Psychiatric symptoms and disorders in extremely preterm young adults at 19 years of age and longitudinal findings from middle childhood

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Facebook text: Babies born more than 14 weeks early doing well as adults. A study following the development of extremely premature babies in the UK and Ireland has found no increased risk for mental health disorders in young adulthood. Building on earlier work published in @JAACAP, researchers of the UK EPICure Study <link to epicure study facebook page> have followed up a cohort of babies born extremely preterm to 19 years of age. Findings reveal that, although extremely preterm young adults are more likely to be shy and anxious, they may overcome earlier mental health difficulties experienced in childhood.

Twitter: Study published today in @JAACAP shows extremely #preterm survivors may overcome earlier mental health difficulties by young adulthood <link to article>. New findings from the @EPICurestudy of outcomes after extremely #preterm birth.

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the study and to interpretation of data, critically revised the letter for important intellectual content, approved the final version for submission, and agrees to be accountable for all aspects of the work.

Dear Editor,

Since the 1980s, the long term outcomes of extremely preterm birth, before 28 weeks of gestation, have garnered considerable interest as a result of significant improvements in neonatal care and the consequent increase in survival rates. Compared with birth at full term, extremely preterm birth places infants at increased risk for neurodevelopmental disorders, intellectual impairments and psychiatric sequelae that persist throughout childhood and adolescence.[1] There is now increasing interest as to the longer term outcomes for these babies; in particular, whether adverse outcomes persist or increase in adulthood, or whether survivors may outgrow earlier problems.

To determine the impact of extremely preterm birth in the era of contemporary neonatal care, we identified all babies born before 26 weeks of gestation in the whole of the UK and Ireland from March through December in 1995 – the EPICure cohort – and subsequently assessed their development at 2, 6 and 11 years of age. At 11 years of age we assessed 219 of the children who were born extremely preterm (71% of survivors) alongside 153 term-born controls[2], and evaluated psychiatric outcomes for the first time in this population. In this journal in 2010, we reported that 23% of extremely preterm children had a psychiatric disorder compared with 9% of children born at term (OR 3.2; 95% CI 1.7 to 6.2).[3] Although there was no difference between groups in the prevalence of conduct disorders, extremely preterm children were at significantly increased risk for attention deficit/hyperactivity disorder (ADHD) inattentive sub-type (11.5% vs. 2.9%), emotional disorders (9.0% v. 2.1%) and autism spectrum disorder (8.0% vs. 0%). These results raised concern about the high prevalence of psychiatric sequelae among extremely preterm survivors and the potential impact on their future health and well-being.

To date, outcomes in adulthood have only been reported for cohorts of babies born with extremely low birthweight (ELBW; <1000g) or very low birthweight (VLBW; <1500g) in the 1970s and 1980s. Whilst registry linkage studies have shown an increased risk for psychiatric disorders in extremely preterm adults[4,5], the results of cohort studies are mixed: some have found an increased risk for ADHD,[6,7] mood and anxiety disorders[8] and psychiatric disorders[8,9], whereas others have not.[10-12] Moreover, these cohorts include very few, if any, survivors born before 26 weeks of gestation, in whom persistent high rates of disorders might be anticipated. As such, outcomes in adulthood for extremely preterm babies born after the advent of contemporary neonatal care are unknown.

Therefore, to determine how some of the first survivors of extreme prematurity have fared over the transition to adulthood, we recently evaluated the EPICure cohort at 19 years of age, at which time 192 of the extremely preterm young adults (42% of survivors) and 65 of the term-born controls (42% of those assessed at 11 years) were re-assessed. This assessment included use of the Achenbach Adult Self Report Scale (ASR)[13] to examine psychiatric symptoms completed by the participants themselves. T-scores (Mean 50; SD 10) were derived for broadband scales (internalising and externalising), syndrome scales (statistically constructed through factor analysis of problem items which identified the following syndromes: anxious/depressed, withdrawn, somatic complaints, thought problems, attention problems, aggressive behaviour, rule-breaking behaviour and intrusive behaviour) and DSM oriented scales (proposed to be consistent with the DSM-IV diagnostic categories of depression, anxiety, somatic problems, avoidant personality, ADHD and antisocial personality). These were compared to empirically derived cut-points to identify participants with clinically significant difficulties.[14]

Participants were also assessed using the Clinical Interview Schedule-Revised (CIS-R)[15] to determine the nature and severity of neurotic symptoms and identify depressive disorders,

anxiety disorders and obsessive-compulsive disorders using ICD-10 diagnostic criteria. In addition, IQ was assessed using the Wechsler Abbreviated Scale of Intelligence 2nd Edition, and severe neurodevelopmental disability (one or more of IQ < -3 SD, blindness, deafness or severe neuro-motor impairment) was assessed by a clinician. Socio-economic status (SES) was also classified using parental occupation. A detailed description of the methods and statistical analysis is provided in the supplementary information and the characteristics of the cohort are shown in Table S1, available online (Supplement 1).

There were no significant differences in age, sex and SES between the extremely preterm and term-born adults assessed at 19 years of age, however preterm adults had significantly lower IQ scores (difference in means -18.0 points; 95% CI -22.5 to -13.5), as expected.

ASR questionnaires were completed for 116 preterm adults and 62 controls, the results of which are shown in Table 1. Differences between groups were analysed before and after adjustment for age, sex and SES. Correction for multiple comparisons was applied using the False Discovery Rate procedure.[16] Extremely preterm adults had significantly higher scores for internalising problems on broadband scales; for anxiety/depression, withdrawn and attention problems on syndrome scales; and similarly for depression, anxiety and avoidant personality on DSM scales. After adjustment for confounders and multiple comparisons, extremely preterm adults had a higher score only on the DSM anxiety scale. However, after additionally excluding participants with neurodevelopmental disability, extremely preterm adults had significantly higher scores on the withdrawn personality syndrome scale, and the depression, anxiety and avoidant personality DSM scales.

Although these mean scores were higher, using cut-offs for clinically significant difficulties, there were no statistically significant between-group differences in the prevalence of problems on any ASR scale.

The CIS-R was completed by 120 extremely preterm adults and 64 controls, the results of which are shown in Table 2. There were no statistically significant differences between preterm and term-born adults in any primary CIS-R diagnosis or in the proportions with sub-clinical symptomatology. Excluding those with neurodevelopmental disability did not alter the results appreciably.

We were also interested in the association between psychiatric disorders at 11 and 19 years of age among the extremely preterm participants, the results of which are shown in Table S2, available online (Supplement 1). In unadjusted analyses, we found that extremely preterm participants with a psychiatric disorder at age 11 were more likely to have a mood or anxiety disorder, or clinically significant symptoms of such, at 19 years of age (RR 1.82; 95% CI 1.02, 3.24) and to have avoidant personality problems (RR 3.32; 95% CI 1.39, 7.94). After adjusting for sex and SES, the association remained significant for avoidant personality problems only.

As high SES may protect against the development of psychopathology, we explored changes in the prevalence of disorders from 11 to 19 years of age stratified by SES for extremely preterm participants assessed at both ages. As shown in Figure S1, available online (Supplement 1), there was no discernible difference in the change in prevalence of disorders over time by SES sub-group. However, these results are for descriptive purposes only given the small number of participants in each SES sub-group and should be interpreted with caution.

Together, these results show that, on a population level, the increased risk for childhood psychiatric disorders does not persist into young adulthood among extremely preterm survivors. These results may be contrary to expectation given the increased risk for mental health disorders reported for extremely preterm/VLBW adults in registry linkage studies.[4,5,17]

However such studies may overestimate the prevalence of disorders as preterm adults may be in contact with healthcare services more often in general and thus results may reflect increased referral to psychiatric services rather than increased presence of disorders. Therefore, cohort studies are needed to avoid such potential bias. Indeed, our results are similar to other cohort studies which have failed to find evidence of increased risk for mood or anxiety disorders in VLBW adults.[7,9-12]

We did however find significantly more frequent symptoms of anxiety and depression and more withdrawn and avoidant personality traits among extremely preterm adults. These results are similar to other studies in which outcomes consistent with a socially withdrawn personality have been reported among VLBW adults.[18-20] This suggests that although mental health disorders may not be more common among extremely preterm young adults, as a group they may be less socially engaged and suffer more social withdrawal and anxiety than their term-born counterparts. Notably, we found that extremely preterm adults with a psychiatric disorder at 11 years of age were significantly more likely to have avoidant personality at 19 years of age. Thus earlier disorders may manifest in adulthood as social withdrawal and avoidant personality problems. The aetiology of these is likely to be multifaceted including genetic influences, alterations in brain structure and function as a consequence of immaturity at birth, environmental influences related to prolonged neonatal care, and adverse peer experiences such as bullying.[21]

The strengths of this study lie in the recruitment of a national cohort of babies born before 26 weeks of gestation in 1995, thus providing the earliest population-based data on adult outcomes for extremely preterm babies born in the 1990s. Limitations include the 42% follow-up rate observed in both groups which represents a trend towards decreased public engagement in research and the difficulty in tracing individuals themselves rather than their parents as before. As those lost to follow-up had lower SES, higher rates of cognitive

impairment and lower developmental test/IQ scores at 2.5, 6 and 11 years of age (Table S1), our results may under-estimate the proportion of extremely preterm adults with disorders. However, there was no significant difference in the prevalence of psychiatric disorders at 11 years of age between those assessed and those lost to follow-up, demonstrating that those assessed were representative of the total cohort in terms of childhood psychiatric problems (Table S1, Supplement 1, available online). We used robust methods to explore differences between groups, including the application of the False Discovery Rate procedure to reduce the risk of Type I error. Therefore any differences observed are likely to be true differences. However, we acknowledge that this may have increased the likelihood of a Type II error given the small sample size and thus limited power for detecting between-group comparisons, as reflected in the confidence intervals.

In conclusion, in the latest follow up of the EPICure cohort, we found no evidence of an increased risk for psychiatric symptoms and disorders among young adults born extremely preterm. These results are reassuring and suggest that extremely preterm survivors may overcome earlier psychiatric difficulties. It is important to interpret these results in light of other outcomes including social outcomes and quality of life which will be the subject of future reports.

Yours faithfully,

<<Authors blinded>>

Table 1 Group Differences in Mean T-Scores and Risk For Clinically Significant Difficulties on the Achenbach Adult Self Report Scale in Extremely Preterm Adults and Term-Born Controls Assessed at 19 Years of Age

			Difference in Mean T score							
	EP Mean (SD) n=116	**Control Mean (SD)** n=62	**Unadjusted Mean Difference (95% CI)**	***P***	**Adjusted for age, sex and SES[a] Mean Difference (95% CI)** EP n= 114; Control n=61	***P***	**Benjamini-Hochberg adjusted P value[c]**	**Adjusted for age, sex, SES[a] and excluding disability[b] Mean Difference (95% CI).** EP n= 104; Control n=61	***P***	**Benjamini-Hochberg adjusted P value[c]**
Broadband Scales										
Internalising problems	52.8 (14.2)	48.0 (13.3)	4.9 (0.5, 9.2)	0.028	3.8 (-0.4, 8.0)	0.076	0.228	4.1 (-0.2, 8.4)	0.065	0.195
Externalising problems	48.1 (11.5)	48.0 (11.7)	0.1 (-3.5, 3.7)	0.959	-0.9 (-4.4, 2.6)	0.600	0.600	-1.2 (-4.7, 2.4)	0.521	0.521
Total problems	49.1 (12.6)	45.8 (12.3)	3.3 (-0.6, 7.2)	0.096	2.3 (-1.5, 6.1)	0.240	0.360	2.4 (-1.5, 6.3)	0.224	0.336
Syndrome Scales										
Anxious/depressed	58.1 (10.1)	54.8 (8.6)	3.3 (0.4, 6.1)	0.025	5.5 (0.8, 10.0)	0.021	0.056	6.1 (1.4, 10.8)	0.012	0.096
Withdrawn	56.5 (9.2)	53.4 (7.6)	3.1 (0.5, 5.6)	0.018	5.4 (1.0, 9.9)	0.017	0.068	5.6 (1.0, 10.1)	0.017	0.045[d]
Somatic complaints	55.0 (8.3)	54.7 (7.8)	0.4 (-2.2, 2.9)	0.777	-1.8 (-5.8, 2.3)	0.386	0.441	-2.2 (-6.2, 1.8)	0.274	0.365
Thought problems	54.5 (7.5)	52.9 (6.0)	1.6 (-0.4, 3.7)	0.113	2.4 (-1.6, 6.4)	0.242	0.323	2.0 (-2.1, 6.1)	0.342	0.391
Attention problems	57.1 (8.2)	53.9 (5.9)	3.2 (1.1, 5.2)	0.003	4.1 (0.8, 7.4)	0.016	0.128	4.1 (0.8, 7.4)	0.015	0.060
Aggressive behaviour	54.7 (6.9)	53.9 (6.5)	0.8 (-1.3, 2.9)	0.457	0.9 (-2.5, 4.3)	0.602	0.602	1.1 (-2.3, 4.6)	0.527	0.527
Rule-breaking behaviour	53.4 (5.2)	54.3 (6.6)	-0.9 (-2.7, 0.9)	0.342	-2.3 (-5.0, 0.4)	0.092	0.184	-2.6 (-5.5, 0.2)	0.070	0.140
Intrusive	52.2 (4.2)	53.0 (5.2)	-0.8 (-2.2, 0.6)	0.273	-2.0 (-4.9, 0.9)	0.170	0.272	-2.5 (-5.3, 0.3)	0.080	0.128
DSM Scales										
Depression	56.7 (9.9)	53.9 (7.2)	2.9 (0.3, 5.4)	0.029	3.8 (-0.9, 8.5)	0.109	0.218	4.4 (-0.3, 9.0)	0.066	0.033[d]
Anxiety	55.9 (7.0)	53.4 (5.8)	2.6 (0.6, 4.5)	0.011	4.0 (0.8, 7.3)	0.016	0.048[d]	4.6 (1.3, 7.8)	0.007	0.001[d]
Somatic problems	54.7 (8.2)	54.5 (7.4)	0.1 (-2.3, 2.6)	0.917	-1.7 (-6.1, 2.6)	0.430	0.516	-2.5 (-6.8, 1.8)	0.325	0.271
Avoidant personality	58.8 (9.6)	55.1 (8.5)	3.7 (1.0, 6.5)	0.008	4.7 (0.9, 8.5)	0.015	0.090	5.1 (1.2, 9.0)	0.011	0.004[d]
Attention deficit/hyperactivity	56.5 (8.8)	54.4 (6.8)	2.1 (-0.2, 4.5)	0.072	2.2 (-1.3, 5.7)	0.210	0.315	2.2 (-1.3, 5.7)	0.217	0.145
Antisocial personality	53.2 (5.9)	53.3 (6.5)	-0.1 (-2.0, 1.8)	0.919	-0.9 (-4.5, 2.7)	0.613	0.613	-1.2 (-5.0, 2.5)	0.518	0.518

			Risk for clinically significant difficulties							
	EP n (%) n=116	**Control n (%)** n=62	**Unadjusted OR (95% CI)**	***P***	**Adjusted for age, sex and SES[a] OR (95% CI)** EP n= 114; Control n=61	***P***	**Benjamini-Hochberg adjusted P value[c]**	**Adjusted for age, sex, SES[a] and excluding disability[b] OR (95% CI)** EP n= 104; Control n=61	***P***	**Benjamini-Hochberg adjusted P value[c]**

Broadband Scales										
Internalising problems	25 (21.6)	8 (12.9)	1.85 (0.78, 4.40)	0.161	1.78 (0.71, 4.44)	0.216	0.648	1.89 (0.75, 4.77)	0.175	0.525
Externalising problems	12 (10.3)	7 (11.3)	0.91 (0.34, 2.43)	0.846	0.81 (0.27, 2.42)	0.703	0.703	0.80 (0.26, 2.47)	0.697	0.697
Total problems	17 (14.7)	5 (8.1)	1.96 (0.69, 5.59)	0.209	1.61 (0.55, 4.77)	0.387	0.581	1.64 (0.55, 4.92)	0.376	0.564
Syndrome Scales										
Anxious/depressed	16 (13.8)	3 (4.8)	3.15 (0.88, 11.25)	0.078	2.99 (0.82, 10.91)	0.098	0.784	3.31 (0.90, 12.12)	0.071	0.568
Withdrawn	15 (12.9)	3 (4.8)	2.92 (0.81, 10.51)	0.101	2.79 (0.75, 10.44)	0.128	0.512	2.83 (0.74, 10.72)	0.127	0.508
Somatic complaints	8 (6.9)	4 (6.5)	1.07 (0.31, 3.72)	0.910	0.87 (0.24, 3.19)	0.838	1.117	0.77 (0.20, 2.96)	0.705	0.940
Thought problems	9 (7.8)	2 (3.2)	2.52 (0.53, 12.06)	0.246	1.87 (0.37, 9.40)	0.449	0.898	2.12 (0.42, 10.76)	0.365	0.973
Attention problems	9 (7.8)	3 (4.8)	1.65 (0.43, 6.35)	0.463	1.67 (0.41, 6.74)	0.471	0.754	1.62 (0.39, 6.73)	0.507	0.811
Aggressive behaviour	3 (2.6)	2 (3.2)	0.80 (0.13, 4.90)	0.806	n/a	n/a	n/a	n/a	n/a	n/a
Rule-breaking behaviour	3 (2.6)	3 (4.8)	0.52 (0.10, 2.67)	0.435	0.37 (0.06, 2.32)	0.288	0.768	0.44 (0.07. 2.83)	0.390	0.780
Intrusive	0 (0.0)	1 (1.6)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
DSM Scales										
Depression	18 (15.5)	4 (6.5)	2.66 (0.86, 8.25)	0.090	2.55 (0.81, 8.03)	0.111	0.333	2.63 (0.82, 8.36)	0.102	0.306
Anxiety	8 (6.9)	2 (3.2)	2.22 (0.46, 10.80)	0.322	2.10 (0.41, 10.78)	0.376	0.752	2.24 (0.44, 11.54)	0.334	0.668
Somatic problems	6 (5.2)	4 (6.5)	0.79 (0.21, 2.92)	0.725	0.65 (0.16, 2.59)	0.537	0.644	0.53 (0.12, 2.28)	0.388	0.582
Avoidant personality	19 (16.4)	4 (6.5)	2.84 (0.92, 8.76)	0.069	2.76 (0.88, 8.67)	0.082	0.492	2.86 (0.90, 9.07)	0.073	0.438
Attention deficit/hyperactivity	9 (7.8)	5 (8.1)	0.96 (0.31, 3.00)	0.942	0.92 (0.28, 3.02)	0.892	0.892	0.90 (0.27, 3.06)	0.868	0.868
Antisocial personality	4 (3.4)	3 (4.8)	0.70 (0.15, 3.24)	0.651	0.52 (0.10, 2.73)	0.438	0.657	0.61 (0.11, 3.26)	0.561	0.673

Note: CI = Confidence Interval; DSM = Diagnostic and Statistical Manual of Mental Disorders; OR = Odds Ratio; SES = Socio-Economic Status.

[a]Classified using Office for National Statistics Socio-Economic Classification System; for the purposes of adjustment of confounding factors in the models above, SES has been categorised into two categories due to complete collinearity between some binary outcome variables and levels of SES: (1) higher managerial/professional occupations; (2) all other.

[b]Disability is defined as one or more of IQ < 55, blind, deaf or severe neuromotor impairment at 19 years of age.

[c]Adjusted *P* value after the Benjamini-Hochberg procedure.

[d]Significant if a false discovery rate of 0.05 was selected.

Table 2 Prevalence and Risk for Primary Diagnoses in Extremely Preterm Young Adults Compared With Term-Born Controls Assessed Using the Clinical Interview Schedule-Revised

	EP n (%) n=120	**Control n (%)** n=64	**Unadjusted OR (95% CI)**	***P*[b]**	**Adjusted age, sex and SES[c] OR (95% CI)** EP n= 116; Control n=63	**P**	**Adjusted for age, sex, SES[c] and excluding disability[d] OR (95% CI)** EP n= 107; Control n=63	***P***
Clinical Interview Schedule-Revised Primary Diagnosis[a]								
Any depression	15 (12.5)	3 (4.7)	2.91 (0.81, 10.44)	0.102	2.42 (0.64, 9.19)	0.194	2.62 (0.69, 9.95)	0.158
Mild depression	4 (3.3)	3 (4.7)	0.70 (0.15, 3.23)	0.649	0.67 (0.14, 3.22)	0.619	0.73 (0.15, 3.53)	0.695
Moderate depression	9 (7.5)	0 (0.0)	n/a	0.028	n/a	n/a	n/a	n/a
Severe depression	2 (1.7)	0 (0.0)	n/a	0.544	n/a	n/a	n/a	n/a
Any anxiety disorder	8 (6.7)	6 (9.4)	0.69 (0.23, 2.09)	0.511	0.81 (0.25, 2.65)	0.725	0.89 (0.27, 2.97)	0.855
Panic disorder	0 (0.0)	1 (1.6)	n/a	0.348	n/a	n/a	n/a	n/a
Generalised anxiety disorder	6 (5.0)	1 (1.6)	3.32 (0.39, 28.16)	0.272	3.00 (0.34, 26.29)	0.321	3.23 (0.37, 28.47)	0.291
Phobias	2 (1.7)	4 (6.3)	0.25 (0.05, 1.43)	0.120	0.34 (0.05, 2.15)	0.252	0.38 (0.06, 2.41)	0.303
Obsessive-Compulsive Disorder	0 (0.0)	0 (0.0)	n/a	n/a	n/a	n/a	n/a	n/a
Mixed anxiety & depression	2 (1.7)	3 (4.7)	0.35 (0.06, 2.12)	0.250	0.35 (0.06, 2.21)	0.266	0.40 (0.06, 2.51)	0.325
Clinical Interview Schedule-Revised Sub-threshold Symptomatology[e]								
	EP n (%) n=120	**Control n (%)** n=64	**Unadjusted RRR (95% CI)**	***P***	**Adjusted age, sex and SES[c] RRR (95% CI)** EP n= 116; Control n=63	***P***	**Adjusted for age, sex, SES[c] and excluding disability[d] RRR (95% CI)** EP n= 107; Control n=63	***P***
No mental disorder or symptoms	78 (65.0)	41 (64.1)	n/a	n/a	n/a	n/a	n/a	n/a
Sub-threshold symptoms	9 (7.5)	10 (15.6)	0.47 (0.18, 1.26)	0.133	0.46 (0.17, 1.24)	0.124	0.51 (0.19,1.39)	0.189
Common mental disorder	33 (27.5)	13 (20.3)	1.33 (0.63, 2.81)	0.448	1.35 (0.61, 2.97)	0.462	1.46 (0.66,3.24)	0.355

Note: CI = Confidence Interval; CIS-R = Clinical Interview Schedule-Revised; OR = Odds Ratio; RRR = Relative Risk Ratio; SES = Socio-Economic Status.
[a]CIS-R Primary Diagnosis: all variables are treated as binary variables.
[b]Where there are no cases the p value is derived from chi-square test of independence.
[c]For the purposes of adjustment of confounding factors in the models above, SES has been categorised into two categories due to complete collinearity between some binary outcome variables and levels of SES: (1) higher managerial/professional occupations; (2) all other.
[d]Disability is one or more of IQ <55, blind, deaf or severe neuromotor impairment assessed at 19 years of age.
[e]CIS-R sub-threshold symptomatology: (1) no common mental disorders: CIS-R scores <6 and no disorder; (2) sub-threshold symptoms: CIS-R score 6-11 and no disorder; (3) common mental disorder: CIS-R score ≥12 or any disorder.

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Online Supplement 1

Participants

The EPICure cohort comprised all babies born ≤25 weeks' gestation in the UK and Ireland from March through December 1995. Of 812 babies admitted for neonatal care, 315 survived to discharge. At 2.5 years corrected age, 283 (92%) were assessed, at 6 years of age 241 (78%) were assessed, and at 11 years 219 (71%) were assessed. These data comprise results of assessments at 19 years of age for 129 (42%) EP young adults.

To provide a term-born reference group, 160 children born ≥37 weeks' gestation were recruited and assessed at the 6-year follow-up. These were matched for age, sex and ethnicity where possible to an EP child in mainstream school. At the 11-year evaluation, 110 were re-assessed and 43 new controls were selected using the same criteria, totalling 153. At 19 years, 65 (42%) of these were re-assessed.

Characteristics of participants assessed at 19 years and those lost to follow-up are shown in Table S1. Compared with extremely preterm adults lost to follow-up, extremely preterm adults assessed had higher SES and higher developmental test/IQ scores at 2.5, 6 and 11 years of age. There was no significant difference in Strengths and Difficulties Questionnaire (SDQ) total scores at 6 and 11 years between those assessed and not assessed at 19 years.

Procedure

Participants attended a 2-day assessment at University College London Hospital. Eleven were assessed at home where travel was limited by disability or prior commitments. Written informed consent was obtained from participants themselves or by a parent/guardian for those with severe intellectual impairment. The study was approved by the South Central Hampshire A Research Ethics Committee (Ref: 13/SC/0514).

Statistical analyses

Scores on ASR scales were converted to T-scores (Mean 50; SD 10) using ASR norms. T-scores ≥70 were used to classify clinically significant difficulties on syndrome and DSM scales and ≥64 on broadband scales. Data were analysed using Stata 14.0. T-scores on ASR broadband scales were analysed using linear regression models and on syndrome and DSM scales using Tobit regression models; estimated coefficients are interpreted in the same way as for linear models but the coefficient refers to the censored latent model rather than the observed outcome. Next, for each model, we adjusted for sex, age and SES and performed additional analyses excluding participants with severe neurodevelopmental disability. Odds ratios (ORs) or relative risk ratios (RRRs) of clinically significant difficulties (ASR) and psychiatric disorders (CIS-R) for EP compared with term-born adults were estimated using binary or multinomial logistic regression models. To assess association between psychiatric disorders in childhood and adulthood, risk ratios (RRs) for clinically significant difficulties on the ASR and common mental disorders on the CIS-R at 19 years of with and without a psychiatric disorder at 11 years of age were calculated using generalised linear models (Table S2). Similar adjusted analyses were performed where possible. Correction for multiple corrections was applied to the ASR scales using the False Discovery Rate procedure.[1] To explore the impact of socio-economic status (SES) on change in the prevalence of psychiatric disorders from 11 to 19 years in extremely preterm participants, SES was classified using the UK Office for National Statistics Socio-Economic Classification System based on parental occupation at 11 years of age, categorised into four levels: Professional/managerial; intermediate occupations; routine/manual occupations; other (full time students/long term unemployed/not classifiable). The proportion of participants with a diagnosis at 11 years of age and any common mental disorder at 19 years of age was plotted by SES sub-group for those assessed at both time points and with SES data available at 11 years (Figure S1).

Table S1 Characteristics of Extremely Preterm Young Adults and Term-Born Controls Assessed at 19 Years of Age, and Association of Birth Characteristics and Neurodevelopmental Outcomes with Loss to Follow-Up at 19 Years of Age

Variable		EP assessed N=129	EP[a] not assessed N=177	Difference EP assessed vs. not assessed	Controls assessed N=65	Controls[b] not assessed N=88	Difference controls assessed vs. not assessed	Difference EP vs. controls assessed at 19 years
Characteristics at 19 years				***P***			***P***	***P***
Age at assessment (years)	Mean (SD)	19.3 (0.55)	-	-	19.2 (0.53)	-	-	0.162
Parent SES category at 19y[c]	n/N (%)	-	-	-	-	-	-	-
Higher professional/managerial		69/125 (55.2)	-	-	39/64 (60.9)	-	-	0.322
Intermediate occupations		22/125 (17.6)	-	-	15/64 (23.4)	-	-	-
Routine/manual occupations		22/125 (17.6)	-	-	7/64 (10.9)	-	-	-
Other		12/125 (9.6)	-	-	3/64 (4.7)	-	-	-
IQ score[d]	Mean (SD)	85.9 (16.7)	-	-	103.9 (10.2)	-	-	<0.001
Severe neurodevelopmental disability[e]	n/N (%)	15/121 (12.4)	-	-	0/65 (0.0)	-	-	-
Birth characteristics								
Male sex	n/N (%)	61/129 (47.3)	87/177 (49.2)	0.747	25/65 (38.5)	39/88 (44.3)	0.440	0.243
Gestational age at birth (weeks)	n/N (%)	-	-	0.280	-	-	-	-
	22weeks	2/129 (1.6)	0/177 (0.0)	-	-	-	-	-
	23 weeks	13/129 (10.1)	13/177 (7.3)	-	-	-	-	-
	24 weeks	37/129 (28.7)	60/177 (33.9)	-	-	-	-	-
	25 weeks	77/129 (59.7)	104/177 (58.8)	-	-	-	-	-
Birthweight	Mean (SD)	740.8 (121.9)	751.4 (108.9)	0.422	-	-	-	-
Outcomes at 2.5 years corrected age								
SES category[f]	n/N (%)	-	-	-	-	-	-	-
Non-manual		54/122 (44.3)	29/146 (19.9)	<0.001	-	-	-	-
Manual		40/122 (32.8)	53/146 (36.3)	-	-	-	-	-
Unemployed		28/122 (23.0)	64/146 (43.8)	-	-	-	-	-
Cognitive test score[g]	Mean (SD)	84.0 (13.0)	79.9 (15.1)	0.022	-	-	-	-
Cognitive impairment[h]	n/N (%)	15/117 (12.8)	27/130 (20.8)	0.097	-	-	-	-
Neurodevelopmental disability[i]	n/N (%)	57/126 (45.2)	78/154 (50.6)	0.367	-	-	-	-
Outcomes at 6 years chronological age								
SES category	n/N (%)	-	-	-	-	-	-	-
High		45/111 (40.6)	20/105 (19.0)	0.003	25/52 (48.1)	13/53 (24.5)	0.040	0.309
Middle		32/111 (28.8)	41/105 (39.0)	-	17/52 (32.7)	27/53 (51.0)	-	-
Low		34/111 (30.6)	44/105 (42.0)	-	10/52 (19.2)	13/53 (24.5)	-	-

IQ score[j]	Mean (SD)	85.6 (17.3)	79.1 (19.9)	0.008	108.4 (11.3)	106.6 (11.5)	0.426	<0.001
Cognitive impairment[k]	n/N (%)	41/122 (33.6)	55/117 (47.0)	0.035	0/54 (0.0)	1/56 (1.8)	1.000	<0.001
Neurodevelopmental disability[i]	n/N (%)	44/122 (36.1)	56/117 (47.9)	0.065	0/54 (0.0)	1/56 (1.8)	0.324	<0.001
SDQ Total difficulties score[l]	Mean (SD)	12.4 (6.7)	12.2 (6.6)	0.850	7.4 (5.0)	7.5 (4.5)	0.993	<0.001
SDQ pervasive total difficulties[m]	n/N (%)	5/103 (4.9)	11/87 (12.6)	0.054	1/54 (1.9)	0/52 (0.0)	1.000	0.665
Outcomes at 11 years chronological age								
SES category[c]	n/N (%)	-	-	-	-	-	-	-
Professional/managerial		57/110 (51.8)	21/69 (30.4)	0.002	36/60 (60.0)	41/78 (52.6)	0.789	0.657
Intermediate occupations		27/110 (24.5)	17/69 (24.6)	-	10/60 (16.7)	13/78 (16.7)	-	-
Routine/manual		24/110 (21.8)	22/69 (31.9)	-	13/60 (21.7)	22/78 (28.2)	-	-
Other		2/110 (1.8)	9/69 (13.0)	-	1/60 (1.7)	2/78 (2.6)	-	-
IQ Score[j]	Mean (SD)	86.3 (16.2)	80.8 (19.3)	0.028	105.7 (11.2)	102.9 (10.9)	0.111	<0.001
Cognitive impairment[k]	n/N (%)	42/121 (34.7)	44/97 (45.4)	0.110	0/65 (0.0)	2/88 (2.3)	0.508	<0.001
Neurodevelopmental disability[i]	n/N (%)	50/121 (41.3)	47/97 (48.5)	0.292	0/65 (0.0)	2/88 (2.3)	0.508	<0.001
SDQ Total difficulties score[l]	Mean (SD)	11.7 (7.9)	10.3 (7.0)	0.166	5.6 (5.8)	6.5 (6.1)	0.365	<0.001
SDQ pervasive total difficulties[m]	n/N (%)	21/107 (19.6)	10/78 (12.8)	0.221	1/61 (1.6)	4/82 (4.9)	0.394	0.001
DAWBA any disorder	n/N (%)	30/121 (24.8)	21/97 (21.7)	0.586	3/65 (4.6)	10/87 (11.5)	0.134	0.001
DAWBA any emotional disorder	n/N (%)	8/116 (6.9)	10/84 (11.9)	0.222	0/62 (0.0)	3/81 (3.7)	0.126	0.034

Note: DAWBA = Development And Well Being Assessment; EP = Extremely Preterm; IQ = Intelligence Quotient; SES = Socio-economic Status; SDQ = Strengths and Difficulties Questionnaire.

[a]Denominator: N=306 survivors at 19 years.

[b]Denominator: N=153 controls assessed at 11 years.

[c]SES Socio-economic category classified using UK Office for National Statistics Socio-Economic Classification System.

[d]IQ score EP assessed n=127; control assessed n=64.

[e]Severe neurodevelopmental disability is one or more of IQ <55, blind, deaf or severe neuromotor impairment at 19 years of age.

[f]SES classified using parent occupation.

[g]Cognitive development assessed using the Bayley Scales of Infant Development 2nd Edition (BSID-II) Mental Development Index (MDI) (Mean 100, SD 15); EP assessed n=117; EP not assessed n=130.

[h]Cognitive impairment is BSID-II MDI scores <70.

[i]Neurodevelopmental disability classified as one or more of cognitive, vision, motor or hearing impairment.

[j]IQ measured using the Kaufman Assessment Battery for Children (Mean 100, SD 15); IQ at 6 years: EP assessed n=122; EP not assessed n=117; control assessed n=54; controls not assessed n=56; IQ at 11 years: EP assessed n=121; EP not assessed n=95; control assessed n=65; controls not assessed n=88.

[k]Classified using scores <-2 SD using term-born controls as the reference.

[l]Parent-completed SDQ Total Difficulties Score; At 6 years: EP assessed n=114; EP not assessed n=106; control assessed n=54; controls not assessed n=53; At 11 years: EP assessed n=119; EP not assessed n=89; control assessed n=62; controls not assessed n=86.

[m]Pervasive behaviour problems defined as both parent and teacher rated clinically significant total difficulties using the SDQ.

Table S2 Group Differences in Risk for Clinically Significant Difficulties on the Achenbach Adult Self Report Scales at 19 Years of Age Among Extremely Preterm Adults With and Without a Psychiatric Disorder at 11 Years of Age

	Risk for clinically significant difficulties[a]										
	No disorder at 11 years n (%) n=83	**Any disorder at 11 years n (%)** n=25	**Unadjusted RR (95% CI)** n=108	***P***	**Benjamini-Hochberg adjusted P value**	**Adjusted for age, sex and SES[b] RR (95% CI)** n=107	***P***	**Benjamini-Hochberg adjusted P value**	**Adjusted for age, sex, SES[b] and excluding disability[c] RR (95% CI).** n=98	***P***	**Benjamini-Hochberg adjusted P value**
DSM Scales											
Depression	11 (13.3)	7 (28.0)	2.11 (0.92, 4.87)	0.079	0.237	2.35 (0.98, 5.64)	0.055	0.165	1.98 (0.79, 4.97)	0.143	0.429
Anxiety	7 (8.4)	1 (4.0)	0.47 (0.06, 3.67)	0.475	0.570	0.69 (0.08, 5.77)	0.728	0.728	0.68 (0.08, 5.73)	0.726	0.871
Somatic problems	4 (4.8)	2 (8.0)	1.66 (0.32, 8.54)	0.544	0.544	2.06 (0.37, 11.30)	0.406	0.487	0.90 (0.10, 8.09)	0.928	0.928
Avoidant personality	8 (9.6)	8 (32.0)	3.32 (1.39, 7.94)	0.007	0.042[e]	4.83 (1.65, 14.09)	0.004	0.024[e]	4.23 (1.40, 12.83)	0.011	0.066
Attention deficit/hyperactivity	6 (7.2)	3 (12.0)	1.66 (0.45,6.16)	0.449	0.674	2.45 (0.61, 9.84)	0.208	0.312	1.55 (0.31, 7.88)	0.596	0.894
Antisocial personality	1 (1.2)	2 (8.0)	6.64 (0.63, 70.21)	0.116	0.232	5.24 (0.48, 57.36)	0.175	0.350	5.13 (0.46, 56.58)	0.182	0.364
CIS-R											
Common mental disorder[d]	21/87 (24.1)	11/25 (44.0)	1.82 (1.02, 3.24)	0.042	n/a	2.08 (0.95, 4.59)	0.068	n/a	1.88 (0.83, 4.25)	0.129	n/a
	No Emotional disorder at 11 n **(%);** n=100	**Any Emotional disorder at 11 n (%);** n=8	**Unadjusted RR (95% CI)** n=108	***P***	**Benjamini-Hochberg adjusted P value**	**Adjusted for age, sex and SES[b] RR (95% CI)** n=105	***P***		**Adjusted for age, sex, SES[b] and excluding disability[c] RR (95% CI)** n=98	***P***	
CIS-R											
Common mental disorder[d]	27 (27.0)	4 (50.0)	1.85 (0.86, 3.97)	0.114	n/a	1.25 (0.49, 3.21)	0.643	n/a	1.29 (0.29, 5.75)	0.742	n/a

Note: CIS-R = Clinical Interview Schedule-Revised; DSM = Diagnostic and Statistical Manual of Mental Disorders; SES: Socio-Economic Status.

[a]Reference group: Extremely preterm participants without psychiatric disorder at 11 years.

[b]SES category classified using Office for National Statistics Socio-Economic Classification System; for the purposes of adjustment of confounding factors in the models above, SES has been categorised into two categories due to complete collinearity between some binary outcome variables and levels of SES.

[c]Disability is defined as one or more of IQ <55, blind, deaf or severe neuromotor impairment at 19 years of age.

[d]Common mental disorder: CIS-R score ≥12 or any disorder; Reference category: no mental disorder or sub-threshold symptoms.

[e]Adjusted P value after application of the Benjamini-Hochberg procedure: significant if a false discovery rate of 0.05 was selected.

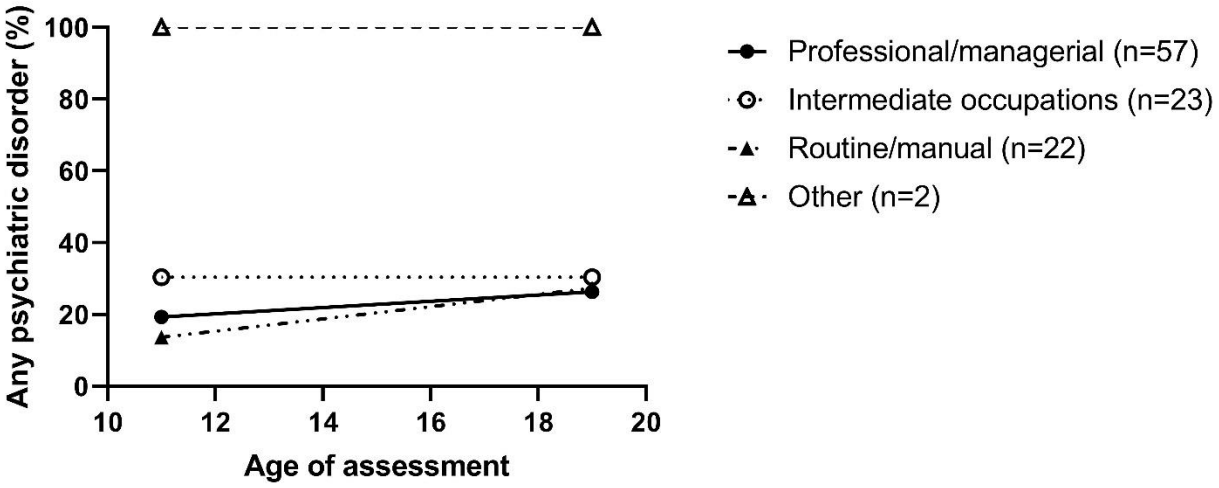

Figure S1. Percent of Participants with a Psychiatric Disorder at 11 Years of Age and Common Mental Disorder at 19 Years of Age Stratified by Parental Socio-Economic Status at 11 Years of Age. (Data are Presented for Participants Assessed at Both Time Points and with Data Available for Classifying Socio-Economic Status at 11 Years.)

References

1. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society*. 1995;51(1):289-300.