

Costs and Health Utilities Associated with Extremely Preterm Birth: Evidence from the EPICure Study

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ABSTRACT

Objective: To estimate costs and health utilities associated with extremely preterm birth at approximately 11 years of age using evidence from a whole population study (the EPICure study).

Methods: The study population comprised surviving children born at 20 through 25 completed weeks of gestation in all 276 maternity units in the United Kingdom and Republic of Ireland from March through December 1995 and a control group of classmates born at full term, matched for age, sex, and ethnic group. Estimates of utilization of health, social, and education services were combined with unit costs derived from primary and secondary sources. Generalized liner regression was used to estimate the impact of extremely preterm birth on public sector costs during the 11th year of life. Suboptimal levels of function for each of the eight attributes of the Health Utilities Index Mark III (cognition, vision, hearing, speech, ambulation, dexterity, emotion, and pain) and multiplicative multi-attribute utility scores were compared between the extremely preterm children and their classmates. Tobit regressions were performed to explore the effects of gestational age at birth on the Health Utilities Index Mark III multiattribute utility score.

Results: Mean (standard deviation [SD]) public sector costs over the 12-month period were £6484 (£5548) for the combined extremely preterm group and £4007 (£2537) for their classmates, generating a mean cost difference of £2477 (bootstrap 95% confidence interval [CI] £1605,

£3360) that was statistically significant ($P < 0.001$). The generalized linear models revealed that compared to birth at term, birth at ≤ 23 completed weeks, 24⁺⁰–24⁺⁶ weeks and 25⁺⁰–25⁺⁶ weeks gestation increased public sector costs by an average of £2417 (95% CI £60, £4774; $P = 0.044$), £1528 (95% CI £129, £2927; $P = 0.032$) and £1501 (95% CI £428, £2574; $P = 0.006$), respectively. In all eight attributes of the Health Utilities Index Mark III, there were significantly higher proportions of suboptimal levels of function among the extremely preterm children ($P \leq 0.05$). The mean (SD) multiattribute utility score for the extremely preterm children as a cohort was 0.789 (0.264), compared to 0.956 (0.102) for the classmates born at term, a mean difference in utility score of 0.167 (95% CI 0.124, 0.209) that was statistically significant ($P < 0.001$). The Tobit regressions revealed that, compared to birth at term, birth at ≤ 23 completed weeks, 24⁺⁰–24⁺⁶ weeks and 25⁺⁰–25⁺⁶ weeks gestation reduced the Health Utilities Index Mark III multi-attribute utility score by an average of 0.312 (95% CI 0.169, 0.455; $P < 0.001$), 0.337 (95% CI 0.235, 0.439; $P < 0.001$) and 0.243 (95% CI 0.159, 0.327; $P < 0.001$), respectively.

Conclusions: The results of this study should be used to inform the development of future economic evaluations of interventions aimed at preventing extremely preterm birth or alleviating its effects.

Keywords: costs, extremely preterm birth, health-related quality of life, health utilities.

Introduction

The incidence of preterm birth, defined as birth before 37 completed weeks of gestation, has been reported at between 5% and 11% throughout the industrialized world with some of the highest rates reported in the United States [1]. The incidence of preterm birth has increased slightly since the 1980s, which has been attributed to increasing rates of multiple births, greater use of assisted reproduction, and increased obstetric intervention, such as induced labor and Caesarean section [2,3]. Developments in clinical practice, such as the use of ultrasonography to estimate gestational age, may also have had a slight effect on the incidence rate as may the trend toward registering a live birth for infants born at the limits of viability whose deaths might previously been classified as stillbirths or miscarriages [2]. Preterm birth has been associated with socioeconomic disadvantage, non-Caucasian ethnic background, substance misuse, and extremes in maternal age, with both teenage and older mothers at an increased risk [4,5].

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Although the majority of preterm births occur between 33 and 36 completed weeks of gestation, it is possible for infants born as early as 22 weeks gestation to survive and the clinical outcomes following birth at extremely low gestational ages are those most widely reported in the literature. A substantial body of literature has reported that infants born at extremely low gestational ages are at an increased risk of a range of adverse neonatal outcomes including chronic lung disease [6], severe brain injury [7], retinopathy of prematurity [8], necrotizing enterocolitis [9], and neonatal sepsis [10]. In later life, these infants are also at an increased risk of motor and sensory impairment [11,12], learning difficulties [13–17], and behavioral problems [18–21].

Although the clinical sequelae of extremely preterm birth are well documented, relatively little is known about its consequences in cost or utility metrics that can be incorporated into cost-effectiveness modeling studies. Two recent systematic reviews of the economic literature in this area highlight the focus of studies upon costs incurred during the neonatal period with few attempts to estimate the costs of preterm birth during later childhood [22,23]. In addition, studies that have estimated the health-related quality of life of premature infants using preference-based measures have tended to categorize children in terms of birth weight, rather than gestational age at birth, despite

the limited prognostic capabilities of the birth weight measure [24–28]. One recent study described the health-related quality of life of British teenagers in mainstream schooling who were born before 29 weeks gestational age using the Health Utilities Index [29]. However, these children were identified from cohorts born in the early 1980s prior to improvements in perinatal practices and intensive care technologies, thus limiting the generalizability of the study results to the current clinical context.

The purpose of this research is to augment the limited economic evidence in this area by estimating costs and health utilities associated with extremely preterm birth during mid-childhood. In so doing, we provide a significant new resource to analysts modeling the cost-effectiveness of preventive or treatment interventions for extremely preterm birth.

Methods

Study Population

Children that participated in the EPICure study formed the basis of this investigation. The EPICure study is a whole population study of all infants born at 20 through 25 completed weeks of gestation in all 276 maternity units in the United Kingdom and Republic of Ireland from March to December 1995. A full description of the study population, recruitment methods, and neonatal assessment procedures is available elsewhere [30]. Of 307 surviving children, 241 (78.2%) were assessed at a median age of 6 years and 4 months (range: 5 years and 2 months to 7 years and 3 months) [31], while 219 (71.3%) were assessed at a median age of 10 years and 11 months (range: 10 years and 1 month to 12 years and 1 month) [32]. At the final follow-up, surviving children underwent a series of assessments of cognitive and functional disability and were then classified into four groups of overall disability (none, mild, moderate, and severe) on the basis of the most severe classification in any domain [32]. A control group of 153 mainstream school classmates who were born at full term and matched for age, sex, and ethnic group was also evaluated using the same assessment procedures. Ethical approval for the study was obtained from the Southampton and South West Hampshire Research Ethics Committee and approved by the Central Office for Research Ethics Committees.

Estimation of Costs

As part of the follow-up assessments conducted at 11 years, the main parent (usually the mother) was asked to complete a detailed postal questionnaire about their child's resource utilization over the previous year. The questionnaire was piloted to ascertain its acceptability, comprehension, and reliability, and reminder letters were sent to parents to increase the response and completion rates. The data collected from the main parent included their child's use of hospital inpatient and day care services, community health services, prescribed medications, social services, and education services. All resource use data were entered directly from the research instruments into a purpose-built data collection program with in-built safeguards against inconsistent entries and then verified by dual coding. Estimates of service provision were derived from these data and usually expressed in terms of contact hours. For all hospital admissions, estimates of service provision were expressed in terms of patient days with part of a day at each level of care counted as a 24-hour period. For education services, estimates of services provision reflected the level of educational assistance within each type of educational establishment (mainstream school, mainstream school with special unit attached, special school for the physically disabled, and special school for children with learning difficulties).

UK unit costs were applied to each resource item to value total resource use for each study child over an annual basis. All unit costs employed followed recent guidelines on costing public services as part of economic evaluation [33–35]. The calculation of these costs was underpinned by the concept of opportunity cost, which can be defined as the value of the next best alternative for using these resources [34]. The costs of hospital inpatient and day care services were largely derived from English Department of Health reference costs based upon National Health Service trust financial returns [36]. The unit costs of community health and social services were largely derived from national sources [37], and took account of time spent by professionals on indirect activities, such as traveling and paper work. Some unit costs of health and social services were calculated from first principles using established accounting methods [33]. Drug costs were obtained from the *British National Formulary* [38]. Educational costs were based upon micro-costing exercises for different types of educational establishment and were obtained from the Department of Education and Skills in England (Department for Education and Skills in London, England, pers. comm.). All costs were expressed in pounds sterling and reflected values for the financial year 2006 to 2007. No inflation or deflation of costs to 2006 to 2007 prices using indices such as the National Health Service Hospital and Community Health Services Pay and Prices Index was required.

Estimation of Health Utilities

The postal questionnaire completed by the main parent around the child's 11th birthday included a preference-based measure of health-related quality of life, namely the Health Utilities Index. The main parent was considered the appropriate subject for describing the child's health-related quality of life as related research had indicated that the comprehension level for the Health Utilities Index is somewhat high for a pediatric sample where a number of children have developmental disabilities [39,40].

The Health Utilities Index is a family of preference-based multi-attribute utility measures [41]. The principal caregiver completed the unedited 15-item questionnaire for proxy-assessed usual health status assessment, which was obtained from the Health Utilities Index developers and covers both Mark II and Mark III health status classification systems. The "usual" health focus of the questions has previously been applied in population health surveys, where short-term illnesses such as the flu are not the major concern [42]. The Mark III classification system is now recommended by the developers because of its broad applicability in both clinical and general population health studies, improvements in a number of definitions, and an increased orthogonality of its attributes for structural independence [42]. It has been used in previous studies of extremely low birth weight children internationally [28]. The Health Utilities Index Mark III health status classification system covers eight attributes: cognition, vision, hearing, speech, ambulation, dexterity, emotion, and pain. Function within each attribute is graded on a 5- or 6-point scale corresponding to level of severity, ranging from normal function (level 1) to severe impairment (levels 5 or 6). Responses to the Health Utilities Index Mark III health status classification system were converted into multiplicative multi-attribute utility scores using a published utility function [43,44]. These multi-attribute utility scores are based on the permutation of responses across the eight attributes and are expressed on an interval scale ranging from –0.36 (representing the health state with the lowest level of function for all attributes) to 1.00 (representing the health state with the highest level of function for all attributes).

The multi-attribute utility scoring algorithm for the Health Utilities Index Mark III can be summarized as $u^* = 1.371(b_1 \times b_2 \times b_3 \times b_4 \times b_5 \times b_6 \times b_7 \times b_8) - 0.371$, where u^* is the utility score for the overall health state being measured and the b_i 's are substituted from a table of coefficients provided by the Health Utilities Index developers for the appropriate attribute and level [44]. To develop the multi-attribute utility scoring algorithm, a random sample of 504 general population adults living in the city of Hamilton, Canada had previously been asked to value selected health states using both a visual analog scaling technique and a standard gamble instrument. Further details on the utility algorithms for the Health Utilities Index Mark III are reported elsewhere [43,44].

Statistical Analysis

Differences in baseline sociodemographic and clinical characteristics between the extremely preterm children and their classmates were tested using the Pearson chi-squared test. Comparisons of each category of public sector costs and of total public sector costs were made between the extremely preterm children and their classmates, as well as between four pre-specified groups of children of varying gestational age at birth (≤ 23 completed weeks, 24^{+0} – 24^{+6} weeks, 25^{+0} – 25^{+6} weeks, term). Comparisons of costs are reported as mean values with standard deviations (SD) and mean differences in costs between the comparison groups with 95% confidence intervals (CIs) where applicable. As the data for costs were skewed, in addition to Student's t -tests of cost differences, nonparametric bootstrap estimation was used to derive 95% CIs for mean cost differences between the comparison groups [45]. The bootstrap method does not rely on parametric assumptions concerning the underlying distribution of data, hence its usefulness for generating CIs for skewed data [46]. Using a large number of simulations, and based on sampling with replacement from the original data, the bootstrap method estimates the distribution of a sampling statistic [46]. Each of the CIs surrounding mean cost differences was calculated using 1000 bias-corrected bootstrap replications. In addition, two generalized linear regressions [46] were performed with total public sector costs over the previous year of life representing the dependent variable in both analyses. In the first model, the main independent variable was defined as a dichotomous variable of gestational age at birth (extremely preterm birth, classmate norms). In the second model, this variable was disaggregated into the four pre-specified gestational age at birth categories (≤ 23 completed weeks, 24^{+0} – 24^{+6} weeks, 25^{+0} – 25^{+6} weeks, term). For both generalized linear regression models, a gamma distribution and linear (identity) link function for costs was selected on the basis of its low Akaike Information Criterion (AIC) statistic (AIC statistic of 19.24 for model 1 and 19.25 for model 2) compared to alternative distributional forms (e.g., Gaussian, Inverse Gaussian and Poisson distributional families) and link functions (e.g., log link function). Covariates included in both models were gender (male, female), maternal marital status (married, single, cohabiting, widowed, separated, or divorced), respondent parent's current age (<30 , 30 – 39 , 40 – 49 , or ≥ 50 years), type of accommodation (owner occupied, rented, or other), access to car (yes or no), highest parental qualification (vocational or equivalent, ordinary level or equivalent, advanced level or equivalent, diploma or equivalent, university degree, postgraduate qualification, other, or none), highest parental occupational status (professional or managerial, intermediate, routine and manual, or long-term unemployed), language spoken at home (English only, or English and other language[s]) and the number of smokers at home (0, 1, or ≥ 2).

For each of the eight attributes of the Health Utilities Index Mark III, we compared the proportion of children with sub-optimal levels of function (defined as below level 1 function) between the extremely preterm children and their classmates using Fisher's exact test for equality of proportions. Differences in the multi-attribute utility scores between the comparison groups were tested using two-sample t -tests for unequal variance. Finally, we performed Tobit regressions to explore the effects of gestational age at birth on the Health Utilities Index Mark III utility score. Tobit regression was required to account for the censoring of the dependent variable, the utility score, which has an upper value of 1.0 [47]. As with costs, two regression models for health utilities were performed, the first applying the dichotomous variable for gestational age at birth, and the second applying the further disaggregated variable for gestational age at birth. The same covariates applied in the generalized linear regressions on costs were applied in the Tobit regressions on health utilities.

All analyses were performed with a microcomputer using the Statistical Package for the Social Sciences (SPSS) (version 15.0; SPSS Inc, Chicago, IL) software and STATA (version 9.0; College Station, TX: StataCorp LP) software. P -values of 0.05 or less were considered statistically significant.

Results

Postal questionnaires reporting costs and health utilities were returned for 190 extremely preterm children (representing 61.9% of eligible surviving children and 86.8% of children assessed for cognitive and functional disability at a median age of 10 years and 11 months) and 141 classmates (representing 92.2% of classmates recruited into the concurrent clinical study [32]). Examination of longitudinal data for the extremely preterm children revealed that those not assessed at a median age of 10 years and 11 months were more likely to be born at 25^{+0} – 25^{+6} weeks, be of nonwhite ethnic origin, have had an operation for necrotizing enterocolitis, to have unemployed parents, and to have had lower cognitive scores or cognitive impairment at 2.5 and 6 years ($P \leq 0.05$). There were no significant differences in the sociodemographic and clinical characteristics at 11 years between the extremely preterm children and their classmates, for whom postal questionnaires were returned, with the exception of language spoken at home, overall disability status and gestational age at birth (Table 1).

The resource use values for each category of resource use for the extremely preterm children and their classmates, and the respective unit costs of each resource item, are presented in Table 2. Mean public sector costs over the 12-month period were £7514 (SD: £5662) among children born at ≤ 23 completed weeks, £6821 (£5984) among children born at 24^{+0} – 24^{+6} weeks, £6132 (£5304) among children born at 25^{+0} – 25^{+6} weeks, and £4007 (£2537) among the classmates born at term. Mean public sector costs over the 12-month period were £6484 (£5548) for the combined extremely preterm group and £4007 (£2537) for their classmates, generating a mean cost difference of £2477 (bootstrap 95% CI £1605, £3360) that was statistically significant ($P < 0.001$) (Table 3). When the data were analyzed by cost category, extremely preterm birth was associated with an increase of £297 in hospital inpatient care costs (bootstrap 95% CI £115, £523; $P = 0.007$), £108 in hospital outpatient and day care costs (bootstrap 95% CI £46, £166; $P = 0.001$), £405 in total hospital costs (bootstrap 95% CI £204, £668; $P = 0.001$), £344 in community health and social care costs (bootstrap 95% CI £223, £461; $P < 0.001$), £760 in total health and social care

Table 1 Sociodemographic and clinical characteristics of study participants; n (%)

Characteristic	Extremely preterm children (n = 190)	Classmates (n = 141)	P-value*
Gender			0.535
Male	86 (45.3)	59 (41.8)	
Female	104 (54.7)	82 (58.2)	
Maternal marital status			0.105
Married	119 (62.6)	104 (73.8)	
Single	10 (5.3)	11 (7.8)	
Cohabiting	24 (12.6)	9 (6.4)	
Widowed	3 (1.6)	1 (0.7)	
Separated/divorced	32 (16.8)	16 (11.3)	
Missing	2 (1.1)	0 (0.0)	
Respondent parent's age (years)			0.525
<30	2 (1.1)	2 (1.4)	
30–39	73 (38.4)	57 (40.4)	
40–49	95 (50.0)	73 (51.8)	
≥50	10 (5.3)	3 (2.1)	
Missing	10 (5.3)	6 (4.3)	
Type of accommodation			0.133
Owner occupied	133 (70.0)	109 (77.3)	
Rented	41 (21.6)	19 (13.5)	
Other	12 (6.3)	12 (8.5)	
Missing	4 (2.1)	1 (0.7)	
Access to car			0.602
Yes	178 (93.7)	133 (94.3)	
No	9 (4.7)	5 (3.5)	
Missing	3 (1.6)	3 (2.1)	
Highest parental qualification			0.688
Vocational/NVQ/CSE	29 (15.3)	17 (12.1)	
O-level/GCSE/Scottish standards	51 (26.8)	40 (28.4)	
BTEC diploma/A-level/Scottish highers	30 (15.8)	16 (11.3)	
Diploma or HND	19 (10.0)	14 (9.9)	
University degree	20 (10.5)	22 (15.6)	
Postgraduate qualification	12 (6.3)	9 (6.4)	
Other	10 (5.3)	12 (8.5)	
None	12 (6.3)	8 (5.7)	
Missing	7 (3.7)	3 (2.1)	
Highest household occupational status			0.064
Professional/managerial	79 (41.6)	77 (54.6)	
Intermediate occupation	44 (23.2)	23 (16.3)	
Routine and manual occupation	46 (24.2)	35 (24.8)	
Long-term unemployed	11 (5.8)	3 (2.1)	
Missing	10 (5.3)	3 (2.1)	
Language spoken at home [†]			0.023
English only	162 (85.3)	132 (93.6)	
English and other language(s)	25 (13.2)	8 (5.7)	
Missing	3 (1.6)	1 (0.7)	
Number of smokers in home			0.437
0	115 (60.5)	91 (64.5)	
1	39 (20.5)	27 (19.1)	
≥2	31 (16.3)	16 (11.3)	
Missing	5 (2.6)	7 (5.0)	
Disability status at 11 years			<0.0001
None	33 (17.4)	102 (72.3)	
Mild	80 (42.1)	37 (26.2)	
Moderate	55 (28.9)	2 (1.4)	
Severe	22 (11.6)	0 (0.0)	
Gestational age at birth			<0.0001
22 ⁺⁰ –22 ⁺⁶ weeks	1 (0.5)	—	
23 ⁺⁰ –23 ⁺⁶ weeks	18 (9.5)	—	
24 ⁺⁰ –24 ⁺⁶ weeks	59 (31.1)	—	
25 ⁺⁰ –25 ⁺⁶ weeks	112 (58.9)	—	
Term	—	141 (100.0)	

* χ^2 test.[†]Distinguished from ethnicity for which the comparison groups were matched. To our knowledge, all study children spoke English with varying levels of proficiency.

A-level, advanced level; BTEC, Business and Technology Education Council; CSE, certificate of secondary education; GCSE, general certificate of secondary education; HND, higher national diploma; NVQ, national vocational qualification; O-level, ordinary level.

costs (bootstrap 95% CI £493, £1052; $P < 0.001$), and £1716 in education costs (bootstrap 95% CI £877, £2517; $P < 0.001$). A more detailed breakdown of the costs of each study group is available upon request.

Relationships between the clinical and sociodemographic characteristics of the study population and total public sector

costs over the 12-month period are shown in Table 4. The generalized linear models revealed that even after controlling for clinical and sociodemographic confounders, extremely preterm birth was associated with significantly increased public sector costs. Model 1 revealed that, compared to birth at term, extremely preterm birth increased public sector costs by an

Table 2 Resource use and unit costs of resource items (UK pound sterling, 2006 to 2007 prices). Resource use values are given as means (SD) unless otherwise stated

Resource use variable, unit	Extremely preterm children (n = 190)	Classmates (n = 141)	Unit cost or range*
Community and social care services			
General practitioner, contacts	1.91 (3.28)	1.24 (1.40)	34.00 per contact [†]
Practice nurse, contacts	0.37 (1.11)	0.27 (0.70)	30.00 per contact [†]
Community nurse, contacts	0.03 (0.19)	0.02 (0.14)	23.00 per contact [†]
Community paediatrician, contacts	0.2 (0.54)	0.06 (0.47)	242.90 per contact [‡]
Dentist, contacts	1.74 (1.22)	1.65 (0.93)	70.02 per contact [‡]
Orthodontist, contacts	0.25 (0.73)	0.29 (1.08)	135.00 per contact [‡]
Optician, contacts	0.86 (1.52)	0.51 (0.76)	26.15 per contact [‡]
Chiropodist, contacts	0.06 (0.54)	0.01 (0.08)	16.00 per contact [‡]
Physiotherapist, contacts	1.35 (6.07)	0.08 (0.56)	40.00 per contact [†]
Speech therapist, contacts	1.20 (4.57)	0.01 (0.12)	40.00 per contact [†]
Audiologist, contacts	0.24 (0.74)	0.04 (0.35)	170.67 per contact [‡]
Social worker, contacts	0.27 (1.25)	0.09 (1.01)	39.00 per contact [†]
Home visitor/volunteer, contacts	0.04 (0.51)	0.00 (0.00)	19.00 per contact [†]
Counselor, contacts	0.26 (2.40)	0.03 (0.34)	34.00 per contact [†]
Psychologist, contacts	0.18 (0.88)	0.04 (0.35)	67.00 per contact [†]
Psychiatrist, contacts	0.03 (0.20)	0.01 (0.17)	256.00 per contact [‡]
Osteopath, contacts	0.14 (1.16)	0.04 (0.51)	42.89 per contact [‡]
Home teacher (portage), contacts	0.11 (1.45)	0.00 (0.00)	36.61 per contact [†]
Home teacher (other), contacts	2.56 (11.74)	0.38 (4.38)	36.61 per contact [†]
Orthoptist, contacts	0.08 (0.46)	0.01 (0.08)	57.57 per contact [†]
Orthotist, contacts	0.16 (0.99)	0.00 (0.00)	30.24 per contact [†]
Other community healthcare professionals, contacts	0.32 (1.52)	0.03 (0.27)	16.00–135.00 per contact ^{†,‡,§}
Hospital outpatient and day care services			
Accident and emergency care, attendances	0.18 (0.46)	0.29 (1.00)	39.25 per attendance [‡]
Hospital day unit, attendances	0.10 (0.77)	0.00 (0.00)	34.00–395.00 per attendance [‡]
Other outpatient care, attendances	0.84 (1.87)	0.22 (0.85)	34.00–395.00 per attendance ^{†,‡}
Hospital inpatient services			
Breathing difficulties, days	0.04 (0.51)	0.00 (0.00)	329.90–6195.11 per day [‡]
Surgery, days	0.17 (1.10)	0.02 (0.19)	329.90–6195.11 per day [‡]
ICU, days	0.00 (0.00)	0.00 (0.00)	329.90–6195.11 per day [‡]
Long-term illness, days	0.28 (3.13)	0.04 (0.51)	329.90–6195.11 per day [‡]
Other, days	0.23 (3.05)	0.01 (0.12)	329.90–6195.11 per day [‡]
Education services			
Mainstream school, n (%)	158 (83.2)	136 (96.5)	3,152.00 per annum
Mainstream school with special unit attached, n (%)	15 (7.9)	5 (3.5)	16,434.00 per annum
Special school, n (%)	17 (8.9)	0 (0.0)	16,434.00 per annum

*Ranges of unit costs are specified where unit costs varied according to type or intensity of care provided.

Source: [†]Netten and Curtis (2007); [‡]National Health Service Reference Costs (2006 to 2007); [§]Primary research; ^{||}Submissions to Department for Children, Schools and Families (2006 to 2007). ICU, intensive care unit; SD, standard deviation.

average of £1608 (95% CI £686, £2530; $P = 0.001$). Model 2 revealed that, compared to birth at term, birth at ≤ 23 completed weeks, 24⁺⁰–24⁺⁶ weeks and 25⁺⁰–25⁺⁶ weeks gestation increased public sector costs by an average of £2417 (95% CI £60, £4774; $P = 0.044$), £1528 (95% CI £129, £2927; $P = 0.032$) and £1501 (95% CI £428, £2574; $P = 0.006$), respectively. No other clinical or sociodemographic covariate had a significant impact upon public sector costs with the exception of long-term unemploy-

ment of both parents, which was associated with an average increase of £5088 (95% CI £193, £9983; $P = 0.042$) in model 1 and £5264 (95% CI £314, £10,213; $P = 0.037$) in model 2.

Comparisons of the frequency and proportion of suboptimal levels of function between the extremely preterm children and their classmates born at term are shown in Table 5 for each of the eight attributes of the Health Utilities Index Mark III. In all eight attributes (vision, hearing, speech, emotion, pain, ambulation,

Table 3 Mean costs and mean cost differences by cost category (UK pound sterling, 2006 to 2007 prices)

	Extremely preterm children (n = 190) Arithmetic mean	Classmates (n = 141) Arithmetic mean	Mean difference	(95% CI)*	P-value [†]
Hospital inpatient care costs	345.9	48.8	297.1	(114.8, 522.5)	0.007
Hospital outpatient and day care costs	158.0	50.2	107.9	(46.1, 165.8)	0.001
Total hospital costs	503.9	99.0	404.9	(203.9, 667.7)	0.001
Community health and social care costs	617.0	273.5	343.5	(223.1, 460.5)	<0.001
Drug/medication costs	23.7	11.7	12.0	(-1.0, 26.7)	0.097
Total health and social care costs	1144.7	384.3	760.4	(493.0, 1052.1)	<0.001
Education costs	5339.2	3623.0	1716.2	(877.3, 2517.2)	<0.001
Total public sector costs	6483.9	4007.3	2476.6	(1604.6, 3360.1)	<0.001

*Bootstrap estimation using 1000 replications, bias corrected.

[†]P-values calculated using Student's *t*-test.

CI, confidence interval.

Table 4 Clinical and sociodemographic factors predicting public sector costs (UK pound sterling, 2006 to 2007 prices) during the 11th year of life, generalized linear model with gamma distribution and linear (identity) link function

Factor	Model 1				Model 2			
	Adjusted regression coefficient ^a	Robust SE	95% CI	P-value	Adjusted regression coefficient ^a	Robust SE	95% CI	P-value
Gestational age at birth								
Classmate norms [†]								
All extremely preterm (model 1)	1,607.9	470.6	(685.5, 2,530.2)	0.001				
≤23 weeks (model 2) [‡]					2,416.8	1,202.7	(59.6, 4,774.0)	0.044
24 weeks (model 2)					1,527.9	714.0	(128.5, 2,927.4)	0.032
25 weeks (model 2)					1,500.9	547.3	(428.2, 2,573.6)	0.006
Gender								
Male [†]								
Female	-360.8	438.7	(-1,220.6, 499.0)	0.411	-382.0	449.8	(-1,263.5, 499.5)	0.396
Maternal marital status [§]								
Married [†]								
Single	2,303.8	1,286.9	(-218.6, 4,826.2)	0.073	2,283.9	1,298.5	(-261.1, 4,829.0)	0.079
Cohabiting	-58.7	730.9	(-1,491.2, 1,373.8)	0.936	-56.0	739.4	(-1,505.2, 1,393.2)	0.940
Widowed	-1,247.2	1,353.8	(-3,900.7, 1,406.2)	0.357	-1,325.4	1,367.0	(-4,004.6, 1,353.9)	0.332
Separated/divorced	436.2	813.4	(-1,158.1, 2,030.5)	0.592	378.2	813.2	(-1,215.7, 1,972.1)	0.642
Respondent parent's age [§]								
<30 [†]								
30-39	-932.9	1,853.4	(-4,565.5, 2,699.7)	0.615	-941.1	1,868.2	(-4,602.7, 2,720.4)	0.614
40-49	-471.3	1,865.6	(-4,127.8, 3,185.1)	0.801	-489.2	1,881.2	(-4,176.1, 3,197.8)	0.795
≥50	-311.1	2,141.8	(-4,508.8, 3,886.7)	0.885	-293.8	2,164.5	(-4,536.2, 3,948.6)	0.892
Type of accommodation [§]								
Owner occupied [†]								
Rented	-2,07.5	771.1	(-1,718.7, 1,303.7)	0.788	-205.6	770.2	(-1,715.1, 1,303.8)	0.789
Other	380.5	926.2	(-1,434.9, 2,196.0)	0.681	470.3	947.1	(-1,385.9, 2,326.5)	0.619
Access to car [§]								
Yes [†]								
No	-1,283.8	1,192.8	(-3,621.7, 1,054.1)	0.282	-1,215.4	1,201.4	(-3,570.1, 1,139.2)	0.312
Highest parental qualification [§]								
Vocational/NVQ/CSE [†]								
O-level/GCSE/Sc standards	30.0	721.4	(-1,383.9, 1,443.9)	0.967	-44.1	730.3	(-1,475.4, 1,387.1)	0.952
BTEC diploma/A-level/Sc highs	351.0	849.7	(-1,314.3, 2,016.3)	0.680	330.6	852.6	(-1,340.5, 2,001.7)	0.698
Diploma or HND	-373.5	885.1	(-2,108.4, 1,361.3)	0.673	-384.8	890.5	(-2,130.2, 1,360.5)	0.666
University degree	-325.5	893.8	(-2,077.2, 1,426.3)	0.716	-362.0	900.3	(-2,126.7, 1,402.6)	0.688
Postgraduate qualification	2,186.7	1,325.9	(-411.9, 4,785.4)	0.099	2,176.2	1,337.2	(-444.6, 4,797.0)	0.104
Other	1,098.5	1,082.1	(-1,022.4, 3,219.4)	0.310	1,029.0	1,093.5	(-1,114.2, 3,172.2)	0.347
None	-503.1	1,046.9	(-2,554.9, 1,548.7)	0.631	-555.4	1,053.2	(-2,619.6, 1,508.9)	0.598
Highest occupational status [§]								
Professional/managerial [†]								
Intermediate occupation	265.1	647.2	(-1,003.4, 1,533.6)	0.682	274.5	656.6	(-1,012.3, 1,561.4)	0.676
Routine and manual occupation	-5.0	571.1	(-1,124.3, 1,114.3)	0.993	23.9	576.5	(-1,106.0, 1,153.8)	0.967
Long-term unemployed	5,088.0	2,497.5	(193.1, 9,983.0)	0.042	5,263.8	2,525.3	(314.2, 10,213.3)	0.037
Language spoken at home [§]								
English only [†]								
English and other language(s)	-231.5	861.3	(-1,919.6, 1,456.6)	0.788	-174.8	921.6	(-1,981.0, 1,631.4)	0.850
Number of smokers in home [§]								
0 [†]								
1	-232.8	587.0	(-1,383.3, 917.7)	0.692	-285.6	589.9	(-1,441.7, 870.6)	0.628
≥2	1,493.6	822.7	(-118.8, 3,106.0)	0.069	1,345.3	844.5	(-309.9, 3,000.5)	0.111
Constant	6,381.1				6,352.3			

^aInterpreted as the additional costs over and above the reference group after adjustment for covariates.[†]Reference group.[‡]Includes child born at 22nd-27th weeks.[§]Cases with missing information omitted from analyses.

A-level, advanced level; BTEC, Business and Technology Education Council; CI, confidence interval; CSE, certificate of secondary education; GCSE, general certificate of secondary education; HND, higher national diploma; NVQ, national vocational qualification; O-level, ordinary level; Sc, Scottish; SE, standard error.

Table 5 Number (%) of children with suboptimal levels of function* within each Health Utilities Index Mark III attribute

Attribute	Gestational age at birth			All extremely preterm	Classmates	P-value‡
	≤23 weeks† (n = 19)	24 weeks (n = 59)	25 weeks (n = 112)	(n = 190)	(n = 141)	
Vision	7 (36.8)	19 (32.2)	35 (31.2)	61 (32.1)	11 (7.8)	<0.001
Hearing	1 (5.3)	5 (8.5)	5 (4.5)	11 (5.8)	1 (0.7)	0.015
Speech	5 (26.3)	16 (27.1)	16 (14.3)	37 (19.5)	5 (3.5)	<0.001
Emotion	5 (26.3)	9 (15.3)	21 (18.8)	35 (18.4)	9 (6.4)	0.002
Pain	3 (15.8)	14 (23.7)	23 (20.5)	40 (21.0)	14 (9.9)	0.007
Ambulation	1 (5.3)	8 (13.6)	7 (6.3)	16 (8.4)	0 (0.0)	<0.001
Dexterity	2 (10.5)	7 (11.9)	10 (8.9)	19 (10.0)	2 (1.4)	0.001
Cognition	9 (47.4)	33 (55.9)	57 (50.9)	99 (52.1)	24 (17.0)	<0.001

*Suboptimal levels of function defined as less than normal (below level 1) function for each attribute.

†Includes child born at 22⁺⁰–22⁺⁶ weeks.

‡Calculated using Fisher's exact test comparing all children born extremely preterm with classmate controls.

dexterity, and cognition), there were significantly higher proportions of suboptimal levels of function among the extremely preterm children ($P \leq 0.05$). When each extremely preterm subgroup was compared to the classmates born at term, there were significantly higher proportions of suboptimal levels of function across all attributes with the exception of hearing ($P = 0.214$), pain ($P = 0.430$), ambulation ($P = 0.119$) and dexterity ($P = 0.070$) for children born at ≤ 23 completed weeks gestation, emotion ($P = 0.058$) for children born at 24⁺⁰–24⁺⁶ weeks gestation and hearing ($P = 0.089$) for children born at 25⁺⁰–25⁺⁶ weeks gestation.

Table 6 presents descriptive statistics for the multi-attribute utility scores for the comparison groups. These multi-attribute utility scores summarize population preferences for the overall health state of the child across the eight attributes of the Health Utilities Index Mark III. The mean (SD) multiattribute utility score for the extremely preterm children as a cohort was 0.789 (0.264), compared to 0.956 (0.102) for the classmates born at term, a mean difference in utility score of 0.167 (95% CI 0.124, 0.209) that was statistically significant ($P < 0.001$). The mean multiattribute utility scores were also significantly lower in each of the three individual extremely preterm subgroups than in the classmates born at term ($P \leq 0.05$).

Finally, the Tobit regressions revealed that even after controlling for clinical and sociodemographic confounders, extremely preterm birth was associated with significantly reduced multi-attribute utility scores (Table 7). Model 1 revealed that, compared to birth at term, extremely preterm birth reduced the Health Utilities Index Mark III multiattribute utility score by an average of 0.280 (95% CI 0.204, 0.357; $P < 0.001$). Model 2 revealed that, compared to birth at term, birth at ≤ 23 completed weeks, 24⁺⁰–24⁺⁶ weeks and 25⁺⁰–25⁺⁶ weeks gestation reduced the Health Utilities Index Mark III multiattribute utility score by an average of 0.312 (95% CI 0.169, 0.455; $P < 0.001$), 0.337 (95% CI 0.235, 0.439; $P < 0.001$) and 0.243 (95% CI 0.159,

0.327; $P < 0.001$), respectively. The only other clinical or socio-demographic covariates associated with significantly reduced multiattribute utility scores were living in rented rather than owner occupied accommodation, a highest parental qualification of "other" compared to vocational or equivalent, a highest parental occupational status of routine and manual compared to professional or managerial, and a highest parental occupational status of long-term unemployed compared to professional or managerial ($P \leq 0.05$).

Discussion

Although the clinical sequelae of extremely preterm birth are well documented, relatively little is known about its consequences in cost or utility metrics that can inform cost-effectiveness modeling studies. Previous studies of the costs of extremely preterm birth have been criticized for their relatively poor methodological quality when assessed against current guidelines for conduct of health economic studies [22,23]. They have also been criticized for their narrow perspective, and their focus upon costs incurred during the neonatal period with few attempts to estimate the costs of the condition during later childhood [22,23]. Previous studies that have estimated the health-related quality of life associated with extremely preterm birth using preference-based measures have tended to categorize children in terms of birth weight, rather than gestational age at birth, and have identified children born prior to recent improvements in perinatal practices and intensive care technologies, thereby limiting their generalizability to the current clinical context [24–29].

This study estimated the costs and health utilities associated with extremely preterm birth on the basis of the largest (to our knowledge) cohort study of extremely preterm children in the world [30–32]. The children were drawn from defined geographical areas, namely the whole of the United Kingdom and Republic of Ireland, rather than clinic-based populations and,

Table 6 Health Utilities Index Mark III multiattribute utility scores

Group	N	Mean	(SD)	Mean decrement from classmates	P-value*
Classmates	141	0.956	(0.102)		
≤23 weeks†	19	0.772	(0.291)	–0.184	0.016
24 weeks	58	0.717	(0.333)	–0.239	<0.001
25 weeks	112	0.830	(0.208)	–0.126	<0.001
All extremely preterm	190	0.789	(0.264)	–0.167	<0.001

*Calculated using two-sample t-test for unequal variance.

†Includes child born at 22⁺⁰–22⁺⁶ weeks.

Table 7 Clinical and sociodemographic factors predicting Health Utilities Index Mark III multiattribute utility scores during the 11th year of life, Tobit regression

Factor	Model 1				Model 2			
	Adjusted regression coefficient*	SE	95% CI	P-value	Adjusted regression coefficient*	SE	95% CI	P-value
Gestational age at birth								
Classmate norms [†]								
All extremely preterm (model 1)	-0.280	0.039	(-0.357, -0.204)	<0.001				
≤23 weeks (model 2) [‡]					-0.312	0.073	(-0.455, -0.169)	<0.001
24 weeks (model 2)					-0.337	0.052	(-0.439, -0.235)	<0.001
25 weeks (model 2)					-0.243	0.043	(-0.327, -0.159)	<0.001
Gender								
Male [†]								
Female	0.098	0.036	(0.028, 0.168)	0.006	0.100	0.035	(0.030, 0.170)	0.005
Maternal marital status [§]								
Married [†]								
Single	0.035	0.105	(-0.172, 0.243)	0.737	0.032	0.105	(-0.175, 0.240)	0.758
Cohabiting	-0.070	0.061	(-0.189, 0.050)	0.253	-0.072	0.060	(-0.191, 0.047)	0.233
Widowed	0.056	0.150	(-0.239, 0.351)	0.708	0.081	0.151	(-0.216, 0.377)	0.592
Separated/divorced	0.028	0.056	(-0.083, 0.138)	0.624	0.017	0.056	(-0.093, 0.127)	0.759
Respondent parent's age [§]								
<30 [†]								
30–39	0.076	0.182	(-0.283, 0.434)	0.678	0.078	0.180	(-0.276, 0.431)	0.665
40–49	0.013	0.183	(-0.347, 0.372)	0.945	0.019	0.180	(-0.335, 0.374)	0.916
≥50	-0.115	0.200	(-0.508, 0.278)	0.564	-0.089	0.197	(-0.478, 0.300)	0.651
Type of accommodation [§]								
Owner occupied [†]								
Rented	-0.131	0.058	(-0.244, -0.017)	0.024	-0.116	0.058	(-0.230, -0.003)	0.044
Other	-0.081	0.071	(-0.220, 0.059)	0.254	-0.093	0.071	(-0.232, 0.046)	0.190
Access to car [§]								
Yes [†]								
No	0.307	0.124	(0.062, 0.552)	0.014	0.276	0.124	(0.032, 0.521)	0.027
Highest parental qualification [§]								
Vocational/NVQ/CSE [†]	-0.095	0.060	(-0.214, 0.024)	0.117	-0.081	0.060	(-0.200, 0.038)	0.183
O-level/GCSE/Sc standards	-0.133	0.069	(-0.268, 0.002)	0.053	-0.130	0.068	(-0.263, 0.004)	0.057
BTEC diploma/A level/Sc highers	-0.181	0.077	(-0.332, -0.030)	0.019	-0.156	0.077	(-0.308, -0.003)	0.045
Diploma or HND	-0.091	0.078	(-0.244, 0.062)	0.245	-0.080	0.077	(-0.232, 0.072)	0.299
University degree	-0.111	0.091	(-0.291, 0.068)	0.224	-0.093	0.091	(-0.273, 0.086)	0.306
Postgraduate qualification	-0.263	0.086	(-0.433, -0.093)	0.003	-0.263	0.085	(-0.431, -0.094)	0.002
Other	-0.195	0.098	(-0.387, -0.003)	0.047	-0.163	0.098	(-0.357, 0.031)	0.099
None								
Highest occupational status [§]								
Professional/managerial [†]	-0.096	0.050	(-0.195, 0.002)	0.055	-0.091	0.050	(-0.189, 0.006)	0.066
Intermediate occupation	-0.134	0.050	(-0.233, -0.036)	0.008	-0.125	0.050	(-0.224, -0.027)	0.013
Routine and manual occupation	-0.304	0.097	(-0.495, -0.113)	0.002	-0.319	0.097	(-0.510, -0.129)	0.001
Long-term unemployed								
Language spoken at home [§]								
English only [†]								
English and other language(s)	-0.013	0.065	(-0.142, 0.115)	0.838	0.011	0.067	(-0.121, 0.142)	0.870
Number of smokers in home [§]								
0 [†]								
1	0.001	0.050	(-0.097, 0.099)	0.986	0.001	0.049	(-0.096, 0.098)	0.988
≥2	-0.017	0.054	(-0.123, 0.089)	0.755	-0.024	0.054	(-0.130, 0.082)	0.658
Constant	0.864				0.846			
Pseudo R ²	40.3%				41.7%			

*Interpreted as the additional utility over and above the reference group after adjustment for covariates.

[†]Reference group.[‡]Includes child born at 22⁺0–22⁺6 weeks.[§]Cases with missing information omitted from analyses.

CI, confidence interval; Sc, Scottish; SE, standard error.

consequently, selection biases are unlikely to represent a major problem. The analysis also used a contemporaneous classroom control group born at full term and matched for age, sex, and ethnic group, rather than control data from siblings, which are prone to biases due to continuously changing developmental profiles throughout childhood, or comparisons with British population norms for which limited data are available [31,48]. The study used validated and reliable approaches to measuring and valuing the costs and health-related quality of life preference-based outcomes associated with extremely preterm birth. The study cost accounting was comprehensive and conducted in line with the methodological requirements for modern health economic evaluation. Notably, in our opinion, the study detected statistically significant differences in each of the broad categories of cost and preference-based health-related quality of life outcomes between the extremely preterm and term born children. The annual cost difference of almost £2500 per annum between the extremely preterm children and their term counterparts exceeds that identified for several other childhood conditions [49]. Similarly, the mean decrement in the multi-attribute utility score of 0.167, or once adjusted for confounders of 0.280, far exceeds the 0.030 minimally important difference in utility score postulated in the literature as clinically important for evaluative purposes [50,51].

There are a number of caveats to the study findings, which should be borne in mind by readers. First, given that the control group comprised solely classmates attending mainstream schools, it might be argued that this is a healthier group than would be expected in the normal population and we have overestimated cost and utility differences between the study groups. However, in the United Kingdom and Republic of Ireland, children with special education needs are largely integrated in mainstream schools. The prevalence of childhood disability requiring education in special schools is 1.1% in England [52]. Consequently, the inclusion of classmates for each extremely preterm child in separate schooling would most likely bias the comparison group. Moreover, separate standardized tests of academic attainment conducted in our study population revealed that classmates achieved mean scores expected for the normal population (reading score: mean 99, SD 12; math score: mean 99, SD 15) [53]. We are therefore confident that our control group adequately reflects the degree of health impairment in 11-year-old children. It is worth further noting that the extremely preterm children lost to follow-up at 11 years in our study were more likely to have had lower cognitive scores or cognitive impairment at 2.5 and 6 years, suggesting that, if anything, we might have underestimated the true extent of health impairment among these children and, by extension, the cost and utility differences between the study groups. A second caveat to the study findings is that the analysis of cost differences was conducted from a public sector perspective and encompassed costs to health, social, and education services. It is likely that birth at the borderline of viability has an economic impact upon other sectors of the economy and upon families and carers [22], suggesting that adopting a broader perspective would increase the cost differences between the study groups. A third caveat is that our cost estimates are based on parental reports of their child's resource utilization over the previous year of life. Previous research has indicated that parents accurately recall their child's hospital service utilization over extended periods when validated against medical records, but tend to under-report their child's community service utilization [54]. If this were the case for our study, our absolute costs for community service utilization may be underestimates. A fourth caveat is that each child's health-related quality of life was assessed by the main parent (usually the

mother) rather than the child itself. At the outset of the study, it was considered on the basis of preliminary research that the comprehension level required for the Health Utilities Index Mark III is somewhat high for our pediatric sample where a number of children have developmental disabilities. Empirical evidence of the concordance between child and parent ratings of attributes of the child's health-related quality of life suggests that parents are able to accurately rate observable behaviors, such as physical functioning and physical symptoms, but are less successful at identifying social or emotional impairments [55,56]. However, there is no consistent evidence to suggest that parents consistently either under-report or over-report social or emotional impairments [57], which suggests that there are unlikely to be systematic biases in the measurement of health-related quality of life in our study. Furthermore, our findings are broadly in keeping with the responses of adolescents aged 12–16 years in an international comparison study of extremely low birth weight adolescents in Canada, Germany, and The Netherlands [28]. A final caveat is that although the Health Utilities Index is the most widely used of the multi-attribute utility measures within the childhood context, the underlying preference weights for the Mark III health status classification system have been derived from a survey of Canadian adults. Recent research suggests that our approach of indirectly estimating health utilities by attaching population-derived utility scores to Health Utilities Index Mark III health states may be a poor substitute for directly measured utility scores at the individual level [58]. However, the cognitive requirements entailed in directly estimating utility scores for health states using techniques such as the visual analog, standard gamble, and time trade-off approaches precluded a direct measurement approach among our pediatric sample [55]. Moreover, many decision-making bodies, such as the National Institute for Health and Clinical Excellence in England and Wales, highlight the importance of valuing health outcomes using population-based preferences of the type we have used for the broader comparative purposes of economic evaluation [59].

How might the results of our study be used to inform economic evaluations of preventive and treatment interventions for extremely preterm birth? It is our view that cost-effectiveness assessments of new interventions in this area should ideally be based on evidence from randomized controlled trials with prospective assessments of costs using a validated client service receipt inventory and outcomes using a multi-attribute utility measure underpinned by population-based preferences. This approach is attractive in terms of its internal validity, minimization of bias and low incremental cost given the large fixed costs incurred by the prospective collection of clinical data [34]. The selection of the appropriate cost and multi-attribute utility measures for such studies should be informed by national technology assessment guidelines and an understanding of their psychometric properties within the childhood context, including their practicality, reliability, and validity. There are many circumstances, however, when prospective cost and utility measurement of this type is either insufficient or unfeasible. For example, within the context of trial-based economic evaluations, the analyst is often faced with extrapolating long-term costs and outcomes beyond the time horizon of the trial. Within the context of decision analytic modeling-based economic evaluations, the analyst is often faced with estimating costs and health utilities for a large number of health conditions or states with limited resources or time. Under such circumstances, our mean results and their associated distributions can act as data inputs for models of cost-effectiveness of preventive or treatment interventions for extremely preterm birth. Indeed, it might be argued that even where estimates of costs and health utilities associated with

extremely preterm birth are already available or can be estimated prospectively as part of an economic evaluation, our results could be viewed as an additional resource that should be pooled with the totality of the evidence base [46]. It should be noted, however, that analysts may face a particular methodological challenge when the time horizon for the cost-effectiveness model spans the entire period of childhood or further into adulthood. Under these circumstances, the impact of age on costs and health utilities should be estimated from data gathered in large-scale longitudinal studies as they become available. When such data are not available, techniques such as meta-regression of data across a number of studies should be considered as a means of disentangling age impacts [27].

In conclusion, the results of this study should be used to inform the development of future economic evaluations of interventions aimed at preventing extremely preterm birth or alleviating its effects. Further research is required that identifies, measures, and values the longer-term economic impacts of the condition in a valid and reliable manner.

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