Examining non-participation in the Maternal Follow-up within the Danish National Birth Cohort

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**Background**

The overall aim of birth cohorts is to follow the participants throughout their life course ideally from conception till death in order to estimate effects in early life exposure on health and disease in later life.

The Danish National Birth Cohort (DNBC) is one of the largest Birth Cohort in the world with initial participation of more than 100,000 women and pregnancies (See [www.dnbc.dk](http://www.dnbc.dk)) (1). Qua individual linkage to the extensive set of Danish registers, estimation of associations between various behavioural, constitutional, and demographic exposure variables and later diseases in midlife are possible in the participating mothers. From the start of the DNBC, repetitive prospective follow-ups were planned and as up until now, several follow-ups focusing on the children have been conducted since the inclusion. Most recently, a maternal follow-up has been conducted in this cohort for the first time.

In order to advocate for high compliance in future follow-ups, women who signed up for participation in the DNBC were asked to join only if they intended to partake in future questionnaires. However, with time passing and changes in life may affect social and health conditions as well as life style, the incentives to participate may diminish. Such changes in conditions may also correlate with outcomes under study and, thus, selection bias may occur (1). Regrettably, non-participation and loss to follow-up in these on-going lifelong cohorts is inevitable and this may lead to bias in estimates if participation in the follow-up is associated with both the exposure and the outcome investigated and adequate adjustments are not included in the analysis (2). Even if participation is not associated with either, bias in estimates may occur (3).

Previously, loss to follow-up in the DNBC in regard to a seven-year follow-up on five exposure-child outcome associations has been examined concluding that bias in effect estimates in all but one analysis were small (4). Since then, time has passed and non-participation in a maternal follow-up from 2013-14 may be both different and larger than at the 7-year follow-up. Focusing on the mothers may include other incentives to participate than in previous questionnaires in the DNBC focusing on the children.

In this current study, we aim to describe selection on maternal characteristics in the Maternal Follow-up within the DNBC. Further, we estimate potential selection bias due to non-participation by estimating the differences in association measures for four maternal exposure-outcome pairs for illustration. Finally, we apply inverse probability weighting (IPW) to illustrate how adjustment for selection bias could be handled.

Non-participation is expected to be systematic and result in difference in prevalence of disease in non-participating and participating women. However, the relative risk of exposures on outcomes is not expected to differ substantially in the two groups. We expect the use of IPW to reduce selection bias due to non-participation.

**Material and method**

This study will use baseline data from the DNBC. From 1996-2002, 100,418 pregnant women in Denmark were recruited to the cohort, and they represent approximately 30% of the women pregnant in that time period and 60% of those invited (5). Thorough information on the DNBC can be found at [www.dnbc.dk](http://www.dnbc.dk). In brief, the overall aim of the DNBC was to establish an extensive cohort with a wide range of early life exposures that may affect the risk of diseases in the offspring throughout life. Furthermore, data on demographics, life style including physical activity and dietary intake, social, mental and physical status was stated to account for systematic biases (1). The enrolled participants were asked to answer four telephone
interviews: Two interviews at gestational week 12 and 30 and two interviews postpartum at 6 and 18 months after delivery.

In 2013-2014, enrolled women were asked to fill in a web-based questionnaire focusing on mental and physical health, occupational health as well as lifestyle, reproduction and strains in motherhood. The questionnaire, referred to as the Maternal Follow-up, was completed 13.7 years after childbirth (interquartile range 12.6-14.5 years). We only use information from this follow-up to identify women who participated in the questionnaire study.

By use of the unique individual person identification number assigned to all Danish individuals (6), each woman in the cohort are already linked to the Danish National Patient Register (7), the Danish Civil Registration System (8), the National Medical Birth Registry (6), and the Danish National Database of Reimbursed Prescriptions (9). The Danish National Patient Registry contains information on all inpatient contacts from 1977 and outpatient contacts and emergency room events from 1995 in Danish hospitals (7). The diagnostic codes used in the Patient registry are classified according to the International Classification of Diseases ICD8 (1977 - 1993) and ICD10 (since 1994). Variables include date, diagnosis codes, and type of hospital admission. The linkage is updated regularly and outcome status for each cohort participant is provided allowing us to estimate associations between selected exposure variables and diagnosed outcomes. The Danish Civil Registration System enabled us to retrieve information on death and migration (8). Information from the National Medical Birth Registry informed on maternal age, parity and birth outcomes (6). Finally, data will be linked to the Danish National Database of Reimbursed Prescriptions, which holds information on prescription medication in Denmark that is provided with partial reimbursement from the Danish Health Care System since 2004 (9). Drugs are categorised according to the Anatomic Therapeutic Chemical (ATC) code, a hierarchical classification system developed by the World Health Organisation (10) and the registry includes data on the date of dispensing, the substance, brand name and quantity. No indication for the prescription is recorded.

We will study if selection by non-participation effects estimates by comparing four different exposure-outcome associations among the baseline population and the participants in the Maternal Follow-up. The four association pairs are chosen while they have been the focus of previous literature and while systematic potential selection may be due to different mechanisms. The four pair are as follows:

1. pre-pregnancy body mass index (BMI) – anxiety and depression disorders (11)
2. physical activity in pregnancy – musculo-skeletal disorders
3. smoking in pregnancy – cardiovascular disease (CVD)
4. alcohol prior to pregnancy – breast cancer (12).

Anxiety and depression disorders will be defined by a diagnosis of one or more of the following ICD10 codes: F30-39 “All affective mental disorders” or F40-48 “All nervous and stress-related disorders/disorders with physical symptoms” and/or by redeemed prescriptions of selective serotonin reuptake inhibitors (SSRIs) (N06AB) or other antidepressants (N06AX). Musculo-skeletal disorders will be identified as any ICD10 code M00-M99. CVD will be identified as any ischemic heart disease (I20-I25) or stroke (I60-I69). Breast cancers are identified by ICD10 codes C50 and D05 (Carcinoma in situ).
**Statistical method**

For distribution of background characteristics, exposures, and outcomes, we will compare the frequencies in the participants in the DNBC cohort and in the Maternal Follow-up by estimating a relative frequency. A bias estimate below 1 will indicate an under-representation in the Maternal Follow-up and equally, estimates above 1 will indicated an over-representation. In continuous variables, bias will be evaluated by the difference in means.

We will use logistic regression analyses with 95% confidence intervals (95% CI) to estimate the odds ratios (OR) between each of the exposure-outcome pairs in the DNBC participants and in the Maternal Follow-up mothers separately. We apply multiple logistic regression analysis to adjust for age, parity, marital status and other potential confounders. To evaluate the magnitude and direction of selection bias, we will estimate the ratio of the ORs for each of the exposure-outcome pairs.

To adjust for potential selection bias due to non-participation in the Maternal Follow-up, we will use IPW (13) to take into account the probability for a woman to participate in the Maternal Follow-up based on her baseline information. The less likely a women is to be participating in the Maternal Follow-up due to her baseline characteristics, the higher weighting score she will be attributed, thus she will not only represent herself but also others like her not participating in the Maternal Follow-up (13).

**Ethics**

Participants in the DNBC initially gave written consent to participate in the longitudinal collection of data and allowed use of their data in research concerning maternal and child health. The Maternal Follow-up collection of data was in accordance with Danish research ethics and involved no intervention or invasive procedures. We will apply for permission to use data by the Danish Data Protection Agency and the DNBC management group.

**Publication**

The results will be sought published in an international peer-reviewed journal and simultaneously, presented at the DNBC webpage.

**Collaborator and co-authors**

PhD student Mette Bliddal will be responsible for the study. The study will be conducted by Mette Bliddal in close collaboration with professor Jørn Olsen (AU), post doc Anton Pottegård (SDU), post doc Helene Kirkegaard (SDU), post doc Zeyan Liew (UCLA) and professor Ellen Nøhr (SDU).

**Economy**

The study is part of Mette Bliddal’s PhD thesis on Obesity-related disease after pregnancy and birth. A follow-up study of 88,000 mothers in the Danish National Birth Cohort (DNBC ref. no 2013-01). Financial support has been granted by the University of Southern Denmark, Odense University Hospital, Department of Gynaecology and Obstetrics, Odense University Hospital, and the Danish Midwife Association. Support for data extraction has been granted by Aase og Einar Danielsens Fond.
Implications
This study will estimate bias from non-participation in a large on-going birth cohort. This knowledge will be valuable for future research in the Maternal Follow-up when evaluating the external validity of findings based on the maternal follow-up in the DNBC.
References


