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## Autism spectrum disorder

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### Abstract

Autism Spectrum Disorder (ASD) is a construct used to describe individuals with a specific combination of impairments in social communication and repetitive behaviours, highly restricted interests and/or sensory behaviours beginning early in life. The worldwide prevalence of autism is just under 1%, but estimates are higher in high-resource countries. Although gross brain pathology is not characteristic of autism, subtle anatomical and functional differences have been observed in postmortem, neuroimaging and electrophysiological studies. Initially it was hoped that accurate measurement of behavioural phenotypes would lead to specific genetic subtypes, but genetic findings have mainly applied to heterogeneous groups that are not specific to autism. Psychosocial interventions in children can improve specific behaviours, such as joint attention, language and social engagement that may affect further development and could reduce symptom severity. However, further research is necessary to identify the long-term needs and treatments and the mechanisms behind them that could result in improved independence and quality of life over time. Families are often the major source of support for people with AUTISM throughout much of life and need to be considered, along with the perspectives of autistic persons, in both research and practice.

### [H1] Introduction

Autism spectrum disorder (ASD) is a common, highly heritable and heterogeneous neurodevelopmental disorder that has underlying cognitive features and commonly co-occurs with other conditions. The

44 behaviours, strengths and challenges of people with autism, have attracted the attention of scientists  
45 and clinicians for at least 500 years (Fig. 1). Autism is a heterogeneous disorder and, reflecting this  
46 heterogeneity, the term autism has been used in various ways to describe both a broader presentation,  
47 and then a specific diagnosis when it was considered to be one subgroup within the general diagnostic  
48 category of ‘pervasive developmental disorders’ (PDDs), a group of disorders that was introduced in  
49 Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM III) in 1980 to convey the idea  
50 of a broader spectrum of social communication deficits. Owing to of lack of clear borders between the  
51 PDDs and difficulties in reliably distinguishing them, the current diagnostic systems, the International  
52 Classification of Diseases 11th Revision (ICD-11) and the DSM-5 use the umbrella term ‘ASD’, and  
53 differentiate individuals using additional clinical specifiers and modifiers. In this paper, we use the term  
54 “autism” to refer to ASD in general, both for brevity and out of respect for the preferences of self-  
55 advocates .

56 Manifestations of autism include impairments in social communication and interaction, sensory  
57 anomalies, repetitive behaviours and varying levels of intellectual disability (Box 1). Together with these  
58 core symptoms, co-occurring psychiatric or neurological disorders are common in people with autism, of  
59 which, hyperactivity and attention disorders (such as attention-deficit/hyperactivity disorder (ADHD)),  
60 anxiety, depression and epilepsy are fairly prevalent. A diagnosis of autism is reached after obtaining a  
61 detailed developmental history, often from the parents, and observation of the individual interacting  
62 with parents or other individuals<sup>1,2</sup>. Early intervention for children with autism is key owing to common  
63 difficulties in communication. The types of interventions used change throughout life and include  
64 parent-mediated interventions and/or therapist-delivered interventions in childhood, school-based  
65 strategies and techniques to promote independence in adulthood. Pharmacological therapies can be  
66 used to treat some of the associated symptoms of autism, such as irritability, and comorbidities, such as  
67 anxiety.

68 This Primer discusses the epidemiology and mechanisms of autism, together with the diagnosis and  
69 treatment of people with this condition. Three themes are addressed: mechanisms of causality and  
70 change over time, heterogeneity within and between individuals with autism, and outcomes across the  
71 lifespan.

72

## 73 [H1] Epidemiology

### 74 [H2] Prevalence

75 Epidemiological administrative and community-based studies have suggested that autism is more  
76 common in males than in females, with reported ratios ranging from 2.1–5. 1, with an estimate of 4.1  
77 in the 2010 Global Burden of Disease study<sup>3,4</sup>. The sex ratio is slightly lower in studies that use population-  
78 wide testing to find community cases within a population compared with the more common passive  
79 case-finding studies that review administrative data (for example, medical or special educational  
80 records), and that may result in less plausible associations and, therefore, artificially increase prevalence  
81 estimates<sup>5</sup>. Active case-finding that does not rely on administrative records has demonstrated an  
82 equivalent community rate of autism in men and women with moderate to profound intellectual  
83 disability<sup>4</sup>. Thus, even the most widely accepted tenet of our understanding of factors associated with  
84 autism is far from straightforward.

85 Estimates of the prevalence of autism in various populations and settings differ according to the method  
86 of ascertainment used in the study, including definition, sampling and the extent of independent  
87 population case assessment in contrast to administratively based sources. Of note, the Global Burden of  
88 Disease study uses all known data from administrative and community survey sources on a disease or  
89 disorder to model associations (particularly with time) to examine trends. In the 2010 GBD study, an  
90 estimated 52 million people had autism globally, equating to a prevalence of 1 in 132 individuals<sup>6</sup>.  
91 Worldwide, little interpretable variation in the prevalence of autism between regions, ethnicities or  
92 services and resource provision has been reported. Indeed, one systematic review did not find a strong  
93 effect of ethnic, cultural or socioeconomic factors on the prevalence of autism<sup>7</sup>. However, statistical  
94 power to detect any effects was limited in the available data sets, particularly in low-income countries.  
95 An increased prevalence of autism has been reported in migrant groups in some studies<sup>8</sup> with few clear  
96 factors that might contribute to a greater prevalence in an Afro-Caribbean population in higher income  
97 countries<sup>9,10,11</sup> in the absence of any evidence of geographical variation<sup>7</sup>. However, a survey of adults in  
98 the general population has shown that rates of autism in black and minority ethnic groups may be lower  
99 than in the rest of the population<sup>12</sup>; data from indigenous and Aboriginal cultures are very limited.

100 Many individuals and groups presume that autism rates are increasing over time, but this supposition is  
101 based on data from administrative records rather community-based studies. Indeed, after accounting  
102 for methodological variations between studies, there was no clear evidence of a change in the  
103 prevalence of autism in the community between 1990 and 2010<sup>13</sup>. In addition, general population and  
104 systematic case-finding community-based surveys (including testing of representative populations) have  
105 also confirm the lack of significant change in prevalence rates in childhood<sup>14</sup> and adulthood<sup>15</sup> over time.  
106 No significant evidence is available supporting that autism is rarer in older people, which provides  
107 further evidence against the suggestion that autism is increasing in prevalence over time<sup>4</sup>. Even in high-  
108 income countries with strong autism public health policies, there is evidence that autism in adults goes  
109 largely unrecognized, whereas administratively recorded diagnoses in children increase year by year<sup>16</sup>.  
110 This finding highlights the importance of obtaining information on autism rates in settings where  
111 professionals may be able to improve its recognition. The prevalence of autism in mental health  
112 inpatient settings is estimated to be far higher than in the general population, ranging from 4–9.9%<sup>17</sup>.

113

## 114 [H2] Environmental factors

115 One review of systematic reviews and meta-analyses of environmental risk factors for autism included a  
116 comprehensive coverage of the literature, a discussion of the limitations of research and the need for  
117 long-term prospective cohort-based studies to begin to address these limitations<sup>18</sup> (Fig. 2). This and  
118 other studies identified environmental risk factors for autism as advanced parental age<sup>19</sup> and birth  
119 trauma, particularly if due to proxies of hypoxia<sup>18</sup>. Moreover, maternal obesity, a short interval between  
120 pregnancies, gestational diabetes mellitus and valproate use during pregnancy have all been associated  
121 with increased risk of autism (Fig. 2). However, it should be noted that these factors cannot be  
122 considered causal, but could be reactive, independent or contributory for autism. Studies evaluating risk  
123 factors for autism that have reported an absence of association are equally, if not more important, to  
124 note, including clear evidence that autism is not associated with vaccination<sup>20</sup>. Other negative  
125 associations include prolonged labour, delivery by caesarian section or assisted vaginal delivery,  
126 premature rupture of membranes and the use of assisted reproductive technologies, among other

127 factors (Fig. 2). Environmental risk factors could underlie risk of autism through several complex  
128 underlying mechanisms, such as genetic and epigenetic related effects (see  
129 Mechanisms/pathophysiology, below), inflammation and oxidative stress, hypoxic and ischemic  
130 damage<sup>18</sup>.

131

## 132 [H1] Mechanisms/pathophysiology

133 Many cognitive theories have been suggested to underlie the behavioural and developmental  
134 manifestations of autism, although the prominence and the consensus on the potential explanatory  
135 value of these theories have declined in the past decade. These theories range from 'social first'  
136 theories, such as the theory of mind (or mentalizing) and social motivational deficit theories, to global  
137 processing deficit theories including attentional control, executive dysfunction and weak central  
138 coherence or enhanced perceptual processing theories<sup>21,22</sup>. Although many of these theories had a  
139 useful descriptive role and provide potential insights into differences in how autistic individuals might  
140 process and experience the world around them, the theories pertain to neurodevelopmental disorders  
141 in general and lack specificity for autism), largely non-developmental, applying only to a single point in  
142 time, and lack evidence as explanatory models. Nevertheless, they have been useful in clinical practice  
143 and underlie some recently proposed interventions, such as CBT-oriented treatments for anxiety<sup>23</sup>.

144 Following cohorts of infants from gestation or birth to 2 or 3 years of age (that is, when a diagnosis of  
145 autism can be established) enables the study of the brain and behavioural manifestations of autism as  
146 they emerge<sup>24</sup>. Indeed, prospective studies of infants with a relative with autism have yielded a number  
147 of insights into the mechanisms of this disorder. For example, infants who develop autism later in  
148 childhood have substantially typical profiles of interest in faces<sup>25</sup> and eyes<sup>26</sup> at 6 months of age, which  
149 have cast doubt on social orienting theories in which autism originates from a primary deficit in innate  
150 patterns of subcortically-mediated social orienting<sup>27</sup>. In addition, subtle but diffuse differences in  
151 encephalography (EEG) and i other measures of brain function have been demonstrated in autistic  
152 people (see 'Findings from electrophysiological studies', below), which could represent alternative  
153 pathways to a common end-state phenotype or to whole-brain alterations in synaptic signalling  
154 pathways that have effects on development<sup>28</sup>. Such considerations highlight the limitations of  
155 deterministic models of autism, in which a genetic change leads to a synaptic change that relates to a  
156 canonical symptom<sup>29</sup>. Rather, there is likely a complex set of developmental interactions, in which the  
157 child's emerging brain activity and behaviour have bidirectional relationships to synaptic signalling and  
158 gene expression<sup>30</sup>.

159

## 160 [H2] Genetics

161 Twin and family studies consistently demonstrate that autism has a particularly large genetic  
162 contribution, with estimated heritability ranging from ~40 to 90%<sup>31,32</sup>. In addition, one analyses  
163 demonstrated that autism is among the most heritable common medical conditions<sup>33</sup>. More than 100  
164 genes and genomic regions have now been confidently associated with autism<sup>34,35</sup>, mostly based on the  
165 study of heterozygous, germ-line, *de novo* mutations. These genetic changes range in size from a single

166 base (or nucleotide)<sup>36-38</sup> to submicroscopic segments of DNA of thousands to millions of bases (also  
167 known as copy number variations (CNVs))<sup>39,40</sup>. Whether these genetic changes lead to alterations in the  
168 sequence of DNA or the structure of the chromosome, changes that have a functional effect on protein-  
169 coding regions of the genome have the strongest and most reliable association with autism risk.  
170 Collectively, these *de novo* heterozygous mutations are rare and confer relatively large risks of autism<sup>41</sup>.  
171 With genetic studies now including cohorts of up to tens of thousands of individuals and the associated  
172 increase in statistical power, common, transmitted alleles of modest effect size, mostly corresponding to  
173 the non-coding regions of the genome, have begun to be identified<sup>42</sup>.

174 Studies of the genetics of autism contrast broadly with studies of adult-onset psychiatric disorders, in  
175 which most successful gene discovery has emerged from genome-wide association studies (GWAS),  
176 which assess common alleles of small effect size. Indeed, the earliest successes in autism presaged a  
177 more general finding that the contribution of rare, *de novo* mutations in coding regions of the genome is  
178 relatively greater among a range of early-onset disorders<sup>43-45</sup> than for typically later-onset common  
179 conditions such as schizophrenia and bipolar disorder, although there is also a surprising degree of  
180 overlap in genetic risk for overtly disparate neuropsychiatric phenotypes that remains to be further  
181 elucidated<sup>31</sup>.

182 The extent to which rare, high effect size mutations account for autism risk raises some important  
183 definitional issues. Considering the overall population, the contribution of *de novo* mutations to autism  
184 risk is quite small (~3%)<sup>32</sup>. Indeed, the vast majority of individuals who harbour genetic risk for a  
185 common condition, particularly those with variants of small effect size, will never develop symptoms or  
186 need clinical attention. By contrast, there is a marked enrichment of individuals with rare and *de novo*  
187 mutations in the clinical autism population. Conservative estimates are that 10–20% of people with  
188 autism harbour a *de novo* rare point mutation or CNV contributing to their presentation<sup>34,46,47</sup>. If the  
189 clinical population is constrained to those with autism who have a combination of factors including  
190 being female, having intellectual disability, multiple unaffected siblings or seizures, ~20-30% have a rare  
191 *de novo* mutation; if an individual has several of these risk factors, the yield of *de novo* sequence and  
192 structural mutations would be expected to be even higher<sup>34</sup>.

193 However, irrespective of the precise proportion of risk conveyed by these mutations, their most  
194 substantial contribution to the understanding of autism is likely to be in elaborating the mechanisms of  
195 this disorder<sup>48,49</sup>. In autism, a single *de novo* germ-line heterozygous loss-of-function point mutation can  
196 convey more risk than the cumulative effect of the top decile of polygenic risk for schizophrenia<sup>47,50</sup>.  
197 Unfortunately, although manifestly more tractable than modelling hundreds of alleles simultaneously,  
198 addressing a single autism mutation at a time is not synonymous with an easy avenue to clinical care of  
199 most people with autism.

200 **[H3] Molecular pathophysiology.** Over the past decade there have been many studies using model  
201 systems to recapitulate so-called single gene (or monogenic) versions of autism, such as fragile X  
202 syndrome and tuberous sclerosis complex – which cumulatively are estimated to account for <10% of  
203 clinical cases of autism<sup>51</sup>. In addition, more recent studies have modelled the effects of rare and *de novo*  
204 mutations identified in idiopathic autism. This literature is far too vast to review comprehensively here  
205<sup>52,53</sup>. Although the study of autism risk genes in model systems has revealed a great deal about general  
206 biology, how these findings relate to the pathophysiology of autism is less clear<sup>48,49</sup>. In general, autism  
207 risk genes tend to have a role in multiple functions in many brain regions that unfold in a

208 spatiotemporally defined manner across development. Consequently, although manipulation of a single  
209 risk gene in a model system may lead to interesting phenotypes—including social-behavioural  
210 phenotypes in evolutionarily distant organisms— it does not necessarily illuminate its contribution to  
211 human social disability. Moreover, although a single mutation can confer a several fold increase in the  
212 risk of autism, these variants do not demonstrate the type of causal clarity that is associated with classic  
213 monogenic neurodevelopmental disorders, such as fragile X syndrome, Angelman syndrome, Rett  
214 syndrome or tuberous sclerosis complex. In addition, the well-established sexual dimorphism of social  
215 disability adds yet another dimension to the expansive search space that exists between risk gene and  
216 human behaviour<sup>48</sup>. The challenges of disentangling the spatiotemporal dynamics of risk gene  
217 expression and protein function are made even more difficult by the reality that these may play out  
218 differently in males versus females.

219 Owing to these challenges, multiple approaches have emerged focusing on convergence<sup>38,40,54–57</sup>, that is,  
220 searching for points of commonality across different autism risk genes, with the reasoning that this  
221 approach could identify shared pathological mechanisms. In fact, the earliest successes in gene  
222 discovery quickly revealed important general properties that have held up well over time, including that,  
223 *prima facie*, most proteins encoded by autism risk genes are involved either in synaptic structure and  
224 function or chromatin modification and regulation of gene expression<sup>38,46,47,58</sup> (Fig. 3). More recently,  
225 there has been an additional focus on spatiotemporal convergence and several studies have supported a  
226 nexus in mid-fetal, glutamatergic neurons during cortical development, with modestly divergent findings  
227 regarding deep<sup>56</sup> versus superficial<sup>54</sup> cortical layers. With improvements in technology, additional  
228 regions, including striatum, have also begun to emerge as points of potential risk convergence for  
229 autism<sup>59</sup>.

230 The ability to constrain future experiments to examine mutations in specific risk-associated regional,  
231 cellular and developmental contexts should allow the narrowing in on relevant mechanisms. Of note,  
232 one study used single cell technologies to examine specific cell types and developmental stages using  
233 brain tissue from people with autism<sup>60</sup>, and demonstrated changes in transcription in multiple cell types  
234 including upper-layer cortical neurons. These types of post-mortem studies ask important but somewhat  
235 broader questions from the approaches described above, such as underlying pathology and how the  
236 brain changes and responds to pathology over time. In these studies, similar to any cross-sectional  
237 study, it can be challenging to differentiate cause from effect. Consequently, the pursuit and  
238 intersection of studies that seek to define convergence early in development and those that examine  
239 subsequent molecular, cellular and circuit level changes will be critical to illuminating pathological  
240 mechanisms.

241 Indeed, given the success and FDA approval of gene therapy for early onset neurological disorders,  
242 particularly spinal muscular atrophy (SMA) type 1<sup>61,62</sup>, targeting single genes of large effect in both  
243 idiopathic and monogenic autism is being viewed as increasingly plausible. As rare syndromes such as  
244 fragile X syndrome, Angelman syndrome and Rett syndrome have offered some of the earliest insights  
245 into autism biology, these disorders are also likely to lead the way in illuminating the practical and  
246 important ethical challenges that will attend such efforts for idiopathic autism. Efforts aimed at the  
247 highest confidence risk genes identified in idiopathic autism, such as *SCN2A* and *CHD8*<sup>34,35</sup>, are almost  
248 certain to soon follow on attempts at gene therapy for monogenic neurodevelopmental disorders, in  
249 light of the growing list of well-defined large-effect targets, the increasing options for addressing  
250 haploinsufficiency<sup>63</sup>, the ability to manipulate gene products without leaving a DNA “scar”<sup>63,64</sup> and the



251 increasing ability to readily detect mutations—and intervene—in utero and very early in post-natal  
252 development.

253

## 254 [H2] Neurobiology

255 **[H3] Findings from MRI Studies.** MRI can facilitate understanding how the brain structurally  
256 and functionally develops differently in people with autism, although to date, MRI results in autism are  
257 not definitive. Although neuroimaging is typically more expensive than EEG and studies are limited by  
258 issues of replication, sometimes that is related to head motion that occurred during the scan which can  
259 erode signal<sup>65</sup>, structural studies including those using diffusion tensor imaging (DTI)<sup>66</sup> and functional  
260 MRI (fMRI)<sup>67</sup> have accelerated our understanding of how altered neural circuits relate to clinical  
261 symptoms of autism<sup>68,69</sup>. Studying circuitry in childhood that is specifically associated with the social  
262 brain (a network of brain areas involved with processing social information), including visual areas, areas  
263 of the prefrontal cortex, subcortex and areas integrating information (such as temporal parietal function  
264 and superior temporal sulcus), could also offer insight into the neural mechanisms of autism<sup>70</sup>. In  
265 addition, MRI may facilitate understanding the heterogeneity of autism demonstrating subgroups of  
266 individuals with specific neurobiological alterations that could account for their symptomology. The  
267 summary of MRI studies in this section focuses on 0-2 years of age addressing biomarkers for autism.  
268 Prospective study designs are largely covered as they represent a significant portion of MRI research in  
269 autism.

270 The first MRI studies of autism focused on cerebral and cerebellar grey matter and white matter  
271 volumes in young children<sup>71,72</sup>, although these studies were limited by studying toddlers and children  
272  $\geq 18$  months, missing the opportunity to detect biomarkers of autism in the first year of life. More  
273 recently, longitudinal studies have obtained multiple brain MRIs of infants at high risk of developing  
274 autism (that is, those with a sibling with autism; known as baby sibling studies) during their first 2 years  
275 of life, and assessed these children for autism at this age. In these studies, detectable differences in  
276 brain structure were observed at 6 months of age in the fractional anisotropy trajectories for 12 of 15  
277 neural fibre tracts in the brain in children diagnosed with autism at 2 years of age compared to children  
278 not diagnosed<sup>73</sup>. Furthermore, abnormal growth in the cortical surface between 6 and 12 months of age  
279 and greater brain volume between 12 and 24 months of age was seen in children who were later  
280 diagnosed with autism, compared with those not diagnosed with autism<sup>74</sup> (Fig. 4). In addition, white  
281 matter integrity in the genu pathway at 6 months of age predicted the presence of restricted and  
282 repetitive behaviours at 2 years of age<sup>75</sup> and computational work demonstrated that whole brain  
283 functional connectivity at 6 months of age predicted a diagnosis of autism at 2 years of age<sup>76</sup>.  
284 Collectively, these studies suggest the presence of disrupted neural pathways before the emergence of  
285 behavioural symptoms in children with autism, and might provide clues about the underlying neural  
286 mechanisms of autism. Although data from MRI studies has revealed differences in neurobiology  
287 between young children diagnosed with autism and those without<sup>77</sup>, given that replication has been  
288 particularly difficult in these studies, more work is required before MRI can be used as a reliable  
289 biomarker of autism<sup>78</sup>.

290 Task-based fMRI studies investigate circuits that are responsible for core challenges in autism (such as  
291 language production and comprehension<sup>79</sup>), and have demonstrated hyper-activation of the superior



292 temporal gyrus and inferior frontal gyrus and hypoactivation of the bilateral middle temporal gyrus<sup>76</sup>. In  
 293 addition, these studies have demonstrated challenges in processing emotions in faces and the “social  
 294 brain”<sup>78</sup>, and deficits in attention<sup>79</sup>. Studies have also shown greater sensitivity to sensory information,  
 295 showing increased connectivity between the anterior insula and sensorimotor areas, and the anterior  
 296 insula and amygdala, together was associated with greater sensitivity to slightly aversive sounds and  
 297 tactile information<sup>80</sup>. Although this area of research has revealed similarities or differences in people  
 298 with autism compared with comparison groups, it has been limited by averaging data across many  
 299 individuals, which can mask heterogeneity and differences across age groups. In addition, the work has  
 300 been limited by small sample sizes and problems with replication that is likely caused by the many  
 301 challenges with MRI data collection in people with autism, such as differences in data processing, inter-  
 302 subject variability and data quality<sup>80</sup>. Longitudinal imaging<sup>81</sup> as well as associating neuroimaging data  
 303 with longitudinal behavioural outcomes<sup>82</sup> can address some of these limitations characterizing  
 304 differences within participants.

305 Resting state functional connectivity MRI studies that require participants to look at a blank screen with  
 306 no task demands have been used to study intrinsic connections in the human brain. Large datasets, such  
 307 as the Autism Brain Imaging Data Exchange (ABIDE<sup>83</sup>), have enabled researchers to pool data to allow  
 308 more highly powered studies to address known limitations of small sample sizes and many dataset have  
 309 relied on resting state studies to study neural connectivity in autism. In these studies, evidence has  
 310 emerged of both hyper-connectivity and hypo-connectivity in short-range and long-range connections  
 311 throughout the brain<sup>84,85</sup>. Differences in results between studies could be due to the age of the  
 312 participants<sup>86</sup>, sex differences, heterogeneity, methodological concerns<sup>87</sup> or that both connectivity  
 313 states exist in autism.

314 In future, MRI could be well suited to categorize subgroups of autism<sup>88</sup>, as well as parsing out  
 315 commonalities and distinctions among other developmental disorders<sup>89</sup>. Using MRI to better understand  
 316 differences between boys and girls on the spectrum<sup>90</sup>, such as differences in whole brain connectivity<sup>90</sup>  
 317 or the social brain<sup>91</sup>, a field in its infancy, or as a marker of biological change due to treatment has  
 318 growing interest<sup>92</sup>.

319 **[H3] Findings from electrophysiological studies.** EEG has been historically used for the  
 320 diagnosis of comorbid epilepsy in people with autism<sup>93</sup> although it can also be used to study the  
 321 mechanisms of autism. Compared with MRI, EEG is more economical, easier to use and less invasive—  
 322 which is particularly important for paediatric populations—whilst granting access to brain dynamics at  
 323 millisecond timescales. Magnetoencephalography (MEG), although more expensive, provides higher  
 324 spatial resolution than EEG.

325 Since the early recordings, the first focus of quantitative EEG was to study people with autism in task-  
 326 free conditions. Pioneering studies have revealed alterations in oscillatory activity during the resting  
 327 state in people with autism, with more slow waves and less alpha waves, as well as less intra-  
 328 hemispheric and inter-hemispheric asymmetry compared to people without autism<sup>94</sup>. More recent  
 329 work has demonstrated the presence of developmental trajectories as revealed through increasingly  
 330 sophisticated spatio-spectral analyses, and has revealed how differences in the trajectories of EEG  
 331 power in high-risk infants may represent an endophenotypes of autism<sup>95,96</sup>.

332 In terms of mechanisms, other studies have started to focus on task-based modulation of cognitive  
333 function, such as low-level perceptual anomalies and action observation that relate to the autism  
334 phenotype. One theory proposing a specific failure in autism of the ability of the brain to ‘mirror’  
335 observed actions of another person (thereby named the ‘broken mirror’ theory) was based on altered  $\mu$ -  
336 wave suppression in autism<sup>97</sup> but was later questioned both theoretically<sup>98,99</sup> and empirically<sup>100,101</sup>,  
337 pointing toward a more complex picture of dysfunctional executive functions and visual attention<sup>102</sup>.  
338 Other studies, particularly those assessing event-related potentials (ERP), have demonstrated the  
339 modulation of sensory processing in people with autism, with observed changes in sensitivities and  
340 latency<sup>103</sup>. Differences in auditory and visual processing could have a role in the development of core  
341 features of autism, such as language delay and difficulty in emotion recognition although this hypothesis  
342 requires further study. Although perceptual processes appear different in people with autism, the  
343 electrophysiological underpinning is still far from clear regarding the main ERPs like the MisMatch  
344 Negativity (MMN)<sup>104</sup> or the N170<sup>105</sup>. Although data from meta-analyses have suggested smaller MMN  
345 amplitudes and delayed N170 latencies on average in people with autism compared to typically  
346 developing controls, additional studies are required that account for the large heterogeneity of this  
347 disorder, by moving away from averaging the data to focus either on specific subgroups<sup>106</sup> or refined  
348 modelling strategies that can capture individual differences in developmental trajectories<sup>95</sup>. Although  
349 this avenue of research has not yet been fully explored, interactive tasks that encompass real-time social  
350 interaction could allow the study of brain activity in experimental contexts that are more relevant for  
351 core autism symptoms, rather than the more passive tasks that are used in most functional imaging  
352 studies<sup>107</sup>. Experiments focusing on human-human interaction<sup>108</sup> and human-machine interaction<sup>109</sup>  
353 have been undertaken but, so far, no study has ever made explicit use of such methods to study the  
354 electrophysiology of autism.

355 In a further search for mechanisms of autism, prospective baby siblings studies have suggested that the  
356 gradual emergence of behavioural symptoms of autism is preceded by earlier subtle alterations in the  
357 activity of regions and networks of the social brain<sup>24</sup>. For example, early work on a small group of 5–6-  
358 month-old infants who later developed autism observed faster but less prolonged neural activation and  
359 delayed sensitization responses to faces compared with infants who did not develop autism<sup>110</sup>, and one  
360 report demonstrated that newborns with an increased familial likelihood of autism showed higher signal  
361 homogeneity within core social brain networks (right fusiform and left parietal cortex<sup>111</sup>). By  
362 comparison, reduced frontal power, particularly in the high-alpha band, during quiet play at 3 months of  
363 age<sup>112</sup> and cortical hyperexcitability in the right tempo-parietal region during auditory repetition of pure  
364 tones at 9–10 months of age have been found in babies at familial risk for autism<sup>113</sup>, suggesting that  
365 atypical patterns occur in brain regions other than those involved in social processing. Such alterations  
366 could have a cascading effect on social learning and contribute to the later emergence of behavioural  
367 symptoms of autism, although a causal link remains to be demonstrated. Replications across different  
368 research centres are needed because many of these studies had small sample sizes, different definitions  
369 of groups and varied measures and time points.

370 Interestingly, results from MEG and EEG studies jointly point toward two physiological mechanisms of  
371 autism: excitation/inhibition (E/I) imbalance and alteration of large-scale functional interactions of brain  
372 systems as quantified through connectivity analysis<sup>114</sup>. An E/I imbalance is supported by results from  
373 computational modelling of how reductions in the amount of inhibition can account for the previously  
374 observed perceptual consequences of autism<sup>115</sup> and transcranial magnetic stimulation (TMS) studies

375 demonstrating a neurophysiological deficit in  $\gamma$ -aminobutyric acid (GABA) receptor-mediated function in  
 376 people with autism<sup>116</sup>. In parallel, decreased long-range functional connectivity has also crystallized as a  
 377 consistent mechanism<sup>117</sup>. MEG studies have especially suggested a complex functional connectivity  
 378 pattern in the somatosensory cortex with reductions in the feedback (top-down) direction, but  
 379 increased in the feed-forward (bottom-up) direction<sup>118</sup>. Clarifying the extent to which this pattern is a  
 380 methodological artifact that could result from the predominant average-brain approach, as suggested by  
 381 fMRI studies, is critical<sup>119</sup>.

382 Beyond use to understand the pathophysiology of autism, the scalability and accessibility of EEG suggest  
 383 that this technique could be an ideal candidate for use as a brain-based biomarker. Measures from  
 384 information theory have already provided promising case-control classification<sup>120</sup>, but developing  
 385 generalizable biomarkers may require a combination of multiple EEG measures supported by robust  
 386 machine learning methods<sup>121</sup>. Against the background of the current reproducibility crisis that  
 387 characterizes many studies<sup>122</sup>, as well as the defining heterogeneity of autism, the next breakthrough  
 388 will certainly demand large-scale collaboration between researchers and clinicians.

389

## 390 **[H1] Diagnosis, screening and prevention**

391 Diagnosis of autism is made on the basis of behavioural presentation. Although substantial  
 392 heterogeneity exists between and within individuals across development, a set of core diagnostic  
 393 features of autism (covering social interaction, communication and flexible or sensory behaviour) can be  
 394 reliably identified by trained clinicians<sup>123,124</sup>.

## 395 **[H2] Diagnostic criteria**

396 The re-formulation of the diagnostic criteria for ASD in the DSM-5 (Box 1)<sup>125</sup>, which is similar to the  
 397 criteria in ICD-11<sup>126</sup>, contains several changes from previous editions that were based on good empirical  
 398 and clinical evidence<sup>127</sup>. First, the sub-classification of ‘Asperger’s disorder’ was subsumed under the  
 399 unitary term ASD as the diagnosis was inconsistently applied even by expert groups<sup>128</sup>. This change is  
 400 controversial, but the evidence supporting the inclusion of Asperger’s disorder as a separate condition is  
 401 very weak<sup>129</sup>. The important questions are how better to consider the factors that characterize  
 402 differences among autistic individuals and ensuring that these differences are measured and addressed  
 403 using neurobiological and clinical research, rather than contained within very poorly defined categories  
 404 of Asperger’s and PDD Not Otherwise Specified (NOS) as defined in DSM-IV<sup>130</sup>. In addition, some  
 405 individuals with social communication problems but not restricted and repetitive behaviours who would  
 406 previously have fallen into the now-removed subcategory of PDD-NOS now receive a different diagnosis  
 407 of Social communication disorder, which is not yet well-validated. Although these changes have led to  
 408 concerns that the DSM-5 ASD criteria are more restrictive than those in DSM-IV, many clinicians feel that  
 409 the changes better reflect clinical consensus and practice. Second, the social and communication  
 410 domains of the diagnostic criteria were unified to reflect the factor structure of symptomatology. Third,  
 411 sensory anomalies (hypersensory and hyposensory responsiveness and sensation-seeking) in DSM-5  
 412 were included under the ‘restricted, repetitive behaviours and interests’ domain to reflect their  
 413 pervasiveness<sup>131</sup>. Fourth, the DSM-IV criteria required symptoms to be present in the first 3 years of life,

414 but criteria in DSM-5 recognise symptom onset occurring in the early developmental period with the  
 415 caveat that symptoms might not fully manifest until social demands exceed limited capacities. This  
 416 change recognizes the developmental nature of autism, wherein for some individuals, clear  
 417 manifestation of autism might not be apparent until mid-childhood, adolescence or even adulthood. In  
 418 addition, late diagnosis (that is, diagnosis beyond early childhood) can occur even in those who received  
 419 intensive early monitoring<sup>132</sup>. In addition, the DSM-5 criteria supports the use of specifiers that can  
 420 denote those with a dual diagnoses, such as individuals with ASD and ADHD or other psychiatric  
 421 disorders, as well genetic conditions such as fragile X syndrome or down syndrome. Beyond the clinic,  
 422 these changes have implications for large-scale data pooling efforts; for considering domains of  
 423 behaviour to be modelled; and for identifying shared and distinct developmental pathways to conditions  
 424 like autism and ADHD.

425

## 426 [H2] Diagnosis and screening in children

427 The two core elements of the diagnostic process of autism in children are a detailed developmental  
 428 history that is usually obtained from parents, covering first concerns and early history to the present  
 429 day, and an observation of the child's interactions with their parents and with unfamiliar adults during a  
 430 combination of structured and unstructured assessments. Ideally, observations of the young person in  
 431 peer-group settings such as school or nursery would also form part of the diagnostic process. Of note, in  
 432 one population-based study in the UK, girls with similar levels of symptom expression to boys were less  
 433 likely to receive a diagnosis of autism from clinical services<sup>133</sup>. This finding might reflect socio-cultural  
 434 factors in the application of the diagnostic criteria, greater resilience or protective factors in girls that  
 435 reduce the need for clinical services at a given symptom level, or the need for the revision of  
 436 instruments used to identify symptoms to more fully cover female autistic traits<sup>127</sup>

437 A number of structured diagnostic interviews and observational assessments for autism exist, but only a  
 438 limited number have been rigorously tested for diagnostic accuracy relative to the gold-standard of  
 439 expert clinician judgement. Although these interviews and assessments have reasonably robust  
 440 sensitivity, specificity and reliability (see<sup>134</sup> for a review) and are widely used in some services in  
 441 communities<sup>135</sup>, there are also challenges to the widespread adoption of the best validated instruments:  
 442 the Autism Diagnostic Interview–Revised (ADI-R<sup>136</sup>) and the Autism Diagnostic Observation Schedule–  
 443 2nd Edition (ADOS-2<sup>123</sup>). These challenges include the cost of the instruments and training, the time  
 444 required to complete them and the need for substantial training to use them reliably<sup>137</sup>. Although expert  
 445 clinical judgement was previously believed to be more reliable than reliance on instrument scores alone  
 446 for the diagnosis of autism<sup>138</sup>, more recent evidence suggests this may not be true at least in toddlers  
 447 and preschool children<sup>139</sup>. The need to take a global perspective on autism is driving attempts to  
 448 develop more scalable tools, but this work is currently in its infancy (Box 2)<sup>140</sup>.

449 The stability of a diagnosis of autism from the preschool years to mid-childhood is relatively high<sup>1</sup>.  
 450 However, although diagnostic systems currently presuppose that autism is a lifelong condition, there is a  
 451 growing recognition that autism has a heterogeneous developmental time course<sup>141</sup>. Indeed, sub-groups  
 452 of individuals with autism and improving or worsening symptoms over time can be identified<sup>142,143</sup>. Such  
 453 developmental trajectories might be a more meaningful phenotype on which to map aetiological  
 454 mechanisms than a static case-control dichotomy<sup>74,144,145</sup>. Some individuals diagnosed as children have

455 no clinically meaningful (or even detectable) impairment later in life (so-called ‘optimal outcome’<sup>146,147</sup>);  
 456 one critical question in identifying mechanisms is whether this profile is associated with successful  
 457 effects of early intervention or is an aetiologically distinct subtype of autism.

458 **[H3] Screening and early identification.** The potential for early testing to prospectively identify children  
 459 with autism at a young age has considerable interest, and several studies have evaluated the  
 460 performance of parent-report instruments between 14 and 24 months of age, such as the Modified  
 461 Checklist for Autism in Toddlers (M-CHAT) and the Early Screening of Autistic Traits (ESAT)<sup>134,148,149</sup>.  
 462 However, there are contrasting views on the strength of the evidence for universal population-wide  
 463 testing, also known colloquially as screening<sup>150,151</sup>. Of note, research is lacking on the effectiveness of  
 464 therapeutic interventions in those identified with autism through universal screening. In addition,  
 465 although it is possible to identify some children with autism before parents or professionals have  
 466 identified concerns, diagnosis is missed in many children<sup>152</sup>, and most tested cohorts have not been  
 467 systematically followed up to identify later-onset autism in children who initially tested negatively<sup>153</sup>.  
 468 Screening also often identifies children with broader developmental difficulties as well as those with  
 469 autism<sup>154</sup>. In general, such instruments could be more useful for identifying possible signs and symptoms  
 470 of autism in high-risk populations, for example in young children with older siblings with autism<sup>155</sup>, or in  
 471 those referred for speech or other developmental concerns to community paediatric services<sup>156</sup>. In  
 472 addition, population-wide testing may also play a part in improving awareness and recognition of the  
 473 early signs and symptoms of autism in both professionals and the general public, which alongside  
 474 ongoing developmental surveillance pathways in community services, could help to bring down the age  
 475 of recognition and diagnosis. These principles also apply in low-income and middle-income countries in  
 476 which testing for autism and other neurodevelopmental disabilities has only just begun to be  
 477 developed<sup>154</sup>. Very little research has been devoted to cultural and ethnic differences in either child  
 478 early presentation and parents’ understanding or the experience of autism, which may in fact affect how  
 479 screening instruments work and thus impact on parents and families as much as autistic individuals.

480

481 **[H3] Early developmental profiles.** Understanding of onset patterns of autism has dramatically  
 482 expanded over the past 10 years, through work on infants with a first degree relative with autism, who  
 483 due to the high heritability of the condition have a 20% chance of developing autism themselves<sup>25</sup>.  
 484 Symptoms of autism have a gradual developmental onset. Indeed, although the average age of autism  
 485 diagnosis remains ~4–5 years of age<sup>157</sup>, parents typically report first concerns to health professionals at  
 486 ~2 years of age<sup>158</sup>. In many individuals, symptoms emerge during the second and third year of life  
 487 (although, as per the DSM-5 onset criteria above, in others, onset might not be noticed until the child  
 488 reaches school-age or later) whereas in others, symptoms become apparent after a seeming period of  
 489 typical development, including a period of regression or stasis. To this end, conceptualization of what  
 490 has been called ‘regression’ prior to 2 years of age has been reconsidered<sup>159,160</sup>. Over the first two years  
 491 of life, a substantial proportion of infants who later receive autism diagnoses show gradually  
 492 accumulating delays across social, communication and language domains, suggesting that ‘regression’  
 493 represents a spectrum ranging from frank loss of acquired skills, to a gradual erosion (or ‘plateauing’) of  
 494 developmental potential to individuals in whom these skills never emerge<sup>161</sup>.

495

## 496 [H2] Diagnosis and screening in adults

497 Information on diagnostic methods to identify autism in adulthood is in its infancy, with little  
 498 methodologically acceptable evaluation of interview methods or screening questionnaires (including  
 499 self-completion questionnaires). Clinical approaches rely heavily on extending methods developed for  
 500 use in childhood to adulthood. These methods tend to rely on childhood developmental data, although  
 501 validation research in adult general population-wide testing suggests good specificity and sensitivity for  
 502 the observationally based ADOS Module 4 (Ref. <sup>162</sup>). However, typically, much research has depended on  
 503 the judgment of expert clinicians and of standardized data collection on early child development that is  
 504 unlikely to be obtainable for many older adults. Given that (undiagnosed) autistic adults presenting for  
 505 an autism assessment are also more likely to have co-occurring adult mental health disorders, any  
 506 method of assessment must be capable of differentiating such abnormalities in symptoms and  
 507 behaviour from abnormalities due to autism. This point has led to the suggestion that clinical  
 508 examination methods to identify adult psychopathology could be extended to include autism in addition  
 509 to depression, anxiety and psychosis, among other disorders<sup>163</sup>. Semi-structured adult psychopathology  
 510 interviewing has been fruitful in the assessment of closely related neurodevelopmental disorders in  
 511 adults, most notably ADHD<sup>164</sup>. Given that most people in the world who are autistic are adults, and as  
 512 many of these individuals have not received a diagnosis of autism<sup>4,15</sup>, the development and evaluation of  
 513 such adult assessment approaches is an urgent research priority.

514

## 515 [H2] Co-occurring disorders

516 In addition to the core features of autism, co-occurring difficulties or disorders (Fig. 5) are much more  
 517 widely recognized in research<sup>165,166</sup>, although they are not necessarily adequately addressed in clinical  
 518 practice<sup>167</sup>. For preschool children with autism, language delays, motor problems, epilepsy, difficulties  
 519 with sleep and eating, and high levels of activity are most commonly observed<sup>168,169</sup>. By comparison,  
 520 ADHD, anxiety, obsessive-compulsive disorder (OCD), intellectual disability, academic challenges,  
 521 irritability and disruptive behaviours become more apparent in school-aged children<sup>170</sup>. The proportion  
 522 of individuals with depressive symptoms becomes higher in adolescents and adults<sup>171</sup>, whereas other  
 523 issues often remain. Moreover, growing evidence (although it is reliant on administrative case-finding  
 524 data) suggests that people with autism have premature mortality<sup>172,173</sup> and increased risk of self-harm  
 525 and possibly suicide, although the mechanisms involved have yet to be elucidated. Studies using  
 526 electronic health records have demonstrated that adults with autism are more likely to be diagnosed  
 527 with many physical health conditions such as immune conditions, sleep disorders and obesity, compared  
 528 with adults in the general population<sup>167</sup>.

529 Collectively, these difficulties and disorders contribute to autism severity<sup>174</sup> and independence and well-  
 530 being at each age<sup>175</sup>. However, it is important to note, in the context of heterogeneity, that the  
 531 prevalence of each of these co-occurring conditions varies considerably with the context of the sample  
 532 (such as from psychiatry referrals, neurological referrals, or schools) and the methodology used  
 533 (administrative, self-report or assessed), as well as with age, level of cognitive function and perhaps  
 534 region<sup>166</sup>). As many of these conditions are treatable, they are very important as clinical considerations  
 535 but are also more complex than sometimes conveyed.

536

## 537 [H1] Management

### 538 [H2] Early intervention

539 Early intervention is seen as a priority because many young children with autism struggle to  
 540 communicate and interact with others, restricting their opportunities to learn and affecting their  
 541 parents who can find their child's behaviour perplexing and challenging to manage. Thus, outcomes of  
 542 such interventions include changes in the individual's availability for learning and increased parent  
 543 understanding. Intervention delivered in the preschool years at an age when there is increased brain  
 544 plasticity might lead to additional benefit, although this theory has not yet been empirically supported.

545 The primary models of psychological intervention for preschool children with autism are developmental  
 546 and behavioural. Although some consensus has been reached on the interventions that have more  
 547 supporting evidence (termed 'naturalistic developmental behavioural interventions'<sup>176</sup>), there is some  
 548 uncertainty and disagreement about the strength of evidence for different approaches, with almost no  
 549 direct comparisons of treatments or studies to assess which child should receive what treatment or  
 550 treatment intensity. Indeed, clinical trials in autism are limited by cost, time, placebo effects and limited  
 551 outcome measures, and are far behind much of the other research. This gap leaves parents and  
 552 practitioners at the mercy of what is available and sometimes marketed in their region. Indeed, access to  
 553 early intervention services is variable in most communities, including in high-income countries, and is  
 554 mostly carried out by non-specialists supervised by specially trained professionals. In low-income and  
 555 middle-income countries, most children and young people with autism — similar to those with  
 556 intellectual and developmental disabilities — will not receive specialized services<sup>177</sup>, although a number  
 557 of groups have begun to test community delivery of early intervention in such settings<sup>178</sup>.

558 Many current interventions build on the original 'Applied Behaviour Therapy'<sup>179</sup> (ABA) and have shifted  
 559 to more natural, child-initiated developmentally appropriate strategies and tasks instead of dependence  
 560 on repeated 'discrete trials' (known as discrete trial training, or DTT). In addition, considerable variation  
 561 exists between different intervention models in terms of mode of delivery (for example, parent-  
 562 mediated versus therapist-implemented), length (12-week versus 2-year programs), intensity (from a  
 563 few hours a week to ~15 hours per week) and the balance between the developmental or dyadic versus  
 564 behavioural components.

565 Lower-intensity approaches include parent-mediated interventions whereby parents are coached to  
 566 become more attuned to their child's communication signals and style (which are considered an  
 567 intermediate child outcome) and to facilitate more joint engagement in play and everyday activities,  
 568 designed to increase social and communication skills in the child<sup>180</sup>. Some studies have demonstrated  
 569 enhanced joint engagement and joint attention (which are considered important intermediate child  
 570 outcomes), with these lower-intensity approaches in preschool children compared to a control group,  
 571 such as the 12-week Joint Attention Symbolic Play Engagement and Regulation (JASPER) program, both  
 572 when delivered by parents in the home<sup>181</sup> and by teaching assistants in school<sup>182</sup>. However, other lower-  
 573 intensity, time-limited parent-mediated interventions such as Focus Playtime Intervention (FPI)<sup>183</sup> have  
 574 not improved child outcomes (such as social orienting and joint attention), although some interventions  
 575 have increased parental responsiveness<sup>184</sup>. A longer program (Preschool Autism Communication Trial  
 576 (PACT)), which consists of fortnightly parent-therapist sessions for 6 months, then monthly sessions for  
 577 another 6 months, demonstrated improvements in parent and child dyadic behaviours such as parental  
 578 synchrony and child initiations when interacting with each other (those close to the intervention target)  
 579 but not symptom reduction at immediate follow-up<sup>185</sup>. A subsequent 6-year follow-up to mid-childhood



580 at age 7 to 11 years identified modest reductions in overall autism symptoms using the ADOS over the  
 581 whole course of the study that were not detectable at the immediate endpoint, suggesting that a  
 582 longer-term perspective is critical in considering outcomes<sup>186</sup>.

583 A higher intensity, more comprehensive approach is the Early Start Denver Model (ESDM), which  
 584 combines behavioural and developmental or dyadic approaches. The ESDM is delivered by therapists for  
 585 ~15 hours per week, and as part of this programme, parents are trained to improve social  
 586 communication and interaction with their child. A small-scale trial demonstrated improvements in child  
 587 developmental and adaptive outcomes, primarily in the language and communication domains,  
 588 following 2 years of ESDM compared with treatment as usual<sup>187</sup>. One larger multi-site trial found  
 589 attenuated benefits with improvement in language outcomes at two of the three trial sites, but no  
 590 differences between the treatment as usual and ESDM groups in overall developmental ability, adaptive  
 591 behaviour or autism severity<sup>188,189</sup>.

592 Many of these early intervention approaches are based on models of typical development. Increasingly,  
 593 studies are using a combination of methods to define treatment outcomes and to better understand the  
 594 mechanisms and models of change of interventions. These methods include analysis of the degree to  
 595 which changes in the direct target of the intervention (for example, parent behaviour) mediate later  
 596 changes in child behaviour<sup>186</sup>, and the use of experimental methods such as EEG to examine whether  
 597 there are accompanying changes in relevant brain networks<sup>190</sup>. Many parents seek complementary  
 598 medical approaches, which to date have not been supported and sometimes are dangerous<sup>191</sup>. A note of  
 599 general caution is that even in the context of significant treatment differences between groups,  
 600 individual outcomes are very variable, and some children do not improve, although reliable predictors of  
 601 response to treatment have not been demonstrated in rigorous, randomized controlled trials. As autism  
 602 is a heterogeneous developmental condition, different interventions may be required at different stages  
 603 throughout life and different individuals might benefit from different interventions. One area which  
 604 many consider to hold much promise, that of neurobiologically or biomarker 'informed' psychological  
 605 intervention, is on the horizon but such targeted therapies have not yet been developed.

606

## 607 [H2] School age children and adolescents

608 Many children and young people with autism can also benefit from interventions at later ages. A  
 609 number of programs and approaches are available that focus on the core social communication  
 610 difficulties of autism; for example, social skills training programs for which moderate evidence of benefit  
 611 exists<sup>192,193</sup>. In addition, non-verbal young people with autism can benefit from use of augmentative  
 612 communication systems, such as the Picture Exchange Communication System (PECS) and more  
 613 sophisticated speech generating devices that use picture symbols and behavioural training methods to  
 614 allow children to request and make choices<sup>194</sup> or other technology-based augmentative communication  
 615 systems. Increasingly, more generic interventions that target co-occurring emotional and behavioural  
 616 problems are being adapted for youths with autism, and initial studies suggest moderate benefits<sup>195</sup>.  
 617 These interventions include modified cognitive behavioural therapy (CBT) for anxiety (modified, for  
 618 example, to include parents, increase the duration of sessions, use more visual materials and specific  
 619 work on understanding one's own emotion states)<sup>196</sup> and parent-mediated interventions for disruptive  
 620 behaviour and ADHD<sup>197</sup>. More recently, there have been efforts to develop and test interventions that  
 621 target aspects of parental wellbeing, such as parental stress and self-efficacy<sup>198</sup>. Increasingly,  
 622 interventions for school-age children and young people with autism are being delivered within the  
 623 school environment, rather than the clinic, which has natural advantages for programmes that consist of

624 groups or peer-to-peer interactions and an emphasis on social skills. Indeed, it is hoped that this  
625 approach may facilitate generalization of the skills learned<sup>199,200</sup>.

626

## 627 **[H2] Adult services**

628 As individuals with autism progress into and through adulthood, the focus of management shifts from  
629 treating the core symptoms of autism to addressing associated symptoms or behaviours and promoting  
630 independence. However, there are few intervention studies to guide treatment options in adulthood.  
631 Indeed, a 2012 systematic review identified only 32 studies published between 1980 and 2010 that  
632 evaluated treatment studies for adolescents and young adults with autism<sup>201</sup>. A more recent review  
633 identified 41 studies of interventions targeting social functioning in adults over a 37-year period<sup>202</sup>.

634 Despite the low number of treatment studies, there is some evidence supporting treatment efficacy for  
635 a limited number of symptoms, behaviors, and functional outcomes such as employment, social skills,  
636 and anxiety; however, in general, the evidence-base is weak<sup>201,202</sup>. For example, only three randomized  
637 controlled trials (all of which included small cohort sizes) that tested job interviewing skills curricula  
638 have been published. Social skills interventions have a somewhat more robust literature base (see<sup>202</sup> for  
639 review), but most of these studies had very small sample sizes and were not well controlled. In addition,  
640 it is unclear whether social skills interventions can be generalized to other social settings and situations,  
641 that is, whether skills learned in the treatment context are used by the participants in other settings,  
642 such as with peers or at work. There is some evidence for the use of cognitive-behavioural therapy (CBT)  
643 for effectively treating anxiety in people with autism who have sufficient cognitive and language skills to  
644 participate in current programs<sup>203</sup>. However, nearly all of the existing research has been conducted with  
645 children and adolescents rather than in adults<sup>202</sup>, and individuals with substantial communication  
646 challenges are excluded from CBT studies. Furthermore, in contrast to the general population, CBT has  
647 not yet been shown to be effective for the treatment of depression in individuals with autism. Given this  
648 weak evidence base, it may be fruitful to explore therapies and treatments tested in other groups that  
649 may benefit those with autism.

650 Formal service systems and social care can help fill in the treatment gaps. Indeed, although many adults  
651 with autism do not receive adequate services and support<sup>204</sup>, their receipt can improve outcomes across  
652 a number of domains<sup>163</sup>. For example, transportation services can allow adults with autism to engage in  
653 employment and access therapies and programs in the community. In addition, comprehensive job  
654 support services can promote finding and maintaining employment, particularly for adults with more  
655 severe impairments<sup>205</sup>. Public health insurance can increase access to psychiatric care for those with co-  
656 occurring mental health problems, and income supports can reduce dependence on families.

657

## 658 **[H2] Medications**

659 All medications that have evidence of benefit for autism treat the associated symptoms or co-occurring  
660 diagnoses, rather than the symptoms of autism directly (including social communication or repetitive  
661 behaviours). As mentioned earlier, autism is an extremely heterogeneous disorder, and individuals with  
662 autism can have a number of common co-occurring disorders that can also vary in severity.

663 Risperidone and aripiprazole (both of which are often termed ‘atypical antipsychotics’) are approved in  
 664 the USA to treat irritability and agitation — including aggression, self-injury and tantrums — in children  
 665 and adolescents with autism<sup>206–208</sup>. However, both treatments are associated with adverse events,  
 666 including sedation, risk of movement disorders and weight gain, which limit their use to people with  
 667 severe irritability with agitation<sup>208</sup>. The anti-diabetes drug metformin has been shown to limit weight  
 668 gain from these medications, possibly broadening their safe use<sup>209</sup>.

669 As mentioned previously (see Co-occurring disorders, above), co-occurring mental health conditions are  
 670 common in people with autism. Methylphenidate, atomoxetine and guanfacine are beneficial for ADHD  
 671 symptoms in autism (Table 1 (Refs. <sup>210–212</sup>)). Although serotonin reuptake inhibitors (SRIs), such as  
 672 fluoxetine and citalopram, are used for the treatment of depression, anxiety and OCD in the general  
 673 population, their efficacy in people with autism is less well established. Indeed, although fluoxetine  
 674 improves symptoms of OCD in adults with autism<sup>213</sup>, citalopram has demonstrated poor tolerability and  
 675 no benefit for repetitive behaviour in children with autism<sup>214</sup>. Medications for depression or anxiety  
 676 have not been tested in people with autism.

677 Some excitement has accompanied the recent studies of medications targeting the neurohormonal  
 678 oxytocin or vasopressin systems, both of which modulates social behaviour across species.  
 679 Underpowered studies of intranasal oxytocin have demonstrated mixed results that are overall not  
 680 supportive of a large effect size<sup>215,216</sup>, with results pending from adequately powered studies  
 681 (NCT01944046). In addition, a pilot study of intranasal vasopressin suggested possible benefit in people  
 682 with autism, although this study was underpowered<sup>217</sup>. A large trial of balovaptan, a vasopressin  
 683 AVPR1A antagonist in adults with autism showed negative results on its primary outcome ( a general  
 684 rating of autism symptoms), with suggestive results on a key secondary parent report measure of  
 685 adaptive behaviour, including social and communication behaviour<sup>218</sup>. A few studies have also focused  
 686 on the hypothesis that, at the level of neural circuits, autism may result from excessive excitation or  
 687 insufficient inhibition<sup>219</sup>, with some promising but inconclusive results for medicines that target the  
 688 GABAergic system<sup>220</sup>. Medications targeting genetic syndromes that can cause autism have not yet  
 689 yielded consistent improvement<sup>221,222</sup>, but there is much hope for a precision medicine approach that  
 690 links genetic subgroups with neurobiology-based treatments.

691

## 692 [H1] Quality of life

### 693 [H2] Objective and subjective measures

694 Several aspects of intervention research speak straight to the heart of current debates within the clinical  
 695 field and broader autism community, including how a good outcome is defined for an individual with  
 696 autism, as well as who should decide what outcomes are used in intervention studies<sup>223</sup>. This point is  
 697 aligned both with the debates about medical versus social models of disability but also with a more  
 698 general shift in medicine away from focusing on symptom reduction to improving the wellbeing and  
 699 quality of life (QOL) of patients. QOL research in adults with autism has focused on two aspects:  
 700 objective and subjective QOL. Objective QOL encompasses social achievements such as employment,  
 701 adequate living conditions, supportive relationships, and good physical and mental health<sup>224</sup>, whereas  
 702 subjective QOL focuses on individuals’ perceptions and subjective assessments of their own lives<sup>225</sup>.

703 Both subjective and objective QOL are often related, but not synonymous, and both are important to  
704 take into account when considering outcomes for individuals with autism (Table 2).

705 *[H3] Objective QOL.* Adults with autism tend to have poor objective QOL. Unemployment is high in this  
706 population, and even among those employed, individuals are often working below their skills and  
707 abilities<sup>226,227</sup>. Moreover, independent living can be a challenge, and adults often lack meaningful  
708 relationships with peers<sup>228</sup>. When aggregating across these domains of life, many adults with autism  
709 have ‘poor’ or ‘very poor’ outcomes<sup>229,230</sup>.

710 Autism is a highly heterogeneous condition and several factors have been associated with higher versus  
711 lower objective QOL. Most of the studied factors associated with higher objective QOL have been  
712 characteristics of the individuals (versus families, service system or communities), and consistent  
713 predictors of higher objective QOL include better early language development, higher IQ and adaptive  
714 behaviour scores, less severe autism symptoms, and fewer challenging behaviours<sup>231</sup>. In addition, more  
715 recent research suggests that women with autism may have a more difficult time maintaining  
716 employment positions<sup>232</sup>, and are more likely to ‘camouflage’ their autism symptoms than men, which  
717 can lead to mental health challenges<sup>233</sup>.

718 *[H3] Subjective QOL.* Meta-analysis have suggested that across the lifespan, subjective QOL tends to be  
719 lower among individuals with autism compared to typically-developing peers<sup>234</sup>, but is often more  
720 positive than indicators of objective QOL<sup>229,235</sup>. Predictors of subjective QOL tend to be inconsistent  
721 across studies, except for perceived stress and supports, the latter of which encompasses services,  
722 family and social support<sup>236–238</sup>.

723

## 724 **[H2] Self-advocate perspective**

725 It is clear that autism has heterogeneous outcomes and biological underpinnings; what is less clear-cut  
726 are the differing and nuanced views of autistic people regarding how autism should be approached and  
727 researched (Box 3, Autistica<sup>239</sup>, see also Ontario Brain Institute<sup>240</sup>). Indeed, some people with a diagnosis  
728 see autism as being a fundamental part of their identity whereas other people do not. In addition, many  
729 people feel that social change is required<sup>241</sup>, whereas other individuals want therapies to meet a range  
730 of their needs<sup>242</sup>. The key is respect for a variety of views and ultimately respect for autistic people.  
731 Researchers can demonstrate respect by considering how autism as a topic is distinct from, for example,  
732 cancer. To this end, terms like ‘disease’ are inappropriate and are scientifically inaccurate when referring  
733 to autism. Ultimately, active participation in the design, implementation and interpretation of research  
734 studies, clear consideration of research ethics and the consequences of research involvement and broad  
735 consultation of autistic people in research is key to authentically addressing the substantial inequalities  
736 autistic people face as a group and ensuring they live long, healthy, happy lives.

737

## 738 **[H2] Family perspectives**

739 Families of people with autism are also heterogeneous, yet, as a group, they experience lower QOL than  
740 families with a member with other neurodevelopmental conditions, even before receiving the formal  
741 diagnosis<sup>243</sup>. For this reason, it is essential that parents, other family members, clinicians, educators, and  
742 the entire external support system coalesce around common goals for outcomes whilst accessing and

743 maximizing resources for the betterment of the child and family. Parents are typically at the centre of  
744 this support network and carry much of the responsibility of direct care, coordination and advocacy,  
745 over and above typical parental responsibilities<sup>244,245</sup>. The exact parental roles are dependent on the  
746 child's strengths and challenges, and frequently shift over time (Fig. 6). During this process, it is  
747 important that parents maintain motivation by setting realistic goals and tracking progress to experience  
748 the many achievements that their loved one with autism can attain.

749 Effective parents often work closely with experienced providers who can track development of the child  
750 with autism and can provide guidance on next actions<sup>246</sup>. Early in childhood, this role includes identifying  
751 and engaging with early and school-based interventions. It is never too early for parents to begin  
752 planning for the adult transition process, including (dependent on the person with autism's capacity)  
753 promoting self-advocacy, preparation for life after secondary education, vocational training and  
754 employment supports, living needs, community participation, and long-term financial considerations.  
755 During adulthood, for cognitively-able adults, parental roles might shift to more traditional  
756 relationships<sup>247</sup>, whereas for those with cognitive disability, parental caregiving often continues and  
757 culminates in planning for late life needs<sup>248</sup>. Although the journey can be challenging, for many parents,  
758 it can be incredibly rewarding and a source of life meaning.

759 Many parents recognize the need to give back to the community through research. Accordingly, it is  
760 crucial that researchers foster this desire carefully, communicating with parents to ensure that any  
761 potential immediate or future risks or benefits are clear. Even if the study period is brief, in many cases,  
762 the goal should be to develop a positive longer-term relationship, as this can lead to parents and people  
763 with autism continually re-engaging in and developing positive feelings about the research process.

764

## 765 [H1] Outlook

766 Autism research has substantially expanded in the past 50 years, particularly the past 20 years, as  
767 reflected in the websites listed in Box 4. Although it seems unlikely that the incidence of autism is truly  
768 rising at the rate suggested in administrative prevalence studies, these data have increased awareness  
769 and the numbers of diagnosed children in schools and clinics, although adult services and recognition  
770 run far behind. The lives of people with autism diagnoses have improved at least in some high-income  
771 countries, with a greater proportion of children using some language<sup>249</sup>, more adults with educational  
772 qualifications and less institutionalization<sup>249</sup>, although the changing nature of diagnoses has to be  
773 considered when interpreting historical trends. Some risk factors for autism have been identified (such  
774 as increased parental age, birth trauma and a positive family history) which has implications at least for  
775 more careful follow-up. In addition, the genetics of autism has yielded surprising discoveries with  
776 substantial implications for heritable neurodevelopmental disorders, such as ADHD, language delay and  
777 named syndromes associated with profound intellectual disability. The perceived value of routine  
778 genetic screening for autism diagnosis is disputed, autism, with American medical academies strongly in  
779 favor whereas those in other countries much more selective. Studies of brain structure and function  
780 have added similarly intriguing findings that are just beginning to be integrated into both developmental  
781 and more mechanistic models of behaviour with possible targets or markers for change. Despite the  
782 intellectual contribution of these studies to research, at this point, neither EEG nor imaging are  
783 recommended as part of standard practice for diagnosis of autism but can be used for other

784 neurological indicators (such as if there are concerns beyond autism symptoms that merit an EEG or  
785 imaging). In this field, replication of findings across sites and even within individuals, as well as larger  
786 samples through collaboration are the promise of the future.

787 One way of bringing the three themes of mechanisms, heterogeneity and outcomes of autism together  
788 is to consider the trajectories of this disorder over time (Fig. 7), and how knowledge of these trajectories  
789 can contribute to investigations of the biological and cognitive underpinnings of autism, and how  
790 treatments and supports could make the lives of children and adults with autism more positive.

791 In terms of mechanisms, despite earlier hopes for simple genetic explanations of autism, instead, we  
792 have identified many single gene germline loss of function point mutations yielding some initial models  
793 of disruption in very basic molecular patterns, as well common genes with small effects that are just  
794 beginning to emerge<sup>29</sup>. Attempts to study genes-first have shown heterogeneity even within highly  
795 specific CNVs, with a few exceptions. In addition, hope exists that genetically based interventions for  
796 autism may be possible, although this will likely involve much further research. Data from genetic  
797 approaches that might yield targeted genetic interventions may be most relevant to rare, severe  
798 neurodevelopmental difficulties in general rather than autism as a specific entity. With more  
799 information about the differing developmental trajectories of autism, more continuous measures of  
800 symptoms and measures of language and intellectual function, behavioural phenotypes and changes  
801 over time can be quantified across different neurobiologically defined subgroups. This approach could  
802 potentially identify different 'routes' to different outcomes, whether autism or not, and could have a  
803 practical benefit in terms of selecting and monitoring appropriate treatments. In addition, with the  
804 heterogeneity of autism, our growing understanding of mechanisms, be they causal or mechanisms for  
805 change, needs to be linked to trajectories in development and not be considered as static<sup>250</sup>.  
806 Researchers modelling autism in other species might find the incorporation of early developmental  
807 manifestations, such as regressions or motor delays, more tractable than the current focus on autism-  
808 related social communication symptoms seen in humans. With collaborations and studies of sufficient  
809 sample sizes, investigators have begun to focus on findings within different developmental periods that  
810 could provide insight into trajectories and targets for intervention. Thus, more study of the development  
811 of autism both in studies of human behaviours and in animal models might have an effect on the  
812 identification and treatment of autism as a neurodevelopmental disorder. Prospective studies, including  
813 epidemiological and direct behavioural work across developmental periods, moving beyond very young  
814 children to later childhood, adolescence, and adulthood are needed.

815 Similarly, limited findings about adult development and patterns that lead into autism (Figs 5 and 7), call  
816 for measurement of different outcomes that respect individual differences in autistic people and in  
817 families (Box 3). By young adulthood, available supports for places to live, employment and mental  
818 health services are needed for individuals who have a range of skill levels, with supports not always well  
819 matched to the needs of individuals; however, comparisons of treatments or treatment intensities have  
820 not historically been made, even though they are continually called for. The types and specific goals of  
821 treatments differ greatly for autistic people who are verbally fluent versus those who have difficulty  
822 speaking for themselves, such that alternative systems need to be in place that take into account co-  
823 occurring conditions, strengths, preferences and challenges. More studies of well-defined, more  
824 homogeneous subgroups of autistic children and adults over time would provide different and more  
825 useful information about real-life issues, as in Table 2 than large-scale surveys of very heterogeneous  
826 samples<sup>251</sup>.

827 Progress in the biology of more generally defined neurodevelopmental disorders may have the greatest  
 828 yield for children with autism in their early years. Clinical trials that compare known treatments (both  
 829 psychosocial and biological), with new ones and treatment as usual would allow us to build on previous  
 830 findings in a more meaningful way and begin to address the priorities listed in Box 3, which strikingly,  
 831 are seldom priorities in autism research. To move from science to practice including evaluation and  
 832 treatment, autism researchers need to find a way to select and fund studies of more mundane, but  
 833 critical evidence gaps in understanding heterogeneity, mechanisms of change and outcome that affect  
 834 practice in any circumstance, not just internationally, within academic systems that reward creativity  
 835 and novelty. Unique methodologies, including the baby sibling studies, accumulation of large data sets  
 836 (such as ABIDE, and the Simons Simplex Collection (SSC)), prospective epidemiological studies and  
 837 mechanistic studies of intermediate biomarkers may begin to bring together information from molecular  
 838 to pathophysiological to cognitive and behavioural levels. However, for now, as for other  
 839 neurodevelopmental and psychiatric disorders including schizophrenia<sup>252</sup>, the distance between science  
 840 and practice remains great, and the amount of research that attempts to address solvable problems for  
 841 autistic people alive today and their families remains modest.

842

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1564

1565 **Table 1:** Evidence-based medication in autism

<b>Medication</b>	<b>FDA or EMA Indication and age</b>	<b>Effect Size (d)<sup>253</sup></b>	<b>Common Adverse Effects</b>
<b>Typically used for ADHD symptoms</b>			
<i>Methylphenidate</i>	FDA and EMA approval for ADHD (not specific for autism) in those $\geq$ 6 years of age	d=0.78 (teacher rated)	Sleep disruption and decreased appetite
<i>Atomoxetine</i>	FDA and individual country approval for ADHD (not specific for autism) in those $\geq$ 6 years of age	d=-0.68-.084	Decreased appetite, nausea and irritability
<i>Guanfacine</i>	FDA and EMA approval for ADHD (not specific for autism) in those 6–17 years of age	d=1.67	Fatigue, sedation and decreased pulse and blood pressure
<b>Typically used to treat agitation and irritability</b>			
<i>Risperidone</i>	FDA approval for irritability associated with autism and EMA approval only for other indications in those 5–17 years of age	d=0.94	Increased appetite, sedation and weight gain
<i>Aripiprazole</i>	FDA approval for irritability associated with autism and EMA approval only for other indications in those 6–17 years of age	d=0.87	Nausea and weight gain

1566 ADHD, attention-deficit/hyperactivity disorder; EMA, European Medicines Agency.

1567

1568 **Table 2:** Factors that affect QOL.

Type of QOL	Factor	Description
Objective QOL	Early language	Follow-up studies of adults with autism who were diagnosed as children have examined the amount of spoken language during early childhood. Individuals with autism who had fluent speech are more likely to have higher levels of objective QOL life in adulthood than those with phrased speech or those with no speech or who spoke in single words.
	Indicators of intelligence	Studies examining IQ scores using standardized IQ tests administered both in early childhood and adulthood find that individuals with autism and higher IQ scores have higher levels of objective QOL than those with lower IQ scores. Other, less-standardized measures of intelligence (such as those used in large cohort studies) have similar findings.
	Adaptive behaviour	Higher levels of adaptive behaviour – and particularly more activities of daily living – are associated with better objective QOL in people with autism. Adaptive behaviour is a challenge for many individuals with autism, who have scores below what would be expected based on IQ <sup>254</sup> . Adaptive behaviour is changeable, making it a promising avenue for interventions to improve objective QOL.
	Autism symptom severity	Individuals with more severe autism symptoms tend to have lower objective QOL in adulthood.
	Challenging behaviours	Higher levels of challenging behaviours in people with autism, which can include both internalizing problems and externalizing problems, are related to lower objective QOL.
	Sex or gender	Sex or gender associations with objective QOL have been demonstrated in terms of employment or post-secondary education. Indeed, women with autism obtain employment and post-secondary educational positions at the same rate as men with autism but have a more difficult time maintaining those positions over time.
	Subjective QOL	Perceived stress
Supports		Several different types of supports have been related to subjective QOL, including formal services, support from family members (most often parents) and more general social support from others.

1569 QOL, quality of life.

1570

1571

1572



1573 **Figure 1.** Theories and findings regarding autism mechanisms, outcomes and heterogeneity.

1574 Original descriptions of the cardinal features of autism were attributed to a range of causes including  
 1575 being raised by wolves (the Wild Boy of Aveyron), inborn limitations in affective contact and unfeeling  
 1576 parenting (such as ‘refrigerator mothers’) and holy people (such as fools for Christ))<sup>255</sup>.  
 1577 Conceptualizations of autism as a common highly heritable neurodevelopmental disorder with  
 1578 underlying cognitive features began with the recognition of differences in brain function and cognition  
 1579 in the 1960s<sup>256–259</sup> and the first twin study in the 1970s<sup>260</sup>. Other proposed mechanisms include  
 1580 maturational lags in neurophysiology<sup>94</sup> and cognitive mechanisms such as joint engagement<sup>176,261</sup>. With  
 1581 the search for pathways to and sometimes out of autism<sup>262</sup> on many levels, conceptualization of  
 1582 positive outcomes has been more recent, but has also varied markedly. In the 1970s, autism societies  
 1583 and collaborative clinical programs focused on community integration and de-institutionalization (such  
 1584 as National Autistic Society (NAS) and National Society for Autistic Children (NSAC))<sup>263</sup>. Priorities shifted  
 1585 in the 1980s and 1990s, with still unreplicated claims of ‘recovery’ in children who participated in  
 1586 intensive behavioural interventions<sup>179</sup>, new advocacy groups focusing on biomedical discoveries to yield  
 1587 potential biological treatments and even ‘cures’ (such as National Alliance for Autism Research (NAAR)  
 1588 and Cure Autism Now<sup>255</sup>) and the neurodiversity movement<sup>264</sup> which rejected ‘cures’ and called for  
 1589 adaptation of environments to support autistic people, using terminology preferred by self-advocates  
 1590 and community participation. Recognition of the marked heterogeneity within autism began in the  
 1591 1970’s with the triad of impairments in language, play and social interaction characterizing many  
 1592 children with intellectual disabilities (ID) or those with classical autism<sup>265</sup>. The first twin study  
 1593 demonstrated that monozygotic twin pairs, though concordant for difficulties associated with autism,  
 1594 differed in specific characteristics and co-occurring conditions including ID<sup>260</sup>. More recently,  
 1595 phenotypic heterogeneity has been the rule in most, though not all, gene-first phenotypic studies<sup>266</sup>.  
 1596 Thus, developmental aspects of differences in strengths, difficulties and trajectories, as well as biological  
 1597 factors, require highly personalized conceptualizations of the needs of autistic individuals and their  
 1598 families. ABA, applied behaviour analysis; AGRE, Autism Genetic Resource Exchange; CDC, US Centers  
 1599 for Disease Control and Prevention; DSM, Diagnostic and Statistical Manual of Mental Disorders; EEG,  
 1600 electroencephalography; GRASP, Global and Regional Asperger Syndrome Partnership ;IDEA, Individuals  
 1601 with Disabilities Education Act; MCEP, the gene associated with Rett Syndrome; PACT, Preschool Autism  
 1602 Communication Trial; PDD, pervasive developmental disorder; SNAP, Special Needs and Autism Project;  
 1603 SPARK, Simons Foundation Powering Autism Research for Knowledge, TEACCH, Treatment and  
 1604 Education of Autistic and Communication related handicapped Children.

1605

1606 **Figure 2.** Environmental risk factors for autism.

1607 Data from studies aiming to identify risk factors for autism can be broadly split into three categories,  
 1608 those with evidence supporting an association (panel a), those with inconclusive evidence (panel b) and  
 1609 importantly, those with no supporting evidence (panel c). Bars represent ranges. \*Represents  
 1610 recurrence risk. Figure adapted from<sup>18</sup> with added findings from select reviews and empirical papers:  
 1611 neonatal hypoxia estimate<sup>267</sup>, childhood vaccines<sup>20</sup>, valporate use during pregnancy<sup>268</sup>, parent age  
 1612 estimates<sup>269</sup>, preterm birth estimate<sup>270,271</sup>, maternal obesity estimate<sup>272</sup>, folic acid intake estimate<sup>273</sup>,  
 1613 siblings estimate<sup>274,275</sup>, interpregnancy interval estimate<sup>276</sup>, assisted reproductive technologies  
 1614 estimate<sup>277,278</sup>, pesticide and air pollution estimate<sup>279</sup>, caesarian section estimate<sup>280</sup>.

1615

1616 **Figure 3.** Encoded proteins associated with autism risk.

1617 Simplified schematic of the major cellular components of a neural circuit in the cerebral cortex, with a  
 1618 focus on pyramid-shaped glutamatergic excitatory projection neurons. Proteins encoded by selected  
 1619 high-confidence (FDR < 0.1) autism risk genes<sup>34</sup> and proteins encoded by selected syndromic autism  
 1620 genes have a role in these neurons during development. These proteins have a diverse intracellular  
 1621 distribution; those at the synapse, have roles in cell adhesion, scaffolding and signalling. In addition,  
 1622 some of these proteins are localized to the nucleus and have been shown, broadly, to mediate  
 1623 chromatin modification and transcriptional control. Syndromic autism genes include *FMR1* (encoding  
 1624 fragile X mental retardation protein; fragile X syndrome), *UBE3A* (encoding Ubiquitin-protein ligase E3A;  
 1625 Angelman syndrome), *TSC1* and *TSC2* (encoding hamartin and tuberlin; tuberous sclerosis complex),  
 1626 *PTEN* (encoding Phosphatase and tensin homolog) and *MECP2* (encoding methyl-CpG-binding protein 2;  
 1627 Rett syndrome). Adapted from <sup>48</sup>.

1628

1629 **Figure 4.** Longitudinal trajectories of total brain volume, surface area and cortical thickness in autism.

1630 Brain trajectories from 6–24 months of age for total brain volume (TBV, panel a), surface area (SA, panel  
 1631 b) and cortical thickness (CT, panel c). Toddlers diagnosed with ASD had significantly greater surface  
 1632 area growth from 6-12 months compared to infants who were high risk for ASD but did not receive a  
 1633 diagnosis as well as compared to typically developing infants. Differences in surface area growth became  
 1634 more pronounced from 12 to 24 months of age for toddlers who received an ASD diagnosis. Corrected  
 1635 age refers to the age corrected by length (body size). Adapted from <sup>74</sup>.

1636

1637 **Figure 5.** Co-occurring disorders.

1638 Primary and secondary disorders and disadvantage can accumulate through development in people with  
 1639 autism. These disorders can form additional targets for treatment and policy. Prevalence estimates are  
 1640 preliminary, derived from QUEST<sup>281</sup> SNAP<sup>282,138</sup> and EDX<sup>147</sup> cohorts, but are limited by the fact that many  
 1641 are based on clinical populations or data that are inherently biased (such as US Medicaid data where  
 1642 billing for treatment is contingent on having a non-ASD diagnosis) and few well-designed population  
 1643 studies exist.

1644 **Figure 6.** Major parental milestones in advocating and supporting their child with autism.

1645 Families of children and adults with autism have many decisions and expectations across the lifespan of  
 1646 their children, from seeking initial diagnostic evaluation and intervention to preparing for aging-related  
 1647 services. These decisions vary across different cultures, regions and countries and depend on many  
 1648 factors, including the resources and services available. However, several decisions are common across  
 1649 all regions, including LMICs, such as choices about who will care for their child if the parents are  
 1650 temporarily unable, the amount of time parents and other family members can spend with the child  
 1651 with autism versus meeting other needs, ways to modify their home environment to ensure the safety  
 1652 and independence of the individual with autism and the kinds of behavioural expectations that are most

1653 helpful for their child or adult. Of note, for many families, these choices and responsibilities are lifelong  
1654 and are relevant, for children, adolescents, adults and elders with autism.

1655

1656 **Figure 7.** Changes in daily living scores as predicted by IQ scores and autistic symptoms.

1657 Changes in independent daily living skills can be observed in people with autism over time. This sample  
1658 consists of ~100 young adults with a mean age of 26 years with autism, who were evaluated at 2, 3 and  
1659 9 years of age and followed up to 26 years of age. Daily living scores are very diverse, ranging from age-  
1660 appropriate levels of independence at adulthood (represented by a daily living score of 100 , assessed  
1661 using the Vineland II<sup>283</sup>) to very limited skills (represented by a score of <30). Increasing divergence  
1662 shows where measurement after 2 years of age is additionally predictive, with the line thickness  
1663 indicating the proportion of early referred children that followed each trajectory. Heterogeneity in  
1664 intellectual functioning and severity of autism symptoms (social communication and restricted,  
1665 repetitive, sensory behaviors) can be observed. In addition, improvements and worsening of autistic  
1666 symptoms and intellectual functioning can occur over time. A, B | Referred children had verbal IQs  
1667 predominantly <50 (over 3 standard deviations below average) but could show improvement in daily  
1668 living standard scores from 2 to 3 years of age that were indicative of eventual greater independence in  
1669 adulthood. Relatively less early change in non-verbal IQ is seen but, like verbal IQ, by adulthood the  
1670 association with eventual adult daily living skills is strong. C, D | Variation in autism symptom severity in  
1671 social-communication (CSS refers to The Autism Diagnostic Observation Schedule, Second Edition  
1672 (ADOS-2) Comparison Scores) showed a stronger association with adult independence than restricted-  
1673 repetitive behaviours and continued to change over the lifespan following more divergent pathways  
1674 than intellectual functioning. Data from the EDX cohort compiled from <sup>1,147,284</sup>.

1675

1676 **Box 1. ASD as defined in DSM-5<sup>a</sup>.**

1677 The Diagnostic and Statistical Manual of Mental disorders, Fifth Edition (DSM-5) criteria for autism  
1678 spectrum disorder (ASD) comprise 5 symptom clusters (A-E)

1679 A. Social communication and social interaction.

1680 • Must have evidence across multiple contexts of all of the following 3 subdomains currently or by  
1681 history

1682 ○ Social reciprocity

1683 ○ Nonverbal communication

1684 ○ Developing, maintaining and understanding relationships  
1685

1686 B. Restricted, repetitive behaviours and interests.

1687 • Must have evidence of 2 of 4 of the following subdomains currently or by history

1688 ○ Stereotyped, repetitive behaviours

1689 ○ Insistence on sameness

1690 ○ Highly restricted, fixed interests

1691 ○ Hyper- or hyposensitivity or interest in sensory inputs  
1692

1693 C. Symptoms must be present in early development but may not be fully manifest until later or may be  
1694 masked later in life by learned strategies

1695

1696 D. Symptoms must cause clinically significant impairment in current functioning

1697

1698 E. Not better explained by intellectual disability or global developmental delay

1699

1700 Note: Previously established DSM-IV diagnoses of any pervasive developmental disorder, including  
1701 Asperger's disorder should be assumed to be equivalent to DSM-5 ASD. ASD may co-occur with many  
1702 other disorders including ADHD, intellectual disability, language delay and genetic syndromes.

1703 <sup>a</sup> Adapted from ref 125.

## 1704 Box 2. Global challenges in autism research

1705 Recently, there have been calls for more attention to global issues in autism research<sup>251</sup> (Global  
1706 Research on Developmental Disabilities Collaboration – Lancet Global Health, 2016), including a number  
1707 of related issues with somewhat different potential solutions. For example, broader populations should  
1708 be included in autism research, including individuals from Lower Resource and Middle Income countries  
1709 (LMICs), but also inclusive representation of the ethnic, linguistic and socio-economic diversity of many  
1710 High Resource countries and people whose autism is unrecognised. Moreover, there should be the  
1711 creation of opportunities to carry out research in LMICs<sup>285</sup>. Open source and shared databanks,  
1712 including autism-specific resources such as the Simons Simplex Collection and Autism Brain Imaging  
1713 Data Exchange (ABIDE), as well as broader collaborations such as PsychENCODE could assist in  
1714 promoting international research. In addition, the science of autism should be disseminated in ways that  
1715 are useful for practice in all countries, but with particular attention to the needs of communities and  
1716 families with fewer resources<sup>286, 287</sup>. More immediately, searches for scalable methods of identification  
1717 and perhaps intervention with children and adults with autism<sup>140,288</sup> have begun. However, the need to  
1718 develop scalable global practices highlights how little is known about when we need population-wide  
1719 testing for autism versus broader neurodevelopmental disorders, the minimal intensity and duration of  
1720 effective interventions, behavioural mechanisms behind changes in behaviour and which treatments  
1721 work with which children and adults and families, all of which have a bearing on interventions locally  
1722 and globally. In addition, global issues of stigma, governance and paucity of resources also have to be  
1723 taken into account<sup>285</sup>.

1724

1725

1726 **Box 3. Top ten questions for autism research proposed by autistic people, family members and**  
 1727 **professionals<sup>a</sup>.**

- 1728 1. Which interventions improve mental health or reduce mental health problems in people with  
 1729 autism? How should mental health interventions be adapted for the needs of people with  
 1730 autism?  
 1731 2. Which interventions are effective in the development of communication and language skills in  
 1732 autism?  
 1733 3. What are the most effective ways to support or provide social care for autistic adults?  
 1734 4. Which interventions reduce anxiety in autistic people?  
 1735 5. Which environment supports are most appropriate in terms of achieving the best education, life  
 1736 and social skills outcomes in autistic people?  
 1737 6. How can parents and family members be supported and/or educated to care for and better  
 1738 understand an autistic relative?  
 1739 7. How can autism diagnostic criteria be made more relevant for the adult population? And how  
 1740 do we ensure that autistic adults are appropriately assessed and diagnosed?  
 1741 8. How can we encourage employers to apply person centred interventions and support to help  
 1742 autistic people maximize their potential and performance in the workplace?  
 1743 9. How can sensory processing in autism be better understood?  
 1744 10. How should service delivery for autistic people be improved and adapted in order to meet their  
 1745 needs?  
 1746

1747 <sup>a</sup>Based on Ref <sup>239</sup>

1748 **Box 4. Examples of autism websites**

1749 **[H1] Sites for health care professionals or research scientists**

- 1750
- 1751 • American Academy of Pediatrics: <https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Pages/autism-initiatives.aspx>
  - 1752
  - 1753 • International Society for Autism Research: <https://www.autism-insar.org>
  - 1754 • National Autistic Society: <https://www.autism.org.uk>
  - 1755 • Royal College of General Practitioners: <https://www.rcgp.org.uk/clinical-and-research/resources/toolkits/asd-toolkit.aspx>
  - 1756
  - 1757

1758 **[H1] Information about treatment, research and advocacy for people with autism and their families:**

- 1759 • Autism Canada: <https://autismcanada.org>
- 1760 • Research Autism: <http://www.researchautism.net/>
- 1761 • Autism Europe: <https://www.autismeurope.org/>
- 1762 • Autism India: <http://www.autism-india.org>
- 1763 • WHO: <https://www.who.int/news-room/fact-sheets/detail/autism-spectrum-disorders>
- 1764 • Autism Spain: <http://www.autismo.org.es>
- 1765 • Autism Speaks: [www.autismspeaks.org](http://www.autismspeaks.org)
- 1766 • Autismus Deutschland : <https://www.autismus.de>
- 1767 • Autistica: <https://www.autistica.org.uk>
- 1768
- 1769

1770 **[H1] Information about research funding, and up-to-date information for people with autism and families**

- 1772 • Simons Foundation: <https://www.sfari.org>
- 1773 • US NIH: <https://www.nlm.nih.gov/health/topics/autism-spectrum-disorders-asd/index.shtml>
- 1774 • Autism Science Foundation : <https://autismsciencefoundation.org>
- 1775
- 1776

1777 **[H1] Epidemiological and surveillance information**

- 1778 • US CDC: <https://www.cdc.gov/ncbddd/autism/index.html>
- 1779 • Adult population autism surveys, England: <https://digital.nhs.uk/data-and-information/publications/statistical/adult-psychiatric-morbidity-survey/adult-psychiatric-morbidity-survey-survey-of-mental-health-and-wellbeing-england-2014>
- 1780
- 1781
- 1782 • Mental Health of Children and Young People (including autism) in England, 2017: <https://digital.nhs.uk/data-and-information/publications/statistical/mental-health-of-children-and-young-people-in-england/2017/2017>
- 1783
- 1784
- 1785 • The University of Queensland Queensland Centre for Mental Health Research: Global Burden of Disease programme (autism): <https://www.uq.edu.au/news/article/2014/08/autism-rates-steady-two-decades>.
- 1786
- 1787
- 1788

1789

1790 **ToC blurb**

1791 Autism spectrum disorder - or autism - is a neurodevelopmental disorder that typically manifests in  
1792 young children. This Primer by Lord and colleagues reviews the epidemiology, mechanisms, clinical  
1793 detection and treatment of autism.