Autism Spectrum Disorder Early Detection Model Development Using Patient Records

Data Science Applied to the NIMH Medical History Questionnaire

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Master's Capstone Project

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Fall 2024 and Spring 2025

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1. Project Overview

This study aims to develop a predictive model for Autism Spectrum Disorder (ASD) using maternal medical history data from the NIMH Medical History Questionnaire. By employing applied statistical modeling and data science techniques, the study will analyze prenatal factors linked to oxidative stress, a pathology implicated in ASD pathogenesis. Key goals include identifying relevant predictors from the dataset. This will include variables pertaining to lifestyle, environmental, and health factors captured by the questionnaire. The study will apply a rigorous and multifaceted approach to data preparation and analysis to refine predictors and assess their contributions to ASD risk. This research seeks to advance understanding of prenatal factors in ASD etiology and establish a framework for early identification. An additional goal of this study is to identify a universal set of predictors by which to construct a general model that can by applied to health care system records for prenatal identification.

2. Background and Significance

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterized by social communication deficits, motor deficits, and repetitive behaviors, with an estimated prevalence of 1 in 54 children (McNally Keehn et al., 2020). Early diagnosis is critical for ASD patients and their families, as interventions applied before three years of age improve developmental outcomes, including cognitive, language, and adaptive skills (Dai et al., 2020). However, the international mean age of diagnosis remains around five years of age, delaying

access to critical interventions during prime periods of neuroplasticity (van ’t Hof et al., 2020; McNally Keehn et al., 2020).

There are challenges in the current state of early ASD diagnosis. Standardized tools like the Modified Checklist for Autism in Toddlers (M-CHAT) have improved early identification but feature false negatives and disparities in application, notably among minority populations and underserved communities (Carbone et al., 2020; Dai et al., 2020). Furthermore, reliance on behavioral assessments introduces variability, often leading to missed or delayed diagnoses for children with subtle or atypical symptom presentations (Carbone et al., 2020).

This study leverages maternal medical records, ensuring that prenatal indicators of ASD, including indicators of oxidative stress, are systematically identified for every child whose mother submits medical records to a hospital system. By applying data science techniques to these records, this approach aims to bridge gaps in screening and create scalable, generalizable models for earlier ASD detection that captures more children.

3. Purpose and Objectives

The purpose of this study is two-fold: to identify relevant prenatal predictors of ASD in maternal health records and to create a durable statistical model that can be applied generally to medical records across many different nodes of care that produce maternal health records.

The objectives include the identification of key prenatal predictors, the development of a generalizable statistical model, and the advancement of clinical the utility of an applied predictive model to digital records systems. This study will conduct analysis to identify variables in maternal medical records linked to oxidative stress that correlate with ASD diagnosis. It will also evaluate the predictive value and applicability of factors in predicting ASD risk. In

developing the generalizable model, the study aims to build a model that integrates prenatal predictors from maternal health records, validate that model using industry standard validation metrics, and ensure applicability across care settings by addressing confounders, feature relevance, and model generalization. Ultimately the goal is to create a framework for integrating a predictive model (or models) into healthcare workflows to assist in early identification of ASD risk and to add to the body of knowledge regarding prenatal factors in ASD etiology.

4. Literature Review

4.1. Introduction

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition influenced by genetic and environmental factors. One environmental factor that has garnered significant attention is maternal oxidative stress, which is characterized by an imbalance between the production of reactive oxygen species (ROS) and the capacity of the body's antioxidant defense system to neutralize them (Liu et al., 2022). This imbalance can lead to cellular damage, affecting critical neurodevelopmental processes in utero. Identifying sources of oxidative stress and their impact on ASD risk is essential for developing predictive models and early intervention strategies.

Maternal oxidative stress arises from a variety of sources, many of which are captured in medical records. These include lifestyle factors such as smoking, psychological stress, socioeconomic conditions, and exposures to environmental toxins. Smoking, for example, is a well-documented contributor to oxidative stress. It increases the production of ROS, leading to oxidative damage that can adversely affect fetal development. Studies have demonstrated that smoking during pregnancy is associated with increased oxidative stress biomarkers, such as

malondialdehyde (MDA) and decreased antioxidant levels, such as glutathione (GSH) (Njotto et al., 2023; Chen et al., 2021). Psychological stress is another contributor to oxidative stress. Chronic stress during pregnancy can elevate cortisol levels, which, in turn, disrupt mitochondrial function and increase ROS production (Alamoudi et al., 2023). This stress-induced oxidative damage has been linked to alterations in fetal brain development, suggesting a potential pathway by which stress may increase ASD risk. The impact of stress on oxidative stress markers has been corroborated in both human and animal studies, highlighting the importance of accounting for maternal stress in predictive models (Usui et al., 2023).

Socioeconomic conditions play a role in oxidative stress. Living in environments with limited access to healthcare, nutritious food, and clean air can exacerbate oxidative stress through mechanisms such as malnutrition and increased exposure to environmental pollutants (Pangrazzi et al., 2020). For instance, trace elements and heavy metals found in industrial pollution can generate ROS and impair antioxidant defense mechanisms. These exposures may disproportionately affect individuals from lower socioeconomic backgrounds, compounding their risk factors for ASD. Obsesity, smoking, alcohol use, diabetes, and other risk factors are more commonly found in low socioeconomic communities.

Pharmacological exposures during pregnancy, such as the use of antiseizure medications like valproic acid, further contribute to oxidative stress. Valproic acid has been shown to increase oxidative damage while reducing antioxidant enzyme activity in cellular and animal models (Terzioğlu Bebitoğlu et al., 2020). Similarly, antibiotics and antidepressants have been implicated as potential confounders in oxidative stress pathways due to their effects on the maternal microbiome and immune system (Njotto et al., 2023; Lee et al., 2024). These findings emphasize

the need for careful consideration of medication use and its impact on oxidative stress when assessing ASD risk.

In addition to these factors, maternal exposure to environmental toxins, such as pesticides and industrial pollutants, has been linked to increased oxidative stress. These toxins can directly generate ROS or impair the activity of antioxidant enzymes, further amplifying oxidative damage (Pangrazzi et al., 2020). The cumulative effect of these exposures, particularly in combination, underscores the complexity of oxidative stress as a multifactorial risk factor for ASD.

By examining these diverse sources of oxidative stress, this study aims to identify key variables within maternal medical records that may serve as predictors of ASD. Incorporating these variables into statistical models will provide a more comprehensive understanding of how oxidative stress contributes to ASD etiology and facilitate the development of targeted interventions for at-risk populations.

4.2. Oxidative Stress and ASD Pathogenesis

Oxidative stress has emerged as a critical factor in the pathogenesis of Autism Spectrum Disorder (ASD), influencing both prenatal neurodevelopment and postnatal neurological function. Oxidative stress results from an imbalance between the production of reactive oxygen species (ROS) and the capacity of antioxidant defense systems to neutralize these reactive molecules, leading to cellular damage. This section examines the mechanisms by which oxidative stress contributes to ASD, focusing on biochemical pathways, evidence from biomarker studies, and the role of oxidative stress in disrupting neurodevelopmental processes.

4.2.1. Mechanisms Linking Oxidative Stress to ASD

The pathophysiology of ASD implicates oxidative stress as a mediator of neural damage during critical periods of brain development. Elevated levels of ROS and reactive nitrogen species (RNS) can impair neuronal proliferation, migration, and synaptic plasticity (Liu et al., 2022). ROS-induced damage to cellular macromolecules, including lipids, proteins, and nucleic acids, disrupts mitochondrial function, exacerbating oxidative stress and creating a self-perpetuating cycle of damage (Chen et al., 2021). This dysfunction is particularly concerning in the context of the developing brain, where mitochondrial activity is crucial for energy production and neurodevelopmental processes. Studies have shown that oxidative stress can disrupt key signaling pathways, such as the phosphoinositide 3-kinase (PI3K)/Akt pathway, which is essential for cell survival and neuroplasticity (Membrino et al., 2023). Additionally, oxidative stress may influence the activity of transcription factors like nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which is involved in inflammatory responses and has been implicated in ASD pathogenesis (Pangrazzi et al., 2020). This interplay between oxidative stress and inflammation further highlights its role in the multifactorial etiology of ASD.

4.2.2. Biomarker Evidence for Oxidative Stress in ASD

Elevated oxidative stress biomarkers have been consistently observed in individuals with ASD. These include increased levels of lipid peroxidation products, such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), as well as reduced concentrations of critical antioxidants, including glutathione (GSH) and superoxide dismutase (SOD) (Chen et al., 2021; Liu et al., 2022). A systematic review by Chen et al. (2021) highlighted significant aberrations in oxidative stress markers across 87 studies, encompassing over 9,000 participants. The findings demonstrated elevated oxidized glutathione (GSSG) levels and decreased GSH:GSSG ratios in

ASD populations, indicating impaired antioxidant capacity. Another critical biomarker, 8-hydroxy-2'-deoxyguanosine (8-OHdG), reflects oxidative damage to DNA and has been found to be significantly elevated in ASD patients compared to neurotypical controls (Usui et al., 2023). Notably, these biomarkers are detectable in peripheral tissues such as blood and urine, suggesting their potential utility in early diagnosis and risk stratification (Pangrazzi et al., 2020).

4.2.3. Impact on Neurodevelopmental Processes

Oxidative stress affects neurodevelopment through multiple pathways, including neuroinflammation, synaptic dysfunction, and disruptions in neural circuitry. Elevated ROS levels can activate microglial cells, the brain's resident immune cells, leading to the release of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) (Usui et al., 2023). These cytokines, in turn, amplify oxidative damage and contribute to the disruption of neural networks critical for social communication and behavioral regulation.

Additionally, oxidative stress impairs synaptic plasticity by disrupting the balance of excitatory and inhibitory neurotransmission. For instance, altered glutamate signaling, exacerbated by oxidative damage, has been observed in ASD and is thought to contribute to the excited neuronal state characteristic of the disorder (Terzioğlu Bebitoğlu et al., 2020). This dysregulation is made worse by mitochondrial dysfunction, as oxidative damage to mitochondrial DNA (mtDNA) reduces the efficiency of energy production, further impairing neural development (Membrino et al., 2023).

4.2.4. Role of Maternal Oxidative Stress

Maternal oxidative stress during pregnancy has a direct impact on fetal neurodevelopment and is considered a critical risk factor for ASD. Exposures to environmental

toxins, lifestyle factors such as smoking and stress, and pharmacological agents like valproic acid contribute to elevated ROS levels in utero (Njotto et al., 2023; Hernández-Díaz et al., 2023). Valproic acid, in particular, has been shown to induce oxidative stress by depleting GSH and increasing lipid peroxidation, highlighting its dual role as both a confounder and a potential contributor to ASD risk (Terzioğlu Bebitoğlu et al., 2020).

Neuroinflammation triggered by maternal immune activation (MIA) further exacerbates oxidative stress. Usui et al. (2023) reported that maternal inflammatory states lead to increased placental production of ROS and cytokines, which cross the blood-brain barrier and disrupt fetal brain development. These findings underscore the importance of addressing maternal health and environmental exposures to mitigate oxidative stress and its downstream effects on ASD pathogenesis.

4.2.5. Summary

Oxidative stress plays a multifaceted role in ASD pathogenesis, influencing neurodevelopmental processes through mechanisms such as mitochondrial dysfunction, neuroinflammation, and synaptic dysregulation. Biomarker studies provide compelling evidence of systemic oxidative stress in individuals with ASD, highlighting potential targets for early diagnosis and intervention.

4.3. Mechanisms of Oxidative Stress in ASD

The pathophysiology of Autism Spectrum Disorder (ASD) involves complex interactions between genetic, environmental, and biochemical factors. Oxidative stress disrupts multiple cellular and molecular pathways critical for neurodevelopment. This section delves into the specific mechanisms through which oxidative stress contributes to ASD, including mitochondrial

dysfunction, neuroinflammation, impaired synaptic plasticity, and disruptions in the redox balance.

4.3.1. Mitochondrial Dysfunction

Mitochondria play a central role in oxidative stress as both generators and targets of ROS. In ASD, evidence suggests that mitochondrial dysfunction exacerbates oxidative damage by impairing energy metabolism and increasing ROS production. Liu et al. (2022) reported that mitochondrial DNA (mtDNA) mutations and reduced mitochondrial enzyme activities are prevalent in ASD patients, leading to an accumulation of ROS. The resulting oxidative damage to mtDNA and mitochondrial membranes further diminishes mitochondrial efficiency, creating a feedback loop that perpetuates oxidative stress (Chen et al., 2021). Mitochondrial dysfunction also disrupts calcium homeostasis and apoptosis signaling, both of which are critical for neuronal health and development. Studies have shown that dysregulated mitochondrial dynamics, including impaired fission and fusion processes, are associated with neuronal apoptosis and synaptic abnormalities in ASD (Usui et al., 2023).

4.3.2. Neuroinflammation and Oxidative Stress

Neuroinflammation is a hallmark of ASD and is closely linked to oxidative stress. Reactive oxygen and nitrogen species generated during inflammatory processes exacerbate oxidative damage, creating a synergistic effect that disrupts neural development. Microglial activation, a key feature of neuroinflammation, is associated with the release of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). These cytokines induce oxidative stress by increasing ROS production and impairing antioxidant enzyme activities (Pangrazzi et al., 2020).

Maternal immune activation (MIA) is a significant contributor to neuroinflammation and oxidative stress in ASD. Usui et al. (2023) highlighted that MIA during pregnancy results in elevated levels of placental ROS and inflammatory cytokines, which can cross the blood-brain barrier and disrupt fetal brain development.

4.3.3. Impaired Synaptic Plasticity

Oxidative stress interferes with synaptic plasticity, a critical process for learning, memory, and overall cognitive function. Elevated ROS levels disrupt the balance of excitatory and inhibitory neurotransmission, leading to synaptic dysfunction. For instance, oxidative stress has been shown to impair the function of N-methyl-D-aspartate (NMDA) receptors, which play a pivotal role in synaptic plasticity and neural network formation (Terzioğlu Bebitoğlu et al., 2020).

Moreover, oxidative damage to presynaptic and postsynaptic proteins compromises synaptic integrity. Proteomic analyses of ASD brain tissue have revealed increased carbonylation of synaptic proteins, a marker of oxidative damage, which correlates with altered synaptic function (Membrino et al., 2023). These disruptions in synaptic signaling could contribute to the cognitive and behavioral deficits observed in ASD.

4.3.4. Disruptions in Redox Balance

The redox balance, regulated by the interplay between ROS and antioxidants, is essential for cellular homeostasis. In ASD, a shift toward an oxidative state is evident from biomarker studies. Reduced levels of glutathione (GSH), the primary cellular antioxidant, and elevated oxidized glutathione (GSSG) levels have been consistently reported in ASD populations (Chen et

al., 2021). This imbalance impairs the detoxification of ROS, leading to oxidative damage to lipids, proteins, and DNA.

Key enzymes involved in the antioxidant defense system, such as superoxide dismutase (SOD) and catalase (CAT), exhibit altered activity in ASD. Liu et al. (2022) noted that decreased SOD activity exacerbates superoxide accumulation, while reduced CAT activity impairs hydrogen peroxide detoxification. These enzymatic deficiencies further disrupt redox homeostasis, amplifying oxidative stress and its pathological effects.

4.3.5. Interaction with Environmental and Genetic Factors

The mechanisms of oxidative stress in ASD are modulated by environmental and genetic factors. Environmental exposures, such as heavy metals and pesticides, directly increase ROS production and impair antioxidant defenses (Pangrazzi et al., 2020). Additionally, genetic variations in oxidative stress-related genes, such as those encoding SOD and glutathione peroxidase, may predispose individuals to heightened oxidative susceptibility (Membrino et al., 2023).

Epigenetic modifications induced by oxidative stress, such as DNA methylation and histone acetylation, further contribute to ASD by altering gene expression patterns critical for neurodevelopment (Usui et al., 2023). These interactions between environmental and genetic factors highlight the multifactorial nature of oxidative stress mechanisms in ASD.

4.3.6. Summary

The mechanisms of oxidative stress in ASD encompass mitochondrial dysfunction, neuroinflammation, impaired synaptic plasticity, and disruptions in redox balance. These processes are influenced by environmental exposures, genetic predispositions, and epigenetic

changes, creating a complex network of interactions that contribute to ASD pathogenesis. Understanding these mechanisms helps to identify potential predictors in the data set.

4.4. Factors Contributing to Oxidative Stress

Oxidative stress, a significant contributor to Autism Spectrum Disorder (ASD) pathogenesis, arises from various endogenous and exogenous factors that disrupt the balance between reactive oxygen species (ROS) production and antioxidant defenses. Maternal medical history forms often capture lifestyle, environmental, and pharmacological variables that can act as sources of oxidative stress. This section explores these factors and their implications for ASD risk, with a focus on smoking, psychological stress, socioeconomic conditions, pharmacological exposures, and environmental toxins.

4.4.1. Smoking

Smoking during pregnancy is one of the most well-documented contributors to oxidative stress. Tobacco smoke contains numerous oxidants and pro-oxidants that can directly generate ROS, overwhelming maternal and fetal antioxidant systems (Njotto et al., 2023). Biomarker studies have linked smoking to increased lipid peroxidation and decreased glutathione (GSH) levels in maternal and fetal tissues, both of which are hallmarks of oxidative stress (Chen et al., 2021). These biochemical changes disrupt fetal neurodevelopment, with smoking during pregnancy being associated with an increased risk of ASD and other neurodevelopmental disorders (Usui et al., 2023). The inclusion of smoking-related variables in maternal medical records provides an opportunity to assess its contribution to oxidative stress and ASD risk in predictive models.

4.4.2. Psychological Stress

Maternal psychological stress during pregnancy is a critical yet often underrecognized contributor to oxidative stress. Chronic stress elevates cortisol levels, which, in turn, impair mitochondrial function and increase ROS production (Alamoudi et al., 2023). This stress-induced oxidative damage has been shown to influence placental function, fetal brain development, and the fetal immune system. Studies have reported that maternal stress correlates with increased oxidative stress biomarkers, including malondialdehyde (MDA), and decreased antioxidant enzyme activities such as superoxide dismutase (SOD) (Pangrazzi et al., 2020).

4.4.3. Socioeconomic Conditions

Socioeconomic conditions can indirectly contribute to oxidative stress by influencing access to healthcare, nutrition, and exposure to environmental hazards. Low socioeconomic status is associated with increased oxidative stress markers due to factors such as malnutrition and exposure to pollutants, including heavy metals and industrial chemicals (Membrino et al., 2023). Poor dietary quality, characterized by low intake of antioxidants such as vitamins C and E, further exacerbates oxidative stress (Liu et al., 2022). Understanding the socioeconomic context of individuals, often captured in medical history forms, could help in evaluating its role in oxidative stress and ASD development.

4.4.4. Pharmacological Exposures

Pharmacological agents, including antiseizure medications, antibiotics, and antidepressants, are prominent contributors to maternal oxidative stress. Valproic acid, an antiseizure medication, has been shown to elevate ROS levels and disrupt antioxidant defenses, thereby increasing oxidative damage in both maternal and fetal tissues (Terzioğlu Bebitoğlu et al., 2020). Similarly, maternal antibiotic use alters the microbiome and may exacerbate oxidative stress through inflammatory pathways (Njotto et al., 2023). While antidepressants have not been

consistently linked to increased oxidative stress, maternal depression—often the underlying indication for these medications—has been associated with elevated oxidative stress markers (Lee et al., 2024). Tracking medication use in maternal medical records is critical for identifying these exposures and assessing their contributions to ASD risk.

4.4.5. Environmental Toxins

Exposure to environmental toxins, including pesticides, industrial chemicals, and air pollutants, represents a significant source of oxidative stress. These toxins directly generate ROS or impair the activity of antioxidant enzymes, leading to oxidative damage at the cellular level (Pangrazzi et al., 2020). For example, heavy metals such as mercury and lead have been implicated in increased lipid peroxidation and mitochondrial dysfunction in ASD populations (Chen et al., 2021). Pesticides, including organophosphates, disrupt cholinergic signaling and induce oxidative stress, compounding their neurotoxic effects.

4.4.6. Combined Effects and Synergistic Interactions

Many of these factors do not act in isolation but interact synergistically to exacerbate oxidative stress. For instance, socioeconomic disadvantage may increase the likelihood of smoking or exposure to environmental pollutants, creating a cumulative burden of oxidative stress (Liu et al., 2022). Similarly, psychological stress may amplify the oxidative effects of pharmacological or environmental exposures through shared inflammatory pathways (Usui et al., 2023). These interactions highlight the importance of examining combinations of variables in maternal medical records to better understand their collective impact on oxidative stress and ASD risk.

4.4.7. Summary

In summary, oxidative stress arises from diverse sources, including smoking, psychological stress, socioeconomic conditions, pharmacological exposures, and environmental toxins, all of which may be captured in maternal medical history forms. Understanding these factors and their interactions is critical for identifying key predictors of oxidative stress and refining statistical models to assess ASD risk. By integrating these variables into predictive frameworks, this research aims to advance the understanding of oxidative stress as a central mechanism in ASD etiology.

4.5. Biomarkers for Early Detection

Biomarkers offer a promising avenue for the early detection of Autism Spectrum Disorder (ASD), particularly those linked to oxidative stress. By identifying and measuring biochemical indicators of oxidative damage or impaired antioxidant capacity, researchers can gain insights into the molecular mechanisms underlying ASD pathogenesis. This section focuses on the biomarkers most relevant to early detection, including oxidative stress markers, antioxidant levels, and neuroinflammatory indicators, with an emphasis on their potential presence in maternal medical records.

4.5.1. Oxidative Stress Markers

Markers of oxidative damage to lipids, proteins, and DNA are among the most studied indicators of oxidative stress in ASD. Malondialdehyde (MDA), a product of lipid peroxidation, is consistently elevated in individuals with ASD (Chen et al., 2021). Studies have shown that increased MDA levels in maternal blood during pregnancy may reflect oxidative damage that affects fetal neurodevelopment. Similarly, 8-hydroxy-2’-deoxyguanosine (8-OHdG), a biomarker of oxidative damage to DNA, is elevated in both ASD populations and their mothers during

pregnancy (Usui et al., 2023). These biomarkers are detectable in blood, urine, and other biofluids, making them practical candidates for inclusion in predictive models.

4.5.2. Antioxidant Capacity

The imbalance between oxidative damage and antioxidant defenses is a hallmark of oxidative stress. Reduced levels of glutathione (GSH), the primary intracellular antioxidant, have been identified in ASD populations and may serve as an early biomarker of risk (Liu et al., 2022). Studies report that a lower ratio of reduced to oxidized glutathione (GSH:GSSG) is associated with increased oxidative stress in both maternal and fetal tissues. This ratio could be a valuable indicator for assessing oxidative balance during pregnancy. Enzymatic antioxidants such as superoxide dismutase (SOD) and catalase (CAT) also play a critical role in mitigating oxidative stress. Decreased SOD activity, which reduces superoxide radicals to hydrogen peroxide, and impaired CAT activity, which further detoxifies hydrogen peroxide, have been observed in ASD populations (Pangrazzi et al., 2020). Assessing these enzymes in maternal samples may help identify disruptions in antioxidant pathways early in pregnancy.

4.5.3. Neuroinflammatory Biomarkers

Oxidative stress and neuroinflammation are closely linked in ASD pathogenesis. Biomarkers such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which are elevated in ASD patients, also reflect systemic inflammation that can exacerbate oxidative damage (Usui et al., 2023). Maternal immune activation (MIA) during pregnancy, indicated by elevated levels of these cytokines, has been associated with increased risk of ASD in offspring. These neuroinflammatory markers, detectable in maternal blood, may serve as early indicators of oxidative stress-related disruptions in fetal neurodevelopment.

4.5.4. Emerging Biomarkers

Emerging biomarkers, such as advanced oxidation protein products (AOPPs) and thiobarbituric acid reactive substances (TBARS), have shown potential for early detection of oxidative stress in ASD. AOPPs, which reflect protein oxidation, are elevated in ASD populations and may provide additional insights into oxidative damage pathways (Membrino et al., 2023). Similarly, TBARS, which measure lipid peroxidation products, could complement traditional biomarkers like MDA in assessing oxidative stress levels. In addition, markers of mitochondrial dysfunction, such as altered mitochondrial DNA (mtDNA) copy number and decreased activity of electron transport chain enzymes, are gaining attention as potential indicators of ASD risk (Liu et al., 2022). These markers may offer a more comprehensive understanding of the role of oxidative stress in ASD and could be incorporated into predictive models alongside traditional oxidative stress biomarkers.

4.5.5. Biomarker Integration into Medical History Forms

The inclusion of oxidative stress biomarkers in maternal medical history forms has the potential to enhance early detection efforts significantly. Routine prenatal testing could measure key biomarkers, such as GSH, MDA, and IL-6, providing clinicians with useful data for assessing ASD risk. Combining these biochemical indicators with self-reported lifestyle and health variables would allow for the development of predictive models that analyze onr or both of molecular and environmental contributions to oxidative stress.

4.5.6. Summary

Biomarkers of oxidative stress and antioxidant capacity, along with neuroinflammatory indicators, hold significant promise for the early detection of ASD. By incorporating these biomarkers into maternal medical records, researchers can better understand the molecular mechanisms underlying ASD and improve the predictive power of statistical models. Continued

research into emerging biomarkers and their integration with existing clinical data will be essential for advancing early intervention strategies and reducing the burden of ASD.

4.6. Confounding Variables in Studies

Understanding the relationship between oxidative stress and Autism Spectrum Disorder (ASD) is inherently complex due to the presence of confounding variables. These factors, which may influence both oxidative stress and ASD risk, can obscure causal relationships and complicate the interpretation of study findings. Maternal medical history forms, while valuable for identifying oxidative stress contributors, often include overlapping variables that must be carefully addressed to ensure robust statistical analyses. This section explores key confounders and their implications for research on oxidative stress and ASD.

4.6.1. Maternal Health Conditions

Maternal health conditions, such as obesity, diabetes, and hypertension, are significant confounders in oxidative stress research. These conditions are associated with elevated levels of reactive oxygen species (ROS) and reduced antioxidant capacity, contributing to oxidative damage in maternal and fetal tissues (Chen et al., 2021). For example, obesity has been linked to increased lipid peroxidation and systemic inflammation, both of which may independently affect fetal neurodevelopment (Liu et al., 2022). Additionally, gestational diabetes has been shown to increase oxidative stress markers such as malondialdehyde (MDA) and decrease antioxidant enzyme activities (Usui et al., 2023). Including these variables in predictive models is essential for disentangling their effects from those of other oxidative stress contributors.

4.6.2. Medication Use During Pregnancy

Medications commonly used during pregnancy, including antiseizure drugs, antibiotics, and antidepressants, present potential confounders in studies of oxidative stress and ASD.

Valproic acid, for instance, has been implicated in both increased oxidative stress and elevated ASD risk (Terzioğlu Bebitoğlu et al., 2020). However, distinguishing the direct effects of the medication from those mediated by underlying maternal conditions, such as epilepsy, is challenging. Similarly, maternal use of antibiotics and antidepressants may influence oxidative stress through alterations in the maternal microbiome or stress-related pathways (Njotto et al., 2023; Lee et al., 2024). Evaluating the interactions between medication use and oxidative stress biomarkers is critical for clarifying these relationships.

4.6.3. Genetic and Familial Factors

Genetic predispositions play a significant role in both ASD and oxidative stress susceptibility. Variations in genes encoding antioxidant enzymes, such as superoxide dismutase (SOD) and glutathione peroxidase, can affect oxidative stress levels and potentially contribute to ASD risk (Membrino et al., 2023). Furthermore, familial factors, including a history of ASD or related neurodevelopmental disorders, may confound associations between oxidative stress and ASD. For example, shared genetic or environmental influences within families could underlie both oxidative stress markers and ASD phenotypes, complicating causal inference (Pangrazzi et al., 2020). Adjusting for familial and genetic factors in statistical models is therefore essential.

4.6.4. Socioeconomic and Environmental Variables

Socioeconomic conditions and environmental exposures are critical overlapping variables that influence oxidative stress and ASD risk. Socioeconomic disadvantage is associated with increased exposure to environmental pollutants, such as heavy metals and pesticides, which are known to generate ROS and impair antioxidant defenses (Chen et al., 2021). Additionally, limited access to healthcare and nutritious food may exacerbate oxidative stress through poor diet quality and chronic stress (Liu et al., 2022). Including socioeconomic variables in analyses

helps contextualize the role of environmental and lifestyle factors in oxidative stress-related outcomes.

4.6.5. Lifestyle Factors

Maternal lifestyle factors, including smoking, alcohol consumption, and dietary habits, are major contributors to oxidative stress and potential confounders in ASD studies. Smoking is a well-established source of ROS, while poor dietary intake of antioxidants such as vitamins C and E can impair oxidative defense mechanisms (Njotto et al., 2023). Alcohol consumption, though less frequently studied, has also been associated with increased oxidative stress and neurodevelopmental risks (Usui et al., 2023). Accurate documentation of these factors in medical history forms is critical for their inclusion as covariates in statistical analyses.

4.6.6. Overlapping Variables and Interactions

Many confounders do not act independently but interact in ways that compound their effects on oxidative stress and ASD risk. For example, maternal stress may amplify the oxidative effects of socioeconomic disadvantage or medication use through shared inflammatory and neuroendocrine pathways (Pangrazzi et al., 2020). Similarly, genetic predispositions to oxidative stress may heighten vulnerability to environmental exposures, creating synergistic interactions that influence neurodevelopment (Membrino et al., 2023). Addressing these overlapping variables requires advanced statistical methods, such as interaction modeling and mediation analysis, to disentangle their combined effects.

4.6.7. Implications for Medical History Form Analysis

The presence of confounders and overlapping variables in maternal medical history forms underscores the need for rigorous variable selection and model design. Identifying and controlling for these factors is essential for isolating the contributions of oxidative stress to ASD

risk. This process may involve stratifying analyses by key confounders, such as maternal health conditions or socioeconomic status, or incorporating interaction terms to account for synergistic effects.

4.6.8. Summary

Confounding variables, including maternal health conditions, medication use, genetic factors, socioeconomic variables, and lifestyle behaviors, complicate the study of oxidative stress and ASD. Their inclusion in maternal medical history forms provides valuable context but requires careful statistical adjustment to ensure valid interpretations. Addressing these confounders is critical for advancing our understanding of oxidative stress as a mechanism in ASD pathogenesis and for developing accurate predictive models.

4.7. Summary and Future Directions

Oxidative stress plays a central role in the pathogenesis of Autism Spectrum Disorder (ASD), acting through mechanisms such as mitochondrial dysfunction, neuroinflammation, synaptic dysregulation, and disruptions in redox balance. This literature review highlights the significant contributions of maternal factors, including lifestyle behaviors, pharmacological exposures, and environmental conditions, to oxidative stress levels during pregnancy (Chen et al., 2021; Liu et al., 2022). Biomarkers such as malondialdehyde (MDA), glutathione (GSH), and pro-inflammatory cytokines have emerged as valuable tools for early detection, with potential applications in predictive modeling (Pangrazzi et al., 2020; Usui et al., 2023).

Despite substantial progress, significant gaps remain in our understanding of how oxidative stress interacts with genetic, environmental, and socioeconomic factors to influence ASD risk. Many studies are limited by cross-sectional designs, small sample sizes, and inadequate adjustment for confounding variables (Njotto et al., 2023). Additionally, the

synergistic effects of multiple oxidative stressors and their interactions with genetic predispositions require further exploration (Membrino et al., 2023).

Future research should prioritize longitudinal studies to capture the dynamic relationship between oxidative stress and neurodevelopment over time. Expanding the use of high-throughput biomarker profiling and integrating findings with detailed maternal medical history forms will enhance the identification of key predictors. Additionally, developing advanced statistical models to account for confounding and interaction effects is essential for refining our understanding of the causal pathways linking oxidative stress to ASD.

By addressing these gaps, the field can move toward more accurate risk stratification and the development of targeted interventions to mitigate oxidative stress during critical periods of neurodevelopment. This effort will not only improve early detection and prevention strategies for ASD but also contribute to a broader understanding of oxidative stress in neurodevelopmental disorders.

5. Statistical Analysis Plan

The NIMH Medical History Questionairre data set is quite large (2243 subjects and 769 variables) and extensive. The purpose of this study will be to identify important prenatal factors related to maternal oxidative stress and to determine whether or not a predictive model can be created based on a medical history questionairre of this type.

I will attempt to use techniques that provide a foundational understanding of variable distributions, relationships, and potential influences on ASD diagnosis while making adjustments to handle the large dataset. Visualizations, summaries, and distributions will help see patterns

and trends, while statistical and correlation analyses will help verify their significance to the study. They will be elucidated in more detail in the sections that follow.

5.1. Description of Tools

This study will be performed in R, SAS, JMP, and Python using applied statistics and data science techniques.

5.2. Exploratory Data Analysis

Exploratory Data Analysis will feature a diverse set of assessments and analyses to try to extract the best possible model from this large data set. This process is discussed in more detail in the continuing narrative below.

5.2.1. Data Cleansing and Inspection

Check for Missing Values. Summary statistics and visualzations such as histograms and scatter plots will be used to identify missing data and its pattern of distribution. Methods involving box plots or z-scores will be used to identify and decide how to handle outliers. Data types such as categorical and numerical data will be verified and converted to functional forms where needed.

5.2.2. Descriptive Statistics

Descriptive statistics such as mean, median, standard deviation, and IQR for continuous variables (e.g., maternal age) and frequency counts for categorical variables (e.g., prenatal complications) will be explored for summary. Frequency tables willl be produced to observe the distribution of categorical variables such as the presence/absence of certain prenatal conditions.

5.2.3. Visualization Techniques

Histograms, bar charts, and density plots can be used for numerical variables such as maternal age, BMI, or gestational weeks, to understand the distribution. Bar plots can also be used for categorical variables like the presence of maternal diabetes, prenatal supplements, or family history of ASD. Box plots can be used to visualize numerical variable distribution across categories (e.g., maternal age distribution by ASD diagnosis). Heatmaps can be used to visually identify possible correlations among continuous variables (like maternal age, weight, BMI) and a potential influence on ASD diagnosis. Violin plots can be used to visualize the numerical variable distribution density for group comparison (groups with/without ASD diagnosis, etc).

5.2.4. Correlation Analysis

Pearson/Spearman Correlation can be run to analyze continuous variable correlations (e.g., maternal age, weight gain, prenatal factors) and their possible linearity with ASD diagnosis. Chi-Square tests can be produced for categorical variables like prenatal exposure to certain conditions and ASD diagnosis toexplore correlation or association.

5.2.5. Univariate Analysis

Vizualisations such as histograms, bar charts, pie charts, etc., can be used to view variable distributions independently with the goal of addressing problematic patterns in those data. Some continuous variables may require transformation (such as Box-Cox) to meet normality assumptions.

5.2.6. Bivariate Analysis

Scatter plots can be produced to visually analyze relationships between two continuous variables (e.g., maternal age vs. child birth weight) and add colorized points by ASD diagnosis to

observe potential patterns. Grouped box plots can be used to explore the effect of categorical variables on numerical variables (such as ASD vs. non-ASD for different prenatal conditions).

5.2.7. Multivariate Analysis

Pair plots (scatterplot matrices) can be used to visualize relationships between multiple continuous variables, potentially by ASD diagnosis. Principal Component Analysis (PCA) can be used for dimensionality reduction and to reveal patterns in this data set with many variables to explore which variables contribute most to the variance. Factor analysis can be used to explore underlying latent factors (e.g., maternal health factors), this will potentially be used to group correlated variables together.

5.2.8. Categorical Data Analysis

Contingency tables can be used to explore the relationships between categorical variables (e.g., prenatal complications and ASD diagnosis). Mosaic plots can be used to visualize joint distributions of pairs of categorical variables and their association with ASD. Decision Trees can be used first as a, non-parametric way to identify which factors split the data best in predicting ASD diagnosis from among the predictor variables.

5.2.9. When Encountering Big Data Processing Problems

The reduction of the data set into stratified sampling could ensure a better representative subset for initial analysis if problems in processing are encountered.

5.2.10. Feature Engineering

Scaled scores or indices could be used to create features like prenatal risk scores or maternal health indices. Creating bins for continuous variables like maternal age or BMI into categories (e.g., age groups) could help further categorical analysis. Interactions between

variables (e.g., maternal age × prenatal health conditions) could be explored with the creation of interaction terms to see if they influence ASD diagnosis.

5.2.10. Dimensionality Reduction

PCA or t-SNE (t-Distributed Stochastic Neighbor Embedding) can be used to visualize high-dimensional data to see cluster patterns related to ASD.

5.2.11. Feature Importance

Random forest models can be run in EDA to determine feature importance (without assumptions) to inform understanding of important factors. Logistic regression can provide knowledge of significant predictors by the comparison of odds ratios.

5.3. Model Building and Validation

After EDA, the project enter into the refinement phase in which will identify predictor variables, compare multiple models (logistic regression, random forest, etc.) and compare their performance (with AUC, sensitivity, specificity, etc.), run model diagnostics (such as normality and multicollinearity) to check model assumptions and validate, apply validation techinques (such as bootstrapping) to validate the chosen model(s), finalize the assessment of predictors (with techniques such as LASSO, Random Forest, PCA, etc.), and ultimately to make an interpretation of the analysis to address the goals of the study.

6. Proposed Project Schedule

Table 1

Proposed Project Schedule

Week	Dates	Activity	Activity Description
1	Jan 1-7	Project initiation	Define objectives and scope; review SAP and dataset characteristics (NIMH Medical History Questionnaire).
2	Jan 8-14	Data Cleaning	Perform initial data cleaning.
3	Jan 15-21	Exploratory Data Analysis (EDA)	Summarize dataset structure, identify missing data, and visualize key variables.
4	Jan 22-28	Feature engineering	Develop variables from raw data related to oxidative stress and other predictors identified in literature.
5	Jan 29-Feb 4	Univariate and bivariate analyses	Examine relationships between key predictors and ASD outcomes.
6	Feb 5-11	Model specification	Define models to test predictive hypotheses (e.g., logistic regression, random forests).
7	Feb 12-18	Initial model training	Test preliminary models and refine based on model diagnostics.
8	Feb 19-25	Model validation	Use cross-validation techniques to assess model stability and predictive performance.
9	Feb 26-Mar 4	Advanced modeling	Explore ensemble techniques.
10	Mar 5-11	Results synthesis	Consolidate model outputs and interpret variable contributions to ASD risk.
11	Mar 12-18	Draft results and discussion	Relate findings to the literature and identify implications.
12	Mar 19-25	Prepare manuscript	Draft introduction, methods, and background sections; integrate analytical results.
13	Mar 26-Apr 1	Submit preliminary results for review	
14	Apr 2-8	Address feedback	Revise analyses and draft based on feedback.
15	Apr 9-15	Prepare presentation materials	Develop slides summarizing key findings, methods, and implications.
16	Apr 16-22	Project Presentation	Refine delivery and address potential questions.

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