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Use of acetaminophen during pregnancy and risk of adverse pregnancy outcomes

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Background Acetaminophen use during pregnancy has been associated with a reduced risk of stillbirth and preterm birth, but findings are based on few studies with small numbers of exposed women.

Methods To examine whether prenatal exposure to acetaminophen reduces the risk of adverse pregnancy outcomes, we used data from the Danish National Birth Cohort. We also examined the combined potential effects of acetaminophen, coffee and tobacco use on pre-eclampsia and preterm birth. The study population consisted of women who provided information on acetaminophen use during pregnancy and gave birth to singletons ($n = 98\,140$). The cohort was linked to the Danish National Hospital Registry and the Medical Birth Registry, which covers all Danish hospitals, miscarriages and births in Denmark.

Results Women using acetaminophen during the third trimester of pregnancy had an increased risk of preterm birth [adjusted hazard ratio (HR) = 1.14, 95% CI: 1.03–1.26]. The risk of preterm birth was increased in mothers with pre-eclampsia (HR = 1.55, 95% CI: 1.16–2.07) but not in women without pre-eclampsia (HR = 1.08, 95% CI: 0.97–1.20). Tobacco smoking and coffee consumption did not modify the effect of acetaminophen in any consistent pattern. No association was found between acetaminophen use and risk of preterm complications, miscarriages, stillbirths, low birth weight or small size for gestational age.

Conclusion Findings do not provide strong support for a change in clinical practice regarding use of acetaminophen during pregnancy, but the increased risk of preterm birth among women with pre-eclampsia should be further investigated.

Keywords Acetaminophen, coffee, low birth weight, pre-eclampsia, premature birth, spontaneous abortion, stillbirth, tobacco

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Introduction

Acetaminophen is one of the most frequently used drugs among pregnant women and is considered the first-choice analgesic and antipyretic in most cases.[1–3] There are few studies on potential teratogenic effects,[4] other pregnancy effects and birth outcomes following acetaminophen use and most of these studies are based on very small numbers of exposed women. A reduced risk of stillbirth[5] and preterm birth[6] has been reported, although not consistently,[5–7] and no association with miscarriage has been reported in the literature.[8] Inhibition of Prostacyclin (PGI_2) synthesis and an imbalance between PGI_2 (a vasodilator) and Thromboxane A2 (TXA_2, a vasoconstrictor) have been suggested as an explanation for these associations.[6,8] In contrast, a reduction in PGI_2 synthesis could also be associated with an increased risk of pre-eclampsia,[9] leading to an increased risk of induced preterm birth which would not be detected in a study using only spontaneous preterm births as endpoints. Induced preterm delivery occurs in 15–25% of all preterm births, with hypertensive disorders as the major proximal cause.[10]

The risk of preterm birth among fetuses exposed to acetaminophen could be related to pre-eclampsia, perhaps mediated through oxidative stress.[11–13] Coffee intake has been shown to enhance acetaminophen oxidation by CYP3A4 to its toxic metabolite, NAPQI[13] and may slow acetaminophen's clearance.[14] Thus, it can be hypothesized that coffee drinkers may have a higher rate of oxidative stress and acetaminophen toxicity due to a higher synthesis of NAPQI, and these toxic effects might be modified by smoking during pregnancy. Glucuronidation capacity is affected in smokers and CYP1A2 activity is significantly correlated to acetaminophen glucuronidation in heavy smokers, suggesting co-regulation of CYP1A2 and acetaminophen conjugating UDP-glucuronosyltranferase isoenzymes.[15]

We evaluated the association between acetaminophen use during pregnancy and the risks of adverse pregnancy outcomes. We also examined the combined potential effects of acetaminophen, coffee and tobacco use on the risk for adverse pregnancy outcomes.

Methods

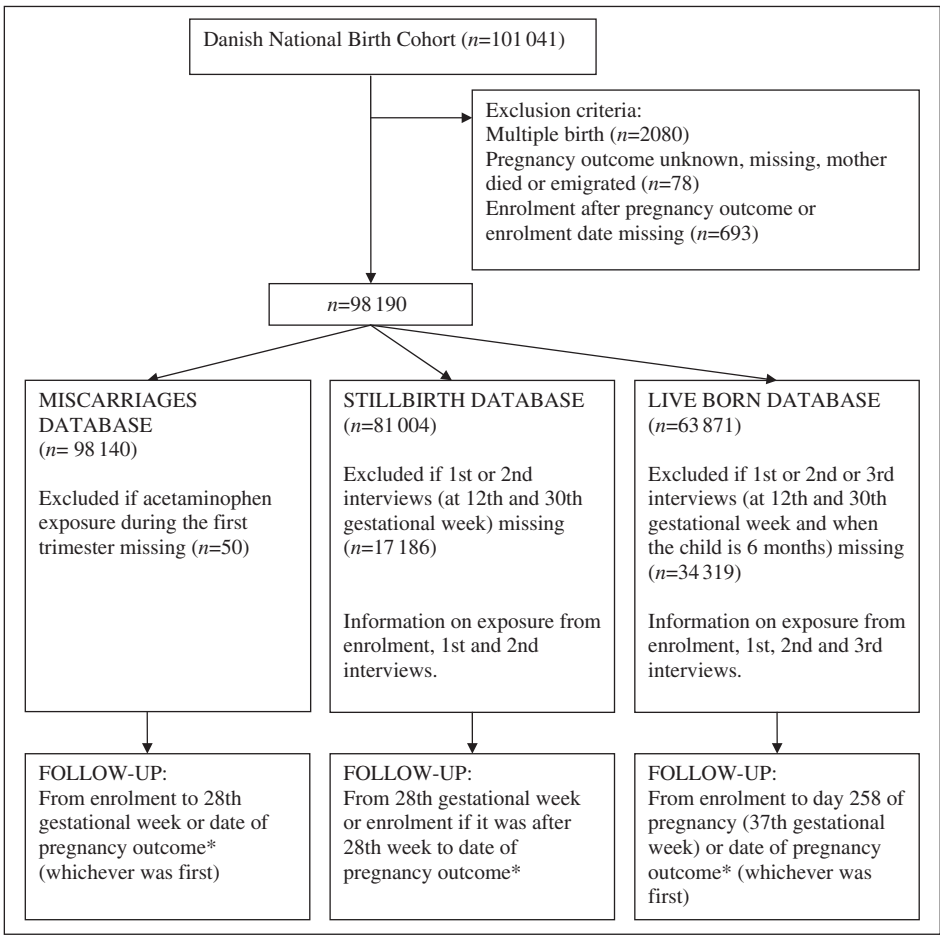
The study draws on data from the Danish National Birth Cohort (DNBC), a population-based cohort. Women were invited to participate in the study between 1996 and 2003, and ~60% of invited eligible pregnant women agreed to take part ($n = 101\,041$ pregnancies). The only inclusion criteria were that women spoke Danish well enough to participate in the interviews and intended to carry their pregnancy to term. The effect of non-participation was evaluated for effect sizes of certain exposures and odds ratios were not biased by non-participation.[16] Participating women were asked to complete a self-administered enrolment questionnaire and four telephone interviews (two during pregnancy and two when their children were 6 and 18 months old). English versions of the questionnaires can be found at http://www.bsmb.dk.[17] Those who gave birth to twins or triplets and those with an unknown outcome or unknown date of outcome were excluded from the analysis. The selection of study subsets used is shown in Figure 1.

Pregnancy outcomes

We used the unique civil registration number assigned to every Danish resident since 1968 to link the study population to the National Hospital Registry (NHR) covering all Danish inpatients and outpatients and to the Medical Birth Registry (MBR). The outcomes were coded using the International Classification of Diseases, 10th version (ICD-10). Low birth weight (LBW) was defined as <2500 g, with birth weight from 2500 to 4500 g serving as the reference category. Preterm birth was defined as occurring (spontaneously or induced) before 37 completed weeks of gestation (or 259 days), with children born at term (excluding post-term births) as the reference group. Information from the registries was used to identify potential causes of preterm delivery: premature rupture of membranes (ICD-10 code O42), preterm labour (code O60), pre-eclampsia (codes O14: gestational hypertension with significant proteinuria and O15: eclampsia) and placenta diseases (codes O43–O45 and P02). Small for gestational age (SGA) was defined as a birth weight below the 10th percentile at a specific gestational age in weeks, based on all live singleton births of the same sex and gestational week recorded in the DNBC. A dead fetus delivered spontaneously before the 28th gestational week (<196 days) was defined as a miscarriage and after that date as a stillbirth, according to the official definition used in Denmark during the study period. Miscarriages were further classified as 'early' when they took place before the 12th gestational week and 'late' when they occurred between the 12th and the 28th gestational week. Although a certain degree of underreporting may be expected, a previous study has found acceptable agreement between information on miscarriages obtained by interview and from registry information.[18] Associations with induced abortions were not evaluated in our study.

Acetaminophen use

Women in the cohort exposed to acetaminophen were identified from responses in the enrolment questionnaire and from the first, second or third interviews. Exposure was categorized as occurring during the first trimester (first to 12th weeks), second trimester (13–24th weeks) or third trimester [25th week to either the 35th week (for preterm births), 39th week (for stillbirths) or delivery (for term births)]. Non-users



*Pregnancy outcomes: live born, stillbirth, miscarriage, induced abortion, hydatidiform mole, and ectopic pregnancy.

Figure 1 Danish National Birth Cohort and population selection for our study

were defined for each specific trimester irrespective of drug use during the other trimesters. The exposure periods of interest for each outcome are shown in Figure 2.

Because women who miscarried tended to leave the cohort early, only the enrolment questionnaire was available to identify exposed and non-exposed pregnancies for most in this group. Women whose pregnancy ended with a stillborn child did not have the third interview. Thus exposed and non-exposed populations were defined without information from this interview. Women in this group who also lacked the first and second interviews were excluded from the analysis. Only mothers who completed the three first interviews (at 12th and 30th gestational weeks and when the child was 6 months old) were included in the analysis of preterm birth, LBW and SGA, as non-response for the third interview was higher among mothers with children born preterm (29.4%) compared mothers with children born at term (23.8%).

Because 35 weeks was the mean gestational age at birth for preterm children (Figures 1 and 2), their mothers' third trimester use of acetaminophen was analysed for weeks 25–35. The mean gestational age for stillborn children was 38.7 weeks and therefore use of acetaminophen during the third trimester was evaluated for weeks 25–39.

Statistical analysis

We used Cox proportional regression models to compute hazard ratios (HRs) of miscarriage, stillbirth, preterm birth, LBW, SGA and other pregnancy outcomes. The models were adjusted for mother's age, socio-economic status, pre-pregnancy body mass index, cigarettes per day, birth order, coffee intake and sex of the child. For miscarriage risk, the model was also adjusted by the history of previous abortions.

Other variables explored as potential confounders and/or effect measure modifiers included gestational age, alcohol consumption during pregnancy, time to pregnancy, pre-eclampsia, abruptio placentae, premature rupture of membranes, preterm labour and mother's history of hypertension, diabetes mellitus

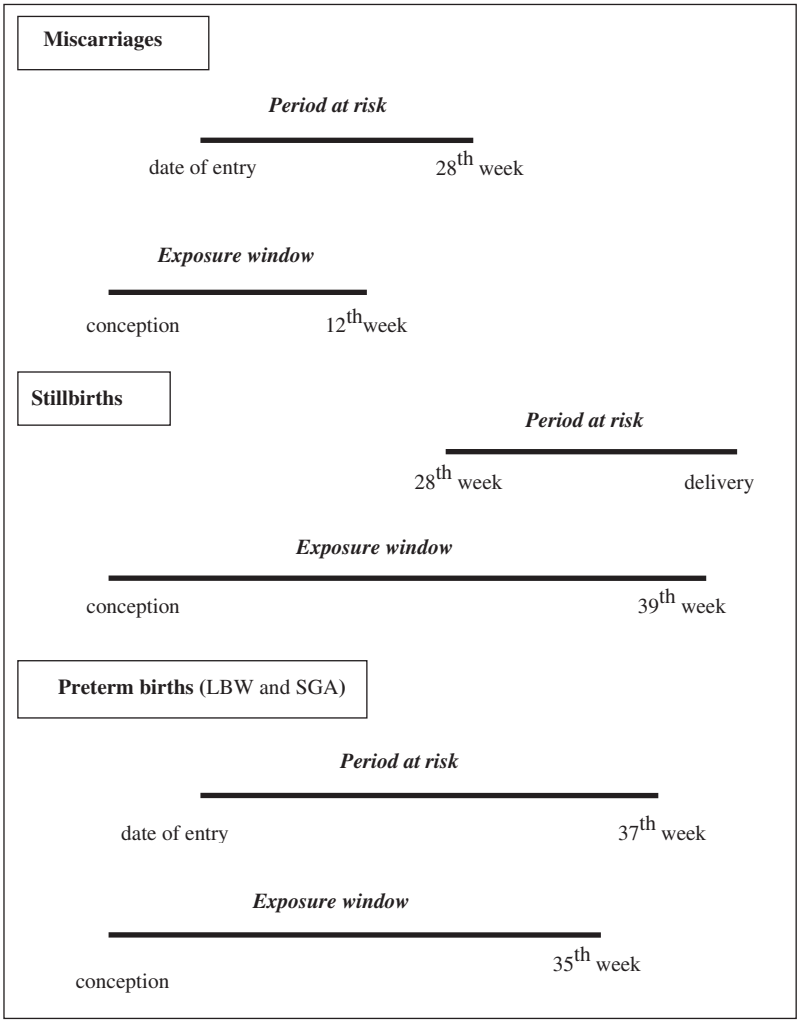


Figure 2 Periods at risk and exposure windows for analyses of selected outcomes

or other diseases that could be associated with acetaminophen use, such as fever, muscle and joint diseases, common cold/influenza, inflammation, infection or antibiotic use. These variables were not included in the final model due to very small (~1%) changes in the estimates of interest. To explore the potential effect of coffee consumption, smoking, hypertension and pre-eclampsia on pregnancy outcomes, we stratified the analyses by each of these variables.

For miscarriages, we started follow-up on the enrolment date and ended on the date of miscarriage, hydatidiform mole, ectopic pregnancy, induced abortion or at gestational week 28, whichever came first. Follow-up for 'early' miscarriages started on the enrolment date and ended at week 12. Follow-up for 'late' miscarriages started at the 12th gestational week and ended at the 28th week. Analyses of stillbirths started at the 28th gestational week and ended at the time of stillbirth or induced abortion. For the remainder of pregnancy outcomes, follow-up started on the date the enrolment questionnaire was completed and ended on the date of live birth, stillbirth, induced abortion or loss to follow-up, or on day 258 of the pregnancy, whichever came first (Figure 2).

Number of weeks exposed during each trimester and during the pregnancy as a whole was evaluated after exclusion of 15 206 pregnancies for which no information was available on acetaminophen use on a week-by-week basis during the first trimester. Linearity of dose–response was assessed using general additive models. Statistical analysis was performed with Stata 8.0 software (Stata Corporation, College Station, TX, USA). Ethics approval was obtained from the Ethics Committee for the Municipalities of Copenhagen and Frederiksberg.

Results

The key characteristics of the eligible study population ($n = 98\,140$) and frequency of the outcomes of interest

Table 1 DNBC study population

	$n = 98\,140$ n^a (%)	Use of acetaminophen ($n = 50\,702$) n (%)	No use of acetaminophen ($n = 47\,438$) n (%)
Mother age (years)			
⩽24	8988 (9.73)	4842 (9.82)	4146 (9.62)
25–29	35 580 (38.50)	18 864 (38.25)	16 716 (38.79)
30–35	34 211 (37.02)	18 298 (37.10)	15 913 (36.93)
⩾36	13 634 (14.75)	7317 (14.84)	6317 (14.66)
Socio-economic status[b]			
High	58 563 (66.74)	30 827 (65.26)	27 736 (68.46)
Medium	25 633 (29.21)	14 290 (30.25)	11 343 (28.00)
Low	3555 (4.05)	2119 (4.49)	1436 (3.54)
Pre-pregnancy body mass index			
<18.5	3921 (4.55)	1911 (4.13)	2010 (5.05)
18.5–25	58 691 (68.18)	30 344 (65.55)	28 347 (71.24)
26–29	16 850 (19.57)	9905 (21.40)	6945 (17.45)
⩾30	6623 (7.69)	4133 (8.93)	2490 (6.26)
Maternal smoking during pregnancy (cigarettes/day)			
Never	67 859 (73.71)	35 159 (71.07)	32 700 (76.77)
<6	13 434 (14.59)	7448 (15.05)	5986 (14.05)
⩾6	10 773 (11.70)	6865 (13.88)	3908 (9.18)
Mother history of previous abortions	16 808 (19.09)	9238 (19.49)	7570 (18.62)
Pregnancy outcomes and child characteristics			
Miscarriages (all <28th week)	4683 (4.77)	1013 (2.00)	3670 (7.74)
Stillbirth	300 (0.31)	140 (0.28)	160 (0.34)
Small for gestational age	8756 (9.53)	4584 (9.34)	4172 (9.74)
Birth weight (g)			
<2500	2836 (3.08)	1391 (2.83)	1444 (3.37)
2500–4500	84 925 (92.33)	45 367 (92.38)	39558 (92.28)
>4500	4217 (4.58)	2350 (4.79)	1867 (4.36)
Gestational age (days)			
<258	4180 (4.54)	2043 (4.06)	2137 (4.98)
259–293	79 658 (86.52)	42 804 (87.04)	36 854 (85.92)
⩾294	8231 (8.94)	4330 (8.80)	3901 (9.09)
Child's sex			
Male	47 396 (51.24)	25 085 (50.81)	22 311 (51.73)
Birth order			
First	41 297 (46.91)	20 709 (43.69)	20 588 (50.67)

Distribution of the main Potential Confounders ($n = 98\,140$).
[a]Numbers do not sum up due to missing values.
[b]Mothers' socio-economic status is derived from mothers' and fathers' educational level and current job title.

are shown in Table 1. Of the 98 190 initially eligible women, 29% ($n = 28\,484$) used acetaminophen during the first trimester, 21% ($n = 20\,501$) during the second, 28% ($n = 25\,792$) during the third up to time of delivery, 20% ($n = 18\,862$) from the 25th to the 35th gestational week, 52% ($n = 50\,727$) at least once up to delivery and 46% ($n = 42\,840$) at least once up to the 35th week of gestation. Women who delivered live born children reported having used acetaminophen on average 9.4 weeks during pregnancy.

Risk of miscarriage

Miscarriages occurred in 4683 (4.8%) pregnancies but acetaminophen use during the first trimester was not associated with an increased risk of this outcome (Table 2); the frequency of miscarriage was 4.83% for users compared with 4.76% for non-users ($P = 0.66$). Women who had a miscarriage tended to end study participation before the first interview [only 886 (19%) had the first interview] as a modified first interview questionnaire was sent to women lacking this interview. Complete information on maternal characteristics was finally obtained for 2496 (53%) women with miscarriages who were included in the fully adjusted analysis (Table 2).

Risk of stillbirth

No increased risk of stillbirth was observed among women exposed to acetaminophen during pregnancy, compared with those with no exposure (Table 2). A similar negative result was found when follow-up was censored at day 271 [corresponding to the mean end of follow up among women with stillbirths (data not shown)].

Risk of preterm birth and other outcomes

Among live born children, whose mothers responded to the first three interviews ($n = 63\,871$), 1371 (2.2%) were born with LBW, 5877 (9.2%) were SGA and 2192 (3.8%) were born preterm. These figures were as expected lower than those of the entire population due to exclusion of women who did not complete the first three interviews. Acetaminophen use during the third trimester (up to the 35th week) was associated with an increased risk of preterm births (HR = 1.14, 95% CI: 1.03–1.26), particularly late preterm birth during the 35th to the 37th weeks (Table 3).

Table 2 HR of miscarriage and stillbirth according to acetaminophen exposure during pregnancy

	Children exposed[a]	%	Children with outcome[b]	HR crude[b]	HR adjusted[b]	95% CI
			Acetaminophen 1st trimester			
Miscarriages (<28th week) ($n = 98\,140$)	955	20.4	2444	1.01	0.97	(0.88–1.06)
Early miscarriages (<12th week)	502	20.0	1578	1.03	1.00	(0.88–1.13)
Late miscarriages (12th to <28th week)	453	20.9	866	1.04	0.88	(0.75–1.03)
Stillbirths (>28th week) ($n = 81\,004$)						
Acetaminophen 1st trimester	65	29.4	209	0.96	0.88	(0.65–1.19)
Acetaminophen 2nd trimester	49	22.2	209	0.91	0.86	(0.62–1.19)
Acetaminophen 3rd trimester[c]	41	18.6	209	1.11	1.06	(0.75–1.50)
Acetaminophen ever in pregnancy[c]	98	44.3	209	0.97	0.90	(0.69–1.19)

[a]Number and percentage of children exposed during the specific trimester of pregnancy, by outcome and number of children with the outcome that were included in the adjusted analysis. Numbers are not exactly the same as in Table 1 because of exclusion criteria for missing interviews (Figure 1) and because of missing values in adjusting variables.
[b]HRs for miscarriages are adjusted by mother age, socio-economic status, history of previous abortion, birth order, pre-pregnancy body mass index, cigarettes/day and coffee intake. HRs for stillbirths are adjusted by mother's age, socio-economic status, pre-pregnancy body mass index and cigarettes/day.
[c]Third trimester and ever use of acetaminophen is defined as use up to the 39th week of gestation. Some women used acetaminophen after 1st trimester of pregnancy.

Table 3 HR for LBW, SGA and preterm birth according to acetaminophen exposure during pregnancy ($n = 63\,871$)

	Acetaminophen 1st trimester		Acetaminophen 2nd trimester		Acetaminophen 3rd trimester[a]		Acetaminophen ever[a]	
	n[b]	HR[c] (95% CI)	n[b]	HR[c] (95% CI)	n[b]	HR[c] (95% CI)	n[b]	HR[c] (95% CI)
LBW	427	1.04 (0.87–1.25)	321	1.15 (0.95–1.40)	247	1.19 (0.98–1.43)	622	1.11 (0.94–1.31)
SGA	1775	0.94 (0.89–0.99)	1321	1.03 (0.96–1.09)	1064	1.03 (0.97–1.09)	2590	0.96 (0.91–1.01)
All preterm (<37 weeks)	662	0.94 (0.86–1.03)	506	1.04 (0.94–1.15)	391	1.14 (1.03–1.26)	967	1.01 (0.93–1.10)
Preterm (35–37 weeks)	480	0.96 (0.86–1.07)	361	1.06 (0.94–1.19)	292	1.21 (1.08–1.36)	697	1.04 (0.94–1.15)
Very preterm (<35 weeks)	182	0.90 (0.75–1.07)	145	0.99 (0.82–1.20)	99	0.98 (0.81–1.19)	270	0.96 (0.82–1.13)

[a]Third trimester use' and 'ever use' were defined as use up to the 35th week of pregnancy.
[b]Number of children by outcome among women exposed to acetaminophen during each trimester.
[c]Adjusted by maternal age, socio-economic status, pre-pregnancy body mass index, cigarettes/day, birth order, coffee intake and sex of the child.

Additional adjustment for the presence during pregnancy of infections, inflammations, use of antibiotics, fever, muscle or joint diseases, pre-eclampsia and hypertensive diseases resulted to a very similar estimate (HR = 1.12, 95% CI: 1.01–1.23) for all preterm births. However, the increased risk of preterm births occurred only in women who also had pre-eclampsia (HR = 1.55, 95% CI: 1.16–2.07); the risk among women without pre-eclampsia was considerably lower (HR = 1.08, 95% CI: 0.97–1.20) (Table 4). After stratifying by coffee intake and smoking, an increased risk of preterm birth after acetaminophen exposure was observed only among children whose mothers did not drink coffee or smoke (HR = 1.34, 95% CI: 1.14–1.57).

When the analysis of preterm birth risk was stratified by hypertension (gestational hypertension and hypertension prior to pregnancy) and pre-eclampsia, acetaminophen use during the third trimester was associated with increased risk of preterm birth only among women who had pre-eclampsia (Table 4). The frequency of preterm phenotypes in the live born population was; 2614 (4%) cases of premature rupture of membranes, 489 (0.8%) cases with preterm labour, 1645 (2.6%) cases of pre-eclampsia and 616 (1%) cases of placenta diseases. When stratifying by causes of preterm birth, acetaminophen use was associated with an increased risk of preterm birth and very preterm birth only among those women with pre-eclampsia (HR = 1.58, 95% CI: 1.17–2.14). This risk changed to HR = 1.41 (95% CI: 1.09–1.81) when using another definition of pre-eclampsia that included cases reported by women during the interviews. No association was found with other potential outcomes including premature rupture of membranes, preterm labour and conditions affecting the placenta (Table 5). Acetaminophen use any time during pregnancy and during the third trimester was associated with a slightly increased risk of hypertension (HR = 1.14: 95% CI: 1.08–1.20 for third trimester use and HR = 1.07, 95% CI: 1.03–1.12 for ever use) and with pre-eclampsia during pregnancy (HR = 1.23: 95% CI: 1.10–1.38 for third trimester use and HR = 1.16, 95% CI: 1.05–1.28 for ever use). There was no linear relation between the number of weeks exposed to acetaminophen during the third trimester of pregnancy and risk of preterm birth. When the number of weeks of exposure was categorized as 0, 1–4 and $\geqslant 5$ weeks, no significant trend for fetal survival was found (data not shown).

Acetaminophen use during pregnancy was not associated with an increased risk of preterm birth complications including bronchopulmonary dysplasia, intracranial hemorrhage, retinopathy of prematurity, perinatal infections and anemia of prematurity.

Acetaminophen use was not associated with the risk of LBW among term children (Table 3). Exposure to acetaminophen during the third trimester was associated with an increased risk for LBW for children also exposed to coffee during gestation (HR = 1.26, 95% CI: 1.00–1.59). The magnitude was slightly

Table 4 HR for adverse pregnancy outcomes according to acetaminophen use during the 3rd trimester (up to 35th week of gestation)[a] adjusted and stratified by hypertension and pre-eclampsia during pregnancy ($n = 63\,871$)

		LBW	SGA	All preterm	Preterm 35–37 weeks	Very preterm <35 weeks
Hypertension	Pre-eclampsia	HR[b] (95% CI)	HR[b] (95% CI)	HR[b] (95% CI)	HR[b] (95% CI)	HR[b] (95% CI)
No	No	1.20 (0.96–1.50)	1.00 (0.94–1.08)	1.09 (0.97–1.22)	1.19 (1.04–1.35)	0.84 (0.66–1.06)
Yes	No	0.92 (0.58–1.45)	1.07 (0.91–1.25)	1.04 (0.78–1.38)	1.06 (0.76–1.49)	0.98 (0.58–1.67)
Yes	Yes	1.15 (0.65–2.02)	1.09 (0.83–1.41)	1.55 (1.16–2.07)	1.45 (1.00–2.09)	1.73 (1.08–2.75)

[a]Adjusted by maternal age, socio-economic status, pre-pregnancy body mass index, cigarettes/day, birth order, coffee intake and sex of the child.
[b]Reference groups are those not exposed during the third trimester, up to the 35th week of pregnancy (HR = 1.00).

Table 5 HR for preterm birth according to acetaminophen use during the 3rd trimester (up to 35th week of gestation)[a] stratified by potential causes of preterm birth ($n = 63\,871$)

		All preterm	Preterm 35–37 weeks	Very preterm <35 weeks
	n[b]	HR[c] (95% CI)	HR[c] (95% CI)	HR[c] (95% CI)
Premature rupture of membranes	2419	1.05 (0.82–1.34)	1.07 (0.80–1.44)	0.96 (0.60–1.54)
Preterm labor	342	1.18 (0.87–1.59)	1.32 (0.93–1.88)	0.89 (0.48–1.64)
Pre-eclampsia	1577	1.58 (1.17–2.14)	1.57 (1.07–2.30)	1.61 (0.98–2.65)
Placenta diseases	566	0.90 (0.58–1.40)	0.96 (0.55–1.68)	0.79 (0.38–1.63)

[a]Reference groups are those not exposed during the 3rd trimester up to 35th week of pregnancy (HR = 1.00).
[b]Total number of pregnancies with the diagnosis of interest (premature rupture of membranes, etc...) and without missing values in adjusting variables.
[c]HR adjusted by maternal age, socio-economic status, pre-pregnancy body mass index, cigarettes/day, birth order, coffee intake and sex of the child.

higher if they were also exposed to tobacco (HR = 1.37, 95% CI: 1.02–1.84).

Acetaminophen use during the pregnancy was not associated with SGA, except for a slightly reduced risk for first-trimester exposure (HR = 0.94, 95% CI: 0.89–0.99) (Table 3). Exposure during the third trimester was not associated with an increased risk of SGA (HR = 1.03, 95% CI: 0.97–1.09), although the risk increased to 1.26 (95% CI: 1.05–1.51) among mothers who smoked but did not consume coffee during pregnancy.

Discussion

Mothers who took acetaminophen during the third trimester of pregnancy were at increased risk of preterm birth following pre-eclampsia. Acetaminophen use during pregnancy was not associated with a change in the risk of miscarriage, LBW or SGA. In contrast to previous reports,[5,6] we found no reduced risk of stillbirth or of preterm birth among pregnancies with acetaminophen exposure. However, our results are based on a large population-based study and included both over-the-counter and prescribed medication. No consistent patterns were observed when the analyses for different outcomes were stratified by coffee and tobacco consumption during pregnancy.

This study has limitations. Though based on a large birth cohort, the sample size is still relatively small for analyses of rare outcomes such as stillbirths. In addition, there was a high number of missing values for covariates in the analysis of miscarriages. In addition, multiple analyses were performed and some significant results are most likely due to chance. Using duration of use as a proxy for dose did not allow us to differentiate between regular daily use and sporadic but frequent use.

Children born at term had a higher probability of exposure because of the longer duration of the third trimester. To avoid length bias, the exposure window was censored at the mean gestational age for preterm births (35 weeks) and for stillbirths (39 weeks). Furthermore, to avoid 'non-response' bias, the analysis was restricted to women who had completed three interviews. Differential recall bias is unlikely since the main data collection took place prior to the outcomes under study, although recall bias could have occurred in the first postpartum interview. Further, participants were asked to note down the drugs they used during pregnancy and to have this information ready at the time of interviewing. Although most of the main outcomes were checked both in the hospital discharge registry and in the DNBC, underreporting and outcome misclassification still occur for pre-eclampsia. This outcome misclassification may bias our results towards the null.

The association of acetaminophen with preterm birth was limited to women with pre-eclampsia and this could reflect reverse causation. Since headache may be caused by hypertension that is an essential symptom of pre-eclampsia, and acetaminophen would be a drug indicated for headache, pre-eclampsia headache may lead to drug use-reverse causation. In addition, women with pre-eclampsia are more likely to deliver preterm for therapeutic reasons. This possibility is also suggested by the fact that preterm birth risk was only marginally increased in women with headache but not pre-eclampsia, and in women who took acetaminophen for causes other than pain, such as fever, inflammation or joint diseases. Alternatively, acetaminophen may cause pre-eclampsia or that the observed association may be due to confounding by indication for migraine treatment.[19] However, there is only very limited evidence suggesting that migraine is a risk factor for pre-eclampsia.[20] There is only experimental evidence suggesting that acetaminophen causes pre-eclampsia, possibly through a reduction of Prostacyclin synthesis[9] and subsequent effects on hypertension. Further studies are needed to examine acetaminophen use and pre-eclampsia as a primary outcome, differentiating between chronic pre-pregnancy hypertension and pregnancy-induced hypertension.

When we stratified the analysis by all indications for acetaminophen use, including pre-eclampsia, only pre-eclampsia was associated with an increased risk of preterm birth. It is noteworthy that when we stratified by causes of preterm birth, the category 'unknown' also presented an increased risk. This could be a real effect of acetaminophen through pathways such as oxidative stress. Residual confounding by other causes of preterm birth or by migraine during pregnancy remains a possibility. However, when we accounted for the main confounders used in previous studies, our estimates did not change.

Our study did not provide strong support for a change in clinical practice regarding use of acetaminophen during pregnancy. The 50% increased risk of preterm birth in women with pre-eclampsia should be critically evaluated.

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KEY MESSAGES

- Acetaminophen use during pregnancy is not associated with a change in risk of miscarriage, stillbirth, LBW or SGA.
- Acetaminophen use during pregnancy is associated with an increased risk of preterm birth in women with pre-eclampsia, but this use need not to be causal.
- Potential importance of these findings for public health is related to the prevalent use of acetaminophen during pregnancy and the potential negative consequences of preterm birth and pre-eclampsia.
- Further research should examine the relation between acetaminophen use during pregnancy and the risk of pregnancy-induced hypertension, pre-eclampsia and other vascular diseases during pregnancy.

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