

ORIGINAL REPORT

Association of prenatal exposure to acetaminophen and coffee with childhood asthma

Xiaoqin Liu^{1*}, Zeyan Liew², Jørn Olsen^{1,2}, Lars Henning Pedersen³, Bodil Hammer Bech¹, Esben Agerbo^{4,5}, Wei Yuan⁶ and Jiong Li⁷

¹Section for Epidemiology, Department of Public Health, Aarhus University, Aarhus, Denmark

²Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, CA, USA

³Department of Obstetrics and Gynecology, Institute of Clinical Medicine, Aarhus University, Aarhus, Denmark

⁴National Centre for Register-based Research, Aarhus University, Aarhus, Denmark

⁵CIRRAU-Centre for Integrated Register-based Research, Aarhus University, Aarhus, Denmark

⁶Department of Epidemiology and Social Science on Reproductive Health, Shanghai Institute of Planned Parenthood Research, WHO Collaborating Center for Research in Human Reproduction, National Population and Family Planning Key Laboratory of Contraceptive Drugs and Devices, Shanghai, China

⁷Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

ABSTRACT

Purpose Some studies have suggested that maternal acetaminophen use during pregnancy is associated with asthma in the offspring, and coffee consumption may modify the toxicity of acetaminophen. We aim to examine whether pregnancy maternal acetaminophen use increases the risk for offspring asthma, and whether such a potential association could be modified by maternal coffee consumption.

Methods We included 63 652 live-born singletons enrolled in the Danish National Birth Cohort. Maternal acetaminophen use and coffee consumption during pregnancy were assessed prospectively via the enrolment questionnaire and three computer-assisted telephone interviews. Asthma cases were identified by using the Danish National Patient Register and the Danish National Prescription Registry. We estimated the hazard ratios (HRs) for asthma according to prenatal acetaminophen and coffee exposure using Cox proportional hazards regression model.

Results After adjusting for potential confounders, acetaminophen use during pregnancy was associated with an increased risk of offspring asthma (HR = 1.16, 95% confidence interval (CI): 1.11–1.22). Coffee drinking during pregnancy was associated with a slightly decreased risk (HR = 0.94, 95%CI: 0.90–0.99). But there was no strong evidence of effect measure modification of acetaminophen use on offspring asthma by coffee consumption.

Conclusions Acetaminophen use during pregnancy was associated with a modest increased risk for offspring asthma, which was not modified by coffee consumption. Copyright © 2015 John Wiley & Sons, Ltd.

KEY WORDS—acetaminophen; asthma; childhood; coffee; paracetamol; pregnancy; pharmacoepidemiology

Received 4 June 2015; Revised 22 September 2015; Accepted 23 November 2015

INTRODUCTION

Acetaminophen, also known as paracetamol, is used as an analgesic or antipyretic agent by more than 50% of pregnant women in the United States and Denmark.^{1,2} Acetaminophen crosses the placenta,³ and risk of adverse health outcomes in the offspring is now under scrutiny.

It has been speculated that acetaminophen depletes glutathione (GSH) and impairs the antioxidant defenses,⁴ favoring increased inflammation of airways and potentially enhanced T-helper (Th) 2 responses.⁵ Such an immune response might predispose children toward asthma. Most,^{6–13} but not all,^{14,15} cohort studies support a modest but consistent association of acetaminophen use during pregnancy and asthma in the offspring. Another study found that acetaminophen use during pregnancy was related to an increased risk of asthma in children at the age of 3–5 years, but not

*Correspondence to: X. Liu, Section for Epidemiology, Department of Public Health, Aarhus University, Bartholins Alle 2, 8000 Aarhus C, Denmark. Email: lxq@ph.au.dk

at the age of 7–10 years.¹⁶ This association may be confounded by maternal respiratory tract infections. Moreover, inconsistency of timing of in utero exposure to acetaminophen and asthma development has been reported,^{6,8–11} possibly because of small effect size, different study populations, or definitions of asthma.

Caffeine may delay acetaminophen's clearance¹⁷ and potentially affect the oxidative stress and acetaminophen toxicity.¹⁸ Thereby, it is possible that caffeine intake may enhance the toxic effect of acetaminophen. Furthermore, caffeine *per se* may have an impact on asthma. Caffeine is found to have anti-inflammatory and immunomodulatory properties in neonatal rats.¹⁹ On the other hand, caffeine intake is suggested to be associated with an increased risk of low birth weight and fetal growth restriction,²⁰ which may predispose children to asthma later in life.²¹ Around 45% of women in Denmark and in the United States continue coffee consumption during pregnancy.^{22–24} To date, evidence on whether coffee consumption during pregnancy influences the risk for asthma in the offspring is sparse. No study has investigated the potential effect modification of acetaminophen use on offspring asthma by maternal coffee consumption.

We aim to estimate the effect of pregnancy acetaminophen use and coffee consumption on asthma in the offspring and to assess whether the association between maternal acetaminophen use and offspring asthma is modified by coffee consumption in a cohort study. In this study, we extended the previous observations in the Danish National Birth Cohort (DNBC)⁶ and defined asthma by using objective medical records and prescription data rather than maternal self-report data.

METHODS

Study population

The study was carried out in the DNBC,²⁵ a nationwide cohort including 101 042 pregnancies. Women were recruited between 6 and 12 weeks of gestation between 1 March 1996 and 1 November 2002 by approximately 50% of all general practitioners in Denmark; 60% of invited women agreed to participate. Women participating in the DNBC were asked to complete a self-administered enrolment questionnaire and to take part in computer-assisted telephone interviews twice during pregnancy (at approximately 16 and 31 weeks of gestation) and when their children were 6 months old (an English version of questionnaires can be found at <http://www.dnbc.dk>). We excluded

2080 non-singleton pregnancies, 6207 unsuccessful pregnancies, 25 pregnancies with unknown birth outcomes, 99 pregnancies with unknown birth dates, 28 254 pregnancies without complete data from one of the three telephone interviews, and 26 pregnancies with unknown coffee consumption during pregnancy. We further excluded 699 infants who emigrated or died before 3 years of age. In total, 63 652 singletons and 60 296 mothers were included in the analyses. All live-born children and new residents in Denmark are assigned a unique personal identification number, which can be used to link information at the individual level between all national registers. The DNBC was linked to the Danish Civil Registration System,²⁶ the Danish Medical Birth Registry,²⁷ the Danish National Prescription Registry,²⁸ and the Danish National Patient Register.²⁹

Data on acetaminophen use and coffee consumption

Information on acetaminophen use during pregnancy was collected by the self-administered enrolment questionnaire and three computer-assisted telephone interviews. In the telephone interviews, women were asked to report use of pain killers during pregnancy. Respondents who answered “yes” were provided a list of 44 common pain killers, including acetaminophen as a singular and combination drug. They were also asked to indicate the specific gestational week of acetaminophen use.

Information on coffee consumption during pregnancy was collected in the first and second computer-assisted telephone interviews. Women were asked, “How many cups of coffee do you drink daily?” Answers were coded in number of cups per day; a mug was coded as two cups. Women who reported coffee consumption in either interview were defined as coffee drinkers. Women who reported coffee consumption in both interviews were considered as constant coffee drinkers during pregnancy, and we averaged the reported cups of coffee in two interviews as the amount of coffee consumption during pregnancy. Women who reported no coffee consumption in both interviews were considered as non-coffee drinkers.

Ascertainment of asthma diagnosis

Asthma in children was identified by using the Danish National Patient Register and the Danish National Prescription Registry. The Danish National Patient Register has collected data on all inpatient contacts since 1977, and from 1995 also for all emergency room and outpatient contacts. Because a definitive diagnosis of asthma cannot be made before

3 years of age,³⁰ we defined asthma cases as at least two prescriptions for inhaled asthma drugs or one hospital contact for asthma (i.e., physician-diagnosed asthma at the hospital) at the age of 3 years or later during 1999–2010. Asthma hospital contact was identified based on the 10th revision of the International Classification of Diseases (ICD-10): J45 and J46. The anatomical therapeutic chemical codes for inhaled anti-asthmatics were: inhaled β_2 -agonists (R03AC02, R03AC03, R03AC04, R03AC12, and R03AC13), inhaled glucocorticoids (R03BA01, R03BA02, and R03BA05), fixed-dose combination of inhaled β_2 -agonists and glucocorticoids (R03AK06 and R03AK07), and leukotriene receptor antagonists (R03DC03). Two or more medications prescribed on the same day were considered as one prescription. The first diagnosis of asthma was defined as the date of first admission, outpatient visit or an emergency room visit for asthma or first anti-asthmatics redeemed in the registers whichever came first after 3 years of age.

Covariates

We adjusted for the following potential confounders in the models: maternal parity (first, second, and higher), maternal age at delivery (<25, 25–29, 30–34, and ≥ 35 years), socioeconomic status (high, medium, and low), maternal history of asthma (yes, no), maternal smoking during pregnancy (never, <10 cigarettes/day, and ≥ 10 cigarettes/day), pre-pregnancy body mass index (<18.5, 18.5–24.9, 25–29.9, and ≥ 30), maternal antibiotic use for respiratory tract infections during pregnancy (yes, no), maternal nausea during pregnancy (yes, no), and sex of the child (boy, girl). Socioeconomic status was a composed variable derived from the mother and father's educational level and occupation. To address potential confounding by indications of acetaminophen use, we further adjusted for maternal fever (yes, no), inflammation or infection (yes, no), or muscle or joint disease during pregnancy (yes, no). Information on maternal antibiotic use for respiratory tract infections was obtained from the Danish National Prescription Registry, and the anatomical therapeutic chemical codes were: J01CA** excluding J01CA08, J01CE**, J01CR**, J01DB**, J01DC**, J01DD**, J01FA**, J01XX08, J04AB**, J04AC**, and J04AK**.

Statistical analysis

All data were analyzed in Stata 11.1 (Statacorp, College Station, TX, USA). Cox proportional hazards regression model was used to estimate the hazard

ratios (HRs) with 95% confidence intervals (CIs) for asthma in children according to maternal pregnancy acetaminophen use and coffee consumption. Follow-up started on the third birthday and ended at the time of first diagnosis of asthma, death, emigration, or the end of 2010, whichever came first. We used robust standard errors to account for the dependency between siblings as 3325 mothers contributed with more than one live singleton.

To examine whether the association between maternal acetaminophen use during pregnancy and asthma depended on timing of exposure to acetaminophen, we divided timing of exposure into four groups: the first trimester (first 12 weeks after the last menstrual period [LMP]) only, the second trimester (13–24 weeks after the LMP) only, the third trimester (25 weeks after the LMP to date of delivery) only, and more than one trimester.

In order to investigate the association between timing of coffee consumption and offspring asthma, we categorized coffee consumption into three groups: reported coffee consumption only in the first interview, only in the second interview, or constant coffee consumption throughout pregnancy. We also examined amount of coffee consumption as average intake of $\frac{1}{2}$ –3 or ≥ 4 cups/day during pregnancy.

To assess whether the association of acetaminophen use and asthma was modified by coffee consumption, we examined the association of acetaminophen use and offspring asthma stratified by amount of coffee consumption. To test for coffee-acetaminophen interaction in the multiplicative scale, we used the Wald chi-square test for heterogeneity between timing of acetaminophen exposure in different amount of coffee consumption groups.

We conducted a sensitivity analysis by further adjustment for the use of aspirin or ibuprofen during pregnancy (yes, no) to explore whether the associations were influenced by the use of other pain killers. We also performed a sensitivity analysis by further adjustment for tea consumption (0, $\frac{1}{2}$ –3, 4–7, and ≥ 8 cups/day) and cola drinks (0, <1, and ≥ 1 liter/week).

ETHICS

The study was approved by the Danish Data Protection Agency and the Central Science Ethics Committee in Denmark. No informed consent is needed for a register-based study of public health interest based on encrypted data according to the legislation in Denmark.

RESULTS

In this cohort, 56.3% of children were born to mothers who used acetaminophen during the index pregnancy. Of 34 962 children born to mothers who reported coffee consumption during pregnancy, 8.1% in the first interview only, 19.3% in the second interview only, and 72.6% in both interviews. The correlation between amounts of coffee consumption reported in two interviews was high ($r=0.83$, $p<0.001$).

Table 1 shows the characteristics of 63 652 children and their mothers according to maternal acetaminophen use and coffee consumption during pregnancy. Compared with mothers who neither used acetaminophen nor drank coffee during pregnancy, mothers who used acetaminophen during pregnancy were characterized by being more often multiparous, having higher pre-pregnancy body mass index and lower socioeconomic status, smoked more, used antibiotics for respiratory tract infections more, had more fever, inflammation or infection, muscle or joint disease, and suffered more

often from nausea during pregnancy. Compared with mothers who neither used acetaminophen nor drank coffee during pregnancy, mothers who drank coffee during pregnancy were older, smoked more, and had more prior pregnancies and less nausea.

In this study, asthma was diagnosed in 7644 children (12.0%) during follow-up in the cohort. An increased risk for asthma was observed in children born to mothers who used acetaminophen during pregnancy (HR = 1.16, 95%CI: 1.11–1.22), compared with children born to mothers who did not use acetaminophen during pregnancy. A slightly higher risks for asthma were observed in children born to mothers who used acetaminophen in the first trimester or more than one trimester; the HRs were 1.21 (95%CI: 1.12–1.31) and 1.20 (95%CI: 1.14–1.27), respectively (Table 2).

A slightly decreased risk for asthma was observed in children born to mothers who drank coffee during pregnancy (HR = 0.94, 95%CI: 0.90–0.99), compared with children born to mothers who did not drink coffee during pregnancy (Table 3).

Table 1. Characteristics of the cohort according to maternal acetaminophen use and coffee consumption during pregnancy ($n=63\,652$)

Characteristics	Acetaminophen + coffee ($n=20\,335$)	Acetaminophen ($n=15\,481$)	Coffee ($n=14\,627$)	Neither acetaminophen nor coffee ($n=13\,209$)
Maternal age at delivery (years)				
<25	6.4	12.6	5.8	11.2
25–29	33.8	44.4	34.5	44.5
30–34	40.7	32.8	40.8	33.8
≥35	19.1	10.2	18.9	10.5
Maternal parity				
1	38.3	49.5	45.4	55.3
≥2	61.7	50.5	54.6	44.7
Pre-pregnancy body mass index				
<18.5	4.0	3.6	4.9	4.5
18.5–24.9	66.4	60.0	71.5	67.7
25–29.9	19.7	23.1	16.4	18.4
≥30	8.3	11.7	5.6	7.8
Unknown	1.6	1.6	1.6	1.6
Socioeconomic status ^a				
High	65.2	64.8	69.0	68.8
Medium	30.3	30.8	27.3	28.0
Low	4.1	4.0	3.4	2.9
Unknown	0.4	0.4	0.3	0.3
Maternal smoking during pregnancy				
Never	66.2	80.5	71.8	85.2
<10 cigarettes/day	18.1	11.3	16.4	8.7
≥10 cigarettes/day	15.7	8.2	11.8	6.1
Pregnancy antibiotic use for respiratory tract infections	22.4	22.2	14.4	14.2
Maternal history of asthma	10.1	11.1	7.5	8.8
Fever during pregnancy	33.0	33.9	22.3	22.9
Inflammation or infection during pregnancy	17.8	17.1	12.6	11.9
Muscle or joint disease during pregnancy	13.1	13.7	8.1	8.8
Nauseas during pregnancy	60.0	66.2	53.6	59.8
Sex of the child				
Boy	51.0	50.2	51.3	51.6
Girl	49.0	49.8	48.7	48.4

^aSocioeconomic status was a composed variable derived from the mother and father's educational level and occupation.

Table 2. Hazard ratios (HRs) for asthma in the offspring according to maternal acetaminophen use during pregnancy ($n = 63\ 652$)

Acetaminophen use during pregnancy	No. of cases (n)	Crude HRs	Adjusted HRs ^a
Never user	2987 (27 836)	1	1 (ref)
Acetaminophen use	4657 (35 816)	1.23	1.16 (1.11–1.22)
1st trimester only	806 (6048)	1.26	1.21 (1.12–1.31)
2nd trimester only	382 (3309)	1.08	1.05 (0.94–1.17)
3rd trimester only	909 (7320)	1.18	1.10 (1.02–1.18)
More than one trimester	2167 (16 002)	1.29	1.20 (1.14–1.27)
Unknown trimester	393 (3137)	1.16	1.12 (1.01–1.25)

^aAdjusted for maternal age at delivery, maternal parity, maternal pre-pregnancy body mass index, socioeconomic status, maternal smoking during pregnancy, maternal history of asthma, maternal fever during pregnancy, maternal inflammation or infection during pregnancy, maternal antibiotic use for respiratory tract infections, maternal muscle or joint disease during pregnancy, maternal nausea during pregnancy, and sex of the child.

Table 4 shows the relation between timing of acetaminophen use and risk for asthma in the offspring stratified by amount of coffee consumption. We found no evidence to suggest that coffee may modify the estimated effect of acetaminophen on offspring asthma (all p -values for interaction were greater than 0.20).

The association between acetaminophen and asthma was similar among children of mothers with and

without pregnancy antibiotic use for respiratory tract infections, and the HRs were 1.15 (95%CI: 1.04–1.28) and 1.16 (95%CI: 1.10–1.23), respectively.

About 5.2% children were born to mothers who used ibuprofen, of whom 443 children developed asthma. A total of 4.6% children were born to mothers who used aspirin and 342 children developed asthma. Maternal use of ibuprofen or aspirin during pregnancy was not associated with asthma in the offspring; the HRs were 1.07 (95%CI: 0.97–1.18) and 0.95 (95%CI: 0.85–1.06), respectively. The results did not change after further adjustment for use of aspirin or ibuprofen during pregnancy (data not shown). Further adjustment for tea consumption and cola drinks gave similar results to those reported here (data not shown).

DISCUSSION

Maternal acetaminophen use during pregnancy was associated with a modest increased risk for asthma, while coffee consumption during pregnancy was associated with a slightly decreased risk. There was no evidence of effect measure modification of acetaminophen use on offspring asthma by coffee consumption.

Table 3. Hazard ratios (HRs) for asthma in the offspring according to coffee consumption during pregnancy ($n = 63\ 652$)

Coffee consumption during pregnancy	No. of cases (n)	Crude HRs	Adjusted HRs ^a
Non-coffee drinker	3563 (28 690)	1	1 (ref)
Coffee drinker	4081 (34 962)	0.93	0.94 (0.90–0.99)
Reported only in the 1st interview	344 (2834)	0.99	0.96 (0.86–1.07)
Reported only in the 2nd interview	789 (6740)	0.93	0.96 (0.89–1.04)
Constant coffee drinker	2948 (25 388)	0.92	0.93 (0.89–0.98)
½–3 cups/day	1919 (17 107)	0.89	0.91 (0.86–0.97)
≥4 cups/day	1029 (8281)	0.99	0.99 (0.92–1.06)

^aAdjusted for maternal age at delivery, maternal parity, maternal pre-pregnancy body mass index, socioeconomic status, maternal smoking during pregnancy, maternal history of asthma, maternal fever during pregnancy, maternal inflammation or infection during pregnancy, maternal antibiotic use for respiratory tract infections, maternal muscle or joint disease during pregnancy, maternal nausea during pregnancy, and sex of the child.

Table 4. Hazard ratios (HRs) for asthma in the offspring according to timing of acetaminophen use stratified by amount of coffee consumption during pregnancy ($n = 54\ 078$)

Acetaminophen use during pregnancy	No coffee consumption		Coffee consumption of ½–3 cups/day		Coffee consumption of ≥4 cups/day	
	No. of cases (n)	Adjusted HRs ^a	No. of cases (n)	Adjusted HRs ^a	No. of cases (n)	Adjusted HRs ^a
Never user	1470 (13 209)	1 (ref)	719 (7307)	1 (ref)	334 (3023)	1 (ref)
Acetaminophen use	2093 (15 481)	1.17 (1.09–1.26)	1200 (9800)	1.20 (1.09–1.31)	695 (5258)	1.14 (1.00–1.30)
1st trimester only	356 (2644)	1.18 (1.05–1.33)	217 (1658)	1.32 (1.13–1.53)	104 (767)	1.20 (0.96–1.50)
2nd trimester only	177 (1419)	1.11 (0.95–1.29)	110 (957)	1.13 (0.92–1.39)	41 (405)	0.90 (0.65–1.24)
3rd trimester only	440 (3257)	1.17 (1.05–1.30)	209 (1918)	1.03 (0.88–1.21)	135 (1068)	1.06 (0.86–1.30)
More than one trimester	941 (6812)	1.19 (1.10–1.30)	563 (4400)	1.24 (1.11–1.39)	355 (2527)	1.20 (1.03–1.40)
Unknown trimester	179 (1349)	1.13 (0.97–1.32)	101 (867)	1.15 (0.93–1.42)	60 (491)	1.07 (0.81–1.41)

^aAdjusted for maternal age at delivery, maternal parity, maternal pre-pregnancy body mass index, socioeconomic status, maternal smoking during pregnancy, maternal history of asthma, maternal fever during pregnancy, maternal inflammation or infection during pregnancy, maternal antibiotic use for respiratory tract infections, maternal muscle or joint disease during pregnancy, maternal nausea during pregnancy, and sex of the child.

Our study corroborates an increased risk for asthma following acetaminophen exposure in utero. The magnitude of the association between acetaminophen exposure in utero and asthma found in the study is moderate but in line with the findings of previous studies.^{10,11} A previous study in the DNBC reported a similar association between prenatal acetaminophen exposure and maternal reported asthma in the children,⁶ which is in line with our finding. In the current study, we ascertained asthma cases from the medical records and prescription registry, and we included a larger study sample size and longer follow-up. Moreover, we adjusted for maternal antibiotic use for respiratory tract infections. Our finding suggests that the association observed cannot be entirely attributed to confounding by maternal respiratory tract infections.

Acetaminophen crosses the placenta and is metabolized by the fetal liver. In adults, acetaminophen is metabolized and excreted through glucuronidation or sulfation pathways. A small proportion is oxidized to a toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI) by cytochrome P450s.³¹ The fetus has a limited ability to metabolize acetaminophen through glucuronidation,³² as glucuronidation pathway of acetaminophen metabolism is catalyzed by uridine 5'-diphospho-glucuronosyltransferase, which cannot be detected in fetal liver before 20 weeks of gestation.³³ Therefore, acetaminophen must be metabolized either to sulfate via sulfation or to NAPQI via cytochrome P450s in early pregnancy.³² NAPQI is detoxified by glutathione S-transferase. It is indicated that fetal liver is able to detoxify acetaminophen as GSH conjugate.³² However, the expression of glutathione S-transferase in the lung of the fetus progressively decreased after 15 weeks of gestation, and at birth, the level of activity was only about 20% of that in samples obtained during the first trimester.³⁴ It was reported that the oxidation of acetaminophen by the fetal liver was approximately 10 times slower than that in the adult liver.³² Excess NAPQI may deplete GSH stores and impair antioxidant defenses.⁴ A depleted GSH in the lung will result in increased oxidative damage to the bronchiolar epithelium and increase the risk for asthma subsequently.³⁵

To our knowledge, there was no previous epidemiological studies that have explored the association between pregnancy coffee consumption and asthma, possibly because of a lack of cohort data with prospective ascertainment of coffee consumption. In our study, we found a slightly decreased risk for asthma following maternal coffee consumption during pregnancy. The weak association may indicate that the effect of coffee consumption is small if it exists, or the association

may be because of chance or confounding. Our findings could also be attributable to the speculative beneficial effect of caffeine on pulmonary surfactant homeostasis. Pulmonary surfactant is suggested to be a modulator of allergic inflammation.³⁶ Its production starts from the canalicular phase (17–26 weeks of gestation).³⁷ Caffeine may stimulate surfactant protein-B mRNA expression and induce total surfactant protein-B levels.³⁸

Even if coffee indeed has no effect on asthma risk, coffee could modify the effect of acetaminophen.¹⁸ However, our study showed no indication of such an effect.

Our study has several strengths. In Denmark, acetaminophen is usually sold as a single drug, and acetaminophen combined with caffeine can only be redeemed with a prescription. Less than 1% of women who reported acetaminophen use during pregnancy bought the drug on prescription, which indicates that more than 99% acetaminophen used by pregnant women does not contain caffeine. This provides a unique opportunity to investigate the effect measure modification of pregnancy acetaminophen use on offspring asthma by coffee consumption. The large sample size allowed us to analyze the association between acetaminophen use, coffee consumption and asthma in the offspring. The mean age of study participants at the end of follow-up was 11.5 years. Information on acetaminophen use and asthma were collected prospectively from different sources, which reduces the chance of recall bias. The availability of data on potential confounding variables, such as indications of acetaminophen use, provides some options for confounder control when studying maternal acetaminophen use during pregnancy and asthma.

Our findings should also be interpreted in the light of limitations. First, we included singletons registered in the DNBC. The participation rate (60%) is low. However, a previous study indicated that the effect of nonparticipation on selected exposure-risk associations is negligible in the DNBC.³⁹ We excluded children without complete data from one of the three telephone interviews. However, the cumulative incidence rate of asthma is comparable in the study population with children excluded from the study. Second, more than 80% of pregnant women did not recall the exact number of dosage, which makes it difficult to accurately calculate the dose consumed, and therefore to estimate dose-response relationship. Because acetaminophen is available as an over the counter medication, prescription register does not adequately capture acetaminophen use. Maternal self-reported acetaminophen use appears to be the only option.⁴⁰ Third, coffee contains varying amounts of caffeine depending on types of coffee (e.g., regular vs. decaffeinated coffee),

coffee beans, and brewing methods. We did not have information on these, but at that time, only a small part came from decaffeinated coffee. Fourth, we did not have information on several potential confounders, such as chocolate consumption, diet, and nutrition, which may be rich sources of caffeine. Our results should be interpreted with caution, especially small differences between acetaminophen exposures in each trimester. The possibility of residual confounding cannot be excluded. Fifth, the using of prescription and hospital registers will not identify asthma cases not seeking medical help.

CONCLUSIONS

In conclusion, our study provides further evidence that acetaminophen use during pregnancy is associated with an increased risk for offspring asthma, which is not modified by coffee consumption.

CONFLICT OF INTEREST

Bodil Hammer Bech has received a fee for acting as a consultant in translating the section on coffee and pregnancy from this website <http://coffeeandhealth.org/> to the Danish website www.kaffe-helbred.dk. The other authors have no conflicts of interest relevant to this article to disclose.

KEY POINTS

- Acetaminophen use during pregnancy is associated with an increased risk for asthma in the offspring, which is not modified by coffee consumption. Coffee consumption during pregnancy *per se* is associated with a slightly reduced risk for asthma in the offspring.

ACKNOWLEDGEMENTS

The Danish National Research Foundation has established the Danish Epidemiology Science Centre that initiated and created the DNBC. The cohort is furthermore a result of a major grant from this Foundation. Additional support for the DNBC is obtained from the Pharmacy Foundation, the Egmont Foundation, the March of Dimes Birth Defects Foundation, the Augustinus Foundation, and the Health Foundation. The funders had no role in study design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

FUNDING SOURCE

The study was supported by the European Research Council (ERC-2010-StG-260242-PROGEURO) and the Nordic Cancer Union (2013–129830). Xiaoqin Liu is supported by a Mobility PhD fellowship from Aarhus University. The funders had no role in study design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Rebordosa C, Kogevinas M, Bech BH, Sorensen HT, Olsen J. Use of acetaminophen during pregnancy and risk of adverse pregnancy outcomes. *Int J Epidemiol* 2009; **38**(3): 706–714. doi:10.1093/ije/dyp151.
2. Werler MM, Mitchell AA, Hernandez-Diaz S, Honein MA. Use of over-the-counter medications during pregnancy. *Am J Obstet Gynecol* 2005; **193**(3 Pt 1): 771–777. doi:10.1016/j.ajog.2005.02.100.
3. Levy G, Garrettson LK, Soda DM. Letter: evidence of placental transfer of acetaminophen. *Pediatrics* 1975; **55**(6): 895.
4. Nuttall SL, Khan JN, Thorpe GH, Langford N, Kendall MJ. The impact of therapeutic doses of paracetamol on serum total antioxidant capacity. *J Clin Pharm Ther* 2003; **28**(4): 289–294.
5. Farquhar H, Stewart A, Mitchell E, *et al.* The role of paracetamol in the pathogenesis of asthma. *Clin exp allergy* 2010; **40**(1): 32–41. doi:10.1111/j.1365-2222.2009.03378.x.
6. Rebordosa C, Kogevinas M, Sorensen HT, Olsen J. Pre-natal exposure to paracetamol and risk of wheezing and asthma in children: a birth cohort study. *Int J Epidemiol* 2008; **37**(3): 583–590. doi:10.1093/ije/dyn070.
7. Garcia-Marcos L, Sanchez-Solis M, Perez-Fernandez V, Pastor-Vivero MD, Mondejar-Lopez P, Valverde-Molina J. Is the effect of prenatal paracetamol exposure on wheezing in preschool children modified by asthma in the mother? *Int Arch Allergy Immunol* 2009; **149**(1): 33–37. doi:10.1159/000176304.
8. Shaheen SO, Newson RB, Sherriff A, *et al.* Paracetamol use in pregnancy and wheezing in early childhood. *Thorax* 2002; **57**(11): 958–963.
9. Perzanowski MS, Miller RL, Tang D, *et al.* Prenatal acetaminophen exposure and risk of wheeze at age 5 years in an urban low-income cohort. *Thorax* 2010; **65**(2): 118–123. doi:10.1136/thx.2009.121459.
10. Shaheen SO, Newson RB, Henderson AJ, *et al.* Prenatal paracetamol exposure and risk of asthma and elevated immunoglobulin E in childhood. *Clin exp allergy* 2005; **35**(1): 18–25. doi:10.1111/j.1365-2222.2005.02151.x.
11. Shaheen SO, Newson RB, Ring SM, Rose-Zerilli MJ, Holloway JW, Henderson AJ. Prenatal and infant acetaminophen exposure, antioxidant gene polymorphisms, and childhood asthma. *J Allergy Clin Immunol* 2010; **126**(6): 1141–1148 e1147. doi:10.1016/j.jaci.2010.08.047.
12. Kallen B, Finnstrom O, Nygren KG, Otterblad OP. Maternal drug use during pregnancy and asthma risk among children. *Pediatric allergy and immunol* 2013; **24**(1): 28–32. doi:10.1111/pai.12034.
13. Andersen AB, Farkas DK, Mehnert F, Ehrenstein V, Erichsen R. Use of prescription paracetamol during pregnancy and risk of asthma in children: a population-based Danish cohort study. *Clin epidemiol* 2012; **4**: 33–40. doi:10.2147/lep.s28312.
14. Kang EM, Lundsberg LS, Illuzzi JL, Bracken MB. Prenatal exposure to acetaminophen and asthma in children. *Obstet Gynecol* 2009; **114**(6): 1295–1306. doi:10.1097/AOG.0b013e3181c225c0.
15. Bakkeheim E, Mowinckel P, Carlsen KH, Haland G, Carlsen KC. Paracetamol in early infancy: the risk of childhood allergy and asthma. *Acta Paediatr* 2011; **100**(1): 90–96. doi:10.1111/j.1651-2227.2010.01942.x.
16. Sordillo JE, Scirica CV, Rifas-Shiman SL, *et al.* Prenatal and infant exposure to acetaminophen and ibuprofen and the risk for wheeze and asthma in children. *J Allergy Clin Immunol* 2015; **135**(2): 441–448. doi:10.1016/j.jaci.2014.07.065.
17. Iqbal N, Ahmad B, Janbaz KH, Gilani AU, Niazi SK. The effect of caffeine on the pharmacokinetics of acetaminophen in man. *Biopharm Drug Dispos* 1995; **16**(6): 481–487.
18. Cameron MD, Wen B, Roberts AG, Atkins WM, Campbell AP, Nelson SD. Co-operative binding of acetaminophen and caffeine within the P450 3A4 active site. *Chem Res Toxicol* 2007; **20**(10): 1434–1441. doi:10.1021/tx7000702.
19. Weichelt U, Cay R, Schmitz T, *et al.* Prevention of hyperoxia-mediated pulmonary inflammation in neonatal rats by caffeine. *Eur Respir J* 2013; **41**(4): 966–973. doi:10.1183/09031936.00012412.

20. Sengpiel V, Elind E, Bacelis J, *et al.* Maternal caffeine intake during pregnancy is associated with birth weight but not with gestational length: results from a large prospective observational cohort study. *BMC Med* 2013; **11**: 42. doi:10.1186/1741-7015-11-42.
21. Liu X, Olsen J, Agerbo E, *et al.* Birth weight, gestational age, fetal growth and childhood asthma hospitalization. *Allergy Asthma Clin Immunol* 2014; **10**(113.10.1186/1710-1492-10-13).
22. Bech BH, Nohr EA, Vaeth M, Henriksen TB, Olsen J. Coffee and fetal death: a cohort study with prospective data. *Am J Epidemiol* 2005; **162**(10): 983–990. doi:10.1093/aje/kwi317.
23. Linn S, Schoenbaum SC, Monson RR, Rosner B, Stubblefield PG, Ryan KJ. No association between coffee consumption and adverse outcomes of pregnancy. *N Engl J Med* 1982; **306**(3): 141–145. doi:10.1056/nejm198201213060304.
24. Weng X, Odouli R, Li DK. Maternal caffeine consumption during pregnancy and the risk of miscarriage: a prospective cohort study. *Am J Obstet Gynecol* 2008; **198**(3): 279 e271–278. doi:10.1016/j.ajog.2007.10.803.
25. Olsen J, Melbye M, Olsen SF, *et al.* The Danish National Birth Cohort—its background, structure and aim. *Scand J Public Health* 2001; **29**(4): 300–307.
26. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011; **39**(7 Suppl): 22–25. doi:10.1177/1403494810387965.
27. Knudsen LB, Olsen J. The Danish Medical Birth Registry. *Dan Med Bull* 1998; **45**(3): 320–323.
28. Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011; **39**(7 Suppl): 38–41. doi:10.1177/1403494810394717.
29. Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999; **46**(3): 263–268.
30. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995; **332**(3): 133–138. doi:10.1056/nejm199501193320301.
31. Prescott LF. Kinetics and metabolism of paracetamol and phenacetin. *Br J Clin Pharmacol* 1980; **10**(Suppl 2): 291S–298S.
32. Rollins DE, von Bahr C, Glaumann H, Moldeus P, Rane A. Acetaminophen: potentially toxic metabolite formed by human fetal and adult liver microsomes and isolated fetal liver cells. *Science (New York, NY)* 1979; **205**(4413): 1414–1416.
33. Strassburg CP, Strassburg A, Kneip S, *et al.* Developmental aspects of human hepatic drug glucuronidation in young children and adults. *Gut* 2002; **50**(2): 259–265.
34. Fryer AA, Hume R, Strange RC. The development of glutathione S-transferase and glutathione peroxidase activities in human lung. *Biochim Biophys Acta* 1986; **883**(3): 448–453.
35. Ballatori N, Krance SM, Notenboom S, Shi S, Tieu K, Hammond CL. Glutathione dysregulation and the etiology and progression of human diseases. *Biol Chem* 2009; **390**(3): 191–214. doi:10.1515/bc.2009.033.
36. Hohlfield JM. The role of surfactant in asthma. *Respir Res* 2002; **3**: 4.
37. Burri PH. Fetal and postnatal development of the lung. *Annu Rev Physiol* 1984; **46**: 617–628. doi:10.1146/annurev.ph.46.030184.003153.
38. Fehrholz M, Bersani I, Kramer BW, Speer CP, Kunzmann S. Synergistic effect of caffeine and glucocorticoids on expression of surfactant protein B (SP-B) mRNA. *PLoS One* 2012; **7**(12): e51575. doi:10.1371/journal.pone.0051575.
39. Nohr EA, Frydenberg M, Henriksen TB, Olsen J. Does low participation in cohort studies induce bias? *Epidemiology* 2006; **17**(4): 413–418. doi:10.1097/01.ede.0000220549.14177.60.
40. Olesen C, Sondergaard C, Thrane N, *et al.* Do pregnant women report use of dispensed medications? *Epidemiology* 2001; **12**(5): 497–501. doi:10.1097/00001648-200109000-00006.