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1 **Antidepressant use during pregnancy and childhood cancer in the offspring**

2 **Running title:** In utero antidepressant exposure and childhood cancer

3

4 Natalie C. Momen,¹ Trine Munk-Olsen,^{2,3} Jiong Li,¹ Katja G. Ingstrup,² Jørn Olsen,^{1,4} Veerle
5 Bergink,^{2,5} Xiaoqin Liu,^{2,*}

6

7 **Author affiliations:** ¹ Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus,
8 Denmark, ² The National Center for Register-based Research, Aarhus University, Aarhus, Denmark,
9 ³ Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Denmark, ⁴
10 Department of Epidemiology, Fielding School of Public Health, University of California, Los
11 Angeles, California, USA, ⁵ The Department of Psychiatry, Erasmus Medical Centre, Rotterdam,
12 The Netherlands

13

14 *** Correspondence:** Xiaoqin Liu, the National Center for Register-based Research, Aarhus
15 University, Fuglesangs Allé 26, 8210 Aarhus V, Denmark. Phone: +45 87166268. E-mail:
16 lxq@econ.au.dk

17

18 **Keywords:** Antidepressant, childhood cancer, depression, epidemiology, in utero, register-based

19 **Key points:** Antidepressant use during pregnancy was not significantly associated with offspring
20 childhood cancer in general, nor with leukemia or nervous system tumors in specific.

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32 **Abstract**

33 **Purpose** Antidepressant use during pregnancy has been increasing in recent years. We evaluated
34 whether in utero exposure to antidepressants increased the risk of childhood cancer.

35 **Methods** This population-based cohort study using national registers in Denmark comprised
36 915,128 liveborn singletons during 1998–2012. We categorised children into three mutually
37 exclusive exposure groups according to maternal redemption of an antidepressant prescription from
38 2 years before pregnancy until delivery of the index child: Unexposed (N=863,033), prior user (use
39 before but not during pregnancy) (N=30,607), and use during pregnancy (N=21,488). The children
40 were followed from birth until first diagnosis of cancer, death, emigration, or December 31st, 2012,
41 whichever came first. The children were followed maximum 14.9 years and contributed to 6.9×10^6
42 person-years at risk. We estimated hazard ratios (HRs) of cancer using Cox regression with 95%
43 confidence intervals (CIs).

44 **Results** In total, 1,298 (0.1%) children were diagnosed with cancer. Antidepressant use during
45 pregnancy was not associated with a significantly increased risk of childhood cancer in general; the
46 HR was 1.03 (95% CI: 0.63–1.68), compared to children born by mothers who discontinued
47 antidepressant use prior to pregnancy. The association between in utero exposure to antidepressants
48 and childhood cancer did not depend on type or duration of antidepressant use. There was no strong
49 evidence indicating a higher risk of leukaemia or nervous system tumours among children exposed
50 to antidepressants in utero.

51 **Conclusion** Antidepressant use during pregnancy was not significantly associated with childhood
52 cancer in general, nor with leukemia or nervous system tumors in specific.

53 **Introduction**

54 Almost 50% of childhood cancers are diagnosed before five years of age,¹ and there is accumulating
55 evidence of early life origins of childhood cancer.^{2, 3} Preconceptional and *in utero* exposures are
56 therefore of interest. Tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs)
57 cross the placental barrier and reach foetal circulation.^{4, 5} There is limited evidence but previous
58 work has indicated fetal antidepressant-exposure could influence childhood cancer risk. As murine
59 models have demonstrated maternal serotonin plays a role in gene expression, proliferation,
60 migration and morphogenesis of the cells from which neuroblastomas derive,⁶ drugs acting on the
61 serotonin pathway could influence cancer risk. Furthermore, epigenetic alternations have been
62 observed in cord blood of antidepressant-exposed infants.⁷

63 A potential association between maternal antidepressant use and risk of childhood cancer has
64 received limited attention. But most studies have not found a statistically significant correlation
65 between the two.⁸⁻¹¹ Neurally active drugs (including antidepressants) have been, however, found to
66 be associated with an increased risk of childhood cancers,¹² and further research is required. We
67 aimed to investigate the association between prenatal exposure to antidepressant medications and
68 risk of childhood cancer.

69

70 **Methods**

71 *Study population*

72 We conducted a cohort study using Danish national registers. All live births and residents in
73 Denmark are registered in the Danish Civil Registration System with a unique identification
74 number, which can be used to link register data. From the Danish Medical Birth Registry, we
75 identified 923,416 live-born singletons born during 1998–2012. We excluded 6,569 children with
76 missing or extreme gestational age (<154 or >315 days). Through linking the Danish Medical Birth

77 Registry to the Danish National Patient Register, we further excluded 1,719 children with
78 chromosomal abnormalities (International Classification of Diseases, 10th revision [ICD-10]: Q90–
79 Q99).

81 ***Exposure—antidepressant use during pregnancy***

82 Information on maternal redemption of a prescription for an antidepressant was retrieved from the
83 Danish National Prescription Registry. The Anatomical Therapeutic Classification (ATC) code for
84 antidepressants was N06A. We defined antidepressant use during pregnancy as one antidepressant
85 prescription from one-month prior to pregnancy until delivery. We also considered history of
86 antidepressant use in the two years prior to pregnancy. Filling date indicated initial use of
87 antidepressants. We calculated the duration of exposure from each prescription by multiplying the
88 number of defined daily doses per package with the number of packages dispensed and adding
89 these.

90 We categorized the children into three mutually exclusive groups according to maternal
91 dispensation of a prescription for an antidepressant from 2 years to 1 month before pregnancy and
92 during pregnancy: 1) unexposed; 2) use before pregnancy but not during pregnancy (prior
93 antidepressant user); 3) use both before and during pregnancy or use only during pregnancy (use
94 during pregnancy).

96 ***Outcome—Childhood cancer***

97 Information on the diagnoses of childhood cancer was obtained from both the Danish National
98 Patient Register and the Danish Register of Causes of Death. The Danish National Patient Register
99 includes information on inpatient visits since 1977, and additionally since 1995 outpatients and
100 emergency room visits. The primary outcome was all incident cancers (ICD-10: C00–C97)

101 diagnosed before age 15 years and the study end. We also looked at the two most common cancer
102 types (secondary outcomes), separately: leukaemia (C91–95) and central and sympathetic nervous
103 system tumours (C47 and C70–72).

104

105 *Statistical analysis*

106 Statistical analyses were performed using Stata 13.1. We followed children from birth until the first
107 diagnosis of cancer, death, emigration, or December 31st, 2012, whichever came first. We used Cox
108 proportional hazards regression to model hazard ratio (HR) of childhood cancer with 95%
109 confidence interval (CIs). The estimated HRs were adjusted for the following covariates: maternal
110 age at delivery (≤ 24 , 25–34, ≥ 35 years), primiparity (yes/no), maternal history of psychiatric
111 disorders at delivery (yes/no), inpatient psychiatric treatment from 2 years before pregnancy up to
112 delivery (yes/no), the dispensation of other psychotropic prescriptions during pregnancy (ATC
113 codes N05 and N06 excluding N06A), smoking during pregnancy (yes/no), maternal highest
114 education (elementary school/above elementary school), calendar year of delivery (1998–2002,
115 2003–2007, 2008–2012), and parental cancer history at time of delivery (yes/no). Information on
116 maternal history of psychiatric disorders (ICD-8: 290–315; ICD-10: F00–F99) and inpatient
117 psychiatric treatment from 2 years before pregnancy up to delivery was obtained from the Danish
118 Psychiatric Central Research Register. Data on remaining covariates were extracted from the
119 registers above as well as from Statistics Denmark’s registers on socioeconomic status. Values for
120 potential confounders were missing for 7.1% of children, and we applied 20 imputations using the
121 Markov Chain Monte Carlo technique for imputing missing values.

122 To minimise confounding by underlying psychiatric disorders, we compared the risk of cancer
123 among children of mothers who used an antidepressant during pregnancy to the prior antidepressant
124 user group. To assess whether associations varied with different antidepressants, we categorised

antidepressants into three types (SSRI monotherapy, non-SSRI monotherapy, or both SSRI and non-SSRI antidepressants). To determine whether associations were modified by the duration of antidepressant use, we divided the duration into three periods (≤ 90 , 91–180, and ≥ 181 days).

Ethics

The study was approved by the Danish Data Protection Agency. No informed consent is required for a register-based study with public health interest based on anonymized data according to Danish legislation.

Results

The resulting dataset consisted of 915,128 singletons born to 555,172 mothers. The mothers of 30,607 (3.3%) children filled at least one prescription before pregnancy (i.e., prior antidepressant user), and 21,488 (2.4%) during pregnancy. Table 1 shows the baseline characteristics of the study population.

Overall, 1,298 children were diagnosed with cancer during the follow-up from birth to maximum 14.9 years, of which 28 were born to mothers who used antidepressants during pregnancy. The median age at first diagnosis of cancer in the whole study population was 3.0 years (interquartile range: 1.3–5.5 years).

Neither antidepressant use before pregnancy nor antidepressant use during pregnancy were associated with a statistically significant increase in the risk of all childhood cancer groups combined; the HRs were 1.14 (95% CI: 0.83–1.57) and 1.15 (95% CI: 0.78–1.72), in comparison to unexposed children. Maternal antidepressant use was not furthermore associated with leukaemia or central and sympathetic nervous system tumours in the offspring (Figure S1 in the supplement).

148 When the data were restricted to the antidepressant user groups, the risk of cancer among
149 antidepressant use during pregnancy group was 1.03 (95% CI: 0.63–1.68), compared to the prior
150 antidepressant user group. Among children exposed to antidepressants *in utero*, 1.8% of them were
151 exposed to SSRIs only, 0.4% to non-SSRI antidepressants, and 0.2% to both SSRI and non-SSRI
152 antidepressants. The risk did not vary by type or duration of antidepressant use (Table 2).

153

154 ***Sensitivity analyses***

155 To minimise the possibility of misclassification of antidepressant exposure during pregnancy, we
156 restricted our analyses to mothers with at least two antidepressant prescriptions, and similar results
157 were obtained (Table S1). The results did not change substantially excluding children whose
158 mothers used antipsychotic (ATC code: N05A) or anticonvulsant agents (ATC code: N03) during
159 pregnancy Table S2).

160

161 **Discussion**

162 In this population-based cohort study, we found no association between maternal antidepressant use
163 and childhood cancer in general, leukaemia, or central and sympathetic nervous system tumours in
164 the offspring, which is consistent with most previous reports.⁸⁻¹¹ Notably, previous studies are of
165 case-control design,⁸⁻¹² which are often susceptible to recall and reporting bias. Moreover, most
166 studies have investigated “neurally active drugs” instead of specific antidepressants. This current
167 study investigated the risk of cancer among 21,488 children exposed to antidepressants *in utero*
168 using a cohort design.

169 Our study is the largest cohort study on this topic so far. The study was based on national
170 registries with complete coverage, which ensures representativeness of the study population.
171 Information on redemption of antidepressant prescriptions during pregnancy came from the

172 prescription register compiled contemporaneously prior to the diagnosis of cancer collected
173 prospectively from the patient register, which minimises the chance of recall bias. Our study also
174 has several limitations. Firstly, we determined antidepressant use during pregnancy based on a
175 redeemed antidepressant prescription. Since some women who redeemed a prescription may not
176 take the drugs, we might have misclassified them as exposed. However, compliance to
177 antidepressant treatment during pregnancy is high in Denmark.¹³ Moreover, when we restricted our
178 analysis to women with at least two antidepressant prescriptions during pregnancy, the results
179 remained unchanged. Secondly, we identified cancer cases using patient and death registers;
180 therefore some cases might not be included, but validation of the cancer data in available patient
181 registry suggests it is of good quality and we speculate that misclassification will be limited.¹⁴ For
182 example, the incidence rate of cancer in our study is comparable to our previous findings.¹⁵ Thirdly,
183 even though our study population is large, we do not have sufficient statistical power to detect
184 moderate association between in utero antidepressant exposure and childhood cancer. On the basis
185 of the upper boundary of the confidence interval, our study could not rule out a relative risk up to
186 1.68. Moreover, small numbers of specific cancer cases do not allow us to further investigation of
187 the associations between antidepressant exposure in utero and specific cancer types.

188

189 **Conclusions**

190 Our findings suggest that antidepressant use during pregnancy is not associated with childhood
191 cancer in the offspring or if it does, the effect is small. Potential concerns about cancer are
192 unsupported.

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226 medications during pregnancy and risk of childhood cancer. *Pharmacoepidemiology and drug*
227 *safety*. 2015; 24:821-829.

228 **Table 1.** Characteristics of study population according to maternal antidepressant use before and
229 during pregnancy

Characteristic	Unexposed group (N=863,033)	Antidepressant user groups	
		Prior user	Use during pregnancy
		(N=30,607)	(N=21,488)
Maternal age at delivery (years)			
≤24	110,984 (12.9)	5,329 (17.4)	3,321 (15.5)
25–34	601,120 (69.6)	19,288 (63.0)	13,393 (62.3)
≥35	150,929 (17.5)	5,990 (19.6)	4,774 (22.2)
Primiparity	378,873 (43.9)	13,755 (44.9)	9,422 (43.8)
Maternal psychiatric history at delivery	38,230 (4.4)	9,676 (31.6)	9,876 (46.0)
Inpatient psychiatric treatment from 2 years before pregnancy up to delivery	1,894 (0.2)	1,350 (4.4)	1,574 (7.3)
Other psychotropic use during pregnancy	4,903 (0.6)	675 (2.2)	1,652 (7.7)
Smoking during pregnancy			
Yes	139,176 (16.1)	9,064 (29.6)	6,694 (31.2)
No	701,278 (81.3)	20,742 (67.8)	14,190 (66.0)
Missing	22,579 (2.6)	801 (2.6)	604 (2.8)
Maternal highest education at delivery			
Elementary school	155,115 (18.0)	10,221 (33.4)	6,784 (31.6)
Above elementary school	675,689 (78.3)	19,787 (64.6)	14,213 (66.1)
Missing	32,229 (3.7)	599 (2.0)	491 (2.3)
Calendar year of delivery			
1998–2002	305,020 (35.3)	5,780 (18.9)	2,995 (13.9)
2003–2007	289,596 (33.6)	10,710 (35.0)	7,152 (33.3)
2008–2012	268,417 (31.1)	14,117 (46.1)	11,341 (52.8)

Parental cancer history at birth			
Yes	10,772 (1.3)	454 (1.5)	318 (1.5)
No	843,518 (97.7)	29,626 (96.8)	20,748 (96.6)
Missing	8,743 (1.0)	527 (1.7)	422 (2.0)
Sex of the child			
Boys	442,637 (51.3)	15,833 (51.7)	11,105 (51.7)
Girls	420,396 (48.7)	14,774 (48.3)	10,383 (48.3)

231 **Table 2.** Hazard ratios of cancer among children whose mothers used antidepressant during
232 pregnancy versus mothers used antidepressants before pregnancy (N=52,095)

Timing of antidepressant use	Cases	Rate (1/100, 000 person-years)	Crude HR	Adjusted HR (95% CI) [†]
Prior antidepressant user	42	23.2	1	1 (Reference)
Antidepressant use during pregnancy	28	24.5	1.03	1.03 (0.63–1.68)
Type of antidepressant use				
SSRIs monotherapy	19	21.4	0.89	0.89 (0.51–1.54)
Non-SSRI antidepressant monotherapy	5	29.3	1.23	1.37 (0.54–3.48)
Both SSRIs and non-SSRI antidepressants	4	49.1	2.00	2.21 (0.77–6.33)
Duration of antidepressant use				
Use for ≤90 days	10	23.3	1.02	1.06 (0.53–2.12)
Use for 91–180 days	6	27.2	1.14	1.14 (0.48–2.70)
Use for ≥181 days	12	24.3	0.98	0.96 (0.50–1.86)

233 The Anatomical Therapeutic Classification codes for selective serotonin reuptake inhibitors (SSRIs) are N06AB and
234 non-SSRI antidepressants N06AA, N06AF, N06AG, and N06AX.

235 † Adjusted for maternal age at delivery, primiparity, maternal psychiatric history at delivery, inpatient psychiatric
236 treatment from 2 years before pregnancy up to delivery, the dispensation of other psychotropic prescriptions during
237 pregnancy, smoking during pregnancy, highest education, calendar year of delivery, and parental cancer history at the
238 time of delivery.