Supplementary Table 1 Correlations with degree of Conditioned Pain Modulation in subgroups based on immersion duration (A) or all extreme preterm birth participants (B).

A: EP and TC subjects tolerating immersion >/=20 secs

	Baseline PPT	**Immersion time**	**Immersion pain**	**CPM %**	**Pain ranking**	**Regular analgesia**	**PCS**	**Anxiety**	**Regular psychotropics**
Baseline PPT (*ln* kPa)	1.0								
Immersion time (s)	0.09	1.0							
Immersion pain (VRS)	-0.25**	-0.24*	1.0						
CPM % (15 sec)	-0.32**	0.04	-0.06	1.0					
Pain ranking (HUI-3) [*n*=104]	-0.09	-0.08	0.02	0.01	1.0				
Regular analgesia	-0.12	-0.12	0.03	0.08	0.35**	1.0			
Pain Catastrophizing [*n*=100]	-0.15	0.01	0.06	0.01	0.30**	0.24*	1.0		
DSM-Anxiety [*n*=104]	-0.06	0.01	0.08	0.21*	0.20*	0.40**	0.40**	1.0	
Regular psychotropics [*n*=101]	-0.05	0.03	0.17	0.14	0.25*	0.33**	0.03	0.28**	1.0

B: All EP only

EP (n=98)	**Baseline PPT**	**Immersion time**	**Immersion pain**	**CPM %**	**Pain ranking**	**Regular analgesia**	**PCS**	**Anxiety**	**Regular psychotropics**
Baseline PPT (*ln* kPa)	1.0								
Immersion time (s)	0.45**	1.0							
Immersion pain (VRS)	-0.38**	-0.38*	1.0						
CPM % (15 sec)	-0.31**	0.16	-0.03	1.0					
Pain ranking (HUI-3) [*n*=94]	-0.17	-0.08	0.06	0.05	1.0				
Regular analgesia	-0.16	-0.11	0.11	-0.01	0.29**	1.0			
Pain Catastrophizing [*n*=89]	-0.24*	-0.09	0.16	-0.05	0.29**	0.29**	1.0		
DSM-Anxiety [*n*=93]	-0.10	0.01	0.01	0.03	0.31**	0.16	0.43**	1.0	
Regular psychotropics [*n*=91]	-0.09	0.01	0.21	0.13	0.24*	0.21	0.22*	0.38**	1.0

Data = two-tailed Spearman's rho bivariate correlation co-efficient: *correlation significant at 0.05; **correlation significant at 0.01 level

Legend: CPM %, conditioned pain modulation % change from baseline at 15 seconds; PCS, Pain Catastrophizing Scale total score DSM-Anxiety, anxiety total score Achenbach Youth Self-Report scale

Supplementary Table 2. Correlations between degree of Conditioned Pain Modulation, immersion time, current pain and psychological variables based on EP status

(A) Extremely Preterm born young adults (all participants)

EXTREMELY PRETERM [n=98]	**CPM %**	**Baseline PPT**	**Immersion time**	**Immersion pain**	**Pain experience**	**Pain VAS**	**Pre-test anxiety**	**Anxiety (T-Ach)**	**PCS**	**FSIQ**	**BMI**	**Time hosp**	**CRIB score**	**Birth weight**
CPM % (15 sec)	1.0													
Baseline PPT (kPa)	-0.31**	1.0												
Immersion time (s)	0.16	0.45**	1.0											
Immersion pain (VRS)	-0.03	-0.38**	-0.38**	1.0										
Pain ranking (HUI-3) [*n*=94]	0.05	-0.17	-0.07	0.06	1.0									
Ave Pain (VAS 0-100)	-0.03	-0.18	-0.11	0.06	0.48**	1.0								
Pre-test anxiety (0-100)	0.01	-0.12	-0.02	0.01	0.03	0.20	1.0							
DSM-Anxiety [*n*=93]	0.03	-0.10	0.01	0.01	0.31**	0.19	0.30**	1.0						
Pain Catastrophizing [*n*=89]	-0.05	-0.24*	-0.09	0.16	0.29**	0.24*	0.23*	0.43**	1.0					
FSIQ	0.09	-0.14	-0.05	-0.05	-0.33**	-0.25*	-0.19	-0.15	-0.05	1.0				
BMI	-0.11	0.15	-0.04	-0.05	0.03	0.12	-0.12	0.01	0.10	-0.08	1.0			
Time hospital [*n*=78]	-0.18	-0.13	-0.08	0.04	0.01	0.23	0.06	0.03	0.10	-0.29**	-0.04	1.0		
CRIB score [*n*=95]	-0.17	-0.12	-0.09	0.07	0.11	0.25*	0.16	-0.12	-0.05	-0.18	-0.02	0.38**	1.0	
Birth weight [*n*=98]	0.03	0.15	-0.03	-0.07	-0.05	-0.19	-0.19	0.05	-0.04	0.15	-0.09	-0.32**	-0.62**	1.0

(B) Term-born control young adults (all participants)

TERM CONTROL [n=48]	**CPM %**	**Baseline PPT**	**Immersion time**	**Immersion pain**	**Pain ranking**	**Pain VAS**	**Pre-test anxiety**	**Anxiety (Ach)**	**PCS**	**FSIQ**	**BMI**
CPM % (15 sec)	1.0										
Baseline PPT (kPa)	-0.28	1.0									
Immersion time (sec)	0.26	-0.09	1.0								
Immersion pain (VRS 0-10)	-0.12	-0.06	-0.24	1.0							
Pain ranking (HUI-3) [*n*=45]	-0.08	0.04	0.04	-0.03	1.0						
Ave. Pain (VAS 0-100)	-0.11	0.12	-0.13	-0.03	0.18	1.0					
Pre-test anxiety (0-100)	-0.21	0.15	-0.08	0.05	-0.23	0.12	1.0				
DSM-Anxiety [*n*=45]	0.01	-0.06	-0.03	0.33*	0.04	0.13	-0.04	1.0			
Pain Catastrophizing [*n*=45]	0.05	0.04	0.14	0.01	0.07	0.23	0.20	0.28	1.0		
FSIQ	0.09	-0.14	0.21	-0.37*	-0.18	-0.03	0.20	-0.24	-0.08	1.0	
BMI	-0.15	0.10	-0.04	0.19	0.17	0.12	-0.24	0.23	-0.32	-0.21	1.0

Data = two-tailed Spearman's rho bivariate correlation co-efficient: *correlation significant at 0.05; **correlation significant at 0.01 level

Legend: CPM %, conditioned pain modulation % change from baseline at 15 seconds; DSM-Anxiety, anxiety total score Achenbach Youth Self-Report scale; Internalizing (Ach), internalizing subscale score Achenbach Youth Self-Report scale; PCS, Pain Catastrophizing Scale total score

Supplementary Table 3. Linear model of CPM Effect (% change in PPT at 15 secs; all participants irrespective of conditioning tolerance)

	Step 1 (n=145)				**Step 2** (n=145)				**Step 3** (n=127)			
Variables	**B**	**SE B**	**β**	***p***	**B**	**SE B**	**β**	***p***	**B**	**SE B**	**β**	***p***
Baseline PPT (*ln* kPa)	-31	6.1	-.40	<0.001	-35	6.7	-.46	<0.001	-37	7.3	-.47	<0.001
Immersion time (s)	1.3	0.45	.24	0.003	1.4	0.47	.24	0.004	1.4	0.5	.23	0.008
EP status					-0.17	7.7	-.002	0.98	4.2	8.4	.04	0.61
Sex					-12.5	8.0	-.13	0.12	-14.8	8.9	-.15	0.09
Pain (HUI-3 ranking)									4.4	5.8	.07	0.46
Regular analgesics									21	19	.10	0.29
Catastrophizing (PCS)									-0.53	0.46	-.12	0.25
DSM-Anxiety									-0.70	0.51	-.15	0.17
Regular psychotropics									49	17	.25	0.006
R^2	**0.17**				**0.18**				**0.27**			
F for R^2	$F_{2,142}$=14.1; P<0.001				$F_{4,140}$=7.6; P<0.001				$F_{9,118}$=4.8; P<0.001			

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page reference and Details Text taken directly from manuscript highlighted in *italics*
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title: *Conditioned Pain Modulation identifies sex-dependent alterations in pain response in extremely preterm born young adults* Abstract: *This observational cohort study..*
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract in suggested format: Background, Methods, Results, Conclusions.
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	*In an observational cohort study, we compared CPM in extremely preterm and term born young adults. The primary outcome was identification of modulatory effects (inhibition, facilitation, no change) in EP and TC groups.*
Methods			
Study design	4	Present key elements of study design early in the paper	*observational cohort study*
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	*Participants were recruited from the EPICure cohort of extremely preterm (EP, <26 weeks gestation) and term controls (TC) born in the United Kingdom and Ireland in 1995...* *The current study at 19 years (EPICure@19; www.epicure.ac.uk)* Following written consent, *participants completed two days of assessments at the NIHR UCLH Clinical Research Facility, London between February 2014 and October 2015.* *CPM was assessed as part of a comprehensive evaluation of somatosensory function in 102 extremely preterm born and 48 term-born control participants in a dedicated sensory testing facility at UCL GOS Institute of Child Health*
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Fig. 1 Recruitment flow chart
		(*b*) For matched studies, give matching criteria and	Figure 1

		number of exposed and unexposed	Table 1 summarises participant demographic data and demonstrates appropriate age and gender match of extreme preterm born (EP, exposed) and term born control (TC, unexposed) groups.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods include details of outcomes. Exposures, predictors, potential confounders included in regression model (Table 3) and Supplementary Tables 1, 2, 3.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Assessments included in Methods. Methods of analysis of CPM effect discussed, and both raw and normalized data included. Validated questionnaire measures.
Bias	9	Describe any efforts to address potential sources of bias	*Testing was performed by a single investigator (SMW) using standardized verbal instructions in a temperature-controlled room at the same time of day.*
Study size	10	Explain how the study size was arrived at	Recruitment discussed. 95%CI rather than post-hoc power analysis to support power.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Statistical analysis section
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Statistical Analyses section in Methods. Additional test in Results, Figure Legends, and Tables.
		(*b*) Describe any methods used to examine subgroups and interactions	Table 2 Correlation matcrix and Table 3 Regression model; Supplementary Tables 1and 2: correlation between variables separated by preterm versus control groups, and by conditioning stimulus tolerance.
		(*c*) Explain how missing data were addressed	Tables: Data cells with missing data contain actual 'n' for available data. No imputation for missing data was performed.
		(*d*) If applicable, explain how loss to follow-up was addressed	EP participants evaluated at 19 years did not differ in birth weight, gestational age or sex from those lost to follow-up, but had higher socio-economic status and higher mean IQ scores at earlier assessments than non-participants.
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for	Figure 1

		eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1 is presented as a flow diagram of participant numbers at each stage of the study.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Tables include sample size (n=) at head of column. Data cells with missing data contain actual 'n' for available data. No imputation for missing data was performed.
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	Recruitment and outcome at different stages of this longitudinal study have been previously reported and are summarised here. 1. Wood NS et al. *N Engl J Med.* 2000;343(6):378-384. 2. Marlow N et al. *N Engl J Med.* 2005;352(1):9-19. 3. Johnson S et al. *Pediatrics.* 2009;124(2):e249-257.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	In tables, data are presented as mean±SD if normally distributed or median and interquartile range. Comparisons and graphs include individual data points and/or mean [95%CI].
		(*b*) Report category boundaries when continuous variables were categorized	Graphs include individual data points and/or mean [95%CI].
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Paragraph in Discussion reports Limitations.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Final paragraph of Discussion: Summary
Generalisability	21	Discuss the generalisability (external validity) of the study results	Included in Discussion
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Funding and Acknowledgements sections included.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.