

# In utero exposure to analgesic opioids and language development in 5-year old children

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## Key points:

- This study assessed the association between prenatal exposure to opioids and development of language competence and communication skills in 5-year old children using three different validated instruments
- In the cohort a small proportion of mothers reported use of analgesic opioids; primarily codeine in very short periods.
- No increase in risk of delayed language development or communication skills was seen in exposed children
- The results should not be generalized to strong opioids, large doses, or long duration of use during pregnancy

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

## ABSTRACT

**Purpose** An increasing consumption of opioids has been reported. The primary aim of the present study was follow-up of neurocognitive development in children exposed to analgesic opioids during pregnancy, using three different validated instruments to assess language and communication development at 5 years.

**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 at 5 years were reported by mothers on three different validated scales; The Ages and Stages Questionnaire (ASQ), The Speech and Language Assessment Scale (SLAS) and The Twenty Statements about Language-Related Difficulties list (Language20Q).

**Results** A total of 27 428 women with 33 407 singleton pregnancies were included. Use of analgesic opioids was reported in 584 pregnancies (1.7%). No associations between opioid use and lower language competence or communication skills were found. For ASQ the OR of being in the lowest category vs the group with maximum mean score was 0.82 (95%CI 0.57, 1.17), for SLAS the OR of scoring worse than typical for age vs better than typical for age was 0.84 (0.61, 1.17) in children exposed to opioids in utero. For Language20Q using the best performance category as reference, the OR of scoring in the lower performance category was 0.57 (0.35, 0.91) with exposure to opioids.

**Conclusion** Use of analgesic opioids in pregnant women does not seem to negatively affect language development or communication skills in children at 5 years.

## Introduction

A remarkable increase in use of opioid analgesics during the last two decades has been documented in the general population worldwide [1-6]. This worrying trend has been accompanied by a rise in abuse of these agents [7]. In the U.S. harm from prescription opioid misuse has increased to epidemic proportions [8]. Even among pregnant women there is a high prevalence of opioid use, especially in the U.S. [9-12]. In Norway the prevalence of use is lower, but opioids have been reported to be the CNS acting drugs most frequently prescribed to pregnant women [13]. Furthermore, studies from the U.S. pregnant population suggest that the opioid crisis in the general population extends to use during pregnancy [9, 11, 14]. Consumption data indicate an increased use of opioids also in Scandinavia [15-17]. In Norway the increased use in the general population is also seen in adolescents (<http://www.norpd.no/Prevalens.aspx>) and the latter might gradually affect use also during pregnancy. Although no increasing trend in analgesic opioid use is so far observed in the population of pregnant women in Norway [18, 19], it is important to gain knowledge on potential harmful effects to the offspring.

Any effect of drug consumption during pregnancy on language and communication development in the offspring would be an important safety issue, as language deficits in children are associated with psychiatric disorders in young adults [20-23] and are also often found to be associated with developmental delay in other domains [20, 24].

In a previous study on language competence and communication skills in 3-year old children no association with prenatal exposure to analgesic opioids was found [25]. Two different instruments, a validated language grammar rating scale [26] and the Ages and Stages Questionnaire (ASQ) [27] were used as markers of neurocognitive development. Although there were no trends towards an effect of analgesic opioids at three years it was considered important to strengthen the conclusion by studying language and communication development in the same cohort at a later stage (five years) using other validated instruments. Language skills have been shown to be more stable from age 4-5 years compared to earlier years [28, 29] and thereby stronger predictors of later outcomes [30]. As language skills in children develop and become increasingly complex with age, it is also possible to measure different aspects of language development such as articulation, syntax, and receptive skills that could be differentially affected by prenatal exposure to analgesic opioids.

The aim of the present study was to assess the effect of exposure to analgesic opioids during pregnancy on development of language and communication skills in 5-year old children.

## Material and methods

### *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 [31, 32]. Data collection is based on detailed self-administered questionnaires both during pregnancy and after birth. In the period from 1999 to 2008 pregnant women in Norway were invited by post to participate in MoBa prior to their first ultrasound scan at week 17/18 and consent to participate was given in 40.6% of pregnancies. Participants answered three questionnaires during pregnancy and 6 months, 18 months, and 3, 5, 7, 8, 13, and 14 years after birth and the study is ongoing. The cohort includes 114.500 children, 95.200 mothers and 75.200 fathers, and follow-up is continuing. 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 [33].

### *Study population*

The present study is based on data from pregnant women and their offspring having reached the age of five years (MoBa data file version 9). The age five questionnaire was returned for 34 065 children from singleton pregnancies and without malformations or chromosomal abnormalities. Pregnancies with no information on one or more language or communication skills questionnaires (n=658) were excluded, resulting in 33 407 pregnancies in 27 428 women.

### *Analgesic opioid use*

Opioids were defined as all analgesics classified in ATC-group N02A based on the Anatomic Therapeutic Chemical classification system as of 2013 [34]. Mothers were asked to report on medication use at pregnancy week 17-18, 30, and 6 months after birth [35], 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. In the two first questionnaires the women reported drug use during pregnancy in separate boxes covering 4-week intervals, and in the last questionnaire drug exposure during pregnancy after week 30. 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. In addition to categorizing opioid use as yes or no (primary analysis), we tried to capture the extent of exposure in different ways: 1) during one period only, or during two or all three pregnancy periods, and 2) repeated use (reported in  $\geq 5$  separate time intervals/tick boxes), occasional use (1-4 separate intervals), and no use during pregnancy. We also stratified opioid use by trimesters.

### *Outcome measures - language and communication development at 5 years*

The primary outcome of this study was language and communication development at five years, and three scales from the five-year questionnaire were included. The Ages and Stages Questionnaire

(ASQ5) was used to measure language function [36]. The Norwegian ASQ has shown good construct validity [36]. Different versions are developed for different age groups and the ASQ for 3-year-olds was used in our previous study on development of language and communication skills in three-year old children prenatally exposed to opioids [25]. The ASQ5 instrument consists of six questions answered by the mother. The items have three response categories (yes, sometimes, and not yet) and were scored 10, 5 and 0, respectively. In accordance with the previous study in 3-year old children [25] the mean score was calculated and grouped in three categories (maximum mean score=10, mean score 8-9.5, and mean score  $\leq 7.5$ ). For sensitivity analyses a cut-off at 1.5 SD below the mean (low score indicating risk) was chosen. This is in accordance with previous analyses of the MoBa data, and in line with ASQ recommendations [25, 27, 37].

The Speech and Language Assessment Scale (SLAS) was used to measure children's articulation, assertiveness, responsiveness, semantics and syntax skills compared with peers [38]. The mothers were asked to rate the statements in a 5-point Likert scale from 'very much lower' to 'very much higher'. A mean score of 3 corresponds to responding "typical of age" on average. The mean score was classified as "lower or very much lower"  $< 3$ , "typical of age" =3, or "higher or very much higher"  $> 3$ .

The Twenty Statements about Language-Related Difficulties list (Language 20Q) was developed to identify children with risk for language impairment [39]. The checklist is a commonly used Norwegian instrument to identify children with language impairment. The checklist consists of 20 statements describing language-related difficulties. All answers were scored on a 5-point Likert scale from 'Doesn't fit the child, absolutely wrong' to 'fits fine with the child, absolutely right'. The Language20Q is validated in a Norwegian sample, in a study of 250 children with typical language development and 48 language impaired children against Language6-16, an established scale [39]. The Language 20Q has shown acceptable fit in a confirmatory factor analysis and satisfactory ability to identify children with language difficulties in a population-based sample [40]. The overall mean score was categorized as "best performance" mean score= 1, "middle performance" mean score=1.01-2, and "lower performance" mean score  $> 2$ .

#### *Potential confounding factors*

Maternal use of opioids during pregnancy has been shown to be less common with increasing maternal and paternal education as well as in working mothers, whereas the proportion of users increased with increasing maternal age, parity and body mass index (BMI, kg/m<sup>2</sup>) [25]. The proportion of opioid users was also higher when the mother reported pain, symptoms of anxiety and depression according to Hopkins Symptom Checklist (HSCL $\geq 2$ ), chronic disease, smoking, paracetamol use, triptans, benzodiazepines, SSRIs and illegal drugs [25]. These variables as well as paternal age, whether the pregnancy was planned or not, and marital status, were considered to be potential confounding factors and were included in adjusted models. Since the three pregnancy questionnaires posed questions on pain slightly differently, all categories of reported pain were merged into a dichotomous pain variable. Maternal chronic disease was defined if the mother reported asthma, diabetes, hypertension, arthritis, lupus, Crohn's disease, epilepsy, multiple sclerosis or cancer in the first questionnaire.

### *Statistics*

The scales were constructed to capture children with specific problems and had highly skewed distributions (i.e. few mothers reported language difficulties) as shown in Figure 1. The variables were therefore transformed into categorical variables. Multinomial logistic regression was applied to estimate the association between prenatal analgesic opioid exposure and language and communication development, respectively. All outcome variables were ordered in three categories in the primary analyses. Cut-offs were chosen based on a combination of clinical reasoning and enough analgesic opioid users in each category. Binary logistic regression was used to estimate the association between prenatal analgesic opioid exposure and ASQ-score below -1.5 SD.

Additional sensitivity analyses of the same outcomes in three to five categories using both ordinal and multinomial logistic regression, and binary logistic regression with different two category cut-offs of the outcome variables were also performed.

Unadjusted as well as adjusted analyses, including all potential confounding factors 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*

The establishment of MoBa and initial data collection was based on a license from the Norwegian Data protection agency and approval from The Regional Committee for Medical Research Ethics. The MoBa cohort is currently regulated by the Norwegian Health Registry Act. The current study was approved by The Regional Committee for Medical Research Ethics 2015/1897/REK sør-øst. Informed consent was obtained from each participant upon recruitment.

## Results

Analgesic opioid use was reported in 584 (1.7%) of the 33 407 pregnancies. The substance primarily used was codeine in combination with paracetamol. Use of codeine was reported in 526 (90%) of the exposed pregnancies, whereas a strong opioid was reported to have been used in 83 (14%). The extent of exposure was limited. Repeated use defined as reported in at least 5 time intervals during pregnancy was reported by 60 mothers. A total of 466 mothers reported analgesic opioid use in one pregnancy period only, and in 28 pregnancies the mother had consumed an opioid one or more times during all three periods of the pregnancy.

The proportion exposed to opioids during pregnancy by parental characteristics is presented in Table 1. Table 2 shows the distribution of language and communication skills according to the three different instruments in children with or without exposure to analgesic opioids during pregnancy. No obvious differences between exposed and unexposed children were observed. On the ASQ, 6.5% of children have a mean score in the lowest development category in both groups. The proportion scoring lower than typical for age on the SLAS is also the same in exposed and unexposed children, 8.4%. There was a small numerical difference in the proportion classified in the lower performance category on Language20Q, 4.5% in children prenatally exposed to opioids and 5.9% in unexposed children. It is demonstrated also in Figure 1 that the distributions of scores on the three different scales are very similar in exposed and unexposed children.

Table 3 shows estimated odds ratios in unadjusted and adjusted analyses of language and communication development. No association with use of analgesic opioids was shown in unadjusted analyses for either of the instruments.

In analyses adjusted for paracetamol, any pain, chronic disease, planned pregnancy, smoking, mother's education, father's education, mother's work situation, mother's age, father's age, parity, marital status, body mass index, alcohol consumption, anxiety and depression, illegal drugs, benzodiazepine use, triptan use, and SSRI use, the results were similar. No association between opioid use and development according to ASQ or SLAS was demonstrated. For Language20Q the OR of the lower performance score category with the best category as reference was estimated to OR=0.57 (95% CI 0.35, 0.91) in children exposed to opioids in utero. Models without adjustment for pain in addition to the other covariates led to the same results as those presented in the table.

The additional ASQ z-score analysis with cutoff 1.5 SD below the mean corresponded exactly to using a cutoff of  $ASQ \leq 7.5$ , OR=0.91 (95% CI 0.65, 1.28). For SLAS and Language20Q various analyses of 3 to 5 categories with different cutoffs gave comparable results to those presented in Table 3. Analyses with exposure classified in number of pregnancy periods or as no, occasional (reported in 1-4 time intervals) or repeated use ( $\geq 5$  time intervals) did not reveal any pattern of increased risk with increased exposure (Supplementary tables 1 and 2). Stratification by trimester led to small numbers exposed, and no pattern in the estimated associations was seen (data not shown).

## Discussion

This prospective study assessed the association between prenatal exposure to analgesic opioids and language and communication development in children at 5 years of age. No associations were found between opioid exposure and scores on three instruments measuring different aspects of language development such as function (ASQ5), a composite of articulation, assertiveness, responsiveness, semantics, and syntax skills (SLAS), or language related difficulties (Language 20Q).

To our knowledge only one study has assessed the association between exposure to analgesic opioids during pregnancy and neurocognitive effects as measured by validated instruments on language development and communication skills [25] and to our knowledge no studies of an association in older children have been performed. Even if no harmful associations were seen in 3-year-olds, it was thus considered important to add longer follow-up and assess any association in the same cohort at five years of age using different instruments.

In line with the results in 3-year old children, we found no association between prenatal exposure to analgesic opioids and language and communication development at the age of five. To increase robustness and sensitivity, three validated instruments measuring different aspects of language development were applied. The estimated associations are relatively precise, and the upper limits of the 95% confidence intervals seem to preclude any large, undetected effect of exposure to analgesic opioids during pregnancy.

A major strength of the present study is its prospective design including three questionnaires on drug consumption during pregnancy which reduces the risk of long-term recall bias. The participants responded to many questions on sociodemographic and health related issues, and it was thus possible to adjust for several potential confounding factors. However, residual confounding cannot be excluded as unmeasured confounders may exist. The apparent protective effect of opioid use according to the adjusted analysis of Language20Q may well be due to residual confounding, or it may be a chance finding. The fact that the upper limit of the 95% CI is below 1 should not receive too much attention since several 95% confidence intervals have been estimated.

Only women agreeing to participate in MoBa have been included in the study. This is probably a selected group of pregnant women. It has been shown that MoBa participants have a healthier lifestyle than the total pregnant population in Norway [41] and these women may also be more cautious about drug use during pregnancy. The prevalence of opioid use is lower in the MoBa cohort than what has been reported in studies based on the Norwegian Prescription Database [18, 19]. One explanation may be that prescribed drugs may not actually be consumed, another that MoBa participants comprise a selected sample of pregnant women in Norway. However, a comparison of MoBa participants and all women giving birth in Norway suggests that estimates of exposure-outcome associations are unbiased [41]. Due to drop out as the child is ageing, as well as missing information of language development on one or more instruments in mothers still participating, the number of pregnancies included in this study is only approximately one third of all pregnancies included in the full MoBa cohort. The dropout does not affect exposure estimates, however. In the full MoBa cohort the percentage reporting exposure to opioids is 1.7%, i.e. identical to the estimate in our study.

The study includes a large number of pregnancies, but only 584 children (1.7%) had been exposed to analgesic opioids during pregnancy according to mothers' self-report. We do not have detailed



information on dosage or duration of use of opioids but have tried to capture extent of exposure by 1) the number of pregnancy periods with reports of opioid use (0-3), and 2) identification of repeated use defined as exposure to an opioid in at least 5 time intervals during pregnancy, not necessarily consecutively. The number of mothers with repeated use according to the above definition was only 60 (<0.2%) and in utero exposure to prescribed analgesic opioids is thus low and rare in this cohort. Our results should therefore not be extended to long-term use or high doses.

Previous studies have demonstrated a lower proportion of self-reported drug use in MoBa compared to data from the NorPD in the same sample [42]. This may partly be due to dispensed drugs not being consumed. However, there is also a risk that mothers underreport their use of drugs in the questionnaires. Nevertheless, it has been shown that self-reported tobacco use in pregnant women in MoBa is a valid marker for actual exposure [43], which supports the validity of self-reported opioid use. Since the questionnaires are filled in three times during pregnancy, the potential for recall bias is reduced. Whereas we cannot preclude some misclassification due to underreporting, we strongly believe that when a pregnant woman states that she has used a specific medication, this is the case. Thus, specificity is believed to be high. It has been shown that when prevalence of exposure is low, specificity is more important than sensitivity. [44] As exposure was registered without knowledge of future outcome, it seems reasonable to assume non-differential misclassification. We therefore regard severe bias of the estimated association as unlikely, but a small bias towards the null cannot be completely ruled out.

In Norway, the weak opioid codeine is the dominating prescribed opioid analgesic (30 mg per tablet [10]) and this is the case also in the MoBa cohort. Only few pregnant women reported use of tramadol or a strong opioid like oxycodone and it was not possible to study specific opioids separately. An exploratory unadjusted analysis of strong opioids was performed in the study of 3-year old children [25] and led to approximately the same results as for all opioids combined.

Parental self-report is generally considered appropriate to measure early expressive vocabulary, especially for severe language delay. We have used validated instruments on language and communication development, and both ASQ and L20Q have been validated in Norwegian. The distributions of mean scores were extremely skewed for all three scales and after inspection of residuals it was not considered appropriate to estimate associations using multiple linear regression analysis. We therefore chose multinomial regression with three categories as the primary analysis of all three scales. Supplementary analyses with different cutoffs and up to five categories resulted in very small numbers in some categories and did not reveal any additional information. A recommended cutoff for clinical follow-up in a screening setting has been established for ASQ (1.5SD) [27] and we performed an additional analysis using this strategy. The recommended z-score cut-off corresponded exactly to the lowest of the three ASQ3 score categories ( $\leq 7.5$ ) and no additional information was achieved.

### *Conclusion*

No association between maternal analgesic opioid use during pregnancy and language and communication development in 5-year old children was detected. The estimated upper limits of the confidence intervals preclude any strong effect on language and communication development. Health care providers should in any case carefully consider the need of analgesic treatment in a

pregnant woman before prescribing an opioid. In this cohort a small proportion reported use of analgesic opioids; primarily codeine in very short periods. The results should thus not be generalized to strong opioids, large doses, or long duration during pregnancy.

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**Table 1** Exposure to opioids during pregnancy by parental characteristics

	Exposed pregnancies		Unexposed pregnancies	
	n	%	n	%
<b>Maternal age in years (n=33 407)</b>				
<25	41	1.6	2 569	98.4
25-29	186	1.7	10 630	98.3
30-34	228	1.7	13 410	98.3
≥35	129	2.0	6 214	98.0
<b>Paternal age in years (n=33 330)</b>				
<25	13	1.2	1 075	98.8
25-29	129	1.8	7 093	98.2
30-34	231	1.7	13 070	98.3
≥35	208	1.8	11 511	98.2
<b>Maternal education (n=33 282)</b>				
≤12	179	2.2	7 915	97.8
≥13	405	1.6	24 783	98.4
<b>Paternal education (n=32 592)</b>				
≤12	269	2.0	13 434	98.0
≥13	304	1.6	18 585	98.4
<b>Marital status (n=33 407)</b>				
Married or living with partner	560	1.7	31 758	98.3
Other	24	2.2	1 065	97.8
<b>Parity (n= 33 407)</b>				
0	252	1.6	15 700	98.4
1	216	1.9	11 387	98.1
≥2	116	2.0	5 736	98.0
<b>Planned pregnancy (n=33 130)</b>				
No	95	1.8	5 221	98.2
Yes	483	1.7	27 331	98.3
<b>Maternal work situation (n=33 290)</b>				
Working	516	1.7	30 500	98.3
Not working	35	2.2	1 571	97.8
Disability pensioner	23	10.2	202	89.8
Other	9	2.0	434	98.0
<b>Maternal BMI (n=32 869)</b>				
<25	356	1.5	22 697	98.5
25-29	143	2.0	6 859	98.0
30-34	52	2.5	1 994	97.5
≥35	28	3.7	740	96.4
<b>Maternal smoking week 17-18 (n=32 076)</b>				
No	506	1.7	29 668	98.3
Sometimes	37	2.9	1 246	97.1
Daily	20	3.2	599	96.8
<b>Maternal alcohol use during pregnancy (n=33 362)</b>				
No	275	1.6	17 056	98.4
Occasionally	281	1.9	14 503	98.1
Regularly	27	2.2	1 220	97.8
<b>Maternal chronic disease (n=33 407)</b>				
No	518	1.6	30 991	98.4
Yes	66	3.5	1 832	96.5
<b>Maternal pain during pregnancy (n=33 407)</b>				
No	21	0.7	2 993	99.3
Yes	563	1.9	29 830	98.1

<b>Maternal anxiety and depression during pregnancy; HSCL <math>\geq</math>2 (n=32 651)</b>				
No	469	1.6	29 432	98.4
Yes	92	3.3	2 658	96.7
<b>Maternal triptan use in pregnancy (n=33 407)</b>				
No	551	1.7	32 559	98.3
Yes	33	11.1	264	88.9
<b>Maternal benzodiazepine use in pregnancy, including z- hypnotics (n=33 407)</b>				
No	551	1.7	32 610	98.3
Yes	26	10.9	213	89.1
<b>Maternal SSRI use in pregnancy (n=33 407)</b>				
No	574	1.7	32 576	98.3
Yes	10	3.9	247	96.1
<b>Maternal paracetamol use in pregnancy (n=33 407)</b>				
No	132	0.7	18 554	99.3
Yes	452	3.1	14 269	96.9
<b>Maternal illegal drug use in pregnancy (n=33 407)</b>				
No	578	1.7	32 742	98.3
Yes	6	6.9	81	93.1
<b>Maternal folic acid supplements in early pregnancy (n=33 407)</b>				
No	124	1.9	6 361	98.1
Yes	460	1.7	26 462	98.3



**Table 2. Distribution of language and communication development at 5 years with and without prenatal exposure to prescribed opioids.**

Performance categories	Opioids during pregnancy, n (%)	
	Yes n=584	No n=32 823
<b>ASQ5</b>		
Lower (mean score $\leq 7.5$ )	38 (6.5)	2 143 (6.5)
Middle (mean score 8-9.5)	196 (33.6)	11 032 (33.6)
Best possible (mean score 10)	350 (59.9)	19 648 (59.9)
<b>SLAS</b>		
Lower or very much lower than typical for age (mean score $>3$ )	49 (8.4)	2 759 (8.4)
Typical for age (mean score=3)	109 (18.7)	6 321 (19.3)
Higher or very much higher than typical for age (mean score $<3$ )	426 (73.0)	23 743 (72.3)
<b>Language 20Q</b>		
Lower (mean score $\geq 2$ )	26 (4.5)	1 924 (5.9)
Middle (mean score 1.01-1.99)	379 (64.9)	19 971 (60.8)
Best (mean score 1)	179 (30.7)	10 928 (33.3)

**Table 3. Association between exposure to opioid during pregnancy and language and communication development at 5 years.**

Performance category	Opioid exposure	Unadjusted model n=33 407	Unadjusted model n=30 000*	Adjusted model** n=30 000*
		OR (95% CI)	OR (95% CI)	OR (95% CI)
<b>ASQ5</b>				
Middle (mean score 8-9.5) vs best possible (mean score 10)	No	1	1	1
	Yes	1.00 (0.84, 1.19)	0.97 (0.80, 1.17)	0.90 (0.74, 1.08)
Lower (mean score ≤7.5) vs best possible (mean score 10)	No	1	1	1
	Yes	1.00 (0.71, 1.39)	0.99 (0.69, 1.41)	0.82 (0.57, 1.17)
<b>SLAS</b>				
Typical for age (mean score 3) vs higher or much higher (mean score <3)	No	1	1	1
	Yes	0.96 (0.78, 1.19)	0.95 (0.76, 1.19)	0.99 (0.79, 1.25)
Lower or very much lower (mean score >3) vs higher or much higher (mean score <3) than typical for age	No	1	1	1
	Yes	0.99 (0.73, 1.33)	0.91 (0.65, 1.26)	0.84 (0.61, 1.17)
<b>Language 20Q</b>				
Middle (mean score 1.01-1.99) vs best performance category (mean score 1)	No	1	1	1
	Yes	1.16 (0.97, 1.39)	1.16 (0.96, 1.40)	1.04 (0.86, 1.26)
Lower (mean score ≥2) vs best performance category (mean score 1)	No	1	1	1
	Yes	0.83 (0.55, 1.25)	0.73 (0.46, 1.17)	0.57 (0.35, 0.91)

\*cases with missing values on one or more covariates excluded \*\* adjusted for paracetamol, any pain, chronic disease, planned pregnancy, smoking, mother's education, father's education, mother's work situation, mother's age, father's age, parity, marital status, body mass index, alcohol consumption, anxiety and depression (mean HSCL), illegal drugs, benzodiazepine use, triptan use, SSRI use

**Supplementary table 1. Distribution of language and communication development at 5 years according to number of pregnancy periods with reported exposure to prescribed opioids.**

Performance categories	Opioids during pregnancy, n (%)		
	No opioid use n=32 823	One period n=466	Two or three periods n=118
<b>ASQ5</b>			
Lower (mean score ≤7.5)	2 143 (6.5)	32 (6.9)	6 (5.1)
Middle (mean score 8-9.5)	11 032 (33.6)	157 (33.7)	39 (33.1)
Best possible (mean score 10)	19 648 (59.9)	277 (59.4)	73 (61.9)
<b>SLAS</b>			
Lower or very much lower than typical for age (mean score >3)	2 759 (8.4)	37 (7.9)	12 (10.2)
Typical for age (mean score=3)	6 321 (19.3)	91 (19.5)	18 (15.3)
Higher or very much higher than typical for age (mean score<3)	23 743 (72.3)	338 (72.5)	88 (74.6)
<b>Language 20Q</b>			
Lower (mean score ≥2)	1 924 (5.9)	23 (4.9)	3 (2.5)
Middle (mean score 1.01-1.99)	19 971 (60.8)	304 (65.2)	75 (63.6)
Best (mean score 1)	10 928 (33.3)	139 (29.8)	40 (33.9)

**Supplementary table 2. Distribution of language and communication development at 5 years according to extent of reported prescribed opioid use during pregnancy.**

Performance categories	Opioids during pregnancy, n (%)		
	No opioid use n=32 823	Occasional use n=524	Repeated use n=60
<b>ASQ5</b>			
Lower (mean score ≤7.5)	2 143 (6.5)	35 (6.7)	3 (5.0)
Middle (mean score 8-9.5)	11 032 (33.6)	179 (34.2)	17 (28.3)
Best possible (mean score 10)	19 648 (59.9)	310 (59.2)	40 (66.7)
<b>SLAS</b>			
Lower or very much lower than typical for age (mean score >3)	2 759 (8.4)	44 (8.4)	5 (8.3)
Typical for age (mean score=3)	6 321 (19.3)	99 (18.9)	10 (16.7)
Higher or very much higher than typical for age (mean score<3)	23 743 (72.3)	381 (72.7)	45 (75.0)
<b>Language 20Q</b>			
Lower (mean score ≥2)	1 924 (5.9)	24 (4.6)	2 (3.3)
Middle (mean score 1.01-1.99)	19 971 (60.8)	340 (64.9)	39 (65.0)
Best (mean score 1)	10 928 (33.3)	160 (30.5)	19 (31.7)

Occasional use: reported in 1-4 tick boxes during pregnancy, repeated use: reported in ≥5 tick boxes during pregnancy

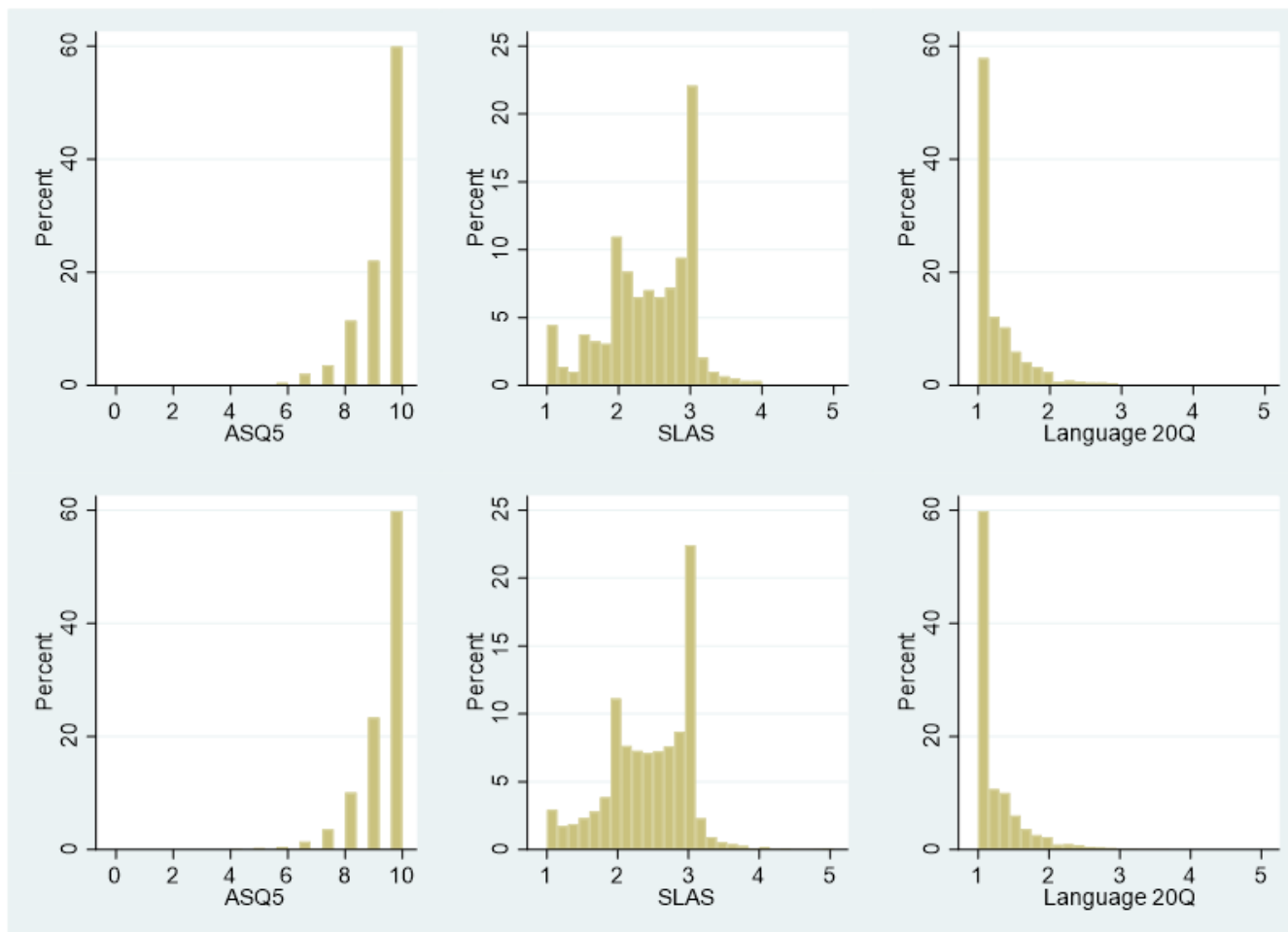


Figure 1. Distribution of language and communication skills in children exposed (upper panels) and not exposed (lower panels) to opioids during pregnancy.