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Feature

From autism to the plural 'autisms': evidence from differing aetiologies, developmental trajectories and symptom intensity combinations

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Autism spectrum disorder is defined by the presence of sustained problems in areas of social cognition and social understanding alongside repetitive and/or restricted patterns of behaviour. Behavioural presentations and developmental trajectories in autism are highly heterogeneous. For most, characteristics variably continue across the lifespan, and, for many, they overlap with numerous overrepresented comorbid combinations spanning behavioural, psychiatric and somatic domains. The current autism diagnostic systems (DSM-5, ICD-11) reflect this heterogeneity, focusing on discerning different assistance needs and symptom severity combinations. An emerging view on the pluralisation of autism – 'the autisms' – based on different severity levels and different developmental trajectories is gaining popularity, bolstered by the introduction of the grouping 'profound autism' and observations of non-persistence of autism for some. We advance the case for expanding the definition of the plural autisms based also on the numerous different aetiological routes that can lead to autism. Various genetic conditions, susceptibility to infectious agents, non-infectious environmental exposures and immune-mediated occurrences have all been observed to culminate in a diagnosis of autism. As a triad, aetiology, presentation intensity and developmental trajectory offer new ways to classify the autisms, with potentially important implications for research and practice.

Keywords

Autism spectrum disorder; environment; genetics; heterogeneity; the autisms.

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Autism spectrum disorder (ASD) is a highly heterogeneous, clinically defined diagnosis based on observable behaviour linked to two core issues: (a) social cognition and social understanding; and (b) the presence of restricted, repetitive patterns of behaviour, interests or activities.[1,2] Referral for assessment for diagnosis is based on struggles and the disabling effects of behaviours on daily living. Diagnosis is exclusively based on observable behaviours and analysis of developmental history.

The estimated prevalence and incidence of autism suggest consistent global increases occurring over several decades. Nowhere is this trend more evident than in data from the US Centers for Disease Control and Prevention Autism and Developmental Disabilities Monitoring (ADDM) Network, which showed an estimated 1 in 36 8-year-olds to have a diagnosis of ASD in 2020.[3] Other data from regional and national initiatives point to similar increases, particularly across child age groups, together with large numbers waiting to access assessment services. The exact causes of the increase are still a matter of debate. 'Increased awareness' and 'diagnostic substitution' have long been preferred explanations. Prevalence data from the California Department of Developmental Services, which are limited to the more affected portion of the autistic population,[4] suggest that awareness is not the sole driver of recent surges, as such 'high-support needs' presentations granting preferential access to services are unlikely to have been previously missed. The possibility of a real increase in autism cases as accounting for some of the sustained uptick in numbers cannot be discounted. Other influences, including looping effects, are also potentially relevant to specific circumstances.[5]

Autism plus and plus and plus

Autism for many is not a stand-alone condition. Multiple behavioural, psychiatric and somatic symptoms are overrepresented alongside a diagnosis of autism,[6] whether they begin at the same time as the initial autism onset or emerge subsequently. Some of these comorbidities are intrinsic, directly relating to the presence of autism. Others come about as a result of autistic behaviours, for instance, scurvy following restricted feeding patterns or weight gain as a side-effect of various pharmacotherapies.

Intellectual disability is present in around one-third of people diagnosed with autism. Epilepsy and/or seizure disorders are estimated to affect a similar proportion. Attention-deficit hyperactivity disorder (ADHD), although a relatively new addition to the diagnostic picture of autism, is increasingly recognised as being another important comorbidity. Schizophrenia and related conditions such as psychoses have important historical links to autism. The possibility of an autism phenotype linked to onset of psychosis has also been suggested. Mood disorders such as depression and bipolar disorder, anxiety and related symptoms, and conditions such as obsessive–compulsive disorder are similarly overrepresented in people with autism.[7]

Various somatic conditions are likewise overrepresented alongside autism. Gastrointestinal issues, including both functional problems and more pathological states such as inflammatory bowel disease and coeliac disease,[6] are more frequently present in autistic versus non-autistic people. Cardiovascular conditions and diseases are also overrepresented, as are various neurological conditions and

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a multitude of immune-related conditions including but not limited to various autoimmune and atopic diseases.

Autism diagnostic criteria are not just about diagnosing autism anymore

Although there are multiple ways of assessing the presence of autism, diagnosis is given on the basis of meeting established behavioural criteria following the current iterations of the DSM[2] or ICD.[1] These manuals have undergone modifications to criteria, but the core features first formally described by Kanner[8] have survived intact.

One notable change to the modern description of autism, manifesting in both the current DSM and ICD instruments (DSM-5, ICD-11), is a focus on how such manuals now provide more than just information about diagnostic criteria. There are several examples of this, including discernment of different levels of 'severity' of autism during assessment. The DSM-5 describes 'levels of support' as part of the diagnostic criteria, alongside offering an alternative diagnosis – Social (Pragmatic) Communication Disorder – for those who show persistent difficulties in social use of verbal communication but do not reach other thresholds for autism. The ICD-11 criteria also focus on 'splitting levels', with the ability to code different degrees of functional language use alongside the presence or absence of learning (intellectual) disability accompanying autistic features. Regression (or plateauing) in previously observed developmental milestones is also mentioned as part of the ICD-11 autism criteria, something not previously seen. Such changes to autism diagnostic criteria indicate a shift away from autism as a universal and uniform label, instead taking into account the huge heterogeneity present.

The move away from just listing diagnostic criteria is also evident in another area of the ICD-11 descriptions of autism: the introduction of boundary conditions. The ICD-11 autism diagnostic criteria list 18 boundary conditions defined under the term 'differential diagnosis'. Several conditions are featured, including disorders of intellectual development, schizophrenia (spectrum disorders) and personality disorder, all of which also represent comorbidities potentially accompanying a diagnosis of autism.[9] All boundary conditions show overlap with autism, with some degree of autistic features being part of their respective manifestations. Autistic traits are therefore no longer exclusive to a diagnosis of autism and require diagnosticians to embrace a wider view when assessing. The inclusion of the term 'Secondary Neurodevelopmental Syndrome' in the ICD-11 autism boundary conditions, denoting specific 'acquired medical conditions' manifesting with autistic traits, also represents an important shift. Diagnostic criteria now incorporate potential causation information too, at least with regard to the presence of autistic traits.

Such shifts in the diagnostic criteria, whether intentional or not, introduce the idea that there may be multiple different types of autism, although united by shared diagnostic criteria: the plural 'autisms'.

The plural autisms

Various scholars have mentioned the plural autisms under one name or another, on the basis that the massive heterogeneity that underlies autism – in presentation, developmental history and prognosis – may be due, in part, to different types of autism all being subsumed under one diagnostic label. This idea continues from Bleuler's 'group of schizophrenias'[10] and draws on other examples defined in the diagnostic manuals, for instance, depression, for which several different codes are used to define on the basis of presentation and context. Pluralisation gathers additional strength from the multiple behavioural, psychiatric and somatic conditions that seem to be overrepresented alongside a diagnosis of autism, with potentially different comorbidity clusters circling around different autism phenotypes,[11] albeit not necessarily in a uniform fashion. More directly, however, the pluralisation of autism can draw on three primary areas or vectors providing description: different symptom intensities, differing developmental trajectories and different aetiologies.

The era of profound autism (and saying farewell to Asperger syndrome)

The ability to detail support levels and/or presentation as a function of intellectual disability and verbal language use in the current DSM and ICD schedules also relates to a new designation: profound autism. 'Profound autism' was introduced in 2022,[12] providing a distinction between those who do and don't need '24-hour access to an adult who can care for them if concerns arise, cannot be left completely alone in a residence' and 'cannot take care of basic everyday adaptive needs.' The rationale behind the term was multifold but in part relates to the 'single spectrum condition' grouping of autism in current diagnostic manuals and the requirement for distinction based on differing support needs. Despite concerns about the introduction of profound autism,[13] the adoption of the term by the US ADDM initiative[14] to provide data on estimated prevalence cemented an initial place for profound autism in the diagnostic lexicon. That an estimated quarter of people with autism fulfilled the criteria for profound autism according to the ADDM report provided important context for how widespread profound autism is. The overrepresentation of profound autism among Black and minority ethnic children similarly provides scope for further investigations.

It is perhaps not coincidental that the introduction of profound autism followed the removal of the diagnosis 'Asperger syndrome' from diagnostic texts.[15] The criteria for Asperger syndrome, last detailed in DSM-IV, provided separation between autism with and without functional language use issues. Removal of Asperger syndrome and other diagnostic options such as childhood disintegrative disorder translated into 'autism is autism' for everyone. For whatever reasons, however, this transition was short-lived.

It is still early days for profound autism. Discussions continue about the terminology used, the definition of profound autism and how one ensures that cognitive abilities are accurately determined (especially when 'nonverbal, were minimally verbal' are part of the diagnostic criteria and the implications for cognitive testing battery selection). What such a designation offers is a valuable and frequent distinction when it comes to the pluralisation of autism. As per the 2022 *Lancet* commission paper[12] that first detailed the conception of profound autism, it offers a way to 'prioritise the needs of this vulnerable and underserved group of autistic individuals.'

Non-persisting autism: meeting diagnostic thresholds is not universally lifelong

The idea that autism is universally a 'lifelong' diagnosis is a mainstay. The diagnosis is, in many quarters, seen as fixed and provides an important anchor for many life events. In recent years, however, emerging evidence has suggested that such a singular view is not representative of every experience of autism.[11] Multiple instances illustrate how well-defined diagnosed cases of autism do

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not seemingly persist temporally, at least in the short and medium terms, based on reaching diagnostic cut-off points. Whereas such non-persistence would previously have been thought to be due to misdiagnosis, recent data suggest that if this were the case, misdiagnosis would be happening on a grand scale.

Rather, there is a growing acceptance that for some, reaching diagnostic thresholds for autism is not a lifelong state. The work of Fein and colleagues,[16] in particular, provides an important starting point for the idea that autism is not immutable for everyone. Their studies and editorials provide important discussion points. The terminology used to denote non-persisting autism has also shifted as acceptance has increased, from 'optimal outcome' to 'loss of autism diagnosis' to 'non-persisting'. This perhaps reflects cultural shifts, in terms of a move away from seeing non-persisting autism as 'optimal' for all and using more scientific language to denote temporal presentation differences.

There is still more to do. Most studies have been short term in their examination of non-persisting autism and could not authoritatively say whether such non-persistence is final, or what remains or might develop if autism abates. Some longitudinal studies have indicated that for some, non-persistence is a closed state, carrying some additional benefits in terms of social variables and relative freedom from comorbid disabling psychiatric issues.[17] Another potentially important question yet to be answered is whether non-persistence is akin to a prodromal period for some, whereby autism abates but other life-changing diagnoses then emerge. Other labels such as ADHD provide hints that diagnostic switching – ADHD to autism – may be important. Likewise, an estimated one in ten people with autism may 'progress' to schizophrenia;[18] this provides further evidence for the potential fluidity of autism and such prodromal tendencies.

What causes the autisms?

As well as the plural autisms encompassing different symptom presentations and different developmental trajectories, there may be different patterns of causation. Aetiology is not a priority for some stakeholders, but it is important to investigate on the basis that clues about prognosis can often be elucidated, allowing better management of health needs, which in turn has an impact on quality of life and premature mortality. Moreover, where autism appears as a consequence of or alongside a life-altering condition, the requirement to treat said condition may well have implications for the presentation and stability of autistic traits.

Genetics and 'syndromic autism'

There is significant support for the idea that autism has a genetic basis in many. Evidence from both simplex and multiplex studies have repeatedly shown autism and the broader autism phenotype to have important heritable underpinnings. Various studies on heritability and the transmission of autistic traits via genetic architecture provide strong evidence of a link. However, that is not to say that the transmission of autism follows a uniform inheritance pattern, nor that genetic architecture or gene expression patterns provide a completely intellectually satisfying account. Despite huge investment of resources, surprisingly few universally reproducible genetic markers for autism have been so far reported. It is more accurate to say that the genetics of autism, although important, are complicated and multifactorial and overlap with those of various other behaviours and conditions.

An important point to make when discussing the genetics of autism concerns the use of the term syndromic autism. It has various meanings, but we define it as autism appearing alongside or as a consequence of a known condition as a syndrome with other relevant comorbidity. Various examples of syndromic autism have been described,[19] including elevated rates of autism following 22q11.2 deletion syndrome, Rett syndrome and fragile X syndrome. Autism has also been reported across various specific duplication and deletion syndromes and is coincident with various genetic conditions affecting, for example, mitochondrial and related biological functions. Many genetic variants involved in autism, including but not limited to single nucleotide polymorphisms,[20] overlap with other behavioural and psychiatric conditions.

Another slightly undervalued area related to syndromic autism is the appearance of autism coincident with various inborn errors of metabolism (IEM). IEM are typically screened for via newborn programmes, covering conditions as diverse as phenylketonuria (PKU), maple syrup urine disease and medium-chain acyl-CoA dehydrogenase deficiency. Whether inherited or spontaneously occurring, various IEM show a strong relationship with autism. PKU has a particularly important relationship with autism,[21] and at least one treatment for PKU, tetrahydrobiopterin, has been examined in the context of autism intervention.[22] Other, more recently discovered IEM also prominently include autism. Branched-chain ketoacid dehydrogenase kinase deficiency is defined by problems with availability of branched-chain amino acids. Early supplementation with such amino acids has been shown to have some important effects on the presentation of autism in these cases. Some have even observed a possible protective role for such supplements.[23]

A wide variety of genetic conditions manifest autism, and an even wider variety manifest subthreshold autistic traits. Many of these genetic conditions can be screened for and, in the case of the IEMs, are already treatable with potentially important effects for the presentation of autistic traits. That such a wide range of genetic conditions, with various different genetic structural and/or gene expression profiles impacting on a multitude of biological pathways, also manifest autism provides evidence for the pluralisation of autism.

Infectious agents and inflammatory sequelae

Humans, like all animals, are in a constant evolutionary struggle with a multitude of viruses, bacteria and related organisms. We are invaded countless times over our lifespan by multiple species, many of which are highly evolved to circumvent our own advancing immune systems and/or our mothers' immune functions during the critical period of development *in utero*. Alongside somatic manifestations following such infections, many different infectious agents can affect behaviour and development. The condition known as paediatric acute-onset neuropsychiatric syndrome is an example of how a relatively innocuous bacterium, *Streptococcus*, can lead to significant and life-changing childhood psychopathology including tics, anxiety and oppositional behaviours. There are several other examples in which organisms affect behaviour, predominantly as a result of neuroinvasion, such as during toxoplasmosis (linked to schizophrenia), with mostly neuroinflammatory effects.

It is not surprising then that various infectious agents have been linked to the onset of cases of autism. The work of Chess provides a template, with her research detailing how congenital rubella – affecting the yet unborn or newborn – is a risk factor for autism.[24] Her work, together with subsequent discussions about the potential value of the rubella vaccination programme in mitigating risk of autism and other outcomes,[25] has been expanded to include a variety of other infectious agents such as cytomegalovirus and (cerebral) malaria that all enhance autism risk in offspring. The scientific jury is still out on whether more recent infectious diseases

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such as Zika virus can lead to autism in some cases. Whether other neurotropic viruses could feasibly cause behavioural outcomes pertinent to autism remains a topic for debate, particularly in these post-pandemic times.

Having already mentioned the term 'neuroinflammatory', we move to the potential processes through which infectious agents may cause some of the autisms and prime roles for conditions such as meningitis and encephalitis. Such states are primarily characterised by inflammatory mechanisms directly affecting the central nervous system. Several studies have observed a link between infectious and post-infectious sequelae such as encephalitis and meningitis and an elevated risk of autism. Enteroviral encephalitis, Hashimoto encephalopathy and other specific neuroinflammatory-linked conditions can seemingly manifest as autism, importantly also including 'autistic regression' as part of their clinical picture.

One particular class of encephalitis, autoimmune encephalitis, is attracting research attention as a consequence of cases of diagnosis of autism following onset and diagnosis.[26] Autoimmune encephalitis, which is distinct from other types of encephalitis, involves a person's own immune system attacking specific cells as part of a misdirected (autoimmune) immune response. Various types of autoimmune encephalitis have been identified (acute demyelinating encephalomyelitis, LGI1/CASPR2-antibody encephalitis and anti-*N*-methyl-D-aspartate (anti-NMDA) receptor encephalitis), with anti-NMDA receptor encephalitis becoming a specific focus. There is growing interest in how autoimmune encephalitis presents and the overlap with autistic features that can accompany such presentations. Again, regression is an important part of onset. Regarding prognosis and treatment, a varied picture is emerging. There are reports of abatement of autistic and other features following correct diagnosis and instigation of treatment regimes focused on various immune-related components including steroids, intravenous immunoglobulin, plasma exchange (plasmapheresis) and monoclonal antibodies. Some of these treatments have, independently from autoimmune encephalitis, been examined as intervention options for autism.

The accumulated literature regarding infectious agents and inflammatory sequelae in autism shows strong evidence of association. Such routes to autism provide important information about how autism might come about and how our specific interactions with the environment can increase autism susceptibility, seemingly without primary genetic involvement. For some cases of autism, however, there does seem to be a genetic vulnerability, with autoinflammatory genes particularly linked to poorly controlled maternal autoimmune disease in pregnancy.

Pollutants and contaminants

Various environmental elements have been linked to the onset of autism. Some correlates have proved controversial; others have, with less attention, slipped quietly into the research literature.[27,28] It is unsurprising that various pollutants and contaminants, in particular, have been linked to autism aetiology on the basis that such agents are ubiquitous, and developing infants are especially prone to the adverse effects of exposure. Exposure to heavy metals such as lead, aluminium and mercury has been a source of speculation. Various hypotheses have been fashioned around exposure events, biological effects, and a myriad of interventions to either remove or negate their biological effects. Some interventions have proved controversial, often involving powerful medications and/or removal (chelating) agents which can, without appropriate clinical knowledge, have serious consequences and side-effects.

The science on this topic is still evolving but provides some important details. Numerous reports suggest that the burden of heavy metals is typically increased alongside a diagnosis of autism. Other studies have linked such heavy metal loads to facets of autistic and other behaviours, in line with what would typically be expected for such metals (many of which have no useful biological purpose in the human body). However, the question of causation with respect to heavy metals is less easy to discuss, not least because – unlike exposure to viral or bacterial agents – there are few cases of specific and detailed heavy metal exposure events and resultant temporal effects. Specific behaviours such as pica are also overrepresented comorbidities in autism, which means that exposure to such materials may be more common as a result of autism. Similar caveats apply to other observations on autism risk, for example, links to exposure to certain classes of pesticides[28] based on geographical and residence data. However, this does not discount data showing that specific pesticide preparations, with known biological actions, are seemingly linked to elevated risk of autistic traits.

Adverse teratogenic events from pregnancy taken medicines and related compounds

Teratogenicity refers to the ability of any compound to inflict structural or functional changes on the unborn child following exposure during conception or critical pregnancy periods. Various compounds show such abilities, including seemingly harmless nutrients such as vitamin A, life-saving medicines such as lithium, and recreational compounds such as alcohol. Perhaps unsurprisingly, medicine use, particularly in pregnancy, has also been discussed in terms of offspring autism risk. One particular drug – sodium valproate – provides perhaps the most clear, evidence-based example of how medication taken during pregnancy can affect offspring behaviour and development; initially, risks were identified relating to neural tube defects in offspring, but the evidence now extends to offspring autism risk.[29] Sodium valproate is a life-saving medicine typically used to control epilepsy. As an anticonvulsant, it has several modes of action, affecting functions of gamma-aminobutyric acid and also acting as a direct histone deacetylase inhibitor. It has also, for many years, been linked to the onset of various behavioural and developmental issues in exposed offspring, including a significantly heightened risk of autism. The magnitude of the risk is such that various health agencies now include warnings on prescription of valproate to women of reproductive age.

Work is still required to unravel the particular effects that influence autism risk in exposed offspring, including evidence suggesting that timing and dosage may play important parts. Such work will be made easier by the already widely used valproate mouse model of autism, in which the biology of the teratogenic effects of valproate can be viewed in exposed cohorts in a controlled manner, albeit with cautions about differences between human and murine physiology. Various findings have been obtained using the valproate mouse model of autism, including the involvement of multiple biological systems following exposure; these findings are potentially pertinent to various overrepresented comorbidities appearing alongside autism.

Other medicines delivered during pregnancy have also been suggested to increase the risk of autism in offspring. Use of various antidepressant medicines during pregnancy has been studied as a function of offspring autism risk. The findings so far from such research are more complicated than those for valproate exposure, owing to confounding of the effects of medicines with the

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underlying reasons for such antidepressant use. Issues such as fetal alcohol syndrome and its clinical overlap with autism, alongside work looking at exposure to acetaminophen (paracetamol), remain under investigation.

Other immune system effects culminating in an autism diagnosis

Alongside viral and/or bacterial pathogens exerting an influence on autism risk, the role of immune functions in relation to autism aetiology has also been expanded. Pregnancy is a time of significant biological effort on the part of the mother. Vital biological pathways are re-engineered to nurture the developing fetus, and the maternal immune system is 'reprogrammed' to avoid risk to the fetus, eliciting an unfavourable maternal immune response. Such immune tolerance does not occur in a vacuum, as a mother's immune system still has to contend with a multitude of viral and bacterial pathogens. In this context, the idea of maternal immune activation (MIA) as potentially important to autism offspring risk is also a consideration. Various studies have found that MIA seems to be important for later risk of offspring schizophrenia, and similar patterns have been considered for offspring autism. A role for inflammatory signalling molecules affecting fetal development has been proposed, particularly during times of maternal infection during pregnancy and covering seasonal periods when such infections are likely to occur. The suggestion is that maternal immune functions and/or responses at critical times reprogramme the developing fetal brain.

Similarly, a related strand of research looking at the role of pathogenic maternal autoantibodies to developing fetal tissues provides further evidence for immune system effects on autism risk in offspring. In such cases, dubbed 'maternal autoantibody-related (MAR) autism', various autoantibodies have been linked to autism risk in offspring, to the point where screening for MAR autism is moving towards being possible, and there is the prospect of 'a prophylactic against MAR autism'.[30] Of particular note with respect to MAR is the associated suggestion that said maternal autoantibodies are able to cross the placenta to reach the developing child, which potentially offers an important clue for intervention.

MIA and MAR autism provide further evidence for the notion of plural autisms on the basis of defined immunological features presenting a potentially causative effect on offspring development. The theme of immune system compounds affecting more than just immune functions opens up new frontiers regarding how immune functions and behaviour (and development) are linked.

Reflecting on causation

We have not covered every single aetiological agent that has hitherto been associated with autism onset. We are only beginning to understand how nutritional issues related to folate metabolism in the context of autoimmunity, vitamin D deficiency and breastfeeding status can act on autism risk and how they may intersect with issues previously discussed. We can, however, be confident that moving to the plural autisms, including aetiological data, offers new avenues for a standardised inspection of autism that partially 'counteracts' some of the issue of heterogeneity. That some of the causative factors are potentially acquired in whole or in part provides an important interface with many different disciplines that have only had a limited part to play in the study of autism. For instance, toxicology and immunology might have as important an input for some as genetics for others, showing how wide the autisms may be in aetiology, which biological systems may be important and their clinical management. The question of whether there may be common underlying mechanisms towards the development of autism or different mechanisms across different autisms but with similar behavioural and developmental outcomes is also posed. At the current time, we are unable to provide an intellectually satisfying answer to this question.

Where next?

How many autisms are there?

Multiple different symptom trajectories are a feature of autism. As these are overlaid with differing symptom intensities and different aetiologies, it is likely that multiple phenotypes make up the plural autisms. Although efforts have already been made to define and diagnose specific autisms, predominantly based on aetiology (MAR autism, branched-chain ketoacid dehydrogenase kinase deficiency), we cannot yet provide a specific figure for how many autisms there may eventually be. One complication is how to standardise what formally constitutes one of the autisms, which themselves are likely to include fuzzy boundaries, changeable behavioural profiles and trajectories, and potentially multiple or overlapping aetiological factors. A similar issue confounds other attempts to counteract the problem of autism heterogeneity, as, for example, introduced in the description 'prototypical autism'[31] and subsequent bifurcation from a 'frank' presentation. For clinical services, in particular, such standardisation will require significant efforts in reorganisation.

Whether comorbidities, particularly less formally defined issues such as pathological demand avoidance, can be successfully mapped on to specific autisms remains to be seen. We also recognise that our preferred term – the autisms – may not eventually be the best description of the multitude of conditions that reflect such heterogeneity.

What does plurality mean for autism research?

Autism research has made progress. Data-driven models that emphasise biological factors as being definitive to the onset and the continuation of symptoms dominate. That is not to say that biology works in a vacuum – a variety of biopsychosocial influences affect the lives of autistic and non-autistic people alike – but, as per the example aetiologies discussed, biology is a common thread. However, aside from such progress, the translation of autism research into tangible benefits for people with autism has not been universally successful. There are several reasons for this breakdown in 'bench to bedside', arguably in large part related to the massive heterogeneity that singular autism encapsulates.

The plural autisms offer a more nuanced view, inviting further inspection of variables outside being diagnosed with autism versus asymptomatic control as a focal point in research. There are already hints that this is happening, as per analysis of characteristics such as regression, which not only offers new ways of differentiating different types of autism but also provides information regarding prognosis and possible intervention pathways. Adoption of the plural autisms would also have important repercussions for specific areas of autism research, including studies of potential biomarkers for early detection of autism and the rise of statistical techniques based on Mendelian randomisation in causational autism and related research. Given the likely increase in the amount of data to be collected and numbers of correlates to be analysed in the context of autism pluralisation, further moves towards the inclusion of machine learning (artificial intelligence) technologies should be embraced.[32]

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Does causation matter?

Causation matters because, as in the example of sodium valproate, there is a need to be alert to how even life-saving medicines can have significant and life-changing effects. Further scrutiny of non-infectious environmental exposures that mothers-to-be and young, developing children are potentially exposed to provide clues as to how to minimise their likely wide-ranging and synergistic effects. Developmental presentations post-infection invite further study on how such pathogens can affect behaviour as well as physiology and influence the development of vaccines and successful treatments of such agents. The range of autisms appearing alongside genetic conditions and IEM provide important information for long-term planning as well as future conversations involving genetic counselling.

Causation also matters from a mechanistic point of view. Epidemiological studies that have found a link between parental psychiatric disorders and likelihood of autism spectrum disorder in offspring provide important data on risk but typically do not provide detailed information about the reason for the risk. It would be easy to infer that there is a shared genetic overlap between various psychiatric conditions and autism. However, given the increasingly important relationship between immune functions and various psychiatric labels, such biological functions also provide an important mechanism from parental psychopathology to offspring developmental and behavioural issues. A focus on mechanisms would also be likely to yield important information, with respect not just to autism but to accompanying comorbidity. Where such comorbidity is potentially life-affecting, such as in the case of epilepsy, information on mechanisms may offer dual intervention options.

Other considerations

Potential sex differences across the presentation of the autisms represents an important topic. Emerging research suggests that the traditional 4:1 male/female ratio has underestimated the number of females with autism[33] on the basis of underdiagnosis or misdiagnosis. Disagreement with the 4:1 or 3:1 male/female ratio of autism following valproate exposure[29] has already surfaced, implying that specific aetiological factors may have different sex profiles. Sex is already an important variable in the presentation of specific developmental conditions such as Rett syndrome; a challenge, therefore, is to establish whether the traditional 4:1 sex ratio holds across the different types of autisms, linking also with gender.

To attempt to reliably define the various autisms, further longitudinal studies are required. That areas as disparate as genetics – including epigenetics[34] – immune functions and even the gut microbiome (or some combinations) are variably important to the aetiology of different autisms implies that research programmes should be multidimensional and transdisciplinary. Longitudinal studies of development and behaviour are also studies of 'moving targets' given the wide range of biological and other changes that can influence them, including puberty and advancing age. As noted by Corbett et al,[35] developmental trajectories in relation to depressive symptoms occurring alongside autism may not follow typical patterns of development. Therefore, fluidity in core autistic traits probably matches fluidity across other comorbid conditions.

The pluralisation of autism would be likely to have important implications for societal views about autism. Issues such as the non-persistence of autism and the introduction of the profound autism classification have not been universally well received. Discussion of further fracturing of the definition of autism, particularly using aetiological information as part of that separation, will not be a priority for many already diagnosed with autism, given the various biopsychosocial influences on their lives. Discussions about preventive strategies for some of the autisms are also likely to elicit strong emotions, despite, for example, the evidence pointing to rubella vaccination as seemingly already having achieved such an effect.[25] Community and stakeholder dialogue, strong ethical oversight, and a commitment to equality in screening and healthcare are important factors. Recognition that across the autisms there will be different challenges facing different groups – including potentially life-changing issues such as the effects of wandering and/or elopement, particularly among those with profound or high-support-needs autism, and the equally serious risks of suicidal behaviours in relation to autism[9] – will similarly affect views.

We have advanced an argument for the pluralisation of autism: the autisms. Various pieces of evidence point to different aetiologies across the singular label of autism, which, combined with differences in symptom intensity and developmental trajectory profiles, lend support to a plural readjustment. The current diagnostic manuals providing rules for bestowing a diagnosis of autism seemingly support such pluralisation. Further discussions on how to implement research and clinical moves towards the plural autisms are required.

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Additional notes on language used

Throughout this manuscript, we have relied on guidance supplied by NHS England (https://www.england.nhs.uk/learning-disabilities/about/get-involved/involving-people/making-information-and-the-words-we-use-accessible/#autism) for language style. We use the term 'autism spectrum disorder' and the acronym 'ASD' sparingly in the body text of the manuscript in the context of the formal clinical descriptions of autism as per DSM and ICD definitions. We have avoided use of words such as 'deficit' (aside from the description of ADHD) in the manuscript, in keeping with some communities' preferences. Our use of the word 'comorbid' over 'co-occurring' is based on the notion that comorbidity implies a relationship between A and B, where one may influence the other and vice versa. Co-occurring by contrast, typically has a different meaning, in which independent issues 'coincidentally' happen at the same time. Our use of the word 'risk' is multiple but specific on the basis that risk = likelihood × impact. We understand that 'risk' can sometimes carry negative connotations. Our use is not intended in such a manner.

Data availability

Data availability is not applicable to this article as no new data were created or analysed in this study.

Author contributions

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Declaration of interest

P.W. and K.C. are directors at and employed by ESPA Research, an autism research organisation. P.S. is chairman of ESPA (Education and Services for People with Autism), a registered charity (no. 1037868) providing specialised autism specific college and residential

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services. M.H. is a trustee of ESPA and a director at ESPA Research. C.S. owns BeginningwithA, offering autism consultancy and training. K.H. is the chief executive of ESPA and company secretary for ESPA Research. B.M. is a paediatric consultant at the Synapse Centre for Neurodevelopment. P.W. and K.C. report grants from the Robert Luff Foundation during the writing of this paper. B.M. is a clinical advisor for Kingdom Therapeutics.

References

1 World Health Organization (WHO). *ICD-11 for Mortality and Morbidity Statistics: 6A02 Autism spectrum disorder*. WHO, 2023 (https://icd.who.int/browse/2024-s01/mms/en#437815624).

2 American Psychiatric Association (APA). *Diagnostic and Statistical Manual of Mental Disorders* (5th edn). APA, 2013.

3 Maenner MJ, Warren Z, Williams AR, Amoakohene E, Bakian AV, Bilder DA, et al. Prevalence and characteristics of autism spectrum disorder among children aged 8 years – autism and developmental disabilities monitoring network, 11 sites, United States, 2020. *MMWR Surveill Summ* 2023; **72**: 1–14.

4 O'Sharkey K, Mitra S, Paik SA, Chow T, Cockburn M, Ritz B. Trends in the prevalence of autism spectrum disorder in California: disparities by socio-demographic factors and region between 1990-2018. *J Autism Dev Disord* [Epub ahead of print] 3 May 2024. Available from: https://doi.org/10.1007/s10803-024-06371-w.

5 Haslam N. Looping effects and the expanding concept of mental disorder. *J Psychopathol* 2016; **22**: 4–9.

6 Sala R, Amet L, Blagojevic-Stokic N, Shattock P, Whiteley P. Bridging the gap between physical health and autism spectrum disorder. *Neuropsychiatr Dis Treat* 2020; **16**: 1605–18.

7 Hossain MM, Khan N, Sultana A, Ma P, McKyer ELJ, Ahmed HU, et al. Prevalence of comorbid psychiatric disorders among people with autism spectrum disorder: an umbrella review of systematic reviews and meta-analyses. *Psychiatry Res* 2020; **287**: 112922.

8 Kanner L. Autistic disturbances of affective contact. *Nervous Child* 1943; **2**: 217–50.

9 Lai MC, Saunders NR, Huang A, Artani A, Wilton AS, Zaheer J, et al. Self-harm events and suicide deaths among autistic individuals in Ontario, Canada. *JAMA Netw Open* 2023; **6**: e2327415.

10 Jablensky A. The diagnostic concept of schizophrenia: its history, evolution, and future prospects. *Dialogues Clin Neurosci* 2010; **12**: 271–87.

11 Whiteley P, Carr K, Shattock P. Is autism inborn and lifelong for everyone? *Neuropsychiatr Dis Treat* 2019; **15**: 2885–91.

12 Lord C, Charman T, Havdahl A, Carbone P, Anagnostou E, Boyd B, et al. The *Lancet* Commission on the future of care and clinical research in autism. *Lancet* 2022; **399**: 271–334.

13 Clarke EB, McCauley JB, Lutz A, Gotelli M, Sheinkopf SJ, Lord C. Understanding profound autism: implications for stigma and supports. *Front Psychiatry* 2024; **15**: 1287096.

14 Hughes MM, Shaw KA, DiRienzo M, Durkin MS, Esler A, Hall-Lande J, et al. The prevalence and characteristics of children with profound autism, 15 sites, United States, 2000–2016. *Public Health Rep* 2023; **138**: 971–80.

15 Czech H. Hans Asperger, National Socialism, and 'race hygiene' in Nazi-era Vienna. *Mol Autism* 2018; **9**: 29.

16 Fein D, Barton M, Eigsti IM, Kelley E, Naigles L, Schultz RT, et al. Optimal outcome in individuals with a history of autism. *J Child Psychol Psychiatry* 2013; **54**: 195–205.

17 Gillberg IC, Helles A, Billstedt E, Gillberg C. Boys with Asperger syndrome grow up: psychiatric and neurodevelopmental disorders 20 years after initial diagnosis. *J Autism Dev Disord* 2016; **46**: 74–82.

18 Hsu TW, Chu CS, Tsai SJ, Hsu JW, Huang KL, Cheng CM, et al. Diagnostic progression to schizophrenia: a nationwide cohort study of 11 170 adolescents and young adults with autism spectrum disorder. *Psychiatry Clin Neurosci* 2022; **76**: 644–51.

19 Benvenuto A, Moavero R, Alessandrelli R, Manzi B, Curatolo P. Syndromic autism: causes and pathogenetic pathways. *World J Pediatr* 2009; **5**: 169–76.

20 Fang Y, Cui Y, Yin Z, Hou M, Guo P, Wang H, et al. Comprehensive systematic review and meta-analysis of the association between common genetic variants and autism spectrum disorder. *Gene* 2023; **887**: 147723.

21 Baieli S, Pavone L, Meli C, Fiumara A, Coleman M. Autism and phenylketonuria. *J Autism Dev Disord* 2003; **33**: 201–4.

22 Klaiman C, Huffman L, Masaki L, Elliott GR. Tetrahydrobiopterin as a treatment for autism spectrum disorders: a double-blind, placebo-controlled trial. *J Child Adolesc Psychopharmacol* 2013; **23**: 320–8.

23 Tangeraas T, Constante JR, Backe PH, Oyarzábal A, Neugebauer J, Weinhold N, et al. BCKDK deficiency: a treatable neurodevelopmental disease amenable to newborn screening. *Brain* 2023; **146**: 3003–13.

24 Chess S. Follow-up report on autism in congenital rubella. *J Autism Child Schizophr* 1977; **7**: 69–81.

25 Berger BE, Navar-Boggan AM, Omer SB. Congenital rubella syndrome and autism spectrum disorder prevented by rubella vaccination – United States, 2001-2010. *BMC Public Health* 2011; **11**: 340.

26 Whiteley P, Marlow B, Kapoor RR, Blagojevic-Stokic N, Sala R. Autoimmune encephalitis and autism spectrum disorder. *Front Psychiatry* 2021; **12**: 775017.

27 Ding M, Shi S, Qie S, Li J, Xi X. Association between heavy metals exposure (cadmium, lead, arsenic, mercury) and child autistic disorder: a systematic review and meta-analysis. *Front Pediatr* 2023; **11**: 1169733.

28 von Ehrenstein OS, Ling C, Cui X, Cockburn M, Park AS, Yu F, et al. Prenatal and infant exposure to ambient pesticides and autism spectrum disorder in children: population based case-control study. *BMJ* 2019; **364**: 1962.

29 Christensen J, Grønborg TK, Sørensen MJ, Schendel D, Parner ET, Pedersen LH, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA* 2013; **309**: 1696–703.

30 Bolandparvaz A, Harriman R, Alvarez K, Lilova K, Zang Z, Lam A, et al. Towards a nanoparticle-based prophylactic for maternal autoantibody-related autism. *Nanomedicine* 2019; **21**: 102067.

31 Mottron L, Gagnon D. Prototypical autism: new diagnostic criteria and asymmetrical bifurcation model. *Acta Psychol* 2023; **237**: 103938.

32 Washington P, Wall DP. A review of and roadmap for data science and machine learning for the neuropsychiatric phenotype of autism. *Annu Rev Biomed Data Sci* 2023; **6**: 211–28.

33 Loomes R, Hull L, Mandy WPL. What is the male-to-female ratio in autism spectrum disorder? A systematic review and meta-analysis. *J Am Acad Child Adolesc Psychiatry* 2017; **56**: 466–74.

34 Khoodoruth MAS, Chut-Kai Khoodoruth WN, Al Alwani R. Exploring the epigenetic landscape: the role of 5-hydroxymethylcytosine in neurodevelopmental disorders. *Camb Prism Precis Med* 2024; **2**: e5.

35 Corbett BA, Muscatello RA, McGonigle T, Vandekar S, Burroughs C, Sparks S. Trajectory of depressive symptoms over adolescence in autistic and neurotypical youth. *Mol Autism* 2024; **15**: 18.

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