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MSc Public Health and Social Care in Practice

Factors influencing the prevalence rate of ASD amongst children, a systematic review.

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Declaration.

This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree

Signed Solomon Lopez Date 10th January 2024.

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This dissertation is being submitted in partial fulfilment of the requirements for the degree of MSc.

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This dissertation is the result of my own independent work/investigation, except where otherwise stated.

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Abstract.

The aim of this SLR is to examine the factors influencing the prevalence rate of ASD amongst children. To obtain literature for this SLR a search strategy was formulated to ensure that relevant, credible and current information was acquired. Using the PEO framework and the relevant Boolean operators', key words were generated to be used in the search for literature. To obtain the relevant literature for this research a search of the PubMed database using the search term 'Children *AND* factors *AND* autism' was conducted resulting in fourty five studies to be used in this SLR. A PRISMA flowchart (see appendix 3) displays how this search was conducted along with the inclusion and exclusion criteria used. The selected studies were then subject to critical appraisal via the Coughlan, Cronin and Ryan (2007) tool in which information regarding the studies is visually displayed to further ensure the research free from bias, credible and presents valid arguments (see appendix 1). With the appropriate studies selected, thematic analysis of the chosen studies took place using the Braun and Clarke method in which the themes and subthemes are created. Air pollution, hereditary influences, chemicals and external factors were identified as themes along with the subthemes of F.A and multivitamins. Examining these themes it was identified that the main themes, air pollution, hereditary influences, chemicals and external factors negatively contributed to the prevalence rate of ASD whilst the subthemes of F.A and multivitamins, particularly vitamin D positively impacted ASD development. This SLR concluded that the increased prevalence rate of ASD is not a result of one factor but aa result of multiple factors working together to increase this rate.

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Abbreviations.

ASD: Autism Spectrum Disorder.

TA: Thematic analysis.

SLR: Systematic literature review.

U.S: United States of America.

U.K: United Kingdom.

CDD: Child Development Disorder.

EG: Electroencephalogram.

DSM-4: Diagnostic and Statistical Manual of Mental Disorders 4th edition.

DSM-5: Diagnostic and Statistical Manual of Mental Disorders 5th edition.

PDD: Pervasive Developmental Disorders.

(MAR) ASD: Maternal autoantibody related Autism Spectrum Disorder.

FA: Folic acid.

RCT: Randomised control trial.

CDC: Center for Disease Control and Prevention.

PCB: Polychlorinated biphenyl.

ECHA: European Chemicals Agency.

BPA: Bisphenol A.

NTP: National Toxicology Program.

C.O: Carbon monoxide.

VOCs: Volatile organic compounds.

PM: Particulate matter.

E.U: European union.

SO2: Sulphur oxides.

GD: Gestational diabetes.

BPA: Bisphenol A.

OPFR: Organophosphate flame retardant.

ICD-10: National Clinical Coding Standards ICD-10 5th Edition (2022).

Chapter 1: Introduction and background.

1.1. Introduction to the topic.

Autism spectrum disorder or ASD is a neurodevelopmental disorder that interferes with social interaction, communication, learning, and behaviour (National Institute of Mental Health, 2023). Although autism can be diagnosed at any age, the disorder typically begins to manifest during the early stages of a child's development, but may not be fully apparent until adulthood, when social interactions exceed the body's capacity to cope with them (WHO, 2023). It may be linked to a variety of cognitive, educational, linguistic, medical, emotive, and behavioural issues, such as a need for consistency, difficulty comprehending others' intentions, emotions, and outlooks, and concurrent mental health issues (NICE, 2021). Depending on the individual's age, educational background, language proficiency, and cognitive abilities, difficulties may manifest differently (Hyman *et al*., 2020). Unfortunately these issues will be serious enough to have a significant impact on a person's life, relationships, education, work, and/or other activities and are typically present in all contexts although they may differ from one situation to another (WHO, 2022). Autism is classified as a "spectrum" disorder due its wide-ranging characteristics and degrees of severity. The disorder can be diagnosed in individuals of any gender, race, ethnicity, and socioeconomic and although a long-term condition, through the implementation of treatments and services individuals may experience an improvement in their symptoms and daily activities (National Institute of Mental Health, 2023). With discrepancies between the official worldwide figures and those presented by researchers coupled with the CDC presenting data showing the prevalence rate of children living with autism more than doubling over the past fifteen years, in depth exploration on what factors may be influencing this upward trend (WHO, 2023; Zeidan *et al.*, 2022).

1.2. Background and current context.

With the prevalence rate of children living with autism increasing examination on the contributing factors as a whole picture is vital. With current studies examining contributing factors as individual entities, this creates a research gap. This research gap limits our understanding on how best to prevent children being born with autism and navigate potential areas of concern. Consequently, this research report aims to examine these factors collectively to gain a deeper understanding into the development of childhood autism. Universally accepted research on the link between genetics and autism has shown that changes in specific genes increase a child's risk of developing autism. These gene changes can be passed to a child through their parent irrespective of whether any parent suffers from

autism. These genetic changes can also occur in an embryo's early development initiated by the sperm and/or egg that combine to create the embryo (Autism Speaks, 2023; Rylaarsdam and Guemez-Gamboa, 2019). Genetics whilst significantly increasing the risk of autism development, cannot do so alone (Chaste and Leboyer, 2012). Alongside genetic changes, numerous research studies have examined the environmental and medicinal factors independently, yet none have examined these factors when occurring in combination. The National Institute of Environmental Health Services (2023) examined autism and the environmental factors that may increase risk but not what these risks coupled with other factors have on the increased prevalence rate. Elemy (2021) researched prescribed medicines links to autism development, and although providing results that will be used in this research report, also failed to identify what these results coupled with the other factors presented by other research studies display. The spread of misinformation leading to parents promoting inaccurate diagnosis causing an increase in the prevalence rate must also be factored into the discussion. Inaccurate information surrounding autism and its causes can be traced back to 1998 when a research paper published by Dr Andrew Wakefield stated that the measles-mumps-rubella (MMR) vaccine caused autism. Although proven to be inaccurate and false by the English General Medical Counsel it initiated the conversation and debate surrounding vaccines and their influence on the cause of autism (Shroff and Fulghum-Bruce, 2022).

1.3. Rationale for research.

Currently there is a negative trend in the numbers of children being diagnosed with autism and developmental disabilities. Statistics on the prevalence of children living with childhood autism in the U.S show one in one hundred and ten in 2006, one in fourty-four in 2021 and one in thirty-six in 2023 (CDC, 2023). With the numbers of children living with autism more than doubling from the first published figures, a deeper understanding into why this is occurring is needed through in-depth research all negative factors impacting the prevalence rate of autism in children will be examined. (Brisendine, 2017). Alongside this examination and analysis of current and past autism assessment procedures will take place. This research paper seeks to better understand how and why every identifiable negative factor is influencing case numbers. Quantitative secondary data will be examined in this review due to time limitations. Published experiences from parents of children with autism will be analysed (where appropriate) alongside research findings and better understand why there is an increase in the rate of child ASD.

1.4. Research question.

What are the factors negatively impacting the prevalence rate of children living with autism?

1.5. Research aim.

In the hope of preventing future cases, this research aims to examine the contributing factors on the increased prevalence rate of children living with autism.

1.6. Research objectives.

- Identify factors negatively impacting the prevalence rate of children living with autism.
- Review past and current autism testing procedures.
- Review all information and data.
- Make recommendations.

1.7. Chapter summary.

The public health issue of the increase in the prevalence rate of children living with autism was highlighted. Contributing factors to be examined were discussed alongside discussing the aims and objectives of this research. In the next chapter examination of ASD as a disorder and the associated implications will be examined in depth.

Chapter 2: Literature review.

2.1 Introduction to literature review.

In this chapter autism as a disorder will be defined alongside its associated implications. Due to the various neurodevelopmental disorders that now make up an autism (ASD) diagnosis, these individual disorders along with their symptoms will be examined and explanation given on the new classification of autism (ASD) and associated disorders. From this point onwards we will refer to autism as ASD as to its new classification (Autism Speaks, 2023).

2.2 Literature review.

2.2.1 Definition

ASD is a wide umbrella term that encompasses several conditions. Some conditions involve some degree of difficulty with social interaction and communication whilst others are characterised by an atypical set of behaviours and patterns of behaviour. Atypical behaviours can include a difficulty with transitions between activities, attention to detail, and unusual reactions to sensations (WHO, 2023).

DSM-4: Subcategories of Autism Spectrum Disorder, 1994.
In the Diagnostic and Statistical Manual of Mental Disorders (DSM-4), autism was classified by five different categories. The five categories were:

- Autism spectrum disorder.

ASD is a developmental disorder caused by brain differences. Some have a known cause of ASD such as a genetic condition, while others seem to have no known cause. Scientists believe there are several causes that work together to alter the normal patterns of development as individuals with ASD may act differently, communicate differently, interact differently, and learn differently from most people. Often, there is nothing about their appearance that makes them different from others other than their differing ability level. Some people may have more advanced conversation skills, while others may not be able to speak. Some people require a lot of support in their day-to-day lives, while others may be able to work and live without much support. Most symptoms of ASD start before age 3 and last for the entirety of a person's life, although they may improve with time. Some children develop ASD symptoms in the first year of life, while others may not develop symptoms until they are 24 months old or older. In addition, some children with ASD develop new skills and

milestones until they are 18-24 months old, after which they may not develop new skills or may have lost the skills they had (CDC, 2022).

- Asperger's Disorder.

Asperger's syndrome is a neurodevelopmental disorder that is sometimes classified as a form of ASD. Doctors sometimes describe Asperger's syndrome as a high-functioning type of ASD meaning its symptoms are less severe than other types of ASD (Ellis and Sheikh, 2023).

- Rett syndrome.

Rett syndrome is a neurodevelopmental disorder that affects both the brain and the nervous system. Most children with Rett Syndrome start off with normal growth and development then experience a period of growth delay (National Institute of Neurological Disorders and Stroke, 2023).

- Childhood Disintegrative Disorder.

Child Development Disorder (CDD) is a rare disorder characterized by delayed language, social, and motor development in children over the age of 3 years. Also known as Heller's syndrome or disintegrative psychosis, CDD was initially thought to be a purely medical disorder with identifiable medical causes. However after review, researchers found that there was no definitive medical or neurological cause for cases of CDD. Subsequently, CDD was added to the 4th edition of the DSM-IV in 1994. About 50% of children with CDD show an EG (Electroencephalogram) abnormality. An EG measures the electrical activity of the brain resulting from nerve transmission (Brain waves) and in some cases, CDD may be accompanied by seizures. Children born with CDD have a normal growth span of at least two years. This growth span includes language comprehension, speech, large and small muscle skills, and social skills. After this normal growth span, CDD children start to lose some of the skills they have learned. CDD typically begins between the ages of 3 and 4 but can occur at any age up to the age of 10 (American Psychiatric Association, 2013; Charan, 2021; Jaydeokar *et al*., 1997; Sadock *et al*., 2009).

- Pervasive Developmental Disorder- Not Otherwise Specified.

Pervasive Developmental Disorders (PDD), also known as ASD is characterised by delays in social and communication development. Symptoms may appear as early as the first year of life, although the typical onset is by the third year of life. (National Institute of Neurological Disorders and Stroke, 2023).

DSM-5: No Subcategories of Autism Spectrum Disorder, 2013.
In the 2013 edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), ASD became the sole classification for autism. With no subcategories in the DSM-5, a child with an existing diagnosis of Asperger's syndrome, Autistic disorder, or PPD would be considered to have ASD. The DSM-5 has three levels of ASD with the level a child is diagnosed at determined by the severity of their symptoms and level of support they require in their day-to-day life.

- Level 3 – requires a high amount of support in everyday life – severe autism.
- Level 2 – mid level support – mid level autism.
- Level 1 autism – minimal support needed – high functioning autism. (American Psychiatric Association, 2000; 2013).

2.2.2 Symptoms.

ASD is a developmental disorder that is caused by abnormalities in the brain causing individuals with ASD to have difficulties with social communication and interaction, limited or repetitive behaviours and/or limited interests. Those with ASD may have different methods of learning, movement, or attention making life very difficult (CDC, 2022). Symptoms of ASD may include:

- Restricted and/ or repetitive behaviours and/or Interests.
- Not responding to their name.
- Avoiding eye contact.
- Emotionally challenged.
- Becoming emotional if they dislike a taste, sound and/or smell.
- Repetitive movements
- Limited communication.
- Limited pretend play.
- Difficulty in routine change.
- Different modes of playing with toys and other objects (CDC, 2022; National Institute of Neurological Disorders and Stroke, 2023; NHS, 2022).

Children with ASD symptoms vary extensively. Some children do not speak at all, others speak in limited phrases or conversations, and some have a relatively average language development. Repetitive play skills and limited social skills are generally evident with

extreme responses to sensory information such as loud noises and lights commonplace (National Institute of Neurological Disorders and Stroke, 2023).

2.2.3 Cost.

From 1990 – 2019 the U.S reported 2 million new cases of ASD with a cost to the state of seven trillion dollars. In the next decade, at this current rate prevalence rate, there will be an additional 1 million cases of ASD culminating in an additional four trillion dollars in social costs. If this rate were to increase forecasters have predicted costs associated with ASD to reach fifteen trillion dollars by 2029 (Cakir *et al*., 2020). In the U.K providing support for children living with autism amounts to two point seven billion pounds each with lifetime costs estimated at just over a million pounds. Those with ASD without intellectual disability is estimated at just over seven hundred and fifty thousand pounds. (Knapp *et al*., 2009) and although the cost of ASD will vary from child to child due to differing factors but on average it will cost sixty thousand dollars per year to raise a child living with ASD (Zauderer, 2022).

2.2.4 Diagnosis and assessments.

Currently there are range of tools used to diagnose autism in the United Kingdom, the main being the ADOS (Autism Diagnostic Observation Schedule), the ADI-R (Autism Diagnostic Interview - Revised), 3Di (Developmental, Dimensional and Diagnostic Interview) and DISCO (Diagnostic Interview for Social and Communication Disorders) (The National Autistic Society, 2023). In the United States of America, the diagnosis tools slightly differ with the ADI-R and ADOS also utilised in ASD diagnosis with the addition of Childhood Autism Rating Scale (CARS) and the Gilliam Autism Rating Scale – Second Edition (GARS-2) (CDC, 2022). Alongside the above-mentioned diagnostic tools, the USA adheres to the standardized criteria supplied by the American Psychiatric Association's Diagnostic and Statistical Manual, Fifth Edition (DSM-VI) in diagnosing autism. The U.K uses the National Clinical Coding Standards ICD-10 5th Edition (2022). This review will use the DSM VI definition for ASD as this was the first diagnostic manual to make the classification change which was then followed by the ICD-10. To meet diagnostic criteria this criterion a child must have a "continuing inconsistencies in each of three areas of social communication and interaction plus at least two of four types of restricted, repetitive behaviours" (CDC, 2022; American Psychiatric Association, 2013).

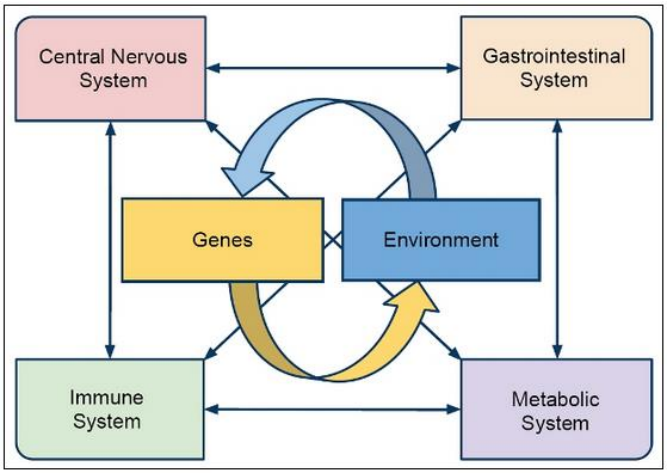
2.2.5 Prevalence.

Official worldwide statistics record one in every one hundred children currently living with ASD (Zeidan *et al*., 2022; WHO, 2023). This figure has been questioned by researchers and seemingly rubbished by a recent multi sex CDC ASD study with ages ranging from three to seventeen. They found one in six parents reported autistic tendencies in their children and sought to secure an autism diagnosis. Boys were also found to be four times more likely to place on the autistic spectrum then girls (CDC, 2022). Official U.S figures have one in thirty-six children not the estimated one in every one hundred reported with the U.K although reporting slightly better figures, still report higher than the estimated numbers with one in fifty-seven (CDC, 2023; Newcastle University, 2021).

2.2.6 Prognosis.

ASD's long-term outcome is difficult to determine as this will vary but regardless ASD is a lifelong condition that in one way or another will impact a person's life. The I.Q. of the child paired with the degree of social interaction impairment and appropriate communication early on are important prognostic factors. To accurately predict the long-term outcome of a child living with autism the progression made within the year of diagnosis will play an important role in assessing this. Utilising early interventions such as behavioural modification and speech therapy can assist in positive outcomes for children living with autism. The lower on the scale a child places will affect their outcome with those lower often living complete and fulfilling lives. Some of the comorbidities associated with autism such as anxiety, depression and obsessive-compulsive disorder may also negatively affect outcomes (Grossman, 2023).

2.2.7 Factors.



(Boston University, 2023).

The above diagram shows the relationship between the factors that influence ASD development. This visual representation highlights the complexities and intertwinement of ASD development and in chapter six discussion will take place on the many identified factors and their causes in an attempt understand their role independently and combined with other identified risk factors.

2.3 Chapter summary.

In this chapter examination has taken place of the developing issue of ASD as a disorder with its associated elements examined. In chapter 3 discussion will take place regarding the methodology used when obtaining relevant literature for this SLR.

Chapter 3: Methodology.

3.1 Introduction to chapter.

In this chapter discussion will take place about the methodology used in obtaining relevant literature for this SLR. A search strategy will be formulated with discussions and explanations had on the rationale and importance of the tools used in conducting these searches. The benefits of conducting systematic searches in ethically considered databases whilst utilizing keywords and synonyms will be explained combined with highlighting those used in the search for literature to be used in this review.

3.2 Systematic literature review.

Dewey and Drahota (2016) define a systematic literature review as a process that identifies, selects and critically evaluates research in the aim of answering a research question. Before any systematic literature review is undertaken, a clearly specified plan that encompasses criteria specifications is essential. Searches of multiple, relevant databases and grey literature will be undertaken in a manner that can be duplicated by other researchers. The systematic literature review seeks to answer a specific research question aided by a considered search strategy. The review determines the type of data to be searched, evaluated and reported within predetermined timelines. All search terms, searches and thresholds must be incorporated into the review (Charles Stuart University, 2023). Pittway (2008) specifies seven fundamental points underlying systematic literature reviews. Transparency, accessibility, coverage, clarity, integration, focus and equality.

3.3 Search strategy.

Before a final literature search commences, a search strategy must be developed to secure the relevant literature. A search strategy will consist of keywords, Boolean operators, synonyms, subject headings and limiters. This strategy and its results should be recorded throughout the search. Each database searched may require an individual strategy to ensure successful searches within them (Bramer *et al*., 2018). To assist in obtaining the relevant literature, the use of the PICO and PEO framework will be employed. Regularly utilised by health researchers, these frameworks allow for key theories to be highlighted to assist in the search for relevant literature as well as the structuring of the literature review.

- PICO

The PICO framework is adopted in research involving an interventions effectiveness by examining discrete and searchable aspects of a condition relating to a patient or population. It contains four main concepts.

1. Patients or population.
2. Intervention.
3. Comparisons.
4. Outcomes (City University of London, 2023; Colorado State University, 2023).

- PEO

Used as a tool to assist in investigative prognosis, condition development likelihood due to a pre-existing condition and/or exposure, the PEO framework is used predominantly in qualitative research and dissects the specified topic into three concepts.

1. Population.
2. Exposure.
3. Outcome (City University of London, 2023; Colorado State University, 2023).

3.4 Search terms.

Search terms allow key words that embody a specified research question to be entered into databases. Often contained in the abstract of an academic writing, they allow readers to quickly identify what an article will contain. Created from the research question, search terms also present researchers with specific words in which to search databases to find relevant literature on a chosen topic (Corrin *et al.,* 2022). Due the way search databases operate, searching for a research question will often yield poor or no results. Hence the need for a variety of search terms that contain all the relevant synonyms relating to that specific word. Ensuring all relevant synonyms are included ensures all searches conducted are as thorough as possible. (California State University Chico, 2023; Royal College of Nursing, 2023).

As discussed in 3.3 Search strategy, the PICO/PEO framework is adopted by health researchers to assist in the identification of related literature and the design of the literature review (Colorado State University, 2023). This systematic literature review will adopt the PEO framework due to the nature of the research question.

Table 1: PEO Framework

Population	Children
Exposure	Factors
Outcome	Autism

The PEO framework enables searches to be conducted in a clear and concise manner. Displayed In Table 1, the research question is categorised into the population effected, the exposure and outcome of said exposure. This allows for concise searches of relevant databases. Once identified, coupled with the relevant Boolean operators, the relevant searches can commence. Boolean Operators are simple words such as AND, *OR, NOT* or *AND NOT*. To maximise search results, they are used to combine or exclude keywords in searches (Alliant Libraries, 2023). Below are the keywords entered into the relevant databases paired with the applicable Boolean operators.

'Children *AND* factors *AND* autism'.

Search 1 (P) – Children.
Search 2 (E) – Factors.
Search 3 (O) – Autism.

3.5 Key words.

Keywords or search terms is the name given to the words that represent the research areas main theories and are entered into relevant database search engines. Failure to highlight and select the appropriate keywords can lead to a lack of the relevant information required. To identify the keywords needed, multiple searches may be required until the required search results are yielded. To obtain the best search results a three-step process should be followed.

1. Identification of the topic areas main theories.
2. Identifying relevant synonyms and antonyms.
3. Highlight abbreviations (California State University, 2023; Walden University, 2023).

To obtain the required literature for this review, the following search terms were used ‘Children *AND* autism *AND* factors’.

3.6 Databases.

Currently there are numerous health and social care databases that researchers can access to locate relevant literature. Whilst searches of one database may yield results, no singular database will provide complete comprehensive results (Betran *et al*., 2005; St George’s University of London, 2023). In a study on database searches and missed relevant studies by Ewald *et al.* (2022), they found that searches conducted over at least two separate search engines yielded the best results. These findings were backed up by another study by Bramer *et al*. (2017) in which they found that alongside searching the relevant databases according to subject area, Google Scholar is a beneficial addition to the usual area specific search engines. To obtain the relevant literature for this report searches of the Google Scholar and PubMed Central databases were conducted. These databases were selected due to literature being published being of an academic nature, credible and relevant to the subject area.

3.7 Inclusion/exclusion criteria.

To establish the confines of a systematic review, formulating an inclusion and exclusion criteria are essential. They are affected by a variety of factors but always established after a research question has been formulated. Contained in the methodology section of a systematic literature review, the criterion for each relevant category is explained. The criteria for inclusion and exclusion can be generalised by one or more of the following categories.

1. Study population.
2. Intervention.
3. Outcome variables.
4. Length of time.
5. Cultural and linguistic range.
6. Methodological quality (The University of Melbourne, 2023; The University of Texas, 2023; Meline, 2023).

3.7.1 Inclusion criteria.

- Studies involving children (under the age of eighteen) diagnosed with autism.
- Articles, journals, papers and studies from developed countries due to the similarities in diagnostic criteria.
- Articles, journals, papers and studies written within the last twenty years.
- Articles, journals, papers and studies from credible sources obtained from the databases specified in 3.6 Databases.
- Mixed method and quantitative studies.

3.7.2 Exclusion criteria.

- Studies involving those aged eighteen or over diagnosed with ASD.
- Children diagnosed with Rett syndrome as the condition has recently been removed from the ASD list (Hoffman and Bhandari, 2023).
- Articles, journals, papers and studies written pre-2003.
- Articles, journals, papers and studies from developing countries due to differing diagnostic and reporting procedure.

3.8 Search results.

A total of fourty five studies were used for this SLR. To obtain these studies a visual aid is contained in appendix 3. via a PRISMA flow chart. A PRISMA flow chart is a visual representation of the systematic process of screening irrelevant studies . The first step in the process being the recording the number of articles acquired through a search database. Secondly, all decisions made regarding the inclusion and exclusion of studies is presented with the number of articles included and excluded recorded at each stage (Macquarie University, 2023). To commence the search for this SLR, the search ‘children *AND* factors *AND* autism’ was entered into the PubMed database which produced ten thousand eight hundred and fifty-six results. In the first stage of the process, one hundred and ninety duplicate records were removed, one hundred and twenty-seven were marked as ineligible by automation tools and sixty-three were removed for other reasons. With the completion of this first stage, the remaining study results were then subject to extensive screening. Of the ten thousand four hundred and seventy-six remaining results, eight thousand nine hundred and eighty-five were excluded. These remaining studies were then subject to the final

screening stage as none were removed at either two previous stages (see appendix 3.). This final screening removed several studies for the following reasons:

- Reason 1 - Relevance to subject area (n = 964)
- Reason 2 – Country of publication (n = 312)
- Reason 3 – Low quality (n = 100)
- Reason 4 – Not RCT (n = 70)

This left a remaining fourty five studies to be used in the writing of this SLR.

3.9 Ethical considerations.

To protect the dignity, rights and welfare of research participants, research ethics is the name for the standards of conduct for researchers. Ethics committees review all research involving humans' participants to ensure these standards are being adhered to (WHO, 2023). Before this SLR commenced, an application for ethical approval was submitted to the University of Wales Trinity Saint David for review. All studies used in this report will be subject to the ethical considerations stated in the said application. Utilising academic databases will help somewhat in ensuring this but will be verified via this literature reviews author to confirm.

3.10 Chapter summary.

In this chapter, discussion has taken place regarding the tools used in searching for the relevant literature needed for this systematic literature review. The rationale of searches and their relevant databases was given alongside the role keywords and synonyms play when searching these databases. An inclusion and exclusion criteria were set to assist in obtaining the most appropriate ethically considered studies. In the following chapter discussion will take place on how data used in this systematic literature review will be evaluated.

Chapter 4: Data evaluation.

4.1 Introduction to chapter.

In this chapter the benefits that critical appraisal tools provide in the extraction and interpretation of data will be discussed. Examination of the chosen critical appraisal tools used in this review will take place alongside the findings these tools generated.

4.2 Brief introduction to critical appraisal and paper quality.

Every study published will have its own set of strengths and weaknesses and at times extracting the relevant data and correctly interpreting it can prove problematic. To address these issues critical appraisal tools provide the facilitation of the systematic examination of research to evaluate its creditability, value and relevance to the intended subject area. Critical appraisals allow researchers to:

- Reduce the amount of unnecessary information available.
- Identify the most pertinent papers.
- Distinguish evidence from preconceived notions, misinterpretation, and belief.
- Evaluate the accuracy of the study.
- Evaluate its usefulness and clinical relevance.
- Identify any potential biases (Mhaskar *et al*., 2009; Morrison, 2023).

4.3 Critical appraisal tools.

Critical appraisal is the systematic evaluation of research evidence to assess its reliability, worthiness and applicability in a specific situation. It enables clinicians to utilise research evidence in a reliable and effective manner. Critical appraisal tools provide analytical assessments of a study's quality, particularly the techniques used to reduce any potential biases in the research process. As these elements may have an impact on the outcome of the study and the interpretation of the findings, these tools are essential for researchers to determine if the results can be trusted and appropriately disseminated to other contexts, including policy, other research projects, education and clinical practice (Elwood, 2017; Katrak *et al.,* 2004; Mhaskar *et al*., 2009).

4.4 Evaluation of quantitative studies.

In 2007 Coughlan, Cronin and Ryan whilst scrutinising critical appraisal tools developed their own to address the shortcomings of the current models. They concluded that critical appraisal should be a process of analysing each phase of a research process. It is not a critique, but rather an objective assessment of research using a balanced and objective methodology. To effectively appraise quantitative research, Coughlan, Cronin and Ryan identified key questions that should be asked to determine whether or not it is credible, impartial and built on sound research (Coughlan *et al*., 2007). Contained in table 2 (see Appendix 1) is a list of the studies used in this report appraised using the Coughlan, Cronin and Ryan critical appraisal tool.

4.5 Chapter summary.

In this chapter discussion has taken place regarding the role critical appraisal tools play in reviewing research used for academic writing. Coughlan, Cronin, and Ryan's 2007 critical appraisal framework for was used as the tool for this SLR and was discussed alongside presenting the studies used in this research in its framework. The next chapter will discuss the role thematic analysis plays in data analysis and synthesis.

Chapter 5: Data analysis and synthesis.

5.1 Introduction to chapter.

This chapter will examine the role thematic analysis plays in data analysis and synthesis. The Braun and Clarke's thematic analysis method will be defined, and the relevant codes and themes found in this research presented alongside their relevance in answering the research question.

5.2 Thematic analysis.

Initially developed in the 1970's by Gerald Holton, thematic analysis (TA) in its simplest form provides a clear method for the identification and interpretation of patterns in qualitative data. In 2006 Victoria Clarke and Virginia Braun published a paper on the area of thematic analysis. Their analysis of thematic analysis concluded that alongside summarising data, an effective thematic analysis provides an interpretative story about said data in relation to answering a research question (Clarke and Braun, 2014; Merton, 1975).

5.3 Data analysis tool.

Since its inception in 2016, the Braun and Clarke's thematic analysis method has been seen as one of the most thorough methods of analysing research. The method has since been amended to address certain aspects of it that were not clearly defined and given the term 'reflexive thematic analysis' (Byrne, 2021; Braun and Clarke, 2019). Braun and Clarke's thematic analysis method is an iterative process consisting of six steps. An iterative process is a set of steps that you repeat continually refining with each cycle (Eby, 2019; Mihas, 2023). Braun and Clarke's thematic analysis method contains six steps:

- Familiarising the data – Continual reading cycles with each cycle generating further information to be extracted.
- Generate codes – Code generation refers to the process of writing codes for as many different topics as possible and then applying that code to a specific context segment, rather than just one phrase.
- Generate themes from the codes – Refers to sorting codes into higher-level topics.
- Review themes.
- Defining and naming themes.

- Identify patterns (Eby, 2019; Mihas, 2023).

5.4 Characteristics of the identified studies.

Of the fourty five studies included in this SLR, thirty four were from the U.S (Arora *et al*., 2017; DeVilbiss *et al*., 2017; Schmidt *et al*., 2012; Schmidt *et al*., 2017; Schmidt *et al*., 2019; Goodrich *et al*., 2018; Schmidt *et al*., 2011; Brown *et al*., 2018; Curtin *et al*., 2018; Brucato *et al*., 2017; Krakowiak *et al*., 2012; Volk *et al*., 2014; Jones and Water, 2019; Volk *et al*., 2011; Thurston, 2017; Ramirez-Celis, 2022; Ramirez-Celis, 2021; Wang and Qian, 2021; Campaign for Safer Cosmetics, 2023; Houlihan *et al*., 2002; Silva *et al*., 2004; Cowell *et al*., 2017; Heacock *et al*., 2016; Leonetti *et al*., 2016; Schecter *et al*., 2012; Rock *et al*., 2020; Poston and Saha, 2019; National Toxicology Program, 2014; Hertz-Picciotto and Delwiche, 2009; King and Bearman, 2009; Mazumdar *et al*., 2010; Liu *et al*., 2010; King *et al*., 2009 and Liu *et al*., 2010). Four were from China (Dong *et al*., 2020; Chen *et al*., 2023; Chen *et al*., 2018 and Wang *et al*., 2022). One from the United Arab Emirates (Eissa *et al*., 2018). One from Sweden (Saeedi *et al*., 2021). One from Australia (Mazumder *et al*., 2022). One from Denmark (Kapur and Seshiah, 2017) and two joint studies between the U.S and Italy (Campbell *et al*., 2007) and the U.S and Canada (Chun *et al*, 2020).

The remaining characteristics of the studies used in this SLR are displayed in the characteristics table contained in appendix 4.

5.5 Emerging themes and sub-themes from included studies.

Themes.

- Air pollution and ASD.

One study (Thurston, 2017) discusses the many health risk associated with air pollution with Volk *et al*. (2011) and Volk *et al*. (2016) both directly link air pollution with an increased risk of ASD. Volk *et al*. (2016) also named genotype MET rs1858830 CC as a hereditary risk factor that when coupled with air pollution further increases the risk of a child being born with ASD. However Chun *et al.* (2020) found not all types of air pollution increase the risk of ASD development with Goodrich *et al*. (2018) finding periconceptional FA intake can reduce the risk of ASD development regardless of air pollution levels.

- Hereditary influences and ASD.

Two studies (Campbell *et a*l., 2007 and Volk *et al*., 2016) directly name the gene MET rs1858830 CC as a hereditary risk factor for ASD. Two studies (Chen *et al*., 2023; Jones and Water, 2022) discuss how the maternal immune systems effectiveness influences ASD development. Chen *et al.* (2018) examines the numbers of overweight and/or obese pregnant women with (Kapur and Seshiah, 2017; Mazumder *et al*., 2022 and Saeedi *et al*., 2021) investigating the associated risk factor of diabetes and in particular GD in ASD development. Similarly Krakowiak *et al.* (2012) and Brucato *et al*. (2017) discuss how and/or if maternal physical health is an area for discussion in the development of ASD. Two studies (Ramirez-Celis *et al*., 2021 and Ramirez-Celis *et al*., 2022) discuss the issue of MAR ASD and its associated causes and effects. One study King *et al*. (2009) examines maternal ages effect on ASD development. Two studies (Eissa *et al*., 2018 and Liu *et al*., 2010) examine if the number of ASD cases are due de novo mutations occurring in children born to parents aged fourty and over. One study (Liu *et al*., 2010) discusses if the projected heritability of autism has been exaggerated.

- Chemicals and ASD.

Two studies (Arora *et al*., 2017 and Curtin *et al*., 2018) discuss how internal metal dysregulation increases ASD risk. With one study by Brown *et al*. (2018) examining insecticides and its contained chemicals effects on ASD development. Three studies (Campaign for Safer Cosmetics, 2023; Houlihan *et al*., 2002; Silva *et al*., 2004 and Wang, 2021) discuss how phthalates affect ASD development whilst five studies (Cowell *et al*., 2019; Dong *et al*., 2021; National Toxicology Program, 2014; Poston and Saha, 2019 and Rock *et al*., 2020) name and examine flame retardants chemicals ion their various forms and asses their role in the development of ASD.

- External factors

Three studies (Hertz-Picciotto and Delwiche, 2009; King and Bearman, 2009 and Rudacille, 2010) discuss the diagnosis criteria changes as a possible cause for the rise in ASD prevalence. With two studies (Liu *et al*., 2010 and Mazumdar *et al*., 2010) examining how and why ASD clusters exist within communities. One study (Liu *et al*., 2010) discusses how demographic change can yield genetic changes resulting in the development of ASD.

Sub-themes.

- F.A and ASD.

Three studies (Goodrich *et al*., 2018; Schmidt *et al*., 2012 and Schmidt *et al*., 2017) examine the role F.A has on the development of ASD as a stand-alone vitamin and when used to address a specific factor of ASD such as air pollution.

- Vitamins and ASD.

Three studies (DeVilbiss *et al*, 2017; Schmidt *et al*., 2011 and Schmidt *et al*., 2019) discuss the benefits using multivitamins periconceptional and during pregnancy can bring alongside reducing ASD occurrence in both normal and high-risk families. With one study (Wang *et al*., 2022) examining the role vitamin D deficiencies play in ASD development.

5.6 Chapter summary.

In this chapter data analysis and synthesis of the studies contained in this SLR has taken place. To achieve this Braun and Clarke's thematic analysis method was selected as a suitable method and as such themes and sub themes extracted from the studies included in this report were subject to this method of data analysis and synthesis. Themes and sub-themes were generated and displayed in their relevant sub chapters. In the following chapter discussion will take place regarding the themes and sub themes generated in this chapter.

Chapter 6: Discussion.

6.1 Discussion

6.1.1 Air pollution and ASD.

In recent years air quality has become such an issue, not only in reference to autism but to the general health conversation, that it has required the introduction of schemes such as clean air zones to combat the issue (Department for Environment, Food & Rural Affairs, 2023). The CDC (2022) found air pollution is mainly caused by six pollutants carbon monoxide, lead, nitrogen oxides, ground-level ozone, particulate matter and sulphur oxides. Carbon monoxide (C.O) is a colourless poisonous gas that can cause health issues is breathed in. It is commonly generated from the burning of gas, wood, coal and/or oil though fires or relevant applications (NHS, 2022). Nitrogen oxides (NOx) are a group of spontaneous gasses that enter the atmosphere through the burning of fuel, the major contributor to this pollutant being motor vehicles (United States Environmental Protection Agency, 2023). Ground-level ozone or tropospheric is a brief pollutant remaining in the atmosphere for hours and at most weeks. It is formed by natural sunlight interacting with volatile organic compounds (VOCs) created by human actions (Climate and clean air coalition, 2023). When researching 'VOCs' the definition supplied by the United States Environmental Protection Agency (2023) describes a compound that has high vapour pressure and low water. They then go on to add '*Many VOCs are human-made chemicals that are used and produced in the manufacture of paints, pharmaceuticals, and refrigerants. VOCs typically are industrial solvents, such as trichloroethylene; fuel oxygenates, such as methyl tert-butyl ether (MTBE); or by-products produced by chlorination in water treatment, such as chloroform. VOCs are often components of petroleum fuels, hydraulic fluids, paint thinners, and dry-cleaning agents. VOCs are common ground-water contaminants*' (United States Environmental Protection Agency, 2023). The two areas of concern noted in this description are VOCs being created as a by-product of chlorination in water treatment and their common place in ground- water contamination. Particulate matter is a combination of solid and liquid droplets formed either directly from a pollutant or because of various pollutants reacting with one another in the atmosphere. PM particles vary in size with ten micrometres considered the largest that can enter the human body causing heath concerns, illnesses and death from heart or lung disease. Both the EU and World Health Organization agree PM10 is PM less than ten micrometres in diameters with PM2.5 or fine PM less than 2.5 micrometres in diameter (European environment Agency, 2023). According to the World Health Organisation (2023) the most harmful of all PMs is PM2.5. Primarily formed as a by-product of the burning of fuels containing sulphur such as coal and/or oil, Sulphur oxides

exist in the atmosphere as primary gaseous SO2 or secondary particulate sulphate (ScienceDirect, 2023; Thurston, 2017). Lead although used for centuries in cables, paints and more notably metal water pipes and pesticides is one of four metals that are proven to have a detrimental effect on human health. Lead can enter the body through air, water and/or food and can be found in products such as fruit, vegetables, meats, grains, seafood, soft drinks, wine and cigarettes. Due to lead entering public drinking water through the corrosion of pipes, regular PH adjustments are required to ensure the safety and quality of public water (Lenntech, 2023). The link between air pollution and ASD was confirmed by a study conducted by Volk *et al*. (2011) in which they found that exposure to air pollution at a young age may be a risk factor for ASD. In this same study children born to mothers living near motorways were also found to be twice as likely to develop ASD. Air pollution combined with a genetic mutation in the gene MET again increases the risk of developing ASD. MET is a tyrosine-binding protein that, upon binding to its ligand (hepatocyte growth factor), activates a variety of cellular signalling pathways. These pathways are involved in proliferative, motile, migration and invasiveness (Organ *et al.,* 2011). A further study conducted by Campbell *et al*. (2007) investigating the link between MET and ASD confirms this direct link. With that being said a study by Chun *et al*. (2020) found that the blanket statement of air pollution being an exacerbating factor of ASD development is not appropriate. They found that *'there is some evidence for PM2.5, weak evidence for NO2 and little evidence for PM10 and ozone'*. Even though a blanket statement might not quite tell the whole story, air pollution still poses a risk. Considering all the factors associated with air pollution, questions must be asked as to the role lead plays in not only entering the body through air pollution but through ground water contamination, water treating processes and corroded pipes (Lenntech, 2023; United States Environmental Protection Agency, 2023). If lead is contained in a mother's food, water and air then lead must be considered to be one of the underlying aggravating factors in the increased prevalence rate of ASD.

6.1.2 Hereditary influences and ASD.

Prenatal conditions and hereditary influences both play a role in the development of ASD. Diseases and health concerns whilst pregnant such as diabetes and obesity have been found to have a direct link with ASD development (Brucato *et al*., 2017; Krakowiak *et al.*, 2012). The World Obesity Federation (2022) lists fourty percent of women worldwide as currently overweight or obese. Chen *et al*. (2018) examined the area of pregnancy and obesity in pregnant women through data supplied by World Health Organization, the World Bank and the Food and Agricultural Organization and found that in the year ending 2014 there were '*38.9 million overweight and obese pregnant women and 14.6 million obese*

pregnant women existed globally in 2014'. These figures coupled with over one hundred and ninety-nine million women living with diabetes present depressing prenatal situation (International Diabetes Federation, 2015; Kapur and Seshiah, 2017). Pregnancies create a variety of changes in the human body such as hormone fluctuations and weight gain and becoming pregnant whilst overweight or obese can promote an environment in where gestational diabetes becomes an issue. Gestational diabetes is developed by women who before their current pregnancy where not diabetes sufferers but due to changes in the body's hormone production become so. Although all pregnant women will have a level of insulin resistance during their final trimester, gestational diabetes It is caused by an insulin deficiency at the beginning of their pregnancy. Produced by the pancreas, insulin is the hormone responsible in allowing blood sugar into cells for the body to consume as energy (CDC, 2022). Although less common than type one or two diabetes, gestational diabetes still effects one in every twenty pregnancies in the U.K, over eight percent of all U.S pregnancies and over fourteen percent of worldwide pregnancies (CDC[1], 2023; CDC[2], 2023; Diabetes UK, 2023; Mazumder *et al*., 2022; Saeedi *et al*., 2021). Risk factors associated with gestational diabetes consist of:

- Obesity.
- Being a previous sufferer.
- Previous pregnancies with a large baby (4.5kg/10lb+).
- Familial history of diabetes.
- Being of South Asian, Black or African Caribbean or Middle Eastern descent.
- Aged over fourty and pregnant (Diabetes UK, 2023).

Obesity. not only a factor in gestational diabetes but proven to weaken immune function regardless of health eating and exercise habits (Deivert, 2013). In a study by Chen *et al.* (2023) they found that the number of children born with ASD was *'significantly higher among the offspring of mothers with autoimmune diseases*.' Pregnancy effects the way the human body would normally respond and as such is already in a state of immunocompromisation. Whilst not at a level of a person born with an immunodeficiency disease or chemotherapy patient the presence of a foetus in the human body presents it with its own internal challenges. A foetuses genetical makeup is from partly from another person and as such the body's immune system must try to adapt and facilitate the changes that are occurring. Due to these the body's reactions to infections changes (Miller and Ghazal, 2022; National Institute of Environmental Health Services, 2023). A relatively new phenotype of ASD has been discovered with maternal autoantibodies that identify proteins in the developing foetal

brain cited as the cause. This type of ASD has been termed maternal autoantibody related (MAR) ASD (Jones and Water, 2022). Autoantibodies are antibodies that mistakenly bind to self-proteins instead of foreign bodies. In MAR-ASD, autoantibodies cross the placenta and bind to targets in the developing brain, changing neuronal development. Due to the recency of the discovery of MAR-ASD data on this phenotype are limited and as such will need further research into the area. The Autism Research Institute (2023) have released figures for the U.S and report between eighteen and twenty six percent of all ASD cases are made up of this phenotype (Mind Institute, 2022). Tackling the problem of being overweight or obese prenatal and whilst pregnant seems to be the underlying issues raised here. Not only weakening the immune system, obesity is a major cause of diabetes with those not diabetic pre pregnancy having an increased risk having Gestational diabetes. As listed in the risk factors associated with gestational diabetes, being aged fourty and over and pregnant also increase the risk of ASD development. This area is complex in nature as the data on the subject has vast fluctuations. In 1992 the risk of being aged fourty and older and having a child with ASD had an eighty percent increase. Data assed after 1994 showed a decrease to between forty and fifty percent (Rudacille, 2010). Researchers attributed this risk to de novo mutations. A de novo mutation is a change in the genetic sequence that has not been inherited from their parents. De novo mutations are new mutations that have not been present in a family in previous generations (King and Bearman, 2009; UCL Institute of Ophthalmology, 2023). King and Bearman (2009) found evidence that these de novo mutations are caused by pathogenic mutations coming from older parents and their study examining twins and ASD this seem to confirm this. Their study assessed twins born between 1992 and 2000 and found genetically identical same sex identical twins faced increasing numbers of ASD whilst opposite-sex and fraternal twins saw their numbers decrease. They attributed de novo mutations to DNA in sperm or eggs as a contributing factor to the development of ASD.

6.1.3 Chemicals and ASD.

Chemicals have been found to play a significant role in the development of ASD. Bisphenol A, phthalates, flame retardants, and polychlorinated biphenyls are being investigated as specific causes of ASD. Current research has proven maternal exposure to insecticides during early pregnancy a cause of ASD development and many of the forementioned chemicals are contained within it (Brown *et al*., 2016; Lener *et al*., 2021; National Institute of Environmental Health Services, 2023). Due to the Stockholm Conventions ban on persistent organic pollutants, PCBs have been banned (unless covered by a specific case related exception) from since 2004 with all old sources of PCB having to be disposed of in an

environmentally responsible way manner by 2028. Due to this PCBs pose a limited threat to ASD development (Environment Agency and Department for Environment, Food and Rural Affairs, 2015; UN Environment Programme, 2023). Bisphenol A or BPA is predominantly found in the production of polycarbonate plastics. BPAs can be found in everyday items such as water bottles, windows and food storage boxes and in commercially produced items such as epoxy resins for food can coatings and water supply pipes. More often than not, BPAs enter the body through ingestion, but traces of BPAs can be found in the air, dust and drinking water. With that being said research has proven the majority of BPA exposure is through the food and drinks consumed. The use of BPA as a coating for water pipes, food storage boxes and bottles are particularly concerning as this chemical is known to leech into food and drink. When examining BPAs most common uses most examples are in a situation where the BPA will be heated as to heat the contents held inside. This becomes a further issue as the rate of leeching into food and drink is increased dependent on the temperature of the BPA and the contents held inside. With food storage containers and baby bottles being predominantly made using BPAs, examination of alternative available products must be examined (CDC, 2017; National Institute of Environmental Health Services, 2023). Referring to its function not chemical composition, fire retardants are a mixture of chemicals used since the 1970's to prevent or slow the natural burn patterns of fire. Due to the multiple combinations of flame retardants they are often grouped by chemical structure and/or properties to allow for easier identification (Houlihan *et al*., 2002). BFRs or brominated flame retardants are predominantly made up of the chemical bromine. It is used in electronics, furniture and building production. Whilst the formulation of BPRs has been replaced by newer less toxic combinations, both old and newer types of BPRs are proven to have toxic endocrine effects (Dong *et al.*, 2021; Leonetti *et al*., 2016). Used as an additive to BPRs, Hexabromocyclododecane or HBCD are found mainly in polystyrene foam building materials. As with BPRs, HBCDs are proven to be toxic and effects such as changes in the immune and reproductive systems, neurotoxic effects, and endocrine disruption have been seen (Schecter *et al*., 2012). OPFRs or organophosphate flame retardants are seen as a modern solution to traditional flame retardants. Also used widely in industry and textile and electronics production, these chemicals pose an increased risk to bone and brain health (Poston and Saha, 2019; Rock *et al*., 2020). Like PCBs, PBDEs or Polybrominated diphenyl ethers were phased out of production in 2004 but unlike PCBs products containing PBDE's are still in circulation. Due to PBDEs not binding with the products they are added to the level of exposure is increased as they can be easily released into the atmosphere. As with most of these types of chemicals, research has linked exposure to neurodevelopmental disorders (Poston and Saha, 2019). TBBPA or Tetrabromobisphenol A has a variety of applications. Found in paints, plastics, electronics and other flame retardants,

Tetrabromobisphenol A whilst not linked to ASD or any other neurological disorder, it has been found to cause cancer in rats and mice (National Institute of Environmental Health Services, 2023; NTP, 2014). Human exposure to flame retardants is usually through leeching into food, water and dust but can also be found in soil due to leeching due to manufacturing. In low-income countries the burning of electrical waste is also an issue, as this directly affects the environment and public health in multiple way (Heacock *et al*., 2016). Phthalates, although being widely used in everyday plastic products has been proven to have a detrimental effect of health on many levels. Despite having a relatively short half-lives in tissues, the effects chronic exposure has is damaging. Cases of failed pregnancies, stunted child development and growth and impaired reproductive systems have all being reported as symptoms of long-term chronic exposure to phthalates (Wang and Qian, 2021). Due to their similarities in chemical makeup, Phthalates are not only used in plastic production but in personal care products. For expectant mothers this is particularly concerning as dibutyl phthalate (DBP) is used in nail polish and is listed by the EU as an endocrine-disrupting compound of high concern, DBP is widely used in scented products to help the scent linger and Di-2-ethylhexylphthalate (DEHP) is found in eyelash glue (ECHA, 2023[1]; ECHA, 2023[2]; ECHA, 2023[3]). Women in general need to made aware the dangers phthalates pose not only potential and expectant mothers. Phthalates contained within cosmetic products are not always listed as an ingredient. In a study by Houlihan *et al.* (2002) they discovered phthalates in nearly three-fourths of the tested products with none of the seventy-two products listing so on their labels. This is a concern as consumers need to be able to make informed decision on the products and their associated risks involved. Phthalates do not break down easily and linger in the environment and body for a substantial amount of time (Cowell, 2019). So much so phthalates are often found in human urine samples. When the CDC (2013) examined two thousand four hundred and fifty samples they found DBPs in ninety nine percent of the samples. They surmised that this was due to the widespread use of fragrances and cosmetic products. More concerning was the levels found in women of colour attributed to the frequency, length of time and types of products used and promoted directly their communities (Archer *et al*., 2008; Chadwick *et al*., 2023; Silva *et al,* 2004; Malkan, 2007). Expectant mothers, regardless of colour must be aware of the chemicals they are exposing their bodies too and the potential effects they have on the risk of ASD development in their child.

6.1.5 Folic acid, vitamins and ASD.

Multivitamins play a vital role in the prevention of ASD and intellectual disability with Schmidt *et al.* (2011; 2019) conducting two separate studies into the area. In the first they found prenatal multivitamin intake during the first month of pregnancy can help reduce the likelihood of a further child being born with ASD in high-risk families (DeVilbiss *et al*, 2017). Multivitamins come in many shapes and forms such as pills and powders and are designed to help to fill the gap in a person's diet. Each multivitamin type and brand will have its own combination of vitamins and minerals (Sheikh and Painter, 2023). In the second study, they compared a group of expectant mothers subsidising their diets with multivitamin tablets with a placebo group. They determined that the risk of a child being born with ASD is reduced when a daily prenatal vitamin supplement is used three months before conception and a month during. More notably they added these effects were felt most in high-risk families due to genetic abnormalities (Schmidt *et al*., 2011; 2019). Natural chemical imbalances occurring within the body have also been proven to assist in the development of ASD. A study by Arora *et al*. (2017) examining twin baby's teeth (one with ASD, one without) to compare lead, manganese, and zinc levels found that the child born with ASD were deficient in essential metals manganese and zinc but had increased levels of the harmful metal lead. These types of chemical imbalances were also found in another study by Curtin *et al*. (2018) that found metal metabolism was disturbed in ASD cases due to disrupted zinc-copper cycles again highlighting the need for close monitoring of expectant mothers' vitamin and mineral levels. As previously stated, multivitamins are made up of different minerals and vitamins and when researchers examined these components singularly, new research has highlighted the role vitamin D may play in ASD development. Vitamin D is responsible for regulating calcium and phosphorus metabolism but also plays a leading role in foetal and early postnatal brain development. Research into the area is ongoing but early signs suggest that vitamin D deficiency may be a contributing factor in the development of ASD (Eissa *et al*., 2018; Wang *et al*., 2022). Another vitamin that is proven to reduce the risk of ASD is folic acid. Folic acid or vitamin B9 is an artificial form of the natural vitamin folate. It assists the body in red cell production and is found naturally in foods such as chickpeas, kidney bean and broccoli (NHS, 2020; NHS, 2023). Schmidt *et al*. (2012) conducted a study on the effects on folic acid as a prenatal vitamin and found that women who consumed the recommended daily dosage during the first month of their pregnancy reduced their risk of birthing a child with ASD. Building on that initial study Schmidt *et al*. (2017) and Goodrich *et al*. (2018) also found early pregnancy intake of folic acid not only reduced the risk of ASD on a whole but particularly in mothers that had been exposed to high levels of air pollutants and pesticides. Whilst the majority of the research supports the supplementation of vitamins, one study conducted by

the Johns Hopkins Bloomberg School of Public Health (2016) argues that whilst beneficial in recommended amounts to aid both mother and child, an excess of any vitamin can result in having the opposite intended effect. The research examined new mother's folate levels after birth and found that if a mother's levels are considered 'very high' or four times a normal amount the risk of her child developing ASD more than doubles. Alongside folate, an excess of vitamin B12 in expectant mothers can also be detrimental with the risk of her child being diagnosed with ASD tripling . An excess of both increases the risk of ASD development to almost eighteen times the normal rate. Whilst providing benefits to mothers suffering from deficiencies, due to both vitamins occurring naturally in fruit and in some countries such as the U.S added to foods to fortify them, if a woman is to use multivitamins at a time in her life where she may intend on becoming pregnant attention must be paid to folate levels as to ensure the correct levels are being consumed as not to enter a state of excess. Whilst examining the research on F.A, vitamins and ASD the only study that had any negative comment regarding F.A was the forementioned Johns Hopkins Bloomberg School of Public Health (2016) study. Due to this, critique on the area is limited and as such research should continue on vitamins relationship with ASD development, particularly F.A to ensure the findings of the study are the only identifiable risk.

6.1.7 Assessments, political and social factors (external factors).

Not only a complex medical disorder, ASD is also a social and political hotbed. Social and political factors are not only helping to fuel the prevalence rate of ASD but effecting the allocation of appropriate treatment. Through the deinstitutionalisation movement, insurance legislation, data collection methods and assessment and diagnostic changes these external factors have a major influence not only on research but also treatments and diagnosis (Gerrard, 2022). Changes in ASD diagnosis has most certainly negatively impacted the prevalence rate of children living with an ASD diagnosis, with a study by King and Bearman (2009) adding further credibility to this argument. In the King and Bearman (2009) study titled, *Diagnostic change and the increased prevalence of autism*, they found that in 2009 one in four children diagnosed with ASD in California today would not have been diagnosed with ASD in 1993. The DSM or Diagnostic and Statistical Manual of Mental Disorders has experienced several changes regarding the diagnosis of ASD helping to negatively fuel the increase in numbers. The latest, the DSM-IV had three major changes to the diagnosis of ASD. The first change combined of autistic disorder, Asperger's disorder, childhood disintegrative disorder, and pervasive developmental disorder under the umbrella term of ASD. Secondly, qualitative impairments in social interaction, qualitative impairments in communication and restricted repetitive stereotyped patterns of behaviour were combined

and the final change was the streamlining and clarification within the social or communication area to assist in the diagnostic process (Leafwing Center, 2022). Due to these changes it was noted that caseloads increased by over twenty six percent as many sole diagnoses of mental retardation are now receiving joint diagnosis of mental retardation as well as ASD (King and Bearman, 2009). In the same year, 2009, Hertz-Picciotto and Delwiche (2009) conducted a study into the average age an ASD diagnosis. They compared the average age of an ASD diagnosis in 1992 and in the year 2000. They found that the average age fell from 5.9 years to 3.8 years respectively and accounted for a twenty four percent rise in ASD diagnosis. Clusters of ASD diagnosis have also been detected and flagged as an area for investigation. In the King and Bearman (2009) study they found children in West Hollywood and Northridge, northwest of downtown Los Angeles were four times more likely to be diagnosed with ASD than children in any other part of the U.S. They noted that one explanation may be due to the wealth of the families involved as the areas West Hollywood and Northridge are made up of predominately affluent white families (Mazumdar *et al.,* 2010). Another explanation could be the proximity effect. King and Bearman (2009) found that children living less than two hundred and fifty meters to a child diagnosed with ASD are fourty two percent more likely to be diagnosed with ASD than the average child. This risk decreases the more the distance increases with children living between two hundred and one and five hundred meters risk falling to twenty two percent (Liu *et al*., 2010). In this same study it was also discovered that when two children with similar symptoms living in different parts of the country were assessed for ASD, the child who lived near another child diagnosed with ASD had a higher likelihood of being diagnosed whilst the other was more likely to be diagnosed with mental retardation. This is most concerning when combined the note made regarding the race and affluency of those being correctly and misdiagnosed. Despite the proximity effect being strongest in younger children and less severe cases of the disorder it is still an area for further research as for younger children the earlier the diagnosis of ASD the sooner the appropriate actions can be taken to offer the relevant support(Rudacille, 2010).

6.2 Strengths and limitations.

Whilst researchers strive to ensure SLRs are transparent, accurate, replicable and free from bias care must be shown to ensure human error does not lead to misleading, harmful and/or biased being published (DistillerSR, 2023). This SLR has sought to seek the strongest evidence on the factors influencing the prevalence rate of children living with autism. Reliable sources of information have been retrieved to present valid arguments on the subject matter using transparent methods of information sourcing visible both in the studies

used and, in the information presented in this SLR. As with all SLRs the methods followed in achieving data are clearly catalogued as to allow fellow researchers an insight into how this was compiled for this review (Bullet-proof reading, 2019). Due to the attributes of a SLR, the risk of bias influencing the research used is almost eliminated as the studies included were not subjectively decided but a result of the processes followed during the relevant searches (Andrews, 2017; Aveyard, 2014). This SLR has summarised a variety of large bodies of evidence, extracting the relevant sections of information allowing simple reading in one publication (Murad *et al*., 2016). As with all SLR's, this SLR has both strengths and weaknesses. ASD is a complex disorder and as such data on the area and associated factors affecting the prevalence rate are constantly changing (Harish, 2020). Due to the nature of SLRs only published studies can be included into the research and as such new relevant theories and/or unpublished work on the area must be excluded which could lead to misinformation due to new findings (Müller *et al*., 2013). The complex, systematic processes that a SLR follows provides great structure and transparency but are also time consuming. Ideally due to its time-consuming nature there would be more than one researcher involved in this SLR to ensure its quality and add insight to the findings contained in other studies and SLRs. Whilst every effort has been taken to ensure this SLR is bias free, the addition of an additional researcher would be an additional benefit (Hagen-Zanker *et al*., 2011; Müller *et al*., 2013).

6.3 Chapter summary.

Using the themes and sub-themes generated in chapter five, this chapter examines the many complex factors negatively affecting the prevalence rate of children living with ASD. As discussed, these complex factors individually increase the risk of ASD development and in the next chapter discussion will take place on these factors as whole with recommendations given at the appropriate stages.

Chapter 7: Recommendations and conclusion.

7.1 Implications of findings.

In Hertz-Picciotto and Delwiche (2009) study's final notes, Hertz-Picciotto comments *"What is causing the increased prevalence, and what is causing autism? The answers are not necessarily overlapping".* Throughout chapter six discussion took place on the variety of risk factors identified to be contributing to the rate of ASD prevalence in children but these factors rarely occur on their own. For example if we take an average expectant mother. The World Population Review (2024) has her average age twenty-eight years old and whilst years away from fourty and as such removing the risk of de novo mutations found in later maternal ages, notes again are made about the increasing number of women having children aged fourty plus due to choosing their careers over motherhood until later in life (King and Nearman, 2009). Aged twenty-eight this expectant mother is over seventy percent more likely to live in an urban than rural area as such subject to higher than the recommended levels of air pollution (WHO, 2024). Although Chun *et al*. (2020) made findings showing not all six pollutants increase the risk of ASD development, exposure is still a risk and should still be highlighted as such. As with most women, this expectant mother will use one or more beauty products at any given time. The beauty industry is huge with the U.K spending seven billion pounds on nail polishes for DIY mani-pedis alone. With developed countries female populations spending up to two hundred and fifty pounds per annum on beauty products, information on the risks associated with use of these products on paternal health must be provided on products containing such chemicals (Hancock, 2023). The rise of social media has played a part in the increased usage of beauty products, this is an area of concern as women on lower incomes may seek to use low quality products to mirror what they see online. These are proven to contain more toxic chemicals such as phthalates than their more expensive counterparts (Duff, 2023; Martin, 2023). Already the risk of ASD development in her child is increased and even the water she drinks will further exacerbate this risk as it contains phthalates, lead, VOCs and BPAs due to water pipes coatings, water treatment and pipe corrosion. If the water she drinks and/or the milk fed to her child is contained in a plastic bottle this again increases her risk due to leeching (CDC, 2017; National Institute of Environmental Health Services, 2023; United States Environmental Protection Agency, 2023). The plastic containers used by many to store and heat up food pose a genuine risk due to leeching caused by the very process they are advertised as suitable for (Zanolli, 2020). Children's play toys are also an area of concern with ninety percent of all children toys being made from plastics (The World Counts, 2024). The toys she purchases for her child will be coated in one of the many flame retardants currently available presenting an ongoing risk to her child due to exploratory play involving the

chewing, sucking and biting of toys. This play can cause chemicals to enter the body through ingestion (NHS Greater Glasgow and Clyde, 2017). If these many factors have resulted in her child displaying symptoms associated with ASD, then a diagnosis can be influenced by several factors. Due to the changes in ASD diagnosis her child may have previously being diagnosed with either Asperger syndrome, pervasive developmental disorder-not otherwise specified (PDD-NOS) or childhood disintegrative disorder but now will fall under the umbrella term of ASD (Wright, 2013). Other children located in the near vicinity that have been diagnosed with ASD will also play a part in ASD diagnosis (Mazumdar *et al*, 2010). These multiple factors all play a part in ASD development and diagnosis. ASD development is a complex issue with multiple factors working negatively to help contribute to the disorder. It cannot be attributed to one factor but a result of them all (Sauer *et al*., 2021).

7.2 Recommendations for practice.

With the increase in ASD prevalence an ongoing global issue, women not only just expectant and current mothers need to be made aware of the risk factors that negatively influence ASD development in children. A health programme addressing the issue of ASD running in clinics and surgeries would help offer information on the area. Those involved in the programme would be girls aged between fourteen and sixteen (dependant on age of consent in the relevant country) and those aged fourty and over who plan on becoming pregnant. Girls aged between fourteen and sixteen were chosen due to this period being when they can legally become sexually active (country dependant) and as such pregnant. This age group is also when beauty habits are formed (Morris and Matta, 2023; Smith, 2014). Those aged fourty were chosen due to an increase in the numbers of pregnant women of this age group coupled with the risk of de novo mutations in the children they birth (Alonso-Gonzalez *et al*., 2018). The programme would offer vitamin supplementation with increased FA to all participants to reduce the risk of ASD to potential children born to them. Those enrolled in the programme that become pregnant would be subject to regular vitamin deficiency tests to ensure the issues found with an excess of foliate consumption do not become an issue (Johns Hopkins Bloomberg School of Public Health, 2016). With an increase in overweight pregnant women, current localised information regarding weight management will be given alongside highlighting the risks that being pregnant and overweight brings i.e. GD and/or maternal immune systems ineffectiveness leading to an increase in the risk of ASD development (Mayo Clinic, 2022; WHO, 2024; Zawadzka *et al*., 2021). One of the most important aspects of the programme will be the information given on chemicals. With one in three women never checking the ingredients contained in their

beauty products, awareness of the risks certain chemicals pose not only to themselves but their potential child will be highlighted (Selby and Pacheco, 2023). The risks of the use of plastics as food containers and bottles to feed their children will be emphasized as well as signposting to alternative options available providing less of a risk such as Borosilicate glass, stainless steel, silicone, and ceramic containers due to their heat resistant and non-leeching properties (Wondrwood, 2024; Goodmann, 2022).

7.3 Recommendations for future research.

ASD as a disorder will need continual research due to its complexities in development and increased prevalence rate. In this SLR five areas have been highlighted as specific areas for future research to address ASD development and diagnosis. They are the use of plastics, vitamin D, de novo mutations, diagnosis and MAR ASD. As discussed in chapter six, the use of plastics is a worldwide health issue not only in respects of ASD development but other health concerns (Gold, 2023). Further research is needed into finding affordable alternatives for food containers and liquid storage bottles particularly in baby feeding bottles. Currently eighty two percent of baby feeding bottles are made from plastics and although BPA's have been removed from bottles post 2004, their frequent heating poses a constant risk due to chemical leeching (Begum and Powell Key, 2023; Godoy, 2020). Alternatives such as Borosilicate glass are available but due to affordability and risk of breakage not a viable common option (Wondrwood, 2024). Research into the benefits vitamin D give in respects of ASD development is in its infancy. With limited research on the area and conflicting views, as with F.A it is important to understand its role as it may provide significant risk reduction but on the other hand an excess may result in other health complications (Hess, 2021; Wang *et al.,* 2022; WebMD, 2024). With first birth rates for women aged 40 and older having more than doubled in the past 30 years, further research in de novo mutations will be needed to ensure potential mothers in this age group are made aware of the risks in becoming pregnant (Alonso-Gonzalez *et al*., 2018). The diagnosis of ASD itself is not the identified issue but the cluster effect seen because of this. Further research is needed to examine if clusters are a result of an ASD assessor in an area willingness to diagnose, widespread misunderstandings in a particular assessment center of the criteria that must be met for an ASD diagnosis and/or if personal bias. MAR ASD is the final area this SLR will recommend for future research. As this phenotype of ASD is a recent discovery by researchers in the U.S there is limited data on this type of ASD worldwide. Research is needed in other countries to assess its prevalence and confirm identifiable causes .

7.4 Conclusion.

This SLR has sought to examine ASD as a disorder and the factors negatively effecting the prevalence rate. As discussed in chapter six, research into the area flagged air pollution, hereditary influences, chemicals, assessments and political and social factors as areas of concern. Each area flagged contains complex sub issues that are not easily solved. Beauty trends, technological advances and a worldwide reliance on plastics whilst on face value have no corelation to one another they all will have an impact on the prevalence rate of children diagnosed with ASD. The increasing pressures on women to have a career resulting in later maternal ages will continue to be an area of increasing risk and finding the balance between career and family planning will be essential in minimising this risk. F.A and potentially vitamin D were the two positives found during the research and a real onus must be on researchers to investigate vitamin D's risk reduction in regards to ASD in both a swift and extensive manner. With the prevalence rate of children living with ASD an ever-present issue constant research into the areas highlighted in this SLR will be vital in attempting to reverse that trend.

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Appendices.

Appendix 1 - Coughlan, Cronin, and Ryan 2007 framework for Quantitative studies.

Author	Arora *et al*., 2017.	Schmidt *et al*., 2019.	Campbell *et al*., 2007.	Schmidt *et al*., 2017.	DeVilbiss *et al*., 2017.	Schmidt *et al*., 2012.	Goodrich *et al*., 2018.	Schmidt *et al*., 2011.	Brown *et al*., 2018.	Curtin *et al*., 2018.	Brucato *et al*., 2017.	Krakowiak *et al*., 2012.	Volk *et al.,* 2014.	Jones and Water, 2019.	Volk *et al.,* 2011.
Purpose/ Research problem	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified
Logical consistency	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear
Literature review	Logically organi	Logically organi	Logically organi	Logically organi	Logically organi	Logically organi	Logically organi	Logically organi	Logically organi	Logically organi	Logically organi	Logically organi	Logically organi	Logically organi	Logically organi

	sed. Majority of the research from 2010-2017. Included primary research.	sed. Majority of the research from 2017-2018. Included primary research.	sed. Majority of the research from 2006-2007. Included primary research.	sed. Majority of the research from 2015-2017. Included primary research.	sed. Majority of the research from 1996-2007. Included primary research.	sed. Majority of the research from 2003-2009. Included primary research.	sed. Majority of the research from 2016-2017. Included primary research.	sed. Majority of the research from 2003-2009. Included primary research.	sed. Majority of the research from 1987-2005. Included primary research.	sed. Majority of the research from 2016-2018. Included primary research.	sed. Majority of the research from 2017. Included primary research.	sed. Majority of the research from 2003-2010. Included primary research.	sed. Majority of the research from 2004-2014. Included primary research.	sed. Majority of the research from 2018. Included primary research.	sed. Majority of the research from 2010-2013. Included primary research.
Aim/Objectives/Hypothesis	Identified and unambiguous. Consistent	Identified and unambiguous. Consistent	Identified and unambiguous. Consistent	Identified and unambiguous. Consistent	Identified and unambiguous. Consistent	Identified and unambiguous. Consistent	Identified and unambiguous. Consistent	Identified and unambiguous. Consistent	Identified and unambiguous. Consistent	Identified and unambiguous. Consistent	Identified and unambiguous. Consistent	Identified and unambiguous. Consistent	Identified and unambiguous. Consistent	Identified and unambiguous. Consistent	Identified and unambiguous. Consistent

	with the content of the literature review.	with the content of the literature review.	with the content of the literature review.	with the content of the literature review.	with the content of the literature review.	with the content of the literature review.	with the content of the literature review.	with the content of the literature review.	with the content of the literature review.	with the content of the literature review.	with the content of the literature review.	with the content of the literature review.	with the content of the literature review.	with the content of the literature review.	with the content of the literature review.
Data analysis/Results	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified

Coughlan, Cronin, and Ryan 2007 framework for Quantitative studies cont.

Author	Chun *et al*., 2020.	Thurston, 2017.	Ramirez-Celis *et al*., 2022.	Ramirez-Celis *et al*., 2021.	Wang and Qian, 2021.	Campaign for Safer Cosmetics, 2023.	Silva *et al*., 2004.	Kapur and Seshiah, 2017.	Cowell *et al*., 2019.	Leonetti *et al*., 2016.	Dong *et al*., 2021.	Rock *et al*., 2020.	Poston and Saha, 2019.	Chen *et al*., 2023.	National Toxicology Program, 2014.	Chen *et al*., 2018.
Purpose/ Research problem	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified
Logical consistency	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear
Literature review	Logically organ	Logically organ	Logically organ	Logically organ	Logically organ	Logically organ	Logically organ	Logically organ	Logically organ	Logically organ	Logically organ	Logically organ	Logically organ	Logically organ	Logically organ	Logically organ

	ised. Majority of the research from 2012-2014. Included primary and secondary research.	ised. Majority of the research from 2017. Included primary research.	ised. Majority of the research from 2000-2003. Included primary research.	ised. Majority of the research from 2020. Included primary research.	ised. Majority of the research from 2019-2020. Included primary research.	ised. Majority of the research from 2009-2022. Included primary research.	ised. Majority of the research from 1999-2000. Included primary research.	ised. Majority of the research from 2013-2016. Included secondary research.	ised. Majority of the research from 1998-2013. Included primary research.	ised. Majority of the research from 2010-2011. Included primary research.	ised. Majority of the research from 2020. Included primary research.	ised. Majority of the research from 2019. Included primary research.	ised. Majority of the research from 2018. Included secondary research.	ised. Majority of the research from 2004-2019. Included primary research.	ised. Majority of the research from 2005-2009. Included primary research.	ised. Majority of the research from 2005-2014. Included secondary research.
Aim/Objectives/Hypothesis	Identified and unambiguo	Identified and unambiguo	Identified and unambiguo	Identified and unambiguo	Identified and unambiguo	Identified and unambiguo	Identified and unambiguo	Identified and unambiguo	Identified and unambiguo	Identified and unambiguo	Identified and unambiguo	Identified and unambiguo	Identified and unambiguo	Identified and unambiguo	Identified and unambiguo	Identified and unambiguo

	us. Consistent with the content of the literature review.	us. Consistent with the content of the literature review.	us. Consistent with the content of the literature review.	us. Consistent with the content of the literature review.	us. Consistent with the content of the literature review.	us. Consistent with the content of the literature review.	us. Consistent with the content of the literature review.	us. Consistent with the content of the literature review.	us. Consistent with the content of the literature review.	us. Consistent with the content of the literature review.	us. Consistent with the content of the literature review.	us. Consistent with the content of the literature review.	us. Consistent with the content of the literature review.	us. Consistent with the content of the literature review.	us. Consistent with the content of the literature review.
Data analysis/Results	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified

Coughlan, Cronin, and Ryan 2007 framework for Quantitative studies cont.

Author	Wang *et al*., 2022.	Mazumder *et al*., 2022.	Eissa *et al*., 2018.	Saeedi *et al*., 2021.	Picciotto and Delwiche, 2009.	King and Bearman, 2009.	Mazumdar *et al*., 2010.	Liu *et al*., 2010.	King *et al*., 2009.	Liu *et al*., 2010.	Rudacille, 2010.
Purpose/ Research problem	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified	Clearly identified
Logical consistency	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear	Logically presented and clear
Literature review	Logically organised. Majority of the research from 2022. Included	Logically organised. Majority of the research from 2017-2018.	Logically organised. Majority of the research from 2018. Included	Logically organised. Majority of the research from 2010-2018.	Logically organised. Majority of the research from 1990-2006.	Logically organised. Majority of the research from 1992-2005.	Logically organised. Majority of the research from 1993-2001.	Logically organised. Majority of the research from 2000-2005.	Logically organised. Majority of the research from 1992-2000.	Logically organised. Majority of the research from 1992-2000.	Logically organised. Majority of the research from 1987-2003.

	primary and secondary research.	Included primary research.	secondary.	Included secondary research.	Included primary and secondary research.	Included primary research.	Included primary and secondary research.	Included primary research.	Included primary research.	Included primary research.	Included secondary research..
Aim/Objectives/ Hypothesis	Identified and unambiguous. Consistent with the content of the literature review.	Identified and unambiguous. Consistent with the content of the literature review.	Identified and unambiguous. Consistent with the content of the literature review.	Identified and unambiguous. Consistent with the content of the literature review.	Identified and unambiguous. Consistent with the content of the literature review.	Identified and unambiguous. Consistent with the content of the literature review.	Identified and unambiguous. Consistent with the content of the literature review.	Identified and unambiguous. Consistent with the content of the literature review.	Identified and unambiguous. Consistent with the content of the literature review.	Identified and unambiguous. Consistent with the content of the literature review.	Identified and unambiguous. Consistent with the content of the literature review.
Data analysis/Results	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified	Clear and identified

Appendix 2 – Themes table.

Themes	Articles where it was extracted	Sub-Themes	Articles where it was extracted
Air pollution	MET rs1858830 CC genotype and air pollutant exposure may interact to increase the risk of autism spectrum disorder (Volk *et al*., 2016). Living near a freeway was associated with autism. Examination of associations with measured air pollutants is needed (Volk *et al*., 2011). For positive association between maternal exposure to ambient air pollution and ASD in children, there is some evidence for PM2.5, weak evidence for NO2 and little evidence for PM10 and ozone. However, patterns in associations over trimesters were inconsistent among studies and among air pollutants (Chun *et al*., 2020).	Folic acid	Periconceptional folic acid may reduce ASD risk in those with inefficient folate metabolism (Schmidt *et al*., 2012). In this study population, associations between pesticide exposures and ASD were attenuated among those with high versus low FA intake during the first month of pregnancy (Schmidt *et al*., 2017). Mothers exposed to higher levels of air pollution during the first trimester of pregnancy and who reported low supplemental FA intake during the first pregnancy month were at a higher ASD risk

	Air pollution presents a difficult worldwide public health challenge because it is so widespread and is emitted by so many different types of sources. This pollution includes both gaseous and particle pollutants. These pollutants can originate as primary pollutants (those exhausted directly into the air by pollution sources) or as secondary pollutants (those formed in the atmosphere, largely from the primary pollutants). The primary pollutants include particulate matter (PM), which includes carbonaceous black soot, and gaseous pollutants, which include: sulfur oxides (such as sulfur dioxide, SO2), nitrogen oxides (such as nitric oxide, NO, and nitrogen dioxide,		compared to mothers exposed to lower levels of air pollution and who reported high first month FA intake. Our results suggest that periconceptional FA intake may reduce ASD risk in those with high prenatal air pollution exposure (Goodrich *et al*., 2018).

	NO2), and carbon oxides (such as carbon monoxide, CO, and carbon dioxide, CO2). Secondary air pollutants include gaseous ozone (a major component of photochemical smog) formed from nitrogen oxides and hydrocarbons, and particulate sulfate (e.g., sulfuric acid) and nitrate (e.g., ammonium nitrate) aerosols created in the atmosphere from sulfur and nitrogen oxide gases, respectively. Combustion and secondary particles are usually very small, too small to see individually with the human eye, and are usually less than 1 micrometer (mm) in diameter. By comparison, a human hair is roughly 70 mm in diameter. Such tiny particles are especially of health		

	concern because they tend to be more enriched in toxic compounds, and because they can also penetrate deeper into the lung than the larger PM generated by natural processes (such as windblown soil particles) (Thurston, 2017).		
Hereditary influences	Multiple genes contribute to autism spectrum disorder (ASD) susceptibility. One particularly promising candidate is the MET gene, which encodes a receptor tyrosine kinase that mediates hepatocyte growth factor (HGF) signalling in brain circuit formation, immune function, and gastrointestinal repair (Campbell *et al*., 2007).	Vitamins	Maternal multivitamin supplementation during pregnancy may be inversely associated with ASD with intellectual disability in offspring (DeVilbiss *et al*, 2017). Periconceptional use of prenatal vitamins may reduce the risk of having children with autism, especially for genetically susceptible

	We found that having the flu or genitourinary tract infections during pregnancy is not related to the child being diagnosed with ASD. However, we did find children were at increased risk for ASD when their mothers had a fever during pregnancy (Brucato *et al*., 2017). Maternal MCs may be broadly associated with neurodevelopmental problems in children. With obesity rising steadily, these results appear to raise serious public health concerns (Krakowiak *et* al., 2012). One potential etiologic pathway through which the maternal immune system can interfere with neurodevelopment is through maternal autoantibodies that recognize proteins in the developing foetal brain. This mechanism of pathogenesis is now thought to lead to a sub phenotype of ASD that has		mothers and children (Schmidt *et al*., 2011). Maternal prenatal vitamin intake during the first month of pregnancy may reduce ASD recurrence in siblings of children with ASD in high-risk families (Schmidt *et al*., 2019). The pathogenesis of ASD is considered to be the interaction of genetic and environmental factors. There is increasing evidence that vitamin D deficiency in pregnancy and early childhood can lead to the occurrence of ASD (Wang *et al*., 2022).

	been termed maternal autoantibody related (MAR) ASD (Jones and Water, 2022). Maternal autoantibody-related ASD (MAR ASD) is a subtype of autism in which pathogenic maternal autoantibodies (IgG) cross the placenta, access the developing brain, and cause neurodevelopmental alterations and behaviors associated with autism in the exposed offspring (Ramirez-Celis *et al*., 2022). The incidence of autism spectrum disorder (ASD) has been rising, however ASD-risk biomarkers remain lacking. We previously identified the presence of maternal autoantibodies to fetal brain proteins specific to ASD, now termed maternal autoantibody-related (MAR) ASD. The current study aimed to create and validate a		

	serological assay to identify ASD-specific maternal autoantibody patterns of reactivity against eight previously identified proteins (CRMP1, CRMP2, GDA, NSE, LDHA, LDHB, STIP1, and YBOX) that are highly expressed in developing brain, and determine the relationship of these reactivity patterns with ASD outcome severity (Ramirez-Celis *et al*., 2021). There are currently over 199 million women living with diabetes, and this is projected to increase to 313 million by 2040. Diabetes is the ninth leading direct cause of death in women globally, causing 2.1 million deaths each year, most of them were pre-mature. The issue of women and diabetes is important for several reasons (Kapur and Seshiah, 2017).		

	Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders which cause long term social and behavior impairment, and its prevalence is on the rise. Studies about the association between maternal autoimmune diseases and offspring ASD have controversial results (Chen *et al*., 2023). We estimated that 38.9 million overweight and obese pregnant women and 14.6 million obese pregnant women existed globally in 2014. In upper middle income countries and lower middle income countries, there were sharp increases in the number of overweight and obese pregnant women (Chen *et al*., 2018). Gestational diabetes mellitus (GDM) has serious consequences for both maternal and neonatal health. The growing number of		

	noncommunicable diseases and related risk factors as well as the introduction of new World Health Organization (WHO) diagnostic criteria for GDM are likely to impact the GDM prevalence (Mazumder *et al*., 2022). Internationally, the prevalence of GDM varies from 1 to 28 %. Even if the same diagnostic criteria and screening method are applied, the prevalence of GDM varies depending on population characteristics such as age, ethnicity, overweight/obesity, lifestyle (physical activity, diet) and type 2 diabetes mellitus prevalence in the background population (Saeedi *et al*., 2021). Pooling data across multiple birth cohorts inflates the risk associated with paternal age. Analyses that do not suffer from problems produced		

	by pooling across birth cohorts demonstrated that advanced maternal age, rather than paternal age, may pose greater risk (King *et al*., 2009).		
Chemical influences. Folic acid. Vitamins.	Significant divergences are apparent in metal uptake between ASD cases and their control siblings, but only during discrete developmental periods. Cases have reduced uptake of essential elements manganese and zinc, and higher uptake of the neurotoxin lead. Manganese and lead are also correlated with ASD severity and autistic traits. Our study suggests that metal toxicant uptake and essential element deficiency during specific developmental windows increases ASD risk and severity, supporting the hypothesis of systemic elemental dysregulation in ASD (Arora *et al*., 2017).	External factors.	Autism incidence in children rose throughout the period. Cumulative incidence to 5 years of age per 10,000 births rose consistently from 6.2 for 1990 births to 42.5 for 2001 births. Age-specific incidence rates increased most steeply for 2- and 3-year olds. The proportion diagnosed by age 5 years increased only slightly, from 54% for 1990 births to 61% for 1996 births. Changing age at diagnosis can explain a 12% increase, and inclusion of milder cases, a 56% increase

	These findings provide the first biomarker-based evidence that maternal exposure to insecticides is associated with autism among offspring (Brown *et al*., 2018). These findings suggest that altered zinc-copper rhythmicity precedes the emergence of ASD, and quantitative biochemical measures of metal rhythmicity distinguish ASD cases from controls (Curtin *et al*., 2018). Phthalates are a series of widely used chemicals that demonstrate to be endocrine disruptors and are detrimental to human health. Phthalates can be found in most products that have contact with plastics during producing, packaging, or delivering. Despite the short half-lives in tissues, chronic exposure to phthalates will adversely influence the endocrine system and functioning of multiple organs, which		(Hertz-Picciotto and Delwiche, 2009). Changes in practices for diagnosing autism have had a substantial effect on autism caseloads, accounting for one-quarter of the observed increase in prevalence in California between 1992 and 2005 (King and Bearman, 2009). Children born in a primary cluster are at four times greater risk for autism than children living in other parts of the state. This is comparable to the difference between males and females and twice the risk estimated for maternal age over 40. In every year roughly 3% of the new caseload of autism in California arises from the

	has negative long-term impacts on the success of pregnancy, child growth and development, and reproductive systems in both young children and adolescents (Wang, 2021). Two are widely used in personal care products: 1) dibutyl phthalate (DBP) is used in nail polish, and is listed by the EU as an endocrine-disrupting compound of high concern. Some companies have phased DBP out of nail products. 2) DEP is widely used in scented products to help the scent linger, although it is rarely found on labels because it is a constituent of the ubiquitous ingredient “fragrance.” A third phthalate, Di-2-ethylhexylphthalate (DEHP) is found in eyelash glue, and is widely used in other consumer products.		primary cluster we identify-a small zone 20 km by 50 km. We identify a set of secondary clusters that support the existence of the primary clusters. The identification of robust spatial clusters indicates that autism does not arise from a global treatment and indicates that important drivers of increased autism prevalence are located at the local level (Mazumdar *et al*, 2010). Despite a plethora of studies, we do not know why autism incidence has increased rapidly over the past two decades. Using California data, this study shows that children living very close to a child previously diagnosed with autism are more likely to

	A significant loophole in federal law allows phthalates (and other chemicals) to be added to fragrances without disclosure to consumers. In field research, the Campaign for Safe Cosmetics only found phthalates listed as an ingredient in nail polish, but our 2002 report, Not Too Pretty, detected phthalates in nearly three-fourths of tested products. None of the 72 products tested had phthalates listed on the labels. Our 2008 follow-up testing found that phthalate levels had dropped in some – though not all – of the products tested previously in 2002 (Campaign for Safer Cosmetics, 2023). Major loopholes in federal law allow the $20-billion-a-year cosmetics industry to put unlimited amounts of phthalates into		be diagnosed with autism. An underlying social influence mechanism involving information diffusion drives this result, contributing to 16% of the increase in prevalence over 2000-2005 (Liu *et al*., 2010). By turning a social demographic lens on the historical patterning of concordance among twin pairs, we identify a central mechanism for this association: de novo mutations, which are deletions, insertions, and duplications of DNA in the germ cells that are not present in the parents' DNA. Along the way, we show that a demographic eye on the rising prevalence of autism leads to

	many personal care products with no required testing, no required monitoring of health effects, and no required labelling (Houlihan *et al*., 2002). We measured the urinary monoester metabolites of seven commonly used phthalates in approximately 2,540 samples collected from participants of the National Health and Nutrition Examination Survey (NHANES), 1999–2000, who were ≥ 6 years of age. We found detectable levels of metabolites monoethyl phthalate (MEP), monobutyl phthalate (MBP), monobenzyl phthalate (MBzP), and mono-(2-ethylhexyl) phthalate (MEHP) in > 75% of the samples, suggesting widespread exposure in the United States to diethyl phthalate, dibutyl phthalate or diisobutylphthalate, benzylbutyl		three major discoveries. First, the estimated heritability of autism has been dramatically overstated. Second, heritability estimates can change over remarkably short periods of time because of increases in germ cell mutations. Third, social demographic change can yield genetic changes that, at the population level, combine to contribute to the increased prevalence of autism (Liu *et al*., 2010). There is strong evidence that individuals who would have solely been diagnosed with mental retardation in the past now receive a dual diagnosis of mental retardation and autism (Rudacille, 2010).

	phthalate, and di-(2-ethylhexyl) phthalate, respectively. We infrequently detected monoisononyl phthalate, mono-cyclohexyl phthalate, and mono-n-octyl phthalate, suggesting that human exposures to di-isononyl phthalate, dioctylphthalate, and dicyclohexyl phthalate, respectively, are lower than those listed above, or the pathways, routes of exposure, or pharmacokinetic factors such as absorption, distribution, metabolism, and elimination are different. Non-Hispanic blacks had significantly higher concentrations of MEP than did Mexican Americans and non-Hispanic whites. Compared with adolescents and adults, children had significantly higher levels of MBP,		

	MBzP, and MEHP but had significantly lower concentrations of MEP. Females had significantly higher concentrations of MEP and MBzP than did males, but similar MEHP levels. Of particular interest, females of all ages had significantly higher concentrations of the reproductive toxicant MBP than did males of all ages; however, women of reproductive age (i.e., 20–39 years of age) had concentrations similar to adolescent girls and women ≥ 40 years of age. These population data on exposure to phthalates will serve an important role in public health by helping to set research priorities and by establishing a nationally representative baseline of exposure with which population levels can be compared (Silva *et al*., 2004)		

	Polybrominated diphenyl ethers (PBDEs) were used extensively as flame retardants in furniture containing polyurethane foam until they were phased out of use, beginning in 2004. We examined temporal changes in plasma PBDE concentrations from 1998 to 2013 and characterized patterns of exposure over the early lifecourse among 334 children (903 samples) between birth and 9 years. We examined time trends by regressing PBDE concentration on year of sample collection in age-adjusted models and characterized developmental trajectories using latent class growth analysis (LCGA). Controlling for age, BDE-47 concentrations decreased 5% (95% confidence interval (CI): -9, -2) per year between 1998 and 2013. When considering only postnatal samples,		

	this reduction strengthened to 13% (95% CI: -19, -9). Findings for BDE-99, 100 and 153 were similar, except that BDE-153 decreased to a lesser extent when both prenatal and postnatal samples were considered (-2%, 95% CI: -7, 0) (Cowell *et al*., 2019). These results suggest BFRs accumulate in the placenta and potentially alter TH function in a sex-specific manner, a possible mechanism to explain the sex-dependent impacts of environmental exposure on children's growth and development (Leonetti *et al*., 2016) Traditional brominated flame retardants (BFRs) negatively affect the environment and human health, especially in the sensitive (developing) nervous system. Considering the physicochemical similarities between novel		

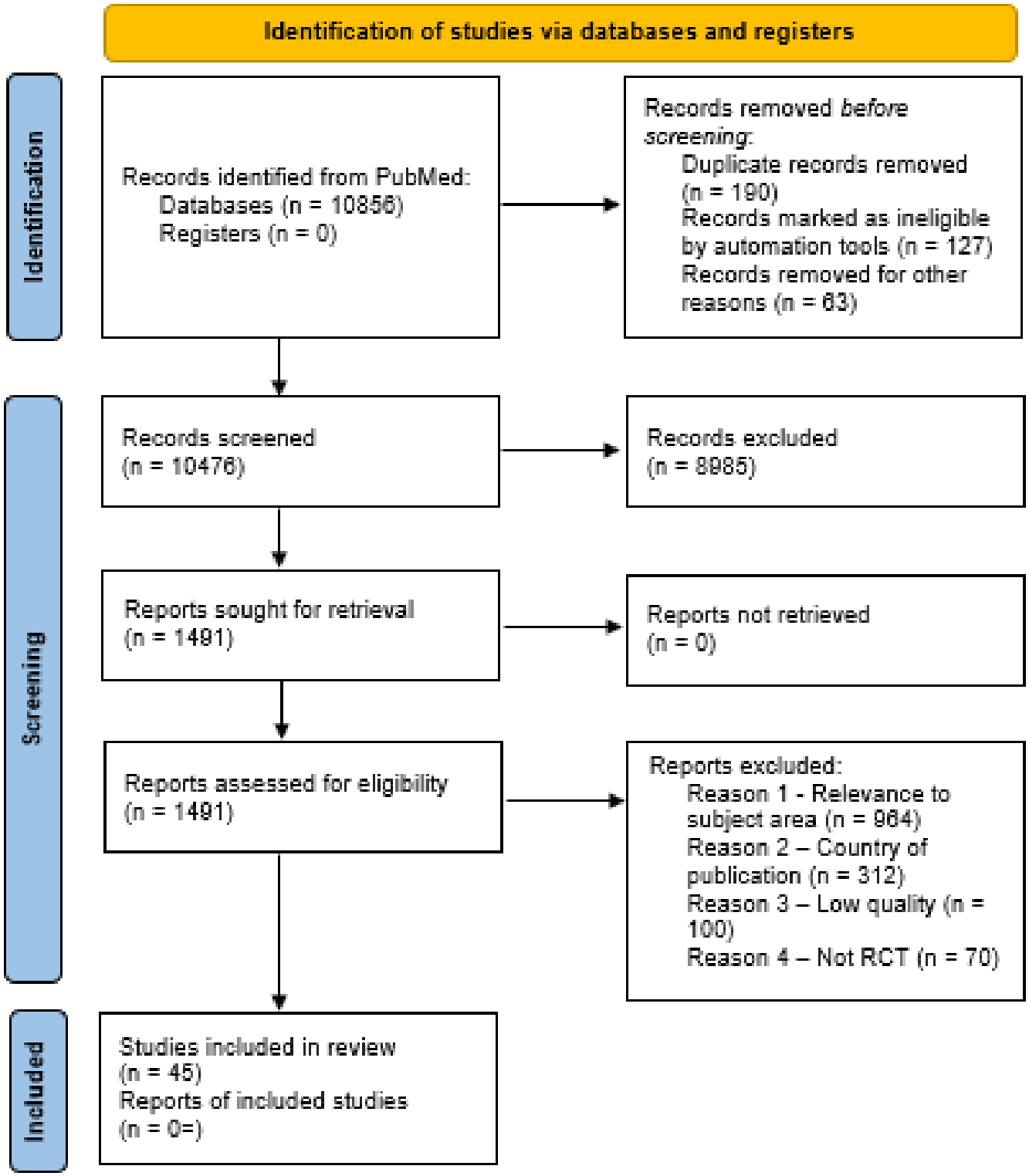
	brominated flame retardants (NBFRs) and BFRs, more and more evidence reveals the neurotoxic effects of NBFRs (Dong *et al*., 2021). These results suggest BFRs accumulate in the placenta and potentially alter TH function in a sex-specific manner, a possible mechanism to explain the sex-dependent impacts of environmental exposure on children's growth and development (Leonetti *et al*., 2016) Traditional brominated flame retardants (BFRs) negatively affect the environment and human health, especially in the sensitive (developing) nervous system. Considering the physicochemical similarities between novel brominated flame retardants (NBFRs) and BFRs, more and more evidence reveals the neurotoxic effects of NBFRs (Dong et al., 2021).		

	There is a growing need to understand the potential neurotoxicity of organophosphate flame retardants (OPFRs) and plasticizers because use and, consequently, human exposure, is rapidly expanding. We have previously shown in rats that developmental exposure to the commercial flame retardant mixture Firemaster 550 (FM 550), which contains OPFRs, results in sex-specific behavioral effects, and identified the placenta as a potential target of toxicity (Rock *et al.,* 2020). Disruption of epigenetic regulation by environmental toxins is an emerging area of focus for understanding the latter's impact on human health. Polybrominated diphenyl ethers (PBDEs), one such group of toxins, are an environmentally pervasive class of		

	brominated flame retardants that have been extensively used as coatings on a wide range of consumer products. Their environmental stability, propensity for bioaccumulation, and known links to adverse health effects have evoked extensive research to characterize underlying biological mechanisms of toxicity. Of particular concern is the growing body of evidence correlating human exposure levels to behavioral deficits related to neurodevelopmental disorders. The developing nervous system is particularly sensitive to influence by environmental signals, including dysregulation by toxins (Poston and Saha, 2019). Administration of tetrabromobisphenol A resulted in increased incidences of non-neoplastic		

	lesions of the uterus and ovary in female rats, the liver and kidney in male mice, and the forestomach in male and female mice (National Toxicology Program, 2014). Among the genetic causes, several chromosomal mutations including duplications or deletions could be possible causative factors of ASD. In addition, the biochemical basis suggests that several brain neurotransmitters, e.g., dopamine (DA), serotonin (5-HT), gamma-amino butyric acid (GABA), acetylcholine (ACh), glutamate (Glu) and histamine (HA) participate in the onset and progression of ASD (Eissa *et al*., 2018).		

Appendix 3 – PRISMA chart.



Appendix 4 – Characteristics table.

Author	Arora *et al*., 2017.	Schmidt *et al*., 2019.	Schmidt *et al*., 2017.	DeVilbiss *et al*., 2017.	Schmidt *et al*., 2012.	Goodrich *et al*., 2018.	Schmidt *et al*., 2011.	Brown *et al*., 2018.	Curtin *et al*., 2018.	Brucato *et al*., 2017.	Krakowiak *et al*., 2012.	Volk *et al.,* 2014.	Jones and Water, 2019.	Volk *et al.,* 2011.
Method	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative
Participants	32	637	516	273	834	606	707	778	n/a	1104	1004	408	n/a	563
Subject	n/a	Vitamins	F.A	Vitamins	F.A	F.A	Vitamins	Pesticides	Zinc and copper	Flu or fever	Diabetes, hypertension, and obesity	MET rs1858830 CC genotype and air pollutant	n/x	n/a
Outcomes	n/a	Maternal prena	Associations betwe	Maternal multivita	Periconceptional folic	Results suggest that	Periconceptional use of	Maternal expos	These findin	We found that	Maternal MCs may be broadly	MET rs1858830	This mechanism of	Living near a freew

		tal vitamin intake during the first month of pregnancy may reduce ASD recurrence in siblings of childr en with	en pesticide exposures and ASD were attenuated among those with high versus low FA intake during the first month	min supplementation during pregnancy may be inversely associated with ASD with intellectual disability in offspring.	acid may reduce ASD risk in those with inefficient folate metabolism.	periconceptional FA intake may reduce ASD risk in those with high prenatal air pollution exposure.	prenatal vitamins may reduce the risk of having children with autism, especially for genetically susceptible mothers and children	ure to insecticides is associated with autism among offspring	gs suggest that altered zinc-copper rhythmicity precedes the emergence of ASD, and quantitative biochemical	having the flu or genitourinary tract infections during pregnancy is not related to the child being diagnosed with ASD. However,	associated with neurodevelopmental problems in children.	CC genotype and air pollutant exposure may interact to increase the risk of autism spectrum disorder.	pathogenesis is now thought to lead to a subphenotype of ASD that has been termed maternal autoantibody related (MAR) ASD	ay was associated with autism. Examination of associations with measured air pollutants is needed.

		ASD in high-risk families.	of pregnancy.						measures of metal rhythmicity distinguish ASD cases from controls.	we did find children were at increased risk for ASD when their mothers had a fever during pregnancy.				

Characteristics table cont.

Author	Chun *et al*., 2020.	Wang and Qian, 2021.	Campaign for Safer Cosmetics, 2023.	Silva *et al*., 2004.	Kapur and Seshiah, 2017.	Cowell *et al*., 2019.	Leonetti *et al*., 2016.	Dong *et al*., 2021.	Rock *et al*., 2020.	Poston and Saha, 2019.	Chen *et al*., 2023.	National Toxicology Program, 2014.	Chen *et al*., 2018.
Method	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative
Participants	n/a	n/a	n/a	2540	n/a	334	95	n/a	n/a	n/a	104325	n/a	n/a
Subject	ASD and air pollution	n/a	Phthalates	Phthalates	Diabetes.	PBDE	BFR	BFR	OPFR	PBDE	Autoimmune disease	Tetrabromobisphenol A	Obesity
Outcomes	For positive association	Phthalates, as endocrine-disrupti		Of particular interest, females	There are currently over	When examining developmental	These results suggest BFRs accumu	Mechanistic studies have shown	These findings suggest that	review the current body of evidence for PBDE-	Mother with autoimmune diseas	Tetrabromobisphenol A was nominated by the	The number of overweight and

	betwe en mater nal expos ure to ambie nt air polluti on and ASD in childre n, there is some eviden ce for PM2.5 , weak eviden	ng chemic als and SVOCs, are detrime ntal to the reprodu ctive, neurolo gical, and develop mental system s of human from multiple exposur e		of all ages had significa ntly higher concent rations of the reprodu ctive toxicant MBP than did males of all ages; howeve r, women of reprodu ctive	199 million wome n living with diabet es, and this is projec ted to increa se to 313 million by 2040	period, PBDE concent rations peaked during toddler years for the majority of children , howeve r, our observa tion of several unique trajector ies suggest s that a	late in the placent a and potenti ally alter TH function in a sex-specific manner , a possibl e mecha nism to explain the sex-depend ent	that the impact of NBFRs is related to the comple x interact ion of neural and endocri ne signals . From disrupti ng the gender differen tiation of the	OPFR s have the potent ial to impact the 5-HTerg ic syste m in the fetal forebr ain by disrup ting placen tal trypto phan metab olism	induced epigenetic disruptions , including DNA methylatio n, chromatin dynamics, and non-coding RNA expression while discussing the potential relationshi p between PBDEs and neurodevel	e might be associ ated with increa sing the risk of autism spectr um disord er in offspri ng.	NIEHS for toxicity and carcinogeni city studies based on its high production volume, the potential for widespread human exposures, and the absence of standard toxicity and carcinogeni city studies reported in the scientific literature.	obese pregna nt women has increas ed in high income and middle income countrie s. Environ mental change s could lead to increas ed caloric supply

	ce for NO2 and little evidence for PM10 and ozone.	pathways.		age (i.e., 20-39 years of age) had concentrations similar to adolescent girls and women 40 years of age.		single measure may not accurately reflect exposure to PBDEs throughout early life	impacts of environmental exposure on children's growth and development.	brain, altering serum thyroid/sex hormone levels, gene/protein expression, and so on, to interfere with the feedback effect between differen		opmental disorders.			and decreased energy expenditure among women.

								t levels of the HPG/HPT axis					

Characteristics table cont.

Author	Wang *et al*., 2022.	Mazumder *et al*., 2022.	Eissa *et al*., 2018.	Saeedi *et al*., 2021.	King and Bearman, 2009.	Mazumdar *et al*., 2010.	Liu *et al*., 2010.	King *et al*., 2009.	Liu *et al*., 2010.	Rudacille, 2010.
Method	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative	Quantitative
Participants	n/a	n/a	n/a	136705	7003	272	n/a	n/a	n/a	n/a
Subject	Vitamins	ASD cluster	Chromosomal mutations	G.D	Diagnostic practices	GD	Social Demographic Change and Autism	Autism Risk and Older Reproductive Age	Social Influence	Social factors

Outcomes	Low vitamin D levels in utero, postnatal, and in early childhood have been hypothesized to be a risk factor for neurodevelopmental disorders, particularly ASD. Animal and human cellular, biological, and physiologic studies have provided compelling evidence for numerous roles of vitamin D in	We identify a set of secondary clusters that support the existence of the primary clusters. The identification of robust spatial clusters indicates that autism does not arise	It is motivating that numerous genes identified so far in human ASD genetic studies generate several valuable transgenic ASD rodent models, which display both ASD-like abnormalities in neuropathology as well as in	The IADPSG criteria increase the prevalence of GDM, but allow movement towards more homogeneity.	Using the probability of change between 1992 and 2005 to generalize to the population with autism, it is estimated that 26.4% (95% CI 16.25–36.48) of the increase	Our study demonstrates that the national prevalence of GDM is very high, which warrants immediate attention of policy makers, health practitioners, public health researchers, and the	social demographic change can yield genetic changes that, at the population level, combine to contribute to the increased prevalence of autism.	Pooling data across multiple birth cohorts inflates the risk associated with paternal age.	information diffusion simultaneously contributed to the increased prevalence, spatial clustering, and decreasing age of diagnosis.	There is good evidence that de novo mutations are a more important contributor to disease risk than we had assumed

	various body processes, some of which are involved in the pathobiology of ASD	from a global treatment and indicates that important drivers of increased autism prevalence are located at the local level.	behavioral phenotypic features. Moreover, several of the abnormalities involve the dysfunction of various neurotransmitter systems.		d autism caseload in California is uniquely associated with diagnostic change through a single pathway—individuals previously diagnosed with MR.	community				

Appendix 5 - Thesis Search Sheet.

My research question:	What are the factors negatively impacting the prevalence rate of children living with autism?
Places to search for information:	PubMed database

Date	Database / Search Engine Name	Search Terms	No of Results	Links to: title, aim, objective number?	Your Comments or notes
	PubMed	Children AND factors AND autism.	10,865	yes	N/a