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Annual Research Review: The role of the environment in the developmental psychopathology of autism spectrum condition

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Background: Although autism spectrum condition (ASC) is strongly genetic in origin, accumulating evidence points to the critical roles of various environmental influences on its emergence and subsequent developmental course. **Methods:** A developmental psychopathology framework was used to synthesise literature on environmental factors associated with the onset and course of ASC (based on a systematic search of the literature using PubMed, PsychInfo and Google Scholar databases). Particular emphasis was placed on gene–environment interplay, including gene–environment interaction (G × E) and gene–environment correlation (rGE). **Results:** Before conception, advanced paternal and maternal ages may independently enhance offspring risk for ASC. Exogenous prenatal risks are evident (e.g. valproate and toxic chemicals) or possible (e.g. selective serotonin reuptake inhibitors), and processes endogenous to the materno-foeto-placental unit (e.g. maternal diabetes, enhanced steroidogenic activities and maternal immune activation) likely heighten offspring vulnerability to ASC. Folate intake is a prenatal protective factor, with a particular window of action around 4 weeks preconception and during the first trimester. These prenatal risks and protective mechanisms appear to involve G × E and potentially rGE. A variety of perinatal risks are related to offspring ASC risk, possibly reflecting rGE. Postnatal social factors (e.g. caregiver–infant interaction, severe early deprivation) during the first years of life may operate through rGE to influence the likelihood of manifesting a full ASC phenotype from a 'prodromal' phase (a proposal distinct to the discredited and harmful 'refrigerator mother hypothesis'); and later postnatal risks, after the full manifestation of ASC, shape life span development through transactions mediated by rGE. There is no evidence that vaccination is a postnatal risk for ASC. **Conclusions:** Future investigations should consider the specificity of risks for ASC versus other atypical neurodevelopmental trajectories, timing of risk and protective mechanisms, animal model systems to study mechanisms underlying gene–environment interplay, large-sample genome–envirome designs to address G × E and longitudinal studies to elucidate how rGE plays out over time. Clinical and public health implications are discussed.
Keywords: Autism spectrum condition; autism spectrum disorder; autism; Asperger's syndrome; genetics; environment; developmental psychopathology.

Introduction

Autism spectrum condition (ASC) encompasses a set of heterogeneous neurodevelopmental syndromes affecting approximately 1% of the population (Lai, Lombardo, & Baron-Cohen, 2014). It arises early in development, persists across the life span, and is characterised by pervasive difficulties with social reciprocity, social communication, flexibility and sensory processing (American Psychiatric Association, 2013). Although a substantial proportion of people with ASC have a measured IQ in the typical range, and show a variety of cognitive strengths (Charman et al., 2011; Howlin, Goode, Hutton, & Rutter, 2009; Mandy, Murin, & Skuse, 2014), ASC is often associated with difficulties of functioning in a range of settings, insufficient quality of life and unsatisfactory adulthood outcomes (van Heijst & Geurts, 2015; Howlin & Moss, 2012).

In the last few decades, autism research has grown exponentially, yet some fundamental questions remain unanswered. For example, there are no established biomarkers for ASC (Ecker, Spooren, & Murphy, 2013), and we do not yet understand its causes (Lai et al., 2014; Mandy, 2013). Furthermore, there is much to be learnt about how to help people with the condition (Wong et al., 2015). These gaps in current knowledge partly reflect the heterogeneity of ASC in terms of its aetiology and phenomenology (Coleman & Gillberg, 2012; Geschwind & State, 2015; Happe, Ronald, & Plomin, 2006; Lai, Lombardo, Chakrabarti, & Baron-Cohen, 2013). Accordingly, attempts to understand ASC must engage with its complexity by seeking to synthesise the multiple factors that influence its aetiologies and emergence (onset) as well as development (course) across the lifespan. In the current review, on the basis of a growing evidence base, we argue that this will require consideration of both environmental and genetic influences on development. We present and

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discuss our findings within the framework of *developmental psychopathology*, as we believe that this approach has much to offer researchers in their efforts to understand the origins and developmental course of ASC, and to design support and interventions.

Integrating autism research: a role for developmental psychopathology

Developmental psychopathology has been defined as 'the study of the origins and course of individual patterns of behavioural maladaptation' (Rutter & Sroufe, 2000). It seeks to investigate 'the mysterious unfolding of disturbance over time' (Fonagy, 2003) by drawing on a set of powerful ideas that include the following:

1. *Psychopathology is maladaptation*: Mental disorders are not well formulated simply as a characteristic of the individual; rather they reflect a mismatch between a person's capacities and the demands placed on them by their environment.
2. *Development is transactional*: Adaptation and maladaptation arise from a dynamic interaction between a person and their environment across the life span, with the individual shaping their environment and the environment shaping the individual.
3. *Outcomes are multiply determined*: The interplay of multiple risk and protective factors, at different levels (biological, psychological, social) shapes the development of psychopathology, and of adaptation.
4. *Sensitivity to risk changes over time*: The magnitude and quality of risk and protective effects vary, depending on when they occur during the life span.

A key idea in contemporary developmental psychopathology is that typical and atypical developmental trajectories emerge from the combined effects of genes (G) and environmental factors (E) (Rutter & Silberg, 2002). It has been further noted that the aetiological roles and developmental influences from G and E are not simply additive. The overall picture should be understood in the light of two key broad forms of gene–environment interplay (GE interplay): (a) gene–environment interaction (G × E) and (b) gene–environment correlation (rGE) (Rutter, 2006; Rutter et al., 1997). Mechanisms underlying GE interplay also include processes whereby the environment exerts influence via the genome (so called 'nurture via nature' effects), either by changing the genotype, or by influencing expression of the genotype, for example, via the epigenome (Tordjman et al., 2014).

In the current context, G × E refers to situations where the effects of G are increased, or decreased, in the presence of a particular environment; similarly, G × E also refers to the case where the effects of E are influenced by the presence or absence of specific genetic predisposition (Rutter, 2006). rGE refers to the effects of G on individual differences in the liability to exposure to particular E, hence reflecting *indirect* G effects operating through E. rGEs can be further classified as *passive* (when parental genotype influences the environment that their offspring experiences), *active* (when the individual's genotype influences their tendency to select, create or shape the environment that they experience) and *evocative* (when genotype creates the tendency for an individual to induce other people to create the environment that they experience) (Rutter & Silberg, 2002). Phenotypic variances of behavioural or clinical characteristics can therefore be parsed into the contribution from the main effects of G (additive, or multiplicative involving G–G interaction), main effects of E (additive, or multiplicative involving E–E interaction), G × E effects and rGE effects. These effects are dynamic rather than static or deterministic. They may have different impacts depending on the life stage of the individual.

In the current review we will use this developmental psychopathology framework to investigate the emergence and development of ASC in the light of the joint effects of G, E and GE interplay (Chaste & Leboyer, 2012; Kim & Leventhal, 2015; Meek, Lemery-Chalfant, Jahromi, & Valiente, 2013; Stoltenberg et al., 2010). Atypical neurodevelopmental conditions (including ASC) are not static. Rather, they evolve dynamically with multiple factors modulating the developmental trajectory of an individual. Thus, our review will consider environmental risk and protective factors both as influences on an individual's chance of presenting with ASC, and as influences on the developmental course of the individual after the emergence of their ASC.

The role of genetic (G) and environmental (E) factors in the emergence of ASC: a historical overview

By the 1940s, soon after the initial clinical case series that gave rise to the current diagnostic formulation of ASC (Asperger, 1944; Kanner, 1943; Ssucharewa & Wolff, 1996), aetiological speculation followed. During the 1950s and 1960s a psychoanalytic theory prevailed, which asserted that autism originated from inadequate opportunities for the child to properly bond with their mother. Specifically, it was argued that autism occurred when a cold, distant and rejecting attitude on the part of mothers resulted in their infants failing to develop a capacity for affective and social reciprocity (Bettelheim, 1967). This idea, known as the 'refrigerator mother theory', came to be widely accepted, including by Kanner himself. It led to the simplistic and harmful misconception that autism is caused by parenting, and resulted in many parents of children with autism blaming themselves for their child's difficulties (Silberman, 2015).

Bernard Rimland, a psychologist and parent of a child with autism, made the first effective challenge to the prevailing idea that autism was 'psychogenic', caused by features of the family environment. In his book 'Infantile Autism: The Syndrome and its Implications for a Neural Theory of Behavior' he challenged what he called 'murky psychoanalytic interpretations masquerade[ing] as truth', proposing that autism is not caused by a 'disturbed early mother–child relationship', but rather is an innate condition with a neurobiological basis (Rimland, 1964). Kanner lent this (at the time) radical idea credibility by writing a forward for Rimland's book. Certainly, its 'neurogenic' hypothesis echoed Kanner's initial conceptualisation that autism stems from 'an innate inability to form the usual biologically provided affective contact with people' (Kanner, 1943).

Rimland's emphasis on innateness was subsequently supported by the first twin studies of autism, which reported substantially higher concordance of autism in monozygotic (MZ) than in dizygotic (DZ) twins, yielding an estimated broad heterogeneity (i.e. phenotypic variance accounted for by additive G effects) of 91%–93% (Bailey et al., 1995; Folstein & Rutter, 1977). Subsequent twin studies before 2010 all showed substantially higher concordance rates for MZ versus DZ twins (median 76% vs. 0% for autistic disorder, and 88% vs. 31% for the broader ASC construct), giving a heritability estimate of 80%–90% (Ronald & Hoekstra, 2011). Such findings were a powerful refutation of the idea that psychogenic factors, such as early parenting, cause autism. Rather, autism has come to be viewed as one of the most genetically driven human conditions (McGuffin, Riley, & Plomin, 2001). Nevertheless, in these twin studies the MZ concordance rate was never 100%, suggesting that there must be some nongenetic factors at play.

Surprisingly, large-scale population genetic studies in the first decade of the 21st century reported a somewhat different picture of the relative contributions of G and E to the phenotypic variance of autism diagnoses or autistic traits. Lichtenstein, Carlstrom, Rastam, Gillberg, and Anckarsater, (2010), in 16,858 Swedish 9- and 12-year-old general population twins (0.9% amongst them diagnosed with ASC), estimated ASC's heritability to be 80% (95% confidence interval, 29%–91%), with the remaining 20% (9%–38%) of aetiological variance being attributed to *non-shared* environmental factors. Hallmayer et al. (2011) found that in 192 twin pairs in the United States, the estimated additive G effect was only moderate: 37% (8%–84%) for narrowly defined autism, and 38% (14%–67%) for broader ASC. In this study, a large portion of phenotypic variance was explained by *shared* E effects: 55% (9%–81%) for narrowly defined autism and 58% (30%–80%) for ASC. Further, Sandin et al. (2014), in a population-based Swedish cohort, estimated the additive G effect was 54% (44%–64%) for narrowly defined autism and 50% (45% –56%) for broader ASC. Their model showed no significant shared E effects, but a substantial contribution from *non-shared* E: 46% (36%–55%) for narrowly defined autism, 50% (44%–55%) for ASC. Gaugler et al., (2014) then similarly showed that in a genotyped Swedish general population sample, additive G effect due to common variants (i.e. SNP-based heritability) was 49.4% (31%–69%); when considering both common and rare variants this rose slightly to 52.4% (35%–71%). All these large-scale studies demonstrate substantially lower G effects and larger E effects than the earlier twin studies.

It is worth noting that how the phenotype is defined might affect the estimation of G versus E effects. For example, Frazier, Thompson et al. (2014) showed that in 568 twins from the Interactive Autism Network, high heritability was estimated using extreme scores (population percentile of 99.9%) on quantitative measures of autistic traits/symptoms, yet the heritability estimates drop substantially when moving even slightly away from the extreme (population percentile ≤99.5%). Further, in a large UK twin sample (n = 203–359 depending on the instrument used), estimated additive G effect varied according to the assessment method used, from 56% (37%–82%) by parental-interview using the Autism Diagnostic Interview-Revised (ADI-R), 76% (41%–86%) by direct observation using the Autism Diagnostic Observation Schedule (ADOS), 78% (48%–87%) by telephone screening interview with parents using the Development and Well-being Assessment (DAWBA), to 78% (77%–79%) by parent-report screening questionnaires using the Childhood Autism Spectrum Test (CAST) (Colvert et al., 2015). In these analyses, shared E effects were negligible, but nonshared E effects were moderate, ranging from 14% (7%–47%) by the ADI-R, 22% (13%–36%) by the DAWBA, 22% (21%–23%) by the CAST, to 24% (14%–39%) by the ADOS. How phenotypic definition and severity of ASC, comorbidities and measurement of autistic characteristics affect the estimation of G and E effects in aetiology has been extensively discussed elsewhere (Ronald & Hoekstra, 2011).

As a summary, Gaugler et al. (2014) synthesise the literature and show that, for aetiological contributions to ASC, 49% are by additive G effect from common inherited variants, 3% by additive G effect from rare inherited variants, 4% by nonadditive G effect and 3% by de novo mutations; however, 41% are not accounted for by the above, and are therefore likely to encompass a variety of E-meditated effects. Although the estimates of G and E effects to date vary, which can be partially explained by variations in sample ethnicity and statistical modelling strategies, a converging message is that although genetic effects account for most aetiological contribution (over 50%), there are also

substantial roles of nongenetic effects for the liability to ASC.

In order to suggest candidates for these nongenetic effects, we now summarise empirical literature on environmental influences on the emergence and development of ASC. Here, we define 'environment' in a broad sense, as any factor that is not directly genetic. The following search strategy was employed. Initially, lists of environmental exposures were independently generated by the two authors, based on scoping searches of the literature. These were combined to set the scope of the review. Searches were then conducted for each type of exposure (using PubMed, PsychInfo and Google Scholar) to identify studies of its relationship with ASC risk and protection. Also, bibliographies of relevant articles were scanned to identify any additional studies. To minimise risk of bias, we drew upon meta-analytic reviews of environmental exposures where available. Our findings are presented chronologically, ordered according to the point of the life span when their effects are likely to be greatest, based on current evidence. This reflects the fact that the timing as well as the nature of environmental influence is crucial.

Preconception environmental risks

One factor that predicts the chances of an individual developing ASC is the age of their parents when they were conceived. Maternal (Sandin et al., 2012) and paternal (Hultman, Sandin, Levine, Lichtenstein, & Reichenberg, 2011) age are independently associated with risks for offspring ASC (Sandin et al., 2015), and this is likely to reflect distinct causal processes. Moreover, there is a joint effect of maternal and paternal age: risk is highest when both parents are older, and risk further increases among disparately aged parents (Sandin et al., 2015). There have also been reports on potential associations between interpregnancy interval (e.g. <12 months) and increased risks of offspring ASC, although the exact relationship and underlying mechanisms remain unclear (Cheslack-Postava, Liu, & Bearman, 2011; Durkin, Dubois, & Maenner, 2015; Gunnes et al., 2013; Werling & Geschwind, 2015).

Paternal age

Hultman et al. (2011) conducted a meta-analysis of 10 studies in seven different countries and found a monotonic relationship between paternal age and ASC. Compared to fathers aged 29 years or below, the risk of autism for offspring of fathers aged 30–39 years was 1.22 (95% CI 1.05–1.42). For offspring of fathers aged 40–49 it was 1.78 (95% CI 1.52–2.07) and for those born to fathers aged over 50 years, it was 2.46 (95% CI 2.20–2.76). The association between paternal age and ASC does not simply reflect a confound by intellectual ability, as it is found for individuals with higher functioning ASC presentations, as well as for individuals diagnosed with ASC with intellectual disability (Croen, Najjar, Fireman, & Grether, 2007; Tsuchiya et al., 2008). Furthermore, the relationship between paternal age and offspring ASC risk persists after controlling for other potential confounds such as maternal age, parental country of birth, parental psychiatric history, perinatal complications, year of birth and socioeconomic status.

One possible explanation is that men who carry a genetic risk for having a child with ASC are more likely to reproduce later than average, perhaps due to having characteristics of the broad autism phenotype that make them less interested in relationships, or less able to attract a mate. If this is true, while we would expect older fathers to have more children with ASC, we would not expect to see a paternal age effect operating within families: younger (later born) siblings would have an equal ASC risk to their older (earlier born) siblings. Hultman et al. (2011) directly tested this by looking at 660 families in which a father had multiple children, one of whom had autism. Within these families the affected child on average had older paternal age than their nonautistic siblings, and this finding persisted even when controlling for parity and maternal age. Also, in a mixed-effect within-family model, time since the birth of the first child significantly predicted autism risk in offspring. These findings make it unlikely that the paternal age effect can be explained by manifestations of the genetic predisposition, such as high autistic traits and shyness, resulting in deferred paternity.

Another possibility is that the paternal age effect occurs because as men age, their spermatozoa contain an increasing number of de novo mutations (Kong et al., 2012; Michaelson et al., 2012). In human males, spermatogonial cells, which are stem cells for the formation of spermatozoa, replicate throughout the life span, every 16 days. Each time these cells divide, there is the possibility of mutations being introduced to their genetic material, arising from copying errors. This accumulation of mutation risk in spermatogenesis across the life span, in combination with the ailing of mechanisms that protect against mutation during DNA replication, explains why the spermatozoa of older males have more mutations. ASC is associated with de novo mutations, and recent studies have shown that when these do occur in people with ASC, they are more often paternal than maternal in origin, and are linked to greater paternal age (Kong et al., 2012). One striking finding that accords with this model is that advanced grandpaternal age, on either the maternal or paternal side, is also associated with greater offspring ASC risk (Frans et al., 2013). Thus, the effect of paternal age may arise from a process of 'nurture via nature'; with nongenetic factors, some present decades before the proband is born, influ-

encing genotype, which in turn directly impacts on ASC risk.

The paternal age effect may be well conceptualised as a form of G × E. In a study of twins in two large nationally representative samples from Sweden and the United Kingdom, it was observed that advancing paternal age increased concordance for ASC and autistic traits in MZ and DZ pairs (Lundstrom et al., 2010). One interpretation of this finding is that the effects of paternal age amplify pre-existing genetic risk, thereby making it more likely that genetically vulnerable individuals develop the autistic phenotype, thereby increasing concordance between twins.

Maternal age

Due to sex differences in gametogenesis, the association between maternal age and offspring ASC risk must reflect, at least in part, a distinct mechanism from the one proposed above to explain the paternal age effect. A meta-analysis of 16 papers, with a combined sample of 25,287 ASC cases and 8,655,576 controls provides compelling evidence that mothers aged over 35 are one and a half times more likely (relative risk 1.52, 95% CI 1.12–1.92) to have a child with ASC compared to mothers aged between 25 and 29 years (Sandin et al., 2012). This estimate of risk remained unchanged when adjustments were made for potential confounds, with all studies controlling for paternal age and sex of the child, and most also accounting for socioeconomic status, birth year, birth order and perinatal factors, such as gestational age, birth weight, Apgar score and foetal distress. Six studies in the meta-analysis controlled for obstetric complications and a subgroup analysis of these revealed that the effect of maternal age persists (relative risk 1.37, 95% CI 1.27–1.49) even when accounting for this important confound. It is also notable that younger-than-average maternal age is a protective factor: adolescent mothers had a 0.76 risk of having a child with ASC, compared to those aged 25–29. The risk conferred by higher maternal age applies across the autism spectrum, including for offspring with Asperger's disorder and pervasive developmental disorder, not otherwise specified (PDD-NOS) (Croen et al., 2007).

One possible explanation for the maternal age effect is that it reflects a higher risk of chromosomal abnormalities. These are associated both with higher maternal age (Martin, 2008) and with some cases of ASC (Marshall et al., 2008). It will be valuable in the future to investigate this in studies that record the presence of chromosomal abnormality in addition to ASC diagnosis. Alternatively, maternal age could operate on ASC risk by altering not the content of the genome, but rather its expression, for example via epigenetic processes (Sandin et al., 2012). Such an idea would be compatible with the fact that older mothers have, on average, had greater exposure to environmental risk factors that could influence methylation in germ cells, with developmental consequences for their offspring (Sandin et al., 2012).

The risk posed by maternal age may interact with other variables. In their meta-analysis, Sandin et al. (2012) noted that effects of maternal age were stronger in studies with a higher male-to-female ratio. This raises the possibility that higher maternal age is a greater risk factor for male than female offspring. Intriguingly, a converse pattern has been observed for paternal age, with paternal age appearing to pose the greatest risk for female offspring (Croen et al., 2007; Reichenberg et al., 2006), in particular simplex autism (Puleo et al., 2012). However, a recent large-scale study failed to find sex-moderating effect on risks for offspring ASC associated with increased parental ages (Sandin et al., 2015). Nevertheless, the study of parental age effects still points to the possibility of sex-specific pathways to ASC that may be associated with different risk mechanisms (Lai, Lombardo, Auyeung, Chakrabarti, & Baron-Cohen, 2015).

Prenatal environmental risks

Exogenous prenatal environmental risks

Valproate. Valproate is an anticonvulsant for people with epilepsy, a mood stabiliser for bipolar disorder, and a prophylactic drug against migraine. It is widely used, including by women of childbearing age: in industrialised nations, around 20% of pregnant women with epilepsy receive valproate (Kulaga, Sheehy, Zargarzadeh, Moussally, & Berard, 2011). When taken during pregnancy, valproate crosses the placenta, and is associated with a 'foetal valproate syndrome' comprising a range of physical and neurodevelopmental difficulties (Shallcross et al., 2011; Tomson et al., 2011). Those exposed in utero to valproate have a 10% chance of being born with congenital malformations, and are also at increased risk of having developmental delay, language problems and impaired executive function (Roullet, Lai, & Foster, 2013). The potential association between in utero valproate exposure and ASC was suggested by clinical observations of autism in children with foetal valproate syndrome (Williams et al., 2001). Subsequently, observations by the Liverpool and Manchester Neurodevelopmental Group of a cohort of women with epilepsy confirmed an association between valproate use in pregnancy and increased risks of ASC, as well as other neurodevelopmental disorders, in offspring (Bromley et al., 2013).

To date, the best epidemiological evidence for a direct link between in utero valproate exposure and subsequent ASC comes from a whole-population study of 655,615 children born in Denmark between 1996 and 2006 (Christensen et al., 2013). Analyses controlled for a range of potential confounds, including maternal and paternal age, epilepsy, parental

psychiatric history, gestational age, birth weight, sex, congenital malformations and parity. In the total sample, 508 children were identified as having been exposed to valproate in utero, and among these there was a 4.42% (95% CI 2.59–7.46) absolute risk of having ASC, in comparison to 1.5% in the general population. Even when analyses were limited to children of mothers with epilepsy, the association between valproate use in pregnancy and ASC persisted, suggesting that this association does not arise from the possibility that maternal epilepsy is associated both with valproate use and having a child with ASC.

The case for in utero valproate as a causal risk factor for ASC has been strengthened by its use to create one of the most influential animal models of the condition: rats and mice exposed to it in utero show a profile of behavioural features that may correspond to the social, communication and flexibility difficulties seen in humans with ASC (Roullet et al., 2013). Furthermore, studies of rodents have begun to suggest possible epigenetic mechanisms, whereby in utero valproate exposure impacts upon postnatal social and communication development. A key mediator of this association is inhibition of histone deacetylase, which impacts upon gene transcription (Moldrich et al., 2013). Also, valporate has been found to cause DNA demethylation in the brains of prenatally exposed rats, which disregulates the Wnt/β-catenin signalling pathway (Wang et al., 2010). This pathway is the key regulator of early central nervous system development (Ciani & Salinas, 2005), and may be involved in the aetiology of some cases of ASC.

The discovery that valproate may impact upon early and fundamental processes of central nervous system development raises the questions of how specific and how direct its effects on ASC risk are. In utero valproate exposure in humans is associated with an array of neurodevelopmental atypicalities beyond ASC, including attention-deficit/hyperactivity disorder (ADHD), dyspraxia and low IQ (Roullet et al., 2013). One possibility is that, in some cases, it causes a general developmental delay, which has the effect of lowering the threshold for the expression of any underlying biological vulnerability to ASC (Skuse, 2007).

Selective serotonin reuptake inhibitors. Between 7% and 13% of pregnant women experience depression, and selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressant (Bennett, Einarson, Taddio, Koren, & Einarson, 2004; Sørensen et al., 2013). In the United Kingdom approximately 4% of pregnant women use SSRIs during their pregnancy (Charlton et al., 2015). In the USA, perinatal SSRI use is more widespread, with estimates ranging from 5% to 10% (Alwan, Reefhuis, Rasmussen, & Friedman, 2011). SSRIs cross the placental barrier, and serotonin plays a role in early brain development (Hviid, Melbye, & Pasternak, 2013). As such, concerns have been raised in the scientific literature about potential effects of in utero SSRI exposure on a range of developmental outcomes, and this has included consideration of whether SSRI exposure in utero increases risk of ASC (Hadjikhani, 2010).

Man et al. (2015) performed a meta-analysis of four high-quality case–control studies, with a combined sample of 79,221 individuals (cases and controls altogether), addressing the question whether in utero SSRI exposure is associated with increased ASC risk. All of these studies compared children diagnosed with an ASC to a control group of children without ASC in terms of maternal use of SSRI during pregnancy, either indexed by prescription records (Croen, Grether, Yoshida, Odouli, & Hendrick, 2011; Rai et al., 2013) or maternal retrospective report (Gidaya et al., 2014; Harrington, Lee, Crum, Zimmerman, & Hertz-Picciotto, 2014). Taken together these studies show a clear association between SSRI use in pregnancy and risk of having a child who is later diagnosed with an ASC, with an unadjusted odds ratio (OR) of 2.12 (95% CI 1.65–2.71).

Nevertheless, the case for in utero SSRI use as a causal risk factor for ASC is not yet proven, due to the problem of 'confounding by indication'. Parents of children with ASC are more likely to use SSRI because they are at higher than average risk of experiencing depression and anxiety before the birth of their child with ASC, perhaps because there are aetiological factors common to ASC and depression/anxiety, or because having the broad autism phenotype makes a person more vulnerable to emotional difficulties (Piven & Palmer, 1999). This raises the possibility that it is the characteristics associated with SSRI use (notably depression and anxiety) that are a risk factor for offspring ASC, rather than SSRI per se. The case–control studies summarised by Man et al. (2015) all sought to account for this possibility by controlling for maternal psychiatric history along with other potential confounds, and the resultant adjusted pooled association between in utero SSRI exposure and ASC continued to be significant, albeit smaller (adjusted OR 1.81, 95% CI 1.47–2.24).

However, findings from a very large and well-controlled Danish cohort study, which were not included in the meta-analysis by Man et al., sound a note of caution (Sørensen et al., 2013). Initial analyses in this study, using data from 655,615 children of 428,407 mothers, sought to control statistically for a range of potential confounds (i.e. parental age at conception, parental psychiatric history at child birth, child gestational age and birth weight, child sex and parity) and replicated the association between in utero SSRI exposure and ASC risk found by earlier reports. However, two subsequent analyses, that were elegantly designed to control more stringently for confounds, failed to

find any risk effect of SSRI. When only mothers with a recorded history of affective disorder prior to the birth of their child were examined (n = 6,080 children), there were no differences in the risk of having a child with ASC for those who took SSRIs when pregnant, and those who did not (Sørensen et al., 2013). Next, a sibling analysis was conducted, whereby mothers were selected who had more than one child, at least one of whom had ASC (n = 6,142 children) (Sørensen et al., 2013). This type of within-person analysis is effective for controlling for confounds that are unmeasured in between-person designs (Rabe-Hesketh & Skrondal, 2008). In this analysis there was no evidence that mothers who used SSRI in their pregnancy had a higher risk of having a child with ASC compared to another pregnancy when they did not use SSRI. Furthermore, others have found that antidepressants, regardless of their composition, are associated with increased ASC risk (Rai et al., 2013), which weakens the argument for a specific mechanism linking SSRI and ASC and strengthens the idea that SSRIs may merely be a marker for an underlying causal risk factor, for example, the genetic propensity to depression.

Further investigation is required before any potential effect of in utero SSRI exposure can be ruled out. It should be acknowledged that if there is a risk of ASC associated with SSRI use in pregnancy, it is small. Rai et al. (2013) calculated that, if they assumed a causal association, SSRI accounted for only 0.6% of the cases of ASC in their sample. Future investigations should account for a number of subtleties, intimated by the extant literature, which may characterise the relationship between SSRI exposure in the womb and risk of developing ASC. First, it may be that SSRI exposure in utero is a focused risk for high-functioning ASC. Rai et al. (2013) found an association between in utero SSRI use and ASC without intellectual disability, but there was no such relationship for children with ASC in combination with an IQ below 70. Second, similar to the effect of maternal age, SSRI risk may be greater for males than females. In their Californian population-based case–control study, Harrington et al. (2014) found an association between SSRI and ASC in males only.

Toxic chemicals. A variety of toxic chemicals have been identified as harmful to foetal neurodevelopment (particularly in the first trimester) and may play causal or contributing roles in the emergence of developmental disabilities. These include (but are not restricted to) heavy metals (e.g. lead, methylmercury, arsenic, manganese), alcohol and chemical pesticides (e.g. polychlorinated biphenyls, organophosphate, DDT) (Landrigan, 2010). Summarising available retrospective and prospective epidemiological and clinical data to date, chemical exposure that may be associated with increased risks for child ASC include pesticides, phthalates, polychlorinated biphenyls (PCBs), solvents, toxic waste sites, air pollutants and heavy metals; the strongest evidence of association is shown by traffic-related air pollutants and pesticides (Kalkbrenner, Schmidt, & Penlesky, 2014; Rossignol, Genuis, & Frye, 2014).

The Childhood Autism Risks from Genetics and Environment (CHARGE) project in California raises the possibility that traffic-related air pollution (TRAP) is an environmental risk factor for ASC. Initially in this line of investigation, distance from a freeway was taken as a proxy measure of exposure to TRAP, and it was found that, controlling for social and demographic factors, children whose mothers had lived near a freeway during pregnancy were more likely to develop ASC (adjusted OR 1.86, 95% CI 1.04–3.45) (Volk, Hertz-Picciotto, Delwiche, Lurmann, & McConnell, 2011). Subsequently, the authors used sophisticated methods to model maternal exposure to TRAP, and confirmed their previous finding (Volk, Lurmann, Penfold, Hertz-Picciotto, & McConnell, 2013). Higher levels of TRAP exposure during pregnancy (adjusted OR 1.98, 95% CI 1.20–3.31) and in the first year of life (adjusted OR 3.10, 95% CI 1.76–5.57) were associated with greater ASC risk. The authors used regional records to estimate exposure to specific pollutants, and found that both nitrogen dioxide (NO_2) and particulate matter exposure in pregnancy and the first year of life were positively associated with ASC risk (Volk et al., 2013). Similar findings have been shown elsewhere. A nation-wide population-based cohort study in Taiwan geographically (by post code) linked ASC diagnoses in the National Health Insurance Research Database with levels of air pollution from 70 Taiwan Environmental Protection Agency monitoring station, including carbon monoxide (CO), NO_2, sulfur dioxide (SO_2), PM10 and ozone (O_3). The study finds that children exposed to O_3, CO, NO_2 and SO_2 in the preceding 1–4 years have increased risk for getting newly diagnosed ASC (Jung, Lin, & Hwang, 2013).

These findings will require replication in different countries and geographical areas, using designs that control for unmeasured confounds that might be related to both living in an area with high traffic pollution and having a child with ASC. The within-family designs used to test for effects of SSRI (Sørensen et al., 2013) and valproate (Christensen et al., 2013) would be instructive. Furthermore, the specificity of the effects of TRAP should be investigated by studies that distinguish between cases of ASC with and without intellectual disability, and which account for cooccurrence of ASC with other neurodevelopmental disorders.

Nevertheless, some initial work on a potential mechanism of action lends plausibility to the finding that prenatal and infant TRAP exposure is a risk factor for ASC. Volk et al. (2014) recently reported data suggesting that exposure to TRAP exerts its effect on ASC risk via an interaction with a promoter

variant of the MET receptor tyrosine kinase (MET) gene. The MET gene mediates a number of molecular signalling pathways during development, playing a role in the proliferation, differentiation and survival of cells in diverse tissues (Peng, Huentelman, Smith, & Qiu, 2013). It is crucial to the regulation of nervous system development, both in utero and after birth, and has been implicated in the development of some cases of ASC (Campbell, Li, Sutcliffe, Persico, & Levitt, 2008; Campbell et al., 2006, 2007; Sousa et al., 2009). One MET allele that has been linked to ASC is the CC genotype at MET rs1858830 (Campbell et al., 2006; Rudie et al., 2012). When Volk et al. (2014) examined whether the MET rs1858830 genotype influenced sensitivity to TRAP they found evidence for a G × E effect. Among those in the high-exposure group for TRAP, individuals who had the CC genotype showed elevated risk of ASC (OR 2.9, 95% CI 1.0–10.6), whereas those with a CG or GG genotype did not (OR 1.3, 95% CI 0.73–2.2). Similarly, for those with the CC genotype, NO_2 exposure was associated with elevated ASC risk (OR 3.2, 95% CI 1.3–9.1), but this was not the case for participants with the CG or GG genotype at this SNP (OR 1.2, 95% CI 0.71–2.1). Thus, air pollution exposure may interfere with a signalling pathway that guides neurodevelopment, and this could be one mechanism that links TRAP and elevated ASC risk. Consistent with this idea is evidence that ASC risk from TRAP peaks in the third trimester and first year of life (Volk et al., 2013), at a time when the MET signalling pathway is thought to be especially influential on neuronal growth, then synaptogenesis and pruning, and then functional maturation and plasticity (Peng et al., 2013).

In terms of pesticides exposure, a large-scale retrospective study shows that in California, family exposure to organochlorine pesticides (measured using geographical mapping) increases risks of offspring ASC (Roberts et al., 2007); with high-vulnerability periods statistically modelled to occur at two points, one from 38 days before conception to 163 days post conception, and a second postnatal peak between 346 and 529 days post conception (Roberts & English, 2013). Prospective studies also show that organophosphate exposure during pregnancy increases risks of offspring autistic symptoms measured at 2–3 years (Eskenazi et al., 2007; Rauh et al., 2006), and that PCBs and dichlorodiphenyldichloroethylene exposure during pregnancy marginally increases risks of offspring ASC diagnosis by childhood (Cheslack-Postava et al., 2013). A recent study from the CHARGE project further shows that residential proximity to organophosphates at some point during pregnancy is associated with a 60% increased risk for offspring ASC (Shelton et al., 2014). Mechanisms of gestational pesticides exposure leading to the pathophysiology of autism may include altered excitation–inhibition regulation for neuronal development, mitochondrial dysfunction in relation to oxidative stress, immune-dysregulation such as immune-suppression or neuro-inflammation, and via maternal hypothyroxinaemia (Shelton, Hertz-Picciotto, & Pessah, 2012). Whether there exists a particularly vulnerable subpopulation that is at greater risk for pesticide exposure (i.e. G × E effects) remains to be clarified using large-scale studies that consider factors broadly associated with both the genome and the envirome.

'Endogenous' prenatal environmental risks

Apart from the exogenous environmental risk factors discussed above, several biological conditions immediately surrounding the foetus, the prenatal environment in the womb, have also been shown to potentially increase risks for developing ASC later in life. These factors, although seemingly 'environmental' for the foetus, can be products of genetic disposition, or parts of recursive, feedback regulatory loops that are under genetic control and involve GE interplay, for both the foetus and the mother. They can therefore be considered 'endogenous' for the materno-foeto-placental unit as a whole.

A US longitudinal cohort study shows that children born to mothers who are severely obese (class II/III, BMI >35) before pregnancy have increased risk for adverse developmental outcomes, including autism and a full range of other conditions such as developmental delay, ADHD and psychosocial problems (Jo et al., 2015). A meta-analysis also shows that risks of offspring ASC are increased in obese compared with normal-weighted mothers (adjusted OR 1.47, 95% CI 1.24–1.74) (Li et al., 2016). The US population-based case–control CHARGE study further shows that maternal metabolic conditions [i.e. obesity, hypertension, pre-existing type II diabetes or gestational diabetes mellitus (GDM)] are broadly associated with increased risks for neurodevelopmental disorders in children, including ASC (adjusted OR 1.61, 95% CI 1.10–2.37) and developmental delay (adjusted OR 2.35, 95% CI 1.43–3.88) (Krakowiak et al., 2012). Specifically, maternal diabetes has long been shown to be a risk factor for a wide range of developmental delays in offspring (Ornoy, Reece, Pavlinkova, Kappen, & Miller, 2015). Maternal weight gain during pregnancy (but not pregnancy BMI itself) seems to be associated with a modest increased risk of ASC for offspring (Bilder et al., 2013). Recently, a large retrospective longitudinal cohort study including 3,388 children with ASC shows that after controlling for other risk factors, maternal GDM diagnosed at 26 weeks or earlier remains to be a significant risk factor for offspring ASC (birth-year-adjusted hazard ratio, HR 1.42, 95% CI 1.15–1.74) (Xiang et al., 2015). Amongst children with ASC, those born to mothers with diabetes have elevated risk of poorer expressive language (Krakowiak et al., 2012). These emerging findings suggest that maternal metabolic profile,

particularly during pregnancy, is associated with an increased risk for offspring ASC.

How exactly maternal metabolic factors increase risks for offspring atypical neurodevelopment is not yet clear, but effects mediated by in utero steroid regulation may be one common biochemical pathway. Steroid hormones in the womb can directly influence gene transcription and expression in the foetus during vulnerable periods of embryonic development (Auyeung, Lombardo, & Baron-Cohen, 2013; Baron-Cohen et al., 2011; Jessen & Auger, 2011). In individuals without clinical ASC, prenatal testosterone level predicts elevated behavioural and cognitive traits associated with autism in both typically developing males and females from early to late childhood (Auyeung et al., 2013), and shows long-lasting effects on brain structural organisation (Lombardo, Ashwin, Auyeung, Chakrabarti, Taylor et al., 2012) and emotional reward processing (Lombardo, Ashwin, Auyeung, Chakrabarti, Lai et al., 2012) in late childhood. Daughters (but not sons) of mothers with hyperandrogenic polycystic ovary syndrome (PCOS) exhibit increased autistic traits compared to those born to mothers without PCOS (Palomba et al., 2012). In a Danish population-based cohort, increased prenatal steroidogenic activity (across Δ4 sex steroids including progesterone, 17α-hydroxyprogesterone, androstenedione and testosterone, as well as cortisol) predicts later ASC diagnosis in childhood in males, with elevations across all prenatal hormones on a latent generalised steroidogenic factor (Cohen's d = .37); this elevation was observed across all ICD-10 diagnostic subgroups (Baron-Cohen et al., 2015). This finding suggests that at least in males, altered steroid hormonal activity (beyond sex steroids) in the womb predisposes to later ASC diagnoses. Furthermore, a recent population-based Swedish study (Kosidou et al., 2015) on 23,748 ASC cases and 208,796 controls matched for birth month and year, sex and region of birth, shows that maternal PCOS increases the odds of offspring ASC (adjusted OR 1.59, 95% CI 1.34–1.88), after adjusting for effects of maternal age, paternal age, parental psychiatric history, household income, parental education and mother's country of birth; the effects are similar for boys (adjusted OR 1.60, 95% CI 1.31–1.94) and girls (adjusted OR 1.58, 95% CI 1.14–2.20). The odds of offspring ASC is even higher when the mothers have both PCOS and obesity (indicating more severe hyperandrogenaemia) (adjusted OR 2.13, 95% CI 1.46–3.10). Overall, there is accumulating evidence indicating that changes in the prenatal hormonal environment play a contributing role in modulating risk and protective mechanisms associated with ASC. As steroid hormonal processes are highly associated with biological sexual differentiation, they may meanwhile underlie the male-preponderance and female-protection of autism (Lai et al., 2015). It has been increasingly shown, from animal work, that sexual differentiation in the brain is not solely neuronal, but inflammatory mediators and immune cells (such as microglia) are also principle regulators (Lenz & McCarthy, 2015; McCarthy, Pickett, Vanryzin, & Kight, 2015). As microglial activation during early brain development is influenced by prenatal sex hormones (Lenz, Nugent, Haliyur, & McCarthy, 2013), the interactions among prenatal hormonal and immune systems may be critical for shaping early atypical neurodevelopment resulting in the emergence of ASC, as well as other neurodevelopmental disorders.

A third endogenous risk condition regards processes triggering maternal immune reactions during pregnancy. As early as in the 1970s, rubella infection during early pregnancy (with greatest risk in the first 8 weeks post conception) was shown to increase risk for autism, in association with other presentations characteristic of congenital rubella syndrome (Chess, 1971). Other viral infections are similarly associated (Libbey, Sweeten, McMahon, & Fujinami, 2005). The timing of infection may influence its effect on ASC risk, as shown by a Danish birth cohort study which showed that it was maternal viral infection during the first trimester that predicted subsequent offspring ASC diagnoses (adjusted HR 2.98, 95% CI 1.24–7.15) (Atladottir et al., 2010). Risks are not confined to viral infection: maternal infection during pregnancy associated with hospitalisation, regardless of whether the infection is bacterial, viral, or other/unknown, is associated with higher odds of offspring ASC (adjusted OR 1.37, 95% CI 1.28–1.47) (Lee et al., 2015). Experiencing multiple infections during pregnancy is also associated with an increased risk of offspring ASC (adjusted OR 1.36, 95% CI 1.05–1.78) (Zerbo et al., 2015).

The pathogenic effects associated with maternal infections may be mediated by the immune responses they evoke. The CHARGE study found that, although offspring clinical diagnoses of ASC or developmental delay are not associated with maternal exposure to influenza virus during pregnancy, both are associated with maternal fever during pregnancy (Zerbo et al., 2013). Also in the CHARGE study, maternal autoimmune conditions are associated with increased risk for combined ASC and developmental delay (adjusted OR 1.46, 95% CI 1.01–2.09), but not ASC alone (Lyall, Ashwood, Van de Water, & Hertz-Picciotto, 2014). In a Finish national birth cohort, elevated maternal serum C-reactive protein (an inflammatory marker) in the first or early second trimester is associated with increased risk of offspring diagnosis of ICD-10 childhood autism (adjusted OR 1.14, 95% CI 1.02–1.27) (Brown et al., 2014). Finally, in a subgroup of children with ASC, the presence of maternal foetal brain-reactive immunoglobulin G (auto)antibodies may be pathogenic (Braunschweig & Van de Water, 2012); lactate dehydrogenase A and B, cypin, stress-induced phosphoprotein 1, collapsin response medi-

ator proteins 1 and 2, and Y-box-binding protein are found to be the seven primary antigens for these 'maternal autoantibody-related' ASC (Braunschweig et al., 2013). The subgroup of mothers (of children with ASC) who have antibrain antibodies are more likely to also have autoimmune diseases, especially systemic lupus erythematosus and rheumatoid arthritis (Brimberg, Sadiq, Gregersen, & Diamond, 2013).

There is now increasing evidence suggesting a central role of immune dysregulation in ASC (Estes & McAllister, 2015). Neuro-immune processes are not only key to the neurobiological characteristics of individuals with ASC themselves (Voineagu et al., 2011), but such processes may also play a contributing' role in atypical neurodevelopment as early as the gestational period and may explain the pathogenesis of the autism phenotype in a subgroup of individuals (McDougle et al., 2015). More broadly, maternal immune activation during pregnancy may serve as shared risk processes affecting neurodevelopment and the emergence of a wide range of conditions beyond ASC (e.g. schizophrenia, epilepsy, cerebral palsy, Alzheimer's or Parkinson's disease), through mechanisms such as microglial activation and priming, cytokine release, altered adaptive immune responses, blood-brain-barrier and white matter injury, altered synaptic and neuronal development, and even transcriptional and epigenetic effects (Knuesel et al., 2014).

Risk mechanisms underlying these endogenous environmental processes can in fact be products of GE interplay. First, rGE can be a critical early mechanism leading to enhanced risk for autism. A candidate risk gene for autism, the nuclear hormone receptor RORA (retinoic acid-related orphan receptor-alpha), plays pivotal roles regulating sex steroid hormones through feedback loops operating via androgen and oestrogen receptors and associated coregulators (Sarachana & Hu, 2013). Dysregulated RORA expression (e.g. deficiency), as a genetic factor, in the foetal brain can impact on the in utero sex steroid hormonal environment (e.g. hyperandrogenic), which further affects the neurodevelopment of the foetus. This could be an example of a *biological* rGE operating very early in development. Furthermore, it has been shown that family history of autoimmune diseases overall is associated with a 28% (95% CI 12%–48%) increased risk for autism in the proband (Wu et al., 2015). Whether genetic disposition of immune dysregulation operates to increase offspring risk for autism through direct inherited genetic effects on foetal neurodevelopment, or through rGE involving maternal immune activation, awaits clarification.

On the other hand, prenatal endogenous environmental risks for autism may participate in G × E. In a large Simons Simplex Collection sample, there are significant interactive effects between the presence of ASC-associated copy number variants (CNVs) and maternal infection or fever during pregnancy on autism symptomatology: Individuals with ASC-associated CNVs and a history of maternal infection show higher levels of social-communicative impairments and repetitive, restricted and stereotyped behaviours, indicating that those with pathogenic CNVs are more susceptible to insults associated with maternal immune activation (Mazina et al., 2015). Such findings highlight the value of considering GE interplay when investigating how environmental risks operate.

Prenatal protective factors

Vitamin B9, commonly known as folate, is a source of 1-carbon units, which are required for a number of basic cellular processes such as DNA replication and methylation. Maternal folate deficiency during and in the 4 weeks after conception is associated with greater risk of having offspring with neural tube defects (NTD) (Blom, 2009). Conversely, supplementation of a mother's diet at the start of pregnancy with folic acid, a synthetic form of folate, reduces the risk of NTD and improves cognitive outcomes for offspring (Veena et al., 2010; Wolff, Witkop, Miller, & Syed, 2009). This protective effect of periconception and prenatal folate on neurodevelopment extends to ASC. In the CHARGE sample, a mean daily folate intake above 0.6 mg during the first month of pregnancy, estimated retrospectively by telephone interview, was associated with a reduced risk of having a child with ASC (adjusted OR 0.62, 95% CI 0.42–0.92) (Schmidt et al., 2012). Similarly, in a large general population study of 85,176 Norwegian children born between 2002 and 2008, folic acid supplementation at the start of pregnancy (4 weeks before conception to 8 weeks after) was associated with a reduced risk of having a child with autistic disorder (adjusted OR 0.61, 95% CI 0.41–0.90); such a protective effect was not found for Asperger's syndrome or PDD-NOS (but the power of these analyses was limited) (Suren et al., 2013).

It has been proposed that this protective effect derives from the role of folate as a methyl donor that contributes to epigenetic processes during early neural development (Schmidt et al., 2011). During early embryogenesis there is a process of DNA demethylation, followed by re-establishment of DNA methylation. This extensive reprogramming of part of the epigenetic code relies on the presence of methyl donors, including folate, and is influential on the risk of NTD (Blom, 2009). Thus, folate may protect against ASC by supporting early epigenetic processes that guide typical neurodevelopment. Such a hypothesis is consistent with the observation that protective effect of folate appears to be limited to a critical period at the very start of pregnancy, when extensive remethylation of the embryo's DNA occurs (Schmidt et al., 2011; Suren et al., 2013). Furthermore, some cases of ASC have been linked to NTD

(Rodier, Ingram, Tisdale, Nelson, & Romano, 1996). One possibility is that folate is not protective against all cases of ASC, but rather is only relevant to those associated with NTD and very early perturbations of the emerging nervous system. This is consistent with the finding of Suren et al. (2013) that prenatal folate reduces risk of autistic disorder, but not milder forms of ASC such as Asperger's syndrome or PDD-NOS.

Another interesting feature of the protective effect of prenatal folate is that it appears to operate as a G × E. Folate supplementation exerts its strongest protective effect for mothers and children who have a genotype associated with inefficient folate metabolism (Schmidt et al., 2011, 2012). This highlights the fact that the aetiologies of ASC involve biological processes that are beyond the nervous system per se, but extend to other interactive systems, and illustrates why the collection of 'genes for autism' is so large and diverse and thus has to be viewed through the lens of GE interplay.

Perinatal risks

Birth can be a critical period for the emergence of atypical neurodevelopment, including ASC (Ben-Ari, 2015). There has been extensive interest in the possibility that events during birth, and characteristics of the baby at and shortly after birth, influence ASC risk. In a comprehensive meta-analysis of 41 papers, Gardener, Spiegelman, and Buka (2011) demonstrated the existence of several perinatal risk factors for ASC. Some of these perinatal risk factors are unlikely to be causal. Instead, they probably reflect an underlying risk for ASC, or mark the presence of other causal risk factors. For example, being born with congenital malformations (OR 1.80, 95% CI 1.42–2.82) almost certainly does not cause a child to develop ASC, but it may indicate that foetal development has been atypical and that the baby may be already on a trajectory towards developing ASC (Bolton et al., 1997).

Other perinatal risk factors may be components of rGE that plays out over time, whereby: (a) inherited risk for ASC places a foetus at risk of having specific experiences at birth; (b) which in turn serve to magnify their already elevated risk for ASC. Evidence for the first part of this causal chain comes from the finding that familial loading for ASC and the broader autism phenotype predict risk of obstetric complications (Bolton et al., 1997). Direct empirical evidence for the second part of the rGE hypothesised above is currently scarce. Nevertheless, it is notable that a number of the strongest perinatal ASC risks identified by Gardener et al. (2011), such as neonatal anaemia (OR 7.87, 95% CI 1.43–43.36), meconium aspiration (OR 7.34, 95% CI 2.30–23.47), birth trauma (OR 4.90, 95% CI 1.41–16.94) and very low (<1.5 kg) birth weight (OR 3.0, 95% CI 1.73–5.20), are all associated with hypoxia before, during or immediately after birth. Hypoxia places the developing brain at risk, and thus could raise the chance of ASC (Kolevzon, Gross, & Reichenberg, 2007). Thus, genetic ASC risk may increase risk of the neonate being exposed to hypoxia, which in turn may magnify their chances of subsequently developing ASC.

It is worth noting that very few perinatal risk factors have been shown to be specific to ASC. Data from the Autism and Developmental Disability Monitoring Network show that many perinatal risk factors for ASC (e.g. preterm birth, low birth weight, small for gestational age, low Apgar score) are also risk factors for intellectual disability (Schieve, Clayton, Durkin, Wingate, & Drews-Botsch, 2015). Similarly, a Danish population-based cohort study shows that neonatal morbidities are risk factors for ASC but also for other neurodevelopmental disorders (e.g. ADHD, intellectual disability, epilepsy, cerebral palsy) (Atladottir, Schendel, Parner, & Henriksen, 2015).

Postnatal environmental risks

When considering postnatal environmental risk factors it is important to distinguish between exposures that potentially play a role in the aetiology of ASC and those that influence ASC's expression and developmental trajectory once it has become established. Current evidence suggests that the full clinical syndrome of ASC manifests as early as the second year of life (Landa, 2008; Ozonoff et al., 2010), so it is possible that environmental exposures occurring early in life (e.g. during the first year) may influence whether or not an individual later presents a full ASC phenotype. By contrast, environmental risks that occur after the 'onset' of the condition, by definition, cannot be implicated in its aetiology, but may play a role in shaping the severity and behavioural manifestations of autistic symptoms and influencing their functional impact. Based on this we divide our discussion of postnatal environmental risks for ASC into those occurring early in life (during the first year), which potentially (but not exclusively) influence an individual's risk of presenting with a full syndrome of ASC, and those occurring after the full emergence of ASC, which may impact upon symptom severity and expression as well as functional outcome.

Early postnatal risks

The notion that subtle variations in maternal care can in any simple sense *cause* autism, as was proposed by the 'refrigerator mother theory', has been discredited (Bailey et al., 1995; Folstein & Rutter, 1977). Nevertheless, characteristics of the social environment, including caregiver–infant interaction, may partially mediate the relationship between ASC susceptibility, present at birth and the emergence and development of an ASC pheno-

type later on. Crucial to this account is the proposal that there is an ASC prodrome in the first year(s) of life characterised by reduced tendency to seek, respond to and evoke social experience; and that this may perturb infant–caregiver social interaction, which in turn may increase the risk of the infant developing social communication and flexibility difficulties characteristic of ASC (Dawson, 2008; Green et al., 2015; Hobson & Lee, 2010). This model, depicted in Figure 1, can be understood *partly* as a rGE, whereby genetic risk for ASC manifests in such a way as to shape experience of the environment (e.g. the infant's ability to attend to aspects of parental care) and to shape the environment itself (e.g. by evoking fewer or different interactions from caregivers), which in turn promotes the emergence of the full autistic phenotype.

There is some evidence to support the rGE shown in Figure 1. Prospective 'infant-sibling' studies have shown differences in early social orienting and engagement between infants who go on to develop ASC compared to those who do not, consistent with the idea of an ASC prodrome. Characteristics of this pre-ASC state include lower levels of activity (Wan et al., 2012), being less attentive to the primary caregiver (Wan et al., 2013), directing less attention to social scenes (Chawarska, Macari, & Shic, 2013), showing a decline in attention to eyes between 2 and 6 months (Jones & Klin, 2013), having an atypical neural response to dynamic eye gaze aged 6–10 months (Elsabbagh et al., 2012) and making fewer requests at 12 months (Rozga et al., 2011).

These 'prodromal' characteristics might plausibly impact upon caregiver–infant interaction (pathway b in Figure 1), as part of an active or evocative rGE, and there is some empirical evidence in support of this. Twelve-month-old infants who go on to develop ASC tend to receive a more directive style of parenting, with parent–infant interactions more likely to be characterised by less mutuality and engagement intensity (Wan et al., 2013). Crucially, in support of the hypothesised pathway c of Figure 1, these features of parent–infant interaction at 12 months predicted ASC diagnosis at 3 years, even when controlling for characteristics of emergent ASC at baseline (Wan et al., 2013).

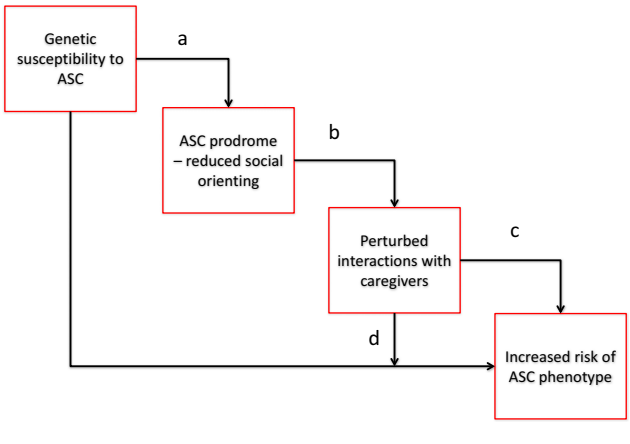

Figure 1 A proposed gene–environment correlation in the emergence of autism spectrum condition

Nevertheless, research on very early signs of ASC is not yet sufficient to conclusively support (or refute) this model. In particular, more work is required to establish whether atypicalities in caregiver–infant interaction actually have any causal influence on the chances of an individual developing the full ASC syndrome (pathway c). The atypicalities of infants in terms of their social engagement and interactions with caregivers could merely be early markers of ASC, without actually influencing its emergence.

Randomised-controlled trials (RCT) of interventions designed to prevent the emergence of ASC in high-risk infants will be instructive for testing pathway c in Figure 1, since they serve as experiments in which caregiver–infant interaction is manipulated (Howe, Reiss, & Yuh, 2002), and so test the hypothesis that caregiver–infant interaction has some causal influence on the emergence of a full ASC phenotype. To date one such RCT has been published. Green et al. (2015) tested an adapted Video Intervention to Promote Positive Parenting (iBASIS-VIPP), which is designed to help parents adapt to their child's style of communication to enhance sensitive parenting. In a sample of infants (7–10 months) at high risk of developing ASC, iBASIS-VIPP was compared to no treatment in a relatively small ($n = 54$ families) but rigorously conducted RCT. There was a large, significant effect on parenting style, with iBASIS-VIPP parents becoming less directive, and a nonsignificant trend towards their infants showing fewer early signs of ASC. These findings require elaboration in larger (better powered) trials with follow-up in toddlerhood and early childhood, to learn more about the size, significance and longevity of any treatment effects. Nevertheless, Green et al. (2015)'s initial findings on very early intervention are consistent with the notion that the caregiver–infant relationship may have some influence on the risk of a child (who has higher-than-average genetic susceptibility to ASC) developing the full ASC phenotype.

The model in Figure 1 proposes that some infants evoke or select to experience certain types of interaction with caregivers, which then impact upon their risk of developing a full ASC phenotype. This raises the question of whether *exogenous* features of the social environment, which do not reflect the infant's pre-existing susceptibility, could ever play a causal role in the emergence of ASC. The study of typical child development, and of the effects of child maltreatment, show that most forms of early environmental deprivation do *not* increase risk for ASC (Sroufe, 2005). However, anecdotal reports have suggested that very severe social deprivation in the first year of life may lead to autistic-like difficulties (Skuse, 1984). A systematic test of this idea came

from the study of Romanian children adopted in the United Kingdom after they had experienced extreme social deprivation in their early years spent in orphanages. Aged six, a substantial proportion (16 of 144; 11.1%) of these children showed a marked pattern of social and communication difficulties in conjunction with sensory abnormalities and circumscribed interests, which closely resembled ASC (Rutter et al., 2007). Such difficulties were more common in the children who had endured an extended period of environmental deprivation, involving very little social and emotional reciprocal contact with adults, lasting at least the first 12 months of their lives (Rutter et al., 1999). Similarly, a comparable condition termed 'post-institutional autistic syndrome' was found in 16% of a sample of 8-year-olds adopted in the Netherlands, who were previously institutionalised in Romania (Hoksbergen, ter Laak, Rijk, van Dijkum, & Stoutjesdijk, 2005).

The syndrome identified in the Romanian adoptees has been labelled 'quasi-autism' as it differed from idiopathic autism in three key respects (Rutter et al., 1999). First, aged 6 years, many of the children showed features that are not classically autistic, namely a capacity for spontaneous and flexible communication and a tendency towards social approach, albeit in a manner that was uninformed by an age-appropriate understanding of social boundaries. Second, the children with quasi-autism experienced substantial alleviation of their difficulties from the age of 4 years onwards, which is in contrast to the trajectory seen in 'ordinary' autism. Only half with quasi-autism at 6 years continued to meet criteria by the age of 12 (Rutter et al., 2007). Third, there was an equal male–female ratio, in contrast to the male-predominance in prevalence in idiopathic autism (Rutter et al., 1999). Similar findings come from studying children who experienced an early lack of reciprocal exchange due, not to poor institutional care, but to their congenital blindness. Brown, Hobson, Lee, and Stevenson (1997) reported high rates of autistic difficulties in children born blind, but noted that even those who met diagnostic criteria for autism gave a clinical impression of having difficulties that were not quite typical of 'ordinary' autism. Furthermore, they had a better prognosis than children with idiopathic autism: at follow-up, like the Romanian adoptees, most of the blind children (8/9) who had met criteria for autism in mid-childhood no longer qualified for a diagnosis by the time they reached adolescence.

A further point to make about the effects of extreme social deprivation early in life is that only a minority of those who suffer from this environmental exposure go on to develop ASC or 'quasi-autism'. Furthermore, and most importantly, the vast majority of individuals with ASC *do not* suffer from a history of childhood social deprivation. On this basis, and taking into account that social deprivation does not lead to a syndrome identical to idiopathic autism, it is clear that the social environment is neither sufficient nor necessary to *cause* ASC. In the model in Figure 1, we should conceptualise the effect of early social experience as, at most, a *modifier* of pre-existing susceptibility to ASC, as signified by pathway d.

However, severe early social deprivation and maltreatment is still associated with increased social-communication and flexibility difficulties that persist later in life, even if not fulfilling an ASC diagnosis. In the cohort of Nurses' Health Study II, women with high autistic traits in adulthood were at significantly increased odds of having experienced childhood sexual, physical or emotional abuse, than women with low autistic traits (Roberts, Koenen, Lyall, Robinson, & Weisskopf, 2015). The Bucharest Early Intervention Project showed that at the age of 10 years, previously institutionalised Romanian children, compared to community children who were never institutionalised, showed increased lifetime scoring on all domains of the Social Communication Questionnaire (Levin, Fox, Zeanah, & Nelson, 2015). When family centred foster care intervention had been provided, however, improved social communication skills were evident. These findings point to the critical role of the social environment in dynamically shaping an individual's general social-communication and flexibility developments.

No evidence for vaccination being a postnatal environmental risk. We finish our consideration of early postnatal environmental risks for ASC by evaluating a notorious proposal about the aetiology of autism; that the combined Measles, Mumps and Rubella (MMR) vaccine causes some cases of ASC, via its effect on the gut. This arose from a paper, since retracted, which described 12 children who developed inflammatory bowel disease and autism subsequent to having the MMR vaccine (Wakefield et al., 1998). These findings, based on a nonrepresentative sample, are consistent with there being no statistical association between MMR and ASC, but despite this they contributed to widespread anxiety about potential harmful effects of MMR. This in turn resulted in a drop in MMR uptake in many developed countries, and so is likely to have increased the incidence of measles, mumps and rubella (Gastanaduy et al., 2014; Gust et al., 2004).

Many large-scale epidemiological studies have refuted the idea that MMR vaccine (Madsen et al., 2002) or thiomersal-containing vaccines (Parker, Schwartz, Todd, & Pickering, 2004) act as postnatal risks for the incidence of ASC. A recent meta-analysis, pooling findings from five case–control studies and five cohort studies, provides evidence that is very clearly contrary to the idea that MMR, thiomersal (aka thimerosal), or mercury are causal agents in the emergence of ASC: none of them are associated with any increased risk for ASC diagnosis

(Taylor, Swerdfeger, & Eslick, 2014). In fact, the pooled estimate suggests a trend (p = .07) towards MMR being associated with *reduced* risk for ASC (OR 0.84, 95% CI 0.70–1.01). This is consistent with the finding that increases or decreases in the population uptake of MMR is not associated with corresponding rises or falls, respectively, in the incidence of ASC (Honda, Shimizu, & Rutter, 2005; Taylor et al., 1999). Furthermore, the notion that MMR could operate as a risk factor among those already at higher genetic susceptibility for ASC is not empirically supported either: MMR is not associated with ASC among the younger siblings of people with ASC (Jain et al., 2015).

Later postnatal risks

One strength of a developmental approach to studying psychopathology is that it takes account of the timing, as well as the nature, of risk and protection. The same risk or protection occurring at different points in development can have distinct effects. A model based on the rGE process in Figure 1 can be applied later in development, as a set of predictions about how people with ASC shape their environments (Figure 2, pathway b), and how the resultant experiences may influence the severity and quality of their symptoms and characteristics (pathway c) (Meek et al., 2013). This causal chain would play out in different ways, depending on the age and context of the person with ASC. For a young child, autistic impairments are associated with a number of atypicalities in parent–child interaction (pathway b) (Hudry et al., 2013). Based on evidence from RCTs of early interventions, it is likely that the quality of caregiver–child interaction can influence the severity and quality of the child's symptoms (pathway c) (Oono, Honey, & McConachie, 2013; Pickles et al., 2015). In later childhood and adolescence, the transaction between the individual and the environment will occur in a wider range of contexts. For example, ASC is a risk factor for being victimised by peers and for social exclusion (pathways b and d), and such experiences likely further

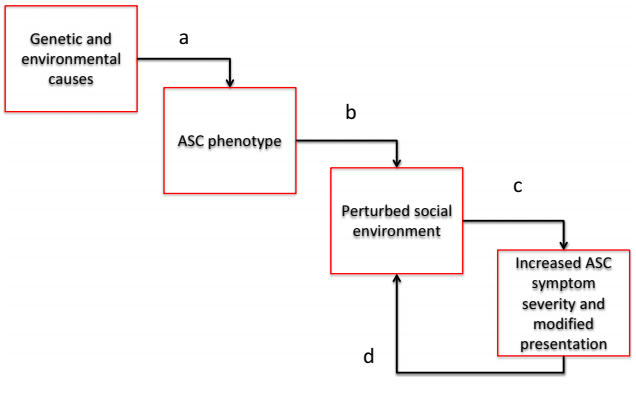

Figure 2 A proposed transaction between the person and the environment impacting upon symptom severity and presentation of autism spectrum condition

diminish social and communication functioning (pathway c) (Fein, 2015; van Roekel, Scholte, & Didden, 2010). The identification of such transactions, whereby the environment is both *shaped by the individual*, and then *shapes the individual*, offers clear targets for environmental intervention across the life span.

Ecological effects on adaptation

Maladaptation is not merely a characteristic of the individual, but rather arises from a misfit between their capacities and the demands placed on them by the environment. This idea offers a way to conceptualise some ecological effects on ASC across the life span, as it highlights the impact of different environments (e.g. primary school, secondary school, university, the work place, local community) on the functioning of people on the autism spectrum (Lai & Baron-Cohen, 2015). The profound impact of ecology on people with ASC is highlighted by difficulties with transition, when the environment undergoes rapid, substantial change. At such moments, for example, when moving from primary to secondary education (Mandy et al., 2016), or attempting to graduate from education to the workplace (Roux et al., 2013), many people with ASC struggle and develop additional difficulties when they attempt to adapt to a new set of challenges posed by their environment. Arguably, given difficulties with flexibility, people with ASC are especially vulnerable to maladaptation after ecological change. This points to the value of developing interventions that aim to shape the environment to fit the needs and abilities of people with ASC (Lai & Baron-Cohen, 2015; Mandy et al., 2015). Unfortunately, to date much empirical work designed to improve the adaption of people with ASC has taken a converse approach, seeking to change the individual to fit the environment better (Wong et al., 2015).

One proposal is that *secular* changes in the social ecology of industrialised countries have influenced the recent increase in diagnosed ASC. Some theorists have argued that, compared to previous generations, social life is ever more dependent on well-developed capacities for empathy and social adroitness (Côté, 1996; Pinker, 2011); and that increasingly 'social affiliations are organized primarily by voluntary choice and contingent upon sustained mutual satisfaction' (p. 83) (Fein, 2015). Such changes would likely disadvantage individuals with innate difficulties in mental perspective taking, social communication and flexibility, and so could result in more people experiencing social impairments that increase their probability of receiving an ASC diagnosis (Fein, 2015). Although this suggested interaction between cultural evolution and biologically determined characteristics of the individual is intriguing, it is speculative and difficult to test empirically. One approach would be to conduct anthropological investigations in countries that are

becoming increasingly 'westernised' to measure whether changes to social life and social demands are occurring, and whether these influence the prevalence and presentation of behavioural and cognitive characteristics associated with ASC (i.e. high autistic traits), and impact upon rates of ASC diagnosis.

Conclusions

The current review has identified evidence for diverse environmental exposures that are associated with risk for or protection from the emergence of ASC, and which may influence subsequent life span development. Our use of a developmental psychopathology framework highlights the following features of the emergence and progression of the autistic phenotype. First, ASC arises from the interplay of multiple risk and protective factors, which can be conceptualised at different levels of analysis. For example, several possible G × E have been identified, whereby the impacts of features of the environment (e.g. folate exposure in utero, TRAP exposure during pregnancy and infancy) appear to be moderated by genotype. Second, ASC emerges from dynamic transactions between the individual and their environment. Such transactions include rGE, for example, when the genetic risk for ASC makes perinatal complications more likely, which in turn enhance the risk of atypical neurodevelopment. Third, the dynamic unfolding of the phenotype does not stop at the moment of diagnosis: risk and protective factors continue to interact across the life span and to influence adaptation long after the individual has developed symptoms that earn them an ASC diagnosis. The efficacy of various supports and interventions at different ages is testament to the lifelong influence of the environment. Fourth, changing features of a person's ecology can have marked effects on their adaptation. One example of this is the impact of transition from education to work, during which many people with ASC experience a decline in their capacity to meet the demands placed on them by the environment.

The study of environmental influences has the potential to identify aetiological mechanisms that partly underlie the emergence of ASC. For example, work on TRAP, if replicated, will enrich understanding of how the MET receptor tyrosine kinase (MET) gene may influence the aetiology of ASC (Volk et al., 2014). The diversity of environmental risks identified, and the different windows of influence they have across the life span, enforces the argument that there are many aetiological routes to ASC, and factors involved in these mechanisms are not solely genetic or environmental, but likely involve GE interplay. Nevertheless, it is possible that once mechanisms associated with environmental risk and protection are better characterised, by a process of triangulation, they may converge on a smaller number of common pathways, for example oxidative stress and DNA methylation (Menezo, Elder, & Dale, 2015), and immune dysregulation (Estes & McAllister, 2015; Knuesel et al., 2014).

Based on the current literature, we suggest the following five areas for further investigation. First, there is some evidence to suggest that maternal age at conception and maternal use of SSRIs during pregnancy may be stronger ASC risk factors for males compared to females and that paternal age might pose greater risk for female than male offspring. This relates to the possibility that there are sex-specific pathways to ASC (Lai et al., 2015; Werling & Geschwind, 2013). Further investigation should take into account potential sex-moderating effects, and results could help elucidate the greater male vulnerability to the condition, and sex/gender-specific ASC symptom profiles (Frazier, Georgiades, Bishop, & Hardan, 2014; Hiller, Young, & Weber, 2014; Lai et al., 2011, 2012, 2015; Mandy & Tchanturia, 2015; Mandy et al., 2012; Messinger et al., 2015; Supekar & Menon, 2015; Szatmari et al., 2012).

Second, some environmental risks, such as in utero SSRI exposure, may be specifically associated with high-functioning ASC (Rai et al., 2013), whereas others, for example parental age at conception, may be associated with the full autism spectrum including developmental disability (Croen et al., 2007). The protective effect of folic acid seems to operate more evidently for classic autism than the milder forms of ASC (Suren et al., 2013). Perinatal risk factors, in addition, seem to increase the vulnerability to a broader spectrum of neurodevelopmental disorders rather than specifically to ASC (Atladottir et al., 2015; Schieve et al., 2015); maternal immune activation during pregnancy appears to have the same broad impact (Knuesel et al., 2014). Such findings point towards different developmental mechanisms that can partially explain the great heterogeneity amongst people with ASC, as well as mechanisms specifically leading to ASC versus other and broader atypical neurodevelopmental outcomes (e.g. ADHD, intellectual and developmental disabilities, epilepsy). Studies have shown that genetic aetiologies of ASC are quite distinct from those of intellectual disability (Ronald & Hoekstra, 2011; Sanders et al., 2015), but whether it is the same for environmental causes remains unknown. It might be the case that broad-impact environmental risks non-specifically 'lower the bar' for specific genetic risks to manifest specific phenotypes. Further investigations to test the specificity of different environmental risks and the underlying reasons will inform the aetiological heterogeneity in atypical neurodevelopment.

Third, further investigation of the precise timing of risk is required, to guide identification of processes that are implicated in the development of ASC. For example, the observation that there is a critical period for the protective effect of folate points towards early reprogramming of the epigenome as a key process influencing risk for ASC.

Fourth, animal models could provide a useful platform for investigating mechanisms underlying potential gene–environment interplay, beyond genetic mutations *per se*, in the aetiologies of ASC. For example, animal model systems are well suited to studying how valproate, SSRI or toxic chemicals exposure, maternal immune activation, or alteration in prenatal hormonal exposure interacts with genetic factors in modifying early neurodevelopment and subsequent behavioural features in relation to ASC.

Finally, as it has become clearer that the aetiological variance of ASC is substantially explained by various nongenetic contributors (Gaugler et al., 2014), which are unlikely simply 'environmental', but possibly involve a wide range of G × E and rGE mechanisms, future studies should be capable of revealing these complexities. For example, both the genome and the envirome need to be measured (Anthony, 2001; Neiderhiser, 2001), and sample size needs to be large to provide sufficient statistical power to detect various G × Es (Kim & Leventhal, 2015). Longitudinal designs capable of capturing timing effects of risk and protective mechanisms are required to test and reveal whether (and how) rGEs shape the emergence and life span development of ASC in an individual (Meek et al., 2013), which potentially provides implications for prevention, intervention and support.

Are there any public health and policy implications as well as clinical recommendations that can be made based on the current literature on environmental risks and protection for ASC? Clearly, it is a good idea for women trying to conceive a child, and in the early weeks of pregnancy, to take folic acid supplements, to reduce the risk of ASC and a range of other neurodevelopmental difficulties (National Institute for Health and Care Excellence, 2008). In terms of avoidance of hazards, it is difficult to make unequivocal recommendations based on current evidence, which is correlational and has not yet conclusively delineated mechanisms of action. However, the carefully controlled analyses of the effects of valproate, in combination with animal model findings, are sufficiently convincing that women considering pregnancy and during pregnancy should avoid the use of valproate, unless none of the alternative treatment options for the underlying disorders (e.g. epilepsy, bipolar disorder) are effective. In these difficult situations, risks of offspring ASC should be discussed in detail with pregnant users of valproate. It is also best to avoid exposure to toxic chemicals (in particular TRAP and pesticides) and to reduce the opportunity of immune activation (e.g. infection) during pregnancy. Finally, our developmental psychopathology analysis emphasises the value of environmental interventions and the importance of recognising the transactional nature of development, in the lens of GE interplay, including those aimed at modifying early caregiver–child interaction as well as later person-environment fit, as these may help mitigate genetically driven effects on the emergence and development of ASC.

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Key points

- Although autism spectrum condition (ASC) is highly genetic, environmental factors play a role in its emergence and development across the life span.
- Susceptibility to some environmental risks for ASC, for example, traffic-related air pollution, may be moderated by genotype.
- Other environmental risks, for example, perinatal complications associated with hypoxia, may be part of gene–environment correlations, whereby genetic risk increases the probability of environmental exposure, which in turn shapes the emergence of the ASC phenotype.
- Although genes are highly influential on the aetiology and development of ASC, environmental interventions have the potential to reduce susceptibility to the condition, alleviate symptoms and modify the developmental course.
- The study of environmental risk and protection can help elucidate aetiological and phenotypic heterogeneity, and will promote the discovery of mechanisms underpinning the emergence and development of ASC.

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