

Combined Analysis of the Association Between Air
Pollution, Urban Green Space, and Neurodevelopmental
Disorders

by

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Abstract

This thesis aimed to test the association between environmental exposures and neurodevelopmental diagnoses, trait, and cognitive scores in a sample of children and adolescents living in Toronto, Canada. The influence of the environment on the prevalence and severity of Attention-Deficit Hyperactivity Disorder (ADHD), Obsessive-Compulsive disorder (OCD), and Autism Spectrum Disorder (ASD) is not yet clear. Studying the effects of these exposures in an urban environment is critical, as they represent potentially important modifiable risk factors. This thesis found evidence of an association between environmental exposures and OCD traits within the community. Consistent results in the analysis are promising; however, the results are preliminary and require further study. The results add to the uncertainty surrounding the effect of the environment on ADHD. Analysis of the combined results support the use of quantitative measures for assessing neurodevelopmental disorders, and the idea that disorders like ADHD and OCD exist at extreme ends of a spectrum of traits within the community.

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Table of Contents

Abstract.....	ii
Acknowledgements.....	iii
Table of Contents.....	iv
List of Tables.....	viii
List of Figures.....	ix
List of Appendices.....	x
Chapter 1 - Introduction.....	11
1.1 Background on Neurodevelopmental Disorders and Environmental Exposures.....	11
1.1.1 Environmental Exposures as Risk Factors.....	11
1.1.2 Framing Neurodevelopmental Disorders and Comorbidity.....	13
1.1.3 The Current State of the Research.....	14
1.1.4 Socioeconomic Status as a Risk Factor for Neurodevelopmental Disorders.....	16
1.1.5 A Network Perspective of Neurodevelopmental Disorders.....	17
1.1.6 Study Objectives and Design.....	18
1.2 Data, Study Design, and Recruitment.....	19
1.2.1 Traits Assessment.....	19
1.2.2 Neurodevelopmental Disorder Diagnosis.....	20
1.2.3 Cognition Assessment.....	21
1.2.4 Data linkage.....	21
1.2.5 Data analysis.....	22
1.2.6 Network Models.....	23

1.3	Thesis Outline.....	24
1.3.1	Key Findings.....	25
Chapter 2 - The Effect of Ambient NO₂ Pollution on the Prevalence and Severity of Neurodevelopmental Disorders.....		27
2.1	Introduction.....	27
2.2	Data and Methods.....	29
2.2.1	Study design and subject recruitment.....	29
2.2.2	Trait assessments and neurodevelopmental disorder diagnosis.....	29
2.2.2.1	Traits.....	29
2.2.2.2	Diagnoses.....	30
2.2.2.3	Cognition.....	30
2.2.3	Air pollution data and environmental exposure assessment.....	32
2.2.4	Data analysis.....	33
2.3	Results.....	35
2.3.1	Sensitivity analysis.....	36
2.4	Discussion.....	37
2.5	Conclusion.....	42
Chapter 3 - A Network Perspective of Environmental Exposures and Neurodevelopmental Disorders.....		43
3.1	Introduction.....	43
3.2	Data and Methods.....	45
3.2.1	Study design and subject recruitment.....	45
3.2.2	Trait assessments and neurodevelopmental disorder diagnosis.....	46
3.2.2.1	Traits.....	46

3.2.2.2	Diagnosis.....	47
3.2.2.3	Cognition.....	47
3.2.3	Environmental exposure and marginalization linkage.....	47
3.2.4	Data Analysis.....	49
3.3	Results.....	51
3.3.1	Sample characteristics.....	51
3.3.2	NO ₂ Networks.....	51
3.3.3	PM _{2.5} Networks.....	52
3.3.4	Green Space Networks.....	53
3.3.5	Full Networks.....	55
3.3.6	Sensitivity analysis.....	56
3.4	Discussion.....	56
3.4.1	NO ₂ Networks.....	56
3.4.2	PM _{2.5} Networks.....	58
3.4.3	Green Space Networks.....	58
3.4.4	Research Implications.....	59
3.4.5	Strengths and Limitations.....	62
3.5	Conclusion.....	63
Chapter 4	Conclusion.....	64
4.1	Combined Results and Discussion of Findings.....	64
4.2	OCD Findings.....	64
4.3	ADHD Findings.....	66
4.4	Cognitive Score Findings.....	68

4.4.1	Evidence that Environmental Exposure Influence Traits, Not Diagnosis.....	69
4.5	Directions for Further Research.....	70
4.5.1	Expand on Analysis Across Traits of Neurodevelopmental Disorders.....	70
4.5.2	Sex Specific Analysis of Neurodevelopmental Traits.....	71
4.5.3	The Need for Multi-pollutant Studies.....	73
4.6	Strengths and Limitations.....	74
4.7	Conclusion.....	75
	Appendices.....	2
	Appendix A.....	2
	References.....	4

List of Tables

Table 1: Demographic and Neurodevelopment Characteristics of Participants.....	31
Table 2: Environmental Exposure Measures.....	33
Table 3: Demographic and Neurodevelopment Characteristics of Participants.....	48
Table 4: Environmental Exposure Measures.....	49
Table 5: Models and Variables Included in Network Analysis.....	50
Table 6: Odds Ratios for Risk of Diagnosis.....	2
Table 7: Effect Estimate for Trait and Cognitive Scores.....	3

List of Figures

Figure 1: Odds Ratios for Multivariate Logistic Regression of Reported Diagnosis.....	35
Figure 2: Effect Estimates for Multivariate Regression of Trait and Cognitive Scores....	37
Figure 3: Single Exposure Network Models for NO ₂	52
Figure 4: Single Exposure Network Models for PM _{2.5}	53
Figure 5: Single Exposure Network Models for Green Space.....	54
Figure 6: Multi-exposure Network Models including NO ₂ , PM _{2.5} , and Green Space.....	55

List of Appendices

Appendix A.....	2
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Chapter 1 - Introduction

1.1 Background on Neurodevelopmental Disorders and Environmental Exposures

Neurodevelopmental disorder (NDD) is a broad term for chronic disorders that affect the central nervous system during developmental periods for motor skills, cognition, communication, or behavior (1). Attention-deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), and autism spectrum disorder (ASD) are three common and impairing childhood neurodevelopmental disorders which frequently co-occur. Research on these disorders has shown a high degree of heritability within and across disorders (2–4).

Despite significant heritability previous research has shown that environmental factors may account for 10-65% of the variance seen within these disorders (5). Environmental exposures such as air pollution have a well-documented effect on population health across a diverse range of outcomes and mechanisms. This has typically been studied in the context of cardiac or respiratory disease, however the impact of the environment on NDDs should not be overlooked (5–7). Identifying and understanding the effects of environmental exposures is important as they may act as important modifiable risk factors.

1.1.1 Environmental Exposures as Risk Factors

Ambient environmental exposures during childhood and adolescence have been identified as a potential factor in the development of NDDs. Ambient air pollution - including Nitrogen Dioxide (NO₂), and fine particulate matter (PM_{2.5}) have been studied as potential risk factors. NO₂ is emitted primarily through combustion, with its main sources being industrial processes and vehicle emissions. As such, locations of roads and vehicle traffic near to residential areas are often significant predictors for the health impacts of ambient NO₂ concentration, and ambient levels are typically several times greater around roadways compared to baseline urban exposures (8,9). This means that NO₂ is a useful proxy for other pollutants that result from traffic and road pollution (8,9). There is a large spatial variability in NO₂ in relation to markers of traffic emissions, including distance from roads, traffic volumes, and road length (8).

PM may be a result of direct emission or conversion from gaseous precursors (10). Similarly, it is emitted from transportation sources, but includes others such as residential combustion, power generation, industry, and agriculture in addition to transportation (10,11). PM is made up of several chemical compounds including nitrates, sulfates, elemental and organic carbon, organic compounds, biological compounds, and metals (12). PM_{2.5} is considered “fine particular matter” and is measured by particulates of less than 2.5 microns in diameter. Biologic mechanisms of action with respect to air pollution and neurodevelopment are not well understood, but there is evidence of inflammation and epigenetic changes influencing risk of NDDs (13–15). Studies of individuals living in cities with high air pollution were found to have increased levels of inflammatory markers, disruption of the blood-brain barrier, endothelial activation, and oxidative stress (16,17). Increased inflammatory markers have been identified in individuals diagnosed with ADHD, OCD, and ASD (15,18). Reviews of this relationship have identified several possible mechanisms including glucocorticoid resistance, blood-brain barrier disruption altered neurotransmitter metabolism, impaired functional connectivity, increased oxidative stress, astrocyte and microglia activation, neuronal damage, and reduced neurotrophic support (19). Epigenetics refers to heritable modifications that affect the expression of a gene but not the underlying genome (20). Common mechanisms include methylation, histone modification, chromosome remodelling, or RNA regulation. Although research of the contributions of epigenetics to NDDs is preliminary, they may play an important role in NDD etiology. Epigenetic modifications may mediate or modify genetic or environmental risk or provide a biological mechanism for gene-environment interactions (21). Research has identified a possible relationship between epigenetic changes and NDDs, including ADHD, OCD, and ASD (22–24). Conversely, green space is hypothesized to act as a protective factor. Potential mechanisms for this relationship include Attention Restoration Theory (ART), reducing maternal stress, encouraging physical activity and social connection), as well as decreasing the effects of noise and traffic pollution (25–29). ART posits that concentrating on a task requires directed or voluntary attention, which may become depleted over time – particularly in more stressful urban

environments. Kaplan proposes that the natural environment helps restore this attention by engaging in activities that are “compatible” with our intrinsic motivations, getting away from everyday stress, engaging with stimuli that are “softly fascinating”, and experiencing expansive spaces and contexts (30).

1.1.2 Framing Neurodevelopmental Disorders and Comorbidity

ADHD, OCD, and ASD occur with high levels of comorbidity (31–33), and have been shown to have similarities in etiology (34–41), impaired executive function (42–44), and phenotype (45–51). Clinical diagnosis of disorders such as ADHD and OCD occur at extremes of widely distributed traits within the general population (52). In the case of diagnosis, ADHD is diagnosed when a child presents with significant symptoms of restlessness, inattentiveness, or impulsiveness. OCD may be diagnosed given a clinically extreme presentation of intrusive thoughts or urges, where individuals may attempt to reduce anxiety by acting out certain rituals (compulsions) (53). ASD involves repetitive behaviours in addition to impairment of social communication, and highly restricted interests and/or sensory behaviours (5). Conceptualizing NDD symptoms as a spectrum within the community by including quantitative neurodevelopmental trait scores in addition to diagnosis may allow us to better understand the effects of exposures. This contrasts with the commonly used diagnostic categories based on number of symptoms. Using a clinical threshold for NDDs reduces this spectrum of traits to two categories: affected and unaffected. Focusing on quantitative neurodevelopmental traits allowed us to identify more subtle effects of the environment on risk and severity.

Impairment to executive function is implicated in a wide range of common mental disorders, including ADHD, OCD, and ASD (43,44,54). This may affect the ability to delay or stop a response, identify and correct errors, or hold information in short-term working memory.

Impairment to executive function may impact the ability to suppress external stimuli or inappropriate actions and impulses (response inhibition). The stop-signal task has been used to measure response inhibition, where response speed and variability reflect consistency of attention and concentration (42,55).

Despite frequently co-occurring, the relationship between different NDDs is still unclear but are related to both symptomology and genetics. Individuals diagnosed with OCD and ADHD have been shown to exhibit higher frequencies of ASD symptoms (56–60). Some studies have concluded that comorbidity alone does not account for this increase in subclinical ASD symptoms (57). Emerging research has pointed to the possibility that existing diagnostic categories do not capture etiologically, biologically, and phenomenologically homogeneous groups (61–68). It has been found that subgroups with shared phenotypes and neurobiologies may exist that cut across existing diagnostic groups (69).

1.1.3 The Current State of the Research

Research on the effects of environmental exposures on the prevalence and severity of ADHD, OCD, and ASD has yielded inconclusive results. Some reviews found that a majority of included studies reported an observation between $PM_{2.5}$ and behavioural problems related to attention, and risk of ADHD (70,71), with some evidence of a dose-response relationship with risk of ADHD (71). However, both concluded that heterogeneity, bias, and a low number of studies as a need for further research (70,71). Further reviews found insufficient evidence of a relationship between $PM_{2.5}$ and ADHD (72,73). Relatively few studies have been conducted on the effects on NO_2 on ADHD. Two reviews found that there was not enough evidence to establish a connection, and the need for further study (70,72). Some research has studied the effects of green space in the context of ADHD. In some studies access to green space improved behaviours and symptoms, and decreased severity of symptoms experienced by children diagnosed with ADHD (74,75). A review on the effect of green space on attention restoration reported a mix of positive, and no change, and in one case – a negative relationship. The authors found that this differed across different attention measures (76).

Reviews of ASD have yielded similarly inconsistent results. Evidence for an association with $PM_{2.5}$ was reported to be strong (72,77,78), limited (79,80), or unclear (73). Of note is the mixed findings with respect to vulnerable windows of exposure. The strongest evidence was for maternal/prenatal exposure (72,77–79), within this period exposure during the third trimester

was found to most associated with ASD (78,79). However, some found evidence of risk for postnatal exposure to PM_{2.5} (72,77,78). Exposure to NO₂ was found to increase risk of ASD during postnatal periods (77,78), while other reviews found weak evidence for postnatal (72) and prenatal exposure (72,79,80). Research on the relationship between exposure to green space and ASD is limited, however one study found that an inverse relationship between urban green space and childhood autism (81).

Despite the relationship between OCD and both ADHD and ASD, research on the contribution of environmental exposures to its development is limited. To our knowledge there have been no previous studies on the effect of either air pollution or green space on OCD. Perinatal and reproductive cycle events, parental styles, stressful or traumatic events, socioeconomic factors, infection, substance abuse, and vitamin deficiency have all been studied as potential risk factors and correlates (82,83). However, no environmental exposure has been linked causatively with OCD (82,83).

Overall, the environmental contributions to development of NDDs is still unclear. Reviews have cited mixed results and heterogeneity of studies as a need for further research. Importantly most studies included in reviews rely on cases or diagnostic outcome variables for assessing risk. While this remains the predominant method for quantifying NDDs, using trait and symptom scores allow us to assess more subtle changes within a quantitative scale. Some research has indicated that multiple susceptibility genetic factors may interact with environmental conditions to lead to a continuous dimension of ASD-like and inattention traits, with neurodevelopmental disorders at the extremes of this continuum (84,85).

1.1.4 Socioeconomic Status as a Risk Factor for Neurodevelopmental Disorders

In addition to environmental variables like air pollution and greenspace consideration of other covariates such as socioeconomic status (SES) and marginalization that may also influence risk is also needed. Lower SES has been shown to affect health and development, and is associated with worse health and psychological well-being, in addition to impaired cognitive and emotional development (86–90). Studies of low SES and NDDs have yielded mixed results. The risk of

diagnosis with ADHD was found to increase with lower socioeconomic status (91–93). Studies of ASD diagnosis, OCD diagnosis, and OCD traits have found mixed and sometimes contradictory results with some finding increased risk for both higher and lower SES (94–101). Relevant to NDDs and executive function – low SES children exhibit larger responses to unattended stimuli, suggesting a decreased ability to suppress distraction (102,103). This may be due to a decreased ability to recruit prefrontal attention circuits in response to stimuli when compared with higher SES children (104). SES related disparities in executive function tasks have been described throughout early adolescence (105–110). Mechanisms for this relationship are still being studied however studies in humans suggest that prenatal factors, parent–offspring interactions and cognitive stimulation at least partly underlie the effects of SES on brain development. Research on ADHD and SES found some evidence of altered brain structure as possible mechanism (111). These effects are somewhat specific, with the level of cognitive stimulation in the home environment best predicting a child’s cognitive development and the quality of parental care more closely related to its emotional development (112). Another hypothesis relates to neurodevelopment, as children of lower socioeconomic status parents were more likely to exhibit neurological abnormalities at 4 months and 1 year, and neurological abnormalities, hard signs, soft signs, and autonomic nervous system dysfunctions at 7 years (113).

1.1.5 A Network Perspective of Neurodevelopmental Disorders

Given the complex relationship between NDDs it may be useful to visualize them as a system as opposed to standalone conditions. Symptoms of NDDs have typically been thought to result from a causal latent disorder (114,115). For example, an individual exhibits obsessive-compulsive symptoms because of the underlying condition of OCD. Conversely, a network theory of mental disorders suggests that disorders arise from a network of causally related symptoms (116). Within this network, symptoms interact and feedback into each other and may result in a self-sustaining disorder state (117). This means that if a symptom is present and is related to other symptoms in a network, it may increase the probability that those symptoms develop (117). This

also increases the importance of identifying and quantifying the most central symptoms in a network, current diagnostic tools weight all symptoms or traits equally. More central symptoms share connections with many other variables within the network, and if influenced by external factors such as environmental exposure, may cause other symptoms to develop

Comorbidity has traditionally been studied as the co-occurrence of distinct disorders; however, network theory hypothesizes that these may arise due to mutual interactions between symptoms across disorders (118). Overlapping phenotype across disorders (45–51) may provide a path to comorbidity, as networks model relationships between symptoms rather than across two latent disorders (119). Shared symptoms may act as “bridge symptoms”, which may spread activation between disorders (118). Network analysis has been used to assess comorbidity across NDDs, however analysis of other mental disorders has been useful in visualizing the effects of environmental exposures. Studies of psychopathology have found that external environmental exposures may increase the degree of symptom connectivity and result in less resilient symptom networks (120–122). Network analysis may provide a useful tool for visualizing the effects of environmental exposures on the development of NDDs.

1.1.6 Study Objectives and Design

The objectives of this thesis are to test the association between environmental exposures and neurodevelopmental diagnoses, trait, and cognitive scores in a sample of children and adolescents living in Toronto, Canada. Studying the effects of these exposures allows for assessing a wide range of exposure within the urban environment and the potential to modify this exposure through policy and interventions. This objective was met by completing two linked studies that have been written as stand-alone papers for submission in peer-reviewed academic journals.

The first study included in this thesis examined the association between NO₂ and ADHD and OCD trait scores, cognitive scores, and reported diagnoses for ADHD, OCD, and ASD. ASD trait scores were not available in this study. It was hypothesized that exposure to higher levels of

ambient NO₂ at residential addresses will increase the risk of a diagnosis of ADHD, OCD, and ASD and be associated with increased ADHD and OCD traits and reduced executive function. The second study in this thesis aimed to model the association between environmental exposures and NDD traits, diagnosis, and cognitive scores using network models. Network analysis may help gain additional insight into the effect of the environment on NDDs and potential pathways that may account for this association. Analyzing changes in both quantitative trait scores and reported diagnosis may quantify more subtle changes in NDD risk and severity within the community.

1.2 Data, Study Design, and Recruitment

The primary data source for the analysis in this thesis are drawn from initial sample consisted of data from 17,263 participants (aged 6-17 years) collected through the *Spit for Science* project at the Ontario Science Centre in Toronto, Canada (42). In this study, parents reported diagnoses/treatment received for OCD, ADHD and ASD and behavior of their children. When a parent report was unavailable, self-reports for participants 12+ years of age were included. The data included the first 4 digits of the residential Postal Code where applicable. The study was approved by The Hospital for Sick Children's research ethics board (42). After linking environmental exposures (see below) and excluding those with missing information the final sample was composed of 6,536 participants all living within Toronto, Canada.

1.2.1 Traits Assessment

ADHD traits were measured using the Strengths and Weaknesses of Attention-Deficit/Hyperactivity Disorder Symptoms and Normal Behavior Scale (SWAN) (123). The SWAN is a seven-point Likert scale that assess both strengths and weaknesses with 3 being far above average (indicating a strength) and -3 being far below average (indicating a weakness). Possible total scores range from -54 to 54, which can be further separated into two 9-item subscales, inattentive and hyperactive/impulsive, both subscales range from -27 to 27. These scores were reversed so that higher scores corresponded with increased ADHD traits. Parent and

self-completed SWAN survey contained the same questions. For more information see Crosbie et al. (42).

OCD traits were assessed using the Toronto Obsessive Compulsive Scale (TOCS) (124), a Likert scale consisting of 21 items. Possible answers ranged from -3 to 3 to assess both strengths and weakness, with a total score from -63 to 63. This scale can be further broken down into 6 subscales based on a previous factor analysis: counting/checking, hoarding, cleaning/contamination, rumination, symmetry/ordering, and superstition. A score of 3 on the SWAN or the TOCS was counted as a symptom for ADHD or OCD respectively. Both TOCS and SWAN scores show good reliability and validity (125,126).

1.2.2 Neurodevelopmental Disorder Diagnosis

Participants were classified as having a diagnosis for ADHD, OCD, or ASD if they reported having a diagnosis or were receiving treatment for ADHD, OCD, or ASD by a health care professional. In addition, participants with six or more reported symptoms of inattention or hyperactivity (or both) were also classified as having an ADHD diagnosis. Participants with four or more parent-reported symptoms or seven or more self-reported symptoms were classified as having an OCD diagnosis. Control groups included participants who did not report a diagnosis, were not receiving treatment for a disorder or had fewer reported symptoms than the cut-off. Participants were classified as having a diagnosis for ASD if they reported having a diagnosis of or treatment for ASD by a health care professional. Control groups included participants who did not report a diagnosis.

1.2.3 Cognition Assessment

Response inhibition, response time and response variability were measured using the stop-signal task (SST) administered on a computer. The SST includes a stop and a go task. The go task requires that the participant respond to stimuli (either an X or an O) presented in the centre of the screen for 500ms as quickly and as accurately as possible by pressing the corresponding button (left for X; right for O). The stop task involved an auditory signal randomly presented by headphones at a comfortable listening level in 25% of the trials.

Response inhibition (stop signal reaction time) was estimated using interpolation (55). Reaction time is the mean response time on Go trials that did not involve a stop signal while response variability is the standard deviation of this mean and reflects sustained attention and arousal (42).

1.2.4 Data linkage

All environmental data (NO₂, PM_{2.5}, and green space) were indexed to DMTI Spatial Inc. postal codes and were provided by the Canadian Urban Environmental Health Research Consortium (CANUE) (127–136). All environmental data between the years of 2000 to 2009 was included. The mean value was calculated over 10 years, and then averaged across four-digit Postal Codes creating a mean value for each four-digit Postal Code grid. The values were then assigned to participants based on the Postal Code at the residential address.

The Canadian Index of Marginalization (CAN-Marg) for 2006 was also included in all models. The CAN-Marg is composed of four dimensions: residential instability, material deprivation, dependency, and ethnic concentration (137). The ethnic concentration subscale was included with the hope that it will allow us to gain greater understanding of the impact of environmental racism in our current study. Each measure is based on census data and is available at the dissemination area level, equivalent to several grouped urban blocks. Participants were linked to the CAN-Marg data set by the centroid of the area encompassed by four-digit Postal Codes and which dissemination area it fell into.

1.2.5 Data analysis

SST data were reported as standardized Z-scores, which included sex, age, and corrected for stimulant medication. All other data was reported in its unstandardized form for ease of comparison. NO₂ and marginalization component scores were included in models as continuous variables – with effect sizes given per unit increase (per ppb NO₂, and quintile of marginalization, respectively).

All data linkage and statistical analysis were conducted using the statistical software R (version 4.0.4) (138). Linear regression was used to assess the association between NO₂ concentration and trait outcome measures. Model 1 included age, sex, and respondent in addition to NO₂

concentration, while Model 2 also included residential instability, material deprivation, dependency, and ethnic concentration as covariates. We have included the ethnic concentration subscale with the hope that it will allow us to understand better the impact of environmental racism in our current study. Ethnic concentration incorporates the proportion of the population who are recent immigrants, and the proportion of the population who identify as a visible minority. While this is a crude measure that does not adequately quantify the damaging effects of racism our hope is that it gives us some insight and accounts for some of the marginalization of racialized communities.

Male sex and self-reported participants were used as reference groups. SST outcome scores already included demographic covariates and a correction for stimulant medication; only marginalization scores and NO₂ concentration were included in these models. Effect estimates were reported per increase in unit of NO₂. Diagnostic tests including residual and Q-Q plots were administered to ensure that models met linear regression assumptions. Variance inflation scores were calculated to assess multicollinearity.

This study used logistic regression to assess the association between ambient NO₂ pollution and reported neurodevelopmental disorder diagnosis. Initial unadjusted models included age, sex, respondent in addition to NO₂ concentration, while final models also included residential instability, material deprivation, dependency, and ethnic concentration as covariates. Male sex and self-respondent were again used as reference groups. Results from this analysis were reported as odds ratios, giving the change in odds of diagnosis per unit increase in the predictor variable.

As the analysis involved multiple hypothesis tests of the same sample significance values were adjusted using the Bonferroni correction to reduce the likelihood of false positives within the results. This correction is applied to both linear and logistic regression results.

1.2.6 Network Models

For the network analysis component, network models were estimated containing all relevant variables with the goal of visualizing the relationship between traits and environmental

exposures. To examine changes in network structure and connections network models increasing in complexity were calculated for each environmental exposure in addition to a final full model. Each model included demographic and marginalization variables.

Network models consist of nodes and edges, where nodes correspond with variables, and edges represent two variables that are not independent after conditioning for all variables in the dataset. As models included continuous, ordinal, and binary data a Mixed Graphical Model (MGMs) was used to estimate networks using the R package *mgm* (139). All network models included pairwise interactions. To avoid false positive findings, *mgm* uses the least absolute shrinkage and selection operator (LASSO) (140). This shrinks small non-zero edges to exactly zero, the strength of this is determined by the tuning parameter lambda. Based on previous analysis of this dataset the less conservative cross validation method was used to estimate the tuning parameter. This allowed visualization of potentially smaller but potentially important associations within the networks. Ten folds were used for cross validation in the LASSO procedure.

After estimating partial correlations between variables, network models were visualized using the R package *qgraph* (141). The layout of node positions was calculated using the Fruchterman Reingold algorithm, which places nodes such that all the edges are approximately the same length and crossing is minimized (142). All analysis was performed in R (version 4.0.4) (138).

1.3 Thesis Outline

The analysis conducted and findings included for thesis are presented across three separate chapters. Chapter Two is a paper that will be submitted for publication (*The Effect of Ambient NO₂ Pollution on the Prevalence and Severity of Neurodevelopmental Disorders*) in the journal *Environmental Health Perspectives*. This analysis looks at the association between NO₂ pollution and trait scores, cognitive scores, and diagnosis. Only one environmental exposure was studied initially, with the goal of conducting an initial analysis without accounting for the complexities of multiple pollutants. NO₂ was chosen based on its spatial variability within an urban setting. Chapter Three is the paper *A Network Perspective of Environmental Exposures and Neurodevelopmental Disorders*, to be submitted to the *Journal of Child Psychology and*

Psychiatry. This study similarly tests the associations between environmental exposures and NDD trait and cognitive scores. However, unlike the previous paper, this study looks at this association through the lens of the network theory of mental disorders. This analysis included all three environmental exposures to assess more complex associations with outcome variables. Finally, Chapter Four will discuss the collective findings of the two previous studies and their place within the wider literature.

1.3.1 Key Findings

The combined papers in this thesis add to increasing amount of literature studying the complex etiology of NDDs. These papers found evidence of an association between environmental exposures and OCD traits within the community. Consistent results between the two studies are promising; however, the analysis is preliminary and requires further study. The results add to the uncertainty surrounding the effect of the environment on ADHD. Despite some previous studies finding evidence of a relationship this study found no evidence of association, and in the first study an inverse relationship with overall SWAN, and inattention scores. Analysis of the combined results support the use of quantitative measures for assessing NDDs, and the idea that disorders like ADHD and OCD exist at extreme ends a spectrum of traits within the community. Subsequent studies should continue to make use of validated, quantitative measures when studying ADHD and OCD especially given the subtle yet potentially significant effect of exposures on symptoms. Future research should also prioritize validating measures and interactions by sex to try and understand the potential similarities and differences with respect to psychopathology and susceptibility in males and females. The results presented in this thesis are promising, although they also show the need for future research to support and expand the findings. Network analysis of exposures and NDDs shows the need for including multiple exposures and trait scores across ADHD, OCD, and ASD. It can be concluded that network analysis may prove a useful tool for visualizing the complex relationship between these and other external factors.

Chapter 2 - The Effect of Ambient NO₂ Pollution on the Prevalence and Severity of Neurodevelopmental Disorders

2.1 Introduction

Environmental exposures have a well-documented effect on population health across a diverse range of outcomes and mechanisms. Identifying and understanding these environmental exposures is critical as they may act as important modifiable risk factors. Previous research indicates that the environment plays a role in the development of neurodevelopmental disorders (NDDs) (5–7) and may account for 10–65% of the variance seen within these disorders (5).

One potentially important exposure is Nitrogen Dioxide (NO₂), which is primarily emitted from industrial sources and vehicle emissions as a result of combustion (8,143). While the effects of NO₂ on neurodevelopment are not well understood, some hypotheses for the mechanisms of action include inflammation and changes in methylation (13–15). Previous research has found evidence of increased inflammatory markers in those diagnosed with attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), and autism spectrum disorder (ASD) (15,18). Research on NO₂ and NDDs has yielded mixed evidence, and in the case of OCD – has not been studied (79,144–148). Notably, few studies have tested the association between current exposure to NO₂ pollution and NDDs.

ADHD, OCD, and ASD are three of the most common and impairing childhood NDDs. Clinical diagnosis of disorders such as ADHD and OCD occur at extremes of widely distributed traits within the general population (52). For example, ADHD is diagnosed when a child presents with significant symptoms of restlessness, inattentiveness, or impulsiveness. OCD may be diagnosed given a clinically extreme presentation of intrusive thoughts or urges, where individuals may attempt to reduce these obsessions by acting out certain rituals (compulsions) (53). Using a clinical threshold for NDDs reduces this spectrum of traits to two categories: affected and unaffected. Including quantitative neurodevelopmental trait scores in addition to diagnosis may allow us to identify more subtle effects of NO₂.

Impairment to executive function is implicated in a wide range of common mental health conditions, including ADHD, OCD, and ASD (43,44,54). This may affect the ability to delay or stop a response, identify and correct errors, or hold information in short-term working memory. This may, in turn, impact the ability to suppress external stimuli or inappropriate actions and impulses (response inhibition). The stop-signal task has been used to measure response inhibition, where response speed and variability reflect consistency of attention and concentration (42,55).

Focusing on quantitative neurodevelopmental traits allowed us to identify more subtle effects of NO₂ on risk and severity. Consideration of other covariates such as socioeconomic status and marginalization that may also influence risk is also needed. The risk of diagnosis with ADHD was found to increase with lower socioeconomic status (91–93), while studies of ASD diagnosis, OCD diagnosis, and OCD traits have found mixed and sometimes contradictory results (94–101). Studying the effects of these covariates and NO₂ pollution allows for greater spatial variability within the urban environment and the potential to modify this exposure through policy and interventions.

The objective of the current study was to test the association between NO₂ pollution and neurodevelopmental diagnoses and trait scores. We examined reported diagnoses for ADHD, OCD, and ASD and trait scores for ADHD and OCD in a large community sample of youth aged 6-17. ASD trait scores were not available in this study. We hypothesize that exposure to higher levels of ambient NO₂ at residential addresses will be associated with increased prevalence of ADHD, OCD, and ASD and be associated with increased ADHD and OCD traits and reduced executive function.

2.2 Data and Methods

2.2.1 Study design and subject recruitment

Our sample consisted of 17,263 participants (aged 6-17) recruited through the Spit for Science project at the Ontario Science Centre in Toronto, Canada (42). Parents reported diagnoses/treatment received for OCD, ADHD, and ASD and their children's behaviour. When

parent report was unavailable, we included self-report for participants 12+ years of age. In addition, the first four digits of participant's residential postal code was collected. Complete information, including environmental data based on Postal Codes (see below for details) within the Greater Toronto Area was available for 8,299 participants. The study was approved by The Hospital for Sick Children's research ethics board (42). Demographic information is shown in Table 1.

2.2.2 Trait assessments and neurodevelopmental disorder diagnosis

2.2.2.1 Traits

To assess ADHD traits, we used the Strengths and Weaknesses of Attention-Deficit/Hyperactivity Disorder Symptoms and Normal Behavior *Scale* (SWAN)(123). The parent (SWAN-Parent) and self-report (SWAN-Self) versions of the SWAN included the same 18 items but differed in terms of the referent ("your child" instead of "me"). The SWAN is a seven-point Likert scale that assesses both strengths and weaknesses, with 3 being far above average (indicating a strength) and -3 being far below average (indicating a weakness). The total possible score ranges from -54 to 54, with two 9-item subscales, inattentive and hyperactive/impulsive; both range from -27 to 27. For ease of comparison, SWAN scores were reversed so that higher scores represented greater ADHD traits. OCD traits were assessed using the Toronto Obsessive Compulsive Scale (TOCS) (126), a Likert scale consisting of 21 items. Possible answers ranged from -3 to 3 to assess strengths and weaknesses, with a total score of -63 to 63. This scale is broken down into six subscales based on previous factor analysis: counting/checking, hoarding, cleaning/contamination, rumination, symmetry/ordering, and superstition. Both TOCS and SWAN scores show good reliability and validity (124,125). Trait scores are summarized in Table 1.

2.2.2.2 Diagnoses

Participants were classified as having a diagnosis for ADHD, OCD, or ASD if they reported having a diagnosis of or treatment for ADHD, OCD, or ASD by a health care professional. In addition, participants with six or more reported symptoms of inattention or hyperactivity (or both) were also classified as having an ADHD diagnosis. Participants with four or more parent-reported symptoms or seven or more self-reported symptoms were classified as having an OCD diagnosis. A score of 3 on the SWAN or the TOCS was counted as a symptom for ADHD or OCD, respectively. Control groups included participants who did not report a diagnosis, were not receiving treatment for a disorder or had fewer reported symptoms than the cut-off. Prevalence of reported diagnosis is reported in Table 1.

2.2.2.3 Cognition

Response inhibition, response time, and response variability were measured using the stop-signal task (SST) administered on a computer. Trait, cognitive score, and reported diagnosis are summarized in Table 1.

Table 1: Demographic and Neurodevelopment Characteristics of Participants

	Measure	Value	Observed Range
Demographics			
	Age [years (mean \pm SD)]	10.75 \pm 2.78	6.0-17.9
	Parent report [frequency. (%)]	7,024 (84.64%)	
Sex [frequency. (%)]			
	Female	4,101 (49.42%)	
	Male	4,198 (50.58%)	
Neurodevelopmental traits (mean \pm SD)			
	TOCS Total Score	-19.04 \pm 21.82	-63-58
	Counting/Checking	-3.75 \pm 3.92	-9-9
	Hoarding	-0.57 \pm 3.1	-6-6
	Cleaning/Contamination	-4.3 \pm 6.43	-15-15
	Rumination	-1.03 \pm 3.03	-6-6

	Symmetry/Ordering	-2.81 ± 5.41	-12-12
	Superstition	-4.59 ± 3.68	-9-9
	SWAN Total Score	-4.62 ± 16.91	-54-54
	Hyperactivity/impulsivity	-2.81 ± 9.34	-27-27
	Inattention	-1.81 ± 9.09	-27-27
Stop-Signal Task Performance [ms. (mean ± SD)]			
	Interpolated stop signal reaction time	308 ± 149.35	1-1266.2
	Reaction Time	601.38 ± 111.00	295.04-1300.41
	Response Variability	160.16 ± 57.10	43.62-553.04
Neurodevelopmental disorder diagnoses [frequency. (%)]			
	OCD	281 (3.39%)	
	ADHD	597 (7.19%)	
	ASD	119 (1.43%)	

The SST involves a stop and a go task. The go task requires that the participant responds to stimuli (either an X or an O) presented in the centre of the screen for 500 ms as quickly and as accurately as possible by pressing the corresponding button (left for X; right for O). The stop task involved an auditory signal randomly presented by headphones at a comfortable listening level in 25% of the trials. Participants were instructed to stop their go signal response on that trial. Stop signals followed a presentation of the go signals by a delay which was adjusted dynamically depending on participant performance. If the participant could stop their response, the delay was increased by 50 ms, making it more difficult to stop on the subsequent stop-signal trial. If they could not stop, the stop-signal delay was decreased by 50 ms, making it easier to stop on the next stop-signal trial.

The SST consists of a practice block and four experimental blocks of 24 trial, each involving 18 go trials and 6 stop trials. Response inhibition (stop-signal reaction time) was estimated using interpolation (55). Reaction time is the mean response time on Go trials that did not involve a

stop signal, while response variability is the standard deviation of this mean and reflects sustained attention and arousal (54). SST data were standardized to include age, sex, and whether the participant was taking stimulant medication. Standardized scores ranged from -3 to 3, with a mean of approximately 0 and a standard deviation of 1.

2.2.3 Air pollution data and environmental exposure assessment

NO₂ data were indexed to DMTI Spatial Inc. postal codes and were provided by CANUE (Canadian Urban Environmental Health Research Consortium) (127,135,136). Ambient NO₂ pollution was estimated using a land-use regression (LUR) model (127,135,136). Data between the years 2000 to 2009 were included. The mean value was calculated over ten years and then averaged across four-digit Postal Codes, creating a mean value for each four-digit Postal Code grid. The values were then assigned to participants based on the Postal Code at the residential address.

To account for socioeconomic factors, we used the Canadian Index of Marginalization for 2006 (CAN-Marg). The CAN-Marg includes four dimensions: residential instability, material deprivation, dependency, and ethnic concentration. Each dimension was divided into quantiles, with five representing the most marginalized (137). We have included the ethnic concentration subscale with the hope that it will allow us to understand better the impact of environmental racism in our current study. Each measure is based on Census data and is available at the dissemination area level, equivalent to several grouped urban blocks. Participants were linked to the CAN-Marg data set by the centroid of the area encompassed by four-digit Postal Codes and which dissemination area it fell into. Environmental data are summarized in Table 2.

Table 2: Environmental Exposure Measures

	Measure	Value	Observed Range
Marginalization Scores (mean ± SD)			
	Residential instability	2.55 ± 1.4	1-5
	Material deprivation	2.47 ± 1.31	1-5

	Dependency	2.62 ± 1.37	1-5
	Ethnic concentration	3.85 ± 1.23	1-5
Environmental Exposures (mean ± SD)			
	NO ₂	17.63 ± 5.94	5.28-44.06

2.2.4 Data analysis

SST data were analyzed as standardized Z-scores, which included sex and age. All other data was reported in its unstandardized form for ease of comparison. NO₂ and marginalization component scores were included in models as continuous variables – with effect sizes given per unit increase (per 1 ppb, and quintile of marginalization, respectively).

All data linkage and statistical analysis were conducted using R (version 4.0.4) (138). Linear regression was used to assess the association between NO₂ concentration and trait outcome measures. Model 1 included age, sex, respondent in addition to NO₂ concentration, while Model 2 also included residential instability, material deprivation, dependency, and ethnic concentration as covariates. Male sex and self-reported participants were used as reference groups. SST outcome scores already included demographic covariates; only marginalization scores and NO₂ concentration were included in these models. Effect estimates were reported per increase in unit of NO₂. Diagnostic tests including residual and Q-Q plots were administered to ensure that models met linear regression assumptions.

Our study used logistic regression to assess the effect of ambient NO₂ pollution on the prevalence of neurodevelopmental disorder diagnosis. Model 1 included age, sex, respondent in addition to NO₂ concentration, while Model 2 also included residential instability, material deprivation, dependency, and ethnic concentration as covariates. Male sex and self-respondent were again used as reference groups. Results from this analysis were reported as odds ratios, giving change in odds of diagnosis per unit of NO₂.

As the analysis involved multiple hypothesis tests of the same sample significance values were adjusted using the Bonferroni correction to reduce the likelihood of false positives within the results. This correction is applied to both linear and logistic regression results.

2.3 Results

Our sample of 8,299 participants was 50.58% male and had a mean age of 10.75 years, where 84.64% of respondents were parents. Mean NO₂ exposure for the study population was 17.63 ± 5.94 ppb. Table 1 shows summary characteristics of the study population, including frequency of neurodevelopmental disorder diagnosis and trait test scores within the sample.

Model 2 results for logistic regression found consistent negative but non-significant associations between NO₂ concentration and odds ratios for diagnosis of OCD (-0.008 per ppb NO₂, 95% CI: -0.03 to 0.002), ADHD (-0.02 per ppb NO₂, 95% CI: -0.03 to 0.002) and ASD (-0.02 per ppb NO₂, 95% CI: -0.06 to 0.02). Odds ratios are shown in Figure 1. Regression results are also available in Appendix A, Table 1.

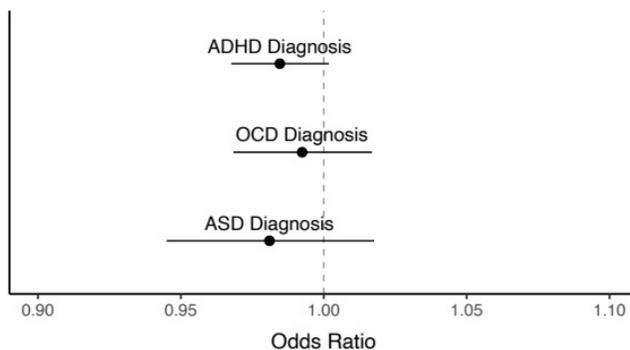


Figure 1: Odds Ratios for Multivariate Logistic Regression of Reported Diagnosis.

Logistic regression models include age, sex, respondent, as well as marginalization component scores. Odds ratios give the change in odds of diagnosis per ppb NO₂.

Adjusted linear regression models of NO₂ pollution and both cognitive scores and trait scores are shown in Figure 2. Results are also displayed with corrected significance and R² values in Appendix A, Table 7. Effect estimates show the change in each respective neurodevelopmental trait score per 1 ppb of NO₂. Model 1 and 2 both showed similar trends for continuous trait test scores, and further regression results will correspond with findings from Model 2. Increased NO₂

concentration was associated with an increased overall TOCS score in the adjusted model (0.14 per ppb NO₂, 95% CI: 0.05 to 0.24) however this was not statistically significant. Component scores counting/checking (0.04 per ppb NO₂, 95% CI: 0.02 to 0.06) and cleaning/contamination (0.05 per ppb NO₂, 95% CI: 0.02 to 0.08) were found to be significantly associated with NO₂ concentration. Symmetry/ordering (0.04 per ppb NO₂, 95% CI: 0.01 to 0.06), rumination (0.0002 per ppb NO₂, 95% CI: -0.01 to 0.01) and superstition (0.01 per ppb NO₂, 95% CI: -0.002 to 0.03) displayed a small and non-significant association. Component score hoarding (-0.01 per ppb NO₂, 95% CI: -0.02 to 0.004) was negatively associated with NO₂ concentration, although not statistically significant. Increased NO₂ concentrations were associated with lower SWAN scores (-0.09 per ppb NO₂, 95% CI: -0.16 to -0.01), inattentive dimensions scores (-0.06 per ppb NO₂, 95% CI: -0.1 to -0.02), and hyperactivity scores (-0.03 per ppb NO₂, 95% CI: -0.07 to 0.01) although these findings were not significant. Increased NO₂ concentration was significantly associated with decreased response inhibition (-0.01 per ppb NO₂, 95% CI: -0.02 to -0.004), while reaction time (0.005 per ppb NO₂, 95% CI: 0.0001 to 0.01), and response variability (-0.001 per ppb NO₂, 95% CI: -0.005 to 0.004) were positively associated but not significant.

2.3.1 Sensitivity analysis

We examined all initial models containing only demographic covariates (sex, age, respondent) and NO₂ concentration, as well as full models, which included marginalization component scores. Models were re-evaluated with quartiles of NO₂ exposure to evaluate any changes in regression results. As socioeconomic status and marginalization were associated with some traits, models were assessed without the lowest quintile of marginalized groups. During data collection many participants were part of family groups that all completed questionnaires and testing. To account for multiple responses from the same parent respondent linear mixed-effects models were included with family ID as a random variable.

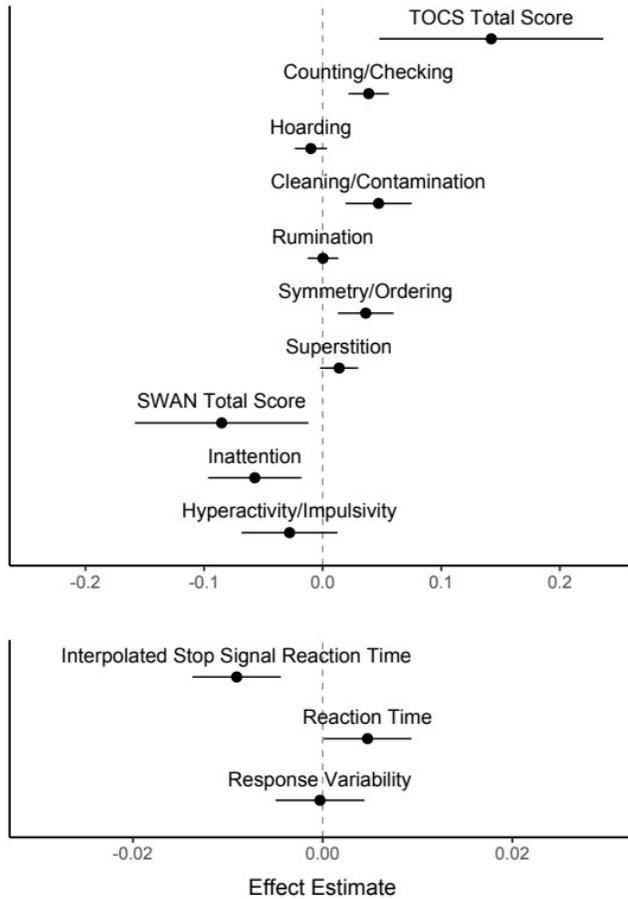


Figure 2: Effect Estimates for Multivariate Regression of Trait and Cognitive Scores

Linear regression models include age, sex, respondent, marginalization scores and NO_2 . Linear regression models of cognitive scores were analyzed as standardized Z-scores and include marginalization scores and NO_2 . Regression coefficients give the change in outcome score per ppb NO_2 .

2.4 Discussion

Our study tested the relationship between ambient NO_2 pollution and neurodevelopmental disorder traits and diagnosis among 8,299 youth living within the Greater Toronto Area. Increased NO_2 concentration was associated with greater expression of OCD traits, specifically counting/checking and cleaning/contamination. Further, increased NO_2 exposure was associated with fewer ADHD traits, including inattention and decreased response inhibition. Although there were associations between NO_2 and behavioural and cognitive traits related to neurodevelopmental disorders, there was no association with reported diagnoses. The cohort's

percentages of diagnosis with each disorder were similar to estimates of epidemiological studies, although the prevalence of OCD was higher (3.39% vs. 2%) (53).

This is the first study of the relationship between ambient NO₂ pollution and OCD. Our study found associations for total TOCS score and its component scores symmetry/ordering, scores rumination, and superstition - although these findings were not significant after correcting for multiple testing. Component scores counting/checking, and cleaning/contamination were found to be significantly associated with NO₂ concentration. Hoarding was negatively associated with NO₂ but was not significant. Previous research has found that both genetic and environmental factors play key roles in the etiology of OCD (149,150). Several studies have found associations between OCD and the environment, including streptococcal infection, traumatic brain injury, stressful and traumatic life events, and parenting styles. Here, we did not find a correlation between ambient NO₂ pollution and OCD diagnosis. Still, the results of trait scores analysis suggest that NO₂ may contribute to OCD traits in the community. Increased risk of OCD through infection may occur via inflammation and damage to brain tissue at a time of critical development (151). NO₂ pollution is thought to affect neurodevelopment through a similar mechanism (13–15). Previous research has found that air pollutants can induce brain damage via neuroinflammation, oxidative stress, and neurochemical or neuropathological changes. Studies of cities with high air pollution found that residents showed signs of neuroinflammation and an altered brain innate immune response (16,17).

Increased NO₂ exposure was associated with reduced ADHD traits, although our findings were not significant after correction. Forns et al. (2016) found that increased NO₂ exposure at school address was associated with an increased total score on the Strengths and Difficulties Questionnaire (SDQ) in children aged 7-10. The authors found some evidence of an association with subdimensions hyperactivity, peer problems, and pro-social dimensions. However, analysis found no evidence of an association between NO₂ and ADHD, assessed using the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (152). Sunyer et al. 2017 used the child Attention Network test (ANT) to assess changes in attention with daily levels of NO₂ exposure at

the school location. The authors found that increases in daily ambient levels of NO₂ were associated with decreased attention (153). Two studies of other gaseous air pollutants found a negative association between hyperactivity scores and overall ADHD. However, the authors were unable to explain this finding (154,155). Although the mechanism driving NO₂ related neurotoxicity is poorly understood, there is not currently a biologically plausible explanation for gaseous air pollutants providing a protective effect against neurodevelopmental disorders like ADHD. In general, reviews of the effect of NO₂ on ADHD have yielded inconclusive evidence of an association (144–146). It is important to note that many of the studies included in reviews include pregnancy and early life rather than current exposure. Future studies should further explore this relationship to identify potential confounders or mechanisms of action.

Response inhibition was found to have a similarly negative relationship, while reaction time and response variability increased with NO₂ concentration. A study by van Kempen et al. (2012) assessed cognition in school-aged children and its association with NO₂ pollution at school and residential addresses. The study found that NO₂ exposure was associated with decreased Digit Memory Span Test (DMST) score, which assesses a child's ability to memorize long sequences. However, the authors found no relationship with other cognitive scores, including reaction speed, switching attention, locomotion, and perceptual coding (156). This result is unexpected; however, these results are preliminary and require further study.

Our study found associations between NO₂ concentration and various trait scores for ADHD and OCD; however, no relationship was found for reported diagnosis. Although no studies have studied NO₂ pollution and OCD, previous literature on ADHD has shown limited evidence of a connection. Min and Min followed a cohort of 8,936 youth from birth to diagnosis of ADHD to assess the relationship between diagnosis and cumulative exposure to air pollution (including NO₂). The authors found that cumulative exposure to NO₂ was associated with an increased incidence of ADHD in childhood (157). A study by Gong et al. on pre and postnatal exposure to NO₂ found no association with ASD or ADHD in 3,426 twins living in Sweden (158).

We did not observe an association between NO₂ and a reported diagnosis of ASD (ASD traits scores were not measured in this study). Previous research has shown some evidence of increased risk of ASD diagnosis with NO₂ exposures. A case-control study comparing children with autism to typically developing controls assessed NO₂ pollution at residential addresses for pregnancy and the first year of life. After adjusting for maternal smoking, socioeconomic, and sociodemographic factors, the authors found that those diagnosed with ASD were more likely to live in residences with the highest quartile exposure to traffic-related air (159). In a systematic review of environmental toxicants – including NO₂, six different studies found an association between ASD and air pollution (160). However, reviews have concluded that research on this relationship has yielded limited or contradictory evidence (79,145,147). Future studies should examine the relationship between ASD traits and NO₂ exposure. This would allow us to assess changes in a spectrum of symptoms that may not be detectable when using a threshold of diagnosis. Although our study relied on self-reported diagnoses of disorders rather than clinician-confirmed diagnoses, their prevalence was comparable to previous epidemiological studies (5,53,161).

Our study has several notable strengths. Including both traits and diagnoses in our study allowed for a more detailed analysis, as quantitative traits offer greater variability and may offset the influence barriers to services/access to care have on diagnoses. ADHD and OCD consist of multiple dimensions of a spectrum of traits rather than a cut-off of the number of symptoms. Analyzing the association between these traits and NO₂ allows us to understand the effect on individual traits and overall disorder. The use of land-use regression measurements of NO₂ concentration also represents a strength as it allows us to capture greater spatial variability. Although our study used four-digit Postal Codes to approximate NO₂ concentration at a participant's residence, we believe this still provides us with sufficiently accurate measures. Postal Codes may have limitations in terms of accurately assessing a residential address, but given the urban context of our study, we can be reasonably confident that we are estimating ambient pollution in the area surrounding participant's homes.

A limitation of the current study is the lack of information on covariates such as maternal smoking and second-hand smoke, noise pollution, parental psychopathology, maternal and child stress/trauma, and birth complications. These variables have been linked to increased risk for neurodevelopmental disorders (94,144,145); future studies should include these covariates to better understand the role of air pollution in the etiology of neurodevelopmental disorders. Additionally, our data for participants was linked based on current residential Postal Codes at the time of the study. We did not have information on previous residences or exposures for locations such as schools. This means that we cannot establish the temporal sequence of exposure to NO₂ pollution before the development of the disorder or confirm exposure levels at critical periods of development. In ADHD and ASD, pregnancy and early life are hypothesized to be vulnerable periods due to rapid brain development (144,160). The last trimester of pregnancy has been identified as a critical period of development of ASD (162). Much of the current research has focused on prenatal and early life exposure; however, further research is required to evaluate the effects of NO₂ pollution at different periods to establish critical periods of exposure.

2.5 Conclusion

Our study is the first to find evidence of an association between increased ambient NO₂ pollution and the severity of OCD traits. Exposure to NO₂ was associated with reduced ADHD traits, improved response inhibition, and increased reaction time. While NO₂ impacted traits related to neurodevelopmental disorders, there was no association with reported diagnoses. Overall, our study adds to the growing body of literature regarding the effects of ambient air pollution on the brain and neurodevelopmental disorders. Further studies are needed to disentangle the effects of NO₂ and socioeconomic marginalization and should include multiple pollutant models.

Chapter 3 - A Network Perspective of Environmental Exposures and Neurodevelopmental Disorders

3.1 Introduction

Attention-deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), and autism spectrum disorder (ASD) are three common and impairing childhood neurodevelopmental disorders (NDDs) which occur with high levels of comorbidity (31–33). Although the etiology of these disorders has been shown to have a strong genetic component, previous research has shown that environmental factors should not be overlooked (5–7). Identifying and understanding the effects of environmental exposures is important as they may act as important modifiable risk factors.

Air pollutants including Nitrogen Dioxide (NO₂), and fine particulate matter (PM_{2.5}) have been studied as a potential risk factor for NDDs. Common sources for these pollutants include fuel combustion, industrial and agricultural processes (8,143). Possible mechanisms for this relationship include methylation and inflammation (17,162). Previous research has found evidence of increased inflammatory markers in individuals diagnosed with ADHD, OCD, and ASD (13–15,18). However, reviews of this relationship have found limited evidence of an association with ADHD and ASD (79,144–148), while OCD has not been studied. Conversely, Attention Restoration Theory (ART) posits that natural environments may restore our ability to concentrate and act as a protective exposure (163). The effects of green space have typically been studied in the context of ADHD, with some studies finding decreased risk of ADHD and increased attention (164–166).

In addition to frequently co-occurring research has shown similarities in etiology (34–41), impaired executive function (42–44), and phenotype (45–51) between ADHD, OCD, and ASD. ADHD typically includes restlessness, inattention, and impulsiveness (42), while OCD is characterized by intrusive urges or obsessions, which may result in a set of compulsions (53).

Similarly, ASD involves repetitive behaviours in addition to impairment of social communication, and highly restricted interests and/or sensory behaviours (5). Clinical diagnosis of these disorders typically occurs at the extreme end of a spectrum of widely distributed traits within the general population (52). By looking at interactions between disorders at both the symptom and diagnosis level we hope to gain additional insight into how NDDs are impacted by the environment.

Symptoms of NDD have typically been thought to result from a causal latent disorder. For example, an individual exhibits obsessive-compulsive symptoms because of the underlying condition of OCD. Conversely, a network theory of mental disorders suggests that disorders arise from a network of causally related symptoms (116). This extends to comorbidity, where networks model relationships between symptoms rather than across two latent disorders (119). The network perspective of disorders suggests that if a symptom appears it will influence the probability of closely related symptoms occurring (117). Within this network symptoms interact and feedback into each other and may result in a self-sustaining disorder state (117). Network analysis may provide a useful tool for visualizing the effects of environmental exposures on the development of NDDs. Exposures may influence symptoms differentially, leading to activation of the network.

Our analysis included trait scores for ADHD and OCD, as well reported diagnosis for ASD (ASD trait scores were not available in this study). Executive function was analyzed using the results of the stop-signal task (SST). Impairment to executive function is implicated in a wide range of common mental disorders, including ADHD, OCD, and ASD (43,44,54). This may affect the ability to delay or stop a response, identify and correct errors, or hold information in short-term working memory. Impairment to executive function may impact the ability to suppresses external stimuli or inappropriate actions and impulses (response inhibition). The stop-signal task has been used to measure response inhibition, where response speed and variability reflect consistency of attention and concentration (42,55). Other external covariates such as

socioeconomic status have been found to influence the development of NDDs (91,93–101,167). We included the Canadian Index of Marginalization in our analysis to account for neighborhood level socioeconomic status (137).

Our study aims to model the association between environmental exposures and NDD traits, diagnosis, and cognitive scores using network models. We hope to gain additional insight into the effect of the environment on NDDs and potential pathways that may account for this association. Network models may allow us to visualize interactions between exposures and traits, while gaining understanding into comorbidity and relationships between NDDs. We hypothesize that NO₂ and PM_{2.5} will be associated with increased ADHD and OCD trait scores, ASD diagnosis, and decreased executive function, while green space serves as a protective factor.

3.2 Data and Methods

3.2.1 Study design and subject recruitment

Our initial sample consisted of data from 17,263 participants (aged 6-17 years) collected through the Spit for Science project at the Ontario Science Centre in Toronto, Canada (42). Parents reported diagnoses/treatment received for OCD, ADHD and ASD and behavior of their children. When parent report was unavailable, we included self-report for participants 12+ years of age. We collected the first 4 digits of the residential Postal Code where applicable. The study was approved by The Hospital for Sick Children's research ethics board (42). After linking environmental exposures (see below) and excluding those with missing information our final sample was composed of 6536 participants all living within Toronto, Canada. Demographic characteristics are summarized in Table 3.

3.2.2 Trait assessments and neurodevelopmental disorder diagnosis

3.2.2.1 Traits

ADHD traits were measured using the Strengths and Weaknesses of Attention-Deficit/Hyperactivity Disorder Symptoms and Normal Behavior *Scale* (SWAN) (123). The SWAN is a seven-point Likert scale that assess both strengths and weaknesses with 3 being

far above average (indicating a strength) and -3 being far below average (indicating a weakness). Possible total scores range from -54 to 54, which can be further separated into two 9-item subscales, inattentive and hyperactive/impulsive, both subscales range from -27 to 27. These scores were reversed so that higher scores corresponded with increased ADHD traits. Parent and self-completed SWAN survey contained the same questions. For more information see Crosbie et al. (42). OCD traits were assessed using the Toronto Obsessive Compulsive Scale (TOCS) (124), a Likert scale consisting of 21 items. Possible answers ranged from -3 to 3 to assess both strengths and weakness, with a total score from -63 to 63. This scale can be further broken down into 6 subscales based on a previous factor analysis: counting/checking, hoarding, cleaning/contamination, rumination, symmetry/ordering, and superstition. A score of 3 on the SWAN or the TOCS was counted as a symptom for ADHD or OCD respectively. Both TOCS and SWAN scores show good reliability and validity (125,126). A summary of trait scores for ADHD and OCD is shown in Table 3.

3.2.2.2 Diagnosis

Participants were classified as having a diagnosis for ASD if they reported having a diagnosis of or treatment for ASD by a health care professional. Control groups included participants who did not report a diagnosis. ASD diagnosis is reported in Table 3.

3.2.2.3 Cognition

Response inhibition, response time and response variability were measured using the stop-signal task (SST) administered on a computer. The SST includes a stop and a go task. The go task requires that the participant respond to stimuli (either an X or an O) presented in the centre of the screen for 500 ms as quickly and as accurately as possible by pressing the corresponding button (left for X; right for O). The stop task involved an auditory signal randomly presented by headphones at a comfortable listening level in 25% of the trials. Response inhibition (stop signal reaction time) was estimated using interpolation (55). Reaction time is the mean response time

on Go trials that did not involve a stop signal while response variability is the standard deviation of this mean and reflects sustained attention and arousal (42). SST data controlled for whether the participant was taking stimulant medication. SST results are summarized in Table 3.

3.2.3 Environmental exposure and marginalization linkage

All environmental data (NO₂, PM_{2.5}, and green space) were indexed to DMTI Spatial Inc. postal codes and were provided by the Canadian Urban Environmental Health Research Consortium (CANUE) (127–136). All environmental data between the years of 2000 to 2009 was included. The mean value was calculated over 10 years, and then averaged across four-digit Postal Codes

Table 3: Demographic and Neurodevelopment Characteristics of Participants

	Measure	Value	Observed Range
Demographics			
	Age [years (mean ± SD)]	10.9 ± 2.8	6-17.9
	Parent report [frequency. (%)]	5396 (84)	
Sex [frequency. (%)]			
	Female	3194 (49.6)	
	Male	3263 (50.4)	
Neurodevelopmental traits (mean ± SD)			
	TOCS Total Score	-18.63 ± 21.79	-63-58
	Counting/Checking	-3.80 ± 3.92	-9-9
	Rumination	-1.03 ± 3.02	-6-6
	Symmetry/Ordering	-2.84 ± 5.43	-12-12
	Superstition	-4.63 ± 3.69	-9-9
	Cleaning/Contamination	-4.37 ± 6.42	-15-15
	Hoarding	-0.59 ± 3.1	-6-6
	SWAN Total Score	-4.65 ± 16.85	-54-54
	Hyperactivity/impulsivity	-2.79 ± 9.37	-27-27
	Inattention	-1.79 ± 9.09	-27-27

Stop-Signal Task Performance [ms. (mean ± SD)]			
	Interpolated Stop signal reaction time	309.9 ± 150.30	56-1266.2
	Reaction Time	602.2 ± 110.9	295.04-1300.41
	Response Variability	160.34 ± 57.37	43.62-553.04
Neurodevelopmental disorder diagnoses [frequency. (%)]			
	ASD	99 (1.5%)	

creating a mean value for each four-digit Postal Code grid. The values were then assigned to participants based on the Postal Code at the residential address.

The Canadian Index of Marginalization (CAN-Marg) for 2006 was also included in all models. The CAN-Marg is composed of four dimensions: residential instability, material deprivation, dependency, and ethnic concentration (137). We have included the ethnic concentration subscale with the hope that it will allow us to gain greater understanding of the impact of environmental racism in our current study. Each measure is based on census data and is available at the dissemination area level, equivalent to several grouped urban blocks. Participants were linked to the CAN-Marg data set by the centroid of the area encompassed by four-digit Postal Codes and which dissemination area it fell into. Environmental exposures and marginalization scores are summarized in Table 4.

Table 4: Environmental Exposure Measures

	Measure	Value	Observed Range
Marginalization Scores (mean ± SD)			
	Residential instability	-0.29 ± 0.93	-2.08-3.57
	Dependency	-0.25 ± 0.78	-2-8.4
	Material deprivation	-0.32 ± 0.91	-2.13-6.06
	Ethnic concentration	0.75 ± 1.29	-1.23-6.33
Environmental Exposures (mean ± SD)			
	NO ₂	17.53 ± 5.94	5.27-44.06

PM _{2.5}	9.27 ± 2.08	3.88-14.03
Green space	0.43 ± 0.04	0.19-0.54

3.2.4 Data Analysis

We estimated network models containing all relevant variables with the goal of visualizing the relationship between traits and environmental exposures. To examine changes in network structure and connections we calculated network models increasing in complexity for each environmental exposure in addition to a final full model. Each model included demographic and marginalization covariates. For a full list of models see Table 5.

Table 5: Models and Variables Included in Network Analysis

Network	TOCS and SWAN Scores	Cognitive Scores	ASD Diagnosis	Environmental Exposures
3a	Total TOCS and SWAN scores	No	No	NO ₂
3b	TOCS and SWAN component scores	Yes	No	NO ₂
3c	TOCS and SWAN component scores	Yes	Yes	NO ₂
4a	Total TOCS and SWAN scores	No	No	PM _{2.5}
4b	TOCS and SWAN component scores	Yes	No	PM _{2.5}
4c	TOCS and SWAN component scores	Yes	Yes	PM _{2.5}
5a	Total TOCS and SWAN scores	No	No	Green space
5b	TOCS and SWAN component scores	Yes	No	Green space
5c	TOCS and SWAN component scores	Yes	Yes	Green space
6a	Total TOCS and SWAN scores	No	No	All
6b	TOCS and SWAN component scores	Yes	No	All
6c	TOCS and SWAN component scores	Yes	Yes	All

Network models consist of nodes and edges, where nodes correspond with variables, and edges represent two variables that are not independent after conditioning for all variables in the dataset. As our models included continuous, ordinal, and binary data, we used Mixed Graphical Models

(MGMs) using the R package *mgm* (139) to estimate networks. To relax the normality assumption for data included in our analysis a nonparanormal transformation was used prior to constructing our networks (168,169). To avoid false positive findings, *mgm* uses the least absolute shrinkage and selection operator (LASSO) (140). This shrinks small non-zero edges to exactly zero, the strength of this is determined by the tuning parameter lambda. Based on previous analysis of this dataset we used the less conservative cross validation method to estimate the tuning parameter as opposed to the stricter Extended Bayesian Information Criterion. This allows us to visualize potentially smaller but potentially important associations within our networks. Ten folds were used for cross validation to calculate the LASSO parameter. After estimating partial correlations between variables network models were visualized using the R package *qgraph* (141). The layout of node positions was calculated using the Fruchterman Reingold algorithm, which places nodes such that all the edges are approximately the same length and crossing is minimized (142). All analysis was performed in R (version 4.0.4) (138).

3.3 Results

3.3.1 Sample characteristics

After removing missing data points our final sample (n = 6457) include 3263 males (50.4%) and 3194 females (49.6%). The mean age was 10.9 years and ranged from 6 to 17.9 years of age. Of all responses 5396 were completed by parents (84%). Total prevalence of reported ASD diagnosis was 99 (1.4%), which is comparable to estimates from previous studies (5). Sample characteristics, including NDD traits and marginalization scores are shown in Table 3.

Unless explicitly stated, connections between nodes are positive. See Table 5 for full list variables included in models.

3.3.2 NO₂ Networks

Edge weights and clustering are reported for those variables most relevant to our research questions. Unless explicitly stated, connections between nodes discussed are positive. See Table 5 for variables included in models.

Network models for NO₂ pollution are shown in Figure 3. In Figure 3A NO₂ was found to be associated with overall TOCS score, notably female sex was positively associated with TOCS, and shared a negative edge with SWAN total score. In Figure 3B NO₂ was associated with counting/checking and symmetry/ordering, and negatively associated with hoarding and rumination. Despite clustering close to ADHD trait scores, it did not share any edges. Figure 3C shows the full network model for NO₂. Connections were similar to our previous model with associations between counting/checking and symmetry/ordering, while still negatively associated with hoarding

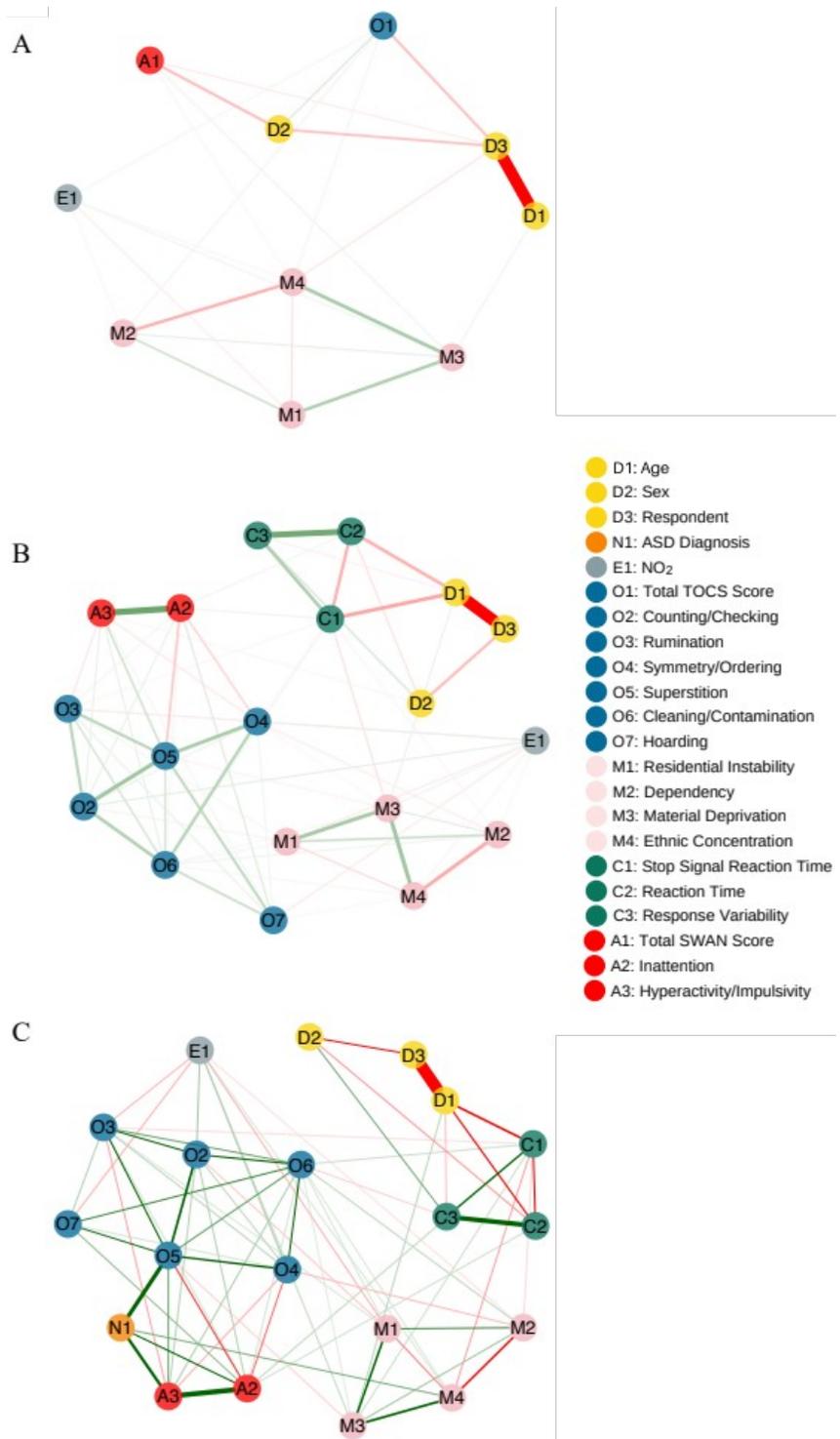


Figure 3: Single Exposure Network Models for NO₂
 Edges indicate pairwise associations between variables. Model 3A includes demographics, marginalization scores, and overall TOCS and SWAN scores. Model 3B includes demographics, marginalization scores, cognitive scores, and TOCS and SWAN component scores. Model 3C additionally includes ASD diagnosis.

and rumination. Diagnosis with ASD was strongly associated with ADHD trait scores and the superstition subscale.

3.3.3 PM_{2.5} Networks

Figure 4 contains network models for PM_{2.5}. In Figure 4A PM_{2.5} did not share edges with either TOCS or SWAN total scores. However, after including trait and cognitive scores in Figure 4B PM_{2.5} was associated with counting/checking and shared a negative edge with rumination. The full network model for PM_{2.5} is shown in Figure 4C. PM_{2.5} was again related to counting/checking, while also being negatively associated with rumination and ASD diagnosis. ASD diagnosis was again strongly associated with superstition and ADHD trait scores.

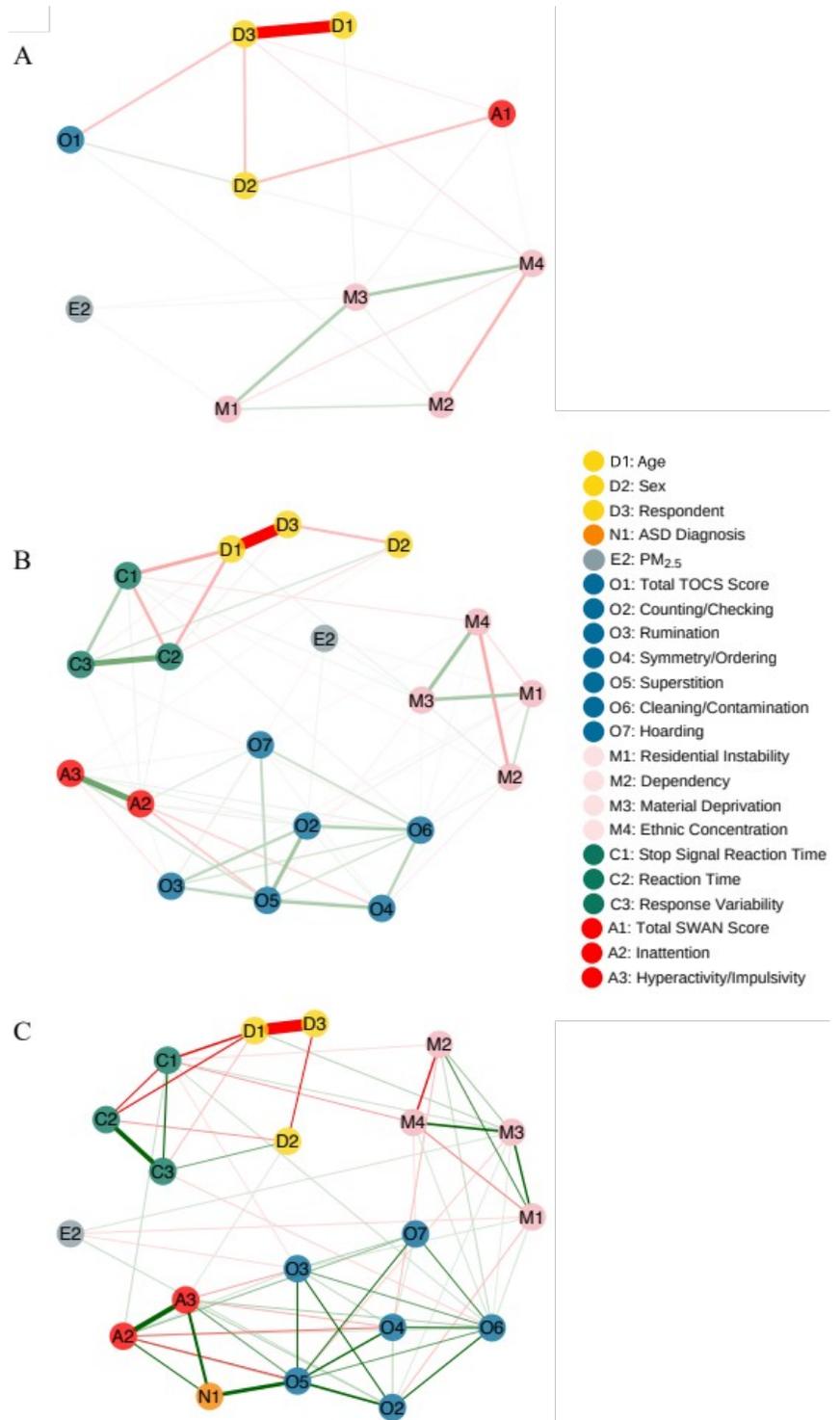


Figure 4: Single Exposure Network Models for PM_{2.5}
 Edges indicate pairwise associations between variables. Model 4A includes demographics, marginalization scores, and TOCS and SWAN total scores. Model 4B includes demographics, marginalization scores, cognitive scores and TOCS and SWAN component scores. Model 4C additionally includes ASD diagnosis.

3.3.4 Green Space Networks

Figure 5A shows the relationship between greenness and total TOCS and SWAN scores and shares a negative edge with both variables. After adding trait and cognitive scores green space was found to be associated with cleaning/contamination and hoarding, while being negatively associated with symmetry/ordering. The full network model for greenspace shown in Figure 5C. Green space was still associated with hoarding after the inclusion of ASD diagnosis, but no longer connected to counting/checking. Green space was negatively associated with superstition and ASD diagnosis.

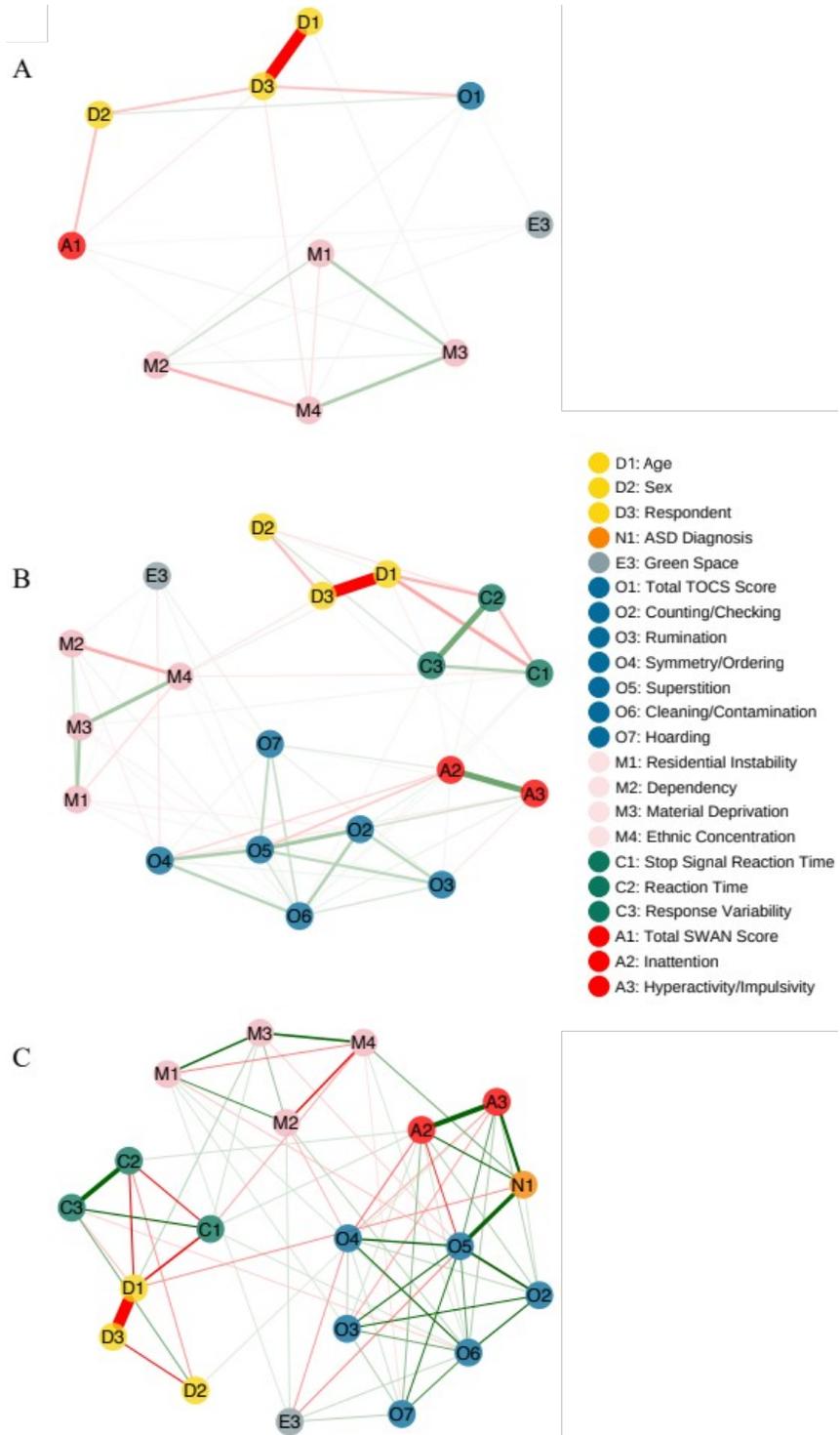


Figure 5: Single Exposure Network Models for Green Space
 Edges indicate pairwise associations between variables. Model 5A includes demographics, marginalization scores, and TOCS and SWAN total scores. Model 5B includes demographics, marginalization scores, cognitive scores, and TOCS and SWAN component scores. Model 5C additionally includes ASD diagnosis.

3.3.5 Full Networks

Figure 6A contains all environmental variables included in our analysis in addition to overall TOCS and SWAN scores. Green space was associated with $PM_{2.5}$ and SWAN total score and negatively associated with NO_2 . After adding trait subscales and cognitive scores green space was found to be associated with hoarding, rumination, and cleaning/contamination, and negatively associated with superstition. NO_2 was positively associated with counting/checking, and symmetry/ordering. It was negatively associated with hoarding, and rumination. $PM_{2.5}$ was negatively associated with symmetry/ordering.

Figure 6C contains all variables of interest. NO_2 was associated with counting/checking, and symmetry/ordering, while

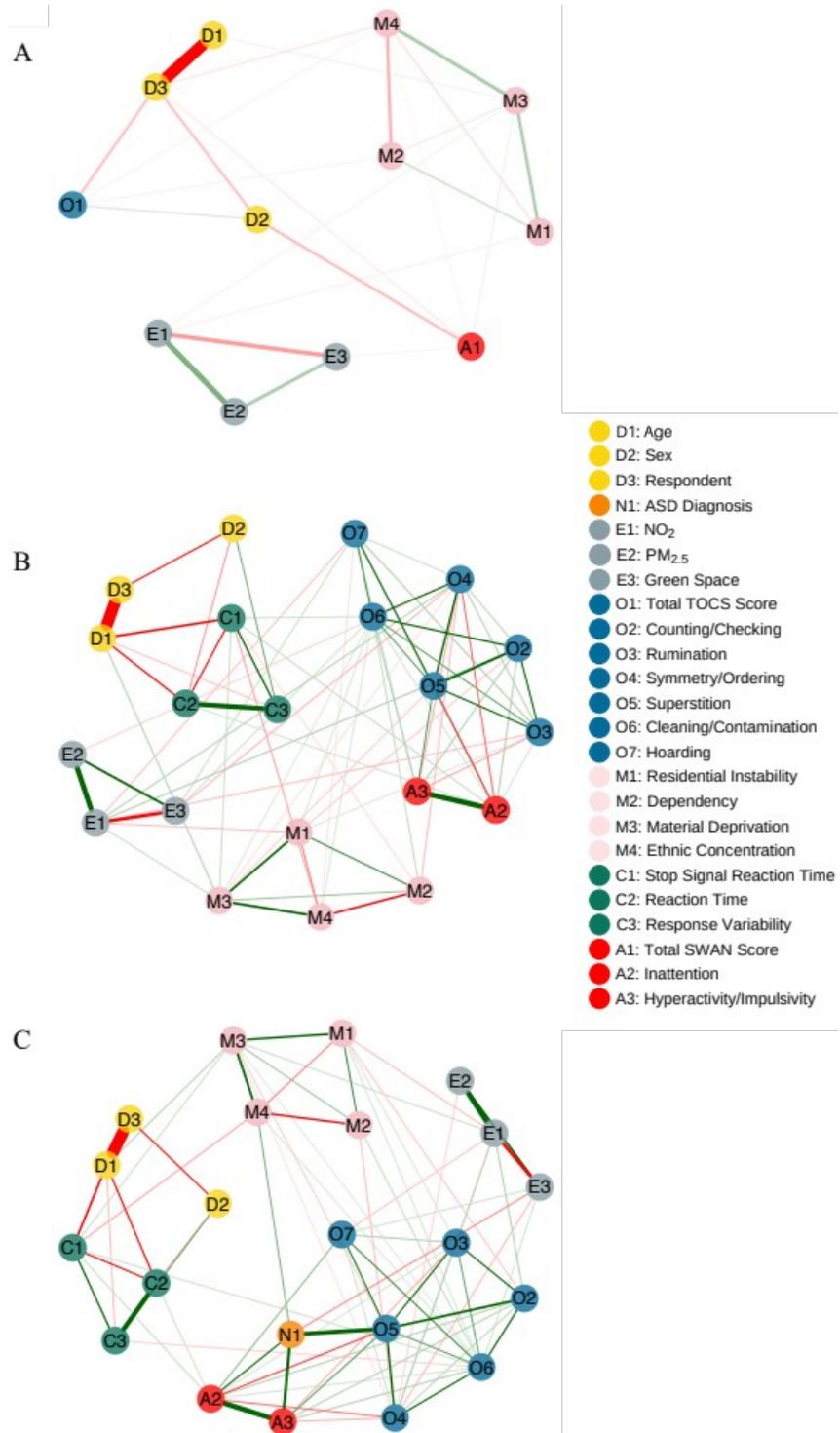


Figure 6: Multiple Exposure Network Models including NO_2 , $PM_{2.5}$, and Green Space

Edges indicate pairwise associations between variables. Model 6A includes demographics, marginalization scores, and TOCS and SWAN total scores. Model 6C includes demographics, marginalization scores, and TOCS and SWAN component scores. Model 6C additionally includes ASD diagnosis.

negatively associated with rumination. Green space was negatively associated with ASD diagnosis and symmetry/ordering, it was positively associated with cleaning/contamination, and hoarding. PM_{2.5} was positively associated with both NO₂, and green space, but did share edges with any other variables.

3.3.6 Sensitivity analysis

The R package *bootnet* was used to assess the stability of measurements in all models. Results of this analysis show stability across network models.

3.4 Discussion

The current study is the first to address the effects of the environment on ADHD, OCD, and ASD through a network perspective. We analyzed NO₂, PM_{2.5}, and green space separately and together in full models. Within each environmental variable we constructed models of increasing complexity to try and understand the how relationships changed as the models became more complex. Our results showed that environmental variables affected trait and cognitive scores in different ways, including positive and negative associations within the same disorder. Edges between exposures and trait scores often changed from individual exposure to full models.

3.4.1 NO₂ Networks

Results from NO₂ network showed relatively consistent results between models. NO₂ concentration shared an edge with overall TOCS score, counting/checking symmetry/ordering, and negative edges with hoarding and rumination. In our final model NO₂ was found to share edges with counting/checking and symmetry/ordering, it shared a negative edge with hoarding. Reviews of environmental risk factors for OCD include streptococcal infection, traumatic brain injury, stressful and traumatic life events, and parenting styles – while citing the need for further research (83,150). Increased risk of OCD through infection may occur via inflammation and damage to brain tissue at a time of critical development (151), similar NO₂ pollution is thought to affect neurodevelopment through a similar mechanism (13–15). Previous research has found that air pollutants can induce brain damage via neuroinflammation, oxidative stress, and neurochemical or neuropathological changes. Studies of cities with high air pollution found that

residents showed signs of neuroinflammation and an altered brain innate immune response (16,17).

The lack of edges between NO₂ pollution and ADHD traits, cognitive scores, or ASD diagnosis is somewhat surprising – however research up until this point has been mixed. Forns et al. (2016) found that increased NO₂ exposure at school address was associated with an increased total score on the Strengths and Difficulties Questionnaire (SDQ) in children aged 7-10. There was some evidence of an association with subdimensions hyperactivity, peer problems, and pro-social dimensions. However, the authors did not find an association between NO₂ and ADHD, assessed using the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (152). Sunyer et al. 2017 used the child Attention Network test (ANT) to assess changes in attention with daily levels of NO₂ exposure at the school location. The authors found that increases in daily ambient levels of NO₂ were associated with decreased attention (153).

A study by van Kempen et al. (2012) assessed cognition in school-aged children and its association with NO₂ pollution at school and residential addresses. The study found that NO₂ exposure was associated with decreased Digit Memory Span Test (DMST) score, which assesses a child's ability to memorize long sequences. However, the authors found no relationship with other cognitive scores, including reaction speed, switching attention, locomotion, and perceptual coding (156). Our results support the findings from some reviews of NO₂ and ADHD, which concluded that there was insufficient evidence of a relationship (70,72).

3.4.2 PM_{2.5} Networks

PM_{2.5} networks found a positive edge between counting/checking, and a negative edge with rumination. PM_{2.5} only shared an edge with one other node – a negative connection with symmetry/ordering. It shared strong positive edges with both NO₂ and greenspace, indicating the presence of multicollinearity. This is an interesting finding in the context of previous research. While there have been no studies of PM_{2.5} and OCD, our network model found correlations with two trait scores. Like the hypothesized mechanism for NO₂, PM_{2.5} may influence OCD symptomology through inflammation, altered immune response, or epigenetic changes (14–

17,170). The negative edge shared with rumination requires further research, there are no known mechanisms through which air pollution would provide a protective effect for neurodevelopmental symptoms. Despite clustering close to ADHD trait scores $PM_{2.5}$ did not share any edges with these or ASD diagnosis. Previous research has shown some evidence of a connection between both ADHD (70,71), and ASD (72,77,78). Notably many of the studies included in these reviews predominately tested prenatal exposure to $PM_{2.5}$, and risk of diagnosis rather than changes in symptomology.

3.4.3 Green Space Networks

Network models for green space showed a negative edge with overall TOCS and SWAN scores, as well as symmetry/ordering in the second model. Our final network model found negative edges with superstition and symmetry/ordering traits, as well as positive edges with cleaning/contamination, and hoarding. The benefits of green space have typically been studied in the context of ADHD. Research has found access to green space improved behaviours and symptoms, and decreased severity of symptoms experienced by children diagnosed with ADHD (74,75). Despite being negatively associated with total SWAN score in our first model, green space did not share any edges with ADHD trait scores in the final models. Interestingly both superstition and symmetry/ordering traits share an edge with the inattention trait, possibly showing the complex relationship between these variables. A review on the effect of green space on attention restoration reported a mix of positive, and no change, and in one case – a negative relationship. The authors found that this differed across different attention measures (76). Similarly green space did not share an edge with ASD diagnosis in the final model but was connected through the symmetry/ordering dimension. The literature on green space and ASD is limited, however one study found that found that urban green space was negatively correlated with childhood autism (81). Although little research has been conducted on green space and OCD specifically our results provide some evidence that it may affect traits within the community. Negative edges were found for overall TOCS score, and superstition and symmetry/ordering traits in final models. Superstition was found to be a central trait and may

provide a mechanism through which green space decreases overall OCD symptomology. A study on the effect of the effect of residential green space on obsessive-compulsive symptoms in a Spanish cohort (171). The authors assessed symptoms using the Spanish version of the Symptom Checklist 90 Revised (SCL-90-R) (172). The authors found an inverse relationship between green space and obsessive-compulsive symptoms; however, the result not statistically significant (171).

3.4.4 Research Implications

Much of the previous research has focused on air pollution and risk of ADHD. However, our study found a consistent lack of edges between environmental variables and ADHD traits, and environmental exposures frequently clustered closer to OCD trait scores. Reviews of NO₂ and ADHD have concluded that there is insufficient evidence of a connection (70,72). Stronger evidence has been collected on PM_{2.5}, with some reviews reporting the majority of included studies reported an observation between PM_{2.5} and behavioural problems related to attention, and risk of ADHD (70,71). However, other reviews found insufficient evidence of a relationship between PM_{2.5} and ADHD (72,73,146). Two studies found a protective effect between green space and symptom severity in children diagnosis with ADHD (74,75). Another study found that increased green space was associated with a lower incidence of ADHD (173). However, this relationship is complex and has been shown to affect different aspects of attention differently. A study by Donovan et al. found that increased minimum exposure to greenness was protective for ADHD, but increased mean exposure was not (174). Our results suggest that environmental exposures do not directly influence ADHD trait scores in youth.

Of note if the position of ASD diagnosis relative to ADHD and OCD trait scores. In all models ASD shared positive edges with both ADHD trait scores, and the most central OCD trait – superstition. The relationship between the three disorders is still unclear, however previous research has found overlapping phenotype and increased severity of symptoms in those diagnosed with NDDs. Studies of individuals diagnosed with ASD, or ADHD were found to exhibit increased symptoms of the other disorder (175–179), while studies of ASD and OCD

traits have found increased rates of cross disorder symptoms (180,181). A study by Anholt et al. found that patients diagnosed with OCD presented with increased ADHD and ASD symptoms when compared to controls (50). However, other research has found a contradictory relationship. A study of a community sample found that those with a sibling with ASD showed more ADHD, but not OCD traits compared to those without a sibling with ASD (182). Increasingly studies have begun analyzing symptoms across disorders using techniques such as factor or cluster analysis. A study by Kushki et al. examined symptoms of ADHD, OCD, and ASD without considering diagnostic label. The authors found that clusters cut across diagnostic categories and resulted in more homogenous subgroups, with social difficulties and inattention commonly seen across ADHD, OCD, and ASD (69). Despite our analysis showing traits clustering largely along diagnostic lines, this finding is still relevant. The identification of subgroups may provide important context for the study of the environment on NDDs. Exposures may influence traits differently and may in turn affect subgroups in different ways. Green space has been shown to affect different types of attention in different ways, although this requires further research (183). Network theory posits that external factors may influence specific symptoms, which in turn influence closely related symptoms, potentially resulting in a feedback cycle that manifests as a clinical disease state. Understanding and quantifying the differential impacts of environmental exposures on specific traits may provide information on mechanism of action, susceptibility of subgroups to environmental exposures, or possible interventions.

Previous reviews of the effects of air pollution and NDDs have cited the need to incorporate multiple pollutants into models to understand the synergistic or antagonistic effects. Individuals are typically exposed to a variety of ambient exposures simultaneously, and many exposures are closely correlated. Several articles have detailed the need to move toward a multi-pollutant approach to better understand the complex nature of exposure, and the individual health impacts of each component exposure (70,72,184–187). Further affecting the relationship between exposures and health is that exposures act as proxies for sources, or other exposures and may reflect their standalone or combined effect (185). Including multiple pollutants to assess the

individual and total effects on NDDs is an important first step, however future studies should use methods which deal with multicollinearity and measurement error. Network analysis which included all environmental exposures found strong associations between all variables, including a positive association between PM_{2.5} and green space. Our study used the LASSO for regularization of networks and estimation of the tuning parameter. Future analysis may benefit from an alternative method, such as elastic net regularization (188). This may reduce the effects of strong correlations between variables within the network. Based on the wide range of exposure and effects the environment has over long periods it is critical to decrease exposure misclassification when assessing an exposures impact on NDDs.

3.4.5 Strengths and Limitations

A notable strength of our study was our sample size. Given the small but potential significant associations between trait scores and environmental exposures our sample size allows us to estimate these connections within the community. Increasingly NDDs are viewed as a spectrum of widely distributed traits within the population, and diagnostic boundaries may not capture the heterogeneity of each respective disorder. Using trait and cognitive scores is a notable strength as it allows us to assess smaller changes and interactions that may be missed when relying on diagnostic labels. Using a network analysis to study the associations between NDDs and the environment provides a different perspective on the complex relationship between symptoms and the many external factors which may influence risk and severity. Although our study used four-digit Postal Codes to approximate environmental exposure at a participant's residence, we believe this still provides us with sufficiently accurate measures. Postal Codes may have limitations in terms of accurately assessing a residential address, but given the urban context of our study, we can be reasonably confident that we are estimating ambient exposure values in the area surrounding participant's homes.

A limitation of the current study is the lack of information on variables such as maternal smoking and second-hand smoke, noise pollution, parental psychopathology, maternal and child stress/trauma, and birth complications. These variables have been linked to increased risk for

neurodevelopmental disorders (94,144,145); future studies should include these variables to better understand the role of air pollution in the etiology of neurodevelopmental disorders. As our study was observational, we are unable to establish the temporal sequence between exposure to each respective environmental variable and reported diagnosis and trait score.

We did not have information on previous residences or exposures for locations such as schools and so are unable to assess levels of exposure during potentially critical times of development. In ADHD and ASD, pregnancy and early life are hypothesized to be vulnerable periods due to rapid brain development (144,160). The last trimester of pregnancy has been identified as a critical period of development of ASD (162).

3.5 Conclusion

Our study provides evidence of an association between environmental exposures and OCD traits within the community; however, we did not find associations with ADHD traits, cognitive scores, or ASD diagnosis. Given the complex nature of the relationship between ADHD, OCD, and ASD, more research is needed to understand the effects the environment has on symptoms within the community. Our study also shows the need for more studies incorporating multiple exposures into analysis. Strong associations were found between all NO₂, PM_{2.5}, and green space and further research is needed to study potential synergistic or antagonistic relationships between these exposures.

Chapter 4 - Conclusion

The concluding chapter of this thesis will summarize the combined findings of the previous chapters and discuss them in the context of current literature. Future directions for research will be discussed, along with strengths and limitations of the current analysis.

4.1 Combined Results and Discussion of Findings

Our study tested the association between ADHD and OCD trait scores, cognitive scores and reported diagnosis with environmental exposure in Toronto, Canada. The first study found that increased NO₂ was positively associated with OCD traits, negatively associated with ADHD traits, and was not associated with prevalence of diagnosis. The second study used network models to assess associations with three environmental exposures: NO₂, PM_{2.5}, and greenspace. This analysis found that environmental exposures were associated with some OCD trait scores and ASD diagnosis, but not associated with ADHD traits, or cognitive scores.

4.2 OCD Findings

Despite the lack of research on environmental exposures and OCD, the findings suggest they may affect traits within the community. The first paper found that increased NO₂ concentration was significantly associated with TOCS component scores counting/checking and cleaning/contamination. Overall TOCS score, symmetry/ordering, rumination, and superstition were positively associated with NO₂ but not statistically significant. NO₂ concentration was negatively associated with hoarding, although this was not significant. Final network models for NO₂ found edges between counting/checking, and symmetry/ordering trait dimensions, in addition to negative edges with rumination and hoarding scores. The final model which included all environmental exposures also found positive edges with counting/checking, as well as rumination, and a negative edge with hoarding.

There are no previous studies on the effects of air pollution on OCD symptoms, however some studies have found an association with streptococcal infection, traumatic brain injury, stressful and traumatic life events, and parenting styles (83,150). Of note is the effect of streptococcal

infection on OCD symptoms in youth. Infection may increase risk for OCD through inflammation and damage to brain tissue at a time of critical development (151). NO₂ is hypothesized to affect neurodevelopment through a similar mechanism of inflammation or epigenetic changes (13–15). Previous research has found that air pollutants can induce brain damage via neuroinflammation, oxidative stress, and neurochemical or neuropathological changes. Studies of cities with high air pollution found that residents showed signs of neuroinflammation, and an altered brain innate immune response (16,17).

Network analysis found that green space was associated with several TOCS component scores in both green space and multiple exposure models. Single exposure network models found that green space shared a positive edge with cleaning/contamination and hoarding, while sharing negative with symmetry/ordering and superstition. Final network models which included all environmental variables found similar results. Green space was again associated with cleaning/contamination and hoarding, but in this model only negatively associated with symmetry/ordering. Little research has looked at protective factors for OCD risk and symptoms, and to our knowledge there has been only one study of the effect of greenspace. The study tested the effect of residential green space on obsessive-compulsive symptoms in a Spanish cohort (171). The authors assessed symptoms using the Spanish version of the Symptom Checklist 90 Revised (SCL-90-R) (172). Residential green space was found to have an inverse relationship with obsessive-compulsive symptoms; however, the result not statistically significant (171). Green space is hypothesized to act as a protective factor, although mechanisms are not well understood. In this context urban green space may reduce maternal stress, encourage physical activity and social connection, as well as decreasing the effects of noise and traffic pollution (25–29). Given the lack of research in this area, these findings require further study, especially using trait or symptom scores. Our analysis did not find a correlation between ambient NO₂ pollution and OCD diagnosis. However, consistency in the associations between NO₂ and OCD trait scores, as well as associations with green space in network analysis suggest that the environment

may affect trait scores in the community. Previous research has found that both genetic and environmental factors play key roles in the etiology of OCD (149,150).

4.3 ADHD Findings

Results from this analysis add to the uncertainty regarding the effect of the environment on ADHD, particularly in the case of NO₂ pollution. The first study found no association with reported ADHD diagnosis, and a negative association with overall SWAN score, inattention, and hyperactivity trait scores although this was not statistically significant. Network analysis did not find a negative association between NO₂ exposure and ADHD trait scores, nor did it show an interaction between environmental exposure and ADHD traits. The finding of a consistent negative association between NO₂ and ADHD traits in this thesis was unexpected. Currently there is not a biologically plausible explanation for gaseous air pollutants providing a protective effect against neurodevelopmental disorders like ADHD. Forns et al. (2016) found that increased NO₂ exposure at school address was associated with an increased total score on the Strengths and Difficulties Questionnaire (SDQ) in children aged 7-10. There was some evidence of an association with subdimensions hyperactivity, peer problems, and pro-social dimensions. However, the authors did not find an association between NO₂ and ADHD, assessed using the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (152). Another study used the child Attention Network test (ANT) to assess changes in attention with daily levels of NO₂ exposure at the school location. The authors found that increases in daily ambient levels of NO₂ were associated with decreased attention (153). However, two studies of other gaseous air pollutants found a negative association between hyperactivity scores and overall ADHD. In both cases the authors were unable to explain this finding (154,155). In general reviews of NO₂ and ADHD have concluded that there is insufficient evidence of a connection (70,72). Interestingly, final networks showed consistent negative edges between NO₂ pollution and the OCD trait score hoarding, which some research has found to associate with ADHD (189,190). In the models presented here, hoarding was in turn associated with increased inattention score. The network theory of mental disorders suggests that if a symptom arises it will influence the

probability of closely related symptoms/nodes from occurring (117). Therefore, external factors may influence symptoms which may in turn influence other symptoms within the network – in this case hoarding and inattention traits. There are no plausible mechanisms by which NO₂ pollution acts as a protective factor for either OCD or ADHD symptoms. However, based on the consistency of these associations the interactions between these variables requires further study. In future studies it may be helpful to break the hoarding and inattention trait scores into component symptoms to further understand this relationship.

Stronger evidence has been collected on PM_{2.5} and some reviews have found that a majority of included studies reported an observation between PM_{2.5} and behavioural problems related to attention, and risk of ADHD (70,71), with some evidence of a dose-response relationship with risk of ADHD (71). However, other reviews found insufficient evidence of a relationship between PM_{2.5} and ADHD (72,73,146). This study did not find any associations between PM_{2.5} and ADHD traits.

The network analysis did not find any edges between green space and ADHD traits. This is a surprising result as green space has primarily been studied as a potential protective exposure for ADHD and inattention. Two studies found a protective effect between green space and symptom severity in children diagnosis with ADHD (191,192). Another study found that increased green space was associated with a lower incidence of ADHD (173). However, this relationship is complex and has been shown to affect different aspects of attention differently. A study by Donovan et al. found that increased minimum exposure to greenness was protective for ADHD, but increased mean exposure was not (174). A review on the effect of green space on different tests of attention found improved performance in working memory, attentional control, and cognitive flexibility. However, improvements in attentional control were not detected when only examining studies with fully balanced baseline measures.

Finally, heightened restoration potential, through fatigue induction or participant characteristics, strengthened the restoration effect on working memory, but not attentional control or cognitive flexibility (183). Given the uncertainty in how green space effects ADHD and attention

restoration more research is needed. The statistically significant negative association between NO₂ and ADHD traits requires further study, as there is not a known mechanism to explain this finding. Given the lack of association between NO₂ and risk of diagnosis future studies should prioritize trait scores rather than overall diagnosis. Additionally, controlling for additional variables such as maternal smoking, noise exposure, and parental psychopathology may improve the accuracy of findings.

4.4 Cognitive Score Findings

Chapter Two found that increased NO₂ exposure was associated with reaction time and response variability, while a statistically significant negative association was found with stop signal reaction time. The subsequent network analysis that included cognitive scores did find any edges with environmental variables. Cognitive scores clustered closely with demographic variables, although this is not surprising as age is known to be a significant predictor of SST performance (193). A study by van Kempen et al. (2012) assessed cognition in school-aged children and its association with NO₂ pollution at school and residential addresses. The study found that NO₂ exposure was associated with decreased Digit Memory Span Test (DMST) score, which assesses a child's ability to memorize long sequences. However, the authors found no relationship with other cognitive scores, including reaction speed, switching attention, locomotion, and perceptual coding (156). A review of air pollution and cognitive function found that NO₂ was associated with impaired working memory, general cognitive function, and psychomotor functions (194). The same review found that PM_{2.5} was linked to difficulties in working memory, short-term memory, attention, processing speed, and fine motor function (194).

4.4.1 Evidence that Environmental Exposure Influence Traits, Not Diagnosis

These results suggest that environmental exposures may be associated with trait scores in the community, but do not directly influence the prevalence of diagnosis. The analysis from Chapters 1 and 2 used trait scores for both OCD and ADHD to assess symptoms in addition to reported diagnosis. Analysis in Chapter 1 found associations with NO₂ pollution and overall TOCS and SWAN scores, as well as several subscales. However, analysis of reported diagnosis

found that increased exposure to ambient NO₂ was not associated with increased diagnosis of ADHD, OCD, or ASD. This finding requires further study, however previous research has suggested that multiple susceptibility genetic factors may interact with environmental conditions to lead to a continuous dimension of traits, with neurodevelopmental disorders at the extremes of this continuum (84,85). In this context it may be unsurprising that exposure to NO₂ was not associated with overall diagnosis, but instead may result in more subtle changes to symptomology. Network analysis found similar results, with associations between environmental exposures and several trait scores, but few edges with ASD diagnosis. In network analysis symptoms/nodes are visualized as causally related elements rather than arising from an underlying latent disorder (116). Although NDDs are diagnosed as discreet disorders based on number of symptoms, research has suggested that clinical diagnosis lies on a spectrum of symptoms that is distributed within the general population (52). Further analysis of symptoms without the use of diagnostic labels has suggested the existence of subgroups that cut across disorders and may include cognitive scores. Complex etiology coupled with the heterogeneity and comorbidity seen across NDDs necessitates the use of more sensitive diagnostic tools when assessing NDDs in the community.

4.5 Directions for Further Research

4.5.1 Expand on Analysis Across Traits of Neurodevelopmental Disorders

The current study used trait scores for analysis of ADHD and OCD symptoms, but analysis of ASD was limited to reported diagnosis. Analysis in Chapters 1 did not find an association between NO₂ pollution and increased odds of reported diagnosis, but final network models found a protective association with green space. Despite this promising finding, further study should analyze this relationship with detailed ASD symptom or trait scores. As mentioned previously, using diagnosis and trait scores allows for more detailed analysis and a greater understanding of how the environment impacts NDDs. Network analysis may provide a new tool for looking at comorbidity and symptoms across NDDs. Previous research has found overlapping phenotype and increased severity of symptoms in those diagnosed with ADHD, OCD, and ASD. Studies of

individuals diagnosed with ASD, or ADHD were found to exhibit increased symptoms of the other disorder (175–179). Some studies of ASD and OCD traits have found increased rates of cross disorder symptoms (180,181), a study by Anholt et al. found that patients diagnosed with OCD presented with increased ADHD and ASD symptoms when compared to controls (50). However, other research has found a contradictory relationship. A study of a community sample found that those with a sibling with ASD showed more ADHD, but not OCD traits compared to those without a sibling with ASD (182). Increasingly studies have begun analyzing symptoms across disorders using techniques such as factor or cluster analysis. A study by Kushki et al. examined symptoms of ADHD, OCD, and ASD using a clustering analysis that did not consider diagnostic label. The authors found that clusters cut across diagnostic categories and resulted in more homogenous subgroups, with social difficulties and inattention commonly seen across ADHD, OCD, and ASD (69). Interestingly, ASD displayed consistent and strong edges with ADHD trait scores, particularly hyperactivity/impulsivity, and the superstition trait score. Network theory has identified bridge symptoms which may link comorbid disorders together and influence symptoms across disorders (119,195). If a symptom appears within a network, it may influence the probability of closely related symptoms occurring (117). Modelling comorbidity in the context of networks of NDDs visualizes relationships between symptoms rather than across two latent disorders (119). Including trait and symptoms scores for multiple NDDs when analyzing the effects of environmental exposure may provide clarity on how these variables interact with each other. Future research should also investigate the relationship between ASD symptoms and other NDD traits to identify bridge symptoms or subgroups.

4.5.2 Sex Specific Analysis of Neurodevelopmental Traits

The analysis from Chapter 1 on the effects of NO₂ found that sex was a significantly associated with odds of diagnosis and several trait scores, however network analysis did not find any shared edges between sex and NDD trait scores or diagnoses. Instead, network models indicated that female sex was negatively associated with cognitive trait score reaction time, and positively associated with response variability. NDDs such as ADHD or ASD have typically been

diagnosed primarily in males, with risk documented to be two to four times higher when compared to females (196–198). The reason for this disparity is unclear, however it is likely a complex combination of genetic, environment, and sociocultural differences. The female protective effect, whereby females are less susceptible or have a higher threshold of risk due to a second X chromosome has been hypothesized (199). Other research has suggested that males are more susceptible to stress and environmental factors. A recent US study of 1479 mother–infant pairs) identified lead exposure as an ADHD risk factor for boys but not girls. For boys exposed to lead, high maternal high-density lipoprotein levels or low maternal stress during pregnancy partially counteracted the increased risk of ADHD diagnosis (200). Research on inflammation in prepubescent males, females, and males with Klinefelter syndrome has suggested the X chromosomes affect inflammatory process, with males more vulnerable (201). Interestingly recent research has suggested that the difference in risk of diagnosis between males and females converges later in life (202,203). Authors concluded that this may be due in part to differences in symptom profile, as males may exhibit more hyperactive traits which arise earlier, while females display more inattentive traits (202,204,205). Among methodological factors, diagnostic criteria, tests, and professional's expertise could have a role in females' under-diagnosis, since diagnostic and screening tests of ASD are developed on the basis of the male-typical phenotype, and assessment of females is restricted to areas where they are most similar to males. Therefore, those who do not meet the male-typical behavioral descriptions are likely to be missed (206–217). In particular, “camouflaging” has been studied in females with ASD. “Camouflaging” is the tendency to cope (consciously or unconsciously mimicking or learning) through conventional and acceptable behaviors and strategies in social situations (218). The disparity in risk of NDD diagnosis between males and females requires further study, especially with a focus on trait scores which are validated in female population. Focusing on traits rather than overall diagnosis may reveal more about the overall structure of NDDs in females, and the potential differential impact of environmental exposures. Despite the lack of edges between NDD traits and sex network analysis may provide a useful technique for visualizing the interactions between

environmental exposures and trait scores across sex. By analyzing sex specific trait interactions, and how these are influenced by the environment will improve our understanding of NDDs generally.

4.5.3 The Need for Multi-pollutant Studies

Analysis in Chapter 1 tested the association between NDDs and NO₂ pollution in part because of the spatial variability of NO₂ within urban centres like Toronto. However, it is understood that rather than being exposed to a pollutant in isolation, individuals are often exposed to multiple exposures simultaneously. Several articles have detailed the need to move toward a multi-pollutant approach to better understand the complex nature of exposure, and the individual health impacts of each component exposure (70,72,184–187). Further affecting the relationship between exposures and health is that exposures act as proxies for sources, or other exposures and may reflect their standalone or combined effect (185). Generally multi-pollutant analysis would improve the quantification of the total health effect associated with the exposure to multiple pollutants. This total health effect requires acknowledgement that the health burden from simultaneous exposure to multiple pollutants may differ from the sum of individual effects estimated from single pollutant models (184). Including multiple pollutants to assess the individual and total effects on NDDs is an important first step, however future studies should use methods which deal effectively with multicollinearity and measurement error. Network analysis which included all environmental exposures found strong associations between all variables, including a positive association between PM_{2.5} and green space. Our study used the LASSO for regularization of networks and estimation of the tuning parameter. Future analysis may benefit from an alternative method, such as elastic net regularization (188). This may reduce the effects of strong correlations between variables within the network. Based on the wide range of exposures and potential effects of the environment has over long periods it is critical to decrease exposure misclassification when assessing an exposures impact on NDDs.

4.6 *Strengths and Limitations*

This study attempted to quantify the effects of environmental exposures on NDD traits and diagnosis within the community. The use of validated scales which can be administered to a non-clinical population represents a strength. Given the previously cited research on subgroups and blurred lines between diagnosis of ADHD, OCD, and ASD it is critical to be able to quantify smaller changes. Similarly, using a network analysis to study the associations between NDDs and the environment provides a different perspective on the complex relationship between symptoms and the many external factors which may influence risk and severity. Although this study used four-digit Postal Codes to approximate environmental exposures at a participant's residence, this still provides sufficiently accurate measures. Postal Codes may have limitations in terms of accurately assessing a residential address, but given the urban context of our study, it is reasonable that ambient exposure values are those from the area surrounding participant's homes.

A limitation of the current study is the lack of information on covariates such as maternal smoking and second-hand smoke, noise pollution, parental psychopathology, maternal and child stress/trauma, and birth complications. These variables have been linked to increased risk for neurodevelopmental disorders (94,144,145); future studies should include these covariates to better understand the role of air pollution in the etiology of neurodevelopmental disorders. Importantly, data was linked based on current residential Postal Codes at the time of the study. As the individual data for this thesis was observational, a temporal sequence between exposure to each respective environmental variable and reported diagnosis and trait score was unable to be established.

The data did not include information on previous residences or exposures for locations such as schools and so are unable to assess levels of exposure during potentially critical times of development. In ADHD and ASD, pregnancy and early life are hypothesized to be vulnerable periods due to rapid brain development (144,160). The last trimester of pregnancy has been

identified as a critical period of development of ASD (162). Future studies should try and replicate these findings and assess critical windows of exposure for OCD.

4.7 Conclusion

This thesis suggests that environmental exposures may be associated with OCD traits within the community. This is particularly true for NO₂ pollution, although our results are preliminary and should be replicated in future studies. Despite previous research suggesting an association between air pollution, ADHD, and ASD this study did not find any evidence of an association. Importantly, no associations between exposures and reported diagnosis, despite statistically significant associations with trait scores provides support for analysis of NDDs as multifaceted, heterogenous conditions. Chapter Three presents research that is the first to use network analysis to study the effect of the environment on NDDs, and subsequent studies should continue to make use of validated, quantitative measures when studying ADHD and OCD. The role of ASD traits as a possible bridge between ADHD and OCD requires further study. Future research should continue to assess sex specific differences in the risk and development of NDDs and utilise a multi-pollutant model.

Appendices

Appendix A

Outcome	NO ₂ [(OR (95% CI)]			
	Model 1	p	Model 2	p
OCD Diagnosis	1.00 (0.98 to 1.02)	1.0	0.98 (0.97 to 1.0)	1.0
ADHD Diagnosis	0.99 (0.97 to 1.00)	1.0	0.99 (0.97 to 1.02)	1.0
ASD Diagnosis	0.98 (0.95 to 1.01)	1.0	0.98 (0.94 to 1.02)	1.0

Note: Effect estimates give the change odds per 1 ppb NO₂ exposure. Model 1 includes age, sex, respondent, and NO₂. Model 2 additionally controls for marginalization.

Table 6: Odds Ratios for Reported Neurodevelopmental Disorder Diagnosis

Table 7: Effect Estimate for Neurodevelopmental Trait and Cognitive Scores

Outcome	NO ₂ [β (95% CI)]					
	Unadjusted	p	R ²	Adjusted	p	R ²
TOCS total score	0.18 (0.11 to 0.26)	>0.001*	0.0339	0.14 (0.05 to 0.24)	0.102	0.0341

Counting/checking	0.04 (0.03 to 0.06)	>0.001*	0.0326	0.04 (0.02 to 0.06)	>0.001*	0.0327
Hoarding	-0.01 (-0.03 to 0.002)	0.620	0.0076	-0.01 (-0.02 to 0.004)	1.0	0.0088
Cleaning/contamination	0.07 (0.05 to 0.1)	>0.001*	0.0259	0.05 (0.02 to 0.08)	0.030*	0.0295
Rumination	-0.001 (-0.01 to 0.01)	1.0	0.0554	0.0002 (-0.01 to 0.01)	1.0	0.0557
Symmetry/ordering	0.05 (0.03 to 0.07)	>0.001*	0.0288	0.04 (0.01 to 0.06)	0.080	0.0288
Superstition	0.01 (0.001 to 0.03)	1.0	0.0236	0.01 (-0.002 to 0.03)	1.0	0.0245
SWAN total score	-0.08 (-0.14 to -0.01)	0.503	0.0331	-0.09* (-0.16 to -0.01)	0.724	0.0345
Hyperactivity/ Impulsivity	-0.02 (-0.06 to 0.01)	1.0	0.0280	-0.03 (-0.07 to 0.01)	1.0	0.0292
Inattention	-0.05** (-0.08 to -0.02)	0.073	0.0331	-0.06 (-0.1 to -0.02)	0.142	0.0341
Stop signal reaction time	-0.01 (-0.01 to -0.01)	>0.001*	0.0036	-0.01 (-0.02 to -0.004)	0.005*	0.0074
Reaction time	0.01 (0.001 to 0.01)	0.249	0.0008	0.005 (0.0001 to 0.01)	1.0	0.0005
Response Variability	0.001 (-0.003 to 0.004)	1.0	- 0.0001	0.001 (-0.005 to 0.004)	1.0	0.0004

Note: Effect estimates give the change in outcome per 1 ppb NO₂ exposure. Model 1 includes age, sex, respondent, and NO₂. Model 2 additionally controls for marginalization. Cognitive scores were measured in standardized Z scores which include age and sex. Statistical significance is given for p > 0.05 and is denoted with an asterisk. R² is given as adjusted for number of predictors in the respective model.

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