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Reproducibility of Reported *In utero* Exposure to Tobacco Smoke

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Abstract

PURPOSE—In studies of the fetal origins of disease and life course epidemiology, measures of fetal exposure may be based on information reported by the adults who were exposed *in utero*. In particular, the full spectrum of consequences of *in utero* exposure to maternal tobacco smoking is now an area of active investigation, and the ability to report such exposure reproducibly is of interest. We evaluated the reproducibility of *in utero* exposure to tobacco smoke, reported by the adult daughter during consecutive pregnancies.

METHODS—This study was based on 11,257 women who enrolled for more than one pregnancy in the Norwegian Mother and Child Cohort Study (MoBa). Participants completed a questionnaire around 17 weeks of gestation, which asked about their *in utero* exposure to tobacco smoke. Kappa statistics were calculated. Determinants of agreement were evaluated using logistic regression.

RESULTS—Weighted Kappa for *in utero* exposure for the first and second reports was 0.80. Determinants of agreement were higher education (better) and longer time between reports (worse).

CONCLUSIONS—Information on *in utero* exposure to maternal tobacco smoking provided by adult women was highly reproducible in this population.

Keywords

tobacco smoking; prenatal exposure; reproducibility

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CONFLICT OF INTEREST: None declared

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INTRODUCTION

About 10–30% of women in western countries smoke during pregnancy (1,2). The short-term risks of maternal smoking to offspring, such as being delivered preterm or small-for-gestational-age, have been well-characterized (3,4). Longer-term consequences of such *in utero* exposure, however, are still under investigation. For example, such exposure may increase risk of early menarche, infertility, premature menopause, obesity, type 2 diabetes, and increased serum cholesterol (5–10). Investigations of longer-term consequences often depend on adults' reports of their exposure *in utero* (11). Information about the reproducibility of adults' reports will enhance the interpretation of data on health effects. In a large pregnancy cohort in Norway, women could enroll for more than one pregnancy, thus providing data on their *in utero* tobacco exposure more than once. We used these data to study the reproducibility of reporting.

MATERIALS AND METHODS

The Norwegian Mother and Child Cohort Study (MoBa)

This study is based on the Norwegian Mother and Child Cohort Study (MoBa), conducted by the Norwegian Institute of Public Health (12). Enrollment was from 1999 to 2008 and included about 107,000 pregnancies from 90,000 women. During enrollment, the proportion of pregnant women in Norway invited to participate gradually increased, to about 71%. This proportion never reached 100% because two large hospitals in Oslo did not enroll subjects, and because women were recruited only through hospitals and maternity units with at least 100 deliveries per year. The response rate was about 44% (13). Pregnant women were recruited with a mailed invitation before a routine ultrasound examination offered to all pregnant women in Norway at 17–18 weeks of gestation (www.fhi.no/morogbarn). Other than noted above there were no exclusion criteria (12). The Regional Committee for Medical Research and the Norwegian Data Inspectorate approved the study and informed consent was obtained from each participant. The present study is based on participants recruited from 1999 to 2007 (MoBa database version 4.201). Participants were asked to complete a questionnaire about demographic characteristics, reproductive health, disease and medication history, lifestyle, and socioeconomic status.

In utero exposure to tobacco smoking

Women were asked: “Did your mother smoke when she was pregnant with you?” Those who answered “yes” to this question were classified as having been exposed to tobacco smoking while *in utero*; those who responded “no” were considered unexposed. Women who answered “don’t know” or who did not respond to this question were classified as unknown exposure.

Among the participants born in 1967 or later (when the Medical Birth Registry of Norway was created [$n=11,082$]), birth weight was available for 90.8%, and was used as a surrogate to validate their reported *in utero* exposure to tobacco smoke.

Data analysis

Among women with more than one pregnancy in MoBa, 11,257 completed the first study questionnaire twice. To evaluate the pairwise agreement between the two reports, we calculated the kappa statistic (κ), the fraction of the observed agreement not due to chance relative to the maximum non-chance agreement (14). Weighted kappa (κ_w) (15) was also calculated for the 3×3 tables using the reported *in utero* exposure to maternal smoking as an ordinal variable as suggested by Maclure & Willett (16) with the following categories:

yes, unknown and no. In this strategy, non-contiguous categories are considered to have worse disagreement than contiguous categories. Standard linear weights were used (17).

We also examined determinants of agreement between responses among women who had completed the questionnaire twice. For this purpose we used the logistic model of agreement where the outcome variable is equal one when the two reports agree (cells in the diagonal of 2×2 or 3×3 tables) and zero if not (18). In a separate analysis, we used logistic regression to assess the determinants of the “unknown” status for *in utero* exposure to maternal smoking. The outcome variable was coded as one if the first or second report had an answer of “unknown” status for *in utero* exposure, and zero otherwise.

RESULTS

The mean age of the study participants was 28.1 years (standard deviation, 3.9) during the reporting period. Women who reported being exposed to tobacco smoke *in utero* were lighter at birth compared to those not exposed; this was observed among all births and among those born after 37 completed weeks of gestation. Among women whose *in utero* exposure was unknown, the mean birth weight were intermediate for all births and term births (Table 1). The adjusted birth weight difference (non exposed-exposed, adjusted for gestational age, age and parity of the participant’s mother) was 178 g for all births and 181 g for term births (data not shown). The overall weighted Kappa for the 3×3 table (yes, unknown, no) was 0.80 for the first and second reports of *in utero* exposure to maternal smoking (Table 1). When the analysis was restricted to those whose responses were either yes or no at both times (2×2 table), the kappa statistic was 0.93.

Results from the logistic model based on 2×2 and 3×3 tables are presented in Table 2. More educated participants (College and > College) were significantly more likely to report the same exposure at both times as compared to those with less than High School. A longer time interval between reports (4 – 8 years) was significantly associated with poorer agreement. An interval of 3 years between reports was also a significant predictor of poorer recall in the 3×3 analysis.

In the analysis of predictors of “unknown” *in utero* exposure status (data not shown), we observed that women with higher education were less likely to report “unknown” status of exposure (College, OR = 0.60, 95%CI: 0.48 – 0.74; > College, OR = 0.62, 95%CI: 0.49 – 0.78) as compared with those with less than a high school education. Those with longer time between reports were more likely to report “unknown” status of exposure (4 – 8 years, OR = 1.21, 95%CI: 1.01 – 1.44). Woman’s age and current smoking status were not significantly associated with “unknown” *in utero* exposure status.

DISCUSSION

In the present study the reproducibility of daughters’ reports on *in utero* smoking exposure was much higher than expected by chance, and consistent with a previous study in the U.S. (19). An offspring’s report about their mother’s smoking status during pregnancy has been previously shown to be reasonably valid (Table 3) (11,20,21). In the present study the reproducibility was affected by whether subjects with unknown exposure to *in utero* tobacco smoking were included in the calculation of κ . When the effect of this inclusion is considered in interpretation of Table 3, the data suggest that the kappa for the reproducibility of reporting this exposure is higher than for the validity. For example, when we excluded the unknown category from the calculations, as was done in the validity studies, we observed a higher coefficient ($\kappa=0.93$).

In one of the studies of agreement between reports from mothers (about her own smoking during pregnancy) and daughters (about her *in utero* exposure), the concordance was lower among older daughters (11). In the present study, participants' age was not a significant predictor of agreement and weighted kappas were comparable across categories of age (Table 2), similar to findings in two previous studies (19,21). Our results showed that college education (and > college) was consistently associated with better agreement, which was not observed in a previous study (21). However, in the study by Sandler and Shore (21) only 28 % had more than high school education, while in our study the corresponding percentage was much higher (69.2 %). Although our study was limited to women, similar agreement was observed by gender in the two previous studies that also included males (19,21). As expected, longer time between reports was associated with poorer reproducibility in this study. However, kappas remained high across categories of time between reports even when the unknown category was included in the calculations. Consistent with this result, we observed that longer time between reports was a significant predictor of unknown status of exposure.

Our study had several limitations. Women who participated in MoBa were not a representative sample of all pregnant women from Norway during the period of interest, and previous analyses suggest that prevalence of exposures and outcomes are biased due to self-selection (e.g. smokers were under-represented and multivitamin users over-represented) (13). An underestimation of the prevalence of *in utero* exposure to maternal smoking was expected, because women who reported being smokers were more likely to report *in utero* exposure to maternal smoking (data not shown). In Norway, during the period when the study participants were born (between 1960 and 1989), the prevalence of smoking among reproductive age females (16 to 55 years) ranged from 26% to 52%. The prevalence of daily smokers among women ages 25 to 34 years was 46% in 1974 and 41% in 1977 (22,23). In the present study, 38% of the participants were born between 1974 and 1977; and the prevalence of reported *in utero* smoking was 23% for those born in 1974 and 26% for those born in 1977. It is also likely that women who participated in MoBa for more than one pregnancy may have been especially health conscious, and therefore may have been better-than-average reporters of early life exposure.

Another limitation is that we did not have data on the number of cigarettes smoked per day by the subject's mother. Previous studies that evaluated the reproducibility or validity of amount of cigarettes found moderate to poor agreement (19,21). In another study, however, agreement was better when the amount of cigarettes smoked by the mother was greater (15 + cig/day) (11).

Although we were not able to evaluate the validity of *in utero* smoking directly, we were able to show that this exposure can be regarded as valid based on the birth weights of a subset of the MoBa participants. Maternal smoking during pregnancy has been associated with an average reduction of 149 g in birth weight (24), and in the present study we observed a 181 g average decrement.

In summary, reports of *in utero* exposure to maternal tobacco smoking have consistently been shown to be highly reproducible, and the degree of reproducibility depends on whether subjects with unknown exposure were included in the analysis.

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List of abbreviations

CI	confidence interval
κ	Kappa statistic
κ_w	Weighted Kappa
MoBa	The Norwegian Mother and Child Cohort Study

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Table 1

Birth weight of the subjects according to self-reported *in utero* exposure to tobacco smoke, and agreement for self-reported *in utero* exposure to tobacco smoke on the first and second completions of the first MoBa questionnaire

	First completion			
	In utero exposure			
	Yes	Unknown	No	Total
Birth weight ^a				
Mean	3,340.7	3,419.0	3,546.1	
SD	491.3	504.6	487.7	
N	2,365	1,080	6,622	
Second completion				
In utero exposure				
Yes	2,236	276	155	2,667
Unknown	229	635	427	1,291
No	110	339	6,850	7,299
Total	2,575	1,250	7,432	11,257
Weighted Kappa ^b	0.80			
Kappa ^c	0.93			

^aBased on a subset of the participants who were born on 1967 or later and had available birth weight in the Norwegian Medical Birth Registry (n = 10,067). Among those born after 37 completed weeks of gestation (n = 9,362), the mean birth weights (SD) were: yes, 3,375.0 (450.8); unknown, 3,461.0 (461.7); no, 3,570.3 (458.8)

^bWeighted Kappa, based on 3 by 3 table that includes all possible answers: yes, unknown and no. Linear weights were estimated as: $1 - |i - j| / (k - 1)$, where i and j index the rows and columns of the ratings by the two reports and k is the maximum number of possible ratings

^cBased on 2 by 2 table that is restricted to answers of either yes or no

Table 2

Characteristics of the women when they first completed the first questionnaire for the Norwegian Mother and Child Cohort Study (MoBa), kappa statistics and adjusted Odds Ratios (OR) of agreement between two reports of *in utero* exposure to tobacco smoke

	N	%	Agreement 2 × 2 ^a			Agreement 3 × 3 ^c		
			κ	OR ^b	95% CI	κ _w	OR ^b	95% CI
All participants	11,257							
Age (years)								
<25	1,954	17.4	0.92	1.00		0.78	1.00	
25 – 29	5,324	47.3	0.93	0.96	0.68, 1.36	0.80	1.02	0.88, 1.20
30 – 34	3,384	30.1	0.93	0.99	0.67, 1.45	0.81	1.09	0.91, 1.29
35 +	595	5.3	0.93	1.13	0.58, 2.20	0.80	0.97	0.74, 1.27
Education								
< High School	593	5.3	0.89	1.00		0.77	1.00	
High School	2,868	25.5	0.92	1.41	0.88, 2.26	0.78	1.15	0.91, 1.45
Some College	5,124	45.5	0.93	2.00	1.23, 3.23	0.81	1.55	1.23, 1.97
College +	2,672	23.7	0.93	2.35	1.37, 4.03	0.80	1.61	1.25, 2.08
Current smoking status								
Never	8,654	76.9	0.92	1.00		0.80	1.00	
Former	1,816	16.1	0.92	0.79	0.58, 1.09	0.81	1.00	0.86, 1.16
Sometimes	175	1.6	0.90	0.66	0.29, 1.52	0.77	0.75	0.51, 1.12
Daily	575	5.1	0.92	0.87	0.52, 1.45	0.81	1.00	0.78, 1.27
Missing	37	0.3	0.84	0.86	0.12, 6.39	0.68	1.04	0.40, 2.69
Time between reports (years)								
< 2	3,167	28.1	0.93	1.00		0.83	1.00	
2	4,660	41.4	0.93	0.92	0.68, 1.26	0.81	0.88	0.77, 1.01
3	2,176	19.3	0.92	0.84	0.58, 1.21	0.79	0.78	0.66, 0.91
4 – 8	1,179	10.5	0.90	0.65	0.43, 0.98	0.75	0.67	0.55, 0.81
Missing	75	0.7	0.89	0.56	0.17, 1.85	0.74	0.64	0.35, 1.15

κ, kappa; κ_w, weighted kappa

^aBased on 9,351 women who completed the questionnaire twice and answered either yes or no on both occasions

^b Odds Ratios are adjusted for all variables listed in the table. The outcome variable is equal one if the two reports agree and zero if not

^c Based on 11,257 women who completed the questionnaire twice regardless of their answers at both occasions

Table 3
Summary of reports on the reproducibility or validity of *in utero* exposure to tobacco smoke

Author	Year	Place	n	Index Reporter (Adults)	Comparison Reporter	κ	Included Unknowns in Calculation
Validity							
Sandler et al. (21)	1986	U.S.	355	Daughters/Sons	Mothers	0.74	no
Sanderson et al. (20)	1998	U.S.	416	Daughters	Mothers	~0.76*	no
Simard et al. (11)	2008	U.S.	32,260	Daughters	Mothers	0.80	no
Reproducibility							
Coultais et al. (19)	1989	U.S.	149	Daughters/Sons	Same subject after 4–6 months	0.73	yes
Present study	201?	Norway	11,257	Daughters	Same subject after 2.4 years (median)	0.80	yes

* Kappa was 0.75 among cases and 0.77 among controls