Prenatal Exposure to Acetaminophen and Overweight in Childhood

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Published in:
Obesity

DOI:
10.1002/oby.22526

Publication date:
2019

Document version
Peer reviewed version

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Article type : Original Article

Title: Prenatal exposure to acetaminophen and overweight in childhood.

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Word count

- Abstract: 200 words
- Paper: 3390 words (main text regardless abstract and references)
- Title: 55 characters without spaces

Number of references: 30

Number of tables: 4

Number of figure: 1

Number of supplementary table (web-only): 5

Number of appendix (web-only): 2

Funding: This work was supported by the Danish Medical Research Council [DFF Project no. 09-3307].

Conflict of Interest Disclosures: All authors reported no conflict of interests.

Key words: acetaminophen (paracetamol), overweight, obesity, prenatal exposure, fetal programming

Author Contribution: Olsen and Liew conceptualized and designed the study. Liew performed data analyses and drafted the manuscript. All co-authors contributed equally in the manuscript revision and interpretation of results.

Acknowledgement: The Danish National Research Foundation established the Danish Epidemiology Science Centre, which initiated and created the Danish National Birth Cohort. The cohort is furthermore a result of a major grant from this Foundation. Additional support for the Danish National Birth Cohort was obtained from the Pharmacy Foundation, the Egmont Foundation, the March of Dimes Birth Defects Foundation and the Augustinus Foundation.

What is already known about this subject?

- Early life exposure to endocrine-disrupting chemicals or "obesogens" could predispose individuals to weight gain.
- Acetaminophen (paracetamol) is the most common over-the-counter medication to treat pain and fever in pregnancy, and it has been suggested to exhibit hormonal effects in recent experimental studies thus a possible "obesogen" that should be evaluated for its potential to promote weight gain.
- Acetaminophen intake in the first 12 months of life was associated with higher child BMI at age 7 in a cross-sectional survey collected from 18 countries, and a case-control study of 25 obese children in the U.S. at age 3-5 years detected elevated levels of acetaminophen metabolites in umbilical cord blood.

What does this study add?

- In this large population-based longitudinal study in Denmark, we found no consistent associations between maternal intake of acetaminophen during pregnancy and BMI z-scores and waist circumferences in the offspring measured at age 7 and 11 years.
- We observed that frequent exposure to acetaminophen during pregnancy (i.e. indicated by intake in all three trimesters or higher cumulative weeks of use) was positively associated with overweight in girls at age 11, but not in boys.

- There was no strong evidence to suggest that prenatal exposure to acetaminophen may influence childhood BMI, but the observed association between frequent prenatal exposure to acetaminophen and overweight in girls warrant further investigation.

ABSTRACT

Objective: Acetaminophen (paracetamol), a medication commonly used in pregnancy, has hormonal effects suggested in experimental studies. Developmental exposure to endocrine disruptors could predispose individuals to weight gain. We evaluated the associations between prenatal acetaminophen exposure and child's overweight.

Methods: We studied 30,127 (age 7) and 24,934 (age 11) children in the Danish National Birth Cohort born during 1996-2002. Mothers reported acetaminophen use in telephone interviews conducted during pregnancy, and children's body-mass-index (BMI) and waist circumference were reported by parents at 7 and 11 years. We estimated differences for BMI z-score and waist circumference, and risk ratio for overweight in girls and boys adjusting for indications of use and other confounders.

Results: We found no consistent associations for prenatal acetaminophen exposure and BMI z-score or waist circumference in girls and boys at both ages. Prenatal acetaminophen exposure was associated with overweight in girls at age 11 (RR 1.31 (95%CI 1.10, 1.56) if exposed in all three trimesters and p-trend <0.001 for cumulative weeks of exposure), but no association was found in boys.

Conclusions: There was no strong association between prenatal acetaminophen exposure and childhood BMI, but the findings on frequent prenatal exposure to acetaminophen and overweight in girls warrant further investigation.

INTRODUCTION

Acetaminophen (paracetamol) is a commonly used over-the-counter medication for pain relief and fever reduction. Unlike other antipyretics and analgesics, acetaminophen is not considered contra-indicated for pregnancy use and about 40-60% of pregnant women reported using acetaminophen at least once during pregnancy in the USA and in Western/Northern European countries (1). Acetaminophen can cross the placental barrier reaching the fetus who has limited capacity to metabolize acetaminophen during early development (2). Recent experimental studies have suggested that acetaminophen exhibits endocrine disruptive effects and in-utero exposure could affect fetal development (3, 4). Intrauterine exposure to acetaminophen inhibited fetal testosterone production in ex vivo fetal rat testes (4, 5), while female mouse fetuses exposed to acetaminophen showed perturbed proliferation of the primordial germ cells resulting in a reduction of ovarian follicle reserves (6). Epidemiological studies have also found that prenatal acetaminophen exposure was associated with increased occurrence of cryptorchidism (7) and shorter anogenital distance (8) in male infants, and earlier pubertal development in the female offspring (9).

Emerging research have suggested that early life exposure to "obesogens", including xenobiotic chemicals and endocrine disruptors, could permanently alter metabolic processes and predispose individuals to weight gain (10, 11, 12). Obesogens can cause weight gain by altering lipid homeostasis to promote adipogenesis and lipid accumulation, increasing the number and the size of adipocytes, or by altering the endocrine pathways responsible for the control of adipose tissue development (13). Acetaminophen is a possible "obesogen" that should be evaluated for its potential to promote weight gain (3, 4). Two epidemiological studies have previously suggested a possible link between early life exposure to acetaminophen and higher BMI in childhood (14, 15). The ISAAC study analyzed cross-sectional surveys collected for a total of 76,216 children in 18 countries found that acetaminophen use in the first 12 months of life was associated with higher BMI at age 7 in affluent countries (14). However, the study did not evaluate prenatal acetaminophen exposure, and the information on infant acetaminophen use was retrospectively reported by the parents when the child was 7 years old thus susceptible to recall bias. Moreover, a recent small matched case-control study conducted in the U.S. also reported elevated levels of acetaminophen metabolites in umbilical cord blood in 25 obese children at age 3-5 years compared to 25 sex-matched non-obese children (15). However,

acetaminophen has a short half-life thus a single measure of metabolites at birth might only indicate exposures shortly before delivery and do not represent exposure throughout pregnancy.

Here, we used longitudinal data collected in the Danish National Birth Cohort (DNBC) and evaluated the associations between maternal acetaminophen use in pregnancy and risks for being overweight in offspring at age 7 and 11 years. All analyses were stratified by boys and girls to evaluate potential sex-specific differences since earlier studies in the cohort reported sex-specific associations of prenatal exposure to acetaminophen and reproductive health outcomes in the offspring (7, 9).

METHODS

Study population

The Danish National Birth Cohort (DNBC) is a nationwide longitudinal study of pregnancies and children (16). Briefly, women were recruited between 6–12 weeks of gestation from 1996 to 2002 by about 50% of all general practitioners in Denmark. Among all pregnant women invited, 60% agreed to participate. The data collection instruments and questionnaires of the DNBC can be found online at http://www.dnbc.dk. There were 100,417 eligible pregnancies in the DNBC and we restricted our analyses to live-born singleton children with both exposure and outcome data available. A total of 64,322 mothers completed the enrollment form and the three telephone interviews (approximately at the gestational weeks of 12 and 30, and 6 months after birth) where information on acetaminophen intake during pregnancy was collected. Among these, BMI and waist circumference data were available in 38,983 (61%) children at age 7 and 31,647 children (49%) at age 11 years. For this study, we further restricted the analyses to 30,127 children at age 7 years and 24,934 children at age 11 years, excluding children if their height and weight measurements were taken for more than 3 months apart or if the timing of when the measurements were taken was missing.

Exposure assessment

At the first contact, women filled out an enrollment form that included questions regarding any supplement and medication use covering the period from four weeks before pregnancy until the gestational week of reporting. In the three computer-assisted telephone interviews, women were

asked to report whether they had taken any pain killers during pregnancy. Respondents who answered 'yes' were provided with a list of 44 common pain killers including acetaminophen whether available over-the-counter or via prescription. Additional questions also gave women the opportunity to report use of pain killers or drugs not specified in the list in an open-ended question. Women were asked to report the gestational week of use on a week-by-week basis. The information on weekly intake was used to calculate trimester specific and duration of use. The first, second and third trimesters were defined by the following time periods, weeks 1 through 12, weeks 13 through 24, and week 25 to delivery, respectively. We categorized the cumulative weeks of acetaminophen use into 1, 2-5, 6-20, and >20 weeks.

Outcome measures

Information on children's BMI and waist circumference were collected at 7 (mean and SD 7.05 ± 0.25) and 11 (mean and SD 11.30 ± 0.63) years of age. At age 7 years, 33% of these measures were taken by the school doctor, public health nurse, or the general practitioner, and for the remaining 67%, measurements were taken by one of the parents. Information on weight, height, and waist circumference at age 11 years was reported by the mother or father. The internal age- and sex-specific BMI *z*-scores were calculated using the Lambda, Median, Sigma (LMS) method (17). We categorized overweight at age 7 and 11 years according to the International Obesity Task Force (IOTF) reference (18). Since less than 1.5% of the children in the cohort were obese, overweight and obesity were combined and are referred to as being 'overweight'.

Covariates

We used directed acyclic graphs to identify potential confounding factors *a priori.* First, we included demographic factors such as child's birth year (categorical), maternal age at child birth (≤24, 25-29, 30-34, and ≥35 years), and parity (1st child, 2nd child, or more children) derived from the Danish medical birth register. Maternal pre-pregnancy BMI (continuous), maternal smoking (never, ≤9, and >9 cigarettes/day) and parental socio-occupational position were collected from the telephone interviews. A four-level socio-occupational variable was created based on the highest among maternal or paternal education and occupation: (1) high grade professional with extensive education, (2) medium grade professional with medium-length

education, (3) skilled worker or works in a position requiring less education, (4) unskilled worker, unemployed, or on financial assistance. To address possible confounding by indication, we controlled for three specific maternal conditions during pregnancy including maternal fever (yes/no), inflammation/infection (yes/no), and musculoskeletal diseases including pain (yes/no), as these conditions may trigger acetaminophen use (19) and also affect child development. Information regarding maternal diseases during pregnancy were reported by the mothers in the second phone interview during pregnancy. Moreover, we also controlled for the most commonly used nonsteroidal anti-inflammatory drugs including the over-the-counter drugs ibuprofen and acetylsalicylic acid (aspirin) to address potential confounding by other medication. Information regarding ibuprofen and aspirin use were collected in a manner similar to acetaminophen, as described above.

Statistical Analyses

We used multivariable linear regression models to estimate the difference (β) of childhood BMI z-score or waist circumference (in cm) at age 7 and 11 years according to prenatal acetaminophen exposure (ever/never, trimester of use, and cumulative weeks of use) with never use as referent. We also used a generalized linear model to estimate the risk ratio (RR) for being overweight in childhood. We calculated p-value in linear-trend tests by fitting cumulative weeks of exposure as a continuous variable. We adjusted for the above mentioned potential confounders in all statistical models. Analyses were conducted for boys and girls separately to evaluate sex-specific exposure effects on the outcomes at these ages. Test for heterogeneity was also conducted by including an interaction term between prenatal acetaminophen exposure (ever/never) and child's sex in the regression model. We performed additional sensitivity analyses restricting to mothers who did not experience fever, inflammation/infection, or musculoskeletal diseases and pain during pregnancy. Mothers who used acetaminophen for more than 30 weeks of gestation (<2%) were excluded in linear trend tests to evaluate the influence of extreme values. In addition, we adjusted for paternal BMI (reported by mothers when the child was 18 months old), maternal use of antibiotics and medications for sleep problems or depression in pregnancy to evaluate possible confounding by these factors. Multiple imputations were used to estimate the missing values of covariates (about 5% of participants were missing at least one covariate value).

To assess possible bias due to loss to follow-up, we first compared the characteristics of the mothers and children who did or did not participate at the 7 and 11 years follow up. Next, we utilized inverse-probability-weights (IPW) technique to account for possible selection bias. We modeled the probability of participation at 7 and 11 years follow up according to a range of measured factors available for all women in the DNBC at baseline. The list of factors found to be predictive of participation in the 7- or 11-year follow-up and included in the IPW is presented in the appendix (see appendix A and B). We incorporated the stabilized IPW in all regression analyses and computed the 95% confidence intervals (CIs) using robust variance estimators. In sensitivity analyses, we compared our results with and without implementing IPW. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Of the children in the 7- and 11-year cohorts, more than half (55%) of the mothers reported ever using acetaminophen during pregnancy (see Table 1 and Table S1). Acetaminophen use was more common among parous women, smokers, those with higher pre-pregnancy BMI, and who experienced fever, infection/inflammation and musculoskeletal diseases in pregnancy. Compared with the baseline cohort in the DNBC, the characteristics of mothers and children who participated in the 7- and 11-year cohorts were similar (see Table S1). There were some differences observed such as women who were generally healthier (i.e. having had a normal pre-pregnancy BMI and did not smoke) and women from higher social classes were more likely to have participated in the follow-ups.

Overall, there was no strong association found between prenatal acetaminophen exposure and the continuous BMI z-scores and waist circumferences in girls and boys at both age 7 and 11 years (Table 2). Some sex-differences were observed that the effect estimates were mostly negative for boys and positive for girls (p-values for the interaction term between ever use of acetaminophen and child's sex were <0.10 for these outcomes), but most of the confidence intervals were wide and included the null. No association was found for cumulative weeks of exposure and BMI z-scores or waist circumference in girls and boys at both ages (Table S2).

We also found no associations between prenatal acetaminophen exposure and overweight in boys and girls at age 7 (Table 3). However, at age 11, we estimated that girls exposed to acetaminophen at least once had an elevated RR for overweight (RR=1.10 95%CI 0.97, 1.24), and a 31% higher risk for being overweight if the girls were exposed in all three trimesters (RR=1.31 95%CI 1.10, 1.56). The estimated RRs for exposure in the first and second trimester were higher than that in the third trimester, but the CIs were wide and overlapped. A linear dose-response like pattern was detected for cumulative weeks of acetaminophen exposure in pregnancy and overweight in girls at age 11 (p-trend < 0.001) (see Figure 1). There was no association for prenatal acetaminophen exposure and overweight in boys at age 11.

Our findings did not change when restricting to women who did not experience fever, infections, musculoskeletal diseases and pain; the risks for overweight were elevated in girls at age 11 who were frequently exposed to acetaminophen during pregnancy among women who did not have these diseases or conditions (Table 4). The results were also remained consistent in sensitivity analyses additionally adjusted for paternal BMI, and maternal use of antidepressants and medications for sleep problems in pregnancy (Table S3) or when excluding the extreme heavy users (Table S4). The effect estimates changed minimally when comparing models with and without implementing IPW accounting for possible selection bias due to non-participation in the follow up (Table S5).

DISCUSSION

We did not find consistent associations between prenatal acetaminophen exposure and BMI z-scores and waist circumferences in the offspring measured at age 7 and 11 years. However, we observed that frequent exposure to acetaminophen during pregnancy was positively associated with overweight in girls at age 11, but not in boys.

Acetaminophen is considered a "safe" medication for pregnant women (20). The guideline of use has not been changed in spite of recent findings that suggested frequent use of acetaminophen in pregnancy might affect a range of adverse health outcomes in the exposed offspring, including reproductive toxicity (7, 21, 22), neurobehavioral disorders (19, 23, 24), asthma (25), and pubertal development (9). Elevated oxidative stress via the depletion of glutathione (26, 27) or interference on steroid hormone functions (4, 28, 29) are proposed as the shared underlying

biological pathways affecting multiple outcomes. Large-scale studies that evaluate additional potential long-term health consequences in the prenatally exposed offspring are urgently needed.

Recently, a large cross-sectional study (the ISAAC study) based on data from 18 countries reported that acetaminophen use in the first 12 months of life was related to a small increase (~0.07 kg/m2) in the mean childhood BMI age 6-7 years in affluent-GNI countries only (14). A cross-sectional association between self-reported frequent acetaminophen exposure and higher BMI among adolescents aged 13-14 was also found but the direction of the association is unclear. Data collected from affluent countries in the ISAAC study might have a higher degree of accuracy, but it is also possible that the exposure-related weight promoting effects are more apparent in developed countries that follow high-calories and high-fat diets (12). The observed early postnatal exposure effect could be confounded by in-utero exposure, which has been suggested as a sensitive period for adiposity promoting effects in animals exposed to synthetic chemicals (12).

Emerging evidence has indicated that in-utero exposure to "obesogens" (11, 12), including various types of endocrine disruptors, can disturb the developmental and homeostatic controls over adipogenesis thus affecting the weight-control mechanisms and energy balance later in life (10, 13). Prenatal exposure to pharmacologic sources of estrogenic agents such as oral contraceptives and diethylstilbestrol (DES) were linked to childhood overweight or obesity in a few studies (30, 31). Acetaminophen has been reported to induce rather strong hormonal effects such as inhibiting androgen or prostaglandin synthesis in experimental settings (4, 28, 29). Further experimental studies are needed to test the possible adiposity-promoting effect of acetaminophen and to elucidate the mechanisms of action.

The positive association observed for girls at 11 years might indicate a sex-hormone specific mechanism of the exposures (32), but it could also be explained by the timing of pubertal growth and outcome measures in our study. Some girls might have started entering puberty at age 11 while for most boys this is still considered a pre-pubertal period (33). Another DNBC study followed a subset of offspring up to age 16 found that prenatal acetaminophen exposure was associated with a 2-3 months earlier attainment of several markers of pubertal development (e.g. pubic hair, axillary hair, and acne) only in the female offspring (9). We only have complete BMI data at age 7 and 11 for this study preventing us to further explore growth trajectories and

account for pubertal development. Studies with longer follow-up time are needed to evaluate whether the estimated sex-specific exposure effects persist into older ages.

Our study has several strengths. First, the analyses were conducted using data from a large nationwide cohort of mothers and their children with up to 11 years of prospective follow-up. Secondly, the exposure information was recorded multiple times during pregnancy using structural telephone interviews and the women were provided with a list of medications which could assist with their reporting. Acetaminophen was mostly sold as a singular drug over-the-counter in Denmark under 3 major brand names (Pamol, Pinex, and Panodil) at the time of the study which limited the challenges of having to estimate exposures for combination drugs that might be common in other countries (34). Moreover, the outcomes were recorded in a large group of offspring at two time points. Finally, we were able to control for a range of potential confounders in our analyses. Maternal pain and fever have been previously estimated to be the main indications for taking acetaminophen in pregnancy (19), but these factors are not demonstrated as risk factors for childhood obesity. Other types of NSAIDs were not recommended in Denmark for pregnant women during the study period thus the prevalence of use was much lower compared to acetaminophen. Controlling for NSAIDs as well as other medications such as antibiotics for infections and medications for sleep problems or depressions did not change our findings.

Limitations of our study should be noted. The results could be affected by exposure and outcome misclassifications. Although the exposure information was queried multiple times with relatively short recall periods, it is possible that mothers have under-reported the use of this commonly used drug (35). Flawed recall of drug names, timing, and frequency of use was likely non-differential to the outcome. We assessed the cumulative weeks of exposure but did not have information on the days of use and the exact number of pills and dosage taken which limited our ability to perform a true exposure dose-response analysis. Parent-reports of BMI might also be subject to errors. A previous validation study showed that the proportion of children categorized as overweight was slightly lower in the DNBC compared to our parent-reported BMI at age 7 with measurements by school doctors in a subgroup of children, but the degree of under-reporting was found to be consistent across the distribution of height and weight of the children (36). We do not expect our main findings to be solely driven by correlated

measurement errors otherwise we would expect a stronger association at age 7 but not at age 11 in girls because the gaps between parental reports for the exposure and outcome are smaller. Overall, the estimated prevalence of childhood obesity is lower in Denmark compared with other European countries according to the WHO surveys (37) potentially limiting the generalizability of our findings to countries with higher rates of obesity.

Our analyses only included women who completed all interviews that collected acetaminophen use information at baseline. The proportion of overweight in the children at age 11 years (~8.7%) was comparable among women who did or did not complete all these interviews suggesting influence from selection bias at baseline is minimal. Nevertheless, influence from loss-to-follow-up bias is possible since only about half of the children were included in the 11 year analyses. The direction of this bias is hard to predict, but we found that in general mothers and children who were healthier were more likely to have participated in the 11 year follow up. If the exposed and overweight children were more likely to drop out that might bias the results towards the null. IPW technique was used to minimize influence from drop out, but we cannot rule out residual biases from unmeasured factors that were not included in the model. Finally, we also cannot rule out possible influence from uncontrolled confounding. Acetaminophen is taken for a variety of reasons which could be mild or severe (19, 20). Some major indications of acetaminophen use such as fever, infections and musculoskeletal diseases and pain did not appear to explain our findings. Genetic factors may also play a role in childhood obesity (38), but it is unknown whether these genes also correlate with acetaminophen use in pregnancy.

In summary, we analyzed a large national sample and did not find strong evidence to suggest maternal intake of acetaminophen during pregnancy affect BMI z-scores and waist circumferences in the offspring. However, we observed that maternal frequent use of acetaminophen was associated with an increased risk for overweight in girls at age 11 years, which warrants further investigation.

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Table 1. Characteristics of study participants by exposure to acetaminophen at least once (ever/never) during pregnancy

	7 year cohort				11 year cohort			
	Exposed (N=16,644)		Unexposed (N=13,483)		Exposed (N=13,681)		Unexposed (N=11,253)	
	n	%	n	%	n	%	n	%
Mother age (years)								
≤ 24	1265	7.6	975	7.2	871	6.4	720	6.4
25-29	6248	37.5	5230	38.8	5118	37.4	4323	38.5
30-34	6450	38.8	5129	38.0	5418	39.6	4347	38.7
≥ 35	2681	16.1	2149	15.9	2274	16.6	1863	16.6
Parity								
1st child	7228	43.4	6705	49.7	5719	41.8	5420	48.2
2nd or more child	8954	53.8	6378	47.3	7576	55.4	5477	48.7
Missing	462	2.8	400	3.0	386	2.8	356	3.2
Child's sex								
Male	8582	51.6	7037	52.2	6730	49.2	5754	51.2
Female	8062	48.4	6446	47.8	6951	50.8	5499	48.9
Child's Birth year								
1997-2000	10091	60.6	8128	60.3	7872	57.5	6459	57.4
2001-2003	6553	39.4	5355	39.7	5809	42.5	4794	42.6
Parental Socio-occupational status								
1 (highest)	5716	34.3	5228	38.8	5093	37.2	4601	40.9
2	5546	33.3	4435	32.9	4637	33.9	3729	33.1
3	4742	28.5	3460	25.7	3535	25.8	2665	23.7
4 (Lowest)	590	3.5	327	2.4	387	2.8	227	2.0
Missing	50	0.3	33	0.2	29	0.2	31	0.3
Maternal drinking during pregnancy								
Never	4342	26.1	3950	29.3	3423	25.0	3244	28.9
1-4 glass(es) per week	6622	39.9	5247	38.9	5624	41.1	4535	40.3
more than 4 glasses per week	5680	34.1	4286	31.8	4634	33.9	3474	30.9
Maternal smoking during pregnancy								
Never	12224	73.4	10647	79.0	1047	76.6	9147	81.4
≤ 9 cigarettes/day	2175	13.1	1529	11.3	1687	12.3	1124	10.0
> 9 cigarettes/day	2245	13.5	1307	9.7	1520	11.1	982	8.7
Mother pre-pregnancy body mass index								
<18.5	558	3.4	581	4.3	515	3.8	494	4.4
18.5-25	11046	66.4	9634	71.5	9396	68.7	8293	73.8
26-29	3363	20.2	2278	16.9	2571	18.8	1765	15.7
≥30	1444	8.7	788	5.8	1022	7.5	544	4.8
Missing	233	1.4	202	1.5	177	1.3	157	1.4
Fever during pregnancy	5515	33.1	2999	22.2	4532	33.1	2492	22.2
Missing	9	0.1	4	0.0	5	0.0	4	0.0
Musculoskeletal diseases and pain during	2166	13.0	1126	8.4	1631	11.9	843	7.5
Missing	22	0.1	9	0.1	19	0.1	9	0.1
Infection and inflammation during	2216	13.3	1244	9.2	1834	13.4	1044	9.3
Missing	2	0.0	2	0.0	1	0.0	1	0.0
Mother use of aspirin during pregnancy	1347	8.1	1005	7.5	1096	8.0	858	7.6
Mother use of ibuprofen during pregnancy	990	5.9	553	4.1	840	6.1	447	4.0

Table 3. Risk ratios for overweight at age 7 and 11 years according to maternal acetaminophen use during pregnancy

Table 2. Adjusted differences for body mass index (BMI) z scores and waist circumference at age 7 and 11 according to maternal acetaminophen use during pregnancy

Acetaminophen use during pregnancy	No. of children	Overweight at age 7 years		No. of children	Overweight at age 11 years	
		N	Adjusted RR and 95% CI [a]		N	Adjusted RR and 95% CI [a]
Among girls						
Never use	6446	694	reference	5499	404	reference
Ever use	8062	960	0.99 (0.91, 1.09)	6951	660	1.10 (0.97, 1.24)
Timing specific [b]						
1st trimester only	1424	174	1.07 (0.92, 1.25)	1227	107	1.10 (0.90, 1.34)
2nd trimester only	752	82	0.96 (0.77, 1.19)	676	81	1.10 (0.85, 1.41)
3rd trimester only	1548	186	0.99 (0.85, 1.15)	1379	121	1.01 (0.84, 1.23)
any 2 trimesters	2118	245	0.95 (0.83, 1.09)	1827	171	1.05 (0.88, 1.24)
all three trimesters	1508	189	0.99 (0.86, 1.15)	1256	152	1.31 (1.10, 1.56)
Among boys						
Never use	7037	555	reference	5754	465	reference
Ever use	8582	802	1.02 (0.92, 1.14)	6730	658	1.03 (0.92, 1.16)
Timing specific [b]						
1st trimester only	1583	137	1.02 (0.86, 1.22)	1279	118	1.10 (0.91, 1.32)
2nd trimester only	768	70	1.04 (0.82, 1.31)	629	59	1.05 (0.82, 1.35)
3rd trimester only	1685	155	1.02 (0.86, 1.21)	1282	108	0.95 (0.78, 1.16)
any 2 trimesters	2308	207	0.97 (0.83, 1.14)	1810	178	1.04 (0.88, 1.22)
all three trimesters	1488	157	1.05 (0.88, 1.25)	1142	136	1.06 (0.86, 1.29)

Acetaminophen use during pregnancy	No. of children	BMI z scores Adjusted difference and 95% CI [a] at 7 years	Waist circumference (cm) at 7 years	No. of children	BMI z scores Adjusted difference and 95% CI [a] at 11 years	Waist circumference (cm) at 11 years
Among girls						
Never use	6446	reference	reference	5499	reference	reference
Ever use	8062	0.02 (-0.01, 0.05)	-0.03 (-0.20, 0.14)	6951	0.01 (-0.02, 0.05)	0.21 (-0.07, 0.49)
Timing specific [b]						
1st trimester only	1424	0.02 (-0.01, 0.05)	0.19 (-0.10, 0.48)	1227	0.01 (-0.05, 0.07)	0.13 (-0.33, 0.59)
2nd trimester only	752	0.05 (-0.01, 0.10)	-0.16 (-0.53, 0.20)	676	0.07 (-0.01, 0.14)	0.31 (-0.30, 0.93)
3rd trimester only	1548	0.02 (-0.05, 0.09)	-0.11 (-0.40, 0.18)	1379	0.00 (-0.06, 0.06)	0.19 (-0.29, 0.66)
any 2 trimesters	2118	0.02 (-0.03, 0.07)	-0.03 (-0.29, 0.23)	1827	0.00 (-0.05, 0.05)	0.20 (-0.22, 0.62)
all three trimesters	1508	-0.00 (-0.05, 0.04)	0.11 (-0.19, 0.42)	1256	0.01 (-0.05, 0.08)	0.33 (-0.20, 0.85)
Among boys						
Never use	7037	reference	reference	5754	reference	reference
Ever use	8582	-0.03 (-0.06, 0.00)	-0.25 (-0.41, -0.10)	6730	-0.04 (-0.07, 0.00)	-0.22 (-0.50, 0.07)
Timing specific [b]						
1st trimester only	1583	-0.05 (-0.10, 0.00)	-0.39 (-0.65, -0.13)	1279	-0.03 (-0.09, 0.03)	-0.12 (-0.60, 0.37)
2nd trimester only	768	0.01 (-0.06, 0.08)	-0.32 (-0.68, 0.04)	629	-0.05 (-0.13, 0.03)	-0.02 (-0.68, 0.64)
3rd trimester only	1685	-0.05 (-0.10, -0.00)	-0.23 (-0.51, 0.04)	1282	-0.07 (-0.13, -0.01)	-0.35 (-0.85, 0.15)
any 2 trimesters	2308	-0.05 (-0.09, -0.01)	-0.26 (-0.49, -0.03)	1810	-0.04 (-0.09, 0.02)	-0.28 (-0.70, 0.13)
all three trimesters	1488	-0.01 (-0.07, 0.04)	-0.13 (-0.41, 0.15)	1142	-0.01 (-0.08, 0.05)	-0.09 (-0.62, 0.45)

[a] Adjusted maternal age, parity, birth year, parental socio-occupational status, maternal pre-pregnancy body mass index, maternal alcohol drinking during pregnancy, maternal smoking during pregnancy, maternal musculoskeletal diseases and pain, fever, or infection/inflammation during pregnancy, maternal use of ibuprofen and aspirin during pregnancy. [b] Timing of exposure analyses included all never users and approximately 91.5% acetaminophen users who indicated their timing of use.

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Table 4. Risk ratios for overweight at age 7 and 11 years according to maternal acetaminophen use during pregnancy, excluding mothers with specific health conditions during pregnancy.

Acetaminophen use during pregnancy	Overweight in girls				Overweight in boys			
	Age 7		Age 11		Age 7		Age 11	
	N	Adjusted RR and 95% CI [a]	N	Adjusted RR and 95% CI [a]	N	Adjusted RR and 95% CI [a]	N	Adjusted RR and 95% CI [a]
Among mothers without fever during pregnancy								
Never used	550	Reference	322	Reference	423	Reference	356	Reference
Ever used	610	0.96 (0.88, 1.06)	418	1.09 (0.96, 1.23)	537	1.00 (0.92, 1.09)	451	1.05 (0.95, 1.17)
in all three trimesters	123	1.00 (0.86, 1.17)	90	1.34 (1.11, 1.63)	96	1.00 (0.86, 1.17)	92	1.06 (0.87, 1.28)
>20 weeks	57	0.89 (0.71, 1.11)	47	1.55 (1.22, 1.97)	46	1.06 (0.85, 1.32)	48	1.04 (0.77, 1.39)
p-trend for cumulative week of exposure		0.68		<.001		0.49		0.74
Among mothers without infections or inflammations during pregnancy								
Never used	630	Reference	360	Reference	506	Reference	417	Reference
Ever used	835	1.01 (0.93, 1.10)	574	1.18 (1.06, 1.33)	702	0.95 (0.87, 1.02)	571	1.04 (0.95, 1.15)
in all three trimesters	163	1.01 (0.87, 1.16)	125	1.46 (1.23, 1.73)	137	0.91 (0.79, 1.04)	117	1.01 (0.85, 1.20)
>20 weeks	70	0.86 (0.69, 1.06)	59	1.47 (1.17, 1.84)	73	0.96 (0.79, 1.16)	61	1.01 (0.78, 1.32)
p-trend for cumulative week of exposure		0.2145		<.001		0.58		0.85
Among mothers without musculoskeletal diseases during pregnancy								
Never used	623	Reference	372	Reference	503	Reference	425	Reference
Ever used	827	1.01 (0.93, 1.10)	557	1.11 (0.99, 1.25)	676	0.97 (0.89, 1.05)	548	1.00 (0.90, 1.10)
in all three trimesters	148	0.97 (0.84, 1.13)	114	1.35 (1.14, 1.61)	129	0.95 (0.82, 1.09)	109	1.00 (0.84, 1.21)
>20 weeks	64	0.86 (0.69, 1.06)	52	1.34 (1.06, 1.71)	66	1.00 (0.82, 1.22)	60	1.06 (0.81, 1.38)
p-trend for cumulative week of exposure		0.2378		<.001		0.91		0.58

[a] Adjusted maternal age, parity, birth year, parental socio-occupational status, maternal pre-pregnancy body mass index, maternal alcohol drinking during pregnancy, maternal smoking during pregnancy, maternal musculoskeletal diseases and pain, fever, or infection/inflammation during pregnancy, maternal use of ibuprofen and aspirin during pregnancy.

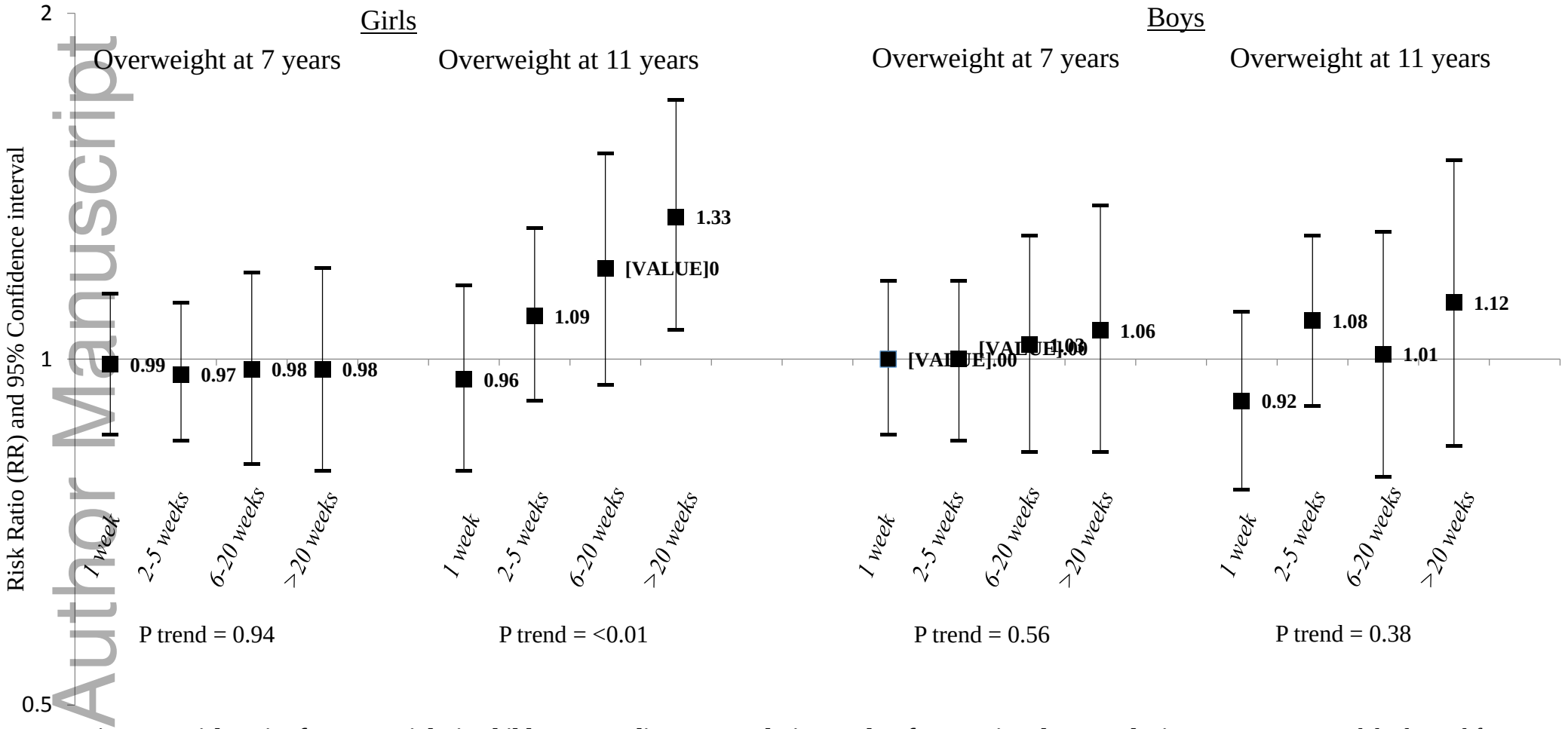

Figure 1. Risk ratios for overweight in children according to cumulative weeks of acetaminophen use during pregnancy. Model adjusted for maternal age, parity, birth year, parental socio-occupational status, maternal pre-pregnancy body mass index, maternal alcohol drinking during pregnancy, maternal smoking during pregnancy, maternal musculoskeletal diseases and pain, fever, or infection/inflammation during pregnancy, maternal use of ibuprofen and aspirin during pregnancy. P-trend was calculated using linear trend tests by fitting weeks of exposure as a continuous variable.

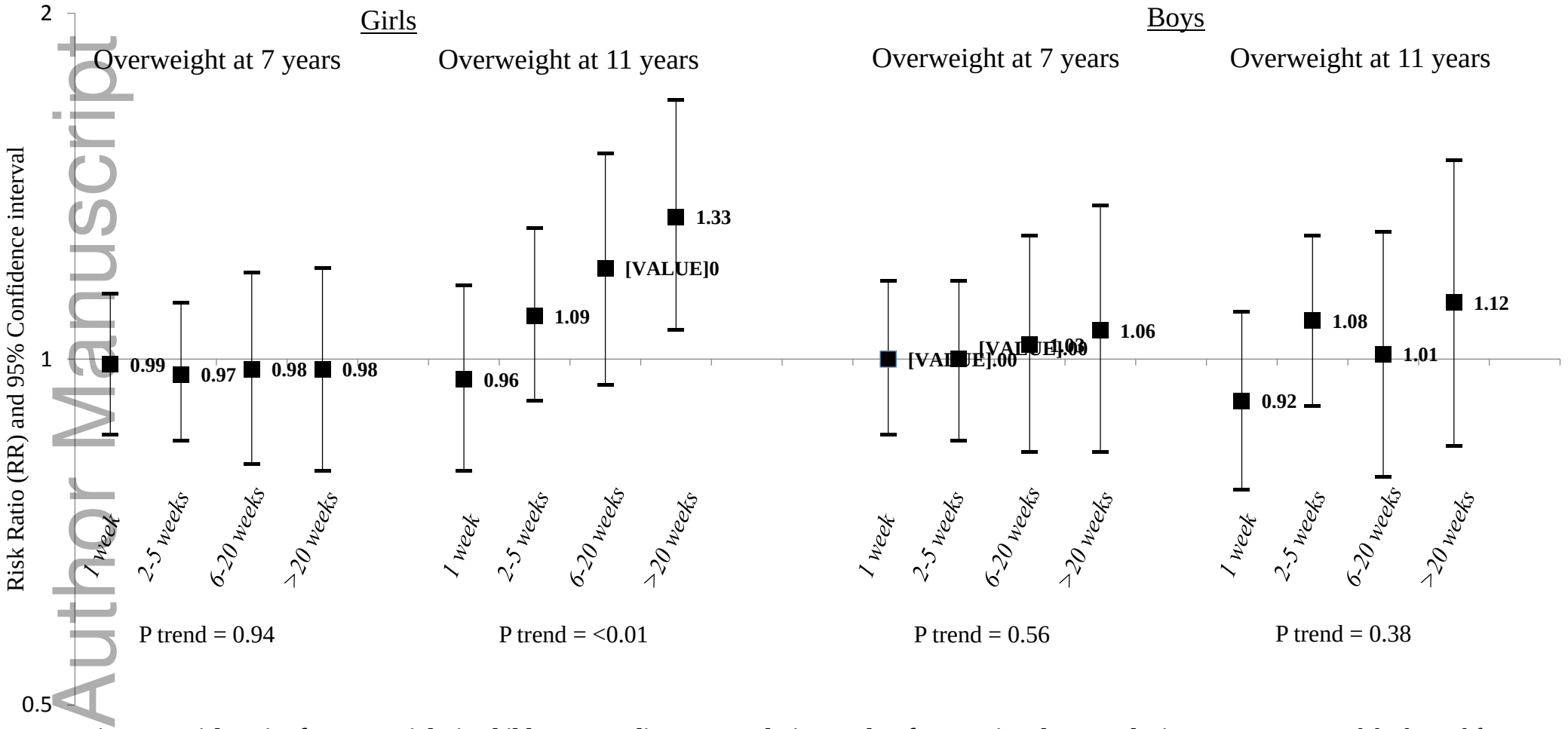

Figure 1. Risk ratios for overweight in children according to cumulative weeks of acetaminophen use during pregnancy. Model adjusted for maternal age, parity, birth year, parental socio-occupational status, maternal pre-pregnancy body mass index, maternal alcohol drinking during pregnancy, maternal smoking during pregnancy, maternal musculoskeletal diseases and pain, fever, or infection/inflammation during pregnancy, maternal use of ibuprofen and aspirin during pregnancy. P-trend was calculated using linear trend tests by fitting weeks of exposure as a continuous variable.