Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.
Study sample:
The MoBa study recruited pregnant women between 1999-2008, however, they youngest children, born in the period 1999-2001, could not be included in the study due to lack of consent as they turned 18 before the end of follow-up in 2018.

Outcome:
National tests were introduced in Norway as part of the national quality assessment system in 2004, however, tests have been performed every year since 2007. National tests are mandatory, and only children with special educational or special language training needs were exempted from a test. National tests are held in the first semester of the fifth, eight, and ninth grade and test the basic skills of reading/literacy, numeracy, and English language. The pupils perform the tests on computers and have 90 minutes to complete one test. The tests are scored from zero and upwards. eTable 2 and eTable 3 shows a simple comparison of scores between the MoBa participants and the complete population of test takers in each subject and each test year. eFigure 1 shows the distribution of scores in literacy, numeracy and English. Below is a more thorough description of what is being tested in each subject.

Literacy
Reading and language is arguably the most important academic skill learned in school. The reading test is done by presenting the student with a text (roughly an A4 sheet 12pt text) and then asking multiple-choice questions in different complexity about the text. This measures speed of reading as well as the ability to decompose a longer segment of coherent text. The exams are designed to test for the following abilities: to find information in a text, to interpret a text, and to reflect and evaluate the content of a text. While volume training and exposure are important for most scholastic skills, this is especially important for reading. Volume training by reading different materials and books of increasing complexity is the primary way of excelling in reading and reflecting over writing content. The raw test scores range between a minimum of 0 points to a maximum of 34 points.

Numeracy
Unlike reading, high volume and exposure is not sufficient for excelling in mathematics, with large volume being potentially detrimental to performance. The test should reflect multiple sub-domains in mathematics, such as numeracy, geometry, and statistics. Numeracy is the basics of number manipulation, but is limited to as addition, subtraction, multiplication, and division. Geometry and measurements, are the two and three dimensional representations of numeracy, where comparing volumes and surfaces of different measurements are evaluated. Statistics is operationalized as a visualization of data, mostly into charts and diagrams, with some data summary, such as mean, median, and factors. The raw test scores range between a minimum of 0 points to a maximum of 45 points.

English
The tests are designed to measure three different aspects of English language; general reading, vocabulary and grammar. The raw test scores range between a minimum of 0 points to a maximum of 50 points.

Covariates:
Family income was assessed by income-to-needs-ratio (ITNR), which is family income after tax divided by the poverty level i.e. consumption equivalents. The EU-60 standard was applied. The higher ITNR level, the better off are the family. ITNR was grouped into 3 levels (ITNR <2, ITNR 2-3, ITNR≥3). ITNR was assessed one year prior to childbirth.

Paternal medication use was collected in the Father’s questionnaire. The fathers could report if they had used medications in the period 6 months before their partner became pregnant. Among our study sample of 64 256 children, we have data on 51 692 of the fathers. Among these, 943 (1.8 %) reported use of opioids. Among the fathers using opioids before their partner became pregnant (n=943), 5.0%, 3.7% and 91.3% had partners that used opioids during pregnancy, pre-pregnancy only and no use, respectively.
Statistical analysis:
In a sub-analysis, we used unexposed children as reference group. For this analysis we used propensity scores with standardized mortality/morbidity ratio weights (SMR), instead of inverse probability of treatment (IPT) weights as were used in the main analysis with discontinuers. According to Stürmer et. al. SMR weights are preferred when we have an unexposed reference group or when the reference group is not well defined. However, when we have an active reference (or disease comparator), the inverse probability of treatment (IPT) weights can be used. This is because with an active reference, we assume that the prevalence of the indication for treatment is somewhat similar between the two groups, thus reducing the potential for violations of the positivity assumption. Then it would make sense to estimate the average treatment effect in the entire population and thus IPT weights can be used. IPT weights creates a pseudo-population of both the exposed and unexposed, which has the same covariate distribution as the overall population of exposed and unexposed. Every person is weighted by the inverse of the probability of receiving the treatment actually received. This answers the question: “what would have happened if everyone had been exposed versus what would have happened if everyone had not been exposed?” Standardized mortality/morbidity ratio (SMR) weights creates a pseudo-population of the unexposed, which has the same covariate distribution as the exposed. Every exposed person receives the weight of 1, while the unexposed are down-weighted and receives the weight of PS odds (PS/1-PS). With the SMR weights, we estimate the average treatment effect in the treated, which answers the question “what would have happened if those actually exposed had not been exposed?”.

Subanalyses and sensitivity analyses:
In a sensitivity analysis, we compared children exposed to opioid analgesics in one period with children exposed in 2 or more intervals during pregnancy to examine associations with length of exposure.

In a sensitivity analysis, we used an alternative model specification (cf. eTable 6). Use of co-medications was measured in the period 6 months before pregnancy, and we removed symptoms of depression and anxiety measured in gestational week 17.

In the last sensitivity analysis, we restricted the study sample to women who had returned the MoBa questionnaire at 6 months post-partum (MoBa Q4), to ensure that every woman had complete information on exposure, and repeated our main analysis.
eResults. Sensitivity Analyses

Children exposed to opioid analgesics in one interval scored similar to those exposed in two intervals or more during pregnancy (eTable 9).

In the analysis with the alternative model specification, point estimates did not differ substantially from the main analysis (data not shown). However, only associations of prenatal exposure in first trimester and in 2-3 4-week intervals with lower scores on the numeracy test remained significant. No other associations were found.

When MoBa Q4-returned was required to enter the study sample, the sample included 57 954 pregnancies. The point estimates were similar to those reported in the main analysis and conclusions remain the same (Data not shown).
eTable 1. Relevant indications for opioid use during pregnancy.

| Indications                  | MoBa Q1 | MoBa Q3 |
|------------------------------|---------|---------|
| Pelvic girdle pain           | ●       | ●       |
| Abdominal pain               | ●       |         |
| Back pain                    | ●       | ●       |
| Neck and shoulder            |         |         |
| Arthritis                    | ●       |         |
| Sciatica                     | ●       |         |
| Fibromyalgia                 | ●       |         |
| Other pains in muscles/joints|         | ●       |
| Migraine                     | ●       |         |
| Other headache               | ●       |         |
| Headache / migraine          |         | ●       |

Abbreviations: MoBa, The Norwegian Mother, Father and Child Cohort; Q1, the first MoBa questionnaire; Q3, the third MoBa questionnaire.
eTable 2. Test scores among children in MoBa and all children in Norway who took the test, according to subject and test year.

| Test year | MoBa children (n=93,416) | General population |
|-----------|---------------------------|---------------------|
|           | N | Raw scores (mean ± SD) | N | Raw scores (mean ± SD) |
|          |   |                          |    |                          |
| **Literacy** | | | | |
| 2011      | 14 | 24.0 ± 3.4 | 54,826 | 21.3 ± 5.9 |
| 2012      | 7434 | 19.3 ± 6.0 | 54,319 | 18.6 ± 6.2 |
| 2013      | 10,869 | 22.4 ± 6.5 | 55,314 | 21.5 ± 6.7 |
| 2014      | 11,707 | 19.7 ± 5.8 | 55,662 | 18.8 ± 6.1 |
| 2015      | 13,484 | 21.5 ± 6.3 | 55,611 | 20.3 ± 6.5 |
| 2016      | 15,421 | 20.1 ± 7.0 | 58,297 | 18.4 ± 7.1 |
| 2017      | 14,197 | 20.7 ± 6.1 | 58,192 | 19.0 ± 6.4 |
| 2018      | 11,822 | 19.1 ± 5.9 | 59,792 | 17.4 ± 6.1 |
| Overall   | 84,948 | 20.5 ± 6.4 | 452,213 | 19.4 ± 6.5 |
| **Numeracy** | | | | |
| 2011      | 14 | 30.1 ± 6.5 | 55,122 | 26.0 ± 8.5 |
| 2012      | 7510 | 27.7 ± 8.4 | 54,790 | 26.7 ± 8.6 |
| 2013      | 11,063 | 26.5 ± 9.1 | 56,298 | 25.2 ± 9.4 |
| 2014      | 11,932 | 25.5 ± 9.1 | 57,235 | 24.1 ± 9.3 |
| 2015      | 13,818 | 25.5 ± 9.0 | 57,117 | 23.8 ± 9.6 |
| 2016      | 15,500 | 25.5 ± 9.0 | 58,829 | 23.3 ± 9.2 |
| 2017      | 14,246 | 25.2 ± 9.3 | 58,710 | 22.8 ± 9.5 |
| 2018      | 11,897 | 27.6 ± 9.1 | 60,478 | 24.8 ± 9.5 |
| Overall   | 85,980 | 26.1 ± 9.2 | 458,579 | 24.6 ± 9.3 |
| **English** | | | | |
| 2011      | - | - | - | - |
| 2012      | 7445 | 27.7 ± 11.3 | 54,426 | 27.3 ± 11.4 |
| 2013      | 10,996 | 27.9 ± 10.5 | 55,978 | 27.5 ± 10.6 |
| 2014      | 11,829 | 27.5 ± 9.8 | 56,764 | 26.8 ± 10.0 |
| 2015      | 13,723 | 26.8 ± 10.4 | 56,625 | 26.3 ± 10.6 |
| 2016      | 15,365 | 26.6 ± 9.3 | 58,229 | 25.7 ± 9.5 |
| 2017      | 14,142 | 27.4 ± 9.6 | 58,080 | 26.4 ± 9.8 |
| 2018      | 11,788 | 27.4 ± 10.4 | 59,795 | 26.4 ± 10.7 |
| Overall   | 85,288 | 27.3 ± 10.1 | 399,897 | 26.6 ± 10.4 |

Abbreviations: MoBa, The Norwegian Mother, Father and Child cohort
* Due to large technical problems the Norwegian directorate of education and training cancelled national tests in English in 2011.5
**eTable 3. National test results of the MoBa children presented as z scores.**

| Test subject             | MoBa children, n=93 416 | N  | Mean scores (SD) | Median scores (P25, P75) |
|--------------------------|-------------------------|----|------------------|--------------------------|
| Literacy 5th grade       | 84 948                  |    | 0.21 (0.97)      | 0.37 (-0.48, 0.97)       |
| Numeracy 5th grade       | 85 980                  |    | 0.20 (0.98)      | 0.23 (-0.54, 0.96)       |
| English 5th grade        | 85 288                  |    | 0.07 (0.98)      | 0.03 (-0.69, 0.88)       |

Abbreviations: MoBa, The Norwegian Mother, Father and Child cohort
P25 indicate the 25th percentile, and P75 indicate the 75th percentile of the z-score.
eTable 4. Overview of data source of covariates.

| Variable                                             | Data Source  |
|------------------------------------------------------|--------------|
| Maternal age                                         | MBRN         |
| Marital status                                       | MoBa Q1      |
| Parity                                               | MBRN         |
| Education level                                      | SSB          |
| Family income                                        | SSB          |
| Pre-pregnancy BMI                                    | MoBa Q1      |
| Smoking status at start of pregnancy                 | MBRN         |
| Alcohol use                                          | MoBa Q1      |
| Symptoms of anxiety depression                       | MoBa Q1      |
| Maternal chronic diseases before pregnancy           | MoBa Q1      |
| Co-medications                                       | MoBa Q1      |
| - Paracetamol                                        |              |
| - Triptans                                           |              |
| - NSAIDS                                              |              |
| - Antidepressants                                    |              |
| - Benzodiazepine and benzodiazepine-like drugs        |              |
| - Antiepileptic                                      |              |
| - Anti-psychotics                                    |              |
| Paternal age                                         | MBRN         |
| Paternal education                                   | SSB          |
| Child sex                                            | MBRN         |
| Time of year the baby was born                       | MBRN         |

Abbreviations: MBRN, The Medical Birth Registry of Norway; MoBa, The Norwegian Mother, Father and Child Cohort; SSB, Statistics Norway; Q1, The first MoBa questionnaire.
eTable 5. Characteristics of generated weights

|                        | Literacy |                                         | Numeracy |                                         | English |                                         |
|------------------------|----------|------------------------------------------|----------|------------------------------------------|---------|------------------------------------------|
|                        | Estimated IPTW |                           | Estimated IPTW |                           | Estimated IPTW |                           |
|                        | Mean (SD) | Min-Max       | Mean (SD) | Min-Max       | Mean (SD) | Min-Max       |
| Pre-pregnancy exposed only | Reference | Reference | Reference | Reference | Reference | Reference |
| Exposed                | 1.0 (0.3) | 0.6-5.6      | 1.0 (0.3) | 0.6-5.3      | 1.0 (0.3) | 0.6-5-8      |
| **Timing of exposure** |          |              |          |              |          |              |
| 1<sup>st</sup> trimester | 1.0 (0.5) | 0.5-9.7      | 1.0 (0.6) | 0.5-8.4      | 1.0 (0.5) | 0.5-9.7      |
| 2<sup>nd</sup> trimester | 1.0 (0.3) | 0.5-4.8      | 1.0 (0.3) | 0.5-5.6      | 1.0 (0.4) | 0.5-6.4      |
| 3<sup>rd</sup> trimester | 1.0 (0.4) | 0.4-5.4      | 1.0 (0.4) | 0.4-5.1      | 1.0 (0.4) | 0.4-6.2      |
| **Duration of exposure** |          |              |          |              |          |              |
| 1 interval             | 1.0 (0.2) | 0.6-3.3      | 1.0 (0.2) | 0.6-3.0      | 1.0 (0.2) | 0.6-3.0      |
| 2-3 intervals          | 1.0 (0.4) | 0.3-4.9      | 1.0 (0.4) | 0.3-4.7      | 1.0 (0.4) | 0.3-4.8      |
| 4 or more intervals    | 1.0 (0.6) | 0.2-11.2     | 0.9 (0.7) | 0.2-13.6     | 1.0 (0.7) | 0.2-16.2     |

Abbreviations: IPTW, Inverse probability of treatment weights; SD, Standard deviation.
eTable 6. Overview of alternative model specifications.

| Model         | Description                                                                                                                                                                                                                                                                                                                                 |
|---------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Main          | 1  | sIPTW:  
Numerator: Probability of exposure.  
Denominator: Maternal age, marital status, parity, maternal and paternal education level (in birth year), family income-to-needs-ratio (1 year prior to child birth), pre-pregnancy BMI, chronic disease pp, alcohol use (Q1), smoking habits at pregnancy start, use of co-medications (Q1), symptoms of anxiety and depression (Q1), time of year the baby was born (before/after summer) and paternal age. |
| Alternative model | 2  | sIPTW:  
Numerator: Probability of exposure.  
Denominator: Maternal age, marital status, parity, maternal and paternal education level (in birth year), family income-to-needs-ratio (1 year prior to child birth), pre-pregnancy BMI, chronic disease pp, smoking habits at pregnancy start, use of co-medications (pp), time of year the baby was born (before/after summer) and paternal age.  
In this model, all covariates included are measured before pregnancy. |

Abbreviations: sIPTW: stabilized inverse probability of treatment weight; BMI, body mass index; pp, pre-pregnancy; Q1, the first MoBa questionnaire. Symptoms of anxiety/depression was measured by a short version of the Hopkins Symptom Checklist (SCL-5) in the first MoBa questionnaire.
**eTable 7. Use of specific opioids during pregnancy.**

| Substance (ATC code)                                      | Exposed during pregnancy, n=1483 (%) |
|----------------------------------------------------------|--------------------------------------|
| Morphine (N02AA01)                                       | 68 (4.6)                             |
| Oxycodone (N02AA05)                                      | 9 (0.6)                              |
| Codeine, combinations excluding psycholeptics (N02AA59)  | 1342 (90.5)                          |
| Ketobemidone (N02AB01)                                   | 54 (3.6)                             |
| Buprenorphine (N02AE01)                                  | 3 (0.2)                              |
| Ketobemidone and antispasmodics (N02AG02)                | 18 (1.2)                             |
| Tramadol (N02AX02)                                       | 41 (2.8)                             |

Women may have used more than one medication.

Abbreviations: ATC, Anatomical Therapeutic Chemical Classification system.
eTable 8. Role of gender on scholastic skills in fifth grade according to exposure status.

| Sample | Boys | | | Girls | | |
|--------|------|---|---|------|---|---|
|        | N    | Crude β (95% CI) | Weighted β (95% CI) | N    | Crude β (95% CI) | Weighted β (95% CI) |
| **Literacy** | | | | | | |
| Pre-pregnancy exposed | 353 Reference | Reference | 368 Reference | Reference |
| Exposed | 717 -0.05 (-0.18, 0.08) | -0.04 (-0.19, 0.11) | 728 -0.07 (-0.18, 0.05) | -0.08 (-0.20, 0.04) |
| Unexposed | 30 608 Reference | Reference | 30 101 Reference | Reference |
| Exposed | 717 -0.04 (-0.11, 0.04) | 0.01 (-0.06, 0.09) | 728 -0.07 (-0.14, -0.01) | -0.03 (-0.10, 0.04) |
| **Numeracy** | | | | | | |
| Pre-pregnancy exposed | 354 Reference | Reference | 368 Reference | Reference |
| Exposed | 731 -0.07 (-0.20, 0.05) | -0.06 (-0.19, 0.08) | 738 -0.11 (-0.23, 0.002) | -0.10 (-0.22, 0.01) |
| Unexposed | 31 125 Reference | Reference | 30 325 Reference | Reference |
| Exposed | 731 -0.04 (-0.12, 0.03) | 0.02 (-0.05, 0.10) | 738 -0.13 (-0.20, -0.06) | -0.06 (-0.13, 0.01) |
| **English** | | | | | | |
| Pre-pregnancy exposed | 353 Reference | Reference | 365 Reference | Reference |
| Exposed | 718 -0.003 (-0.14, 0.13) | -0.03 (-0.17, 0.12) | 726 -0.04 (-0.16, 0.08) | -0.05 (-0.18, 0.07) |
| Unexposed | 30 765 Reference | Reference | 30 211 Reference | Reference |
| Exposed | 718 0.02 (-0.06, 0.09) | 0.04 (-0.04, 0.11) | 726 -0.08 (-0.14, -0.01) | -0.06 (-0.13, 0.01) |

β: indicates standardized mean difference in test scores.
eTable 9. Association between duration of prenatal exposure to opioid analgesics and scholastic skills in fifth grade.

|                        | Literacy |              | Numeracy |              | English |              |
|------------------------|----------|--------------|----------|--------------|---------|--------------|
|                        | N        | Crude β (95% CI) | Weighted β (95% CI) | Crude β (95% CI) | Weighted β (95% CI) | Crude β (95% CI) | Weighted β (95% CI) |
| Exposed in 1 interval  | 917      | Reference    | Reference | Reference    | Reference    | Reference    | Reference    |
| Exposed in 2 or more intervals | 527      | -0.08 (-0.19, 0.02) | -0.09 (-0.20, 0.02) | -0.07 (-0.18, 0.03) | -0.06 (-0.17, 0.05) | -0.01 (-0.11, 0.10) | -0.03 (-0.14, 0.09) |

β: indicates standardized mean difference in test scores
eFigure 1. Distribution of test scores in the complete population of test takers in fifth grade between 2011 and 2018, according to subject (A, B, C).

A) Test scores on the literacy test.
Mean (SD): 19.4 ± 6.5
Median (Range): 20 (0-34)

B) Test scores on the numeracy test
Mean (SD): 24.6 ± 9.3
Median (Range): 25 (0-45)
C) Test scores on the English test
Mean (SD): 26.6 ± 10.4
Median (Range): 26 (0-50)
eFigure 2. Directed acyclic graph.

Simplified directed acyclic graph showing assumed relationship between the exposure (prenatal opioid analgesics), the outcome (school performance in children) and different covariates (e.g., sociodemographic and lifestyle factors, use of co-medications etc.).

Abbreviations: NAS, neonatal abstinence syndrome; BMI, body mass index.
eFigure 3. Overview of exempted children and their exposure status.

Indication sample
Pregnancy-child dyads with test scores in literacy, numeracy and / or English in 5th grade between 2011 and 2018
n=64 256

Exempted, n=484 (%)
Exposed, n=15 (3.1)
Pre-pregnancy exposed only, n=2 (0.4)
Unexposed, n=467 (96.5)

Exempted, n=221 (%)
Exposed, n=6 (2.7)
Pre-pregnancy exposed only, n=5 (2.3)
Unexposed, n=210 (95.0)

Exempted, n=561 (%)
Exposed, n=20 (3.6)
Pre-pregnancy exposed only, n=4 (0.7)
Unexposed, n=537 (95.7)

Cancelled exam, n=262
Failed to appear, n=384
Missing, n=251

Cancelled exam, n=121
Failed to appear, n=165
Missing, n=108

Cancelled exam, n=182
Failed to appear, n=209
Missing, n=166

Literacy
n=62 875

Numeracy
n=63 641

English
n=63 138
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