BMC Medicine

RESEARCH

Open Access

Disease and mortality trajectories of cognitively able autistic individuals in mid- and later adulthood

Yiwei Pu[1†], Feng Li[1†], Tailin Zhu[1†], Jiong Li[1,2], Wei Zhou[1], Lingli Zhang[1], Jingyu Chen[1], Qianlong Zhang[1], Tai Ren[1*] and Fei Li[1*]

Abstract

Background An increasing number of autistic adults have entered their later life, but little is known about the disease trajectory in mid- and later adulthood. We aimed to examine the patterns of comorbidity progression in adults with autism spectrum disorder (ASD) that may affect their mortality.

Methods Participants were identified from the UK Biobank study. We first identified individuals with ASD diagnosis, each of whom was randomly matched to up to 10 participants without ASD diagnosis. Cox regression was used to estimate the hazard ratio (HR) of mortality. Disease trajectory analysis was performed to investigate temporal sequencing of medical conditions and mortality associated with ASD. A multistate model was used to investigate the association patterns between ASD and three common chronic conditions: cardiovascular disease/hypertension, type 2 diabetes and disorders of lipoprotein metabolism, and depression/anxiety.

Results The study included 659 ASD cases (66.8% male; mean age 52.0 [SD, 8.1]) and 6590 matched non-autistic individuals. ASD were associated with a 90% higher all-cause mortality (HR, 1.90, 95% CI, 1.41–2.55) and also higher risks of 45 medical conditions across almost all body systems (all Bonferroni-adjusted $P < 0.05$). Trajectory analyses exhibited three clusters of medical conditions that predisposed autistic adults to excess mortality: cardiometabolic diseases, external conditions, and infectious diseases. Autistic adults showed not only an overall increased risk of progression of multimorbidity but also distinctive association patterns across different disease transitions.

Conclusions Our findings show patterns of comorbidities among autistic adults in their mid- and later adulthood, which could provide information to their caregivers to implement appropriate disease management and prevention strategies.

Keywords Autistic adult, Disease trajectory, Multicomorbidity, Cohort study

†Yiwei Pu, Feng Li and Tailin Zhu contributed equally to the study and were considered as co-first authors.

*Correspondence:
Tai Ren
rt@shsmu.edu.cn
Fei Li
feili@shsmu.edu.cn
Full list of author information is available at the end of the article

Background

An increasing number of individuals diagnosed with autism spectrum disorder (ASD) have entered their midlife and elderhood. [1] ASD has been recognized to be associated with a variety of mental and somatic comorbidities and almost double the risk of premature mortality during childhood and young adulthood not limited to certain causes of death [2, 3]. In a meta-analysis of 340 studies, developmental coordination disorder, attention-deficit/hyperactivity disorder, overweight/obesity, and epilepsy were identified as common prevalent psychiatric and somatic comorbidities, respectively, in ASD patients [3]. Understanding the progression of comorbidities associated with ASD would provide crucial information to prevent future health decline for autistic adults, their families, and caregivers. However, empirical evidence is limited in middle-aged and elderly autistic individuals [4]. In particular, the progression of the comorbidities and mortality associated with ASD have not been addressed.

Previous studies have predominantly focused on comorbidities during early adulthood [5]. Only three longitudinal studies reported comorbidity patterns among middle-aged and elderly autistic individuals, in which significantly elevated premature mortality rates were observed among autistic adults without intellectual disability, driven by such medical conditions as depression, anxiety, ischemic heart disease, type 2 diabetes, self-harm, etc. [2, 6, 7]. However, the temporal progression of comorbidities and the complex interplay of these concurrent conditions remain under-explored.

This study used longitudinal data from the UK Biobank, linked with National Health Service (NHS) primary care and hospital inpatient records, to characterize disease progression patterns and comorbidity profiles in individuals with ASD. As an exploratory analysis without a priori hypotheses, we aimed to (1) identify medical conditions that may mediate the association between ASD and mortality risk and (2) examine the longitudinal relationship between ASD status and multimorbidity development.

Methods

Study design

Data for this study were based on the UK Biobank, a prospective cohort recruiting over 500,000 individuals aged 40 to 69 years across the UK between 2006 and 2010 [8]. Data on diagnosis and death was identified from national registers in the UK (details in Table S1) [8]. Participation of the study needed voluntarily informed consent and travel to designated locations to complete comprehensive questionnaires and assessments. This process inherently selected individuals with higher cognitive and functional abilities, leading to what has been termed a "healthy volunteer" effect in prior research [9]. Thus, the study population was considered as "cognitively able autistic adults." Autistic individuals were defined by (1) an inpatient diagnosis of ASD coded by ICD-10 (F84.0/1/5/8/9) or (2) a self-reported "diagnosis of ASD by a professional," which was collected in 2016 (responded by ~ 50,000 participants) and 2022 (responded by ~ 170,000 participants), respectively. For each autistic individual, we randomly selected up to 10 non-autistic participants individually matched by birth year (continuous), sex (male or female), Townsend deprivation index (continuous), and respondence status of the self-reported ASD question (yes or no). As the participants who responded at follow-up were necessarily alive and on average healthier than the non-respondents [10], the respondence status was involved in the matching procedure (workflow for details, Fig. S1).

This study included three parts: first, we investigated whether ASD patients had a higher mortality compared with their matched non-ASD individuals. The follow-up started at the date of recruitment or the date of response to the diagnostic question, whichever came later. The follow-up ended on the date of death or 30th December 2022, whichever came first. Data on ASD collected in 2022 were not involved in this analysis because of the short follow-up period. Second, we investigated disease trajectories that linked ASD to mortality using inpatient diagnoses, which were first available in 1997. Follow-up ended on the date of death or 30th December 2022, whichever came first. Third, we investigated the association between ASD and risk of multimorbidity, including three main chronic conditions (cardiovascular disease/hypertension [CVD/HTN], type 2 diabetes mellitus/disorders of lipoprotein metabolism [T2D/DLP], and depression/anxiety [DEP/ANX]) identified in the trajectory analysis. The chronic diseases were identified from both the inpatient and primary care registers [11]. Follow-up started at the first date recorded in the medical record system after the 10th birthday or recruitment time, whichever came first. Follow-up ended on death or 30th December 2022, whichever came first.

Diagnoses of medical conditions and mortality

All UK Biobank participants were regularly linked to the National Death Registries of the UK to update the mortality data [8].The participants were considered to be included in the hospital inpatient data since 1997 [8].

Diagnosis of medical conditions and the date of diagnosis in the trajectory analysis were identified from the primary and secondary diagnoses recorded with ICD-10 in the UK Biobank inpatient data (Data-Field 41,270). The ICD-10 codes were used according to an established method considering the clinical or biological

similarities, resulting in a total of 470 3-digits codes [12]. Only inpatient diagnosis was included in trajectory analysis because it had generally higher validity than the diagnosis in the primary care settings [13]. Based on findings from the disease trajectory analyses, we were further interested in the patterns of multimorbidity of three main chronic conditions: CVD/HTN, T2D/DLP, and DEP/ANX [14–16]. For chronic diseases, diagnoses in the primary care settings have been shown to exhibit comparable or better validity when determine the time of disease onset [11]. Thus, diagnoses of these chronic conditions and dates of diagnoses were identified from the first occurrence data (Category 1712), which integrated information from the primary care data (Category 3000), the hospital inpatient data (Category 2000), death register records (Field 40,001, Field 40,002), and self-reported medical condition (Field 20,002). Diagnostic codes for the three chronic conditions were detailed in Table S2.

Covariates

Covariates for disease and multimorbidity trajectory analyses included birth year (continuous) or age (continuous), sex (male or female), Townsend deprivation index (continuous), and ethnicity/race (white or not-white). Due to the limited number of non-white individuals (< 5% in autistic participants), specific analyses in the disease trajectory included exclusively white individuals, violating the positivity assumption. Thus, we did not adjust for ethnicity/race in disease trajectory analyses. Additional covariates at baseline were described and adjusted for in the survival analysis, including current smoker (yes or no), current drinker (yes or no), body mass index (kg/m^2), number of days per week of moderate physical activity with at least 10 min (continuous), diagnosed intellectual disability (ID; ICD-10 codes F70/F79), and age-adjusted Charlson comorbidity index (0, 1, or ≥ 2) [17]. ID was identified from the first occurrence data. Notably, among the 20 individuals diagnosed with ID, six had completed university education. This finding suggests the possibility of misclassification in ID diagnoses, which may reflect the historically common misdiagnosis of ID and autism [18]. As autistic individuals are commonly comorbid with cognitive problems, we additionally performed a variety of analyses to assess the cognitive functioning, including fluid intelligence scores, reaction time, and prospective memory (specific definition detailed in the supplementary methods).

Statistical analysis

Continuous variables were compared with *t*-test and categorized variables with chi-square test. Cox regression was applied to estimate the hazard ratio (HR) and its confidence interval (CI) of mortality associated with ASD, adjusting for sex, birth year, Townsend deprivation index, respondence status of the self-reported ASD question in 2016, and the covariates as described above.

Disease and mortality trajectory analyses

We evaluated the pattern of progression of medical conditions associated with ASD following an established method [12]. Briefly, we identified (1) diagnoses associated with ASD from 470 medical conditions (of which we selected conditions that occurred in at least 30 autistic individuals [~ 5% of total]) by logistic regression; (2) the sequence of each pair of diagnoses in step 1 by binomial test (> 50%); and (3) the magnitude of associations between each sequential pair in step 2 by logistic regression. Bonferroni corrections for multiple testing were applied in each step. Due to the incomplete records of the diagnoses during childhood in the study population (the earliest record in the inpatient register was of 30 years old), we were unable to determine the exact date of the diagnosis for ASD for Cox regression. Nevertheless, as ASD mostly developed during childhood [19], we a priori assumed that ASD developed before all outcomes in step 2 and measured the associations by odds ratios (ORs) estimated by logistic regression. For comparability, all-cause mortality was also regarded as one condition in this analysis and the associations between other conditions and mortality were also measured by ORs. To enhance interpretability, we categorized the observed disease and mortality trajectories into distinct clusters based on established clinical patterns from previous literature [3, 12, 20].

Multimorbidity trajectory analyses

To evaluate the pattern of progression of multimorbidity associated with ASD, we considered a multistate model that characterized the rate of accumulation of three chronic conditions during the development of multimorbidity and estimate hazard ratios (HRs) for ASD with adjustment for age, sex, and Townsend deprivation index [21]. In this model, states represented all possible combinations of the three conditions (8 states) or death that was the terminal state and could be reached from any other state (Fig. 3a). A state-to-state transition was assumed from a state with fewer conditions to a state with more conditions. Each individual was presumed to have no underlying diseases at the initial state. We assumed that the three chronic conditions were persistent throughout life once diagnosed. For two or more events happening on the same day, the transition would be counted in multiple transitions to the next states, while the individual would move to a state that matched the individual's condition after transition. According to the results from disease trajectory analyses and prior knowledge, we

consider the following conditions in the multimorbidity: depression, anxiety, CVD/HTN (including ischemic heart disease and hypertension), type 2 diabetes mellitus, disorders of lipoprotein metabolism, and cancer. Cancer was excluded from the multistate model due to lack of significant association with ASD (Table S3). To ensure adequate sample sizes for each disease state in the multistate model, we consolidated other conditions according to the ICD-10 classification into three states: depression/anxiety, CVD/HTN, and diabetes mellitus/disorders of lipoprotein metabolism. For example, if individual A was diagnosed with CVD/HTN and T2D/DLP at day 10, this transition would contribute to both "none to CVD/HTN" and "none to T2D/DLP." At the same time, individual A would move from the state "none" to "CVD/HTN + T2D/DLP" at day 10; thus, individual A would not contribute to any transition from "CVD/HTN to CVD/HTN + T2D/DLP" and "T2D to CVD/HTN + T2D/DLP." Individual event-time models were established for each transition, with the time parameter representing the duration from one diagnosis to the subsequent diagnosis or death [21–23]. We employed the "flexsurv" package in the R software environment for implementation.

To account for potential misclassification of ASD due to self-reported diagnosis, we additionally restricted to only inpatient diagnosis of ASD for sensitivity analysis. Given evidence that autistic individuals were disproportionately affected by COVID-19 in terms of mental and physical health outcomes, we conducted sensitivity analyses restricting the follow-up period to December 31, 2019 (pre-pandemic) to evaluate potential temporal effects. Sensitivity analyses of multimorbidity trajectory analyses were also performed to remove self-reported diagnoses to exclude the effect of self-reported time errors on diseases progression analyses. Statistical analyses were conducted using R (version 4.2.2) during the time period October 2023 to March 2024.

Results

The 659 autistic adults (66.8% male; mean age 52.0 [SD, 8.1]) showed comparable baseline characteristics to the matched 6590 non-autistic individuals, such as age, sex, Townsend deprivation index, body mass index, level of physical exercise, and age-adjusted Charlson comorbidity index (Table 1; specific comorbidities were shown in Table S4). Autistic adults were slightly more likely be white and less likely to be a current drinker. Among autistic adults, 2.6% received a diagnosis of intellectual disability (ID), compared with less than 0.1% in the matched control group (Table 1). In addition, autistic adults had a slightly higher fluid intelligence score than the reference group, though this measure was only available in 30% of the study population at baseline. ASD individuals have marginally longer reaction times than controls, with no significant differences in prospective memory (Table S5).

During a median follow-up time of 6.4 years, 52 (11.6%) of the autistic adults died compared to 279 (6.2%) in the reference group (mortality, 12.7 versus 6.7 per 1000 person-years, Fig. 2). ASD was associated with a 90% increased all-cause mortality (HR, 1.90, 95% CI, 1.41–2.55) adjusting for sex, Townsend deprivation index, birth year, and response to the questions collected in 2016. Additional adjustment of race, alcohol consumption, smoking status, fluid intelligence, diagnosis of intellectual disability, reaction time, prospective memory, diagnosis of ID, BMI, and age-adjusted CCI yielded similar results (Table S6).

The median follow-up time for the trajectory analysis was 15.0 years, starting at a mean age of 48.6 (SD, 9.0; range, 28 to 71) years and ended at 65.6 (SD, 8.1; range, 43 to 85) years of age. During the follow-up period, ASD was associated with a higher risk of 45 medical conditions across almost all organ systems (all Bonferroni-adjusted $P < 0.05$; Fig. 1; Table S7). Specifically, ASD was most prominently associated with depression, anxiety, poisoning due to external causes, and malnutrition (ORs > 4). Regarding prevalence, three conditions showed a prevalence exceeding 20% among autistic individuals, including primary hypertension (32%; OR, 1.52, 95% CI, 1.27–1.82), depression (26%; OR, 6.08, 95% CI, 4.96–7.46), and injuries due to external causes (23%; OR, 1.95, 95% CI, 1.60–2.36).

By trajectory analyses, we identified 16 ASD → D1 → Death routes and 2 ASD → D1 → D2 → Death routes (Fig. 2). Among medical conditions that were both associated with ASD and all-cause mortality, we noted three main clusters base on clinical opinion including cardiometabolic diseases (primary hypertension and diabetes mellitus), external conditions (falls, external causes of morbidity related to medical treatment, injuries due to external causes, and complications due to medical treatment), and infectious diseases (bacterial infection, pneumonia, and possible urinary infection). Additionally, we observed a mortality trajectory of cardiometabolic diseases followed by acute renal failure.

We then investigated the association between ASD and the progression pattern of cardiovascular disease/hypertension, diabetes mellitus/disorders of lipoprotein metabolism, and depression/anxiety. The point estimates of HRs were higher than 1 among most progression routes (Fig. 3). Autistic individuals without the diagnosis of CVD/HTN and diabetes mellitus/disorders of lipoprotein metabolism had a 222% increased risk of depression/anxiety (HR, 3.22, 95% CI, 2.70–3.84). Autistic individuals with diabetes mellitus/disorders of lipoprotein metabolism or both CVD/HTN and diabetes mellitus/disorders of lipoprotein metabolism showed 137 to 191% increased

Table 1 Characteristics of individuals at recruitment with and without diagnosis of ASD

Variables	Individuals with no diagnosis of ASD (*N* = 6590)	Individuals diagnosed with ASD (*N* = 659)	*P* value
Age, y			
Mean (SD)	52.0 (8.13)	52.0 (8.18)	0.98
Sex (male)	4409 (66.9%)	440 (66.8%)	0.98
Birth year			
Mean (SD)	1960 (8.18)	1960 (8.22)	0.95
Townsend deprivation index			
Mean (SD)	−0.267 (3.31)	−0.162 (3.35)	0.44
Missing	11 (0.2%)	1 (0.2%)	
Body mass index, kg/m^2			
Mean (SD)	27.3 (4.70)	27.7 (5.89)	0.15
Missing	37 (0.6%)	9 (1.4%)	
White	6070 (92.1%)	618 (93.8%)	0.03
Missing	36 (0.5%)	9 (1.4%)	
Current drinker	6106 (92.7%)	550 (83.5%)	< 0.001
Missing	29 (0.4%)	7 (1.1%)	
Current smoker	807 (12.2%)	86 (13.1%)	0.59
Missing	38 (0.6%)	4 (0.6%)	
Number of days per week of moderate physical activity with 10 + min			
Mean (SD)	3.51 (2.29)	3.39 (2.44)	0.23
Missing	252 (3.8%)	34 (5.2%)	
Intellectual disability			
Yes	3 (0.0%)	17 (2.6%)	< 0.001
No	6587 (100.0%)	642 (97.4%)	
Fluid intelligence			
Mean (SD)	6.26 (2.24)	6.62 (2.59)	0.04
Missing	4212 (63.9%)	411 (62.4%)	
aCCI			
0	2816 (42.7%)	271 (41.1%)	0.24
1	2005 (30.4%)	191 (29.0%)	
≥ 2	1769 (26.8%)	197 (29.9%)	

This table shows the basic characteristics of the depression individuals and their matched individuals without ASD, including age, sex, race, birth year, Townsend deprivation index, body mass index, drinking status, smoking status, level of physical exercise, diagnosis of intellectual disability, fluid intelligence and age-adjusted Charlson comorbidity index. Numbers were expressed as frequency (percentage), unless otherwise indicated. Specific comorbidities were shown in Table S4

ASD autism spectrum disorder, *aCCI* age-adjusted Charlson comorbidity index, *SD* standard deviation

risks of depression/anxiety, though the CIs were wide. The patterns for developing depression/anxiety were similar and the risks were 2- to threefold higher among autistic individuals with CVD/HTN or diabetes mellitus/disorders of lipoprotein metabolism (HR for CVD/HTN, 2.98, 95% CI, 2.04–4.35; HR for diabetes mellitus/disorders of lipoprotein metabolism, 2.37, 95% CI, 1.24–4.52).

In the sensitivity analyses restricted on only inpatient diagnosis of ASD, the associated medical conditions, mortality trajectories, and multimorbidity patterns were consistent (Figs. S3–S7, Tables S8–S11). Patterns of multimorbidity also remained consistent in sensitivity analyses excluding self-reported diagnoses (Fig. S8). Sensitivity analyses excluding post-December 31, 2019 diagnoses (comprising approximately 20% of total diagnoses; Table S12) demonstrated consistency with primary findings (Figs. S9–S10).

Discussion

This study showed a 90% higher all-cause mortality in autistic adults in the UK Biobank study. Given the established link between comorbidity and multimorbidity with increased mortality in older populations, our study sequentially examined the co-occurrence of conditions alongside ASD, the disease and mortality trajectory, and the patterns of multimorbidity progression. ASD was

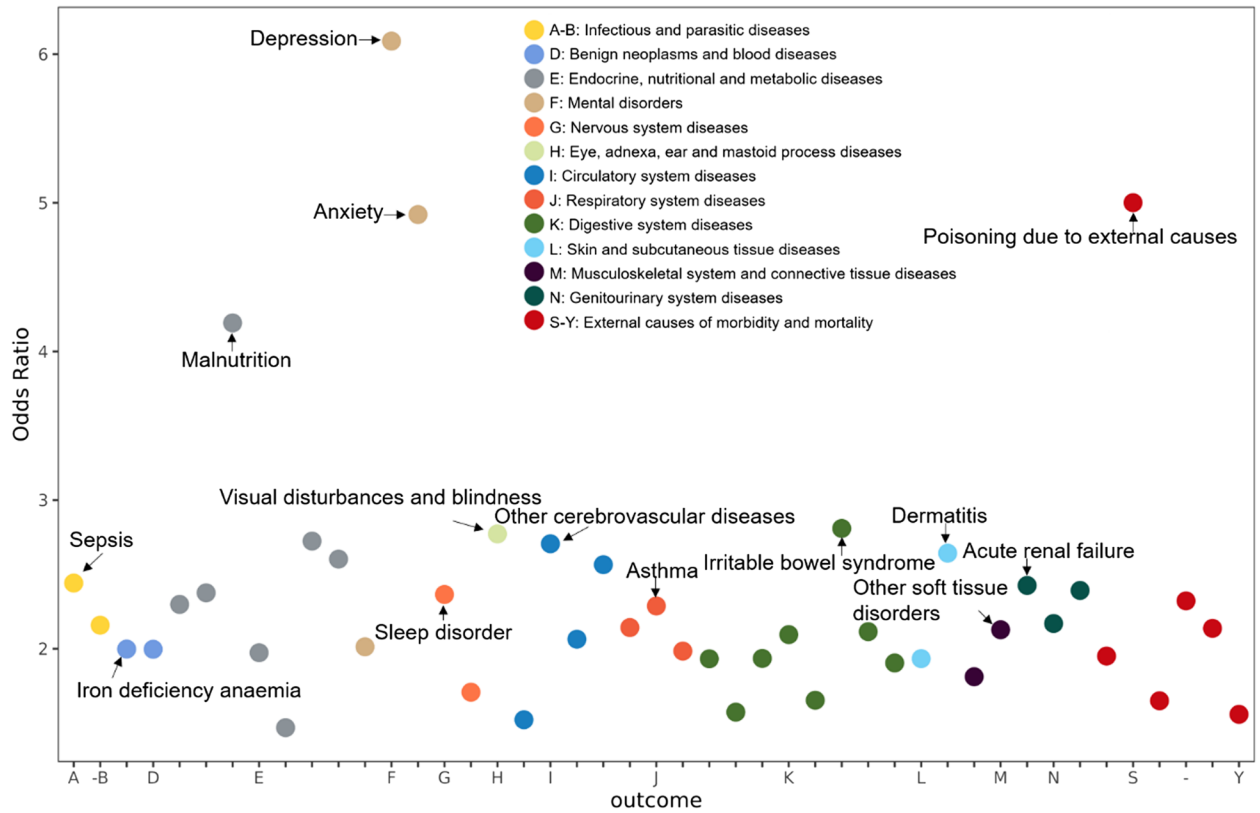

Fig. 1 Odds ratios of medical conditions associated with autism spectrum disorder in the UK Biobank study. The X axis shows the disease categories according to the ICD-10 system. The Y axis shows the odds ratios of medical conditions associated with autism spectrum disorder in the UK Biobank study. Only medical conditions that passed Bonferroni corrected $P < 0.05$ were presented. Detailed risk estimates were listed in Supplementary Table 5

associated with higher risks for 45 medical conditions across almost all organ systems, most prominently with depression, anxiety, poisoning due to external causes, and malnutrition. The disease trajectory analysis highlighted cardiometabolic diseases, external conditions, and infectious diseases to predispose autistic adults to the excess mortality. Regarding multimorbidity, we observed up to threefold risks of depression/anxiety among autistic adults without CVD/HTN and T2D/DLP and 3- to fivefold risk of CVD/HTN and T2D/DLP among autistic adults with preexisting depression or anxiety.

Disease trajectory analysis is a novel approach to understand disease progression and comorbidities using longitudinal data [12, 24, 25], which may reveal the key pathways leading to the deterioration in general health after autism. Consistent with previous studies, we observed that autistic adults had high comorbid rates of psychological disorders and a wide spectrum of somatic problems [4, 26, 27]. Moreover, our study extends previous knowledge by identifying medical conditions that potentially linking ASD to an increased mortality in their later lives. Autistic adults who died were more likely to have been hospitalized for three main clusters of conditions: cardiometabolic diseases, external causes, and infectious diseases during their lifetime [7, 28, 29]. Additionally, we provided novel evidence that autistic adults were at higher risk of multimorbidity, with a pattern of ASD → DEP/ANX → CVD/HTN or T2D/DLP. Though we could not rule out possible common genetic factors between ASD and these conditions, the findings were likely to attribute to suboptimal disease management among autistic adults [7].

ASD contributes significantly to health loss throughout the lifespan for physical and psychological issues. Communication difficulties and impaired social interaction, core symptoms of ASD, can impede healthcare access. Individuals with ASD face challenges in accessing non-emergency medical services, attending healthcare appointments, and seeking emergency care when confronted with external conditions and chronic physical issues [30, 31]. Previous studies highlighted an under-representation of autistic adults in primary care psychological therapy services, leading to worsening of their depressive and anxious symptoms [32]. These

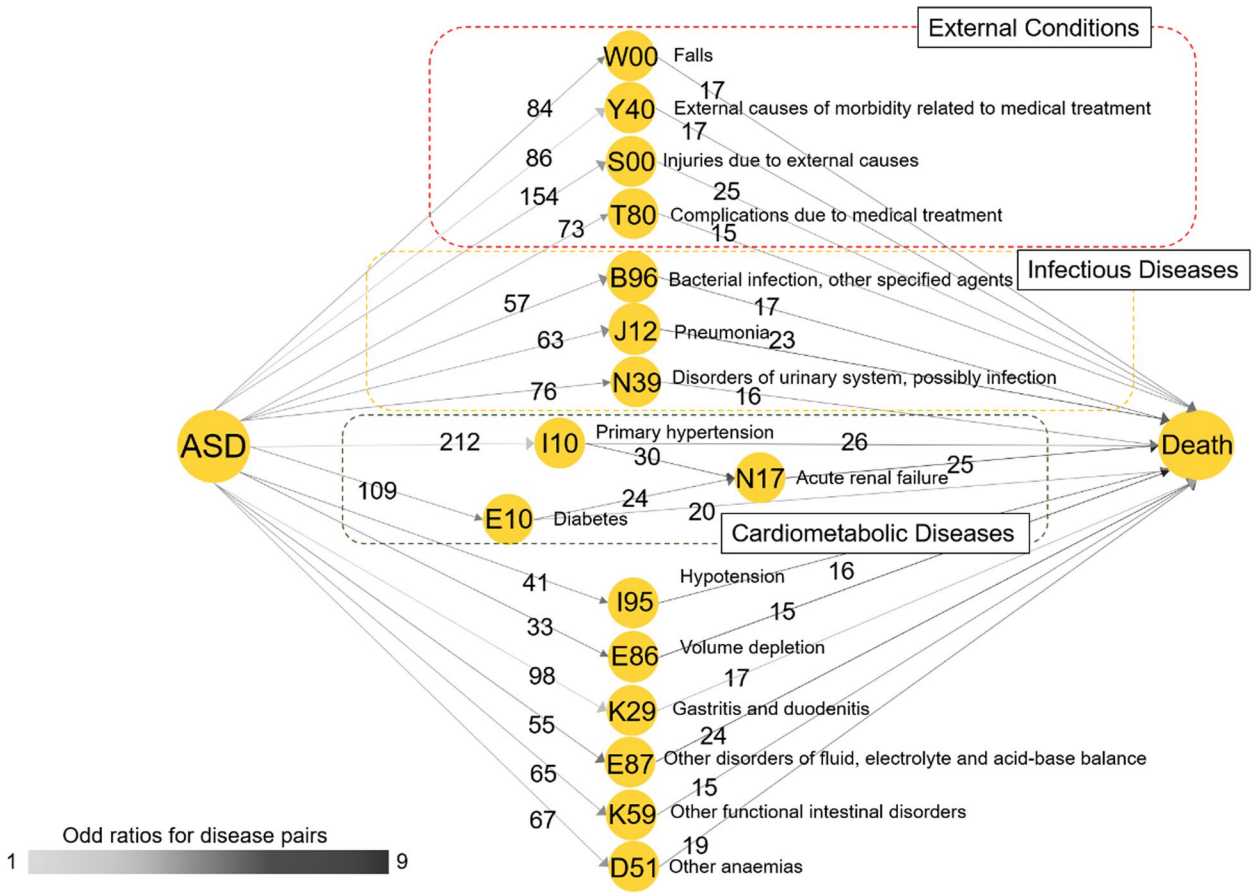

Fig. 2 Disease and mortality trajectories of autism spectrum disorder. Each circle containing a three-digit ICD-10 code represents one type of medical condition. The number above the arrow connecting two circles corresponds to the number of disease pairs among ASD individuals. The color of the arrows indicates the odds ratio of the sequential association between the two medical conditions. We identified three clusters of medical conditions: external conditions, infectious diseases, and cardiometabolic diseases. Red box indicates medical conditions that were related to external conditions. Yellow box indicates medical conditions that were related to infectious diseases. Green box indicates medical conditions that were related to cardiometabolic diseases. ASD, autism spectrum disorder

challenges may delay diagnoses and lead to suboptimal outcomes for both psychiatric and somatic comorbidities. From a healthcare delivery perspective, this highlights the potential inadequacy of the current healthcare system in meeting the needs of autistic adults [33]. The growing population of aging adults with ASD necessitates improved health care services that could address their specific medical needs. In the UK, the Health and Care Act 2022 has taken steps in this direction through the Oliver McGowan training initiative to ensure medical stuff receive training on medical needs for learning disability and ASD. [35, 35] Furthermore, our study also provides information on preventing health declines and premature mortality among autistic adults and their families in their later lives.

Our study observed a nearly twofold higher mortality in autistic adults, consistent with previous studies in younger populations [2, 35]. To be noted, autistic adults in our study were followed-up to their later life and were cognitively able for daily life, evidenced by cognitive function tests such as fluid intelligence, reaction time, and prospective memory. Our finding was in line with a cohort study in England involving ~ 20,000 ASD patients aged 18 to 70 years with no diagnosis of intellectual disability, with a median length of follow-up around 2.3 years [4]. Considering the elevated mortality rates observed in cognitively able autistic adults, it is hypothesized that autistic adults with intellectual disabilities may encounter more severe health challenges as they age. Consequently, there is a pressing need for further research dedicated to the health trajectories of autistic adults with intellectual disabilities.

The study period extending through December 2022 captured the COVID-19 pandemic's impact. Evidence suggests that individuals with ASD experienced disproportionate health effects during this period [35, 35].

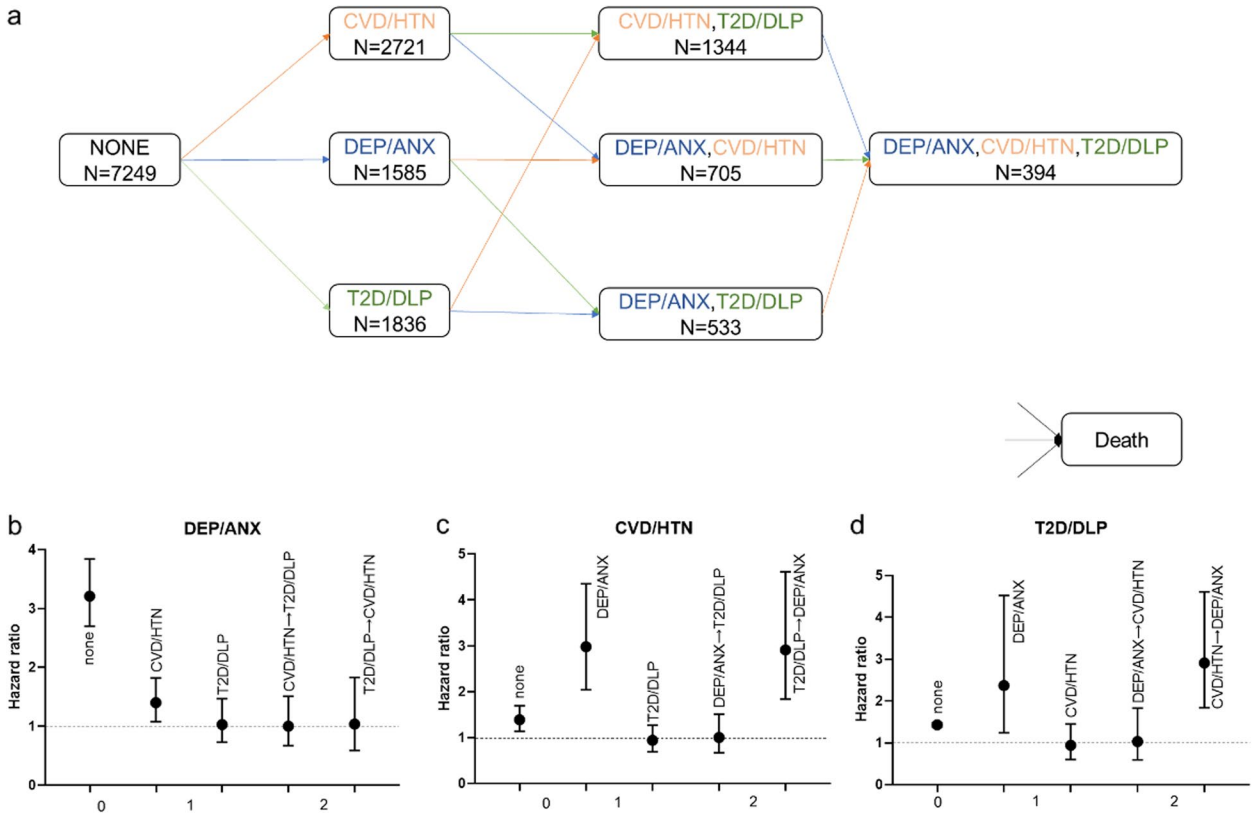

Fig. 3 A multistate model to estimate association between ASD and the rate of morbidity progression. **a** The initial condition, labeled "None," represents participants with no comorbidities at baseline. Intermediate comorbidity states are color coded as follows: cardiovascular disease/hypertension (CVD/HTN, orange), type 2 diabetes and disorders of lipoprotein metabolism (T2D/DLP, green), and depression/anxiety (DEP/ANX, blue). Each colored arrow indicates a transition, with the color corresponding to the condition diagnosed at the time of transition (e.g., blue arrows indicate transitions to a MH diagnosis). The final state "death" is directly accessible from all other states. The "*N*" below each comorbidity state indicates the total number of participants who entered that state during the follow-up period. Figures **b** to **d** show the hazard ratios (HRs) of the association of ASD with an incident diagnosis of **b** DEP/ANX, **c** CVD/HTN, and **d** T2D/DLP, respectively. X axis shows the number of pre-existing comorbidities. HRs were estimated adjusted for age, sex, Townsend deprivation index, and ethnicity. ASD, autism spectrum disorder; DEP/ANX, depression and anxiety; CVD/HTN, cardiovascular disease/hypertension; T2D/DLP, type 2 diabetes and disorders of lipoprotein metabolism; HR, hazard ratio; CI, confidence interval

Given the widespread COVID-19 infection rates in the UK, isolating pandemic-specific effects from underlying health disparities presents methodological challenges. Though our analyses showed consistent results restricting to the time preceding the COVID-19 pandemic [35], the ongoing global presence of COVID-19 may further amplify existing health disparities between individuals with ASD and the general population.

Our findings indicate that ASD participants had higher fluid intelligence scores than non-ASD participants at both baseline and follow-up assessments. This finding, together with the matching procedure for socioeconomic factors, suggests that the ASD group in this study represented a specific subgroup of cognitively able autistic individuals. As a result, it would be inappropriate to generalize these findings to the broader autistic population, particularly those with co-occurring intellectual disabilities.

This study has several strengths. First, the validity of the data from the inpatient registers in the UK Biobank study has been established [8]. Second, we applied novel approaches, including disease trajectory analysis and multimorbidity trajectory analysis, to extend current understanding of the disease and mortality trajectory of ASD. Third, the follow-up covered a period from mid-adulthood to elderhood, addressing an underreported medical need in a growing population of aging autistic adults [4].

Our results should be interpreted in light of several limitations. First, we had no data on the diagnosis date for ASD, which might introduce misclassification in the trajectory analysis when determining the sequence

of medical conditions. Still, as the earliest record in the inpatient register was 30 years of age, the assumption that ASD happened before all inpatient diagnoses were highly likely to be true. Second, autistic participants in the UK Biobank might only represent a subgroup of autistic adults who were cognitively able autistic adults at recruitment [9, 10]. However, the UK Biobank may not capture a representative sample of individuals with low-functioning ASD, which could limit the scope of analyses related to this specific subgroup. Considering the patterns of specific causes of death exhibited notable differences between individuals with low-functioning and high-functioning ASD [2], there is a pressing need for further research dedicated to the health trajectories of autistic adults with intellectual disabilities. Third, the length of follow-up of 6.4 years was relatively short to understand the mortality in the elder populations. We acknowledged this limitation and applied different follow-up windows in the two following trajectory analyses, which covered a follow-up period of 15 years. Fourth, due to the limited sample size in this study, stratified analysis by sex or age was not feasible for analysis. Fifth, the accuracy of the observed mortality may have been affected by the relatively short follow-up period. Last, we had no data to further investigate the potential mechanism underlying the observed patterns of disease progression.

Conclusions

The cognitively able autistic adults in the UK Biobank study showed a 90% higher all-cause mortality. The disease trajectory analysis highlighted cardiometabolic diseases, external conditions, and infectious diseases to predispose autistic adults to the excess mortality. Regarding multimorbidity including CVD/HTN, T2D/DLP, and depression/anxiety, autistic adults showed not only an overall increased risk of progression but also distinctive association patterns. This study presented novel evidence on the disease, multimorbidity, and mortality trajectory of ASD in midlife and elderhood. These findings may inform autistic adults, their families, and primary care providers to implement better disease management and prevention strategies.

Abbreviations

aCCI	Age-adjusted Charlson comorbidity index
ASD	Autism spectrum disorder
CI	Confidence interval
CVD/HTN	Cardiovascular disease/hypertension
DEP/ANX	Depression/anxiety
HR	Hazard ratio
NHS	National Health Service
OR	Odds ratio
T2D/DLP	Type 2 diabetes mellitus/disorders of lipoprotein metabolism

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04095-x.

Additional file 1: Supplementary methods—fluid intelligence test. Fig. S1. Workflow. Fig. S2. Survival analysis. Fig. S3. Survival analysis, restricting on only inpatient diagnosis of autism spectrum disorder. Fig. S4. Odds ratios of medical conditions associated with autism spectrum disorder, restricting on only inpatient diagnosis of autism spectrum disorder. Fig. S5. Disease trajectories of ASD individuals, restricting on only inpatient diagnosis of autism spectrum disorder. Fig. S6. The multistate diagram depicting disease progression restricting on only inpatient diagnosis of autism spectrum disorder. Fig. S7. Estimated association between ASD and the rate of next disease transition, restricting on only inpatient diagnosis of autism spectrum disorder. Fig. S8. A multistate model to estimate association between ASD and the rate of morbidity progression excluding diagnoses from self-reported data. Fig. S9. Odds ratios of medical conditions associated with autism spectrum disorder in the UK Biobank study before COVID. Fig. S10 A multistate model to estimate association between ASD and the rate of morbidity progression before COVID. Table S1. Details of data on diagnoses and deaths. Table S2. Codes for the three chronic conditions. Table S3. Prevalence of malignant neoplasm. Table S4. Comorbidities at recruitment of individual with or without diagnosis of autism spectrum disorder in hospital inpatient records. Table S5. Cognitive function tests. Table S6. Survival analysis. Table S7. Medical conditions associated with autism spectrum disorder. Table S8. Characteristics of individuals at recruitment with and without diagnosis of ASD, restricting on only inpatient diagnosis of autism spectrum disorder. Table S9. Comorbidities at recruitment of individual with or without diagnosis of autism spectrum disorder in hospital inpatient records, restricting on only inpatient diagnosis of autism spectrum disorder. Table S10. Survival analysis, restricting on only inpatient diagnosis of autism spectrum disorder. Table S11. Medical conditions associated with autism spectrum disorder restricted on only inpatient diagnosis of ASD. Table S12. Distribution of diagnoses before and after the COVID-19 pandemic.

Acknowledgements

This research has been conducted using the UK Biobank Resource under Application Number 94522. The computations in this paper were run on the π 2.0 (or the Siyuan-1) cluster supported by the Center for High Performance Computing at Shanghai Jiao Tong University.

Role of the funder/sponsor

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Authors' contributions

FL1 (Fei Li) and TR designed the study. TR and YP conducted data analysis. YP, TZ, and FL2 (Feng Li) drafted the manuscript. YP, TR, TZ, FL1, and FL2 contributed to data interpretation and critically revised the manuscript. JL performed linguistic revision and editorial refinement of the manuscript. FL1, TR, and TZ acquired funding. WZ, LZ, JC and QZ provided administrative, technical, or material support. provided administrative, technical, or material support. FL1 and TR supervised the research. The corresponding author attests that all the listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors read and approved the final manuscript.

Funding

This study was supported by grants from the National Natural Science Foundation of China (82125032, 81930095, 82204048, and 82301729), the China Brain Initiative Grant (STI2030-Major Projects 2021ZD0200800), China Postdoctoral Science Foundation (2022M712125), the Science and Technology Commission of Shanghai Municipality (23Y21900500, 19410713500, and 2018SHZDZX01), the Shanghai Municipal Commission of Health and Family Planning (GWV-11.1-34, 2020CXJQ01, and 2018YJRC03), Innovative research team of high-level local universities in Shanghai (SHSMU-ZDCX20211100), and the Guangdong Key Project (2018B030335001).

Data availability
This research has been conducted using the UK Biobank Resource under Application Number 94522. All researchers who wish to access the research resource must register with UK Biobank by completing the registration form in the Access Management System (AMS- https://bbams.ndph.ox.ac.uk/ams/).

Declarations

Ethics approval and consent to participate
Ethical approval for the UK Biobank study protocol was granted by the Northwest Multi-center Research Ethics Committee (MREC reference: 21/NW/0157). Written informed consent was obtained from all participants prior to their enrollment in the research program.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Developmental and Behavioural Paediatric & Child Primary Care & Ministry of Education—Shanghai Key Laboratory of Children's Environmental Health, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China. [2]Department of Epidemiology, Nanjing Medical University, Nanjing, China.

Received: 12 June 2024 Accepted: 24 April 2025
Published online: 13 May 2025

References

1. Hirota T, King BH. Autism spectrum disorder: a review. JAMA. 2023;329(2):157–68.
2. Hirvikoski T, Mittendorfer-Rutz E, Boman M, Larsson H, Lichtenstein P, Bölte S. Premature mortality in autism spectrum disorder. Br J Psychiatry. 2016;208(3):232–8.
3. Micai M, Fatta LM, Gila L, et al. Prevalence of co-occurring conditions in children and adults with autism spectrum disorder: a systematic review and meta-analysis. Neurosci Biobehav Rev. 2023;155: 105436.
4. O'Nions E, Lewer D, Petersen I, et al. Estimating life expectancy and years of life lost for autistic people in the UK: a matched cohort study. Lancet Reg Health Eur. 2024;36:100776.
5. Mason D, Stewart GR, Capp SJ, Happé F. Older age autism research: a rapidly growing field, but still a long way to go. Autism Adulthood. 2022;4(2):164–72.
6. Vohra R, Madhavan S, Sambamoorthi U. Comorbidity prevalence, healthcare utilization, and expenditures of Medicaid enrolled adults with autism spectrum disorders. Autism. 2017;21(8):995–1009.
7. Liu S, Larsson H, Kuja-Halkola R, Lichtenstein P, Butwicka A, Taylor MJ. Age-related physical health of older autistic adults in Sweden: a longitudinal, retrospective, population-based cohort study. Lancet Healthy Longev. 2023;4(7):e307–15.
8. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12(3): e1001779.
9. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. Am J Epidemiol. 2017;186(9):1026–34.
10. Legge SE, Pardiñas AF, Woolway G, et al. Genetic and phenotypic features of schizophrenia in the UK Biobank. JAMA Psychiatry. 2024;81(7):681–90.
11. Clifton L, Liu X, Collister JA, Littlejohns TJ, Allen N, Hunter DJ. Assessing the importance of primary care diagnoses in the UK Biobank. Eur J Epidemiol. 2024;39(2):219–29.
12. Han X, Hou C, Yang H, et al. Disease trajectories and mortality among individuals diagnosed with depression: a community-based cohort study in UK Biobank. Mol Psychiatry. 2021;26(11):6736–46.
13. Sarkar U, Bonacum D, Strull W, et al. Challenges of making a diagnosis in the outpatient setting: a multi-site survey of primary care physicians. BMJ Qual Saf. 2012;21(8):641–8.
14. Cortese S, Gabellone A, Marzulli L, et al. Association between autism spectrum disorder and diabetes: systematic review and meta-analysis. Neurosci Biobehav Rev. 2022;136: 104592.
15. Goldstein BI, Korczak DJ. Links between child and adolescent psychiatric disorders and cardiovascular risk. Can J Cardiol. 2020;36(9):1394–405.
16. Stadnick NA, Martinez K, Coleman KJ, et al. Mental health screening in pediatric primary care for children with autism. Autism. 2022;26(5):1305–11.
17. Koppie TM, Serio AM, Vickers AJ, et al. Age-adjusted Charlson comorbidity score is associated with treatment decisions and clinical outcomes for patients undergoing radical cystectomy for bladder cancer. Cancer. 2008;112(11):2384–92.
18. Fusar-Poli L, Brondino N, Politi P, Aguglia E. Missed diagnoses and misdiagnoses of adults with autism spectrum disorder. Eur Arch Psychiatry Clin Neurosci. 2022;272(2):187–98.
19. Geschwind DH. Advances in autism. Annu Rev Med. 2009;60:367–80.
20. Li J, Xia D, Cui M, et al. Disease trajectories before dementia: evidence from a large-scale community-based prospective study. Br J Psychiatry. 2024;225(6):538–46.
21. Chen S, Marshall T, Jackson C, et al. Sociodemographic characteristics and longitudinal progression of multimorbidity: a multistate modelling analysis of a large primary care records dataset in England. PLoS Med. 2023;20(11): e1004310.
22. Crowther MJ, Lambert PC. Parametric multistate survival models: flexible modelling allowing transition-specific distributions with application to estimating clinically useful measures of effect differences. Stat Med. 2017;36(29):4719–42.
23. Jackson CH. Flexsurv: a platform for parametric survival modeling in R. J Stat Softw. 2016;70:i08.
24. Siggaard T, Reguant R, Jorgensen IF, et al. Disease trajectory browser for exploring temporal, population-wide disease progression patterns in 7.2 million Danish patients. Nat Commun. 2020;11(1):4952.
25. Kjærsgaard Andersen R, Jørgensen IF, Reguant R, Jemec GBE, Brunak S. Disease trajectories for hidradenitis suppurativa in the Danish population. JAMA Dermatol. 2020;156(7):780–6.
26. van Heijst BF, Deserno MK, Rhebergen D, Geurts HM. Autism and depression are connected: a report of two complimentary network studies. Autism. 2020;24(3):680–92.
27. Ward JH, Weir E, Allison C, Baron-Cohen S. Increased rates of chronic physical health conditions across all organ systems in autistic adolescents and adults. Mol Autism. 2023;14(1):35.
28. Lai MC, Kassee C, Besney R, et al. Prevalence of co-occurring mental health diagnoses in the autism population: a systematic review and meta-analysis. Lancet Psychiatry. 2019;6(10):819–29.
29. Schott W, Tao S, Shea L. Co-occurring conditions and racial-ethnic disparities: Medicaid enrolled adults on the autism spectrum. Autism Res. 2022;15(1):70–85.
30. Schott W, Tao S, Shea L. Emergency visits for autistic children and children with ADHD. Pediatrics. 2022;149(Suppl 4):e2020049437V.
31. Weir E, Allison C, Baron-Cohen S. Autistic adults have poorer quality healthcare and worse health based on self-report data. Mol Autism. 2022;13(1):23.
32. El Baou C, Bell G, Saunders R, et al. Effectiveness of primary care psychological therapy services for treating depression and anxiety in autistic adults in England: a retrospective, matched, observational cohort study of national health-care records. Lancet Psychiatry. 2023;10(12):944–54.
33. Catchpole J. Navigating a system not built for us: autism and primary care talking therapies. Lancet Psychiatry. 2023;10(12):913–4.
34. NHS England. The Oliver McGowan Mandatory Training on Learning Disability and Autism. 2024. https://www.hee.nhs.uk/our-work/learning-disability/current-projects/oliver-mcgowan-mandatorytraining-learning-disability-autism/background.
35. Murray SA, Boyd K, Moine S, et al. Using illness trajectories to inform person centred, advance care planning. BMJ (Clinical research ed). 2024;384: e067896.

36. Catalá-López F, Hutton B, Page MJ, et al. Mortality in persons with autism spectrum disorder or attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. JAMA Pediatr. 2022;176(4):e216401.
37. Zhang L, Ren T, He H, et al. Protective factors for children with autism spectrum disorder during COVID-19-related strict lockdowns: a Shanghai autism early developmental cohort study. Psychol Med. 2024;54(6):1102–12.
38. Randall KN, McKown GL. Perceived impact of the COVID-19 pandemic on adults with intellectual and developmental disability: a qualitative study. J Intellect Disabil. 2024;28(1):118–36.
39. Li J, Zhou Y, Ma J, et al. The long-term health outcomes, pathophysiological mechanisms and multidisciplinary management of long COVID. Signal Transduct Target Ther. 2023;8(1):416.

Publisher's Note