Health-related quality of life and emotional and behavioral difficulties after extreme preterm birth: developmental trajectories

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Background: Knowledge of long-term health related outcomes in contemporary populations born extremely preterm (EP) is scarce. We aimed to explore developmental trajectories of health-related quality of life (HRQoL) and behavior from mid-childhood to early adulthood in extremely preterm and term-born individuals. **Methods**: Subjects born at gestational age ≤ 28 weeks or with birth weight ≤ 1000 grams within a region of Norway in 1991-92 and matched term-born control subjects were assessed at 10 and 18 years. HRQoL was measured with the Child Health Questionnaire (CHQ) and behavior with the Child Behavior Checklist (CBCL), using parent assessment at both ages and self-assessment at 18 years. **Results**: All eligible EP (n = 35) and control children participated at 10 years, and 31 (89%) and 29 (83%) at 18 years. At 10 years, the EP born boys were given significantly poorer scores by their parents than term-born controls on most CHQ and CBCL scales, but the differences were minor at 18 years; i.e. significant improvements had occurred in several CHQ (self-esteem, general health and parental impact-time) and CBCL (total problem, internalizing and anxious/depressed) scales. For the girls, the differences were smaller at 10 years and remained unchanged by 18 years. Emotional/behavioral difficulties at 10 years similarly predicted poorer improvement on CHQ-scales for both EP and term-born subjects at 18 years. Self-assessment of HRQoL and behavior at 18 years was similar in the EP and term-born groups on most scales. **Conclusions**: HRQoL and behavior improved towards adulthood for EP born boys, while the girls remained relatively similar, and early emotional and behavioral difficulties predicted poorer development in HRQoL through adolescence. These data indicate that gender and a longitudinal perspective should be considered when addressing health and wellbeing after extremely preterm birth.

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Introduction

Children born extremely preterm (EP) are at increased risk of cognitive and social shortcomings, neurosensory deficiencies, psychiatric disorders, lung problems, and cardiovascular disease (Doyle and Anderson 2010; Hack 2009). While early outcome studies of EP-born survivors focused mainly on those with major impairments, more attention is now being paid to consequences of less severe dysfunctions with high prevalence (Aylward 2005) that may have unfavorable consequences for later health-related quality of life (HRQoL) and social functioning. The sparse knowledge on functional issues and HRQoL in adults born preterm is largely based on studies of subjects born in the 1970-80s, and the impression is that the majority of those without major disabilities do well and live fairly normal lives (Doyle and Anderson 2010; Hack 2009; Moster and others 2008; Saigal 2013). However, neonatal intensive care went through major changes in the early 1990s, improving survival for the most immature and conceivably also the most vulnerable infants (Doyle and Anderson 2010; Wilson-Costello and others 2005). Thus, in Norway approximately 80% of all infants born more than 12 weeks preterm in 1999-2000 survived to discharge if resuscitated and admitted to neonatal intensive care (Markestad and others 2005).

Emotional and behavioral problems and reduced HRQoL have been described in children born EP in the 1990s (Berbis and others 2012; Johnson and Wolke 2013; Stahlmann and others 2009), but we do not know to what extent and in what ways such challenges persist to adulthood and how these issues relate to each other. Moreover, it is not known if potentially modifiable traits and characteristics may affect these outcomes, such as perceived self-efficacy. Adolescence is an important period in life, characterized by a pace in growth and development second only to that of infancy. Behavioral patterns established in this period have long-lasting effects on future health and well-being, for better or worse. In a cross-sectional study of 10 year old children born EP in

39   1991-92,we found that parent reported HRQoL was reduced in boys but not in girls (Vederhus

40   and others 2010). We know from other studies on HRQoL and behavior of children in general

41   that there are age-and gender-related differences which are particularly striking through puberty

42   (Bongers and others 2003; Michel and others 2009). Therefore our primary aim was to explore

43   gender-related development of HRQoL and emotional and behavioral difficulties through puberty

44   from 10 to 18 years of age in EP and term-born individuals, as reported by their parents.

45   Secondarily, we addressed these same issues by means of self-reports at 18 years of age, and

46   investigated the significance of perceived self-efficacy and associations between neonatal

47   variables and outcome at age 18.

Methods

Design and participants

50   A longitudinal cohort comparison design was applied. At first follow-up at 10 years of age in

51   2001-02, all survivors born at gestational age (GA) ≤ 28 weeks or with birth-weight (BW) ≤ 1000

52   g in 1991-92 within a defined area of Western Norway Health Authority and cared for at the only

53   neonatal intensive care unit in the region (Haukeland University Hospital) were invited (n = 35).

54   A matched comparison group was established by inviting the temporally nearest term-born child

55   (GA ≥ 37 weeks) of the same gender with BW between 3 and 4 kg (Norwegian 10th to 90th

56   percentile) for each EP-born participant. If that person declined, the next was approached and so

57   on, until a full 1:1 control group was recruited. A second follow-up was performed at 18 years of

58   age in 2008-09. A standard clinical examination was performed by the same pediatrician (TH) at

59   both ages and the medical history was obtained from parents, or in cases of doubt, from medical

60   records. Perinatal characteristics of the group born EP were obtained from medical records (Table

61   S1). Results from the first follow-up have been published (Vederhus and others 2010).

62   **Outcome measures - questionnaires**

63   Participants and parents completed the questionnaires in private, either at the site of the

64   examination or at home. Socio-demographic data were obtained from validated questionnaires

65   used in population studies in Norway, including questions of bullying, physical activity and

66   interaction with friends (The Nord-Trøndelag Health Study 2012; Wold, Smith, and Aaroe 1994).

67   *The Child Health Questionnaire (CHQ)*

68   HRQoL was assessed by using the CHQ-questionnaires which are generic instruments designed

69   to measure functional health and well-being of children by parent or self-report (Landgraf and

70   others 1999). The CHQ-scales address physical functioning, limitations in social functioning due

71   to physical, emotional or behavioral constraints, general health, pain, self-esteem, mental health

72   and behavior, impact on the parents in terms of emotional strain and time available for

73   themselves, and significance of the child's health on family activity and cohesion. A recall period

74   of the preceding four weeks is used, except for family cohesion and general health. Each item is

75   scored on a 4-6 point Likert scale, and the items in each sub-scale are summarized and

76   transformed into a scale ranging from 0 (poor) to100 (optimal). A validated Norwegian version

77   was used (Selvaag and others 2001). The parent version (CHQ-PF50) consists of 50 questions

78   within 13 scales and was completed at 10 and 18 years. The child form (CHQ-CF87) consists of

79   87 questions within 12 scales and was completed by self-assessment at 18 years.

80   *Child Behavior Checklist (CBCL) and Youth Self-Report (YSR)*

81   Emotional and behavioral difficulties and competencies were measured using validated

82   Norwegian versions of CBCL (parent) and YSR (self-report) (Achenbach and Rescorla 2001;

83   Novik 1999). The 1991 CBCL version was completed by the parents at 10 and 18 years, while the

84   2001 YSR version was completed by the children at 18 years. Based on the preceding 6 months

85   each problem-item is scored on a scale ranging from 0 (not true) to 2 (very true or often true),

86   making a total problem score ranging from 0-236 for the CBCL and 0-210 for the YSR. Two

87   broadband scales are composed from five of the eight derived syndrome scales, the internalizing

88   (withdrawn, somatic complaints, anxious/depressed) and externalizing (delinquent or rule-

89   breaking, aggressive behavior). The competence scales measure the amount and the quality of the

90   child's participation in organized activity, sports and hobbies, connection with friends and family,

91   and school performance. *Higher score* on each scale means *more* problems or *better*

92   competencies.

93   ***General Self-Efficacy (GSE)***

94   GSE denotes the perception of one's capacity to achieve a certain goal. It reflects confidence in

95   being able to cope across a wide range of challenging situations and seems to be important to

96   psychosocial functioning (Schwarzer and others 1997). A validated Norwegian 5-item version of

97   the original 10-item GSE scale was completed at 18 years (Roysamb, Schwarzer, and jer 1999).

98   Responses are rated from 'not at all true' (1) to 'exactly true' (4) and an overall mean value

99   ranging from 1 to 4 is calculated.

100   **Statistical methods**

101   Multiple linear, binary logistic and ordinal logistic regression analyses were used to analyse

102   continuous, binary and ordinal response variables. The mixed linear and generalized linear

103   regression modules in *SPSS* were used, taking the matched structure of EP and term-born subjects

104   (gender and age) and the repeated responses (10 and 18 years) into account. These methods allow

105   for contribution also from pairs with declines. Separate analyses for gender were applied for the

106   CHQ-PF50 and CBCL and as sub-analysis for the YSR. Interaction terms were used to assess

107   differences regarding effects of time by group, and gender by group when appropriate. The

108   regression models with self-reported outcomes were adjusted for gender, GSE, maternal

109   education, mild mental retardation and/or ADHD. Further, the regression models with parent-

110   reported changes from 10 to 18 years in the CHQ-scales as dependent variable and the CBCL

111   total problem score at 10 years as predictor variable were adjusted for gender, CHQ-PF50-scores

112   and maternal education at 10 years, and mild mental retardation and/or ADHD. In the group born

113   EP, backward stepwise linear regression analysis was applied to assess associations between

114   outcomes at 18 years and selected neonatal variables (gender, BW $\leq$ 10 percentile, intra-

115   ventricular hemorrhage, days on mechanical ventilation, and steroid treatment for

116   bronchopulmonary dysplasia). The parent-reported gender-related trajectories of CHQ-PF50 and

117   CBCL were also graphically displayed.

118   Power analyses were originally done when the present study was launched at age 10, based on

119   CHQ-PF50 summary scores (Vederhus and others 2010). Applying post-hoc analyses, the study

120   had 80% power to detect group differences of approximately 5.5 points, providing a significance

121   level of 0.05. Findings from that study suggested that stratification on gender would provide

122   important hypothesis-generating pilot data; hence, the present design despite loss of statistical

123   power. Group mean values are given with 95% confidence intervals to provide measures of

124   uncertainty.

125   **Ethics**

126   The study was approved by the Regional Committee on Medical Research Ethics of the Western

127   Norway Regional Health Authority (file no. 99.2000), and was performed in accordance with the

128   Helsinki Declaration. Informed consent was obtained for each participating subjects and their

129   parents.

130   **Results**

131   **Participants**

132   All eligible EP-born subjects (n = 35) participated at 10 years of age. On average, 1.3 term-born

133   children were approached to recruit a full 1:1 matched control group. Clinical and socio-

134   demographic characteristics at 10 and 18 years of age are presented in Table S1.

135   At 18 years, 31 (89%) of the EP and 29 (83%) of the term-born controls participated (four EP-

136   born females and four males and two females born at term declined). Twenty-three mothers and

137   seven fathers completed the questionnaires in the EP-born group vs. 22 mothers, five fathers and

138   one parent couple in the control group. There were one single parent and five divorced/separated

139   couples in both the EP and term-born group.

140   **Development from 10 to 18 years of age as reported by parents**

141   Results from the mixed linear regression of the CHQ-PF50-scales are presented in Table 1 and

142   illustrated in "Fig. 1". Parents of the EP-born subjects tended to give lower scores than parents of

143   the term-born peers at both 10 and 18 years. Split by gender, the differences were smaller for girls

144   than boys. For EP-born boys, the parents' scores tended to improve from 10 to 18 years on all

145   scales relative to those of the term-born controls; however, significant only for self-esteem,

146   general health and parental impact-time (group by age interaction). For the EP-born girls the

147   score trajectories did not differ from those of the controls.

148   Results from the mixed linear regression of the CBCL-scales are presented in Table 2 and

149   illustrated in "Fig. 2". Similarly to that of CHQ-PF50, the parents of the EP-born subjects tended

150   to give their children poorer scores than the parents of the term-born controls on all scales at both

151   ages, but the differences were largely greater for the boys. Relative to the controls the scores

152   tended to improve from 10 to 18 years for the boys, although this relative improvement was

153   significant only for the total problem, internalizing and anxious/depressed scales (group by age

154   interaction). For the EP-born girls the score trajectories did not differ from those of the controls.

155   Competence scores remained significantly poorer for both genders at 18 years.

156   **Factors influencing development of HRQoL from 10 to 18 years**

157   When adjusting for gender, ADHD/mild mental retardation, maternal education and CHQ-PF50-

158   scores at 10 years in the mixed linear regression model, higher CBCL total problem score at 10

159   years predicted poorer development of CHQ-PF50 scale-scores from 10 to 18 years. This effect

160   was statistically significant for the scales role/social-emotional/behavioral, bodily pain, mental

161   health, self-esteem, emotional impact on the parents and family cohesion (Table 3). The effects

162   were similar for the subjects born EP and at term. However, the effect of gender was different in

163   the EP vs. the term-born subjects, in that EP-born boys showed significantly greater improvement

164   in the domains mental health and self-esteem while girls showed no such improvement.

165   **Self-reported CHQ and YSR at 18 years**

166   The EP-born and term-born adolescents scored themselves similarly on CHQ-CF87, and the

167   scores were also similar after adjusting for gender, GSE, ADHD/mild mental retardation and

168   maternal education in regression models (Table 4). Split by gender, EP-born females had lower

169   scores on self-esteem in the unadjusted but not in the adjusted model. For the males, there were

170   no group differences in the unadjusted analyses, but in the adjusted model males born EP scored

171   better than males born at term on the scales role/social emotional and self-esteem (group by

172   gender interaction).

173   On the YSR, the EP and term-born males scored themselves similarly while the EP-born females

174   gave poorer scores than term-born females on the withdrawn and anxious/depressed scales (1.5;

175   95% CI: -0.0 to 3.1; $p = 0.05$ and 2.7; 95% CI: 0.2 to 5.1; $p = 0.03$, respectively) and the social

176   competence scale (-1.6; 95% CI: -2.7 to -0.5; $p = 0.008$). In the adjusted model, EP-born subjects

177   reported significantly fewer externalizing problems than their term-born peers (Table 4).

178   GSE score was positively associated with most of the CHQ-CF87-scales and negatively

179   associated with the internalizing, externalizing and total problem scale on the YSR in both EP

180   and term-born adolescents (Table 4).

181   **Influence of neonatal variables in EP-born subjects at 18 years**

182   In the backward stepwise linear regression analysis, only number of days of mechanical

183   ventilation remained a significant predictor of the three CBCL scales social, thought and

184   attention; $b = 0.09$; 95% CI: 0.03 to 0.15 (adjusted $R^2 = 0.22$), $b = 0.06$; 95% CI: 0.03 to 0.09

185   (adjusted $R^2 = 0.29$), and $b = 0.16$; 95% CI: 0.07 to 0.25 (adjusted $R^2 = 0.28$), respectively. No

186   significant associations were found with any of the CHQ-scales.

187   **Discussion**

188   To our knowledge, this is the first controlled study reporting longitudinal parent assessments of

189   HRQoL and emotional and behavioral difficulties from mid-childhood to early adulthood in

190   subjects born EP in the 1990s. At 10 years of age, boys born EP were assessed as having

191   substantially more problems with emotion/behavior, competence and HRQoL than peers born at

192   term, while at 18 these differences were considerably smaller. For the girls, differences were

193   generally smaller and did not change much during puberty. Emotional and behavioral difficulties

194   at 10 years of age were associated with less favorable development of HRQoL through puberty in

195   both the EP and the term-born group. However, judged by self-reports at 18 years, HRQoL and

196   emotional/behavioral issues were scored relatively similar in the EP and term-born groups, except

197   that EP-born girls reported more withdrawal, anxiety and depression and lower social

198   competence. GSE was associated with better HRQoL and less emotional and behavioral

199   difficulties irrespective of group.

200   **Developmental trajectories**

201   Our longitudinal data obtained from the parents suggest that negative consequences of preterm

202   birth on HRQoL and behavior tend to diminish over time for boys. A positive development of

203   HRQoL corresponds with data presented in a review article, but in that paper it was discussed

204   whether improvements reflected a shift from parent to self-report which is known to give

205   different assessments (Zwicker and Harris 2008). Contrary to our findings a previous study of

206   EP-born and term-born subjects born in 1977-82 reported that all participants perceived a small

207   decrease in HRQoL from adolescence to young adulthood, but that was by self-reports (Saigal

208   and others 2006). A decline in general health was reported also by children born with extremely

209   low birth-weight in 1992-95 and their term-born controls from 8 to 14 years of age (Hack and

210   others 2012). The difference in HRQoL and behavior trajectories between EP-born boys and girls

211   observed in our study may be due to the fact that girls were assessed as having fewer difficulties

212 at 10 years and therefore had less room for improvement. Also to be considered is that girls in

213 general, tend to have a less favorable development of HRQoL and mental health through puberty

214 than boys (Bongers and others 2003; Michel and others 2009). There were, however, still

215 differences in scores between EP and term-born subjects of both genders at 18 years. It is

216 therefore likely that some differences in HRQoL and behavior will remain towards young

217 adulthood. Regarding the significance of gender, studies of EP-born subjects have been

218 inconsistent in that more emotional/behavioral difficulties have been described for males at 17

219 years (Grunau and others 2004) as well as for females at 20 years (Hack and others 2004).

220 Internalizing symptoms in eight year old EP-born girls predicted persistent internalizing

221 symptoms at 20 years in a study by Hack et al. (Hack and others 2005), which is in accord with

222 our observation.

223 Normal behavior and HRQoL are important premises for social functioning, and the

224 improvements towards that of peers born at term at young adulthood are reassuring in terms of

225 the likelihood of living normal self-supportive lives. This notion is supported by a register-based

226 study of adults in Norway which, after excluding people on disability pensions, demonstrated that

227 level of education and chance of having a paid job only marginally decreased with degree of

228 prematurity (Moster and others 2008). However, these adults were born during 1967-83 when

229 few EP-born infants survived.

230 Inferior HRQoL has been reported in children and adolescents with behavioral problems (Klassen

231 and others 2004), also in children born EP (Saigal and others 2006; Verrips and others 2012). In

232 one study, internalizing behavior at eight years predicted poorer HRQoL at 13 years in children

233 born with very low birth-weight or very preterm, but not in the term-born control children (Wolke

234 and others 2013). In contrast, we found that emotional/behavioral difficulties at 10 years

235 predicted less improvement in HRQoL at young adulthood both for EP-born and term-born

236   subjects, suggesting that the effect of behavior is a general phenomenon and not related to

237   prematurity *per se.*

Self-assessment at 18 years

239   The finding that EP and term-born individuals scored their HRQoL similarly is in agreement with

240   most reports on survivors of preterm birth (Hack and others 2007; Indredavik and others 2005;

241   Roberts and others 2013; Saigal and others 2006), but in contrast to some who report inferior

242   mental health and well-being (Lund and others 2012; Methusalemsdottir and others 2013; Saigal

243   and others 2007). Earlier reports on behavior are more inconsistent (Boyle and others 2011; Dahl

244   and others 2006; Grunau and others 2004; Hack and others 2004; Lund and others 2012; Saigal

245   and others 2003). Interestingly, the EP-born males reported their self-esteem to be better than the

246   term-born males, whereas the scores were opposite for the females. This gender difference was in

247   agreement with their parents' assessments. Others have also reported that self-esteem of EP-born

248   adolescents was comparable to that of controls, but not the gender difference observed in the

249   present study (Roberts and others 2013; Saigal and others 2002).

250   Contrary to a previous study (Verrips and others 2012), we found that confidence in the ability to

251   achieve goals (GSE score) was positively associated with self-reported HRQoL and emotional

252   health irrespective of group. This finding may be important because GSE is a trait that can be

253   modified and strengthened by interventions (Axelsson and others 2012). Moreover, it was

254   encouraging that EP-born subjects reported fairly similar levels of leisure time activities and

255   social interaction as term-born peers, which is contrary to previous reports of disadvantages in

256   sports and friendship (Dahan-Oliel and others 2012; Hallin and Stjernqvist 2010). Bullying in

257   preterm born adolescents have been reported (Grindvik and others 2009), but was not found in

258   the present study.

259   Little is known concerning the significance of neonatal exposures on later HRQoL and emotional

260   issues. Neonatal morphine exposure and neonatal procedural pain predicted internalizing

261   behavior in 7-year old very preterm born children in one study (Ranger and others 2013). We

262   found an association between duration of mechanical ventilation and emotional problems at 18

263   years. In the present we have previously reported on a negative association between neonatal

264   corticosteroid treatment and social functioning at ten years (Vederhus and others 2010), but no

265   such association was found at 18 years.

266   **Strengths and weaknesses**

267   The major strengths of this study were the population-based and controlled design and high

268   follow-up rate, and that the assessments were made by the same research team on both occasions.

269   No subjects in this birth-cohort had major impairments, and there were no exclusions for medical

270   reasons, thus the results may not be generalized to those with severe neurodevelopmental

271   impairments. The use of both parent- and self-reports facilitated better understanding of

272   developmental patterns.

273   The limitation of this study was primarily a relatively low number of participants, and positive as

274   well as negative findings must therefore be cautiously interpreted. HRQoL research is

275   characterized by a high number of endpoints, challenging a priori power calculations, which was

276   further complicated in this study by partly unknown distributions in preterm born populations,

277   and by the longitudinal perspective. Although debatable (Fayers and Machin 2007), a post hoc

278   power analysis was reported at age 10 (Vederhus and others 2010), indicating a between-group

279   detection limit of 5.5 for CHQ-PF50 summary scores, a figure considered adequate by the creator

280   (Landgraf and others 1999). Stratifying by gender reduced the size of the groups, and therefore

281   also statistical power. Nevertheless, this was considered important and necessary, given the

282   findings at age 10 and the known influence from gender during puberty on the issues under study.

283   Given the relatively small sample size, the present findings should primarily be considered

284   hypothesis-generating pilot data and an incitement for future research, preferably in larger

285   population samples. To a large extent we have given 95% confidence intervals for calculated

286   group mean values, in order to indicate the reliability of the estimates.

Conclusion

287

288   For EP-born boys, parents' assessments of HRQoL, emotion and behavior improved towards that

289   of term-born controls from 10 to 18 years of age, and for both genders and for children born EP

290   and at term emotional/behavioral difficulties at 10 predicted less improvement in HRQoL at age

291   18. As there were still some important group differences at age 18, we are concerned that our

292   findings may herald difficulties in a complex and demanding adult life. The present pilot data

293   imply that gender and a longitudinal perspective are important aspects when addressing HRQoL

294   and behavioral issues after preterm birth, and that these issues should be considered in clinical

295   work as well as in future and preferably larger studies.

Acknowledgements

We sincerely thank the children and their parents who gave of their time to take part in this

follow-up study.

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Parent-reported Child Health Questionnaire at 10 and 18 years of age in EP-and term-born children

Table 1. Parent-reported **C**hild **H**ealth **Q**uestionnaire at 10 and 18 years in EP- and term-born children

	Boys			Girls		
Age at follow-up:	10 years (n = 26)	18 years (n = 22)		10 years (n= 44)	18 years (n = 38[a])	
CHQ-PF50 scales	Estimated mean difference (95% CI) EP vs. term-born	Estimated mean difference (95% CI) EP vs. term-born	Tests of interaction group by age p-values[b]	Estimated mean difference (95% CI) EP vs. term-born	Estimated mean difference (95% CI) EP vs. term-born	Tests of interaction group by age p-values[b]
Physical functioning	-7.9 (-15.7,-0.2)	-2.3 (-10.9,6.3)	0.33	-2.3 (-6.3,1.8)	-5.4 (-9.8,-0,9)	0.31
Role/social - emotional/behavioral	-23,9 (-42,2,-5.7)	-8.4 (-28.5,11.8)	0.25	-4.0(-11.5,3.4)	-3.8 (-11.9,4.3)	0.96
Role/social - physical	-10.3 (-19.8,-0.7)	-4.4 (-15.0,6.2)	0.56	-0.8 (-7.6,6.1)	-1.1(-8.6,6.4)	0.95
Bodily pain	-8.5 (-22.6,5.7)	-6.8[c] (-23.1,9.5)	0.96	-2.7 (-15.2,9.8)	-3.9[c] (-17.8,9.9)	0.89
Behavior	-24.2 (-37.7,-10.6)	-7.8 (-22.7,7.2)	0.11	-6.4 (-13.4,0.6)	-4.8 (-12.5,2.9)	0.76
Mental health	-8.8 (-18.3,0.6)	-0.5(-11.0,9.9)	0.24	-3.9 (-8.8,1.1)	-7.0 (-12.5,-1.6)	0.39
Self-esteem	-8.3 (-19.8,3.1)	11.3 (-1.6,24.1)	0.03	-5.5 (-13.6,2.6)	-7.5(-16.4,1.3)	0.74
General health	-27.8 (-39.2,-16.5)	-7.5 (-20.2,5.2)	0.02	-17.2 (-26.3,-8.2)	-11.2 (-21.2,-1.3)	0.38
Parental impact -emotional	-35.3 (-52.9,-17.6)	-11.7 (-31.3,7.8)	0.08	-12.5 (-20.3,-4.7)	-8.0 (-16.6,0.6)	0.44
Parental impact - time	-21.4(-31.9,-10.8)	-3.8 (-15.6,8.1)	0.03	-7.1 (-12.3,-1.8)	-2.1 (-7.8,3.7)	0.21
Family activity	-23.1 (-38.6,-7.5)	-2.8 (-20.2,14.6)	0.09	-6.7 (-14.6,1.2)	-5.5 (-14.2,3.2)	0.84
Family cohesion	-2.3 (-16.9,12.3)	5.1 (-11.3,21.5)	0.50	-3.2 (-13.1,6.8)	-0.6 (-11.5,10.3)	0.73

EP = extremely preterm. Higher scores in each of the CHQ scales reflect better outcome (range 0-100).
a) One report was missing
b) From mixed linear model: interaction-term testing if development from 10 to 18 years differed in the EP vs. the term-born group
c) One missing

Parent-reported Child Behavior Checklist at 10 and 18 years in EP- and term-born children.

Table 2. Parent-reported **C**hild **B**ehavior **C**heckli**st** at 10 and 18 years in EP- and term-born children

	Boys			Girls		
Age at follow-up:	10 years (n = 26)	18 years (n = 22)		10 years (n= 44[a])	18 years (n = 38[b])	
CBCL scales	Estimated mean difference (95% CI) EP- vs. term-born	Estimated mean difference (95% CI) EP- vs. term-born	Tests of interaction group by age p-values[c]	Estimated mean difference (95% CI) EP- vs. term-born	Estimated mean difference (95% CI) EP- vs. term-born	Tests of interaction group by age p-values[c]
Total problem	37.3 (20.7,54.0)	9.8 (-8.9,28.5)	0.03	9.6 (2.4,16.8)	9.8 (2.1,17.4)	0.97
Internalizing	10.3 (5.3, 15.3)	2.1 (-3.5,7.7)	0.03	2.6 (-0.7,5.8)	5.6 (2.2,9.1)	0.20
Externalizing	11.1(4.9,17.3)	2.2 (-4.8,9.2)	0.06	2.3 (-0.7,5.2)	1.8 (-1.4,5.0)	0.82
Withdrawn	2.8 (1.1,4.5)	0.3 (-1.6,2.2)	0.06	1.3 (0.1,2.5)	2.4 (1.2,3.7)	0.21
Somatic complaints	1.8 (0.4,3.2)	0.6 (-1.0,2.2)	0.28	0.04 (-1.3,1.4)	0.1 (-1.4,1.6)	0.96
Anxious/depressed	6.2 (3.1,9.2)	1.0 (-2.4,4.4)	0.03	1.3 (-0.3,3.0)	3.4 (1.7,5.2)	0.08
Social problems	3.9 (2.3,5.5)	1.7 (-0.1,3.5)	0.07	2.6 (1.6,3.6)	1.3 (0.2,2.4)	0.09
Thought problems	2.2 (1.0,3.3)	0.7 (-0.7,2.0)	0.09	0.2 (-0.1,0.5)	0.2 (-0.2,0.5)	0.75
Attention problems	6.2 (3.7,8.7)	2.8 (-0.03,5.6)	0.07	2.2 (0.9,3.4)	1.2 (-0.2,2.6)	0.30
Delinquent behavior	2.2 (0.8,3.7)	0.2 (-1.4,1.8)	0.07	-0.02 (-0.8,0.8)	0.1 (-0.7,1.0)	0.78
Aggressive behavior	8.8 (3.8,13.8)	2.0 (-3.6,7.7)	0.08	2.3 (-0.2,4.8)	1.6 (-1.0,4.3)	0.73
Total competence	-3.2[d] (-6.1,-0.4)	-3.7[e] (-7.1,-0.2)	0.84	-3.8[f] (-5.8,-1.7)	-5.0[e] (-7.3,-2.8)	0.39
Activities	-0.5[g] (-1.7,0.6)	-0.8[g] (-2.1,0.5)	0.78	-1.4[g] (-2.4,-0.3)	-1.4[g] (-2.5,-0.3)	0.93
Social competence	-1.0[d] (-2.4,0.5)	-1.2 (-2.8,0.3)	0.81	-1.6[g] (-2.7,-0.5)	-2.0[d] (-3.2,-0.7)	0.66
School competence	-2.0 (-2.9,-1.0)	-2.0[h] (-3.2,-0.8)	0.96	-1.0[g] (-1.6,-0.4)	-0.6[f] (-1.3,0.0)	0.38

EP = extremely preterm. Higher score on each of the CBCL scales reflects more problems or better competencies.
a) Two reports were missing
b) One report was missing
c) Mixed linear model. Interaction-terms assessing if the differences between the EP and the matched term-born control groups were different at ten and 18 years of age
d) Two missing e) Five missing f) Three missing g) One missing h) Four missing

Predictors for changes in parent reported health-related quality of life from 10 to 18 years of age for EP- and term-born children

Table 3. Predictors for changes in parent reported health-related quality of life from 10 to 18 years of age for EP- and term-born children

Response variable	Explanatory variables[a]		
CHQ-PF50 scale changes (score range 0-100)	**Gender**[b]	**EP- vs. term-born** (n = 57) **b (95%CI)**	**CBCL total problem score at 10 years**[c] **b (95% CI)**
Physical functioning		-2.0 (-6.7,2.7)	-0.1 (-0.2,0.1)
Role/social – emotional/behavioral		0.8 (-9.2,10.9)	-0.7 (-1.0,-0.3)***
Role/social – physical		0.9 (-6.0,7.8)	-0.1 (-0.3,0.1)
Bodily pain[d]		7.1 (-4.1,18.3)	-0.4 (-0.7,-0.02)*
Behavior		1.9 (-5.9,9.6)	-0.2 (-0.5,0.03)
Mental health	Boys Girls	8.5[e] (-1.1,18.2) -4.8 (-10.8,1.2)	-0.3 (-0.5,-0.04)*
Self-esteem	Boys Girls	19.3[f](8.9,29.6) -5.0 (-11.6,1.5)	-0.3 (-0.5,-0.1)**
General health		-2.7 (-10.0,4.4)	-0.03(-0.2,0.2)
Parental impact – emotional		1.5 (-6.8,9.8)	-0.3 (-0.6,-0.1)*
Parental impact - time		0.9 (-2.9,4.8)	-0.1 (-0.3,0.01)
Family activity		1.4 (-6.4,9.3)	-0.2 (-0.5,0.1)
Family cohesion		3.5 (-6.5,13.5)	-0.4 (-0.6,-0.1)*

EP = extremely preterm, CHQ = Child Health Questionnaire-Parent Form50
a) Mixed linear regression model adjusted for CHQ-scores at 10 years, gender, maternal education at 10 years and attention deficit hyperactivity disorder/mild mental retardation (n=5).
P-values given as * $\leq$ 0.05; ** $\leq$ 0.01; *** $\leq$ 0.001, positive b indicates improved outcome.
b) Estimates are given specifically for boys and girls when there was a significant interaction group by gender.
c) Child Behavior Checklist – total problem score: negative association of total problem score indicates that high level of problems at 10 years of age predicts less improvement in CHQ-scores to 18 years.
d) Two missing
e) Interaction p-value = 0.017
f) Interaction p-value < 0.001

Self-reports at 18 years of age in adolescents born EP and at term

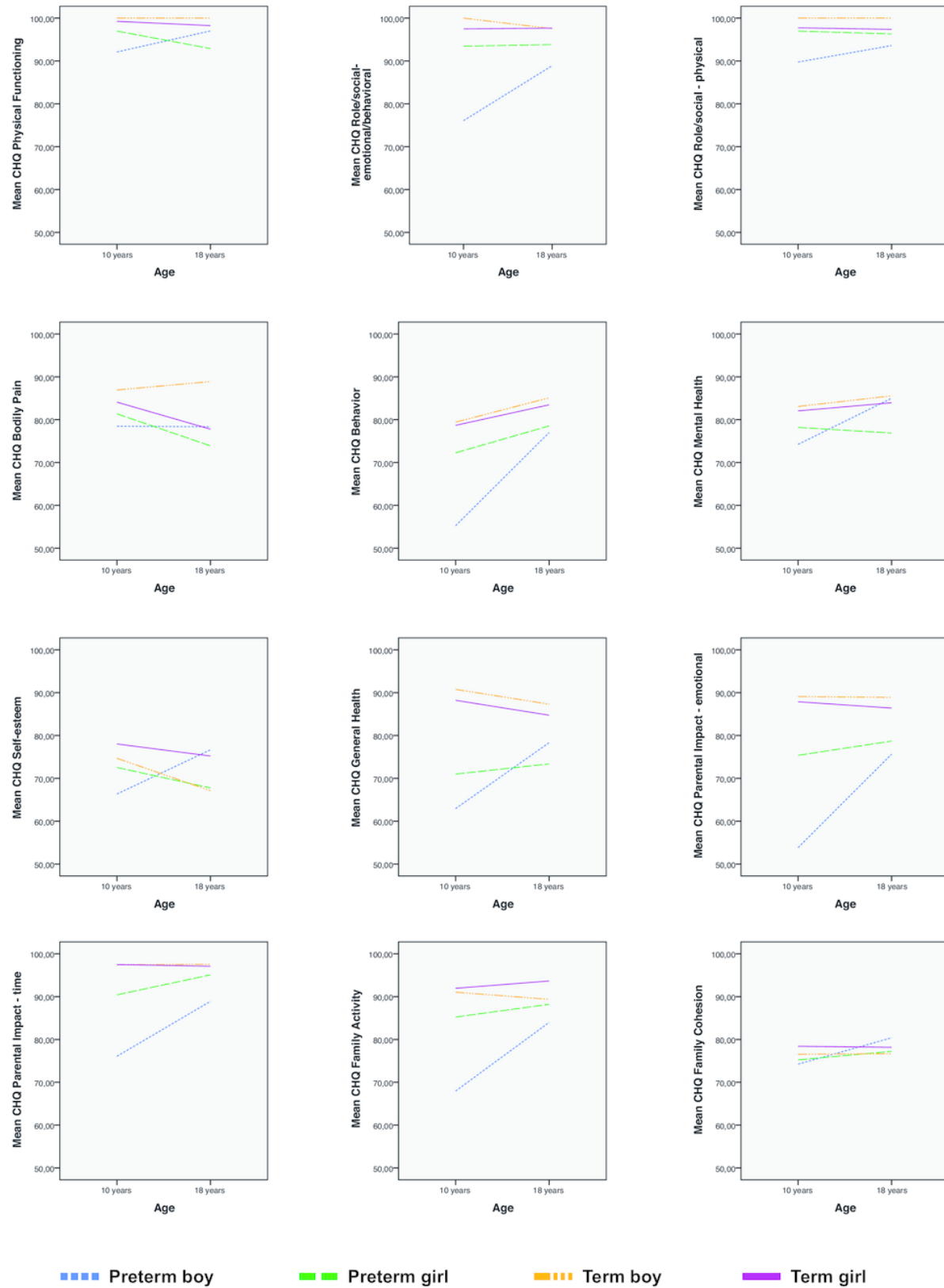
Table 4. Self-reports at 18 years of age in adolescents born EP and at term

Response variable CHQ-CF87 (range 0-100)	Unadjusted results				Adjusted results[a]		
	EP-born (n = 31) mean (SE)	Term-born (n = 29) mean (SE)	EP- vs. term-born estimated mean differences (95% CI)	P-value	EP- vs. term-born b (95% CI)	GSE score b (95% CI)	Interaction term group by gender EP- vs. term-born b (95% CI)
Physical functioning	93.7 (2.9)	98.5 (0.6)	-4.4 (-9.0,0.2)	0.06	-0.4 (-5.4,4.7)	5,4 (1.3,9.6)*	
Role/social-emotional	88.9 (3.9)	92.7 (2.7)	-3.9 (-14.2,6.3)	0.44		13.6 (6.1,21.1)**	Boys: 17.9 (1.8,34.0)[b] Girls: -1.7 (-12.9,9.5)
Role/social-behavioral	95.0 (2.8)	99.2 (0.5)	-6.7 (-16.4,2.9)	0.16	2.0 (-2.8,6.7)	5.2 (0.6,9.8)*	
Role/social-physical	94.6 (2.9)	100.0 (0.0)	-5.4 (-11.6,0.8)	0.09	-0.1 (-6.4,6.3)	8.7 (3.9,13.6)**	
Bodily pain	74.2 (4.4)	76.6 (4.2)	-2.1 (-13.8,9.6)	0.71	5.4 (-6.6,17.4)	-0.4 (-10.8,10.0)	
Behavior	76.2 (3.0)	78.2 (1.9)	-1.9 (-9.1,5.3)	0.59	4.6 (-2.6,11.8)	9.9 (3.9,15.8)**	
Mental health	72.9 (3.2)	75.1 (2.1)	-2.1 (-10.1,5.8)	0.59	2.5 (-5.9,10.9)	10.6 (4.1,17.1)**	
Self-esteem	69.7 (2.9)[d]	75.4 (2.6)	-6.1 (-14.4,2.3)	0.15		15.1 (9.4,20.9)***	Boys: 14.2 (3.4,25)[c] Girls: -5.2 (-12.7,2.2)
General health	70.4 (3.3)	73.7 (3.1)	-3.0 (-11.6,5.6)	0.49	3.7 (-5.9,13.3)	11.6 (3.8,19.5)**	
Family activity	88.0 (3.3)	91.4 (2.5)	-3.8 (-13.1,5.5)	0.40	1.0 (-8.6,10.6)	3.4 (-3.8,10.7)	
Family cohesion	74.5 (4.9)	74.5 (4.7)	0.1 (-13.9,14.0)	0.99	7.6 (-7.5,22.7)	15.1 (2.7,27.5)*	
YSR:							
Total problems (range 0-210)	33.0 (5.2)	29.1 (3.1)	3.7 (-8.7,16.1)	0.54	-9.9 (-21.6,1.9)	-20.7 (-30.3,-11.1)***	
Internalizing (range 0-62)	10.2 (2.0)	8.2 (1.2)	1.9 (-2.8,6.6)	0.41	-2.9 (-7.4,1.5)	-9.4 (-12.8,-6.0)***	
Externalizing (range 0-64)	8.4 (1.3)	9.8 (1.0)	-1.4 (-4.7,1.9)	0.39	-3.9 (-7.4,-0.5)*	-3.3 (-6.1,-0.4)*	

EP = extremely preterm, CHQ = Child Health Questionnaire-Child Form87, YSR = Youth Self-Report, GSE = General Self-Efficacy (score range 1-4). Higher scores reflect better outcome on the CHQ, but more problems on the YSR.
a) Mixed linear model adjusted for gender, maternal education at 10 years of age, and attention deficit hyperactivity disorder/mild mental retardation. If interaction term group by gender was not significant (p > 0.05) model without is reported. P-values given as * p < 0.05, ** p < 0.01 *** p < 0.001
b-c) Test of interaction assessing if differences between boys and girls were different in the EP and the term-born group; p= 0.040 and p=0.003, respectively.
d) Split by gender, EP female 66.6 vs. term-born female 78.8, p-value = 0.009

1

Parent-reported changes on the Child Health Questionnaire-scales from 10 to 18 years

Displayed for extremely preterm- and matched term-born control subjects split by gender: increasing scores imply improvements

Parent-reported changes on the Child Behavior Checklist-scales from 10 to 18 years

Displayed for extremely preterm- and matched term-born control subjects split by gender: decreasing scores imply improvements