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Maternal characteristics and pregnancy outcomes in the NICE birth cohort: an assessment of self-selection bias

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ABSTRACT

Background: Prospective birth cohorts are essential for identifying associations between exposures and outcomes. However, voluntary participation introduces a potential bias due to self selection since the persons that chose to participate may differ in background characteristics and behaviors.

Objectives: To investigate potential bias due to self-selection in the ***N****utritional impact on* ***I****mmunological maturation during* ***C****hildhood in relation to the* ***E****nvironment* (NICE) birth cohort in northern Sweden.

Methods: Women in the NICE birth cohort ($N = 621$) were compared to nonparticipating pregnant women in Norrbotten County in northern Sweden who were eligible for participation ($N = 4976$) regarding maternal characteristics and lifestyle. Maternal characteristics and pregnancy outcomes were compared between the groups and associations between exposures (smoking, folic acid, BMI, parity, education) and pregnancy outcomes (birth weight and gestational age) were analyzed by linear regression analyses, examining any interaction with the group.

Results: NICE participants were more highly educated, older and more likely to cohabit than the non-participants. They more often took folic acid and multivitamin supplements and less often smoked during early pregnancy. Pregnancy outcomes (mode of delivery, gestational age at delivery, birth weight and APGAR score) did, however, not differ significantly between participants and non-participants. Smoking, BMI, education and parity affected gestational age and birth weight, but the associations were of similar magnitude in participants and non-participants, with no significant effect on the group.

Conclusion: Self-selection to the NICE study was evident in some factors related to lifestyle and socioeconomic characteristics but did not appear to skew pregnancy outcomes or alter well-known effects of certain lifestyle parameters on pregnancy outcomes.

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NICE birth cohort; enrollment bias; pregnancy cohort; self-selection; self selection bias

Introduction

Prospective birth cohorts are important for finding associations between exposures during pregnancy and pregnancy outcome and future child health, but self-selection and low participation may pose problems [1]. The prevalence of exposures, such as smoking, as well as outcomes, such as birth weight and gestational age at birth may differ between individuals who choose to participate in cohort studies and those who decline to participate. Selection bias occurs if an

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underlying factor is associated both with an exposure, an outcome, as well as with the willingness to participate, which reduces the generalizability of the results [2].

One method to assess selection bias in epidemiological studies is to compare exposure-outcome associations between the study participants and the nonparticipating individuals from the same population as that from which the study participants were recruited [3,4]. This method requires registry data for both the participants and the nonparticipating population. Differences in effect estimates between the study participants and the nonparticipating population would likely reflect selection bias, which would limit the generalizability of results obtained in the cohort study.

The ***N****utritional impact on* ***I****mmunological maturation during* ***C****hildhood in relation to the* ***E****nvironment* (NICE) study is a Swedish, prospective birth cohort, the primary objective of which is to study the effects of environmental exposures during pregnancy and infancy, including diet, lifestyle, microbiota and toxicants, on the maturation of the infant's immune system and development of allergies [5]. Neurodevelopment, growth and oral health are secondary outcomes.

The aim of the present study was to investigate potential bias due to self-selection in the NICE birth cohort by comparing: i) the means and prevalence estimates of the background characteristics, exposures and outcomes; and ii) the exposure-outcomes associations of the women in the NICE cohort with the nonparticipating population of pregnant women in Norrbotten County in northern Sweden who were eligible for participation in the cohort.

Subjects and methods

Overview of the birth cohort

The NICE cohort is a prospective birth cohort that recruited pregnant women in northern Sweden in the period from February 2015 through March 2018. The women gave birth between 3 June 2015, and 16 August 2018. The birth cohort has been described in detail in the study protocol [5]. Briefly, all pregnant women with planned delivery at the Sunderby Hospital in Luleå, the largest maternity hospital in Norrbotten County in northern Sweden, were invited to participate in the study. Exclusion criteria were the inability to understand written and spoken Swedish. Recruitment occurred in two steps. Oral and written information about the study was given at a visit to the maternity clinic at gestational weeks 10–12. In conjunction with the scheduled ultrasound in gestational week 18–20 at the Sunderby Hospital, the prospective parents were provided a more detailed written description of the study with an attached informed consent form and invited to participate in the study. Parents who wished to participate returned a signed consent form by regular mail. No contact was made with parents who did not respond to the invitation.

Study population

In this study, the 621 women who agreed to participate in the NICE cohort were compared to 4967 nonparticipating women who gave birth at the same hospital (Sunderby Hospital) during the same period (3 June 2015, to 16 August 2018). In total, 6352 infants were born at Sunderby Hospital and registered in the digital medical record system Partus during this period, 645 of whom were part of the NICE cohort (Figure 1). The NICE cohort included a total of 655 pregnancies, although the deliveries for 10 of these pregnancies were not registered in Partus, either because the deliveries took place at another hospital or that they were late miscarriages or intrauterine fetal deaths. We excluded twin and triplet births, i.e. 6 infants (3 twin pairs) from the participant group and 177 infants from the nonparticipating group. Furthermore, we excluded, based on an *a priori* decision, pregnancies other than the first one if the woman gave birth more than once during the inclusion period (18 in the participating group and 554 in the nonparticipating group).

Ethics approvals and informed consent

Signed informed consent forms were collected from all the parents in the NICE cohort, and these covered access to information from different hospital records. The study was approved by the Regional Ethical Review Board in Umeå (REK: 2013/18-31 M). Additional ethical approval was obtained for the extraction of hospital records, including information on maternal characteristics and pregnancy outcomes, from the nonparticipating group (REK: 2018/265-32 M).

Data variables

Data regarding maternal and delivery characteristics were extracted from electronic hospital records and anonymized before processing. Data regarding the pregnant women included age, education,

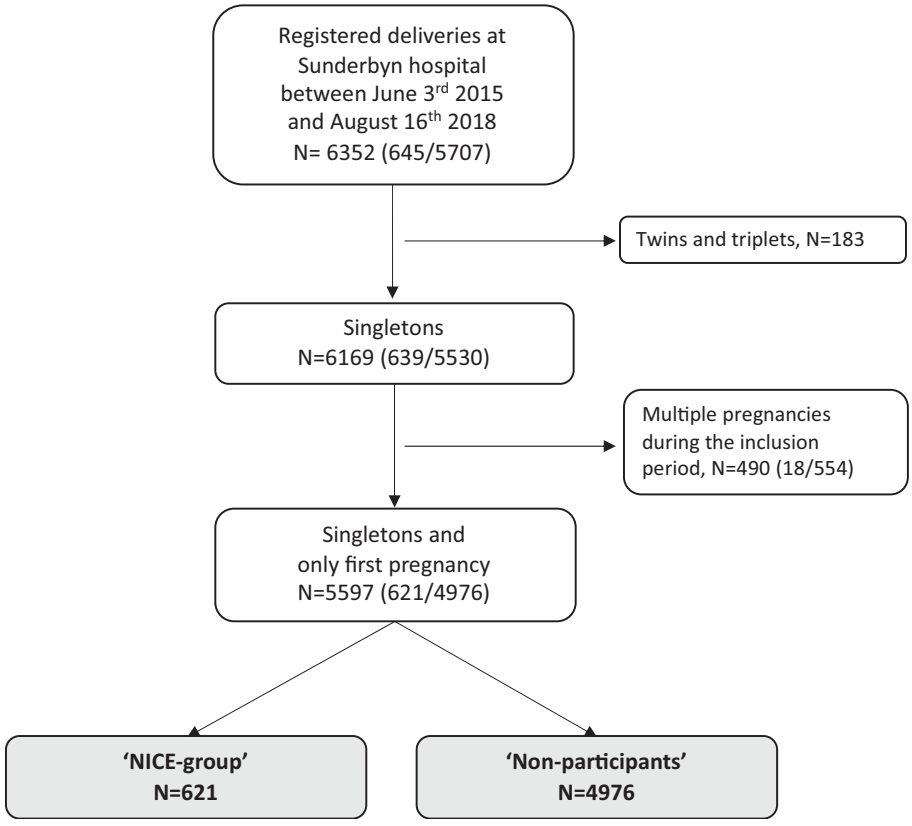

Figure 1. Flow chart of the inclusion and exclusion process used in the current study. N = total population ('NICE-group'/'Non-participants').

cohabitation with a partner, ethnicity ("Swedish" or "other", self-reported), and BMI (measured at admission to maternity care), number of pregnancies, parity and *in vitro* fertilization, smoking during early/late pregnancy, and intake of alcohol or folic acid and multivitamin supplements. Obstetric data included mode of delivery, gestational age, infant sex, birth weight, and APGAR score. The categories of the different variables are shown in Tables 1 and 2.

Statistical analyses

Differences in means and relative frequencies between women in the NICE cohort and the nonparticipating population of pregnant women in Norrbotten County during the inclusion period were evaluated using unpaired Student's *t*-test for continuous data and Pearson's Chi-square test for categorical data. Multivariable-adjusted linear regression models with an interaction term between exposure and participation were used to compare differences in exposure-outcome associations between the participants and non-participants. The exposures that were studied in the linear regression models are shown in Table 3 and included maternal education, maternal BMI, parity, maternal smoking and folic acid supplementation use. The outcomes that were studied included birth weight and gestational age at delivery. The models were adjusted for maternal age (continuous) and parity (continuous but categorized into five levels: 0, 1, 2, 3, $\geq$4), except when these variables were the exposure or outcome. By adding the "participation" variable as a factor, we obtain the information of whether participation has an effect on the outcome while keeping other variables constant. The data were extracted directly from the electronic hospital records and included some unrealistic data points and some extreme outliers that could not be validated. The cleaning up of the data and the amount of missing data are described in detail in Supplementary Tables 1 and 2. Statistical analyses were performed using the IBM SPSS Statistics ver. 25.0 and R ver. 3.5.0 software packages.

Results

Characteristics in the NICE cohort group versus in the nonparticipating population

The women in the NICE cohort were on average 2 years older than the non-participants (31 vs. 29 years,

Table 1. Maternal characteristics among the women in the NICE cohort compared with the non-participant population.

	NICE birth cohort ($N = 621$)	Non-participants ($N = 4967$)	p-value*
Maternal characteristics	N (%) or mean (25^{th}–75^{th} percentile)		
Age, years[a]	31 (28–34)	29 (26–33)	<.001
Age, years (categorical)[b]			<.001
<25	46 (7)	991 (18)	
25–30	290 (45)	2446 (44)	
31–35	201 (31)	1445 (26)	
>35	108 (17)	743 (13)	
Education[b]			<.001
Elementary school	15 (3)	446 (10)	
High school	168 (29)	2111 (47)	
Higher education after high school	403 (69)	1964 (43)	
Civil status[b]			.001
Co-habitant	588 (98)	4404 (95)	
Single	13 (2)	252 (5)	
Ethnicity[b]			<.001
Swedish	523 (93.7)	3519 (78.3)	
Other	35 (6.3)	977 (21.7)	
Maternal BMI, kg/m^{3} [a]	25 (22–28)	26 (22–28)	.500
Maternal BMI, kg/m^{3} [b]			.393
Underweight, <18.5	10 (2)	108 (2)	
Normal weight, 18.5–24.9	329 (56)	2476 (52)	
Overweight, 25.0–29.9	165 (28)	1340 (28)	
Obese, ≥30.0	89 (15)	799 (17)	
Pregnancy			
Previous pregnancy history[b]			.496
No previous pregnancies	188 (30)	1438 (29)	
≥1 previous pregnancies	431 (70)	3512 (71)	
Parity[b]			.307
No previous children	302 (49)	2312 (47)	
≥1 previous children	319 (51)	2664 (54)	
In vitro fertilisation/insemination[b]			.002
Yes	51 (9)	253 (6)	
No	519 (91)	4253 (94)	
Intake/exposures during pregnancy			
Smoking during early pregnancy[b]			.001
Yes	10 (2)	227 (5)	
No	599 (98)	4658 (95)	
Smoking during late pregnancy[b]			.152
Yes	8 (2)	104 (3)	
No	460 (98)	3541 (97)	
Alcohol use[b]			.157
Yes	0 (0)	20 (0)	
No	607 (100)	4753 (100)	
Folic acid supplements[b]			<.001
Yes	449 (81)	3181 (71)	
No	107 (19)	1332 (30)	
Multi-vitamin supplements[b]			<.001
Yes	321 (59)	2195 (50)	
No	228 (41)	2188 (50)	

*Pearson's Chi-square test for categorical data and unpaired Student's t-test for continuous data.
Abbreviations: BMI: body mass index; IVF: *in vitro* fertilization.
Education was categorized as elementary school (9 years of full-time education), senior high school (12 years) or higher education (university level or similar). Women categorized themselves as being co-habitant or single. Ethnicity was self-reported and categorized as Swedish or "Other". Smoking during early pregnancy and alcohol use at any stage during pregnancy were self-reported. *In vitro* fertilization (IVF) refers to intra-cytoplasmic sperm injection (ICSI), sperm or egg donation, hormonal treatment or insemination.
Some characteristics included in this table have been published in previous publications from the NICE cohort, but only in a selected number of participants in the NICE cohort and not in this specific set of participants [32–34].
[a]Mean (25^{th}–75^{th} percentile).
[b]Number (percent).

$p < .001$). In accordance with the generally high level of education of Swedish women, the majority had at least 12 years of education. However, in the participating group, 69% had >12 years of education compared to 43% in the nonparticipating group ($p < .001$) (Table 1). The vast majority in both groups lived with a partner, although this was more common in the participating group (98% vs. 95%, $p < .001$). A larger proportion of the women in the nonparticipating group classified themselves as "not Swedish" (22% vs. 6%), this was likely related to the fact that the ability to understand both written and spoken Swedish was required for participation in the NICE cohort. There were no differences in pre-pregnancy BMI between the groups (Table 1).

Most women (70%) had been pregnant before, and slightly more than half already had a child/children, with no differences between participants and non-

Table 2. Delivery and infant birth outcomes among the women and infants in the NICE cohort compared with the non-participant population.

	NICE birth cohort ($N = 621$)	Non-participants ($N = 4967$)	p-value*
Pregnancy and delivery characteristics	N (%) or mean (25^{th}–75^{th} percentile)		
Vaginal delivery[a]	541 (87)	4285 (86)	.749
Planned Cesarean delivery[a]	28 (5)	259 (5)	.458
Acute Cesarean delivery[a]	53 (9)	435 (9)	.863
Gestational age at birth, days[b]	280 (275–288)	279 (274–287)	.343
Infant characteristics			
Sex[a]			
Female	330 (53)	2439 (49)	.053
Male	291 (47)	2537 (51)	
Birth weight (grams)[b]	3585 (3250–3955)	3585 (3235–3920)	.395
APGAR $\leq$7 at 5 minutes[a]			
Yes	17 (3)	178 (4)	.269
No	603 (97)	4747 (96)	

*Pearson's Chi-square test for categorical data and unpaired Student's t-test for continuous data.
The cutoff for the APGAR score has changed in Sweden since the NICE study data were collected. Here, we use the definitions that were valid at the time of recruitment. Some characteristics included in this table have been published in previous publications from the NICE cohort, but only in a selected number of participants in the NICE cohort and not in this selection of participants [32–34].
[a]Mean (25^{th}–75^{th} percentile).
[b]Number (percent).

participants. Participating women were more likely to have undergone *in vitro* fertilization or insemination (9% vs. 6%, $p = .002$).

Overall, very few women smoked during early pregnancy (2% in the participating group and 5% in the nonparticipating group, $p = .001$). Half of the women in the nonparticipating group quit smoking and, during late pregnancy, there was no longer any significant difference between the groups in terms of the prevalence of smoking (2% vs. 3%). None of the women in the participating group reported alcohol intake, and this was exceptionally uncommon also in the nonparticipating group (0.4%, N.S.). More women in the participating than in the nonparticipating group reported intake of folic acid supplements ($p < .001$) or multi-vitamins ($p < .001$) during pregnancy (Table 1).

Pregnancy outcomes in the NICE cohort group versus in the nonparticipating population

The majority delivered vaginally; only 5% by planned and 14% by acute sectio delivery, with no differences between the groups (Table 2). Most of the infants (86% and 87%, respectively) were delivered at term, with no differences in gestational age between the participants and non-participants (Table 2). The proportions of children who were born with a low APGAR score at 5 min after birth, did not differ significantly between the groups (Table 2).

Comparison of differences in exposure-outcome associations between the two groups

Well-known associations between maternal characteristics and pregnancy exposures on the one hand, and pregnancy outcome, on the other hand, were studied in the NICE cohort and the nonparticipating population. We analyzed whether these associations were more or less pronounced in the two groups by comparing the β-coefficients, and examined whether or not there was a significant interaction between the groups (NICE participants/non-participants) and the studied exposure (Table 3).

Mothers with a university education delivered infants who were somewhat heavier than women with <12 years of education. This association was seen in both the NICE cohort and the non-participant group in the models adjusted for maternal age and parity (Table 3). Women who had at least one child previously (multipara) gave birth to infants who were 100–200 g heavier, an effect observed both in the NICE cohort and in the non-participant group and in both crude and adjusted models (Table 3). As expected, heavier women delivered heavier children (Table 3). Adding maternal education as an additional confounder did not affect the association (data not shown). Smoking was associated with lower birth weight in both groups, but only significantly so in the non-participant group (Table 3). Maternal intake of folic acid was associated with higher infant birth weight, both without and with adjustment for maternal age and parity, albeit only in the NICE group (p-values for interaction = .084 and .069, respectively; Table 3).

Discussion

The results from this study indicate that the pregnant women who accepted the invitation to participate in

Table 3. Differences in exposure-outcome associations among the women and infants in the NICE birth cohort, as compared with the non-participant population.

		NICE birth cohort			Non-participants			*p*-value for interaction	
Exposure	Outcome	*N*[a]	Crude β-coefficient (95% CI)	Adjusted β-coefficient (95% CI)[b]	*N*[a]	Crude β-coefficient (95% CI)	Adjusted β-coefficient (95% CI)[b]	Crude	Adjusted
Maternal education >12 years[c]	Birth weight (g)	584	87 (−13; 190)	110 (8.1; 210)	4513	38 (4.4; 71)	58 (23; 95)	.354	.433
Maternal education >12 years[c]	Gestational age (days)	586	1.9 (−0.30; 4.1)	2.0 (−0.21; 4.3)	4515	0.93 (0.20; 1.7)	0.93 (0.13; 1.7)	.425	.417
Maternal BMI <18.5[d]	Birth weight (g)	591	−61 (−420; 300)	−55 (−410; 300)	4713	−100 (−210; 6.7)	−100 (−210; 7.0)	.828	.847
Maternal BMI: 25–30[d]	Birth weight (g)	591	34 (−72; 140)	51 (−54; 160)	4713	110 (71; 150)	100 (66; 140)	.193	.282
Maternal BMI: >30[d]	Birth weight (g)	591	100 (−30; 240)	110 (−18; 240)	4713	210 (160; 250)	200 (150; 240)	.150	.212
Multiparity[e]	Birth weight (g)	619	190 (100; 280)	190 (100; 280)	4964	120 (90; 150)	130 (97; 170)	.149	.162
Multiparity[e]	Gestational age (days)	620	−1.7 (−3.7; 0.24)	−1.8 (−3.9; 0.26)	4968	−1.3 (−2.0; −0.53)	−1.1 (−1.8; −0.28)	.664	.638
Maternal smoking[f]	Birth weight (g)	607	−120 (−470; 240)	−190 (−540; 160)	4875	−230 (−300; −150)	−240 (−320; −160)	.553	.649
Maternal smoking[f]	Gestational age (days)	608	−4.1 (−12; 3.7)	−3.7 (−12; 4.2)	4878	−1.0 (−2.7; 0.67)	−0.83 (−2.5; 0.86)	.450	.517
Using folic acid supplements[g]	Birth weight (g)	574	123 (3.9; 240)	120 (4.0; 240)	4505	−5.9 (−30; 42)	26 (−12; 63)	.065	.084
Using folic acid supplements[g]	Gestational age (days)	575	2.3 (−0.29; 4.9)	2.3 (−0.39; 4.9)	4509	−0.05 (−0.85; 0.74)	−0.52 (−1.3; 0.30)	.088	.069

[a]Number of subjects included in the adjusted models.
[b]Adjusted for maternal age, and parity (categorized into 0, 1, 2, 3, ≥4) except when parity or maternal age was the exposure.
[c]Maternal education >12 years compared to maternal education ≤12 years.
[d]Reference body mass index (BMI): 18.5–25.0.
[e]Multiparity compared to Nulliparity.
[f]During the first trimester of pregnancy.
[g]Maternal-reported intake of folic acid supplements during pregnancy.

the NICE cohort were somewhat older, more educated, more often lived co-habited and less often smoked in early pregnancy compared to the nonparticipating population of women who gave birth at the same hospital during the same period. However, the differences between the groups were relatively small and did not result in any significant difference in pregnancy outcome between the groups.

Participation

The primary aim of the NICE cohort is to examine how a combination of multiple exposures during early life (diet, microbes, toxicants, environment, lifestyle) influence immune maturation and allergy development. To be able to answer these questions, many biological samples and a large volume of questionnaire data have been collected from the participants in the NICE study. Thus, the participants agreed to an extensive study protocol. This, together with the fact that no reminders were sent out to the parents who did not respond to the invitation, is likely to have influenced the participation rate by around 12%. This is low compared to national population-based birth cohorts [1,6,7]. However, the NICE cohort did not aim to be population-based but rather to collect comprehensive questionnaire data and many biological samples from a lower number of families. Further, the ability to understand written and spoken Swedish was required for enrollment in the study.

Assessing self-selection bias in the NICE cohort

In concordance with reports from other birth cohorts, the women in the NICE cohort were older, more highly educated, more likely to take folic acid and multivitamin supplements, and less likely to smoke than the nonparticipating women [1,8–10]. This implies a potential bias due to self-selection in the NICE cohort in some factors related to lifestyle and socioeconomic characteristics. However, no differences were found in pregnancy and birth outcomes, such as mode of delivery, gestational age, and birth weight, which indicates that there was no influence of any potential selection bias on these outcomes.

Assessing bias in exposure-outcome associations

To analyze bias in association measures, exposure-outcome associations were compared among the women and infants in the NICE cohort and the nonparticipating population. In accordance with previously

published methodology [11], we assessed the difference in associations using an interaction term between the exposure variables and participation. None of the interaction terms were significant, which suggests that none of the tested associations differed significantly between the NICE participants and the non-participants. Not even associations between outcomes and exposures that were over-/under-represented in the NICE cohort, such as maternal education, maternal smoking and intake of folic acid supplements, differed significantly between the two groups. However, when examining the results from the exposure-outcome associations it should be noted that when the exposure or outcome of interest was different between the groups, results of the exposure-outcome association might be less generalizable compared to exposure or outcome that do not differ between groups. In other words, selection bias does not affect all exposure-outcome associations in the same way. It is further important to notice that the confidence intervals for the regression coefficients are large for many of the associations among the NICE cohort participants. This lowers the power of the comparison and limits the conclusion.

Results from the exposure-outcome associations

It is well-recognized that maternal smoking during pregnancy is associated with several adverse health effects on the fetus, including shorter gestational length and reduced fetal growth [12–14]. In accordance with the previous literature [12], we found that women who reported smoking during early pregnancy gave birth to lighter infants. The association was only significant in the non-participant group which is probably due to the low power in the NICE cohort where only 10 women smoked. Lighter infant weight predicts some adverse outcomes later in life, such as obesity, diabetes and cardiovascular disease [15–19].

Maternal overweight and obesity have been associated with increased birth weight [20,21]. Indeed, we found that overweight and obese women gave birth to infants with higher birth weights. The associations did not differ between the women in the NICE cohort and the non-participant women and were only significant in the non-participant group. A higher level of maternal education ($<$12 years vs. $\leq$12 years) was associated with higher infant birth weight, which is in line with the results from other studies [22–24]. The women in the NICE cohort were, in general, more highly educated than the non-participant population, and the effect sizes for the associations between maternal education and the different studied outcomes differed between the two groups, being larger in the NICE cohort. Still, the association did not differ significantly between the participating and the non-participating groups.

Multiparity was associated with a higher infant birth weight [25,26]. The women in the NICE cohort did not differ from the nonparticipating women regarding the frequency of either the outcomes multiparity or infant birth weight. Similarly, the associations did not differ between the women in the NICE cohort and the non-participant group.

Women in Sweden who are planning a pregnancy or being pregnant are advised to consume folate-containing supplements to prevent neural tube defects. The women participating in the NICE cohort had significantly higher intakes of folic acid and multivitamins than nonparticipating women. Except for neural tube defects, it has been suggested that folate supplementation and higher maternal folate status during pregnancy are also beneficial for other birth outcomes such as low birth weight [27–31]. Here we found folic acid supplement intake to be associated with a significantly increased birth weight of 120 grams in the NICE cohort. However, no association between folic acid and birth weight was found in the non-participant group.

Strengths and weaknesses of the present study

The main strength of this study is the ready access to both exposures and outcomes in the nonparticipating population of eligible women, which enabled analyses of differences in exposure-outcome associations between the women who agreed to participate in the NICE cohort and the women who declined to participate (or did not receive the study information). Therefore, we were not only able to describe the study population but also to assess selection bias. As we currently have data on differences in exposure-outcome associations between the NICE cohort participants and the rest of the population, this can be taken into account when interpreting results from future analyses of exposures and outcomes in the NICE birth cohort.

The low number of participants in the NICE cohort (compared to the non-participant population) made investigations of associations between exposures and rare outcomes underpowered, e.g. preterm birth, SGA, LGA. As a consequence of this, we were not able to analyze these binary outcomes, only the continuous outcomes of birth weight and gestational age.

Another limitation is the lack of data regarding the maternal history of chronic diseases, as it was not possible to extract these data from the electronic medical hospital records. Therefore, bias may still be present in exposure-outcome associations other than those that it was possible to study here.

One inclusion criterion in the NICE cohort was to be able to understand spoken and written Swedish. We did not have information about how well the non-participant population understood spoken and written Swedish and, therefore, we could not select a "non-participant population" that was similar to the NICE cohort in this aspect. This resulted in significantly more women who reported their nationality as Swedish in the NICE cohort than in the non-participant population. This is a limitation of the present study, since bias due to self-selection because of ethnicity/nationality could not be assessed. Furthermore, it reduces the overall generalizability of the results from the NICE birth cohort, as the cohort is selected and is not population-based.

The recruitment of the NICE cohort took place in Norrbotten County in northern Sweden. In this study, we have compared the participants to all other women giving birth at the same hospital. Since we have not compared the NICE participants to women in other regions of Sweden, we are not able to draw any conclusions regarding the generalizability of our population in relation to the rest of the country.

Conclusion

In summary, the women in the NICE cohort were older, had a higher educational level, were more likely to live together with a partner, were less frequently smokers, and used folic acid and multivitamin supplements more often than the nonparticipating population of women. This suggests bias due to self-selection in some lifestyle and socioeconomic characteristics in the NICE cohort. Still, none of the studied exposure-outcome associations differed between the women in the NICE cohort and the women in the nonparticipating population giving birth at the same hospital, suggesting that the generalizability of these outcomes was good.

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Authors' contribution

All the authors participated in the planning and execution of this study and approved the final version. LEÖ, BJ and MB conceived the study. FM and RL extracted data from records. LEÖ and MB wrote the first draft of this manuscript. LEÖ, MB, DM, SN and RL conducted the statistical analyses. All the authors revised several versions of this manuscript and approved the final version for publication.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The dataset used in this study originates from the Nutritional impact on Immunological maturation during Childhood in relation to the Environment (NICE) cohort.

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