Pre-Existing Differences in Mothers of Children with Autism Spectrum Disorder and/or Intellectual Disability: A Review

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1. Introduction

The autism spectrum disorders (ASD) represent a group of severe and chronic neuro-developmental disorders often simply referred to as autism. [1] Using the criteria provided by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, ASD are diagnosed by impairments within the three strands of DSM-4: *social interaction*, *communication* and *repetitive behaviours or interests*. [2] The aetiology of autism is complex. [3] Research has implicated a strong genetic basis [4-7] involving multiple genes [5, 7, 8] and possible gene-environment interactions. [9-13] Advances in chromosomal microarray analysis and gene sequencing technologies have improved diagnoses and suggest that aetiologies of ASD will continue to be uncovered. [9] In addition, a child presenting with autistic symptoms may be found to have a certain genetic mutation which accounts for their true underlying biological diagnosis. For example, a diagnosis of Rett syndrome would be confirmed when a girl with ASD and intellectual disability was found to have a mutation of the *MECP2* gene on the X-chromosome. [14] Children with ASD and intellectual disability have been found to have an expansion of the *FMR1* gene confirming a diagnosis of Fragile X syndrome. [15]

Autism and intellectual disability commonly coexist with 30-80% of persons with ASD reported as also having ID. [16, 17] Currently, the relationship between ASD and comorbid ID is poorly understood. [18] However, it is known that phenotypically, persons with these disorders can be grouped into the three categories of ASD without ID, ASD with ID and ID only. [18] Intellectual disability (ID) is characterized by an intelligence quotient (IQ) of less than 70 which is associated with limitations in at least two areas of adaptive skill and which

is manifest before 18 years. [19] The level of ID is generally grouped into the five levels of mild, moderate, severe, profound and unspecified by IQ score. In research it is common to stratify ID to the following three levels defined by the American Psychiatric Association [2] (Table 1).

Descriptor/level of ID	IQ score
Mild or moderate ID	35-40 up to 69 points
Severe or profound ID	< 35-40 points
Unspecified ID	< 70*

*Here the person has been assessed as having ID but has not been assessed adequately to determine the level.

Table 1. Levels of intellectual disability

In terms of aetiology, ID can be broadly divided into cases of known biomedical cause and those of unknown cause. The biomedical causes may be divided into genetic and non-genetic causes. Further subdivisions are given in Figure 1.
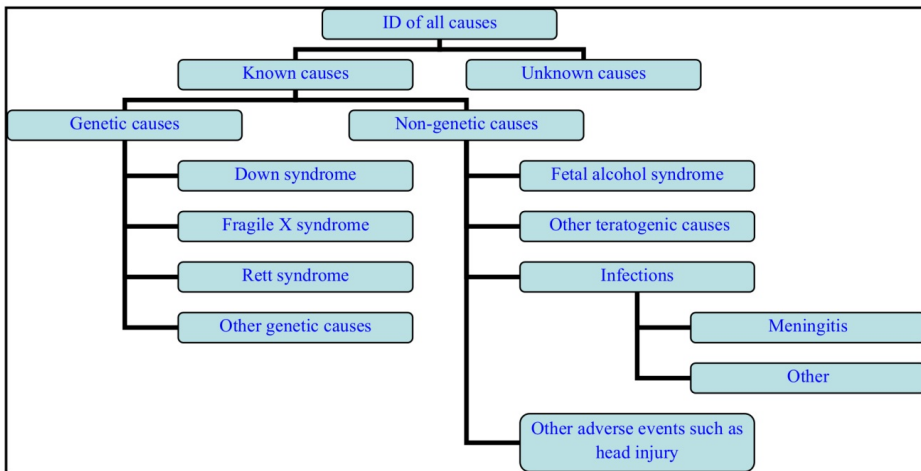
Figure 1. Commonly known aetiologies of intellectual disability

In addition to genetic and non-genetic causes of ASD and ID, relationships with socio-demographic factors such as a mother's education, [20, 21] immigration, [17, 22] and ethnicity, [23] have also been identified. Other reported associations involve aspects of a mother's health including physical characteristics [24] physical [25, 26] and mental health [27, 28] and health behaviours. [29, 30]

It has also been reported that milder autistic traits are present in other family members of individuals diagnosed with ASD. This phenomenon has been coined the Broad Autism

Phenotype [31] and includes qualitatively similar, but milder traits in areas such as language, personality and social behaviour. Some researchers believe that identification of the Broad Autism Phenotype in family members might provide a complementary strategy for detecting genes which contribute to the likelihood of ASD. [32, 33] When comparing family members of a child with ASD to persons from the general population, subtle differences within the Broad Autism Phenotype could be associated with specific brain regions, particular neural pathways, and ultimately with particular genes. [33]

The above factors have been used as guides in choosing terms for our literature search to examine pre-existing characteristics of mothers of children with autism and mothers of children with intellectual disability of unknown cause. Inherent characteristics of mothers of children with a specific disability could be associated with the genetic, environmental or genetic-environmental aetiology of their child's condition. It is therefore important to separate pre-existing factors, particularly in relation to mental health, from morbidities such as depression [34] which might develop due to the more intense demands of caring for a child with ASD and/or ID.

The aim of this study is to review research on the pre-existing characteristics which differentiate mothers of children with ASD and/or ID of unknown cause from each other and from mothers of children without these disabilities. Such an investigation may help to further clarify the determinants of ASD and/or ID including the role of genetic and modifiable risk factors. Improving our understanding of the genetic and environmental causes of ASD and ID may reduce the future burden of these disabilities [35] by hastening the development of effective prevention and treatment strategies.

2. Literature search and selection

The papers considered for this review resulted from a search of the Medline, Web of Knowledge, Scopus and Google scholar databases. Combinations of the search terms below were chosen.

- Terms associated with ASD and/or ID: autis*, pervasive development disorder*, intellectual disability, mental retardation, disab*;

- Terms associated with ASD and/or ID aetiology: immigra*, migra*, ethnic*, age, socio-demographic, prenatal, perinatal, auto*, immun*, anti*, psych* and phenotype*; and

- Terms associated with mothers of children with ASD and/or ID: traits, characteristics, parents, mothers, children, persons.

A paper was included in the review if:

- It was accepted for publication between 1st January 1990 and 31st October, 2012 inclusive;

- It was a full text article in English;

- It described new research and was published in a peer-reviewed journal;

- It described the results of a cohort, case-control, correlation or cross-sectional study of at least 15 subjects;

- It compared a characteristic of parents or mothers of children with ASD and/or ID with parents or mothers of children without disability or with a population norm;

- It assessed characteristics that were pre-existing and not likely to be a result of caring for a child with ASD and/or ID; and

- It used methods of ascertainment and measurement of the characteristic(s) of interest that were assessed as unlikely to lead to bias.

Eighty papers were retained for the review. We stress that these papers do not represent the entire literature pool in the area. Had we chosen different search terms or used different combinations of terms in our searches, the basis for our review would possibly have been different. The three categories for our analyses were; *socio-demographic factors*, *immigrant status and ethnicity* and *health and physical characteristics* and we sorted papers by these categories. An additional 61 articles were used to provide background information and possible explanations of some of the reported associations.

3. Socio-demographic factors

There are a number of considerations which impinge on the effect of socio-demographic factors on the prevalence of ASD and/or ID. Firstly, in persons with ASD with ID and those with just ID, the features overlap to some degree. A child with ASD with ID, particularly in the past, may often have been diagnosed with only ID as there have been secular changes in the identification of children with ASD. Secondly, persons who could be diagnosed with ASD without ID are most often able to function independently and may remain undiagnosed in a range of scenarios. Thirdly, the process through which children are assigned a diagnosis of ASD is much more complex than for ID. Whilst elsewhere, the gold standard might be the considered judgement of an expert clinician who had seen many patients with autism [36], in Western Australia, a diagnosis of ASD in a child requires an assessment by a team comprising a paediatrician, psychologist, and speech pathologist. Waiting times for this assessment can be prolonged in the Western Australian public system [37] and even longer in the US. [38] One effect of these considerations is that in some countries a child whose parents are socioeconomically disadvantaged may oft times be diagnosed with ID when a diagnosis of ASD could be more appropriate.

3.1. Socio-economic status

Thirteen articles researched the parental socio-economic status (SES) of children with ASD and/or ID [17, 20, 21, 39-48] and all but two [42, 43] supported a different association of SES with ASD than ID. Children with ASD were more likely to be from higher SES families but children with ID were more likely to be from lower SES families.

A range of measures of high SES were consistently associated with ASD. In a large telephone interview study in the US, family wealth was used as a measure of SES. [40] The researchers

found that children from higher income families were more likely to have a diagnosis of ASD. Similarly, others using family income as a marker for SES, found a significant association between high family SES and ASD in the offspring. [47] Further analyses, using the dual markers of high family income and high maternal education, found a particular association between high SES and ASD without ID. [47] Using population data and deriving SES from mother's place of residence at time of the child's birth, Australian researchers also found that ASD, ASD with ID and particularly ASD without ID were associated with higher SES. [17]

The overall association between high SES and ASD without ID could result from the increased empowerment of parents of high SES to pursue a diagnosis where their children have a milder variant of ASD. [49] In families of low SES, higher functioning children with autistic traits might be informally labelled by family and contemporaries as unusual, difficult or emotionally damaged. In a comparable way, lower functioning children with autistic traits might be formally or informally given a diagnosis of ID. Others have suggested that children of lower SES parents might be more likely to be diagnosed at a later age than those of higher SES and hence not be included in studies of ASD and SES with lower ages of cut-off. [49]

Further evidence of the possible social contributions to the likelihood of an ASD diagnosis was found in a large multi-based national study in the US. [39] Undiagnosed children who met the criteria for ASD had a lower SES than children who had been previously diagnosed. [39] Area-level SES indicators derived from census data were used in another study where the researchers elucidated that increasing SES and the increasing prevalence of ASD were associated in a dose-response fashion. [39]

King et al. [41] provided evidence that an interaction of social factors was affecting the likelihood of an ASD diagnosis. They examined factors influencing the likelihood of an ASD diagnosis using data on around five million births in Californian cohorts from 1992 to 2000. They found that an interaction between high and low level SES measures influenced the likelihood of an ASD diagnosis. Medi-Cal is a program providing medical assistance to the needy in California and these researchers used family use of Medi-Cal as a binary measure of SES. Property values in the area of a mother's residence were also used as a measure of SES. These researchers reported that children whose families were enrolled with Medi-Cal births and living in wealthier neighbourhoods were two and a half times more likely to receive a diagnosis of ASD than their counterparts living in poorer areas. [41] This could indicate that for parents of limited resources, living in a higher SES neighbourhood had benefits in terms of the likelihood of their child being diagnosed with ASD. Possibly, this results from the parents' increased access to support persons such as paediatricians and child health nurses and to educational programs such as parent classes and interventions for children, compared to that of similar parents in less affluent areas.

In contrast, a Danish study accessing linked population data, used maternal education and parental wealth as a measure of SES and found no association between SES and ASD diagnosis. [42] In neighbouring Sweden, a population-based study published in 2012, used low income, manual occupation and less education as measures of low SES. The researchers concluded that low, not high SES, was a risk factor for ASD. [43] There may be a number of reasons for the differing findings of these studies. The universal health-care and routine screenings offered in

Denmark and Sweden may eliminate the ascertainment bias associated with high SES which may exist in other Western countries. [43]

By comparison with ASD, low SES was often identified as a risk factor for ID [21, 44-46, 48] and especially mild or moderate ID. [17, 20, 48] One of these studies was a cross-sectional study of over five million children. [48] It concluded that children with mild or moderate ID had an increased risk of exposure to social conditions which were detrimental to their development. [48] Another study examined SES and ID prevalence in the 1966 and 1985-6 Finnish birth cohorts. [46] The researchers concluded that the association of low SES with ID was present in both cohorts. Plausible hypotheses for this persisting association are that there had been no improvements in antenatal and obstetric care in those of lower SES over the twenty years in question or, alternatively, there is a prominent genetic involvement in the aetiology of ID. Another, is that the higher risk of exposure to a developmentally unfavourable environment has persisted over the 20 year interval in the children of mothers of lower SES. [48]

In total, ten studies [20, 21, 23, 41, 45, 47, 50-53] used education alone as a measure of SES. All four of the studies investigating ASD reported positive associations between high maternal education and the risk of ASD in the offspring. Three of these studies were from California and each reported that parents of children with ASD were more educated than the general population. [21, 41, 50] The fourth reported that mothers with more than 16 years education were more than twice as likely to have a child with ASD without ID than mothers of a child with only 12 years education. [47] The relationship was reversed with maternal education and ID where all research ascertained a negative association between high maternal education and the risk of ID in the offspring. For instance, with children with unspecified ID [20, 21, 23, 45, 51, 53] and developmental delay without ASD [24](which may include those with known genetic syndromes), seven studies concluded that their mothers were of a lower educational status. One of these, a population study, established that mothers of children with ID were less likely to have more than 13 years of education. [23]

The association of maternal education with varying levels of ID has been investigated including for severe ID and on the basis that risk factors for Down syndrome differed from those of other forms of ID, children with Down syndrome were excluded. Mothers of children with severe ID were found to be more likely to have a lower educational status than mothers in the general population. [52] Comparable results were found for mothers of children with mild or moderate ID [20, 21] of unknown cause. These mothers had increased odds of a lower educational status than mothers in the general population. One of these studies used Californian service agency records and a sample of more than 27 000 mothers of children with mild or moderate ID or severe or profound ID. [21] Less maternal education was also associated with an increased risk of severe or profound ID in the offspring.

3.2. Marital status

Four papers, describing five studies, examined marital status in relation to the odds of ASD and/or ID. [17, 20, 46, 54] At the time of their child's birth, it is uncertain whether a woman's marital status is associated with her odds of a child with ASD. However, mothers of children with ID were more likely to be without partners.

In Australia, a retrospective cohort study, using linked health registries assessed marital status in terms of living with a partner. They reported that at their child's birth, women living with a partner were 35% more likely to have a child with ASD and particularly ASD with ID. [17] On the other hand, a similar Canadian study found that mothers not living with a partner at the time of their child's birth were 19% more likely to have a child with ASD than those mothers who were living with a partner. [54]

With ID, women without a partner had increased odds of having a child with ID [17] and particularly mild or moderate ID. [20] Similarly, a cohort study using UK data, concluded that compared to typically developing children, those with early cognitive delay were less likely to have their biological parents living together during the first five years of their lives compared to families with a typically developing child. [55] However, in Finland, the negative association between living with a partner and the odds of ID in the offspring, present in a 1966 birth cohort, was absent in the 1985-6 cohort. [46] The reduction of the association in the second cohort may have been a reflection of the improved SES of single mothers over the 20 year period.

3.3. Parental age

In most studies, increasing maternal age, sometimes along with increasing paternal age, was associated with ASD. A minority of studies found relationships only with paternal age or found no association with either maternal or paternal age. Contrasting results were reported with ID where teenage mothers were more likely to have children with mild or moderate ID were older mothers and particularly likely to have children with severe or profound ID. Socio-demographic and biological explanations are offered.

All ten studies investigating the association of maternal age with the prevalence of ASD found that advanced maternal age was associated with an increasing prevalence of ASD [17, 29, 47, 56-61] and sometimes ASD without ID. [17, 47] Four of these studies, reported an additional association with paternal age. [17, 56, 58, 61] For instance, a population-based study using data from multiple sites throughout the US, found associations with both maternal and paternal age after adjustment for the other parent's age, birth order and maternal education. [58]

Five of the cited studies specifically reported an association between paternal but not maternal age and ASD in the offspring. [58, 62-65] One of these studies was a small Japanese case-control study of 84 father-child dyads. The researchers reported that advanced parental age was associated with nearly twice the risk of ASD without ID. [65] Another was a population-based Israeli cohort study which used data from a medical registry. [63] The remaining studies used population data from Sweden and another, population data from Denmark. [62, 64] After an adjustment for maternal age, the Swedish researchers identified a linear association of increasing paternal age and the risk of ASD. These researchers commented that if no adjustment was made for paternal age it would appear as though maternal age, rather than paternal was the risk factor for ASD. They added that paternal age could be a risk factor as generally the male was considered to be the origin of new mutations in the gene pool and their production increased with age. [62]

By comparison, three studies from Northern Europe, and UK identified that neither of advancing maternal nor advancing paternal age was a risk factor for ASD. [42, 43, 66] One of the studies from Denmark and another from Sweden used linked data from national registries. [42, 43] The third was a much smaller UK study of around 5 000 participants and parents provided data by completing self-reports. As with broader measures of SES, the results from Denmark and Sweden might reflect the model of health service provision in Scandinavia. Moreover, there is evidence that children with ASD are diagnosed later in younger mothers. [67] Thus there may be a bias of ascertainment in some studies where younger children are included. In the UK study, [66] younger mothers may been included more often since they were recruited when pregnant. Further, a diagnosis of ASD was not required for their child but instead, a parent completed the *Social and Communication Disorders Checklist*. In other studies from the US, [41, 47, 58, 59] Canada [29] and Australia, [17, 57] ASD may be under-ascertained in the children of younger parents, possibly as a result of their lesser confidence to be pro-active in the diagnostic process.

Maternal age had a dual association with ID of unknown cause. Firstly, teenage mothers were more likely to have children with mild or moderate ID. [17, 20, 21] Secondly, older women were more likely to have children with severe or profound ID. [21, 68] The results of a Finnish cohort study which investigated ID of both known and unknown cause [46] was discounted because of the inclusion of ID of known cause. With Down syndrome, the most common cause of ID, it is known that the risk increases very abruptly with advancing maternal age. [69] This might explain the researchers' finding of an association between increased maternal age and ID in the offspring seen in the 1966 birth cohort. [46] The finding that the association no longer existed in 1985-6 cohort may have been because of the introduction or increased uptake of prenatal screening for Down syndrome.

The association of parental and particularly maternal age with ASD and/or ID suggests that both social and biological forces are operating. Younger parents may find a diagnosis of ASD more difficult to obtain for their children because of inexperience and navigational require-ments of local systems. Thus, some of the ID diagnoses of their children may be undiagnosed cases of ASD. Further, the excess of older mothers of children with ASD and to a lesser extent ID may result from increased de novo mutations in older women and their partners [70] or the increase of epigenetic mechanisms which are associated with ageing. [71]

3.4. Parity

Parity describes the number of live-born children and stillbirths at more than 20 weeks gestation of a woman. [72] Two strong relationships of low parity with ASD and high parity with ID have been demonstrated in the majority of studies.

In women of lower parity, the risks of ASD, [29, 41, 73] ASD with ID [17] and ASD without ID [17, 74] were found to be increased in a number of studies. One of these was a Canadian cohort study using linked data-bases and with nearly 1 000 case mothers. [29] The authors identified that nulliparous women (that is women having their first child) were at the greatest risk of having a child with ASD. Moreover, a national, population-based study in the US reported

that older nulliparous women with older partners were around three times more likely to have a child with ASD. [58]

However, two studies found other associations between parity and the risk of ASD. The first, a Danish case-control study nested in population data, found no association. [42] The second, a prospective cohort study using linked health data of more than 110 000 mothers in the US, asserted that mothers of parity greater than two were more likely to have a child with ASD than other mothers. [25] Possibly, socio-demographic factors were also operating in this circumstance. In relation to SES and the odds of ASD, it is possible once again that the disparate findings of this same Danish study may have been due to less ascertainment bias which set them apart from other studies in the area. [42] The second study involved nearly 120 000 nurses who were followed via their completion of mailed questionnaires over sixteen years. [25] Hence, all mothers were educated and due to their involvement with nursing, could be expected, on average, to have more knowledge of ASD than other mothers. Further, parity was assessed as a binary variable with the two values of greater than two and less than or equal to two. Commonly, other studies have defined parity as either a continuous variable or one with more than two possible values and this difference might account for variations in study findings.

Mothers of higher parity had increased odds of having a child with mild or moderate ID. [17, 20, 21] One of the research groups concluded that fourth or subsequent children had an increased risk of mild-moderate ID. [20] A Finnish study of two birth cohorts, twenty years apart, found that high parity persisted as a risk factor for ID over time. [46] A large cohort study compared the parity of the mothers of Californian children with ID to the parity of mothers of typically developing children born between 1987 and 1994. [21] These researchers reported that mothers of parity of three or more were 30-50% more likely to have a child with mild or moderate ID or unspecified ID. [21] Both this study and another Californian study reported that mothers of children with severe or profound ID had an elevated but not significantly increased parity compared to mothers of typically developing children. [21, 52]

3.5. Summary

Socio-demographic factors often operate quite differently for ASD and ID. For example, high parental SES was positively associated with the risk of ASD and negatively associated with the risk of ID in the offspring. Marital status, as defined by living with a partner, has different associations. At the time of their child's birth, there was no consistent association of marital status with mothers of a child with ASD compared to the mothers of typically developing children. On the other hand, mothers of a child with ID were less likely to be living with a partner than mothers of typically developing children. Parity appeared to have reverse associations for ASD and ID. Compared to mothers of typically developing children, mothers of low parity were more likely to have a child with ASD and mothers of high parity were more likely to have a child with ID. Similar patterns exist for maternal age. Mothers of an advanced age were more likely to have a child with ASD than mothers of typically developing children. In contrast, mothers of a younger age were more likely to have a child with ID than mothers

of typically developing children. However, an additional association exists with older mothers being also more likely to have a child with severe ID.

An under-ascertainment of ASD due to social factors and, to a lesser extent an over-ascertainment of ID could be contributing to the socioeconomic effects seen with ASD and ID. For instance, in terms of the severity of ASD, researchers in California, with birth cohorts from 1992 to 2000, divided the children with ASD into two groups of equal size where the less severe group comprised children in the top 50% of cases according to level of functioning and the most severe group was the lower 50%. [41] They found that the children from the less severe group were more often found in neighbourhoods which housed wealthier and more educated individuals. Conversely, the same researchers reported that where low SES was measured by a Medi-Cal payment for the birth, the ratio of more severe to less severe cases was always greater than one. The researchers' interpretation was that the most difficult to diagnose cases of ASD, that is the less severely affected, were under-ascertained in lower SES populations. [41]

The association of high SES with ASD also might be compounded by some of the characteristics known to be related to mothers of children with ASD. Older women with the support of a partner and with fewer children would seem more likely to achieve a more complex diagnosis requiring more assessments for their child than younger single mothers. Socio-demographic associations with ASD in most Western countries do not appear to operate as strongly and might even be absent in some Northern European countries. This might be due to a different social welfare structure in this region and specifically related to the universal screening for developmental disability. In addition to these and other social factors which could bias ascertainment, biological factors may be operating with older parents.

4. Immigrant status and ethnicity

Immigrant describes mothers who give birth while residing in a country which is not their own country of birth. *Ethnic* describes mothers who belong to a minority racial group in their country of residence which may or may not be their country of birth. To some extent, the groups of immigrant and ethnic mothers overlap. When examining social forces in relation to ASD and ID, it is important to take into account the often complex process associated with making a diagnosis of ASD.

4.1. Immigrant status

4.1.1. Immigrant mothers and autism

In all of the eight studies of immigrant mothers of children and ASD, [17, 22, 30, 57, 62, 75-77] the research concluded that immigrant mothers were more likely to have a child with ASD and particularly ASD with ID. [17, 22] In relation to immigrant mothers from Asia one of these studies was conducted by an Australian research group from New South Wales and used birth records and active surveillance to ascertain children with ASD. The group found that immigrant mothers born in South-East or North-East Asia were more likely to have a child with

ASD than other immigrant mothers. [57] A Western Australian study, using linked population data, also found that immigrant mothers from South-East or North-East Asia were at increased risk of having a child with ASD with ID. [17] A similar situation was described in Sweden where immigrant mothers from East Asia were more than three times as likely to have a child with ASD. [76]

Black immigrant mothers and immigrant mothers from developing countries were also found to be more likely to have a child with ASD compared to other immigrant mothers. One study from the UK [75] and another from Sweden [76] reported that black immigrant mothers [75] and immigrant mothers from sub-Saharan Africa [76] were much more likely to have a child with ASD compared to non-immigrant mothers. Further, a small Swedish case-control study compared the prevalence of autistic disorder and pervasive development disorder not otherwise specified (PDDNOS) in black African children with at least one parent born in Somali to the prevalence in children without a Somali background. [77] The researchers reported that these 17 black mothers were from three to four times more likely to have a child with ASD compared to the mothers without a Somali background. [77]

There is evidence that 'the intensity of the mother's skin colour' is related to her risk of having a child with ASD. A Swedish study compared the risk of ASD in the children of immigrants from each of North, East and other parts of Africa. [22] The mothers from North Africa were predominantly Moroccan and hence were probably fairer than the other two groups of mothers. For example, the East African group was predominantly from Somalia and Ethiopia while the ethnicity of the group from other parts of Africa was not described. The risk of ASD in the North African group was elevated (1.5) but not significantly higher than that of non-immigrant parents. On the other hand, the risk in the East African mothers and mothers from other parts of Africa of having a child with ASD was 1.9 and 3.5. [22]

Immigrant mothers from distant countries and those who emigrated during pregnancy were more likely to have a child with ASD than other immigrant mothers. For instance, researchers from the UK and Denmark found that immigrant mothers born outside of Europe were more likely to have a child with ASD. [62, 75] Similarly, a Swedish study found that immigrant mothers who were not from either of the US or Europe were nearly three times as likely to have a child with ASD compared to mothers from Nordic countries. [30] Another Swedish study ascertained that immigrant mothers who emigrated during pregnancy were even more likely to have a child with ASD than mothers who emigrated at other times. [22]

There is evidence that immigrant mothers are at different risks of ASD without ID and ASD with ID. Two Swedish studies found that immigrant mothers, excepting those from neigh-bouring Northern Europe, were less likely to have a child with ASD without ID [22] and Asperger syndrome [76] compared to non-immigrant mothers. One of these studies, along with an Australian study, reported that immigrant mothers were more likely to have a child with ASD with ID. [17, 22] In addition, the Swedish study found that the African immigrant mothers were more likely to have a child with ASD with ID compared to non-immigrant mothers. [22] Similar results were found in a small Swedish case-control study, where all seventeen of the Somali children with autism presented with ASD with ID. [77]

Another group of researchers reported that certain immigrant mothers were less likely to have a child with ASD than non-immigrant mothers. The US study conducted a national telephone survey which chose respondents who resided with their biological child and the child's other parent. [78] These researchers reported that non-immigrant Hispanic children had about twice the prevalence of ASD of immigrant Hispanic children. [78] These results were at variance to those in the previous studies of immigrant mothers. The lower likelihood of ASD in immigrant Hispanics compared to non-immigrant Hispanics could be explained by the relative ease of access of Mexican Hispanics to the US. With many countries, immigrants must meet stringent criteria prior to entry and some of these relate to the health of their offspring, their age, wealth, education and occupation. However, Mexican Hispanics would be less likely to experience the same stress, climatic change and exposure to new infections as most other immigrants groups. Moreover, immigrant parents from some of the other studies have usually relocated from more distant locations. For example, one reported findings which related to immigrants from Somali to Sweden, [77] another to non-European immigrants to Britain [75] and another to immigrants to the isolated continent of Australia. [57]

Overall, immigrant mothers and particularly black or Asian immigrant mothers, mothers from distant, developing countries and those who travelled while pregnant were at a higher risk of having a child with ASD. The mothers at highest risk of a child with ASD were from groups who would be expected to experience the most stress. For example, those relocating from a developing country and those pregnant at the time might be expected to experience higher stress than mothers who are relocating from a developed country or are not pregnant. This stress, along with the environmental changes associated with immigration, may have specific and negative effects on the developing fetal central nervous system. [22]

The risk of immigrant mothers having a child with ASD might be further exacerbated by an increased exposure to novel viruses [75] and intrauterine infections. [57] Other hypotheses to explain this association relate to low vitamin D levels [75, 79] and these have been further fuelled by animal studies. One study of rat pups with gross vitamin D deficiencies reported that they had structural brain abnormalities which were similar to those in children with ASD. [80] Furthermore, ASD was particularly common in black or Asian immigrant women and darker women more often have a vitamin D deficiency. [80] Generally, immigrant mothers are more likely to have a child with ASD with ID and less likely to have a child with ASD without ID. This may indicate different aetiologies for these subgroups.

Along with these biologically–based hypotheses, social factors may affect the likelihood of an immigrant mother having a child diagnosed with one of ASD, ASD with ID or ASD without ID. For instance, a diagnosis of ASD without ID would be particularly difficult where the child's parents were in an unfamiliar country, with a different language and where unusual behaviours might be explained by cultural differences. [22] In Australia, excluding the relatively small group of refugees, and in the US, Asian immigrants and their children are more often of a higher SES than other immigrant mothers. [81, 82] This might explain why the association with ASD was greater in this group than in other immigrant groups.

4.1.2. Immigrant mothers and intellectual disability

Compared to ASD, there was a reverse scenario identified with ID. Overall, immigrant mothers were 20-50% less likely to have a child with mild or moderate ID than non-immigrant mothers. [17, 20, 21] In Australia, Asian immigrant mothers were less likely to have a child with mild or moderate ID than non-immigrant mothers. [17, 20] As with ASD, the reversal with mild or moderate ID might be due to their higher SES compared to other immigrant groups. [81-83]

Differing results were found with the association of ID in the children of Mexican immigrants in a similar manner to the unexpected lower likelihood of Hispanic immigrant mothers having a child with ASD. A study of children with severe or profound ID, and born in California, found that immigrant mothers from Mexico, who would have been likely to be Hispanic, were nearly twice as likely to have a child with severe or profound ID compared to parents born in the US. [52] The idiosyncrasies associated with this immigrant group, compared to those immigrants from more distant locations, might explain this finding. They are likely to be less empowered than their non-immigrant counterparts and, as mentioned previously, their immigration was likely to be less regulated. Hence, from a socio-demographic viewpoint, they are more likely to present with low SES which is a risk factor for ID.

4.2. Ethnicity

In many studies, immigrant status and ethnicity were not differentiated. Therefore, within the ethnic group of mothers, there would have been mothers who, due to their country of birth, were both ethnic and immigrant. A recurrent trend of the research is that mothers from minority ethnic groups were less likely to have a child with ASD and more likely to have a child with ID than mothers who were not from minority ethnic groups.

Epidemiologists have found that mothers from ethnic minorities and particularly Aboriginal mothers were less likely to have a child with ASD. For example, in the US, the Hispanic mothers were less likely to have a child with ASD compared to non-Hispanic mothers. [23, 59, 84] In New York, the prevalence in Latinos was around half that in non-Latinos. [40] Some of these mothers from minority ethnic groups would have also been immigrant and, as reported, immigrant mothers usually have higher rates of ASD. This means that mothers from ethnic minority groups and who are native to their country might be expected to have the lowest likelihood of a child with ASD. This is the case in both Australia and Canada, where Aboriginal mothers had about half the odds of having a child with ASD compared to non-Aboriginal mothers [17, 29]

Compared to ASD, there was a reverse situation with ID since overall mothers from ethnic minority groups were more likely to have a child with ID. Asian mothers giving birth in California were 40% more likely to have a child with severe or profound ID although this result was not significant. [21] Hispanic mothers were more likely to have a child with either mild or moderate ID or severe or profound ID than Caucasian mothers. Again, in each of the ID groups, the results narrowly failed to achieve significance. [21] By comparison, Australian Aboriginal mothers were more than three times more likely to have a child with mild or moderate ID and were 60% more likely to have a child with severe or profound ID. [17, 20]

The higher rates of ID and the lower rates of ASD found in most ethnic minority and particularly indigenous communities may relate to the differing gene frequencies of these groups from the general population. However, differences could be exacerbated by environmental factors such as maternal alcohol consumption [85] without this being specifically identified as an aetiological factor. [86] Another consideration could be that marginalized groups are less empowered than others to pursue a diagnosis of ASD in contrast to a diagnosis of ID and that the infrastructures established for diagnostic assessment do not meet their needs. This second factor may also account for the lower prevalence of ASD and higher prevalence of ID with respect to the Australian Aboriginal community. [87]

In two Californian studies, contrasting findings were found for the previously described associations of ethnicity with ASD. Firstly, a cohort study found that Hispanic mothers were no less likely to have a child with ASD with ID than white mothers. [52] The same study also reported that Californian black mothers were more than five times as likely to have a child with ASD with ID as white mothers. [52] Furthermore, Californian Asian mothers were almost four times as likely to have a child with ASD with ID as white mothers. [52] Again, this may be a reflection of the higher proportion of immigrants in these groups. A second explanation in relation to the Asian mothers could be the fact that Asian mothers in US tend to have a higher SES than most other ethnic mothers. The second of the two Californian studies reported that Asian mothers giving birth in California were 30% less likely to have a child with mild or moderate ID. [21] This may also be a reflection of their higher SES.

4.3. Summary

Generally, immigrant mothers, and especially black and Asian immigrant mothers, were more likely to have a child with ASD compared to non-immigrant mothers. Furthermore, immigrant mothers were more likely to have a child with ASD with ID and less likely to have a child with ASD without ID compared to non-immigrant mothers. Immigrant mothers from distant or developing countries and mothers who emigrated when they were pregnant were even more likely to have a child with ASD. By contrast, in the US, Hispanic immigrant mothers were less likely to have a child with ASD than non-immigrant Hispanic mothers. Furthermore, non-immigrant mothers and particularly Aboriginal mothers were more likely to have a child with ID and especially mild or moderate ID than mothers who were not ethnic.

5. Health and associated characteristics

5.1. Mental health

The *World Health Organisation* describes mental health as a state of mental well-being. [88] This state of well-being can be enhanced by the prevention of mental disorders and the treatment and rehabilitation of those with mental disorders. Compromised mental health has been reported in the mothers of children with ASD and to a lesser extent in the mothers of children with ID compared to mothers of children without these disorders. For example, researchers found that mothers of a child with ASD were more likely to have a pre-existing psychiatric [62,

64, 89] or personality [62, 89, 90] disorder than mothers of typically developing children. Further, parents of a child with ASD were more likely to have increased rates of disorders which were related to affective disorder, [42] obsessive compulsive disorder, [27] anxiety, [27] paranoia, [27] and somatization [27] than the parents of typically developing children. One of these studies was conducted by a Californian team and recruited 269 parents of children with ASD via an existing university research program and control parents of typically developing children who were students (or their contacts) at the university. Self-reported mental health measures were obtained via questionnaire. [27] Other reported associations with parents of a child with ASD were increased rates of schizophrenia, [42, 89, 91] psychosis [42] and depression, [27, 64, 89] compared to the parents of typically developing children. Mothers of a child with ASD were more likely to have had pregnancies complicated by depression [92, 93] than mothers of typically developing children. Another research group explored mental health by comparing the rates of mental disorders in parents of people with ASD to those in parents of people with Down syndrome. [94] Parents of a child with ASD were more likely to have had an anxiety disorder than the parents of children with Down syndrome.

Studies have most commonly investigated the mental health of mothers of children with disabilities rather than the developmental outcomes in children born to mothers with mental health diagnoses. In one case-control study, the latter approach was employed and linked data from population-based registries was used to compare the likelihood of ASD with ID or ID in the children of more than 3 000 mothers with schizophrenia, bipolar disorder or unipolar major depression to the likelihood of these disorders in control mothers. Of these, around 1 300 mothers had bipolar disorder and these were assessed as nearly ten times more likely to have a child with ASD with ID than mothers without these disorders. [95] However, there were only four children with a mother with pre-existing bipolar disorder so these large odds are associated with particularly wide confidence intervals and only just reached significance.

The same study found that children of mothers with either schizophrenia, unipolar major depression or bipolar disorder or a combination of these disorders were about three times as likely to have a child with ID as mothers without these disorders. [95] Furthermore, mothers with ID themselves were more likely to have a child with ID compared to mothers with no history of psychiatric disorder or ID. [95]

5.2. Personality traits

Personality traits have been more often identified in the parents of children with ASD. For instance, parents of children with ASD were more likely to manifest a range of subtle autistic-like characteristics than parents of typically developing children. These characteristics have been grouped together as the Broad Autism Phenotype and include social cognition deficits, such as reasoning about the emotions of others, [96] autistic-like traits, [97] and impaired aspects of executive function. [98, 99]

A questionnaire entitled the Autism Spectrum Quotient (AQ) [100] was designed to assess the Broad Autism Phenotype in the five domains of social skills, communication, attention to detail, attention switching and imagination. [101] Researchers from the UK conducted a case-control study comprising parents of children with and without ASD from more than 1 500

families. Parents of children with ASD were more likely to exhibit autistic-like traits in all domains except that of attention to detail [102] than parents of typically developing children. Furthermore, these researchers and others found that a Broad Autism Phenotype occurred more commonly in parents of children with simplex ASD [97, 102] (where only one family member has ASD) and multiplex ASD [100, 103] (where more than one family member has ASD) than in parents of typically developing children. A dose-response effect was also described with parents in multiplex ASD families expressing a Broad Autism Phenotype significantly more often than parents in simplex ASD families. [32]

Some factors associated with maternal mental health may have a deleterious effect on the fetus and increase the likelihood of a child developing ASD or ID. For example, mothers with schizophrenia may remain on antipsychotic drugs during their pregnancies and these drugs, perhaps along with lower levels of maternal self-care (such as diet and medical care) and genetic factors related to the disease may adversely affect the development in the fetus. The milder autistic features in the parents of children with ASD might also be attributable to genetic factors associated with ASD. [33] In their affected children, these factors, along with additional genetic factors from the other parent, may sometimes produce the clinical phenotype of ASD.

5.3. Physical characteristics

Here are a group of diverse findings pertaining to the physical attributes of the mothers of interest. One study identified that mothers of children with ASD were significantly taller, particularly those of children with ASD without ID compared to the mothers of typically developing children. [17] This study population comprised more than 300 000 mothers and the mean heights of mothers of children with ASD with ID and mothers of children with ASD without ID were 164.3 and 164.9 cm. These means were significantly higher than the mean of the mothers of typically developing children (163.4cm). Another study found that mothers of children with ASD were both taller and heavier than mothers of typically developing children. [93] Similarly, a Canadian population study found that among non-smoking women, taller and heavier women were more likely to have a child with ASD compared to the mothers of typically developing children. [29]

Compared to the mothers of children with ASD, differing associations between maternal height and the mothers of children with ID were identified. Using population data, researchers identified that shorter women and those of medium height were more likely to have a child with mild or moderate ID than other mothers. [20] Further, the shortest group of women were more likely to have a child with severe or profound ID than other women. [20] Others found that mothers of children with mild or moderate ID, with a mean height of 162.1 cm were significantly shorter then than the mothers of typically developing children whose mean was 164.3 cm. However, the mothers of children with severe or profound ID were not significantly shorter than the mothers of typically developing children. [17] However, associations have also been described between SES and height, [104] and so the observed height differences between the mothers of children with ASD and ID may be a reflection of the different mean SES of these groups.

5.4. Health behaviours

Smoking during pregnancy has been associated with both ASD and ID in the offspring. In one study, mothers who smoked during pregnancy were reported to be more likely to have a child with ASD than mothers who did not smoke. [30] In 2011, a Swedish nested case-control study using medical registry data, found that mothers who smoked during early pregnancy were 70% less likely to have a child with ASD but almost twice as likely to have a child with Asperger syndrome. [76] This raises the possibility that Asperger syndrome has a distinct aetiology from other forms of ASD.

On the other hand, differing results were found in a US population-based, case-cohort study which explored the association of mothers who smoked during pregnancy and ASD. [105] Data from more than 6 000 000 mothers and their children were adjusted for potential confounders such as maternal age, education, and marital status. The definition of smoking during pregnancy was not described in the paper, so presumably this encompasses all mothers who had admitted to smoking one or more cigarettes during their pregnancy. The researchers reported that mothers who smoked during pregnancy were no more likely to have a child with ASD than mothers who did not smoke. Two large recently published cohort studies published in 2010 and 2011 also found no association between mothers who smoked during pregnancy and ASD. [29, 106] However, the first study examined only associations between maternal smoking and ASD generally [29] Hence, any associations between the relatively small group of mothers of children with Asperger syndrome may have been lost in the broader analysis. In addition, smoking was defined as *any smoking during pregnancy* which may have lessened the likelihood of an association with ASD. These were different outcomes to the second study, where mothers of children with ASD with ID and ASD without ID were considered separately and mothers who smoked ten or more cigarettes a day were a distinct group from the less intense smokers. [106] The first research group suggested that associations found with other studies were attributable to a confounding by maternal socio-demographic characteristics. [29]

The findings of associations between smoking during pregnancy and ID are also limited. A population study in the US ascertained that mothers who smoked 20 or more cigarettes a day were more likely to have a male child, but not a female child, with ID than mothers who did not smoke during pregnancy. [107] A large Finnish cohort study found that mothers who smoked after 2 months of pregnancy were no more likely to have a child with ID than mothers who did not smoke after this time. [46] This definition of smoking is broader than that of the first study so the likelihood of identifying an association between maternal smoking and ID may be reduced. Further, smoking during the first two months of pregnancy or gender of the fetus was not considered for inclusion in the model. An alternative study, with a more stringent definition of maternal smoking and which addressed these omissions, would be more likely to discern an association between smoking and ID.

Mothers who consume excessive alcohol during pregnancy were assessed as more likely to have a child with ID (but not ASD). This cause of ID is termed fetal alcohol syndrome (FAS) or fetal alcohol spectrum disorder (FASD). Fetal alcohol syndrome is at the most severe end of the spectrum and is diagnosed by characteristic facial features, brain dysmorphology, intellectual and other disabilities. [108] The milder diagnosis of FASD [109] does not require

the presence of all of the characteristic physical features required for FAS. [110] Studies from Sweden and the US attributed between 2-10% of mild or moderate ID to FAS or FASD. [111, 112] While the US study considered that a further 3% of severe or profound ID was caused by FAS or FASD. [112]

In a Western Australian record linkage study heavy prenatal alcohol exposure was found to be an important cause, accounting for 2.5% of non-genetic intellectual disability. [85] Under-ascertainment, particularly of FASD, may result from non-disclosure of alcohol consumption during pregnancy due to the associated stigma. [113] In addition, perhaps due to inadequate training, [114] clinicians may lack awareness and confidence in making this diagnosis. [113] Also, clinicians may be concerned at the psychological effect on the mother of a FASD diagnosis and may not pursue this in situations where it is not conclusive or they feel it would not be beneficial to the mother or child.

Large cohort studies and linked data have provided researchers with the opportunity to study whole populations of mothers and their children with and without ASD and/or ID. Data can also be adjusted for a range of possible confounders such as SES and age. This enables the identification of new risk factors for ASD and/or ID and the elimination of others. For example, the association of smoking during pregnancy with ASD and/or ID in the offspring has weakened in the most recent studies using linked population data. Persisting associations are an increased risk of Asperger syndrome or PDD-NOS in mothers who smoked during pregnancy and an increased risk of ID in the male children of mothers who smoked heavily during pregnancy. Maternal alcohol consumption during pregnancy remains a risk factor for ID.

The remaining associations of maternal smoking with ASD and ID in the offspring could result from the effect of this exposure on overall fetal development and particularly growth restriction, [115, 116] preterm birth [115] and low birth-weight [117] Moreover, sub-optimal fetal growth has been associated with mild or moderate ID in Caucasian children. [118] The association of maternal alcohol consumption with ID might be due the multiple effects of alcohol on the fetus and placenta. [119] For example, alcohol can induce oxidative stress in placental villous tissue. Other demonstrated effects are an increase in neural tube defects and increased heart rate and cortisol levels in the exposed infant.

5.5. Physical health

The research literature has provided evidence that maternal physical health, both prior to and during pregnancy is related to the likelihood of a mother having a child with ASD and/or ID. Various pre-existing conditions in the mother and related or unrelated complications of her pregnancy increase the likelihood of a mother having a child with ASD and/or ID compared to mothers who do not have the condition.

Pre-pregnancy obesity is an example of a condition which increases the likelihood of a woman having a child with ASD and/or ID. Obese women were more likely to have a child with ASD, [24, 54, 120] or ID [24, 46] than women who were not obese. One of these studies was a Finnish study which used linked data from the birth cohorts of 1966 and

1985-6 and included around 250 mothers of children with ID in each of the cohorts. [46] In both cohorts, mothers with obesity prior to their pregnancies were more likely to have a child with ID than women without pre-pregnancy obesity. However, the association of ID with pre-pregnancy obesity was an increasing risk reflected in the greater odds in the latter cohort(2.4) compared with the original cohort(1.8). [46] Another of the research groups reported that women with an early age of menarche were more likely to have a child with ASD than other women. [120] Early menarche, along with pre-pregnancy obesity, could indicate the possibility of maternal hormonal involvement in the risk of ASD and ID. [120] Then again, the relationship with ID may be resulting from confounding by the association between socioeconomic disadvantage and obesity in highly developed countries. [121] In the light of the increasing prevalence of obesity in these countries, these associations with ASD and ID are an important future research direction. [122]

Women with an auto-immune disorder or anomalies of the immune system were more likely to have a child with ASD and/or ID than women who did not. [25, 26, 123] Furthermore, the majority of associations in this area were with ASD rather than ID. For example, in a case-control study using linked data with more than 1 200 cases, mothers with an auto-immune disorder were 60% more likely to have a child with ASD than mothers without an auto-immune disorder. [26] These findings were supported by a small case-control study of 61 mothers of children with ASD. [123] Other studies have found that women with a particular auto-immune disease were more likely to have a child with ASD than women who did not have the disease. For instance, a case-control study with 407 cases found that women with psoriasis were more likely to have a child with ASD than mothers without this disorder. [124] Another research group used linked population data with more than 3 000 mothers of a child with ASD and nearly 700 000 control mothers. They reported that women with rheumatoid arthritis or celiac disease were more likely to have a child with ASD than mothers who did not have one of these disorders. [125]

One study found that women with pre-existing diabetes were more likely to have a child with ASD than women without pre-existing diabetes [29] However, a study used linked data from the national birth and inpatient registries and reported that women with pre-existing diabetes were no more likely to have a child with ASD than other mothers. [30] In relation to ID, a group of US researchers investigated a possible association with diabetes by comparing more than 160 000 mother-child dyads. The researchers identified that mothers with pre-existing diabetes were more than 10% more likely to have a child with ID. [126] Diabetes during pregnancy was also associated with both ASD and ID. For instance, two studies found that mothers with diabetes during pregnancy were more likely to have a child with ASD [25] and ASD with ID [127] than mothers without the disorder. The first of these was a Canadian population study which included nearly 800 cases of ASD and more than 66 000 births. Mothers who developed gestational diabetes were associated with a 76% increased risk of ASD compared to women who did not develop the condition. [25] The second was an Australian population study which found that mothers who had diabetes during pregnancy were nearly three times as likely to have a child with ASD with ID than mothers without diabetes. [127] More attenuated results were

ascertained by Californian researchers who conducted a case-control study and compared the mothers of more than 500 children with ASD, 172 mothers of children with developmental disabilities other than ASD to typically developing children. [24] They found that mothers with gestational diabetes were more likely (but not significantly more likely) to have a child with ASD than mothers without the disorder. The lack of significance may be due to the reduced power of this smaller study. Two studies identified an association between gestational diabetes and ID or a condition similar to ID. [24, 127] One was a large retrospective cohort study using linked registry data. Here the researchers found that mothers with diabetes during pregnancy were nearly 70% more likely to have a child with mild or moderate ID [127] compared to mothers without this disorder. The other research group found that mothers with diabetes during pregnancy were nearly two and a half times more likely to have a child with a developmental disability other than ASD than mothers without diabetes during pregnancy. [24]

Further, differences have been identified relating to the immunological status of mothers of children with ASD prior to their pregnancies. An independent case-control study identified fetal brain antibodies in mothers of children with ASD but not in controls mothers. [128] This study found that mothers of children with ASD were significantly more likely to have an auto-antibody reactivity pattern for human fetal brain proteins than mothers of typically developing children.

Cytokines are regulators of immune response and maternal immune dysfunction has been associated with the neurological development of the fetus. [129] A case-control study identified that mothers of children with ASD and/or ID were more likely to have aberrant cytokine profiles compared to the mothers of typically developing children. [130] In this study, the concentration of serum cytokines at mid-pregnancy in the mothers of children with ASD with ID, developmental disabilities other than ASD and typically developing children were compared. Mothers of a child with ASD with ID were more likely to have higher concentrations of three particular cytokines than mothers of a typically developing child. In addition, mothers of a child with a developmental disability other than ASD were more likely to have higher concentrations of a different set of three different cytokines (to the ASD group) than mothers of typically developing children. [130]

Auto-immune diseases and other immune dysfunction might impinge on the immature nervous system of the developing fetus. This could have a deleterious effect on future cognitive function [131] and increase the likelihood of ASD and ID. [130]

Hypertension or high blood pressure is either a temporary or sustained elevation of the blood pressure in the arteries. [132] Moreover, the elevation is at a level where cardiovascular or other damage may occur. Hypertension during pregnancy was associated with an increased risk of ASD in the child. Three studies provided evidence that women who experienced hypertension during pregnancy were more likely to have a child with ASD [24, 30, 54] than women who had not suffered hypertension. In one of the studies, Swedish researchers conducted a nested, matched case-control study with data from over 400 children with ASD and over 2 000 controls. [30] Records of children's hospitalisation over 10 years were linked to birth records. The researchers concluded that mothers who suffered a hypertensive disease

during pregnancy were 60% more likely to have a child with ASD than other mothers. In contrast, a large cohort study of more than 650 000 nurses found that mothers with hypertension during pregnancy were no more likely to have a child with ASD than mothers without with hypertension during pregnancy. [25] Possibly, these nurses, with their increased medical knowledge, sought treatment before their blood pressure reached a level which would have been damaging to the unborn child.

Hypertension and oedema are two common symptoms of pre-eclampsia or toxaemia [132] which is a condition occurring in about 8% of first pregnancies. [133] Women who experience this condition, along with those who suffer oedema, were more likely to have a child with ASD and/or ID. Three groups of researchers found that women with pre-eclampsia [25, 29, 134] and those suffering oedema [92] during their pregnancies were more likely to have a child with ASD than women without these conditions during their pregnancies. In contrast, a much smaller case-control study, found that woman with pre-eclampsia had reduced (though not significantly so) likelihood of a child with ASD. [60] Pre-eclampsia was also associated with ID. [135] This association was found by researchers in a population-based, retrospective cohort study in South Carolina. Here, women who suffered pre-eclampsia were nearly 60% more likely to have a child with ID.

Associations of maternal epilepsy have been demonstrated with both ASD and ID. Women who experienced epilepsy during pregnancy were more likely to have a child with ASD with ID [127] or mild or moderate ID. [127] These Australian researchers conducted a retrospective cohort study of nearly 3 000 mothers of children with ASD and/or ID of unknown cause and around 237 000 mothers of typically developing children using linked population data from medical registries. They established that mothers with epilepsy during pregnancy were more than four and a half times as likely to have a child with ASD with ID [127] and more than three and a half times as likely to have a child with mild or moderate ID compared to mothers without epilepsy during their pregnancies. [127] A case-control study in US had only 61 control mothers of a child with ASD. [123] Here, mothers who had experienced seizure prior to their pregnancies were nearly six times as likely to have a child with ASD. However, possibly due to the small size of the study, results did not reach significance.

In addition to epilepsy, mothers who experienced a range of other conditions during pregnancy were found to be more likely to have a child with ASD than other mothers. Overall, health issues during pregnancy were associated with a higher risk of ASD. Researchers reported that women who had allergies, [124] asthma, [124] bleeding, [30] or high body temperature [93] during their pregnancies were more likely to have a child with ASD than women who had not experienced these conditions during their pregnancies. Asthma during pregnancy was also associated with ID, with pregnant women with asthma being more likely to have a child with mild or moderate ID than mothers without this condition during pregnancy. [127]

Other conditions during pregnancy have been associated with ID. For instance, an Australian population study found that women who had renal or urinary conditions during pregnancy were more than twice as likely to have a child with mild or moderate ID as women without these conditions during pregnancy. [127] Furthermore, women who suffered anaemia during their pregnancies were more than five times as likely to have a child with severe or profound ID than

women without anaemia during pregnancy. [127] Two research groups ascertained that infections during pregnancy were associated with ASD. They found that women whose pregnancies were complicated by urinary tract infection, [93] or any bacterial or viral infection [93, 136] were more likely to have a child with ASD than mothers who did not experience an infection.

Infections during pregnancy were also associated with ID. For example, one study reported that mothers who suffered trichomoniasis during pregnancy were more likely to have a child with ID than mothers without this condition during pregnancy. [137] A cohort study used Medicaid claims and linked infant records to investigate the association of treated and untreated urinary tract infections during pregnancy with later ID in the child. [138] The researchers reported that pregnant women with untreated urinary tract infections were 30% more likely to have a child with ID than pregnant women without these infections. Moreover, mothers with untreated urinary tract infections were 22% more likely to have a child with ID than mothers with antibiotic treated urinary tract infections. [138]

There is always a risk that the use of certain medications during pregnancy may have adverse effects on a developing fetus. This use is likely to be related to a woman's health and the decision to use a particular medication at this time must be difficult. Sometimes, medications initially considered safe have been later implicated to adversely affect the future health of the unborn child. For instance, six studies found that the children of mothers who used anti-depressants, [64, 139] anti-convulsants, [140] psycho-active drugs, [64] prescribed medications [54, 93] and medications generally [141] had a higher risk of a child with ASD. One of these was a population-based case-control study in Stockholm. [64] Using registry data, the researchers assessed that mothers who took psycho-active drugs or anti-depressants during their pregnancies were more than four times as likely to have a child with ASD.

It is also possible that the increased use of prescribed medications in mothers of children with ASD may have resulted from a bias in data collection. In one of the studies which found an increased use of prescribed medications, case mothers were recruited via their response to an advertisement in a support agency newsletter or via their membership of a support agency. [93] Each of these methods might have resulted in a bias in the direction of a high SES. This, in turn, may have produced an increased use of prescribed medications in the case mothers. On the other hand, the study which found an increased use of medications generally was a population study using medical registries. [141] The reported associations are likely to be mediated by a complex interaction of factors. For instance, in addition to possible SES bias, there could be a genetic association such as the familial link of depressive disorders or epilepsy with ASD. Another possibility is an environmental effect which results from the physiological impact of maternal medication use on the uterine environment.

5.6. Summary

Before the birth of their affected children, certain socio-demographic, health and physical attributes differentiate mothers of children with ASD and/or ID from those of mothers in the general population. Further, these attributes often vary by the disability group of their child. In Tables 2 to 4, these differences are grouped into categories according to their associations with groups of mothers. An examination of Table 2 shows that with socio-demographic factors,

the relationships with ASD and ID are most often reversed. High SES was most often associated with the ASD groups of mothers and low SES, most often associated with ID.

Different associations of marital status were found with each of ASD and ID. With ASD, the only two studies found in the area had opposing results. With all but one study, single mothers were at increased risk of unspecified ID and mild or moderate ID, compared to women who were living with a partner.

In the majority of the studies, increased maternal age, along with increased paternal and parental age, were associated with ASD and ASD without ID. With ID, two associations emerged. Younger mothers had an increased risk of bearing a child with mild or moderate ID. But severe or profound ID was associated with increased maternal age.

Lower parity had a consistent positive association with ASD in most studies. With mild or moderate ID and unspecified ID, the relationship was reversed and the association was with greater parity. However, with severe or profound ID, there was no association.

In Table 3, the associations with immigrant status and ethnicity are summarized. Most often, immigrant mothers are more likely to have a child with ASD or ASD with ID than non-immigrant mothers. On the other hand, ASD without ID was associated with non-immigrants, excepting those immigrants from nearby countries. The Mexican/Hispanic immigrant mothers in the US were a separate group since these mothers were less likely to have a child with ASD than Mexican/Hispanic non-immigrant mothers.

With ethnicity, the associations differed from those with immigrant status, in spite of the overlap between the groups. Except for Asian and black mothers, mothers from ethnic minority groups were at a lower risk of children with ASD compared to Caucasian mothers. With the exception of Asian mothers, the relationship with ID was reversed since mothers from ethnic minority groups, and particularly Aboriginal mothers, were at an increased risk of a child with ID.

Table 4 shows the many associations of health and behavioural traits with ASD and highlights the quite small proportion common to both ASD and ID. With mental health, ten research groups reported associations with ASD. Contrastingly, only one study found an association with the mothers of children with ID. Autistic-like traits were associated only with the parents of children with ASD.

As with other socio-demographic factors, ASD and ID had an overall reverse association with height. Taller and heavier women were more likely to have offspring with ASD and shorter women to have offspring with ID. The associations with maternal smoking during pregnancy were minimal. Excessive alcohol consumption during pregnancy was only associated with offspring with ID. Obesity though was associated with both ASD and ID.

Both ASD and ID had associations with immune function, though the association with ASD was broader. Both pre-existing diabetes and diabetes during pregnancy were associated with ASD and/or ID. Further, abnormal levels of cytokines during pregnancy were also associated with each of ASD and ID. Other associations were with only ASD and were auto-immune disorder generally, psoriasis, rheumatoid arthritis, celiac disease and maternal fetal brain antibodies.

Seven studies associated hypertension, oedema and pre-eclampsia with ASD whereas only one study associated pre-eclampsia with ID. Epilepsy and asthma had associations with both of ASD and ID but no other associations during pregnancy were common to both disorders. Medication use during pregnancy was only found to be associated with ASD.

	ASD			ID		
Category	ASD without ID	Undifferentiated ASD	ASD with ID	Mild ID	Unspecified ID	Severe ID
SES	+veassoc [17,47]	+veassoc [17,39-41,47]	+veassoc [17]	-veassoc [17,20,48]	-veassoc [21,44-46,48]	
In Denmark & Sweden		No assoc[42] -veassoc[43]				
Education as a measure of SES	+veassoc [47]	+veassoc [21,41,50]		-veassoc [20,21]	-veassoc [20,21,32,44,45,51, 53] -veassoc (DD)[24]	-veassoc [21,52]
Marital status at child's birth (Women with partners)		+veassoc [17] -veassoc [54]	+veassoc [17]	-veassoc [20]	-veassoc[17] -veassoc (early cognitive delay) [55]	
Age Maternal	+veassoc [17,47]	+veassoc [17,21,29,47,56-61]		-veassoc [17,20,21]	No assoc [46]	+veassoc [21,68]
Paternal & maternal		+veassoc [17,56,58,61]				
Only paternal	+veassoc [65]	+veassoc [58,62-65]				
Maternal & paternal (Denmark, Sweden & UK)		No assoc [42,43,66]				
Lower parity	+veassoc [17,74]	+veassoc [29,41,73] -veassoc [25] No assoc [42]	+veassoc [17]	-veassoc [17,20,21]	-veassoc [21,46]	No assoc [21,52]
Age & lower parity		+veassoc [58]				

ASD, autism spectrum disorder; ID, intellectual disability; Mild ID, Mild or moderate ID; Severe ID, Severe or profound ID; SES, socio-economic status; +ve, positive; -ve, negative; assoc, association.

Table 2. Associations of socio-demographic factors in the mothers of children with ASD and/or ID

		ASD		ID	
Category	ASD without ID	Undifferentiated ASD	ASD with ID	Mild ID	Severe ID
Immigrant status (Immigrant vs non-immigrant)		+veassoc[17,22,30,57,62,75-77]	+veassoc [17,22]	-veassoc[17,20,21]	
North Europe & UK	-veassoc (except other North Europeans)[22,76]		+veassoc in Somalis[77] & Africans [22]		
US		-veassoc immigrant Hispanic vs non-immigrant Hispanics [78]			+veassoc Mexican immigrants in California [52]
Asian		+veassoc in SE & NE Asians [17,57]+veassoc in East Asians[76]		-veassoc for Asians in Aus& US [17,20]	
Ethnicity(Non-Caucasian vs Caucasians)		-veassoc in Hispanics [23,59,84] & Latinos [40]		+veassoc in Aboriginals [17,20]	+veassoc in Aboriginals [17,20]
		-veassoc in Aboriginals [17,29]			
		+veassoc in Asians [52] +veassoc in Blacks [52]	No assoc in Hispanics [52]	-veassoc in Asians [21]	

ASD, autism spectrum disorder; ID, intellectual disability; Mild ID, Mild or moderate ID; Severe ID, Severe or profound ID; +ve, positive; -ve, negative;assoc, association; SE, south eastern; NE, north eastern; Aus, Australia; NHW, non-Hispanic white.

Table 3. Associations of immigrant status and ethnicity in the mothers of children with ASD and/or ID

		ASD	ID
Category	ASD without ID, [Asperger syndrome] [ASD with ID]	Undifferentiated ASD	Unspecified ID[Mild ID], [Severe ID]
Mental health		Schizophrenia [42,89,91]	Schizophrenia [95] or
		Depression [27,64,89]	Unipolar major depression [95] or
	Bipolar disorder [ASD with ID] [95]		Bipolar disorder [95]
		Psychiatric, [62,64,89] personality disorders, [62,89,90] affective [42] & obsessive compulsive disorders,[27] anxiety, [27,94] & paranoia [27]Somatization, [27] psychosis,[42] depression,[27, 64, 89] & depression during pregnancy [92,93]	ID in mother [95]
Personality traits		Autistic-like traits [97,100,102,103]	
Physical characteristics	Taller[ASD without ID] [17 17]Taller[ASD with ID] [17]	Taller and heavier [93] Taller and heavier (non-smoking mothers only) [29]	Shorter, medium height [20]Shortest[Severe ID] [20] & shorter[Mild ID] [17]
Health behaviours During pregnancy	Smoking[Asperger syndrome] [76]	Smoking [30]Smoking(-veassoc) [76] Smoking(no assoc) [29,105,106]	In male children with ≥ 20 cigs/day in mother[107]Smoking (no assoc)[46]
			Alcohol[85]Alcohol[Mild ID] [111, 112] Alcohol[Severe ID] [112]
Physical health	Obesity[ASD with ID] [24]	Obesity [24,54,120]	Obesity [24,46]
		Early menarche[120]	
Immune function	Diabetes during pregnancy [ASD with ID] [127]	Diabetes[24,29] & diabetes during pregnancy[25]	Diabetes[126] & diabetes during pregnancy(Mild ID)[127] & (DD no ASD)[24]
		Higher conc of 3 cytokines[130]	Higher conc of 3 other cytokines(DD) [130]
		Any auto-immune disorder, [256,26,123] psoriasis,[124] & rheumatoid arthritis[125] celiac disease, [125] &fetal brain antibodies [128]	

ASD, autism spectrum disorder; ID, intellectual disability; Mild ID, mild or moderate ID; Severe ID, severe or profound ID; UTI, urinary tract infection,

Table 4. Associations of mental health, personality traits, physical characteristics, health behaviours and physical health in the mothers of children with ASD and/or ID

	ASD		ID
Category	ASD without ID[ASD with ID]	**Undifferentiated ASD**	**Unspecified ID[Mild ID], [Severe ID]**
Other areas during pregnancy		Hypertension[24,30,54] Oedema[92]	
		Pre-eclampsia[25,29,134]	Pre-eclampsia[135]
	Epilepsy[ASD with ID) [127]		Epilepsy(Mild ID)[127]
		Allergies,[124] bleeding,[30] & high temperature[93] UTI[93] & any infection[93,136]	Renal/urinary conditions,[127] [Mild ID][126] Anaemia [Severe ID] [127]Trichomoniasis[137] & untreated UTI[138]
		Asthma [124]	Asthma (Mild ID) [127]
		Anti-depressants,[64,139] prescribed[54,93] & other medications[141] Anticonvulsants[140] & psycho-active drugs[64]	

ASD, autism spectrum disorder; ID, intellectual disability; Mild ID, mild or moderate ID; Severe ID, severe or profound ID; UTI, urinary tract infection.

Table 5. Associations of health during pregnancy in the mothers of children with ASD and/or ID

6. Conclusion

This chapter provides a review of the research pertaining to the pre-existing characteristics of mothers of a child with ASD and/or ID. Some consistent and enduring associations have emerged across the published reports. With socio-demographic factors, these are the contrasting associations of maternal education, age, immigrant status and ethnicity with ASD and ID. With maternal health; aspects of mental health, personality traits, immune function and the use of medication during pregnancy have stronger associations with the mothers of children with ASD than ID. Some of these differences may be reflections of distinct aetiologies for ASD and/or ID of unknown cause and provide directions for future research. As such, primary and secondary prevention strategies may be refined and/or developed which will contribute to lower prevalence, reduced levels of severity and better outcomes for affected children.

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