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# BMJ Open Childhood neurodivergent traits, inflammation and chronic disabling fatigue in adolescence: a longitudinal case-control study

Lisa Quadt <sup>1</sup>, Jenny Csecs,<sup>2</sup> Rod Bond,<sup>3</sup> Neil A Harrison,<sup>4</sup> Hugo D Critchley,<sup>1</sup> Kevin A Davies,<sup>5</sup> Jessica Eccles <sup>1,6</sup>

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<sup>1</sup>Department of Clinical Neuroscience, Brighton and Sussex Medical School, Brighton, UK

<sup>2</sup>Berkshire Healthcare NHS Foundation Trust, Bracknell, UK

<sup>3</sup>School of Psychology, University of Sussex, Brighton, UK

<sup>4</sup>Cardiff University Brain Research Imaging Centre, Cardiff University, Cardiff, UK

<sup>5</sup>Department of Clinical and Experimental Medicine, Brighton and Sussex Medical School, Brighton, UK

<sup>6</sup>Sussex Partnership NHS Foundation Trust, Worthing, UK

## Correspondence to

Dr Lisa Quadt;  
[l.quadt@bsms.ac.uk](mailto:l.quadt@bsms.ac.uk)

## ABSTRACT

**Objectives** To test whether inflammatory processes link the expression of childhood neurodivergent traits to chronic disabling fatigue in adolescence.

**Design** Longitudinal case-control study.

**Setting** We analysed data from The Avon Longitudinal Study of Parents and Children (ALSPAC).

**Participants** 8115 and 8036 children of the ALSPAC cohort at ages 7 and 9 years, respectively, 4563 of whom also completed self-report measures at age 18 years.

**Primary and secondary outcome measures** We assessed if children scoring above screening threshold for autism/attention deficit hyperactivity disorder (ADHD) at ages 7 and 9 years had increased risk of chronic disabling fatigue at age 18 years, computing ORs and CIs for effects using binary logistic regression. Mediation analyses were conducted to test if an inflammatory marker (interleukin 6 (IL-6)) at age 9 years linked neurodivergent traits to chronic disabling fatigue at age 18 years.

**Results** Children with neurodivergent traits at ages 7 and 9 years were two times as likely to experience chronic disabling fatigue at age 18 years (likely ADHD OR=2.18 (95% CI=1.33 to 3.56); p=0.002; likely autism OR=1.78 (95% CI=1.17 to 2.72); p=0.004). Levels of IL-6 at age 9 were associated with chronic disabling fatigue at age 18 (OR=1.54 (95% CI=1.13 to 2.11); p=0.006). Inflammation at age 9 years mediated effects of neurodivergent traits on chronic disabling fatigue (indirect effect via IL-6: ADHD b=1.08 (95% CI=1.01 to 1.15); autism b=1.06; (95% CI=1.03 to 1.10)). All effects remained significant when controlling for the presence of depressive symptoms.

**Conclusions** Our results indicate higher risk of chronic disabling fatigue for children with neurodivergent traits, likely linked to higher levels of inflammation. The implementation of transdiagnostic screening criteria to inform support strategies to counteract risk early in life is recommended.

## INTRODUCTION

There is an increasing interest in the aetiology and maintenance of chronic fatigue, including experiences of fatigue symptoms associated with medical conditions, and chronic fatigue syndromes such as myalgic encephalomyelitis (ME/CFS).<sup>1</sup> Fatigue has

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ A large, longitudinal data set was used to assess potential mechanisms underlying the association between childhood neurodivergent traits and chronic disabling fatigue.
- ⇒ Sample size was too small for subgroup analysis to detect risk according to sex.
- ⇒ Neither neurodivergent traits nor chronic disabling fatigue was clinically assessed, but based on self-report and parent report.

particularly come into focus in the wake of the COVID-19 pandemic and the emergence of Long COVID, where prolonged fatigue is a major symptom in both children<sup>2</sup> and adults.<sup>3-4</sup> However, there is still substantial debate about which risk factors may make certain groups more susceptible to developing chronic fatigue throughout the lifespan.

‘Neurodivergence’ describes neurodevelopmental conditions such as autism and attention deficit hyperactivity disorder (ADHD) and supersedes the traditional, deficit-based view of these conditions.<sup>5</sup> In this article, we align our language with the preferences of the neurodivergent community, including using identity-first language where appropriate and avoiding ableist and pathologising terms.<sup>6-8</sup> The prevalence for autism is estimated at 1%<sup>9</sup> and between 2.7% and 5.4% for ADHD.<sup>10</sup> However, recent reports estimate that at least 10%–15% of the population is neurodivergent.<sup>11-12</sup> Conservative diagnostic criteria perhaps contribute to underdiagnosis of individuals assigned female at birth<sup>13</sup> and ethnic minorities,<sup>14</sup> making accurate prevalence estimates difficult.

Neurodivergent individuals are likely at higher risk of experiencing chronic fatigue. A substantial evidence base indicates that neurodivergence frequently co-occurs with

mental and physical health conditions. These include chronic pain (eg, fibromyalgia),<sup>15</sup> conditions related to hereditary connective tissue disorders (eg, Ehlers-Danlos syndrome/hypermobility spectrum disorder),<sup>16</sup> digestive and gut issues,<sup>17 18</sup> frequent dental complaints,<sup>19</sup> and common psychiatric conditions, such as anxiety and depression.<sup>20 21</sup> Increasingly, it is suggested that ADHD and chronic fatigue share transdiagnostic clinical features, such as executive dysfunction in personal, occupational and social domains,<sup>22–24</sup> atypical attention and sleep patterns<sup>25 26</sup> and increased risks for co-occurring health conditions.<sup>27 28</sup> Previous studies have investigated the overlap between ADHD and (chronic) fatigue, with a focus on symptomatic overlap,<sup>29–32</sup> and neurochemical mechanisms.<sup>33</sup> A study comparing patients with ME/CFS, autistic participants, and a comparison group without diagnoses of these conditions, found that ME/CFS patients did not score higher on an autism screening tool than the comparison group.<sup>34</sup> Recent qualitative research may suggest symptomatic overlap between (chronic) fatigue and ‘autistic burnout’,<sup>35 36</sup> and one empirical study found increased rates of ‘central sensitivity syndromes’, including ME/CFS, in autistic adults.<sup>37</sup>

Research into the potential co-occurrence of neurodivergence and chronic fatigue has focused hitherto on adult populations, although neurodivergent children are likely also at higher risk. Crucially, there is evidence that children with chronic fatigue present differently to adults,<sup>38</sup> and it is important to differentiate the experience of (chronic) fatigue from fatigue syndromes, such as ME/CFS. One classification criterion for fatigue conditions is the duration of fatigue, ranging from acute fatigue (<1 month), prolonged (>1 month, <6 months) to chronic fatigue (>6 months).<sup>39</sup> ME/CFS, in contrast to acute and prolonged fatigue, has very specific diagnostic criteria, and is characterised by unrefreshing sleep and rest, chronic widespread pain, memory, attentional and cognitive dysfunction.<sup>40</sup> In many countries, a medical diagnosis of ME/CFS requires the presence of postexertional malaise (PEM) as a cardinal feature.<sup>41</sup>

Despite its evident detrimental impact on quality of life, prolonged or chronic fatigue as a medical symptom is frequently described as an ‘unexplained’ symptom,<sup>42</sup> and patients regularly report being dismissed about their experience. However, there is robust evidence<sup>43</sup> for a variety of biological mechanisms, including inflammation in the pathobiology of fatigue.<sup>44</sup> Dysregulated immunological and inflammatory processes are likely implicated in the development of fatigue symptomatology, including persisting production of proinflammatory cytokines after viral or bacterial infections, or other stressors.<sup>40 44</sup> In chronic fatigue syndrome, mitochondrial, T cells, B cells and natural killer cells dysfunction and dysregulated circulating cytokines in combination with dysfunctional activation of the hypothalamic–pituitary–adrenal axis may be involved in the onset of chronic fatigue.<sup>45</sup> A recent case–control study with Long COVID patients shows that exercise resulted in attenuated mitochondrial

enzyme activity, reduced T-cell response and tissue infiltration in skeletal muscle, strongly indicating that local and systemic metabolic disturbances underlie PEM.<sup>46</sup> Aberrant immune responses and increased inflammation may underlie fatigue in the general population, where increased interleukin 6 (IL-6) is associated with so-called ‘sickness behaviours’.<sup>47</sup> Sickness behaviours are a normal reaction to signals from peripheral inflammatory cytokines, and include fatigue, anhedonia and social withdrawal.<sup>48</sup> The production of the proinflammatory cytokine IL-6 is part of an immediate immune response to homeostatic threats, and its synthesis usually ceases when homeostasis is restored. When IL-6 synthesis is dysregulated and persists, however, fatigue may persist, making IL-6 a target for clinical and interventional research.<sup>49</sup>

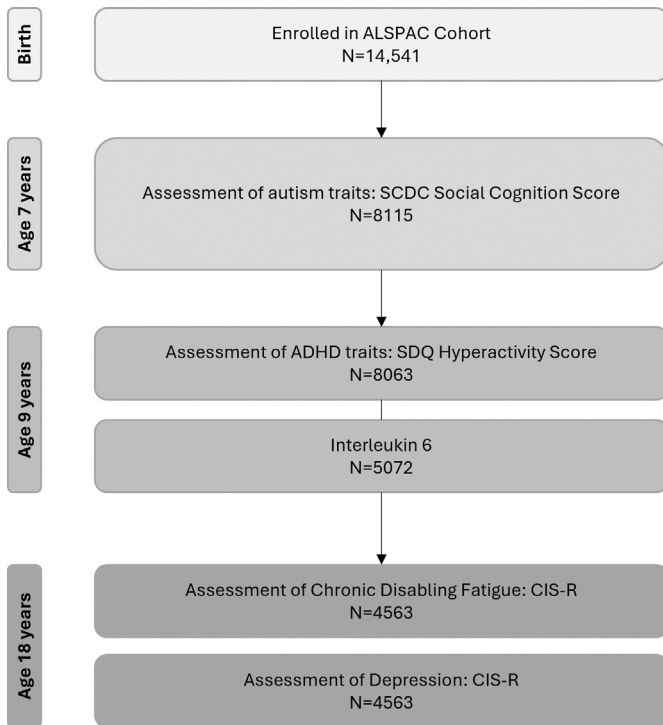
Both neuroinflammatory and peripheral inflammatory dysfunction may further provide a mechanistic link between neurodivergence and chronic fatigue. Dysregulation of peripheral inflammatory cytokines is documented for autism<sup>50</sup> and ADHD,<sup>51</sup> where higher levels of IL-6 are found in both populations. It is also suggested that neuroinflammation links ADHD with pain disorders.<sup>52</sup> Additionally, increased inflammation mediated by mast cell activation is proposed to play a mechanistic role in the neurodevelopment of autism<sup>53 54</sup> and ADHD.<sup>55</sup> Mast cells are blood cells reacting to immune stressors, often described as the ‘immune gate to the brain’.<sup>56</sup> Mast cell activation syndrome (MCAS) describes a range of mast cell disorders, typically characterised by overactivation of mast cell mediators in response to internal or external triggers. Symptoms range widely from mild allergic reactions to life-threatening anaphylaxis.<sup>57</sup> There is furthermore increasing evidence to suggest a mechanistic and symptomatic overlap between variant connective tissue, MCAS and chronic fatigue.<sup>58</sup> These conditions are over-represented in neurodivergent populations,<sup>16</sup> strengthening a potential role of aberrant inflammatory processes involved in chronic fatigue experienced by neurodivergent individuals.

We aimed to investigate the relationship between increased experiences of chronic fatigue and neurodivergent traits in a longitudinal birth cohort. We hypothesised a neurodevelopmental pathway from childhood neurodivergent (autism, ADHD) traits to experiencing chronic disabling fatigue in adolescence and tested whether increased peripherally circulating inflammatory markers (IL-6) impacted on this relationship. We chose IL-6 as previous studies showed increased levels in both autistic<sup>50</sup> and ADHD populations.<sup>51</sup>

## METHODS

### Study design and participants

We used data from The Avon Longitudinal Study of Parents and Children (ALSPAC), a birth cohort that records data of 14 541 live births from women in Avon County in southwest England between April 1991 and December 1992.<sup>59</sup> Parents and children regularly



**Figure 1** Participant Flow and available data at each timepoint. ADHD, attention deficit hyperactivity disorder; ALSPAC, Avon Longitudinal Study of Parents and Children; CIS-R, Clinician Interview Schedule Revised; SCDC, Social and Communication Disorders Checklist; SDQ, Strengths and Difficulties Questionnaire.

completed postal questionnaires about a comprehensive number of aspects of their child's and their own health and development from birth. Children attended annual assessment clinics from the age of 7 years, during which a series of physiological tests and face-to-face interviews was conducted.

Data from assessments at ages 7, 9 and 18 years were used for this study, as variables of interest were tested at these timepoints (figure 1). At age 7 years, parents and carers of 8115 children filled out the Social and Communication Disorders Checklist (SCDC),<sup>60</sup> of which the Social Cognition Score was used as an indication of autistic traits. At age 9 years, parents or carers of 8063 children completed the Strengths and Difficulties Questionnaire (SDQ),<sup>61</sup> of which we used the Hyperactivity Score to get an estimate of ADHD traits. 5072 of these children also attended a clinic where IL-6 was assessed. At age 18 years, the same participants were asked to complete the Clinical Interview Schedule Revised (CIS-R),<sup>62</sup> 4563 respondents provided data.

## Outcomes

### Childhood neurodivergent traits at ages 7 and 9 years

Neurodivergent traits were measured at ages 7 and 9 through parent report using the SCDC<sup>60</sup> for autistic traits and the SDQ<sup>61</sup> Hyperactivity subsection for ADHD traits. The SDQ entails five subscales (hyperactivity, conduct problems, emotional symptoms, peer problems

and prosocial behaviour), of which we used the hyperactivity subscale as an index of ADHD traits. Scores range between 0 and 40, with higher scores indicating greater difficulties. In the case of missing data at the item level, scores were prorated. The SCDC is a brief, 12-item questionnaire assessing autistic traits. Scores range between 0 and 24, with higher scores indicating higher likelihood of meeting diagnostic criteria for autism. The SCDC and SDQ were completed by parents when children were 7 years and 7 months, and 9 years and 7 months old, respectively.

We calculated binary variables for presence/absence of likely autism and ADHD using the recommended cut-off scores of  $\geq 8$  for likely presence of ADHD<sup>63</sup> and  $\geq 9$  for likely presence of autism.<sup>64</sup>

### IL-6 at age 9 years

Blood draws for serum IL-6 concentrations were taken during assessment clinic visits from non-fasting participants. Blood draws were taken either in the morning or early afternoon, depending on whether the child attended a morning or afternoon clinic. We excluded cases that had reported very recent or current infections at the time of the blood draw to avoid confounding by higher inflammation markers.

### Chronic disabling fatigue and depression at age 18 years

Chronic disabling fatigue and depression were assessed at age 18 years using the self-administered computerised version of the CIS-R.<sup>62</sup> We included a measure of depression to test for potential confounding effects of depressed mood. Participants were classified as experiencing 'chronic disabling fatigue' as defined by Collin *et al.*<sup>65</sup> if they met the following criteria: (1) they had been lacking energy and getting tired during the last month, (2) they responded 'yes' to more than two of the following four items: (a) feeling tired or lacking energy for 4 days within the past 7 days; (b) feeling tired or lacking energy for more than 3 hours in total on any day in the past 7 days; (c) feeling so tired or lacking in energy that they had to push themselves to get things done on one or more occasions in the past 7 days; (d) feeling tired or lacking energy when doing things they enjoy in the past 7 days, (3) their fatigue lasted longer than 6 months, (4) their fatigue was not explained by exercise or medication, (5) their fatigue was not alleviated by rest and (6) their fatigue was worse after exercise.<sup>65</sup> We use the term 'chronic disabling fatigue' instead of ME/CFS to indicate that this was based on self-report instead of a clinical assessment by a physician following a diagnosis of ME/CFS.<sup>66</sup>

### Statistical analyses

Statistical analyses were conducted using IBM SPSS Statistics V.26 and MPlus V.8.<sup>67</sup> We tested whether scoring above cut-off for autism and ADHD traits at ages 7 and 9 years predicted subsequent chronic disabling fatigue at age 18 years by using logistic regression to calculate ORs and 95% CIs for chronic disabling fatigue separately



for ADHD and autistic traits. We used logistic regression to explore the association between IL-6 at age 9 years and subsequent chronic disabling fatigue at age 18. We repeated these analyses controlling for depression.

As a sensitivity analysis, we repeated these analyses again using continuous SDQ and SCDC scores to test whether we would get similar results.

We also performed two separate mediation analyses<sup>68</sup> with chronic disabling fatigue at 18 years as binary outcome (present/absent), or SCDC or SDQ scores (continuous) at 7 and 9 years as predictors, and levels of IL-6 at 9 years as the potential mediating variable. We repeated mediation analyses to control for CIS-R Depression Score. For the mediation analysis, we used probit regression with full information maximum likelihood (MPlus estimator command *ML* with Monte Carlo integration), applying bootstrapping (n=2000) with the generation of 95% bias-corrected bootstrap CIs to test inferentially for direct and indirect mediation effects.

We applied full information maximum likelihood estimation,<sup>69</sup> where a likelihood function calculates the relationship between a probability estimate based on observed data from variables in the respective analytical model and different estimate values. Full information maximum likelihood estimation chooses parameter estimates that maximise this likelihood function based on complete cases, thereby providing robust parameter estimates, despite missing data.<sup>70</sup>

### Patient and public involvement

This research was motivated by ongoing patient and public involvement work, where neurodivergent young people, and parents and caregivers of neurodivergent children and young people often express their concerns about physical and mental health conditions. Chronic fatigue and fatiguing conditions in adolescence are specific concerns that are exacerbated by the COVID-19 pandemic and the emergence of Long COVID. In conversation with patients, parents and caregivers, it was often expressed that postviral or postinflammatory fatigue was experienced but dismissed and underappreciated by healthcare professionals. Two patient representatives commented on this manuscript. Our patient and public involvement members will support the dissemination of our findings among public stakeholders in an accessible

manner, and the author team includes neurodivergent individuals.

## RESULTS

### Frequency of chronic disabling fatigue and neurodivergent traits

Table 1 shows frequency of scoring above threshold for autism and ADHD traits at ages 7 and 9 years, and for chronic disabling fatigue at age 18 years.

### Risk of chronic disabling fatigue at age 18 years according to neurodivergent traits at ages 7 and 9 years

Children who met criteria for likely autism or ADHD showed higher frequency of chronic disabling fatigue at age 18 years in comparison to children who did not meet criteria (figure 2).

Children who showed an indication of autism at age 7 years were almost two times as likely (OR=1.78 (95% CI=1.17 to 2.72; p=0.008)) to experience chronic disabling fatigue at age 18 years. Children who scored above threshold for ADHD at age 9 years were two times as likely (OR=2.18 (95% CI=1.33 to 3.56; p=0.002)) to experience chronic disabling fatigue at age 18 years. These effects remained significant when controlling for depression (autism: OR=1.65 (95% CI=1.04 to 2.61; p=0.34); ADHD: OR=1.88 (95% CI=1.09 to 3.22; p=0.022)).

Sensitivity analyses showed that when using continuous SCDC and SDQ scores, differential relationships remained and likelihood of experiencing chronic disabling fatigue at age 18 years increased with higher SCDC (OR=1.06 (95% CI=1.03 to 1.09; p<0.001)) and SDQ (OR=1.08 (95% CI=1.03 to 1.14; p=0.003)). These effects remained significant when controlling for depression (SDQ: OR=1.07 (95% CI=1.02 to 1.14; p=0.013); SCDC: OR=1.05 (95% CI=1.02 to 1.09; p=0.003)).

### Association between inflammation at age 9 years and subsequent presence of chronic disabling fatigue at age 18 years

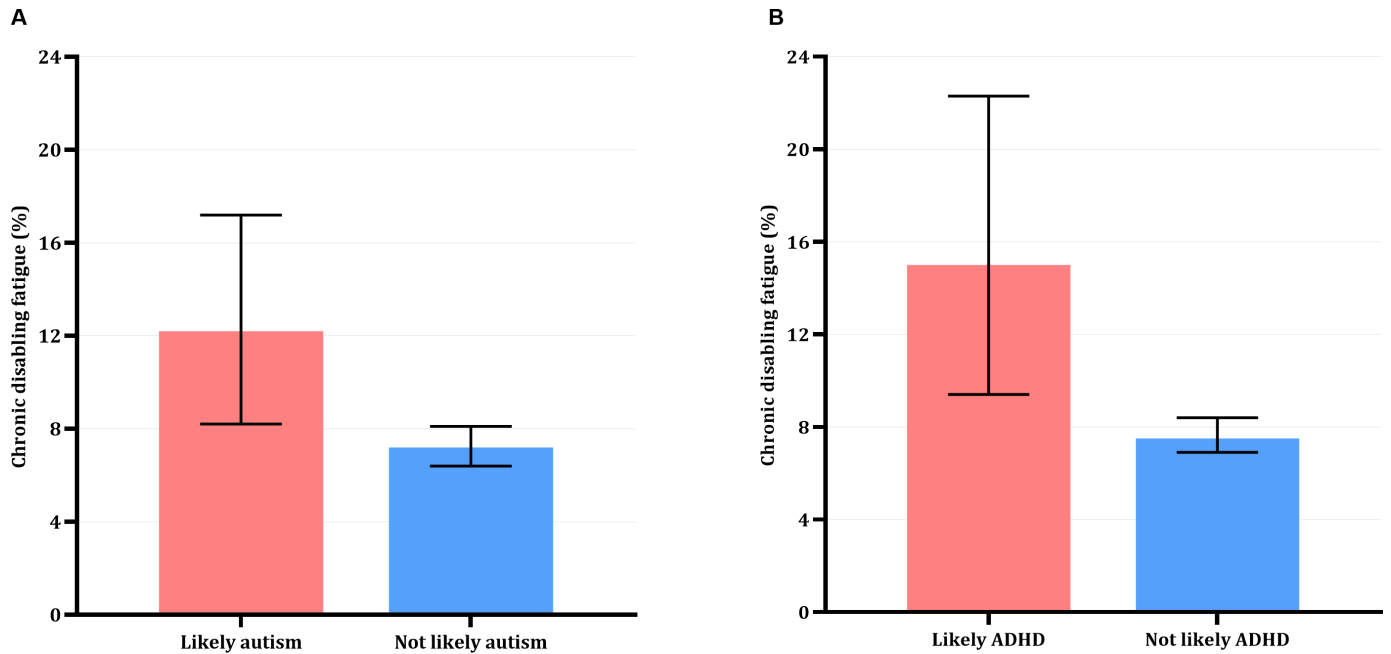
IL-6 levels at age 9 years were significantly associated with a higher likelihood of chronic disabling fatigue at age 18 years (OR=1.54 (95% CI=1.13 to 2.11); p=0.006; figure 3). This indicates a 1.5 times higher likelihood of experiencing chronic disabling fatigue at age 18 years per

**Table 1** Frequency of neurodivergent traits and chronic disabling fatigue

	Data available for ages 7 and 9 years	Above cut-off	Data available for age 18 years	Above cut-off
Autism	8115	629 (7.8)		
ADHD	8063	373 (4.6)		
Chronic disabling fatigue			4563	367 (8.0)

Data are n (%) or n/N (%) unless otherwise specified. N=14 541 originally enrolled in Avon Longitudinal Study of Parents and Children cohort. ADHD cut-off≥9 on hyperactivity subscale on Strengths and Difficulties Questionnaire. Autism cut-off≥8 on Social and Communication Disorders Checklist.

ADHD, attention deficit hyperactivity disorder.



**Figure 2** Frequency of chronic disabling fatigue in percent at age 18 years for children with likely neurodivergence (likely autism (A); likely ADHD (B); red bars) and without likely neurodivergence (blue bars). Error bars are 95% CIs.

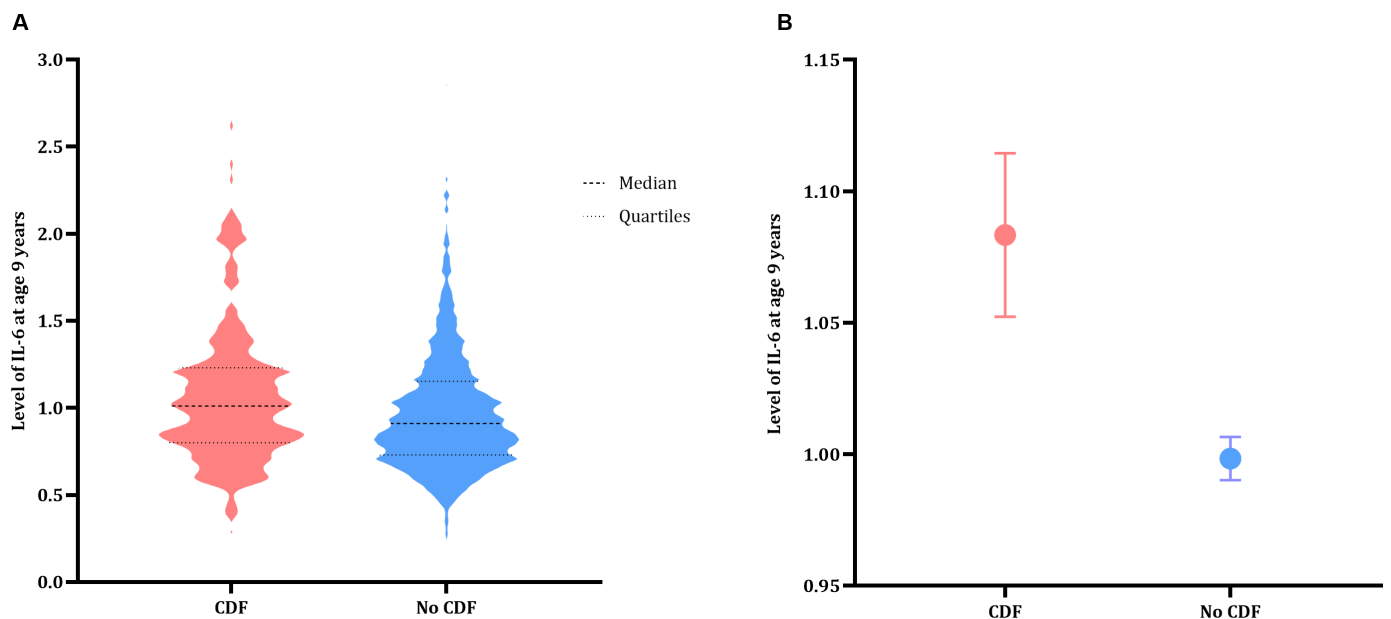
unit increase of IL-6 levels at age 9 years. This remained significant when controlling for depression (OR=1.59 (95% CI=1.34 to 2.22); p=0.006).

### Mediation analysis

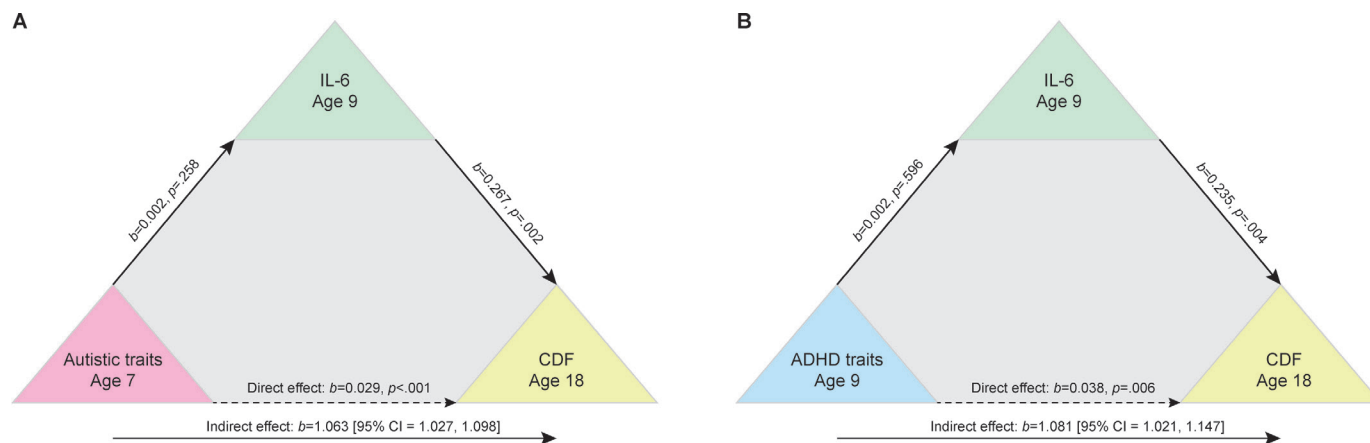
Both mediation models showed that continuous scores of neurodivergent traits (SCDC at age 7 years/SDQ at age 9 years) and IL-6 at age 9 years were significantly associated with presence of chronic disabling fatigue at age 18 years. This was demonstrated by significant indirect effects of IL-6 on the relationship between autistic traits and chronic

disabling fatigue (b=1.06 (95% CI=1.03 to 1.10); figure 4A), and on the relationship between ADHD traits and chronic disabling fatigue (b=1.08 (95% CI=1.02 to 1.15); figure 4B). This indicates that per unit increase in IL-6, the odds that children with higher neurodivergent traits at ages seven and nine years would experience chronic disabling fatigue at age 18 years increased by 1.06 and 1.08.

Both effects remained significant after controlling for levels of depression at age 18 years (autistic traits: b=1.06 (95% CI=1.02 to 1.10); ADHD traits: b=1.08 (95% CI=1.01 to 1.16)).



**Figure 3** Group comparison of participants at age 18 years old who scored above threshold for chronic disabling fatigue (CDF) (CDF; red) and who did not (no CDF; blue). (A) A violin plot displaying the distribution of IL-6 levels at age 9 years old. (B) The mean IL-6 values and SEM in each group at age 9 years old. CDF, chronic disabling fatigue; IL-6, interleukin 6.



**Figure 4** Two separate mediation analyses showing significant indirect effects of autistic traits at age 7 years (Social and Communication Disorders Checklist scores (A)) and attention deficit hyperactivity disorder traits (Strengths and Difficulties Questionnaire Hyperactivity subscale scores (B)) at age 9 years on chronic disabling fatigue at age 18 through IL-6. ADHD, attention deficit hyperactivity disorder; CDF, chronic disabling fatigue; IL-6, interleukin 6.

## DISCUSSION

Using a large birth cohort, we found a link between neurodivergent traits in childhood and increased frequency of experiencing chronic disabling fatigue in adolescence, mediated by levels of childhood inflammation. We found that children who scored above cut-off on parent-reported autism and ADHD measures at ages 7 and 9 years were approximately two times as likely to meet self-reported criteria for chronic disabling fatigue at age 18 years. Increased inflammation, as indicated by IL-6 levels at age 9 years, provides a potential mechanistic explanation for this link, even when controlling for depression.

Adding to previous research indicating that there is a transdiagnostic overlap between (chronic) fatigue and ADHD, we provide evidence that also extends to autism, where little research has hitherto shown such a relationship. In line with findings that fatigue conditions may be inflammation-related,<sup>47</sup> heightened IL-6 in childhood was found to be a potential explanatory link between childhood neurodivergent traits and chronic disabling fatigue.

There is ample evidence of increased inflammation in neurodivergent children and young people. Most prominently, digestive and gut issues have been associated with increased local and systemic inflammation,<sup>71</sup> but frequent dental issues may also be connected with inflammatory conditions.<sup>72</sup> Additionally, higher biopsychosocial stress in neurodivergent children perhaps accounts for increased levels of inflammation and subsequent experience of chronic disabling fatigue. In the ALSPAC cohort, blood samples from which IL-6 levels were detected were drawn at a clinical appointment. It is possible that this session and the blood draw itself introduced stress to young participants, especially those with higher neurodivergent traits, which may have impacted on IL-6 levels.

Research shows that neurodivergent children experience higher levels of loneliness,<sup>73 74</sup> and are more likely to experience bullying.<sup>75</sup> Neurodivergent children are also more vulnerable to experience pain.<sup>76–78</sup> Different reasons are suggested in the literature,

including differences in pain perception,<sup>79</sup> dopaminergic dysregulation,<sup>52</sup> and increased prevalence of hereditary connective tissue disorders, such as (hypermobile) Ehlers-Danlos syndrome.<sup>80</sup> Variant connective tissue is linked to increased pain<sup>16</sup> and a higher risk for psychiatric disorders in adolescents.<sup>81</sup> Neurodivergence and chronic fatigue are conditions with complex individual neurodevelopmental pathways. It is therefore likely that inflammation is not the only mediating or moderating factor that plays into the over-representation of (chronic) fatigue in neurodivergent individuals. Additional mechanistic insights are needed to disentangle the intricacies of this relationship. It is likely that a convergence of exogenous factors in a vulnerable body increases the risk of experiencing chronic fatigue in neurodivergent young people, as evidence from our results suggests.

## Strengths and limitations

Although both SDQ and SCDC have good psychometric properties in identifying indications of ADHD and autism,<sup>64 82</sup> it is important to note that they cannot replace clinical evaluations for neurodivergent conditions. Additionally, these were not child-completed questionnaires. Parents' report on neurodivergence in their children has been shown to be biased depending on race<sup>83</sup> and sex<sup>84</sup> of the child and may thus be a biased resource. Autistic advocates and researchers call for using measurement tools that meaningfully reflect the autistic experience, which may not always align with their psychometric properties.<sup>85</sup> Furthermore, the concept of chronic disabling fatigue was carefully conceptualised in this study, but again cannot replace clinical assessment. Future research can improve robustness by testing associations between clinically evaluated diagnoses.

Although we used a large birth cohort, we did not perform a subgroup analysis to detect risk according to sex, as sample size was too small.

ALSPAC blood sample collection clinics ran both morning and afternoon sessions. As IL-6 exhibits diurnal variation with

decreasing levels throughout the day, the collection time may have impacted on IL-6 levels in participant blood samples depending on time of attendance and blood draw.

We found a rather large incidence of chronic disabling fatigue in cohort participants at age 18 years (8%). In contrast, a systematic review and meta-analysis found for ME/CFS ‘an average prevalence of 1.40%±1.57%, with a pooled prevalence of 0.39% and a meta-analysis prevalence of 0.68%’.<sup>86</sup> However, chronic fatigue conditions, including ME/CFS, are likely largely underdiagnosed or misdiagnosed,<sup>87</sup> with one study citing up to 91% of patients being undiagnosed or misdiagnosed.<sup>88</sup> Additionally, our sample was not clinician tested for ME/CFS, perhaps also accounting for a higher number of chronic disabling fatigue.

## Conclusion

Our findings call for transdiagnostic screening practices to support health and well-being during development and adolescence. Critically, children who are suspected to be or diagnosed as neurodivergent should routinely be screened for physical and mental health concerns. Earlier integration of brain-body concerns in a holistic framework can facilitate tailored support and improve quality of life of neurodivergent individuals of all ages. We therefore call for timely access to healthcare, extra attention, and early intervention targeting health concerns at critical timepoints for neurodivergent children.

X Jessica Eccles @BendyBrain

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**Contributors** RB advised on data analysis, conducted initial mediation analyses and data interpretation. He approved the initial draft of this manuscript but did not approve the full and final versions of this manuscript. JE conceived, planned and designed this study and obtained data from ALSPAC. LQ conducted all final data analyses. RB, LQ and JE interpreted data. JC drafted an initial version of the manuscript. LQ drafted the final full manuscript. KAD advised on introduction and discussion, and overall reporting. JE, HDC and NAH revised the manuscript. LQ, JC, NAH, KAD, HDC and JE approved the final version. JE acts as guarantor and accepts full responsibility for the work and conduct of the study, had access to the data, and controlled the decision to publish.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication** Consent obtained from parent(s)/guardian(s).

**Ethics approval** Ethical approval for the study was obtained from the ALSPAC ethics and law committee and the local research ethics committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC ethics and law committee at the time. Children were invited to give assent where appropriate. Study participants have the right to withdraw their consent for elements of the

study or from the study entirely at any time. Full details of the ALSPAC consent procedures are available on the study website (<http://www.bristol.ac.uk/alspac/researchers/research-ethics/>). Initial Approval Reference numbers: Bristol and Weston Health Authority: E1808, Southmead Health Authority: 49/89 and Frenchay Health Authority: 90/8. 7 Year Clinic Approval Reference numbers: United Bristol Healthcare Trust: E4168 ALSPAC Hands on Assessments at Age Seven (30 September 1998), Southmead Health Services: 67/98 Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC)—Hands on Assessments at Age Seven (14 September 1998) and Frenchay Healthcare Trust: 98/52 Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC). Hands on Assessments at Age Seven (8 December 1998). 9 Year Clinic Approval Reference numbers: United Bristol Healthcare Trust: E5018, Southmead (North Bristol Trust): 008/01 and Frenchay (North Bristol Trust): 2001/35 Avon Longitudinal Study of Parents and Children (ALSPAC) Assessments at Age Nine (9 May 2001). 17 Year Clinic Approval Reference numbers: North Somerset & South Bristol Research Ethics Committee: 08/H0106/9.

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## ORCID iDs

Lisa Quadt <http://orcid.org/0000-0002-5896-916X>

Jessica Eccles <http://orcid.org/0000-0002-0062-1216>

## REFERENCES

- Noor N, Urits I, Degueure A, *et al*. A comprehensive update of the current understanding of chronic fatigue syndrome. *Anesth Pain Med* 2021;11.
- Fainardi V, Meoli A, Chiopris G, *et al*. Long COVID in children and adolescents. *Life (Basel)* 2022;12:285.
- Hartung TJ, Neumann C, Bahmer T, *et al*. Fatigue and cognitive impairment after COVID-19: A prospective Multicentre study. *EClinicalMedicine* 2022;53:101651.
- Sukocheva OA, Maksoud R, Beeraka NM, *et al*. Analysis of post COVID-19 condition and its overlap with Myalgic Encephalomyelitis/chronic fatigue syndrome. *J Adv Res* 2022;40:179–96.
- Fletcher-Watson S. Transdiagnostic research and the Neurodiversity paradigm: commentary on the Transdiagnostic revolution in neurodevelopmental disorders by Astle *et al*. *J Child Psychol Psychiatry* 2022;63:418–20.
- Flowers J, Dawes J, McCleary D, *et al*. Words matter: language preferences in a sample of autistic adults. *Neurodiversity* 2023;1.
- Keating CT, Hickman L, Leung J, *et al*. Autism-Related language preferences of English-Speaking individuals across the globe: A mixed methods investigation. *Autism Res* 2023;16:406–28.
- Potts B, Smith N, Malamateniou C. Respectful language in autism research: in response to Abdelrahman *et al*. ‘exploration of Radiographers’ knowledge, attitudes, and practices in delivering Healthcare to children with autism spectrum disorder. *Radiography (Lond)* 2024;30:702–3.
- Zeidan J, Fombonne E, Scora J, *et al*. Global prevalence of autism: A systematic review update. *Autism Res* 2022;15:778–90.
- Cortese S, Song M, Farhat LC, *et al*. Incidence, prevalence, and global burden of ADHD from 1990 to 2019 across 204 countries: data, with critical re-analysis, from the global burden of disease study. *Mol Psychiatry* 2023;28:4823–30.
- Embracing Complexity. Embracing Complexity: Towards New Approaches for Supporting People with Neurodevelopmental Conditions 2019, Available: <https://www.autistica.org.uk/downloads/files/Embracing-Complexity-in-Diagnosis.pdf>
- Doyle N. Neurodiversity at work: a Biopsychosocial model and the impact on working adults. *Br Med Bull* 2020;135:108–25.
- Burrows CA, Grzadzinski RL, Donovan K, *et al*. A data-driven approach in an unbiased sample reveals equivalent sex ratio of autism spectrum disorder-associated impairment in early childhood. *Biol Psychiatry* 2022;92:654–62.
- Ames JL, Morgan EH, Onaiwu MG, *et al*. Racial/ethnic differences in psychiatric and medical diagnoses among autistic adults. *Autism Adulthood* 2022;4:290–305.



- 15 Asztély K, Kopp S, Gillberg C, *et al.* Chronic pain and health-related quality of life in women with autism and/or ADHD: A prospective longitudinal study. *J Pain Res* 2019;12:2925–32.
- 16 Csecs JLL, Iodice V, Rae CL, *et al.* Joint Hypermobility links Neurodivergence to Dysautonomia and pain. *Front Psychiatry* 2021;12:786916.
- 17 Buie T, Campbell DB, Fuchs GJ III, *et al.* Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with Asds: A consensus report. *Pediatrics* 2010;125:S1–18.
- 18 Ming X, Chen N, Ray C, *et al.* A gut feeling: A hypothesis of the role of the Microbiome in attention-deficit/hyperactivity disorders. *Child Neurol Open* 2018;5:2329048X18786799.
- 19 Corridore D, Zumbo G, Corvino I, *et al.* Prevalence of oral disease and treatment types proposed to children affected by autistic spectrum disorder in pediatric dentistry: a systematic review. *Clin Ter* 2020;171:e275–82.
- 20 Mutluer T, Aslan Genç H, Özcan Morey A, *et al.* Population-based psychiatric Comorbidity in children and adolescents with autism spectrum disorder: A meta-analysis. *Front Psychiatry* 2022;13:856208.
- 21 D'Agati E, Curatolo P, Mazzone L. Comorbidity between ADHD and anxiety disorders across the LifeSpan. *Int J Psychiatry Clin Pract* 2019;23:238–44.
- 22 Biederman J, Petty C, Fried R, *et al.* Impact of Psychometrically defined deficits of executive functioning in adults with attention deficit hyperactivity disorder. *Am J Psychiatry* 2006;163:1730–8.
- 23 Ali S, Matcham F, Irving K, *et al.* Fatigue and Psychosocial variables in autoimmune rheumatic disease and chronic fatigue syndrome: A cross-sectional comparison. *J Psychosom Res* 2017;92:1–8.
- 24 Sacchetti GM, Lefler EK. ADHD Symptomology and social functioning in college students. *J Atten Disord* 2017;21:1009–19.
- 25 Konofal E, Lecendreux M, Cortese S. Sleep and ADHD. *Sleep Med* 2010;11:652–8.
- 26 Zielinski MR, Systrom DM, Rose NR. Fatigue, sleep, and autoimmune and related disorders. *Front Immunol* 2019;10:1827.
- 27 Janssens KAM, Zijlema WL, Joustra ML, *et al.* Mood and anxiety disorders in chronic fatigue syndrome, Fibromyalgia, and irritable bowel syndrome: results from the Lifelines cohort study. *Psychosom Med* 2015;77:449–57.
- 28 Kessler RC, Adler L, Barkley R, *et al.* The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity survey replication. *Am J Psychiatry* 2006;163:716–23.
- 29 Sáez-Francàs N, Alegre J, Calvo N, *et al.* Attention-deficit hyperactivity disorder in chronic fatigue syndrome patients. *Psychiatry Res* 2012;200:748–53.
- 30 Rogers DC, Dittner AJ, Rimes KA, *et al.* Fatigue in an adult attention deficit hyperactivity disorder population: A Trans-diagnostic approach. *Br J Clin Psychol* 2017;56:33–52.
- 31 Young JL. Chronic fatigue syndrome: 3 cases and a discussion of the natural history of attention-deficit/hyperactivity disorder. *Postgrad Med* 2013;125:162–8.
- 32 Young JL, Redmond JC. Fibromyalgia, chronic fatigue, and adult attention deficit hyperactivity disorder in the adult: a case study. *Psychopharmacol Bull* 2007;40:118–26.
- 33 Yamamoto T. The relationship between central fatigue and attention deficit/hyperactivity disorder of the inattentive type. *Neurochem Res* 2022;47:2890–8.
- 34 Bileviciute-Ljungar I, Maroti D, Bejerot S. Patients with chronic fatigue syndrome do not score higher on the autism-spectrum quotient than healthy controls: comparison with autism spectrum disorder. *Scand J Psychol* 2018;59:428–32.
- 35 Keville S, Meek C, Ludlow AK. Mothers' perspectives of Co-occurring fatigue in children with autism spectrum disorders. *Fatigue: Biomedicine, Health Behav* 2021;9:209–26.
- 36 Raymaker DM, Teo AR, Steckler NA, *et al.* Having all of your internal resources exhausted beyond measure and being left with no clean-up crew": defining autistic burnout. *Autism Adulthood* 2020;2:132–43.
- 37 Grant S, Norton S, Weiland RF, *et al.* Autism and chronic ill health: an observational study of symptoms and diagnoses of central sensitivity syndromes in autistic adults. *Mol Autism* 2022;13:7.
- 38 Collin SM, Nuevo R, van de Putte EM, *et al.* Chronic fatigue syndrome (CFS) or Myalgic Encephalomyelitis (ME) is different in children compared to in adults: a study of UK and Dutch clinical cohorts. *BMJ Open* 2015;5:e008830.
- 39 Son C-G. "Differential diagnosis between "chronic fatigue" and "chronic fatigue syndrome". *Integr Med Res* 2019;8:89–91.
- 40 Cortes Rivera M, Mastronardi C, Silva-Aldana CT, *et al.* Myalgic Encephalomyelitis/chronic fatigue syndrome: A comprehensive review. *Diagnostics (Basel)* 2019;9:91.
- 41 Carruthers BM, Jain AK, De Meirleir KL, *et al.* Myalgic Encephalomyelitis/chronic fatigue syndrome. *J Chronic Fatigue Syndrome* 2003;11:7–115.
- 42 Luty J. Medically unexplained syndromes: irritable bowel syndrome, Fibromyalgia and chronic fatigue. *BJPsych Advances* 2018;24:252–63.
- 43 Komaroff AL, Lipkin WI. Insights from Myalgic Encephalomyelitis/chronic fatigue syndrome may help unravel the pathogenesis of Postacute COVID-19 syndrome. *Trends Mol Med* 2021;27:895–906.
- 44 Grygiel-Górniak B, Puszczewicz M. Fatigue and Interleukin-6 – a multi-Faceted relationship. *Reumatologia* 2015;53:207–12.
- 45 Yang T, Yang Y, Wang D, *et al.* The clinical value of Cytokines in chronic fatigue syndrome. *J Transl Med* 2019;17:213.
- 46 Appelman B, Charlton BT, Goulding RP, *et al.* Muscle abnormalities worsen after post-Exertional malaise in long COVID. *Nat Commun* 2024;15:17.
- 47 Karshikoff B, Sundelin T, Lasselin J. Role of inflammation in human fatigue: relevance of multidimensional assessments and potential neuronal mechanisms. *Front Immunol* 2017;8.
- 48 Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. *Brain Behav Immun* 2007;21:153–60.
- 49 Tanaka T, Kishimoto T. The biology and medical implications of Interleukin-6. *Cancer Immunol Res* 2014;2:288–94.
- 50 Saghazadeh A, Ataeinia B, Keynejad K, *et al.* A meta-analysis of pro-inflammatory Cytokines in autism spectrum disorders: effects of age, gender, and latitude. *J Psychiatry Res* 2019;115:90–102.
- 51 Ferencova N, Visnovcova Z, Ondrejka I, *et al.* Peripheral inflammatory markers in autism spectrum disorder and attention deficit/hyperactivity disorder at adolescent age. *Int J Mol Sci* 2023;24:11710.
- 52 Kerekes N, Sánchez-Pérez AM, Landry M. Neuroinflammation as a possible link between attention-deficit/hyperactivity disorder (ADHD) and pain. *Med Hypotheses* 2021;157:S0306-9877(21)00236-X.
- 53 Theoharides TC, Kavalioti M, Tsilioni I. Mast cells, stress, fear and autism spectrum disorder. *Int J Mol Sci* 2019;20:3611.
- 54 Theoharides TC, Stewart JM, Panagiotidou S, *et al.* Mast cells, brain inflammation and autism. *Eur J Pharmacol* 2016;778:96–102.
- 55 Song Y, Lu M, Yuan H, *et al.* Mast cell-mediated Neuroinflammation may have a role in attention deficit hyperactivity disorder (review). *Exp Ther Med* 2020;20:714–26.
- 56 Ribatti D. The crucial role of mast cells in blood-brain barrier alterations. *Exp Cell Res* 2015;338:119–25.
- 57 Theoharides TC, Perlman AI, Twhair A, *et al.* Mast cell activation: beyond histamine and Tryptase. *Expert Rev Clin Immunol* 2023;19:639–54.
- 58 Kucharik AH, Chang C. The relationship between Hypermobile Ehlers-Danlos syndrome (hEDS), postural orthostatic tachycardia syndrome (POTS), and mast cell activation syndrome (MCAS). *Clinic Rev Allerg Immunol* 2020;58:273–97.
- 59 Boyd A, Golding J, Macleod J, *et al.* Cohort profile: the 'children of the 90S'—The index offspring of the Avon longitudinal study of parents and children. *Int J Epidemiol* 2013;42:111–27.
- 60 Skuse DH, James RS, Bishop DV, *et al.* Evidence from Turner's syndrome of an imprinted X-linked locus affecting cognitive function. *Nature* 1997;387:705–8.
- 61 Goodman R. The strengths and difficulties questionnaire: A research NOTE. *J Child Psychol Psychiatry* 1997;38:581–6.
- 62 Brugha TS, Bebbington PE, Jenkins R, *et al.* Cross validation of a general population survey diagnostic interview: a comparison of CIS-R with SCAN ICD-10 diagnostic categories. *Psychol Med* 1999;29:1029–42.
- 63 Silva TBF, Osório FL, Loureiro SR. SDQ: Discriminative validity and diagnostic potential. *Front Psychol* 2015;6:811.
- 64 Skuse DH, Mandy WPL, Scourfield J. Measuring autistic traits: Heritability, Reliability and validity of the social and communication disorders checklist. *Br J Psychiatry* 2005;187:568–72.
- 65 Collin SM, Norris T, Gringras P, *et al.* Childhood sleep and adolescent chronic fatigue syndrome (CFS/ME): evidence of associations in a UK birth cohort. *Sleep Med* 2018;46:26–36.
- 66 Collin SM, Norris T, Nuevo R, *et al.* Chronic fatigue syndrome at age 16 years. *Pediatrics* 2016;137:e20153434.
- 67 Muthén L, Muthén B. Statistical analysis with latent variables: Mplus user's guide: Muthén & Muthén, Los Angeles, CA. 2012.
- 68 Muthén B, Asparouhov T. Causal effects in mediation modeling: an introduction with applications to latent variables. *Struct Equat Model: A Multidisciplinary J* 2015;22:12–23.
- 69 Enders CK. Applied Missing Data Analysis. New York, NY: Guilford Press, 2010.
- 70 Newman DA. Missing data: five practical guidelines. *Organ Res Methods* 2014;17:372–411.

- 71 Bundgaard-Nielsen C, Knudsen J, Leutscher PDC, *et al.* Gut Microbiota profiles of autism spectrum disorder and attention deficit/hyperactivity disorder: A systematic literature review. *Gut Microbes* 2020;11:1172–87.
- 72 Sharma D, Bhandary S, Prabhu V. Evaluation of salivary biomarker levels in children with autism spectrum disorder having dental Caries. *J Orofac Sci* 2023;15:61.
- 73 Houghton S, Roost E, Carroll A, *et al.* Loneliness in children and adolescents with and without attention-deficit/hyperactivity disorder. *J Psychopathol Behav Assess* 2015;37:27–37.
- 74 Bauminger N, Kasari C. Loneliness and friendship in high-functioning children with autism. *Child Development* 2000;71:447–56.
- 75 Hoover DW, Kaufman J. Adverse childhood experiences in children with autism spectrum disorder. *Curr Opin Psychiatry* 2018;31:128–32.
- 76 Battison EAJ, Brown PCM, Holley AL, *et al.* Associations between chronic pain and attention-deficit hyperactivity disorder (ADHD) in youth: A Scoping review. *Children (Basel)* 2023;10:142.
- 77 Mundal I, Schei J, Lydersen S, *et al.* Prevalence of chronic and Multisite pain in adolescents and young adults with ADHD: a comparative study between clinical and general population samples (the HUNT study). *Eur Child Adolesc Psychiatry* 2024;33:1433–42.
- 78 Lipsker CW, Bölte S, Hirvikoski T, *et al.* Prevalence of autism traits and attention-deficit hyperactivity disorder symptoms in a clinical sample of children and adolescents with chronic pain. *J Pain Res* 2018;11:2827–36.
- 79 Failla MD, Gerdes MB, Williams ZJ, *et al.* Increased pain sensitivity and pain-related anxiety in individuals with autism. *PAIN Rep* 2020;5:e861.
- 80 Cederlöf M, Larsson H, Lichtenstein P, *et al.* Nationwide population-based cohort study of psychiatric disorders in individuals with Ehlers-Danlos syndrome or Hypermobility syndrome and their siblings. *BMC Psychiatry* 2016;16:207.
- 81 Eccles JA, Quadt L, McCarthy H, *et al.* Variant connective tissue (joint Hyerprmobility) and its relevance to depression and anxiety in adolescents: a cohort-based case-control study. *BMJ Open* 2022;12:e066130.
- 82 Goodman R. Psychometric properties of the strengths and difficulties questionnaire. *J Am Academy Child Adolescent Psych* 2001;40:1337–45.
- 83 Donohue MR, Childs AW, Richards M, *et al.* Race influences parent report of concerns about symptoms of autism spectrum disorder. *Autism* 2019;23:100–11.
- 84 Ramsey RK, Nichols L, Ludwig NN, *et al.* Brief report: sex differences in parental concerns for toddlers with autism risk. *J Autism Dev Disord* 2018;48:4063–9.
- 85 Jones SC. Measuring the wrong thing the right way? time to rethink autism research tools. *Autism in Adulthood* 2022;4:104–9.
- 86 Lim E-J, Ahn Y-C, Jang E-S, *et al.* Systematic review and meta-analysis of the prevalence of chronic fatigue syndrome/Myalgic Encephalomyelitis (CFS/ME). *J Transl Med* 2020;18.
- 87 Jason LA, Mirin AA. Updating the National Academy of medicine ME/CFS prevalence and economic impact figures to account for population growth and inflation. *Fatigue: Biomed Health Behav* 2021;9:9–13.
- 88 Bateman L, Bested AC, Bonilla HF, *et al.* Myalgic Encephalomyelitis/chronic fatigue syndrome: essentials of diagnosis and management. *Mayo Clin Proc* 2021;96:2861–78.