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Social Context of Preterm Delivery in France in 2011 and Impact on Short-Term Health Outcomes: the EPIPAGE 2 Cohort Study

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Abstract

Background: Low socio-economic context increases the risk of preterm delivery and may affect short-term outcomes in children born preterm. We described the social context of preterm delivery in France in 2011 and compared it with the general population of deliveries over the same period. We also studied how social context influenced pregnancy and delivery characteristics in the preterm population, and how it affected mortality and short-term morbidity in liveborn preterm children (<35 weeks).

Methods: We created an individual socio-economic vulnerability index, derived from multiple correspondence analysis based on maternal social information in the French National Perinatal Survey (NPS-2010). Weighted coordinates were applied to families from the EPIPAGE 2 study, a population-based cohort of preterm infants born in 2011, to quantify the infant's exposure to socio-economic vulnerability. Multivariable logistic models were used to relate the socio-economic context to pregnancy and delivery characteristics, and to assess its impact on short-term outcomes of the infants.

Results: Among mothers of preterm infants, gestational age decreased as socio-economic conditions worsened. In the most deprived group, women had more irregular pregnancy care, a higher prevalence of infection during pregnancy, and a lower rate of antenatal corticosteroid administration. The most deprived group was associated with a higher risk of severe morbidity for the preterm neonates.

Conclusion: Our results emphasise the need for a large population-based surveillance system to identify the most deprived mothers, and to propose appropriate follow-up and care to these women and their infants in order to enhance long-term health.

Keywords: *socio-economic conditions, preterm delivery, maternal infection, short-term outcomes.*

Preterm delivery (PTD) remains a worldwide public health concern.[1,2] It is the leading cause of perinatal and neonatal mortality and morbidity, resulting in neurodevelopmental impairments and respiratory and gastrointestinal complications,[2,3] which in turn have a major lifelong impact.[4,5] Overall, previous research primarily focused on very preterm deliveries (VPTD < 32 weeks), even though moderate preterm deliveries (MPTD 32–34 weeks) have been increasing faster than VPTD. In addition, in school-aged children born preterm, a continuum has been observed in the frequency of cognitive deficits across gestational ages

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(GA),[2,4,5] demonstrating that analysis of the consequences of PTD needs to include all GA groups.

PTD is a complex condition influenced by a variety of socio-economic or environmental factors. Adverse socio-economic factors increase the occurrence of maternal health problems, such as genital maternal tract infections, which may affect the duration of pregnancy.[6] Socio-economic factors also have an impact through cumulative '*life course*' exposure to adverse situations, including crowded housing conditions, unemployment, and severe financial difficulties. Individuals are, thus, at greater risk of chronic stress. In turn, this may lead to careless behaviours during pregnancy, such as smoking and delayed or reduced prenatal care.[7] The cumulative effects of socio-economic disadvantages on the increased risk of PTD have been consistently documented.[8,9] However, little is known about their independent impact on early childhood health outcomes.

In recent years, in France and in other developed countries, there has been a steady increase in the prevalence rate of PTD and MPTD,[10–13] while at the same time the social context for women has worsened.[13,14] Using data from the EPIPAGE 2 cohort of PTD, our objectives were (1) to describe the social context of PTD in France in 2011 and compare it with that of the general population of deliveries during the same period, (2) to document the association of social factors with pregnancy and delivery characteristics and short-term morbidity among liveborn preterm children, and (3) to determine whether socio-economic disadvantages have an independent effect on short-term morbidity in liveborn preterm children.

Methods

Design and participants

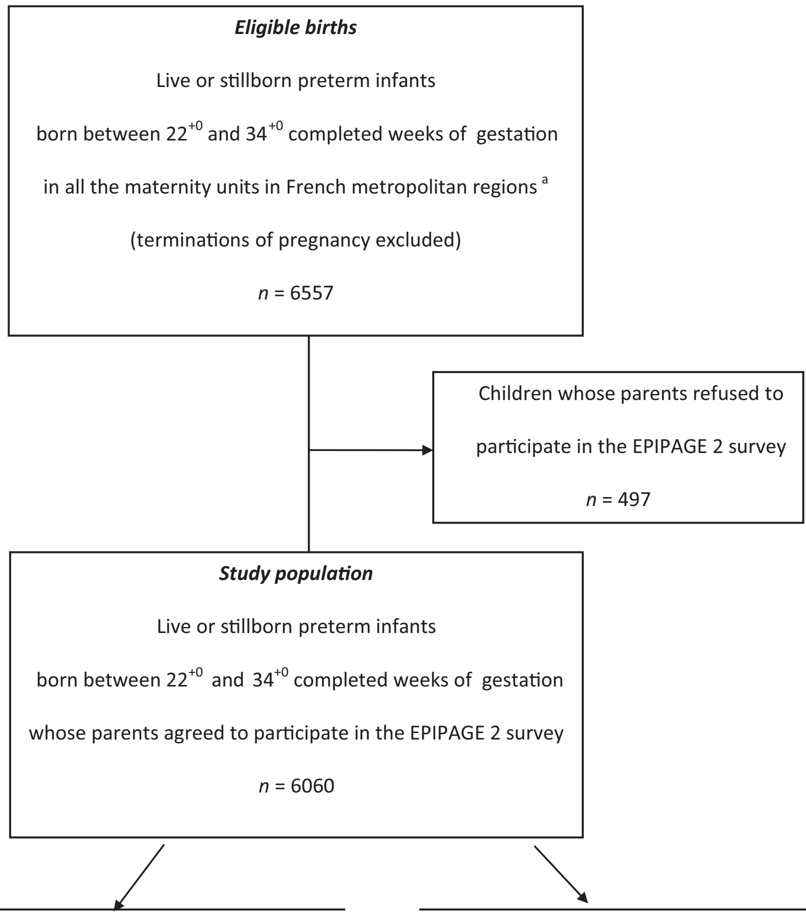
The EPIPAGE 2 study is a French observational prospective cohort study designed to describe the medical and social context in which PTD occurred in 2011. This study aims to improve our understanding of the short- and long-term outcomes in preterm children and their families, and also to identify early predictors of health and developmental problems related to PTD. The detailed protocol has been published elsewhere.[15] At birth and during the neonatal period, data were prospectively collected from medical records, and were related to families' social context, pregnancy complications and context of delivery, child's condition at birth, neonatal diseases, management of care, and medications. Mothers were also interviewed to complete the information on family socio-economic status. Written consent was obtained for all participants. As required by French law, the study was approved by the appropriate ethics committees and by the national data protection authority.[15]

The current analysis excluded 1324 terminations of pregnancy, most for congenital malformation. Of 6557 eligible births, 445 families (497 infants, 7.6%) refused to participate. The total study sample consisted of live or stillbirths delivered at 22–26 weeks ($n = 1875$), 27–31 weeks ($n = 3007$), and 32–34 weeks ($n = 1178$). Figure 1 summarises the number of mothers and of births in the study population according to GA group.

Measure of social context

Social context information at birth comprised the following: mother's nationality (French, other European countries, North Africa, others African countries, other countries), maternal educational level classified into three groups (high: university graduate; intermediate: post-secondary education; and low: less education or none), mother living alone (or not), mother living in their own home or not (the latter category being mother living with her parents or another family member, in a friend's home, foster home centre, or in a hostel), health insurance (social security, the French equivalent of Medicare-*Couverture Médicale Universelle* or *CMU*-, or no insurance), and occupation (e.g. higher professional, intermediate, public or corporate employee, shop and service worker, employee in skilled or unskilled occupations, or unemployed). Occupation was collected separately for mothers and fathers. Data for all births were collected from medical records with the exception of maternal educational level and mother living in their own home, which were collected from maternal interviews. Only mothers with surviving newborns were interviewed.

To quantify exposure to socio-economic vulnerability, an individual socio-economic index (ISEI) was derived from the above indicators available for all births. These indicators were also available in a representative sample of all live and stillbirths (≥22 weeks of gestation or ≥500 g birthweight) in 2010 across France [French National Perinatal Survey (NPS) – 14 903 births],[13] which served as a reference population for births in this study. Using the NPS-2010 data,



All births

Weeks[b]	Infants (*n*)	Mothers (*n*)
22–26	1875	1627
27–31	3007	2533
32–34	1178	954
Total	6060	5114

Livebirths

Weeks[b]	Infants (*n*)	Mothers (*n*)
22–26	980	827
27–31	2717	2280
32–34	1152	932
Total	4849	4039

Figure 1. Study population according to gestational age group, born during the inclusion periods of the EPIPAGE 2 survey. [a]The participating French metropolitan regions were Alsace, Aquitaine, Auvergne, Basse-Normandie, Bourgogne, Bretagne, Centre, Champagne-Ardenne, Franche-Comté, Haute-Normandie, Ile-de-France, Languedoc-Roussillon, Limousin, Lorraine, Midi-Pyrénées, Nord-Pas-de-Calais, Pays-de-Loire, Picardie, Provence-Alpes-Côte-d'Azur and Corsica, and Rhône-Alpes. [b]Completed weeks of gestation.

multiple correspondence analysis was performed to estimate weighted coordinates. The ISEI was then calculated by adding the terms of weighted coordinates obtained from the most discriminant axis. The weighted coordinates that were retained were then applied to EPIPAGE 2 data. All the indicators selected corresponded to a single concept as shown in the eigenvalues graphs, although internal consistency remained poor with an estimated Cronbach's alpha at around 0.60. Additional information about the score's construction and its external validity is given in Tables S1 and S2 and in Figures S1 and S2. The ISEI score was estimated for 91.0% and 81.6% (after taking into account the variation in the duration of recruitment according to GA) of the mother–child dyads in the NPS-2010 and EPIPAGE 2 studies, respectively. In

EPIPAGE 2, the ISEI score was estimated for 4589 preterm children, of whom 3970 (86.5%) were alive at birth. In one out of two cases, missing values for the ISEI score were due to the absence of the father's occupation.

Pregnancy, delivery characteristics, and neonatal outcomes

Maternal data included age, parity, pre-pregnancy body mass index (<18.5, 18.5–24.9, 25–29.9, ≥30 kg/m^2), tobacco consumption during pregnancy (non-smokers, 1–9 cigarettes per day, ≥10 cigarettes per day), and regular pregnancy care (defined as at least seven prenatal visits and three ultrasound examinations during pregnancy as recommended). This item was directly assessed by the practitioner in a yes/no question in order to take the length of pregnancy into account in PTDs. We also collected the mother's obstetrical history, pregnancy management, and complications, including infertility treatment, hypertension during pregnancy (pregnancy-induced hypertension or pre-eclampsia), severe second- or third-trimester haemorrhage, hospitalisation during pregnancy, premature rupture of membranes (PROM) at least 12 h before the onset of labour, infection (with or without chorioamnionitis), and antenatal corticosteroid administration. Delivery data consisted of spontaneous delivery (yes/no) and caesarean section (yes/no). Neonatal outcomes first considered total mortality.[3] We also studied liveborn infants' outcomes, including in-hospital mortality and a composite indicator of severe neonatal morbidity, defined as any of the following outcomes: severe intraventricular haemorrhage (IVH) (grades III–IV IVH or intraparenchymal haemorrhage),[16] cystic periventricular leukomalacia, severe bronchopulmonary dysplasia [defined as mechanical ventilator support, continuous positive airway pressure – at 36 weeks' postmenstrual age or ≥30% supplementary oxygen at 36 weeks postmenstrual age],[17] stage II or III necrotising enterocolitis, stage 3 or more retinopathy of prematurity, or laser treatment. If a single outcome was missing (i.e. was not marked as either absent or present) and all the other severe outcomes were absent, the child survivor was considered as having no severe morbidity. Growth retardation [small-for-gestational age – defined using customised birthweight standards] was also recorded.[18]

Statistical analysis

The social context of PTD before 35 weeks [percentages of each indicator and their 95% confidence intervals (CI)] and the distribution of the index score (split into tertiles according to its observed distribution in NPS-2010, the highest tertile indicating the most deprived population) were described in comparison to the general population of deliveries. The relationships between socio-economic deprivation and pregnancy and delivery characteristics were explored using logistic regression models, while controlling for maternal age and tobacco consumption during pregnancy, as these covariates are known confounders. Using these models, we compared the frequencies of maternal characteristics in the tertiles of the deprivation score (tertiles obtained by splitting the ISEI according to its observed distribution in EPIPAGE 2 data) and sought a linear trend where appropriate (after verification of the assumption of linearity of the ISEI score). Interaction terms between ISEI and type of birth (singleton/multiple) were further added to the models. For each neonatal outcome, from unadjusted and multivariable (adjusted for GA) models, we tested the homogeneity of the odds ratios (ORs) in the three ISEI groups. Interaction terms between ISEI and GA were then explored. Data on morbidity for babies born between 22 and 24 weeks were combined because of small numbers in each group. To assess the impact of missing ISEI values on adjusted estimates, we conducted analysis on datasets where these missing values were imputed using multiple imputation by chained equations.[19] Given that the duration of recruitment varied according to GA, all the percentages presented were weighted. Clustered robust standard errors were estimated to take into account the clustering of children with mothers who had multiple pregnancies, when multiple births and all births were considered for bivariate tests and regression models. All tests were two-sided and P values < 0.05 were considered statistically significant. Analyses were done with STATA software version 11.0 (StataCorp, 2011, College Station, Texas 77845-4512, USA).

Results

Social characteristics differed markedly between mothers of preterm children ($n = 6060$) and those in the general population (Table 1). Preterm infants were

Table 1. Parents' characteristics and distribution of the individual socio-economic index (ISEI) in the EPIPAGE 2 survey (children $n = 6060$) of live or stillborn preterm infants: comparison with French National Perinatal Survey (NPS-2010)

	EPIPAGE 2-2011		EPIPAGE 2-2011			NPS-2010	
	22–34 weeks		22–26 weeks	27–31 weeks	32–34 weeks	All	
	(n = 6060[a])		(n = 1875)	(n = 3007)	(n = 1178)	(n = 14 903[b])	
Children (n)	%[c]	[95% CI][c]	%	%	%	%	[95% CI]
Maternal age (years)							
<25	16.0	[14.7, 17.5]	20.4	18.6	13.8	16.9	[16.3, 17.5]
25–29	32.6	[30.7, 34.6]	31.5	31.9	33.2	33.1	[32.4, 33.9]
30–34	29.0	[27.2, 31.0]	28.1	27.1	30.2	30.7	[29.9, 31.4]
35–39	17.0	[15.5, 18.7]	14.7	16.5	17.8	15.8	[15.2, 16.4]
≥40	5.3	[4.4, 6.3]	5.5	5.8	5.0	3.5	[3.2, 3.8]
Parity							
Nulliparous	50.7	[48.3, 53.1]	50.3	47.9	52.2	43.5	[42.7, 44.3]
1	38.1	[35.7, 40.4]	37.3	40.3	37.1	34.5	[33.7, 35.3]
2	7.0	[5.9, 8.2]	7.1	7.7	6.6	14.2	[13.7, 14.8]
≥3	4.3	[3.5, 5.3]	5.4	4.2	4.1	7.8	[7.4, 8.2]
Pre-pregnancy body mass index (kg/m^2)							
<18.5	8.5	[7.2, 9.8]	8.0	8.3	8.8	8.2	[7.8, 8.7]
18.5–24.9	58.5	[56.3, 60.6]	56.8	56.2	59.9	64.6	[63.8, 65.4]
25–29.9	19.4	[17.8, 21.2]	20.2	19.8	19.1	17.3	[16.7, 18.0]
≥30	13.6	[12.2, 15.1]	15.0	15.7	12.3	9.9	[9.4, 10.4]
Regular pregnancy care[d]							
No	5.2	[4.4, 6.1]	8.5	6.0	4.1	9.5	[9.0, 10.0]
Smoking during pregnancy (cig/day)							
None	79.6	[77.9, 81.2]	79.3	77.8	80.5	83.0	[82.4, 83.7]
1–9	8.9	[7.8, 10.1]	8.8	10.1	8.4	12.2	[11.6, 12.7]
≥10	11.5	[10.3, 12.9]	11.9	12.2	11.1	4.8	[4.5, 5.2]
Maternal educational level[e]							
Low	29.4	[27.0, 31.9]	29.8	30.3	28.9	28.2	[27.4, 28.9]
Intermediate	21.0	[18.9, 23.2]	20.8	21.3	20.8	19.9	[19.2, 20.5]
High	49.7	[46.9, 52.4]	49.4	48.4	50.2	52.0	[51.2, 52.8]
Own home							
No	6.4	[5.3, 7.8]	7.8	6.8	6.2	7.2	[6.7, 7.6]
Mother's nationality[f]							
French	79.3	[77.5, 80.9]	74.8	76.7	81.4	86.7	[86.1, 87.2]
Other European country	3.3	[2.6, 4.1]	3.0	3.0	3.5	3.4	[3.1, 3.7]
North Africa	6.8	[5.9, 7.9]	7.4	8.3	6.0	4.8	[4.4, 5.1]
Other African country	6.4	[5.5, 7.4]	10.5	7.3	5.1	2.9	[2.7, 3.2]
Other countries	4.3	[3.4, 5.3]	4.3	4.7	4.0	2.3	[2.0, 2.5]
Mother living alone[f]							
Yes	8.9	[7.8, 10.2]	9.3	8.8	8.9	7.2	[6.8, 7.7]
Mother's occupation[f]							
Higher professional occupations	10.6	[9.2, 12.1]	7.9	9.0	12.0	12.4	[11.8, 12.9]
Intermediate occupations	15.6	[14.0, 17.3]	13.62	14.7	16.4	20.9	[20.2, 21.6]
Public or corporate employee, craftsman, trader, farmer	19.3	[17.5, 21.1]	16.2	18.9	20.1	25.6	[24.9, 26.3]
Shop and service workers	15.2	[13.7, 16.9]	16.8	15.1	15.0	18.7	[18.1, 19.4]
Skilled or unskilled manual workers	6.6	[5.7, 7.7]	7.4	7.2	6.2	7.5	[7.1, 8.0]
Unemployed or other jobless	32.7	[30.8, 34.7]	38.2	35.2	30.4	14.9	[14.3, 15.5]
Father's occupation[f]							
Higher professional occupations	14.1	[12.6, 15.8]	13.7	14.0	14.2	18.3	[17.6, 18.9]
Intermediate occupations	14.2	[12.6, 16.0]	12.6	12.4	15.3	16.7	[16.1, 17.3]
Public or corporate employee, craftsman, trader, farmer	21.4	[19.6, 23.4]	20.0	20.6	22.0	21.9	[21.2, 22.6]
Shop and service workers	9.2	[8.0, 10.6]	7.7	9.3	9.2	4.7	[4.3, 5.0]
Skilled or unskilled manual workers	30.5	[28.5, 32.4]	34.0	32.3	29.0	33.7	[32.9, 34.5]
Unemployed, other jobless	10.6	[9.3, 12.0]	12.0	11.0	10.2	4.9	[4.5, 5.2]
Health insurance[f]							
None or French Medicare equivalent	15.3	[13.9, 16.9]	14.3	15.9	15.3	13.9	[13.3, 14.5]
ISEI							
–	n = 4589		n = 1141	n = 2426	n = 1022	n = 13 463	
Tertile 1 (least deprived)	26.2	[23.4, 27.0]	21.9	21.2	27.5	32.8	[32.0, 33.6]
Tertile 2	29.9	[28.2, 31.9]	28.5	31.0	29.8	31.3	[30.5, 32.1]
Tertile 3 (most deprived)	44.8	[42.9, 46.8]	49.6	47.7	42.8	35.9	[30.1, 36.7]

[a]All live and stillborn children born between 22 and 34 completed weeks of gestation in a maternity hospital in metropolitan France and participating at EPIPAGE 2 survey in 2011.
[b]All live and stillborn children born between 22 and 42 completed weeks of gestation in a maternity hospital in metropolitan France and participating in the NPS survey in 2010. Gestational age was missing for 71 children.
[c]Weighted percentage taking into account the varying duration of recruitment according to gestational age in the EPIPAGE 2 survey, and the non-independence of data between siblings.
[d]Regular pregnancy monitoring, defined as at least seven prenatal visits and three ultrasound examinations during pregnancy in NPS-2010, was directly assessed by the practitioner in a yes/no question as pregnancy duration was shortened in preterm deliveries in EPIPAGE 2.
[e]Maternal educational level was classified into three groups: high (university graduates), intermediate (post-secondary education), and low (less or no education).
[f]Indicators included in the construction of the individual socio-economic index (ISEI).
95% CI: exact confidence intervals of the proportion.

more often born to mothers belonging to extreme age groups, nulliparous, obese, of foreign nationality, living alone, unemployed, and with an unemployed father. Smoking during pregnancy and irregular pregnancy care were also more prevalent in PTDs. Similar figures were found when considering livebirths only (data not shown). Nearly half of PTDs (44.8%) belonged to the most deprived socio-economic group, defined as the highest ISEI tertile in the general population. Results suggested a socio-economic gradient in PTDs, as the most deprived group accounted for 49.6% of children born at 22–26 weeks, 47.7% born at 27–31 weeks, and 42.8% born at 32–34 weeks (Table 1). This gradient was observed in both single and multiple births (Table 2).

Table 3 presents pregnancy and delivery characteristics of live PTDs according to ISEI levels separately in single ($n = 2587$) and multiple births ($n = 1383$) because a significant interaction was found between ISEI score and type of birth ($P = 0.020$). Irregular pregnancy care was more prevalent in the most deprived group than in the two less deprived groups, and this result was found both in single ($P < 0.001$) and multiple births ($P = 0.028$). Hospitalisation during pregnancy was also less common in the most deprived group, especially among singletons. There was no consistent socio-economic gradient in pregnancy complications (hypertension during pregnancy, PROM, or severe haemorrhage), except for infection where a significant linear trend across the tertiles of ISEI score was found, with the highest prevalence reported in multiple births in the most deprived group ($P_{\text{trend test}} = 0.007$). Among multiple births, antenatal corticosteroid administration was less common in the most deprived group ($P_{\text{trend test}} = 0.013$) than in the two less deprived groups.

Table 4 compares short-term outcomes between the three ISEI groups in single and in multiple births. The unadjusted ORs, ORs adjusted for GA (model 1), and ORs adjusted for all confounders (model 2) are presented. We found no significant interaction at the 5% level between ISEI and GA. The unadjusted risk for total mortality (live and stillbirths) was significantly increased among children born in multiple pregnancies and exposed to the most deprived conditions (OR = 1.75, [95% CI 1.08, 2.83]). After adjusting for all confounders, the increase in total mortality risk was no longer significant. We found no socio-economic gradient for in-hospital mortality neither in singletons nor in multiple births. Belonging to

Table 2. Distribution of the individual socio-economic index (ISEI) in EPIPAGE 2 according to gestational age groups ($n = 4589$): weighted percentages and [95% CI: confidence intervals]

	Single births						Multiple births					
	($n = 3091$)						($n = 1498$)					
	22–26 weeks[a]		27–31 weeks		32–34 weeks		22–26 weeks		27–31 weeks		32–34 weeks	
	%	[95% CI]	%	[95% CI]	%	[95% CI]	%[b]	[95% CI][b]	%[b]	[95% CI][b]	%[b]	[95% CI][b]
Tertile1 (least deprived)	20.8	[18.2, 23.7]	19.1	[17.2, 21.1]	22.2	[20.1, 27.1]	24.8	[20.3, 30.0]	25.6	[22.7, 28.737]	36.2	[31.5, 41.1]
Tertile 2	28.5	[25.6, 31.7]	30.3	[28.1, 32.6]	29.1	[23.0, 32.4]	28.4	[23.6, 33.7]	32.6	[29.4, 35.9]	30.8	[26.4, 35.5]
Tertile 3 (most deprived)	50.7	[47.3, 54.0]	50.7	[48.2, 53.1]	48.7	[44.8, 52.6]	46.8	[41.3, 52.4]	41.8	[38.5, 45.3]	33.1	[28.6, 37.9]

[a]Completed weeks of gestation.
[b]Weighted percentage taking into account the varying duration of recruitment according to gestational age in the EPIPAGE 2 survey, and the non-independence of data between siblings.

Table 3. Pregnancy and delivery characteristics of preterm single or multiple livebirths by level of individual socio-economic index (ISEI) in EPIPAGE 2-2011 ($n = 3970$): weighted percentages and [95% CI]

	Preterm children liveborn between 22 and 34 weeks (single births)							Preterm children liveborn between 22 and 34 weeks (multiple births)						
	$n = 2587$							$n = 1383$						
	ISEI tertiles from EPIPAGE 2							ISEI tertiles from EPIPAGE 2						
	First (Least deprived)		Second		Third (Most deprived)		Adjusted trend test	First (Least deprived)		Second		Third (Most deprived)		Adjusted trend test
	%	[95% CI]	%	[95% CI]	%	[95% CI]	*P* value[a]	%	[95% CI]	%	[95% CI]	%	[95% CI]	*P* value[a]
Mother's adverse obstetrical history[b]	21.7	[17.0, 27.3]	20.7	[16.4, 25.8]	24.9	[20.6, 29.9]	0.113	8.1	[4.0, 15.7]	14.6	[7.9, 25.2]	7.8	[3.8, 15.1]	ND[e]
Pre-pregnancy	25.1	[20.1, 30.8]	37.6	[31.9, 43.6]	38.1	[33.1, 43.5]	ND[e]	32.6	[22.9, 44.1]	37.8	[27.0, 50.0]	36.4	[25.6, 48.8]	ND[e]
Body mass index ≥ 25 (kg/m^2)														
Infertility treatment	10.6	[8.3, 13.9]	5.1	[3.5, 7.3]	3.7	[2.4, 5.9]	0.025	44.2	[36.6, 52.1]	42.2	[33.8, 51.5]	20.7	[13.7, 29.9]	0.032
Irregular pregnancy care	1.6	[0.8, 3.3]	2.3	[1.4, 3.96]	11.1	[8.6, 14.1]	<0.001	1.1	[0.2, 4.7]	0.2	[0.0, 1.3]	4.7	[1.8, 11.7]	0.028
Hypertension during pregnancy[c]	23.2	[19.7, 27.1]	27.3	[23.4, 31.6]	22.2	[18.7, 26.1]	ND[e]	11.8	[7.2, 18.1]	12.2	[7.3, 19.8]	9.8	[5.0, 18.4]	ND[e]
Premature rupture of membranes	39.8	[35.3, 44.4]	36.4	[32.0, 41.1]	36.7	[32.5, 41.1]	0.445	37.1	[30.1, 44.8]	35.9	[28.0, 44.7]	40.6	[31.2, 50.8]	0.977
Infection during pregnancy[d]	11.5	[9.1, 14.3]	11.3	[9.0, 14.0]	15.7	[13.1, 18.7]	0.206	7.7	[5.2, 11.1]	11.2	[7.4, 16.6]	16.5	[10.8, 24.4]	0.007
Spontaneous delivery	47.4	[42.7, 52.2]	42.4	[37.7, 47.2]	46.0	[41.4, 50.6]	ND[e]	59.2	[51.2, 66.7]	67.6	[58.3, 75.6]	66.3	[55.4, 75.7]	0.370
Severe haemorrhage	18.1	[14.9, 21.8]	14.0	[11.3, 17.3]	14.3	[10.7, 16.4]	ND[e]	10.4	[6.8, 15.7]	7.3	[4.0, 12.8]	7.2	[3.8, 13.4]	ND[e]
Hospitalisation during pregnancy	32.0	[27.8, 36.6]	25.4	[21.5, 29.8]	29.8	[25.8, 34.1]	ND[e]	46.4	[38.7, 54.4]	49.5	[40.5, 58.4]	34.6	[25.4, 45.1]	ND[e]
Antenatal corticosteroid administration	75.3	[70.9, 79.2]	76.5	[72.2, 80.4]	70.9	[66.5, 74.9]	ND[e]	89.7	[83.9, 93.6]	82.5	[74.8, 88.2]	81.1	[71.3, 88.0]	0.013
Caesarean section	57.7	[53.7, 62.2]	59.5	[54.8, 64.1]	55.0	[50.0, 59.5]	0.796	60.7	[53.0, 67.9]	54.1	[45.1, 62.9]	59.2	[48.7, 63.2]	0.588

[a]*P* value for adjusted trend test compared proportions by ISEI level, estimated using logistic regression taking weighting into account. The model was adjusted for maternal age and smoking during pregnancy and included ISEI as a continuous variable.

[b]Mother's adverse obstetrical history was defined as previous adverse pregnancy outcomes (infant small-for-gestational age, or multigravida with previous preterm delivery, or multigravida with previous stillborn).

[c]Hypertension during pregnancy included pregnancy-induced hypertension and pre-eclampsia.

[d]Infections excluded asymptomatic bacterial infection during pregnancy and included all other types of infection with or without chorioamnionitis.

[e]ND, not done. As the assumed linearity of the ISEI level was not verified, a trend test was not performed.

Table 4. Infants' short-term outcomes by level of individual socio-economic index in EPIPAGE 2-2011 among (a) preterm single births and among (b) preterm multiple births: unadjusted and adjusted odds ratios [95% CI]

(a) Preterm single births

22–34 weeks

			Unadjusted		Model 1[c]		Model 2[d]	
	%[a]	[95% CI][a]	OR[a]	[95% CI][a]	OR[a]	[95% CI][a]	OR	[95% CI][a]
Total mortality (AB)					(n = 744/3091)			
ter1	11.5	[9.8, 13.5]	1.00	[Reference]	1.00	[Reference]	1.00	[Reference]
ter2	13.0	[11.0, 15.3]	1.14	[0.88, 1.49]	1.20	[0.83, 1.72]	1.35	[0.87, 2.10]
ter3	13.0	[11.1, 15.2]	1.15	[0.89, 1.49]	1.03	[0.72, 1.48]	0.97	[0.60, 1.57]
In-hospital mortality (LB)					(n = 240/2587)			
ter1	4.1	[3.0, 5.4]	1.00	[Reference]	1.00	[Reference]	1.00	[Reference]
ter2	5.2	[3.9, 7.0]	1.30	[0.84, 2.00]	1.29	[0.75, 2.22]	1.54	[0.85, 2.77]
ter3	4.1	[3.2, 5.3]	1.02	[0.68, 1.52]	0.74	[0.45, 1.22]	0.88	[0.52, 1.54]
Composite indicator of morbidity[e] (LB)					(n = 383/2289)			
ter1	6.9	[5.6, 8.4]	1.00	[Reference]	1.00	[Reference]	1.00	[Reference]
ter2	10.1	[8.2, 12.4]	1.52	[1.09, 2.09]	1.52	[1.10, 2.11]	1.48	[1.05, 2.14]
ter3	10.8	[8.7, 13.4]	1.63	[1.18, 2.27]	1.63	[1.13, 2.34]	1.58	[1.07, 2.45]
Small-for-gestational age (SGA) (LB)					(n = 813/2424)			
ter1	26.6	[22.8, 30.8]	1.00	[Reference]	1.00	[Reference]	1.00	[Reference]
ter2	36.7	[32.2, 41.3]	1.59	[1.20, 2.12]	1.62	[1.22, 2.16]	1.53	[1.11, 2.13]
ter3	31.2	[27.1, 35.5]	1.25	[0.94, 1.66]	1.24	[0.92, 1.66]	1.14	[0.83, 1.60]

(b) Preterm multiple births

22–34 weeks

			Unadjusted		Model 1[c]		Model 2[d]	
	%[a,b]	[95% CI][a,b]	OR[a,b]	[95% CI][a,b]	OR[a,b]	[95% CI][a,b]	OR[a,b]	[95% CI][a,b]
Total mortality (AB)					(n = 244/1498)			
ter1	6.1	[4.6, 8.2]	1.00	[Reference]	1.00	[Reference]	1.00	[Reference]
ter2	6.9	[5.0, 9.6]	1.15	[0.71, 1.84]	0.79	[0.44, 1.42]	0.72	[0.37, 1.42]
ter3	10.2	[7.3, 14.1]	1.75	[1.08, 2.83]	1.32	[0.69, 2.53]	0.99	[0.39, 2.53]
In-hospital mortality (LB)					(n = 129/1383)			
ter1	3.8	[2.6, 5.7]	1.00	[Reference]	1.00	[Reference]	1.00	[Reference]
ter2	4.2	[2.8, 6.1]	1.09	[0.62, 1.91]	0.64	[0.36, 1.16]	0.52	[0.26, 1.06]
ter3	4.8	[2.8, 7.9]	1.25	[0.64, 2.47]	0.95	[0.40, 2.24]	0.54	[0.17, 1.70]
Composite indicator of morbidity[e] (LB)					(n = 189/1207)			
ter1	7.1	[5.2, 9.6]	1.00	[Reference]	1.00	[Reference]	1.00	[Reference]
ter2	8.7	[6.2, 12.1]	1.25	[0.76, 2.04]	1.12	[0.66, 1.90]	1.02	[0.60, 1.73]
ter3	8.8	[5.9, 13.1]	1.27	[0.73, 2.21]	0.91	[0.48, 1.71]	0.52	[0.25, 1.07]
Small-for-gestational age (SGA) (LB)					(n = 413/1316)			
ter1	33.6	[28.0, 39.7]	1.00	[Reference]	1.00	[Reference]	1.00	[Reference]
ter2	35.4	[29.1, 42.3]	1.08	[0.73, 1.61]	1.10	[0.74, 1.64]	1.18	[0.76, 1.81]
ter3	32.2	[24.9, 40.4]	0.94	[0.60, 1.46]	0.96	[0.62, 1.51]	1.19	[0.73, 1.96]

[a]Weighted percentage reflecting varying duration of recruitment according to gestational age in the EPIPAGE 2 survey.
[b]The estimated link took into account both the weight and the non-independence of the data within siblings.
[c]Model 1, adjusted for gestational age.
[d]Model 2 was the full model, adjusted for gestational age + sex + pre-pregnancy body mass index ≥ 25 + irregular pregnancy care + infertility treatment + infection during pregnancy + antenatal corticosteroid administration + smoking during pregnancy + maternal age.
[e]A composite indicator of severe outcomes was defined by the presence of at least severe brain lesion (III–IV IVH or cystic periventricular leukomalacia) on brain ultrasonography or bronchopulmonary dysplasia or severe retinopathy of prematurity or diagnosis of necrotising enterocolitis. If a single outcome was missing (i.e. was not marked as either absent or present) and all the other severe outcomes were absent, the child survivor was considered as having no severe morbidity.
AB, all births; live and stillborn preterm infants born between 22 and 34 completed weeks of gestation; LB, livebirths, preterm infants born alive between 22 and 34 completed weeks of gestation.

the most deprived group was associated with a significantly elevated risk of severe morbidity among singletons (unadjusted OR = 1.63, [95% CI 1.18, 2.27]; adjusted OR = 1.58, [95% CI 1.07, 2.45]). The aetiological risk fraction, indicating the proportion of singletons affected by severe morbidity and born <35 weeks that can be attributed to exposure to the poorest socio-economic conditions, was estimated at slightly below 37.0%.

Comment

Overall, we reported that poorer socio-economic conditions were associated with a higher prevalence of irregular care during pregnancy, a higher frequency of maternal infection, and a lower rate of antenatal corticosteroid administration. With regard to the infants' outcomes, we found significant trends in total mortality rates (live and stillbirths) in multiple births and severe morbidity rates (measured with a composite indicator) in single births across ISEI tertiles. After adjusting for all confounders, the social gradient remained significant only for severe morbidity.

Socio-economic condition was assessed by individual indicators and summarised in a composite score. This was constructed with the same indicators collected in two large national representative samples of PTDs (EPIPAGE 2) and of all deliveries (NPS-2010) over the same period of time, thus ensuring the comparability of the score within the same time frame. This methodology allowed us to characterise the PTD population compared with all deliveries. As suggested by previous studies,[20,21] we found that socio-economic conditions were significantly more prevalent in the preterm group than in the general population. Our composite score was based on the conceptual model described by Townsend and by Wrezinski, which provided the relevant parameters to be included.[22,23] However, due to study constraints, this score does not cover all areas of socio-economic deprivation. First, in both studies, only socio-economic variables extracted from medical records were available for all live and stillbirths. Therefore, maternal educational level, which was recorded during in-depth interviews proposed only to mothers of liveborn infants in the EPIPAGE 2 study, was not included in the score calculations. Second, the father's data are rarely recorded in medical files on a routine basis. As the use of paternal indicators when describing the socio-economic situation of the family is recommended in the literature,[24] we chose to retain the father's occupation in the score despite a high rate of missing values. To clarify the impact of adding the father's component in the score, we conducted additional analysis, first without the father's occupation in the composite score and second using imputed completed datasets for ISEI. All analyses showed consistent results and confirmed the one-dimensionality of the score.

The main strength of our score is that it comprehensively combined various individual indicators, given a satisfactorily complete assessment of the socio-economic situation of the family in line with recommendations.[24] Our approach has the potential to improve international comparisons, which are difficult because most studies have used a single indicator that differs from one study to another. However, the weighted coordinates that we used were calculated using a French reference and cannot therefore be directly applied to other reference populations, which may have different characteristics. Another strength of our approach is that the combination of relevant aspects of deprivation in a single score makes it easy to identify a vulnerable population that generally combines a number of difficulties, and this approach may permit the use of more parsimonious statistical models. Of course, combining ISEI with a neighbourhood-level socio-economic measure in multi-level modelling would yield better understanding of the underlying mechanisms, and clarify any variations between children with different individual levels of socio-economic deprivation but living in the same neighbourhood.

As previously noted in the literature, maternal and pregnancy characteristics vary with socio-economic status. Of concern is the higher frequency of infections during pregnancy in mothers whose social and economic conditions were poorer.[7,20] Several studies have investigated the complex mechanisms linking infections during pregnancy and PTD.[6,25] Genital infections are one of the main causes of premature rupture of fetal membranes and consequently of PTD, especially at lower GA.[26] In our study, we observed a high frequency of irregular care during pregnancy and a low hospitalisation rate in the most deprived group, while the incidence of diseases was not lower than in the more socially advantaged populations. It is well known that disadvantaged women who experience problems during pregnancy are less likely to access the care that they need.[27] For these women, the concerns are to promote early detection and to monitor pregnancy regularly so that preventive actions may be more effective. Our findings support this need, as they show low coverage with antenatal administration of corticoids in the most deprived group, which was not fully explained by a greater proportion of very low GAs at birth, a group where policies remain variable in France especially before 25 weeks of gestation.[28] The efficacy of antenatal corticosteroid administration to women at risk for PTD in order to reduce neonatal mortality and to improve neonatal outcomes, such as respiratory distress syndrome, IVH, and NEC in infants born between 24 and 34 weeks of gestation, has been consistently documented in the literature.[29,30] Therefore, it is essential to enable these women to benefit from this treatment.

Like Bonet and collaborators,[31] we found no socio-economic gradient in in-hospital mortality. However, among multiple births, we did observe a socio-economic gradient across ISEI score tertiles for unadjusted risk of total mortality (live and stillbirths), which was no longer significant after controlling for GA. These results suggest that GA principally mediates the pathway between social context and mortality. On the other hand, among single births, the association between socio-economic position and morbidity remained significant after adjusting for all confounders, suggesting that deprivation has a direct and independent impact. Further work is needed to explore this effect. To summarise, our study demonstrated that health inequalities may arise very early in life and require early paediatric care. In addition to the inherent difficulties associated with PTD, children born in the worst socio-economic context combine from birth the triple disadvantages of poor socio-economic status, the consequences of less effective maternal prevention (more irregular pregnancy care with a tendency to more pathologies and lower rate of administration of antenatal corticosteroids), and more adverse outcomes in the short term, especially among singletons. Early identification of socio-economically vulnerable pregnant women remains a challenge. One possible mode of action is to allow data sharing between social benefit databases and medical databases,[32] which could encourage women to attend regular medical follow-ups and to adopt healthier habits that are beneficial to both the mother and the child. Compared with other developed countries, France remains backward in collaboration between agencies, although some initiatives have been undertaken.[33] Knowledge of the socio-economic context could significantly improve clinical planning and implementation of social measures to enable early interventional strategies for the child in order to prevent developmental disorders and to improve the overall functional outcomes for these infants.

Although intervention programmes are diverse and vary in their period of application, intensity, setting, and degree of parental involvement, they have provided evidence of their benefits.[34,35] Based on a neurosensory approach that emphasises the transactional nature of development, one strategy to prevent developmental delay in both disadvantaged children and preterm infants may be home visiting at an early stage by a health care practitioner, trained to raise parents' awareness of their infant's cues, who can teach the parents to respond appropriately and facilitate mutually satisfying interactions. Such a programme, financed by health insurances funds and implemented on a large scale, already exists in Amsterdam.[35] In France as yet, there are only regional initiatives by perinatal care networks, offering early post-discharge interventions to vulnerable infants; however, they are not developed with the same intensity. In view of budget cuts in health and research and the lack of national policy of early intervention, perinatal networks are forced to make choices regarding the interventions and the follow-up proposed to vulnerable children. Results from our study suggest that the burden of high socio-economic vulnerability will also manifest in the long term. Socio-economically vulnerable babies need particular attention, and it is important to provide them with long-term follow-up, supported by national policy.

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Supporting Information

Additional Information may be found in the online version of this article at the publisher's web-site:

Figure S1. Graph of eigenvalues after MCA in EPIPAGE 2 data ($n = 4589$); Cronbach's alpha = 0.60.
Figure S2. Distribution of the individual socio-economic index (ISEI) in EPIPAGE 2 data ($n = 4589$): (a) density, (b) boxplot.
Table S1. Parents' socio-economic indicators included in the individual socio-economic index (ISEI) and weighted coordinates obtained from the most discriminant axis from NPS-2010.
Table S2. External validity of the individual socio-economic index (ISEI) from NPS-2010 data ($n = 14\,903$, 1440 missing).
Appendix S1. EPIPAGE 2 study group.