Published in final edited form as:

Pediatr Allergy Immunol. 2011 August ; 22(5): 528–536. doi:10.1111/j.1399-3038.2010.01135.x.

Oral contraceptive pill use before pregnancy and respiratory outcomes in early childhood

Dana B. Hancock¹, Siri E. Håberg³, Kari Furu^{3,4}, Kristina W. Whitworth¹, Per Nafstad^{3,5}, Wenche Nystad³, and Stephanie J. London^{1,2}

¹Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC, USA

²Laboratory of Respiratory Biology, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC, USA

³Division of Epidemiology, Norwegian Institute of Public Health, Oslo, Norway

⁴Department of Pharmacy, University of Tromsø, Tromsø, Norway

⁵Department of General Practice and Community Medicine, Medical Faculty, University of Oslo, Oslo, Norway

Abstract

Oral contraceptive pills (OCPs) are often used soon before, and sometimes during, pregnancy. A few studies have suggested that OCP use before pregnancy may increase risks for childhood respiratory outcomes, but data are inconclusive. No studies have analyzed the two types of OCPs, estrogen-progestin combined pills and progestin-only pills, separately. In the Norwegian Mother and Child Cohort Study (MoBa), we prospectively examined associations of OCP use before pregnancy, by type, with lower respiratory tract infections in 60,225 children followed to 6 months old, lower respiratory tract infections and wheezing in 42,520 children followed to 18 months old, and asthma in 24,472 children followed to 36 months old. We used logistic regression to estimate odds ratios and their 95% confidence intervals crudely and with adjustment for a wide range of potential confounders. Combined pills were used much more commonly than progestin-only pills. Taking combined pills before pregnancy was not associated with lower respiratory tract infections, wheezing, or asthma. Progestin-only pill use in the year before pregnancy had a slight positive association with wheezing at 6–8 months old [adjusted odds ratio (95% confidence interval)=1.19 (1.05–1.34)]. Our finding that combined pill use before pregnancy was not related to respiratory outcomes should provide reassurance to the vast majority of mothers using OCPs before becoming pregnant. The small association with progestin-only pill use and early respiratory outcomes may reflect uncontrolled confounding or other bias but does suggest that these two types of pills should be examined separately in future analyses of respiratory and other childhood outcomes.

Introduction

Oral contraceptive pills (OCPs) are widely used among women of reproductive age (1). Intended pregnancies often occur shortly after discontinuing OCPs, and almost half of unintended pregnancies occur when women are using contraceptives (2). Some biological

effects of OCPs linger in women months to years after discontinuation, such as effects on hormone levels (3–5). Given that progesterone helps to orchestrate the shifting immunological environment during pregnancy (6, 7), it is conceivable that use of progestin-containing OCPs before pregnancy could disrupt the immunological balance and influence fetal respiratory development. Wjst and Dold first postulated that the mother's OCP use may increase the risk of asthma in the child (8). Since then, a few studies have supported the positive association between maternal OCP use before pregnancy and risk for asthma and other respiratory outcomes in children, but data are inconclusive (9–13).

OCPs include estrogen-progestin pills (referred to as combined pills) and progestin-only pills (referred to as mini-pills). The less frequently used mini-pills are recommended to breastfeeding mothers and to women with contraindications or clinical side effects from combined pills (14). Despite their differences, combined pills and mini-pills have not been examined separately in previous studies of OCP use before pregnancy and respiratory outcomes in children. We examined whether OCP use before pregnancy is associated with an increased risk of respiratory outcomes (lower respiratory tract infections, wheezing, and asthma) in 24,472 to 60,225 children participating in the prospective Norwegian Mother and Child Cohort Study (MoBa) – the largest study of maternal OCP use and childhood respiratory outcomes to date.

Subjects and Methods

Study Design

MoBa is a pregnancy cohort of over 100,000 pregnancies enrolled from 1999 to 2009, and it is conducted by the Norwegian Institute of Public Health (15). During the second trimester of pregnancy, pregnant women were recruited through a postal invitation in connection with a routine ultrasound examination offered to all pregnant women in Norway. Pregnant women in urban and rural sectors from all geographical areas of Norway were invited to participate, and approximately 44% of the women agreed to participate (15). The current study is based on version 4 of the quality-assured data files released for research in February 2009. The study was approved by the Regional Committee for Medical Research, the Norwegian Data Inspectorate, and Institutional Review Board of the National Institute of Environmental Health Sciences, USA. Informed consent was obtained from each participant.

The pregnant women were asked to complete an enrollment questionnaire (around week 15 of pregnancy) and a series of five follow-up questionnaires (around weeks 22 and 30 of pregnancy and 6, 18, and 36 months after birth). Questionnaires included items on maternal and child health and nutrition, child development, socio-economic status, lifestyle habits, and environmental exposures. The questionnaires are accessible at the MoBa website (16). Additional information on maternal and neonatal characteristics was obtained from birth records in the Medical Birth Registry of Norway, which were completed by hospital health professionals (17).

We analyzed data from singleton children born between November 1999 and May 2007 with follow-up data available through February 2009. The analyses included 60,225 children born to 54,256 mothers with 6-month follow-up questionnaire data. Of these, 42,520 children had 18-month follow-up questionnaire data, and 24,472 children had 36-month follow-up questionnaire data. We also conducted analyses considering only mothers with one child in MoBa and found similar patterns of association (data not shown).

Oral contraceptive pill use before pregnancy

In the enrollment questionnaire around week 15 of pregnancy, women were asked “Have you/your partner at any time during the last year used the following methods to avoid

becoming pregnant?” The list of contraceptives included combined pills and mini-pills separately. Women were not asked to report the specific OCP brand. We classified women into the following mutually exclusive categories for reported OCP use in the year before pregnancy: both combined pills and mini-pills, combined pills only, mini-pills only, or no OCPs. Because only a small proportion of women reported use of both combined pills and mini-pills in the year before getting pregnant (1.0%), we do not present effect estimates for this category.

A subsequent question asked women “were you taking the pill/mini-pill during the last four months before this pregnancy?” Women who reported using combined pills only (or mini-pills only) in the year before pregnancy and responded “yes” to this question were classified as using combined pills only (or mini-pills only) in the four months before pregnancy. We could not classify the OCP use of women who reported using both combined pills and mini-pills in the year before pregnancy and responded “yes” to the question regarding the four months before pregnancy. Women who responded “no” to this question were classified as using no OCPs in the four months before pregnancy.

Childhood respiratory outcomes

Children were classified as having lower respiratory tract infections (including respiratory syncytial virus, bronchiolitis, bronchitis, or pneumonia) based on maternal report on the 6-month and 18-month follow-up questionnaires. Mothers were asked about lower respiratory tract infection episodes in 6-month intervals (<6, 6–11, and 12–18 months old). In the 18-month follow-up questionnaire, but not in the earlier questionnaire, mothers were asked about wheezing in their child (worded as chest congestion/tightness or whistling/wheezing in the chest) in 3-month intervals (6–8, 9–11, 12–14, and 15–18 months old). Mothers were queried about the child’s asthma on the 36-month follow-up questionnaire.

Covariates

Maternal and child characteristics were selected as potential confounders based on their inclusion in previous studies of maternal OCP use with childhood respiratory outcomes (9–12, 18) or studies of childhood respiratory outcomes in MoBa (19, 20). The following maternal characteristics from the enrollment questionnaire were used: history of asthma and atopy including hay fever, atopic dermatitis, pollen allergy, animal hair allergy, or other allergy (neither asthma nor atopy, atopy only, asthma only, or both asthma and atopy), age (<25, 25–30, or >30 years old), smoking during the first trimester of pregnancy (yes/no), folate supplementation during the first trimester of pregnancy (yes/no), number of previous live births (0, 1, or >1), pre-pregnancy body mass index (<18.5, 18.5–24.9, 25.0–29.9, or >29.9), level of education (<13, 13–16, or >16 years completed or ongoing), and income (<150,000, 150,000–299,000, or >299,000 Nkr). Nearly 10% of mothers had an ongoing education, so income and educational level were believed to measure distinct socio-economic characteristics. Child characteristics of sex, gestational age (<37, 37–38, 39–41, or >41 weeks), parental smoking in the first 3 months after birth (yes/no), breastfeeding at the age of 6 months (yes/no), season of birth (March-May, June-August, September-November, or December-February), and year of birth were obtained from the 6-month follow-up questionnaire or the Medical Birth Registry of Norway. Some covariates occurred during pregnancy or after birth, and these were included to reflect the correlated lifestyle factors and exposures occurring before OCP use that potentially confound the association between maternal OCP use and childhood respiratory outcomes. Covariates with two categories were coded as dichotomous variables, and covariates with more than two categories were coded with dummy variables.

Statistical analyses

Logistic regression models were used to examine associations of OCP use (by type) in the year before pregnancy with lower respiratory tract infections (<6, 6–11, or 12–18 months old), wheezing (6–8, 9–11, 12–14, or 15–18 months old), or asthma (<36 months old). Associations were also examined for OCP use in the four months before pregnancy. All models were analyzed using SAS version 9.1 (SAS Institute, Inc., Cary, NC) to generate odds ratios (ORs) and 95% confidence intervals (CIs). Results from crude and adjusted models are presented.

To evaluate confounding, we applied an iterative change-in-estimate procedure (21, 22) to the model examining the association of OCP use in the year before pregnancy with lower respiratory tract infections at <6 months old. The mother's number of previous live births was the only covariate to exhibit a substantial confounding effect with change-in-effect estimates ranging between 23.1% and 29.1% across iterations. The remaining covariates each resulted in change-in-effect estimates <3.6%: maternal history of asthma and atopy, maternal age, smoking during first trimester of pregnancy, folate supplementation during first trimester of pregnancy, pre-pregnancy body mass index, maternal education, maternal income, child's sex, child's gestational age, parental smoking in the first 3 months after birth, breastfeeding at 6 months, season of birth, and year of birth.

We tested for interaction between number of previous live births and OCP use in the year before pregnancy using lower respiratory tract infections at <6 months old as the outcome, and we found no evidence for an interaction between number of previous live births and combined pill use ($P=0.22$) or between number of previous live births and mini-pill use ($P=0.36$).

Results

The demographic and clinical characteristics of the 60,225 children followed to 6 months old and their mothers are presented in Table 1. Mothers who used combined pills [$N=19,786$ (33%)] were younger and more often nulliparous and not breastfeeding 6 months after birth compared with mothers who used mini-pills [$N=3,286$ (5%)]. Patterns of OCP use were similar for the other maternal and child characteristics.

In the 60,225 children followed to 6 months old, crude ORs suggested an inverse association of combined pill use before pregnancy and a positive association of mini-pill use before pregnancy with lower respiratory tract infections at <6 months old (Table 2). However, these associations were reduced after adjustment for covariates [the adjusted OR for combined pill use in the year before pregnancy was 1.03 (95% CI: 0.94–1.13, $P=0.51$), and the adjusted OR for mini-pill use in the year before pregnancy was 1.10 (95% CI: 0.95–1.28, $P=0.21$)]. Results were similar when considering OCP use in the four months before pregnancy (Table 2). In the 42,520 children followed to 18 months old, there were no associations between combined pill use and lower respiratory tract infections or between mini-pill use and lower respiratory tract infections after adjustment (Table 2).

In the 42,520 children followed to 18 months old, crude ORs suggested an inverse association of combined pill use before pregnancy and a positive association of mini-pill use before pregnancy with wheezing at 6–8 months and 9–11 months (Table 3). After adjustment, combined pill use in the year before pregnancy was not associated with wheezing [OR (95% CI)=0.97 (0.90–1.04) for wheezing at 6–8 months], but mini-pill use in the year before pregnancy had a small positive association with wheezing [OR (95% CI)=1.19 (1.05–1.34) for wheezing at 6–8 months]. Findings were generally similar when considering the four months before pregnancy. Associations of mini-pill use before

pregnancy with wheezing diminished at older ages. There were no associations between use of OCPs (combined pills or mini-pills) before pregnancy and asthma at <36 months (Table 4).

Discussion

In our large, prospective study, use of combined pills in the year before pregnancy was not associated with early childhood respiratory outcomes (lower respiratory tract infections, wheezing, or asthma). We found a small positive association between use of mini-pills in the year before pregnancy and increased risk for wheezing in the child's first year of life, but this may be due to uncontrolled confounding. Of note, mini-pills represent less than one-sixth of OCP use in this cohort.

Three previous studies have supported the hypothesis that OCP use before pregnancy may increase risks for respiratory outcomes in children (10–12). Brooks et al. found that OCP use before pregnancy was associated with an increased risk of childhood asthma/wheezing [adjusted OR (95% CI)=1.81 (1.25–2.61)] and coughing [adjusted OR (95% CI)=2.72 (1.41–5.24)] (10). Osman et al. also found a positive association between OCP use in the 6 months before pregnancy with asthma in children [adjusted OR (95% CI)=1.16 (1.06–1.27)], but the association was restricted to children with uncharacteristic features of asthma (12). Keski-Nisula et al. found no association of OCP use in the year before pregnancy with childhood asthma, but they reported a positive association with allergic rhinitis when considering OCPs with a less androgenic or antiandrogenic progestin [adjusted OR (95% CI)=1.67 (1.07–2.59)] (11). Conversely, Frye et al. found no association between OCP use before pregnancy and childhood asthma (9), and Xu et al. found no association between maternal hormone concentrations during early pregnancy (progesterone, total estradiol, and free estradiol) and childhood asthma (13). In our study, examination of OCP use before pregnancy without considering combined pills and mini-pills separately indicated no increased risks for respiratory outcomes in early childhood (data not shown).

The progestin contained in different mini-pill brands have varying androgenic properties (anti-androgenic, less androgenic, or androgenic), and the slight positive association of mini-pill use with early wheezing may reflect an effect related to mini-pills with specific androgenic properties (or lack thereof), given the findings of Keski-Nisula et al. (11). During our study period, four mini-pill brands were dispensed in Norway according to the Norwegian Drug Wholesalers Database (23): norethindrone, lynestrenol, levonorgestrel, and desogestrel. The androgenic mini-pills norethindrone, lynestrenol, and levonorgestrel dominated the market until 2004, when the less androgenic desogestrel was introduced to the market and became the leading mini-pill representing >80% of mini-pills dispensed as of 2007 (23, 24). We were not able to examine associations of mini-pills with specific androgenic properties, since the mothers were not asked to report their specific OCP brand.

Some hormonal influences of OCPs diminish within two months of discontinuing use (25), but effects on other hormone levels persist months to years after discontinuation (3–5). Biological mechanisms to explain recent OCP use lingering into pregnancy and influencing fetal respiratory development remain speculative. Brooks et al. hypothesized two alternative mechanisms involving the mother's immunological shift from a T helper 1 (T_H1) to a T_H2 environment during pregnancy (10). They proposed either a prolonged T_H2 effect (increased T_H2 activity present from the onset of pregnancy) or a prolonged endocrine effect (increased progesterone or estrogen levels resulting later in increased T_H2 activity) (10). However, a prolonged endocrine effect seems less likely given that fetuses are naturally exposed to much higher levels of progesterone than the levels used in OCPs.

In epidemiologic studies, very modest associations, such as the association we observed among the relatively small proportion of women using mini-pills, are subject to bias that may occur from selection or confounding. Comparison of crude and adjusted models gave evidence for confounding – apparent protective effects of combined pill use on several outcomes were eliminated with adjustment. Likewise, positive association with mini-pill use and various outcomes were attenuated with adjustment and generally became statistically nonsignificant. Although a few associations with mini-pill use remained statistically significant after adjustment, in this setting, we cannot rule out residual confounding. None of the associations were statistically significant after adjustment, when considering Bonferroni correction for multiple testing.

The reliance on maternal report of OCP use is a limitation of our study. The report of OCP use in the four months before pregnancy may be more accurate than the report of OCP use in the year before pregnancy due to a shorter recall period. However, our findings are not subject to bias from differential recall of OCP use according to the child's respiratory illness, because the mother's oral contraceptive pill use was assessed prospectively during pregnancy. With regard to the outcomes, mothers were asked about the presence of asthma, not asthma diagnosis. However, they were asked to list any medications the child took in the previous 12 months. Approximately 84% of reported asthma cases in our analyses were also reported to use prescribed inhaler medication. In a pilot study, we have found that maternal reports of asthma medication have high validity compared with pharmacy registry data (26). A new pharmacy registry in Norway includes all prescriptions after January 1 2004 and linkage to this resource will be available for future analyses in MoBa (26).

There were around 75,000 singleton pregnancies enrolled in MoBa resulting in births between November 1999 and May 2007. These participants had children who turned six months old by November 2007 and were thus eligible to have returned a six-month follow-up questionnaire by the end of follow-up for this analysis. Over 85% of the children had 6-month follow-up questionnaire data available for our analysis (15). Respondents to the six-month questionnaire were slightly more likely to have used combined pills in the year before pregnancy than non-respondents; 33% of those returning the six-month questionnaire used the combined pill compared with 29% of those who did not return the questionnaire ($P<0.0001$). Respondents and non-respondents did not differ in use of the mini-pill ($P=0.19$). As expected, women with more children were slightly less likely to return the six-month questionnaire; 53% of women returning the six-month questionnaire had previous live births compared to 57% of women who did not return the questionnaire ($P<0.0001$).

The main advantages of our study included the large sample size and the prospective nature of the MoBa pregnancy cohort. In addition, the proximity of the mother's OCP use was known in discrete time intervals before pregnancy (one year before pregnancy, four months before pregnancy, and the start of pregnancy), and with the extensive questionnaire data, many covariates were examined for potential confounding. Children in the MoBa study are being followed to older childhood ages, and future studies can examine whether OCPs are associated with later childhood respiratory outcomes and whether associations differ by wheezing patterns throughout childhood [e.g., transient, persistent, and late-onset as previously proposed (27, 28)].

Our findings suggest that maternal use of the much more commonly prescribed combined pill was not associated with respiratory outcomes (lower respiratory tract infections, wheezing, or asthma) in early childhood, thus providing reassurance to the vast majority of mothers who may have taken OCPs prior to conception. Although our finding of a small positive association with mini-pill use may not be causal, it does suggest that future investigations of effects of OCP use before pregnancy in relation to health outcomes in the

offspring should consider the two types of OCPs, estrogen-progestin combined pills and progestin-only mini-pills, separately.

Acknowledgments

We are grateful to the MoBa families for their study participation. We thank Ethel Sanniez and Dr. Grace Chiu for analytical assistance and Dr. Donna Baird for insightful comments on the manuscript.

Funding

This research was supported in part by the Intramural Research Program of the NIH, National Institute of Environmental Health Sciences (Z01-ES-49019). This work was also supported by contract no. ES044008 with the National Institute of Environmental Health Sciences. The Norwegian Mother and Child Cohort Study is supported by the Norwegian Ministry of Health and the National Institute of Environmental Health Sciences (National Institutes of Health, USA, grant no. N01-ES-85433), the National Institute of Neurological Disorders and Stroke (National Institutes of Health, USA, grant no. 1 U01-NS-047537), and the Norwegian Research Council/FUGE (grant no. 151918/S10).

References

1. Mosher WD, Martinez GM, Chandra A, Abma JC, Willson SJ. Use of contraception and use of family planning services in the United States: 1982–2002. *Advance data*. 2004; 10(350):1–36. [PubMed: 15633582]
2. Finer LB, Henshaw SK. Disparities in rates of unintended pregnancy in the United States, 1994 and 2001. *Perspect Sex Reprod Health*. 2006; 38(2):90–96. [PubMed: 16772190]
3. Jernstrom H, Knutsson M, Olsson H. Temporary increase of FSH levels in healthy, nulliparous, young women after cessation of low-dose oral contraceptive use. *Contraception*. 1995; 52(1):51–56. [PubMed: 8521715]
4. Moore JW, Key TJ, Wang DY, Bulbrook RD, Hayward JL, Takatani O. Blood concentrations of estradiol and sex hormone-binding globulin in relation to age at menarche in premenopausal British and Japanese women. *Breast Cancer Res Treat*. 1991; 18 Suppl 1:S47–S50. [PubMed: 1873557]
5. Barbieri RL, Gao X, Xu H, Cramer DW. Effects of previous use of oral contraceptives on early follicular phase follicle-stimulating hormone. *Fertil Steril*. 1995; 64(4):689–692. [PubMed: 7672135]
6. Piccinni MP, Giudizi MG, Biagiotti R, Beloni L, Giannarini L, Sampognaro S, et al. Progesterone favors the development of human T helper cells producing Th2-type cytokines and promotes both IL-4 production and membrane CD30 expression in established Th1 cell clones. *J Immunol*. 1995; 155(1):128–133. [PubMed: 7541410]
7. Szekeres-Bartho J, Wegmann TG. A progesterone-dependent immunomodulatory protein alters the Th1/Th2 balance. *Journal of reproductive immunology*. 1996; 31(1–2):81–95. [PubMed: 8887124]
8. Wjst M, Dold S. Is asthma an endocrine disease? *Pediatr Allergy Immunol*. 1997; 8(4):200–204. [PubMed: 9553986]
9. Frye C, Mueller JE, Niedermeier K, Wjst M, Heinrich J. Maternal oral contraceptive use and atopic diseases in the offspring. *Allergy*. 2003; 58(3):229–232. [PubMed: 12653797]
10. Brooks K, Samms-Vaughan M, Karmaus W. Are oral contraceptive use and pregnancy complications risk factors for atopic disorders among offspring? *Pediatr Allergy Immunol*. 2004; 15(6):487–496. [PubMed: 15610361]
11. Keski-Nisula L, Pekkanen J, Xu B, Putus T, Koskela P. Does the pill make a difference? Previous maternal use of contraceptive pills and allergic diseases among offspring. *Allergy*. 2006; 61(12):1467–1472. [PubMed: 17073879]
12. Osman MF, Black C, Jick S, Hannaford P. Previous maternal oral contraception and the risk among subsequent offspring of asthma diagnosis in early childhood. *Paediatr Perinat Epidemiol*. 2009; 23(6):567–573. [PubMed: 19840293]
13. Xu B, Pekkanen J, Husman T, Keski-Nisula L, Koskela P. Maternal sex hormones in early pregnancy and asthma among offspring: a case-control study. *J Allergy Clin Immunol*. 2003; 112(6):1101–1104.

14. Erkkola R, Landgren BM. Role of progestins in contraception. *Acta Obstet Gynecol Scand*. 2005; 84(3):207–216. [PubMed: 15715527]
15. Magnus P, Irgens LM, Haug K, Nystad W, Skjaerven R, Stoltenberg C. Cohort profile: the Norwegian Mother and Child Cohort Study (MoBa). *Int J Epidemiol*. 2006; 35(5):1146–1150. [PubMed: 16926217]
16. The Norwegian Institute of Public Health. MoBa Website – The Mother and Child Cohort Study: Questionnaires. Available at: http://www.fhi.no/eway/default.aspx?pid=238&trg=MainArea_5811&MainArea_5811=5903:0:15,3138:1:0:0::0:0. Retrieved June 1, 2010
17. Irgens LM. The Medical Birth Registry of Norway. Epidemiological research and surveillance throughout 30 years. *Acta Obstet Gynecol Scand*. 2000; 79(6):435–439. [PubMed: 10857866]
18. Xu B, Jarvelin MR, Pekkanen J. Prenatal factors and occurrence of rhinitis and eczema among offspring. *Allergy*. 1999; 54(8):829–836. [PubMed: 10485386]
19. Haberg SE, Stigum H, London SJ, Nystad W, Nafstad P. Maternal obesity in pregnancy and respiratory health in early childhood. *Paediatr Perinat Epidemiol*. 2009; 23(4):352–362. [PubMed: 19523082]
20. Haberg SE, London SJ, Stigum H, Nafstad P, Nystad W. Folic acid supplements in pregnancy and early childhood respiratory health. *Arch Dis Child*. 2009; 94(3):180–184. [PubMed: 19052032]
21. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. *Am J Epidemiol*. 1993; 138(11):923–936. [PubMed: 8256780]
22. Weng HY, Hsueh YH, Messam LL, Hertz-Picciotto I. Methods of covariate selection: directed acyclic graphs and the change-in-estimate procedure. *Am J Epidemiol*. 2009; 169(10):1182–1190. [PubMed: 19363102]
23. Rønning, M., editor. Drug Consumption in Norway 2003–2007. Oslo: Norwegian Institute of Public Health; 2008 March.
24. Carr BR. Uniqueness of oral contraceptive progestins. *Contraception*. 1998; 58(3 Suppl) 23S-7S quiz 67S.
25. Liukko P, Erkkola R, Bergink EW. Progestagen-dependent effect on some plasma proteins during oral contraception. *Gynecol Obstet Invest*. 1988; 25(2):118–122. [PubMed: 2967233]
26. Furu K, Karlstad O, Skurtveit S, Haberg SE, Nafstad P, London SJ, et al. High validity of mother-reported use of anti-asthmatics among children: a comparison with a population-based prescription database. *J Clin Epidemiol*. 2010 in press.
27. Henderson J, Granell R, Heron J, Sherriff A, Simpson A, Woodcock A, et al. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax*. 2008; 63(11):974–980. [PubMed: 18678704]
28. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med*. 1995; 332(3):133–138. [PubMed: 7800004]

Demographic and clinical characteristics of 60,225 children followed to 6 months old and their mothers, stratified by use of oral contraceptive pills (OCPs) in the year before pregnancy.

Table 1

	No OCPs		Combined pills and mini-pills		Combined pills only		Mini-pills only	
	N	% ^a	N	% ^a	N	% ^a	N	% ^a
Total	36,548		605		19,786		3,286	
<i>Maternal characteristics</i>								
<i>History of asthma and atopy</i>								
No asthma or atopy	24,903	68	412	68	12,958	65	2,296	70
Atopy, no asthma	9,126	25	146	24	5,196	26	790	24
Asthma, no atopy	822	2	16	3	515	3	51	2
Asthma and atopy	1,697	5	31	5	1,117	6	149	5
<i>Age (years)</i>								
<25	3,207	9	82	14	4,009	20	245	7
25–30	14,574	40	326	54	10,607	54	1,497	46
>30	18,766	51	197	33	5,170	26	1,544	47
<i>Smoking during first trimester of pregnancy</i>								
No	33,119	91	564	94	17,796	91	3,072	94
Yes	3,153	9	38	6	1,860	9	189	6
<i>Folate supplementation during first trimester pregnancy</i>								
No	8,728	24	134	22	4,510	23	701	21
Yes	27,820	76	471	78	15,276	77	2,585	79
<i>Number of previous live births</i>								
0	13,912	38	126	21	13,540	68	406	12
1	13,955	38	363	60	4,206	21	2,046	62
≥1	8,680	24	116	19	2,040	10	834	26
<i>Body mass index</i>								
Underweight (<18.5)	1,051	3	19	3	573	3	83	3
Normal (18.5–24.9)	22,608	64	384	65	12,977	67	2,174	68
Overweight (25.0–29.9)	8,075	23	153	26	4,238	22	717	22
Obese (≥30)	3,706	10	38	6	1,621	8	245	8

	No OCPs		Combined pills and mini-pills		Combined pills only		Mini-pills only	
	N	% ^a	N	% ^a	N	% ^a	N	% ^a
<i>Level of education (years completed or ongoing)</i>								
≤12	11,845	33	185	31	6,695	35	862	27
13–16	15,283	43	264	44	8,543	44	1,514	47
>16	8,620	24	147	25	4,165	22	853	26
<i>Income (Nkr)</i>								
<150,000	6,489	18	109	19	3,938	20	549	17
150,000–299,000	17,717	49	307	52	9,763	50	1,665	52
≥300,000	11,599	32	172	29	5,756	30	1,006	31
<i>Child characteristics</i>								
<i>Sex</i>								
Male	17,727	49	299	49	9,701	49	1,663	51
Female	18,759	51	306	51	10,063	51	1,618	49
<i>Birth weight</i>								
<2500 g	906	2	10	2	630	3	59	2
≥2500 g	35,575	98	595	98	19,130	97	3,221	98
<i>Breastfeeding at 6 months</i>								
No	6,911	19	108	18	4,556	23	417	13
Yes	29,637	81	497	82	15,230	77	2,869	87
<i>Year of birth</i>								
1999	18	<1	1	<1	6	<1	1	<1
2000	889	2	13	2	462	2	92	3
2001	1,731	5	31	5	892	5	196	6
2002	4,046	11	74	12	2,269	11	361	11
2003	5,975	16	106	18	3,474	18	525	16
2004	6,377	17	101	17	3,688	19	562	17
2005	7,457	20	107	18	3,933	20	618	19
2006	8,285	23	135	22	4,202	21	757	23
2007	1,770	5	37	6	860	4	174	5
<i>Season of birth</i>								

	No OCPs		Combined pills and mini-pills		Combined pills only		Mini-pills only	
	N	% ^a	N	% ^a	N	% ^a	N	% ^a
Mar-May	9,129	25	161	27	4,920	25	911	28
Jun-Aug	9,349	26	153	25	5,171	26	805	25
Sep-Nov	8,745	24	135	22	4,945	25	771	23
Dec-Feb	9,325	26	156	26	4,772	24	799	24

^aPercentages are based on non-missing data. Percentage column totals may exceed 100 due to rounding.

Table 2

Associations of oral contraceptive pill (OCP) use before pregnancy with lower respiratory tract infections in 60,225 children followed to 6 months old and 42,520 children followed to 18 months old.

		N (%)* of children with:					
Lower respiratory tract infections	Timing of OCP use	Type of OCP	Lower respiratory tract infections	No lower respiratory tract infections		Crude OR (95% CI)	Adjusted ^c OR (95% CI)
<6 months		Total	3,021	57,204			
	Year before pregnancy	No OCPs	1,927 (64)	34,621 (61)		1.00 (referent)	1.00 (referent)
		Combined pills only	808 (27)	18,978 (33)		0.77 (0.70–0.83)	1.03 (0.94–1.13)
		Mini-pills only	240 (8)	3,046 (5)		1.42 (1.23–1.63)	1.10 (0.95–1.28)
	4 months before pregnancy	No OCPs	2,417 (80)	44,685 (78)		1.00 (referent)	1.00 (referent)
		Combined pills only	441 (15)	10,230 (18)		0.80 (0.72–0.88)	1.07 (0.96–1.20)
		Mini-pills only	121 (4)	1,600 (3)		1.40 (1.16–1.69)	1.09 (0.89–1.34)
6–11 months		Total	2,863	38,515			
	Year before pregnancy	No OCPs	1,765 (62)	23,134 (60)		1.00 (referent)	1.00 (referent)
		Combined pills only	866 (30)	12,934 (34)		0.88 (0.81–0.96)	1.00 (0.91–1.09)
		Mini-pills only	194 (7)	2,083 (5)		1.22 (1.05–1.43)	1.05 (0.89–1.24)
	4 months before pregnancy	No OCPs	2,271 (79)	29,961 (78)		1.00 (referent)	1.00 (referent)
		Combined pills only	457 (16)	6,988 (18)		0.86 (0.78–0.96)	0.95 (0.85–1.07)
		Mini-pills only	99 (4)	1,121 (3)		1.17 (0.95–1.44)	0.95 (0.76–1.19)
12–18 months		Total	3,480	38,063			
	Year before pregnancy	No OCPs	2,058 (59)	22,919 (60)		1.00 (referent)	1.00 (referent)
		Combined pills only	1,180 (34)	12,700 (33)		1.04 (0.96–1.12)	1.03 (0.95–1.12)
		Mini-pills only	199 (6)	2,083 (6)		1.06 (0.91–1.24)	1.07 (0.91–1.26)
	4 months before pregnancy	No OCPs	2,712 (78)	29,643 (78)		1.00 (referent)	1.00 (referent)
		Combined pills only	632 (18)	6,855 (18)		1.01 (0.92–1.10)	1.00 (0.91–1.11)
		Mini-pills only	99 (3)	1,123 (3)		0.96 (0.78–1.19)	0.98 (0.79–1.22)

^dNumber and percentage of children correspond to the crude models. For lower respiratory tract infections at <6 months, analyses included 60,225 children in crude models and 54,234 children in adjusted models. Analyses for lower respiratory tract infections at 6–11 months included 41,378 children in crude models and 37,574 children in adjusted models. Analyses for lower respiratory tract infections at 12–18 months included 41,543 children in crude models and 37,737 children in adjusted models.

^b Percentages were calculated using the total number of cases or controls as the denominator. The small category of children whose mothers reported using both combined pills and mini-pills in the year before pregnancy is not shown. For OCP use in the four months before pregnancy, data is missing for a small proportion of the children.

^c Estimates were adjusted for maternal history of asthma and atopy (neither, asthma only, atopy only, both), maternal age (<25, 25–30, >30 years), smoking during first trimester of pregnancy (yes/no), folate supplementation during first trimester of pregnancy (yes/no), number of previous live births (0,1,>1), pre-pregnancy body mass index (<18.5, 18.5–24.9, 25.0–29.9, >29.9), maternal education (<13, 13–16, >16 years), maternal income (<150,000, 150,000–299,000, >299,000 Nkr), child's sex, child's gestational age (<37, 37–38, 39–41, >41 weeks), parental smoking in the first 3 months after birth (yes/no), breastfeeding at 6 months (yes/no), season of birth (Mar-May, Jun-Aug, Sep-Nov, Dec-Feb), and year of birth.

Table 3

Associations of oral contraceptive pill (OCP) use before pregnancy with wheezing in 42,520 children followed to 18 months old.

Wheezing	Timing of OCP use	Type of OCP	N (%) <i>a,c</i> of children with:			Crude OR (95% CI)	Adjusted ^d OR (95% CI)
			Wheezing	No Wheezing	Total		
6–8 months		Total	5,356	36,535			
	Year before pregnancy	No OCPs	3,321 (62)	21,897 (60)		1.00 (referent)	1.00 (referent)
		Combined pills only	1,584 (306)	12,377 (34)		0.84 (0.79–0.90)	0.97 (0.90–1.04)
	4 months before pregnancy	Mini-pills only	388 (7)	1,920 (5)		1.33 (1.19–1.50)	1.19 (1.05–1.34)
		No OCPs	4,219 (79)	28,415 (78)		1.00 (referent)	1.00 (referent)
		Combined pills only	860 (16)	6,685 (18)		0.87 (0.80–0.94)	0.98 (0.90–1.06)
9–11 months		Total	7,634	34,257			
	Year before pregnancy	No OCPs	4,630 (61)	20,588 (60)		1.00 (referent)	1.00 (referent)
		Combined pills only	2,408 (32)	11,553 (34)		0.93 (0.88–0.98)	1.02 (0.96–1.09)
	4 months before pregnancy	Mini-pills only	497 (7)	1,811 (5)		1.22 (1.10–1.35)	1.11 (0.99–1.24)
		No OCPs	5,945 (78)	26,689 (78)		1.00 (referent)	1.00 (referent)
		Combined pills only	1,304 (17)	6,241 (18)		0.94 (0.88–1.00)	1.01 (0.94–1.09)
12–14 months		Total	9,576	32,315			
	Year before pregnancy	No OCPs	5,715 (60)	19,503 (60)		1.00 (referent)	1.00 (referent)
		Combined pill only	3,181 (33)	10,780 (33)		1.01 (0.96–1.06)	1.06 (1.00–1.12)
	4 months before pregnancy	Mini-pill only	573 (6)	1,735 (5)		1.13 (1.02–1.24)	1.10 (0.99–1.22)
		No OCPs	7,475 (78)	25,159 (78)		1.00 (referent)	1.00 (referent)
		Combined pills only	1,684 (18)	5,861 (18)		0.97 (0.91–1.03)	1.03 (0.96–1.10)
15–18 months		Total	8,930	32,961			
	Year before pregnancy	No OCPs	5,302 (59)	19,916 (60)		1.00 (referent)	1.00 (referent)
		Combined pills only	3,033 (34)	10,928 (33)		1.04 (0.99–1.10)	1.02 (0.97–1.08)
	4 months before pregnancy	Mini-pills only	490 (6)	1,818 (6)		1.01 (0.91–1.12)	0.99 (0.88–1.11)
		No OCPs	7,475 (78)	25,159 (78)		1.00 (referent)	1.00 (referent)
		Combined pills only	1,684 (18)	5,861 (18)		0.97 (0.91–1.03)	1.03 (0.96–1.10)

N (%) ^{a,c} of children with:						
Wheezing	Timing of OCP use	Type of OCP	Wheezing	No Wheezing	Crude OR (95% CI)	Adjusted ^c OR (95% CI)
	4 months before pregnancy	No OCPs	6,943 (78)	25,691 (78)	1.00 (referent)	1.00 (referent)
		Combined pills only	1,610 (18)	5,935 (18)	1.00 (0.94–1.07)	0.99 (0.93–1.06)
		Mini-pills only	264 (3)	963 (3)	1.01 (0.88–1.17)	1.02 (0.88–1.18)

^aNumber and percentage of children correspond to the crude models. There were 42,520 children followed to 18 months with data for lower respiratory tract infections or wheezing from 6 to 18 months. For wheezing, analyses included 41,891 children in crude models and 38,037 children in adjusted models.

^bPercentages were calculated using the total number of cases or controls as the denominator. The small category of children whose mothers reported using both combined pills and mini-pills in the year before pregnancy is not shown. For OCP use in the four months before pregnancy, data is missing for a small proportion of the children.

^cEstimates were adjusted for maternal history of asthma and atopy (neither, asthma only, atopy only, both), maternal age (<25, 25–30, >30 years), smoking during first trimester of pregnancy (yes/no), folate supplementation during first trimester of pregnancy (yes/no), number of previous live births (0,1,>1), pre-pregnancy body mass index (<18.5, 18.5–24.9, 25.0–29.9, >29.9), maternal education (<13, 13–16, >16 years), maternal income (<150,000, 150,000–299,000, >299,000 Nkr), child's sex, child's gestational age (<37, 37–38, 39–41, >41 weeks), parental smoking in the first 3 months after birth (yes/no), breastfeeding at 6 months (yes/no), season of birth (Mar–May, Jun–Aug, Sep–Nov, Dec–Feb), and year of birth.

Associations of oral contraceptive pill (OCP) use before pregnancy with asthma in 24,472 children followed to 36 months old.

Table 4

Timing of OCP use	Type of OCP	N (%) ^{a,c} of children with:		Crude OR (95% CI)	Adjusted ^c OR (95% CI)
		Asthma	No Asthma		
Total		2,155	22,317		
Year before pregnancy	No OCPs	1,242 (58)	13,339 (60)	1.00 (referent)	1.00 (referent)
	Combined pills only	754 (35)	7,581 (34)	1.07 (0.97–1.17)	1.05 (0.95–1.17)
	Mini-pills only	130 (6)	1,190 (5)	1.17 (0.97–1.42)	1.00 (0.81–1.23)
4 months before pregnancy	No OCPs	1,659 (77)	17,286 (78)	1.00 (referent)	1.00 (referent)
	Combined pills only	399 (19)	4,150 (19)	1.00 (0.89–1.12)	1.03 (0.91–1.16)
	Mini-pills only	71 (3)	641 (3)	1.15 (0.90–1.48)	1.01 (0.76–1.33)

^a Number and percentage of children correspond to the crude models. Analyses included 24,472 children in crude models and 22,201 children in adjusted models.

^b Percentages were calculated using the total number of cases or controls as the denominator. The small category of children whose mothers reported using both combined pills and mini-pills in the year before pregnancy is not shown. For OCP use in the four months before pregnancy, data is missing for a small proportion of the children.

^c Estimates were adjusted for maternal history of asthma and atopy (neither, asthma only, atopy only, both), maternal age (<25, 25–30, >30 years), smoking during first trimester of pregnancy (yes/no), folate supplementation during first trimester of pregnancy (yes/no), number of previous live births (0,1,>1), pre-pregnancy body mass index (<18.5, 18.5–24.9, 25.0–29.9, >29.9), maternal education (<13, 13–16, >16 years), maternal income (<150,000, 150,000–299,000, >299,000 Nkr), child's sex, child's gestational age (<37, 37–38, 39–41, >41 weeks), parental smoking in the first 3 months after birth (yes/no), breastfeeding at 6 months (yes/no), season of birth (Mar–May, Jun–Aug, Sep–Nov, Dec–Feb), and year of birth.