Socioeconomic inequalities in reproductive outcomes in the Italian NINFEA birth cohort and the Piedmont Birth Registry

Disuguaglianze socioeconomiche negli esiti riproduttivi nella coorte italiana di nuovi nati NINFEA e nel Registro delle nascite piemontese

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ABSTRACT

BACKGROUND: socioeconomic inequalities in reproductive outcomes have been consistently reported in several countries. In a European collaborative study conducted in 2012 whose aim was to investigate the association between socioeconomic position (SEP), measured through maternal education, and preterm delivery inconsistent results were found for the NINFEA birth cohort. However, NINFEA contributed to that study with the first 2,500 pregnancies only, and estimates were not adjusted for any potential confounders assuming that SEP is a distal exposure, that could not be affected by other preterm risk factors.

OBJECTIVES: to investigate the relationship between SEP and the reproductive outcomes using the entire NINFEA cohort and compare the results with the population-based Piedmont Birth Registry (PBR), accounting for potential baseline collider bias both in the cohort and in the registry.

DESIGN: observational study.

SETTING AND PARTICPANTS: 5,323 NINFEA singletons, whose mothers registered into the study before the 36th week of gestation, were analysed. Analyses on maternal education were replicated in the 2011 PBR of 35,318 singletons live births. Factors affecting the likelihood of being a member of the NINFEA study or becoming pregnant in the general population were treated as potential confounders to adjust for baseline collider bias.

MAIN OUTCOME MEASURES: the association of maternal education and a recently developed household income indicator with both preterm delivery (<37th weeks of gestation) and low birth weight (<2,500 gr) were analysed.

RESULTS: in the NINFEA cohort, low SEP was positively associated with both preterm delivery and low birth weight, with slightly stronger associations for household income, especially on low birth weight. Results were consistent with those obtained in the PBR data, where an inverse relationship between maternal education and the two reproductive outcomes was found. In both populations, there was confounding due to maternal age and parity, showing that independently of the nature of the source population, baseline factors that affect the probability of being a member of such source population have to be accounted for to allow causal inference.

CONCLUSIONS: low SEP is associated with adverse reproductive outcomes in a contemporary Italian population.

Keywords: socioeconomic position, birth cohorts, premature birth, low birth weight, income

WHAT IS ALREADY KNOWN

- **Low socioeconomic position (SEP) has been associated with adverse reproductive outcome in different countries. Inconsistent results were observed in the NINFEA study in an analysis conducted in 2012.**
- **In birth cohort studies, maternal education is often used as the only indicator of child SEP, however different indicators might capture different SEP dimensions.**
- **Typically, SEP-outcome estimates are not adjusted for potential confounders based on the assumption that SEP is a distal exposure not affected by other outcome risk factors.**

WHAT THIS PAPER ADDS

- **Low maternal education and low household income are positively associated with adverse reproductive outcomes in the NINFEA study and results are consistent with those found in the Piedmont Birth Registry.**
- **The SEP-reproductive outcomes estimates are confounded by the outcome risk factors influencing the probability of being a member of the study source population (i.e., baseline collider bias), irrespectively of whether the analyses were based on NINFEA birth cohort data or population-based registry data (Piedmont Birth Registry).**

RIASSUNTO

INTRODUZIONE: numerosi studi condotti in diversi Paesi hanno rilevato disuguaglianze socioeconomiche negli esiti riproduttivi. In uno studio collaborativo europeo condotto nel 2012 per studiare l'associazione tra la posizione socioeconomica (PSE), misurata attraverso il livello di istruzione materno, e l'occorrenza di parti pretermine, le stime ottenute nella coorte di nuovi nati NINFEA non erano del tutto coerenti con la maggioranza degli studi. Tuttavia, la coorte NINFEA ha partecipato allo studio del 2012 solamente con le prime 2.500 gravidanze e le stime non erano aggiustate per nessun potenziale confondente, basandosi sul presupposto che la SEP sia un'esposizione distale, non influenzabile da altri fattori di rischio del parto pretermine.

OBIETTIVO: analizzare la relazione tra PSE ed esiti riproduttivi, utilizzando i dati dell'intera coorte NINFEA, e di confrontare i risultati con quelli ottenuti dal Registro delle nascite piemontese, tenendo conto del *baseline collider bias* sia nella coorte sia nel Registro.

DISEGNO: studio osservazionale.

SETTING E PARTECIPANTI: sono stati analizzati 5.323 bambini (gravidanze singole) della coorte NINFEA, le cui madri sono state arruolate nello studio prima della 36ª settimana di gestazione. Le analisi sulla scolarità materna sono state repli-

cate nei dati del Registro delle nascite piemontese del 2011, che includeva 35.318 nati vivi da gravidanze singole. Per tenere conto del *baseline collider bias*, i fattori che influenzano la partecipazione allo studio NINFEA o la probabilità di avere una gravidanza nella popolazione generale sono stati trattati come potenziali confondenti.

PRINCIPALI MISURE DI OUTCOME: è stata analizzata l'associazione del livello di istruzione materno e di un indicatore di reddito familiare, recentemente sviluppato, con il parto pretermine (<37 settimane di gestazione) e il basso peso alla nascita (<2.500 g).

RISULTATI: nella coorte NINFEA, una bassa PSE era positivamente associata sia al parto pretermine sia al basso peso alla nascita, con associazioni leggermente più forti per il reddito familiare, in particolare con il basso peso alla nascita. I risultati sono coerenti con quelli ottenuti dai dati del Registro, dove si è osservata una relazione inversa tra il livello d'istruzione materno e i due esiti di interesse. In entrambe le popolazioni era necessario aggiustare per età e parità materna, suggerendo che, indipendentemente dal tipo di popolazione in studio (selezionata *vs* rappresentativa), per ottenere stime non distorte vanno considerati i fattori che influenzano la probabilità di rientrare in questa popolazione.

CONCLUSIONI: in una popolazione italiana contemporanea, una bassa PSE è associata con esiti riproduttivi avversi.

Parole chiave: stato socioeconomico, coorti di nascita, parto pretermine, basso peso alla nascita, reddito

INTRODUCTION

The relationship between socioeconomic position (SEP) and birth outcomes has been extensively explored across different countries, with evidence of low SEP being positively associated with adverse reproductive outcomes.[1-3]

In a large European collaborative study involving several birth cohorts recruited between 1990 and 2011 conducted to investigate the association between SEP and preterm delivery, the authors observed educational disparities in the risk of premature birth in 8 of the 12 cohorts analysed and no association in four cohorts.[3] In particular, in the Italian NINFEA (*Nascita e Infanzia: gli Effetti dell'Ambiente*) study, although there was no evidence of an association, the direction of the relationship was inconsistent; relative risk and 95% confidence interval (CI) for the low maternal education class of 0.7 (0.2-1.9). However, at the time the NINFEA cohort contributed with the first 2,500 pregnancies (singletons, enrolled before the 37th week of gestation) recruited by the beginning of 2011. Moreover, the authors did not adjust for any potential confounders, based on the assumption that SEP is a distal exposure, that could not be affected by other preterm risk factors. However, the selection mechanisms that lead individuals to be a member of a specific source population – namely pregnant women in a given place and a given time period, and a specific study population, i.e., those who voluntarily participate in the NINFEA study – should be considered when analysing the data. This is because, as depicted in figure 1, if both the exposure of interest (i.e., SEP) and some other outcome risk factors (e.g., maternal age) affect the probability of being a part of the source and study populations (S in figure 1), baseline selection may induce an association between the exposure and the outcome risk factors generating lack of exchangeability (baseline collider bias – for further details please refer to the paper by Richiardi et al.)[4]. In many populations, SEP affects the probability of becoming pregnant as well as it typically affects the likelihood to participate in a study; the same applies to other premature birth risk factors, such as maternal age, country of birth, and family size.[4,5] These outcome risk factors should thus be considered as additional variables to adjust for in order to obtain an unbiased estimate of the SEP-preterm delivery relationship.

The aim of this study was to re-analyse the SEP-preterm delivery association using the entire NINFEA cohort, that now includes more than 6,500 singletons recruited up to 2016, accounting for potential baseline collider bias. It was decided to extend the analysis by including low birth weight as an additional reproductive outcome of interest and by using a second indicator of SEP, a recently developed indicator of disposable household income,[6] that might capture a different dimension of the child SEP. Moreover, in order to compare the NINFEA results with those based on a full population-based study, these analyses were replicated in the Piedmont Birth Registry (PBR) data.

METHODS

STUDY POPULATION

■ **NINFEA.** The NINFEA study is an Italian internet-based mother-child cohort that recruited approximately 7,500 pregnant women (www.progettoninfea.it).[7] Recruitment has been carried out in the period 2005-2016, with the study advertised both actively, through obstetrics clinics, and passively, via Internet and the media. Members of the cohort are children born to women who had access to the Internet, enough knowledge of the Italian language to complete on-line questionnaires, and volunteered to participate any time during pregnancy by completing the first baseline questionnaire. The follow-up questionnaires are completed at 6 and 18 months after delivery and when the child turns 4, 7, 10, and 13 years. The Ethical Committee of the San Giovanni Battista Hospital and CTO/CRF/Maria Adelaide Hospital of Turin approved the NINFEA study (approval No. 0048362 and following amendments) and the informed consent was obtained from all the participants.

For this study, the NINFEA database used was the version 2019.11. The study population included 5,323 sin-

gletons, whose mothers registered into the study before the 36th week of gestation and completed the 6-months questionnaire, which collects information on reproductive outcomes.

■ **PBR.** Computerized birth registration was established in Italy since 2001 (Certificate of Delivery Assistance – CeDAP). The 2011 Piedmont Birth Registry data, completed by midwives at the time of the delivery, was used.[8] The Piedmont Region includes approximately 4,500,000 inhabitants and 64% of the NINFEA children were born in Piedmont. The study population consists of 35,318 live-born singletons delivered after the 28th week of gestation.

EXPOSURE, OUTCOME, AND CONFOUNDING VARIABLES

In the NINFEA study, two child SEP indicators were used: maternal education during pregnancy as in the paper by Poulsen at al.[3] (low: lower than secondary education; medium: secondary education; high: university degree or higher) and an indicator of the equivalised (i.e., standardized for the household size and composition) total disposable monthly household income at birth. As described in the paper by Pizzi et al.,[6] the latter was derived using external data from the Italian 2011 "European Union Statistics on Income and Living Conditions" (EUSILC) survey[9] and individual and household characteristics available in the NINFEA cohort (namely, parental age, cohabitation status, education, country of birth and occupation, house size and type and family size). The derived household income was categorized in three classes using as cut-offs the first and third quartiles of the equivalised total disposable monthly household income distribution of the Italian 2011 EUSILC population (low: lower than 933 euros; medium: between 933 and 1,810 euros; high: above 1,810 euros). In the PBR, data maternal education, categorized as in the NINFEA study, was used as the only SEP indicator.

The two outcomes of interest were preterm birth, defined as the birth of an alive baby at fewer than 37 weeks of gestation, and low birth weight, defined as babies weighting at birth less than 2,500 grams.

Maternal age at delivery (continuous), nulliparity (yes/no), maternal country of birth (Italy, other European countries, other countries), and child region of birth (Piedmont, Tuscany; other Northern Italian regions, other Italian regions) are known to affect the likelihood of being a member of the NINFEA study[5] and/or affect the SEP, and are potential risk factors of adverse reproductive outcomes; thus, they were selected as potential confounders in the NINFEA study. These factors also likely to influence the probability of becoming pregnant or act as confounders in the general population (e.g., country of birth), so they were treated as potential confounders in the PBR analyses as well. In the PBR data, maternal country of birth is classified as Italy *vs* not-Italy.

STATISTICAL ANALYSIS

Logistic regression models were used to estimate odds ratios (OR) and 95%CI, using a complete case analysis approach. High maternal education and household income were used as reference categories in all models. For each exposure-outcome association in both the NINFEA and the PBR datasets, two models were fitted: unadjusted and fully adjusted. The latter model included maternal age, country of birth, and nulliparity and, for the NINFEA study, also region of birth of the child. All the analyses were performed using STATA version 15 (STATA Corp., Texas, USA).

RESULTS

In the 5,323 singletons included in the NINFEA study population, the prevalence of preterm delivery was 4.5%, while the prevalence of low birth weight was 4.7% (table 1). There was a low proportion of children with low SEP, both in terms of low maternal education (4.8%) and in terms of low household income (3.5%). Most of the mothers were nulliparous, 4% were born outside Italy and the mean age was 33.3 years (table 1).

The complete case approach led to the exclusion of 417 subjects (8%) for the preterm analysis and 555 (10%) for the birth weight analyses, leaving a total of 4,906 and 4,768 children for the two analyses, respectively. The estimated associations of SEP with the two outcomes in the NINFEA study are shown in table 2. Higher risks of both premature birth and low birth weight were observed among children with low SEP, although all the 95% CIs included the null value. The associations were slightly stronger for the household income, especially for low birth weight (fully-adjusted OR of preterm and low birth weight for low *vs* high income of 1.63; 95%CI 0.77-3.46 and 2.02; 95%CI 0.98-4.18, respectively). Adjustment for maternal age and for maternal age and parity had a considerable impact on the effect of maternal education and income, respectively, especially on low birth weight (table 2).

Among the 35,318 singletons included in the PBR study population, the prevalence of preterm delivery was 5.6%, while the prevalence of low birth weight was 5.2%; 30% of the mothers had a low education level, 28% were born outside Italy, 52% were nulliparous, and the mean age was 31.7 years (table 1). Due to missing data in the maternal education variable and in the outcome data, the complete case approach led to the exclusion of 1,141 subjects (3%), leaving a total of 34,177 children for the analyses. The associations between maternal education and reproductive outcomes based on this data are presented in table 3. There was an inverse association between maternal education and both outcomes, with the effect of low maternal education on premature births very similar to that observed in the NINFEA data (fully adjusted OR 1.46; 95%CI 0.81;2.66 in the NINFEA study and 1.41; 95%CI 1.22;1.62 in the PBR data). The association between low maternal education and low birth weight was slightly stronger in the

CHARACTERISTICS	NINFEA		PBR	
	No.	MEAN (SD) OR %	No.	MEAN (SD) OR %
MATERNAL AGE AT DELIVERY				
Total	5,323	33.3 (4.3)	35,317	31.7 (5.5)
Missing values	0	–	1	–
NULLIPARITY				
No	1,620	31.2%	16,837	47.7%
Yes	3,572	68.8%	18,481	52.3%
Missing values	131	–	0	–
MATERNAL COUNTRY OF BIRTH[a]				
Italy	5,115	96.1%	25,315	71.7%
Other European countries	140	2.6%	10,003	28.3%
Other countries	68	1.3%	–	–
CHILD REGION OF BIRTH				
Piedmont	3,303	62.2%		
Tuscany	1,182	22.3%		
Other Northern Regions	479	9.0%		
Other	343	6.5%		
Missing values	16	–		
MATERNAL EDUCATION LEVEL[b]				
Low	254	4.8%	10,107	29.5%
Medium	1,769	33.5%	16,739	48.9%
High	3,255	61.7%	7,390	21.6%
Missing values	45	–	1,082	–
HOUSEHOLD INCOME[c]				
Low	177	3.5%		
Medium	2,935	58.8%		
High	1,882	37.7%		
Missing values	331	–		
PRETERM BIRTH				
No	5,083	95.5%	33,295	94.4%
Yes	239	4.5%	1,958	5.6%
Missing values	1	–	65	–
LOW BIRTH WEIGHT				
No	4,914	95.3%	33,438	94.8%
Yes	245	4.7%	1,815	5.2%
Missing values	164	–	65	–

a In the PBR data, maternal country of birth is classified as Italy vs not-Italy / *Nei dati del Registro delle nascite piemontese, il Paese di nascita della madre è classificato come Italia vs non Italia*

b Low: lower than secondary education; medium: secondary education; high: university degree or higher / *Basso: istruzione elementare o media inferiore; medio: istruzione media superiore; alto: laurea universitaria o livello superiore*

c Equivalised total disposable monthly household income. Low: lower than 933 euros; medium: between 933 and 1,810 euros; high: above 1,810 euros / *Reddito familiare mensile disponibile equivalente. Basso: meno di 933 euro; medio: fra 933 e 1,810 euro; alto: maggiore di 1,8110 euro.*

Table 1. Characteristics of mother-child dyads included in the NINFEA and Piedmont Birth Registry (PBR) study populations.
Tabella 1. Caratteristiche delle coppie madre-figlio incluse nel Progetto Ninfea e nel Registro delle nascite piemontese (PBR).

CHARACTERISTICS	PRETERM BIRTH (NO. 4,906)		LOW BIRTH WEIGHT (NO. 4,768)	
	OR_{CRUDE} (95%CI)	OR_{ADJ} (95%CI) [a]	ORC_{CRUDE} (95%CI)	OR_{ADJ} (95%CI) [a]
MATERNAL EDUCATION				
High	–	–	–	–
Medium	0.87 (0.65-1.18)	0.93 (0.69-1.27)	0.71 (0.52-0.98)	0.78 (0.57-1.07)
Low	1.26 (0.70-2.27)	1.47 (0.81-2.66)	1.21 (0.67-2.17)	1.49 (0.82-2.71)
HOUSEHOLD INCOME				
High	–	–	–	–
Medium	0.95 (0.71-1.26)	1.07 (0.80-1.44)	0.93 (0.70-1.24)	1.10 (0.82-1.48)
Low	1.17 (0.58-2.37)	1.63 (0.77-3.46)	1.30 (0.66-2.56)	2.02 (0.98-4.18)

a Adjusted for maternal age, nulliparity, country of birth, and child region of birth / *Aggiustato per età della madre, nulliparità, Paese di nascita, regione di nascita del bambino*

Table 2. Associations of maternal education and household income with reproductive outcomes in the NINFEA study.
Tabella 2. Associazioni dell'istruzione della madre e del reddito famigliare con gli esiti riproduttivi nello studio NINFEA.

CHARACTERISTICS	PRETERM BIRTH (NO. 34,177)		LOW BIRTH WEIGHT (NO. 34,177)	
	OR_{CRUDE} (95%CI)	OR_{ADJ} (95%CI) [a]	OR_{CRUDE} (95%CI)	OR_{ADJ} (95%CI) [a]
MATERNAL EDUCATION				
High	–	–	–	–
Medium	1.14 (1.01-1.30)	1.22 (1.07-1.39)	1.16 (1.02-1.33)	1.29 (1.13-1.47)
Low	1.28 (1.11-1.46)	1.41 (1.22-1.62)	1.30 (1.13-1.49)	1.68 (1.46-1.95)

a Adjusted for maternal age, nulliparity, country of birth / *Aggiustato per età della madre, nulliparità, Paese di nascita*

Table 3. Association of maternal education with reproductive outcomes. Piedmont Birth Registry data, 2011.
Tabella 3. Associazione fra livello di istruzione della madre ed esiti riproduttivi. Registro delle nascite piemontese, 2011.

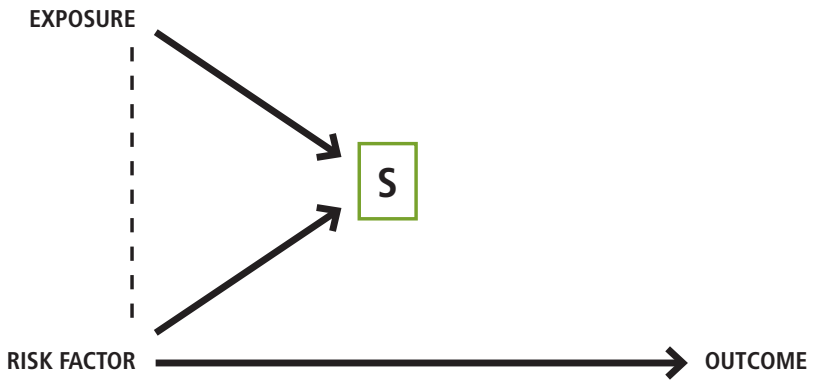

Figure 1. Directed acyclic graph of baseline collider bias. The exposure of interest and another outcome risk factor affect the probability of selection in the source/study population S. When conditioning on S (square around S), a spurious association between the exposure and the outcome risk factor is induced (dashed line).
Figura 1. *Baseline collider bias* rappresentato attraverso un diagramma causale. L'esposizione di interesse e un altro fattore di rischio per l'esito di interesse influenzano la probabilità di fare parte della popolazione in studio S. Quando si condiziona su S (quadrato attorno a S), viene indotta un'associazione spuria tra l'esposizione e il fattore di rischio (linea tratteggiata).

PBR data. Similarly to the NINFEA, the PBR estimates changed when adjusting for maternal age and parity, with the crude OR of low birth weight among the less educated mothers increasing from 1.30 to 1.68 (table 3).

DISCUSSION

In the NINFEA study, socioeconomic disparities in reproductive outcomes, namely preterm delivery and low birth weight, were explored using two different measures of child SEP – maternal education and household income, accounting for baseline collider bias. To further investigate this issue, the analyses on maternal education in the PBR population, again accounting for baseline collider bias, were replicated.

In the NINFEA cohort, low SEP was positively associated with both outcomes, with slightly stronger associations for household income, especially with low birth weight. Although the 95% confidence intervals were quite wide, due to the low prevalence of both the exposures and the outcomes, the direction of the associations was consistent with previous findings[1,2] and with the effects estimated in the PBR data, where an inverse relationship between maternal education and the two reproductive outcomes was found. The inconsistent results observed for the NINFEA cohort in the European collaborative study conducted in 2012[3] were likely due to two factors:

- random variation, as the NINFEA contributed to the 2012 analyses only with the first 2,500 pregnancies;
- lack of adjustment for the risk factors of preterm delivery that also affect the probability of being a member of the cohorts analysed (i.e., adjustment for potential collider bias).

Here, it was shown that, when models were adjusted for maternal age and parity, factors known to affect the probability of being pregnant and the participation into the NINFEA study,[5] the estimates for low SEP increased. The same effect of adjustment for potential determinants of being pregnant in Piedmont in 2011 was observed in the PBR data, supporting the recent notion that baseline collider bias is ubiquitous in cohort studies, irrespectively of whether they are based on a selected or representative sample.[4]

In conclusion, after adjustment for baseline collider bias, the results of the two sources consistently indicate that low SEP is associated with adverse reproductive outcomes in contemporary pregnancies. The persistence of socioeconomic inequalities in adverse reproductive outcomes is of concern, given the strong implications that newborns' characteristics may have over the life-course.

Conflicts of interest: none declared.

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