A Systematic Review into the Association Between Maternal Hypothyroidism and Neurodevelopmental Disorders in Childhood

Submitted by William David Thompson to the University of Exeter as a thesis for the degree of

Master by Research in Medical Studies

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Signature………………………………………………..
Abstract

Background
In the previous 20 years, numerous studies have shown associations between maternal hypothyroidism during pregnancy and various types of neurodevelopmental disorders in children. However, other studies have not found significant associations and the field is complicated by differing definitions of hypothyroidism.

Aim
This systematic review aimed to collect all articles on this topic, both observational studies and RCTs, and where possible perform meta-analysis to find out the overall significance of a given association, with a particular focus on the outcomes of intellectual disability, autism and attention deficit hyperactivity disorder (ADHD) with the exposure as the three types of hypothyroidism (overt, subclinical and hypothyroxinaemia).

Method
This involved searching through MEDLINE, EMBASE, PSYCHINFO, CINAHL, AMED, BNI, Cochrane, Scopus and Web of Science, as well as grey literature searching and citation chasing. Articles were screened for inclusion by two reviewers, and data extraction and quality appraisal was carried out by the primary reviewer and checked by a secondary reviewer. Random-effects meta-analysis and narrative analysis were used.

Results
37 relevant articles were discovered and underwent data extraction. In total, we found that the association between indicators of intellectual disability and maternal hypothyroxinaemia was significant, with a combined odds ratio of 2.69 (1.47-4.95). However, we did not find an association between subclinical hypothyroidism and indicators of intellectual disability or with maternal hypothyroidism with autism and ADHD.
Conclusion
This study shows that the evidence supports the link between intellectual disability and maternal hypothyroxinaemia. Future studies should focus more on school age children and on autism and ADHD, and have larger cohorts.

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</tr>
<tr>
<td>AMED</td>
<td>Allied and Complementary Medicine Database</td>
</tr>
<tr>
<td>APoER2</td>
<td>Apolipoprotein E Receptor 2</td>
</tr>
<tr>
<td>ASD</td>
<td>Autistic Spectrum Disorder</td>
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<tr>
<td>BNI</td>
<td>British Nursing Index</td>
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<tr>
<td>Brief-P</td>
<td>Behaviour Rating Inventory of Executive Function-Preschool edition</td>
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<td>CBCL</td>
<td>Child Behaviour Checklist</td>
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<td>CINAHL</td>
<td>Cumulative Index to Nursing and Allied Health Literature</td>
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<tr>
<td>Cochrane</td>
<td>Cochrane Library</td>
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<tr>
<td>CRD</td>
<td>Centre for Reviews and Dissemination</td>
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<tr>
<td>DSM</td>
<td>Diagnostics and Statistics Manual</td>
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<td>EMBASE</td>
<td>Excerpta Medica Database</td>
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<td>fT₄</td>
<td>Free Thyroxine</td>
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<td>HcG</td>
<td>Human Chorionic Gonadotrophin</td>
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<td>ICD-10</td>
<td>International Classification of Diseases, 10th edition</td>
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<td>ID</td>
<td>Intellectual Disability</td>
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<td>IQ</td>
<td>Intelligence Quotient</td>
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<td>MEDLINE</td>
<td>Medical Literature Analysis and Retrieval System Online</td>
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<td>NDD</td>
<td>Neurodevelopmental Disorder</td>
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<tr>
<td>PICO</td>
<td>Population, Interventions/Exposures, Comparators and Outcomes</td>
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<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
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<tr>
<td>T₃</td>
<td>Triiodothyronine</td>
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<td>T₄</td>
<td>Thyroxine</td>
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<td>TBG</td>
<td>Thyroid Binding Globulin</td>
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<td>TSH</td>
<td>Thyroid Stimulating Hormone</td>
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<tr>
<td>tT₄</td>
<td>Total Thyroxine</td>
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<tr>
<td>VLDLR</td>
<td>Very Low Density Lipoprotein Receptor</td>
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Chapter 1: Introduction

It has been known since the 19th century\textsuperscript{1} that a severe lack of iodine (less than 50 µg a day in diet\textsuperscript{2}), the key component of thyroxine, during pregnancy and early childhood can result in the syndrome of cretinism, characterized by severe lack of development, as well as deafness. Whilst cretins are known to have TSH levels between 31\textsuperscript{2} and 150 mIU/l\textsuperscript{3}, most cretinism occurs in endemic “goitre belts” such as Central Africa, where the natural intake of iodine is less than 50µg (the US Institute of Medicine recommends an intake of 150µg for adults plus 220µg for pregnant women, the World Health Organisation recommends 250 µg for pregnant and lactating women)\textsuperscript{4}. The terms cretinism and congenital hypothyroidism are often used interchangeably, though there are some key differences. Congenital hypothyroidism, caused by a genetic inability of the fetus to produce thyroxine, is often less severe than cretinism caused by iodine deficiency, as the fetus can use thyroxine from the mother during development. At birth, further problems can be avoided by immediately treating the child with levothyroxine (congenital hypothyroidism is something that is routinely checked for)\textsuperscript{5}. Though hypothyroidism in young children is relatively rare in developed countries these days, hypothyroidism in adults, linked to advanced age and autoimmunity is much more common, with roughly 2% of the UK women having the condition\textsuperscript{6}. However, thyroid function changes in women during pregnancy, in part because thyroid-binding-globulin levels increase (reducing the detectable level of thyroxine)\textsuperscript{16}, possibly in order to transport more thyroxine to the placenta\textsuperscript{17}. As a result, the thresholds for hypothyroidism in non-pregnant individuals do not apply, and there is disagreement among physicians as to what thresholds to use in pregnancy (such as whether to diagnose hypothyroidism at TSH levels higher than 4.2 mIU/l or 2.5 mIU/l)\textsuperscript{16}. 
In recent years there has been increased concern in the literature that adult hypothyroidism during pregnancy could result in more mild forms of neurodevelopmental disorder in the child (relative to cretinism). A key article was published by Haddow et al in 1999 showing an association between maternal hypothyroidism and reduced IQ scores in the children, with an IQ difference of 7 points between the children of untreated hypothyroid mothers and euthyroid mothers\(^7\). Maternal hypothyroidism has been implicated in other neurodevelopmental disorders, for example Román et al in 2013 showed that children born to hypothyroid mothers (namely mothers hypothyroid between the 8\(^{th}\) and 12\(^{th}\) week of pregnancy) had a 4 times greater risk of developing autism than children born to euthyroid mothers\(^8\). Furthermore in 2004 Vermiglio et al found that in one cohort, 68.7% of children born to mothers with hypothyroxinaemia (due to living in a low iodine area) developed Attention Deficit Hyperactivity Disorder (ADHD), compared to 0% for mothers without the condition\(^9\). However, results have been conflicting, with Craig et al showing no significant difference in infant development between children born to euthyroid mothers and those born to mothers with hypothyroxinaemia\(^10\). Furthermore, Lazarus et al found no difference in IQ between those children whose mothers were treated for hypothyroidism (both subclinical and overt hypothyroidism) during pregnancy and those who weren’t\(^11\). Therefore, it is debatable whether mothers with milder forms of hypothyroidism (namely subclinical hypothyroidism and isolated hypothyroxinaemia, which often doesn’t present symptoms) should be treated with levothyroxine to reduce the incidence of Neurodevelopmental Disorders (NDD).

In the next section, the basic nature of human thyroid function will be discussed, and how thyroid homeostasis is different in pregnancy (and how hypothyroidism can affect pregnancy). The following section (page 19) will introduce the differing types of neurodevelopmental disorders, and relevant issues regarding their diagnosis and aetiology. This will be followed by an analysis of possible mechanisms by which maternal hypothyroidism could result in neurodevelopmental disorders (page 26) followed by a summary of the aims of this project (page 39).
Hypothyroidism and pregnancy

Thyroxine and Thyroid homeostasis

The Thyroid gland is a butterfly shaped organ found in the neck next to the trachea (i.e. windpipe). Thyroxine (T4) is a key hormone for speeding up the body’s metabolic rate (in part due to priming the body to respond to adrenaline\(^{12}\)) and is a key hormone for development, in particular the brain (in part due to promoting neuronal migration via the Reelin pathway \(^{13}\)). The active form of Thyroxine in the body is Triiodothyronine (T3). Most of the T\(_4\) and T\(_3\) is bound in plasma proteins, including Thyroid Binding Globulin (TBG)\(^{17}\) which keeps them inactive, hence the active hormones are unbound and referred to as free thyroxine (fT\(_4\)) and free Triiodothyronine (fT\(_3\)). Thyroxine is regulated via a negative feedback pathway, in which Thyroid Stimulating Hormone (TSH) from the pituitary gland (a small gland below the brain) stimulates the production of the active hormone fT\(_3\) and the inactive fT\(_4\) (which is converted to fT\(_3\) on site) in the thyroid gland, the fT\(_4\)/fT\(_3\) then inhibiting the production of TSH \(^{14}\). TSH is ultimately released from the pituitary gland due to the release of Thyrotropin Releasing Hormone (TRH) from the hypothalamus in the brain, which is released in response to low TSH. TRH is released in response to numerous other stimuli, including cold temperatures, as thyroxine raises the body temperature \(^{15}\) (see Figure 1 for more details).

Thyroid homeostasis in pregnancy

TSH is often suppressed during pregnancy, as Human Chorionic Gonadotrophin can also stimulate fT\(_4\) production, reciprocally suppressing TSH in the process \(^ {16}\). Furthermore increased levels of thyroid-binding-globulin (TBG) are released during pregnancy, making the measurement of T\(_4\) levels more difficult \(^ {16}\). It has been suggested that these changes during pregnancy are to help facilitate the transport of T\(_4\) to the placenta and on to the fetus \(^ {17}\). However, the placenta is also known to produce deiodinase enzymes to convert the T\(_4\) to inactive rT\(_3\) (reverse triiodothyronine) \(^ {18}\), hence the transport of iodine to the fetus may be more important. \(^ {17}\)

Forms of hypothyroidism

The symptoms of hypothyroidism include fatigue, weight gain without eating as much and sensitivity to the cold \(^ {19}\). There are three different recognised forms of
hypothyroidism, based on variations on the levels of both fT$_4$ and TSH. One form is overt hypothyroidism, which is characterised by low levels of fT$_4$ and, due to reduced negative feedback, increased TSH. This form of hypothyroidism is associated with full onset of the symptoms and doctors will treat this condition with levothyroxine$^{16}$. There is also the form of subclinical hypothyroidism, characterised by normal levels of fT$_4$ but elevated levels of TSH$^{16}$. There are often no visible symptoms of subclinical hypothyroidism$^{20}$, and treatment of this condition is not universally agreed upon$^{16}$ (though it is often treated during pregnancy), even though some studies have linked it to health problems, such as elevated cholesterol$^{21}$. Furthermore there is the form known as isolated hypothyroxinaemia, which occurs in pregnancy and is characterized by normal TSH but low levels of fT$_4$$^{16}$. A problem with all of these forms is that different researchers use differing definitions of what “low” fT$_4$ and “high” TSH levels mean. In an attempt to bring standardisation, the American Thyroid Association states that during pregnancy, low fT$_4$ is defined as levels below the 10$^{th}$ percentile average, and elevated TSH is defined as levels above 2.5 mIU/l in the first trimester and 3 mIU/l in the second and third trimesters$^{22}$.

**Causes of hypothyroidism**

There are many different ways that hypothyroidism can be caused, and different causes bring different levels of severity. Overt hypothyroidism is often associated with Hashimoto’s disease, also known as Autoimmune Thyroid Disease, in which the immune system attacks the thyroid gland$^{16}$. This involves a T-cell with an antigen for a thyroid protein being activated, stimulating the B-cells to secrete antibodies against thyroid proteins$^{23}$. This often occurs following a bout of thyroiditis, the inflammation of the thyroid gland. It is theorised that Hashimoto’s disease originates from the immune system attacking a thyroid protein that resembles a viral protein, though clear evidence is lacking$^{23}$. Thyroiditis can be brought about in many ways, the most common being postpartum thyroiditis, where a mothers immune system becomes hyperactive after being suppressed during pregnancy, allowing existing autoimmunity to become manifest$^{24}$.$^{25}$. It has been proposed that postpartum thyroiditis could result from an immune response to fetal cells that have migrated from the fetus to settle in the thyroid gland$^{23}$. Though often seen as a temporary phenomenon,
one study showed that in 64% of cases, postpartum thyroiditis lead to long term thyroid failure\textsuperscript{26}.

Thyroiditis can also be caused by infections to the thyroid gland, this includes subacute thyroiditis (characterised by pain in the thyroid) which is believed to be caused by enterovirus infection (due to the fact that it often follows respiratory infections and peaks in occurrence in the summer) \textsuperscript{21}. Another infection includes suppurative thyroiditis, characterized by long term bacterial, fungal or parasitic infections of the thyroid gland. This rarely happens as the thyroid is quite resistant to infection, hence suppurative thyroiditis is often associated with AIDS patients\textsuperscript{23}. Certain drugs are also known to cause thyroiditis\textsuperscript{23}, these include Amiodarone, which has a high iodine content, which can overload the thyroid gland, causing a Wolff-Chaikoff effect (where the thyroid blocks uptake of iodine), followed by an immune system attack\textsuperscript{27}. Other drugs that can cause thyroiditis include Lithium (used in mental health treatment) which can stimulate B-cell activity and inhibit thyroxine synthesis\textsuperscript{28} and Interferon alpha (used in Cancer treatment\textsuperscript{29}) by stimulating B-Cell activity\textsuperscript{25}.

Subclinical hypothyroidism can be caused by all the things that cause overt hypothyroidism, but to a reduced extent. In fact, subclinical hypothyroidism is known to progress to overt hypothyroidism in many cases \textsuperscript{21}. Subclinical hypothyroidism is also linked to old age\textsuperscript{30}; this may be linked to changes the immune system undergoes during aging. In particular, there are a group of B-cells (carrying the CD19+CD24hiCD38hi phenotype) that are able to suppress other B-cells and T-cells by secreting Interleukin-10. This group of B-Cells have been shown in one study to decrease with advanced age, and this decrease correlates with increasing autoimmune disease (in this study rheumatoid arthritis) \textsuperscript{31}. Furthermore, isolated hypothyroxinaemia is linked to iodine deficiency in the mother; however a firm cause of isolated hypothyroxinaemia is unknown\textsuperscript{32}.

**Hypothyroidism and Pregnancy Outcomes**

Hypothyroidism during pregnancy has been linked to numerous negative outcomes for both the mother and the child. Overt hypothyroidism is associated with an increased risk of miscarriage, pre-term delivery, pre-eclampsia, placental abruption, gestational hypertension, congestive heart failure, fetal
respiratory distress syndrome, increased need for caesarean section, low birthweight and neonatal death\textsuperscript{16}. Subclinical hypothyroidism is also associated with miscarriage and pre-term delivery, however only one study has shown levothyroxine treatment of subclinical hypothyroidism to reduce these phenomena \textsuperscript{16,33}. Considering the association between subclinical hypothyroidism and advanced age, this is relevant information for women having children at an older age or perimenopause. Isolated hypothyroxinaemia has been associated with increased risk of placental abruption, pre-term delivery and increased use of caesarean section\textsuperscript{32}, however most studies have not shown a risk associated with isolated hypothyroxinaemia and as such isn’t treated\textsuperscript{16}. Pre-term birth and miscarriage are both associated with the presence of thyroid autoantibodies regardless of whether the mothers showed signs of hypothyroidism, this possibly being linked to a general association between maternal autoimmunity and pre-term delivery/miscarriage, where the immune system initiates labour\textsuperscript{34}. Furthermore hypothyroidism could contribute to placental abruption by increasing the coagulation rate of the blood, reducing the oxygen reaching the placenta\textsuperscript{35}.

Overt hypothyroidism, sub-clinical hypothyroidism and isolated hypothyroxinaemia have all been associated with decreased IQ and behavioural problems in the offspring, which is the main focus of this thesis.
TRH from the brain stimulates the pituitary gland to release TSH, which stimulates the thyroid gland to release thyroid hormones (T3 and T4), which then represses TSH and TRH secretion in a negative feedback loop.

### Neurodevelopmental Disorders in Childhood

Neurodevelopmental disorders (NDD) are defined by Diagnostics and Statistics Manual 5 (DSM5) as “a group of conditions with onset in the developmental period [i.e. children]” going on to say, “The disorders typically manifest at
an early stage in development, often before the child enters grade school, and are characterized by developmental deficits that produce impairments of personal, social, academic, or occupational functioning” 37(p31). According to government figures, between 3 and 4% of UK children have an NDD, which are often co-morbid with each other and physical disabilities38. Furthermore, neurological studies often point to overlapping brain structure anomalies in NDD’s, namely a difficulty in forming long distance neuron connections within the brain39 40 41 42 43 44.

An editorial in 2012 by Michael J Owen proposed that all NDD are part of a continuum of brain dysfunction, ranging from neonatal death due to severe brain abnormalities up to mild behavioural difficulties. From this he suggested that all NDD’s share a common aetiology. This was based on the observation that intellectual disability is three to five times more prevalent in the schizophrenic population than the general population, and that numerous gene polymorphisms linked to schizophrenia are also linked to other psychiatric and neurodevelopmental conditions45.

Types of neurodevelopmental disorder

There are about 12 basic types of NDD that are currently recognised by DSM-V, with numerous subcategories37. Of key significance to this thesis are intellectual disability, autism spectrum disorders (ASD), language disorder, attention deficit hyperactivity disorder (ADHD), specific learning disorders such as dyslexia and dyscalculia, developmental coordination disorder (i.e. dyspraxia) and Tourettes Syndrome.

Intellectual disability, historically known as mental retardation (a term still used by ICD-1046), is characterised by severe deficits in abstract reasoning, resulting in difficulty living independently. DSM5 measures it in terms of adaptive function37; whilst ICD-10 identifies it by an IQ less than 70 (DSM5 also measures IQ, but sees it as less important than adaptive function). Intellectual disability often co-occurs with global developmental delay, the failure to meet key developmental milestones (such as walking, talking and toilet training) at the appropriate age, used on children younger than 5 years.
Autism spectrum disorders are characterized by deficits in social behaviour (such as a lack of reciprocity and understanding of non-verbal communication), delayed (or in some cases absent) language development and repetitive, restrictive behaviour. This is linked to Language Disorder, characterized by an inability to pick up language skills (like vocabulary and grammar) that is substantially below what is expected for their age and not explained by another condition i.e. deafness.

ADHD (also known as hyperkinetic disorder in ICD-10) is characterized by severe inattention (missing details, poor focus, losing things, not listening, failure to complete tasks etc.) combined with hyperactivity and impulsivity (fidgeting, inability to sit still, movement in inappropriate/dangerous contexts, excessive talking etc.) Symptoms have to be present before the age of twelve, and that the symptoms occur in two or more settings.

Specific learning disorders are difficulties in a specific academic skill over a period of six months despite interventions. This includes dyslexia (a specific disorder of reading and writing, characterized by reading words slowly and incorrectly) and dyscalculia (a specific disorder of arithmetic skills).

Developmental coordination disorder, or dyspraxia, is characterized by acquisition and executive control of motor functions (i.e. movement) that is substantially lower than what would be expected for that age (such as clumsiness and difficulty catching objects).

Tourettes syndrome is characterized by rapid, uncontrolled, non-rhythmic motor or vocal movements, which is similar to other stereotypic movement disorders, characterized by repetitive and seemingly purposeless movement.

**Overlap between neurodevelopmental disorders**
Increasing evidence suggests that the rate of co-morbidity between NDD is very high. In particular, studies suggest that between 28 and 53 percent of autism patients show ADHD symptoms depending on the population sample. This may seem strange, considering that autism and ADHD are often seen as opposite behavioural symptoms, with autism being an inability to shift focus and ADHD an inability to hold focus. However one study did show that many
children with ADHD have difficulty shifting focus in response to social cues\textsuperscript{47}, a trait shared with autism. It has also been suggested that hyperactivity could result in a child being less able to form stable relationships with peers, thus delaying social development, resulting in autistic like behaviour later in life\textsuperscript{48}. There is also an association between dyslexia and behavioural problems (one study found that 40% of children with ADHD also had reading difficulties) \textsuperscript{49}, and connections between childhood NDD and adult mental health, such as a link between autism and schizophrenia (some studies showing 34.8% of autistic patients having schizophrenia and 60% of schizophrenic patients having autism) \textsuperscript{50}. A key (though not only) link in this is intellectual disability, which is known to be highly comorbid with autism, ADHD and schizophrenia\textsuperscript{51}. It has recently been suggested that much of the increase in autism diagnosis in recent years is due to the reclassification of children with intellectual disability as autistic\textsuperscript{52}, though other researcher’s disagree\textsuperscript{53}. This level of overlap suggests that there are blurred boundaries between differing NDD, rather than the discrete categories they are often presented as. Therefore this study aims to look at all neurodevelopmental disorders mentioned in DSM5 and 4, as a possible aetiology in one NDD may apply to others.

Further evidence for a shared aetiology comes from the fact that there are shared brain structure abnormalities in these NDs. For one thing, corpus callosum abnormalities are observed in autism\textsuperscript{40}, ADHD\textsuperscript{41} and Tourettes syndrome\textsuperscript{44}, and hemisphere specific actions (hinting at a role of the corpus callosum in those processes) have been noted in language development\textsuperscript{39}, pragmatic language disorder (linked to autism)\textsuperscript{54} and dyslexia\textsuperscript{55}. Considering the role that the corpus callosum plays in the function of the brain, in terms of both coordinating movement on both sides of the body and allowing the reactive right hemisphere to influence the routine left hemisphere (more in the Mechanisms of Action section), it is not surprising that defects therein would be linked to NDD. An even more common abnormality found are frontal lobe abnormalities, observed in autism\textsuperscript{37}, ADHD\textsuperscript{38}, Tourettes\textsuperscript{44}, other motor stereotypies\textsuperscript{43}, developmental coordination disorder\textsuperscript{42} and dyslexia\textsuperscript{54}. The frontal lobe acts as the main regulator for the brain, activating other parts of the brain when needed and inhibiting parts when not needed. Therefore its underdevelopment is likely to cause multiple cognitive and emotional problems,
hence its role in many types of NDD. Both of these commonly found abnormalities could be linked to a decreased ability of the brain to form long distance connections within the brain. This could be linked to decreased myelination, abnormal neuronal migration (more in the Mechanisms of Action section) or differences in chemoattractant levels needed for axons and dendrites to locate each other\textsuperscript{56}. Therefore, it is easy to see how disruption to brain development at an early stage can lead to multiple behavioural characteristics (manifesting as multiple, overlapping NDD), hence separating NDD into discrete diagnosis may be a false dichotomy.

The overlapping nature of NDD could be exaggerated due to the methodologies used. For example it may represent a sampling bias, namely that the more severe patients of a type of NDD (in terms of both cognition and behaviour), who may be more likely to be comorbid, are possibly more likely to be brought to clinics, whilst less severe patients (who may be less comorbid) are more likely to be ignored\textsuperscript{48}. However, population based studies have also shown high levels of comorbidity\textsuperscript{49}, meaning the risk of sampling bias may be less significant.

It should also be pointed out that many of these studies are based on parental report of the symptoms of NDD. It is known that parental report can introduce bias into a study, as shown by evidence relating children’s sugar consumption and hyperactivity. Here it was shown that where mothers, who believed their children became hyperactive when consuming sugar, believed their child had consumed sugar (when in fact it was a placebo) reported more hyperactive behaviour than mothers who were told their child was given a placebo\textsuperscript{57}. This raises the possibility that over-concern on behalf of the parents could in turn result in over-diagnosis of patients with NDD, thus reducing the validity of the claim that NDDs overlap. At the same time, there are benefits to parental report, as parents may be able to observe behavioural trends that clinicians may miss, likewise clinicians may pick up traits that parents may miss\textsuperscript{58}.

All of this means that when investigating the link between maternal hypothyroidism and NDD’s, focussing on one diagnosis could result in much relevant information being lost, as it may be being investigated in an overlapping diagnosis instead. Hence for this project we are investigating all
neurodevelopmental disorders. Furthermore, if all NDD’s are found to be linked to maternal hypothyroidism, it would strengthen Owens claim that all NDD have a common aetiology and form less distinct categories as conventional psychiatry makes out.

**Mixed aetiology for autism**

Despite the evidence of a shared aetiology between multiple NDD, due to overlapping diagnosis and shared brain structure alterations, there is also evidence for a mixed aetiology for autism. Key evidence for this comes from the fact that single gene defects, like Fragile X and tuberous sclerosis, only account for 10% of autism cases. Other evidence for this comes from brain structure studies, where regions all across the brain have been implicated in autism, yet few have been implicated consistently (for a list of some key brain regions, see Figure 2). This suggests that the autistic population consists of patients with insults to differing regions of the brain, yet showing the same outward behavioural phenotype (speculatively because the brain regions are part of a shared brain network). Twin studies have indicated that autism is highly genetic, up to 80% genetic in one study; however a recent, larger population study found the genetic component to be closer to 50%. Twin studies only measure how much genetics accounts for the variability of a trait in a given population. This means that twin studies in different populations can produce different results, for example height is 80% genetic within the Western World but 65% genetic in developing countries, most likely owing to differing shared environmental conditions between the two populations. Even within a population, if a study says autism is 80% genetic, it could mean that for each individual it is 80% genetic and 20% environmental, or it could mean that for 80% of the autistic population it is entirely genetic whilst for 20% of the autistic population it is entirely environmental, or it could mean any mid-point between those two alternatives. This means there is still room for an environmental influence on autism to be measured, and indeed, environmental factors in autism have already been found.

This all means that if a link between maternal hypothyroidism and autism (or indeed any other NDD) is found, it may only explain a small percentage of the
overall population of patients, even if the phenomena cuts across multiple NDD categories. However, if the link is found in multiple NDD categories, this would still suggest a common aetiology, strengthening Owens position.

Figure 2: Names for different structures in the brain.

The Cerebrum is the outer layer of the brain, where most cognitive processes take place, the forward facing part of the cerebrum is known as the frontal lobe, which is key to cognitive and emotional control. The Corpus Callosum is a large nerve that connects the two hemispheres of the brain. The striatum is a component of the Basal Ganglia, which is key to motivation to movement. The Hippocampus is a key memory centre in the brain, particularly for verbal and spatial memory. The Cerebellum is key to voluntary movement and fine motor ability. Less relevant to this study, the thalamus relays signals within each hemisphere, the hypothalamus is key to endocrine control (such as TRH) and the Amygdala is key for emotional memory, particularly fear.64

Mechanisms of action for the association between maternal hypothyroidism and neurodevelopmental disorders

24
This section will review and discuss contemporary hypotheses on how hypothyroidism during pregnancy could impact brain development, and how the subsequent brain abnormalities could result in various NDD.

There are many ways that maternal hypothyroidism could result in NDD’s, most likely is the role thyroxine plays in promoting neuronal migration within the developing brain. FT₃ is believed to stimulate cells in the brain (namely Cajal-Retzius neurons in the cortex and granule cells in the cerebellum) to produce the protein Reelin. Reelin acts as a scaffold for radial glial cells (by helping them maintain their shape) which in turn act as a scaffold for neurons migrating from the inner brain to the outer brain⁶⁵. Reelin does this by inactivating Dab-1 (via ApoE and VLDL receptors), Dab-1 being an inhibitor of cell migration and filopodia formation⁶⁶ (for more details, see Figure 3). Linked to migration, fT₃ is more generally key in stimulating the production of the extracellular membrane, of which Reelin is part of. This includes stimulating the astrocytes to secrete many compounds, including laminin, fibronectin, basic fibroblast growth factor, epidermal growth factor and nerve growth factor (the growth factors stimulating further membrane protein secretion)⁶⁷. In the event of an absence of fT₃, this can result in a smaller cerebellum and a smaller cortex that is dense in grey matter⁶⁵, as the neurons are less able to form white matter connections due to being closer together.

As well as neuron migration, thyroxine is also key in neuron differentiation, stimulating asymmetric cell division in the radial glial cells into apical progenitors, which migrate upwards towards the ventricles, and basal progenitors, which migrate along the basement membrane, forming a layer of cells under the apical progenitors (basal progenitors are largely found in the telencephalon/cerebrum)⁶⁸.⁶⁹. This cell differentiation is possibly regulated by downregulating E2F-1 and Cyclin D1 whilst upregulating p27, all of these genes being linked to the cell cycle⁶⁷.

Thyroxine is thus key to both the migration of glutamatergic cells in the cortex⁶⁸ and to the differentiation of GABA-ergic cells in the cerebellum from Pax-2 precursor cells⁷₀.

The fetus begins producing thyroid hormone receptors during the 8th week of pregnancy, but the fetal thyroid gland is not active until the 12th week of
pregnancy. In that time the fetus is dependent on the thyroxine of the mother. This time period also correlates with the first arm movements a foetus makes, suggesting a key role in psychomotor development. Whilst the mother may provide the fetus with a source of fT₄, it seems likely that the fT₃ is produced in the foetus, probably within the brain itself, as the D2 enzyme is expressed in the fetal brain. The placenta also expresses the D3 enzyme to create inactive rT₃, whilst this is seen by some as evidence of maternal thyroxine’s unimportance in fetal development, it could simply be an attempt to prevent the fetus becoming hyperthyroid rather than blocking off maternal thyroxine altogether.

At later stages in pregnancy and childhood, thyroxine promotes the maturation of oligodendrocytes and stimulates them to produce myelin, allowing the white matter to become more efficient at sending signals within the brain. This later function is probably unconnected to maternal thyroid function; however it could be affected by iodine deficiency, which in pregnancy could be linked to maternal hypothyroxinaemia.

Given the role thyroxine (particularly maternal thyroxine) has in the developing brain, it does seem probable that maternal hypothyroidism would have a negative effect on the child’s brain development.

**Intellectual Disability and Psychomotor development**

The hippocampus is a brain structure required for the formation of long term memories, and is associated with verbal and spatial IQ. Though some studies link larger hippocampi to greater IQ (see Table 1), others associated smaller hippocampi to greater IQ, possibly due to increased dendritic pruning (removing unused brain connections so that used ones can be used more efficiently). The hippocampus is itself a part of the cortex, the outer layer of the cerebrum, the cerebrum being the most advanced (and largest) region of the brain, which controls voluntary movement in the body. Increased cortical thickness is associated with increased IQ in some studies, particularly in younger children (see Table 1). However, other studies have shown that increasing thinness of the cortex at different stages of development correlate more strongly with increased IQ, particularly in older children and adolescence. This can be linked to dendritic pruning.
The corpus callosum is also important in IQ (see Table 1), being the main nerve connecting the two hemispheres of the cerebrum (likely consisting of many smaller white matter connections). A larger corpus callosum is often associated with a higher IQ\(^8\) (especially spatial IQ); most likely because the increased hemispheric connection allows for the more specialized hemisphere in a given subject to be activated when appropriate (i.e. the left hemisphere for language processing) plus allowing both hemispheres to be used when faced with a challenging task\(^9\). However, one study (Ganjavi et al) disagrees with the association with larger corpus callosum volumes and IQ, showing that in boys under 12, a smaller corpus callosum was associated with increased IQ\(^10\). They suggest that this is due to a combination of more efficient use of a single hemisphere and dendritic pruning.

In 1999, Haddow et al found an association between maternal hypothyroidism and lowered IQ scores in the child (including scores below 85 IQ points)\(^7\). This may in part be linked to underdevelopment of the hippocampus in children born to hypothyroid mothers. Thyroxine is important in hippocampi development, mostly by stimulating the differentiation of hippocampal cells from dentate granule cells, this being achieved by upregulating the protein doublecortin\(^8\) (a microtubule linked protein). Cell migration is also important in the formation of connections within the hippocampus, thus nerve fibre malfunctions are observed in the hippocampi of hypothyroid rats, linked to increased expression of cell adhesion protein NCAM-180 (causing the cells to stick in place)\(^9\). Thyroxine plays a big role in promoting cell migration towards the cortex, allowing for the cortex to become thicker and for forming the layers of the cortex\(^6\). Thyroxine is important in the formation of the corpus callosum (as shown by many studies), largely because the formation of the corpus callosum is dependent on migrating glial, glutamatergic and GABA-ergic cells\(^8\). In fact, the first migration of cells begins between the 8\(^{th}\) and 12\(^{th}\) week of pregnancy (disruption at this point can result in corpus callosum agenesis)\(^8\), the same time when the fetus is dependent on maternal thyroxine.

As well as IQ, maternal hypothyroidism is also linked to delayed development of motor skills (or psychomotor development) in the children\(^8\). Much of this can be linked to the deficits in the corpus callosum, which is important in bimanual coordination\(^8\) (though individuals without the corpus callosum can find
compensatory mechanisms to achieve bimanual action\textsuperscript{90}). A much more important part of the brain for controlling movement is the cerebellum, which is linked to both fine motor skills and balance\textsuperscript{91} (see Table 1). However, much like with the corpus callosum, individuals lacking a cerebellum can find compensatory mechanisms to achieve motor performance, such as one individual who can ride a bicycle\textsuperscript{92}. Thyroxine is key to the development of the cerebellum, being important to the maturation of the Purkinje cells\textsuperscript{93} (the only output neurons in the cerebellum, thus centre of motor control\textsuperscript{94}) and to the migration of granule cells (a group of key input neurons\textsuperscript{95}), mostly through repression of the Thyroid receptor apha1\textsuperscript{96}. 
Table 1: Summary of relevant brain regions significantly linked to neurodevelopmental disorders

<table>
<thead>
<tr>
<th></th>
<th>Hippocampus</th>
<th>Cortex/Cerebrum</th>
<th>Corpus Callosum</th>
<th>Cerebellum</th>
<th>Enhanced Cortex-Subcortex connectivity</th>
<th>Decreased Frontal Lobe-striatum connectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual Disability (IQ)</td>
<td>Yes (decreased volume)</td>
<td>Yes (decreased volume)</td>
<td>Yes (decreased volume)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Autism</td>
<td>No</td>
<td>Yes (Increased Volume, increased density)</td>
<td>Yes (decreased volume)</td>
<td>Yes (decreased volume in parts)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>ADHD</td>
<td>No</td>
<td>No</td>
<td>Yes (decreased volume)</td>
<td>Yes (decreased volume in parts)</td>
<td>No</td>
<td>Yes (particularly in girls)</td>
</tr>
<tr>
<td>Developmental Motor Coordination</td>
<td>No</td>
<td>No</td>
<td>Yes (decreased volume)</td>
<td>Yes (decreased volume)</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Autism

At the time of writing, the most recent review on the brain structure and function in autistic spectrum disorders was published by Sungji Ha et al in 2015 in Experimental Neurobiology. It describes how autism seems to be characterised by rapid total brain growth during early stages of development, followed by a decline in growth (relative to typically developing brains) around 10 and 15 years of age. This growth is characterised by increased size of the cortex surface area (see Table 1), but not in thickness, a phenomena possibly caused by underdevelopment of white matter connections (causing the neurons to arrange themselves evenly and unconnected rather than tightly and connected). This suggestion is further supported by abnormalities in brain gyriﬁcation observed in autism, with increased gyriﬁcation in some brain areas (i.e. the frontal lobe) and decreased gyriﬁcation in others (i.e. the medial parieto-occipital cortices). The review also discussed white matter in autism, and the general association in autism with decreased long distance connections (i.e. inter-hemispheric) and increased short distance connections (i.e. striatal-cortical connections, see Table 1), though a few studies did find more general hyper-connectivity in ASD children.

Due to the cerebellums role in movement, it was believed to play a role in shifting attention from one object to another. An inability to do so would result in autism like symptoms, such as being focussed on a single area whilst being “disinterested” in others (see Table 1). However, more recent studies have suggested that the cerebellums role in attention seems to be entirely motor based, and thus irrelevant when discussing psychological behaviour. Nonetheless, the cerebellum has been implicated in other symptoms of autism, such as motor stereotypies, fine motor skills (a common deficit in autism) and language development (language in particular being linked to fine motor skills). However, most studies seem to link autism to a larger (rather than smaller) cerebellum, though the cerebellar vermals lobules are smaller. The cerebellar vermal lobules connect the cerebellum to the spinal cord (allowing the cerebellum to perceive movement of the body) and to the brain itself (allowing for conscious awareness of movement) and are linked to eye movement. Thus it is possible that the symptoms of autism could arise less from...
reduced ability to move due to the cerebellum entirely, but from reduced perception of movement due to the cerebellar vermal lobules.

Autism has also been associated with thickening of the cortex\textsuperscript{106}, though studies are conflicted\textsuperscript{107} (see Table 1). This could result in autism by increasing the density of grey matter in the cortex, making it difficult to form long distance white matter connections within the brain. This would result in decreased connections between the frontal and temporal lobes, weakening social behaviour, and decreased inter-hemispheric connections, affecting cognitive functions. Also it could result in increased short distance white matter connections within each hemisphere. This could include increased connections between the cortex and sub-cortical regions, resulting in motor stereotypies, and increased connections within the primary sensory cortex, altering sensory responses\textsuperscript{40}.

The role of cortex thickness is closely linked to that of the corpus callosum (see Table 1), which can be used as a marker of the amount of long distance white matter connections within the brain\textsuperscript{81}. Much like the cerebellum, the corpus callosum plays a key role in motor skills development, namely bimanual coordination\textsuperscript{89}, immediately linking it to autistic symptoms. In particular, the corpus callosum is important in learning new motor skills, whilst old skills are ingrained within the motor system (including the cerebellum). The corpus callosum is also important in directed gaze, by controlling the bimanual movement of the eyes\textsuperscript{108}. This is important in social behaviour, for recognising faces, emotions and in learning from other people, all things reduced in autism.

Outside of its role in motor control, the corpus callosum is also important in cognitive control. It is believed that the two hemispheres of the brain are specialized to performing differing tasks, namely that the left hemisphere is specialized for carrying out routine behaviour and the right hemisphere for responding to novel behaviour\textsuperscript{109}. Therefore, in the event of the corpus callosum being weakened, it is possible for one hemisphere to become too dominant, leading to autism like behaviour. For example, if the left hemisphere becomes too dominant, it could result in Asperger syndrome like behaviour, with language and writing skills functioning, but with the patient being unable to “break routine” (i.e. respond to novel stimuli) and with reduced sensory perception. On the other hand, if the right hemisphere becomes too dominant, it
could result in symptoms closer to dyslexia and classical autism, where many routine behaviours (including language and self-care functions) are highly underdeveloped or absent but with heightened sensory perception, possibly allowing some to have advanced visuospatial skills (such as drawing).

In 2013, Román et al linked maternal hypothyroidism to an increased risk of autistic spectrum disorders\textsuperscript{8}. This is possibly linked to deficits in the cerebellum, a part of the brain dependent on thyroxine and linked to autism. The thickening of the cortex associated with autism could result from decreased neuronal migration, causing the neurons to build up in one layer of the cortex rather than spreading to others, hence the role of thyroxine. Furthermore, hyperthyroidism is known to inhibit the proliferation of neural progenitor cells\textsuperscript{110}, hence hypothyroidism could result in an increase of such cells. Indeed, increased numbers of immature cells have been found in autopsies of autistic brains\textsuperscript{111}. However, congenital hypothyroidism is associated with a decrease in grey matter in the cortex rather than an increase\textsuperscript{112}. Other studies have associated congenital hypothyroidism with increased cortex thickening in some areas with cortex thinning in others, consistent with reduced neuronal migration\textsuperscript{113}. The corpus callosum is known to be smaller in both autism\textsuperscript{110} (agenesis of the corpus callosum results in autism like behaviour\textsuperscript{114}) and in maternal hypothyroidism\textsuperscript{115}. In fact, the main role of maternal hypothyroidism in autism could be reducing the size of the corpus callosum, thus reducing the bimanual coordination and cognitive control associated with the corpus callosum. However, the roles of cortical thickness and the cerebellar vermis are still relevant to the link between maternal hypothyroidism and autism.

**ADHD**

An underdeveloped cerebellum could contribute to ADHD symptoms in a similar way to how it could contribute to autism, which is by affecting attention, albeit preventing the patient from holding attention rather than shifting it. This may seem paradoxical, considering that holding attention and shifting attention are seen as opposite functions; however the same phenomena can be interpreted differently by whoever is carrying out the diagnosis. For example, if a child is gazing towards a window during lessons, one psychologist could claim they are unable to hold attention, thus cannot focus on the teacher, another psychologist may claim they are unable to shift
attention, and is heavily focussed on something outside or on the window. Furthermore, the cerebellar vermis is also reduced in ADHD\textsuperscript{116}, as it is in autism.

More generally, ADHD seems to be associated with decreased white matter volumes and thus reduced connectivity between different parts of the brain. As well as the frontal lobes and the cerebellum, this also includes the frontal lobe with the striatum and parietal lobe (linked to decreased motor control, see Table 1), within the “default mode network” (linked to inability to focus on a task) and between the two hemispheres i.e. reduced corpus callosum size\textsuperscript{41}. The corpus callosum itself could play a role in ADHD symptoms, both with its role in directed gaze\textsuperscript{108} (needed to hold attention) and that some of the symptoms of ADHD could be linked to increased right hemisphere activity\textsuperscript{109} i.e. responding more dramatically to novel stimuli, resulting in hyperactive behaviour.

A recent study showed that there is a brain structure difference in boys and girls with ADHD, with ADHD boys showing decreased white matter in the primary motor area, with ADHD girls showing increased white matter in the medial orbitofrontal cortex (part of the prefrontal cortex, see Table 1). Considering that girls are believed to mature faster than boys, and that posterior parts of the brain mature before anterior parts, it seems probable that girls would use the prefrontal cortex more than boys of the same age, hence the differing structures\textsuperscript{117}. The increased white matter measured in ADHD girl’s medial orbitofrontal cortex could reflect decreased branching of the white matter, forming thick cables that affect fewer areas of the brain. This study means that there are potentially differing aetiologies for ADHD in girls and boys.

In 2014 Päkkilä et al linked maternal TSH levels to ADHD\textsuperscript{118}. Furthermore, many studies have linked ADHD to decreased connectivity between the frontal lobe and the cerebellum\textsuperscript{41}, the cerebellum’s development being dependent on thyroxine. The deficit in white matter associated with ADHD could be linked to decreased neuronal migration, hence the role of thyroxine. However, unlike autism, cortex thickening and increased local connections of white matter don’t seem to play as big a role in ADHD (it isn’t mentioned in the main review on the topic\textsuperscript{41}). This hints at a possible mechanism for the differentiation of autism and ADHD in hypothyroidism. Namely, that autism may result from maternal hypothyroidism in an iodine sufficient context,
whilst ADHD could result from maternal hypothyroxaemia in an iodine deficient context. Speculatively in autism, whilst the fetus lacks maternal thyroxine during the critical 8 to 12 week period (resulting in reduced neuronal migration thus an underdeveloped corpus callosum), once its own thyroid gland is active, it can use its own thyroxine to develop novel white matter connections. By contrast in ADHD, due to the fetus’ own thyroxine defects due to iodine deficiency, the white matter network remains undeveloped. This would prevent the more autism typical behaviour (namely repetitive behaviour) from developing in ADHD, and links to the observation that ADHD brains are often less mature (as the white matter network is universally stunted).

Päkkilä et al found that in girls, elevated maternal TSH levels were more strongly associated with ADHD symptoms than low fT₄, with no association found for boys. They suggested the increased association in girls could hint at a separate mechanism for ADHD in girls compared to boys, boys being diagnosed 3 times as often. This is not surprising; the brain structure abnormalities in girls with ADHD could easily be brought about by a decrease in neuronal migration, hence the role of thyroxine. Furthermore, Ghassabian et al in 2011 found that elevated TSH levels in mothers, but not lowered fT₄ in mothers, was associated with increased externalising behaviour in children. They suggested the reason for this was because increased TSH levels were a better indicator of mild low thyroid function than directly measuring fT₄.

Confounding Factors

Whilst maternal thyroxine could be important in the development of intellectual disability, autism and ADHD, it is possible that there are confounding factors linked to hypothyroidism that are causing the phenomena described, rather than low thyroxine levels itself. One potential factor could be low socioeconomic status, which is associated with low iodine intake and hypothyroidism in developing countries, and to some extent in developed countries. Low socioeconomic status is linked to intellectual disability and to ADHD, however autism is linked to increased socioeconomic status. This could be accounted for by differing diagnostic trends linked to social sensibilities, for example an autism diagnosis carrying fewer stigmas than an intellectual disability diagnosis. Other studies have failed to show a link between socioeconomic status and autism.
Another confounding factor could be parental obesity, as hypothyroidism is commonly associated with obesity. Maternal obesity is associated with many neurodevelopmental impairments, including cognitive impairments, autism and ADHD. This link is further strengthened if the mother also has diabetes. Maternal obesity is believed to impact brain development largely through inflammation against the fetal brain.

A major confounding factor (especially in the case of autism) is the impact of autoimmune responses (including inflammation) against the fetal brain. Hypothyroidism is often caused by autoimmunity, and is often linked to other autoimmune diseases like type 1 diabetes. Autoimmunity (or more accurately, maternal immune attack) is widely believed to be associated with autism, with antibodies interacting with the fetal brain, in particular attacking the cerebellum. However, in a recent systematic review into the link between autism and autoimmunity, autoimmune hypothyroidism was the condition with the strongest link to autism. Thyroid autoantibodies have been linked to damage to white matter, which could contribute to symptoms of autism. Autoimmune disease has also been associated with ADHD and to intellectual disability via autism.

Hypothyroidism is also associated with advanced age, and autism is associated with advanced maternal age. Advanced age is believed to be linked to autism due to an increased mutation rate in the gametes, leading to alterations in the genes responsible for brain development. Advanced maternal age is also hypothesized to be linked to increased concentrations of neurotoxins in the mother. A recent systematic review found that ADHD was linked to younger parentage (itself linked to low socioeconomic status).

Another confounding factor is the role of Polycystic Ovarian Syndrome (PCOS), a condition found in between 5 and 10% of women of reproductive age, which is also linked to hypothyroidism. Autism has been controversially linked to increased fetal testosterone. As PCOS results in increased testosterone in the mother, it is therefore possible that it could then result in autism in the child. A major study in Sweden found such a link, with maternal PCOS increasing the odds of autism by 59%. Testosterone is believed to contribute to autism symptoms by increasing the overall size of the brain (hence the thickening of the cortex) whilst altering the
dendritic connections (hence the reduced size of the corpus callosum)\textsuperscript{139}. Prenatal testosterone has also been associated with increased externalising behaviour\textsuperscript{140}, though it has also been linked to increased development\textsuperscript{141}.

**Conclusion**

In summary, it seems that maternal hypothyroidism may contribute to intellectual disability, autism and ADHD in three overlapping ways. One is by reducing neuronal migration within the cortex, reducing the formation of the hippocampus (needed for long term memory formation) and reducing connectivity within the cortex. The other is by reducing the size of the corpus callosum (also by reduced neuronal migration), reducing the patients’ capacity for bimanual motor control, directed gaze and efficient cognitive control of the left and right hemispheres. The other is by reducing the size of the cerebellar vermis, reducing the patient’s ability to perceive and respond to movement, thus reducing their motor development and potentially their language and social development. Furthermore, differences between the three diagnostic criteria’s could emerge due to differences in the exposure to maternal hypothyroidism, with acute exposure resulting in autism and chronic exposure resulting in ADHD and intellectual disability. Therefore, maternal hypothyroidism could be a common aetiology for these three NDD (hence this review will focus on these three NDD), strengthening Owens hypothesis. Despite these possibilities, there are still potential confounding factors in the form of socio-economic status, parental obesity, maternal autoimmunity, parental age and PCOS.
Figure 3: Neuronal Migration and Reelin.

Part A shows the direction of neuronal migration within the brain; whilst part B shows the migrating neurons travelling up the glial cells. Part C shows how Reelin interacts with the Very Low Density Lipoprotein Receptor (VLDLR) and the Apolipoprotein E Receptor 2 (APoER2) to promote actin reformation and thus glial cell formation and neuronal migration.
Purpose of this Systematic Review

Though the Haddow\textsuperscript{7}, Román\textsuperscript{8} and Päkkilä\textsuperscript{118} studies have shown links between maternal hypothyroidism and NDD's, the evidence is inconsistent. For example, a study by Craig et al in 2012 showed no significant association between maternal hypothyroidism and cognitive development in infants after adjusting for confounders\textsuperscript{10}. Therefore there is a need to examine all the evidence on the topic to see if there is a pattern, and why deviations from that pattern occur.

At present, there are debates going on among clinicians on issues related to maternal hypothyroidism, in particular the issues on iodine supplementation\textsuperscript{144} and universal screening during pregnancy of thyroid disorders\textsuperscript{145}. At present, the UK is one of the few countries that do not fortify salt with iodine, despite some estimates that doing so could increase the average IQ by 1.22 points per child, saving up to £4495 per pregnancy in wider society\textsuperscript{144}. At the same time, there are potential risks to iodine consumption (i.e. the Wolf-Chaikoff effect\textsuperscript{27}), plus such a decision would have its own monetary costs. It has also been proposed that all pregnant women be screened for thyroid disorders (including hypothyroidism) and those found with elevated TSH levels be treated with levothyroxine\textsuperscript{145}. However, most cases of elevated TSH are subclinical hypothyroidism\textsuperscript{19}, and at what level of TSH elevation should be treated is disputed\textsuperscript{16}. Furthermore, some studies have found universal screening no more effective at reducing negative pregnancy outcomes than targeted screening\textsuperscript{33}, and whether levothyroxine treatment can prevent NDD has also been questioned\textsuperscript{11}.

This study thus aimed to search the literature on the link between hypothyroidism in the mother and neurodevelopmental disorders in the child, to see if the evidence for such an association is robust. If the link is robust, it would be strong evidence in favour of universal screening of thyroid disorders. This study also aimed to examine the association between maternal hypothyroidism and numerous NDD (in particular autism, ADHD and intellectual disability), as there is considerable comorbidity between NDDs and they may share a common pathway in development. There have been non-systematic reviews on the topic most recently by Amed in 2015\textsuperscript{146}. 
However this review mostly focussed on the synthesis and transport of thyroxine within the developing brain, with a particular focus on the MCT8 transporter, rather than the impact of maternal hypothyroidism. A more relevant recent review was by Rovet in 2014\textsuperscript{147}, which compared children born to hypothyroid mothers (HYPO) with children with congenital hypothyroidism (CH). Many differences were noticed, in particular that HYPO children have a somewhat less developed cortex whilst CH children have somewhat less developed cerebellums. Considering the link between cortex development and corpus callosum development\textsuperscript{81}, and how the corpus callosum is strongly linked to most NDDs, this observation supports the mechanisms reviewed above.

Furthermore a systematic review has been carried out on the link between maternal hypothyroidism and cognitive development by Wang et al in 2015\textsuperscript{148}. The review found a strong association, though it did find evidence of publication bias.

The current review aimed to search more databases (Wang et al\textsuperscript{148} only looked at Medline and Embase), and examine more neurodevelopmental outcomes (namely diagnosis of ND) and also analyse randomised controlled trials on the topic of whether levothyroxine treatment can prevent or reduce the severity of symptoms of NDD in children born to hypothyroid mothers, something that has not been done before. Wang et al\textsuperscript{148} can also be criticized for forcing studies measuring different outcomes into the same meta-analysis, which this study hopes to avoid.

Another recent systematic review was by Spencer et al in 2015\textsuperscript{149}, which looked at randomised controlled trials (RCT) to see how much does screening for thyroid disorders (and subsequent treatment) reduce negative outcomes in pregnancy, including low IQ. The review found only one RCT on the topic of IQ, which came up with a negative association.

The current review also looked for observational studies, and was specialized for looking for neurodevelopmental disorders (Spencer et al also looked into pre-eclampsia and pre-term birth, among other things).

Another recent systematic review was by Chen et al in 2016\textsuperscript{150}, which looked into the association between autism and maternal autoimmune disease. Not only did they find a strong association, they also found that the strongest, and only statistically
significant association was between autism and maternal autoimmune thyroid disease. Much of this association seemed to be weighted due to the presence of the Andersen et al 2014 study, which had a population sample of 857,014\textsuperscript{151}, however even after removing that study, the association between autism and maternal autoimmune disease remained strong.

The current study did not examine the impact of thyroid antibodies (though that could be the basis of a future systematic review) and instead focused on the presence of thyroid hormones (fT\textsubscript{4} and TSH) on both autism and other neurodevelopmental disorders.

Therefore, the current review asked two main research questions.

1. Is there an association between hypothyroidism in mothers and neurodevelopmental disorders in their children?

2. Does levothyroxine treatment of pregnant mothers lead to a significant drop in diagnosis and/or reduction in the severity of symptoms of neurodevelopmental disorders in children?

As part of the discussion, we looked into how differences in methodology account for different conclusions between articles on the topic. This study also studied mothers who had overt hypothyroidism, sub-clinical hypothyroidism and isolated hypothyroxinaemia during pregnancy and their children from those pregnancies.

We planned to conduct a number of sub-group analyses if there is enough data (that is two or more articles per subgroup with compatible data), which included:

1. Different types of hypothyroidism (overt, subclinical and isolated hypothyroxinaemia).

2. Different definitions of hypothyroidism (fT\textsubscript{4} levels in the 10th, 5th and 2.5th percentiles etcetera)

3. Each specific neurodevelopmental disorder individually (autism, ADHD, intellectual disability)
Chapter 2: Methods

A pre-defined protocol was developed following consultation with topic experts and is registered with PROSPERO (2016:CRD42016032790).

Research questions and PICO's

The first thing done when starting the systematic review was to decide precisely what information was being searched for. This required clear research questions, and from that an understanding of the populations, interventions or exposures, controls or comparisons and patient outcomes (PICO) that were being studied.

After much discussion, two research questions were decided upon.

*Research Question 1: Is there an association between hypothyroidism in the mothers and neurodevelopmental disorders in their children?*

Population: All mothers where thyroid function tests were carried out during pregnancy, either as defined as overt hypothyroidism (high TSH with low fT₄), subclinical hypothyroidism (high TSH with normal fT₄) and/or hypothyroxinaemia (normal TSH with low fT₄) or as continuous measures. The population also included all children where neurodevelopmental outcomes were measured after birth (no lower age limit was used, as neurodevelopmental symptoms can appear any time after birth), either as an explicit diagnosis or as measured on a continuous scale. The NDD's being measured were the ones listed in Diagnostics and Statistics Manual 5th edition (DSM5)³⁷, with additional terminology from International Classification of Diseases 10th edition (ICD-10)⁴⁶. There was a particular focus on autism, ADHD and intellectual disability due to the high rate of co-morbidity, and these NDDs appeared a lot in scoping searches. Adult men and women without children were excluded from the population.

Exposure: Maternal hypothyroidism as indicated by high TSH levels and/or low fT₄, measured either at a cut-off point (such as fT₄ below the 10th percentile) or as the lower half of a continuous measure.

Control (i.e. Unexposed): Euthyroid mothers (as determined by the researchers in the articles).
Outcome: The frequency of diagnosis and/or the severity of symptoms of neurodevelopmental disorders in children. This included measuring the symptoms in undiagnosed children as a continuum.

Studies: Observational studies were chosen for this research question.

Research Question 2: Does levothyroxine treatment of pregnant mothers lead to a significant drop in diagnosis and/or reduction in the severity of symptoms of neurodevelopmental disorders in children?

Population: All mothers with any diagnosis of hypothyroidism as defined by the researchers (including levels of fT4, TSH and hospital diagnosis). As with question 1, the population also included all children where neurodevelopmental outcomes were measured after birth (no lower age limit was used, as neurodevelopmental symptoms can appear any time after birth), whilst excluding adult men and childless women.

Intervention: Treatment of the mother with levothyroxine to eliminate the symptoms of hypothyroidism. We considered looking into iodine treatment as well, however iodine treatment is of little use to mothers with autoimmune hypothyroidism (the main focus of this study) hence to decrease work load we focussed on levothyroxine treatment.

Control: Mothers whose hypothyroidism was left untreated.

Outcome: The frequency of diagnosis and/or the severity of symptoms of neurodevelopmental disorders in children. This included measuring the symptoms in undiagnosed children as a continuum.

Studies: Randomised controlled trials (RCTs) were chosen for this research question.

It was decided that a systematic review would be the best way to answer these two questions, as systematic reviews reduce the risk of selection bias by the researchers, due to the fact that they provide “explicit, pre-specified and reproducible methods”\textsuperscript{152} on how to search for articles and extract data from those articles. Systematic reviews thus collect all available evidence on a given topic\textsuperscript{152}. They are considered “gold standard” evidence.
Searches

Searches were carried out between November 2015 and February 2016. To search the literature, a core set of search terms were used based on the PICOS used above, which were then adapted for the map terms used in each database, hence a slightly different search strategy was used for each database (the search terms are available in the appendix section (see appendix 1 to 7). At its core, the search strategy consisted of three blocks, the first terms for hypothyroidism, the second terms for NDD’s and the third terms for mothers and pregnancy. The three blocks were joined together in the searches using AND operators, and were held together internally using OR operators.

The search terms we used for neurodevelopmental disorders were the standardized terms, namely those from the 4th and 5th edition of the Diagnostics and Statistics Manual for Mental Disorders (DSM-IV and DSM-V)\textsuperscript{37} with additional terminology from International Classifications of Diseases 10\textsuperscript{th} edition (ICD-10)\textsuperscript{46}. DSM terms are established in systematic reviews dealing with neurodevelopmental disorders\textsuperscript{153}.

9 databases were searched using 6 interfaces. MEDLINE, EMBASE and PsychInfo were searched using OVID. CINAHL and AMED were searched using EBSCOhost; the British Nursing Index was searched using ProQuest, the Cochrane Central Register of Controlled Trials was searched using Wiley, Scopus was searched using Elsevier and Web of Science was searched using Thomson Reuters.

To reduce the risk of publication bias, we decided to look for information outside of academic journals on top of our database searches.

Alerts were also set up to inform of any new articles of the topic. This included Google alerts, and Web of Science also sent alerts linked to the saved search to the account holder.

Only titles and abstracts were searched for. See appendices 1 to 7 for the list of search terms used for each database.

The results from the searches were stored on EndNote\textsuperscript{154} before deduplication took place.
Methods for Grey literature searching

A Grey Literature search was also carried out using GreyLit, OpenGrey and Grey source.

For searching Grey Literature Report, Boolean operators were not allowed, thus the individual search terms were used, and a title screening (plus quick full text analyses where available) was used to pick out any relevant reports. The relevant hits were then downloaded as Bibtex and then opened on EndNote, though the data often had to be filled into the reference manually.

For Greysource, a list of directories to other grey literature sites was given. When checking the biological and medical sciences section on GreySource, it seemed to link back to OpenGrey. Here OpenGrey seemed to work, without producing a white screen.

We had planned to search OpenGrey directly (rather than through GreySource), however due to a technical fault with the website; we were unable to do so.

For institutions linked to neurodevelopment, we checked the following charity websites linked to autism: Autistica, Autism Speaks, Dame Shirley Foundation, INSAR, Simons Foundation, Waterloo foundation and NAS. These foundations also look into wider neurodevelopmental topics. For searching Autistica and the Simons Foundation, the same search term was used as for Scopus. For the other websites, we simply searched for hypothyroidism, thyroid and thyroxine separately. A title screening was then performed to see if an article was relevant. For the Dame Shirley Foundation, we were unable to search the site, so a title screening of the ‘Articles Press and Media’ section was performed.

For institutions linked to thyroid dysfunction, we checked the following institution websites: British Thyroid Foundation, British Thyroid Association, Society for Endocrinology and the American Thyroid Association. We used the same search terms as we used for Scopus. Where this was not possible, we searched for each of the neurodevelopment terms separately. A title and report screening was done on the results to see if anything relevant appeared. We were unable to search the website of the British Thyroid Association. When an article was found, the original
library was checked to see if it had already been found in the earlier literature searches. The American Thyroid Association mostly linked to and commented on published articles, hence searching it was abandoned.

Methods for Backwards Citation Chasing
Here the primary reviewer went to the reference section of each agreed article. They then did a title search of the references, and if a reference seemed to match the protocol criteria, that title was selected. It was then checked to see if the article had already been found in the full library, or if it had already been excluded. If not, the article would then be located, and an abstract and full text screening would take place. If it still matched the protocol criteria, it would be added to a new library for backwards citation chasing.

Methods for Forwards Citation Chasing
Here the primary reviewer used the database Scopus. There the title of each agreed article was placed into the Document search. Once the title was found, the “papers citing this” section was chosen, showing all the articles that had cited the article. A title screening was done to see if any of the references matched the protocol criteria. It was then checked to see if the article had already been found in the full library, or if it had already been excluded. If not, the article would then be located, and an abstract and full text screening would take place. If it still matched the protocol criteria, it would be added to a new library for forwards citation chasing.

Methods for Results screening
The following process was based on guidelines from the CRD handbook, chapter 1.3.2155.

Removing Duplicates
All the citations found during the systematic searches were placed in one combined EndNote library for all of the databases. The duplicate results were removed in two waves, firstly by using the “find duplicates” function in EndNote, followed by a sifting through of the duplicates to retain the citation with the most information (for example one duplicate may have an abstract whilst the other wouldn’t). This was followed by manually sifting through the citations to delete duplicates the in-built function missed.
Title and Abstract Screening

The de-duplicated citations were then read, and were included and/or excluded for full text analysis. Citations were excluded if: they were an animal (rather than human) study, they were before 1994 (when DSM-IV was released\(^ {156} \)), environmental pollution, cancer, iodine deficiency rather than thyroid hormone imbalance, single genes or diseases/syndromes other than hypothyroidism, vitamins and minerals in diet, Graves’ disease or hyperthyroidism without mention of hypothyroidism, assays, children with hypothyroidism but not the mothers, antibodies, cost-effectiveness, women’s mental and physical health but not the child’s, brain structure, neurodevelopment and mental health without hypothyroidism and if it was a Review, Commentary, Editorial, Letter or Erratum.

After the primary reviewer had included and excluded the citations as they saw fit, two half libraries were created and sent to two secondary reviewers to analyse. Once they completed their analysis, they sent their results back to the primary reviewer. The primary reviewer then merged their results and the original results into a new library, and used smart groups (an EndNote function) to arrange the citations into four groups: those the primary and secondary reviewers agreed to include, those they agreed to exclude, those the primary but not secondary reviewers wanted to include and those the secondary reviewers but not the primary reviewer wanted to include. A meeting was then held looking at the citations they disagreed on (to see if those citations should be included after all), and all the citations they agreed on went on to full text screening. This method was used to improve inter-rater reliability.

Full text screening

For the agreed citations, the full texts were searched for and attached to the EndNote citation as PDF files. Most of the full texts were extracted using the in-built full text finder function on EndNote. Some full texts failed to be picked up by the in-built function (such as those published to the Journal of Clinical Endocrinology and Metabolism) and had to be attached to the citation manually. Some full texts were not available for free online, thus had to be ordered from the British Library. Some of the agreed citations on closer screening turned out to be Conference abstracts, thus had no full text available, and had to be excluded.
With the full texts assembled, they were read sequentially and included or excluded for data extraction. This was done by filling the in/ex column with 0 for include or a special number for exclude depending on the reason they were excluded. The full texts were excluded if: the wrong population was being analysed (designated 2), the wrong intervention was given/exposure measured (3), the wrong comparison group was used (4), the wrong outcome was being measured (5), it was the wrong study design (6), it was a review or editorial or commentary (7), it was a duplicate (particularly a foreign language duplicate, 8) or it was a Conference abstract.

After the primary reviewer had included or excluded the full texts, they halved the full text library and created two new libraries to send to the two second reviewers. They also included and excluded the full texts, using the same principle, but put their results in column 8 in the citation. The second reviewers sent their libraries back to the primary reviewer after completing their analysis, one library at a time. The primary reviewer then arranged the full texts into (non-smart) groups within the libraries sent to them based on four premises: those articles both the primary and secondary reviewers agreed to include, those they agreed to exclude, those the primary reviewer but not the secondary reviewers wanted to include and those the secondary reviewers but not the primary reviewer wanted to include. All disagreements were dealt with via Email, and the agreed full texts went on to data extraction.

**Methods for Data Extraction**

Once the final selection of articles was assembled, the key information had to be selected for data analyses. Therefore, the primary reviewer read through each article again, and copied the key information into a readily prepared data extraction form (a blank version of the one used can be found in appendix 8). The data extraction form used was a modified version of a data extraction form used for a systematic review into the use of mindfulness therapy. Use of a data extraction form helps reduce bias in the study, as it forces the reviewer to choose specific data about the article. It also saves time as only the most necessary data has to be extracted (to fill in each form).

Initially, a pilot data extraction form was used on one article (to test whether more or less information needs extracting), with the aim of extracting the following key data: Bibliographic information, the setting of the study (i.e. the country and the
intervention site), the time of the study, the study design, the funding sources, the
study aims, the age of the mother during pregnancy (if available), the age of the child
when assessed, the type of hypothyroidism being assessed, how that
hypothyroidism was defined, the neurodevelopmental disorder being measured, how that
neurodevelopmental disorder was measured, excluded groups, who and where
was the study carried out, whether levothyroxine treatment was measured, the
control group used, the follow up period, the statistical analyses, the number of
people in the study, the number lost to follow-up and how much more likely were the
case children to have neurodevelopmental disorder diagnosis and symptoms
compared to control children (as measured via odds ratios, beta values and p-
values).

After the pilot was used, it was further modified to include new information, namely
how were the thyroid hormones measured and demographic differences between
groups (either the case and control groups or the included and excluded groups).

This process of copying the key information into the form continued until there was a
form for each selected article. During the process, similarities between some articles
(such as using the same population sample) were noticed that had been missed
during the screening process. These articles were subsequently merged as “sister
papers”. When a data extraction form was completed, it was sent to the secondary
reviewers to check for mistakes and for alternative decisions. Discussions would
take place, and the data extraction results would be modified as seen fit. This later
process also reduces bias in the process by providing a second opinion on the
matter.

**Methods for Quality Assessment**

As the data extraction process was undertaken, simultaneously the quality
assessment of the articles was taking place. This process assessed the risk of bias
in the articles, for further analysis at a later part of the study. It is important to tell if
the study is biased in terms of selecting candidates and in methodology, as that can
artificially inflate or deflate the results. Furthermore, if studies with one type of results
(i.e. positive) turn out to have a higher risk of bias than another set of type of results
(i.e. negative) then this would be used as a key talking point during the discussion.
The quality assessment process involved answering questions about the article using sub-forms within the data extraction forms (see Appendix 8). As the second reviewers checked the data extraction forms, they also performed their own quality assessment on the articles. Where disagreements were had, a discussion would be had and the risk or bias would be adjusted as seen fit (further reducing bias in the process). The results of the quality assessment would later be put into a Risk of Bias table using a different table for each of the methods used.

**Quality Assessment for Observational Studies**

For the observational studies used to answer question 1, the Downs and Black Checklist was used to assess the risk or bias\(^{157}\), as recommended by the Cochrane Handbook Chapter 13.5.2.3\(^{158}\). Here a list of 27 questions had to be answered Yes, No or Unable to Determine (UTD) about the article. These included questions like “Were the subjects asked to participate in the study representative of the entire population from which they were recruited?” A full version of the checklist used can be seen in the data extraction form in appendix 8.

**Quality Assessment for Randomized Controlled Trials**

For the Randomised Controlled Trials used to answer question 2, the Cochrane checklist was used\(^{159}\). This checklist assesses the key risks of bias in an RCT (as discussed by the CRD Handbook chapter 1.3.4\(^{160}\)), namely: selection bias, performance bias, detection bias, attrition bias and reporting bias. Here the reviewer has to rank 8 entries linked to these biases as having either low, high or unclear risk of bias, and use information from the article to justify why it was ranked as such. A full version of the checklist used can be seen in the data extraction form in appendix 8.

**Methods for Data Analysis**

**Choosing Data for Meta-Analysis**

Many of the studies provided multiple sets of results, some with over 20 sets. To avoid bias, we had to choose carefully which set of results to use in the data analysis, rather than simply choosing the most positive result. Hence the following criterion was used.
1. For studies using multiple tests for the same outcome, the most commonly used test would be used (i.e. the Wechsler Intelligence Test would be used over an experimental intelligence test).

2. Where available, the total score of the test would be used rather than a subset of that test.

3. Where a trait was measured over multiple time periods, the latest point of measuring would be chosen, as this is when the child is older, and neurodevelopmental traits at an older age tend to be more stable. Whilst some NDD’s recede by adulthood (making measuring at that stage less reliable) over 18s were excluded in this meta-analysis, hence this is irrelevant.

4. When multiple cut-offs of TSH and fT₄ were measured, the most extreme cut-off was used. Similarly, when an outcome was measured both against a continuous thyroid hormone measure and against a cut off value (i.e. cut off of the 10th percentile fT₄ for hypothyroxinaemia) the cut off value was used.

5. When thyroid hormone samples were collected at multiple times in pregnancy, the earliest time was chosen, owing to the theory that hypothyroidism in early pregnancy is more problematic than later pregnancy.

6. Where both fT₄ and tT₄ were measured, the fT₄ measure was used, as fT₄ is the more commonly measure for hypothyroxinaemia, and according to one study is as accurate a way to detect hypothyroxinaemia as tT₄. Studies where only tT₄ was measured were included under hypothyroxinaemia.

7. When a choice between an adjusted and unadjusted result was given, the adjusted result was used.

Pääkkilä et al 2014¹¹⁸ presented ADHD scores for girls and boys separately, but not in total. In that particular case we contacted the authors for gender merged results. We aimed to carry out 9 sets of meta-analysis, equating to the three primary NDD outcomes (ASD, ADHD and intellectual disability) multiplied by the three types of hypothyroidism (overt, subclinical and hypothyroxinaemia). We also decided to carry out a meta-analysis of hypothyroxinaemia as defined by the 5th percentile fT₄ levels or lower.
Though there are roughly 12 basic recognized types of NDD, for pragmatic reasons we decided to stick to autism, ADHD and intellectual disability for the meta-analysis, due to the high levels co-morbidity between those three NDD.

Externalising behaviour measures were included in the ADHD meta-analysis, as that has predictive value for future ADHD\textsuperscript{162}.

Studies on infant cognition were included in the intellectual disability meta-analysis, as infant-cognition can weakly predict later intellectual disability\textsuperscript{163}. We decided to include measures of language as outcomes for intellectual disability. Whilst language scores could be used as outcome measures for autism and autistics traits, full autism diagnosis requires measures of other attributes like social behaviour and repetitive behaviour. Likewise whilst IQ usually measures a range of verbal and non-verbal attributes, verbal and non-verbal IQ are known to correlate strongly with each other\textsuperscript{164}, hence a score of one can potentially predict the other. For this reason, performance IQ measures were also included as outcomes.

We also decided to include studies of Developmental Delay as outcomes for intellectual disability, including the Mullen Scale of Early Learning and the Vineland Adaptive Behaviour Scale (both used by Yau et al\textsuperscript{194}). These studies are contentious as they include motor development measures as well as cognitive measures. However, developmental delay is linked to intellectual disability (DSM-V uses global developmental delay as a diagnosis for children too young to be diagnosed with intellectual disability\textsuperscript{34}). Furthermore the Mullen Scale of Early Learning can be used to predict IQ\textsuperscript{165}, and the Vineland Adaptive Behaviour Scale is used to diagnose Intellectual Disability\textsuperscript{166}. Thus the developmental delay outcomes were included, and for this reason the combined Bayley Scales (Mental and Psychomotor) was also included.

All of these measures constituted as indicators of intellectual disability, but not as explicit diagnosis of intellectual disability.

Studies measuring autism and ADHD using both discrete diagnosis and validated continuous scales were included in this study.
Threshold Graphs
In order to check for any outliers in the studies, and to check that a study was measuring the type of hypothyroidism it claimed to be measuring, graphs of the threshold values for the studies were constructed.

In order to confirm that a given study measured the type of hypothyroidism it claimed to be measuring, a graph was plotted of all the studies, with the maximum absolute fT4 level measured to be diagnosed with hypothyroidism (in that study) against the minimum absolute TSH level needed to be diagnosed with hypothyroidism (in that study). If no fT4 was measured in a study, the study was given a 0 for its fT4 value in the graph, if no TSH was measured in a study, 0 was given for its TSH value in the graph.

In order to check for outliers in the studies measures of neurodevelopmental outcomes, a graph was plotted of all the relevant outcome measures in the studies (thus only outcome measures for ASD, ADHD and intellectual disability) against the diagnostic/significance threshold for the measure, either as specified by the study or using the standard deviation of the population mean for that outcome (see Appendix 9 for more details).

Both of these graphs were made using Excel.

Meta-Analysis
Though many of the studies in the results gave odds ratios in the results, many of them gave continuous results and regression coefficients. Hence a key part of the meta-analysis was converting the continuous results and regression coefficients into odds ratios.

To convert the continuous results, we used two equations, one by Suissa to gain the risk estimates and their variances\textsuperscript{167}, the other one by Whitehead et al\textsuperscript{168} (based on Suissa et al) to gain the odds ratios and the variance of the odds ratios, from which the standard deviation (for the odds ratios) and confidence intervals could be calculated (see Figure 4 for further explanation). If we were defining positive results if the score was lower than threshold (as with IQ when measuring intellectual disability) the reciprocal of the odds ratio was used instead. In some cases, the studies did not
give an explicit threshold, in these cases the population mean minus the standard deviation of the population mean was used as a threshold. Many studies have used 1 standard deviation below the population mean as a threshold in their investigations (including Haddow et al7) hence this decision is supported by researcher practice.

Suissa et al claim their method is more accurate when dealing with small population sizes (such as less than 100 subjects) when compared to a binary approach to dichotomized data167. It is also an intuitive method, in that it is clearer where the final result comes from in the original data.
Figure 4: A graph showing the estimation of risk using methods from Suissa et al and data from Liu et al\textsuperscript{169}.

In this graph, the mean of IQ is 108 and the standard deviation is 9. The Suissa method is based on the assumption that the sample is selected from a Gaussian distribution, with the risk (from which odds ratios can be calculated) being the proportion of the normal curve below the threshold (in this graph the threshold is 99 and specified by the red line).

No established method could be found to convert the linear regression results to Odds Ratios; hence eight studies were excluded from the meta-analysis (though
they were included in narrative analysis alongside the meta-analysis). Linear regression can be reported in many different ways, the outcome can be measured against a continuous or discrete exposure, the outcome variable can be transformed, and the regression coefficient can be standardized or adjusted (or not). This high level of variation makes it difficult to find a consistent method to accurately convert them to odds ratios.

For the linear regression results, we decided to use narrative analysis instead. Here, text without figures or calculations is used to summarise the nature and results of each study, with a conclusion based on the net number of results for or against an association.

Where discrete results were presented in the study but no Odds Ratios were given, Odds Ratios were calculated in the standard method\(^\text{170}\); that is according to this equation.

\[
\frac{(a*d)}{(b*c)}
\]

Where \(a\) is the total exposed and with the disease, \(d\) is the total unexposed without the disease, \(b\) is the total exposed without the disease and \(c\) is the total unexposed with the disease.

Once the odds ratios were calculated, they were then used to produce forest plots (using the metan function on STATA\(^\text{171}\)) of the results. Forest plots display the pooled estimate of multiple odds ratios from different studies on a given topic (as well as the component odds ratios) showing the overall level of significance on a given topic. Each study was weighted using inverse variance and a random model, so that studies with a lower risk of bias will have a greater impact on the pooled estimate. Inverse variance means the greater the confidence intervals of an odds ratio, the lower its weight, and a random model means the weight from odds ratios that deviate from the other odds ratios is reduced\(^\text{171}\).

A result was considered significant if it produced a \(p\)-value less than 0.05.

Funnel plots (using the metafunnel function on STATA\(^\text{172}\)) were also produced to measure publication bias. In order to use metafunnel, standard error had to be calculated, which was done using this equation.
SE = (lnUCI – lnOR)/1.96

Where lnUCI is the log upper confidence interval and lnOR is the log Odds Ratio.

The statistical analysis was done using a combination of Excel\textsuperscript{173} and STATA\textsuperscript{174}. 
Chapter 3: Results

Search results
After searching all databases, 6041 articles were discovered. After removing the duplicate results, 3448 hits remained and after Title and Abstract screening, 59 articles met the inclusion criteria. Of those 59 articles, nine were conference abstracts with no traceable journal article associated with them, meaning the methods could not be studied in depth, thus were excluded from study. A further five measured the wrong outcomes (such as psychiatric disorders and seizures), four were reviews, editorials or commentary, one measured the wrong exposure (maternal iodine deficiency) and one was a duplicate result (see Figure 5, a PRISMA diagram which shows the pathway to the included articles). One article, Noten et al 2014\cite{175}, was accepted into the study, but had to be ordered from the British Library, and could not be delivered until late into the project, thus was excluded. This left 37 remaining full texts, of which one (Klein et al 2001\cite{176}) used the same data as Haddow et al 1999\cite{7}, whilst two articles (Williams et al 2013\cite{177} and Korevaar et al 2015\cite{178}) used the same outcome measures on differing individuals from the same cohort as two other studies (Williams et al 2012\cite{179} and Ghassabian et al 2014\cite{180} respectively). Haddow et al\cite{7} and Klein et al\cite{176} were merged as sister papers (the other articles were different enough to be treated separately), leaving 36 full texts in total (see Figure 5).

During Grey Literature searches, no relevant articles were found on GreyLit and 1 article was found on OpenGrey via GreySource which was unrelated to the protocol. No relevant articles could be found searching the institution websites either.

During the forwards and backwards citation chasing, one other relevant article was discovered (Si et al 2012\cite{181}), however the article was written in Traditional Chinese script. It was a British Library order, so could not be machine translated, and the one Chinese speaker available had difficulty understanding Traditional script, and had other academic commitments, hence to save time this article was excluded.

Thus, 36 articles were included in this review (see Figure 5 and Table 2).

Of those studies, only one, Lazarus et al\cite{11}, was a Randomised Controlled Trial.
Exposure Characteristics of Observational Studies

To make sure that the studies were measuring the type of hypothyroidism they claimed to be studying, and that the differing types of hypothyroidism were distinct, threshold graphs for the absolute cut-off values for the thyroid hormone measurements were created.

When the first threshold graph was made, the tT₄ values (from the studies Oken et al¹⁸² and Li et al¹⁸³) were so vast that they made the rest of the graph unreadable. They were thus removed from Figure 6, though the tT₄ values were still included in the analysis, as tT₄ is another way of measuring hypothyroxinaemia. Figure 6 showed that the studies measuring overt hypothyroidism, subclinical hypothyroidism and hypothyroxinaemia occupied distinctly different thresholds. An exception to this was Päkkilä et al 2015¹⁸⁴, whose thresholds for overt hypothyroidism overlap with studies for hypothyroxinaemia. However, Päkkilä et al 2015¹⁸⁴ is still an overt hypothyroidism study, because in hypothyroxinaemia those with TSH higher than the threshold are excluded from the diagnosis, whilst with overt hypothyroidism those with TSH higher than the threshold are included in the diagnosis, hence they are measuring different things (see Table 2).
**Figure 5:** the PRISMA diagram showing search strategy and exclusion criteria at each step.

Database searches:
- Medline: 1683
- Embase: 1476
- PsychInfo: 210
- AMED: 1
- CINAHL: 101
- British Nursing Index: 42
- Cochrane: 58
- Web of Science: 801
- Scopus: 1689
- Total: 6041

Duplicate results: 2593

Results after deduplication: 3448

Excluded after Title and Abstract screening: 3389

Results after Title and Abstract screening: 59

Papers excluded for:
- Wrong population: 0
- Wrong intervention/exposure: 1
- Wrong comparison: 0
- Wrong outcomes: 5
- Inappropriate study design: 1
- Review, editorial or commentary: 4
- Duplicate: 1
- Conference abstracts: 9
- Unavailable paper: 1

Results from Grey literature: 8
Results from citation chasing: 1

Results after Full Text screening: 37

Merged as sister papers: 1

Final Results: 36

Excluded due to language: 1
<table>
<thead>
<tr>
<th>Name</th>
<th>Study type</th>
<th>N</th>
<th>Male/ Female %</th>
<th>Region/ Country</th>
<th>Thyroid Dysfunction Assessed</th>
<th>fT4 measurements</th>
<th>TSH measurements</th>
<th>Age at Psychological assessment</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994 Liu</td>
<td>Matched Cohort</td>
<td>8</td>
<td>hypothyroidism and 9 siblings of hypothyroidism</td>
<td>NK</td>
<td>China and Japan</td>
<td>OH</td>
<td>control range 6.40-24.50 pmol/l, case range 2.30-6.30 pmol/l, control &lt;5 mU/l, case range 25-190 mU/l</td>
<td>4-15 years</td>
<td>The Suzuki-Binet Intelligence Scale</td>
</tr>
<tr>
<td>1999 Pop</td>
<td>Cohort</td>
<td>220</td>
<td>55/45</td>
<td>Netherlands</td>
<td>HR</td>
<td>NA</td>
<td>NA</td>
<td>10 months</td>
<td>Bayley Scales of Infant Development</td>
</tr>
<tr>
<td>1999 Haddow</td>
<td>Matched Cohort</td>
<td>62</td>
<td>hypothyroidism and 124 controls</td>
<td>1:1.4 ratio</td>
<td>Maine, United States</td>
<td>OH</td>
<td>control 12.48 pmol/l mean, case 9.14 pmol/l mean</td>
<td>7-9 years</td>
<td>WISC, 3rd edition and Conners Continuous Performance test</td>
</tr>
<tr>
<td>2000 Smit</td>
<td>Cohort</td>
<td>7</td>
<td>hypothyroid, 6 euthyroid and 7 hyperthyroid</td>
<td>1:1 ratio</td>
<td>Netherlands</td>
<td>SH</td>
<td>NA</td>
<td>6, 12 and 24 months</td>
<td>Bayley Scale of Infant Development (Touwens method at 6 and 12 months, Hempel's method at 24 months)</td>
</tr>
<tr>
<td>2003 Pop</td>
<td>Matched Cohort</td>
<td>63 HR and 62 controls</td>
<td>Cases 42/58, controls 53/47</td>
<td>Netherlands</td>
<td>HR</td>
<td>&lt;10th Percentile (12.10 pmol/l)</td>
<td>range 0.15-2.0 mU/l</td>
<td>1-2 years</td>
<td>Bayley Scale of Infant Development</td>
</tr>
</tbody>
</table>

Table 2: All studies for this project (sister papers merged). 1
<table>
<thead>
<tr>
<th>Year</th>
<th>Reference</th>
<th>Cohort Type</th>
<th>Sample Size</th>
<th>Country</th>
<th>Hormones &amp; Ranges</th>
<th>Maternal Report</th>
<th>Follow-up</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>Kasatkina</td>
<td>Cohort</td>
<td>17 HR and 18 controls</td>
<td>Russia</td>
<td>HR reference range: 12.0-22.0 pmol/l</td>
<td></td>
<td>6,9 and 12 months</td>
<td>Gnome method, in particular the Coefficient of Mental Development (CMD).</td>
</tr>
<tr>
<td>2006</td>
<td>Kooistra</td>
<td>Matched Cohort</td>
<td>108 HR and 96 controls</td>
<td>The Netherlands</td>
<td>HR &lt;10th Percentile (11.40-12.0 pmol/l)</td>
<td></td>
<td>3 weeks</td>
<td>Neonatal Behavioural Assessment Scale</td>
</tr>
<tr>
<td>2009</td>
<td>Oken</td>
<td>Cohort</td>
<td>500</td>
<td>Massachusetts, USA</td>
<td>Co tT4 range: 4.50-10.90 μg/dl (57.92-140.28 nmol/l)</td>
<td></td>
<td>6 months and 3 years</td>
<td>Visual Recognition Memory at 6 months, Peabody Picture Vocabulary Test and Wide Range Assessment of Visual Motor Ability at 3 years</td>
</tr>
<tr>
<td>2009</td>
<td>Munoz</td>
<td>Matched Cohort</td>
<td>29 HR and 30 controls</td>
<td>Spain</td>
<td>HR &lt;10th Percentile (10.17 pmol/l)</td>
<td>NA</td>
<td>2 years</td>
<td>Parental report based on the criteria in DSM-IV for ADHD</td>
</tr>
<tr>
<td>2010</td>
<td>Henrichs</td>
<td>Cohort</td>
<td>3659</td>
<td>Netherlands</td>
<td>HR and Co TSH 10th percentile tT4 &lt;11.76 pmol/l, 5th percentile tT4 &lt;10.96 pmol/l</td>
<td></td>
<td>18 and 30 months</td>
<td>MacArthur Communicative Development Inventory at 18 months, Language Development Survey at 30 months</td>
</tr>
<tr>
<td>2010</td>
<td>Li</td>
<td>Matched Cohort</td>
<td>19 HR, 18 SH and 77 controls</td>
<td>China</td>
<td>SH and HR Hypo-tT4&lt;2.50th percentile (101.79 nmol/l)</td>
<td>SH=&gt;97.50th percentile (4.21 mU/l)</td>
<td>25-30 months</td>
<td>Bayley Scale of Infant Development</td>
</tr>
<tr>
<td>2011</td>
<td>Ghassabian</td>
<td>Cohort</td>
<td>3736</td>
<td>Netherlands</td>
<td>Co tT4 and TSH &lt;10th percentile (11.76 pmol/l)</td>
<td></td>
<td>18 months and 3 years</td>
<td>The Child Behaviour Checklist was used by mothers at 18</td>
</tr>
<tr>
<td>Year</td>
<td>Study</td>
<td>Cohort</td>
<td>Sample Size</td>
<td>Country</td>
<td>Test</td>
<td>Hormone Range</td>
<td>Hormone Definition</td>
<td>Duration</td>
</tr>
<tr>
<td>--------</td>
<td>-------</td>
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<td>-------------</td>
<td>---------</td>
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<td>-------------------</td>
<td>----------</td>
</tr>
<tr>
<td>2011</td>
<td>Su</td>
<td>196</td>
<td>1017</td>
<td>China</td>
<td>SH</td>
<td>&lt;5th percentile</td>
<td>&lt;10.40-8.51 pmol/l</td>
<td>6 months</td>
</tr>
<tr>
<td>2011</td>
<td>Chevrier</td>
<td>201</td>
<td>287</td>
<td>California, USA</td>
<td>CoFT4 and TSH</td>
<td>Low FT4 defined as &lt;6.44 pmol/l</td>
<td>High TSH 2.50 mU/l</td>
<td>6 months and 1, 2 and 5 years</td>
</tr>
<tr>
<td>2011</td>
<td>Behrooz</td>
<td>199</td>
<td>19 SH and 19 controls</td>
<td>Iran</td>
<td>SH</td>
<td>NA</td>
<td>SH=&gt;3.0 mU/l control 1.40 mU/l mean, case 11.30 mU/l mean</td>
<td>7.9 years for cases, 7.5 years for controls</td>
</tr>
<tr>
<td>2012</td>
<td>Williams</td>
<td>179</td>
<td>166 children and 143 mothers</td>
<td>United Kingdom</td>
<td>SH and HR</td>
<td>&lt;10th percentile (11.6 pmol/l)</td>
<td>3.0 mU/l</td>
<td>5.5 years</td>
</tr>
<tr>
<td>2012</td>
<td>Suárez-Rodríguez</td>
<td>207</td>
<td>37 HR and 33 controls</td>
<td>Spain</td>
<td>HR</td>
<td>&lt;10th Percentile (9.5 pmol/l)</td>
<td>range 1.07-1.88 mU/ml</td>
<td>38 months and 5 years</td>
</tr>
<tr>
<td>2012</td>
<td>Craig</td>
<td>10</td>
<td>98 HR and 98 controls</td>
<td>Maine, United States</td>
<td>HR</td>
<td>&lt; 3rd Percentile (11.84 pmol/l)</td>
<td>range 0.10-3.5 mU/l</td>
<td>2 years</td>
</tr>
<tr>
<td>2012</td>
<td>Lazarus</td>
<td>11</td>
<td>Randomized Trial 390 interventions and 404</td>
<td>United Kingdom and Italy</td>
<td>OH and SH and HR</td>
<td>Hypo and overt &lt;2.5th percentile (95% range)</td>
<td>SH and overt &gt;97.5th percentile (95% range)</td>
<td>3 years</td>
</tr>
<tr>
<td>Year</td>
<td>Author</td>
<td>Cohort Size</td>
<td>Country</td>
<td>Test</td>
<td>Description</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>--------</td>
<td>------------</td>
<td>---------</td>
<td>------</td>
<td>-------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>Williams</td>
<td>97</td>
<td>United Kingdom</td>
<td>SH</td>
<td>NA</td>
<td>2.50 mU/l</td>
<td>5.5 years</td>
<td>The McCarthy Scales of Children's Abilities.</td>
</tr>
<tr>
<td>2013</td>
<td>Julvez</td>
<td>1761</td>
<td>Spain</td>
<td>Co fT4 and TSH</td>
<td>10th percentile fT4 &lt;8.89 pmol/l, 5th percentile fT4 &lt;8.39 pmol/l, 2.5th percentile fT4 &lt;8.10 pmol/l</td>
<td>90th percentile TSH &gt;2.59 mU/l, 95th percentile TSH &gt;3.20 mU/l, 97.5th percentile TSH &gt;4.18 mU/l</td>
<td>14 months average (range 11-23 months)</td>
<td>Bayley Scales of Infant Development</td>
</tr>
<tr>
<td>2013</td>
<td>Finken</td>
<td>1765</td>
<td>Netherlands</td>
<td>Co fT4 and TSH</td>
<td>fT4 10th percentile &lt;7.70 pmol/l, 5th percentile fT4 &lt;7.0 pmol/l, 2.5th percentile fT4 &lt;6.50 pmol/l</td>
<td>90th percentile TSH &gt;2.30 mU/l, 95th percentile TSH &gt;2.90 mU/l, 97.50th percentile TSH &gt;3.80 mU/l</td>
<td>5-6 years</td>
<td>The Amsterdam Neuropsychological Tasks (ANT), a series of video game style tests measuring visuo-motor skills, such as baseline speed (the first task)</td>
</tr>
<tr>
<td>2013</td>
<td>Roman</td>
<td>4039</td>
<td>Netherlands</td>
<td>HR</td>
<td>&lt;10th Percentile (11.82 pmol/l), &lt;5th Percentile (10.99 pmol/l)</td>
<td>NA</td>
<td>6 years</td>
<td>Pervasive Developmental Problems on the Child Behavior Checklist for Toddlers (CBCL 1.5-5), parent reported</td>
</tr>
<tr>
<td>2013</td>
<td>Andersen</td>
<td>857014</td>
<td>Denmark</td>
<td>OH</td>
<td>Hospital Diagnosis (Denmark diagnosis &lt;9.10 pmol/l)</td>
<td>Hospital Diagnosis (Denmark diagnosis &gt;5.0 mU/l)</td>
<td>3 years</td>
<td>Hospital diagnosis of ADHD and Autism. Also prescription of ADHD medication.</td>
</tr>
<tr>
<td>2014</td>
<td>Ghassabian</td>
<td>3737</td>
<td>Netherlands</td>
<td>Co fT4 and TSH and HR</td>
<td>&lt;5th percentile (10.99 pmol/l)</td>
<td>High TSH &gt;2.50 mU/l</td>
<td>6 years</td>
<td>Snijders-Oomen Niet-verbale intelligentie test,</td>
</tr>
<tr>
<td>Year</td>
<td>Study</td>
<td>Design</td>
<td>Cases with autism and developmental delay</td>
<td>Controls</td>
<td>Study Site</td>
<td>Primary Outcome</td>
<td>TSH Level</td>
<td>Follow-up (years)</td>
</tr>
<tr>
<td>------</td>
<td>-------</td>
<td>--------</td>
<td>------------------------------------------</td>
<td>----------</td>
<td>------------</td>
<td>----------------</td>
<td>-----------</td>
<td>------------------</td>
</tr>
<tr>
<td>2014</td>
<td>Yau</td>
<td>Nested Case-Control</td>
<td>78 with autism, 45 with developmental delay and 149 controls</td>
<td>ASD 87.18/12.82, DD 60/40, controls 89.26/10.74</td>
<td>California, USA</td>
<td>SH</td>
<td>NA</td>
<td>Neurodevelopment measured first, then compared to TSH levels (TSH in general population 0.42-3.69 mU/l)</td>
</tr>
<tr>
<td>2014</td>
<td>George</td>
<td>Case-Control</td>
<td>143 with autism and 200 controls</td>
<td>Cases 83.7/16.3, controls 57.5/42.5</td>
<td>Kerala, India</td>
<td>OH</td>
<td>Hospital Diagnosis (India reference 9.48-19.58 pmol/l)</td>
<td>Hospital Diagnosis (India reference 0.60-5.78 mU/l)</td>
</tr>
<tr>
<td>2014</td>
<td>Pakkila</td>
<td>Cohort</td>
<td>348 High TSH, 66 HR and 5131 controls</td>
<td>High TSH 52/48, Hypo 59.1/40.9, controls 50.6/49.4</td>
<td>Finland</td>
<td>SH and HR and Co TSH</td>
<td>Low fT4 &lt;11.40-11.10 pmol/l gestation dependent</td>
<td>high TSH &gt;3.10-3.50 mU/l gestation dependent</td>
</tr>
<tr>
<td>2015</td>
<td>Korevaar</td>
<td>Cohort</td>
<td>3839</td>
<td>49/51</td>
<td>Netherlands</td>
<td>Co fT4 and TSH</td>
<td>Low fT4 &lt;10.4 pmol/l</td>
<td>High TSH &gt;4.04 mU/l</td>
</tr>
<tr>
<td>2015</td>
<td>Modesto</td>
<td>Cohort</td>
<td>127 HR, 3873 controls (Generation R)</td>
<td>1:1 ratio</td>
<td>Netherlands</td>
<td>HR</td>
<td>&lt;5th percentile (10.94 pmol/l) range 0.03-4.04 mU/l</td>
<td>8 years</td>
</tr>
<tr>
<td>2015</td>
<td>Grau</td>
<td>Cohort</td>
<td>39 controls, 47 subgroup 1 (HR) and</td>
<td>51.2/48.8</td>
<td>Spain</td>
<td>HR</td>
<td>&lt;10th Percentile (13.7-11.5 pmol/l) range 0.01-5.0 mU/l</td>
<td>1 and 6-8 years</td>
</tr>
</tbody>
</table>

revise (Mosaics and Categories) Autism diagnosis based on DSM-IV specifications Childhood Autism Rating Scale The Rutters B2 scale Snijders-Oomen Niet-verbale intelligentie test, revise (Mosaics and Categories) The Conners’ Parent Rating Scale-Revised Short Form (mother ranked) Brunet-Lezine scale and WISC-IV
<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Study Type</th>
<th>Sample Size</th>
<th>Country</th>
<th>SH</th>
<th>OH</th>
<th>Control</th>
<th>Exclusion Criteria</th>
<th>Follow-up</th>
<th>Assessment Instrument</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>Ganaie</td>
<td>Cohort</td>
<td>369 subgroup 2 (other iodine and thyroid problems)</td>
<td>Kashmir Valley, India</td>
<td>OH</td>
<td>NA</td>
<td>Control &lt;10 mU/l, borderline 10-20 mU/l, abnormal &gt;20 mU/l</td>
<td>3-4 weeks</td>
<td>Neonatal Behavioral Assessment Scale</td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>Pakkila</td>
<td>Cohort</td>
<td>5295</td>
<td>Finland</td>
<td>OH and SH and HR</td>
<td>Hypo and overt &lt;11.40-11.09 pmol/l</td>
<td>SH and overt &gt;3.10-3.50 mU/l</td>
<td>8 and 16 years</td>
<td>Strengths and Weaknesses of ADHD Symptoms and Normal Behavior, Teacher reported child school performance, Youth Self Report and WISC-Revised</td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>Murphy</td>
<td>Cohort</td>
<td>23 SH and 47 controls</td>
<td>Ireland</td>
<td>SH</td>
<td>&lt;2nd percentile excluded</td>
<td>&gt;98th percentile (&gt;4.0-3.50 mU/l)</td>
<td>7-8 years</td>
<td>WISC-IV</td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>Chen</td>
<td>Cohort</td>
<td>106 cases and 106 controls</td>
<td>China</td>
<td>SH</td>
<td>range 5.55-15.8 pmol/l</td>
<td>&gt;3.47-4.99 mIU/l</td>
<td>12-24 months</td>
<td>The Gesell development test (as revised by the Beijing Child’s Health Care Unit)</td>
<td></td>
</tr>
</tbody>
</table>

1. OH=Overt Hypothyroidism, SH=Subclinical Hypothyroidism, HR=Hypothyroxinaemia, Co=Continuous, WISC=Wechsler Intelligence Scale for Children, WPPSI= Wechsler Preschool and Primary Scale of Intelligence
For Haddow et al, the values used in Figure 6 were not the absolute threshold values, but the average values of the cases. The actual threshold for 76% of the cases was having a TSH level above the 99.7th percentile, the absolute value for which was not specified. For the remaining cases, the threshold was having a TSH level between the 98th and 99.6th percentile (absolute values not given) with a tT4 count lower than 7.75 µg/dl (99.7 nmol/l). Thus within the study there was a mixture of participants with a measure of T4 and those without, with those without predominating. Although physicians often recommend levothyroxine treatment for TSH levels higher than 10 mIU/l regardless of fT4 levels, for this thesis subclinical hypothyroidism was defined as elevated TSH with normal fT4, including studies where fT4 wasn’t measured. Furthermore, the Haddow et al study has been described before as a subclinical hypothyroidism study in the literature (even if it describes itself as an overt hypothyroidism study), hence Haddow et al was analysed under subclinical hypothyroidism. Ganaie et al was also viewed as a subclinical hypothyroidism study, as no T4 was measured at all in that study.

Though Chen et al seems to stand out from the other subclinical hypothyroidism studies, that is because it was the only study specialising in subclinical hypothyroidism that mentioned the absolute fT4 threshold values it used to exclude overt hypothyroidism (lowest being 5.55 pmol/l). Murphy et al provided details of the percentile threshold values it used (2nd percentile) but not the absolute value, Li et al provided the threshold value in tT4 (101.79 nmol/l, which would be difficult to graph), the rest did not factor in T4 into their diagnosis or where continuous measures of TSH. Hence Chen et al was analysed as a subclinical hypothyroidism study.

Andersen et al and George et al used hospital diagnosis for their measures of overt hypothyroidism rather than direct measures, hence the thyroid hormone values used in Table 2 and Figure 6 are based on data from Carlé et al (hypothyroidism thresholds for Denmark) and Unnikrishnan et al (hypothyroidism thresholds for India) respectively.
Figure 6: Thyroid hormone threshold graph without tT₄ values
Outcome Characteristics of Observational Studies

In order to check for outlier studies that defined NDD in a substantially different way, graphs were made of the thresholds used for NDD diagnosis by study.

Figure 7 shows the chosen outcome measures for intellectual disability. Here a case was significant if they scored lower than threshold in any of these tests. For Kasatkina et al\textsuperscript{191} (which used the Coefficient of Mental Development, Gnome Method) a threshold was given for the overall scale out of 100 (80) but not for the subscales (it was the Cognitive subscale that was used for meta-analysis). Therefore for the subscales in Kasatkina et al\textsuperscript{191}, we used 16 as a threshold, as the subscales were out of 20, and 16 multiplied by five is 80 (much as 20 multiplied by five is 100), thus 16 gave a good approximation of the total value.

The Language Development Survey (used by Henrichs et al\textsuperscript{192}) had a threshold substantially lower than the other studies, since the threshold is not the individual score on the test, but the percentile score of the individual (in this case the 15\textsuperscript{th} percentile of the population). Most of the other studies had fairly consistent cut-off points (only three are outside of the 80 to 90 radius). As most of the studies used a threshold of 1 standard deviation below the population mean, whilst official diagnosis of Intellectual Disability requires an IQ lower than 2 standard deviations, it was decided the meta-analysis should be named “indicators of intellectual disability” rather than intellectual disability itself.
Figure 7: Intellectual disability thresholds
Figure 8 shows the chosen outcome measures for ADHD. Andersen et al\textsuperscript{151} based their study on hospital diagnosis of ADHD (and prescription of ADHD medication) therefore did not have a threshold and was not included in Figure 8. The Child Behaviour Checklist (externalising) has a much higher threshold than the other outcome scales as it measured against a population percentile rather than a cut-off in the outcome measure, hence is probably not an outlier.

Figure 9 shows the chosen outcome measures for autism. Unlike Munoz et al\textsuperscript{193} (which used a DSM-IV diagnosis and gave a threshold), Yau et al\textsuperscript{194} used DSM-IV to diagnose autism yet did not give a threshold value; hence it was not included in Figure 9 (same with Andersen et al\textsuperscript{151} which used hospital diagnosis). The Childhood Autism Rating Scale (used by George et al\textsuperscript{195}) seems to use a seemingly lower threshold than the Clinical Pervasive Developmental Problems, though it is the only study to use an absolute cut-off on a given scale, Clinical Pervasive Development Problems being a population percentile measure and the other two (not in Figure 9) being absolute values; hence it was probably not as much of an outlier as it appeared.
A case was unhealthy if they scored higher than the threshold.
A case was unhealthy if they scored higher than the threshold
Risk of Bias for Observational Studies

A summary of the risk of bias for the observational studies is shown in Table 3. Questions 23 and 24 (which were about the randomization process, see Appendix 8) were irrelevant to this study, and questions 14 (about blinding the subjects to the intervention) and 19 (about compliance with the intervention) were also largely irrelevant. The lowest scoring question in this study was question 8, about whether adverse effects of the intervention were recorded, though this was also largely irrelevant.

The lowest scoring relevant question was 27, since very few studies reported on the statistical power of the studies. Also low scoring was question 26, as many studies did not take into account the attrition to their population samples, and question 15, as many studies did not explicitly blind subjects as to whether they were in the hypothyroidism group or the control group.

The two studies with the highest risk of bias were Liu et al\textsuperscript{169} and Kasatkina et al\textsuperscript{191}, mostly because those studies gave inadequate information as to where their study subjects came from. The study with the lowest risk of bias was Su et al\textsuperscript{196}, which answered positively on all relevant Downs and Black questions (except question 27).

In total, the overall risk of bias is acceptably low as the majority of relevant criteria for the majority of studies have been met.
### Table 3: Risk of Bias results.

The rows are questions on the Downs and Black Checklist, the Columns are the studies. Green signifies reduced risk of bias, red increased risk of bias, orange intermediate risk and yellow uncertain or irrelevant risk.

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Meta-Analysis for Observational Studies

Studies Excluded from Meta-Analysis

7 studies were outright excluded for the major part of the meta-analysis. Klein et al\textsuperscript{176} was deemed a sister paper to Haddow et al. Data was not used from Klein et al\textsuperscript{176} because although that study produced odds-ratios, it focussed on the untreated mothers (Haddow et al included mixed results for treated and untreated\textsuperscript{7}) and to use that data would require a separate set of meta-analysis that could alter the statistical significance of the results. Data was not used from Korevaar et al\textsuperscript{178} as no numerical data (other than p-values) was given, only graph data.

Finken et al\textsuperscript{197} used the Amsterdam Neuropsychological Tasks (ANT), a series of computer game style tests designed to measure cognitive functions in the form of response speed, response speed stability, visuomotor skills, response selection, and response inhibition. The study presented 11 sets of outcomes for the ANT (88 sets of outcomes were presented in Finken et al\textsuperscript{197} in total) with none of them being given as the total value of the ANT. Finken et al\textsuperscript{197} is the only study in the results to use the ANT method, and whilst Finken et al\textsuperscript{197} cite articles associating ANT scores with brain damage, it is not as well validated as other neurodevelopmental measures in this study. It is also unclear what NDD the ANT was actually measuring (it seems to measure symptoms of both intellectual disability and ADHD). Due to the confusion surrounding this study, it was excluded from the meta-analysis.

Pop et al\textsuperscript{199}, Kooistra et al\textsuperscript{198} and Ganaie et al\textsuperscript{186} were excluded as they were measures of psycho-motor development rather than cognitive development. Pop et al\textsuperscript{199} looked at the association between maternal hypothyroxinaemia and Bayley’s Psychomotor Development index, Kooistra et al\textsuperscript{198} looked at maternal hypothyroxinaemia and the Neonatal Behavioural Assessment Scale (NBAS, which largely measures reflexes rather than cognitive functions) and Ganaie et al\textsuperscript{186} looked at overt hypothyroidism and NBAS.

For Behrooz et al\textsuperscript{199}, the IQ results from that study were used in the meta-analysis. Table 4 of Behrooz et al\textsuperscript{199} contained results for other psychometric tests, including
results for a continuous performance test. However, 3 outcomes for the continuous performance test were given, none of which was described as the total value. There were 38 outcomes displayed on table 4, equal to the 38 participants in the study, seriously questioning the statistical significance of any result in table 4. Hence all the results from Behrooz et al\textsuperscript{199} table 4 were excluded.

Though the studies that used Beta values as results were excluded from the statistical analysis (including Ghassabian et al 2011\textsuperscript{119}, Williams et al 2012\textsuperscript{179}, Julvez et al\textsuperscript{200}, Chevrier et al\textsuperscript{201}, Oken et al\textsuperscript{182}, Modesto et al\textsuperscript{202}, Craig et al\textsuperscript{10} and Murphy et al\textsuperscript{190} (which used confidence intervals rather than standard deviations for its mean results, hence was treated as a beta value despite using the Mann-Whitney U test) these studies were included as narrative analysis for this thesis (see page 55). The narrative analysis appears after the summary of the meta-analysis in each section.

Having searched the literature, the following sets of narrative and meta-analysis will demonstrate whether the association between a given NDD and maternal hypothyroidism is robust based on the evidence found, thus answering the research questions of this thesis.

**Nature of studies not formally analysed**

Finken et al\textsuperscript{197} showed that maternal hypothyroxinaemia in the 10\textsuperscript{th} percentile resulted in a 41.3 (20.3 to 62.4) ms slower response speed on the Amsterdam Neuropsychological Tasks in the least adjusted model (down to 39.5 (17.6 to 61.4) ms in the most adjusted model), with decreased statistical significance at lower percentiles (possibly due to a smaller number of children). Furthermore, the study also associated on an increased risk with overt hypothyroidism, with those children born to mothers in both the 10\textsuperscript{th} percentile FT\textsubscript{4} and 90\textsuperscript{th} percentile TSH had 71.3 (14.7 to 127.9) ms slower response speed, the model used not shown. The study was also quite large with 1765 participants. However, it is not clear whether mean reaction time is the most important feature of the ANT, and it is certainly not the total, hence this result may be the result of selective reporting (most of the other results in the study were insignificant).

Behrooz et al\textsuperscript{199} did find a negatively significant association between subclinical hypothyroidism and commission errors in the continuous performance task (p=0.04). However, this result was not mentioned in the text of the article, and considering the
large number of outcomes reported in Table 4 of Behrooz et al\textsuperscript{199} (38, equal to the number of participants) was likely to be a statistical false positive (a hypothesis further supported by the fact that the other two outcomes related to the continuous performance task gave insignificant associations). If this result was allowed in, the cases scored lower than the controls, possibly indicating a reduced risk of ADHD, which could have affected the results for the ADHD and subclinical hypothyroidism meta-analysis.

The Noten et al\textsuperscript{175} article was unavailable for data extraction, hence was excluded from this study, however some information was available from a scientific poster. The study measured the association between maternal hypothyroxinaemia and their children’s school performance (similar to Päkkilä et al 2015\textsuperscript{184}). The study found a negatively significant association between maternal hypothyroxinaemia and their children’s arithmetic skills, with an odds ratio of 1.86 (1.24-2.79). Our study did not do a meta-analysis on school performance; hence whether it could have been fitted into the study is questionable. Noten et al also measured Language development in the children (which could have been included in the indicative of intellectual disability meta-analysis), there the odds ratio was 1.36 (0.9-2.06), thus insignificant\textsuperscript{175}.

The Si et al\textsuperscript{181} article was available, but was written in Traditional Chinese script, and though a Chinese speaker was available, they had difficulty with Traditional script, hence to save time this article was excluded. Some information could be gained from the abstract, which was available in English. In this study, after the mothers had their thyroid hormones measured and had given birth, the mother-child pairs were grouped according to the child’s Denver Development Screen Test (DDST) that is with a delay group and a control (normal) group. The differences in maternal thyroid hormones between the groups were then measured. The delay group had significantly higher TSH levels than the control group ($t=4.906$, $p <0.05$), though whether this is selective reporting for the abstract is not clear. This article could have been fitted into the indicative of intellectual disability and subclinical hypothyroidism meta-analysis, and may have strengthened the association.

We found two conference abstracts studying the link between maternal hypothyroidism and neurodevelopmental disorders (Alvarez et al\textsuperscript{203} and Naiki et al\textsuperscript{204}) but were unable to find full articles linked to these studies; hence these studies
were excluded in the results. Alvarez et al studied the association between maternal thyroid levels and the children’s Bayley Scale scores. The study found an association between high maternal TSH and reduced Psychomotor development (adjusted beta value = -1.05, p = 0.038), whilst finding no association between any thyroid hormone and Mental development. Whilst the analysis of motor development was not a major part of this meta-analysis, the results could have been important for the indicators of intellectual disability meta-analysis, possibly weakening the association. However, considering that this study used regression coefficients to present their results, this information probably couldn’t go into the forest plot. Naiki et al studied the association between maternal thyroid dysfunction (and maternal thyroid hormone levels) and the IQ of the children (measured using the Wechsler Intelligence Scale for Children IV). All of the children born were within the normal range of IQ (82 to 127) and no linear association between the thyroid hormones and IQ was found (TSH p =0.08, fT4 p=0.36). If a full article was found, this study could have provided an extra study for the overt hypothyroidism and indicators of intellectual disability meta-analysis (which was lacking in studies), though the meta-analysis would still have come out as weak.

Overall, it seems the studies not formally included in the analysis were unlikely to have made that much difference to the overall results.

**ADHD and overt hypothyroidism**

Only one study dealing with overt hypothyroidism and ADHD was found, hence no meta-analysis could be performed. Andersen et al\textsuperscript{151} investigated the link between hospital diagnosed thyroid disease and ADHD, either based on hospital diagnosis or by prescription of ADHD medication. It estimated a hazard ratio for ADHD and maternal overt hypothyroidism (after adjustments) as 1.10 (0.98-1.25).

Though Andersen et al\textsuperscript{151} was a large data-base study (857,014 singletons were screened) it is only one study, thus the observational association between overt hypothyroidism and ADHD remains unclear, though it appears there is no evidence.

**ADHD and subclinical hypothyroidism**

Figure 10 shows the two studies investigating the link between ADHD and subclinical hypothyroidism used in the meta-analysis (Haddow et al and Päkkilä et al 2014\textsuperscript{118}). Two separate outcomes were given for boys and girls in Päkkilä et al 2014\textsuperscript{118};
however the original research team donated us an odds ratio with the genders merged. Figure 10 showed that the pooled odds ratio for these studies was 1.58 (0.50-5.00), making the association between ADHD and subclinical hypothyroidism insignificant.

Modesto et al\textsuperscript{202} analysed the association between maternal subclinical hypothyroidism (defined as normal fT\textsubscript{4} with TSH higher than 2.5 mIU/l) and ADHD as measured by the Conners Parent Rating Scale-Revised at 8 years. After fully adjusting their model, they came to a beta value of -0.01 (-0.07 to 0.05), deeming the association insignificant. Chevrier et al\textsuperscript{201} analysed the association between continuous TSH levels in the mother and ADHD in the child. This was measured using both the Child Behaviour Checklist and the Kiddies Continuous Performance Test at 5 years, the latter outcome being used in this analysis (namely as it is a direct test rather than a parent reported test, thus less biased). The beta value came out as -0.75 (-4.61 to 3.12), deeming it insignificant. Ghassabian et al 2011\textsuperscript{119} analysed the association between continuous TSH in the mother and externalising behaviour in the child, as measured by the Child Behaviour Checklist. The beta value came out as 0.22 (0.04 to 0.40), deeming it significant.

Considering the result of the forest Plot (see Figure 10) it seems that there is no evidence for an association.
Figure 10: Forest plot of ADHD and subclinical hypothyroidism studies.

A circle before the Study means the odds ratio was calculated by the authors of this thesis, the absence of a circle means the odds ratio was taken from the study. A green circle means the study shows the same significance as the authors of the study demonstrated, a red circle means the study shows greater significance than the authors of the study demonstrated.
ADHD and hypothyroxinaemia

Figure 11 shows the two studies measuring the association between maternal hypothyroxinaemia and ADHD used in the meta-analysis (Munoz et al and Päkkilä et al 2014\textsuperscript{118}). The odds ratio for Munoz et al\textsuperscript{193} was calculated using the Suissa and Whitehead method. For the Päkkilä et al 2014\textsuperscript{118} results, an odds ratio for both genders merged was given to us by the original research team. Figure 11 showed that the pooled odds ratio for these studies was 3.58 (0.07-172.66), making the association between maternal hypothyroxinaemia and ADHD insignificant.

Modesto et al\textsuperscript{202} investigated the link between maternal hypothyroxinaemia (defined as fT\textsubscript{4} below the 5\textsuperscript{th} percentile and TSH between 0.1-2.5 mIU/l) and ADHD. They also used alternative definitions of hypothyroxinaemia, the one chosen for this analysis being the one where thyroid hormone samples were taken at less than 13 weeks (as maternal thyroxine is believed to be more important in early pregnancy). The fully adjusted beta value came out as 0.13 (-0.01 to 0.26), deeming the association insignificant. Chevrier et al\textsuperscript{201} investigated the link between continuous fT\textsubscript{4} and ADHD. The beta value came out as 7.52 (-4.86 to 19.91), deeming the association insignificant. Ghassabian et al 2011\textsuperscript{119} investigated the link between continuous fT\textsubscript{4} and externalising behaviour. The beta value came out as -0.02 (-0.16 to 0.2), deeming the association insignificant.

Considering the result of the forest plot (see Figure 11), it seems there is no evidence for an association.
A circle before the Study means the odds ratio was calculated by the authors of this thesis, the absence of a circle means the odds ratio was taken from the study. A green circle means the study shows the same significance as the authors of the study demonstrated, a red circle means the study shows greater significance than the authors of the study demonstrated.
**ASD and overt hypothyroidism**

Figure 12 shows the two studies that investigated the link between autism and overt hypothyroidism (Andersen et al\textsuperscript{151} and George et al\textsuperscript{195}). Figure 12 showed that the pooled odds ratio for these studies was 2.05 (0.66-6.35), deeming the association insignificant.

Considering the forest Plot (see Figure 12) it seems there is no evidence for an association between maternal overt hypothyroidism and autism (despite both studies giving a positive result), however with only two studies it is still unclear (even though Andersen et al\textsuperscript{151} was a very large study).
Figure 12: Forest plot of ASD and overt hypothyroidism studies.

- Study: Andersen 2014 3 years Autism diagnosis
  - ES (95% CI): 1.30 (1.11, 1.53)
  - Weight: 61.48

- Study: George 2014 2-6 years Autism (CARS > 30)
  - ES (95% CI): 4.25 (1.38, 13.07)
  - Weight: 38.52

- Overall (I-squared = 75.1%, p = 0.041)
  - ES (95% CI): 2.05 (0.66, 6.35)
  - Weight: 100.00

NOTE: Weights are from random effects analysis.
**ASD and subclinical hypothyroidism**

Figure 13 shows the two studies that investigated the link between maternal subclinical hypothyroidism and autism (Yau et al\(^{194}\) and Román et al\(^{8}\)). Both of these studies measured continuous TSH against those with predefined autism. Figure 13 showed that the pooled odds ratio of the studies was 0.62 (0.23-1.65), deeming the association insignificant.

Considering the forest plot (see Figure 13), it seems that there is no evidence for an association between subclinical hypothyroidism and autism; however with only two studies the result is unclear.
Figure 13: Forest plot of ASD and subclinical hypothyroidism studies.

Study | ES (95% CI) | Weight
--- | --- | ---
Yau 2014 3-4 years Autism Diagnosis | 0.33 (0.12, 0.91) | 38.02
Roman 2013 6 years Clinical Pervasive Developmental Problems | 0.92 (0.72, 1.17) | 61.98
Overall (I-squared = 73.1%, p = 0.054) | 0.62 (0.23, 1.65) | 100.00

NOTE: Weights are from random effects analysis
**ASD and hypothyroxinaemia**

There was only one study investigating the link between maternal hypothyroxinaemia and autism, hence no meta-analysis could be performed. Román et al investigated the link between severe hypothyroxinaemia (defined as fT₄ below the 5th percentile with TSH between 0.03 and 2.5 mIU/l) and autism (defined as those who scored within the 98th percentile of the Pervasive Developmental Problems subscale of the Child Behaviour Checklist). It estimated the odds ratio between maternal hypothyroxinaemia and autism to be 2.6 (1.3-5.18).

As there is only one study on the link between maternal hypothyroxinaemia and autism, the evidence is unclear, though the one study did find a strong effect.

**Indicators of intellectual disability and overt hypothyroidism**

Figure 14 shows the two studies that investigated the link between maternal overt hypothyroidism and indicators of intellectual disability (Liu et al¹⁶⁹ and Päkkilä et al 2015¹⁸⁴). We attempted to calculate an odds ratio for Liu et al¹⁶⁹ directly from discrete data in the study. However, none of the children born to mothers with overt hypothyroidism had IQs below the threshold of 90; hence the odds ratio came out as zero. Despite attempts to rectify this, the metan function in STATA automatically excluded Liu et al¹⁶⁹ (see Figure 14).

Thus, the only available odds ratio for maternal overt hypothyroidism and indications of intellectual disability was Päkkilä et al 2015¹⁸⁴. Päkkilä et al 2015¹⁸⁴ measured the association between hypothyroidism (overt and subclinical hypothyroidism were mixed in the study, overt hypothyroidism defined as fT₄ lower than 11.09 pmol/l and TSH greater than 3.5 mIU/l) and IQ (as measured using the Wechsler Intelligence Scale for Children-Revised). It came to an odd ratio of 1.05 (0.55-2.02), deeming the association insignificant.

It seems that there is no evidence for an association between maternal overt hypothyroidism and indicators of intellectual disability, but with only two studies the results are unclear.
Figure 14: Forest plot of indicators of intellectual disability and overt hypothyroidism studies.

A circle before the Study means the odds ratio was calculated by the authors of this thesis, the absence of a circle means the odds ratio was taken from the study. A green circle means the study shows the same significance as the authors of the study demonstrated, a red circle means the study shows greater significance than the authors of the study demonstrated.
**Indicators of intellectual disability and subclinical hypothyroidism**

Figure 15 shows the 9 studies in total used in the meta-analysis. Smit et al\(^{205}\), Behrooz et al\(^{199}\) and Williams et al 2013\(^{177}\) all had their odds ratios calculated using the Suissa and Whitehead methods, whilst for Chen et al\(^{187}\) we calculated the odds ratios directly from the data. Behrooz et al\(^{199}\) presented the results given as insignificant (no child came out with an IQ <85), however after conversion, the odds ratios came out showing positive associations. The pooled odds ratio of the studies came out as 2.01 (0.80-5.08), deeming the association insignificant (see Figure 15). Figure 16 suggested that there may be a strong publication bias in favour of the association.

Julvez et al\(^{200}\) investigated the link between maternal subclinical hypothyroidism (measured as TSH at the 90\(^{th}\), 95\(^{th}\) and 97.5\(^{th}\) percentiles, with an ordinal value showing the trend) and infant cognitive development (as measured using the Bayley Scales Mental Development Index at 14 months). For TSH in the 97.5\(^{th}\) percentile, the beta value came out as 2.29 (-2.78 to 7.36), deeming the association insignificant. Oken et al\(^{182}\) investigated the link between maternal subclinical hypothyroidism (measured as TSH higher than 2.5 mU/l) and intellectual development (as measured using the Peabody Picture Vocabulary Test at 3 years). The beta value came out as 2.5 (-0.8 to 5.7), deeming the association insignificant. Murphy et al\(^{188}\) investigated the link between maternal subclinical hypothyroidism (defined as either TSH higher than 4 mIU/l or fT\(_4\) levels in the 2nd percentile, having both these traits constituted overt hypothyroidism and were excluded, thus half of the case sample technically had hypothyroxinaemia) and IQ (measured using the Wechsler Intelligence Scale for Children-IV). The mean difference between the controls and cases IQs was 5.24 (Mann-Whitney confidence intervals= 0.144 to 10.330), deeming the association positively significant. Chevrier et al\(^{201}\) investigated the link between continuous maternal TSH and numerous measures of cognitive development at 5 years, the chosen one for this thesis being the Wechsler Preschool and Primary Scale of Intelligence 3\(^{rd}\) edition, Performance IQ subscale. The beta value was estimated to be -2.26 (-5.57 to 0.74), deeming the association insignificant.
Williams et al 2012\textsuperscript{179} deals with preterm births (with thyroid hormones measured at birth) whilst Williams et al 2013\textsuperscript{177} deals with full term births (with thyroid hormones measured at 10 weeks, 34 weeks and at birth). Williams et al 2012\textsuperscript{179} measured the association between maternal subclinical hypothyroidism (defined as TSH greater than 3 mIU/l) against intellectual development (as measured by the McCarthy Scales). The beta value came out as -13.541 (-23.931 to -3.151), deeming the association negatively significant (subclinical hypothyroidism associated with decreased McCarthy score).

Considering the results of the forest plot (see Figure 15), it seems there is no evidence for an association between maternal subclinical hypothyroidism and indicators of intellectual disability.
Figure 15: Forest plot of indicators of intellectual disability and subclinical hypothyroidism studies.

A circle before the Study means the odds ratio was calculated by the authors of this thesis, the absence of a circle means the odds ratio was taken from the study. A green circle means the study shows the same significance as the authors of the study demonstrated, a red circle means the study shows greater significance than the authors of the study demonstrated.
Figure 16: Funnel plot of indicators of intellectual disability and subclinical hypothyroidism studies.
**Intellectual disability and hypothyroxinaemia**

Figure 17 shows the 8 studies used for the meta-analysis. Pop et al 2003, Kasatkina et al, Suarez-Rodriguez et al, Grau et al and Ghassabian et al 2014 had their odds ratios calculated using the Suissa and Whitehead method. The pooled odds ratio of the studies came out as 2.69 (1.47-4.95), deeming the association positively significant (see Figure 17). Figure 18 showed some evidence of publication bias in favour of an association, most likely driven by one study with both a high odds ratio and high standard error, namely Suarez-Rodriguez et al.

Craig et al investigated the link between maternal hypothyroxinaemia (defined as fT₄ lower than the 3rd percentile with TSH between 0.1-3.5 mIU/l) and infant cognitive development (measured using Bayley Scale 3, Cognitive subscale). The beta value came out after adjustments as -1.4 (-4.9 to 2.0), deeming the association insignificant. Julvez et al investigated the link between maternal hypothyroxinaemia (defined as fT₄ in the 10th, 5th and 2.5th percentiles, with an ordinal value showing the trend) and infant cognitive development. For fT₄ in the 2.5th percentile, the beta value came out as -4.20 (-8.62 to 0.22), deeming the association insignificant. Williams et al 2012 investigated the link between maternal hypothyroxinaemia (defined as fT₄ lower than 11.7 pmol/l) and intellectual development. The beta value came out as 14.466 (0.453 to 28.479), meaning there was a significant positive association between maternal hypothyroxinaemia and IQ (decreased fT₄ led to a decreased risk of intellectual disability). Chevrier et al investigated the link between continuous fT₄ and IQ at 5 years. The beta value came out as -4.12 (-13.73 to 5.49), deeming the association insignificant. Oken et al investigated the link between continuous tT₄ and intellectual development. The beta value came out as -0.1 (-0.7 to 0.5), deeming the association insignificant.

Considering the forest plot (see Figure 17), it seems there is some evidence for an association between maternal hypothyroxinaemia and indicators intellectual disability.

Note that many differing thresholds were used to define hypothyroxinaemia (see Figure 6). In Figure 19 the meta-analysis was limited to hypothyroxinaemia as defined as fT₄ below the 5th percentile, here the pooled odds ratio came to 2.83 (1.41-5.68), also deeming the association positively significant. Figure 20 showed
evidence of publication bias in favour of an association, driven by one study with both a high odds ratio and high standard error, namely Li et al\textsuperscript{183}. Julvez et al\textsuperscript{200} and Craig et al\textsuperscript{10} both used fT\textsubscript{4} thresholds below the 5\textsuperscript{th} percentile and both showed insignificant results. Despite this, it does seem that there is some evidence for an association between 5\textsuperscript{th} percentile fT\textsubscript{4} in pregnancy and indicators of intellectual disability.
A circle before the Study means the odds ratio was calculated by the authors of this thesis, the absence of a circle means the odds ratio was taken from the study. A green circle means the study shows the same significance as the authors of the study demonstrated, a red circle means the study shows greater significance than the authors of the study demonstrated.
Figure 18: Funnel plot of indicators of intellectual disability and hypothyroxinaemia studies.
Figure 19: Forest plot of indicators of intellectual disability and hypothyroxinaemia (5\textsuperscript{th} percentile fT4 levels) studies.

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<td>Henrichs 2010 30 months Language Development Survey</td>
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<tr>
<td>Ghassabian 2014 6 years Snijders-Oomen Niet Verbale intelligentie test</td>
<td>2.10 (1.58, 2.79)</td>
<td>43.02</td>
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<tr>
<td>Overall (I-squared = 78.7%, p = 0.009)</td>
<td>2.83 (1.41, 5.68)</td>
<td>100.00</td>
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NOTE: Weights are from random effects analysis

A circle before the Study means the odds ratio was calculated by the authors of this thesis, the absence of a circle means the odds ratio was taken from the study. A green circle means the study shows the same significance as the authors of the study demonstrated, a red circle means the study shows greater significance than the authors of the study demonstrated.
Figure 20: Funnel plot of indicators of intellectual disability and hypothyroxinaemia (5th percentile fT4 levels) studies.
Results for Randomized Controlled Trials
In total, only one Randomized Control Trial was found for question 2, that being Lazarus et al. This was not enough to perform a meta-analysis, though this study was analysed.

Exposure Characteristics for Randomized Controlled Trials
In Lazarus et al, the threshold values used were fT₄ lower than the 2.5th percentile and/or TSH higher than the 97.5th percentile. The absolute values for these thresholds is not given, however the 95% confidence ranges are given, and the lower value for fT₄ is 8.4 pmol/l, and the higher value for TSH is 3.65 mIU/l. This range of values meant that overt hypothyroidism, subclinical hypothyroidism and hypothyroxinaemia were all included at once. Those people assigned to the screening group were immediately tested for hypothyroidism, and those with thyroid hormones beyond the thresholds were put on a course of levothyroxine treatment. Those people assigned to the control group had their serum samples taken, yet their thyroid hormones were only measured after delivery of the child.

Outcome Characteristics for Randomized Controlled Trials
Three outcome measures were used in this study: the Wechsler Preschool and Primary Intelligence Scale-3rd edition, the Child Behaviour Checklist (CBCL) and the Behaviour Rating Inventory of Executive Function-preschool version (Brief-P). The CBCL and Brief-P were measured in case those aspects of the child’s behaviour affected their IQ score. A threshold value was given for the Wechsler scale of an IQ less than 85, for the CBCL the significance threshold was above the 98th percentile (though mean values are what were presented) and for Brief-P the threshold was greater than 65. These characteristic were measured once the child was 3 years old.

Risk of Bias for Randomized Controlled Trials
With Lazarus et al, the main concern is that no placebo was put in place for the control group, they were simply untreated (as opposed to say, making them go
through a dummy procedure followed by giving them a placebo). However, given the nature of the study, where the psychological assessments were performed by psychologists on young children (rather than testing the effects of a drug on adults) this aspect may be less relevant. With an attrition rate higher than 20%, there is a strong possibility that there was attrition bias going on in this study, and no attrition analysis was provided in the article. Despite these things, the overall risk of bias in Lazarus et al seemed low (see Table 4).

<table>
<thead>
<tr>
<th>Table 4: Cochrane Checklist for Lazarus et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry</td>
</tr>
<tr>
<td>Random sequence generation (selection bias)</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) (patient-reported outcomes)</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) (Mortality)</td>
</tr>
<tr>
<td>Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))</td>
</tr>
<tr>
<td>Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (&gt;6 weeks))</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
</tr>
</tbody>
</table>
Data Analysis for Randomized Controlled Trials

In total, none of the outcomes measured were deemed significant by the authors of Lazarus et al (see Table 5). When we converted the scores for IQ less than 85 into odds ratios, we came to an odds ratio of 0.834 (0.551-1.262), confirming that the association was insignificant. How the confidence intervals for the difference values were calculated is not clear, though it was probably the standard method\(^\text{209}\). Most of the p-values were calculated using a t-test, though the IQ less than 85 was tested using a \(\chi^2\)-squared test.

Lazarus et al also used Risk ratios showing the different relative risks of low IQ between the screening and control groups depending on differing IQ thresholds, and based on whether the screening group had actually complied with the intervention or not. None of these results were significant.

In conclusion, the one RCT on whether levothyroxine treatment during pregnancy reduces the incidence and/or symptoms of a neurodevelopmental disorder has come out with a negative result.
Table 5: Results from Lazarus et al

<table>
<thead>
<tr>
<th>Test</th>
<th>Screening Group (N = 390)</th>
<th>Control Group (N = 404)</th>
<th>Difference (95% CI) (Control Group − Screening Group)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IQ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>99.2±13.3</td>
<td>100.0±13.3</td>
<td>0.8 (−1.1 to 2.6)</td>
<td>0.40</td>
</tr>
<tr>
<td>&lt;85 (% of children)</td>
<td>12.1</td>
<td>14.1</td>
<td>2.1 (−2.6 to 6.7)</td>
<td>0.39</td>
</tr>
<tr>
<td>CBCL T score‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>44.4±12.4</td>
<td>45.1±13.6</td>
<td>0.7 (−1.2 to 2.5)</td>
<td>0.49</td>
</tr>
<tr>
<td>Brief-P T score§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>40</td>
<td>40</td>
<td>0</td>
<td>0.59</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>47–55</td>
<td>47–55</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Chapter 4: Discussion

The first research question of this thesis was “Is there an association between hypothyroidism in mothers and neurodevelopmental disorders in their children?” Our evidence shows that there is some evidence for an association between maternal hypothyroxinaemia and indicators of intellectual disability. Our meta-analysis shows that there is no evidence for an association between all types of maternal hypothyroidism and ADHD. The association between autism and overt hypothyroidism is insignificant owing to large confidence intervals (despite both studies (Andersen et al\textsuperscript{151} and George et al\textsuperscript{196}) showing a positive result). The association between subclinical hypothyroidism and autism shows an insignificant reverse association, and only one study has investigated the link between autism and hypothyroxinaemia (Román et al\textsuperscript{8}), which showed a positive result. There is no evidence for an association between subclinical hypothyroidism with indicators of intellectual disability, and not enough studies have been done on the link between overt hypothyroidism and indicators of intellectual disability for a clear outcome to be determined.

The fact that there was only a significant association between intellectual disability and hypothyroxinaemia is evidence against the claim that autism, ADHD and intellectual disability share a common aetiology, weakening the claims made by Owen\textsuperscript{45}. Whilst these findings do support the mechanisms
proposed for the aetiology of intellectual disability and psychomotor impairment (see pages 28-29) and marginally support the proposed mechanism for autism (mostly due to Román et al⁸), they do not support the proposed mechanism for ADHD.

The second research question of this thesis was “Does levothyroxine treatment of pregnant mothers lead to a significant drop in diagnosis and/or reduction in the severity of symptoms of neurodevelopmental disorders in children?” Only one randomized controlled trial was found on the topic, Lazarus et al¹¹, which gave a negative outcome. Therefore from the current evidence it seems the levothyroxine treatment of hypothyroid mothers does not reduce the severity of NDD, though with only one RCT the evidence is not clear. These findings do not support the case for universal screening of pregnant mothers for hypothyroidism.

Strengths and Limitations compared to other Meta-Analysis’
In 2015, Wang et al¹⁴⁸ carried out a systematic review entitled “Maternal Thyroxine Levels During Pregnancy and Outcomes of Cognitive Development in Children”¹⁴⁵. Whilst no explicit question was given for the review, the review aimed to answer the question of whether low maternal thyroxine was associated with delayed cognitive skills in the children, for which they searched EMBASE and Medline. They found that using a random effects analysis (much like we did) that there was a combined Risk Ratio of the studies they used of 3.08 (1.83-5.18), deeming the evidence for the association strong. All the studies found in Wang et al¹⁴⁸ appear in our study, including Haddow et al⁷ (which is interesting considering it was mostly based around TSH levels rather than thyroxine levels).

Compared to Wang et al¹⁴⁸, this systematic review looked at more databases, performed grey literature searches and forward and backward citation chasing, allowing a truly comprehensive look at what studies on the link between maternal hypothyroidism and neurodevelopmental disorders exist. Unlike Wang et al¹⁴⁸, which based their statistical analysis on risk ratios, we based ours on odds ratios. Odds ratios have an advantage over risk ratios when dealing with rare diseases²¹⁰ (overt hypothyroidism and diagnosed neurodevelopmental disorders being fairly rare). However, conventionally odds ratios are used for
case-control studies, whilst risk ratios are used for cohort studies\textsuperscript{210}. The majority of studies found were cohort studies; hence the use of odds ratios could affect the validity of the results.

Wang et al\textsuperscript{148} based their searches on a very specific question, namely is there an association between maternal thyroxine levels and child cognitive development. Our study by contrast looked into TSH as well as T\textsubscript{4}, differing types of hypothyroidism (overt, subclinical and hypothyroxinaemia) and into many different neurodevelopmental disorders, including indicators of intellectual disability (the closest to what Wang et al\textsuperscript{148} did). However, despite searching for many types of neurodevelopmental disorders, due to reasons of statistical significance (and pragmatic reasons) we only did meta-analysis for ADHD, autism and (indicators of) intellectual disability (due to the co-morbidity of these NDD). We did not do a meta-analysis on neurodevelopmental traits like reading and mathematics (i.e. dyslexia and dyscalculia) though we did examine psychomotor development in the appendix section (see Results, pages 80-81).

Much of the data extracted from the studies (such as whether the study took place in a hospital or not) was not used in the final analysis. Much of the data that was used in this thesis is displayed in the summary table (see Table 2). Performing a systematic review is a learning curve; hence with the knowledge gained from this review, a more streamlined, relevant data extraction process can be developed for later systematic reviews.

For this thesis we used the Downs and Black Checklist to measure the quality of the studies. Some of the questions on Downs and Black (such as the one about “data dredging”) were difficult to interpret, which may have affected the results. Furthermore, there was uncertainty on which Downs and Black questions were relevant and which were not, further questioning the validity of the quality assessment. However, many of these issues were reduced by the fact that two people examined the data and performed quality assessment; hence this risk to validity may be irrelevant. Wang et al\textsuperscript{148} used the Newcastle-Ottawa scale to assess quality, a scale that has been criticized for having low inter-rater reliability\textsuperscript{211}.

Whilst the Suissa and Whitehead method has been an effective way of converting continuous data into odds ratios, it has not been 100% accurate, as
shown by the false positive result for Behrooz et al\textsuperscript{199}. However, some statistical outliers are expected when dealing with a fairly large number of studies.

The biggest issue in the meta-analysis is probably the inability to find an agreed upon method to convert the regression coefficients into odds ratios, meaning that eight studies could not be included in the meta-analysis. A possible method was found, but that required the standard error of the regression coefficients to be presented, and only one study (Williams et al 2012\textsuperscript{179}) provided the standard error, hence this method was abandoned. This issue was partly overcome by the use of narrative analysis of the regression coefficient results, and from the results, it seems unlikely that they would have affected the meta-analysis substantially.

When choosing whether to classify a study by which type of hypothyroidism (overt, subclinical or hypothyroxinaemia) there were some issues. For example, in many of the studies, T\textsubscript{4} and TSH levels were measured, but were measured and displayed separately rather than in conjunction. Hence rather than view these studies as overt hypothyroidism studies, we treated them as joint subclinical hypothyroidism and hypothyroxinaemia studies, with the outcomes for both used in separate meta-analysis. However, if the results of this thesis go to publication, we may choose to contact the authors of these studies to discuss the classification issue in more depth.

Both the issues of the regression coefficients and classifying hypothyroidism both stem with heterogeneity and lack of clarity in how the studies reported their results. This heterogeneity in reporting outcomes is something that is difficult for a review team to overcome, though hopefully it may advise future studies to be clearer and more homogenous in their reporting.

**Risk of Publication Bias**

As part of our systematic search, we performed grey literature searches, during which no new articles were found. This suggests that unpublished articles are not a major risk in the associations, however there is still a risk of unpublished results within published studies (possibly a decision by researchers to make their articles easier to publish).
The association with the highest risk of publication bias (in the results section) seems to be the association between subclinical hypothyroidism and indicators of intellectual disability (see Figure 20). This is probably due to a large number of low weight (small population sample and/or high levels of variance) studies in this association, the heaviest included study being Henrichs et al\textsuperscript{192} that included 3659 mother-child pairs. Larger scale studies into subclinical hypothyroidism and intellectual disability could correct this bias.

The publication bias risk for hypothyroxinaemia and indicators of intellectual disability is also pretty weak (see Figure 22), probably due to a much higher number of high weight (large population sample and/or low levels of variance) studies compared to the subclinical hypothyroidism meta-analysis (though it is still possibly biased by Suarez-Rodriguez et al\textsuperscript{207} and Li et al\textsuperscript{183}).

**ADHD and hypothyroidism**

An insignificant association was observed for both subclinical hypothyroidism and hypothyroxinaemia (and for the one study on overt hypothyroidism, Andersen et al\textsuperscript{151}), thus it seems that the evidence for an association between maternal hypothyroidism and ADHD is weak. It is possible that the association between maternal hypothyroidism and ADHD is confounded by the child’s IQ (which is associated with maternal hypothyroxinaemia), hence irrelevant for ADHD children with normal IQ.

There was much discussion on how to present the results from Päkkilä et al 2014\textsuperscript{118}. In Päkkilä et al 2014\textsuperscript{118}, separate outcomes were given for boys and girls, something no other study did. It was suggested that we calculate our own odds ratios from the data given, however the odds ratios in the study were adjusted odds ratios, and it was questionable if we could adjust them in the same way. Indeed, the study gave no discrete data on the number of children born into families with more than two children, which was one of the factors Päkkilä et al 2014\textsuperscript{118} adjusted for. For the subclinical hypothyroidism results, we experimented with merging the odds ratios using a fixed effect model, and use that in the meta-analysis (see Appendix 12). We tried contacting the research team in Finland for their own, merged gender odds ratios; and after much delay these results were delivered to us. Considering that these results will have been adjusted in the same way as the results presented in the article, these were the
most accurate outcomes available for the Päkkilä et al 2014\textsuperscript{118} study, hence these were the ones used in this thesis.

Interestingly with Modesto et al\textsuperscript{202}, whilst they found the association between maternal hypothyroxinaemia before 13 weeks gestation and ADHD to be insignificant (beta value $0.13 \, (-0.01 \text{ to } 0.26)$), they found that the overall association of maternal hypothyroxinaemia with ADHD was significant (beta value $0.07 \, (0.003 \text{ to } 0.14)$) if somewhat weaker. This suggests that hypothyroxinaemia later in pregnancy (rather than earlier, as previously assumed) has a stronger association with ADHD. Munoz et al\textsuperscript{194} never specified when the fT\textsubscript{4} levels were measured, and Haddow et al\textsuperscript{7} measured thyroid hormones on average at 17 weeks, well into the second trimester of pregnancy.

2 studies (Ghassabian et al 2011\textsuperscript{119} and Päkkilä et al 2014\textsuperscript{118}) did find an association between continuous TSH levels and ADHD symptoms (for Päkkilä et al\textsuperscript{118} the association was only significant in girls). This raises the question of why would continuous TSH levels show an association but not subclinical hypothyroidism and hypothyroxinaemia (neither of those studies found such associations). ADHD has been associated in the past with thyroid hormone resistance, where the T\textsubscript{4} levels are high yet the TSH levels are unsuppressed\textsuperscript{212}. Thyroid hormone resistance is often associated with mutations to the $\beta$ thyroid receptor, resulting in the receptor being unable to bind to thyroxine whilst forming an inactive complex with the DNA\textsuperscript{213}. Thyroid hormone resistance results in elevated T\textsubscript{4} levels, which could overstimulate the functional $\alpha$ thyroid receptors, leading to symptoms of hyperthyroidism and ADHD (as suggested by Andersen et al\textsuperscript{151}). Thus the association between continuous maternal TSH and ADHD could be the result of genetic thyroid resistance found in both the mother and child. However, these mutations are believed to be rare in the population, making this hypothesis less probable, though a weaker polymorphism causing weaker thyroid resistance than could be more common, which raises possibilities of a genome wide association study (GWAS) into ADHD and thyroid receptors. Then again, the most recent GWAS into ADHD did not find any thyroid receptor genes associated with ADHD at population level\textsuperscript{214}.
Andersen et al\textsuperscript{151} had the advantage of being a very big study, being the biggest study in terms of population sample of all the studies in the meta-analysis. However it also had weaknesses, namely the fact that it was based on records from Denmark’s public health system, yet most children diagnosed with ADHD and Denmark are diagnosed privately\textsuperscript{215}.

Overall, it seems that more studies need to be done to investigate the link between maternal hypothyroidism and ADHD. The small number of studies investigating the link between hypothyroidism and ADHD isn’t surprising, whilst Munoz et al\textsuperscript{193} measured ADHD at 2 years of age; ADHD largely becomes significant once the child is in school, meaning the follow-up time for a study is much longer than measuring infant development. ADHD is generally not measured at 2 years of age (most children that age are hyperactive and inattentive) hence it is largely diagnosed at 7 years of age.

**Autism and hypothyroidism**

Despite both studies showing a significant positive association (Andersen et al\textsuperscript{151} and George et al\textsuperscript{195}), the overall odds ratio for maternal overt hypothyroidism and autism came to 2.05 (0.66-6.35), deeming the association insignificant.

The reason the meta-analysis came out insignificant was probably due to the high level of variability in the George et al\textsuperscript{195} study. This raises the possibility that the link between maternal hypothyroidism and autism could be being confounded by some other association(s). Some of these associations have already been mentioned in this thesis, these include: socioeconomic status, parental obesity, autoimmune responses against the brain, advanced parental age and polycystic ovarian syndrome. This study also suggests that the link between maternal hypothyroidism and autism may be being confounded by the child’s IQ (which is associated with maternal hypothyroxaemia), thus irrelevant to autistic children with normal IQ.

Indeed, George et al\textsuperscript{195} measured the association between multiple factors with autism risk, the most significant factors (excluding maternal hypothyroidism) were: excess fetal movement (11.44 (2.85-45.98)), maternal respiratory infection and/or asthma (6.11 (1.56-24.02)), maternal vaginal infection (5.2 (1.72-15.73)) and family history of neurodevelopmental disorders (2.9 (1.72-
The fact that maternal infections (as well as maternal hypothyroidism) were associated with increased autism risk strongly implicates a role of autoimmunity in the aetiology of autism. However, a recent systematic review on the association between autoimmunity and autism showed that autoimmune hypothyroidism had the strongest link to autism\(^{132}\), though whether that is due to the low thyroxine levels or the thyroid autoantibodies or some other autoimmune or genetic link (many genes implicated in autoimmunity are also implicated in brain development\(^{216}\)) is not clear.

George et al\(^{195}\) suggested (due to their own data and previous research) that the main cause of autism could be increased stress exposure to the fetus. This hypothesis is supported by recent research (Haas et al) which showed that methylation of the \(OXT\) gene (which encodes the neuropeptide Oxytocin) was associated with decreased general sociability\(^{217}\) (decreased oxytocin function has been associated with autism\(^{218}\)). Haas et al suggested that the cause of this epigenetic modification was in part exposure to social stress. This links into other recent research that showed an association between maternal stress and autism in the child, as long as the mother had the short allele of the serotonin transporter promoter region (\(5\text{HTTLPR}\))\(^{219}\). This link between maternal stress and autism could be confounding the results, especially considering research that showed that high TSH is associated with increased levels of cortisol\(^{220}\), a key stress hormone.

Our results suggest that the overall odds ratio for subclinical hypothyroidism and autism is 0.62 (0.23-1.65), deeming the evidence for an association weak, with both studies showing a negative result. The sole study on autism and hypothyroxinaemia showed a positively significant result, with an odds ratio of 2.6 (1.3-5.18). However, the association was only significant if the fT\(_4\) levels were lower than the 5\(^{th}\) percentile, continuous fT\(_4\) and fT\(_4\) in the 10\(^{th}\) percentile was not significantly associated with autism. This suggests that the fetus will only begin to experience problems once a critical level of fT\(_4\) is reached, possibly because the mother’s body will actively transport T\(_4\) to the fetus\(^{221}\).

Overall, it seems that more studies need to be done on the association between maternal hypothyroidism and autism diagnosis before a firm conclusion can be reached. The small number of studies into autism and hypothyroidism isn’t
surprising considering that fully diagnosed autism is much rarer than below average IQ, meaning that finding cases can be difficult.

**Intellectual disability and hypothyroidism**

For this study, we used one standard deviation (s.d.) from the population mean IQ to mean intellectual disability (however, Yau et al\(^{194}\) used a cut-off of 70, which could signify two standard deviations below the mean). Usually this meant one standard deviation from the general population, though for Kasatkina\(^{191}\) that meant one standard deviation from the control sample. Historically, one standard deviation was used to diagnose intellectual disability, which meant that 16% of the population would be diagnosed as having intellectual disability whilst being fully functional and not requiring special care\(^{222}\). For this reason, the diagnosis of intellectual disability was adjusted to two standard deviations, which only includes 3% of the population\(^{222}\). However, IQ one s.d. below the mean is still associated with many negative outcomes, in one study it was found that only 10% of people with an IQ one s.d. below the mean had incomes higher than $34,000\(^{223}\) (the average income in the USA). There are other advantages to using one s.d. below the mean; it means you have a much larger sample size (allowing for greater statistical significance) and it allows you to investigate more subtle effects on brain development, hence we are justified in using IQ one s.d. below the mean as our cut-off.

Only three studies claim to have investigated the link between overt hypothyroidism and intellectual disability, and one of these (Haddow et al) was reclassified as a subclinical hypothyroidism study (even though it probably had some overt hypothyroidism cases in the population sample). Considering that Pakkila et al 2015 used a mixture of overt and subclinical hypothyroidism in their definition of hypothyroidism, it is arguable that the only true study on overt hypothyroidism and intellectual disability was Liu et al\(^{169}\). Crucially, in Liu et al\(^{169}\) all the participant mothers in the study were treated with levothyroxine, questioning whether they were fully hypothyroid during pregnancy. The lack of studies into overt hypothyroidism and intellectual disability isn't surprising considering that overt hypothyroidism is a much rarer phenomenon than subclinical hypothyroidism (with 1.9% of women with overt hypothyroidism against 7.5% of women with elevated TSH\(^{6}\), meaning that finding cases is more difficult. Overt hypothyroidism is also more closely linked to the symptoms
of hypothyroidism, hence is more likely to be treated before pregnancy, restoring the mother to a euthyroid state when tested.

In total, 5 studies show a positive association between hypothyroxinaemia and indicators of intellectual disability, compared to 8 studies that show an insignificant association. Despite this, the meta-analysis for the association showed a strong association, with an overall odds ratio of 2.69 (1.47-4.95) for hypothyroxinaemia.

Kasatkina et al\textsuperscript{191} were measuring the difference in development between children of euthyroid mothers and hypothyroxinaemic mothers \textit{treated} with levothyroxine, hence it could be expected for the difference to be insignificant (Kasatkina et al\textsuperscript{191} also found a positively significant association between continuous fT\textsubscript{4} and the Coefficient of Mental Development at 12 months (R=0.708, p=0.014)). Though Julvez et al\textsuperscript{200} reported an insignificant association between Bayley Mental Development and fT\textsubscript{4} below the 2.5\textsuperscript{th} percentile; they found a significant association between Bayley Mental Development and the fT\textsubscript{4} below the 5\textsuperscript{th} percentile (beta value -3.41 (-6.67 to -0.15)) and with the ordinal value (beta value -1.38 (-2.28 to -0.17) which measures the trend from the 10\textsuperscript{th} to 2.5\textsuperscript{th} percentiles. Considering this, it is arguable that 7 against 6 studies show a positive association between hypothyroxinaemia and indicators of intellectual disability.

There is also the issue of cut-offs used in defining hypothyroidism. For hypothyroxinaemia defined as fT\textsubscript{4} below the 5\textsuperscript{th} percentile, the association with indicators of intellectual disability are stronger (odds ratio 2.83 (1.41-5.68)). The one exception to this trend seems to be Craig et al\textsuperscript{10}, which defined hypothyroxinaemia as fT\textsubscript{4} below the 3\textsuperscript{rd} percentile, yet ultimately gave an insignificant association. However, the value of the 3\textsuperscript{rd} percentile in Craig et al was 11.84 pmol/l, when the other studies gave values lower than 11 pmol/l. Thus it seems that fT\textsubscript{4} levels lower than 11 pmol/l could be critical in the development of indicators of intellectual disability. This is arguably irrelevant, considering that different studies use different assay techniques to measure fT\textsubscript{4}. Indeed, all the cohorts that had their T\textsubscript{4} measured below the 5\textsuperscript{th} percentile were measured using different techniques. Thus the percentile value is probably more important.
Furthermore, the cut-off value used to define subclinical hypothyroidism could be critical. Separate from the results, a statistical analysis on subclinical hypothyroidism as defined as TSH 4mIU/l or higher was done (see Appendices 10 and 11). Of these studies, 3 studies reported a positively significant result against 2 that didn’t. The overall odds ratio for this association between indicators of intellectual disability and subclinical hypothyroidism over 4 mIU/l was positively significant (5.98 (1.17-30.69)). Furthermore Murphy et al\textsuperscript{188} included a lot of hypothyroxinaemic mothers alongside the subclinical hypothyroid mothers, though they did not give the absolute fT\textsubscript{4} cut-offs used and there were more subclinical hypothyroid mothers in the sample.

When looking at these associations, the age of the child can be significant. For example, in Smit et al\textsuperscript{203}, a positive association was found between maternal subclinical hypothyroidism and low Bayley Mental Development at 6 and 12 months, but not at 24 months (the age we chose for the meta-analysis). This suggests that maternal hypothyroidism has a stronger impact on the child at very early stages of development (namely before school age) which then wears off as the child gets older. This is possibly due to the child consuming more iodine after birth, allowing their own thyroxine to repair the delay in brain development (indeed, iodine consumption in childhood is strongly associated with IQ\textsuperscript{224}).

The association between maternal hypothyroxinaemia and indicators of intellectual disability is stronger than the association with subclinical hypothyroidism, supporting the hypothesis that maternal thyroxine is important in brain development, and that maternal hypothyroxinaemia is not harmless and that treatment options should be considered (currently maternal hypothyroxinaemia treatment is not widely recommended).

Despite these associations, the hypothesis that maternal hypothyroidism negatively effects brain development is called into question by the results of Lazarus et al\textsuperscript{11}, in which screening and treating maternal hypothyroidism made no difference to the children’s IQ, according to their own results. Furthermore, there is a study in the pipeline by Casey et al (also a Randomized Control Trial) and early results suggest that levothyroxine treatment for maternal subclinical hypothyroidism and hypothyroxinaemia does \textit{not} result in a decreased
incidence of low IQ. This combined with the fact that the two studies on overt hypothyroidism and IQ gave insignificant outcomes (Liu et al. and Päkkilä et al. 2015), suggests either that the association between maternal hypothyroidism and intellectual disability is largely insignificant, or that it operates by an alternative mechanism.

**Recommendations for Policy, Practice and Contribution of Findings to Theory**

**Hypothesis: Early stage hypothyroidism leads to autism, late stage iodine deficiency leads to ADHD/intellectual disability**

Our evidence suggests that hypothyroxinaemia (which may be caused by iodine deficiency) in the later stages of pregnancy has a bigger impact on child development than hypothyroidism in the early stages of pregnancy.

The most recent systematic review found on the topic (Taylor et al.) found that iodine supplementation during pregnancy following mild iodine deficiency (a urinary iodine content of between 99 µg/l and 50 µg/l) in developed countries did result in improved cognitive abilities for the children. Furthermore, an observational study by Moleti et al found that iodine supplementation had a much greater impact on child cognitive abilities than levothyroxine treatment. This suggests that iodine, which allows the fetus to synthesize its own thyroxine once their thyroid gland is developed, is more important in intellectual development than maternal thyroxine. Considering that hypothyroxinaemia has been proposed to be caused by iodine deficiency, it would explain why our findings show the association between intellectual disability and hypothyroxinaemia to be stronger than the association between ID and subclinical hypothyroidism. Vermiglio et al also demonstrated that mothers living in an iodine deficient area were more likely to have children with ADHD.

ADHD has also been linked to thyroid hormone resistance, caused by non-responsive mutations in the thyroid β receptor. Interestingly, Forrest et al demonstrated in developing chick brains that the thyroid β and α receptors had differing functions in the developing brain. In particular, the α receptors were expressed throughout brain development and were associated with neuron
migration, whilst the β receptors were expressed in the latter stages of brain development and were associated with white matter\textsuperscript{228}. This is significant considering the association between denser cortices and increased short distance connections (indicative of low neuronal migration) with autism\textsuperscript{103} and of reduced long and short distance connections (indicative of low white matter) with low IQ\textsuperscript{81} and ADHD\textsuperscript{41}.

Modesto et al\textsuperscript{202} found the association between maternal hypothyroxinaemia before 13 weeks gestation and ADHD was insignificant after adjustments, however they found that maternal hypothyroxinaemia measured at any stage of gestation and ADHD did have a significant association (beta value 0.07 (0.003 to 0.14)). This possibly means that ADHD had a stronger association with hypothyroxinaemia at later stages of gestation than it did at earlier stages of gestation. Furthermore, Pop et al 2003\textsuperscript{206} reported that the most significant association to Bayley scores was with those mothers who were hypothyroxinaemic consistently throughout pregnancy (hinting that the fetus can recover from bouts of hypothyroxinaemia). Though the overall odds ratio was insignificant, both studies on overt hypothyroidism and autism gave a positive result.

This evidence supports the hypothesis (proposed in the introduction) that hypothyroidism in the early stages of pregnancy (when the fetus is dependent on its mothers thyroxine) results in autism and hypothyroxinaemia (linked to iodine deficiency) in the latter stages of pregnancy (when iodine is needed for the fetus’ own thyroxine) results in ADHD and intellectual disability. The hypothesis goes that in autism, low thyroxine levels from the mother during early pregnancy results in under stimulation of the neural α receptors, resulting in decreased neuronal migration, making the formation of long distance brain connections more difficult, thus stunting corpus callosum formation (resulting in reduced bimanual coordination resulting in most autistic symptoms). Once the fetus is able to synthesize its own thyroxine, if the mother is iodine sufficient, the β receptors will stimulate the formation of white matter connections, but only over short distances (this includes within the hippocampus, restoring IQ, and between the cortex and sub-cortex, resulting in motor stereotypies). This is supported by the findings of Román et al\textsuperscript{8}, Andersen et al\textsuperscript{151} and George et
al\textsuperscript{[195]}, but not from the meta-analysis on autism. Note that iodine deficiency has been associated with autism\textsuperscript{[229]}.

By contrast with ADHD/intellectual disability, low iodine levels mean the fetus is less able to synthesize its own thyroxine, meaning the β receptors remain unstimulated. This means the hippocampus is left undeveloped, resulting in reduced IQ, and the white matter connections to the frontal lobe are considerably less developed, resulting in ADHD symptoms. This is largely supported by the meta-analysis for intellectual disability and hypothyroxinaemia and by the results of Modesto et al\textsuperscript{[202]}, but not by the meta-analysis for ADHD.

Reverse Significance
A few studies in this thesis reported a negatively significant result, in which measures of maternal hypothyroidism measures were associated with a decreased risk of neurodevelopmental disorders. Chevrier et al\textsuperscript{[201]} reported an inverse correlation between TSH and scores on the Child Behaviour Checklist (though this method may be subject to parental bias, hence the Kiddie's Continual Performance Task was used as the main measure in the meta-analysis), with a regression coefficient of -0.65 (-1.26 to -0.04). Chevrier et al\textsuperscript{[201]} also reported a positive correlation between TSH and Mental scores on the Bayley Scale and Auditory comprehension on the Preschool Language Scale, both at 12 months of age (regression coefficients of 1.71 (0.05 to 3.37) and 2.92 (0.59 to 5.25) respectively. Yau et al\textsuperscript{[194]} reported that children with autism and developmental delay (measured separately) were born to mothers with significantly lower TSH levels than the general population (adjusted odds ratios of 0.33 (0.12-0.91) and 0.09 (0.02-0.42) respectively). Williams et al 2012\textsuperscript{[179]} reported a positive association between maternal hypothyroxinaemia and McCarthy score in children born prematurely, the regression coefficient being 14.466 (0.453 to 28.479).

The only one of these studies that could have affected the forest plots is Yau et al\textsuperscript{[194]}, however it would be wise to analyse these reverse significance studies in depth. The results of Chevrier et al\textsuperscript{[201]} corroborate evidence from Andersen et al\textsuperscript{[151]}, which reported a positively significant association between maternal hyperthyroidism and ADHD, with a reported hazard ratio of 1.18 (1.03-1.36). Also of significance is the age of gestation the thyroid hormones were sampled.
at, Chevrier et al\textsuperscript{201} measured at 27 weeks, Williams et al 2012\textsuperscript{179} measured at 34 weeks (or 1 hour after pre-term birth at 34 weeks) and Yau et al\textsuperscript{194} measured at 15-19 weeks. These studies were measuring thyroid hormones well into the second trimester of pregnancy. This supports a hypothesis (mentioned in Williams et al 2012\textsuperscript{179}) that at later stages of pregnancy, hyperthyroidism becomes as bad a factor in neurodevelopment as hypothyroidism. Indeed, Korevaar et al\textsuperscript{178} reported a U-shaped curve for IQ <85 and maternal fT\textsubscript{4} levels, highlighting the risks of maternal hyperthyroidism further (see Figure 21).

At the later stages of pregnancy, when the fetus’ own thyroid gland is beginning to become active\textsuperscript{8}, it is less dependent of the thyroxine of its mother; hence increases in thyroid hormone levels could be more damaging than decreases by this stage. Andersen et al\textsuperscript{151} discussed the possible mechanisms linking maternal hyperthyroidism to ADHD. One possible mechanism being that thyroxine increases the concentrations of dopamine in the developing brain\textsuperscript{230}, with dopamine levels showing an inverse U shaped curve association with working memory scores\textsuperscript{231} (hence too much dopamine due to maternal hyperthyroidism could cause ADHD symptoms). Hyperthyroidism has also been shown to be associated with increased differentiation of the neurons (as indicated by changes in the cytoskeletal structure\textsuperscript{232}), which in turn could slow down the proliferation of the neurons (hyperthyroidism being linked to reduced neuron proliferation\textsuperscript{233}), which could result in the thinner brain cortices reported in ADHD\textsuperscript{234}. Furthermore, reduced glucose metabolism in the prefrontal cortex (part of the frontal lobe) has been associated with adults with a history of hyperactivity\textsuperscript{235}; reduced glucose metabolism in the frontal lobe has also been associated with hyperthyroidism in adults\textsuperscript{236}, suggesting that maternal hyperthyroidism could induce a similar hyperthyroid state in the child. These mechanisms could also result in the developmental delay seen in the Chevrier et al\textsuperscript{201}, Yau et al\textsuperscript{194} and William’s et al 2012\textsuperscript{181} studies. It could also potentially explain why none of the meta-analysis’ for ADHD and hypothyroidism showed a positive result.

Whilst our meta-analysis showed no reverse significance was seen for intellectual disability and ADHD, a weak reverse significance was found for the association between autism and subclinical hypothyroidism (0.62 (0.23-1.65), see Results). Though the reverse association was weak, both studies (Yau et
al\textsuperscript{194} and Román et al) showed some level of negative association, thus it is necessary to look deeper.

The Yau et al\textsuperscript{194} study proposed a differing mechanism for their reverse significance result, placental abnormalities. Trophoblast inclusions (abnormal folding’s of the placenta) have in one study (Walker et al) been strongly associated with subsequent ASD risk in the child, with 4 inclusions meaning a 74\% probability of being at risk of ASD\textsuperscript{237}. Trophoblast inclusions have been used in the past as markers of triploid gestations and of other fetal chromosome abnormalities and spontaneous abortions, and seem to be caused by increased cell proliferation in the Cytotrophoblast\textsuperscript{237}(the placenta’s inner layer). Walker et al hypothesized that the link between Trophoblast inclusions and ASD could be a shared overgrowth phenotype (leading to increased Cytotrophoblast growth and to the increased early stage brain growth reported in autism), or possibly to increased serotonin synthesis in the placenta affecting the brain development of the fetus (increased circulating serotonin has been reported in autism\textsuperscript{238}). Furthermore, overgrowth of the trophoblast can result in increased levels of Human Chorionic Gonadotrophin (HcG)\textsuperscript{239}, a hormone known to result in decreased levels of TSH\textsuperscript{16}, hence the association. However, a generation R study found no association between HcG levels and either IQ or autism in relation to thyroid hormones\textsuperscript{240}. Nonetheless, placental overgrowth could explain the weak reverse association between autism and subclinical hypothyroidism our evidence has shown, and it could be a confounding factor in the association between overt hypothyroidism and autism.

These reverse significance results may just be random error in the overall picture in the link between maternal hypothyroidism and NDD’s. However, the mechanisms they suggest do deserve further study at a later date, possibly in the form of more systematic reviews.
This graph shows a U-shaped curve for IQ <85 and thyroxine levels (B and D) and a reverse U-shaped curve for mean IQ and thyroxine levels (A and C). With inclusion of overt hypothyroidism and hyperthyroidism (A and B), it seems that overt hyperthyroidism has a much greater negative impact on the child’s IQ than overt hypothyroidism.
Recommendations for Future Research

Most of the studies found in this thesis have been short follow up studies, measuring the child’s neurodevelopment when they are still an infant, with small population sizes. What are needed are more long term studies, studying the impact of maternal hypothyroidism of the child at primary school age (5-11 years), involving larger population cohorts. There should also be more studies on autism and ADHD rather than simply IQ and infant development. However such studies would be more expensive, though the lack of certainty surrounding the link between autism and maternal hypothyroidism should warrant such studies. It would also be worth checking if the association holds for both high IQ and low IQ children with autism and ADHD, in case studies are biased in favour of high IQ children (who may be easier to recruit into studies).

To test the hypothesis regarding early vs late hypothyroidism, one would be required to measure maternal thyroid levels at least twice during pregnancy, once before 12 weeks (when the fetus’s own thyroid gland is inactive) and once after 12 weeks. This would then be followed up after 5-6 years to measure the diagnosis of autism, ADHD and intellectual disability and/or to measure traits associated with these NDD. If the hypothesis is correct, those children born to mothers who were overtly hypothyroid before 12 weeks would have an increased incidence of autism, whilst those children born to mothers with hypothyroxinaemia after 12 weeks would have an increased incidence of ADHD and low IQ. This would be a very expensive experiment due to the many measures, and having a long follow up period will make it difficult to keep hold of all the participants.

Also, for the Lazarus study, it may be useful to follow up the children in the screening group to see if they have a decreased frequency of autism diagnosis (despite having normal IQs).
Recommendations for Clinical Practice

As the association between maternal hypothyroxinaemia and indicators of intellectual disability is so much stronger than that with subclinical hypothyroidism, there should be a shift towards measuring T4 levels when diagnosing hypothyroidism than TSH levels. During pregnancy, diagnosis and treatment of hypothyroidism is recommended if TSH is above 2.5 mIU/l. This is according to the Endocrine Society\textsuperscript{241} and American Thyroid Association\textsuperscript{22}, but these guidelines do not recommend treating isolated hypothyroxinaemia, though the European Thyroid Association does\textsuperscript{242}. The reference range for fT4 in the UK is 10-24 pmol/l\textsuperscript{243}, 10 being well under the 11 pmol/l threshold this meta-analysis suggested as being significant, potentially meaning that “at risk” mothers are being missed (though this may be irrelevant due to assay variability). Either way, there should be trimester specific minimum values for fT4, much as there already is for TSH.

There seems to be no evidence that treatment of maternal hypothyroidism with levothyroxine reduces the risk of low IQ. There is however evidence of a link between hypothyroxinaemia and indicators of intellectual disability, and this opens up room for a later systematic review on the association between maternal iodine levels and NDD's (currently the UK has no guidelines on iodine consumption during pregnancy).
Chapter 5: Conclusion

It has been widely suggested that maternal hypothyroidism contributes to NDDs in the child, based largely on the results of the Haddow et al\textsuperscript{7} study. It is hypothesized that between the 8\textsuperscript{th} week of pregnancy (when thyroid hormone receptors are first detected) and the 12\textsuperscript{th} week of pregnancy (when the fetus’ own thyroid gland is active) that the fetus is dependent on the thyroxine of the mother, which is needed by the fetus to promote neuronal migration in the cortex and to promote the development of the cerebellum. In this thesis, the meta-analysis has shown no significant association between hypothyroidism and ADHD or autism (though this is still contentious, especially for autism and overt hypothyroidism). It also found no significant association between both overt or subclinical hypothyroidism and indicators of intellectual disability (ID), and the only Randomized Controlled Trial on the topic found that levothyroxine treatment made no difference to IQ scores. However, the meta-analysis has shown a positively significant association between hypothyroxinaemia and indicators of intellectual disability.

The two studies on overt hypothyroidism and autism (which though insignificant when combined, individually were both significant) combined with the results of Modesto et al\textsuperscript{203} and the association between hypothyroxinaemia and ID suggest a possible mechanism in which early stage maternal hypothyroidism leads to autism (due to reduced neuronal migration due to reduced stimulation of the thyroid α receptor) whilst late stage maternal hypothyroxinaemia leads to lower IQ and ADHD symptoms (due to reduced myelination due to reduced stimulation of the thyroid β receptor). In the latter scenario, the hypothyroxinaemia is probably the result of iodine deficiency rather than autoimmune hypothyroidism.

For future studies, there should be an increased follow-up period, focussing on children of primary school age (5-11 years) with an increased focus on more explicit diagnosis of NDD’s (like autism and ADHD) rather than measuring traits associated with intellectual disability. Whilst such an endeavour would be costly, the evidence of a link between overt hypothyroidism and autism is tantalising.
enough to pursue further investigations. There should also be an increased emphasis on T4 measurements in general practice in addition to TSH measurements, as T4 (whether fT4 or tT4) seems to be more closely linked to neurodevelopmental outcomes than TSH.
Appendices

Appendix 1: Basic Search Terms (modified depending on which data base used)

(hypothyroidism OR hypo thyroid OR hypothyroxinaemia OR hypothyroxinemia OR levo thyroxine OR levo thyroxin OR thyrotropin OR Liothyronine OR (thyroid disease) OR (thyroid deficiency) OR (thyroid diseases) OR thyroid OR (thyroid deficient) OR (thyroid dysfunction) OR (hashimoto's thyroiditis) OR (hashimotos thyroiditis) OR (hashimoto thyroiditis) OR (hashimotos disease) OR (hashimoto's disease) OR (hashimoto disease) OR thyroiditis OR (thyroid neoplasms)) AND (neurodevelopment OR neurodevelopmental OR neuropsychological OR neurocognitive OR (cognitive function) OR performance OR neurobehavioral OR neurobehavioural OR (nervous system development) OR (developmental disorders) OR Autism OR Autistic OR (brain development) OR (neurologic disease) OR (neurologic diseases) OR IQ OR (intelligence quotient) OR (learning disorders) OR (special educational needs) OR (intellectual disability) OR (mental retardation) OR (mentally retarded) OR (mental deficiency) OR (global developmental delay) OR language OR (speech sound disorder) OR stuttering OR (communication disorders) OR (theory of mind) OR cognition OR (pervasive development disorder) OR (pervasive developmental disorder) OR PDD OR Aspergers OR Asperger OR (social behaviour) OR (social behaviour) OR (childhood disintegrative disorder) OR (attention deficit hyperactivity disorder) OR (attention deficit disorder with hyperactivity) OR (attention deficit disorder) OR (hyperactivity disorder) OR (hyperkinetic disorder) OR hyperkinesis OR (child behaviour disorders) OR ADHD OR ADD OR ASD OR ASC OR AD OR dyslexia OR dyscalculia OR (learning difficulties) OR (reading disorder) OR (spelling disorders) OR (disorder of written expression) OR (specific disorder of arithmetic skill) OR (specific disorder of scholastic skill) OR coordination OR dyspraxia OR psychomotor OR motor OR (stereotypic movement disorder) OR (tic disorder) OR (Tourette syndrome) OR stereotypy OR (stereotyped repetitive motor movements) ) AND (maternal OR mother OR mothers OR pregnancy OR pregnant OR gestation OR gestational OR utero OR uterine OR placenta OR placental)
Appendix 2: Search Terms for MEDLINE Data Base Search

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Ovid MEDLINE(R) Daily Update <November 18, 2015>

Search Strategy:

1 hypothyroid*.ti,ab. (28893)
2 hypothyroxinemia.ti,ab. (456)
3 Thyroid Disease*.ti,ab. (11143)
4 Thyroid Hormone*.ti,ab. (30862)
5 Triiodothyronin*.ti,ab. (15160)
6 Thyroxin*.ti,ab. (26649)
7 Thyroid.ti,ab. (146841)
8 thyroid deficiency*.ti,ab. (309)
9 Thyrotropin.ti,ab. (15626)
10 thyroid dysfunction.ti,ab. (3672)
11 Hashimoto*.ti,ab. (5822)
12 Thyroiditis.ti,ab. (11843)
13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (185372)
14 Autis*.ti,ab. (29378)
15 Language development disorder*.ti,ab. (36)
16 Child development disorder*.ti,ab. (7)
17 Attention Deficit Disorder with Hyperactivity.ti,ab. (233)
18 Asperger*.ti,ab. (1826)
19 Pervasive Development* Disorder*.ti,ab. (1843)
20 Social responsiveness scale.ti,ab. (214)
21 Social behavior?.ti,ab. (7152)
22 childhood disintegrative disorder*.ti,ab. (70)
23 ASD.ti,ab. (11422)
24 ASC.ti,ab. (5335)
25 AD.ti,ab. (99735)
26 PDD.ti,ab. (2588)
27 ADHD.ti,ab. (16749)
28 Attention Deficit Hyperactivity Disorder.ti,ab. (17139)
29 Attention Deficit Disorder.ti,ab. (1543)
30 Hyperactivity Disorder.ti,ab. (17415)
31 Hyperkinetic disorder.ti,ab. (193)
32 Child Behavior disorder.ti,ab. (5)
33 Child Behavior disorders.ti,ab. (34)
34 Hyperkinesis.ti,ab. (678)
35 Neurodevelopment*.ti,ab. (18701)
36 Prenatal Exposure Delayed Effects/ or Brain/ or Nervous System/
   (450441)
37 prenatal exposure delayed effects.ti,ab. (2)
38 Brain.ti,ab. (761560)
39 Nervous System.ti,ab. (215524)
40 neuropsychological.ti,ab. (36232)
41 neurocognitive.ti,ab. (12078)
42 neurobehavioral.ti,ab. (9323)
43 Cognition/ (72569)
44 cognition.ti,ab. (41565)
45 Developmental Disabilities/ (16439)
46 Developmental disabilities.ti,ab. (3169)
47 IQ.ti,ab. (16510)
48 intelligence quotient.ti,ab. (2166)
49 Intellectual Disability/ or Intelligence/ (67891)
50 intelligence.ti,ab. (24040)
51 intellectual disability.ti,ab. (6741)
52 mental* retard*.ti,ab. (30942)
53 mental* deficient*.ti,ab. (1775)
54 developmental disorder*.ti,ab. (6391)
55 learning disorder*.ti,ab. (922)
56 special education* need*.ti,ab. (235)
57 Global developmental delay.ti,ab. (533)
58 language disorder.ti,ab. (751)
59 language disorders.ti,ab. (1322)
60 Speech Sound Disorder.ti,ab. (86)
61 Stutter*.ti,ab. (3778)
62 Auditory Perception/ or Phonetics/ or Speech/ (52187)
Auditory Perception.ti,ab. (1173)
Phonetics.ti,ab. (449)
Speech.ti,ab. (60348)
Fluency Disorder*.ti,ab. (66)
communication disorder*.ti,ab. (1041)
dyslexia.ti,ab. (4206)
dyscalculia.ti,ab. (315)
Mathematics/ or Cognition Disorders/ (131979)
Mathematics.ti,ab. (4906)
cognition disorder*.ti,ab. (158)
cognition.ti,ab. (41565)
Reading Disorder*.ti,ab. (383)
spelling disorder*.ti,ab. (45)
Writing/ or Agraphia/ or Verbal Learning/ or Pattern Recognition, Visual/ or Reading/ (68671)
Writing.ti,ab. (19457)
Agraphia.ti,ab. (663)
Verbal Learning.ti,ab. (3580)
Pattern Recognition.ti,ab. (11614)
Reading.ti,ab. (92607)
Disorder of Arithmetic Skill*.ti,ab. (5)
Brain Diseases/ (50429)
brain disease*.ti,ab. (4303)
Disorder of scholastic skill*.ti,ab. (3)
Developmental Coordination Disorder.ti,ab. (694)
Motor Skills Disorders/ (2345)
Motor Skills Disorder*.ti,ab. (6)
Dyspraxia.ti,ab. (418)
Apraxias/ (2447)
Apraxia*.ti,ab. (3167)
Disorder of Motor function.ti,ab. (10)
Movement Disorders/ (14472)
movement disorder*.ti,ab. (10556)
Stereotyp* movement disorder*.ti,ab. (51)
Stereotyped Behavior/ (8135)
Stereotyp* behavior.ti,ab. (1993)
Tic disorder.ti,ab. (486)
tic disorders.ti,ab. (645)
Tourette's syndrome.ti,ab. (1571)
Tourette syndrome.ti,ab. (2363)
102 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 37 or 38 or 39 or 40 or 41 or 42 or 44 or 45 or 46 or 47 or 48 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 71 or 72 or 73 or 74 or 75 or 77 or 78 or 79 or 80 or 81 or 82 or 84 or 85 or 86 or 88 or 89 or 91 or 92 or 94 or 95 or 97 or 98 or 99 or 100 or 101 (1370075)
maternal.ti,ab. (190120)
mother*.ti,ab. (169278)
pregnan*.ti,ab. (404068)
gestation*.ti,ab. (162703)
uter*.ti,ab. (160526)
Placent*.ti,ab. (85965)
109 103 or 104 or 105 or 106 or 107 or 108 (807033)
110 13 and 102 and 109 (1663)
Appendix 3: Search Terms for EMBASE Data Base Search

1. hypothryoid*.ti,ab. (38340)
2. hypothyroxin?emia.ti,ab. (566)
3. levothyroxin*.ti,ab. (3799)
4. thyroxin*.ti,ab. (30822)
5. thyrotropin.ti,ab. (17306)
6. liothyronin*.ti,ab. (258)
7. thyroid.ti,ab. (180454)
8. Hashimoto*.ti,ab. (7629)
9. Thyroiditis.ti,ab. (15033)
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (223305)
11. Neurodevelopment*.ti,ab. (24045)
12. Neuropsychological.ti,ab. (51588)
13. neurocognitive.ti,ab. (17465)
14. cognitive function.ti,ab. (30904)
15. cognition.ti,ab. (55856)
16. language.ti,ab. (120827)
17. performance.ti,ab. (751432)
18. neurobehavio?ral.ti,ab. (11776)
19. nervous system development.ti,ab. (2783)
20. development* disorder*.ti,ab. (8984)
21. Autis*.ti,ab. (37855)
22. brain development.ti,ab. (15037)
23 neurologic disease*.ti,ab. (5914)
24 IQ.ti,ab. (22348)
25 Intelligence Quotient.ti,ab. (2637)
26 Learning disorder*.ti,ab. (1343)
27 Special education* need*.ti,ab. (465)
28 intellectual disability.ti,ab. (9371)
29 mental retard*.ti,ab. (31544)
30 mental* retard*.ti,ab. (38965)
31 Global Developmental Delay.ti,ab. (879)
32 mental* deficien*.ti,ab. (2128)
33 Speech sound disorder*.ti,ab. (186)
34 Stutter*.ti,ab. (4497)
35 communication disorder*.ti,ab. (1403)
36 theory of mind.ti,ab. (3415)
37 Pervasive Development* Disorder*.ti,ab. (2488)
38 Pervasive Child Development Disorders.ti,ab. (1)
39 Asperger*.ti,ab. (2491)
40 Social behavio?r.ti,ab. (8668)
41 behavio?r disorder*.ti,ab. (5906)
42 Attention Deficit Disorder with Hyperactivity.ti,ab. (273)
43 Attention Deficit Hyperactivity Disorder.ti,ab. (21064)
44 Attention Deficit Disorder*.ti,ab. (2216)
45 Hyperactivity Disorder*.ti,ab. (21977)
46 Hyperkinetic Disorder*.ti,ab. (538)
47 Hyperkinesis.ti,ab. (842)
48 ADHD.ti,ab. (23295)
49 ASD.ti,ab. (16322)
50 ASC.ti,ab. (7555)
51 AD.ti,ab. (134395)
52 PDD.ti,ab. (3887)
53 dyslexia.ti,ab. (4985)
54 dyscalculia.ti,ab. (428)
55 learning difficulty.ti,ab. (226)
56 Disorder of Scholastic Skill*.ti,ab. (7)
57 Disorder of Arithmetic Skill*.ti,ab. (5)
Reading disorder*.ti,ab. (473)
Spelling disorder*.ti,ab. (51)
Coordination disorder*.ti,ab. (995)
Dyspraxia.ti,ab. (659)
Psychomotor disorder*.ti,ab. (130)
Motor coordination.ti,ab. (4934)
Motor dysfunction.ti,ab. (3919)
Coordination.ti,ab. (74060)
Stereotyp* movement disorder*.ti,ab. (69)
Tic disorder*.ti,ab. (1325)
Tourette*.ti,ab. (5379)
Motor stereotyp*.ti,ab. (233)
Stereotyp* movement*.ti,ab. (697)
11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 (1329872)
Maternal.ti,ab. (231685)
Mother*.ti,ab. (208091)
Pregnant*.ti,ab. (503979)
Gestation*.ti,ab. (208439)
Uter*.ti,ab. (196411)
Placenta*.ti,ab. (104825)
72 or 73 or 74 or 75 or 76 or 77 (980275)
10 and 71 and 78 (1476)
Appendix 4: Search Terms for PsychInfo Data Base Search

1. hypothyroid*.ti,ab. (1350)
2. exp Hypothyroidism/ (616)
3. hypothyroxin?emia.ti,ab. (35)
4. exp Cerebral Cortex/ or exp "Migration of Nerve Cells"/ or exp Environmental Effects/ or exp Pregnancy/ or exp Autism/ or exp Neurotoxicity/ or exp Thyroid Hormones/ or exp Thyroxine/ or exp Thyroid Disorders/ or exp Thyrotropin/ (182139)
5. Thyroxin*.ti,ab. (927)
6. thyroid.ti,ab. (4102)
7. Thyrotropin.ti,ab. (1113)
8. Hashimoto*.ti,ab. (212)
9. Thyroiditis.ti,ab. (159)
10. 1 or 3 or 5 or 6 or 7 or 8 or 9 (5793)
11. Autis*.ti,ab. (35730)
12. exp Mind/ or exp Cognitive Processes/ or exp Pervasive Developmental Disorders/ or exp Mother Child Relations/ or exp Learning/ or exp Attention/ or exp Brain/ or exp Childhood Development/ or exp Intellectual Development Disorder/ (830329)
13. Mind.ti,ab. (59009)
14. cognitive processes.ti,ab. (15194)
15. pervasive development* disorder*.ti,ab. (2584)
17. Learning.ti,ab. (286133)
18. Attention.ti,ab. (197221)
20. Childhood Development.ti,ab. (926)
21. intellectual development disorder*.ti,ab. (1)
22. Asperger*.ti,ab. (3175)
23. exp Interpersonal Relationships/ or exp Attention Deficit Disorder with Hyperactivity/ or exp Social Skills/ or exp Learning Disabilities/ (185528)
24. interpersonal relation*.ti,ab. (12474)
25. Attention Deficit Disorder with Hyperactivity.ti,ab. (371)
Social Skill*.ti,ab. (11714)  
social responsiveness scale.ti,ab. (205)  
exp Social Behavior/ (575826)  
social behavior.ti,ab. (13371)  
childhood disintegrative disorder.ti,ab. (107)  
exp Developmental Disabilities/ or exp Childhood Psychosis/ (14042)  
developmental disabilities.ti,ab. (6413)  
childhood psychosis.ti,ab. (205)  
Attention Deficit Hyperactivity Disorder.ti,ab. (18748)  
exp Hyperkinesis/ or exp Cognitive Ability/ or exp Executive Function/ or exp Attention Deficit Disorder/ (102865)  
hyperkinesis.ti,ab. (416)  
cognitive ability.ti,ab. (6118)  
executive function.ti,ab. (8071)  
Attention Deficit Disorder.ti,ab. (2072)  
Hyperactivity Disorder.ti,ab. (19002)  
Hyperkinetic disorder.ti,ab. (170)  
exp Behavior Disorders/ (142400)  
Behavior disorder*.ti,ab. (5601)  
ADHD.ti,ab. (20137)  
ASD.ti,ab. (9156)  
ASC.ti,ab. (568)  
AD.ti,ab. (37093)  
PDD.ti,ab. (1567)  
Neurodevelopment*.ti,ab. (8627)  
exp Brain Development/ or exp Cognitive Development/ or exp Neural Development/ or exp Infant Development/ or exp Motor Processes/ (173981)  
Cognitive development.ti,ab. (9707)  
nervous system.ti,ab. (941)  
infant development.ti,ab. (2378)  
motor processes.ti,ab. (748)  
cerebral cortex.ti,ab. (8293)  
migration of nerve cells.ti,ab. (3)  
Neurotoxicity.ti,ab. (3414)  
neuropsychological.ti,ab. (37403)
neurocognitive.ti,ab. (8910)
exp Cognitive Impairment/ or exp Neuropsychology/ or exp Neurocognition/ (45766)
Cognitive Impairment*.ti,ab. (24706)
Neuropsychology.ti,ab. (7317)
Neurocognition.ti,ab. (964)
neurobehavio?ral.ti,ab. (5224)
exp Behavioral Neuroscience/ or exp Neurology/ (17177)
Behavio?ral neuroscience.ti,ab. (600)
neurology.ti,ab. (9539)
cognition.ti,ab. (56347)
IQ.ti,ab. (24238)
exp Gifted/ or exp Wechsler Intelligence Scale for Children/ or exp Intelligence Quotient/ or exp Intelligence/ or exp Academic Achievement/ (101611)
Gifted.ti,ab. (9928)
Intelligence.ti,ab. (62168)
Academic Achievement.ti,ab. (15990)
mental* retard*.ti,ab. (24541)
mental* deficien*.ti,ab. (2725)
intellectual disability.ti,ab. (6173)
exp Behavior Problems/ (25623)
behavio?r problem*.ti,ab. (12627)
development* disorder*.ti,ab. (5586)
special education* need*.ti,ab. (1373)
Global developmental delay.ti,ab. (152)
exp Delayed Development/ or exp Nervous System Disorders/ or exp Ataxia/ (242053)
Delayed development.ti,ab. (329)
nervous system disorder*.ti,ab. (362)
Ataxia.ti,ab. (4569)
language disorder*.ti,ab. (2823)
Speech sound disorder*.ti,ab. (225)
exp Phonological Awareness/ or exp Phonology/ or exp Oral Communication/ or exp Speech Disorders/ or exp "Articulation (Speech)"/ or exp Reading/ (67364)

Phonological.ti,ab. (14653)
Phonology.ti,ab. (2921)
oral communication.ti,ab. (513)
Speech disorder*.ti,ab. (1322)
Articulation.ti,ab. (7533)
Stutter*.ti,ab. (5068)
fluency disorder*.ti,ab. (137)
exp Communication Disorders/ or exp Verbal Fluency/ or exp Language/ (127413)
communication disorder*.ti,ab. (1435)
verbal fluency.ti,ab. (3625)
language.ti,ab. (150888)
dyslexia.ti,ab. (5749)
dyscalculia.ti,ab. (420)
exp Acalculia/ (404)
Acalculia.ti,ab. (167)
Reading.ti,ab. (93555)
spelling disorder*.ti,ab. (64)
exp Orthography/ or exp Spelling/ or exp Agraphia/ (6402)
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Agraphia.ti,ab. (524)
Orthography.ti,ab. (1694)
Disorder of Arithmetic Skill*.ti,ab. (5)
exp Mathematical Ability/ or exp Mathematics/ (23631)
Mathematical Ability.ti,ab. (471)
Mathematics.ti,ab. (24119)
Disorder of scholastic skill*.ti,ab. (4)
exp Special Needs/ (3257)
Special needs.ti,ab. (5172)
Developmental Coordination disorder*.ti,ab. (736)
exp Dyspraxia/ (639)
Dyspraxia.ti,ab. (355)
Disorder of Motor function.ti,ab. (9)
exp Motor Performance/ or exp Cerebral Palsy/ (19331)
performance.ti,ab. (290919)
Cerebral Palsy.ti,ab. (5321)
Stereotyp* movement disorder*.ti,ab. (64)
exp Aggressive Behavior/ or exp Eye Movements/ or exp Tourette Syndrome/ or exp Social Interaction/ or exp Neuropsychiatry/ (350606)
Aggressive behavio?r.ti,ab. (10725)
eye movement*.ti,ab. (18030)
Tourette*.ti,ab. (3350)
social interaction.ti,ab. (14480)
neuropsychiatry.ti,ab. (2008)
Tic disorder*.ti,ab. (960)
exp Obsessive Compulsive Disorder/ (11181)
Obsessive Compulsive Disorder.ti,ab. (11459)
maternal.ti,ab. (42987)
mother*.ti,ab. (101585)
pregnan*.ti,ab. (35990)
gestation*.ti,ab. (10051)
uter*.ti,ab. (3834)
exp Prenatal Exposure/ (5397)
prenatal.ti,ab. (14198)
placent*.ti,ab. (1114)
135 or 136 or 137 or 138 or 139 or 141 or 142 (153974)
10 and 134 and 143 (210)
Appendix 5: Map Terms for CINAHL and AMED

1. Congenital hypothyroidism
2. Triiodothyronine
3. Thyrotropin
4. Thyroiditis, autoimmune
5. Developmental Disabilities
6. Child Development Disorders, Pervasive
7. Articulation Disorders, Organic
8. Motor Skills Disorders
9. Gait Disorders, Neurologic
10. Deaf-Blind Disorders
11. Disorders of Excessive Somnolence
12. Sleep Disorders, Circadian Rhythm
13. Social Behavior
14. Social Readjustment Rating Scale
15. Dystonic Disorders
16. Feeding and Eating Disorders of Childhood
17. Mental Disorders Diagnosed in Childhood
18. Reactive Attachment Disorder
19. Night Terrors
20. Dysphonia, Muscle Tension
21. Child Behavior Disorders
22. Neuromuscular Facilitation
23. Diagnosis, Neurologic
24. Neuropsychology
25. Intelligence
26. Learning Disorders
27. Students, Disabled
28. Organic Mental Disorders, Substance-Induced
29. Hypersensitivity, Delayed
30. Apraxia, Developmental
31. Prenatal Exposure Delayed Effects
32. Agraphia
33. Education, Special
34. Schools, Special
35. Communicative Disorders
36. Articulation Disorders, Functional
37. Speech Disorders
38. Apraxia of Speech (Developmental)
39. Phonetics
40. Fluency Disorders
41. Voice Disorders
42. Alternative and Augmentative Communication
43. Apraxia
44. Sleep-Wake Transition Disorders
45. Movement Disorders
46. Duane Retraction Syndrome
47. Stiff-Person Syndrome
48. Prenatal Diagnosis
49. Umbilical Cord Blood Banks
Appendix 6: Map Terms for BNI

1. Social Problems
2. Spasticity
3. Special Needs
4. Speech disorders
5. Attention Deficit Disorder
6. Hyperactivity
7. Hypersensitivity
8. Neurological Systems and Disorders
9. Neuroscience nursing
10. Neurology nursing
11. Neuroses and Phobias
12. Learning disabilities
13. Mental Handicap
14. Mentally Disordered Offenders
15. Deafness
16. Delirium
17. Dependency Scales
18. Learning Problems
19. Language
20. Swallowing
21. Communication
22. Dysphagia
23. Eating Disorders
24. Disabilities
25. Prenatal care

Appendix 7: Map Terms for Cochrane

1. Adrenal glands
2. Gonads
3. Parathyroid glands
4. Pineal gland
5. Pituitary gland
6. Pituitary-adrenal gland
7. Dextrothyroxine
8. Thyrotropin
9. Thyroxine
10. Triiodothyronine
11. Iodine peroxidase
12. Glycoprotein Hormones
13. Goiter
14. (Euthyroid Sick Syndrome)
15. Akinetic Mutism
16. Child Development Disorders, Pervasive
17. Anxiety, Separation
18. Child Behavior Disorders
19. Developmental Disabilities
20. Communication disorders
21. Learning disorders
22. Intellectual disability
23. Mutism
24. Schizophrenia, Childhood
25. Tic Disorders
26. Stereotypic Movement Disorder
27. Motor Skills Disorder
28. Attention Deficit and Disruptive Behaviour Disorders
29. Feeding and Eating Disorders of Childhood
30. Elimination Disorders
31. Reactive Attachment Disorder
32. Language Development Disorder
33. Adjustment Disorders
34. Affective Disorders
35. Anxiety Disorders
36. Articulation Disorders
37. Attention Deficit Disorder with Hyperactivity
38. Auditory Perception Disorders
39. Child Reactive Disorders
40. Cognition Disorders
41. Consciousness Disorders
42. Conduct Disorders
43. Memory Disorders
44. Attention
45. Conversion disorder
46. Sleep Initiation and Maintenance Disorders
47. Dysphonia
48. Emotional Intelligence
49. Perceptual Disorders
50. Psychomotor Disorders
51. Anhedonia
52. Confusion
53. Catatonia
54. Neurologic Manifestations
55. Apraxias
56. Polydipsia, Psychogenic
57. Mental Fatigue
58. Mental Recall
59. Mental Competency
60. Mental Processes
61. Delirium, Dementia, Amnestic, Cognitive Disorders
62. Agraphia
63. Anomia
64. Dyslexia
65. Speech Disorders
66. Child Language
67. Disorders of Excessive Somnolence
68. Impulse Control Disorders
69. Aphasia
70. Echolalia
71. Awareness
72. Consciousness
73. Imagination
74. Intuition
75. Comprehension
76. Cognitive (Dissonance + Reserve)
77. Higher Nervous Activity
78. Learning
79. Perception
80. Thinking
81. Volition
82. Mind-Body Relations
83. Intention
84. Executive Function
85. Theory of Mind
86. Anticipation
87. Mindfulness
88. Spatial Navigation
89. Psychomotor Agitation
Appendix 8: Maternal Hypothyroidism and Neurodevelopmental Disorders Data extraction form

Bibliographic Information

<table>
<thead>
<tr>
<th>First Author</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Title</td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td></td>
</tr>
<tr>
<td>Citation</td>
<td></td>
</tr>
</tbody>
</table>

Study

Country:  
Setting:  
Recruitment dates:  
Study design:  
Funding source:  
Notes:  

Primary Study Aims (1=yes, 0=no)

| To find an association with neurodevelopmental disorders (Q1) |  |
| To study the effects of maternal hypothyroidism (Q1) |  |
| To reduce the frequency of ND diagnosis (Q2) |  |
| To reduce the symptoms of ND (Q2) |  |
| Other |  |

Notes:  

Primary selection criteria (1=yes, 0=no)
### Main site of intervention (1=yes, 0=no)

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Community-based</th>
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<tbody>
<tr>
<td>Research Centre/University</td>
<td>Organisations/other community locations</td>
</tr>
<tr>
<td>Outdoor Environment</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Not Described</td>
<td></td>
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</tbody>
</table>

### Intervention Delivered by... (1=yes, 0=no)

<table>
<thead>
<tr>
<th>Medical doctors/medical assistants</th>
<th>Research team (unspecified)</th>
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</thead>
<tbody>
<tr>
<td>Psychologists</td>
<td>Other Professional</td>
</tr>
<tr>
<td>Other allied health professional</td>
<td>Not described</td>
</tr>
<tr>
<td>Non-professionals</td>
<td></td>
</tr>
</tbody>
</table>

### Exposure/intervention measured (1=yes, 0=no, N.A.=non-applicable)

#### Demographics
- **Age of mother**
- **Age of child (when assessed)**
- **Selected ethnic group**

#### Type of hypothyroidism measured
- **Overt hypothyroidism**
- **Sub-clinical hypothyroidism**
- **Maternal hypothyroxinaemia**

### Comparator description (1=yes, 0=no, N.A.=non-applicable)

- **ADHD**
- **Other**

### Notes:

- Exposure/intervention measured (1=yes, 0=no, N.A.=non-applicable)

- Comparator description (1=yes, 0=no, N.A.=non-applicable)

- Demographics

- Type of hypothyroidism measured

- Neurodevelopmental disorder measured

- Excluded groups
<table>
<thead>
<tr>
<th>Low fT₄</th>
<th>Cut off value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High TSH</td>
<td>Cut off value</td>
</tr>
<tr>
<td></td>
<td>Hormones measured at</td>
</tr>
<tr>
<td>Levothyroxine treatment</td>
<td>Dosage</td>
</tr>
<tr>
<td></td>
<td>Onset of treatment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparator group described</th>
<th>Normal fT₄</th>
<th>Normal TSH</th>
<th>Hyperthyroidism</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Untreated</td>
<td>Iodine treatment</td>
<td>Other</td>
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</tbody>
</table>

Notes:

How was TSH/fT4/thyroid outcomes measured?:

Demographic Differences between Case and Control group
Outcomes

Primary

Secondary

Method of Assessment

Duration of Follow Up

Analysis (statistics)
Results

Number lost to follow up:

Results of analysis for neurodevelopmental outcomes (Effect size with 95% CI, p-values where available)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
<th>Answer</th>
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<tbody>
<tr>
<td>1</td>
<td>Is the hypothesis/aim/objective of the study clearly described? Must be explicit</td>
<td></td>
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<tr>
<td>2</td>
<td>Are the main outcomes to be measured clearly described in the Introduction or Methods section? If the main outcomes are first mentioned in the Results section, the question should be answered no. ALL primary outcomes should be described for YES</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Are the characteristics of the patients included in the study clearly described? In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given. Single case studies must state source of patient</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Are the interventions of interest clearly described? Treatments and placebo (where relevant) that are to be compared should be clearly described.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Are the distributions of principal confounders in each group of subjects to be compared clearly described? A list of principal confounders is provided. YES = age, severity</td>
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<tr>
<td>6</td>
<td>Are the main findings of the study clearly described? Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions.</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Does the study provide estimates of the random variability in the data for the main outcomes? In non normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported.</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Have all important adverse events that may be a consequence of the intervention been reported? This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events (COMPLICATIONS BUT NOT AN INCREASE IN PAIN).</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Have the characteristics of patients lost to follow-up been described? If not explicit = NO. RETROSPECTIVE – if not described = UTD; if not explicit re: numbers agreeing to participate = NO. Needs to be &gt;85%</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Have actual probability values been reported (e.g. 0.035 rather than &lt;0.05) for the main outcomes except where the probability value is less than 0.001?</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Were the subjects asked to participate in the study representative of the entire population from which they were recruited? The study must identify the source population for patients and describe how the patients were selected.</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Were those subjects who were prepared to participate representative of the entire population from which they were recruited? The proportion of those asked who agreed should be stated.</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? For the question to be answered yes the study should demonstrate that the</td>
<td></td>
</tr>
<tr>
<td>Question</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>-------------</td>
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<tr>
<td>14</td>
<td>Was an attempt made to blind study subjects to the intervention they have received? For studies where the patients would have no way of knowing which intervention they received, this should be answered yes. Retrospective, single group = NO; UTD if &gt; 1 group and blinding not explicitly stated.</td>
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<tr>
<td>15</td>
<td>Was an attempt made to blind those measuring the main outcomes of the intervention? Must be explicit.</td>
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<tr>
<td>16</td>
<td>If any of the results of the study were based on “data dredging”, was this made clear? Any analyses that had not been planned at the outset of the study should be clearly indicated. Retrospective = NO. Prospective=Yes.</td>
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<tr>
<td>17</td>
<td>In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in casecontrol studies, is the time period between the intervention and outcome the same for cases and controls? Where follow-up was the same for all study patients the answer should yes. Studies where differences in follow-up are ignored should be answered no. Acceptable range 1 yr follow up = 1 month each way; 2 years follow up = 2 months; 3 years follow up = 3 months...........10 years follow up = 10 months.</td>
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<tr>
<td>18</td>
<td>Were the statistical tests used to assess the main outcomes appropriate? The statistical techniques used must be appropriate to the data. If no tests done, but would have been appropriate to do = NO.</td>
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<tr>
<td>19</td>
<td>Was compliance with the intervention/s reliable? Where there was non compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. Surgical studies will be YES unless procedure not completed.</td>
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<tr>
<td>No.</td>
<td>Question</td>
<td>Answer</td>
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<tr>
<td>-----</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------</td>
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<td>20</td>
<td>Were the main outcome measures used accurate (valid and reliable)? Where outcome measures are clearly described, which refer to other work or that demonstrates the outcome measures are accurate = YES. ALL primary outcomes valid and reliable for YES</td>
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<tr>
<td>21</td>
<td>Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? Patients for all comparison groups should be selected from the same hospital. The question should be answered UTD for cohort and case control studies where there is no information concerning the source of patients</td>
<td></td>
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<tr>
<td>22</td>
<td>Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same time? For a study which does not specify the time period over which patients were recruited, the question should be answered as UTD. Surgical studies must be &lt;10 years for YES, if &gt;10 years then NO</td>
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<tr>
<td>23</td>
<td>Were study subjects randomised to intervention groups? Studies which state that subjects were randomised should be answered yes except where method of randomisation would not ensure random allocation.</td>
<td></td>
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<tr>
<td>24</td>
<td>Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.</td>
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<tr>
<td>25</td>
<td>Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? In nonrandomised studies if the effect of the main confounders was not investigated or no</td>
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adjustment was made in the final analyses
the question should be answered as no. If
no significant difference
between groups shown then YES

26 Were losses of patients to follow-up taken
into account? If the numbers of patients
lost to follow-up are not
reported = unable to determine.

27 Did the study have sufficient power to
detect a clinically important effect where
the probability value for a
difference being due to chance <5%
Sample sizes have been calculated to
detect a difference of x% and y%.

For randomised controlled trials, the Cochrane checklist (risk of bias
measured as low risk, high risk or unclear risk)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Judgement</th>
<th>Support for judgement</th>
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<td>Random sequence generation (selection bias)</td>
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<td>Allocation concealment (selection bias)</td>
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<td>Blinding of participants and personnel (performance bias)</td>
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<tr>
<td>Blinding of outcome assessment (detection bias) (patient-reported outcomes)</td>
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<td>Blinding of outcome assessment (detection bias) (Mortality)</td>
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<td>Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))</td>
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<tr>
<td>Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (&gt;6 weeks))</td>
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<td>Selective reporting (reporting bias)</td>
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Data extracted by:
### Appendix 9: Outcomes used for Meta-Analysis

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<thead>
<tr>
<th>Category</th>
<th>DSM-specifications</th>
<th>Selection Criteria</th>
<th>Outcome Measures used</th>
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<tbody>
<tr>
<td>Intellectual Disability</td>
<td>• Reduced conceptual skills (such as reading, writing, maths and language)</td>
<td>• Measures of Intelligence Quotient (IQ).</td>
<td>• Bayley Scale</td>
</tr>
<tr>
<td></td>
<td>• Reduced social skills (such as social judgement, empathy and communication skills)</td>
<td>• Measures of Infant Cognitive Development.</td>
<td>• Bayley Scale 3, Cognitive</td>
</tr>
<tr>
<td></td>
<td>• Reduced self-management (such as personal care, job responsibilities and money management)</td>
<td>• Measures of Language Development</td>
<td>• Bayley Scale Mental Development</td>
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<tr>
<td></td>
<td></td>
<td>• Measures of Non-verbal IQ</td>
<td>• Coefficient of Mental Development, Cognition (Gnome Method)</td>
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<tr>
<td></td>
<td></td>
<td>• Measures of general Development Delay</td>
<td>• Mullen Scales of Early Learning</td>
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<td>• Vineland Adaptive Behavior Scales</td>
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<td>• Gesell Development Test, Language</td>
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<td>• Language Development Survey</td>
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<td></td>
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<td>• McCarthy Scales of Children’s Abilities</td>
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<tr>
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<td>• Peabody Picture Vocabulary Test</td>
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<td>• Snijders-Oomen Niet-Verbale</td>
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<tr>
<td>ADHD</td>
<td>Inattention (such as failure to pay attention to details and difficulty organising tasks and activities)</td>
<td>Hyperactivity and Impulsivity (such as excessive talking, fidgeting and an inability to remain still)</td>
<td>Studies that recorded ADHD as diagnosed or used a validated scale were selected. Measures of externalising behaviour were also included.</td>
</tr>
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</table>
| Autism | - Communication Deficits (such as delayed language and responding inappropriately in a conversation)  
- Overt dependence on routines (possibly resulting in being highly sensitive to their environment and being fixated on inappropriate things) | Studies that recorded Autism as diagnosed or used a validated scale were selected. | - Rutters scale B2  
- Autism DSM-IV  
- Childhood Autism Rating Scale (CARS)  
- Clinical Pervasive Development Problems  
- Hospital Diagnosis |
### Appendix 10: Forest Plot for indicators of intellectual disability and subclinical hypothyroidism (greater than 4 mIU/l only)

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<tr>
<th>Study</th>
<th>ES (95% CI)</th>
<th>Weight</th>
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<td>Su 2011 6 months Bayley Scale</td>
<td>10.49 (1.01, 119.19)</td>
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<tr>
<td>Chen 2015 12-24 months Gesell Language score</td>
<td>1.65 (0.52, 5.22)</td>
<td>38.50</td>
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<tr>
<td>Li 2010 25-30 months Bayley Mental score</td>
<td>15.63 (4.70, 51.99)</td>
<td>37.86</td>
</tr>
<tr>
<td>Overall (I² = 72.9%, p = 0.025)</td>
<td>5.98 (1.17, 36.69)</td>
<td>100.00</td>
</tr>
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</table>

**NOTE:** Weights are from random effects analysis
Appendix 11: Funnel Plot for indicators of intellectual disability and subclinical hypothyroidism (greater than 4 mIU/l only)
Appendix 12 Forest plot to calculate merged gender subclinical hypothyroidism odds ratio for Pääkkilä et al 2014.18
References


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