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Examining Nonparticipation in the Maternal Follow-up Within the Danish National Birth Cohort

Mette Bliddal*, Zeyan Liew, Anton Pottegård, Helene Kirkegaard, Jørn Olsen, and Ellen A. Nohr

* Correspondence to Dr. Mette Bliddal, Odense Patient Data Explorative Network (OPEN), Department of Clinical Research, University of Southern Denmark and Odense University Hospital, J.B. Winsløw Vej 9a, 3, 5000 Odense C, Denmark (e-mail: mette.bliddal@rsyd.dk).

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A follow-up questionnaire on maternal health was distributed within the Danish National Birth Cohort (established in 1996–2002) 14 years after the index birth. Responses were obtained from 41,466 (53.2%) of 78,010 eligible mothers. To ensure the appropriate use of these data, the possibility of selection bias due to nonparticipation had to be evaluated. We estimated 4 selected exposure-outcome associations (prepregnancy weight–depression; exercise–degenerative musculoskeletal conditions; smoking–heart disease; and alcohol consumption–breast cancer). We adjusted for several factors associated with participation and applied inverse probability weighting. To estimate the degree of selection bias, we calculated relative odds ratios for the relationship between the baseline cohort and the subset participating in the Maternal Follow-up. Participating women were generally healthier, of higher social status, and older than the baseline cohort. However, selection bias in the chosen scenarios was limited; ratios of the odds ratios ranged from −14% to 5% after adjustment for age, parity, social status, and, if the variable was not the exposure variable, prepregnancy body mass index, exercise, smoking, and alcohol consumption. Applying inverse probability weighting did not further reduce bias. In conclusion, while participants differed somewhat from the baseline cohort, selection bias was limited after factors associated with participation status were accounted for.

birth cohorts; cohort studies; inverse probability weighting; longitudinal studies; nonparticipation; selection bias

Abbreviations: BMI, body mass index; CI, confidence interval; DNBC, Danish National Birth Cohort; ICD-8, *International Classification of Diseases, Eighth Revision*; ICD-10, *International Classification of Diseases, Tenth Revision*; IPW, inverse probability weighting.

The Danish National Birth Cohort (DNBC) is one of the largest birth cohorts in the world, with initial participation of more than 100,000 pregnant women (see www.dnbc.dk) (1). While most birth cohort studies have focused on the children's health outcomes, the DNBC also provides the opportunity to study the health of women after they have given birth, with detailed information being collected during their pregnancies and in early motherhood. From the inception of the DNBC, regular prospective follow-ups of the children were planned, and several have been conducted.

From December 2013 to December 2014, an average of 14 years after childbirth, the first follow-up focusing on the health of the mothers—the Maternal Follow-up—was conducted. With the passage of time, the incentive to participate in the DNBC may vary due to changes in life situations, social or health conditions, and lifestyle. Differences in participation are likely to correlate with exposures and health outcomes under study, and thus selection bias may occur (1–3), making it imperative to evaluate the possibility of bias due to nonparticipation. Fortunately, the extensive nationwide health registers in Denmark allow formal assessment of the influence of potential selection, as they also hold information about DNBC participants who chose not to participate in the Maternal Follow-up.

In this study, we aimed to describe selection based on maternal characteristics in the Maternal Follow-up within the DNBC. We selected 4 maternal exposure-outcome pairs and examined the direction and magnitude of potential selection bias due to nonparticipation. Further, we examined whether using the inverse probability weighting (IPW) technique could reduce the possible influence of selection bias.

METHODS

Danish National Birth Cohort

This study was based on the DNBC. From 1996 to 2002, a total of 91,389 women with 100,421 pregnancies in Denmark were recruited into the cohort, corresponding to approximately 30% of all pregnancies in Denmark during the study recruitment period (4) (Figure 1). Baseline information on demographic factors and lifestyle was collected using computer-assisted telephone interviews (1). The Maternal Follow-up was conducted during 2013 and 2014, with the majority of women being in their forties, having ended childbearing but not yet having reached menopause. A questionnaire was developed by researchers familiar with the DNBC and relevant experts within the fields of mental and physical health, occupational health and lifestyle, reproduction, and stresses associated with motherhood. From January 2013 to November 2014, an invitation to fill out a Web-based questionnaire was sent to all eligible mothers in the DNBC. Mothers who provided an e-mail address in connection with previous follow-ups regarding the children were contacted by e-mail (54%); the rest were contacted by regular mail (46%). The women were reminded twice by e-mail or letter (depending on the group) at fortnight (2-week) intervals if they did not respond to the initial invitation.

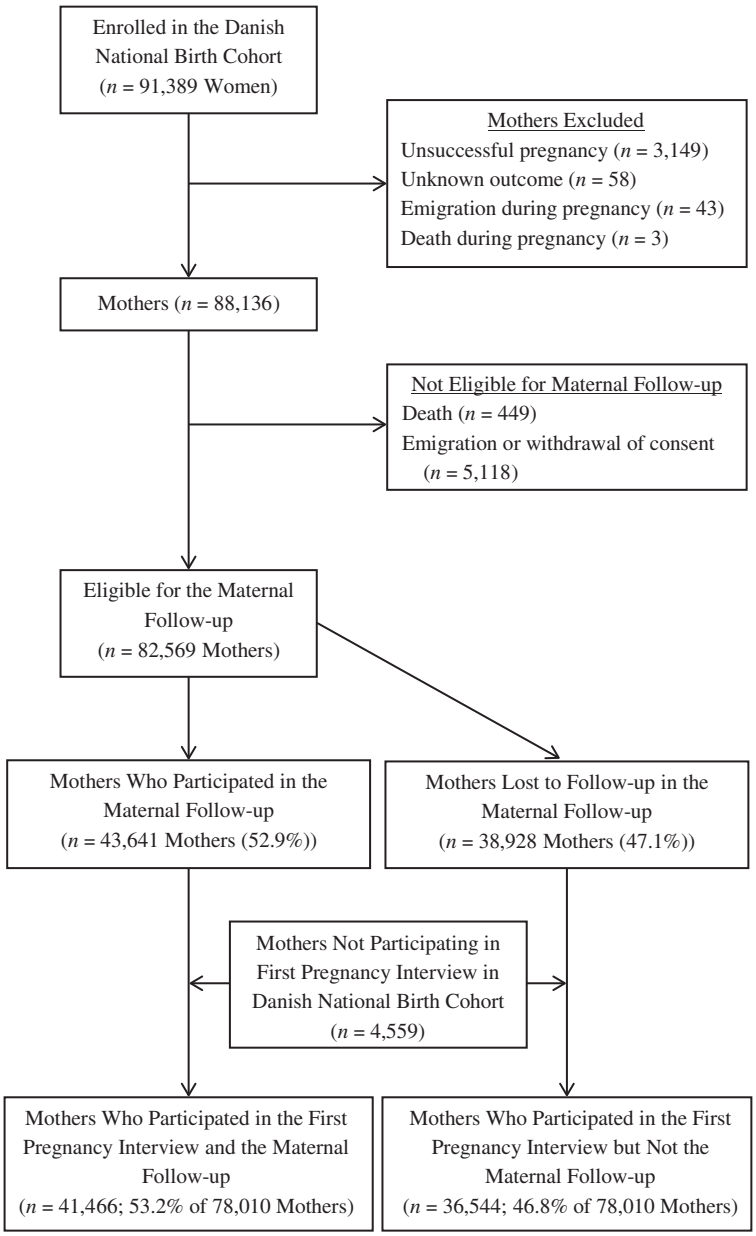

Figure 1. Selection of the baseline population for the Danish National Birth Cohort (1996–2002) and of participants and nonparticipants in the Maternal Follow-up (2013–2014).

From the initial cohort, women were excluded if they had had only unsuccessful pregnancies in the cohort study ($n = 3,149$), had had only unknown outcomes in the cohort study ($n = 58$), had emigrated ($n = 43$), or had died during pregnancy ($n = 3$). This left us with a sample of 88,136 mothers. If a woman had more than 1 pregnancy in the cohort leading to a liveborn child, the first pregnancy served as the index pregnancy.

A total of 5,567 mothers were not eligible for the Maternal Follow-up due to death ($n = 449$), emigration, or withdrawal of consent to participate in future data collections. In all, 82,569 mothers were invited to participate in the Maternal Follow-up (46% by mail, 54% by e-mail), and 43,641 completed the Maternal Follow-up questionnaire. The overall response rate was 52.9% (26% by mailed invitation, 68% by e-mail invitation). The questionnaire was completed a median of 13.8 years after childbirth (interquartile range, 12.7–14.6), and the data collection concluded in February 2015. For this study, we excluded mothers who did not complete the first interview in the DNBC ($n = 4,559$); this left us with a study population of 78,010 mothers (baseline cohort), of whom 53.2% ($n = 41,466$) responded to the Maternal Follow-up questionnaire (Maternal Follow-up subset).

Other data sources

Through use of the unique individual personal identification number assigned to all Danish individuals (5), the baseline cohort (including mothers who did not participate in the Maternal Follow-up) was linked to the Danish National Patient Register (6), the Danish Civil Registration System (5), and the National Medical Birth Registry (7, 8). Due to the individual linkage and the quality of the Danish health registers, the linkage rate was very high, and linkage was virtually complete (9). The Danish National Patient Register contains information on all inpatient contacts made from 1977 onward and on outpatient contacts and emergency room events occurring in Danish hospitals from 1995 onward (6). The diagnostic codes used in the patient register are classified according to the *International Classification of Diseases, Eighth Revision* (ICD-8; 1977–1993) and the *International Classification of Diseases, Tenth Revision* (ICD-10; 1994 to the present). These data allowed us to identify diseases diagnosed in hospital settings for each woman in the cohort. The Danish Civil Registration System enabled us to retrieve information on death and migration (5). Information on parity and birth outcomes was obtained from the National Medical Birth Registry (7).

Exposure-outcome associations

We studied whether selection by nonparticipation in the follow-up affected relative risk estimates by comparing 4 different exposure-outcome associations in the baseline cohort and the Maternal Follow-up subset. The 4 selected associations were: 1) prepregnancy body mass index (BMI)–anxiety and depression disorders (10–12); 2) leisure-time exercise during pregnancy–degenerative musculoskeletal disorders (13–15); 3) smoking during pregnancy–stroke/ischemic heart disease (16); and 4) alcohol consumption prior to pregnancy–breast cancer (17, 18). These associations were chosen because they have previously been subjects of interest in the literature and because each of the selected exposures and outcomes could have influenced participation in the Maternal Follow-up. Further, different types of diseases may affect selection differently, and the outcomes chosen cover 4 major areas of disease that are all relevant to the study of women in midlife and are sufficiently common to allow meaningful assessment in this still fairly young population. Finally, the chosen diseases represent both common and rare diseases, which again may affect the impact of selection differently.

Study variables

All exposure information was self-reported from the first interview at a median 17 weeks of gestation in the DNBC. Prepregnancy BMI was calculated on the basis of prepregnancy weight (kg) and height (m) as weight divided by the square of height and was categorized according to the World Health Organization (19) obesity definition as underweight (BMI <18.5), normal-weight (BMI 18.5–24.9), overweight (BMI 25.0–29.9), or obese (BMI ≥30.0). Leisure-time exercise during pregnancy was categorized as no exercise, 1–180 minutes/week, or >180 minutes/week. Smoking during pregnancy was categorized according to smoking status at the first interview (no smoking, smoking cessation in early pregnancy, or current smoking). Alcohol consumption before pregnancy was categorized as no alcohol intake/<1 drink per week, 1–4 drinks per week, or ≥5 drinks per week.

Outcome data were obtained from the Danish registers, and all outcome variables were dichotomous. Diagnoses of anxiety and depression disorders were defined by 1 or more of the following ICD-10 codes: F30–F39 ("all affective mental disorders") or F40–F48 ("all nervous and stress-related disorders/disorders with physical symptoms"). Degenerative musculoskeletal disorders were identified as any ICD-10 code M related to degenerative musculoskeletal conditions. Cardiovascular diseases were identified as diagnosis of any ischemic heart disease (ICD-10 codes I20–I21 or I24–I25) or stroke (ICD-10 codes I60–I64). Breast cancer cases were identified by ICD-10 code C50. Before focusing on each outcome, we excluded women with any record of the actual outcome before the day of conception by either ICD-8 codes or ICD-10 codes (see Web Table 1 (available at https://academic.oup.com/aje) for ICD-8 and ICD-10 specifications for definition of exclusions and outcomes).

Other variables were defined at the time of the index pregnancy and included age (years; continuous), parity (0, 1, or ≥2 children), and social status (defined by type of job, or by type of education if still attending school; low, middle, or high) (20). Finally, parity after the index child's birth (i.e., number of children born after the index child; 0, 1, or ≥2) up to June 2011 was recorded.

Statistical methods

Exposures and background characteristics at baseline, as well as parity during follow-up and selected outcomes, were described by marginal frequencies for the baseline cohort and for the Maternal Follow-up subset. We used multiple logistic regression analyses with 95% confidence intervals to estimate odds ratios for each of the exposure-outcome pairs in the baseline cohort and in the Maternal Follow-up subset, respectively. Adjustments were made for age, parity, and social status at baseline and, if the variable was not the exposure variable, prepregnancy BMI, leisure-time exercise during pregnancy, smoking in pregnancy,

and alcohol consumption prior to pregnancy. We chose traditional models often applied to examine causal relationships, but we abstained from applying sophisticated models to maintain the focus on the bias analyses. Adjusting for the chosen factors may block confounding and selection paths via these factors (21).

To evaluate the magnitude and direction of selection bias, we compared the distributions of the exposures, covariates, and outcomes in the baseline cohort and the Maternal Follow-up subset, computing the relative differences (prevalence ratios) between the baseline cohort and the Maternal Follow-up subset (22). We also obtained selection bias estimates by use of the ratio of the odds ratios for each of the exposure-outcome pairs by dividing the adjusted odds ratio in the Maternal Follow-up subset with the adjusted odds ratio in the baseline cohort (23). Bias estimates (i.e., relative odds ratios) below 1 indicate underestimation of the association in the Maternal Follow-up subset; conversely, estimates above 1 indicate overestimation. The adjusted relative odds ratio was used for the evaluation of selection bias, as a crude relative odds ratio would have represented a mix of both selection and confounding bias. To calculate the 95% confidence intervals of the prevalence ratios and relative odds ratios for the associations between the 2 dependent study populations (the Maternal Follow-up participants inherently being a subset (Sub) of the baseline cohort (Tot)), we used an equation method presented by Nohr et al. (22) as

$$\mathrm{SE}(\hat{\theta}_{\mathrm{Sub}} - \hat{\theta}_{\mathrm{Tot}}) = \sqrt{\mathrm{SE}(\hat{\theta}_{\mathrm{Sub}})^2 - \mathrm{SE}(\hat{\theta}_{\mathrm{Tot}})^2},$$

which was found in a simulation study to be valid, especially when the expected bias is modest (22). The θ's represent odds ratios, and SE represents the standard error.

In addition, we performed weighted regression analysis using IPW (24) by estimating the probability of participation in the Maternal Follow-up based on the women's information collected at baseline, to account for potential selection bias in analyses of women participating in the Maternal Follow-up. A participating woman was thus assigned a weight so that she accounted not only for herself in the analyses but also for those who were similar to her in terms of characteristics but did not answer the follow-up questionnaire (24). We first used logistic regression to predict the odds of participation in the Maternal Follow-up using a wide range of baseline factors—that is, all 4 exposure variables of interest, the selected covariates, and the number of children (1 or ≥2) enrolled in the DNBC. These factors were all associated with participation in both univariate analyses and mutually adjusted analyses (see Web Table 2). An IPW variable for each woman was then computed and included in the regression model for the Maternal Follow-up subset with a robust error estimator to obtain the 95% confidence interval. All analyses were performed using STATA 13.0 (StataCorp LP, College Station, Texas).

Ethics

Participants in the DNBC initially gave written consent to participate in the longitudinal collection of data and allowed use of their data for research in maternal and child health. Permission to use the data was granted by the Danish Data Protection Agency.

RESULTS

Characteristics of the baseline cohort and of participants in the Maternal Follow-up are presented in Table 1. The Maternal Follow-up subset differed from the baseline cohort, as mothers who were older at baseline or had more than 1 child in the DNBC were overrepresented in the Maternal Follow-up. In addition, they were healthier in regard to weight and exercise than all participants at baseline. Some subgroups were less likely to participate in the Maternal Follow-up. Young mothers (age <20 years) were underrepresented with a prevalence ratio of 0.55 (95% confidence interval (CI): 0.50, 0.61), women of low social status with a prevalence ratio of 0.74 (95% CI: 0.71, 0.76), and women who smoked during pregnancy with a prevalence ratio of 0.75 (95% CI: 0.74, 0.77) (Table 1). Parity during follow-up was similar in the baseline cohort and the subsample.

Women with incident disease diagnosed during the follow-up period tended to be less likely to participate in the Maternal Follow-up. Underrepresentation was most pronounced for women with depression/anxiety and for women with stroke/ischemic heart disease (prevalence ratios were 0.80 (95% CI: 0.77, 0.82) and 0.83 (95% CI: 0.78, 0.89), respectively) (Table 2). Women who had received a diagnosis of breast cancer were overrepresented with a prevalence ratio of 1.13 (95% CI: 1.07, 1.20).

Table 3 shows the crude and adjusted odds ratios for the baseline cohort and the Maternal Follow-up subset for each of the 4 exposure-outcome pairs along with the adjusted relative odds ratios comparing the adjusted odds ratios for the baseline cohort and the Maternal Follow-up subset. Associations in the chosen exposure-outcome pairs were as expected. Risk of a diagnosis of depression was higher for both underweight and overweight/obese women than for normal-weight women. Risk of degenerative musculoskeletal conditions was slightly increased with increasing leisure-time exercise during pregnancy. Smoking in pregnancy was associated with a higher risk of cardiovascular disease than nonsmoking only in the baseline cohort. Finally, results indicated no association between alcohol consumption and breast cancer.

Overall, selection bias was generally limited in the chosen scenarios, with relative odds ratios ranging from −0.86 to 1.05. For the relationship between prepregnancy BMI and depression, the risk among underweight women was underestimated in the Maternal Follow-up subset compared with the baseline cohort (relative odds ratio = 0.90, 95% CI: 0.73, 1.07), whereas for overweight and obese women, there was a slight overestimation (relative odds ratios of 1.04 (95% CI: 0.96, 1.14) and 1.05 (95% CI: 0.93, 1.20), respectively). Point estimates were slightly higher in the Maternal Follow-up subset for exercise and musculoskeletal disorders and slightly lower for smoking and CVD compared with those in the baseline cohort. When we examined the relationship between smoking and cardiovascular disease, women reporting smoking cessation in the Maternal Follow-up had a ratio of odds ratios of 0.86 (95% CI: 0.65, 1.14) compared with the baseline cohort. Note, however, that for all associations the 95% confidence intervals were largely overlapping. When IPW was applied to the adjusted analyses, the bias estimates were largely unchanged.

DISCUSSION

More than half of the baseline cohort in the DNBC participated in the Maternal Follow-up 14 years after childbirth. Of

Table 1. Characteristics of the Baseline Cohort (1996–2002) and the Maternal Follow-up Subset (2013–2014) in the Danish National Birth Cohort

Variable	Baseline Cohort (n = 78,010)		Maternal Follow-up (n = 41,466)		Participation Rate, %	Prevalence Ratio[a]	95% Confidence Interval[b]
	No. of Mothers	%[c]	No. of Mothers	%[c]			
% of study population		100.0		53.2	53.2		
Maternal age at index conception, years							
<20	843	1.1	247	0.6	29.3	0.55	0.50, 0.61
20–24	9,655	12.4	4,134	10.0	42.8	0.81	0.79, 0.82
25–29	32,512	41.7	17,321	41.8	53.3	1.00	0.99, 1.01
30–34	26,107	33.5	14,543	35.1	55.7	1.05	1.04, 1.06
35–39	8,113	10.4	4,741	11.4	58.4	1.10	1.08, 1.12
≥40	779	1.0	479	1.2	61.5	1.16	1.09, 1.22
Parity at baseline							
0	39,771	51.0	21,423	51.7	53.9	1.01	1.01, 1.02
1	26,376	33.8	13,901	33.5	52.7	0.99	0.98, 1.00
≥2	11,862	15.2	6,141	14.8	51.8	0.97	0.96, 0.99
No. of children born during follow-up[d]							
0	35,119	45.0	18,843	45.4	53.7	1.01	1.00, 1.02
1	31,622	40.5	16,794	40.5	53.1	1.00	0.99, 1.01
≥2	9,993	12.8	5,227	12.6	52.3	0.98	0.97, 1.00
No. of children enrolled in DNBC							
1	70,309	90.1	36,997	89.2	52.6	0.99	0.99, 0.99
>1	7,701	9.9	4,469	10.8	58.0	1.09	1.07, 1.11
Index-pregnancy prepregnancy BMI[e]							
<18.5 (underweight)	3,420	4.4	1,692	4.1	49.5	0.93	0.90, 0.96
18.5–24.9 (normal-weight)	52,110	66.8	28,809	69.5	55.3	1.04	1.04, 1.04
25.0–29.9 (overweight)	14,909	19.1	7,600	18.3	51.0	0.96	0.95, 0.97
≥30.0 (obese)	6,267	8.0	2,745	6.6	43.8	0.82	0.80, 0.85
Social status at baseline[f]							
Low	6,766	8.7	2,647	6.4	39.1	0.74	0.71, 0.76
Middle	28,391	36.4	13,590	32.8	47.9	0.90	0.89, 0.91
High	39,668	50.8	23,872	57.6	60.2	1.13	1.13, 1.14
Smoking during index pregnancy							
Nonsmoking	57,102	73.2	32,290	77.9	56.5	1.06	1.06, 1.07
Smoking cessation	7,603	9.7	3,857	9.3	50.7	0.95	0.93, 0.97
Smoking	13,275	17.0	5,309	12.8	40.0	0.75	0.74, 0.77
Exercise during pregnancy, minutes/week							
0	49,001	62.8	24,911	60.1	50.8	0.96	0.95, 0.96
1–179	22,779	29.2	13,060	31.5	57.3	1.08	1.07, 1.09
≥180	6,122	7.8	3,442	8.3	56.2	1.06	1.03, 1.08
Alcohol consumption prior to index pregnancy, drinks/week							
0/<1	17,480	22.4	8,200	19.8	46.9	0.88	0.87, 0.90
1–4	42,634	54.7	23,184	55.9	54.4	1.02	1.02, 1.03
>4	17,487	22.4	9,906	23.9	56.6	1.07	1.05, 1.08

Abbreviations: BMI, body mass index; DNBC, Danish National Birth Cohort.

[a] Ratio of percentage in the Maternal Follow-up to percentage in the baseline cohort. Values above 1 indicate that women with this characteristic were overrepresented in the Maternal Follow-up; values below 1 indicate underrepresentation.

[b] Computed using an equation method presented by Nohr et al. (22); see text for details.

[c] Percentages may not add up to 100 due to missing information. Number (%) of mothers with missing information in the baseline cohort: age, 1 (<0.01%); parity, 1 (<0.01%); number of children enrolled in DNBC, 1 (<0.01%); prepregnancy BMI, 1,304 (1.7%); social status, 3,185 (4.1%); smoking during pregnancy, 30 (0.04%); exercise during pregnancy, 108 (0.1%); alcohol consumption during pregnancy, 409 (0.5%).

[d] Information on subsequent births was available only until June 2011.

[e] Weight (kg)/height $(m)^2$.

[f] Social status was defined by type of job, or by type of education if still attending school (20).

Table 2. Distribution of Selected Diseases in the Baseline Cohort and the Maternal Follow-up Subset, Danish National Birth Cohort, 1996–2014

Disease[a]	Baseline Cohort		Maternal Follow-up		Participation Rate, %	Prevalence Ratio[b]	95% Confidence Interval[c]
	No. of Mothers	%	No. of Mothers	%			
Depression/anxiety	76,668		40,925				
Yes	5,458	7.1	2,319	5.7	42.5	0.80	0.77, 0.82
No	71,210	92.9	38,606	94.3	54.2	1.02	1.01, 1.02
Degenerative musculoskeletal conditions	72,922		39,026				
Yes	16,408	22.5	8,367	21.4	51.0	0.95	0.94, 0.97
No	56,514	77.5	30,659	78.6	54.3	1.01	1.01, 1.02
Stroke or ischemic heart disease	77,902		41,412				
Yes	981	1.3	435	1.1	44.3	0.83	0.78, 0.89
No	76,921	98.7	40,977	98.9	53.3	1.00	1.00, 1.00
Breast cancer	77,987		41,452				
Yes	757	1.0	455	1.1	60.1	1.13	1.07, 1.20
No	77,230	99.0	40,997	98.9	53.1	1.00	1.00, 1.00

[a] Cases arising prior to conception were excluded.
[b] Ratio of percentage in the Maternal Follow-up to percentage in the baseline cohort. Values above 1 indicate that women with this characteristic were overrepresented in the Maternal Follow-up; values below 1 indicate underrepresentation.
[c] Computed using an equation method presented by Nohr et al. (22); see text for details.

all invited mothers, those who chose to participate were generally older and healthier at baseline and at follow-up. The only exception was an overrepresentation of women with breast cancer, which is noteworthy for future studies of cancer in the cohort. In addition, we found that maternal social status and several lifestyle factors at baseline were associated with participation in the Maternal Follow-up. However, in the 4 selected exposure-outcome associations that we evaluated, the possible influence of selection bias in the effect estimates was limited after we adjusted for factors that may influence selection. Additionally applying IPW had virtually no impact on the bias estimates.

Although nonparticipation in the Maternal Follow-up was as high as 47.1%, it was not substantially larger than the 39.9% nonparticipation in the 7-year follow-up focusing on the health of the children within the same cohort (21), and 40.2% of mothers participated in both follow-ups, indicating that many women willing to participate once in a follow-up also participate in subsequent follow-ups. This is also supported by the fact that women who had once been contacted via their e-mail address had a much higher response rate (68%) than women invited by mailed letter (26%). The fact that the most healthy and well-educated mothers were more willing to participate in follow-ups is consistent with findings from other large longitudinal cohort studies of younger women (25–27).

Estimates of associations in the 4 exposure-outcome pairs were as expected, except for alcohol consumption prior to pregnancy and breast cancer, where we found no association, in contrast to other investigators who observed that alcohol intake was significantly related to breast cancer risk (18, 28). This may be explained by the fact that the alcohol consumers in the DNBC Maternal Follow-up were "healthy alcohol consumers"—with most women in this category having a glass of wine at dinner several times per week but with few heavy drinkers. Our upper category of alcohol consumers was set at >5 drinks per week—a fairly low cutoff. This lack of association with breast cancer among light users of alcohol is supported by another study that did not find an association between alcohol intake of up to 6 drinks per week and breast cancer in premenopausal women (29). Even though we adjusted for other lifestyle factors, the finding may also have been due to residual confounding.

Despite differences in prevalence estimates and risk of disease between the baseline cohort and the subset, the chosen associations between exposure and disease were only slightly affected by selection after adjustment for the few factors associated with participation. This corresponds with other studies that have examined effects of selection on measures of association in longitudinal studies (21, 25, 30). In the DNBC cohort, Greene et al. (21) found selection bias to be small, with relative ratios of −10% to 8% when examining childhood outcomes 7 years postpartum. Additionally, in other large longitudinal cohort studies, such as the Norwegian Mother and Child Cohort Study (30) and the Avon Longitudinal Study of Parents and Children (22), dropout or self-selection was systematic, yet it only biased selected exposure-outcome associations marginally. We found little indication of selection bias in the 4 associations we evaluated, and we cannot rule out the possibility that simple stochastic variation drove some or all of our findings. Because the sample size and number of cases were smaller in the Maternal Follow-up subset, the 95% confidence intervals were wider and the variance of the estimates increased. Hence, odds ratios were not different in the larger baseline cohort but were more accurate. Interestingly, the largest difference in odds ratios was found for women who reported cessation of smoking during pregnancy and stroke/ischemic heart disease. Smoking is a time-varying

Table 3. Odds Ratios and Adjusted Relative Odds Ratios Comparing Associations Between Risk Factors and Chronic Diseases in the Baseline Cohort and the Maternal Follow-up Subset, Danish National Birth Cohort, 1996–2014

Association	Crude OR		Adjusted[a] OR or ROR									
	Baseline Cohort	Maternal Follow-up	Baseline Cohort		Maternal Follow-up		ROR	95% CI[b]	Maternal Follow-up With IPW[c]		ROR With IPW[c]	
			OR	95% CI	OR	95% CI			OR	95% CI	ROR	95% CI[b]
Prepregnancy BMI[d]–depression[e]												
<18.5 (underweight)	1.43	1.21	1.19	1.05, 1.36	1.07	0.87, 1.33	0.90	0.73, 1.07	1.10	0.88, 1.37	0.92	0.75, 1.10
18.5–24.9 (normal-weight)	1.00	1.00	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
25.0–29.9 (overweight)	1.16	1.22	1.08	1.00, 1.16	1.13	1.01, 1.26	1.04	0.96, 1.14	1.13	1.00, 1.26	1.04	0.96, 1.14
≥30.0 (obese)	1.35	1.41	1.14	1.03, 1.26	1.20	1.02, 1.41	1.05	0.93, 1.20	1.19	1.00, 1.41	1.04	0.91, 1.19
Exercise during pregnancy (minutes/week)–degenerative musculoskeletal conditions[f]												
0	1.00	1.00	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
1–179	0.95	0.99	1.06	1.02, 1.10	1.10	1.04, 1.16	1.04	1.00, 1.08	1.09	1.03, 1.15	1.03	0.90, 1.07
≥180	0.96	0.99	1.10	1.03, 1.18	1.15	1.05, 1.26	1.04	0.98, 1.11	1.16	1.05, 1.27	1.05	0.98, 1.12
Smoking during pregnancy–stroke or ischemic heart disease[g]												
No smoking	1.00	1.00	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Cessation in first trimester	1.01	0.86	1.17	0.92, 1.50	1.01	0.69, 1.47	0.86	0.65, 1.14	0.94	0.65, 1.37	0.80	0.60, 1.07
Smoking	2.30	2.05	2.16	1.85, 2.51	2.02	1.59, 2.57	0.94	0.78, 1.13	2.02	1.58, 2.58	0.94	0.77, 1.13
Alcohol consumption prior to conception (drinks/week)–breast cancer[h]												
0/<1	1.00	1.00	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
1–4	1.10	1.07	0.94	0.77, 1.15	0.95	0.73, 1.23	1.00	0.85, 1.19	0.93	0.72, 1.22	0.99	0.83, 1.18
≥5	1.39	1.27	0.99	0.79, 1.25	0.98	0.72, 1.32	0.98	0.81, 1.20	0.97	0.72, 1.32	0.98	0.80, 1.20

Abbreviations: BMI, body mass index; CI, confidence interval; IPW, inverse probability weighting; OR, odds ratio; ROR, relative odds ratio.

[a] Adjusted for age, social status, parity, and, if the variable was not the exposure variable, prepregnancy BMI, exercise during pregnancy, smoking during pregnancy, and alcohol consumption prior to conception.

[b] Computed using an equation method presented by Nohr et al. (22); see text for details.

[c] Generated on the basis of variables used for adjustment and numbers of children enrolled in the Danish National Birth Cohort.

[d] Weight (kg)/height $(m)^2$.

[e] Baseline population: $n = 76,668$; Maternal Follow-up: $n = 40,925$.

[f] Baseline population: $n = 72,922$; Maternal Follow-up: $n = 39,026$.

[g] Baseline population: $n = 77,902$; Maternal Follow-up: $n = 41,412$.

[h] Baseline population: $n = 77,987$; Maternal Follow-up: $n = 41,452$.

factor, and it is likely that some mothers started to smoke again after their pregnancy; our finding may indicate that these women were less likely to participate in the Maternal Follow-up.

We have presented adjusted relative odds ratios with full awareness that by adjusting for potential confounders one also removes some selection bias when the covariates are also associated with selection, which was the case here. Adjusting for a sufficient set of measured covariates that influence selection could appropriately close the open collider path that would otherwise induce a spurious association between the exposure and the outcome (24, 31). In our chosen examples, we included a few important covariates in the regression model, and only minor selection bias was present. Regression adjustment is convenient and easy to implement. Additionally applying the IPW technique did not reduce the bias estimates notably. This again indicates that IPW may just slightly add to the regression model in terms of addressing possible direct influence of the exposure on the selection that cannot be removed by adjusting for other covariates (24). If it requires a large number of covariates to predict selection, however, the regression model becomes ineffective having to include all of these independent variables in the outcome regression, and using IPW may then be an advantage (24).

The principal strengths of this study were the large sample size and the almost complete information on covariates collected at baseline in the baseline cohort. Further, disease ascertainment was register-based and nearly complete for the baseline cohort, which allowed us to estimate the effect of nonparticipation related to both exposures and outcomes (6).

A limitation was that some of the outcomes of interest were rare, leading to uncertainty in bias estimates, and we cannot rule out the possibility of some selection bias. We chose a limited set of measured covariates to predict participation, and clearly, levels of many of these factors may vary over time. However, looking at (for instance) parity, childbirth during follow-up did not seem to be associated with participation, and our selected baseline covariates appeared to be sufficient to predict participation. We recognize that time-varying factors' status at the time of the Maternal Follow-up would likely be more related to Maternal Follow-up participation than only using the status at baseline. However, we did not have such information on, for instance, social status for the full cohort—only among those who participated in the Maternal Follow-up study and provided this information.

Further, we expect that any uncontrolled confounding might have affected the estimates in the same direction in the full cohort and the Maternal Follow-up cohort, allowing us to distinguish the bias due to selection effects. The associations investigated involve potentially fatal outcomes (e.g., breast cancer or stroke), but only 449 of the baseline cohort members were not eligible for the Maternal Follow-up study due to death (0.51%); thus, potential influence from survival bias was probably minimal. Notably, we studied 4 exposure-outcome associations and found no evidence of strong selection bias. While this is generally reassuring, we cannot exclude the possibility that for other associations, selection bias may differ substantially from the −14 to 5% range found in our analysis. Future studies using data from the DNBC Maternal Follow-up should always reflect this possibility. Further, residual selection bias may be present due to factors not accounted for both when selecting covariates to control for and when performing IPW (24).

In conclusion, several exposure and outcome factors that we evaluated appeared to be associated with participation in the Maternal Follow-up within the DNBC; mothers with favorable baseline social and lifestyle factors were the most likely to adhere to long-term participation. Reassuringly, the influence of selection bias in the exposure-outcome effect estimates was limited after factors that affect participation were accounted for in the analysis, and application of IPW techniques did not decrease this bias any further. Our findings add to previous literature which suggests that despite systematic nonparticipation according to baseline characteristics in large population-based birth cohort studies, the resultant selection bias is often relatively small if these factors can be accounted for in the analysis. Our results may inform bias analyses for longitudinal studies of women's health that are prone to selective participation in follow-ups.

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Author affiliations: Odense Patient Data Explorative Network (OPEN), Department of Clinical Research, University of Southern Denmark and Odense University Hospital, Odense, Denmark (Mette Bliddal); Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, Los Angeles, California (Zeyan Liew); Research Unit of Clinical Pharmacology and Pharmacy, Department of Public Health, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark (Anton Pottegård); Research Unit of Gynecology and Obstetrics, Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark (Helene Kirkegaard, Ellen A. Nohr); and Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark (Jørn Olsen).

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