**PDS-16-0281 revised
Language competence and communication skills in 3 year old children after prenatal exposure to analgesic opioids**

**Running head:** Development after prenatal opioid exposure

Eva Skovlund1,2, Marte Handal1, Randi Selmer1, Ragnhild Eek Brandlistuen1, Svetlana Skurtveit1,3

1 Norwegian Institute of Public Health, Oslo, Norway.
2 Department of Public Health and General Practice, NTNU, Norwegian University of Science and Technology, Trondheim, Norway.
3 Norwegian Centre for Addiction Research, University of Oslo, Oslo, Norway.

**Corresponding author:** Eva Skovlund, Department of Public Health and General Practice, NTNU, Norwegian University of Science and Technology, PO Box 8905, 7491 Trondheim, Norway. eva.skovlund@ntnu.no

**Keywords:** Opioids, Language competence, Communication skills, Neurodevelopment, MoBa

**Key points:**

* In this Norwegian cohort study use of analgesic opioids was reported in 892 of the 51 679 included pregnancies (1.7%).
* No association between prenatal exposure and reduced language competence or communication skills at 3 years of age was found.
* No firm conclusion can be drawn with regard to prolonged use of strong opioids or high doses.

**Conflict of interest disclosures** None

**Word count: 3641**

**ABSTRACT**

**Purpose** An increasing consumption of opioids in the general population has been reported in several countries also among pregnant women. Limited information is available regarding the effect of prenatal exposure to analgesic opioids on long-term neurocognitive function in children. The primary aim of the study was to determine the association between prenatal exposure to analgesic opioids and language competence and communication skills at 3 years of age.

**Methods** The Norwegian Mother and Child Cohort Study (MoBa) prospectively included pregnant women 1999-2008. Participants reported medication use at pregnancy week 17/18 and 30, and 6 months after birth. Children’s language competence and communication skills were reported by mothers on validated scales.

**Results** A total of 45 211 women with 51 679 singleton pregnancies were included. Use of analgesic opioids was reported in 892 pregnancies (1.7%). In adjusted analyses no association between opioid use and reduced language competence or communication skills was found, OR=1.04 (95% CI: 0.89-1.22) and OR=1.10 (95% CI: 0.95-1.27), respectively. Both pain and use of paracetamol were associated with a small reduction in communication skills. No such association was found for language competence.

**Conclusion** Use of analgesic opioids in pregnant women does not seem to affect language development or communication skills in children at 3 years.

**Introduction**

Data from the general population suggest increasing consumption of prescription opioids in several countries 1-5. Also among pregnant women there is a high prevalence of opioid use 6, 7. In studies from the US, 14-28% of pregnant women report opioid use during pregnancy 6, 8, 9.

In Norway opioids have been reported to be the CNS acting drugs most frequently prescribed to pregnant women 10, but with a lower prevalence of use than reported in the US. Analgesic opioid use is reported in about 3% of all pregnant women in Norway 11 and below 2% during all three trimesters in Sweden 12, 13.

For chronic pain the American Pain Society Guidelines recommend no or minimal use of prescribed opioids in pregnancy, if possible 14. The Norwegian Medical Association has recommended that opioids be used sporadically for severe pain during the first and second trimesters, but warn about treatment close to term due to potential perinatal complications, the most studied being Neonatal Abstinence Syndrome (NAS) 15. Limited information is available regarding the effect of prenatal exposure to analgesic opioids on long-term neurocognitive function in children.

Language development plays a fundamental role in cognition, social development and learning. Early language deficits may impair long-term social adaptation, cognitive development and academic achievement and are associated with psychiatric disorders in young adults 16-19. Developmental delay in the language domain is also often found to be associated with delay in other domains 16, 20. Thus a potential effect of drug intake during pregnancy on language and communication development in the offspring would be an important safety issue. There are some reports on cognitive development after use of illicit opioids or medication assisted maintenance therapy during pregnancy but the results are conflicting 21, 22. No population based estimates are available regarding the risk of delayed language development children born to mothers using opioid analgesics during pregnancy.

The aim of the present study was to assess the effect of exposure to analgesic opioids during pregnancy on language competence and communication skills in 3 year old children.

**Material and method**

*The MoBa cohort*

The Norwegian Mother and Child Cohort Study (MoBa) is a prospective population-based pregnancy cohort run by the Norwegian Institute of Public Health 23, 24. During the period from 1999 to 2008 pregnant women in Norway received a postal invitation to participate in MoBa prior to the first ultrasound scan at week 17/18. The women consented to participation in 40.6% of the pregnancies. Data collection is based on detailed self-administered questionnaires both during pregnancy and after birth on questions regarding in utero exposures that may increase the likelihood of delayed neurodevelopment such as alcohol consumption, smoking, illicit drug use and use of prescription medication like opioids, SSRI, and benzodiazepines 25, 26. Participants answered three questionnaires during pregnancy as well as 6 months, 18 months, and 3, 5, 7 and 8 years after birth. Follow-up of children in MoBa is still ongoing. The cohort now includes 114.500 children, 95.200 mothers and 75.200 fathers. Some of the information in MoBa is obtained by linkage to the Medical Birth Registry of Norway (MBRN) which is a nationwide registry based on mandatory notification of all births or late abortions in Norway 27.

*Study population*

The present study is based on data from pregnant women and their offspring having reached the age of three years (MoBa data file version 7). The age three questionnaire was returned for 58 410 children. Children from pregnancies with multiple fetuses (n=1748) and children with malformations and/or chromosomal abnormalities (n=1555) were excluded, as were pregnancies where the mother did not answer all three questionnaires on drug use during pregnancy (n=3069). Pregnancies with missing data on language competence and/or communication skills (n=359) were also excluded, resulting in 51 679 pregnancies in 45 211 women.

*Opioid use*

Opioids were defined as all analgesics classified in ATC-group N02A based on the Anatomic Therapeutic Chemical classification system as of 2013 28. Opioid containing cough medications (R05DA01 and R05DA04) were registered for sensitivity analyses. Mothers were asked to report on medication use at pregnancy week 17-18, 30, and 6 months after birth 25, covering the period from 6 months before pregnancy to week 17-18, the period from week 19-29, and the period from week 30 to birth. Complete questionnaires are available from the Norwegian Institute of Public Health (<http://www.fhi.no/enmoba>)

Mothers were defined as analgesic opioid users if they had reported use of any analgesic opioid on at least one of the three questionnaires by naming a drug as well as ticking a box indicating that they had used the drug during pregnancy. To try to capture extent of exposure we classified use as none, during one period only, or during two or all three pregnancy periods. In addition binary exposure in each pregnancy period was registered.

*Language competence*

Language competence at three years of age was evaluated by a validated language grammar rating scale 29. The mother classified her child’s language competence according to six different categories;

1. not yet talking
2. talking, but unintelligible
3. talking in one-word utterances such as “milk” or “down”
4. talking in 2-3 word phrases, such as “me got ball” or “give doll”
5. talking in fairly complete sentences, such as “I got a doll” or “Can I go outside?”
6. talking in long and completed sentences, such as “When I went to the park, I went on the swings” or “I saw a man standing on the corner”

Categories a) to d) were combined in the analyses due to small numbers. If the mother had marked several categories, the child was classified in the most advanced language category. The validity of the language grammar rating scale has been evaluated by Roth et al 30.

*Communication skills*

Communication skills were assessed by 6 items from the Ages and Stages Questionnaire (ASQ) which is considered to be an effective screening tool for detecting developmental impairments or disturbances 31. Mothers rated the child’s ability to master different skills (described in Supplementary table 1) using the categories *yes*, *sometimes*, or *not yet*, scored 10, 5, and 0, respectively, as suggested by Squires 32. Mean scores were estimated if the mother had filled in at least 3 of the 6 items constituting the scale, and thereafter grouped in three ordinal categories for statistical analysis. In addition a z-score was calculated with a cut-off of 1.5 for supplementary analyses 32.

*Potential confounding factors*

A large number of factors may be associated with opioid use during pregnancy as well as with language competence and communication skills in the offspring. Maternal and paternal education level, marital status and maternal work situation during pregnancy, information on whether the pregnancy was planned or not, use of folic acid supplements in early pregnancy, pre-pregnancy body mass index (BMI, kg/m2) and chronic diseases were retrieved from the first pregnancy questionnaire. Reports on other drug use, smoking and alcohol use as well as pain were retrieved from all three questionnaires. Information regarding maternal and paternal age and parity was retrieved from the MBRN.

The three questionnaires posed questions on pain slightly differently. All categories of pain reported were therefore merged into one binary pain variable (yes/no). Maternal chronic disease was defined if a pregnant woman reported asthma, diabetes, hypertension, arthritis, lupus, Crohn’s disease, epilepsy, multiple sclerosis or cancer in the first questionnaire.

Associations between potential confounding factors and opioid use during pregnancy (exposure) and language and communication skills (separate outcomes) were estimated. All factors shown to be independent explanatory variables for outcome as well as explanatory variables for exposure were included in the final model.

*Statistics*

Ordinal logistic regression (proportional odds model) 33 was applied to estimate the association between prenatal analgesic opioid exposure and language competence or communication skills, respectively. Both outcome variables were ordered in three categories, with scores ranging from 1 to 3. The outcome can then be categorised in two ways; development category 1 *vs* 2-3 or 1-2 *vs* 3. The interpretation of the odds ratio (OR) is the change in the odds of being in a lower development category per unit increase in the independent variable, regardless of how the outcome has been dichotomised.

The assumption of proportionality of odds for the ordinal models was checked by an approximate likelihood ratio test. Additional sensitivity analyses of the same outcomes in three to five categories using multinomial logistic regression, and binary logistic regression with different two category cut-offs of the outcome variables were also performed. To study if there was a sensitive period during pregnancy we also modelled the effect of binary exposure during three time intervals. Separate analyses of opioid containing cough medications compared to the reference group with no opioid use were also performed.

For communication skills, a supplementary analysis using the z-score with a cut-off of 1.5 SD below the mean was conducted.

Unadjusted as well as adjusted analyses, including all potential confounding factors (see above), were performed, and 95% confidence intervals (CI) for the OR were calculated. Standard errors were estimated using the clustered sandwich estimator to handle multiple pregnancies in the same woman. Statistical analyses were conducted using Stata 14.

*Ethics*

MoBa has a license from the Norwegian Data Inspectorate. Informed consent was obtained from each participant upon recruitment.

**Results**

*Pain*

In 47 058 (91.1%) pregnancies the woman reported pain on at least one questionnaire. Back pain or pelvic pain was reported in 44 877 pregnancies (86.8%), and in 20 249 pregnancies (39.4%) the woman reported that pelvic pain made her wake up at night. Headache or other pain was reported in 29 220 pregnancies (56.5%).

*Opioid use*

Use of analgesic opioids was reported in 892 of the 51 679 pregnancies (1.7%). Opioid use during one period only was reported in 720 pregnancies (1.4%), whereas drug use in at least two periods was reported in 172 (0.3%).

The dominating substance was codeine in combination with paracetamol; reported in 799 (89.6%) of the 892 pregnancies. Use of a strong opioid was reported in 117 (13.1%) of exposed pregnancies. In 653 pregnancies use of opioid containing cough medication was reported.

Table 1 shows maternal use of analgesic opioids during pregnancy according to parental characteristics. Use of opioids was less common with increasing maternal education and age as well as in working mothers, whereas the proportion of users increased with increasing parity and BMI. The proportion of opioid users was also higher when the mother reported pain, chronic disease, smoking, use of triptans, benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), and illegal drugs.

Maternal work situation, parity, paternal education, maternal smoking, maternal BMI as well as maternal use of benzodiazepine or SSRI during pregnancy were independent explanatory variables for both outcome and exposure.

*Language competence*

Table 2 shows the number and proportion of children in the different language competence categories reported by the mothers in the 3 years questionnaire by maternal use of analgesic opioids during pregnancy. Only very small differences were observed between children prenatally exposed to opioids during either one or two to three periods and children prenatally not exposed.

Table 3 shows estimated odds ratios of lower language competence when exposed to analgesic opioids in utero. In unadjusted analyses, there was a trend towards a small detrimental effect of prenatal exposure to opioids, but there was no effect of opioid use on language competence in adjusted analyses. The odds ratio of language competence in a lower category was 1.04 (95% CI: 0.89-1.22) with use of analgesic opioids whether or not pain was included in the model.

Unadjusted analyses show small increases in the odds of being in a lower language development category in children exposed to paracetamol or maternal pain, respectively. In adjusted analyses including all potential confounding factors, however, there was no effect of number of periods with reported use of paracetamol or pain during pregnancy.

Sensitivity analyses using binary logistic regression models with different cut-offs as well as multinomial logistic regression models with different numbers of categories of language development supported the results from the ordinal models. So did the model assessing exposure during different periods. There was no association between use of opioid containing cough medication and language development, OR=1.00 (95%CI: 0.82, 1.22).

*Communication skills*

The number and proportion of children in the different categories of communication skills are shown in Table 2. Small differences were observed between children prenatally exposed to analgesic opioids and children not exposed.

There were small effects of prenatal exposure to opioids, paracetamol, and maternal pain in unadjusted analyses (Table 4). However, no effect of analgesic opioid use on communication skills was found in adjusted analyses; the estimated odds ratio of being in a lower category being 1.10 (95% CI: 0.95, 1.27). Categorizing opioid use into one period or two or three periods gave OR=1.10 (95% CI: 0.94, 1.28) and OR=1.12 (95% CI: 0.82, 1.53), respectively. On the other hand, both pain and use of paracetamol were associated with a small reduction in communication skills. Again, supplementary sensitivity analyses supported the results from the ordinal model.

|  |
| --- |
| Binary logistic regression analyses using the z-score with a cut-off of -1.5, corresponding to a cut-off of 7.5 in mean ASQ3 score, did not reveal an association between analgesic opioid use and communication skills, OR=1.27 (95% CI: 0.96, 1.68). No association between use of cough medication and communication skills was found, OR=0.96 (95% CI: 0.81, 1.13). |

**Discussion**

In this large prospective study, we have assessed the association between prenatal exposure to analgesic opioids and language competence or communication skills at 3 years of age.

An increase in opioid use during the last two decades has been documented in several populations 1, 2, 4, 5. This trend has been accompanied by a rise in abuse of these agents 34. Studies from the U.S. pregnant population suggest that the epidemic use of prescribed opioids in the general population extends to use during pregnancy 6, 8, 35. Even if no increasing trend in opioid use is evident in Norway or other Scandinavian countries 10, 36, neither in the general population (www.norpd.no) 2 nor in the population of pregnant women 11 it is highly important to gain knowledge on potential harmful effects to the offspring.

There is a growing body of evidence that opioids may be associated with specific birth defects, and codeine is potentially an important contributor 7, 37. In a review of the literature no association between opioid exposure and head circumference or birth length was found 7, but results regarding a potential effect on birth weight and preterm birth have been inconclusive.

To our knowledge, no studies have been performed with respect to neurocognitive effects of prescribed analgesic opioids. Some studies have found children exposed to opioid maintenance treatment (OMT) to have reduced cognitive function compared to unexposed 22. The presence of several other risk factors may have confounded the association, and a firm conclusion on causality cannot be drawn.

In the present study there was no association between analgesic opioid use during pregnancy and language competence or communication skills in 3 year old children, respectively. Since both exposure and outcome are rare events, a large sample is required to obtain sufficient power to detect associations. A major strength of this study is the large number of pregnancies leading to relatively precise estimates. The upper limits of the 95% confidence intervals seem to preclude any large effect of prenatal exposure to analgesic opioids. As MoBa participants responded to detailed questions regarding drug use as well as a large number of other health related and sociodemographic factors, it was possible to control for several important potential confounders. The prospective design to some extent reduces the risk of recall bias as the women reported on drug use before assessing the outcomes of interest.

Whereas there seems to be no relevant association between prenatal exposure to opioids and neurocognitive development at 3 years, there was an association between prenatal exposure to paracetamol and communication skills, the odds of being in a lower development category increasing with number of pregnancy periods with reported use of paracetamol. Residual confounding cannot be excluded, but this finding is supported by an earlier MoBa study, which showed a weak association between long-term use of paracetamol and communication skills both in the cohort and in sibling-adjusted analyses 38.

A large proportion of pregnant women reports pain during pregnancy. Maternal pain in itself might affect neurodevelopment, but to our knowledge, such effects have not been studied. The results of this study did not indicate any substantial effect of maternal pain on the child’s language competence. However, there was a small association with communication skills. Unfortunately, the questions on pain during pregnancy are not identical in the different MoBa questionnaires, and refined and consistent classification of duration and type of pain was not possible. A majority reported pregnancy related pain, such as back pain or pelvic girdle pain.

In Norway, the weak opioid codeine is the dominating prescribed opioid analgesic, and the products on the market contain 30 mg per tablet 9. As codeine was reported in approximately 90 % of the 892 exposed pregnancies, our results are most representative for this substance. The prevalence of opioid use in MoBa is rather small (1.7%), and we chose to classify all analgesic opioids together. The value of studying subgroups of opioids as e.g. oxycodone would be very limited. A separate exploratory analysis of strong opioids led to approximately the same results as for all opioids combined, but the number of women was too low for appropriate adjustment for confounding, and no firm conclusion can be drawn. Cough medications (R05D) were not included in the main analyses as the dose is low and duration of use expected to be very short. In light of our findings on analgesic opioids, it is no surprise that supplementary analyses of use of opioid containing cough medications *vs* no opioid use revealed no association with neurocognitive development.

We do not have information on dosage or duration of use of opioids. A mother who has reported use of opioids during a period may have used the drug once only or possibly every day, and any conclusions with regard to duration should be dealt with cautiously. However, mothers reporting use during two or more periods are more likely to have consumed a higher total dose. This assumption is also supported by the fact that a larger proportion of women using opioids in more periods also use benzodiazepines 11.

In a nation-wide registry study 2.9 % of pregnant women filled at least one prescription of opioid analgesics 11. The discrepancy between that estimate and the prevalence of opioid use of 1.7% reported in the present study may partly be explained by selection bias39. Only women agreeing to participate in MoBa have been included in the study, and it has been shown that MoBa participants have a healthier lifestyle than the total pregnant population in Norway. They may also be more cautious with regard to drug use during pregnancy. However, a comparison of MoBa participants and all women giving birth in Norway suggests that estimates of exposure-outcome associations are unbiased 39.

In addition to the effect of self-selection, there is the possibility of misclassification of drug consumption. Previous studies have demonstrated a lower proportion of self-reported drug use in MoBa compared to data from the NorPD in the same sample 40. In that study 2.1% filled opioid prescriptions during pregnancy whereas 1.6% self-reported opioid use. It is not surprising that the prevalence estimate is lower using self-reports than in the prescription database as dispensed drugs need not be consumed. However, there is also a risk that mothers underreport their use of drugs in the questionnaires. Underreporting of exposure is on the other hand, assumed to have little effect on the estimated odds ratios. It has been shown that when the prevalence of exposure is low, high specificity, i.e. classification of true unexposed as unexposed is highly important whereas sensitivity is less important 41.

Parental self-report is generally considered a valid measure of early expressive vocabulary, especially for severe language delay and a validation against clinical assessment has been described for this instrument in our cohort 30. The Ages and Stages Questionnaire at the age of three years has also been validated 32 . The distribution of ASQ3 scores originally comprises 21 categories and could in principle have been treated as a continuous variable. However, the distribution was heavily skewed, and ordinal logistic regression with three categories was therefore applied. Sensitivity analyses with a larger number of categories led to very small numbers in the lowest category and violation of the assumption of proportionality. Using a z-score as recommended for screening led to the same conclusion since the recommended cut-off corresponds exactly to the lowest of the three ASQ3 score categories (≤7.5). In adjusted analyses of language competence use of four categories instead of three led to the same estimates, but with slightly less certain fulfilment of the proportionality assumption. Language competence was registered in six ordinal categories, but the number of children in the three lowest categories was small, and we decided to restrict the primary analysis to three ordinal categories. Supplementary analyses with the outcome ordered in four categories did not affect the results.

*Conclusion*

No association between maternal analgesic opioid use during pregnancy and language competence or communication skills in 3 year old children was detected. Our findings are based on a cohort of pregnant women where a small proportion report use of analgesic opioids, and primarily codeine in short periods and probably small doses. Therefore, the results are not necessarily applicable to strong opioids, large doses, or long duration during pregnancy. Even if any strong effect on language competence or communication skills seems unlikely, health care providers should carefully consider both the underlying disease of the pregnant women and potential harm to the developing fetus before prescribing an opioid. Future research, especially on heavy use of prescribed opioids and neurodevelopment of the child, is necessary.

**Acknowledgment**

The Norwegian Mother and Child Cohort Study is supported by the Norwegian Ministry of Health and the Ministry of Education and Research, NIH/NIEHS (contract no N01-ES-75558), NIH/NINDS (grant no.1 UO1 NS 047537-01 and grant no.2 UO1 NS 047537-06A1). We are grateful to all the participating families in Norway who take part in this on-going cohort study.

**Table 1 M**aternal use of analgesic opioids during pregnancy by parental characteristics

|  |  |  |  |
| --- | --- | --- | --- |
|  | No opioid use | One period | Two or three periods |
|  | n | % | n | % | n | % |
| **Maternal age in years (n=51 610)** |  |  |  |  |  |  |
| <25 | 4 550 | 98.2 | 75 | 1.6 | 7  | 0.2 |
| 25-29 | 16 960 | 98.4 | 234 | 1.4 | 45 | 0.3 |
| 30-34 | 20 218 | 98.4 | 261 | 1.3 | 74 | 0.4 |
| ≥35 | 8 990 | 97.9 | 150 | 1.6 | 46 | 0.5 |
| **Paternal age in years (n=51 487)** |  |  |  |  |  |  |
| <25 | 1 890 | 98.3 | 29 | 1.5 | 3 | 0.2 |
| 25-29 | 11 311 | 98.3 | 168 | 1.5 | 28 | 0.2 |
| 30-34 | 20 152 | 98.3 | 284 | 1.4 | 63 | 0.3 |
| ≥35 | 17 245 | 98.2 | 236 | 1.3 | 78 | 0.4 |
| **Maternal education (n=50 598)** |  |  |  |  |  |  |
| <12 | 8 310 | 97.7 | 146 | 1.7 | 49 | 0.6 |
| 12 | 7 145 | 98.1 | 112 | 1.5 | 24 | 0.3 |
| 13-16 | 21 834 | 98.3 | 310 | 1.4 | 61 | 0.3 |
| >16 | 12 425 | 98.6 | 145 | 1.1 | 37 | 0.3 |
| **Paternal education (n=48 643)** |  |  |  |  |  |  |
| <12 | 16 107 | 98.0 | 267 | 1.6 | 66 | 0.4 |
| 12 | 6 153 | 98.0 | 102 | 1.6 | 24 | 0.4 |
| 13-16 |  13 960 | 98.3 | 199 | 1.4 | 39 | 0.3 |
| >16 | 11 575 | 98.7 | 113 | 1.0 | 38 | 0.3 |
| **Marital status (n=51 453)** |  |  |  |  |  |  |
| Married or living with partner | 49 222 | 98.3 | 692 | 1.4 | 162 | 0.3 |
| Single | 887 | 97.0 | 22  | 2.4 | 5 | 0.6 |
| Other | 454 | 98.1 | 6 | 1.3 | 3  | 0.7 |
| **Parity (n= 51 610)** |  |  |  |  |  |  |
| 0 | 24 272 | 98.4 | 329 | 1.3 | 55 | 0.2 |
| 1 | 17 363 | 98.2 | 243 | 1.4 | 75 | 0.4 |
| ≥2 | 9 083 | 98.0 | 148 | 1.6 | 42 | 0.5 |
| **Planned pregnancy (n=51 143)** |  |  |  |  |  |  |
| No | 8 478 | 98.0 | 144 | 1.7 | 27 | 0.3 |
| Yes | 41 782 | 98.3 | 569 | 1.3 | 143 | 0.3 |
| **Maternal work situation (n=51 470)** |  |  |  |  |  |  |
| Working | 46 774 | 98.4 | 642 | 1.3 | 139 | 0.3 |
| Not working | 2 787 | 97.6 | 51 | 1.8 | 19 | 0.7 |
| Disability pensioner | 342 | 92.2 | 18 | 4.9 | 11 | 3.0 |
| Other | 677 | 98.5 | 7 | 1.0 | 3 | 0.4 |
| **Maternal BMI (n=50 561)** |  |  |  |  |  |  |
| <25 | 34 625 | 98.5 | 430 | 1.2 | 103 | 0.3 |
| 25-29 | 10 663 | 98.0 | 178 | 1.6 | 38 | 0.4 |
| 30-34 | 3 248 | 97.3 | 72 | 2.2 | 17 | 0.5 |
| ≥35 | 1 148 | 96.7 | 28 | 2.4 | 11 | 0.9 |
| **Maternal smoking week 17-18 (n=49 598)** |  |  |  |  |  |  |
| No  | 44 990 | 98.4 | 606 | 1.3 | 137 | 0.3 |
| Yes | 3 747 | 97.0 | 86 | 2.2 | 32 | 0.8 |
| **Maternal alcohol use during pregnancy (n=51 584)** |  |  |  |  |  |  |
| No | 25 245 | 98.4 | 338 | 1.3 | 79 | 0.3 |
| Some | 17 985 | 98.3 | 252 | 1.4 | 62 | 0.3 |
| Weekly in periods | 7 462 | 97.9 | 130 | 1.7 | 31 | 0.4 |
| **Maternal chronic disease (n=51 679)**  |  |  |  |  |  |  |
| No | 45 366 | 98.4 | 604 | 1.3 | 144 | 0.3 |
| Yes | 5 421  | 97.4 | 116 | 2.1 | 28 | 0.5 |
| **Maternal pain during pregnancy (n=51 679)** |  |  |  |  |  |  |
| No | 4 597 | 99.5 | 22 | 0.5 | 2 | 0.1 |
| Yes  | 46 190  | 98.2 | 698 | 1.5 | 170 | 0.4 |
| **Maternal triptans use in pregnancy (n=51 679)**  |  |  |  |  |  |  |
| No | 50 440 | 98.3 | 697 | 1.4 | 157 | 0.3 |
| Yes | 347 | 90.1 | 23 | 6.0 | 15 | 3.9 |
| **Maternal benzodiazepine use in pregnancy, including z-hypnotics (n=51 679)** |  |  |  |  |  |  |
| No | 50 428 | 98.3 | 696 | 1.4 | 160 | 0.3 |
| Yes | 359 | 90.9 | 24 | 6.1 | 12 | 3.0 |
| **Maternal SSRI use in pregnancy (n=51 679)** |  |  |  |  |  |  |
| No | 50 417 | 98.3 | 707 | 1.4 | 169 | 0.3 |
| Yes | 370 | 95.9 | 13 | 3.4 | 3 | 0.8 |
| **Maternal paracetamol use in pregnancy (n=51 679)** |  |  |  |  |  |  |
| No | 27 801 | 99.1 | 212 | 0.8 | 30  | 0.1 |
| **Yes** | 22 986 | 97.3 | 508 | 2.1 | 142 | 0.6 |
| **Maternal illegal drug use in pregnancy (n=51 679)** |  |  |  |  |  |  |
| No | 50 675 | 98.3 | 717  | 1.4 | 168 | 0.3 |
| Yes | 112 | 94.1 | 3 | 2.5 | 4 | 3.4 |
| **Maternal folic acid supplements in early pregnancy (n=51 679)** |  |  |  |  |  |  |
| No | 13 655 | 98.2  | 202 | 1.5 | 46 | 0.3 |
| Yes | 37 132  | 98.3 | 518 | 1.4 | 126 | 0.3 |

**Table 2** Number and proportion of children with different levels of language competence and communication skills reported by the mothers in the 3 years questionnaire by use of analgesic opioids

|  |  |  |  |
| --- | --- | --- | --- |
|  | No opioid use | One period | Two or three periods |
| **Language competence** | n | % | n | % | n | % |
| Long complicated sentences | 39 132 | 77.0 | 531 | 73.8 | 131 | 76.2 |
| Fairly complicated sentences | 9 637 | 19.0 | 162 | 22.5 | 31 | 18.0 |
| Two to three word phrases or less | 2 018 | 4.0 | 27 | 3.8 | 10 | 5.8 |
| Two to three word phrases | 1 696 | 3.3 | 21 | 2.9 | 7 | 4.1 |
| One word  | 187 | 0.4 | 3 | 0.4 | 0 | 0 |
| Unintelligible | 68 | 0.1 | 1 | 0.1 | 2 | 1.2 |
| Not yet talking | 67 | 0.1 | 2 | 0.3 | 1 | 0.6 |
|  |  |  |  |  |  |  |
| **Communication skills** |  |  |  |  |  |  |
| ASQ3 score 10 (maximum mean score) | 30 829 | 60.7 | 412 | 57.2 | 93 | 54.1 |
| ASQ3 score 8-9.5  | 17 366 | 34.2 | 259 | 36.0 | 66 | 38.4 |
| ASQ3 score ≤7.5 | 2 592 | 5.1 | 49 | 6.8 | 13 | 7.6 |
| ASQ3 score 5.8-7.5 | 2 183 | 4.3 | 40 | 5.6 | 8 | 4.7 |
| ASQ3 score ≤5  | 409 | 0.8 | 9 | 1.3 | 5 | 2.9 |
|  |  |  |  |  |  |  |

ASQ3: Ages and stages questionnaire 3 years

**Table 3** Odds ratios of having a child with lower language competence according to use of analgesic opioids, paracetamol, and pain during pregnancy (ordinal logistic regression)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | N |  | Unadjusted OR (95% CI) | Adjusted OR (95% CI) a | Adjusted OR (95% CI) a |
| Opioid use |  |  |  |  |  |
| No | 44 842 |  | 1  | 1  | 1  |
| Yes | 804 |  | 1.15 (0.98, 1.34) | 1.04 (0.89, 1.22) | 1.04 (0.89, 1.22) |
| One period | 643 |  | 1.17 (0.98, 1.39) | 1.07 (0.90, 1.28) | 1.07 (0.90, 1.28) |
| Two or three periods | 161 |  | 1.06 (0.72, 1.56) | 0.91 (0.62, 1.35) | 0.92 (0.62, 1.35) |
|  |  |  |  |  |  |
| Paracetamol |  |  |  |  |  |
| No | 24 627 |  | 1 | 1  | 1  |
| One period | 11 945 |  | 1.03 (0.98, 1.09) | 0.99 (0.94, 1.05) | 1.00 (0.95, 1.05) |
|  Two periods | 7 457 |  | 1.06 (1.00, 1.13) | 0.99 (0.93, 1.05) | 0.99 (0.93, 1.06) |
| Three periods | 1 617 |  | 1.17 (1.04, 1.31) | 1.04 (0.93, 1.17) | 1.05 (0.93, 1.18) |
|  |  |  |  |  |  |
| Pain |  |  |  |  |  |
| No | 4 042 |  | 1  | 1  |  |
| Yes | 41 604 |  | 1.13 (1.05, 1.23) | 1.05 (0.97, 1.14) |  |

a Adjusted for the two other variables presented as well as maternal work situation, paternal education, maternal BMI, parity, maternal smoking, benzodiazepine, and maternal SSRI use during pregnancy (n=45 646)

**Table 4** Odds ratios of having a child with lower communication skills according to use of analgesic opioids, paracetamol, and pain during pregnancy (ordinal logistic regression)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | N |  | Unadjusted OR (95% CI) | Adjusted OR (95% CI) a | Adjusted OR (95% CI) a |
| Opioid use |  |  |  |  |  |
| No | 44 842 |  | 1  | 1  | 1  |
| Yes | 804 |  | 1.22 (1.05, 1.40) | 1.10 (0.95, 1.27) | 1.10 (0.96, 1.27) |
| One period | 643 |  | 1.20 (1.02, 1.40) | 1.10 (0.94, 1.28) | 1.10 (0.94, 1.29) |
|  Two or three periods | 161 |  | 1.29 (0.94, 1.77) | 1.12 (0.82, 1.53) | 1.13 (0.83, 1.53) |
| Paracetamol |  |  |  |  |  |
| No | 24 627 |  | 1 | 1  | 1  |
| One period | 11 945 |  | 1.04 (0.99, 1.08) | 1.00 (0.96, 1.05) | 1.01 (0.96, 1.05) |
|  Two periods | 7 457 |  | 1.14 (1.08, 1.21) | 1.08 (1.03, 1.14) | 1.09 (1.04, 1.15) |
| Three periods | 1 617 |  | 1.25 (1.13, 1.38) | 1.16 (1.04, 1.28) | 1.17 (1.06, 1.30) |
|  |  |  |  |  |  |
| Pain |  |  |  |  |  |
| No | 4 042 |  | 1  | 1  |  |
| Yes | 41 604 |  | 1.22 (1.14, 1.30) | 1.13 (1.06, 1.21) |  |

a Adjusted for the two other variables presented as well as maternal work situation, paternal education, maternal BMI, parity, maternal smoking, benzodiazepine, and maternal SSRI use during pregnancy (n=45 646)

**Supplementary Table 1** Items on communication skills constituting the ASQ-score

|  |
| --- |
| Items |
| Without showing him/her first, does your child point to the correct picture when you say ‘Where is the cat’ or ‘Where is the dog’? Your child must point at the correct picture. |
| When you ask your child to point at his/her eyes, nose hair, feet, ears etc., does he/she point correctly at least seven parts of the body? (The child can point at himself/herself, you or a doll. |
| Does your child use sentences made up of three or four words? |
| Without giving him/her help by pointing or using gestures, ask your child to ‘Put the shoe on the table’ and ‘Put the book under the chair’. Does your child carry out both of these actions correctly? |
| When looking at a picture book, does your child tell you what is happening or what action is taking place in the picture? (For example, ‘Barking’, ‘Running’, ‘Eating’, and ‘Crying’?) You may ask ‘What is the dog (or boy) doing?’ |
| Can your child tell you at least two things about an object he/she is familiar with? If you say, for example, ‘Tell me about your ball’, will your child answer by saying something like ‘It is round, I can throw it, it is big’? |

**References**

1. Clausen TG. International opioid consumption. *Acta Anaesthesiol Scand* 1997; 41: 162-5.

2. Fredheim OM, Skurtveit S, Breivik H, Borchgrevink PC. Increasing use of opioids from 2004 to 2007 - pharmacoepidemiological data from a complete national prescription database in Norway. *Eur J Pain* 2010; 14: 289-94. doi:10.1016/j.ejpain.2009.05.006.

3. Garcia del Pozo J, Carvajal A, Viloria JM, Velasco A, Garcia del Pozo V. Trends in the consumption of opioid analgesics in Spain. Higher increases as fentanyl replaces morphine. *Eur J Clin Pharmacol* 2008; 64: 411-5. doi:10.1007/s00228-007-0419-9.

4. Sullivan MD, Edlund MJ, Fan MY, Devries A, Brennan Braden J, Martin BC. Trends in use of opioids for non-cancer pain conditions 2000-2005 in commercial and Medicaid insurance plans: the TROUP study. *Pain* 2008; 138: 440-9. doi:10.1016/j.pain.2008.04.027.

5. Karanges EA, Blanch B, Buckley NA, Pearson SA. Twenty-five years of prescription opioid use in Australia: A whole-of-population analysis using pharmaceutical claims. *Br J Clin Pharmacol* 2016. doi:10.1111/bcp.12937.

6. Epstein RA, Bobo WV, Martin PR, Morrow JA, Wang W, Chandrasekhar R, et al. Increasing pregnancy-related use of prescribed opioid analgesics. *Ann Epidemiol* 2013; 23: 498-503. doi:10.1016/j.annepidem.2013.05.017.

7. Yazdy MM, Desai RJ, Brogly SB. Prescription Opioids in Pregnancy and Birth Outcomes: A Review of the Literature. *J Pediatr Genet* 2015; 4: 56-70. doi:10.1055/s-0035-1556740.

8. Desai RJ, Hernandez-Diaz S, Bateman BT, Huybrechts KF. Increase in prescription opioid use during pregnancy among Medicaid-enrolled women. *Obstet Gynecol* 2014; 123: 997-1002. doi:10.1097/aog.0000000000000208.

9. Bateman BT, Hernandez-Diaz S, Rathmell JP, Seeger JD, Doherty M, Fischer MA, et al. Patterns of opioid utilization in pregnancy in a large cohort of commercial insurance beneficiaries in the United States. *Anesthesiology* 2014; 120: 1216-24. doi:10.1097/aln.0000000000000172.

10. Engeland A, Bramness JG, Daltveit AK, Ronning M, Skurtveit S, Furu K. Prescription drug use among fathers and mothers before and during pregnancy. A population-based cohort study of 106,000 pregnancies in Norway 2004-2006. *Br J Clin Pharmacol* 2008; 65: 653-60. doi:10.1111/j.1365-2125.2008.03102.x.

11. Handal M, Engeland A, Ronning M, Skurtveit S, Furu K. Use of prescribed opioid analgesics and co-medication with benzodiazepines in women before, during, and after pregnancy: a population-based cohort study. *Eur J Clin Pharmacol* 2011; 67: 953-60. doi:10.1007/s00228-011-1030-7.

12. Stephansson O, Granath F, Svensson T, Haglund B, Ekbom A, Kieler H. Drug use during pregnancy in Sweden - assessed by the Prescribed Drug Register and the Medical Birth Register. *Clin Epidemiol* 2011; 3: 43-50. doi:10.2147/clep.s16305.

13. Kallen B, Borg N, Reis M. The use of central nervous system active drugs during pregnancy. *Pharmaceuticals (Basel)* 2013; 6: 1221-86. doi:10.3390/ph6101221.

14. Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain* 2009; 10: 113-30. doi:10.1016/j.jpain.2008.10.008.

15. Retningslinjer for smertelindring. The Norwegian Medical Association: [http://legeforeningen.no/PageFiles/44914/Retningslinjer%20smertebehandling%20dnlf.pdf;](http://legeforeningen.no/PageFiles/44914/Retningslinjer%20smertebehandling%20dnlf.pdf) 2009.

16. Wang MV, Lekhal R, Aaro LE, Schjolberg S. Co-occurring development of early childhood communication and motor skills: results from a population-based longitudinal study. *Child Care Health Dev* 2014; 40: 77-84. doi:10.1111/cch.12003.

17. Young AR, Beitchman JH, Johnson C, Douglas L, Atkinson L, Escobar M, et al. Young adult academic outcomes in a longitudinal sample of early identified language impaired and control children. *J Child Psychol Psychiatry* 2002; 43: 635-45.

18. Snowling MJ, Adams JW, Bishop DV, Stothard SE. Educational attainments of school leavers with a preschool history of speech-language impairments. *Int J Lang Commun Disord* 2001; 36: 173-83.

19. Beitchman JH, Wilson B, Johnson CJ, Atkinson L, Young A, Adlaf E, et al. Fourteen-year follow-up of speech/language-impaired and control children: psychiatric outcome. *J Am Acad Child Adolesc Psychiatry* 2001; 40: 75-82. doi:10.1097/00004583-200101000-00019.

20. Hill EL. Non-specific nature of specific language impairment: a review of the literature with regard to concomitant motor impairments. *Int J Lang Commun Disord* 2001; 36: 149-71.

21. Bandstra ES, Morrow CE, Mansoor E, Accornero VH. Prenatal drug exposure: infant and toddler outcomes. *J Addict Dis* 2010; 29: 245-58. doi:10.1080/10550881003684871.

22. Konijnenberg C, Melinder A. Prenatal exposure to methadone and buprenorphine: a review of the potential effects on cognitive development. *Child Neuropsychol* 2011; 17: 495-519. doi:10.1080/09297049.2011.553591.

23. 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: 1146-50. doi:10.1093/ije/dyl170.

24. Magnus P, Birke C, Vejrup K, Haugan A, Alsaker E, Daltveit AK, et al. Cohort Profile Update: The Norwegian Mother and Child Cohort Study (MoBa). *Int J Epidemiol* 2016. doi:10.1093/ije/dyw029.

25. Skurtveit S, Selmer R, Roth C, Hernandez-Diaz S, Handal M. Prenatal exposure to antidepressants and language competence at age three: results from a large population-based pregnancy cohort in Norway. *BJOG* 2014; 121: 1621-31. doi:10.1111/1471-0528.12821.

26. Odsbu I, Skurtveit S, Selmer R, Roth C, Hernandez-Diaz S, Handal M. Prenatal exposure to anxiolytics and hypnotics and language competence at 3 years of age. *Eur J Clin Pharmacol* 2015; 71: 283-91. doi:10.1007/s00228-014-1797-4.

27. Irgens LM. The Medical Birth Registry of Norway. Epidemiological research and surveillance throughout 30 years. *Acta Obstet Gynecol Scand* 2000; 79: 435-9.

28. *ATC Classification Index with DDDs*. WHO Collaborating Centre for Drug Statistics Methodology., 2013.

29. Dale PS, Price TS, Bishop DV, Plomin R. Outcomes of early language delay: I. Predicting persistent and transient language difficulties at 3 and 4 years. *J Speech Lang Hear Res* 2003; 46: 544-60.

30. Roth C, Magnus P, Schjolberg S, Stoltenberg C, Suren P, McKeague IW, et al. Folic acid supplements in pregnancy and severe language delay in children. *JAMA* 2011; 306: 1566-73. doi:10.1001/jama.2011.1433.

31. Richter J, Janson H. A validation study of the Norwegian version of the Ages and Stages Questionnaires. *Acta Paediatr* 2007; 96: 748-52. doi:10.1111/j.1651-2227.2007.00246.x.

32. Squires J, Bricker D, Potter L. Revision of a parent-completed development screening tool: Ages and Stages Questionnaires. *J Pediatr Psychol* 1997; 22: 313-28.

33. McCullagh P. Regression models for ordinal data. *J Roy Statist Soc, Series B* 1980; 42: 109-42.

34. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016. *MMWR Recomm Rep* 2016; 65: 1-49. doi:10.15585/mmwr.rr6501e1.

35. Patrick SW, Dudley J, Martin PR, Harrell FE, Warren MD, Hartmann KE, et al. Prescription opioid epidemic and infant outcomes. *Pediatrics* 2015; 135: 842-50. doi:10.1542/peds.2014-3299.

36. Olesen C, Sorensen HT, de Jong-van den Berg L, Olsen J, Steffensen FH. Prescribing during pregnancy and lactation with reference to the Swedish classification system. A population-based study among Danish women. The Euromap Group. *Acta Obstet Gynecol Scand* 1999; 78: 686-92.

37. Broussard CS, Rasmussen SA, Reefhuis J, Friedman JM, Jann MW, Riehle-Colarusso T, et al. Maternal treatment with opioid analgesics and risk for birth defects. *Am J Obstet Gynecol* 2011; 204: 314 e1-11. doi:10.1016/j.ajog.2010.12.039.

38. Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. *Int J Epidemiol* 2013; 42: 1702-13. doi:10.1093/ije/dyt183.

39. Nilsen RM, Vollset SE, Gjessing HK, Skjaerven R, Melve KK, Schreuder P, et al. Self-selection and bias in a large prospective pregnancy cohort in Norway. *Paediatr Perinat Epidemiol* 2009; 23: 597-608. doi:10.1111/j.1365-3016.2009.01062.x.

40. Skurtveit S, Selmer R, Odsbu I, Handal M. Self-reported data on medicine use in the Norwegian Mother and Child Cohort Study compared to data from the Norwegian Prescription Database. *Norsk Epidemiologi* 2014; 24: 209-16.

41. Greenland S. Basic methods for sensitivity analysis of biases. *Int J Epidemiol* 1996; 25: 1107-16.