Title Page

Authors: Frances M Cronin[1], Ricardo Segurado[2], Fionnuala M McAuliffe[3], Cecily C Kelleher[1], Richard E Tremblay[1, 4].

Affiliations:

[1] School of Public Health, Physiotherapy and Sports Science, University College Dublin, Ireland

[2] UCD CSTAR, School of Public Health, Physiotherapy and Sports Science, University College Dublin, Ireland.

[3] UCD Obstetrics & Gynaecology, School of Medicine and Medical Science, University College Dublin, National Maternity Hospital, Dublin, Ireland.

[4] Departments of Pediatrics and Psychology, University of Montreal, Canada.

Manuscript title: Gestational age and chronic 'body-mind' health problems in childhood: Dose-response association and risk factors

Corresponding Author: Frances M Cronin. School of Public Health, Physiotherapy and Sports Science, University College Dublin, Ireland. T: + 353 1 716 3478 E: fran.cronin@ucd.ie.

Conflicts of Interest and Source of Funding: This work was supported by the Health Research Board, Ireland [grant number HRA_PHS/2011/35] to RT. There are no conflicts of interest to disclose.

Abstract

Understanding the developmental course of all health issues associated with preterm birth is important from an individual, clinical and public health point-of-view. Both the number of preterm births and proportion of survivors have increased steadily in recent years. The UK Millennium Cohort Study (n=18 818) was used to examine the association of gestational age with maternal ratings of general health and behavior problems at ages 5 and 11 years using binary and multinomial logistic regression analyses. The association between mothers' ratings of general health and behavior problems was relatively weak at each time point. Children rated as being in poor general health remained constant over time (4.0% at age 5, 3.8% at age 11), but children rated as having behavioral problems increased by almost 100% (5.6% at 5; 10.5% at 11). A gradient of increasing risk with decreasing gestational age was observed for a composite health measure (general health problems and/or behavior problems) at age 5, amplified at age 11 and was strongest for those with chronic problems (poor health at both age 5 and age 11). This association was found to be compounded by child sex, maternal characteristics at birth (education, employment, marital status) and duration of breast feeding. Integrated support to at-risk families initiated during, or soon after pregnancy, may prevent chronic problems and might potentially reduce long term health costs for both the individual and health services.

Keywords Preterm Birth, Behavior Problems, Health Problems, Sex Differences, Breast Feeding, Millennium Cohort Study.

Introduction

A recent worldwide study of the increase in premature births estimated that every year 15 million babies are born preterm (PT). Of these, over one million babies a year die from prematurity, and survivors are at high risk of long term health impairments [1]. However, while the World Health Organisation (WHO) defines health as a 'state of complete physical, mental and social well-being' [2], it is striking that, to the best of our knowledge, most studies of health issues associated with being born prematurely have focused either on physical health outcomes only or mental health outcomes only. Thus, the extent of the impact of PT birth on health and health services is difficult to ascertain as a distinction between mental and physical illness continues in both lay and medical circles, and persists in scientific publications [3].

This silo mentality regarding the consequences of PT birth is well illustrated in a recent paper published in a high impact medical journal [4]. The Boyle et al., (2012) paper used the Millennium Cohort Study (MCS) - a longitudinal study with a large population sample - and described an increase in health problems during early childhood as gestational age (GA) decreases. However, while numerous aspects of physical health (e.g. hospital admissions, longstanding illnesses, asthma etc.) were assessed, the study did not include any dimension of mental health, although data on the children's behavior problems were available.

Unless physical and mental outcomes are extensively comorbid in most cases, the silo approach to understanding the consequences of prematurity is underestimating the number of premature babies that suffer long term adverse health outcomes. Furthermore, to plan appropriate preventive and treatment services it is important to understand the developmental courses of both physical and mental health problems related to PT births.

There appears to be a general consensus that PT children of school-going age - compared to their full term (FT) peers - are at increased risk of symptoms associated with behavior problems [5, 6]. However, study findings for behavior problems outcomes have been inconsistent [7]: some report those born PT as being at a ‘significantly higher risk’ of later behavioral problems [5], and others report a relatively ‘modest’ risk of later behavioural problems (e.g. [8]). Clarity in this area is especially needed as behaviour problems in childhood have been identified as risk factors for later adult mental health problems [9-12].

An additional challenge to synthesising studies of children’s physical health and studies of behavior problem outcomes related to prematurity is the use of a variety of methodologies, instruments, sample recruitment criteria [13-16], and overlapping gestation categories [17]. For example, while most studies compare cohorts of children born FT (39-41 weeks) with cohorts of PT children, the selection of ‘preterm’ categories can differ between studies (e.g. ≤33 weeks gestation [8]; <30 weeks [6]; <26 weeks [18]; <25 weeks [19]). Others focus only on the higher-risk children (e.g. those born <22 weeks [20]), or compare specific ranges of GAs (e.g. 22–32 weeks [5], or ‘mature preterm’ 32-36 weeks gestation [4]) with FT births. Finally, possibly due to the financial and organizational challenges inherent in long-term, population-based follow-ups, most long-term studies of children born PT have assessed health outcomes at only one point in time [21]. Repeated assessments of outcomes are important in order to understand to what extent adverse health outcomes are of a chronic nature and how the different types of problems might be associated with each other (e.g. [22, 23]).

The main objective of the present study was to replicate, as far as possible the methodological approach of the Boyle *et al*., (2012) paper on physical health to investigate the association of PT birth with both physical health problems and behavioral problems. Their population-based longitudinal study compared children born at FT with PT children categorized by GA: namely 37-38 weeks, 34-36 weeks, 32-33 weeks, and 23-31 weeks [24]. They reported a ‘dose-response’ effect of prematurity on children’s health: as GA decreased, parents were more likely to assess their child's general health as 'Poor' or 'Fair', and report more *physical* health problems (i.e. hospital admissions, longstanding illnesses and asthma) up to age five years. Studies of the effect of GA commonly adjust for factors known to affect children's health and development [4]. Multiple studies conducted over the past decade have demonstrated the significant impact of a variety of demographic and environmental factors on the health outcomes of children of school-going age. Factors include the child's sex [25], ethnicity [26] and age at time of interview; maternal characteristics at time of the pregnancy including maternal education [27], marital status, occupation and age at delivery and maternal behavior including smoking and/or drinking during pregnancy [28] and duration of breastfeeding [29].

The MCS gathered a wealth of information on a wide range of factors that have been associated with childhood health, including familial and parental living arrangements, use and type of early childcare facilities used by the family, and parental psychosocial well-being, including self-esteem, life satisfaction, feeling of control, quality of their relationship and social support. However, these (and others available) factors were not included in the present study in order to facilitate comparison of sample descriptives, and results of modelling with the Boyle et al (2012) study on which the current study is based.

Thus, the present study used the same dataset, established the same sample, and matched adjustment variables and outcomes, in order to extend the 'health outcome' findings reported by Boyle et al (2012) to an assessment of behavior problem.

In summary, this research had three aims: Firstly, to examine the association between a general assessment of health and a general assessment of behavioral problems at the start and at the end of middle childhood (age 5 and age 11). Secondly, to describe the association between categories of GA and a composite measure of chronic general health problems and/or behavioral problems at age 5 and at age 11. The third aim was to identify within this sample what perinatal risk factors were associated with chronic ’composite’ health problems at ages 5 and 11.

Materials and Methods

Sample

The MCS is a well-documented, on-going, nationally representative prospective cohort study begun in 2002, and based in the United Kingdom (UK). Full details of the study have been reported previously [30]. The population-based cohort study (n=18818) comprised all children born in the UK who were living in the jurisdiction at the time of the first survey, and the UK register of social payment of child benefit was used as eligibility criterion. The present study used the data on behavior and general health collected at age 5 (first year of primary school) and at age 11 (final year of primary school).

In order to extend the outcome to include behavioral problems, and thereby facilitate comparison with Boyle *et al.*, previously published findings [4] their baseline measures, categorical estimators, adjustment variables and specific selection strategies were replicated.

As this research involved secondary analysis of the MCS, ethical approval was not required.

Gestational age

GA categories replicate those used in Boyle *et al.* [4] and are consistent with commonly used categories stratified on established guidelines set out by the European Foundation for the Care of Newborn Infants (EFCNI, [24]: very preterm (VPT, <31 weeks), moderate preterm (MPT, 32-33 weeks), late preterm (LPT, 34-36 weeks), early term (ET, 37-38 weeks) and FT (39-41 weeks).

Outcome measures

General Health Status

General health at each time point was assessed by using a parent's response (usually the mother) to the question 'How would you rate your child's health?' using a five-point Likert scale: 'Excellent', 'Very good', 'Good', 'Fair' or 'Poor' [5]. Responses to this question have been shown to be strongly correlated with alternative or 'hard' measures of children's health including number of episodes of hospitalization in the previous 12 months, chronic childhood conditions (e.g. asthma, epilepsy, heart condition) and number of bed days due to illness [31], and has been used previously to ascertain health status in a non-clinical sample [4, 5].

Behavioral Health Status

Behavior problems at both 5 and 11 years were assessed using a parent's rating of behavior (usually the mother) on the Strengths and Difficulties Questionnaire (SDQ, Goodman [32]). The SDQ asks the respondent (primary care giver) to rate the child over 20 items, divided equally between four behavior problem categories: Emotional problems (e.g. 'Many fears, easily scared'); Conduct problems (e.g. 'Has temper tantrums or hot tempers'); Hyperactivity-inattention (e.g. 'Restless, overactive, cannot stay still for long'); and Peer problems (e.g. 'Picked on or bullied by other children') [32, 33]. Scored on a three point scale: 'not true' (scoring 2), 'somewhat true' (scoring 1) and 'certainly true' (scoring 0) (and with items reverse scored as appropriate), the Total Difficulties (TD) score ranges from 0 to 40. A TD score of 17 (90^{th} centile) or more is considered 'abnormal' and of use to screen for child psychiatric disorders in a community sample [34]. Furthermore, it is regarded as helpful in identifying the course and prediction of mental health problems in children and adolescents in the general population [35].

The internal consistency of the TD score for both age 5 (α coefficient = .79; [36]) and age 11 (.88) were in line with Goodman (.82) [32].

Composite health

This binary variable created two groups at each time point (age 5 and 11 years): a) those who were rated as having 'Poor' or 'Fair' health and/or given a rating of 17 or higher on the SDQ Total Difficulties score: b) those who were not rated as having 'Poor' or 'Fair' health and/or given a rating of 17 or higher on the SDQ Total Difficulties score.

Longitudinal health

To capture the changes in the 'composite health' assessment from age 5 to age 11, a second binary variable of 'longitudinal health' status was created. This variable identified children who had poor composite health at both time points and those who did not.

Statistical methods

The sample design of the MCS was such that a representation of the total population was possible, while at the same time sufficient numbers of key subgroups (areas of high child poverty, ethnic minorities and residents of smaller countries) were included for analysis.

It included geographical clustering (at UK electoral ward level) and disproportionate stratification (using nine different strata - each country in the UK (England, Wales, Scotland and Northern Ireland) having two strata: advantaged and disadvantaged and one additional strata for ethnic minorities for England). Multiple births (twins and triplets) were included for comparison purposes in the descriptive overview of the MCS sample, but were excluded from the regression analyses as multiple births are more likely to be PT - or induced PT [37].

Because of the MCS sampling design, methods employed for simple random sampling or independence of observations could not be used as this would lead to an underestimation of standard errors and subsequent invalid significance tests. All analyses were therefore completed using Complex Sampling Plans (CSPLAN; SPSS Statistics 20) commands (for further details see [38])) resulting in all reported numbers, percentages and means being appropriately weighted for non-response and attrition for each particular survey dataset(s). Furthermore, it was necessary to analyze the subpopulation of 'singleton births only' using a 'subgroup' function within the CSPLAN that adjusts the non-response and attrition weights appropriately. It should be noted that failure to employ a 'subgroup' function when interrogating any subset of these MCS datasets leads to incorrect variance estimation and misleading significance testing because of the misapplication of the pre-defined weighting scheme [38].

Baseline measures of interest in predicting child health at ages 5 and 11 were those identified and reported by Boyle [4]. These comprised established risk factors which were dichotomized. Adjustment variables included child gender, child race/ethnicity (White British/Other), mother's marital status (Single mother/Other), maternal use of alcohol during pregnancy (≥3 units per week or ≥3 units per occasion), maternal smoking during pregnancy, breastfeeding (3-level variable 'Never tried', 'Breastfed for less than 4 months' (reference level) and 'Breastfed for at least 4 months'). Adjustments were also made for mother's education (Degree/No degree) and work status (3-level variable 'Professional/Managerial' (reference level), Long-term unemployed (Y/N), all others). Finally the mother's age at time of birth was also included.

Poor physical health was identified by primary care-giver rating of the child's general health as being 'Poor' or 'Fair' on the General Health measure [31]. Behavior problems at age 5 and age 11 were identified by using a dichotomized score of ≥17 on the TD score of the SDQ

[32]. These two outcomes were used to create one binary variable showing the child's 'composite health status' at each time point (age 5, age 11 and at both age 5 and 11). This group (with difficulty in at last one area of health during at least one time point) was compared to the cohort of children whose parents had rated them with both a TD score of <17 and also a general health rating as 'Excellent', 'Very good' or 'Good' at all time points.

Logistic regression with appropriate CSPLANS and subgroup analyses for 'singleton births only' was used to investigate the associations of adverse composite health outcomes (physical and/or mental health) with GA category at both age 5 and age 11. Unadjusted (results not shown) and fully-inclusive models were run for each exposure-outcome group in order to adjust for potential confounders. The FT group was used as the reference level for each GA category. For the longitudinal analysis, multinomial logistic regression was applied to avoid assumptions of proportional odds in the outcome groups.

Results and Discussion

The Sample

Subject-level exclusions were matched to those made by Boyle *et al.*, [4] and included: children with missing GA, those born later than 42 weeks gestation, those whose birth weight and GA were deemed improbable (i.e. outside twice the interquartile range from the median birth weight centile based on Bonellie's [39] centile charts for GA, sex and parity) and respondents other than the natural birth mother.

Table 1 presents the characteristics of the mothers of children who were included in the analysis and replicate the findings from Boyle *et al*. This confirmed the same baseline measurements from which to continue the current longitudinal investigation. Mothers of children born <32 weeks (VPT) were, on average, younger than mothers of children born closer to term. They were least likely to be educated to degree level, and most likely to have no formal qualification. They were found to be most likely to have smoked during pregnancy and least likely to have breastfed for longer than four months.

Table 1 Characteristics of mothers of children included in the analysis. Values are n(%) unless otherwise stated.

Mother's Characteristics[a]	**Gestation at birth (weeks)** VPT (<32) (n=206)	MPT (32-33) (n=184)	LPT (34-36) (n=1058)	ET (37-38) (n=3607)	FT (39-41) (n=12565)	**P values comparing GA groups**[b]
Age at time of child's birth (years) Mean: (95% CI)	28.4 (27.3, 29.5)	29.7 (28.5, 30.9)	28.9 (28.4, 29.5)	29.2 (28.9, 29.5)	28.7 (28.5, 29.0)	0.001
Single mother	41 (18.5)	26 (9.4)	208 (16.4)	603 (14.0)	2104 (14.1)	0.065
Moderate/heavy alcohol use during pregnancy[c]	12 (7.0)	12 (6.8)	61 (6.9)	237 (6.7)	885 (7.3)	0.917
Smoked during pregnancy	59 (29.4)	46 (17.9)	286 (25.0)	824 (21.3)	2734 (20.2)	0.003
Socioeconomic status:						
Managerial/Professional	50 (24.6)	45 (27.9)	275 (30.6)	922 (29.0)	3356 (30.5)	0.414
Long term unemployed	21 (7.5)	21 (8.8)	118 (8.6)	417 (8.6)	1422 (8.2)	
Education:						
Degree	59 (29.8)	50 (31.3)	297 (30.0)	994 (30.2)	3752 (33.7)	<0.001
No qualifications	47 (21.6)	28 (11.3)	184 (14.1)	626 (14.4)	1948 (12.3)	
Duration of breastfeeding						
Never	62 (28.2)	52 (27.9)	415 (35.1)	1327 (33.4)	4220 (29.5)	<0.001
≥ 4 months	39 (19.2)	36 (23.0)	222 (23.6)	951 (28.9)	3883 (34.6)	

CI Confidence Interval; ET Early term; FT Full term; LPT Late preterm; MPT Moderate preterm; VPT Very preterm.

[a]Numbers, means and percentages are weighted with appropriate sampling and non-response weights for the dataset(s) used.

[b]χ^2 tests for categorical variables and F tests for continuous variables; calculated for weighted, clustered data.

[c]≥ 3 units/week or ≥ 3 units/occasion.

Characteristics of the children involved in this study are reported in Table 2 and match those reported by Boyle [4]. The average birth weight of the children increased as GA increased. A greater proportion of those born at <32 weeks were from ethnic groups other than 'White British'. Being of multiple birth and/or first born increased the likelihood of being born <34 weeks.

Table 2 Characteristics of children from the Millennium Cohort Study included in this analysis. Values are n(%) unless otherwise stated.

Child's Characteristics[a]	**Gestation at birth (weeks)** VPT (<32) (n=206)	MPT (32-33) (n=184)	LPT (34-36) (n=1058)	ET (37-38) (n=3607)	FT (39-41) (n=12565)	**P values comparing**

						GA groups[b]
Birth weight (kg) Mean: (95% CI)	1.3 (1.2, 1.3)	1.9 (1.9, 2.1)	2.6 (2.5, 2.6)	3.1 (3, 3.2)	3.5 (3.5, 3.5)	<0.001
Male sex	123 (57.9)	96 (57.3)	566 (53.7)	1882 (51.9)	6370 (50.6)	0.081
Multiple birth	39 (20.3)	43 (28.3)	178 (17.1)	178 (5.2)	59 (0.4)	<0.001
First born	103 (51.3)	93 (52.9)	497 (47.9)	1342 (37.6)	5369 (42.5)	<0.001
Length of neonatal hospital stay (weeks) Mean (95% CI)	9.1 (8.0, 10.2)	3.3 (3.0, 3.6)	1.4 (1.3, 1.6)	0.5 (0.5, 0.6)	0.4 (0.4, 0.4)	<0.001
Ethnic group:						
White British	156 (79.5)	153 (88.4)	880 (88.1)	2919 (85.6)	10516 (87.9)	<0.001
Other[c]	50 (20.5)	30 (11.6)	178 (11.9)	683 (14.4)	2029 (12.1)	

CI Confidence Interval; ET Early term; FT Full term; LPT Late preterm; MPT Moderate preterm; VPT Very preterm.

[a]Numbers, means and percentages are weighted with appropriate sampling and non-response weights for the dataset(s) used.

[b]χ^2 tests for categorical variables and F tests for continuous variables; calculated for weighted, clustered data.

[c]Mixed, Indian, black Caribbean/black African, Bangladeshi/Pakistani, Other.

General and Behavioral Health problems over time

At age 5 and at age 11, the proportion of children who were rated as being in ‘Poor’ or ‘Fair’ health remained constant across the two time points (4.0% of the population at 5 (n=601), 3.8% at 11 (n=403)). However, across these same two time points there was almost 100% increase in the proportion of children rated as having behavior problems (5.6% at 5 (n=745); 10.4% at 11 (n=996)).

Interestingly, of the singletons with both health and behavior ratings (n=13051), the association between ratings of general health and behavior problems was relatively low at each time point. At age 5, 745 (5.6%) of the children were rated as having behavior problems. However, only 14.0% of these (n=103) were amongst the 601 (4.0%) children who had been rated as having ‘Poor’ or ‘Fair’ health. Similarly at age 11, 994 (10.5%) of the children were rated as having behavior problems. However, still only 12.6% of these (n=125) were amongst the 403 (3.8%) children who had been rated as having ‘Poor’ or ‘Fair’ health at this time point.

Association between gestational age categories and the composite physical/behavioral health outcome

Three logistic regression analyses were conducted – two binary logistic models with the cross-sectional datasets (data at age 5 and data at age 11) and one multinomial logistic model with the longitudinal dataset (combining data from age 5 and age 11) – using, where necessary, the subgroup function available in SPSS CSPLANs. A small dose-response of significant GA group effects at age 5 was observed, with a larger dose-response effect at age 11 (see Table 3a). Table 3b reports the same dose-response trend - albeit stronger - for those with health problems at both age 5 and age 11.

Early predictors of the composite physical/behavioral health problem outcomes

Table 3a shows the associations between the composite (physical and/or behavioral) health problem outcomes and the early risk factors included in the logistic regression analysis for the cross sectional data at age 5 and age 11 and for the longitudinal analysis (to identify chronic cases).

The significant risk factors for poor outcome at age 5 were: being other than 'White British'; mother not in managerial/professional role; mother smoking during pregnancy; mother being long-term unemployed; mother being single, mother not being educated to degree level; child being breastfed for less than 4 months and child being male. The significant risk factors at age 11 were: mother smoking during pregnancy; mother not being educated to degree level; mother being single; mother not in managerial/professional role; child being breastfed for less than 4 months and child being male.

Results from the longitudinal analysis (chronic problems i.e. occurring at both age 5 and age 11) indicate that while fewer risk factors were significant, effects were stronger than at a single time point (i.e. at age 5 only or age 11 only). Significant factors were mother being single; mother smoking during pregnancy; mother not being educated to degree level; mother's age at time of birth; mother being long-term unemployed; child not being breastfed for at least 4 months and child being born male.

Associations between individual outcomes ('Poor'/'Fair' health or behavior problem) and the early risk factors for each, at each age (5 and 11 years) are reported in Supplementary Table 1.

Table 3 a) Binary Logistic Regression for Cross-Sectional Data on Physical and/or Behavioral Health Problems at Age 5 and at Age 11 Adjusted for all Covariates. b) Multinomial Logistic Regression Analysis for Chronic General and/or Behavioral Health Problems (both Age 5 and Age 11) Adjusted for all Covariates.

	a) Cross-Sectional data		**b) Longitudinal data**
	Age 5[a]	**Age 11[a]**	**Ages 5 & 11 [a]**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**
Gestational Categories[b]			
Very preterm (<32 weeks)	2.0 (1.2, 3.2)[c]	3.9 (2.2, 7.1)[c]	4.2 (1.7, 10.3)[c]
Moderate preterm (32-33 weeks)	2.7 (1.5, 4.8)	2.6 (1.4, 4.7)	3.9 (1.8, 8.8)
Late preterm (34-36 weeks)	1.4 (1.0, 1.8)	1.7 (1.3, 2.3)	1.8 (1.0, 3.2)
Early term (37-38 weeks)	1.3 (1.0, 1.5)	1.1 (0.9, 1.3)	1.2 (0.9, 1.6)
Additional Perinatal Risk Factors			
Child sex (Male)	1.5 (1.3, 1.7)[c]	1.7 (1.4, 1.9)[c]	2.4 (1.8, 3.2)[c]
Ethnic group: not White British	1.8 (1.4, 2.2)[d]	1.1 (0.9, 1.4)	1.4 (0.9, 2.2)
Not firstborn	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)	1.0 (0.8, 1.3)
Mother's age at time of birth	1.0 (1.0, 1.0)	0.98 (0.96, 0.99)	1.0 (1.0, 1.0)[d]
Single mother	1.5 (1.3, 1.8)[c]	1.5 (1.2, 1.8)[c]	2.1 (1.5, 2.8)[c]
Not manager/professional role	1.7 (1.4, 2.1)[c]	1.3 (1.0, 1.6)[d]	1.5 (0.9, 2.3)
Being long term unemployed	1.6 (1.3, 1.9)[c]	1.2 (1.0, 1.6)	1.7 (1.1, 2.6)[d]
Not degree level education	1.5 (1.2, 1.8)[c]	1.6 (1.4, 2.0)[c]	1.8 (1.3, 2.6)[c]
Alcohol use during pregnancy[e]	1.0 (0.8, 1.3)	1.2 (0.9, 1.6)	1.2 (0.8, 1.9)
Smoked during pregnancy	1.7 (1.5, 5.0)[c]	1.6 (1.3, 1.8)[c]	1.9 (1.5, 2.5)[c]
Breastfed <4 months	1.4 (1.2, 1.8)[c]	1.3 (1.0, 1.5)[d]	1.5 (1.1, 2.2)[d]
Child age at assessment (age 5)	0.8 (0.6, 1.1)	n/a	0.7 (0.3, 1.5)
Child age at assessment (age 11)	n/a	0.8 (0.6, 1.0)	0.9 (0.5, 1.7)

OR Odds Ratio; CI Confidence Interval.

[a]Results are weighted with the sampling and non-response weights appropriate for the dataset(s) used.

[b]Full term used as reference level.

[c]Sig @ < 0.001.

[d]Sig @ ≤ 0.05.

[e]≥ 3 units/week or ≥ 3 units/occasion.

Discussion

This study used a very large population-based cohort to examine the association between gestational age (GA) and childhood health problems at age 5 and 11 years as well as changes in this association from age 5 to age 11 years. To the best of our knowledge this is the first large scale longitudinal study to assess both general health problems and behaviour problems in their association with GA.

Results showed that the comorbidity between parental assessments of general health problems and behaviour problems is relatively small - both at age 5 and 11 years - suggesting that parents (and most likely the general public) do not consider serious behaviour problems as 'health' problems. This suggests that studies which aim to assess health problems according to the WHO comprehensive definition [2] are generally missing a crucial health component which is estimated to affect more children than physical health problems. This tendency might hamper early identification of, and therefore delay early interventions for, behavior problems that have been identified as risk factors for later adult mental health problems (see [11, 40, 41]).

The associations between GA and poor general health and/or clinically relevant behavior problem ratings showed a dose-response trend of GA at age 5 and at age 11. The strongest dose-response of GA was observed for children with chronic general and/or behavioral health problems (i.e., problems at both age 5 and age 11). These results indicate that the negative associations of low GA with comprehensive health problems during the elementary school years is more clearly estimated by using a composite physical and mental health index over an extended period of time. This is an important finding with reference to understanding the long term impact of low GA. Previous studies which focus on either physical or mental health problems have clearly underestimated the amplitude of the negative consequences of low GA.

Further analyses - with this longitudinal study and others - are needed to identify the developmental course of the different health components within our composite health assessments as well as to identify their putative interactions. For example, a sub-group may have physical health problems at age 5 which lead to an onset of behavioral problems during the elementary school years (or vice versa), while another sub-group may have one or other forms of health problems during the elementary school years only. It is important to identify these different developmental courses and their predictors in order to put in place effective preventive and therapeutic measures.

The study also identified perinatal factors that are associated with chronic general and/or behavioral health problems during childhood: child sex, maternal education, maternal employment, single motherhood, maternal smoking during pregnancy and duration of breast feeding. Except for child sex and single motherhood, these risk factors are also significantly associated with low GA (Table 1). Thus, our results suggest that preventive interventions targeting pregnant women with these risk factors might reduce not only the risk of low GA [42], but also the long term negative outcomes associated with low GA [43-46].

A major advantage of using the MCS to examine the association between GA, chronic behavior problems and general health problems during middle childhood is that the sample size allows a comparison of relatively small GA groups. However, despite being one of the largest, on-going, population-based longitudinal studies of children's development from early childhood onwards, the number of children in the lowest GA categories is still relatively small. Furthermore, as in many other studies of this type, the reliance on the maternal ratings of child health might also be considered a limitation as maternal ratings alone have been shown to be influenced by factors including maternal characteristics and socio economic status [13, 47, 48]. Finally, further studies using this cohort might consider expanding crucial developmental variables (e.g. breast feeding duration and/or socioeconomic status of the family) beyond the binary versions preferred by Boyle *et al*. and possibly including other crucial developmental variables that are available including parental habitation status, childhood caregiving arrangements etc. However, considerations on extending the number of adjustments must be cognizant of the small sample size in some of the GA groups, and the possibility of ‘over-adjusting’ for factors which may be on the causal chain from early GA (and its own causes) to health outcomes.

In summary, this study indicates that GA - or degree of prematurity - has a strong ‘dose-response’ association with chronic health problems over the period of middle childhood. While studies at one single time point and/or employing a single dimension (general health or behavioral health) reflect this trend, longitudinal analyses of a composite measure of health provides a clearer picture of the strength of association of poor health outcomes with prematurity. This dose-response association is compounded by child sex (males of low GA are at more risk than females), maternal characteristics at birth (education, employment, marital status) and duration of breast feeding. Integrated support to the at-risk families initiated during the perinatal period and appropriate corrective interventions during early childhood may reduce the adverse outcomes, and in turn substantially reduce long term physical/mental health costs to both the individual and health services. Further analyses of the joint developmental trajectories of the different components of the composite health assessment with the MCS and similar studies might also provide insight into the developmental interactions between physical and mental health problems, thus providing useful information to plan preventive and corrective interventions from early childhood to pre-adolescence.

Supplementary Information

Supplementary Table 1 Binary Logistic Regression for Cross-Sectional Data. Odds ratios (OR) and Confidence Intervals (95% CI) for A) Physical Health Problems only and B) Behavior Health Problems only at Age 5 and at Age 11 Adjusted for All Covariates.

	Odds ratios of parent rating (OR (95% CI)			
	A) Child's health as 'Poor' or 'Fair' compared with 'Good', 'Very good' or 'Excellent'		**B) Child's behavior with Total Difficulty score ≥ 17 compared with a Total Difficulty score of <17**	
	Age 5 only [a]	**Age 11 only [a]**	**Age 5 only [a]**	**Age 11 only [a]**
Very preterm (<32 weeks)	2.04 (1.05-3.95) [c]	6.11 (2.77-13.50) [c]	2.24 (1.27-3.93) [d]	2.02 (1.09-3.77) [d]
Moderate preterm (32-33 weeks)	3.64 (1.86-7.14)	3.32 (1.66-6.64)	1.49 (0.64-3.51)	2.15 (1.06-4.34)
Late preterm (34-36 weeks)	1.55 (1.05-2.30)	1.84 (1.24-2.72)	1.24 (0.87-1.78)	1.66 (1.21 – 2.27)
Early term (37-38 weeks)	1.44 (1.12-1.84)	1.40 (1.04-1.87)	1.10 (0.84-1.43)	1.06 (0.87 – 1.29)
Additional perinatal risk factors				
Gender	0.81 (0.66-0.98) [d]	0.83 (0.65 – 1.06)	0.60 (0.50-0.72) [c]	0.55 (0.47-0.65) [c]
Ethnicity: not White British	1.83 (1.39-2.42) [c]	1.79 (1.27 – 2.52) [d]	1.40 (1.06-1.83) [d]	0.88 (0.65-1.17)
Not firstborn	0.91 (0.73-1.13)	0.87 (0.66 – 1.15)	0.89 (0.72-1.10)	0.89 (0.74 – 1.06)
Mother's age	1.0 (0.98-1.02)		0.97 (0.95-0.99) [d]	0.96 (0.94-0.98) [c]
Single mother	1.30 (1.00-1.70) [d]	1.21 (0.88 – 1.66)	1.55 (1.27-1.89) [c]	1.51 (1.21-1.89) [c]
Not managerial/professional	1.37 (1.02-1.85) [d]	1.09 (0.73 – 1.61)	1.93 (1.44-2.58) [c]	1.29(1.01-1.65) [d]
Long term unemployed	1.20 (0.90-1.60)	1.12 (0.75 – 1.69)	1.75 (1.40-2.18) [c]	1.23 (0.93-1.62)
Not educated to degree level	1.45 (1.08-1.94) [d]	1.98 (1.34 – 2.94) [d]	1.48 (1.14-1.93) [d]	1.56(1.24-1.96) [c]
Used alcohol during pregnancy [e]	0.88 (0.61-1.27)	0.97 (0.60 – 1.57)	1.05 (0.78-1.42)	1.28(0.99-1.66)
Smoked during pregnancy	1.71 (1.35-2.16) [c]	1.51 (1.13 – 2.02) [d]	1.75 (1.45-2.13) [c]	1.58 (1.31-1.92) [c]
Breastfed for < 4 months	1.34 (1.04-1.74) [d]	1.22 (0.91 – 1.64)	1.40 (1.07-1.82) [d]	1.30 (1.06-1.60) [d]
Child age at age 11 interview	n/a	1.09 (0.79 – 1.50)	n/a	0.71 (0.54-0.94) [d]
Child age at age 5 interview	0.86 (0.58-1.29)	n/a	0.76 (0.52-1.11)	n/a

[a] Results are weighted with the sampling and non-response weights appropriate for the dataset used.

[b] Full term was used as the reference level.

[c] p < 0. 001

[d] p ≤ 0.05

[e] ≥ 3 units/week or ≥ 3 units/occasion

References

1. Chang HH, Larson J, Blencowe H, Spong CY, Howson CP, Cairns-Smith S, Lackritz EM, Lee SK, Mason E, Serazin AC, Walani S, Simpson JL, Lawn JE (2013) Preventing preterm births: analysis of trends and potential reductions with interventions in 39 countries with very high human development index. The Lancet 381:223-234
2. World Health Organization (WHO) (2005) *Mental health: Facing the challenges, building solutions. Report from the WHO European Ministerial Conference, 2005*. In:WHO Regional Office for Europe, Copenhagen, Denmark
3. Kendell RE (2001) The distinction between mental and physical illness. Br J Psychiatry 178:490-493
4. Boyle EM, Poulsen G, Field DJ, Kurinczuk JJ, Wolke D, Alfirevic Z, Quigley MA (2012) Effects of gestational age at birth on health outcomes at 3 and 5 years of age: population based cohort study. BMJ 344
5. Delobel-Ayoub M, Arnaud C, White-Koning M, Casper C, Pierrat V, Garel M, Burguet A, Roze JC, Matis J, Picaud JC, Kaminski M, Larroque B, Group ES (2009) Behavioral problems and cognitive performance at 5 years of age after very preterm birth: the EPIPAGE Study. Pediatrics 123:1485-1492
6. Potharst ES, van Wassenaer AG, Houtzager BA, van Hus JW, Last BF, Kok JH (2011) High incidence of multi-domain disabilities in very preterm children at five years of age. J Pediatr 159:79-85
7. Arpi E, Ferrari F (2013) Preterm birth and behaviour problems in infants and preschool-age children: a review of the recent literature. Dev Med Child Neurol 55:788-796
8. Bora S, Pritchard VE, Moor S, Austin NC, Woodward LJ (2011) Emotional and behavioural adjustment of children born very preterm at early school age. J Paediatr Child Health 47:863-869
9. Broidy LM, Nagin DS, Tremblay RE, Bates JE, Brame B, Dodge KA, Fergusson D, Horwood JL, Loeber R, Laird R, Lynam DR, Moffitt TE, Pettit GS, Vitaro F (2003) Developmental trajectories of childhood disruptive behaviors and adolescent delinquency: a six-site, cross-national study. Dev Psychol 39:222-245
10. Caspi AM, TE. Newman, DL. Silva, PA. (1996) Behavioral observations at age 3 years predict adult psychiatric disorders. Longitudinal evidence from a birth cohort. Arch Gen Psychiatry 53:1033-1039
11. Moffitt TE, Arseneault L, Belsky D, Dickson N, Hancox RJ, Harrington H, Houts R, Poulton R, Roberts BW, Ross S, Sears MR, Thomson WM, Caspi A (2011) A gradient of childhood self-control predicts health, wealth, and public safety. PNAS 108:2693-2698
12. Castellanos-Ryan N, Seguin JR, Vitaro F, Parent S, Tremblay RE (2013) Impact of a 2-year multimodal intervention for disruptive 6-year-olds on substance use in adolescence: randomised controlled trial. Br J Psychiatry 203:188-195
13. Pugliese M, Rossi C, Guidotti I, Gallo C, Della Casa E, Bertoncelli N, Coccolini E, Ferrari F (2013) Preterm birth and developmental problems in infancy and preschool age Part II: cognitive, neuropsychological and behavioural outcomes. J Matern Fetal Neonatal Med 26:1653-1657

14. Ritchie K, Bora S, Woodward LJ (2015) Social development of children born very preterm: a systematic review. Dev Med Child Neurol 57:899-918
15. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ (2002) Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. JAMA 288:728-737
16. Johnson S, Marlow N (2011) Preterm birth and childhood psychiatric disorders. Pediatr Res 69:11r-18r
17. Mwaniki MK, Atieno M, Lawn JE, Newton CR (2012) Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. The Lancet 379:445-452
18. Johnson S, Hollis C, Kochhar P, Hennessy E, Wolke D, Marlow N (2010) Psychiatric disorders in extremely preterm children: longitudinal finding at age 11 years in the EPICure study. J Am Acad Child Adolesc Psychiatry 49:453-463 e451
19. Samara M, Marlow N, Wolke D (2008) Pervasive behavior problems at 6 years of age in a total-population sample of children born at </= 25 weeks of gestation. Pediatrics 122:562-573
20. Elgen SK, Leversen KT, Grundt JH, Hurum J, Sundby AB, Elgen IB, Markestad T (2012) Mental health at 5 years among children born extremely preterm: a national population-based study. Eur Child Adoles Psy 21:583-589
21. van der Pal-de Bruin KM, van der Pal SM, Verloove-Vanhorick SP, Walther FJ (2015) Profiling the preterm or VLBW born adolescent; implications of the Dutch POPS cohort follow-up studies. Early Hum Dev 91:97-102
22. van Kessel-Feddema B, Sondaar M, de Kleine M, Verhaak C, van Baar A (2007) Concordance between school outcomes and developmental follow-up results of very preterm and/or low birth weight children at the age of 5 years. Eur J Pediatr 166:693-699
23. de Kleine MJ, den Ouden AL, Kollee LA, Nijhuis-van der Sanden MW, Sondaar M, van Kessel-Feddema BJ, Knuijt S, van Baar AL, Ilsen A, Breur-Pieterse R, Briet JM, Brand R, Verloove-Vanhorick SP (2003) Development and evaluation of a follow up assessment of preterm infants at 5 years of age. Arch Dis Child 88:870-875
24. European Foundation for the Care of Newborns and Infants (2011) EU Benchmarking Report 2009/2010: Too Little, Too Late? Why Europe Should Do More For Preterm Infants. In: Keller M LH, Merialdi M, Poets C, Saugstad OD (ed), Karlsfeld, Germany
25. Baillargeon RH, Zoccolillo M, Keenan K, Cote S, Perusse D, Wu HX, Boivin M, Tremblay RE (2007) Gender differences in physical aggression: A prospective population-based survey of children before and after 2 years of age. Dev Psychol 43:13-26
26. Yasui M, Dishion TJ (2007) The ethnic context of child and adolescent problem behavior: implications for child and family interventions. Clin Child Fam Psychol Rev 10:137-179
27. Harding JF (2015) Increases in maternal education and low-income children's cognitive and behavioral outcomes. Dev Psychol 51:583-599
28. Linnet KM, Dalsgaard S, Obel C, Wisborg K, Henriksen TB, Rodriguez A, Kotimaa A, Moilanen I, Thomsen PH, Olsen J, Jarvelin MR (2003) Maternal lifestyle factors in pregnancy risk of attention deficit hyperactivity disorder and associated behaviors: review of the current evidence. Am J Psychiatry 160:1028-1040
29. Oddy WH, Kendall GE, Li J, Jacoby P, Robinson M, de Klerk NH, Silburn SR, Zubrick SR, Landau LI, Stanley FJ (2010) The long-term effects of breastfeeding on child and

adolescent mental health: a pregnancy cohort study followed for 14 years. J Pediatr 156:568-574
30. Hansen K, Johnson J, Joshi H, Calderwood L, Jones E, McDonald J (2010) Millennium Cohort Study first, second, third and fourth surveys: A guide to the datasets (5th edition). In:Centre for Longitudinal Studies, Institute of Education, University of London, London
31. Case A, Lubotsky D, Paxson C (2002) Economic status and health in childhood: The origins of the gradient. Am Econ Rev 92:1308-1334
32. Goodman R (1997) The Strengths and Difficulties Questionnaire: a research note. J Child Psychol Psychiatry 38:581-586
33. Goodman R, Scott S (1999) Comparing the Strengths and Difficulties Questionnaire and the Child Behavior Checklist: is small beautiful? J Abnorm Child Psychol 27:17-24
34. Goodman R (2001) Psychometric properties of the Strengths and Difficulties Questionnaire. J Am Acad Child Adolesc Psychiatry 40:1337-1345
35. Becker A, Rothenberger A, Sohn A (2015) Six years ahead: a longitudinal analysis regarding course and predictive value of the Strengths and Difficulties Questionnaire (SDQ) in children and adolescents. Eur Child Adolesc Psychiatry 24:715-725
36. Cronbach LJ (1951) Coefficient alpha and the internal structure of tests. psychometrika 16:297-334
37. Vogel JP, Lee AC, Souza JP (2014) Maternal morbidity and preterm birth in 22 low- and middle-income countries: a secondary analysis of the WHO Global Survey dataset. BMC Pregnancy and Childbirth 14:56
38. Jones E, Ketende S (2010) User Guide to Analysing MCS Data Using SPSS. In:University of London, London
39. Bonellie S, Chalmers J, Gray R, Greer I, Jarvis S, Williams C (2008) Centile charts for birthweight for gestational age for Scottish singleton births. BMC Pregnancy and Childbirth 8:5
40. Egger HL, Angold A (2006) Common emotional and behavioral disorders in preschool children: presentation, nosology, and epidemiology. J Child Psychol Psychiatry 47:313-337
41. Fontaine N, Carbonneau R, Barker ED, Vitaro F, Hebert M, Cote SM, Nagin DS, Zoccolillo M, Tremblay RE (2008) Girls' hyperactivity and physical aggression during childhood and adjustment problems in early adulthood: a 15-year longitudinal study. Arch Gen Psychiatry 65:320-328
42. Gwin KM, Schrader R, Peters K, Moreno A, Thiel KW, Leslie KK (2012) An exploratory study of the variables impacting preterm birth rates in New Mexico. BMC Pregnancy Childbirth 12:53
43. McCormick MC, Brooks-Gunn J, Buka SL, Goldman J, Yu J, Salganik M, Scott DT, Bennett FC, Kay LL, Bernbaum JC, Bauer CR, Martin C, Woods ER, Martin A, Casey PH (2006) Early intervention in low birth weight premature infants: results at 18 years of age for the Infant Health and Development Program. Pediatrics 117:771-780
44. Olds DL, Holmberg JR, Donelan-McCall N, Luckey DW, Knudtson MD, Robinson J (2014) Effects of home visits by paraprofessionals and by nurses on children: follow-up of a randomized trial at ages 6 and 9 years. JAMA Pediatr 168:114-121
45. Larson CP (2007) Poverty during pregnancy: Its effects on child health outcomes. Paediatr Child Health 12:673-677

46. Spittle A, Orton J, Anderson P, Boyd R, Doyle LW (2012) Early developmental intervention programmes post-hospital discharge to prevent motor and cognitive impairments in preterm infants. Cochrane Database Syst Rev 12:Cd005495
47. Larsson H, Sariaslan A, Langstrom N, D'Onofrio B, Lichtenstein P (2014) Family income in early childhood and subsequent attention deficit/hyperactivity disorder: a quasi-experimental study. J Child Psychol Psychiatry 55:428-435
48. Stone SL, Speltz ML, Collett B, Werler MM (2013) Socioeconomic Factors in Relation to Discrepancy in Parent versus Teacher Ratings of Child Behavior. J Psychopathol Behav Assess 35:314-320