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Complete List of Authors:	Nusinovici, Simon OLLIAC, Bertrand; Centre Hospitalier Esquirol, Child and adolescent psychiatry Flamant, Cyril muller, jean-baptiste; CHU Nantes, neonatology Olivier, Marion Bureau, Valérie Gascouin, Geraldine; Angers University Hospital, Department of Neonatology Basset, Hélène Bouvard , Charlotte Roze, JC; Centre Hospitalier Universitaire de Nantes Pole d\'information medicale evaluation et sante publique Hanf, Matthieu
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Risk factors for parental separation in preterm children: a population-based study

Simon Nusinovici[1], Bertrand Olliac[2,3], Cyril Flamant[1,4], Jean-Baptiste Müller[4], Marion Olivier[5], Valérie Rouger[5], Géraldine Gascoin[6], Hélène Basset[7], Charlotte Bouvard[8], Jean-Christophe Rozé[1,4,5], Matthieu Hanf[1]

Affiliations: 1 National Institute of Health and Medical Research CIC 1413, Nantes University Hospital, F-44000 Nantes, France; 2 Department of Child and Adolescent Psychiatry, Centre Hospitalier Esquirol, Limoges, France; 3 National Institute of Health and Medical Research UMR1094, Tropical Neuroepidemiology, Limoges, France; 4 Department of Neonatal Medicine, Nantes University Hospital, F-44000 Nantes, France; 5 Réseau "Grandir Ensemble", Nantes University Hospital, F-44000 Nantes, France; 6 Department of Neonatal Medicine, Angers University Hospital, F-49100 Angers, France; 7 Department of Neonatal Medicine, Le Mans Hospital, F-72037 Le Mans, France; 8 SOS Prema (parents of French preterm children organization), 32, rue du Chemin Vert, 92100 Boulogne-Billancourt, France

Contact details: Simon Nusinovici; National Institute of Health and Medical Research CIC 1413, 5 allée de l'Ile Gloriette, F-44000 Nantes, France; Email: simon.nusinovici@chu-nantes.fr; Phone: 00332 53 48 21 10; Fax: 00332 53 48 28 67

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ABSTRACT

Objective: The objective of this study was to investigate both the effects of low gestational age and child's neurodevelopmental outcome on the risk of parental separation within seven years of giving birth.

Design: prospective.

Setting: 24 maternity clinics in the Pays-de-la-Loire region.

Participants: This study included 5,732 infants delivered at <35 weeks of gestation born between 2005 and 2013 who were enrolled in the population-based LIFT cohort and who had a neurodevelopmental evaluation at two years.

Outcome measure: risk of parental separation.

Results: Ten percent (572/5,732) of the parents reported having undergone separation during the follow-up period. A mediation analysis showed that low gestational age had no direct effect on the risk of parental separation. Moreover, a non-optimal neurodevelopment at 2 years was associated with an increased risk of parental separation corresponding to a HR=1.49 [1.23; 1.80]. Finally, the increased risk of parental separation was aggravated by low socio-economic conditions.

Conclusions: The effect of low gestational age on the risk of parental separation was mediated by the child's neurodevelopment. This finding could be used to target at risk situations and offer support to help prevent the consequences of a child's neurodevelopmental disabilities on the family.

Key words: parental separation, low gestational age, neurodevelopment outcome, cohort

Strength and limitations of the study:

- This study was based on a large prospective population-based cohort of preterm infants (n=5,732).
- Appropriate multivariable statistical analyses were used to properly model the complex relationships between low gestational age, neurodevelopmental outcome and the risk of parental separation (mediation analyses and survival Cox models).
- The socio-economic factors known to influence the risk for parental separation were taken into account in order to limit possible confounding bias.
- No information was available regarding the relationship between the parents before the birth of their infants.
- Given that the gestational age of our reference population was between 32 and 34 weeks, we cannot exclude the existence of a small effect of preterm birth on the risk of parental separation.

INTRODUCTION

Understanding the consequences of preterm birth on parental separation is critical as parental separation can strongly affect a child's development[1]. The increasing number of preterm births makes these questions more and more topical. Moreover, these questions are of great concern in public health and for structures such as preterm infants' parental organizations.

The birth of a preterm[2–7] or very low birthweight child (VLBW)[5,8–10] is a stressful event for the parents. Compared to mothers of full term infants, mothers of preterm infants have been shown to have a higher risk of experiencing psychological distress and depressive symptoms following the child's birth[11–13]. In addition to psychological distress, the birth of a preterm child frequently has a substantial economic impact on the family involved[14,15]. All these factors that affect the life of the family can have negative consequences for the relationship between the parents.

A neurodevelopmental disability following a preterm birth could mediate, at least partly, the effect of preterm birth on parental separation. Preterm births are indeed associated with a high risk of neurodevelopmental disabilities[16,17] that can also increase the risk of parental separation[18–25]. However, no longitudinal study using appropriate methods has investigated the complex relationships between low gestational age, neurodevelopmental outcome, and parental separation. The objective of this study was to investigate, in a large longitudinal population-based cohort of preterm infants, both the effects of low gestational age and the child's neurodevelopmental outcome on the risk of parental separation within seven years of giving birth.

MATERIALS AND METHODS

Study population

The study population was composed of surviving preterm infants enrolled in the Loire Infant Follow-up Team (LIFT), born at less than 35 weeks of gestation between January 2005 and December 2013, and who were evaluated at two years of corrected age to assess their neurodevelopmental outcomes (Figure 1). The LIFT network includes 24 maternity clinics in the Pays-de-la-Loire region (one of the 13 administrative regions in France) with the objective to screen for early clinical anomalies associated with preterm births and to provide specifically adapted care. The follow-up consisted of standardized visits by trained physicians at 3, 6, 9, 18, and 24 months as well as at 3, 4, 5, 6, and 7 years after the birth of the child.

Perinatal data

Perinatal data was comprised of the date of birth, gender, gestational age (GA), and birthweight. The birthweight Z-score was computed according to the Olsen standards[26].

Parental situation

Information regarding relationship status was binary (i.e. as parents living together or parents living separately). For parents who had separated, the first date at which they were reported to be separated was used. Relationship status was not available at the time of inclusion. Consequently, for the separations reported at the 3-month visit, there was the possibility that the parents had already undergone separation at the time of the child's birth. Therefore, to ensure temporality between preterm birth and parental separation, separations reported at the 3-month visit were excluded.

Neurodevelopmental outcome at two years

Children were evaluated at two years of corrected age. Assessment to define optimal and non-optimal neurodevelopmental outcomes included a physical examination by a LIFT-trained pediatrician, a psychomotor evaluation by a LIFT network psychologist, and a parent-completed questionnaire. Neuromotor evaluation was regarded as non-optimal in case of cerebral palsy or when the physical examination revealed relatively milder signs of abnormal movement during independent walking according to the Amiel-Tison criteria[27]. Psychomotor evaluation was assessed with the revised Brunet-Lézine test (four domains: movement/posture, coordination, language, and socialization)[28]. The mean and maximal global scores were 100 and 140, respectively, and values of <85 were considered non-optimal psychomotor development. Children who were not able to perform the revised Brunet-Lézine test were considered to have non-optimal psychomotor development. Furthermore, neurodevelopmental outcome was assessed with the parent-completed “Ages and Stages Questionnaire” (ASQ)[29,30]. The ASQ assesses development in the following five areas: communication, gross motor, fine motor, problem solving, and sociopersonal skills. The maximal overall ASQ score is 300 and a score of <185 was considered non-optimal[31]. Finally, sensory disabilities such as blindness or children that required a hearing aid were taken into account. Overall, children with a non-optimal neuromotor and/or psychomotor assessment and/or a sensory disability were regarded as having a “non-optimal neurodevelopmental outcome.” Children without a documented physical examination or psychomotor assessment were considered as non-assessable at two years except for children with severe neurological disabilities. This definition of non-optimality has been used in other studies[32–34]. To simplify matters, a non-optimal neurodevelopmental outcome will be referred to as non-optimality.

Socioeconomic information

The socioeconomic data consisted of the socioeconomic level and eligibility for social security benefits for those with low incomes. The socioeconomic level took into account the parent with the more highly rated job according to a scale based on the official classification developed by the French Institute for Statistics and Economic Studies (INSEE). The socioeconomic level and eligibility for social security benefits for those with low incomes were considered as two-level categorical variables.

Urbanicity of the residential municipality

The residential municipality was considered either urban or rural based on definitions developed by the INSEE[1]. Municipalities were considered rural or urban depending on the distance between buildings and the number of inhabitants.

Statistical analysis

The statistical analyses were conducted in three steps. Firstly, the crude associations between gestational age and non-optimality at 2 years and the risk of parental separation were investigated with Kaplan-Meier curves and log-rank tests.

Secondly, a mediation analysis was used to estimate the proportion of the effect of low gestational age on the risk of parental separation that was mediated by non-optimality at 2 years. The aim of a mediation analysis is to decompose the effect of an exposure on an outcome into a direct effect and an indirect effect that is mediated by an intermediate variable (the mediator). Mediation analyses used were based on the counterfactual framework. A counterfactual variable describes what would have happened if we had intervened on exposure. This framework allows the decomposition of the causal effect into a so-called natural direct and natural indirect effect. A natural direct effect measures the change in outcome (the risk of parental separation) that would be observed if we could change the exposure (low gestational age) but leave the mediator (optimality at 2 years) at the value it naturally takes when the exposure is left unchanged. A natural indirect effect measures the

[1] http://www.insee.fr/en/methodes/default.asp?page=definitions/unite-urbaine.htm. Date accessed: February 2016.

change in outcome (the risk of parental separation) that would be observed if we could change the mediator (optimality at 2 years) as much as it would naturally change when exposure was changed without actually changing the exposure (low gestational age). Gestational age was considered as a three-level categorical variable: GA 32-34 (reference), GA 28-31, and GA 24-27 weeks. The estimations of natural direct and indirect effects were done while adjusting for the possible confounding factors: gender, multiple pregnancies ("yes" or "no"), Z-score of birthweight (<-1, between -1 and 0, between 0 and 1, and ≥1), socioeconomic level ("high" or "intermediate"), social security benefits for those with low incomes ("yes" or "no"), and urbanicity of the residential municipality ("urban" versus "rural"). Moreover, this analysis accounted for the censored nature of the outcome. The possible interaction between the exposure and the mediator was tested. Mediation models used here are based on natural effect models[35] implemented in the R package medflex.

Thirdly, the effect of the non-optimality at 2 years on the risk of parental separation was estimated using the multivariable Cox model. Furthermore, the effect of gestation age on non-optimality at 2 years was estimated using logistic regression. For these two models, the same adjustment variables as those considered in the mediation analysis were included in the models. All analyses were performed using R software[2].

Three sensitivity analyses were performed. In the first one, parental separations occurring before the 24-month visit were excluded to ensure the temporality between neurodevelopmental outcome and parental separations. In the second analysis, an imputation of the missing data was performed using a multiple imputation method. The last analysis concerned the comparison of the characteristics of the children that were lost to follow-up between two and five years and those who were still followed at five years.

[2] R Core Team (2016). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org/

Ethic approval

Written consent was obtained for each patient before inclusion in the study, and the cohort was registered at the French data protection authority in clinical research ("Commission Nationale de l'Informatique et des Libertés" or CNIL, No. 851117).

RESULTS

Between January 2005 and December 2013, 6,937 infants born at less than 35 weeks of gestation in the Pays-de-la-Loire region, France, were enrolled in the LIFT cohort. The following infants were excluded from the study population: infants whose parents were separated at the three-month (n=185) or 84-month visit (n=20), children without neurodevelopmental evaluation at two years but still followed (n=392), and children lost to follow-up at two years (n=315). In light of these exclusions, the study population consisted of 5,732 preterm infants, corresponding to 83% of the infants initially enrolled in the cohort (Figure 1).

During the follow-up, 10.0% of the parents reported having undergone separation (n=572), corresponding with an incidence rate of 23.8 separations per 1000 children-year. The median time at which separations were reported was 22 months following the birth of the child with an interquartile range (IQR) of 10.3–43.3 months. 30.2% (n=1,730) and 8.9% (n=508) of the infants were born very or extremely preterm, respectively. 19.1% (n=1,096) of the children were considered non-optimal at two years. Lastly, the median length of the total follow-up was 56 months (IQR=32.1–69.2) (Table 1).

In the bivariable analysis, both gestational age and non-optimality at 2 years were associated with an increased risk of parental separation (Supplementary Table 1, Figure 2). However, the mediation analysis showed that all the effect of low gestational age in very and extremely preterm infants on the risk of parental separation was mediated by the non-optimality at 2 years of age (Supplementary Figure 1). Preterm birth were associated with a higher risk of non-optimal neurodevelopment at two years, corresponding to OR=2.1 [1.8, 2.4] and OR=4.2 [3.4, 5.2] for very and extremely preterm infants, respectively (Supplementary Table 2). The non-optimality at 2 years was associated with an increased risk of parental separation corresponding to a HR=1.49 [1.23, 1.80] (Table 2, Figure 3). Furthermore, a significant interaction was found between non-optimality and social security benefits due to low income on the risk of parental separation (Supplementary Table 3). Finally, a lower parental socioeconomic level, receiving social security benefits due to low income, and living in urban areas were associated with a higher risk of parental separation. The results of the relationships between gestational age, non-optimality, and parental separation are summarized in Figure 3.

DISCUSSION

Using a large population-based cohort study, we found that the effect of low gestational age on the risk of parental separation was entirely mediated by the neurodevelopmental outcome at two years. Parents of preterm infants with a non-optimal neurodevelopment at two years were 50% more likely to have undergone separation in the years following the birth of the child, independently of the socio-economic factors. This increased risk was further aggravated by low socio-economic conditions.

A strength of this study was the use of mediation analysis. Because of the association between gestational age and neurodevelopmental outcome at two years, mediation analysis is a relevant approach to investigate the effects of gestational age and neurodevelopmental outcome on the risk of parental separation. An alternative approach would have been to build a single model predicting parental separation with these two risk factors and the adjustment variables. However, this model would not have accounted for the strong association between gestational age and neurodevelopmental outcome and, therefore, could have led to biased results. A further strength of this study was the large number of infants included, which allowed a high statistical power to be attained. In addition, the longitudinal data and the corresponding survival analyses allowed us to account for the timing of parental separations, rather than simply distinguishing between whether the parents were living together or not. Furthermore, the socio-economic factors known to influence the risk for parental separation were taken into account. For children whose parents underwent separation before the 24-month visit (n=221), there was a doubt regarding the temporality between the neurodevelopmental outcome and the parental separation. The sensitivity analysis showed that without these children, the results were exactly the same, probably due to the early occurrence of neurodevelopment impairments during the child's development (Supplementary Table 4). Finally, a sensitivity analysis was performed after imputation of the missing data (n=1,000) using a multiple imputation method. The robustness of the results demonstrated the absence of bias related to missing data (Supplementary Table 5).

The present study has several limitations. Firstly, this study may underestimate the proportion of parental separation due to a bias in the declaration of relevant information; for example, during the examination of the child by the pediatrician there could a degree of reluctance from the parents to reveal that they are no longer living together. In our study, 12.3% of the parents were found to have undergone separation within an average follow-up time span of 5 years (including separations occurring at the 3-month and 80-month visits that were excluded from analyses). National statistics from the INSEE state that 9.9% of marriages entered into in the year 2000 ended in divorce within 5 years[3], suggesting that absence of bias in parental separation declaration. Secondly, the characteristics of children that were excluded

[3] http://www.insee.fr/fr/ffc/tef/tef2015/T15F033/T15F033.pdf. Date accessed: February 2016

from the study population were not comparable to those who were included (Table 1). For example, late preterm infants born to families with a lower socioeconomic level were overrepresented in the category that was not included for the analysis. However, the absolute differences in the perinatal characteristics were rather small, thus indicating that inclusion criteria did not result in an obvious selection bias. Thirdly, given that the gestational age of our reference population was between 32 and 34 weeks, we cannot exclude the existence of a small effect of preterm birth on the risk of parental separation, albeit one that is not detectable with our study design. Further studies using a population of full-term infants as reference are needed to confirm our results. Fourthly, no information was available regarding the relationship between the parents before the birth of their infants. A very conflictual relationship might be associated with a higher risk of giving birth to a preterm child. Our study could, therefore, overestimate the effect of a non-optimal neurodevelopment on the risk of parental separation. Finally, some children were lost between two and five years of follow-up (1,518 out of 4,813). These children had slightly different characteristics (Supplementary Table 6). However, no difference was observed for the proportion of parents that underwent separation.

In the present study, optimality was defined using neuromotor, psychomotor, and sensory evaluations, thereby revealing particularly severe pathologies or clinical symptoms. The association between optimality and parental separation is in accordance with the results of previous studies demonstrating negative consequences on the parent's relationship in case of a severe disease [19–21]. Interestingly, parents of extremely preterm infants with an optimal neurodevelopment at two years did not have a higher risk of separation. The increased risk of separation by parents of VLBW (<1500g) [36] in a US national survey conducted on 6,016 births might be due to the fact that occurrences of disability were not taken into account during the follow-up. Therefore, we agree with the authors' statement that their values may be regarded as conservative estimates of the effect of child disability on parental separation. While a preterm birth may not, on average, be directly responsible for the disruption of a couple's relationship, the discovery of associated severe child disabilities or neurodevelopmental delays could profoundly challenge the parent's relationship. The increased risk of parental separation seems to be due to the presence of repeated stressful events within the first years of the child's life. Lastly, this study provides evidence for a major impact of socioeconomic factors on the risk of parental separation. This result is in accordance with several studies that showed no or limited parental education and low family income are strong risk factors for separation [21,24,37,38], for parental stress [8–10], and for psychological distress [11].

CONCLUSIONS

The effect of low gestational age on the risk of parental separation was mediated by the child's neurodevelopment, with 50% more separations among parents of children with non-optimal neurodevelopment. This increased risk was aggravated by low socio-economic conditions. This finding could be used to target at risk situations and offer specific support to help prevent the negative consequences of a child's neurodevelopmental disabilities on the family.

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Declaration of interest

The authors have declared that they have no conflict of interest

Author's contributions

Matthieu Hanf had the original idea, provided guidance for the statistical analysis and reviewed and revised the manuscript. Simon Nusinovici performed the statistical analysis, the literature searches and wrote the paper. Jean-Baptiste Müller, Géraldine Gascoin, Hélène Basset, Cyril Flamant, Bertrand Olliac, Valérie Rouger, Charlotte Bouvard and Jean-Christophe Rozé participated to the data collection, reviewed and revised the manuscript. Marion Pérennec participated to the analysis and interpretation of the data, reviewed and revised the manuscript. All the authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data sharing statement:

Data are available from the scientific Committee of the LIFT cohort for researchers who meet the criteria for access to confidential health data. Interested researchers have to comply with the French legislation i.e. require the advice of the "Comité consultatif sur le traitement de l'information en matière de recherché sur le domaine de la santé" (CCTIRS) as well as the authorization of the "Commission nationale de l'information et des libertés" (CNIL) for the treatment of personal health data. Research projects have also to be approved by an independent Ethics Committee. Contact information is available at: http://www.reseau-naissance.fr/module-pagesetter-viewpub-tid-2-pid-21.html

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Table 1. Descriptive characteristics of the study population and comparison between preterm infants included in the study and those not included.

		Included (n=5,732)	Not included (n=1,205)	
Variable	Category	Number (%)	Number (%)	P value
Gestational age (weeks)	32–34	3,494 (61.0)	802 (66.6)	< 0.001
	28–31	1,730 (30.2)	321 (26.6)	
	24–27	508 (8.9)	82 (6.8)	
Gender	Female	2,640 (46.1)	589 (48.9)	0.079
	Male	3,092 (53.9)	616 (51.1)	
Multiple pregnancy	No	3,617 (63.1)	830 (68.9)	< 0.001
	Yes	2,115 (36.9)	375 (31.1)	
Z score of birth weight	<-1	1,378 (24.0)	285 (23.9)	0.999
	-1 to 0	2,044 (35.7)	426 (35.7)	
	0 to 1	1,787 (31.2)	371 (31.1)	
	>1	523 (9.1)	110 (9.2)	
Socio-economic level	Intermediate	4,254 (74.2)	1,024 (85.0)	< 0.001
	High	1,478 (25.8)	181 (15.0)	
Social security benefits due to low income	No	5,031 (87.8)	968 (80.3)	< 0.001
	Yes	701 (12.2)	237 (19.7)	
Urbanicity	Rural	2,104 (36.7)	376 (31.2)	< 0.001
	Urban	3,628 (63.3)	829 (68.8)	
Length of follow-up (months) [Median (IQR)]		56 [32.1, 69.2]	16.6 [8.1, 56.9]	< 0.001

IQR: interquartile range

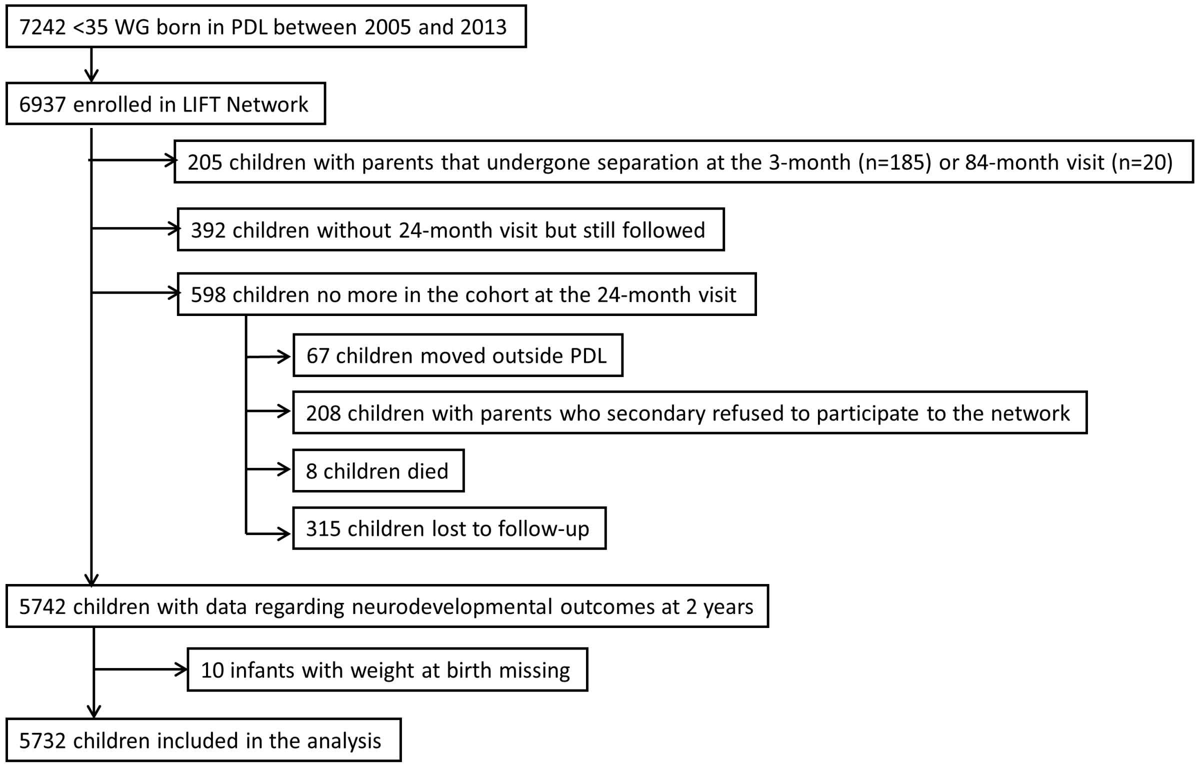
Table 2. Crude and adjusted association between the neurodevelopment of preterm infants and the risk of parental separation. Adjustment was made on perinatal characteristics of the infants, the socio-economic level of the family, and the urbanicity of the residential municipality (n=5,732).

	Category	N (%)	Raw HR [95% CI]	Adjusted HR [95% CI]
Optimality at 2 years*	Yes	4,636 (80.9)	1	1
	No	1,096 (19.1)	1.58 [1.31, 1.90]	1.49 [1.23, 1.80]
Gender	Female	2,640 (46.1)	1	1
	Male	3,092 (53.9)	1.07 [0.90, 1.26]	1.07 [0.91, 1.27]
Multiple pregnancy	No	3,617 (63.1)	1	1
	Yes	2,115 (36.9)	0.94 [0.79, 1.11]	0.97 [0.81, 1.15]
Z score of birthweight	<-1	1,378 (24.0)	1	1
	-1 to 0	2,044 (35.7)	1.03 [0.84, 1.28]	1.1 [0.89, 1.36]
	0 to 1	1,787 (31.2)	0.9 [0.72, 1.12]	0.96 [0.77, 1.20]
	>1	523 (9.1)	0.96 [0.70, 1.33]	1.03 [0.75, 1.43]
Socio-economic level	Intermediate	4,254 (74.2)	1	1
	High	1,478 (25.8)	0.62 [0.50, 0.76]	0.64 [0.52, 0.79]
Social security benefits (SSB) due to low income	No	5,031 (87.8)	1	1
	Yes	701 (12.2)	4.09 [3.43, 4.86]	3.68 [3.09, 4.39]
Urbanicity	Rural	2,104 (36.7)	1	1
	Urban	3,628 (63.3)	1.91 [1.57, 2.31]	1.81 [1.49, 2.20]

HR: hazards ratio; CI: confidence interval

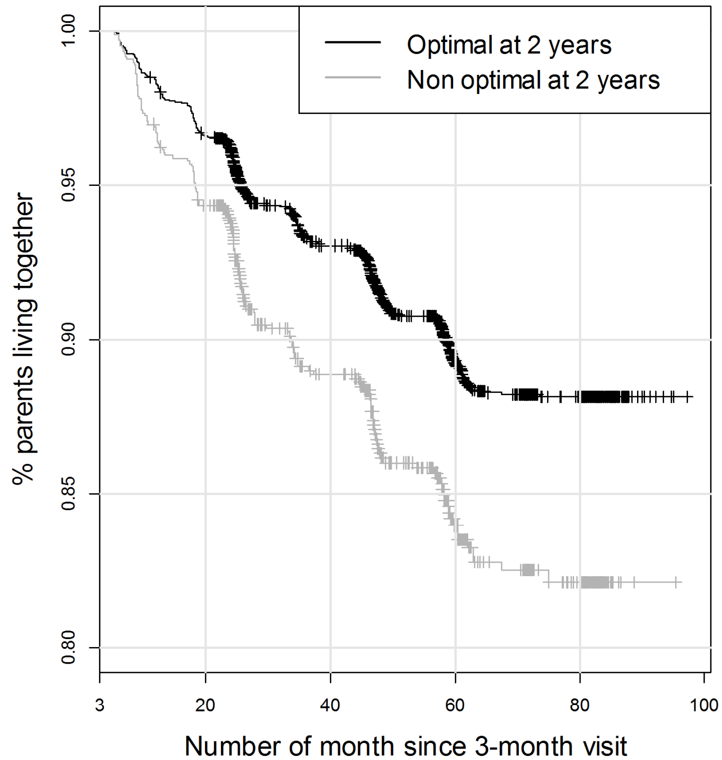
*Children with a non-optimal neuromotor and/or psychomotor assessment and/or sensorial disability at two years were considered as non-optimal.

Figure 1. Flowchart



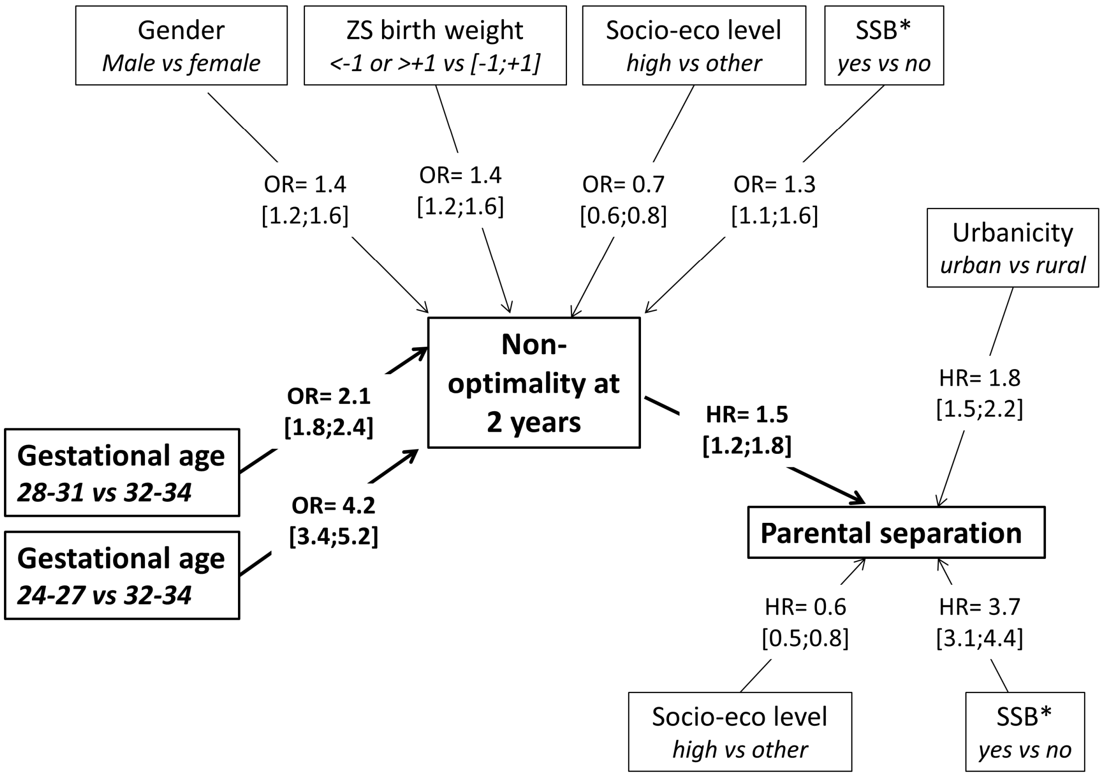
WG: weeks of gestation; PDL: Pays-de-la-Loire region; LIFT: Loire Infant Follow-up Team.

Figure 2. Relationship between the neurodevelopment of preterm infants and the occurrence of parental separation, using Kaplan-Meier curves (n=5,732).



N at risk					
Optimal at 2 years	4636	4406	3248	1755	543
Non-optimal at 2 years	1096	1004	694	335	119

Figure 3. Summary of the relationships between low gestational age, neurodevelopment of preterm infants (non-optimality at two years), and the risk of parental separation.

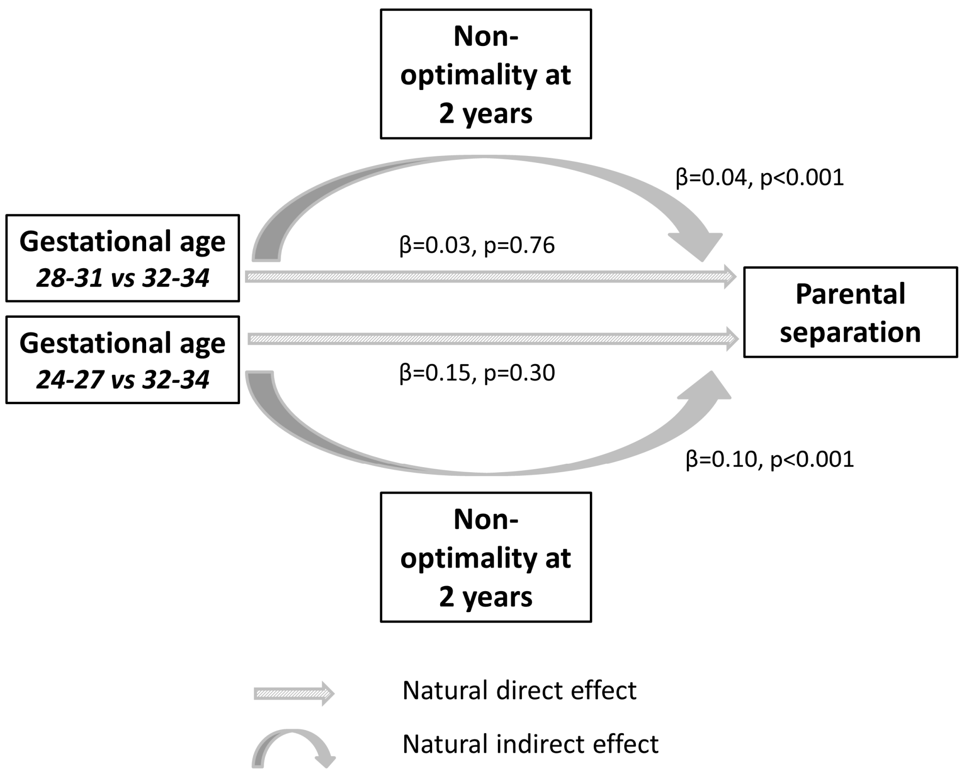


*SSB: Social security benefits due to low income; ZS: Z-score.

Odds ratio (OR) and hazard ratio (HR) were estimated using two different models (because of the absence of direct effect of low gestational age on the risk of parental separation). Model 1: logistic regression with outcome = non-optimality at two years and exposure = gestational age. Model 2: Cox model with outcome = parental separation and exposure = non-optimality at two years. Adjustment variables for both models: gender, multiple pregnancies, Z-score of birthweight, socioeconomic level, social security benefits for those with low incomes, and urbanicity of the residential municipality. Only significant adjustment variables were reported in this figure.

Supplementary materials

Supplementary Figure 1. Decomposition of the effect of low gestational age on the risk of parental separation into a direct effect and an indirect effect mediated by the neurodevelopment of preterm infants (non-optimality at two years). This mediation model was adjusted for gender, multiple pregnancy, Z-score of birthweight, socioeconomic level, social security benefits for those with low incomes, and urbanicity of the residential municipality.



Supplementary Table 1. Incidence risks and incidence rates of parental separation in preterm infants population according to the perinatal characteristics of the child, the socio-economic level of the family and the urbanicity of the residential municipality (n=5,732).

Variable	Category	Incidence risk of parental separation (N events/N at risk) x 100	Incidence rate of parental separation for 1000 children-year	P value**
Gestational age (weeks)	32–34	9.6	22.6	0.030
	28–31	9.9	24.1	
	24–27	13.0	31.6	
Optimality at 2 years*	Yes	9.2	21.5	< 0.001
	No	13.4	34.2	
Gender	Female	9.6	23.0	0.450
	Male	10.3	24.5	
Multiple pregnancy	No	10.2	24.3	0.460
	Yes	9.6	22.9	
Z score of birthweight	<-1	10.3	24.3	0.570
	-1 to 0	10.5	25.3	
	0 to 1	9.2	21.8	
	>1	9.6	23.5	
Socio-economic level	Intermediate	10.8	26.7	< 0.001
	High	7.5	16.4	
Social security benefits due to low income	No	7.6	17.7	< 0.001
	Yes	27.4	73.6	
Urbanicity	Rural	6.6	15.2	< 0.001
	Urban	12.0	29.1	

*Children with a non-optimal neuromotor and/or psychomotor assessment and/or sensorial disability at two years were considered as non-optimal.

**log-rank test

Supplementary Table 2. Adjusted associations between the risk of non-optimal neurodevelopment at two years and gestational age with adjustment variables for preterm infants born between 2005 and 2013 followed in the LIFT cohort (n=5,732).

Variable	Category	N (%)	Adjusted OR [95%CI]
Gestational age (weeks)	32–34	3,494 (61.0)	1
	28–31	1,730 (30.2)	2.06 [1.78, 2.39]
	24–27	508 (8.9)	4.23 [3.43, 5.20]
Gender	Female	2,640 (46.1)	1
	Male	3,092 (53.9)	1.38 [1.2, 1.59]
Multiple pregnancy	No	3,617 (63.1)	1
	Yes	2,115 (36.9)	0.94 [0.82, 1.09]
Z score of birthweight	<-1	1,378 (24.0)	1
	-1 to 0	2,044 (35.7)	0.73 [0.61, 0.87]
	0 to 1	1,787 (31.2)	0.72 [0.6, 0.87]
	>1	523 (9.1)	0.99 [0.77, 1.26]
Socio-economic level	Intermediate	4,254 (74.2)	1
	High	1,478 (25.8)	0.72 [0.61, 0.85]
Social security benefits (SSB) due to low income	No	5,031 (87.8)	1
	Yes	701 (12.2)	1.31 [1.07, 1.59]
Urbanicity	Rural	2,104 (36.7)	1
	Urban	3,628 (63.3)	0.90 [0.78, 1.04]

OR: odds ratio; CI: confidence interval.

Supplementary Table 3. Crude and adjusted associations between the risk of parental separation and neurodevelopment of preterm infants (optimality at two years) with adjustment variables and interaction term between optimality at two years and social security benefits due to low income (n=5,732).

Variable	Category	N (%)	Adjusted HR [95% CI]
Optimality at 2 years*	Yes	4,636 (80.9)	1
	No	1,096 (19.1)	1.27 [0.99, 1.63]
Gender	Female	2,640 (46.1)	1
	Male	3,092 (53.9)	1.07 [0.91, 1.26]
Multiple pregnancy	No	3,617 (63.1)	1
	Yes	2,115 (36.9)	0.96 [0.81, 1.14]
Z score of birthweight	<-1	1,378 (24.0)	1
	-1 to 0	2,044 (35.7)	1.10 [0.89, 1.36]
	0 to 1	1,787 (31.2)	0.97 [0.77, 1.21]
	>1	523 (9.1)	1.04 [0.76, 1.44]
Socio-economic level	Intermediate	4,254 (74.2)	1
	High	1,478 (25.8)	0.64 [0.52, 0.79]
Social security benefits (SSB) due to low income	No	5,031 (87.8)	1
	Yes	701 (12.2)	3.27 [2.65, 4.04]
Urbanicity	Rural	2,104 (36.7)	1
	Urban	3,628 (63.3)	1.80 [1.49, 2.19]
Optimality at 2 years * SSB	Yes * No	4,102 (71.6)	1
	No * Yes	167 (2.9)	1.52 [1.03, 2.23]

HR: hazards ratio; SSB: social security benefits; CI: confidence interval.

*Children with a non-optimal neuromotor and/or psychomotor assessment and/or sensorial disability at two years were considered as non-optimal.

Supplementary Table 4. Adjusted associations between the risk of parental separation occurring from the 24-month visit and neurodevelopment of preterm infants (optimality at two years) with adjustment variables (n=5,511). In this analysis, the separations occurring between the 6-month and the 18-month visit were excluded.

	Category	N (%)	Adjusted HR [95% CI]
Optimality at 2 years*	Yes	4,477 (81.2)	1
	No	1,034 (18.8)	1.49 [1.17, 1.91]
Gender	Female	2,549 (46.3)	1
	Male	2,962 (53.7)	0.98 [0.79, 1.21]
Multiple pregnancy	No	3,479 (63.1)	1
	Yes	2,032 (36.9)	0.90 [0.72, 1.13]
Z score of birthweight	<-1	1,326 (24.1)	1
	-1 to 0	1,952 (35.4)	1.01 [0.77, 1.32]
	0 to 1	1,729 (31.4)	0.98 [0.74, 1.30]
	>1	504 (9.1)	1.02 [0.68, 1.54]
Socio-economic level	Intermediate	4,068 (73.8)	1
	High	1,443 (26.2)	0.67 [0.52, 0.87]
Social security benefits (SSB) due to low income	No	4,903 (89.0)	1
	Yes	608 (11.0)	3.01 [2.38, 3.81]
Urbanicity	Rural	2,054 (37.3)	1
	Urban	3,457 (62.7)	1.82 [1.43, 2.32]

HR: hazards ratio; CI: confidence interval.

*Children with a non-optimal neuromotor and/or psychomotor assessment and/or sensorial disability at two years were considered as non-optimal.

Supplementary Table 5. Adjusted associations between the risk of parental separation and neurodevelopment of preterm infants (optimality at two years) with adjustment variables after imputation of missing values (13 infants with weight at birth missing and 990 infants with neurodevelopmental outcome at two years missing) using the multiple imputation method (n=6,732).

Variable	Category	Adjusted HR [95% CI]
Optimality at 2 years*	Yes	1
	No	1.45 [1.21, 1.73]
Gender	Female	1
	Male	1.06 [0.91, 1.24]
Multiple pregnancy	No	1
	Yes	0.97 [0.83, 1.14]
Z score of birthweight	<-1	1
	-1 to 0	1.06 [0.87, 1.29]
	0 to 1	0.92 [0.74, 1.13]
	>1	0.98 [0.72, 1.33]
Socio-economic level	Intermediate	1
	High	0.68 [0.56, 0.82]
Social security benefits due to low income	No	1
	Yes	3.91 [3.32, 4.60]
Urbanicity	Rural	1
	Urban	1.81 [1.51, 2.18]

HR: hazards ratio; CI: confidence interval.

*Children with a non-optimal neuromotor and/or psychomotor assessment and/or sensorial disability at two years were considered as non-optimal.

Supplementary Table 6. Comparison of the infants born <35 weeks between 2005 and 2011 still followed at the 60-month visit (n=3,295) and those lost to follow-up between the 24-month and the 60-month visit (n=1,518).

Variable	Category	Children still followed at the 60-month visit (n=3295)	Children lost to follow-up between the 24-month and the 60-month visit (n=1518)	P value
Parental separation	Living together	2,868 (87.0)	1,309 (86.2)	0.469
	Separated	427 (13.0)	209 (13.8)	
Gestational age (weeks)	32–34	2,025 (61.5)	949 (62.5)	0.772
	28–31	978 (29.7)	440 (29.0)	
	24–27	292 (8.9)	129 (8.5)	
Optimality at 2 years*	Yes	2,719 (82.5)	1,190 (78.4)	< 0.001
	No	576 (17.5)	328 (21.6)	
Gender	Female	1,507 (45.7)	693 (45.7)	0.982
	Male	1,788 (54.3)	825 (54.3)	
Multiple pregnancy	No	2,063 (62.6)	949 (62.5)	0.976
	Yes	1,232 (37.4)	569 (37.5)	
Z score of birthweight	<-1	816 (24.8)	357 (23.6)	0.192
	-1 to 0	1,156 (35.1)	579 (38.2)	
	0 to 1	1,030 (31.3)	444 (29.3)	
	>1	291 (8.8)	135 (8.9)	
Socio-economic level	Intermediate	2,318 (70.3)	1,191 (78.5)	< 0.001
	High	977 (29.7)	327 (21.5)	
Social security benefits due to low income (SSB)	No	2,864 (86.9)	1,292 (85.1)	0.099
	Yes	431 (13.1)	226 (14.9)	
Urbanicity	Rural	1,221 (37.1)	550 (36.2)	0.604
	Urban	2,074 (62.9)	968 (63.8)	

*Children with a non-optimal neuromotor and/or psychomotor assessment and/or sensorial disability at two years were considered as non-optimal.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5,7,8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-8
Bias	9	Describe any efforts to address potential sources of bias	7,8 + sup tab 4, 5 6
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	Sup tab 3
		(*c*) Explain how missing data were addressed	Sup tab 5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking	Sup tab 6

		account of sampling strategy	
		(*e*) Describe any sensitivity analyses	**Sup mat**
Results			**Page**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	**Fig1**
		(b) Give reasons for non-participation at each stage	**9**
		(c) Consider use of a flow diagram	**Fig1**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**Tab1**
		(b) Indicate number of participants with missing data for each variable of interest	**Tab1, Fig1**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	**Tab1**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	**9**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**Tab2**
		(*b*) Report category boundaries when continuous variables were categorized	**Tab1**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	**Sup mat**
Discussion			
Key results	18	Summarise key results with reference to study objectives	**10**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	**11,12**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**11-13**
Generalisability	21	Discuss the generalisability (external validity) of the study results	**12**
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**13**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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

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Impact of preterm birth on parental separation: a French population based longitudinal study

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Complete List of Authors:	Nusinovici, Simon OLLIAC, Bertrand; Centre Hospitalier Esquirol, Child and adolescent psychiatry Flamant, Cyril muller, jean-baptiste; CHU Nantes, neonatology Olivier, Marion Bureau, Valérie Gascouin, Geraldine; Angers University Hospital, Department of Neonatalogy Basset, Hélène Bouvard , Charlotte Roze, JC; Centre Hospitalier Universitaire de Nantes Pole d\'information medicale evaluation et sante publique Hanf, Matthieu
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Impact of preterm birth on parental separation: a French population based longitudinal study

Simon Nusinovici[1], Bertrand Olliac[2,3], Cyril Flamant[1,4], Jean-Baptiste Müller[4], Marion Olivier[5], Valérie Rouger[5], Géraldine Gascoin[6], Hélène Basset[7], Charlotte Bouvard[8], Jean-Christophe Rozé[1,4,5], Matthieu Hanf[1]

Affiliations: 1 INSERM CIC 1413, Clinical Investigation Center, Nantes University Hospital, F-44000 Nantes, France; 2 Department of Child and Adolescent Psychiatry, Centre Hospitalier Esquirol, Limoges, France; 3 National Institute of Health and Medical Research UMR1094, Tropical Neuroepidemiology, Limoges, France; 4 Department of Neonatal Medicine, Nantes University Hospital, F-44000 Nantes, France; 5 Réseau "Grandir Ensemble", Nantes University Hospital, F-44000 Nantes, France; 6 Department of Neonatal Medicine, Angers University Hospital, F-49100 Angers, France; 7 Department of Neonatal Medicine, Le Mans Hospital, F-72037 Le Mans, France; 8 SOS Prema (parents of French preterm children organization), 32, rue du Chemin Vert, 92100 Boulogne-Billancourt, France

Contact details: Simon Nusinovici; National Institute of Health and Medical Research CIC 1413, 5 allée de l'Ile Gloriette, F-44000 Nantes, France; Email: simon.nusinovici@chu-nantes.fr; Phone: 00332 53 48 21 10; Fax: 00332 53 48 28 67

Word count: 2,758

ABSTRACT

Objective: The objective of this study was to investigate both the effects of low gestational age and infant's neurodevelopmental outcome at two years of age on the risk of parental separation within seven years of giving birth.

Design: prospective.

Setting: 24 maternity clinics in the Pays-de-la-Loire region.

Participants: This study included 5,732 infants delivered at <35 weeks of gestation born between 2005 and 2013 who were enrolled in the population-based LIFT cohort and who had a neurodevelopmental evaluation at two years. This neurodevelopmental evaluation was based on a physical examination, a psychomotor evaluation and a parent-completed questionnaire.

Outcome measure: risk of parental separation (parents living together or parents living separately).

Results: Ten percent (572/5,732) of the parents reported having undergone separation during the follow-up period. A mediation analysis showed that low gestational age had no direct effect on the risk of parental separation. Moreover, a non-optimal neurodevelopment at 2 years was associated with an increased risk of parental separation corresponding to a HR=1.49 [1.23; 1.80]. Finally, the increased risk of parental separation was aggravated by low socio-economic conditions.

Conclusions: The effect of low gestational age on the risk of parental separation was mediated by the infant's neurodevelopment.

Key words: parental separation, low gestational age, neurodevelopment outcome, cohort

Strength and limitations of the study:

- This study was based on a large prospective population-based cohort of preterm infants (n=5,732).
- Appropriate multivariable statistical analyses were used to properly model the complex relationships between low gestational age, neurodevelopmental outcome and the risk of parental separation (mediation analyses and survival Cox models).
- The socio-economic factors known to influence the risk for parental separation were taken into account in order to limit possible confounding bias.
- No information was available regarding the relationship between the parents before the birth of their infants.
- Given that the gestational age of our reference population was between 32 and 34 weeks, we cannot exclude the existence of a small effect of preterm birth on the risk of parental separation.

INTRODUCTION

Understanding the impact of preterm birth on parental separation is critical as parental separation have negative consequences in childhood[1–3], notably on cognitive and psychological developments that can persist in the adolescence[4] and adulthood[5,6]. In France, 9.9% of marriages entered into in the year 2000 ended in divorce within 5 years (National statistics from the French Institute for Statistics and Economic Studies[1] - INSEE). The increasing number of preterm births makes these questions more and more topical. Moreover, these questions are of great concern in public health and for structures such as preterm infants' parental organizations.

The birth of a preterm[7–12] or very low birthweight infant (VLBW)[10,13–15] is a stressful event for the parents. Compared to mothers of full term infants, mothers of preterm infants have been shown to have a higher risk of experiencing psychological distress and depressive symptoms following the infant's birth[16–18]. In addition to psychological distress, the birth of a preterm infant frequently has a substantial economic impact on the family involved[19,20]. All these factors that affect the life of the family can have negative consequences for the relationship between the parents.

A neurodevelopmental disability following a preterm birth could mediate, at least partly, the effect of preterm birth on parental separation. On the one hand, preterm births are indeed associated with a high risk of neurodevelopmental disabilities[21,22]. On the other hand, neurodevelopmental disabilities have been shown to be associated with an increased risk of parental separation[23–30]. However, no longitudinal study has investigated the complex relationships between low gestational age, neurodevelopmental outcome, and parental

[1] http://www.insee.fr/en/methodes/default.asp?page=definitions/unite-urbaine.htm. Date accessed: February 2016.

separation. The objective of this study was to investigate, in a large longitudinal population-based cohort of preterm infants, both the effects of low gestational age and the infant's neurodevelopmental outcome at two years of age on the risk of parental separation within seven years of giving birth.

MATERIALS AND METHODS

Study population

The study population was composed of surviving preterm infants enrolled in the Loire Infant Follow-up Team (LIFT)[31], born at less than 35 weeks of gestation between January 2005 and December 2013, and who were evaluated at two years of corrected age to assess their neurodevelopmental outcomes (Figure 1). The LIFT network includes 24 maternity clinics in the Pays-de-la-Loire region (one of the 13 administrative regions in France) with the objective to screen for early clinical anomalies associated with preterm births and to provide specifically adapted care. The follow-up consisted of standardized visits by trained physicians at 3, 6, 9, 18, and 24 months as well as at 3, 4, 5, 6, and 7 years after the birth of the infant. Data used in this study were routinely collected (i.e. not collected for the purpose of the study).

Perinatal data

Perinatal data was comprised of the date of birth, gender, gestational age (GA), and birthweight. The birthweight Z-score was computed according to the Olsen standards[32].

Parental situation

Information regarding relationship status was binary (i.e. as parents living together or parents living separately). For parents who had separated, the first date at which they were reported to be separated was used. Relationship status was not available at the time of inclusion. Consequently, for the separations reported at the 3-month visit, there was the possibility that the parents had already undergone separation at the time of the infant's birth. Therefore, to ensure temporality between preterm birth and parental separation, separations reported at the 3-month visit were excluded.

Neurodevelopmental outcome at two years

Infants were evaluated at two years of corrected age. Assessment to define optimal and non-optimal neurodevelopmental outcomes included a physical examination by a LIFT-trained pediatrician, a psychomotor evaluation by a LIFT network psychologist, and a parent-completed questionnaire. Neuromotor evaluation was regarded as non-optimal in case of cerebral palsy or when the physical examination revealed relatively milder signs of abnormal movement during independent walking according to the Amiel-Tison criteria[33]. Psychomotor evaluation was assessed with the revised Brunet-Lézine test (four domains: movement/posture, coordination, language, and socialization)[34]. The mean and maximal global scores were 100 and 140, respectively, and values of <85 were considered non-optimal psychomotor development. Infants who were not able to perform the revised Brunet-Lézine test were considered to have non-optimal psychomotor development. Furthermore, neurodevelopmental outcome was assessed with the parent-completed "Ages and Stages Questionnaire" (ASQ)[35,36]. The ASQ assesses development in the following five areas: communication, gross motor, fine motor, problem solving, and sociopersonal skills. The maximal overall ASQ score is 300 and a score of <185 was considered non-optimal[37]. Finally, sensory disabilities such as blindness or infants that required a hearing aid were taken into account. Overall, infants with a non-optimal neuromotor and/or psychomotor assessment and/or a sensory disability were regarded as having a "non-optimal neurodevelopmental outcome." Infants without a documented physical examination or psychomotor assessment were considered as non-assessable at two years except for infants with severe neurological disabilities. This definition of non-optimality has been used in other studies[38–40]. To simplify matters, a non-optimal neurodevelopmental outcome will be referred to as non-optimality.

Socioeconomic information

The socioeconomic data consisted of the socioeconomic level and eligibility for social security benefits for those with low incomes. The socioeconomic level took into account the parent with the more highly rated job according to a scale based on the official classification developed by the INSEE institute. The socioeconomic level and eligibility for social security benefits for those with low incomes were considered as two-level categorical variables.

Urbanicity of the residential municipality

The residential municipality was considered either urban or rural based on definitions developed by the INSEE institute. Municipalities were considered rural or urban depending on the distance between buildings and the number of inhabitants.

Statistical analysis

The statistical analyses were conducted in three steps. Firstly, the crude associations between gestational age and non-optimality at 2 years and the risk of parental separation were investigated with Kaplan-Meier curves and log-rank tests.

Secondly, a mediation analysis was used to estimate the proportion of the effect of low gestational age on the risk of parental separation that was mediated by non-optimality at 2 years. The aim of a mediation analysis is to decompose the effect of an exposure on an outcome into a direct effect and an indirect effect that is mediated by an intermediate variable (the mediator). Mediation analyses used were based on the counterfactual framework. A counterfactual variable describes what would have happened if we had intervened on exposure. This framework allows the decomposition of the causal effect into a so-called natural direct and natural indirect effect. A natural direct effect measures the change in outcome (the risk of parental separation) that would be observed if we could change the exposure (low gestational age) but leave the mediator (optimality at 2 years) at the value it naturally takes when the exposure is left unchanged. A natural indirect effect measures the change in outcome (the risk of parental separation) that would be observed if we could change the mediator (optimality at 2 years) as much as it would naturally change when exposure was changed without actually changing the exposure (low gestational age). Gestational age was considered as a three-level categorical variable: GA 32-34 (reference), GA 28-31 (very preterm birth), and GA 24-27 weeks (extremely preterm birth). The estimations of natural direct and indirect effects were done while adjusting for the possible confounding factors: gender, multiple pregnancies ("yes" or "no"), Z-score of birthweight (<-1, between -1 and 0, between 0 and 1, and ≥1), socioeconomic level ("high" or "intermediate"), social security benefits for those with low incomes ("yes" or "no"), and urbanicity of the residential municipality ("urban" versus "rural"). Moreover, this analysis accounted for the censored nature of the outcome. The possible interaction between the exposure and the mediator was tested. Mediation models used here are based on natural effect models[41] implemented in the R package medflex.

Thirdly, the effect of the non-optimality at 2 years on the risk of parental separation was estimated using the multivariable Cox model. Furthermore, the effect of gestation age on non-optimality at 2 years was estimated using logistic regression. For these two models, the same adjustment variables as those considered in the mediation analysis were included in the models. All analyses were performed using R software[2].

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[2] R Core Team (2016). *R: A Language and Environment for Statistical Computing.* R Foundation for Statistical Computing, Vienna, Austria. http://www.R-project.org/

Four sensitivity analyses were performed. In the first one, parental separations occurring before the 24-month visit were excluded to ensure the temporality between neurodevelopmental outcome and parental separations. In the second analysis, an imputation of the missing data was performed using a multiple imputation method. The third analysis concerned the comparison of the characteristics of the infants that were lost to follow-up between two and five years and those who were still followed at five years. Finally, a last analysis was performed by keeping only one infant from each twins' pair to check the robustness of the results regarding the assumption of non-independence between twins.

Ethic approval

Written consent was obtained for each patient before inclusion in the study, and the cohort was registered at the French data protection authority in clinical research ("Commission Nationale de l'Informatique et des Libertés" or CNIL, No. 851117).

RESULTS

Between January 2005 and December 2013, 6,937 infants born at less than 35 weeks of gestation in the Pays-de-la-Loire region, France, were enrolled in the LIFT cohort. The following infants were excluded from the study population: infants whose parents were separated at the three-month (n=185) or 84-month visit (n=20), infants without neurodevelopmental evaluation at two years but still followed (n=392), and infants lost to follow-up at two years (n=315). In light of these exclusions, the study population consisted of 5,732 preterm infants, corresponding to 83% of the infants initially enrolled in the cohort (Figure 1).

During the follow-up, 10.0% of the parents reported having undergone separation (n=572), corresponding with an incidence rate of 23.8 separations per 1000 infant-year. The median time at which separations were reported was 22 months following the birth of the infant with an interquartile range (IQR) of 10.3–43.3 months. 30.2% (n=1,730) and 8.9% (n=508) of the infants were born very or extremely preterm, respectively. 19.1% (n=1,096) of the infants were considered non-optimal at two years. Lastly, the median length of the total follow-up was 56 months (IQR=32.1–69.2) (Table 1).

In the bivariable analysis, both gestational age and non-optimality at 2 years were associated with an increased risk of parental separation (Supplementary Table 1, Figure 2). However, the mediation analysis showed that all the effect of low gestational age in very and extremely preterm infants on the risk of parental separation was mediated by the non-optimality at 2 years of age (Supplementary Figure 1). Preterm birth were associated with a higher risk of non-optimal neurodevelopment at two years, corresponding to OR=2.1 [1.8, 2.4] and OR=4.2 [3.4, 5.2] for very and extremely preterm infants, respectively (Supplementary Table 2). The non-optimality at 2 years was associated with an increased risk of parental separation corresponding to a HR=1.49 [1.23, 1.80] (Table 2, Figure 3). Furthermore, a significant interaction was found between non-optimality and social security benefits due to low income on the risk of parental separation (Supplementary Table 3). Finally, a lower parental socioeconomic level, receiving social security benefits due to low income, and living in urban areas were associated with a higher risk of parental separation. The AUC of this model was 0.69. The results of the relationships between gestational age, non-optimality, and parental separation are summarized in Figure 3.

DISCUSSION

Using a large population-based cohort study, we found that the effect of low gestational age on the risk of parental separation was entirely mediated by the neurodevelopmental outcome at two years. Parents of preterm infants with a non-optimal neurodevelopment at two years were 50% more likely to have undergone separation in the years following the birth of the infant, independently of the socio-economic factors. This increased risk was further aggravated by low socio-economic conditions.

A strength of this study was the use of mediation analysis. Because of the association between gestational age and neurodevelopmental outcome at two years, mediation analysis is a relevant approach to investigate the effects of gestational age and neurodevelopmental outcome on the risk of parental separation. An alternative approach would have been to build a single model predicting parental separation with these two risk factors and the adjustment variables. However, this model would not have accounted for the strong association between gestational age and neurodevelopmental outcome and, therefore, could have led to biased results. A further strength of this study was the large number of infants included, which allowed a high statistical power to be attained. In addition, the longitudinal data and the corresponding survival analyses allowed us to account for the timing of parental separations, rather than simply distinguishing between whether the parents were living together or not. Furthermore, the socio-economic factors known to influence the risk for parental separation were taken into account. For infants whose parents underwent separation before the 24-month visit (n=221), there was a doubt regarding the temporality between the neurodevelopmental outcome and the parental separation. The sensitivity analysis showed that without these infants, the results were exactly the same, probably due to the early occurrence of neurodevelopment impairments during the infant's development (Supplementary Table 4). Moreover, a sensitivity analysis was performed after imputation of the missing data (n=1,000) using a multiple imputation method. The robustness of the results demonstrated the absence of bias related to missing data (Supplementary Table 5). Finally, the analysis performed by keeping only one infant from each twins' pair showed similar results (Supplementary Table 6).

The present study has several limitations. Firstly, this study may underestimate the proportion of parental separation due to a bias in the declaration of relevant information; for example, during the examination of the infant by the pediatrician there could a degree of reluctance from the parents to reveal that they are no longer living together. In our study, 12.3% of the parents were found to have undergone separation within an average follow-up time span of 5 years (including separations occurring at the 3-month and 84-month visits that were excluded from analyses). National statistics from the INSEE institute state that 9.9% of marriages entered into in the year 2000 ended in divorce within 5 years, suggesting that absence of bias in parental separation declaration. Secondly, the characteristics of infants that were excluded from the study population were not comparable to those who were included (Table 1). For example, late preterm infants born to families with a lower socioeconomic level were overrepresented in the category that was not included for the analysis. However, the absolute differences in the perinatal characteristics were rather small, thus indicating that inclusion criteria did not result in an obvious selection bias. Thirdly, given that the gestational age of our reference population was between 32 and 34 weeks, we cannot exclude the existence of a small effect of preterm birth on the risk of parental separation, albeit one that is not detectable with our study design. Further studies using a population of full-term infants as reference are needed to confirm our results. Fourthly, no information was available regarding the relationship between the parents before the birth of their infants. A very conflictual relationship might be associated with a higher risk of giving birth to a preterm infant. Our study could, therefore, overestimate the effect of a non-optimal neurodevelopment on the risk of parental separation. Fifthly, some factors that may be associated with parental separation were not available in this study and were thus not accounted for, such as the age of the parents or the number of children living in the household. Finally, some infants were lost between two and five years of follow-up (1,518 out of 4,813). These infants had slightly different characteristics (Supplementary Table 7). However, no difference was observed for the proportion of parents that underwent separation.

In the present study, optimality was defined using neuromotor, psychomotor, and sensory evaluations, thereby revealing particularly severe pathologies or clinical symptoms. The association between optimality and parental separation is in accordance with the results of previous studies demonstrating negative consequences on the parent's relationship in case of a severe disease [24–26]. Interestingly, parents of extremely preterm infants with an optimal neurodevelopment at two years did not have a higher risk of separation. The increased risk of separation by parents of VLBW (<1500g) [42] in a US national survey conducted on 6,016 births might be due to the fact that occurrences of disability were not taken into account during the follow-up. Therefore, we agree with the authors' statement that their values may be regarded as conservative estimates of the effect of infant disability on parental separation. While a preterm birth may not, on average, be directly responsible for the disruption of a couple's relationship, the discovery of associated severe infant disabilities or neurodevelopmental delays could profoundly challenge the parent's relationship. The increased risk of parental separation seems to be due to the presence of repeated stressful events within the first years of the infant's life. Lastly, this study provides evidence for a major impact of socioeconomic factors on the risk of parental separation. This result is in accordance with several studies that showed no or limited parental education and low family income are strong risk factors for separation [26,29,43,44], for parental stress [13–15], and for psychological distress [16].

CONCLUSIONS

The effect of low gestational age on the risk of parental separation was mediated by the infant's neurodevelopment, with 50% more separations among parents of infants with non-optimal neurodevelopment. This increased risk was aggravated by low socio-economic conditions.

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Declaration of interest

The authors have declared that they have no conflict of interest

Author's contributions

Matthieu Hanf had the original idea, provided guidance for the statistical analysis and reviewed and revised the manuscript. Simon Nusinovici performed the statistical analysis, the literature searches and wrote the paper. Jean-Baptiste Müller, Géraldine Gascoin, Hélène Basset, Cyril Flamant, Bertrand Olliac, Valérie Rouger, Charlotte Bouvard and Jean-Christophe Rozé participated to the data collection, reviewed and revised the manuscript. Marion Pérennec participated to the analysis and interpretation of the data, reviewed and revised the manuscript. All the authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data sharing statement:

Data are available from the scientific Committee of the LIFT cohort for researchers who meet the criteria for access to confidential health data. Interested researchers have to comply with the French legislation i.e. require the advice of the "Comité consultatif sur le traitement de l'information en matière de recherché sur le domaine de la santé" (CCTIRS) as well as the authorization of the "Commission nationale de l'information et des libertés" (CNIL) for the treatment of personal health data. Research projects have also to be approved by an independent Ethics Committee. Contact information is available at: http://www.reseau-naissance.fr/module-pagesetter-viewpub-tid-2-pid-21.html

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Table 1. Descriptive characteristics of the study population and comparison between preterm infants included in the study and those not included.

		Included (n=5,732)	Not included (n=1,205)	
Variable	Category	Number (%)	Number (%)	P value
Gestational age (weeks)	32–34	3,494 (61.0)	802 (66.6)	< 0.001
	28–31	1,730 (30.2)	321 (26.6)	
	24–27	508 (8.9)	82 (6.8)	
Gender	Female	2,640 (46.1)	589 (48.9)	0.079
	Male	3,092 (53.9)	616 (51.1)	
Multiple pregnancy	No	3,617 (63.1)	830 (68.9)	< 0.001
	Yes	2,115 (36.9)	375 (31.1)	
Z score of birth weight	<-1	1,378 (24.0)	285 (23.9)	0.999
	-1 to 0	2,044 (35.7)	426 (35.7)	
	0 to 1	1,787 (31.2)	371 (31.1)	
	>1	523 (9.1)	110 (9.2)	
Socio-economic level	Intermediate	4,254 (74.2)	1,024 (85.0)	< 0.001
	High	1,478 (25.8)	181 (15.0)	
Social security benefits due to low income	No	5,031 (87.8)	968 (80.3)	< 0.001
	Yes	701 (12.2)	237 (19.7)	
Urbanicity	Rural	2,104 (36.7)	376 (31.2)	< 0.001
	Urban	3,628 (63.3)	829 (68.8)	
Length of follow-up (months) [Median (IQR)]		56 [32.1, 69.2]	16.6 [8.1, 56.9]	< 0.001

IQR: interquartile range

Table 2. Crude and adjusted association between the neurodevelopment of preterm infants and the risk of parental separation. Adjustment was made on perinatal characteristics of the infants, the socio-economic level of the family, and the urbanicity of the residential municipality (n=5,732).

	Category	N (%)	Raw HR [95% CI]	Adjusted HR [95% CI]
Optimality at 2 years*	Yes	4,636 (80.9)	1	1
	No	1,096 (19.1)	1.58 [1.31, 1.90]	1.49 [1.23, 1.80]
Gender	Female	2,640 (46.1)	1	1
	Male	3,092 (53.9)	1.07 [0.90, 1.26]	1.07 [0.91, 1.27]
Multiple pregnancy	No	3,617 (63.1)	1	1
	Yes	2,115 (36.9)	0.94 [0.79, 1.11]	0.97 [0.81, 1.15]
Z score of birthweight	<-1	1,378 (24.0)	1	1
	-1 to 0	2,044 (35.7)	1.03 [0.84, 1.28]	1.1 [0.89, 1.36]
	0 to 1	1,787 (31.2)	0.9 [0.72, 1.12]	0.96 [0.77, 1.20]
	>1	523 (9.1)	0.96 [0.70, 1.33]	1.03 [0.75, 1.43]
Socio-economic level	Intermediate	4,254 (74.2)	1	1
	High	1,478 (25.8)	0.62 [0.50, 0.76]	0.64 [0.52, 0.79]
Social security benefits (SSB) due to low income	No	5,031 (87.8)	1	1
	Yes	701 (12.2)	4.09 [3.43, 4.86]	3.68 [3.09, 4.39]
Urbanicity	Rural	2,104 (36.7)	1	1
	Urban	3,628 (63.3)	1.91 [1.57, 2.31]	1.81 [1.49, 2.20]

HR: hazards ratio; CI: confidence interval

* Infants with a non-optimal neuromotor and/or psychomotor assessment and/or sensorial disability at two years were considered as non-optimal.

Figure's caption

Figure 1. Flowchart

WG: weeks of gestation; PDL: Pays-de-la-Loire region; LIFT: Loire Infant Follow-up Team.

Figure 2. Relationship between the neurodevelopment of preterm infants and the occurrence of parental separation, using Kaplan-Meier curves (n=5,732).

Figure 3. Summary of the relationships between low gestational age, neurodevelopment of preterm infants (non-optimality at two years), and the risk of parental separation.

*SSB: Social security benefits due to low income; ZS: Z-score.

Odds ratio (OR) and hazard ratio (HR) were estimated using two different models (because of the absence of direct effect of low gestational age on the risk of parental separation). Model 1: logistic regression with outcome = non-optimality at two years and exposure = gestational age. Model 2: Cox model with outcome = parental separation and exposure = non-optimality at two years. Adjustment variables for both models: gender, multiple pregnancies, Z-score of birthweight, socioeconomic level, social security benefits for those with low incomes, and urbanicity of the residential municipality. Only significant adjustment variables were reported in this figure.

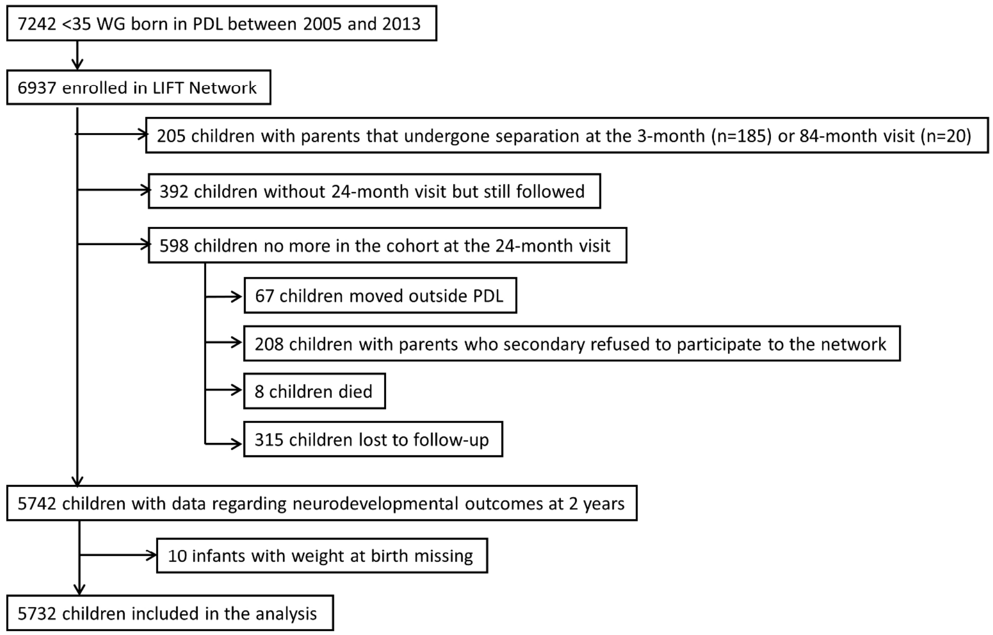

Figure 1. Flowchart
WG: weeks of gestation; PDL: Pays-de-la-Loire region; LIFT: Loire Infant Follow-up Team.

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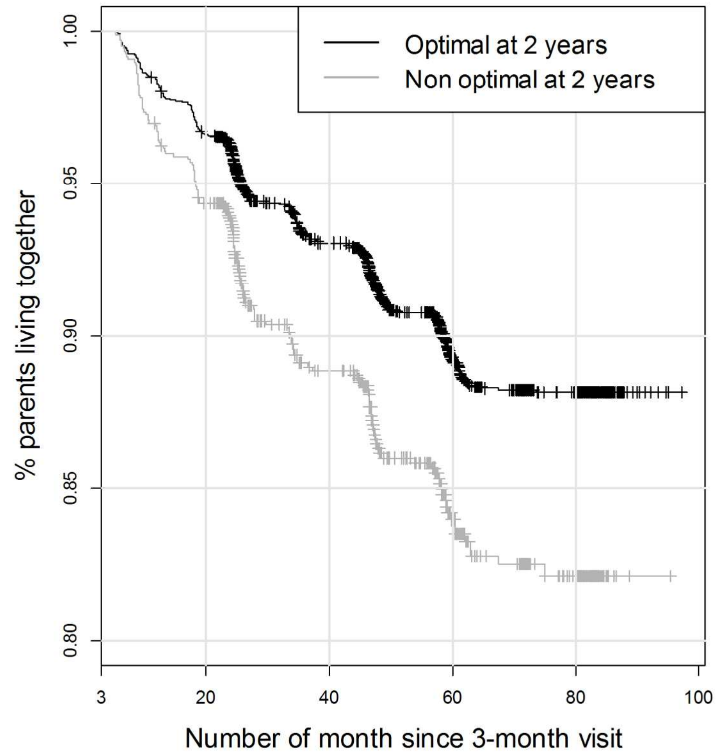


N at risk	3	20	40	60	80
Optimal at 2 years	4636	4406	3248	1755	543
Non-optimal at 2 years	1096	1004	694	335	119

Figure 2. Relationship between the neurodevelopment of preterm infants and the occurrence of parental separation, using Kaplan-Meier curves (n=5,732).

193x171mm (300 x 300 DPI)

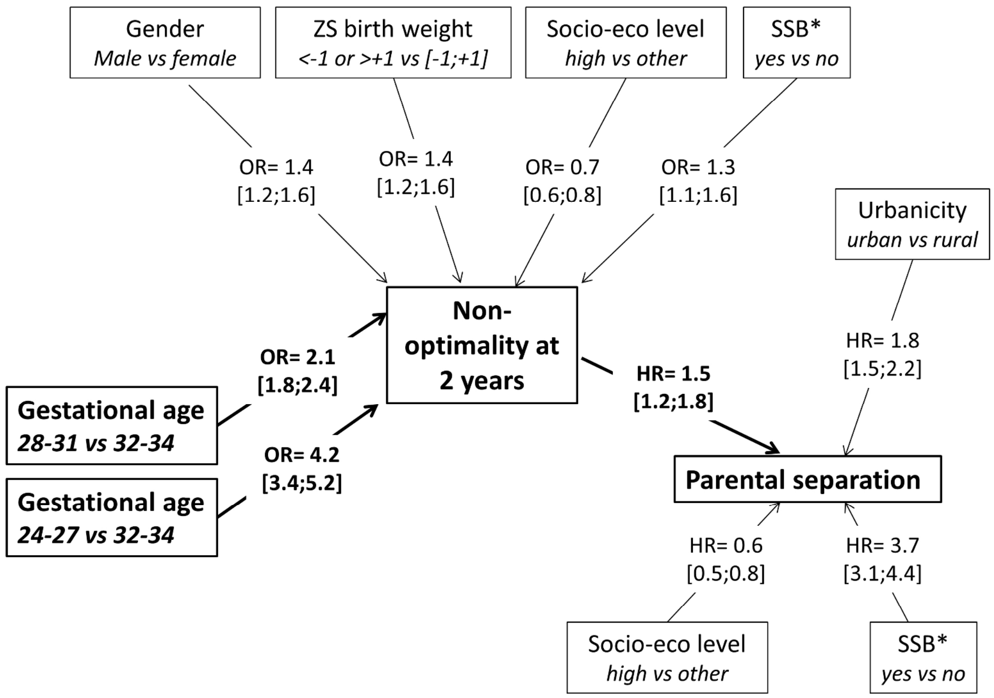
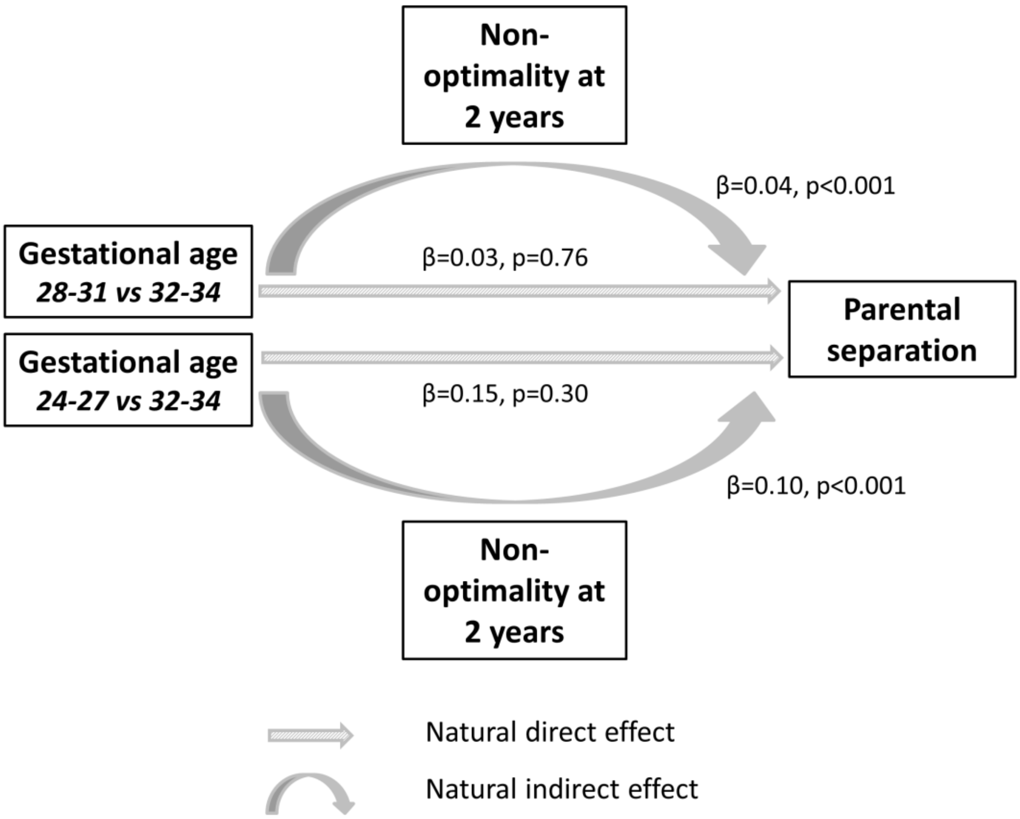


Figure 3. Summary of the relationships between low gestational age, neurodevelopment of preterm infants (non-optimality at two years), and the risk of parental separation.
*SSB: Social security benefits due to low income; ZS: Z-score.
Odds ratio (OR) and hazard ratio (HR) were estimated using two different models (because of the absence of direct effect of low gestational age on the risk of parental separation). Model 1: logistic regression with outcome = non-optimality at two years and exposure = gestational age. Model 2: Cox model with outcome = parental separation and exposure = non-optimality at two years. Adjustment variables for both models: gender, multiple pregnancies, Z-score of birthweight, socioeconomic level, social security benefits for those with low incomes, and urbanicity of the residential municipality. Only significant adjustment variables were reported in this figure.

242x171mm (300 x 300 DPI)

Supplementary materials

Supplementary Figure 1. Decomposition of the effect of low gestational age on the risk of parental separation into a direct effect and an indirect effect mediated by the neurodevelopment of preterm infants (non-optimality at two years). This mediation model was adjusted for gender, multiple pregnancy, Z-score of birthweight, socioeconomic level, social security benefits for those with low incomes, and urbanicity of the residential municipality.



Supplementary Table 1. Incidence risks and incidence rates of parental separation in preterm infants population according to the perinatal characteristics of the child, the socio-economic level of the family and the urbanicity of the residential municipality (n=5,732).

Variable	Category	Incidence risk of parental separation (N events/N at risk) x 100	Incidence rate of parental separation for 1000 children-year	P value**
Gestational age (weeks)	32–34	9.6	22.6	0.030
	28–31	9.9	24.1	
	24–27	13.0	31.6	
Optimality at 2 years*	Yes	9.2	21.5	< 0.001
	No	13.4	34.2	
Gender	Female	9.6	23.0	0.450
	Male	10.3	24.5	
Multiple pregnancy	No	10.2	24.3	0.460
	Yes	9.6	22.9	
Z score of birthweight	<-1	10.3	24.3	0.570
	-1 to 0	10.5	25.3	
	0 to 1	9.2	21.8	
	>1	9.6	23.5	
Socio-economic level	Intermediate	10.8	26.7	< 0.001
	High	7.5	16.4	
Social security benefits due to low income	No	7.6	17.7	< 0.001
	Yes	27.4	73.6	
Urbanicity	Rural	6.6	15.2	< 0.001
	Urban	12.0	29.1	

*Children with a non-optimal neuromotor and/or psychomotor assessment and/or sensorial disability at two years were considered as non-optimal.

**log-rank test

Supplementary Table 2. Adjusted associations between the risk of non-optimal neurodevelopment at two years and gestational age with adjustment variables for preterm infants born between 2005 and 2013 followed in the LIFT cohort (n=5,732).

Variable	Category	N (%)	Adjusted OR [95%CI]
Gestational age (weeks)	32–34	3,494 (61.0)	1
	28–31	1,730 (30.2)	2.06 [1.78, 2.39]
	24–27	508 (8.9)	4.23 [3.43, 5.20]
Gender	Female	2,640 (46.1)	1
	Male	3,092 (53.9)	1.38 [1.2, 1.59]
Multiple pregnancy	No	3,617 (63.1)	1
	Yes	2,115 (36.9)	0.94 [0.82, 1.09]
Z score of birthweight	<-1	1,378 (24.0)	1
	-1 to 0	2,044 (35.7)	0.73 [0.61, 0.87]
	0 to 1	1,787 (31.2)	0.72 [0.6, 0.87]
	>1	523 (9.1)	0.99 [0.77, 1.26]
Socio-economic level	Intermediate	4,254 (74.2)	1
	High	1,478 (25.8)	0.72 [0.61, 0.85]
Social security benefits (SSB) due to low income	No	5,031 (87.8)	1
	Yes	701 (12.2)	1.31 [1.07, 1.59]
Urbanicity	Rural	2,104 (36.7)	1
	Urban	3,628 (63.3)	0.90 [0.78, 1.04]

OR: odds ratio; CI: confidence interval.

Supplementary Table 3. Crude and adjusted associations between the risk of parental separation and neurodevelopment of preterm infants (optimality at two years) with adjustment variables and interaction term between optimality at two years and social security benefits due to low income (n=5,732).

Variable	Category	N (%)	Adjusted HR [95% CI]
Optimality at 2 years*	Yes	4,636 (80.9)	1
	No	1,096 (19.1)	1.27 [0.99, 1.63]
Gender	Female	2,640 (46.1)	1
	Male	3,092 (53.9)	1.07 [0.91, 1.26]
Multiple pregnancy	No	3,617 (63.1)	1
	Yes	2,115 (36.9)	0.96 [0.81, 1.14]
Z score of birthweight	<-1	1,378 (24.0)	1
	-1 to 0	2,044 (35.7)	1.10 [0.89, 1.36]
	0 to 1	1,787 (31.2)	0.97 [0.77, 1.21]
	>1	523 (9.1)	1.04 [0.76, 1.44]
Socio-economic level	Intermediate	4,254 (74.2)	1
	High	1,478 (25.8)	0.64 [0.52, 0.79]
Social security benefits (SSB) due to low income	No	5,031 (87.8)	1
	Yes	701 (12.2)	3.27 [2.65, 4.04]
Urbanicity	Rural	2,104 (36.7)	1
	Urban	3,628 (63.3)	1.80 [1.49, 2.19]
Optimality at 2 years * SSB	Yes * No	4,102 (71.6)	1
	No * Yes	167 (2.9)	1.52 [1.03, 2.23]

HR: hazards ratio; SSB: social security benefits; CI: confidence interval.

*Children with a non-optimal neuromotor and/or psychomotor assessment and/or sensorial disability at two years were considered as non-optimal.

Supplementary Table 4. Adjusted associations between the risk of parental separation occurring from the 24-month visit and neurodevelopment of preterm infants (optimality at two years) with adjustment variables (n=5,511). In this analysis, the separations occurring between the 6-month and the 18-month visit were excluded.

	Category	N (%)	Adjusted HR [95% CI]
Optimality at 2 years*	Yes	4,477 (81.2)	1
	No	1,034 (18.8)	1.49 [1.17, 1.91]
Gender	Female	2,549 (46.3)	1
	Male	2,962 (53.7)	0.98 [0.79, 1.21]
Multiple pregnancy	No	3,479 (63.1)	1
	Yes	2,032 (36.9)	0.90 [0.72, 1.13]
Z score of birthweight	<-1	1,326 (24.1)	1
	-1 to 0	1,952 (35.4)	1.01 [0.77, 1.32]
	0 to 1	1,729 (31.4)	0.98 [0.74, 1.30]
	>1	504 (9.1)	1.02 [0.68, 1.54]
Socio-economic level	Intermediate	4,068 (73.8)	1
	High	1,443 (26.2)	0.67 [0.52, 0.87]
Social security benefits (SSB) due to low income	No	4,903 (89.0)	1
	Yes	608 (11.0)	3.01 [2.38, 3.81]
Urbanicity	Rural	2,054 (37.3)	1
	Urban	3,457 (62.7)	1.82 [1.43, 2.32]

HR: hazards ratio; CI: confidence interval.

*Children with a non-optimal neuromotor and/or psychomotor assessment and/or sensorial disability at two years were considered as non-optimal.

Supplementary Table 5. Adjusted associations between the risk of parental separation and neurodevelopment of preterm infants (optimality at two years) with adjustment variables after imputation of missing values (13 infants with weight at birth missing and 990 infants with neurodevelopmental outcome at two years missing) using the multiple imputation method (n=6,732).

Variable	Category	Adjusted HR [95% CI]
Optimality at 2 years*	Yes	1
	No	1.45 [1.21, 1.73]
Gender	Female	1
	Male	1.06 [0.91, 1.24]
Multiple pregnancy	No	1
	Yes	0.97 [0.83, 1.14]
Z score of birthweight	<-1	1
	-1 to 0	1.06 [0.87, 1.29]
	0 to 1	0.92 [0.74, 1.13]
	>1	0.98 [0.72, 1.33]
Socio-economic level	Intermediate	1
	High	0.68 [0.56, 0.82]
Social security benefits due to low income	No	1
	Yes	3.91 [3.32, 4.60]
Urbanicity	Rural	1
	Urban	1.81 [1.51, 2.18]

HR: hazards ratio; CI: confidence interval.

*Children with a non-optimal neuromotor and/or psychomotor assessment and/or sensorial disability at two years were considered as non-optimal.

Supplementary Table 6. Crude and adjusted association between the neurodevelopment of preterm infants and the risk of parental separation. Adjustment was made on perinatal characteristics of the infants, the socio-economic level of the family, and the urbanicity of the residential municipality. Only one infant from each twins' pair was kept in the analyses (n=3,654).

	Category	N (%)	Adjusted HR [95% CI]
Optimality at 2 years*	Yes	2,919 (79.9)	1
	No	735 (20.1)	1.39 [1.10, 1.74]
Gender	Female	1,676 (45.9)	1
	Male	1,978 (54.1)	1.09 [0.89, 1.33]
Multiple pregnancy	No	2,763 (75.6)	1
	Yes	891 (24.4)	0.90 [0.71, 1.15]
Z score of birthweight	<-1	869 (23.8)	1
	-1 to 0	1,283 (35.1)	1.08 [0.84, 1.39]
	0 to 1	1,147 (31.4)	0.84 [0.64, 1.10]
	>1	355 (9.7)	0.95 [0.64, 1.40]
Socio-economic level	Intermediate	2,705 (74)	1
	High	949 (26)	0.72 [0.56, 0.92]
Social security benefits (SSB) due to low income	No	3,153 (86.3)	1
	Yes	501 (13.7)	3.48 [2.82, 4.29]
Urbanicity	Rural	1,297 (35.5)	1
	Urban	2,357 (64.5)	1.81 [1.43, 2.31]

HR: hazards ratio; CI: confidence interval

* Infants with a non-optimal neuromotor and/or psychomotor assessment and/or sensorial disability at two years were considered as non-optimal.

Supplementary Table 7. Comparison of the infants born <35 weeks between 2005 and 2011 still followed at the 60-month visit (n=3,295) and those lost to follow-up between the 24-month and the 60-month visit (n=1,518).

Variable	Category	Children still followed at the 60-month visit (n=3295)	Children lost to follow-up between the 24-month and the 60-month visit (n=1518)	P value
Parental separation	Living together	2,868 (87.0)	1,309 (86.2)	0.469
	Separated	427 (13.0)	209 (13.8)	
Gestational age (weeks)	32–34	2,025 (61.5)	949 (62.5)	0.772
	28–31	978 (29.7)	440 (29.0)	
	24–27	292 (8.9)	129 (8.5)	
Optimality at 2 years*	Yes	2,719 (82.5)	1,190 (78.4)	< 0.001
	No	576 (17.5)	328 (21.6)	
Gender	Female	1,507 (45.7)	693 (45.7)	0.982
	Male	1,788 (54.3)	825 (54.3)	
Multiple pregnancy	No	2,063 (62.6)	949 (62.5)	0.976
	Yes	1,232 (37.4)	569 (37.5)	
Z score of birthweight	<-1	816 (24.8)	357 (23.6)	0.192
	-1 to 0	1,156 (35.1)	579 (38.2)	
	0 to 1	1,030 (31.3)	444 (29.3)	
	>1	291 (8.8)	135 (8.9)	
Socio-economic level	Intermediate	2,318 (70.3)	1,191 (78.5)	< 0.001
	High	977 (29.7)	327 (21.5)	
Social security benefits due to low income (SSB)	No	2,864 (86.9)	1,292 (85.1)	0.099
	Yes	431 (13.1)	226 (14.9)	
Urbanicity	Rural	1,221 (37.1)	550 (36.2)	0.604
	Urban	2,074 (62.9)	968 (63.8)	

*Children with a non-optimal neuromotor and/or psychomotor assessment and/or sensorial disability at two years were considered as non-optimal.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**2**
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	**4**
Objectives	3	State specific objectives, including any prespecified hypotheses	**4**
Methods			
Study design	4	Present key elements of study design early in the paper	**5,7,8**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**5-7**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	**5**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	**Not applicable**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	**5-8**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	**5-8**
Bias	9	Describe any efforts to address potential sources of bias	**7,8 + sup tab 4, 5 6**
Study size	10	Explain how the study size was arrived at	**Not applicable**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**8**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	**7,8**
		(*b*) Describe any methods used to examine subgroups and interactions	**Sup tab 3**
		(*c*) Explain how missing data were addressed	**Sup tab 5**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking	**Sup tab 6**

		account of sampling strategy	
		(*e*) Describe any sensitivity analyses	**Sup mat**
Results			**Page**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	**Fig1**
		(b) Give reasons for non-participation at each stage	**9**
		(c) Consider use of a flow diagram	**Fig1**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**Tab1**
		(b) Indicate number of participants with missing data for each variable of interest	**Tab1, Fig1**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	**Tab1**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	**9**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**Tab2**
		(*b*) Report category boundaries when continuous variables were categorized	**Tab1**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	**Sup mat**
Discussion			
Key results	18	Summarise key results with reference to study objectives	**10**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	**11,12**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**11-13**
Generalisability	21	Discuss the generalisability (external validity) of the study results	**12**
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**13**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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