International Journal of Epidemiology, 2016, 1998–2008
doi: 10.1093/ije/dyw192
Advance Access Publication Date: 31 August 2016
Original article

Prenatal exposure to paracetamol and SSRIs

Neurodevelopmental problems at 18 months among children exposed to paracetamol *in utero*: a propensity score matched cohort study

Richelle Vlenterie,[1,2]* Mollie E Wood,[2] Ragnhild Eek Brandlistuen,[2,3] Nel Roeleveld,[1,4] Marleen MHJ van Gelder[1,5] and Hedvig Nordeng[2,6]

[1]Department for Health Evidence, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands, [2]PharmacoEpidemiology & Drug Safety Research Group, School of Pharmacy, University of Oslo, Oslo, Norway, [3]Department of Child Development and Mental Health, Norwegian Institute of Public Health, Oslo, Norway, [4]Department of Pediatrics, Radboudumc Amalia Children's Hospital, [5]Radboud REshape Innovation Center, Radboud University Medical Center, Nijmegen, The Netherlands and [6]Domain for Mental and Physical Health, Norwegian Institute of Public Health, Oslo, Norway

*Corresponding author. Department for Health Evidence (HP 133), Radboud University Medical Center, PO Box 9101, 6500 HB Nijmegen, The Netherlands. E-mail: Richelle.Vlenterie@radboudumc.nl

Accepted 15 June 2016

Abstract

Background: Previous studies showed that children exposed to paracetamol during fetal life might have an increased risk of neurodevelopmental problems. Since paracetamol is one of the most commonly used medications during pregnancy, even small increases in the risk of neurodevelopmental problems may have considerable implications for public health.

Methods: Using data from the Norwegian Mother and Child Cohort Study, we applied propensity score (PS) matching to examine associations between prenatal paracetamol exposure and neurodevelopmental problems among children at 18 months of age. Paracetamol use was classified into short-term ($<$ 28 days) and long-term ($\geq$ 28 days) of exposure.

Results: Of the 51 200 pregnancies included in our study, 40.5% of mothers ($n = 20\,749$) used paracetamol at least once during pregnancy. In the PS-matched analyses, long-term paracetamol exposure during pregnancy was associated with communication problems [odds ratio (OR): 1.38, 95% confidence interval (CI) 0.98–1.95) and delayed motor milestone attainment (OR: 1.35, 95% CI 1.07–1.70). We did not observe increased risks after short-term exposure. Sensitivity analyses for several indications showed similar effects as the PS-matched analyses, suggesting no confounding by indication.

Conclusion: Long-term exposure to paracetamol *in utero* was associated with modestly increased risks of motor milestone delay and impaired communication skills among children at 18 months. Caution is warranted when considering long-term use of paracetamol

during pregnancy; however, women with severe pain conditions should not be deprived of appropriate pharmacotherapy.

Key words: Paracetamol, acetaminophen, milestones, neurodevelopment, propensity scores, pregnancy, Norwegian Mother and Child Cohort Study, MoBa

Key Messages

- Long-term exposure ($\geq$ 28 days) to paracetamol during pregnancy was associated with modestly increased risks of motor milestone delay and impaired communication skills among children at 18 months, in PS-matched analyses.
- Sensitivity analyses for headache or migraine, fever and infections showed no confounding by indication for long-term paracetamol use during pregnancy.
- Women with severe pain conditions should not be deprived of appropriate pharmacotherapy; however, caution is warranted for long-term use of paracetamol during pregnancy.

Introduction

Previous studies indicated that one out of two women use paracetamol during pregnancy.[1] In our most recent study published, we found that 3-year-old children, who had been exposed to paracetamol for 28 days or more during fetal life, had poorer gross motor development and communications skills and more externalizing problems, compared with their unexposed siblings.[2] The effect size was approximately one-quarter of a standard deviation, which is of similar magnitude as the negative effects on cognition and neurodevelopment seen in children exposed to lead *in utero*.[3,4] This is a substantial effect, especially after controlling for shared familial and genetic factors by using a sibling design. Moreover, these effect estimates should be considered in light of the public health perspective, in which a shift in the population central tendency of one-quarter of a standard deviation results in a much larger proportion of the population experiencing behavioural problems.[5]

A study from the Danish National Birth Cohort linked prenatal paracetamol exposure to attention-deficit hyperactivity disorder (ADHD)-like behaviours in children at the age of 7 years [risk ratio: 1.13, 95% confidence interval (CI) 1.01–1.27).[6] Similar findings have recently been published from a New Zealand birth cohort, in which prenatal exposure to paracetamol was also associated with more symptoms of ADHD at the age of 7 years.[7] Moreover, a Swedish experimental animal study showed that mice exposed to repeated doses of paracetamol (30 + 30 mg/kg body weight) expressed altered motor activity and failure to acquire spatial learning in adulthood, with observed changes in key brain regions.[8] The results of these studies caused concerns about neurodevelopmental side effects at the level of the European Medicines Agency,[9] and have been debated by the scientific community.[10–14]

The mechanisms through which the effects of paracetamol exposure could be mediated are still unknown, but several hypotheses have been proposed. Animal studies showed changes in the levels of brain-derived neurotropic factors in mice, leading to altered behaviour and learning abilities in adulthood.[8] It is also believed that paracetamol could interfere with maternal hormones which are related to fetal brain development.[15–17] Another plausible biological mechanism that may explain paracetamol's effect on brain development is oxidative stress. In animals, the fetus is capable of generating the toxic metabolite N-acetyl-p-benzoquinone imine that is produced by paracetamol use.[18] Previous studies have found that a therapeutic dose of paracetamol in human adults is related to a reduced capacity to manage oxidative stress.[19,20] As fetal brains inherently have a greater vulnerability to oxidative stress, an effective antioxidant system is important for the development of brain functions in the fetus. All of these plausible mechanisms might cause differences in brain development after prenatal paracetamol exposure.[21]

In this study, we investigated whether neurodevelopmental problems were also present in children at 18 months of age following prenatal exposure to paracetamol, in order to detect these problems as early as possible in childhood, using advanced statistical methods. Because sibling designs may be biased in the presence of non-shared confounding,[22] we conducted a study using propensity score (PS) matching to adjust for important confounders.

Methods

Study population and data collection

The Norwegian Mother and Child Cohort Study (MoBa) is a prospective cohort study conducted by the Norwegian

Institute of Public Health, following over 100 000 pregnancies, which was previously described in detail.[23] Enrolment in the study started in 1999 and was completed in 2008. The participation rate at first assessment was 40.6%. Mothers provided a range of socio-demographical, medical and psychological information during and after the index pregnancy by completing five paper-based questionnaires (at gestational week (GW) 17, GW30, and 6, 18 and 36 months post-partum). Via the woman's personal identification number, MoBa was linked with the Medical Birth Registry of Norway (MBRN), which includes information on pregnancy, delivery and neonatal health for all births in Norway.[24] MoBa was approved by the Regional Committee for Ethics in Medical Research, Region South, and the Norwegian Data Inspectorate. Written informed consent was obtained from all participants, and all data were coded.

The current study was based on MoBa version 6, which was released in 2012 including mothers giving birth before 2009. All live-born singletons of these mothers were included in the study population, except for infants born with major congenital malformations and infants with missing questionnaire information from GW17, GW30 or at 18 months post-partum. Figure 1 shows a flow chart of the eligible study population, including the number of participants with complete outcome data.

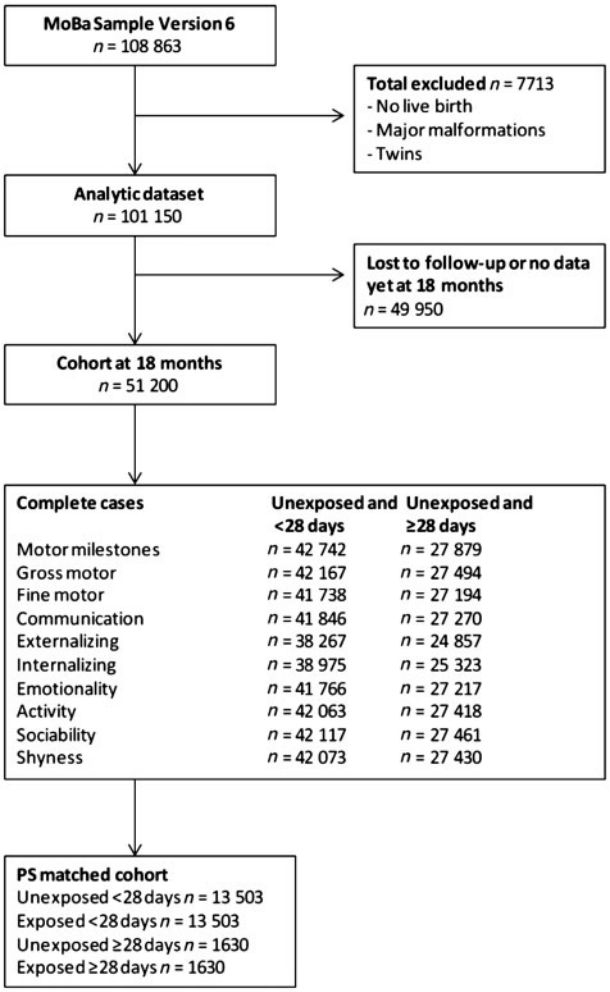

Figure 1. Flow chart displaying the MoBa sample matched by PS.

Paracetamol exposure

Women reported information about illnesses they experienced throughout pregnancy and the medication used for these illnesses, in the two prenatal and first post-partum questionnaire. Indications such as pain, fever and infections were included in the questionnaires to improve the reporting of medication use. Medication use was coded according to the Anatomical Therapeutic Chemical (ATC) Classification System developed by the World Health Organization,[25] and paracetamol exposure was defined as use of a drug with ATC-code N02BE01. We stratified paracetamol exposure into short-term exposure (1–27 days) and long-term exposure (28 days or more), using the same exposure categories as in our previous study.[2] We assumed that when multiple medications and multiple time periods were reported, all medications were used for all time periods indicated.

Neurodevelopmental outcomes

Psychomotor problems

Psychomotor development among infants at the age of 18 months was assessed by the Ages and Stages Questionnaire (ASQ), which had been translated and validated in a Norwegian sample.[26] The ASQ covers gross motor impairment (three items), fine motor impairment (three items) and communication skills (four items). In addition, the age at which the child started walking unaided was included as a separate outcome. This motor milestone is believed to be an objective measure and therefore a reliable maternal report on motor development.[27]

Behavioural problems

The Child Behaviour Checklist (CBCL/11/2-5/LDS) was used to assess behaviour at 18 months.[28] This questionnaire covers externalizing and internalizing behaviour. Externalizing behaviour (nine items) includes two different subscales: aggressive behaviour and attention problems. Internalizing behaviour (seven items) consists of four different subscales: anxiety, emotional reactivity, sleep problems and somatic complaints.

Temperamental problems

Temperament among infants at the age of 18 months was assessed with the short-form Emotionality, Activity and Shyness Temperament Questionnaire (EAS). This version of the EAS used in MoBa was as reliable and precise as the original questionnaire.[29] The questionnaire consists of four different subscales: emotionality (three items), activity (three items), sociability (two items) and shyness (three items). All neurodevelopmental outcomes were reported by the mother. Standardized z-scores were computed for all outcomes, and children with z-scores ≥ 1.5 were classified as having clinically significant problems.

Potential confounders

Potential confounders were identified by means of a literature review and through directed acyclic graphs[30,31] [daggity.net] (Figure 1S, available as Supplementary data at *IJE* online). We included maternal age at delivery, pre-pregnancy body mass index (BMI), parity, marital status or cohabiting, maternal education, smoking and alcohol consumption and folic acid use during pregnancy as potential confounders. Furthermore, maternal depressive symptoms were included using the validated short version of the Hopkins Symptom Checklist, the SCL-5, which recorded maternal psychological distress throughout pregnancy (mean score > 2 at week 17 and/or week 30).

Several other health conditions of the mother during pregnancy were included as potential confounders as well, in order to adjust for confounding by indication: infections (genital, urinar, and respiratory), fever, headache or migraine, pelvic girdle pain, back pain, neck pain, abdominal pain and other pain. In addition, we included a number of concomitant medications as potential confounders: non-steroidal anti-inflammatory drugs (NSAIDs) (ATC code M01A and N02BA), antiepileptics (N03A), antidepressants (N06A), opioids (N02A), triptans (N02CC) and benzodiazepines (N05CD and N05BA). All potential confounders are listed in Table 1, including their categorization for the statistical analysis.

Statistical analysis

We estimated the prevalence of short-term and long-term paracetamol use and the prevalence of psychomotor, behavioural and temperamental problems. Following this, PS were determined using logistic regression models in the complete case cohort [with either short-term or long-term paracetamol use as outcome variable and all 23 variables previously mentioned as confounders (all maternal characteristics in Table 1)], as predictors during multivariable model building.[32] We also considered interaction terms, but the final models included only main effects. Balance of measured confounders between the exposed and unexposed groups was assessed by calculating the standardized differences, which showed that the covariates were for the most part well balanced after matching (Table 1; and Table 2S, available as Supplementary data at *IJE* online). Visual inspection of the PS distribution also showed substantial overlap between the exposed and unexposed women. Using a nearest neighbour approach, PS-matching was implemented in the complete case cohort without replacement. Calipers of width equal to 0.2 standard deviation of the logit of the propensity score were calculated separately per outcome[33] (Table 1S, available as Supplementary data at *IJE* online).

Complete case analyses were conducted using logistic regression to estimate odds ratios (ORs) with 95% confidence intervals (CIs) for the associations between the neurodevelopmental outcomes and *in utero* paracetamol exposure. In addition, logistic regression analyses in which we used the PS as a covariate were performed in the total cohort. The number needed to harm (NNH) was also calculated for each outcome measure.

To evaluate the effects of potential confounding by indication, we performed sensitivity analyses in women with the following health conditions: headache or migraine, fever and infections. Because most women in the study used paracetamol for more than one indication, we did not create indication categories that were mutually exclusive; as a result, women with more than one indication of interest could be part of multiple strata. We also asymmetrically trimmed the range of PS according to the percentile of PS at the upper end (0–99th and 0–95th percentile), in order to reduce bias due to unmeasured confounding;[34] because the trimmed and untrimmed results were similar, we elected to present the untrimmed estimates.

All analyses were performed using Stata Version 11 (Stata Corporation, College Station, TX, USA).

Results

In the 51 200 pregnancies included in our study, 40.5% ($n = 20\,749$) of women used paracetamol at least once during pregnancy. These women were classified into two exposure groups: short-term use ($n = 18\,962$) and long-term use ($n = 1787$). The most common indication reported for long-term paracetamol use was headache or migraine (80.2%), back pain and pelvic girdle pain were reported by 66.0% and 49.9%, respectively, fever by 24.9% and infections by 53.0%, often in combination with fever. For women exposed to paracetamol, 78.9% ($n = 16\,377$) women reported more than one indication.

Table 1. Maternal and child characteristics of the total cohort and the study population matched on PS for non-users and ≥ 28 days of paracetamol (PCM) use during pregnancy

	Total cohort				PS-matched cohort			
	No PCM use	≥ 28 days of PCM use	*P*- value	St. Diff.[b]	No PCM use	≥ 28 days of PCM use	*P*-value	St. Diff.[b]
Maternal characteristics[a]	*n* = 30 451	*n* = 1787			*n* = 1630	*n* = 1630		
Maternal age (years)			0.00				0.86	
< 25	3069 (10.1)	155 (8.2)		−0.06	127 (7.8)	128 (7.9)		0.02
25–29	10 183 (33.4)	594 (31.3)		−0.06	490 (30.1)	497 (30.5)		−0.03
30–34	11 870 (39.0)	805 (42.4)		0.08	715 (43.9)	715 (43.9)		−0.02
≥ 35	5329 (17.5)	345 (18.2)		0.01	298 (18.3)	290 (17.8)		0.02
Pre-pregnancy BMI (kg/m^2)			0.00				0.97	
< 18	939 (3.2)	53 (2.8)		−0.01	42 (2.6)	47 (2.9)		−0.01
18–25	20 067 (67.7)	1023 (54.9)		−0.28	914 (56.1)	894 (54.9)		0.00
≥ 25	8618 (29.1)	789 (42.3)		0.28	674 (41.4)	689 (42.3)		0.00
Parity			0.00				0.72	
0	14 469 (47.5)	666 (35.1)		−0.26	570 (35.0)	575 (35.3)		−0.01
≥ 1	15 982 (52.5)	1233 (64.9)		0.26	1060 (65.0)	1055 (64.7)		0.01
Married/cohabiting			0.80				0.59	
No	934 (3.1)	56 (3.0)		−0.01	58 (3.6)	46 (2.8)		0.02
Yes	29 392 (96.9)	1826 (97.0)		0.01	1572 (96.4)	1584 (97.2)		−0.02
Education (years)			0.00				0.99	
< 13	10 089 (34.9)	695 (38.3)		0.08	610 (37.4)	617 (37.9)		0.04
13–17	12 217 (42.2)	777 (42.8)		0.01	715 (43.9)	701 (43.0)		0.00
≥ 18	6639 (22.9)	344 (18.9)		−0.11	305 (18.7)	312 (19.1)		0.00
Smoking[c]			0.00				0.70	
No	26 162 (88.3)	1565 (83.8)		−0.13	1388 (85.2)	1377 (84.5)		−0.01
Yes	3461 (11.7)	302 (16.2)		0.13	242 (14.9)	253 (15.5)		0.01
Alcohol use[d]			0.00				0.49	
No	24 403 (83.3)	1403 (76.3)		−0.19	1241 (76.1)	1251 (76.8)		0.02
Yes	4901 (16.7)	437 (23.8)		0.19	389 (23.9)	379 (23.3)		−0.02
Folate use			0.25				0.81	
No	13 915 (45.7)	842 (44.3)		−0.02	704 (43.2)	710 (43.6)		0.01
Yes	16 536 (54.3)	1057 (55.7)		0.02	926 (56.8)	920 (56.4)		−0.01
Health conditions								
Headache/migraine	6482 (21.3)	1523 (80.2)	0.00	1.47	1335 (81.9)	1302 (79.9)	0.18	−0.05
Pelvic girdle pain	10 446 (34.3)	948 (49.9)	0.00	0.59	847 (52.0)	814 (49.9)	0.67	−0.06
Back pain	15 221 (50.0)	1254 (66.0)	0.00	0.32	1104 (67.7)	1065 (65.3)	0.69	−0.02
Neck pain	3169 (10.4)	666 (35.1)	0.00	0.62	556 (34.1)	554 (34.0)	0.40	−0.03
Abdominal pain	6046 (19.9)	545 (28.7)	0.00		476 (29.2)	480 (29.5)	1.00	0.00
Other pain	3744 (12.3)	471 (24.8)	0.00	0.33	363 (22.3)	387 (23.7)	0.54	0.02
Fever	3769 (12.4)	473 (24.9)	0.00	0.33	412 (25.3)	403 (24.7)	0.25	0.04
Infections	11 271 (37.0)	1007 (53.0)	0.00	0.33	862 (52.9)	859 (52.7)	0.78	−0.01
Psychotropic co-medication								
Opioids	281 (0.9)	172 (9.1)	0.00	0.38	102 (6.3)	111 (6.8)	0.57	0.02
NSAIDS	1276 (4.2)	341 (18.0)	0.00	0.45	263 (16.1)	272 (16.7)	0.32	0.01
Antidepressants	249 (0.8)	55 (2.9)	0.00	0.17	38 (2.3)	44 (2.7)	0.91	0.00
Anti-epileptics	47 (0.2)	6 (0.3)	0.09	0.02	1 (0.1)	4 (0.3)	0.71	0.01
Benzodiazepines	106 (0.4)	31 (1.6)	0.00	0.13	17 (1.0)	20 (1.2)	0.88	−0.01
Triptans	130 (0.4)	108 (5.7)	0.00	0.33	64 (3.9)	77 (4.7)	0.22	0.01
Depressive symptoms[e]			0.00				0.32	
No	27 761 (91.9)	1599 (84.3)		−0.13	1405 (86.2)	1392 (85.4)		−0.01
Yes	2441 (8.1)	298 (15.7)		0.13	225 (13.8)	238 (14.6)		0.01

(continued)

Table 1. Continued

	Total cohort				PS-matched cohort			
	No PCM use	≥ 28 days of PCM use	*P*- value	St. Diff.[b]	No PCM use	≥ 28 days of PCM use	*P*-value	St. Diff.[b]
Child characteristics								
Gestational age (weeks)			0.38				0.56	
< 37	1391 (4.6)	95 (5.0)		−0.02	80 (4.9)	77 (4.7)		−0.02
≥ 37	29 060 (95.4)	1804 (95.0)		0.02	1550 (95.1)	1553 (95.3)		0.02
Birthweight (g)			0.17				0.51	
< 2500	686 (2.3)	52 (2.8)		−0.02	42 (2.6)	44 (2.7)		−0.02
≥ 2500	29 765 (97.8)	1847 (97.3)		0.02	1588 (97.4)	1586 (97.3)		0.02
Gender			0.01				0.65	
Boy	15 672 (51.5)	919 (48.4)		−0.02	800 (49.1)	788 (48.3)		−0.02
Girl	14 779 (48.5)	980 (51.6)		0.02	830 (50.9)	842 (51.7)		0.02

[a]The numbers of women within the strata do not add up to the total number of women for all variables due to missing values.
[b]Standardized differences, to compare the distribution of the covariates between the treatment groups.
[c]Smoking daily or sometimes during pregnancy.
[d]Use of one or more alcohol units reported during pregnancy.
[e]Mean score of > 2 on the Hopkins Symptom Checklist (SCL-5) at week 17 and/or week 30.

The exposure rates and baseline characteristics of the study population and the 49 950 women lost to follow-up were compared. The long-term exposure rate was somewhat higher in the drop-outs (4.2% vs 3.7%; *P*-value 0.00). The baseline characteristics were similar, except for a slightly higher depression rate in the drop-outs (*P*-value 0.00). Furthermore, these women were somewhat older (*P*-value 0.00) and more often 'not married or cohabiting' (*P*-value 0.00). Women with long-term paracetamol use during pregnancy had higher BMIs, were more often multiparous and were more likely to smoke and use alcohol compared with non-users. In addition, they used more concomitant medication including opioids, NSAIDs and triptans, and had a higher prevalence of selected health conditions, including a higher prevalence of depressive symptoms (Table 1). Women with short-term paracetamol exposure used NSAIDS more often and had a higher prevalence of headache or migraines and infections compared with non-users (Table 2S).

We retained 91% of the long-term exposed women in the PS-matched analyses, with a good balance between the covariates after the PS match (Table 1). Comparing the women in the PS-matched cohort with the women excluded by matching ($n = 61$), the former were slightly younger, were more often primiparous, reported fewer health conditions and used less concomitant medication (Table 3S, available as Supplementary data at *IJE* online).

Neurodevelopmental problems

Among children with long-term exposure to paracetamol *in utero*, psychomotor problems were present in 21.8%, behavioural problems in 17.7%, and temperamental problems in 23.5%. Among children with no prenatal paracetamol exposure, psychomotor problems were present in 19.7%, behavioural problems in 14.7% and temperamental problems in 23.6%.

The results from the total cohort and PS-matched analyses are presented in Table 2. In the crude total cohort analyses, long-term paracetamol exposure was associated with six neurodevelopmental problems (delayed age of starting to walk, impaired gross and fine motor skills and communication skills, externalizing behaviour and shyness problems). In the PS-matched analyses, long-term paracetamol exposure during pregnancy was associated with a delayed age of starting to walk (OR: 1.35, 95% CI 1.07–1.70) and communication problems (OR: 1.38, 95% CI 0.98–1.95), although the latter 95% CI included the null value. The 95% CIs were wider for the other outcomes and included the null value, but long-term exposure to paracetamol may also be weakly associated with gross motor impairment, sociability problems and shyness.

We also conducted logistic regression analyses in the total cohort in which we included the PS as a covariate and found that the results were consistent with the PS-matched models (results not shown). We did not find associations between short-term paracetamol exposure and neurodevelopmental outcomes in the PS-matched (Table 4S, available as Supplementary data at *IJE* online) or PS-adjusted models (results not shown).

The number needed to harm (NNH) for motor milestones and communication problems indicated that 48 and 67 women, respectively, had to be exposed to long-term paracetamol use to result in one child developing neurodevelopmental problems (Table 2).

Table 2. Risk estimates for psychomotor, behavioural and temperamental outcomes in 18-month-old infants associated with *in utero* paracetamol exposure: no use vs ≥ 28 days' use in the total cohort and in the PS-matched cohort

		≥ 28 days of paracetamol use					
		Total cohort			PS-matched cohort[a]		
	NNH[b]	Exp. cases	Unexp. cases	Crude OR (95% CI)	Exp. cases	Unexp. cases	PS-matched OR (95% CI)
Psychomotor problems							
Motor milestone	48	186	2537	1.16 (0.99–1.36)	182	139	1.35 (1.07–1.70)
Gross motor	125	49	585	1.31 (0.98–1.76)	47	37	1.28 (0.83–1.98)
Fine motor	39	220	2970	1.17 (1.01–1.36)	210	190	1.12 (0.91–1.38)
Communication	67	84	998	1.32 (1.05–1.66)	79	58	1.38 (0.98–1.95)
Behavioural problems							
Externalizing	28	168	1791	1.50 (1.26–1.76)	163	154	1.07 (0.85–1.35)
Internalizing	83	127	1807	1.09 (0.91–1.32)	125	121	1.04 (0.80–1.35)
Temperamental problems							
Emotionality	143	68	1387	0.75 (0.58–0.96)	66	85	0.77 (0.55–1.07)
Activity	100	170	2605	1.01 (0.86–1.19)	168	155	1.09 (0.87–1.38)
Sociability	67	151	2113	1.12 (0.94–1.33)	145	125	1.18 (0.92–1.51)
Shyness	83	87	1117	1.22 (0.98–1.53)	83	70	1.20 (0.86–1.66)

Exp., exposed; unexp., unexposed.

[a]The propensity scores included the following maternal characteristics: maternal age, pre-pregnancy BMI, parity, married/cohabiting, education, smoking, alcohol use, folate use, specific health conditions, psychotropic co-medication and depressive symptoms.

[b]How many women on average need to be exposed to long-term paracetamol use in pregnancy to result in one child developing neurodevelopmental problems, who would not otherwise have been harmed.

Sensitivity analyses

Analyses conducted within the main indications for paracetamol use (i.e. headache or migraine, fever, infection) revealed point estimates that were generally very close to those observed in the total PS-matched sample. An exception to this trend was the effect of paracetamol on sociability problems in children whose mother had fever during pregnancy, in which the ORs increased to 2.28 (95% CI 1.39–5.18) (Table 3).

The point estimates based on PS-range restrictions at the upper end (0–99th and 0–95th percentile) resulted in similar point estimates for all outcomes. For most outcomes, however, the CIs were slightly wider and the null value was included (Table 5S, available as Supplementary data at *IJE* online).

Discussion

In this study, we observed modestly increased risks of delayed age at starting to walk and impaired communication skills among children at the age of 18 months born to mothers who used paracetamol for 28 days or more during pregnancy. Less strong evidence was found for some other neurodevelopmental outcomes after long-term exposure to paracetamol. No increased risks were observed for paracetamol use of less than 28 days.

From a public health perspective, it is important to study such a common exposure as paracetamol, which is available over the counter for pregnant women. Also, neurodevelopmental problems in early childhood are associated with mental health problems in childhood, adolescence and adulthood,[35,36] and should therefore be identified as early as possible to provide early intervention opportunities. Risk factors for developing neurodevelopmental problems should be examined and well understood in order to implement preventive measures. In our previous study, we found an association for long-term paracetamol exposure during pregnancy for gross motor and communication development, behaviour and activity problems at the age of 3 years.[2] Our results at 18 months are similar, except for activity problems and externalizing behaviour, where we did not find an association. This can be explained by the fact that these behaviours are more easily observable at 3 years of age, as the parents start to expect the children to be able to control their behaviour better.[37] Follow-up studies should be performed in these children to investigate whether symptoms further diminish into preschool and school age.

This study is the first to examine the risks of long-term paracetamol use during pregnancy and neurodevelopmental problems as early as the age of 18 months, and has several important strengths. First, MoBa has a large sample size and extensive information on medication use and the

Table 3. Risk estimates for psychomotor, behavioural and temperamental outcomes in 18-month-old infants associated with *in utero* paracetamol exposure: no use vs ≥ 28 days' use in the total cohort and in the PS-matched cohort, stratified for women with headache or migraine, fever and infections

	Women with headache or migraine					
	≥ 28 days of paracetamol use					
	Total cohort			PS-matched cohort[a]		
	Exp. cases	Unexp. cases	Crude OR (95% CI)	Exp. cases	Unexp. cases	PS-matched OR (95% CI)
Psychomotor problems						
Motor milestone	154	535	1.21 (1.00–1.46)	150	115	1.34 (1.04–1.74)
Gross motor	41	128	1.33 (0.93–1.90)	39	31	1.27 (0.78–2.04)
Fine motor	171	624	1.15 (0.96–1.37)	162	148	1.11 (0.87–1.41)
Communication	69	197	1.46 (1.10–1.94)	65	55	1.19 (0.82–1.72)
Behavioural problems						
Externalizing	138	457	1.23 (1.00–1.51)	132	125	1.06 (0.82–1.38)
Internalizing	106	468	0.90 (0.73–1.13)	104	102	1.03 (0.77–1.38)
Temperamental problems						
Emotionality	56	277	0.82 (0.61–1.10)	55	64	0.85 (0.59–1.23)
Activity	142	500	1.18 (0.97–1.44)	137	131	1.05 (0.82–1.35)
Sociability	125	453	1.14 (0.93–1.41)	120	100	1.22 (0.92–1.61)
Shyness	70	230	1.26 (0.96–1.66)	68	58	1.18 (0.83–1.69)
	Women with fever					
	≥ 28 days of paracetamol use					
	Total cohort			PS-matched cohort[a]		
	Exp. cases	Unexp. cases	Crude OR (95% CI)	Exp. cases	Unexp. cases	PS-matched OR (95% CI)
Psychomotor problems						
Motor milestone	49	301	1.27 (0.92–1.75)	43	29	1.54 (0.94–2.53)
Gross motor	12	71	1.29 (0.70–2.41)	12	5	2.24 (0.77–6.50)
Fine motor	53	336	1.22 (0.90–1.67)	46	38	1.21 (0.77–1.91)
Communication	17	108	1.20 (0.71–2.03)	12	14	0.85 (0.34–1.87)
Behavioural problems						
Externalizing	52	223	1.77 (1.28–2.44)	49	39	1.30 (0.83–1.03)
Internalizing	42	278	1.13 (0.80–1.58)	35	34	1.07 (0.65–1.74)
Temperamental problems						
Emotionality	17	166	0.77 (0.46–1.28)	16	17	0.94 (0.47–1.89)
Activity	42	327	0.96 (0.69–1.35)	38	34	1.10 (0.67–1.79)
Sociability	39	243	1.24 (0.87–1.77)	35	13	2.68 (1.39–5.18)
Shyness	28	144	1.51 (1.00–2.30)	26	22	1.20 (0.66–2.15)
	Women with infections					
	≥28 days of paracetamol use					
	Total cohort			PS-matched cohort[a]		
	Exp. cases	Unexp. cases	Crude OR (95% CI)	Exp. cases	Unexp. cases	PS-matched OR (95% CI)
Psychomotor problems						
Motor milestone	100	941	1.17 (0.94–1.46)	98	72	1.41 (1.02–1.94)
Gross motor	23	213	1.18 (0.76–1.82)	23	16	1.45 (0.76–2.76)

(continued)

Table 3. Continued

	Women with infections					
	≥28 days of paracetamol use					
	Total cohort			PS-matched cohort[a]		
	Exp. cases	Unexp. cases	Crude OR (95% CI)	Exp. cases	Unexp. cases	PS-matched OR (95% CI)
Fine motor	108	1065	1.11 (0.90–1.37)	107	103	1.04 (0.78–1.39)
Communication	47	399	1.29 (0.94–1.76)	45	35	1.70 (0.83–2.05)
Behavioural problems						
Externalizing	94	649	1.58 (1.26–1.99)	90	83	1.10 (0.80–1.50)
Internalizing	68	717	1.01 (0.78–1.30)	66	69	0.95 (0.67–1.36)
Temperamental problems						
Emotionality	32	462	0.74 (0.51–1.06)	30	39	0.76 (0.47–1.23)
Activity	87	975	0.96 (0.76–1.20)	85	84	1.01 (0.74–1.39)
Sociability	78	748	1.13 (0.89–1.45)	73	57	1.31 (0.91–1.87)
Shyness	47	413	1.25 (0.91–1.70)	46	45	1.02 (0.67–1.56)

Exp., exposed; unexp., unexposed.

[a]The propensity scores included the following maternal characteristics: maternal age, pre-pregnancy BMI, parity, married/cohabiting, education, smoking, alcohol use, folate use, specific health conditions, psychotropic co-medication and depressive symptoms.

medical reasons for use. This enabled us to examine the effects of confounding by indication, and appropriately adjust for the use of concomitant medication, in order to make sure that the effects found after long-term paracetamol exposure were independent from these factors. It is important to take confounding by indication into consideration, especially since certain indications for which paracetamol is used may have direct effects on fetal health.[38] Second, the extensive information on neurodevelopmental problems in the MoBa cohort made it possible to examine a range of important outcomes, including psychomotor problems, behavioural problems and temperamental problems. Well-known and internationally recognized measurements in the field of child psychology were used.[29,39,40] In addition, the motor milestones correlated well with the diagnostics.[27]

A limitation of this study is the possibility of selection bias in MoBa.[23] Children born to women in the MoBa cohort are somewhat healthier compared with children born in the total population in Norway, although the absolute differences are small.[41] Of the 61 women with long-term paracetamol use excluded from the PS-matched analyses, 59 women suffered from headaches or migraines, of which almost 50% used concomitant medications, such as opioids, NSAIDS or triptans. This might suggest that the women who were excluded, suffered from more severe headaches or migraines than the women who were included in the PS-matched analyses. Therefore, we should be careful extending our findings to women suffering from the most severe forms of headaches or migraines. Another limitation is that we could not include information on severity and type of infections during pregnancy in the sensitivity analyses, due to small numbers for certain infections, which may have led to confounding by severity. Due to the possibility of residual confounding in other variables as well, it is not possible to rule out confounding as a possible alternative explanation for the results. We also should not understate the possibility of chance findings, because we explored a relatively large number of outcomes, which can result in an increased type II error rate. The use of parent-reported behaviour outcomes can also be prone to differential misclassification and do not have simple clinical interpretation. In future studies, more objective neurocognitive and neurobehavioural measures are therefore recommended. Additionally, substantial loss to follow-up at the 18-month questionnaire may have introduced selection bias, but the differences between the drop-outs and the study population were limited.

In this study, long-term exposure to paracetamol *in utero* was associated with modestly increased risks of delay in motor milestones and communication problems among children at 18 months of age. Although these findings are based on weak associations, we should still consider a possible harm of long-term paracetamol use during pregnancy. These results should be interpreted carefully, however, and should not be used as an argument not to treat pregnant women with severe pain conditions pharmacologically when such treatment is necessary. Before strong conclusions can be drawn, these findings should be replicated in other birth cohorts.

Supplementary Data

Supplementary data are available at *IJE* online

Funding

This work was supported by grant number 836011020 from ZonMw Program Rational Pharmacotherapy. The Norwegian Mother and Child Cohort Study is supported by the Norwegian Ministry of Health, the Ministry of Education and Research, and National Institutes of Health/National Institute of Environmental Health Sciences (contract no N01-ES 75558), National Institutes of Health/National Institute of Neurological Disorders and Stroke (grants UO1 NS 047537-01 and UO1 NS 047537-06A1) and the Norwegian Research Council/FUGE (the National Programme for Research in Functional Genomics in Norway) (grant number 151918/S10).

Acknowledgements

We want to thank all the families in Norway who have been participating in this ongoing cohort study.

Conflict of interest: The authors have no conflict of interest.

References

1. Nordeng H. Drug utilisation studies in pregnancy. In: *Drug Utilization Studies*. Hoboken, NJ: Wiley, 2016.
2. Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. *Int J Epidemiol* 2013;**42:** 1702–13.
3. Bellinger D, Leviton A, Waternaux C, Needleman H, Rabinowitz M. Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development. *N Engl J Med* 1987;**316:**1037–43.
4. Chiodo LM, Jacobson SW, Jacobson JL. Neurodevelopmental effects of postnatal lead exposure at very low levels. *Neurotoxicol Teratol* 2004;**26:**359–71.
5. Bellinger DC. Perspectives on incorporating human neurobehavioural end points in risk assessments. *Risk Anal* 2002;**22:** 487–98.
6. Liew Z, Ritz B, Rebordosa C, Lee PC, Olsen J. Acetaminophen use during pregnancy, behavioural problems, and hyperkinetic disorders. *JAMA Pediatr* 2014;**168:**313–20.
7. Thompson JM, Waldie KE, Wall CR, Murphy R, Mitchell EA. Associations between acetaminophen use during pregnancy and ADHD symptoms measured at ages 7 and 11 yearsPLoS One 2014;**9:**e108210.
8. Viberg H, Eriksson P, Gordh T, Fredriksson A. Paracetamol (acetaminophen) administration during neonatal brain development affects cognitive function and alters its analgesic and anxiolytic response in adult male mice. *Toxicol Sci* 2014;**138:**139–47.
9. European Medicines Agency. *Highlights of the Pharmacovigilance Risk Assessment Committee (PRAC) Meeting, 5–8 May 2014, London*. London: EMA, 2014.
10. Thiele K, Kessler T, Arck P, Erhardt A, Tiegs G. Acetaminophen and pregnancy: short- and long-term consequences for mother and child. *J Reprod Immunol* 2013;**97:**128–39.
11. Damkier P, Pottegard A, dePont Christensen R, Hallas J. Pregnancy and paracetamol: Methodological considerations on the study of associations between in utero exposure to drugs and childhood neurodevelopment. *Basic Clin Pharmacol Toxicol* 2014;**116:**2–5.
12. Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Authors' Response: More research on paracetamol is required. *Int J Epidemiol* 2014;**43:**975–76.
13. Cannell JJ. Paracetamol, oxidative stress, vitamin D and autism spectrum disorders. *Int J Epidemiol* 2014;**43:**974–75.
14. Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Annotations & Reflections. *Basic Clin Pharmacol Toxicol* 2015;**116:**6–8.
15. Frye CA, Bo E, Calamandrei G *et al*. Endocrine disrupters: a review of some sources, effects, and mechanisms of actions on behaviour and neuroendocrine systems. *J Neuroendocrinol* 2012;**24:**144–59.
16. Colborn T. Neurodevelopment and endocrine disruption. *Environ Health Perspect* 2004;**112:**944–49.
17. Howdeshell KL. A model of the development of the brain as a construct of the thyroid system. *Environ Health Perspect* 2002;**110(Suppl 3):**337–48.
18. 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:**1141–48.
19. Nuttall SL, Khan JN, Thorpe GH, Langford N, Kendall MJ. The impact of therapeutic doses of paracetamol on serum total antioxidant capacity. *J Clin Pharmacol Ther* 2003;**28:**289–94.
20. 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* 1979;**205:**1414–16.
21. de Fays L, Van Malderen K, De Smet K *et al*. Use of paracetamol during pregnancy and child neurological development. *Dev Med Child Neurol* 2015;**57:**718–24.
22. Frisell T, Oberg S, Kuja-Halkola R, Sjolander A. Sibling comparison designs: bias from non-shared confounders and measurement error. *Epidemiology* 2012;**23:**713–20.
23. Magnus P, Irgens LM, Haug K, Nystad W, Skjaerven R, Stoltenberg C. Cohort Profile: The Norwegian Mother and Child Cohort Study (MoBa). *Int J Epidemiol* 2006;**35:**1146–50.
24. Irgens LM. The Medical Birth Registry of Norway. Epidemiological research and surveillance throughout 30 years. *Acta Obstet Gynecol Scand* 2000;**79(:**435–39.
25. World Health Organization. *Classifications. The Anatomical Therapeutic Chemical Classification System with Defined Daily Doses (ATC/DDD)*. Geneva: WHO, 2012.
26. Handal M, Skurtveit S, Furu K *et al*. Motor development in children prenatally exposed to selective serotonin reuptake inhibitors: a large population-based pregnancy cohort study. *BJOG* 2015. Sep 15. doi: 10.1111/1471-0528.13582. [Epub ahead of print.]
27. Bodnarchuk JL, Eaton WO. Can parent reports be trusted? Validity of daily checklists of gross motor milestone attainment. *J Appl Dev Psychol* 2004;**25:**481–90.
28. Novik TS. Validity of the Child Behaviour Checklist in a Norwegian sample. *Eur Child Adolesc Psychiatry* 1999;**8:** 247–54.
29. Mathiesen KS, Tambs K. The EAS temperament questionnaire-factor structure, age trends, reliability, and stability in a Norwegian sample. *J Child Psychol Psychiatry* 1999;**40:**431–39.

30. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology* 1999;**10:**37–48.
31. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. *BMC Med Res Methodol* 2008;**8:**70.
32. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;**70:**41–55.
33. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat* 2011;**10:** 150–61.
34. Sturmer T, Rothman KJ, Avorn J, Glynn RJ. Treatment effects in the presence of unmeasured confounding: dealing with observations in the tails of the propensity score distribution – a simulation study. *Am J Epidemiol* 2010;**172:**843–54.
35. Beyer T, Postert C, Muller JM, Furniss T. Prognosis and continuity of child mental health problems from preschool to primary school: results of a four-year longitudinal study. *Child Psychiatry Hum Dev* 2012;**43:**533–43.
36. Lavigne JV, Arend R, Rosenbaum D, Binns HJ, Christoffel KK, Gibbons RD. Psychiatric disorders with onset in the preschool years: I. Stability of diagnoses. *J Am Acad Child Adolesc Psychiatry* 1998;**37:**1246–54.
37. Naerde A, Ogden T, Janson H, Zachrisson HD. Normative development of physical aggression from 8 to 26 months. *Dev Psychol* 2014;**50:**1710–20.
38. Dreier JW, Andersen AM, Berg-Beckhoff G. Systematic review and meta-analyses: fever in pregnancy and health impacts in the offspring. *Pediatrics* 2014;**133:**e674–88.
39. Achenbach TM, Ruffle TM. The Child Behaviour Checklist and related forms for assessing behavioural/emotional problems and competencies. *Pediatr Rev* 2000;**21:**265–71.
40. Squires J, Bricker D, Potter L. Revision of a parent-completed development screening tool: Ages and Stages Questionnaires. *J Pediatr Psychol* 1997;**22:**313–28.
41. Nilsen RM, Vollset SE, Gjessing HK. Self-selection and bias in a large prospective pregnancy cohort in Norway. *Paediatr Perinat Epidemiol* 2009;**23:**597–608.