

## LETTER

## NSAID use during pregnancy: maternal characteristics and prescription patterns. A nationwide cohort study

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Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs (1). To identify the characteristics of pregnant women who redeemed at least one prescription of an NSAID, we performed a nationwide cohort study including all registered pregnancies resulting in a birth in Denmark from 1997 to 2010. All births were identified using the Medical Birth Registry (2). Information on women redeeming an NSAID was retrieved from the National Prescription Register (3). Information on diseases of the musculoskeletal system and connective tissue (ICD-10 DM group) were from the National Hospital Register (4). Differences in baseline characteristics between exposed and unexposed were calculated using a logistic regression model where maternal age, education, parity, number of offspring in the current pregnancy, smoking during pregnancy, diagnosis of a disease of the musculoskeletal system and connective tissue, and year of birth were included in the model. As information on body mass index (BMI) was only available from 2004, a separate logistic regression model was constructed further including BMI. For all analyses, a p-value of < 0.05 was considered statistically significant. The Danish Data Protection Agency approved the study (No. 2008-41-2517).

We identified 911 569 pregnancies resulting in a birth between 1997 and 2010. A total of 24841 (2.7%) redeemed at least one prescription of an NSAID, mainly ibuprofen (63%), at some point during pregnancy. Women redeeming NSAID prescriptions were characterized by being younger, having a lower educational level, lower household income, more prior pregnancies, fewer multiple births, higher BMI, and smoked more during pregnancy compared to unexposed women (Table 1). It is known that, for example, low socio-economic status is associated with higher disease prevalence, which could partly explain our findings (5). Women exposed to NSAIDs were more likely to have a diagnosis of a disease of the musculoskeletal system and connective tissue (0.9%) than unexposed (0.2%), which was to be expected because NSAIDs are

often used in the treatment of rheumatic diseases. The rates could be underestimated because they are solely based on hospital diagnoses.

From 1997 to 2004 the overall exposure to any NSAID increased from 2.4% to 3.1% ( $p < 0.0001$ ) and decreased to 2.3% in 2010 ( $p < 0.0001$ ) (Figure 1). In 2004, The Danish Medicines Agency drew attention to a possible small increased risk of birth defects for NSAID during pregnancy, and the patient information leaflets were edited (6). This awareness could explain the decrease in exposure to NSAIDs.

Fewer women were exposed to an NSAID during pregnancy than before pregnancy ( $p < 0.0001$ ). The exposure rates decreased throughout pregnancy (1.9% in the first, 0.6% in the second, and 0.4% in the third trimester) compared to before pregnancy (4.4%) and increased again after delivery (3.2%).

This decline is probably due to guidelines warning about risk of harmful effects to the foetus, or general fear of medication during pregnancy. Exposure in early pregnancy has been associated with increased risk of miscarriage and birth defects, although the findings are conflicting (1). It is therefore recommended to use NSAID during the first and second trimesters with caution (7). Women with unrecognized pregnancies could account for some of the exposure seen during the first trimester. NSAID exposure in late pregnancy has been associated with adverse foetal effects (1) and NSAID use is contraindicated during the third trimester (7). However, 0.4% of the women in our cohort were exposed to an NSAID during the third trimester. This could indicate a need for NSAID use during the third trimester, despite contraindications, because some inflammatory conditions such as ankylosing spondylitis may, without pharmacological treatment, worsen during pregnancy (8). Furthermore, some women suffering from migraine continue to use NSAIDs during pregnancy (9). Another reason for NSAID exposure in pregnancy is lack of knowledge of potential adverse effects (10).

Table 1. Basic maternal characteristics.

	Use of NSAIDs	No use of NSAIDs	Adjusted p-value
Total number	24 841	886 728	
Age (years)			0.0008
< 20	446 (1.8)	13 167 (1.5)	
20–24	3705 (14.9)	101 741 (11.5)	
25–29	8258 (33.2)	299 924 (33.8)	
30–34	8041 (32.4)	318 849 (36.0)	
≥ 35	4391 (17.7)	153 047 (17.3)	
Education (no. of months)			< 0.0001
< 144	9162 (37.8)	200 881 (23.9)	
144–155	3803 (15.7)	137 556 (16.0)	
156–179	6601 (27.3)	253 721 (29.5)	
> 179	4655 (19.2)	262 751 (30.6)	
Income (quartiles)			< 0.0001
Lowest quartile	7768 (31.3)	220 343 (24.9)	
Low quartile	7090 (28.5)	220 726 (24.9)	
Medium quartile	5509 (22.2)	222 313 (25.1)	
High quartile	4474 (18.0)	223 346 (25.2)	
Parity			< 0.0001
1	9858 (39.9)	388 217 (44.0)	
2	8482 (34.4)	324 946 (36.8)	
3	4112 (16.7)	122 976 (14.0)	
≥ 4	2228 (9.0)	45 024 (5.1)	
Number of offspring			0.016
1	23 892 (96.2)	849 172 (95.8)	
2	915 (3.7)	36 626 (4.1)	
≥ 3	34 (0.1)	930 (0.1)	
Body mass index (kg/m <sup>2</sup> )*			< 0.0001
< 18.5	424 (3.7)	17 638 (4.3)	
18.5–24.9	5998 (52.5)	258 918 (63.2)	
25.0–29.9	2726 (23.8)	85 208 (20.8)	
30.0–34.9	1348 (11.8)	31 493 (7.7)	
≥ 35	934 (8.2)	16 325 (4.0)	
Smoking during pregnancy	6939 (27.9)	156 886 (17.8)	< 0.0001
Disease of the musculoskeletal system and connective tissue †	230 (0.9)	1906 (0.2)	< 0.0001

\* Information on pre-gestational body mass index only available from 2004 to 2010.

† Defined as a diagnosis of a disease of the musculoskeletal system and connective tissue within the ICD-10 classification system in the 5-year period before birth.

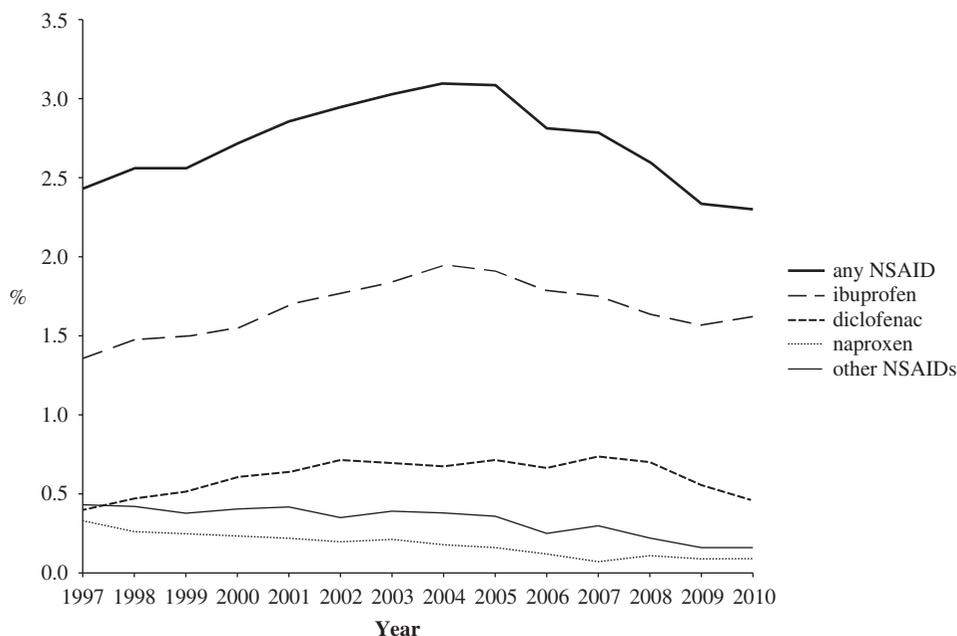


Figure 1. Number of pregnant women giving birth redeeming one or more prescriptions of non-steroidal anti-inflammatory drugs (NSAIDs) during pregnancy between 1997 and 2010. The total number of pregnant women in the period was 911 569. The y-axis represents the percentage of all pregnant women.

The registers used in the present study have previously been validated and found to be accurately recorded. More than 99% of all births in Denmark have been recorded in the Medical Birth Registry (11) and the completeness of the National Prescription Register has been estimated to be 98% (12). Unfortunately, we have no information on adherence, dosage, and treatment indication, or on over-the-counter drugs.

In conclusion, we found that women redeeming at least one NSAID prescription during pregnancy differed in several characteristics compared to unexposed. Furthermore, NSAID exposure during pregnancy increased until 2004, and then decreased. Despite NSAIDs being contraindicated in the third trimester, several thousand women were exposed in this period of the pregnancy.

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