Prenatal exposure to non-steroidal anti-inflammatory drugs and child behavior at 36 months: the role of birth weight and gestational age as mediators

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Background

- Non-steroidal anti-inflammatory drugs (NSAIDs) are analgesic medications that are used by approximately 10% of pregnant women.
- No prior studies have investigated effects of prenatal NSAID exposure on neurodevelopment, although several have observed low birth weight and gestational age.

Objective: Understand the direct and indirect effects of prenatal exposure to NSAIDs on neurodevelopment, using causal mediation analysis.

Methods

- **Design**
  Prospective birth cohort (Norwegian Mother and Child Cohort Study).
- **Exposure**
  Self-reported use of non-steroidal antiinflammatory drugs (NSAIDs) in first trimester, second/third trimester, or at any time during pregnancy.
- **Outcome**
  Maternal report of internalizing or externalizing behavior problems, as measured by the Child Behavior Checklist. Outcome categorized as "clinically significant" behavior problems (z>1.50).
- **Mediator(s)**
  Gestational age (in weeks) and birth weight (in grams), captured on the Medical Birth Registry of Norway (MBRN).
- **Confounders**
  Maternal characteristics (age, pre-pregnancy BMI, smoking in pregnancy, parity), illnesses during pregnancy (depressive symptoms, fever or pain), concomitant medication use (paracetamol, opioids, antidepressants).
- **Analytic Strategy**
  Logistic regression was used to estimate odds ratios and 95% confidence intervals for 3 groups of NSAID exposure: Use during pregnancy, use prior to pregnancy only, and no use. Effect decomposition was used to quantify marginal total (MTE), natural direct (NDE) and natural indirect (NIE) effects of prenatal NSAID exposure on behavior using the SAS macro *%mediation*, adjusting simultaneously for confounders and allowing for exposure-mediator interaction.
  Mediators were used as continuous variables fixed at 39 weeks (for gestational age) and 4000 grams (for birth weight). We performed sensitivity analyses, including (1) limiting analyses to women with self-reported NSAID use before or during pregnancy, and (2) restricting analysis to women who did not also use paracetamol.

	Self-reported NSAID Use		
	During Pregnancy N=2907	Pre-Pregnancy Only N=3503	No History N=37263
Maternal Age >35	18	17	18
Pre-pregnancy BMI >25	37	34	30
Smoking	18	11	11
Parity >1	52	37	55
Illnesses During Pregnancy			
Fever	19	17	16
Pelvic Girdle Pain	42	41	37
Neck or Back Pain	66	67	55
Migraine/ Headache	59	43	32
Rheumatoid Arthritis	2	1	<1
Other Medications During Pregnancy			
Paracetamol	68	45	43
Opioids	6	2	2
Antidepressants	2	1	1

Numbers are column percentages.

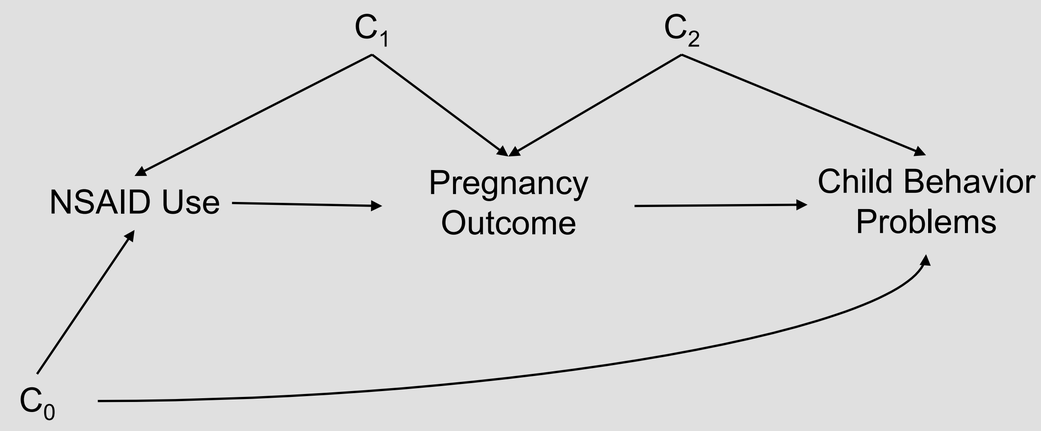
	Full Cohort (N=43673)		No Paracetamol Use (N=23945)	
	N Cases	OR(95%CI)	N Cases	OR(95%CI)
Externalizing Problems				
NSAIDs in pregnancy	287		85	
Vs. PP only	320	1.05 (0.89 to 1.25)	172	1.02 (0.78 to 1.34)
Vs. No NSAIDs	2872	**1.17 (1.03 to 1.34)**	1571	1.11 (0.88 to 1.40)
Internalizing Problems				
NSAIDs in pregnancy	205		75	
Vs. PP only	260	0.97 (0.80 to 1.18)	146	1.11 (0.83 to 1.49)
Vs. No NSAIDs	2366	1.01 (0.87 to 1.17)	1319	1.16 (0.90 to 1.48)

Models adjusted for maternal characteristics, illnesses, and concomitant medication use.

The authors have no financial conflicts of interest to declare. MoBa is supported by the Norwegian Ministry of Health and the Ministry of Education and Research, the National Institutes of Health/National Institute of Environmental Health Sciences, National Institutes of Health/National Institute of Neurological Disorders and Stroke, and the Norwegian Research Council/FUGE.

CONCLUSIONS

- Initial results suggested increased risk of externalizing problems associated with NSAID exposure.
- No apparent mediation by pregnancy outcomes.
- Prenatal exposure to NSAIDs was not associated with behavioral problems in 36 month old children when the appropriate comparison group is used.
- Sensitivity analysis suggests underlying condition, not concomitant paracetamol use, may be the more important confounder.



Directed Acyclic Graph (DAG) showing NSAID exposure, possible pregnancy outcome mediators (birth weight or gestational age), neurodevelopmental outcomes, and common causes of exposure and behavior (C_0), exposure and mediator (C_1), and mediator and outcome (C_2).

Full Cohort (N=43673)			
	Total Effect	Direct Effect	Indirect Effect
Mediator: Birth weight			
Externalizing Problems	**1.15(1.01 to 1.31)**	**1.14(1.00 to 1.30)**	**1.01(1.00 to 1.02)**
Internalizing Problems	1.00(0.85 to 1.15)	0.98(0.84 to 1.14)	1.01(1.00 to 1.02)
Mediator: Gestational Age			
Externalizing Problems	**1.14(1.00 to 1.30)**	**1.13(0.99 to 1.29)**	**1.01 (1.00 to 1.01)**
Internalizing Problems	1.00(0.86 to 1.16)	0.99 (0.85 to 0.15)	1.00(1.00 to1.01)
Women with NSAID History (N=6410)			
	Total Effect	Direct Effect	Indirect Effect
Mediator: Birth weight			
Externalizing Problems	1.07(0.90 to 1,27)	1.06(0.89 to 1.26)	1.01(1.00 to 1.02)
Internalizing Problems	1.00(0.82 to 1.21)	0.99(0.81 to 1.20)	1.01(1.00 to 1.02)
Mediator: Gestational Age			
Externalizing Problems	1.06(0.89 to 1.26)	1.05(0.88 to 1.26)	1.01(1.00 to 1.01)
Internalizing Problems	1.00(0.82 to 1.21)	0.99(0.81 to 1.21)	1.00(1.00 to 1.01)

Estimates are Odds Ratios (95% Confidence Intervals)

ABSTRACT

Background. Non-steroidal anti-inflammatory drugs (NSAIDs) are analgesic medications that are used by approximately 10% of pregnant women. No prior studies have investigated effects of prenatal NSAID exposure on neurodevelopment, although several have observed low birth weight and gestational age.
Objectives. To examine the direct and indirect effects of NSAIDs on child neurodevelopment, using causal mediation analysis.
Method. The Norwegian Mother and Child Cohort Study is a questionnaire-based longitudinal study. We identified 101 625 live non-malformed singleton births, of which 43 673 completed 36 month post-partum follow-up. NSAIDs exposure was ascertained by self-report; outcome (internalizing and externalizing behavior) was measured using the Child Behavior Checklist (CBCL); birthweight (BW) and gestational age (GA) were gathered from birth registry linkage. Effect decomposition was used to quantify marginal total (MTE), natural direct (NDE) and natural indirect (NIE) effects of prenatal NSAID exposure on behavior using the SAS macro *%mediation*, adjusting simultaneously for confounders and allowing for exposure-mediator interaction. Results reported are mean differences in standard deviation units, with 95% confidence intervals (CI) calculated using the delta method.
Results. Of 43 673 pregnancies included, 2907 (6.7%) used NSAIDs during pregnancy. NSAID exposure was associated with an increase in both externalizing (TME: .08, 95% CI .04 to .11) and internalizing (TME: .04, 95% CI .01 to .08) behaviors. These effects were not mediated by BW (NIE for externalizing: -.0009, 95% CI -.0030 to .0020; NIE for internalizing: .0017, 95% CI -.0005 to .0037) or GA (NIE for externalizing: .0017, 95% CI -.0005 to .0039; NIE for internalizing: -.0009, 95% CI -.0011 to .0027).
Conclusion. Prenatal NSAID exposure was associated with increased internalizing and externalizing behaviors in 3-year-old children, and these effects are not attributable to associations between NSAID exposure and BW or GA. The effects are small, but given the frequency of NSAID use during pregnancy, warrant further attention to better understand possible public health implications.

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