by ICD-10 codes in the Danish Psychiatric Central Register. ASD cases and controls were linked to parental Danish International Standard Classification (DISCO-88) job codes. Parental occupational asthmagen exposure was estimated by linking to an asthma-specific job-exposure matrix using the DISCO-88 codes. We performed maternal and paternal analyses separately.

Results: Our maternal analyses included 6,830 case mothers and 29,670 control mothers employed during the pregnancy period. We found an inverse association between ASD and any maternal occupational asthmagen exposure, adjusting for sociodemographic covariates (adjusted OR: 0.88, 95% CI: 0.82 – 0.95). The paternal analysis was restricted to employed fathers and included 7,799 cases and 32,335 controls. In adjusted analyses, paternal occupational asthmagen exposure was also inversely with ASD in the children (adjusted OR: 0.92, 95% CI: 0.86 – 0.98).

Conclusion: We find an inverse association between maternal and paternal occupational asthmagen exposure and ASD in the children. We do not believe that occupational asthmagen exposure protects against ASD, but suggest that unmeasured confounding may bias results in an inverse direction, such that the results are consistent with a null association.
3.2. Introduction

Autism spectrum disorder (ASD) includes a diverse group of neurodevelopmental conditions characterized by repetitive or stereotypic behaviors and impairments in social communication and interactions. Studies suggest that there could be a link between maternal immune conditions and ASD (Comi, Zimmerman et al. 1999, Sweeten, Bowyer et al. 2003, Croen, Grether et al. 2005, Keil, Daniels et al. 2010), though studies linking ASD to specific maternal immune conditions have been inconsistent (Micali, Chakrabarti et al. 2004, Croen, Grether et al. 2005, Mouridsen, Rich et al. 2007, Lyall, Ashwood et al. 2014). Furthermore, the biological mechanism underlying the connection between the maternal immune system and ASD in the child is unclear. Environmental and occupational agents potentially capable of causing a maternal immune reaction have also been linked to ASD in epidemiologic studies (Windham, Zhang et al. 2006, Roberts, English et al. 2007, Kalkbrenner, Daniels et al. 2010, Volk, Hertz-Picciotto et al. 2011, McCanlies, Fekedulegn et al. 2012, Becerra, Wilhelm et al. 2013, Roberts, Lyall et al. 2013, Volk, Lurmann et al. 2013, Windham, Sumner et al. 2013, Raz, Roberts et al. 2014, von Ehrenstein, Aralis et al. 2014).

Exposures to occupational asthmagens, agents that trigger or exacerbate asthma, occur in a wide variety of job settings. Examples of possibly exposed jobs include nurses, nursing aids, cleaners, carpenters, crop and animal producers, bakers, hairdressers, and beauticians. Asthmagens may either directly cause an immune response or cause irritation that results in airway damage and downstream inflammation. We suggest that asthmagen exposure could alter in the maternal in utero environment and increase risk for ASD in the offspring by (1) stimulating production of maternal cytokines or by (2) decreasing oxygen supply to the fetus.

Air pollutant studies have examined the association between certain types of asthmagen exposure, such as aldehydes, styrene, and ethylene oxide, in relation to ASD. Acetaldehyde, formaldehyde, styrene, and metals air pollutant exposures have been linked to ASD, though the results are not consistent (Windham, Zhang et al. 2006, Kalkbrenner, Daniels et al. 2010, Roberts,
Lyall et al. 2013, von Ehrenstein, Aralis et al. 2014). In contrast to air pollutant exposures, occupational exposures can be more intense, and can be estimated based on individual employment. Windham et al (2013) and McCanlies et al (2012) examined occupational exposures in relation to ASD, though neither study focused on exposure to agents that can cause asthma.

Despite evidence suggesting a role for environmental agents in triggering maternal immune responses that might alter risk of ASD, few studies have explicitly tested such hypotheses. In chapter 2, we examined the association between maternal occupational asthmagen exposure during the pregnancy and ASD in the Study to Explore Early Development (SEED) study and found no evidence of a detectable association. However, it is possible that the study size of our sample in SEED would make it challenging to detect a modest effect. Furthermore, in the chapter 2 analysis we did not consider paternal exposures. Fathers may bring asthmagens home from the workplace, thereby resulting in mothers being indirectly exposed to paternal occupational asthmagens (Krakowiak, Szulc et al. 1999, Krop, Doekes et al. 2007, Tagiyeva, Anua et al. 2012). Also, SEED is a case-control study with retrospective recall of occupational exposures during pregnancy, which could introduce bias. Thus, we sought to conduct a larger study examining both maternal and paternal occupational exposure to asthmagens in relation to ASD in a population-based case control study using data from the Danish Registers. Since the association between asthmagen exposure and ASD may differ depending on whether or not the mother has a history of asthma, we also examined whether history of an asthma diagnosis modified the association between asthmagen exposure and ASD.

3.3. Methods

3.3.a. Study design

All live-born children and new Danish residents are assigned a unique personal identification number that links information across different national registers. We linked
children to parents using the Danish Civil Registration System (Pedersen 2011). We linked to the Danish Psychiatric Central Register (DPCR) (Mors, Perto et al. 2011) for information on psychiatric diagnoses, Medical Birth Registry (Knudsen and Olsen 1998) for birth-related covariates, the National Patient Register (Lynge, Sandegaard et al. 2011) for medical diagnoses, and Statistics Denmark registers for information on employment, education, and finance (Petersson, Baadsgaard et al. 2011, Thygesen, Daasnes et al. 2011). The Statistics Denmark employment, education, and finance registers are updated each year.

3.3.b. Selection of eligible participants

We identified all children in the Danish Civil Registration System born between January 1, 1993 and December 31, 2007 (n=1,099,463). We excluded children who could not be linked back to the mother through the Danish Civil Registration System (n=15,404); children who were not born in Denmark, had an unknown birthplace, or could not be matched to the Medical Birth Registry (n=88,908); children who were missing gestational age or with gestational ages at birth of less than 23 weeks or greater than 43 weeks (n=8,945); and children from multiple births or missing information on multiplicity of birth (n=38,638). Thus, we selected our sample from a population of 947,568 individuals meeting the above study inclusion criteria (Figure II-1). The study was approved by the Danish Data Protection Agency.

3.3.c. Case and control selection

The Danish Psychiatric Central Register (DPCR) (Pedersen 2011) contains diagnoses from every inpatient psychiatric admission from 1970 to present, and from every outpatient contact or treatment from January 1, 1995 (Mors, Perto et al. 2011). Prior to 1994, diagnoses were reported according to the International Classification of Diseases, 8th Revision (ICD-8). International Classification of Diseases, 10th Revision (ICD-10) classification has been used for reporting of psychiatric diagnoses since January 1, 1994. In Denmark, school psychologists or
general medical practitioners will refer children suspected of having an ASD to a psychiatric ward. Referred children will undergo diagnostic evaluation and then receive a diagnosis from a psychiatrist that is then entered into the DPCR (Hansen, Schendel et al. 2015). Cases were defined as having a reported diagnosis of Autism Spectrum Disorder (ICD-10 codes: F84.0, F84.1, F84.5, F84.8 and F84.9) from January 1, 1995 into April 2013. Due to time lags in reporting diagnoses to the DPCR, the diagnosis data are considered complete through the end of 2012. For every case (n=12,500), we randomly sampled four controls without a diagnosis of ASD and meeting the study inclusion criteria. The study sample was further restricted to only include the oldest child for each mother in situations where mothers had multiple children in the study population and to exclude those lost to follow-up before age one, children with inconsistent maternal identification numbers across different registers, and children with likely erroneous birth weights for gestational age (defined as birth weight more than six standard deviations above or below the mean sex-specific birth weight for each week of gestational age calculated from singletons born from 1980-2007 in Denmark). The final study sample consisted of 11,869 ASD cases and 48,045 controls (Figure II-2).

3.3.d. Employment status definition

We chose to use job information for the year that overlapped most with the pregnancy. Thus, for children born between January and May, we used job information from the year prior to the year of birth of the child. For children born between June and September, we used job information from the year of birth. For the reminder of the text, we refer to the year of job information as the “occupational year.” We classified parents as employed or unemployed based on an employment status variable from the Integrated Database for Market Research (IDA). Since the employment status variable in the IDA represents whether or not an individual was employed at a given point at the end of November for each year, a person was defined as employed if the individual was employed in the November prior to the occupational year.
3.3.e. Occupational asthmagen exposure assessment

We estimated parental occupational asthmagen exposure during the pregnancy period by linking job codes from the occupational year of interest in the Employment Classification Module (AKM) (Petersson, Baadsgaard et al. 2011) to an asthma-specific job exposure matrix (JEM) developed by Kennedy et al (2000). Job codes are in the format of the Danish International Standard Classification of Occupations (DISCO-88), the Danish version of the International Standard Classification of Occupations (ISCO-88). During the time period of this study, the DISCO-88 codes represent the person’s primary employment during a year as determined by the job for which the person has the highest income.

The asthma-specific JEM matches ISCO-88 codes to categories of asthmagen exposures (Kennedy, Le Moual et al. 2000). Each job code in the asthma-specific JEM is given a classification of “yes” or “no” as to whether or not an individual employed in the job would have a high probability of being exposed to that particular occupational asthmagen. The JEM contains four different subgroups of occupational agents that would put an individual at risk of developing asthma: (1) high molecular weight agents, (2) low molecular weight agents, (3) mixed environment agents, and (4) irritants, as well as compounds or mixtures that belong to each category. We assigned exposure on the basis of crosswalk between ISCO-88 and DISCO-88 for the occupational year.

The developers of the asthma-specific JEM suggest completing a two-step verification step in order to improve classification of the exposure where (1) ISCO-88 codes are checked and (2) asthmagen exposure classifications are checked based on additional information available regarding industry and job tasks. Since we did not have information on job tasks, we did not have sufficient information to do any additional ISCO-88 code checking, but where possible we used industrial codes from the registers to re-classify occupational asthmagen exposures according to the comment code specifications in the JEM. In addition to the re-coding occupational asthmagen exposures according to industry codes, we also decided to code carpenters and joiners.
(ISCO-88 code 7124) as exposed to wood dust because there is evidence that both hard and soft
woods can cause allergy (Demers, Teschke et al. 1997, Bernstein 1999). For these analyses, all
nursing associate professionals (ISCO-88 code 3231) were considered exposed to pharmaceutical
drugs, based on data available in March 2015. Refinement of this classification is possible
pending further review of specific job details, as recommended by the JEM authors. These
assessments were made without consideration of case or control status.

3.3.f. Creation of other covariates

The variables for index child’s sex, child’s year of birth, maternal age at the time of
child’s birth, paternal age at the time of child’s birth, and parity were derived from the Danish
Civil Registration System. Parental income and education were derived from the Statistics
Denmark personal finance and education databases. To calculate parental income, we summed
maternal income and paternal income. In situations where maternal income was missing, we
assumed that the parental income was the paternal income, and vice versa. Highest level of
education was defined as the highest level of education of either the mother or the father. In
cases where the education level of one of the parents was missing, we used the education level of
the other parent. History of parental psychiatric diagnosis was defined as any ICD-8 diagnosis in
the range of 290-315 or any ICD-10 diagnosis in the F group in the Danish Psychiatric Central
Register in either parent prior to the birth of the child. The Danish National Patient Register,
which contains all medical diagnoses by a specialist, was used to define variables for maternal
asthma and paternal asthma. A parent had a history of asthma if he or she had an ICD-8
diagnosis of 493 or an ICD-10 diagnosis of J45 or J46 any time prior to the birth of the child.

3.3.g. Statistical analysis

We restricted the analysis of maternal occupational asthmagen exposure and ASD to
mothers who were employed or not missing the employment status variable. Similarly, analysis
of paternal occupational asthmagen exposure and ASD was restricted to fathers who were employed or not missing the employment status variable. All children born prior to June 1993 were omitted because parental employment status information was not available. We also excluded parents for whom we could not estimate occupational asthmagen exposure because the DISCO-88 codes did not have a match to an ISCO-88 code in the asthma-specific JEM. We restricted our analyses to parent-child pairs for which we had complete covariate information.

We tabulated and calculated the percentages of occupational asthmagen unexposed and exposed parents by various sociodemographic characteristics. We used logistic regression to model the association between parental exposure to any occupational asthmagen and ASD, adjusting for previously identified possible confounders including: year of birth of child (dummy categories for each year), child’s sex, maternal age at birth (continuous), paternal age at birth (continuous), parity (one, two, greater than 2), total parental income during the occupational year (<200,000 DKK, 200,000-399,999 DKK, 400,000 DKK-599,999 DKK, ≥600,000 DKK), highest parental education as of the occupational year (basic school, upper secondary school, vocational school, higher education), and psychiatric diagnosis for either parent prior to the child’s birth (yes, no). Maternal and paternal analyses were performed separately. Analyses were also adjusted for parental asthma diagnosis prior to birth of the child. Logistic regression was also used to model the association between specific occupational asthmagens and ASD.

The association between parental occupational asthmagen exposure and ASD may differ depending on whether or not a parent has a history of asthma. As such, we also fit logistic regression models with an interaction term for occupational asthmagen exposure and history of asthma diagnosis prior to the birth of the child, and estimated the independent and joint effects of occupational asthmagen exposure and asthma. These analyses were conducted using SAS 9.3.

We assessed sensitivity to an unobserved confounder using the methods described in Lin et al. (1998). We were particularly concerned that an unmeasured confounder, such as a health factor (e.g. undocumented allergy or respiratory disease) may lead to avoidance of asthmagen
exposed jobs and may also be a risk factor for ASD. Thus, for our sensitivity analyses we assumed that unmeasured confounder, U, is positively associated with ASD and inversely associated with maternal occupational asthmagen exposure. We assumed that the underlying prevalence of the unmeasured confounder among the unexposed was 0.30. We were then able to estimate corrected adjusted odds ratios and 95% confidence intervals for the association between maternal occupational asthmagen exposure and ASD, using the observed adjusted odds ratio and 95% confidence intervals and assuming different plausible values for the association between the unmeasured confounder and ASD (ORyu), and for the association between the unmeasured confounder and maternal occupational asthmagen exposure (ORxu). These analyses were conducted in R version 3.1.1.

3.4. Results

Of the 11,869 cases and 48,045 controls, mothers of 8,180 (68.9%) cases and 35,084 (73.0%) controls were employed in the November prior to the occupational year of interest. Fathers of 9,437 (79.5%) cases and 39,481 (82.2%) controls were employed. We excluded an additional 6,535 children from maternal and 8,710 children from paternal analyses because we could not estimate occupational asthmagen exposures from DISCO-88 codes. We had complete covariate information on 99.4% of employed mothers and 99.8% of employed fathers, so our maternal analyses ultimately included 6,830 cases and 29,670 controls, and our paternal analyses included 7,799 cases and 32,335 controls.

In the occupational year, 20.3% of mothers and 21.0% of fathers were exposed to occupational asthmagens (Figure 1). Nursing associate professionals, institution-based personal care workers, cleaning staff in non-domestic settings, and hairdressers and beauticians were the most prevalent maternal asthmagen exposed jobs. The most common types of maternal occupational asthmagen exposure were latex, pharmaceutical drugs, LMW reactive agents, and cleaning products. The four most prevalent paternal jobs with asthmagen exposures were
carpenters and joiners, market-oriented crop and animal producers, meat and fish processing machine operators, and machine-tool setters and setter-operators. The most common forms of paternal occupational asthmagen exposures were metals, mixed environment agricultural antigens, wood dusts, LMW reactive agents, metal working fluids, and bioaerosols.

Maternal and paternal occupational asthmagen exposure was associated with lower parental age at the time of the child’s birth, lower parental income, and higher maternal parity at the birth of the index child (Table 3-1). The prevalence of maternal occupational asthmagen exposure was higher in families where the highest level of parental education was basic school. Paternal occupational asthmagen exposure was more prevalent in families where basic or vocational schooling was the highest levels of educational attainment. The percent of parents exposed to occupational asthmagens decreased over time. Parents with exposure to occupational asthmagens in the occupational year were not any more likely to have had an asthma diagnosis prior to the birth of the child. However, mothers exposed to occupational asthmagens during the occupational year were more likely to later be diagnosed with asthma by a specialist than non-exposed mothers (2.8% vs 2.0%).

Mothers of cases were less likely to have been exposed (18.9%) (Table II-1). We observed an inverse association between any maternal occupational asthmagen exposure and ASD in the children (adjusted OR (aOR): 0.88, 95% CI: 0.82 – 0.95) (Figure 3-1). This inverse association was largely driven by the exposures to latex (aOR: 0.89, 95% CI: 0.81 – 0.97) and pharmaceuticals (aOR: 0.77, 95% CI: 0.68 – 0.86). There was no overall association between any low molecular weight maternal occupational asthmagen exposure and ASD, but in crude analyses we saw an association between cleaning products and ASD that decreased after adjustment for sociodemographic factors (crude OR (cOR): 1.18, 95% CI: 1.07 – 1.31; aOR: 1.07, 95% CI: 0.96 – 1.20).

The paternal occupational asthmagen exposure prevalence in cases and controls was 20.2% and 21.2%, respectively (Table II-2). Paternal exposure to any occupational asthmagen
was also inversely associated with ASD in the children in adjusted analyses (aOR: 0.92, 95% CI: 0.86 – 0.98) (Figure 3-1). In contrast to the maternal occupational asthmagen analyses, the inverse association was largely explained by exposure to agricultural antigens. Similar to the maternal analyses, we see some suggestion of an association between paternal exposure to occupational cleaning products and ASD, though this association weakened after adjustment (cOR: 1.25, 95% CI: 1.05 – 1.49; aOR: 1.12, 95% CI: 0.93 – 1.34).

In models that included an interaction term between maternal occupational asthmagen exposure and maternal asthma diagnosis prior to the child’s birth, we did not find evidence that the asthma diagnosis modified the association between maternal asthmagen exposure and ASD (Table 3-2). The adjusted odds ratio between maternal occupational asthmagen exposure and ASD among mothers without an asthma diagnosis and mothers with an asthma diagnosis was 0.89 (95% CI: 0.83 – 0.95) and 0.66 (95% CI: 0.39 – 1.12), respectively. There was evidence of a multiplicative interaction between paternal occupational asthmagen exposure and paternal asthma diagnosis in relation to ASD (Table 3-2). The odds ratio for paternal occupational asthmagen exposure and ASD was 0.91 (95% CI: 0.85 – 0.97) among fathers without an asthma diagnosis, and was 1.64 (95% CI: 1.08 – 2.48) among fathers with an asthma diagnosis.

We did not see evidence of an association between parental asthma diagnosis prior to the birth of the child and ASD, but we do see a suggestion of association between parental asthma diagnosis after the birth of the child and ASD (data not shown).

Our sensitivity analyses for unobserved confounders suggest that the inverse association between maternal occupational asthmagen exposure and ASD could be sensitive to an unobserved confounder that would increase the odds ratio estimate such that the 95% confidence interval would include 1 (Figure 3-2). Assuming that the prevalence of the unobserved confounder among the unexposed is 0.30, a confounder that increases the odds of ASD by 2 times and decreases the odds of maternal occupational asthmagen exposure 0.6 times would bring the observed adjusted odds ratio of 0.88 (95% CI: 0.82 – 0.95) to the unmeasured confounder
adjusted odds ratio to 0.95 (95% CI: 0.88 – 1.03) (Figure 2). However, an unmeasured confounder with an OR of 2 with ASD would need to decrease the odds of maternal occupational asthmagen exposure 0.15 times to pull the 95% confidence interval of the unmeasured confounder adjusted odds ratio above one.

3.5. Discussion

We observed an inverse association between maternal and paternal occupational exposure to asthmagens and ASD, when adjusting for sociodemographic factors. There were similar weak protective effects for both paternal and maternal exposures despite different profiles of asthmagen exposed jobs and asthmagenic agents for mothers and fathers. The inverse association between occupational asthmagen exposures and ASD was largely explained by pharmaceutical drug and latex exposures in mothers, but by agricultural antigens in fathers.

These inverse associations might be explained by health of the parent influencing employment decisions and ASD risk in the children. Individuals with medical complications resulting from asthmagen exposures may be more likely to either change jobs or stop working, a phenomenon known in the literature as the healthy worker effect (HWE) (Pearce, Checkoway et al. 2007). The HWE has been observed in the context of studies examining occupational risk factors for asthma (Le Moual, Kauffmann et al. 2008, Dumas, Le Moual et al. 2013). If the parents of cases are more likely to either avoid occupations with asthmagen exposure or not work because of a history of health effects from asthmagen exposure, then HWE could explain our inverse results if poor health related to selection out of the workforce is related to elevated risk of ASD in children.

Other forms of confounding may explain these inverse associations. For example, previous studies have observed associations between technical jobs and ASD (Windham, Fessel et al. 2009, Dickerson, Pearson et al. 2014), so it is possible that the inverse association we see may be reflecting a common cause of ASD in children and phenotypic features in parents that
affect job selection into technical occupations. While we restricted the analyses to employed parents, we did find that mothers and fathers of ASD cases were less likely to be employed during the pregnancy period than parents of controls, which could also potentially reflect differences in the health of case parents as compared to control parents. Finally, ASD has been linked to higher urbanicity (Lauritsen, Astrup et al. 2013), so it is possible that the inverse association between occupational asthmagen exposure and ASD could be explained by under-ascertainment of cases in rural areas. In particular, this could explain the protective association between paternal occupational asthmagen exposure and ASD, which is largely driven by agricultural asthmagen exposure.

Our sensitivity analyses revealed that an unmeasured confounder that doubles odds of ASD, but decreases the odds of maternal occupational asthmagen exposure would increase the 95% confidence interval to such a degree that it would include one. However, the associations between the latent confounder and both ASD and maternal asthmagen exposure would need to be unrealistically strong to bring the 95% confidence interval entirely above the null.

Alternatively, it is possible that the inverse association is a result of selection bias. Our outcome requires that the child survive the pregnancy. If occupational asthmagen exposure is associated with risk of pregnancy loss and other factors associated with both risk of pregnancy loss and ASD, then it is possible to observe an inverse association between occupational asthmagen exposure and ASD. This form of selection bias has been described in the context of other environmental chemical exposures during the pregnancy and early life outcomes (Liew, Olsen et al. 2015). The plausibility of this explanation is ambiguous given the uncertainty of the impact of asthmagen exposure on fetal loss. Also, selection bias due to fetal loss likely does not explain the inverse association between paternal occupational asthmagen exposure and ASD.

While our approach was to focus specifically on occupational agents that cause asthma, other air pollution and occupational epidemiology studies have examined a wide array of toxicants, some of which are asthmagens, in relation to ASD (Windham, Zhang et al. 2006,
Examples of air pollutants that can induce or exacerbate asthma include certain metals (cadmium, chromium, cobalt, manganese, nickel), aldehydes, styrene and ethylene oxide (Leikauf 2002). While our results suggest a null association between parental occupational asthmagenic metal or metalworking fluid exposures and ASD, some studies report positive associations between air pollutant exposures to metals and ASD (Windham, Zhang et al. 2006, Roberts, Lyall et al. 2013), including asthmagenic metals such as cadmium (Windham, Zhang et al. 2006, Roberts, Lyall et al. 2013), manganese (Roberts, Lyall et al. 2013), and nickel (Windham, Zhang et al. 2006, Roberts, Lyall et al. 2013). Other studies suggested no association between hazardous air pollutant exposure to asthmagenic metals and ASD (Kalkbrenner, Daniels et al. 2010, von Ehrenstein, Aralis et al. 2014). ASD has also been linked to acetaldehyde and formaldehydes (von Ehrenstein, Aralis et al. 2014), agents that could be classified as highly reactive agents, cleaning agents, or irritants in the asthma specific job exposure matrix (Windham, Zhang et al. 2006, Kalkbrenner, Daniels et al. 2010, Roberts, Lyall et al. 2013, von Ehrenstein, Aralis et al. 2014). We did not see any association between these specific asthmagen categories and ASD.

In agreement with our results, McCanlies et al (2012) did not see associations between parental occupational exposure to metals or disinfectants and ASD. Another study reported an association between maternal occupational exposure to disinfectants and ASD (Windham, Sumner et al. 2013). This was based on occupational information from birth certificate data and only had 9 disinfectant exposed cases and 6 disinfectant exposed controls. In our study, unadjusted analyses showed an association between both maternal and paternal occupational exposure to cleaning and disinfectant products and ASD, but this was attenuated upon adjusting
for confounders. We also saw no evidence of association between occupational asthmagen exposure and ASD in the SEED case-control study (Chapter 2).

Even in the absence of an association between asthmagen exposure and ASD, there could still be a link between maternal asthma and ASD. Asthma and ASD may share similar genetics or be associated as a result of other health conditions or asthma medications. In this case-control study, we do not see evidence of a link between parental asthma diagnosis by a specialist prior to the birth of the child and ASD, but observed a suggestion of an association between ASD and maternal asthma diagnosis after the child’s birth. This temporal distinction may indicate that it is not change in the in utero environment from asthmatic inflammation that explains associations between asthma and ASD, but rather other shared health conditions or common genetic underpinning. Alternatively, mothers may not have been diagnosed by the specialist until after the pregnancy but may still have experienced subclinical or undiagnosed asthma during the gestational period. Even if asthmatic pathophysiology does somehow impact neurodevelopment, it may not be entirely surprising that we do not see an association between asthmagen exposure and ASD because occupational asthmagen exposure has been estimated to explain only 10-25% of adult-onset asthma (Kogevinas, Zock et al. 2007).

Asthma has a strong genetic component (London and Romieu 2009). In particular, gene-environment interactions have been reported between specific types of asthmagen exposures, single nucleotide polymorphisms, and occupational asthma (Bernstein 2011, Acouetey, Zmirou-Navier et al. 2013) and atopy is an established risk factor for asthma, including occupational asthma resulting from exposure to certain asthmagens (Dykewicz 2009, Holgate, Arshad et al. 2010). This suggests that it may be difficult to identify links between occupational asthmagens and health outcomes without consideration of different genetic backgrounds. We do not have genetic information on the study population so we could not consider differential genetic susceptibility to asthma in our analysis. We examined the interaction between parental occupational asthmagen exposures and parental asthma prior to the child’s birth under the
hypothesis that mothers with a history of asthma may be more likely to mount a biological immune response to asthmagens. We did not, however, see any evidence of an interaction between maternal occupational asthmagen exposure and asthma in relation to ASD. Intriguingly, the association between paternal occupational asthmagen exposure and ASD was stronger among fathers with asthma. This does not fit with existing hypotheses and may be a chance association since only 124 controls and 46 cases had fathers with an asthma diagnosis prior to birth and an occupational asthmagen exposure during the occupational year. Alternatively, this association may result from confounding by factors that we did not adjust for in our analysis.

Although we adjusted for many possible confounders, our study is limited by the possibility of residual confounding, given that covariates were acquired from nationwide registries and may not include other important confounders found in more detailed medical record data or from parent report. Health conditions, such as asthma, might be particularly challenging to account for in our analyses because they are likely under-reported in the National Patient Register, which only includes diagnoses by a specialist. However, our sensitivity analyses revealed that any unmeasured confounders would need to be very strongly associated with exposure and outcome to see a positive association between occupational asthmagens and ASD. Furthermore, individuals with the most serious asthma symptoms would likely be receiving specialist evaluations for asthma. We did not adjust for seasonality or air pollutant exposures in our analyses, but these are unlikely to be strong confounders of associations between occupational exposures and ASD.

Occupational exposure assessment in the Danish registries was limited. Companies supply job codes to Danish authorities for tax purpose and Statistics Denmark then validates and imputes other DISCO-88 codes based on a variety of different sources, such as union membership records and educational registers (Agerbo, Gunnell et al. 2007). While we tried to incorporate knowledge of industry into our exposure information, we do not have detailed information on job tasks which limited our ability to complete the expert assessment review steps recommended by
the developers of the asthma JEM. We also are not certain how well the DISCO-88 codes from Statistic Denmark would correspond to self-reported jobs. The DISCO-88 codes from Statistics Denmark represent the most likely job for any given year; thus, we were also unable to do any more exact analyses looking at occupational exposure in relation to the time period in the pregnancy. We were also not able to include secondary jobs. The JEM assumes that all people with the same job and industry codes have the same binary value for occupational asthmagen exposure: it does not account for individual differences in factors such as intensity of exposure and use of personal protective equipment that may differ among individuals with the same job and industry codes. The JEM was designed to favor high specificity at the price of sensitivity (Kennedy, Le Moual et al. 2000) with prior information suggesting a sensitivity of 0.4 and specificity close to 1 (Liu, Gustafson et al. 2009, Beach, Burstyn et al. 2012). Given these limitations of the JEM, in chapter 4 we present sensitivity analyses to determine the possible impact of imperfect sensitivity and specificity of the JEM on the estimate.

Despite these limitations with the asthma JEM, we do see that mothers with maternal occupational asthmagen exposure during the pregnancy period were more likely have a diagnosis of asthma after the birth of the child (2.8% vs 2.0%), which suggests that the asthma JEM is measuring exposure well enough to capture some signal of an association with a known consequence of exposure. We note that asthmagen exposed mothers were not any more likely to have a diagnosis of asthma prior to the birth of the child than unexposed mothers. The lack of an association between occupational asthmagen exposure and earlier asthma is not surprising given that we do not know whether the job preceded the asthma or asthma affected the job choice.

Strengths of our study include the large sample size, lack of potential for recall bias because of the use of administrative records, and minimal concern of selection bias related to control selection. The ASD cases are identified through ICD-10 codes in the Danish Psychiatric Central Register that includes both inpatient and outpatient admissions for the period under study. Strict childhood autism diagnoses (F84.0) in the Danish Psychiatric Central Register were
validated in one study (Lauritsen, Jørgensen et al. 2010). The broader class of ASD diagnoses, however, has not been validated, so there is some possibility of a lack of standard case assessment. Since Denmark has a national health system and diagnostic assessments and interventions are free, we suspect that most cases of ASD likely appear in the Register.

In conclusion, our results from this population-based case-control study do not suggest an association between parental occupational asthmagen exposure and ASD, despite previous reports of associations between air pollutants and other occupational exposures and ASD. We specifically examined asthmagen exposures, but future studies might harness the registers to examine other parental occupational patterns and exposures in relation to neurodevelopmental disorders. Future investigation of environmental risk factors for ASD may also benefit from individual measurement of exposure biomarkers and consideration of genetic background.
3.6. References


Table 3-1: Parent and child characteristics by maternal occupational asthmagen exposure and paternal occupational asthmagen exposure in the Danish case-control study.

<table>
<thead>
<tr>
<th></th>
<th>Maternal Asthmagen Exposure, N (%)</th>
<th>Paternal Asthmagen Exposure, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n=29109)</td>
<td>Yes (n=7391)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No (n=31713)</td>
</tr>
<tr>
<td>Child’s Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16411</td>
<td>4103 (20.0)</td>
</tr>
<tr>
<td>Female</td>
<td>12698</td>
<td>3288 (20.6)</td>
</tr>
<tr>
<td>Child’s Year of Birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1993-1997</td>
<td>9284</td>
<td>3044 (24.7)</td>
</tr>
<tr>
<td>1998-2002</td>
<td>10791</td>
<td>2343 (17.8)</td>
</tr>
<tr>
<td>2003-2007</td>
<td>9034</td>
<td>2004 (18.2)</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>14122</td>
<td>3316 (19.0)</td>
</tr>
<tr>
<td>2</td>
<td>10714</td>
<td>2707 (20.2)</td>
</tr>
<tr>
<td>≥3</td>
<td>4273</td>
<td>1368 (24.3)</td>
</tr>
<tr>
<td>Parent’s Age at Child’s Birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤25 years</td>
<td>4243</td>
<td>1226 (22.4)</td>
</tr>
<tr>
<td>26-30 years</td>
<td>11822</td>
<td>3062 (20.6)</td>
</tr>
<tr>
<td>31-35 years</td>
<td>9574</td>
<td>2312 (19.5)</td>
</tr>
<tr>
<td>≥36 years</td>
<td>3470</td>
<td>791 (18.6)</td>
</tr>
<tr>
<td>Total Parental Income</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200,000 DKK</td>
<td>512</td>
<td>140 (21.5)</td>
</tr>
<tr>
<td>200,000-399,999 DKK</td>
<td>7091</td>
<td>2280 (24.3)</td>
</tr>
<tr>
<td>400,000-599,999 DKK</td>
<td>14238</td>
<td>3591 (20.1)</td>
</tr>
<tr>
<td>≥600,000 DKK</td>
<td>7268</td>
<td>1380 (16.0)</td>
</tr>
<tr>
<td>Highest Parental Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic School</td>
<td>1524</td>
<td>585 (27.7)</td>
</tr>
<tr>
<td>Upper Secondary School</td>
<td>1392</td>
<td>261 (15.8)</td>
</tr>
<tr>
<td>Vocational School</td>
<td>12513</td>
<td>3105 (19.9)</td>
</tr>
<tr>
<td>Higher Education</td>
<td>13680</td>
<td>3440 (20.1)</td>
</tr>
<tr>
<td>Parental Psychiatric Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>27638</td>
<td>7029 (20.3)</td>
</tr>
<tr>
<td>Yes</td>
<td>1471</td>
<td>362 (19.8)</td>
</tr>
<tr>
<td>Maternal Asthma Diagnosis Prior to Birth of Child</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>28542</td>
<td>7253 (20.3)</td>
</tr>
<tr>
<td>Yes</td>
<td>567</td>
<td>138 (19.6)</td>
</tr>
<tr>
<td>Paternal Asthma Diagnosis Prior to Birth of Child</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Maternal analyses included 6,830 cases and 29,670 controls
Paternal analyses included 7,799 cases and 32,335 controls
Table 3-2: Independent and joint effects of parental occupational asthmagen exposure and parental asthma diagnosis by a specialist prior to child’s birth in the Danish case-control study.

<table>
<thead>
<tr>
<th>Maternal Asthmagen</th>
<th>Maternal Asthma</th>
<th>CONTROL</th>
<th>N</th>
<th>%</th>
<th>ASD</th>
<th>N</th>
<th>%</th>
<th>aOR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>23127</td>
<td>77.95</td>
<td>5415</td>
<td>79.28</td>
<td>REF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>5984</td>
<td>20.17</td>
<td>1269</td>
<td>18.58</td>
<td>0.89</td>
<td>0.83 – 0.95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>442</td>
<td>1.49</td>
<td>125</td>
<td>1.83</td>
<td>1.23</td>
<td>1.00 – 1.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>117</td>
<td>0.39</td>
<td>21</td>
<td>0.31</td>
<td>0.81</td>
<td>0.50 – 1.32</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Paternal Asthmagen</th>
<th>Paternal Asthma</th>
<th>CONTROL</th>
<th>N</th>
<th>%</th>
<th>ASD</th>
<th>N</th>
<th>%</th>
<th>aOR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>24952</td>
<td>77.17</td>
<td>6108</td>
<td>78.32</td>
<td>REF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>6719</td>
<td>20.78</td>
<td>1532</td>
<td>19.64</td>
<td>0.91</td>
<td>0.85 – 0.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>540</td>
<td>1.67</td>
<td>113</td>
<td>1.45</td>
<td>0.95</td>
<td>0.77 – 1.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>124</td>
<td>0.38</td>
<td>46</td>
<td>0.59</td>
<td>1.56</td>
<td>1.09 – 2.23</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A Maternal model includes maternal asthmagen exposure, child’s year of birth, child’s sex, maternal age at birth, paternal age of birth, total income of parents, parity, highest parental education, history of parental psychiatric diagnosis prior to child’s date of birth, maternal asthma diagnosis by a specialist prior to child’s date of birth, and interaction term between maternal asthmagen exposure and maternal asthma diagnosis by a specialist prior to the child’s date of birth (6,830 cases and 29,670 controls).

B Model includes paternal asthmagen exposure, child’s year of birth, child’s sex, maternal age at birth, paternal age of birth, total income of parents, parity, highest parental education, history of parental psychiatric diagnosis prior to child’s date of birth, paternal asthma diagnosis by a specialist prior to child’s date of birth, and interaction term between paternal asthmagen exposure and paternal asthma diagnosis by a specialist prior to the child’s date of birth (7,799 cases and 32,335 controls).
Figure 3-1: Adjusted odds ratios and 95% confidence intervals for parental occupational asthmagen exposure and ASD in the Danish case-control study.

^ Adjusted maternal model is adjusted for child’s year of birth, child’s sex, maternal age at birth, paternal age of birth, total income of parents, parity, highest parental education, history of parental psychiatric diagnosis prior to child’s date of birth, and maternal asthma diagnosis by a specialist prior to child’s date of birth (6,830 cases and 29,670 controls).

\(^{b}\) Adjusted paternal model is adjusted for child’s year of birth, child’s sex, maternal age at birth, paternal age of birth, total income of parents, parity, highest parental education, history of parental psychiatric diagnosis prior to child’s date of birth, and paternal asthma diagnosis by a specialist prior to child’s date of birth (7,799 cases and 32,335 controls).

\(^{c}\) Paternal mites odds ratio could not be estimated.
Figure 3-1: Adjusted odds ratios and 95% confidence intervals for parental occupational asthmagen exposure and ASD in the Danish case-control study.
Figure 3-2: Sensitivity to unobserved confounder for the association between maternal occupational asthmagen exposure and ASD for fixed prevalence of unmeasured confounder among unexposed of 0.30.

ORyu = association between the unmeasured confounder and ASD
ORxu = association between the unmeasured confounder and maternal occupational asthmagen exposure
Chapter 4. The importance of exposure misclassification:

Using Bayesian correction methods to assess maternal occupational asthmagen exposures

and risk of autism spectrum disorder
4.1. Abstract

Background: Inference in epidemiologic studies is plagued by exposure misclassification. Several methods exist to correct for misclassification error. One approach is to “correct” for misclassification using point estimates for the sensitivity (Sn) and specificity (Sp) of the tool used for exposure assessment. Unfortunately, we typically do not know the Sn and Sp of the tool with certainty, and effect estimates may be sensitive to small discrepancies between the guessed and actual values of the Sn and Sp. Bayesian methods for correction of exposure misclassification exist that allow us to assume distributions for Sn and Sp instead of exact point estimates. These methods have been applied in epidemiologic literature, but are not considered a mainstream approach, especially in the fields of occupational and environmental epidemiology. Here we illustrate an occupational epidemiology application of this Bayesian approach and show the striking difference in effect size estimates with and without accommodation of exposure measurement error.

Methods: We applied Bayesian models to correct for misclassification error in data from two case-control studies (the Study to Explore Early Development, SEED study, and a study nested within the Danish registers) examining the association between autism spectrum disorder (ASD) and occupational asthmagens, agents capable of triggering an asthmatic response. In both of these studies, we assessed for occupational asthmagen exposure using an asthma-specific job-exposure matrix (JEM) for which we had some prior understanding of the degree of exposure misclassification.

Results: In the SEED study using Bayesian models accounting for exposure misclassification, we generated posterior distributions for the adjusted odds ratio (OR) with medians of 1.22 (95% credible interval (CrI): 0.50 – 2.62) and 0.65 (95% CrI: 0.23 - 1.85) assuming non-differential and differential exposure misclassification, respectively. When we apply misclassification correction using Sn and Sp priors from the SEED study to the Danish data, we observed posterior OR distributions with medians of 0.28 (95% CrI: 0.01 – 4.92) when we assume an uninformative
prior on the OR, and 0.60 (95% CrI: 0.23 – 1.70) when we set an informative prior on the OR based on the posterior distribution from the SEED model allowing for differential misclassification.

**Conclusion:** These Bayesian models build upon the conclusions of the previous chapters that there is no association between maternal occupational asthmagen exposures and ASD. This chapter also illustrates how Bayesian methods for exposure misclassification correction can be easily applied to occupational epidemiology. We argue that such analyses that account for exposure misclassification should become more commonplace to improve inference.
4.2. **Introduction**

Misclassification of a binary exposure may have a profound effect on study inference. If non-differential misclassification of exposure is ignored, the association between exposure and disease is expected to be attenuated towards the null. This can greatly reduce power and lead to missed associations as well as paradoxical false positives (Burstyn, Yang et al. 2014) with important biological and policy implications. In the case of differential exposure misclassification, effect estimates can be biased towards or away from the null, making interpretation particularly perilous. Differential misclassification is of particular concern in retrospective studies where exposure assessment is collected following disease ascertainment. An individual may be more likely to over-report or under-report exposure or circumstances giving rise to exposure (e.g. more detailed description of job duties) as a result of their health condition. Differential exposure misclassification can also result from dichotomizing continuous exposure that is known imprecisely (Flegal, Keyl et al. 1991, Gustafson 2004). Thus, misclassification may have severe and unanticipated results on study inference. As an historical example, Brownson et al. (1992) found no association between workplace exposure to environmental tobacco smoke (ETS) and lung cancer. However, they relied on a high percentage of surrogate reports of occupation for exposure classification, given the high mortality of lung cancer. Unfortunately, this may have resulted in high misclassification of exposure, biasing the true association towards the null. Associations between workplace ETS and lung cancer were detectable in later studies with a higher percentage of self-respondents, and thus, lower exposure measurement error (Fontham, Correa et al. 1994, Boffetta, Agudo et al. 1998, Wu 1999).

Given the important impact of measurement error on inference in environmental epidemiology, it is surprising that most reports do not routinely present error-corrected results (Jurek, Maldonado et al. 2006), or even the validity measures of the exposure assessment tools used. A number of methods have been proposed to account for misclassification in the context of retrospective case-control studies in situations where validity metrics are known. One can
implement a simple calculation to “correct” for misclassification using point estimates for the sensitivity (Sn) and specificity (Sp) of the exposure assessment tool. This method is relatively straightforward and has been applied in numerous settings. For example, Burstyn et al. (2010) applied such corrections in examining the association between self-reported maternal substance use (smoking, alcohol use, and drug dependence) and early neonatal morbidity. Upon “correcting” for poor Sn assuming non-differential misclassification error, ORs for neonatal morbidity were higher (Burstyn, Kapur et al. 2010).

However, the true values of Sn and Sp are not generally known, and must be taken as theoretical guesses, or from estimates obtained in other studies that had the measurement tool of interest and a gold standard measured simultaneously. Further, measurement error-corrected odds ratios obtained using a particular point estimate of Sn and Sp can be highly sensitive to small differences between the actual and guessed estimates (Marshall 1989, Gustafson, Le et al. 2001).

An alternative approach, that allows for differential misclassification and does not rely on point estimates, is to correct for exposure misclassification assuming distributions for Sn and Sp. This allows for correction based on theoretical or empirical data, while taking into account the uncertainty regarding the actual values of the misclassification parameters. In practice, this can be accomplished by implementing a Bayesian approach where one posits prior distributions for the Sn and Sp based on prior knowledge of the exposure assessment tool (Gustafson, Le et al. 2001). Intuitively, the procedure samples from these distributions and corrects for misclassification over many iterations. The procedure can distinguish between “good” and “poor” guesses of Sn and Sp by reconciling them with observed data and other parameters involved via likelihood methods. Such methods obtain samples from the posterior distribution of the true (misclassification-corrected) odds ratio relating exposure to outcome. A detailed description of the approach, Bayesian Markov Chain Monte Carlo (MCMC) algorithms, can be found in Gustafson (2004). In recent years, these Bayesian methods have been used to address
misclassification of exposures, such as smoking (MacLehose, Olshan et al. 2009, Luta, Ford et al. 2013), radiotherapy (Luta, Ford et al. 2013), occupational exposures (Liu, Gustafson et al. 2009, Beach, Burstyn et al. 2012), flea and tick treatment (Keil, Daniels et al. 2014), cannabis use (van Gelder, Donders et al. 2014), and self-report of men who have sex with men (Goldstein, Burstyn et al. in press). However, they have still not been widely applied in environmental epidemiology, and are particularly sparse in occupational epidemiology, despite knowledge that measurement error is potentially high for classification of certain occupational exposures.

We show here the application of a Bayesian approach for measurement error correction, described by Gustafson et al (2001), that has been applied in epidemiologic literature, but is not yet considered a mainstream approach. As an illustration, we show how Bayesian methods for correction for exposure misclassification can be applied in occupational epidemiology through an example of the study of the relationship between maternal exposure to occupational asthmagens, agents that can trigger an asthmatic response, and risk of autism spectrum disorder (ASD). We hypothesized that maternal exposure to asthmagens at the workplace might trigger a maternal immune response or reduce oxygen supply to the fetus that might lead to altered neurodevelopment (see Chapter 1 for details). We have examined the association between occupational asthmagen exposure and ASD in two population-based case-control studies: the Study to Explore Early Development (SEED) (Chapter 2) and a study nested within the Danish Registers (Chapter 3). In each, we estimated occupational asthmagen exposure using an asthma-specific job exposure matrix (JEM) (Kennedy, Le Moual et al. 2000) for which we had some prior knowledge of the quality of exposure classification. Here we illustrate how priors for Sn and Sp can inform our effect size estimates and interpretation of results. We demonstrate that these models can be easily applied in existing software packages and argue that these techniques should become more standard practice in the field of environmental epidemiology, as asserted by Burns et al. (2014) in discussing how epidemiology can be made more useful for risk assessment and policy-making.
4.3. Methods

4.3.a. Motivating epidemiological studies

We used two case-control studies in this analysis. The first is the Study to Explore Early Development (SEED), a United States multi-site, population-based case-control study designed to investigate risk factors, co-morbidities, and phenotypes of ASD (Schendel, Diguiseppi et al. 2012). The description of the study population is detailed elsewhere (Chapter 2), but briefly the study consists of three outcome groups: (1) an ASD case group, (2) a general population (POP) control group, and (3) a control group with non-ASD developmental delays (DDs). We only present comparisons between the ASD case group and POP control group in this analysis because it is the most directly relevant for illustrating our measurement error application. Participants were required to be born and reside in one of six study catchment areas in California, Colorado, Georgia, Maryland, North Carolina, and Pennsylvania between September 1, 2003 and August 31, 2006. Children in the ASD were ascertained through service and educational providers for children with developmental disabilities, whereas POP children were identified through random sampling of vital records (Schendel, Diguiseppi et al. 2012). Children completed developmental assessments between the ages of 30 to 68 months. ASD classification was based on results from the Autism Diagnostic Observation Study (ADOS) and the Autism Diagnostic Interview Revised (ADI-R). Maternal job histories were collected as part of computer assisted telephone interview shortly after enrollment in the study. Mothers reported jobs held for one month or more for at least ten hours per week from three months prior to the end of the pregnancy until the child was born or the mother stopped breastfeeding. Based on job title, task, and industry information, we coded jobs according to the International Labor Organization’s International Standard Classification of Occupations 1988 (ISCO-88) (International Labor Organization 1991). Analyses were restricted to mothers reporting at least one job that overlapped with the pregnancy.

Our second case-control study is nested in the Danish Registers. The study sample consists of 29,670 controls and 6,830 ASD cases singleton births born in Denmark between June
1, 1993 and December 31, 2007 with an employed mother in the year representing the majority of
the pregnancy. Details of the selection of the study sample are described elsewhere (Chapter 3).
ASD cases were defined as having a reported ICD-10 diagnosis of autism spectrum disorder
(ICD-10 codes: F84.0, F84.1, F84.5, F84.8 and F84.9) in the Danish Central Psychiatric Register
(DPCR) (Mors, Perto et al. 2011) from January 1, 1995 into early 2013. We linked the ASD
cases and controls to maternal occupation (Danish International Standard Classification of
Occupation, DISCO-88) and industry codes (NACE codes) from the Employment Classification
Module (AKM) (Petersson, Baadsgaard et al. 2011) to determine maternal occupation and
industry in the year that overlapped most with the pregnancy.

4.3.b. Occupational exposure assessment

We estimated maternal occupational asthmagen exposure job codes with an asthma-
specific job exposure matrix (JEM) (Kennedy, Le Moual et al. 2000). In the SEED study, we
linked the ISCO-88 codes with the JEM, and then completed a two-step procedure where we
revised ISCO codes and asthmagen exposure classification for flagged jobs based on comments
in the JEM and job descriptions in the SEED data. In the Denmark study, we merged DISCO-88
codes with the asthma JEM. Since we did not have job descriptions, we did not revise any job
codes based on the JEM comments. However, where possible, we used industry codes to re-
classify asthmagen exposure for flagged jobs based on suggestions included in the JEM.
4.3.c. Statistical analysis to accommodate misclassification of exposure

Overview of statistical analysis

In the first portion of the analysis, we illustrate how one can fit Bayesian models that correct for exposure misclassification in an individual-level analysis that includes adjustment for covariates in the SEED study comparing maternal occupational asthmagen exposure in ASD cases to POP controls. We contrast models where we assume near perfect exposure classification, as is typical in the majority of epidemiological studies, to those in which we assume exposure misclassification based on prior knowledge about the performance of the JEM in different settings. The extent of differential misclassification by case status is not possible to anticipate (it may be trivial or substantial), so we also present results from models that allow for differential exposure misclassification as compared to those that do not. Thus, we present four different models (Table 1): (1) assuming almost perfect classification of asthmagen exposure and non-differential exposure misclassification (model S_A; SEED study, model A), (2) adopting priors on misclassification parameters based on previous studies and non-differential exposure misclassification (model S_B; SEED study, model B), (3) assuming almost perfect classification of exposure but allowing for differential misclassification (model S_C), and (4) setting priors on misclassification parameters based on previous studies and allowing for differential exposure misclassification (model S_D).

In the second portion of the analysis, we apply misclassification correction using data from a two-by-two contingency table of maternal occupational asthmagen exposure by ASD case-control status from the Danish study, with Sn and Sp priors set by the SEED study. (We do not conduct individual-level analysis in the Danish study because of limitations on software available for individual level analyses.) We show two examples of updating priors based on SEED posteriors with Danish data to obtain new posteriors incorporating results from both studies. In the first scenario, we set priors on Sn and Sp based on posterior distributions on these parameters from SEED model S_D and assume no prior knowledge of the odds ratio (model D_D1;
Denmark, model 1). In the next model, we set priors on Sn, Sp and the odds ratio based on posterior distributions from the SEED model S_D (model D_D2). In both of these models we allow for differential misclassification of exposure as dictated by theory and evidence from the SEED study (Table 3).

Since we use individual level data for the SEED Bayesian analyses and only a contingency table as data for the Denmark Bayesian analyses, the model specification is different in Models S_A through S_D as compared to models D_D1 and D_D2. We start by explaining the model specification, priors and implementation of the analysis of SEED. We then address the specifics of the analysis of the Danish case-control study separately.

SEED: Model specification

For the SEED Bayesian misclassification correction, we specify three models: (1) an exposure model, (2) a measurement model and (3) an outcome model, following Gustafson (2004). We express these three models below, where X indicates being “truly” exposed (X=1) or unexposed (X=0) to an occupational asthmagen; X* represents those classified (i.e. assigned by JEM) as exposed (X*=1) or unexposed (X*=0) to an occupational asthmagen; Sn is the overall sensitivity of X* assuming sensitivity is the same in cases and controls; Sp is the overall specificity of X* assuming specificity is the same in cases and controls; Sn_0 is the sensitivity of X* among controls; Sn_1 is the sensitivity of X* among ASD cases; Sp_0 is the specificity of X* among controls; Sp_1 is the specificity of X* among ASD cases; Y represents being an ASD case (Y=1) or a control (Y=0); Z represents a vector of confounders with coefficients \( \alpha \) representing the log-odds of true asthmagen exposure, and coefficients \( \beta \) representing the log-odds of being an ASD case.
(1) Exposure model:
\[
\text{logit}(\Pr(\text{X}=1)) = \alpha_0 + \alpha \text{Z}
\]

(2) Measurement model:

(a) Non-differential exposure misclassification
\[
\Pr(\text{X}^*=1) = \Pr(\text{X}=1)Sn + (1 - \Pr(\text{X}=1))(1 - Sp)
\]

(b) Differential exposure misclassification
\[
\Pr(\text{X}^*=1) = \begin{cases} 
\text{If } Y = 0: \Pr(\text{X} = 1)Sn_0 + (1 - \Pr(\text{X} = 1))(1 - Sp_0) \\
\text{If } Y = 1: \Pr(\text{X} = 1)Sn_1 + (1 - \Pr(\text{X} = 1))(1 - Sp_1)
\end{cases}
\]

(3) Outcome model:
\[
\text{logit}(\Pr(\text{Y}=1)) = \beta_0 + \beta \text{X} + \beta \text{Z}
\]

The exposure model expresses the log odds of the true occupational asthmagen exposure conditional on the confounders in the model. The measurement model specifies probability of observed (misclassified) occupational asthmagen exposure as a function of the probability of true occupational asthmagen exposure, the sensitivity, and the specificity. We denote two possible misclassification models above. In models S_A and S_B, we assume that misclassification of occupational asthmagen exposure by the JEM is non-differential as depicted above in measurement model option (a). In models S_C and S_D, we relax this assumption to allow for differential misclassification by ASD case status as depicted in measurement model option (b) above, such that our observed (misclassified) occupational asthmagen exposure is also conditional on case status. In the outcome model, we model the log odds of having a child with ASD as a function of the true maternal occupational asthmagen exposure status and the potential confounders. Confounders in our analysis included maternal age at child’s birth (continuous), parity (1, 2, >2), child’s sex, maternal race/ethnicity (white, black, Asian, Hispanic, multiracial or other), maternal education (less than high school, high school, some college/trade school, bachelors, advanced degree), current total household income (<$30,000, $30,000-70,000,
SEED: Selection of priors

In models S_A and S_C, we assumed almost perfect classification of exposure by setting prior distributions of \( \text{Beta}(1000,1) \) on sensitivity and specificity (Table 4-1). These distributions have a mean of 0.999 and standard deviation of 0.001. We conceptualize these as models where we assume virtually no exposure misclassification and suspect that the results should be roughly equivalent to typical uncorrected analyses.

In models S_B and S_D, we correct for measurement error based on priors for sensitivity and specificity of the JEM from previous literature. Since incorporating prior knowledge is an important aspect of Bayesian inference, we detail here the origin of the sensitivity and specificity priors for the asthma-specific JEM, which were initially elucidated through expert opinion and then were updated with data from two analyses. Liu et al (2009) asked experts (two occupational physicians and one occupational hygienist) to report the best guess, upper bound, and lower bound of true value for the sensitivity and specificity of the asthma-specific JEM. Liu et al (2009) obtained posterior distributions for sensitivity and specificity for JEM by updating these priors using data from workers’ compensation claims and physician billing records from Alberta, Canada, to examine the association between asthmagen exposure and new adult onset asthma. Beach et al (2012) further updated the sensitivity and specificity posteriors from the Liu et al (2009) in a comparable analysis using similar data from British Columbia, Canada. We used the posterior distributions of sensitivity and specificity of the JEM from Beach et al (2012) as a basis for our prior distributions in this analysis.

Beach et al (2012) reported sensitivity and specificity posterior distributions for 16 categories of asthmagen exposures. Since there was not much variability across the asthmagen
categories for these misclassification parameters, we averaged the medians, 2.5\textsuperscript{th} percentiles, and 97.5\textsuperscript{th} percentiles to obtain a best guess of the mode, 2.5\textsuperscript{th} percentile, and 97.5\textsuperscript{th} percentile for sensitivity and specificity distributions for any asthmagen. The best guess of the 2.5\textsuperscript{th} percentile, mode, and 97.5\textsuperscript{th} percentile was 0.133, 0.381, and 0.728 for sensitivity and 0.990, 0.992, and 0.994 for the specificity, respectively. We used the \textit{betaExpert} function in R to determine parameters for beta distributions roughly corresponding to the above percentiles and then used these \textit{Beta} distributions as priors for sensitivity and specificity. The parameters for these \textit{Beta} distributions for Sn and Sp as well as the mean and SD of these distributions are listed in Table 1. The sensitivity and specificity distributions were centered on means of 0.41 and 0.991, respectively (Table 4-1).

In all models, we assumed a normally distributed uninformative prior with a mean of 0 and variance of 0.5 for all coefficients (log-odds ratios) in the outcome and measurement models, except for the intercept of the outcome model and the coefficient for sex. For these two coefficients, we set an uninformative normally distributed prior with a mean of 0 and a variance of 1. The \textit{N}(0, 0.5) distribution implies that the true odds ratio is roughly between 1/4 and 4 while a \textit{N}(0, 1) distribution implies that the true odds ratio is roughly between 1/7 and 7. We judged these to be sufficiently vague and realistic while not informing the direction the associations. Flatter priors are possible to specify in principle but in practice we encountered problems with convergence with less informative priors.

\textit{SEED: Model convergence and characterizing posteriors}

We ran a complete case analysis with 437 ASD cases and 660 controls. Bayesian analysis was implemented in Winbugs 1.4 (Lunn, Thomas et al. 2000) through the R2WinBUGS (Sturtz, Ligges et al. 2005) package in R version 3.1.2. We ran 3 chains for 25,000 iterations of the simulation, removing the initial 5,000 iterations to allow for a burn-in period. In order to reduce autocorrelation between neighboring iterations, we only sampled every 20\textsuperscript{th} iteration of
accepted samples from the posterior distribution. For model S_B we ran only 2 chains for 15,000 iterations with a 1,500 burn-in period because we received WinBUGS errors for models that were run with more chains or for more iterations. We reviewed trace plots, autocorrelation plots, density plots, and Gelman plots to check for convergence. Code and convergence diagnostics are included in Appendix III. The Bayesian approach generated posterior distributions for the adjusted odds ratio, consisting of a summary odds ratio (median of the posterior distribution) and a 95% credible interval (corresponding to the 2.5th and 97.5th percentiles of the posterior distribution). Posterior distributions were also obtained for the Sn and the Sp of the JEM, and the maternal occupational asthmagen exposure prevalence among controls.

*Denmark: Model specification and selection of priors*

In the second series of Bayesian analyses, we update beliefs from the SEED study with a contingency table of data from a Denmark register study. Crude and adjusted odds ratios for the association between maternal asthmagen exposure and ASD in the Denmark register study are very similar (Chapter 3), so we are not concerned that confounders are not considered in these Bayesian analyses.

No effect size prior: If we have no prior knowledge about the magnitude of the odds ratio relating exposure and the outcome, we proceed as follows. In our contingency table, we have observed asthmagen exposure prevalences, \( X_0 \) and \( X_1 \), for controls and cases, respectively, for \( N_0 \) controls and \( N_1 \) cases. We assume that observed prevalences follow binomial distributions: 
\[
X_0 \sim Bin(p_0, N_0) \quad \text{and} \quad X_1 \sim Bin(p_1, N_1).
\]
If \( r_0 \) and \( r_1 \) are the true exposure prevalences for cases and controls, respectively, then allowing for differential exposure misclassification we can calculate the true exposure prevalence among controls, 
\[
r_0 = \frac{(p_0 + Sp_0 - 1)}{(Sn_0 + Sp_0 - 1)},
\]
and the true prevalence among cases, 
\[
r_1 = \frac{(p_1 + Sp_1 - 1)}{(Sn_1 + Sp_1 - 1)}.
\]
Over many MCMC iterations, we sample candidate values for Sn and Sp for cases and controls from prior distributions based on the SEED analyses and generate posterior distributions for corrected exposure prevalences, \( r_0 \) and \( r_1 \). We
then use these corrected values for exposure prevalences to calculate corrected odds ratios as $\theta = \text{expit}(r_1)/\text{expit}(r_0)$ if they were accepted by the Gibbs sampler.

**Effect size prior:** When we do have prior knowledge about the magnitude of the odds ratio ($\theta$) relating the exposure and outcome, we set prior distributions on $r_0$ and log odds ratio to induce a prior distribution on the true exposure prevalence among cases, $r_1 = ((\theta)(r_0))/(((\theta)(r_0)+1-r_0))$. The distributions for $r_0$ and $r_1$ are then reconciled with the observed exposure prevalences. Selected candidate values for sensitivity, specificity, and $\theta$ are retained for the posterior distributions if they are deemed plausible based on the likelihood of the data given the model and priors. The rest of the model specification is the same as for the set-up where there was no prior information about association of exposure and ASD ($\theta$).

Prior distributions for models D_D1 and D_D2 are listed in Table 4-3. In both model D_D1 and D_D2, we set priors on sensitivity of Beta(15.6, 55.8) for controls and Beta(8.2, 17.8) for cases. The prior on specificity for both cases and controls was Beta(718, 8.2), based on posterior distributions from model S_D. In model D_D1 we assume a non-informative prior on the log odds ratio, so we assume a uniform prior distributions (expressed as Beta(1, 1)) on the true exposure prevalences, $r_0$ and $r_1$, for cases and controls, respectively. In model D_D2, we set a uniform prior only on the true exposure prevalence among the controls, $r_0$, and set an informative normal prior with a mean of -0.43 with a variance of 0.29 on the log odds ratio based on the odds ratio posterior for SEED model S_D.

**Denmark: Model convergence and characterization of posteriors**

The contingency table consisted of 6,101 exposed controls, 23,569 unexposed controls, 1,290 exposed cases, and 5,540 unexposed cases. For models D_D1 and D_D2, we ran 200,000 iterations, removing the initial 10,000 iterations to allow for a burn-in period and selected every 100th iteration for inclusion in the posterior distribution in order to reduce auto-correlation. We
generated posterior distributions for the odds ratio, sensitivity, specificity and exposure prevalence.

4.4. Results

The uncorrected, adjusted, odds ratio (OR) for maternal occupational asthmagen exposure comparing ASD cases to population controls in the SEED study was 1.32 (95% confidence interval (CI): 0.90 - 1.94) (Chapter 2). When we assumed near perfect classification of exposure, which is essentially equivalent to not adjusting for exposure misclassification, we observed posteriors of 1.29 (95% CrI: 0.89 – 1.86) and 1.30 (95% CrI: 0.88 – 1.89) for models assuming non-differential (model S_A) and differential exposure (model S_C) misclassification, respectively (Table 4-2). The Bayesian analysis (model S_B) accounting for exposure misclassification and assuming non-differential misclassification generated a median OR of 1.22 with a 95% credible interval (CrI) of 0.50 – 2.62 (Table 2). In the analysis allowing for differential exposure misclassification (Model S_D), the median adjusted OR was 0.65 (95% CrI: 0.23 - 1.85). These results suggest that the analyses not adjusted for exposure misclassification are positively biased. We also note that the posterior distribution of OR for the model that assumes non-differential misclassification is slightly more concentrated with narrower credible interval.

The Bayesian analyses in models S_B and S_D yielded lower sensitivity distributions compared to prior distributions for sensitivity, but priors and posteriors were similar for the specificity (Table 4-2). We also observe that the median of the posterior distribution for the Sn in cases was higher than the median of the Sn posterior distribution for the controls in the model that allowed for differential exposure misclassification. Though the posterior Sn distributions produced for Sn for cases and controls from Model S_D overlap, this suggests that measurable differential misclassification could be at play. Regardless of the assumptions regarding the
misclassification model, we conclude that there is no evidence of a measurable association between maternal asthmagen exposure and ASD in SEED.

In the Danish case-control analysis, we found an inverse association between maternal asthmagen exposure and ASD (crude OR: 0.90, 95% CI: 0.84-0.96) (Chapter 3). The posterior distributions for sensitivity and specificity resulting from models D_D1 and D_D2 are similar to the posteriors from SEED model S_D (Table 4). In Model D_D1, we observed a posterior OR distribution with a median of 0.28 and a 95% CrI of 0.01 – 4.92 (Table 4-4). The median OR is pulled further from the null compared to the uncorrected estimate because of the lower sensitivity of controls compared to cases. Even though the Denmark study has a large sample size, in the absence of an informative prior on the credible interval of the posterior distribution is broad. In model D_D2 were we set an informative prior on the odds ratio based on the posterior from SEED model S_D, we generate a posterior odds ratio with a median at 0.60 (95% CrI: 0.23 – 1.70). The posterior odds ratio is pulled towards the SEED result by inclusion of this prior. The credible interval is narrower in comparison to the model D_D1 as a consequence of setting this informative prior. The posterior distribution for the Denmark model D_D2 is nearly identical to SEED model S_D and only a little more concentrated around the median. Thus, despite the large sample size from this second study we learn little new because of the poor exposure classification by the JEM.

**4.5. Discussion**

In this paper, we illustrate a Bayesian method for correcting for exposure misclassification in the context of two studies examining the association between maternal occupational asthmagen exposure and ASD in the children. Inferentially, our models suggest that there is no measurable association between maternal asthmagen occupational exposure around the time of pregnancy and ASD.
Our results illustrate key points regarding exposure misclassification in epidemiologic studies. First, we demonstrate here that the odds ratio estimate can move in unexpected ways depending on whether or not one assumes that misclassification is differential. In the epidemiologic literature, authors often assert the belief that exposure misclassification is non-differential and thus results are biased to the null, and argue that reported associations are likely not “spurious” under this rationale. However, in practice it may be difficult to know the true extent of differential misclassification. In the SEED study, we may suspect that differential recall for many self-reported variables because mothers who have a child with an ASD may recall the pregnancy differently than mothers of typically developing controls. However, theoretically, it is also possible for differential misclassification to occur through the process of dichotomizing a continuous exposure measured with error, regardless of the timing of exposure query (Flegal, Keyl et al. 1991, Gustafson 2004). Thus, we assert that it is important to consider the potential impact of both differential and non-differential exposure misclassification error. The extent to which exposure misclassification is non-differential by dichotomizing a continuous exposure measure depends on the strength of exposure-outcome association (Flegal, Keyl et al. 1991). If the true association does not exist or is very weak, then we do not expect exposure misclassification to deviate from non-differential. The fact that we observe little evidence for measurable differential misclassification in the Denmark study is concordant with the observation of no measurable association between exposure and outcome.

Second, we illustrate that even in situations of relatively large sample sizes, such as in the Danish study, we learn little if exposure assessment is poor, and may be falsely confident in relative precise uncorrected effect estimates. In that study, there was a precise protective effect estimate of occupational asthmagen exposure on ASD risk in the Denmark study when we did not account for exposure misclassification. Yet, when we corrected for exposure misclassification, we observed a more protective effect and the credible intervals widened. Specifically, without setting a prior on the log odds ratio, our 95% credible interval for the exposure OR ranged from 0.01 to
4.92, despite the large sample size. When a prior distribution on the OR based on the SEED study was implemented, we observed nearly identical results to the posterior OR from the SEED study. The JEM we chose is among the best of its kind, yet the low sensitivity limits our ability to confidently identify new associations. The inability to improve our estimates and precision in the very large Danish study illustrates that without improving exposure measurements and assessment methods we have perhaps reached the limit of what we can discover with tools like JEMs when the associations are weak. Conversely, these imperfect tools may also generate spurious associations if exposure misclassification is treated as perfect.

One note of concern regarding these models is that we must be careful in setting prior distributions, especially given problems with non-identifiability. Recall that $p_i = r_i * S_n + (1 - r_i) * (1 - Sp)$ where $p_i$ is observed exposure prevalence and $r_i$ is the true exposure prevalence; $i=0$ denotes controls and $i=1$ denotes cases. If we observe an exposure prevalence, $p_i$, of 0.21, and specificity, $Sp$, is approximately 1, then there are two possible solutions for $(r_i, S_n)$: $(0.3, 0.7)$ and $(0.7, 0.3)$. The priors will determine the solution that is selected. Thus, if we place a prior on sensitivity that is concentrated on 0.3, the solution for the true exposure prevalence will converge upon 0.7. Since we have prior knowledge of the performance of the JEM and not true exposure prevalence in the selected samples, we place an informative prior on the sensitivity and specificity instead of the true exposure prevalence. In our analysis, the particular identifiability issue only emerges when the specificity is close to one, but illustrates that use of these models should be guided by knowledge. Prior knowledge may also be complicated by the fact model parameters may not be directly transportable across different study populations, suggesting the importance of perhaps considering a few plausible priors.

This paper illustrates the sensitivity of effect size estimates, and statistical inference, to exposure misclassification in occupational epidemiology. We show how Bayesian procedures can be readily applied to address this misclassification. These methods are true to the theoretical assumption that exposure misclassification is ubiquitous and accommodates our uncertainty in the
amount of misclassification as specified by assumed sensitivity and specificity, and indeed treats these parameter assumptions as random variables, rather than known quantities. We acknowledge that by assuming misclassification error, and particularly assuming distributions for the misclassification parameters instead of point estimates, we potentially sacrifice precision for validity. In situations where little misclassification error exists, this may be an unnecessary sacrifice that results in inefficiency. However, in true situations of error, this is the more appropriate inferential framework. Although we illustrate these methods through use of WinBUGS and R, there are alternative packages that can be used for Bayesian inference, including OpenBUGS (an open-source version of BUGS software) (Thomas, O'Hara et al. 2006), Just Another Gibbs Sampler (JAGS) (Plummer 2003), and STAN (Stan Development Team 2014). In epidemiologic studies we often present results as if there is no measurement error despite the fact that it exists. Thus, we argue that analyses that account for this misclassification should become more commonplace within the epidemiologic literature in general. Though ultimately, these misclassification error methods cannot replace investing in the development of better exposure assessment tools and validating the quality of currently existing exposure assessment tools.
4.6. References


Goldstein, N. D., I. Burstyn and S. Welles (in press). "To be or not to be: Bayesian correction for misclassification of self-reported sexual behaviors among men who have sex with men." Epidemiology.


Table 4-1: Prior distributions for SEED maternal occupational asthmagen exposure misclassification correction.

<table>
<thead>
<tr>
<th>Allow differential misclassification?</th>
<th>Model S_A</th>
<th>Model S_B</th>
<th>Model S_C</th>
<th>Model S_D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>Beta (1000, 1)</td>
<td>Beta (3.6, 5.2)</td>
<td>Beta (1000, 1)</td>
<td>Beta (3.6, 5.2)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.999 (0.001)</td>
<td>0.41 (0.16)</td>
<td>0.999 (0.001)</td>
<td>0.41 (0.16)</td>
</tr>
<tr>
<td>Specificity</td>
<td>Beta (1000, 1)</td>
<td>Beta (1000, 9.1)</td>
<td>Beta (1000, 1)</td>
<td>Beta (1000, 9.1)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.999 (0.001)</td>
<td>0.991 (0.003)</td>
<td>0.999 (0.001)</td>
<td>0.991 (0.003)</td>
</tr>
</tbody>
</table>
Table 4-2: Posterior distributions, median (95% Credible Interval), for SEED maternal occupational asthmagen exposure misclassification correction.

<table>
<thead>
<tr>
<th></th>
<th>Model S_A</th>
<th>Model S_B</th>
<th>Model S_C</th>
<th>Model S_D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds Ratio(^1)</td>
<td>1.29 (0.89 – 1.86)</td>
<td>1.22 (0.50 – 2.62)</td>
<td>1.30 (0.88 – 1.89)</td>
<td>0.65 (0.23 – 1.85)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>0.999 (0.997 – 1.00)</td>
<td>0.23 (0.17 – 0.35)</td>
<td>0.999 (0.996 – 1.00)</td>
<td>0.21 (0.15 – 0.33)</td>
</tr>
<tr>
<td>Cases</td>
<td>0.999 (0.996 – 1.00)</td>
<td>0.99 (0.98 – 1.00)</td>
<td>0.999 (0.996 – 1.00)</td>
<td>0.99 (0.98 – 1.00)</td>
</tr>
<tr>
<td>Specificity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability of true exposure among controls</td>
<td>0.14 (0.14 – 0.14)</td>
<td>0.60 (0.38 – 0.80)</td>
<td>0.14 (0.14 – 0.14)</td>
<td>0.65 (0.41 – 0.91)</td>
</tr>
</tbody>
</table>

\(^1\): adjusted for covariates as described in text
Table 4-3: Prior distributions for Denmark contingency table exposure misclassification correction; differential exposure misclassification is assumed and modeled.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Model D_D1</th>
<th>Model D_D2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity Controls Mean (SD)</td>
<td>Beta (15.6, 55.8)</td>
<td>Beta (15.6, 55.8)</td>
</tr>
<tr>
<td>Sensitivity Cases Mean (SD)</td>
<td>Beta (8.2, 17.8)</td>
<td>Beta (8.2, 17.8)</td>
</tr>
<tr>
<td>Specificity Mean (SD)</td>
<td>Beta (718, 8.2)</td>
<td>Beta (718, 8.2)</td>
</tr>
<tr>
<td>Log Odds Ratio</td>
<td>Uninformative</td>
<td>N(-0.43, 0.29)</td>
</tr>
<tr>
<td>P(exposure</td>
<td>controls)</td>
<td>Beta (1,1)</td>
</tr>
</tbody>
</table>
Table 4-4. Posterior distributions, median (95% Credible Interval), for Denmark contingency table maternal occupational asthmagen exposure misclassification correction.

<table>
<thead>
<tr>
<th></th>
<th>Model D_D1</th>
<th>Model D_D2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds Ratio</td>
<td>0.28 (0.01 – 4.92)</td>
<td>0.60 (0.23 – 1.70)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>0.24 (0.21 – 0.32)</td>
<td>0.25 (0.21 – 0.33)</td>
</tr>
<tr>
<td>Cases</td>
<td>0.30 (0.20 – 0.48)</td>
<td>0.26 (0.19 – 0.41)</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.99 (0.98 – 1.00)</td>
<td>0.99 (0.98 – 1.00)</td>
</tr>
<tr>
<td>Probability of true exposure among controls</td>
<td>0.86 (0.62 – 0.99)</td>
<td>0.82 (0.62 – 0.98)</td>
</tr>
<tr>
<td>Probability of true exposure among cases</td>
<td>0.62 (0.38 – 0.96)</td>
<td>0.73 (0.44 – 0.98)</td>
</tr>
</tbody>
</table>
Chapter 5. General Discussion and Concluding Remarks
5.1. Summary of results

The main goal of this work was to examine the association between parental exposure to occupational asthmagens and risk of autism spectrum disorder (ASD). We evaluated this relationship in the Study to Explore Early Development (SEED) (Schendel, Diguisepi et al. 2012) and a newly established case-control study sampled from the Danish population via register linkage. In both studies, we estimated whether or not a parent was exposed to an occupational asthmagen during the pregnancy using an asthma-specific job exposure matrix (JEM) (Kennedy, Le Moual et al. 2000). Below we discuss and compare the results of these studies with a particular aim towards understanding strengths and limitations of examining the hypothesized associations in the two study designs. We also conducted Bayesian analyses adjusting for misclassification of exposure, given the particular susceptibility of occupational asthmagen exposure to misclassification.

In the SEED study (Chapter 2), we did not observe a marginal association between maternal occupational asthmagen exposure and ASD. The adjusted odds ratio (aOR) for maternal occupational asthmagen exposure was 1.32 (95% confidence interval (CI): 0.90 - 1.94) comparing 437 ASD cases to 660 population controls. Occupational asthmagen exposure varied by socio-demographic characteristics, such that women with higher parity, lower education, lower household income, younger age, or of Black, Hispanic, or other minority race were more likely to have at least one asthmagen exposed job during the pregnancy. We did not see any evidence of an interaction between maternal occupational asthmagen exposure and either maternal history of asthma or child’s sex. There was some suggestion of a weak association between maternal asthma diagnosis prior to the child’s birth and ASD, and a potential for effect modification of occupational asthmagen exposure risk by maternal allergy. The positive point estimate of the adjusted odds ratio comparing ASD cases to population controls was largely driven by families where the mother reported a history of allergy: aOR=1.87, 95% CI: 1.01 – 3.48 in mothers with a history of allergy versus aOR=1.06, 95% CI: 0.65 – 1.73 in mothers without a history of asthma).
However, we caution against over-interpreting these stratified results given the overlapping confidence intervals. We did not see a difference between associations estimated when ASD with or without intellectual disability was considered.

In the Danish study (chapter 3), we examined association of parental exposure to occupational asthmagens in relation to risk of ASD among 6,830 cases and 29,670 controls in maternal analyses and 7,799 cases and 32,335 paternal analyses sampled from population registers born between 1993 and 2007. We observed weakly protective associations between ASD in the child and both maternal and paternal occupational asthmagen exposure, with adjusted ORs of 0.88 (95% CI: 0.82 – 0.95) and 0.92 (95% CI: 0.86 – 0.98), respectively. We found that the socio-demographic determinants of parental occupational asthmagen exposure were similar to those in the SEED study. Parental occupational asthmagen exposure was associated with lower parental age, lower parental income, higher maternal parity, and basic or vocational parental education. Maternal asthma prior to the child’s birth did not modify the association between maternal occupational asthmagen exposure; however, we did see evidence of an interaction between paternal occupational asthmagen exposure and paternal asthma in relation to ASD in the children.

We do not believe that parental exposure to occupational asthmagens protects against ASD in the children. Rather, we suspect that there may be some underlying bias at play in the Danish study. First, if parents with certain health conditions are more likely to have a child with an ASD and are less likely to work in an asthmagen exposed job, then there may be a negative confounding bias and we may estimate an inverse association between occupational asthmagen exposure and ASD. Ideally, we could attempt to adjust for this manifestation of the healthy worker effect by accounting for possible confounding by parental health conditions prior to the pregnancy year. We tried to do this by adjusting for asthma diagnosis prior to the birth of the child, but unfortunately we do not know for certain that these diagnoses preceded occupational asthmagen exposure, given limitations of the registry data. In addition, since our knowledge of
history is based on specialist report of asthma diagnosis to a health registry, we are likely lacking complete information on parental health conditions. Second, since the ASD outcome necessitates restricting the study population to live-born children, it is possible that we have created a selection bias if asthmagen exposure is associated with poor birth outcomes. This form of bias has been described in other literature examining the impact of toxicant exposures during pregnancy on childhood health outcomes (Liew, Olsen et al. 2015). This is a plausible bias for maternal exposure in our study because maternal asthma is associated with poor pregnancy outcomes but it does not account for the apparent protective effect of paternal exposure. There also may be differences in case ascertainment in urban as opposed to rural areas, which could possibly explain the inverse association between occupational asthmagen exposure and ASD, particularly for paternal asthmagen exposure and ASD where this association is largely driven by agricultural exposures. Finally, in estimating this association between parental occupational asthmagen exposures and ASD in chapters 2 and 3, we do not account for exposure misclassification, which is an inevitable consequence of using any JEM in exposure assessment.

In chapter 4, we present an example of Bayesian correction for exposure misclassification in the SEED and Danish studies. Overall, we conclude that once we correct for exposure misclassification the results are consistent with there being no detectible association (positive or negative) between occupational asthmagen exposure and ASD. We also illustrate through use of these techniques that results can be biased in unexpected ways depending on whether or not non-differential misclassification is at play. Unfortunately, differential misclassification may occur as a result of recall bias or for theoretically reasons when one dichotomizes a continuous exposure that has been measured with error (Flegal, Keyl et al. 1991, Gustafson 2004), so it is impossible a priori to ascertain which type of misclassification error is likely in any given setting. We also illustrate that even with the large Danish study, we gain little in terms of new information because of the low sensitivity of the JEM. We use this example to assert the importance of investing efforts in improving exposure assessment methods in environmental and occupational
epidemiology and to argue the use of these Bayesian methods in determining robustness of study findings to measurement error.

5.2. Strengths and weaknesses: comparing SEED and Danish case-control studies

Though our results converge upon the conclusion that there is no marginal association between occupational asthmagen exposure and ASD, there are numerous reasons why we may see different patterns in the SEED analysis compared to the Danish analysis. First, selection of participants into the studies differs. In the SEED study, controls were recruited from random sampling of vital records, but had to actively agree to participate. DiGuisepi et al. (submitted) show that the distribution of socio-demographic characteristics in the control group is different than the demographics of the source population. In the Danish case-control study, we randomly selected controls born during the same time period as the cases without requiring active participation, thus cases and controls in this study are more likely to represent the underlying exposure prevalence in the source population.

Second, though we used the same asthma-specific job exposure matrix (JEM) to estimate occupational asthmagen exposure in both studies, the quality of occupational information greatly differed. In the case of SEED, we manually coded jobs based on string-text descriptions from self-reported questionnaires detailing job titles and tasks during the pregnancy period. We were also able to use these descriptions to further refine exposure assessment based on comment codes in the JEM and we were also able to narrowly pinpoint which jobs overlapped with the pregnancy. In contrast, the Danish occupational codes were generated from administrative sources, so we cannot be as certain of their accuracy. We attempted to further refine exposure assessment using industry codes, but we did not have any description of job tasks, so this could have led to additional misclassification of exposure. Also, we selected the job from the year that we thought best represented the pregnancy period, but we cannot be certain that the mother was actually employed at the job during the pregnancy. Since the jobs in the Denmark study were
from administrative records, the exposure assessment was not subject to recall bias. Recall bias may be a concern in the SEED study where parents with children with ASD might recall jobs with greater detail than typically developing children. This source of information bias may in fact explain the slight positive association in SEED.

Third, the outcome assessment methods in the two studies may reflect different populations of ASD cases. In the SEED study, case status is determined by clinical assessments based on ADOS criteria, ADI-R criteria, and in some cases clinical judgment. Trained professionals administered the assessments, and completed exercises to establish and maintain reliability (Wiggins, Reynolds et al. 2014). However, there is some discrepancy between the SEED ASD criteria and the DSM-IV diagnostic criteria (Wiggins, Reynolds et al. 2014). In contrast, ASD case status in the Danish study was based on registration of ICD-10 codes in the Danish Psychiatric Central Register. In Denmark, children with suspected ASD are referred to specialists. Child psychiatrists determine and then register the diagnosis. One study has validated autism diagnoses in the Danish Psychiatric Central Register (Lauritsen, Jorgensen et al. 2010) (Lauritsen, Jorgensen et al. 2010), but the validity of the broader category of ASD diagnoses is unknown. While universal healthcare in Denmark may reduce barriers to receiving diagnoses, we are uncertain of the degree to which diagnoses may be missed and what factors predict missed diagnoses. Thus, the criteria for case status and the mechanism for ascertaining cases are different in the two studies.

Overall, the major strengths of the SEED study are the richness of information on occupation history during the pregnancy period, the detailed case ascertainment and the availability of a wide-array of other covariates. Limitations include the relatively small sample size and concerns related to sample selection. The Denmark case control study is much larger and the population controls likely represent the employed women in the underlying Danish population, but we are less confident in the exposure assessment. A concern with both studies is the misclassification inherent in the asthma-specific JEM, where we assume that all similar jobs
have the same exposure status. Nevertheless, this works demonstrates the investigation of a biologically plausible hypothesis using existing data sources and used epidemiologic tools capable of detecting true associations because the JEM was capable of replicating the known association between asthmagen exposures and asthma.

5.3. Challenges in ASD epidemiology research

The field of ASD environmental epidemiology is still in its infancy. In order to better characterize environmental risk factors for ASD, we must understand and surmount a number of challenges. First, it is important to measure valid individual level exposures during etiologically relevant time windows. Administrative records, such as employment records described in the Danish study, may be used for assessment of exposure though these may be lacking in detail or potentially even inaccurate. Questionnaire data could be used to assess exposure, though this method of exposure assessment may be subject to recall bias if questionnaires are administered following disease ascertainment. If samples are available, biomarker measurements are a better method of exposure assessment as they are not subject to these recall concerns. The challenge with biomarkers is that they necessitate sample collection during a relevant time window (e.g. the pregnancy), which may not be available, and they may tell us little about exposure pathways. Biomarker measurement is expensive and requires consideration of the biological half-lives of specific toxicants as they are excreted from the body. Occupational epidemiology may provide some advantage in identifying risk factors for ASD because occupational exposures are generally much higher than environmental exposures. However, it can be challenging to assess occupational exposures.

Another challenge to autism epidemiology research is outcome assessment. There are no known biomarkers for ASD so case definitions are based on clinical assessment and judgment. Thus, outcome misclassification is of concern because it degrades power and biases effect estimates. In addition, individuals with ASD display heterogeneous symptoms and co-
morbidities. By collapsing all individuals with ASD into a single category for research purposes, we may dilute our chances of observing an effect if etiology differs depending on the type of ASD.

Large studies are needed to have adequate power to identify small environmental effects in the context of possible effect modifiers, such as genetic susceptibility. However, as demonstrated in this work, large studies may converge on biased results if exposure measurement is poor. The bias can be in unexpected direction, yielding either false positives, or false negatives. This problem would be further aggravated by outcome misclassification. Thus, studies must balance this sample size demand with valid measurements of individual exposures or at least measures of exposure with known and acceptable error rates. Since ASD is relatively rare, large cohort studies measuring exposure measurements during the pregnancy may not yield enough cases to tease apart these etiologic mechanisms. One way to combat this challenge is to establish enriched risk cohorts where women who already have a child with an ASD are enrolled during a new pregnancy and the child is followed through the first few years of life. Two enriched autism longitudinal studies currently exist, the Early Autism Risk Longitudinal Investigation (EARLI) (Newschaffer, Croen et al. 2012) and the Markers of Autism Risk in Babies – Learning Early Signs (MARBLES) study. Alternate approaches include linking registry data with bio-banked samples or combining data from multiple existing cohort studies.

5.4. Future directions

Though we do not find much evidence supporting a link between occupational asthmagen exposures and ASD, our results do not negate a role for the maternal immune system in relation to ASD. In our study, we did not address differential susceptibility to occupational asthmagen exposures. One approach to further this line of research is to examine the association between asthmagen exposure and ASD accounting for maternal genes involved in asthmagen susceptibility. Another approach to testing the hypothesis that there may be a link between
maternal immune activity and ASD is to measure biomarkers of immune activity in maternal bio-
samples from the pregnancy. Two studies have linked differences in cytokine levels in maternal
serum during pregnancy or in amniotic fluid to ASD (Abdallah, Larsen et al. 2011, Goines, Croen
et al. 2011). Since maternal immunoglobulin E (IgE) levels are associated with a mothers
tendency towards producing an allergic response, measurement of total and/or specific IgE may
be useful in determining if there is any suggestion of a link between maternal atopy or allergy and
ASD in the children. The disadvantage of total IgE approach is that no specific exposures could
be implicated. If one wishes to focus on identifying specific exposures to asthmagens implicated
in ASD, one can measure a panel of asthmagen-specific antibodies that capture most common
causes of occupational asthma and allergies.

While cytokine studies may yield information about potential pathways collecting
immune activity and ASD, they are not particularly informative in identifying upstream factors
that trigger these responses. More work needs to be done to identify the specific immune
pathways that impact neurodevelopment. This may narrow the field of possible toxicants that
may modulate the immune system in such a way as to effect neurodevelopment. This is
important for the efficient design of studies because the cost and resources associated with
measuring biomarkers in human population studies.

We noted that in both the SEED and Danish case-control studies, mothers who later went
on to have a child with ASD were less likely to be employed during the pregnancy. Further work
could explore this observation to determine if this discrepancy is explained by other
socioeconomic factors, health conditions of older children, or health conditions of the parents. To
our knowledge, though there are studies suggesting reduced maternal employment (Kogan,
Strickland et al. 2008, Montes and Halterman 2008, Cidav, Marcus et al. 2012) and loss of family
income (Montes and Halterman 2008, Cidav, Marcus et al. 2012) for families with a child with an
ASD, we do not know of studies describing lower percentages of parental employment prior to
the birth of the affected child. This also heightens the importance of developing better
understanding of the socioeconomic and geographic distributions of ASD because of the concern that ascertainment bias may influence study inference.

Finally, occupational epidemiology is an efficient approach to evaluating a wide variety of exposures in relation to ASD because much is known about levels and determinants of occupational exposure, and these tend to be much greater than exposures from other environmental sources. Therefore, we could capitalize on the existing data sources described in this work to estimate other occupational exposures in relation to ASD by linking occupational histories or administrative job codes to a plethora of existing JEMs and databases of workplace exposure measurements. However, given our concerns regarding current methods for exposure assessment in occupational epidemiology, we should focus studies on occupational toxicants for which we can assess exposure relatively well and have biological reason to believe could impact risk of ASD. In this respect, toxicants with known reproductive or neuro-toxicant effects may be a good place to start. Many exposure assessment tools exist for assessment of occupational exposure to carcinogens, so this may also be another option.

5.5. Public health significance

As described in chapter 1, some individuals with ASD may have reduced capacity to function independently in society. Parents of children with ASD experience great stress, and the high cost of behavioral interventions and other healthcare expenditures can be financially devastating (Amendah, Gross et al. 2011, Buescher, Cidav et al. 2014). Despite the impacts of ASD on individuals and society, little is known about the etiology of the disorder. This dissertation is part of only a small number of studies to examine the relationship between parental occupational exposures in relation to ASD. We do not find an association between occupational asthmagen exposure and ASD in both population-based U.S. and Danish case-control studies. These null results should encourage parents that exposure to these asthmagenic agents during
pregnancy does not appear to put the child at a measurable risk of ASD. Given the current state of concern regarding autism in the media, communication of such null findings is critical.

The section of this work devoted to showing Bayesian methods for exposure misclassification correction has important implications for population health research. We suggest that consideration of measurement error is essential in epidemiologic research and caution that under certain circumstances our inferential conclusions can be led astray if we do not take this source of bias into account. This also emphasizes the importance of investing additional resources in improving exposure assessment so that we can truly begin to understand the etiology of complicated conditions, such as ASD.
5.6. References


Appendix I. Additional tables and figures for manuscript entitled:

Maternal exposure to occupational asthmagens and risk of autism spectrum disorder in the
Study to Explore Early Development
Table I-1. Maternal employment during the pregnancy by participant characteristics among mothers starting the occupational section of the caregiver interview with a child in the ASD case, DD, or POP group in the SEED study, part 1. (674 ASD, 1036 DD, 953 POP)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Unemployed, N (%)</th>
<th>Employed, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child’s Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>266 (29.04)</td>
<td>650 (70.96)</td>
</tr>
<tr>
<td>Male</td>
<td>478 (27.36)</td>
<td>1269 (72.64)</td>
</tr>
<tr>
<td>Parity (Missing, n=8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>180 (15.5)</td>
<td>981 (84.5)</td>
</tr>
<tr>
<td>2</td>
<td>321 (33.72)</td>
<td>631 (66.28)</td>
</tr>
<tr>
<td>3 or greater</td>
<td>239 (44.1)</td>
<td>303 (55.9)</td>
</tr>
<tr>
<td>Maternal Race (Missing, n=18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>478 (26.37)</td>
<td>1335 (73.63)</td>
</tr>
<tr>
<td>Black</td>
<td>124 (27.37)</td>
<td>329 (72.63)</td>
</tr>
<tr>
<td>Asian</td>
<td>55 (39.29)</td>
<td>85 (60.71)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>43 (40.57)</td>
<td>63 (59.43)</td>
</tr>
<tr>
<td>Multiracial or other</td>
<td>36 (27.07)</td>
<td>97 (72.93)</td>
</tr>
<tr>
<td>Maternal Education (Missing, n=5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>80 (57.55)</td>
<td>59 (42.45)</td>
</tr>
<tr>
<td>High school</td>
<td>109 (42.75)</td>
<td>146 (57.25)</td>
</tr>
<tr>
<td>Some college/ trade</td>
<td>207 (28.55)</td>
<td>518 (71.45)</td>
</tr>
<tr>
<td>Bachelor’s degree</td>
<td>216 (25.12)</td>
<td>644 (74.88)</td>
</tr>
<tr>
<td>Advanced degree</td>
<td>131 (19.29)</td>
<td>548 (80.71)</td>
</tr>
<tr>
<td>Current Household Income</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>55 (58.51)</td>
<td>39 (41.49)</td>
</tr>
<tr>
<td>&lt;$30,000</td>
<td>192 (37.5)</td>
<td>320 (62.5)</td>
</tr>
<tr>
<td>$30,000 – 70,000</td>
<td>162 (24.62)</td>
<td>496 (75.38)</td>
</tr>
<tr>
<td>$70,000 – 110,000</td>
<td>166 (24.7)</td>
<td>506 (75.3)</td>
</tr>
<tr>
<td>&gt;$110,000</td>
<td>169 (23.25)</td>
<td>558 (76.75)</td>
</tr>
<tr>
<td>Child’s Year of Birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>42 (25.3)</td>
<td>124 (74.7)</td>
</tr>
<tr>
<td>2004</td>
<td>249 (26.43)</td>
<td>693 (73.57)</td>
</tr>
<tr>
<td>2005</td>
<td>310 (26.59)</td>
<td>856 (73.41)</td>
</tr>
<tr>
<td>2006</td>
<td>143 (36.76)</td>
<td>246 (63.24)</td>
</tr>
<tr>
<td>Maternal Age at Birth (Missing, n=2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 years old</td>
<td>121 (35.91)</td>
<td>216 (64.09)</td>
</tr>
<tr>
<td>25-29 years old</td>
<td>166 (27.17)</td>
<td>445 (72.83)</td>
</tr>
<tr>
<td>30-34 years old</td>
<td>239 (25.48)</td>
<td>699 (74.52)</td>
</tr>
<tr>
<td>≥35 years old</td>
<td>216 (27.87)</td>
<td>559 (72.13)</td>
</tr>
</tbody>
</table>
Table I-2. Maternal employment during the pregnancy by participant characteristics among mothers starting the occupational section of the caregiver interview with a child in the ASD case, DD, or POP group in the SEED study, part 2. (674 ASD, 1036 DD, 953 POP)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Employment</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unemployed, N (%)</td>
<td>Employed, N (%)</td>
<td></td>
</tr>
<tr>
<td>Maternal Asthma Prior to Child’s Birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>53 (30.46)</td>
<td>121 (69.54)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>515 (27.99)</td>
<td>1325 (72.01)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>176 (27.12)</td>
<td>473 (72.88)</td>
<td></td>
</tr>
<tr>
<td>Maternal Allergy Prior to Child’s Birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>58 (33.14)</td>
<td>117 (66.86)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>432 (29.47)</td>
<td>1034 (70.53)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>254 (24.85)</td>
<td>768 (75.15)</td>
<td></td>
</tr>
<tr>
<td>Maternal Psychiatric Condition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>532 (28.07)</td>
<td>1363 (71.93)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>212 (27.6)</td>
<td>556 (72.4)</td>
<td></td>
</tr>
<tr>
<td>Gestational Age (Missing, n=18)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35 weeks</td>
<td>44 (19.13)</td>
<td>186 (80.87)</td>
<td></td>
</tr>
<tr>
<td>35-&lt;37 weeks</td>
<td>53 (25.73)</td>
<td>153 (74.27)</td>
<td></td>
</tr>
<tr>
<td>≥37 or greater weeks</td>
<td>640 (28.97)</td>
<td>1569 (71.03)</td>
<td></td>
</tr>
<tr>
<td>Maternal Smoking During Pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Missing, n=3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>684 (28.14)</td>
<td>1747 (71.86)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>60 (26.2)</td>
<td>169 (73.8)</td>
<td></td>
</tr>
</tbody>
</table>
Table I-3: Occupational asthmagen exposure by participant characteristics in population controls (POP) and ASD cases (ASD) in the SEED study, part 1.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>POP controls, N (%)</th>
<th>ASD cases, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unexposed (n=568)</td>
<td>Exposed (n=92)</td>
</tr>
<tr>
<td>Child’s Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>258 48 (15.69)</td>
<td>46 15 (24.59)</td>
</tr>
<tr>
<td>Male</td>
<td>310 44 (12.43)</td>
<td>316 60 (15.96)</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>307 42 (12.03)</td>
<td>205 34 (14.23)</td>
</tr>
<tr>
<td>2</td>
<td>186 33 (15.07)</td>
<td>105 26 (19.85)</td>
</tr>
<tr>
<td>3 or greater</td>
<td>75 17 (18.48)</td>
<td>52 15 (22.39)</td>
</tr>
<tr>
<td>Maternal Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>441 66 (13.02)</td>
<td>230 42 (15.44)</td>
</tr>
<tr>
<td>Black</td>
<td>72 14 (16.28)</td>
<td>79 19 (19.39)</td>
</tr>
<tr>
<td>Asian</td>
<td>22 1 (16.28)</td>
<td>25 3 (10.71)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>11 3 (16.28)</td>
<td>10 8 (44.44)</td>
</tr>
<tr>
<td>Multiracial or other</td>
<td>22 8 (12.90)</td>
<td>18 3 (14.29)</td>
</tr>
<tr>
<td>Maternal education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>11 7 (38.89)</td>
<td>9 6 (40.00)</td>
</tr>
<tr>
<td>High school</td>
<td>27 4 (12.90)</td>
<td>26 11 (29.73)</td>
</tr>
<tr>
<td>Some college/ trade</td>
<td>119 25 (17.36)</td>
<td>116 31 (21.09)</td>
</tr>
<tr>
<td>Bachelor’s degree</td>
<td>216 32 (12.90)</td>
<td>114 18 (13.64)</td>
</tr>
<tr>
<td>Advanced degree</td>
<td>195 24 (17.36)</td>
<td>97 9 (44.44)</td>
</tr>
<tr>
<td>Current Household Income</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;$30,000</td>
<td>61 17 (21.79)</td>
<td>77 24 (23.76)</td>
</tr>
<tr>
<td>$30,000 – 70,000</td>
<td>138 20 (12.66)</td>
<td>86 26 (23.21)</td>
</tr>
<tr>
<td>$70,000 – 110,000</td>
<td>156 24 (13.33)</td>
<td>104 14 (11.86)</td>
</tr>
<tr>
<td>&gt;$110,000</td>
<td>213 31 (12.70)</td>
<td>95 11 (10.38)</td>
</tr>
<tr>
<td>Child’s Year of Birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>31 5 (13.89)</td>
<td>32 7 (17.95)</td>
</tr>
<tr>
<td>2004</td>
<td>226 43 (15.99)</td>
<td>110 24 (17.91)</td>
</tr>
<tr>
<td>2005</td>
<td>269 35 (11.51)</td>
<td>146 33 (18.44)</td>
</tr>
<tr>
<td>2006</td>
<td>42 9 (17.65)</td>
<td>74 11 (12.94)</td>
</tr>
<tr>
<td>Maternal Age at Birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 years old</td>
<td>53 8 (13.11)</td>
<td>44 11 (20.00)</td>
</tr>
<tr>
<td>25-29 years old</td>
<td>130 31 (19.25)</td>
<td>81 19 (19.00)</td>
</tr>
<tr>
<td>30-34 years old</td>
<td>219 32 (12.75)</td>
<td>127 24 (15.89)</td>
</tr>
<tr>
<td>≥35 years old</td>
<td>166 21 (11.23)</td>
<td>110 21 (16.03)</td>
</tr>
</tbody>
</table>
Table I-4: Occupational asthmagen exposure by participant characteristics in population controls (POP) and ASD cases (ASD) in the SEED study, part 2.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>POP controls, N (%)</th>
<th>ASD cases, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unexposed (n=568)</td>
<td>Exposed (n=92)</td>
</tr>
<tr>
<td>Maternal Asthma Prior to Child’s Birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>426 65 (13.24)</td>
<td>267 53 (16.56)</td>
</tr>
<tr>
<td>Yes</td>
<td>142 27 (15.98)</td>
<td>95 22 (18.80)</td>
</tr>
<tr>
<td>Maternal Allergy Prior to Child’s Birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>308 60 (16.30)</td>
<td>208 44 (17.46)</td>
</tr>
<tr>
<td>Yes</td>
<td>260 32 (10.96)</td>
<td>154 31 (16.76)</td>
</tr>
<tr>
<td>Maternal Psychiatric Condition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>429 69 (13.86)</td>
<td>227 57 (20.07)</td>
</tr>
<tr>
<td>Yes</td>
<td>139 23 (14.20)</td>
<td>135 18 (11.76)</td>
</tr>
<tr>
<td>Gestational Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;35 weeks</td>
<td>30 4 (11.76)</td>
<td>39 4 (9.30)</td>
</tr>
<tr>
<td>35-&lt;37 weeks</td>
<td>28 5 (15.15)</td>
<td>30 8 (21.05)</td>
</tr>
<tr>
<td>≥37 or greater weeks</td>
<td>510 83 (14.00)</td>
<td>293 63 (17.7)</td>
</tr>
<tr>
<td>Maternal Smoking During Pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>540 83 (13.32)</td>
<td>319 66 (17.14)</td>
</tr>
<tr>
<td>Yes</td>
<td>28 9 (24.32)</td>
<td>43 9 (17.31)</td>
</tr>
</tbody>
</table>
Appendix II. Additional tables and figures for manuscript entitled:

Parental exposures to occupational asthmagens and risk of autism spectrum disorder in a Danish population-based case-control study
Table II-1: Associations between maternal occupational exposure to asthmagens during pregnancy and risk of ASD in a sample from the Danish population.

<table>
<thead>
<tr>
<th>Maternal Occupational Exposure</th>
<th>Controls (N=29,670)</th>
<th>ASD cases (N=6,830)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR&lt;sup&gt;A&lt;/sup&gt; (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Asthmagen</td>
<td>6101 20.56</td>
<td>1290 18.89</td>
<td>0.90 (0.84 – 0.96)</td>
<td>0.88 (0.82 – 0.95)</td>
</tr>
<tr>
<td>Any HMW</td>
<td>4420 14.90</td>
<td>914 13.38</td>
<td>0.88 (0.82 – 0.95)</td>
<td>0.89 (0.82 – 0.96)</td>
</tr>
<tr>
<td>Animals</td>
<td>261 0.88</td>
<td>55 0.81</td>
<td>0.92 (0.68 – 1.23)</td>
<td>0.84 (0.62 – 1.14)</td>
</tr>
<tr>
<td>Fish</td>
<td>126 0.42</td>
<td>31 0.45</td>
<td>1.07 (0.72 – 1.59)</td>
<td>0.86 (0.57 – 1.29)</td>
</tr>
<tr>
<td>Flour</td>
<td>69 0.23</td>
<td>21 0.31</td>
<td>1.32 (0.81 – 2.16)</td>
<td>1.20 (0.72 – 2.00)</td>
</tr>
<tr>
<td>Plants</td>
<td>9 0.03</td>
<td>4 &lt;0.01</td>
<td>1.94 (0.60 – 6.29)</td>
<td>1.73 (0.51 – 5.84)</td>
</tr>
<tr>
<td>Mites</td>
<td>16 0.05</td>
<td>4 &lt;0.01</td>
<td>1.09 (0.36 – 3.25)</td>
<td>0.93 (0.30 – 2.89)</td>
</tr>
<tr>
<td>Enzymes</td>
<td>45 0.15</td>
<td>17 0.25</td>
<td>1.65 (0.94 – 2.88)</td>
<td>1.56 (0.87 – 2.80)</td>
</tr>
<tr>
<td>Latex</td>
<td>3305 11.14</td>
<td>681 9.97</td>
<td>0.88 (0.81 – 0.96)</td>
<td>0.89 (0.81 – 0.97)</td>
</tr>
<tr>
<td>Bioaerosols</td>
<td>203 0.68</td>
<td>44 0.64</td>
<td>0.94 (0.68 – 1.31)</td>
<td>1.00 (0.71 – 1.41)</td>
</tr>
<tr>
<td>Drugs</td>
<td>2221 7.49</td>
<td>382 5.59</td>
<td>0.73 (0.66 – 0.82)</td>
<td>0.77 (0.68 – 0.86)</td>
</tr>
<tr>
<td>Any LMW</td>
<td>2989 10.07</td>
<td>721 10.56</td>
<td>1.05 (0.97 – 1.15)</td>
<td>1.00 (0.91 – 1.09)</td>
</tr>
<tr>
<td>Reactive</td>
<td>2280 7.68</td>
<td>515 7.54</td>
<td>0.98 (0.89 – 1.08)</td>
<td>0.94 (0.85 – 1.04)</td>
</tr>
<tr>
<td>Isocyanate</td>
<td>49 0.17</td>
<td>13 0.19</td>
<td>1.15 (0.63 – 2.13)</td>
<td>1.13 (0.60 – 2.14)</td>
</tr>
<tr>
<td>Cleaning</td>
<td>1837 6.19</td>
<td>495 7.25</td>
<td>1.18 (1.07 – 1.31)</td>
<td>1.07 (0.96 – 1.20)</td>
</tr>
<tr>
<td>Wood</td>
<td>45 0.15</td>
<td>11 0.16</td>
<td>1.06 (0.55 – 2.06)</td>
<td>1.08 (0.54 – 2.15)</td>
</tr>
<tr>
<td>Metals</td>
<td>336 1.13</td>
<td>82 1.20</td>
<td>1.06 (0.83 – 1.35)</td>
<td>1.11 (0.86 – 1.43)</td>
</tr>
<tr>
<td>Any Mixed Environment</td>
<td>499 1.68</td>
<td>108 1.58</td>
<td>0.94 (0.76 – 1.16)</td>
<td>0.87 (0.70 – 1.08)</td>
</tr>
<tr>
<td>Metal working fluids</td>
<td>78 0.26</td>
<td>25 0.37</td>
<td>1.39 (0.89 – 2.19)</td>
<td>1.43 (0.89 – 2.29)</td>
</tr>
<tr>
<td>Textile</td>
<td>163 0.55</td>
<td>33 0.48</td>
<td>0.88 (0.60 – 1.28)</td>
<td>0.67 (0.46 – 0.99)</td>
</tr>
<tr>
<td>Agricultural antigens</td>
<td>258 0.87</td>
<td>50 0.73</td>
<td>0.84 (0.62 – 1.14)</td>
<td>0.86 (0.63 – 1.18)</td>
</tr>
<tr>
<td>Irritants</td>
<td>69 0.23</td>
<td>12 0.18</td>
<td>0.76 (0.41 – 1.40)</td>
<td>0.82 (0.43 – 1.54)</td>
</tr>
</tbody>
</table>

<sup>A</sup> Adjusted model is adjusted for child’s year of birth, child’s sex, maternal age at birth, paternal age of birth, total income of parents, parity, highest parental education, history of parental psychiatric diagnosis prior to child’s date of birth, and maternal asthma diagnosis by a specialist prior to child’s date of birth.
### Table II-2: Associations between paternal occupational exposure to asthmagens during pregnancy and risk of ASD in a sample from the Danish population.

<table>
<thead>
<tr>
<th>Maternal Occupational Exposure</th>
<th>Controls (N=32,335)</th>
<th></th>
<th>ASD cases (N=7,799)</th>
<th></th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR\textsuperscript{A} (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Asthmagen</td>
<td>6843</td>
<td>21.16</td>
<td>1578</td>
<td>20.23</td>
<td>0.95 (0.89 - 1.01)</td>
<td>0.92 (0.86 - 0.98)</td>
</tr>
<tr>
<td>Any HMW</td>
<td>2002</td>
<td>6.19</td>
<td>543</td>
<td>6.96</td>
<td>1.13 (1.03 - 1.25)</td>
<td>1.09 (0.98 - 1.21)</td>
</tr>
<tr>
<td>Animals</td>
<td>649</td>
<td>2.01</td>
<td>139</td>
<td>1.78</td>
<td>0.89 (0.74 - 1.07)</td>
<td>0.89 (0.74 - 1.08)</td>
</tr>
<tr>
<td>Fish</td>
<td>155</td>
<td>0.48</td>
<td>49</td>
<td>0.63</td>
<td>1.31 (0.95 - 1.81)</td>
<td>1.24 (0.89 - 1.74)</td>
</tr>
<tr>
<td>Flour</td>
<td>153</td>
<td>0.47</td>
<td>38</td>
<td>0.49</td>
<td>1.03 (0.72 - 1.47)</td>
<td>1.05 (0.72 - 1.51)</td>
</tr>
<tr>
<td>Plants</td>
<td>25</td>
<td>0.08</td>
<td>7</td>
<td>0.09</td>
<td>1.16 (0.50 - 2.69)</td>
<td>1.31 (0.56 - 3.11)</td>
</tr>
<tr>
<td>Mites</td>
<td>9</td>
<td>0.03</td>
<td>0</td>
<td>0</td>
<td>NA\textsuperscript{B}</td>
<td>NA\textsuperscript{B}</td>
</tr>
<tr>
<td>Enzymes</td>
<td>123</td>
<td>0.38</td>
<td>29</td>
<td>0.37</td>
<td>0.98 (0.65 - 1.47)</td>
<td>1.02 (0.67 - 1.55)</td>
</tr>
<tr>
<td>Latex</td>
<td>361</td>
<td>1.12</td>
<td>115</td>
<td>1.48</td>
<td>1.33 (1.07 - 1.64)</td>
<td>1.14 (0.91 - 1.42)</td>
</tr>
<tr>
<td>Bioaerosols</td>
<td>840</td>
<td>2.60</td>
<td>225</td>
<td>2.89</td>
<td>1.11 (0.96 - 1.29)</td>
<td>1.11 (0.95 - 1.30)</td>
</tr>
<tr>
<td>Drugs</td>
<td>118</td>
<td>0.36</td>
<td>39</td>
<td>0.50</td>
<td>1.37 (0.96 - 1.97)</td>
<td>1.46 (1.00 - 2.13)</td>
</tr>
<tr>
<td>Any LMW</td>
<td>4305</td>
<td>13.31</td>
<td>1071</td>
<td>13.73</td>
<td>1.04 (0.97 - 1.11)</td>
<td>0.99 (0.92 - 1.07)</td>
</tr>
<tr>
<td>Reactive</td>
<td>971</td>
<td>3.00</td>
<td>256</td>
<td>3.28</td>
<td>1.10 (0.95 - 1.26)</td>
<td>1.00 (0.86 - 1.16)</td>
</tr>
<tr>
<td>Isocyanate</td>
<td>539</td>
<td>1.67</td>
<td>123</td>
<td>1.58</td>
<td>0.95 (0.78 - 1.15)</td>
<td>0.91 (0.74 - 1.12)</td>
</tr>
<tr>
<td>Cleaning</td>
<td>555</td>
<td>1.72</td>
<td>167</td>
<td>2.14</td>
<td>1.25 (1.05 - 1.49)</td>
<td>1.12 (0.93 - 1.34)</td>
</tr>
<tr>
<td>Wood</td>
<td>1132</td>
<td>3.50</td>
<td>242</td>
<td>3.10</td>
<td>0.88 (0.77 - 1.02)</td>
<td>0.88 (0.76 - 1.02)</td>
</tr>
<tr>
<td>Metals</td>
<td>1708</td>
<td>5.28</td>
<td>449</td>
<td>5.76</td>
<td>1.10 (0.98 - 1.22)</td>
<td>1.06 (0.95 - 1.19)</td>
</tr>
<tr>
<td>Any Mixed Environment</td>
<td>2314</td>
<td>7.16</td>
<td>474</td>
<td>6.08</td>
<td>0.84 (0.76 - 0.93)</td>
<td>0.80 (0.72 - 0.89)</td>
</tr>
<tr>
<td>Metal working fluids</td>
<td>915</td>
<td>2.83</td>
<td>252</td>
<td>3.23</td>
<td>1.15 (1.00 - 1.32)</td>
<td>1.08 (0.93 - 1.25)</td>
</tr>
<tr>
<td>Textile</td>
<td>83</td>
<td>0.26</td>
<td>22</td>
<td>0.28</td>
<td>1.10 (0.69 - 1.76)</td>
<td>0.89 (0.55 - 1.45)</td>
</tr>
<tr>
<td>Agricultural antigens</td>
<td>1316</td>
<td>4.07</td>
<td>200</td>
<td>2.56</td>
<td>0.62 (0.53 - 0.72)</td>
<td>0.61 (0.52 - 0.72)</td>
</tr>
<tr>
<td>Irritants</td>
<td>836</td>
<td>2.59</td>
<td>203</td>
<td>2.60</td>
<td>1.01 (0.86 - 1.18)</td>
<td>1.07 (0.91 - 1.26)</td>
</tr>
</tbody>
</table>

\textsuperscript{A} Adjusted model is adjusted for child’s year of birth, child’s sex, maternal age at birth, paternal age of birth, total income of parents, parity, highest parental education, history of parental psychiatric diagnosis prior to child’s date of birth, and paternal asthma diagnosis by a specialist prior to child’s date of birth.  

\textsuperscript{B} Could not be estimated.
Danish Civil Registration System: Born 1993-2007
n=1,099,463

- No ID on mother
  n=15,404

- No match in birth registry or not born in DK
  n=88,908

- Gestational age missing or outside 23-43 weeks
  n=8,945

- Multiple births or missing information on multiple births
  n=38,638

Meeting Study Inclusion Criteria: 947,568 Individuals

Figure II-1: Inclusion criteria for the Danish case-control study.
Four controls were randomly selected for each case. The study was restricted so as to only include the oldest child per mother in cases where more than one child was included among the initial 12,500 cases and 50,000 controls. Children were also excluded if they were lost to follow-up before age one, had inconsistent maternal identification across different registers, or had likely erroneous birth weights for gestational age.

Figure II-2: Selection of cases and controls for the Danish case-control study.
Appendix III. Code and model diagnostics for manuscript entitled:

The importance of exposure misclassification:
Using Bayesian correction methods to assess maternal occupational asthmagen exposures and risk of autism spectrum disorder
III.1 Code

## R packages ##

library(R2WinBUGS)
library(coda)

## Read in data ##

case1pop0 <- read.table("case1pop0.txt", header=TRUE)

## Re-format data as list ##

data <-
list(N=N,asthmagen_preg=asthmagen_preg,DR_AGEBIRTH_MX=DR_AGEBIRTH_MX,
DR_AST_MP=DR_AST_MP,DR_ALG_MP=DR_ALG_MP,
DR_PSYALL_MX=DR_PSYALL_MX, parity_2=parity_2,
parity_3=parity_3, sexm0f1=sexm0f1,mrace_bla=mrace_bla, mrace_asl=mrace_asl,
mrace_his=mrace_his, mrace_oth=mrace_oth, medu_hs=medu_hs, medu_sc=medu_sc,
medu_ba=medu_ba, medu_ad=medu_ad,ti_2=ti_2, ti_3=ti_3, ti_4=ti_4, gest_1=gest_1,
cest_2=cest_2, actsmk_preg=actsrk_preg, y=y, p0=p0)

## Model S A ##

## Initial values are based on coefficients from frequentist regressions: define initial values for 3 chains ##

inits = list(
list(b0=-1.25, b1=0.28, b2=0.05, b3=0.01, b4=-0.07, b5=0.62, b6=-0.27, b7=-0.36,
b8=-1.73, b9=0.59, b10=1.12, b11=0.43, b12=0.15, b13=0.05, b14=0.07, b15=-0.48,
b16=-0.51, b17=-0.38, b18=-0.40, b19=-0.75, b20=0.67, b21=0.50, b22=1.71,
g1=-1.1, g2=0.01, g3=1.27, g4=0.79, g5=-0.31, g6=0.24, g7=0.24, g8=0.2, g9=-0.04,
g10=-0.58, g11=0.62, g12=0.41, g13=-0.51, g14=-0.67, g15=-0.98, g16=1.26,
g17=-0.04, g18=-0.22, g19=-0.19, g20=0.62, g21=1.29, g22=1.12, SN=0.4, SP=0.99),
list(b0=-1.25, b1=0.28, b2=0.05, b3=0.01, b4=-0.07, b5=0.62, b6=-0.27, b7=-0.36,
b8=-1.73, b9=0.59, b10=1.12, b11=0.43, b12=0.15, b13=0.05, b14=0.07, b15=-0.48,
b16=-0.51, b17=-0.38, b18=-0.40, b19=-0.75, b20=0.67, b21=0.50, b22=1.71,
g1=-1.1, g2=0.01, g3=1.27, g4=0.79, g5=-0.31, g6=0.24, g7=0.24, g8=0.2, g9=-0.04,
g10=-0.58, g11=0.62, g12=0.41, g13=-0.51, g14=-0.67, g15=-0.98, g16=1.26,
g17=-0.04, g18=-0.22, g19=-0.19, g20=0.62, g21=1.29, g22=1.12, SN=0.4, SP=0.99),
list(b0=-1.25, b1=0.28, b2=0.05, b3=0.01, b4=-0.07, b5=0.62, b6=-0.27, b7=-0.36,
b8=-1.73, b9=0.59, b10=1.12, b11=0.43, b12=0.15, b13=0.05, b14=0.07, b15=-0.48,
b16=-0.51, b17=-0.38, b18=-0.40, b19=-0.75, b20=0.67, b21=0.50, b22=1.71,
g1=-1.1, g2=0.01, g3=1.27, g4=0.79, g5=-0.31, g6=0.24, g7=0.24, g8=0.2, g9=-0.04,
g10=-0.58, g11=0.62, g12=0.41, g13=-0.51, g14=-0.67, g15=-0.98, g16=1.26,
g17=-0.04, g18=-0.22, g19=-0.19, g20=0.62, g21=1.29, g22=1.12, SN=0.4, SP=0.99))
## This code calls WinBUGS to start iterations ##

```r
casepopS_A.sim = bugs(data, inits=inits, 
model.file="E:/WORKING_DIRECTORY/Model_S_A.txt", 
parameters=c("b1","OR","SN","SP","r0"), n.chains=3, n.iter=25000, n.burnin=5000, n.thin=20, 
working.directory="E:/WORKING_DIRECTORY/", 
bugs.directory="c:/Program Files/WinBUGS14/", codaPkg=TRUE, debug=TRUE)
```

## This is the content of the Model_S_A.txt file ##

```r
model {
    for (i in 1:N) {
        # Outcome model: Log odds of ASD as a function of the true variable for asthmagen exposure (astpregt) and covariates
        y[i] ~ dbern(pt[i])
        logit(pt[i]) <- b0 + b1*astpregt[i] + b2*DR_AGEBIRTH_MX[i] + b3*DR_AST_MP[i] + b4*DR_ALG_MP[i] + b5*DR_PSYALL_MX[i] + b6*parity_2[i] + b7*parity_3[i] + b8*sexm0f1[i] + b9*mrace_bla[i] + b10*mrace_as[i] + b11*mrace_his[i] + b12*mrace_oth[i] + b13*medu_hs[i] + b14*medu_sc[i] + b15*medu_ba[i] + b16*medu_ad[i] + b17*ti_2[i] + b18*ti_3[i] + b19*ti_4[i] + b20*gest_1[i] + b21*gest_2[i] + b22*actsmk_preg[i]

        # Measurement model: probability of observed asthmagen exposure as a function of true asthmagen exposure, sensitivity, and specificity
        # Assumes non-differential exposure misclassification
        asthmagen_preg[i] ~ dbern(pm[i])
        pm[i] <- SN*(astpregt[i]) + (1-SP)*(astpregt[i])

        # Exposure model: Log odds of true asthmagen exposure as a function of covariates
        astpregt[i] ~ dbern(prop[i])
        logit(prop[i]) <- g1 + g2*DR_AGEBIRTH_MX[i] + g3*DR_AST_MP[i] + g4*DR_ALG_MP[i] + g5*DR_PSYALL_MX[i] + g6*parity_2[i] + g7*parity_3[i] + g8*sexm0f1[i] + g9*mrace_bla[i] + g10*mrace_as[i] + g11*mrace_his[i] + g12*mrace_oth[i] + g13*medu_hs[i] + g14*medu_sc[i] + g15*medu_ba[i] + g16*medu_ad[i] + g17*ti_2[i] + g18*ti_3[i] + g19*ti_4[i] + g20*gest_1[i] + g21*gest_2[i] + g22*actsmk_preg[i]
    }
}
```
# Calculate odds ratio

OR <- exp(b1)

# Calculate prevalence of exposure among unexposed #
r0 <- (p0 + SP - 1)/(SN + SP - 1)

# PRIORS

b0 ~ dnorm(0,1)  
b1 ~ dnorm(0,2)  
b2 ~ dnorm(0,2)  
b3 ~ dnorm(0,2)  
b4 ~ dnorm(0,2)  
b5 ~ dnorm(0,2)  
b6 ~ dnorm(0,2)  
b7 ~ dnorm(0,2)  
b8 ~ dnorm(0,1)  
b9 ~ dnorm(0,2)  
b10 ~ dnorm(0,2)  
b11 ~ dnorm(0,2)  
b12 ~ dnorm(0,2)  
b13 ~ dnorm(0,2)  
b14 ~ dnorm(0,2)  
b15 ~ dnorm(0,2)  
b16 ~ dnorm(0,2)  
b17 ~ dnorm(0,2)  
b18 ~ dnorm(0,2)  
b19 ~ dnorm(0,2)  
b20 ~ dnorm(0,2)  
b21 ~ dnorm(0,2)  
b22 ~ dnorm(0,2)  
g1 ~ dnorm(0,2)  
g2 ~ dnorm(0,2)  
g3 ~ dnorm(0,2)  
g4 ~ dnorm(0,2)  
g5 ~ dnorm(0,2)  
g6 ~ dnorm(0,2)  
g7 ~ dnorm(0,2)  
g8 ~ dnorm(0,2)  
g9 ~ dnorm(0,2)  
g10 ~ dnorm(0,2)  
g11 ~ dnorm(0,2)  
g12 ~ dnorm(0,2)  
g13 ~ dnorm(0,2)  
g14 ~ dnorm(0,2)  
g15 ~ dnorm(0,2)  
g16 ~ dnorm(0,2)  
g17 ~ dnorm(0,2)  
g18 ~ dnorm(0,2)
g19 ~ dnorm(0,2)
g20 ~ dnorm(0,2)
g21 ~ dnorm(0,2)
g22 ~ dnorm(0,2)
SN ~ dbeta(1000,1)
SP ~ dbeta(1000,1)
}

## Model S_B ##

## Initial values are based on coefficients from frequentist regressions: define initial values for 2 chains ##

inits = list(
  list(b0=-1.25, b1=0.28, b2=0.05, b3=0.01, b4=-0.07, b5=0.62, b6=-0.27, b7=-0.36, b8=-1.73, b9=-0.59, b10=-1.12, b11=0.43, b12=0.15, b13=0.05, b14=0.07, b15=-0.48, b16=-0.51, b17=-0.38, b18=-0.40, b19=-0.75, b20=0.67, b21=0.50, b22=1.71, g1=-1.1, g2=0.01, g3=1.27, g4=0.79, g5=-0.31, g6=0.24, g7=0.24, g8=0.2, g9=-0.04, g10=-0.58, g11=0.62, g12=0.41, g13=-0.51, g14=-0.67, g15=-0.98, g16=-1.26, g17=-0.04, g18=-0.22, g19=-0.19, g20=0.62, g21=1.29, g22=1.12, SN=0.4, SP=0.99),
  list(b0=-1.25, b1=0.28, b2=0.05, b3=0.01, b4=-0.07, b5=0.62, b6=-0.27, b7=-0.36, b8=-1.73, b9=-0.59, b10=-1.12, b11=0.43, b12=0.15, b13=0.05, b14=-0.07, b15=-0.48, b16=-0.51, b17=-0.38, b18=-0.40, b19=-0.75, b20=0.67, b21=-0.50, b22=1.71, g1=-1.1, g2=0.01, g3=1.27, g4=0.79, g5=-0.31, g6=0.24, g7=0.24, g8=0.2, g9=-0.04, g10=-0.58, g11=0.62, g12=0.41, g13=-0.51, g14=-0.67, g15=-0.98, g16=-1.26, g17=-0.04, g18=-0.22, g19=-0.19, g20=-0.62, g21=1.29, g22=1.12, SN=0.4, SP=0.99))

## This code calls WinBUGS to start iterations ##

casepopS_B.sim = bugs(data, inits=inits, model.file="E:/WORKING_DIRECTORY/Model_S_B.txt", parameters=c("b1","OR","SN","SP","r0"), n.chains=2, n.iter=15000, n.burnin=1000, n.thin=20, working.directory="E:/WORKING_DIRECTORY/", bugs.directory="c:/Program Files/WinBUGS14/", codaPkg=TRUE, debug=TRUE)
**## This is the content of the Model_S_B.txt file ##**

```r
model {
  for (i in 1:N) {

    # Outcome model : Log odds of ASD as a function of the true variable for asthmagen exposure (astpregt) and covariates
    y[i] ~ dbern(pt[i])
    logit(pt[i]) <- b0 + b1*astpregt[i] + b2*DR_AGE_BIRTH_MX[i] + b3*DR_AST_MP[i] + b4*DR_ALG_MP[i] + b5*DR_PS_YALL_MX[i] + b6*parity_2[i] + b7*parity_3[i] + b8*sexm0f1[i] + b9*mrace_bla[i] + b10*mrace_asi[i] + b11*mrace_his[i] + b12*mrace_oth[i] + b13*medu_hs[i] + b14*medu_sc[i] + b15*medu_ba[i] + b16*medi_ad[i] + b17*ti_2[i] + b18*ti_3[i] + b19*ti_4[i] + b20*gest_1[i] + b21*gest_2[i] + b22*actsmk_preg[i]

    # Measurement model: probability of observed asthmagen exposure as a function of true asthmagen exposure, sensitivity, and specificity
    # Assumes non-differential exposure misclassification
    asthmagen_preg[i] ~ dbern(pm[i])
    pm[i] <- SN*(astpregt[i]) + (1-SP)*(astpregt[i])

    # Exposure model: Log odds of true asthmagen exposure as a function of covariates
    astpregt[i] ~ dbern(prop[i])
    logit(prop[i]) <- g1 + g2*DR_AGE_BIRTH_MX[i] + g3*DR_AST_MP[i] + g4*DR_ALG_MP[i] + g5*DR_PS_YALL_MX[i] + g6*parity_2[i] + g7*parity_3[i] + g8*sexm0f1[i] + g9*mrace_bla[i] + g10*mrace_asi[i] + g11*mrace_his[i] + g12*mrace_oth[i] + g13*medu_hs[i] + g14*medu_sc[i] + g15*medu_ba[i] + g16*medi_ad[i] + g17*ti_2[i] + g18*ti_3[i] + g19*ti_4[i] + g20*gest_1[i] + g21*gest_2[i] + g22*actsmk_preg[i]

  }

  # Calculate odds ratio
  OR <- exp(b1)

  # Calculate prevalence of exposure among unexposed
  r0 <- (p0+SP-1)/(SN+SP-1)

  # PRIORS
  b0 ~ dnorm(0,1)
  b1 ~ dnorm(0,2)
  b2 ~ dnorm(0,2)
  b3 ~ dnorm(0,2)
  b4 ~ dnorm(0,2)
  b5 ~ dnorm(0,2)
}
```

160
b6 ~ dnorm(0,2)
b7 ~ dnorm(0,2)
b8 ~ dnorm(0,1)
b9 ~ dnorm(0,2)
b10 ~ dnorm(0,2)
b11 ~ dnorm(0,2)
b12 ~ dnorm(0,2)
b13 ~ dnorm(0,2)
b14 ~ dnorm(0,2)
b15 ~ dnorm(0,2)
b16 ~ dnorm(0,2)
b17 ~ dnorm(0,2)
b18 ~ dnorm(0,2)
b19 ~ dnorm(0,2)
b20 ~ dnorm(0,2)
b21 ~ dnorm(0,2)
b22 ~ dnorm(0,2)
g1 ~ dnorm(0,2)
g2 ~ dnorm(0,2)
g3 ~ dnorm(0,2)
g4 ~ dnorm(0,2)
g5 ~ dnorm(0,2)
g6 ~ dnorm(0,2)
g7 ~ dnorm(0,2)
g8 ~ dnorm(0,2)
g9 ~ dnorm(0,2)
g10 ~ dnorm(0,2)
g11 ~ dnorm(0,2)
g12 ~ dnorm(0,2)
g13 ~ dnorm(0,2)
g14 ~ dnorm(0,2)
g15 ~ dnorm(0,2)
g16 ~ dnorm(0,2)
g17 ~ dnorm(0,2)
g18 ~ dnorm(0,2)
g19 ~ dnorm(0,2)
g20 ~ dnorm(0,2)
g21 ~ dnorm(0,2)
g22 ~ dnorm(0,2)
SN ~ dbeta(3.6,5.2)
SP ~ dbeta(1000, 9.1)
## Model S_C ##

## Initial values are based on coefficients from frequentist regressions: define initial values for 3 chains ##

\[
\text{inits} = \text{list}\left(\begin{array}{l}
\text{list}(b0=-1.25, b1=0.28, b2=0.05, b3=-0.01, b4=-0.07, b5=0.62, b6=-0.27, b7=-0.36, 
b8=-1.73, b9=-0.59, b10=1.12, b11=0.43, b12=0.15, b13=0.05, b14=0.07, b15=-0.48, 
b16=-0.51, b17=-0.38, b18=0.40, b19=-0.75, b20=0.67, b21=-0.50, b22=1.71, 
g1=-1.1, g2=0.01, g3=1.27, g4=0.79, g5=-0.31, g6=0.24, g7=0.24, g8=0.2, g9=-0.04, 
g10=-0.58, g11=-0.62, g12=-0.41, g13=-0.51, g14=-0.67, g15=-0.98, g16=-1.26, 
g17=-0.04, g18=-0.22, g19=-0.19, g20=0.62, g21=1.29, g22=1.12, SN=0.4, SP=0.99), 

\text{list}(b0=-1.25, b1=0.28, b2=0.05, b3=-0.01, b4=-0.07, b5=0.62, b6=-0.27, b7=-0.36, 
b8=-1.73, b9=-0.59, b10=1.12, b11=0.43, b12=0.15, b13=0.05, b14=0.07, b15=-0.48, 
b16=-0.51, b17=-0.38, b18=-0.40, b19=-0.75, b20=0.67, b21=-0.50, b22=1.71, 
g1=-1.1, g2=0.01, g3=1.27, g4=0.79, g5=-0.31, g6=0.24, g7=0.24, g8=0.2, g9=-0.04, 
g10=-0.58, g11=-0.62, g12=-0.41, g13=-0.51, g14=-0.67, g15=-0.98, g16=-1.26, 
g17=-0.04, g18=-0.22, g19=-0.19, g20=0.62, g21=1.29, g22=1.12, SN=0.4, SP=0.99), 

\text{list}(b0=-1.25, b1=0.28, b2=0.05, b3=-0.01, b4=-0.07, b5=0.62, b6=-0.27, b7=-0.36, 
b8=-1.73, b9=-0.59, b10=1.12, b11=0.43, b12=0.15, b13=0.05, b14=0.07, b15=-0.48, 
b16=-0.51, b17=-0.38, b18=-0.40, b19=-0.75, b20=0.67, b21=-0.50, b22=1.71, 
g1=-1.1, g2=0.01, g3=1.27, g4=0.79, g5=-0.31, g6=0.24, g7=0.24, g8=0.2, g9=-0.04, 
g10=-0.58, g11=-0.62, g12=-0.41, g13=-0.51, g14=-0.67, g15=-0.98, g16=-1.26, 
g17=-0.04, g18=-0.22, g19=-0.19, g20=0.62, g21=1.29, g22=1.12, SN=0.4, SP=0.99)\right)
\]

## This code calls WinBUGS to start iterations ##

\[
\text{casepopS.C.sim} = \text{bugs(data, inits=inits,} \\
\text{model.file=quote("E:/WORKING\_DIRECTORY/Model\_S\_C.txt"),} \\
\text{parameters=c("b1","OR","SN0","SN1","SP0","SP1","r0"), n.chains=3, n.iter=25000,} \\
\text{n.burnin=5000, n.thin=20, working.directory="E:/WORKING\_DIRECTORY/",} \\
\text{bugs.directory="c:/Program Files/WinBUGS14/", codaPkg=TRUE, debug=TRUE)}
\]

## This is the content of the Model\_S\_C.txt file ##

\[
\text{model} \{ \\
\text{for (i in 1:N) \{} \\
\text{y[i] \sim dbern(pt[i])} \\
\text{logit(pt[i]) <- b0 + b1*astpregt[i] + b2*DR\_AGEBIRTH\_MX[i] + b3*DR\_AST\_MP[i] +} \\
\text{b4*DR\_ALG\_MP[i] + b5*DR\_PSYALL\_MX[i] + b6*parity\_2[i] + b7*parity\_3[i] +} \
\text{\}}
\]
# Measurement model: probability of observed asthmagen exposure as a function of true asthmagen exposure, sensitivity, and specificity
# Allows differential exposure misclassification

asthmagen_preg[i] ~ dbern(pm[i])

pm[i] <- SN0*(astpregt[i])*(1-y[i]) + (1-SP0)*(astpregt[i])*(1-y[i]) + SN1*(astpregt[i])*(y[i]) + (1-SP1)*(astpregt[i])*(y[i])

# Exposure model: Log odds of true asthmagen exposure as a function of covariates

astpregt[i] ~ dbern(prop[i])

logit(prop[i]) <- g1 + g2*DR_AGE_BIRTH_MX[i] + g3*DR_AST_MP[i] + g4*DR_ALG_MP[i] + g5*DR_PS_Y_ALL_MX[i] + g6*parity_2[i] + g7*parity_3[i] + g8*sexm0f1[i] + g9*mrace_bla[i] + g10*mrace_asi[i] + g11*mrace_his[i] + g12*mrace_oth[i] + g13*medu_hs[i] + g14*medu_sc[i] + g15*medu_ba[i] + g16*medu_ad[i] + g17*t_i_2[i] + g18*t_i_3[i] + g19*t_i_4[i] + g20*gest_1[i] + g21*gest_2[i] + g22*actsmk_preg[i]

# Calculate odds ratio

OR <- exp(b1)

# Calculate prevalence of exposure among unexposed

r0 <- (p0+SP0-1)/(SN0+SP0-1)

# PRIORS

b0 ~ dnorm(0,1)
b1 ~ dnorm(0,2)
b2 ~ dnorm(0,2)
b3 ~ dnorm(0,2)
b4 ~ dnorm(0,2)
b5 ~ dnorm(0,2)
b6 ~ dnorm(0,2)
b7 ~ dnorm(0,2)
b8 ~ dnorm(0,1)
b9 ~ dnorm(0,2)
b10 ~ dnorm(0,2)
b11 ~ dnorm(0,2)
b12 ~ dnorm(0,2)
b13 ~ dnorm(0,2)
b14 ~ dnorm(0,2)
b15 ~ dnorm(0,2)
b16 ~ dnorm(0,2)
b17 ~ dnorm(0,2)
b18 ~ dnorm(0,2)
b19 ~ dnorm(0,2)
b20 ~ dnorm(0,2)
b21 ~ dnorm(0,2)
b22 ~ dnorm(0,2)
g1 ~ dnorm(0,2)
g2 ~ dnorm(0,2)
g3 ~ dnorm(0,2)
g4 ~ dnorm(0,2)
g5 ~ dnorm(0,2)
g6 ~ dnorm(0,2)
g7 ~ dnorm(0,2)
g8 ~ dnorm(0,2)
g9 ~ dnorm(0,2)
g10 ~ dnorm(0,2)
g11 ~ dnorm(0,2)
g12 ~ dnorm(0,2)
g13 ~ dnorm(0,2)
g14 ~ dnorm(0,2)
g15 ~ dnorm(0,2)
g16 ~ dnorm(0,2)
g17 ~ dnorm(0,2)
g18 ~ dnorm(0,2)
g19 ~ dnorm(0,2)
g20 ~ dnorm(0,2)
g21 ~ dnorm(0,2)
g22 ~ dnorm(0,2)
SN0 ~ dbeta(1000,1)
SN1 ~ dbeta(1000,1)
SP0 ~ dbeta(1000,1)
SP1 ~ dbeta(1000,1)
}

## Model S_D ##

## Initial values are based on coefficients from frequentist regressions: define initial values for 3 chains ##

```r
inits = list(
  list(b0=-1.25, b1=0.28, b2=0.05, b3=0.01, b4=-0.07, b5=0.62, b6=-0.27, b7=-0.36, b8=-1.73, b9=0.59, b10=1.12, b11=0.43, b12=0.15, b13=0.05, b14=0.07, b15=-0.48, b16=-0.51, b17=-0.38, b18=-0.40, b19=-0.75, b20=0.67, b21=0.50, b22=1.71, g1=-1.1, g2=0.01, g3=1.27, g4=0.79, g5=-0.31, g6=0.24, g7=0.24, g8=0.2, g9=-0.04, g10=-0.58, g11=0.62, g12=0.41, g13=-0.51, g14=0.67, g15=-0.98, g16=-1.26, g17=-0.04, g18=-0.22, g19=-0.19, g20=-0.62, g21=1.29, g22=1.12 , SN=0.4, SP=0.99),
  list(b0=-1.25, b1=0.28, b2=0.05, b3=0.01, b4=-0.07, b5=0.62, b6=-0.27, b7=-0.36, b8=-1.73, b9=0.59, b10=1.12, b11=0.43, b12=0.15, b13=0.05, b14=0.07, b15=-0.48, b16=-0.51, b17=-0.38, b18=-0.40, b19=-0.75, b20=0.67, b21=0.50, b22=1.71, g1=-1.1, g2=0.01, g3=1.27, g4=0.79, g5=-0.31, g6=0.24, g7=0.24, g8=0.2, g9=-0.04, g10=-0.58, g11=0.62, g12=0.41, g13=-0.51, g14=0.67, g15=-0.98, g16=-1.26, g17=-0.04, g18=-0.22, g19=-0.19, g20=-0.62, g21=1.29, g22=1.12 , SN=0.4, SP=0.99),
  list(b0=-1.25, b1=0.28, b2=0.05, b3=0.01, b4=-0.07, b5=0.62, b6=-0.27, b7=-0.36, b8=-1.73, b9=0.59, b10=1.12, b11=0.43, b12=0.15, b13=0.05, b14=0.07, b15=-0.48, b16=-0.51, b17=-0.38, b18=-0.40, b19=-0.75, b20=0.67, b21=0.50, b22=1.71, g1=-1.1, g2=0.01, g3=1.27, g4=0.79, g5=-0.31, g6=0.24, g7=0.24, g8=0.2, g9=-0.04, g10=-0.58, g11=0.62, g12=0.41, g13=-0.51, g14=0.67, g15=-0.98, g16=-1.26, g17=-0.04, g18=-0.22, g19=-0.19, g20=-0.62, g21=1.29, g22=1.12 , SN=0.4, SP=0.99)
)
```
list(b0=-1.25, b1=0.28, b2=0.05, b3=0.01, b4=-0.07, b5=0.62, b6=-0.27, b7=-0.36, b8=-1.73, b9=0.59, b10=1.12, b11=0.43, b12=0.15, b14=0.07, b15=-0.48, b16=-0.51, b17=-0.38, b18=-0.40, b19=-0.75, b20=0.67, b21=0.50, b22=1.71, g1=-1.1, g2=0.01, g3=1.27, g4=0.79, g5=-0.31, g6=0.24, g7=0.24, g8=0.2, g9=-0.04, g10=-0.58, g11=0.62, g12=0.41, g13=-0.51, g14=-0.67, g15=-0.98, g16=1.26, g17=-0.04, g18=-0.22, g19=-0.19, g20=0.62, g21=1.29, g22=1.12, SN=0.4, SP=0.99)

## This code calls WinBUGS to start iterations ##

casepopS_D.sim = bugs(data, inits=inits, model.file="E:/WORKING_DIRECTORY/Model_S_D.txt", parameters=c("b1","OR","SN0","SN1","SP0","SP1","r0"), n.chains=3, n.iter=25000, n.burnin=5000, n.thin=20, working.directory="E:/WORKING_DIRECTORY/", bugs.directory="c:/Program Files/WinBUGS14/", codaPkg=TRUE, debug=TRUE)

## This is the content of the Model_S_D.txt file ##

model {
  for (i in 1:N) {
    # Outcome model: Log odds of ASD as a function of the true variable for asthmagen exposure (astpregt) and covariates
    y[i] ~ dbern(pt[i])
    logit(pt[i]) <- b0 + b1*astregs[i] + b2*DR_AGBIRTH_MX[i] + b3*DR_AST_MP[i] + b4*DR_ALG_MP[i] + b5*DR_PSYALL_MX[i] + b6*parity_2[i] + b7*parity_3[i] + b8*sexm0f1[i] + b9*mrace_bla[i] + b10*mrace_asi[i] + b11*mrace_his[i] + b12*mrace_oth[i] + b13*medu_hs[i] + b14*medu_sc[i] + b15*medu_ba[i] + b16*medu_ad[i] + b17*ti_2[i] + b18*ti_3[i] + b19*ti_4[i] + b20*gest_1[i] + b21*gest_2[i] + b22*actsmk_preg[i]

    # Measurement model: probability of observed asthmagen exposure as a function of true asthmagen exposure, sensitivity, and specificity
    # Allows differential exposure misclassification
    asthmagen_preg[i] ~ dbern(pm[i])
    pm[i] <- SN0*(astregs[i])*(1-y[i]) + (1-SP0)*(astregs[i])*(1-y[i]) + SN1*(astregs[i])*(y[i]) + (1-SP1)*(astregs[i])*(y[i])

    # Exposure model: Log odds of true asthmagen exposure as a function of covariates
    astregs[i] ~ dbern(prop[i])
    logit(prop[i]) <- g1 + g2*DR_AGBIRTH_MX[i] + g3*DR_AST_MP[i] + g4*DR_ALG_MP[i] + g5*DR_PSYALL_MX[i] + g6*parity_2[i] + g7*parity_3[i] + g8*sexm0f1[i] + g9*mrace_bla[i] + g10*mrace_asi[i] + g11*mrace_his[i] + g12*mrace_oth[i] + g13*medu_hs[i] + g14*medu_sc[i] + g15*medu_ba[i] + g16*medu_ad[i] + g17*ti_2[i] + g18*ti_3[i] + g19*ti_4[i] + g20*gest_1[i] + g21*gest_2[i] + g22*actsmk_preg[i]
  }
}
# Calculate odds ratio

\[ \text{OR} \leftarrow \exp(b1) \]

# Calculate prevalence of exposure among unexposed

\[ r0 \leftarrow \frac{(p0 + SP0 - 1)}{(SN0 + SP0 - 1)} \]

# PRIORS

\[ b0 \sim \text{dnorm}(0, 1) \]
\[ b1 \sim \text{dnorm}(0, 2) \]
\[ b2 \sim \text{dnorm}(0, 2) \]
\[ b3 \sim \text{dnorm}(0, 2) \]
\[ b4 \sim \text{dnorm}(0, 2) \]
\[ b5 \sim \text{dnorm}(0, 2) \]
\[ b6 \sim \text{dnorm}(0, 2) \]
\[ b7 \sim \text{dnorm}(0, 2) \]
\[ b8 \sim \text{dnorm}(0, 1) \]
\[ b9 \sim \text{dnorm}(0, 2) \]
\[ b10 \sim \text{dnorm}(0, 2) \]
\[ b11 \sim \text{dnorm}(0, 2) \]
\[ b12 \sim \text{dnorm}(0, 2) \]
\[ b13 \sim \text{dnorm}(0, 2) \]
\[ b14 \sim \text{dnorm}(0, 2) \]
\[ b15 \sim \text{dnorm}(0, 2) \]
\[ b16 \sim \text{dnorm}(0, 2) \]
\[ b17 \sim \text{dnorm}(0, 2) \]
\[ b18 \sim \text{dnorm}(0, 2) \]
\[ b19 \sim \text{dnorm}(0, 2) \]
\[ b20 \sim \text{dnorm}(0, 2) \]
\[ b21 \sim \text{dnorm}(0, 2) \]
\[ b22 \sim \text{dnorm}(0, 2) \]
\[ g1 \sim \text{dnorm}(0, 2) \]
\[ g2 \sim \text{dnorm}(0, 2) \]
\[ g3 \sim \text{dnorm}(0, 2) \]
\[ g4 \sim \text{dnorm}(0, 2) \]
\[ g5 \sim \text{dnorm}(0, 2) \]
\[ g6 \sim \text{dnorm}(0, 2) \]
\[ g7 \sim \text{dnorm}(0, 2) \]
\[ g8 \sim \text{dnorm}(0, 2) \]
\[ g9 \sim \text{dnorm}(0, 2) \]
\[ g10 \sim \text{dnorm}(0, 2) \]
\[ g11 \sim \text{dnorm}(0, 2) \]
\[ g12 \sim \text{dnorm}(0, 2) \]
\[ g13 \sim \text{dnorm}(0, 2) \]
\[ g14 \sim \text{dnorm}(0, 2) \]
\[ g15 \sim \text{dnorm}(0, 2) \]
\[ g16 \sim \text{dnorm}(0, 2) \]
\[ g17 \sim \text{dnorm}(0, 2) \]
\[ g18 \sim \text{dnorm}(0, 2) \]
g19 ~ dnorm(0,2)  
g20 ~ dnorm(0,2)  
g21 ~ dnorm(0,2)  
g22 ~ dnorm(0,2)  
SN0 ~ dbeta(3.6,5.2)  
SN1 ~ dbeta(3.6,5.2)  
SP0 ~ dbeta(1000, 9.1)  
SP1 ~ dbeta(1000, 9.1)  
{

## Model D_D1 ##

## Danish data: x0=exposed controls, x1=exposed cases, n0=total number of controls, n1=total number of cases ##

data <- list(x0=6101, x1=1290, n0=29670, n1=6830, a.sn0=15.6, b.sn0=55.8, a.sp0=718, b.sp0=8.2, a.sn1=8.2, b.sn1=17.8, a.sp1=718, b.sp1=8.2, aa=1, bb=1)

## This code calls WinBUGS to start iterations ##

DK.modelD_D1.sim = bugs(data, inits=NULL,  
model.file="E:/WORKING_DIRECTORY/Model_D_D1.txt",  
parameters=c("lor","SN0","SN1","SP0","SP1","r0","r1","OR"),  
n.chains=3, n.iter=200000, n.burnin=10000, n.thin=100,  
working.directory="E:/WORKING_DIRECTORY/",  
bugs.directory="c:/Program Files/WinBUGS14/", codaPkg=TRUE, debug=TRUE)

## This is the content of the Model_D_D1.txt file ##

model{

# Distribution of observed data
# n0/n1=count of controls/cases

x0 ~ dbin(p0, n0)  
x1 ~ dbin(p1, n1)  

# Misclassification model: allow differential exposure misclassification

p0 <- r0*SN0 + (1-r0)*(1-SP0)  #controls  
p1 <- r1*SN1 + (1-r1)*(1-SP1)  #cases  

# Disease model

lor <- logit(r1) - logit(r0)  
OR <- exp(lor)  

}
# Uninformative prior on exposure prevalence

\[ r_0 \sim \text{dbeta}(a,a) \]
\[ r_1 \sim \text{dbeta}(a,a) \]

# Priors on SN and SP

\[ \text{SN}_0 \sim \text{dbeta}(a_{\text{SN}_0}, b_{\text{SN}_0}) \]
\[ \text{SN}_1 \sim \text{dbeta}(a_{\text{SN}_1}, b_{\text{SN}_1}) \]
\[ \text{SP}_0 \sim \text{dbeta}(a_{\text{SP}_0}, b_{\text{SP}_0}) \]
\[ \text{SP}_1 \sim \text{dbeta}(a_{\text{SP}_1}, b_{\text{SP}_1}) \]

## Model D_D2 ##

## Danish data: \(x_0=\)exposed controls, \(x_1=\)exposed cases, \(n_0=\)total number of controls, \(n_1=\)total number of cases ##

data <- list(x0=6101, x1=1290, n0=29670, n1=6830, a.sn0=15.6, b.sn0=55.8, a.sp0=718, b.sp0=8.2, a.sn1=8.2, b.sn1=17.8, a.sp1=718, b.sp1=8.2, aa=1, bb=1, mu=-0.43, tau=3.39)

## This code calls WinBUGS to start iterations ##

DK.modelD_D2.sim = bugs(data, inits=NULL, model.file="E:/WORKING_DIRECTORY/Model_D_D2.txt", parameters=c("lor","SN0","SN1","SP0","SP1","r0","r1","OR"), n.chains=3, n.iter=200000, n.burnin=10000, n.thin=100, working.directory="E:/WORKING_DIRECTORY/", bugs.directory="c:/Program Files/WinBUGS14/", codaPkg=TRUE, debug=TRUE)

## This is the content of the Model_D_D2.txt file ##

model{
  # Distribution of observed data
  # \(n_0/n_1=\)count of controls/cases
  x0 ~ dbin(p0, n0) #distribution of observed data
  x1 ~ dbin(p1, n1) #n0/n1=count of controls/cases

  # Misclassification model: allow differential exposure misclassification
  p0 <- r0*SN0 + (1-r0)*(1-SP0) #controls
  p1 <- r1*SN1 + (1-r1)*(1-SP1) #cases

  # Uninformative prior on exposure prevalence in controls
  r0 ~ dbeta(aa,bb)
# Informative prior on odds ratio derived from posterior distribution of SEED analysis

lor ~ dnorm(mu, tau) #log-mean and 1/log-variance

# Priors on SN and SP

SN0 ~ dbeta(a.sn0, b.sn0)
SN1 ~ dbeta(a.sn1, b.sn1)
SP0 ~ dbeta(a.sp0, b.sp0)
SP1 ~ dbeta(a.sp1, b.sp1)

# Disease model
OR <- exp(lor)
r1 <- (OR*r0)/(1-r0+OR*r0)

}
III.2. Convergence diagnostics

III.2.a. Model S_B

Model S_B: Trace Plots

- OR chains 1:2
- SN chains 1:2
- SP chains 1:2
- b1 chains 1:2
Model S_B: Density Plots

deviance chains 1:2

r0 chains 1:2

OR chains 1:2 sample: 1400

SN chains 1:2 sample: 1400

SP chains 1:2 sample: 1400

b1 chains 1:2 sample: 1400

r0 chains 1:2 sample: 1400
Model S_B: Autocorrelation Plots

- OR chains 1:2
- SN chains 1:2
- SP chains 1:2
- b1 chains 1:2
- deviance chains 1:2
- r0 chains 1:2
Model S_B: Gelman Plots

![Gelman Plots](image)

The plots above show the Gelman plots for various parameters in Model S_B. Each plot represents a different parameter: OR, SN, SP, b1, deviance, and r0. The plots display the trace of the parameter values over the iterations of the Markov chain, with the median and 95% quantiles indicated. The trace helps to assess the convergence of the MCMC sampling process.
III.2.b. Model S_D

*Model S_D: Trace Plots*

![Trace Plot OR chains 1:3](image)

![Trace Plot SN0 chains 1:3](image)

![Trace Plot SN1 chains 1:3](image)

![Trace Plot SP0 chains 1:3](image)
Model $S_D$: Density Plots

- **OR chains 1:3 sample: 3000**
- **SN0 chains 1:3 sample: 3000**
- **SN1 chains 1:3 sample: 3000**
- **SP0 chains 1:3 sample: 3000**
- **SP1 chains 1:3 sample: 3000**
- **b1 chains 1:3 sample: 3000**
- **deviance chains 1:3 sample: 3000**
- **r0 chains 1:3 sample: 3000**
Model S_D: Autocorrelation Plots
Model S_D: Gelman Plots
III.2.c. Model D D1

Model D_D1: Trace Plots

OR chains 1:3

SN0 chains 1:3

SN1 chains 1:3

SP0 chains 1:3
Model D_D1: Density Plots

OR chains 1:3 sample: 5700

SN0 chains 1:3 sample: 5700

SN1 chains 1:3 sample: 5700

SP0 chains 1:3 sample: 5700

SP1 chains 1:3 sample: 5700

device chains 1:3 sample: 5700

lor chains 1:3 sample: 5700

r0 chains 1:3 sample: 5700

r1 chains 1:3 sample: 5700
Model D_D1: Autocorrelation

OR chains 1:3

SN0 chains 1:3

SN1 chains 1:3

SP0 chains 1:3

SP1 chains 1:3

device chains 1:3

lor chains 1:3

r0 chains 1:3

r1 chains 1:3
Model D_D1: Gelman Plots

- OR
- SN0
- SN1
- SP0
- SP1
- deviance
- lor
- r0
- r1
III.2.d. Model D D2

*Model D_D2: Trace Plots*

![Trace Plots for OR chains 1:3](image1)

![Trace Plots for SN0 chains 1:3](image2)

![Trace Plots for SN1 chains 1:3](image3)

![Trace Plots for SP0 chains 1:3](image4)
r1 chains 1:3

iteration

0.2 0.4 0.6 0.8 1.0

101 500 1000 1500 2000
Model D_D2: Density Plots

OR chains 1:3 sample: 5700

SN0 chains 1:3 sample: 5700

SN1 chains 1:3 sample: 5700

SP0 chains 1:3 sample: 5700

SP1 chains 1:3 sample: 5700

deviance chains 1:3 sample: 5700

lor chains 1:3 sample: 5700

r0 chains 1:3 sample: 5700

r1 chains 1:3 sample: 5700
Model D_D2: Autocorrelation Plots

OR chains 1:3

SN0 chains 1:3

SN1 chains 1:3

SP0 chains 1:3

SP1 chains 1:3

deviance chains 1:3

lor chains 1:3

r0 chains 1:3

r1 chains 1:3
Model D_D2: Gelman Plots
Curriculum Vitae
Alison B. Singer

Johns Hopkins Bloomberg School of Public Health
Department of Epidemiology
615 N. Wolfe Street
Baltimore, MD 21205
Email: asinge12@jhu.edu

EDUCATION:

PhD Candidate in Epidemiology, Expected May 2015
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Concentration: Occupational and Environmental Epidemiology
Advisor: M. Daniele Fallin, PhD
Thesis: Parental exposure to occupational asthmagens and risk of autism spectrum disorder

Master of Health Science in Epidemiology, May 2011
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Concentration: Occupational and Environmental Epidemiology
Completed Certificate in Risk Sciences and Public Policy

Bachelor of Science in Biology, May 2007
Brown University, Providence, RI
Concentrations: Biology, History

RESEARCH EXPERIENCE:

Graduate Student Researcher,
Wendy Klag Center for Autism and Developmental Disabilities,
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 06/2012 – Present

Research Assistant,
Welch Center for Prevention, Epidemiology and Clinical Research,
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 06/2010 – 10/2011

Research Technician, Laboratory of Joseph G. Gall,

Undergraduate Research Assistant, Laboratory of Susan A. Gerbi,
Department of Molecular Biology, Cell Biology and Biochemistry,
Brown University, Providence, RI 04/2006 – 05/2007
**PEER-REVIEWED PUBLICATIONS:**


**BOOK CHAPTERS:**


**SUBMITTED PUBLICATIONS:**


**IN PREPARATION PUBLICATIONS:**

**Singer AB**, Windham GC, Croen LA, Daniels JL, Lee BK, Schendel DE, Fallin MD, Burstyn I. Maternal exposure to occupational asthmagens and risk of autism spectrum disorder in the Study to Explore Early Development (*in preparation*).

**Singer AB**, Burstyn I, Fallin MD, Schendel DE. Parental exposures to occupational asthmagens and risk of autism spectrum disorder in a Danish population-based case-control study (*in preparation*).

Croen LA, Qian Y, **Singer A**, Zerbo O, Levy S, Schendel D, Schieve L, Daniels J, Fallin D. Family history of immune conditions and risk of autism spectrum disorders in the SEED study (*in preparation*).
CONFERENCE ABSTRACTS:
*Presenting Author


TEACHING EXPERIENCE:

Lecture, “Early Life Environmental Health”,
in Environmental and Occupational Epidemiology Course, 
*Johns Hopkins Bloomberg School of Public Health, Baltimore, MD* 04/2014

Teaching Assistant, “Epidemiologic Methods III”,
*Johns Hopkins Bloomberg School of Public Health, Baltimore, MD* 01/2013 – 03/2013

Teaching Assistant, “Methods and Applications of Cohort Studies”,
*One-week Class, Summer Institute in Epidemiology and Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD* 06/2012, 06/2013

Teaching Assistant, “Multilevel Statistical Models in Public Health”,
*Johns Hopkins Bloomberg School of Public Health, Baltimore, MD* 03/2012 – 05/2012
Teaching Assistant, “Analysis of Longitudinal Data”,
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 01/2012 – 03/2012

Teaching Assistant, “Epidemiologic Methods II”,

Course Faculty, “Occupational and Environmental Epidemiology”,
One-week Summer Workshop, Fudan University
School of Public Health, Shanghai, China 08/2011

Teaching Assistant, “Environmental and Occupational Epidemiology”,
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 03/2011 – 05/2011

Teaching Assistant, “Principles of Epidemiology”,
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 08/2010– 10/2010

LEADERSHIP AND SERVICE ROLES:

Joseph Gall 85th Birthday Symposium Student Co-organizer,
Carnegie Institution, Baltimore, MD 04/2013

Epidemiology Department Curriculum Committee Representative,
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 09/2012 – 08/2014

Environmental Epidemiology Journal Club Coordinator,
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 08/2010 – Present

President, Brown Film Society, Brown University, Providence, RI 05/2006 – 05/2007

Publicity Coordinator/ Special Events Coordinator,
Brown Film Society, Brown University, Providence, RI 05/2005 – 05/2006

HONORS AND AWARDS:

Autism Speaks Dennis Weatherstone Predoctoral Fellowship, 2013 – 2015

Wendy Klag Scholar, Received funding for research proposal “Maternal total serum
immunoglobulin E and early developmental indicators of autism spectrum disorders,” May 2013

Marilyn Menkes Book Award, Epidemiology Department, Johns Hopkins Bloomberg School of
Public Health, May 2013

NIEHS Travel Scholarship to attend the Environmental Epidemiology of Autism Risk Network
Meeting in Donostia/San Sebastian, Spain, May 2013

NIEHS Travel Scholarship to attend the Environmental Epidemiology of Autism Risk Network
Meeting in Toronto, ON, Canada, May 2012
Charlotte Ferencz Award, Epidemiology Department, Johns Hopkins Bloomberg School of Public Health, 2012

Graduated *Magna Cum Laude* from Brown University with Honors in Biology, May 2007

Elizabeth Leduc Prize in Biology, Brown University Cell Biology Award, May 2007

Sigma Xi, Scientific Honor Society, Elected Associate Member, Brown University, May 2007

“Undergraduate Teaching and Research Award,” Laboratory of Dr. Susan Gerbi, Summer 2006

Phi Beta Kappa, Elected Junior Year, Brown University, February 2006