Paracetamol use prior to and in early pregnancy

Prevalence and patterns among women with and without chronic medical diseases

Taagaard, Mille; Rode, Line; de Wolff, Mie Gaarskjær; Damm, Peter; Hagen, Casper P.; Fisher, Margit Bistrup; Hegaard, Hanne Kristine; Rom, Ane Lilleøre

Published in:
British Journal of Clinical Pharmacology

DOI:
10.1111/bcp.15732

Publication date:
2023

Document version:
Final published version

Received: 7 December 2022 | Revised: 26 March 2023 | Accepted: 28 March 2023

DOI: 10.1111/bcp.15732

ORIGINAL ARTICLE

Paracetamol use prior to and in early pregnancy: Prevalence and patterns among women with and without chronic medical diseases

Mille Taagaard[1,2] | Line Rode[2,3] | Mie Gaarskjær de Wolff[4] | Peter Damm[1,5] | Casper P. Hagen[6,7] | Margit Bistrup Fisher[6,7] | Hanne Kristine Hegaard[1,8,9] | Ane Lilleøre Rom[1,9,10]

[1]Department of Obstetrics, The Juliane Marie Centre, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

[2]Department of Clinical Biochemistry, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

[3]Department of Obstetrics, Center for Fetal Medicine, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

[4]Department of Gynaecology and Obstetrics, Copenhagen University Hospital, Amager–Hvidovre, Denmark

[5]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

[6]Department of Growth and Reproduction, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

[7]International Center for Research and Research Training in Endocrine Disruption of Male Reproduction and Child Health (EDMaRC), Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

[8]Faculty of Health Sciences, Copenhagen University, Copenhagen, Denmark

[9]The Interdisciplinary Research Unit of Women's, Children's and Families' Health, The Juliane Marie Centre, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark

[10]Research Unit of Gynaecology and Obstetrics, Department of Clinical Research, University of Southern Denmark, Odense, Denmark

Correspondence
Ane Lilleøre Rom, Department of Obstetrics, The Juliane Marie Centre, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark.
Email: ane.lilleoere.rom@regionh.dk

Funding information
This work was funded by Danish Regions and The Danish Health Confederation.

Aims: Paracetamol is commonly consumed by pregnant women, even though recent data have questioned its safety. Having chronic medical diseases (CMDs) may influence the prevalence of use during pregnancy. We aimed to assess the prevalence and patterns of use 3 months prior to pregnancy and in the first trimester among women with and without CMDs and the potential influence of CMDs on frequent use in the first trimester.

Methods: We used patient-reported data from the Copenhagen Pregnancy Cohort from 1 October 2013 to 23 May 2019 with information on CMDs and paracetamol use. Prevalence and patterns of use were assessed descriptively and by multivariable logistic regression models.

Results: We included 24 019 pregnancies. Use of paracetamol prior to and in early pregnancy was significantly higher among women with CMDs compared to women without (40.7% *vs*. 35.8% and 9.1% *vs*. 5.1%, respectively). Women with CMDs were 2.7 times more likely to have a frequent intake compared to women without [aOR 2.69 (95% CI 2.05–3.32)]. Migraine, rheumatoid arthritis and mental disease were

associated with a higher use of paracetamol [aOR 4.39 (3.20–6.02), aOR 4.32 (2.41–7.72) and aOR 2.74 (1.67–4.49), respectively].

Conclusions: Women with CMDs had a higher paracetamol use before and during pregnancy than women without CMDs. Women with migraine, rheumatoid arthritis and mental disease showed the highest risk of frequent use. This study highlights the importance of discussing pain relief in pregnancy and evaluating the influence of maternal CMDs when assessing adverse effects of paracetamol use during pregnancy.

KEYWORDS

acetaminophen, chronic medical disease, paracetamol, pregnancy

1 | INTRODUCTION

Paracetamol (acetaminophen) is globally known as an over-the-counter drug and is increasingly used, not only by the general population but also during pregnancy, where reported use has been 65% among American women and 35%–50% among European women.[1-5] Paracetamol is the first choice of analgesic during pregnancy, probably due to the assumed low teratogenicity in addition to the antipyretic properties,[1,3] and since non-steroidal anti-inflammatory drugs (NSAIDs) should be cautiously used during the first and second trimesters and avoided in the third.[6] Over the last decade, use of paracetamol during pregnancy has, however, been associated with adverse health outcomes in the offspring including attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASD),[1,3,5,7-14] as well as asthma and wheezing in infancy.[13] Further, in vivo studies, animal models and epidemiological studies suggest adverse effects on gonadal development, including a reduced number of ovarian follicles decisive of the female reproductive lifespan as well as an increased risk of cryptorchidism.[15,16] The building evidence of these potentially detrimental effects is a cause for concern, and recently, several experts have called for precautionary action regarding the use of paracetamol during pregnancy.[17]

As clinicians, we lack information on the magnitude of use, especially in early pregnancy, and knowledge on to which degree maternal morbidity may influence the use of paracetamol during pregnancy. In addition, the detected unfavourable associations between the use of paracetamol and offspring health must be carefully interpreted, since confounding by indication (e.g. maternal chronic medical disease [CMD]) might interfere with the associations.[1,18-21] Today, more women with CMDs are capable of conceiving compared to earlier, that is, the prevalence of pregnant women with CMDs in Denmark increased from approximately 4% in 1989 to 16% in 2013.[22] Even though women with CMDs are highly encouraged to plan their pregnancy and adjust their medication use accordingly,[23] we expect these women to have a more frequent use of paracetamol before and during pregnancy compared to women without CMDs. Since 2012, self-reported clinical data on, for example, health, lifestyle and use of medication before pregnancy and in the first trimester have been collected at the Department of Obstetrics, Copenhagen University Hospital, Rigshospitalet. In present study, we aimed to describe the prevalence and patterns of use of paracetamol prior to pregnancy and in the first trimester among women with and without CMDs and to assess associations between CMDs and frequent use of paracetamol in the first trimester.

What is already known about this subject

- More than 50% of pregnant women worldwide use paracetamol.
- Recently, use of paracetamol in pregnancy has been highly debated due to the associated adverse health outcomes in offspring.
- Chronic medical disease (CMD) in pregnancy may influence the need for pain management in pregnancy.

What this study adds

- Use of paracetamol among women with and without chronic medical diseases was markedly reduced in the first trimester.
- Frequent use of paracetamol was more than doubled for women with CMDs especially among cases of migraine, rheumatoid arthritis and mental diseases.
- This study highlights the importance of discussing pain management during pregnancy.

2 | METHODS

We used patient-reported data from the Copenhagen Pregnancy Cohort based on information from online clinical questionnaires. These were filled out by pregnant women at the Department of

Obstetrics at the Copenhagen University Hospital, Rigshospitalet, in relation to booking a first trimester screening for chromosomal abnormalities, in the period from 1 October 2013 to 23 May 2019. The Department serves as a primary birth facility of the central Copenhagen area and as a tertiary referral hospital for the eastern part of Denmark. Information from the questionnaires was used for individual antenatal care and for research purposes following legislation.

Women were categorized with a CMD (yes/no), if they listed one or more of the following diseases: migraine, thyroid disease, pulmonary disease, mental disease, rheumatoid arthritis, hypertension, neurologic disorders, type 1 or 2 diabetes, cardiac disease, bowel disease, haematologic disease, endometrioses, hepatic disease, renal disease or other CMDs not included in the previously mentioned diseases.

Intake of paracetamol (yes/no) was assessed 3 months prior to pregnancy and in the first trimester. Upon a positive answer, the women were asked to specify the frequency of use, divided into three subgroups: 'daily', '1–2 times per week' and 'rarely'. When the women reported use of 'painkillers' without giving a description of the generic name, the use was classified as 'unspecified'.

Information on socio-demographic characteristics included maternal age, educational level, pre-pregnancy body mass index (BMI), parity, use of assisted reproductive technology, smoking status, and a Danish language barrier.

2.1 | Statistical analyses

Descriptive statistics were applied to describe the socio-demographic characteristics of the study population in relation to CMD. Further, the overall intake of paracetamol among women with and without CMDs, and specific groups of CMDs, was described. The data were presented as numbers (*n*) and percentages (%). Pearson's chi-squared test was used to assess the distributions of the various covariates across CMD status. We used the chi-squared test for trend to test for a potential increase in prevalence of paracetamol intake during the period from 2013 to 2019. Statistical significance was defined as a two-sided $P \leq .05$.

Univariable and multivariable logistic regression analyses were performed to assess potential associations between CMD (yes/no) and frequent paracetamol intake (daily or 1–2 times per week). Adjustment was made based on the a priori selected confounders; maternal age (≤25 years, 26–30 years, 31–35 years, 36–40 years and ≥41 years), educational level (higher degree ≥5 years, intermediate degree [3–4 years], short degree [1–2 years], technical degree and compulsory education), parity (nulliparous/multiparous), and Danish language barrier (yes/no). Both crude odds ratios (ORs) and adjusted odds ratios (aORs) with 95% confidence intervals (95% CI) were given. Unspecified use of painkillers was not included in the analyses (Table S1).

To test the association between a specific chronic medical disease/disease group and frequent intake of paracetamol, univariable and multivariable logistic regression analyses with adjustment for maternal age, educational level, parity and other remaining CMDs were performed. In these analyses, the reference group included women not reporting the specific disease, respectively.

To account for the correlation between more pregnancies by each individual woman in the cohort, generalized estimating equations (GEE) were applied. All analyses were performed using SPSS (IBM Statistics SPSS version 25, Armonk, NY, USA).

2.2 | Ethical approval

The study was approved by the Danish Data Protection Agency (file no.: 2012-58-0004.RH- RH-2016-202, I-Suite no.: 04778, 18 December 2017). The Medical Records Research, Health Research, the Capital Region of Denmark, granted permission to disclose patient information from medical records for research (file no. R-21043472, 5 January 2022).

2.3 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.

3 | RESULTS

From 1 October 2013 to 23 May 2019, a total of 27 522 women received an email invitation with a link to fill in the clinical questionnaire (gestational age 6–12 weeks). Women who moved to another birth facility ($n = 186$) or had a miscarriage before completing the questionnaire ($n = 1119$) were excluded. A total of 2198 women did not return the questionnaire. The final study population thus consisted of 24 019 pregnancies with a response rate of 87.3%. Of these, 7233 women (30.1%) were included with more than one pregnancy. Most women were ≥31 years old (64.1%), academically educated (53.2%), non-smokers (93.2%), nulliparous (62.6%), and had a normal BMI (73.0%) (Table 1). Almost one-fourth of the study population reported having a CMD (22.6%), and compared to women without a CMD, these women were more often obese (14.9% *vs.* 12.1%), assisted by reproductive technology (16.2% *vs.* 10.8%), smokers (2.0% *vs.* 1.3%), older ≥31 years (68.4% *vs.* 63%), and less likely to be academically educated (49.6% *vs.* 54.3%) (Table 1).

Three months prior to pregnancy, the overall use of paracetamol was reported to be 40.7% among women with CMDs compared to 35.8% of women without ($P < .001$). Frequent use (daily or 1–2 times per week) was 6.7% compared to 3.1% ($P < .001$) (Table 2). In the first trimester, overall use was 9.9% among women with CMDs compared to 5.1% of women without CMDs ($P < .001$), while frequent use was 1.9% compared to 0.4% ($P < .001$) (Table 2).

During the study period, the use of paracetamol in the first trimester (any and frequent, respectively) was relatively stable among

TABLE 1 Socio-demographic characteristics of the total study population ($n = 24\,019$) and among women with and without chronic medical diseases.

Characteristics	Total	Pregnancies of women with chronic medical diseases	Pregnancies of women without chronic medical diseases	*P*-value
	$n = 24\,019$	$n = 5422$ (22.6%)	$n = 18\,597$ (77.4%)	
	n	*n* (%)		
Age				<.001
≤25 years	1023 (4.3)	206 (3.8)	817 (4.4)	
26–30 years	7497 (31.2)	1497 (27.6)	6000 (32.3)	
31–35 years	9567 (39.8)	2211 (40.8)	7356 (39.6)	
36–40 years	4765 (19.8)	1192 (22.0)	3573 (19.2)	
≥41 years	1091 (4.5)	301 (5.6)	790 (4.2)	
Missing data	*76*	*15*	*61*	
Educational level				<.001
Higher degree (≥5 years)	12 789 (53.2)	2687 (49.6)	10 102 (54.3)	
Intermediate degree (3–4 years)	6990 (29.1)	1672 (30.8)	5318 (28.6)	
Short degree (1–2 years)	1418 (5.9)	399 (7.6)	1019 (5.5)	
Technical degree	755 (3.1)	192 (3.5)	563 (3.0)	
Compulsory education	1470 (6.1)	359 (6.6)	1111 (6.0)	
Missing data	*587*	*113*	*484*	
BMI pre-pregnancy				<.001
<18.5 kg/m^2	1079 (4.5)	243 (4.5)	836 (4.5)	
18.5–24.9 kg/m^2	17 534 (73.0)	3723 (68.7)	13 811 (74.3)	
25–29.9 kg/m^2	3068 (12.8)	809 (14.9)	2259 (12.1)	
≥30 kg/m^2	1068 (4.4)	372 (6.9)	696 (3.7)	
Missing data	*1270*	*275*	*995*	
Parity				.359
Nulliparous	15 043 (62.6)	3367 (62.1)	11 676 (62.8)	
Multiparous	8976 (37.4)	2055 (37.9)	6921 (37.2)	
Assisted reproductive technology				<.001
Yes	2892 (12.0)	879 (16.2)	2013 (10.8)	
No	20 786 (86.6)	4473 (82.5)	16 313 (87.7)	
Missing data	*341*	*70*	*271*	
Smoking first trimester				.001
Yes	355 (1.5)	107 (2.0)	248 (1.3)	
No	22 378 (93.2)	5256 (97.0)	18 122 (97.4)	
Missing data	*1286*	*59*	*227*	

(Continues)

TABLE 1 (Continued)

Characteristics	Total	Pregnancies of women with chronic medical diseases	Pregnancies of women without chronic medical diseases	*P*-value
	n = 24 019	*n* = 5422 (22.6%)	*n* = 18 597 (77.4%)	
	n	*n* (%)		
Danish language barriers				.324
Yes	1094 (4.6)	234 (4.3)	860 (4.6)	
No	22 668 (95.5)	5138 (94.8)	17 530 (94.3)	
Missing data	*257*	*50*	*207*	

TABLE 2 Prevalence and frequency of paracetamol use 3 months prior to pregnancy and in the first trimester in pregnancies of women with and without chronic medical diseases.

Paracetamol intake	Pregnancies of women with chronic medical diseases	Pregnancies of women without chronic medical diseases	*P*-value
	n = 5422 (22.6%)	*n* = 18 597 (77.4%)	
Prior to pregnancy *n* (%)			
Yes	2207 (40.7)	6653 (35.8)	<0.001
Frequency			
Daily	58 (1.1)	96 (0.5)	<0.001
1–2 times per week	304 (5.6)	476 (2.6)	<0.001
Rarely	1801 (33.2)	6028 (32.4)	0.267
Frequency not reported	*44*	*53*	
No	3215 (59.3)	11 944 (64.2)	<0.001
First trimester *n* (%)			
Yes	539 (9.9)	945 (5.1)	<0.001
Frequency			
Daily	22 (0.4)	31 (0.2)	0.001
1–2 times per week	80 (1.5)	97 (0.2)	<0.001
Rarely	435 (8.0)	804 (4.6)	<0.001
Frequency not reported	*3*	*13*	
No	4883 (90.1)	17 652 (94.6)	<0.001

women with and without CMDs, despite a statistically significant increase from 2017 to 2018 among women with CMDs ($P = .01$ and $P = .03$, respectively) (Figures 1 and 2). Regarding any use of paracetamol 3 months prior to pregnancy, the prevalence increased over time in both women with and without CMD (P for trend <.001) (Figure S1). Frequent paracetamol intake 3 months prior to pregnancy increased in women with CMD during the same time period (P for trend = .003) but not in women without CMD ($P = .07$) (Figure S2).

Migraine was the most frequent disease among the CMDs included (6.5%), followed by thyroid disease (4.7%), mental disease (3.0%), pulmonary disease (2.4%) and rheumatoid arthritis (1.3%) (Table 3). Other CMDs were reported by 1.9% of the women and included diseases not pre-specified in the questionnaire (Table S2). Of all the CMDs, migraine was associated with the highest use of paracetamol 3 months prior to pregnancy and in the first trimester (49.8% and 17.0%, respectively) (Tables 3 and S3). Use of paracetamol in the first trimester was reduced three- to fourfold among women with specific CMDs compared to 3 months prior to pregnancy, for example, migraine from 49.8% to 17.0%, thyroid disease from 33.6% to 7.1%, mental disease from 42.7% to 11.1%, pulmonary disease from 44.2% to 11.3%, and rheumatoid arthritis from 43.9% to 10.8% (Tables 3 and S3).

After adjusting for potential confounders, the logistic regression analyses demonstrated that women with CMDs were approximately 2.7 times more likely to have a frequent intake of paracetamol in the first trimester than women without CMDs: aOR 2.69 (95% CI 2.05–3.32) (Table 4). A similar tendency was present 3 months prior to pregnancy: aOR 2.21 (95% CI 1.92–2.54) (Table S4). Analyses on the individual CMDs demonstrated that women with migraine and rheumatoid arthritis were four times more likely to have a frequent intake of paracetamol in the first trimester, respectively, compared to women without the specific disease: aOR 4.39 (95% CI 3.20–6.02)

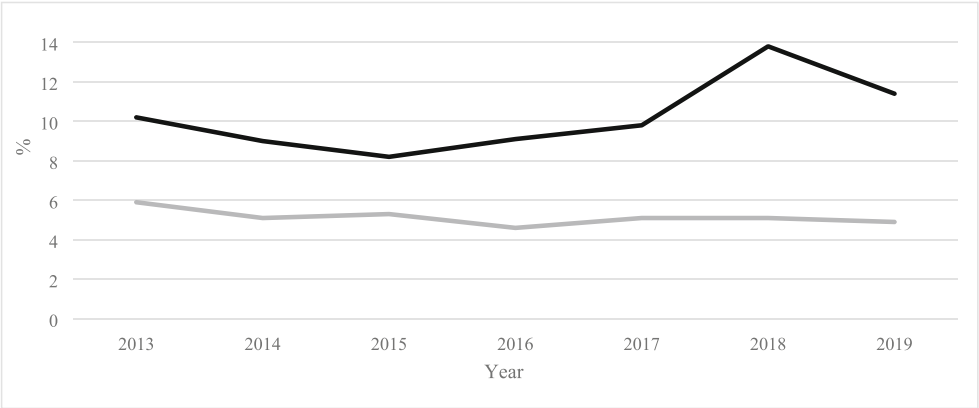

FIGURE 1 Prevalence of any paracetamol intake in the first trimester according to calendar time for pregnancies of women with chronic medical diseases (black) and for pregnancies of women without chronic medical diseases (grey).

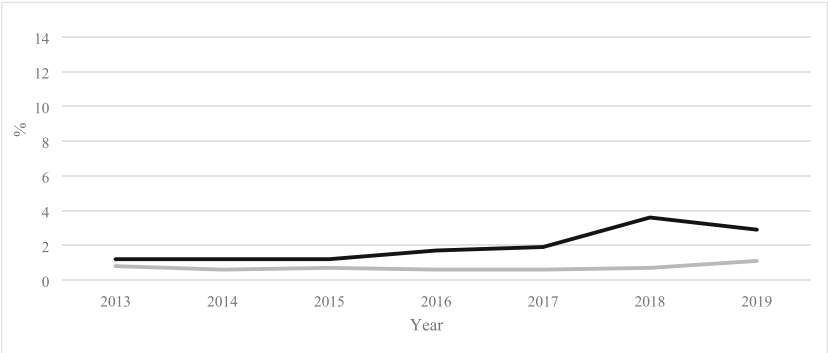

FIGURE 2 Prevalence of frequent paracetamol intake (daily or 1–2 times per week) in the first trimester according to calendar time for pregnancies of women with chronic medical diseases (black) and for pregnancies of women without chronic medical diseases (grey).

TABLE 3 Prevalence and frequency of use of paracetamol in the first trimester according to specific diseases/subgroup of chronic medical diseases.

	Total	No	Yes	Daily	1–2 times per week	Rarely	Frequency not reported
Chronic medical disease	***n*** **(%)**	***n*** **(%)**			***n*** **(%)**		***n***
Migraine	1558 (6.5)	1293 (83.0)	265 (17.0)	6 (0.4)	46 (3.0)	211 (13.5)	3
Thyroid disease	1117 (4.7)	1033 (92.9)	84 (7.1)	5 (0.4)	8 (0.7)	71 (6.4)	0
Mental disease	710 (3.0)	631 (88.9)	79 (11.1)	5 (0.7)	13 (1.8)	61 (8.76)	0
Pulmonary disease	576 (2.4)	514 (89.2)	62 (10.8)	3 (0.5)	7 (1.2)	52 (9.0)	0
Rheumatoid arthritis	305 (1.3)	273 (89.5)	32 (10.5)	8 (2.6)	5 (1.6)	18 (5.9)	0
Hypertension	280 (1.2)	256 (91.4)	24 (8.6)	0 (0.0)	2 (0.7)	21 (7.5)	0
Neurological disease	267 (1.1)	247 (92.5)	20 (7.5)	0 (0.0)	3 (1.1)	17 (6.4)	0
Diabetes type 1	253 (1.1)	241 (95.3)	12 (4.7)	1 (0.4)	2 (0.8)	9 (3.6)	0
Cardiac disease	217 (0.9)	199 (91.7)	18 (8.3)	0 (0.0)	2 (0.9)	16 (7.4)	0
Bowel disease	195 (0.8)	179 (91.8)	16 (8.2)	0 (0.0)	2 (1.0)	14 (7.2)	0
Haematological disease	189 (0.8)	181 (95.8)	8 (4.2)	1(0.5)	0 (0.0)	7 (3.7)	0
Diabetes type 2	91 (0.4)	82 (90.1)	9 (9.9)	1 (1.1)	3 (3.3)	5 (5.5)	0
Endometriosis	89 (0.4)	81 (91.0)	8 (9.0)	1 (1.1)	1 (1.1)	6 (6.7)	0
Hepatic disease	46 (0.2)	42 (91.3)	4 (8.7)	1 (2.2)	2 (4.3)	1 (2.2)	0
Renal disease	39 (0.2)	34 (87.2)	5 (12.8)	0 (0.0)	0 (0.0)	5 (12.8)	0
Other disease[a]	471 (1.9)	429 (89.8)	42 (8.9)	4 (0.7)	5 (1.1)	33 (7.3)	0

[a]Other diseases not specified above are listed in Table S2.

TABLE 4 Association between chronic medical disease status and frequent use of paracetamol in the first trimester.

Frequent use of paracetamol (daily or 1–2 times per week)						
			Crude analyses		Adjusted analyses	
Chronic medical disease	*n*	%	OR	95% CI	aOR[a]	95% CI
Yes	102	1.9	2.74	2.10–3.57	2.69	2.05–3.53
No	128	0.7	1	Ref	1	Ref

Abbreviations: CI, confidence interval; OR, odds ratio.
[a]Adjusted for maternal age, parity, educational level and Danish language barrier.

TABLE 5 Associations between the largest subgroups of chronic medical disease and frequent use of paracetamol in the first trimester.

Frequent use of paracetamol (daily or 1–2 times per week)					
		Crude analyses		Adjusted analyses	
Chronic medical disease	*n*	OR	95% CI	aOR[a]	95% CI
Migraine	52	4.31	3.15–5.90	4.39	3.20–6.02
Thyroid disease	13	1.20	0.65–2.22	1.22	0.65–2.72
Mental disease	18	2.87	1.76–4.69	2.74	1.67–4.49
Pulmonary disease	10	1.86	0.98–3.54	1.53	0.74–3.14
Rheumatoid arthritis	13	4.67	2.62–8.30	4.32	2.41–7.72

Abbreviations: CI, confidence interval; OR, odds ratio.
[a]Adjusted for maternal age, parity, educational level and remaining chronic conditions.

and aOR 4.32 (95% CI 2.41–7.72) (Table 5). In addition, frequent use among women with mental diseases was more than twice as high compared to women without mental diseases: aOR 2.74 (95% CI 1.67–4.49) (Table 5). Prior to pregnancy, significant associations with frequent use were found in women with migraine, mental disease, pulmonary disease and rheumatoid arthritis (Table S5).

4 | DISCUSSION

Based on a large cohort of Danish pregnant women, we found significantly higher use of paracetamol among women with CMDs compared to women without, 3 months prior to pregnancy and in the first trimester. In both groups, a marked reduction in the overall use of paracetamol was reported from 3 months prior to pregnancy to the first trimester; that is, the prevalence decreased from 40% to 10% in women with CMDs. In addition, these women had an approximately 2.5-fold increased risk of frequent use of paracetamol in early pregnancy compared to women without CMDs. Migraine, rheumatoid arthritis and mental diseases were associated with the highest risk of frequent use.

Our findings demonstrated a noticeable reduction in the use of paracetamol during pregnancy, in line with previous research, either indicating that most women are already aware of potential negative consequences and/or a general awareness to use as little medicine as possible during pregnancy.[24] The prevalence of paracetamol intake in the first trimester has previously been reported to be up to 30% among Danish women based on data from the Danish National Birth Cohort including 100 000 births from 1996 to 2003 of both women with and without CMDs.[25] Our study, performed more than 10 years later, displayed a prevalence of 9.9% in pregnancies of women with CMDs and only 5.1% in women without. A national cohort may indicate a more representative estimate, as Copenhagen differs in terms of welfare, social equality and healthcare status from the rest of Denmark.[26] Contrarily, our findings may depict a more recent tendency to reduce paracetamol consumption in early pregnancy among women in general. The latter may have been induced by the restriction on over-the-counter sales of paracetamol made by the Danish Health Authorities in 2013, where large-scale paracetamol sales were minimized.[27] In the present study, the prevalence of use of paracetamol was relatively stable over the years included, prior to pregnancy and in the first trimester, despite an increase in 2018 among women with CMDs. The increase could potentially be explained by the association between cardiac thrombosis and intake of NSAIDs highlighted nationally in 2017.[28] This awareness might have led to a reduction in use of NSAIDs among women with CMDs and an increase in use of paracetamol instead to relieve chronic pain.

As expected, we found a higher prevalence in the use of paracetamol 3 months prior to pregnancy and in early pregnancy among women with CMDs compared to women without CMDs, most likely due to a higher level of pain in women with CMDs.[29,30] Some of these women are treated with teratogenic medication prior to pregnancy, for example, women with rheumatoid arthritis,[31,32] potentially making paracetamol seem like the milder and safer alternative during pregnancy. Even though paracetamol has been associated with adverse pregnancy outcomes,[7,11,13] paracetamol has also been claimed to be the safest analgesic during pregnancy.[33,34]

Migraine was the most common CMD with frequent use of paracetamol in the present study. We found that women with migraine reduced their intake of paracetamol in the first trimester compared to

prior to pregnancy. This potentially indicates an improvement in disease activity during pregnancy, which is reported to be present for 60%–80% of women with migraine while pregnant.[33,35] However, having migraine was also associated with a fourfold risk of frequent use of paracetamol in the first trimester, possibly indicating a need for pain management for some women during pregnancy. This is in line with prior studies showing that 20%–40% of women report either a worsening or an unchanged condition during pregnancy.[35] In addition, prior studies also found that less than a third of women with migraine report an optimal treatment during pregnancy and that 70% report a need for antimigraine agents.[33,34]

Among women with rheumatoid arthritis, who are also known to suffer from increased pain levels during pregnancy,[31,32,36] we also observed a fourfold likelihood of frequent use in the first trimester compared to women without rheumatoid arthritis. Prior studies report that 40%–60% of women with rheumatoid arthritis might experience a reduction in disease activity during pregnancy and thereby a decrease in the use of medical treatment.[37,38] However, many women might still need paracetamol as well as NSAIDs in order to handle chronic pain issues in pregnancy.[31,32] In the present study, we observed a decrease in the prevalence of use of paracetamol among women with rheumatoid arthritis from prior to pregnancy to first trimester, which might reflect either reduced disease activity or an overall concern related to medication use in pregnancy. Presumably, these women have already minimized their use of medication in relation to pregnancy, making paracetamol and NSAIDs a necessity, especially among women with chronic pain due to remaining disease activity.[31,32] Information on potential concomitant use of medication was not available in this dataset.

Among women with mental diseases, frequent use in the first trimester was more than twice as high compared to women without mental diseases. This may be explained by a higher level of chronic pain among psychiatric patients[30] and by an overall elevated use of medical treatment among pregnant women with a psychiatric history.[39] In addition, we used patient-reported information on mental diseases, including psychiatric diagnoses as well as milder cases of depression, anxiety and stress-related disorders. We found, however, a similar reduction in paracetamol intake from prior to pregnancy to the first trimester in this group, which might, similar to migraine and rheumatoid arthritis, reflect a concern related to medication use in pregnancy.

Overall, we observed a higher intake of paracetamol 3 months prior to pregnancy compared to the first trimester. Whether the period of paracetamol intake also included the first weeks of pregnancy and continued until a verified pregnancy cannot be further elucidated from the present study. This information could, however, be valuable, as adverse effects on ovarian development are suspected to be most pronounced in the early part of the first trimester when the pool of primordial follicles is established. This process is essential for the longevity of the female reproductive lifespan and also important for future reproductive health.[16]

The routinely collected clinical data allowed for the inclusion of more than 24 000 unselected pregnancies from the Department of Obstetrics, Copenhagen University Hospital, Rigshospitalet, representing a large strength of our study. Using patient-reported information on paracetamol is also considered a strength, since paracetamol is primarily sold over-the-counter and may therefore not be sufficiently covered in prior studies based on data from national registries, including only prescribed medication.[40] Further, this data collection method reduced the risk of information bias due to recall or misclassification, that is, the women hiding or providing false information on, for example, use of paracetamol, since all information was routinely collected without a specific focus on CMDs and paracetamol. Further, we believe that a potential misclassification of use of paracetamol would be non-differential and bias our findings towards the null.

Our study may be limited by the combination of very different chronic medical diseases, leaving no room for separating the effects of different diseases in some estimates. However, we also describe patterns of use and an association with frequent use according to specific (and the most common) diseases. Our data were limited to assess use of paracetamol prior to pregnancy and in early pregnancy, since the clinical questionnaire was filled out in the first trimester only. Further, we did not have access to information on potential concomitant use of medication in this dataset. Reported use of unspecified painkillers was not included in the regression analyses of CMDs and frequent use of paracetamol. These numbers were, however, low and would not change the conclusions. Even though the response rate was high (87.3%), selection bias related to non-participants may be present.[41] Additionally, our study was based on a high-income population. Thus, our findings may not be representative of the general Danish background population.

The findings of the present study are valuable for clinicians in antenatal care to initiate important discussions on the use of paracetamol during pregnancy and to offer women the most optimal treatment during pregnancy as well as relevant information. We are aware that pain relief during pregnancy is a complex matter and difficult to manage, especially among women with CMDs. It is important to emphasize that advocating antenatal counselling does not encourage excluding pharmacological pain management strategies. These women may already have reduced their use of medical treatments, and in some diseases, the continuation may have been more important. Further, a previous study has shown that unmanaged pain can lead to adverse pregnancy outcomes such as depression and hypertension.[42] However, more research is needed to disclose whether this form of pain could negatively affect fetal development. We believe that the optimal treatment include pharmacological and non-pharmacological strategies, as prior studies also show positive effects of exercise on certain types of pain during pregnancy.[43]

5 | CONCLUSION

All women included in the study considerably reduced the use of paracetamol in the first trimester compared to 3 months prior to pregnancy. Women with CMDs had a significantly higher overall use of paracetamol at both time points compared to women without CMDs.

Frequent use of paracetamol in early pregnancy was 2.5-fold higher in women with CMDs compared to women without. Women with migraine, rheumatoid arthritis or mental diseases had the highest risk of frequent use. This study advocates important discussions on use of paracetamol during pregnancy and highlights the importance of evaluating the potential influence of maternal CMDs when assessing adverse effects of paracetamol use during pregnancy.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the study. Mille Taagaard and Line Rode conducted the analyses. Mille Taagaard, Hanne Kristine Hegaard and Ane Lilleøre Rom drafted the manuscript. All authors contributed to interpretation of the results and to the critical revision of the manuscript for important intellectual content.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

The research data cannot be shared due to limitations in the permission granted from the Danish Patient Safety Authorities.

ORCID

Mille Taagaard https://orcid.org/0000-0003-3119-017X
Ane Lilleøre Rom https://orcid.org/0000-0003-2474-2677

REFERENCES

1. Zafeiri A, Mitchell RT, Hay DC, Fowler PA. Over-the-counter analgesics during pregnancy: a comprehensive review of global prevalence and offspring safety. *Hum Reprod Update*. 2021;27(1):67-95. doi:10.1093/humupd/dmaa042
2. Liew Z, Ernst A. Intrauterine exposure to acetaminophen and adverse developmental outcomes: epidemiological findings and methodological issues. *Curr Environ Health Rep*. 2021;8(1):23-33. doi:10.1007/s40572-020-00301-5
3. Bauer AZ, Kriebel D, Herbert MR, Bornehag CG, Swan SH. Prenatal paracetamol exposure and child neurodevelopment: a review. *Horm Behav*. 2018;101:125-147. doi:10.1016/j.yhbeh.2018.01.003
4. Ersbøll AS, Hedegaard M, Damm P, Johansen M, Tabor A, Hegaard HK. Changes in the pattern of paracetamol use in the periconception period in a Danish cohort. *Acta Obstet Gynecol Scand*. 2015;94(8):898-903. doi:10.1111/aogs.12667
5. Petersen TG, Liew Z, Andersen AMN, et al. Use of paracetamol, ibuprofen or aspirin in pregnancy and risk of cerebral palsy in the child. *Int J Epidemiol*. 2018;47(1):121-130. doi:10.1093/ije/dyx235
6. Bisson DL, Newell SD, Laxton C, Royal College of Obstetricians and Gynaecologists. Antenatal and postnatal analgesia: scientific impact paper no. 59. *BJOG*. 2019;126(4):e114-e124. doi:10.1111/1471-0528.15510
7. 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(6):1702-1713. doi:10.1093/ije/dyt183
8. Eyers S, Weatherall M, Jefferies S, Beasley R. Paracetamol in pregnancy and the risk of wheezing in offspring: a systematic review and meta-analysis. *Clin Exp Allergy*. 2011;41(4):482-489. doi:10.1111/j.1365-2222.2010.03691.x
9. Ernst A, Brix N, Lauridsen LLB, et al. Acetaminophen (paracetamol) exposure during pregnancy and pubertal development in boys and girls from a nationwide puberty cohort. *Am J Epidemiol*. 2019;188(1):34-46. doi:10.1093/aje/kwy193
10. Liew Z, Ritz B, Virk J, Olsen J. Maternal use of acetaminophen during pregnancy and risk of autism spectrum disorders in childhood: a Danish national birth cohort study. *Autism Res*. 2016;9(9):951-958. doi:10.1002/aur.1591
11. Liew Z, Ritz B, Rebordosa C, Lee PC, Olsen J. Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. *JAMA Pediatr*. 2014;168(4):313-320. doi:10.1001/jamapediatrics.2013.4914
12. Alemany S, Avella-García C, Liew Z, et al. Prenatal and postnatal exposure to acetaminophen in relation to autism spectrum and attention-deficit and hyperactivity symptoms in childhood: meta-analysis in six European population-based cohorts. *Eur J Epidemiol*. 2021;36(10):993-1004. doi:10.1007/s10654-021-00754-4
13. Rebordosa C, Kogevinas M, Sørensen 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
14. Zafeiri A, Raja EA, Mitchell RT, Hay DC, Bhattacharya S, Fowler PA. Maternal over-the-counter analgesics use during pregnancy and adverse perinatal outcomes: cohort study of 151 141 singleton pregnancies. *BMJ Open*. 2022;12(5):e048092. doi:10.1136/bmjopen-2020-048092
15. Holm JB, Mazaud-Guittot S, Danneskiold-Samsøe NB, et al. Intrauterine exposure to paracetamol and aniline impairs female reproductive development by reducing follicle reserves and fertility. *Toxicol Sci*. 2016;150(1):178-189. doi:10.1093/toxsci/kfv332
16. Dean A, van den Driesche S, Wang Y, et al. Analgesic exposure in pregnant rats affects fetal germ cell development with intergenerational reproductive consequences. *Sci Rep*. 2016;6(1):19789. doi:10.1038/srep19789
17. Bauer AZ, Swan SH, Kriebel D, et al. Paracetamol use during pregnancy—a call for precautionary action. *Nat Rev Endocrinol*. 2021;17(12):757-766. doi:10.1038/s41574-021-00553-7
18. Rom AL, Wu CS, Olsen J, Jawaheer D, Hetland ML, Mørch LS. Parental rheumatoid arthritis and autism spectrum disorders in offspring: a Danish nationwide cohort study. *J Am Acad Child Adolesc Psychiatry*. 2018;57(1):28-32.e1. doi:10.1016/j.jaac.2017.10.002
19. Rom AL, Wu CS, Olsen J, et al. Parental rheumatoid arthritis and long-term child morbidity: a nationwide cohort study. *Ann Rheum Dis*. 2016;75(10):1831-1837. doi:10.1136/annrheumdis-2015-208072
20. Andersen SL, Andersen S, Vestergaard P, Olsen J. Maternal thyroid function in early pregnancy and child neurodevelopmental disorders: a Danish nationwide case-cohort study. *Thyroid*. 2018;28(4):537-546. doi:10.1089/thy.2017.0425
21. Jølving LR, Nielsen J, Beck-Nielsen SS, et al. The association between maternal chronic inflammatory bowel disease and long-term health outcomes in children—a nationwide cohort study. *Inflamm Bowel Dis*. 2017;23(8):1440-1446. doi:10.1097/MIB.0000000000001146
22. Jølving LR, Nielsen J, Kesmodel US, Nielsen RG, Beck-Nielsen SS, Nørgård BM. Prevalence of maternal chronic diseases during pregnancy—a nationwide population based study from 1989 to 2013. *Acta Obstet Gynecol Scand*. 2016;95(11):1295-1304. doi:10.1111/aogs.13007
23. De Wolff MG, Johansen M, Rom AL, Midtgaard J, Tabor A, Hegaard HK. Degree of pregnancy planning and recommended pregnancy planning behavior among women with and without chronic medical conditions—a large hospital-based cross-sectional study. *Acta Obstet Gynecol Scand*. 2021;100(6):1051-1060. doi:10.1111/aogs.14069

24. de Castro CT, Pereira M, Dos Santos DB. Association between paracetamol use during pregnancy and perinatal outcomes: prospective NISAMI cohort. *PLoS ONE*. 2022;17(4):e0267270. doi:10.1371/journal.pone.0267270
25. Rebordosa C, Kogevinas M, Horváth-Puhó E, et al. Acetaminophen use during pregnancy: effects on risk for congenital abnormalities. *Am J Obstet Gynecol*. 2008;198(2):178.e1-178.e7. doi:10.1016/j.ajog.2007.08.040
26. Copenhagen Municipality. Status på København 2022. https://www.kk.dk/sites/default/files/2022-08/Status%20på%20København%202022.pdf. Published 2022. Accessed April 7, 2023.
27. Danish Health Authority. Begræns recepter på store pakninger af smertestillende håndkøbsmedicin. https://www.sst.dk/da/udgivelser/2013/rationel-farmakoterapi-7-2013/begraens-recepter-paa-store-pakninger-af-smertestillende-haandkoebsmedicin. Published 2013. Accessed July 15, 2022.
28. Zahle M. Ipren eller panodil? Disse hovedpinepiller kan du dø af Jyllands-Posten. https://jyllands-posten.dk/livsstil/familiesundhed/ECE9436402/professor-ibuprofen-fordobler-risikoen-for-blodprop-i-hjertet/. Published March 16, 2017. Accessed September 6, 2022.
29. Ray-Griffith SL, Wendel MP, Stowe ZN, Magann EF. Chronic pain during pregnancy: a review of the literature. *Int J Womens Health*. 2018;10:153-164. doi:10.2147/IJWH.S151845
30. IsHak WW, Wen RY, Naghdechi L, et al. Pain and depression: a systematic review. *Harv Rev Psychiatry*. 2018;26(6):352-363. doi:10.1097/HRP.0000000000000198
31. Østensen M, Andreoli L, Brucato A, et al. State of the art: reproduction and pregnancy in rheumatic diseases. *Autoimmun Rev*. 2015;14(5):376-386. doi:10.1016/j.autrev.2014.12.011
32. Götestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis*. 2016;75(5):795-810. doi:10.1136/annrheumdis-2015-208840
33. Aukes AM, Yurtsever FN, Boutin A, Visser MC, de Groot CJM. Associations between migraine and adverse pregnancy outcomes: systematic review and meta-analysis. *Obstet Gynecol Surv*. 2019;74(12):738-748. doi:10.1097/OGX.0000000000000738
34. Amundsen S, Øvrebø TG, Amble NMS, Poole AC, Nordeng H. Use of antimigraine medications and information needs during pregnancy and breastfeeding: a cross-sectional study among 401 Norwegian women. *Eur J Clin Pharmacol*. 2016;72(12):1525-1535. doi:10.1007/s00228-016-2127-9
35. Maggioni F, Alessi C, Maggino T, Zanchin G. Headache during pregnancy. *Cephalalgia*. 1997;17(7):765-769. doi:10.1046/j.1468-2982.1997.1707765.x
36. Killion JA, Chambers C, Smith CJF, Bandoli G. Prenatal acetaminophen use in women with autoimmune disorders and adverse pregnancy and birth outcomes. *Rheumatology (Oxford)*. 2022;61(4):1630-1638. doi:10.1093/rheumatology/keab623
37. Littlejohn EA. Pregnancy and rheumatoid arthritis. *Best Pract Res Clin Obstet Gynaecol*. 2020;64:52-58. doi:10.1016/j.bpobgyn.2019.09.005
38. de Man YA, Dolhain RJEM, van de Geijn FE, Willemsen SP, Hazes JMW. Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. *Arthritis Rheum*. 2008;59(9):1241-1248. doi:10.1002/art.24003
39. Ingstrup KG, Liu X, Gasse C, Debost JCP, Munk-Olsen T. Prescription drug use in pregnancy and variations according to prior psychiatric history. *Pharmacoepidemiol Drug Saf*. 2018;27(1):105-113. doi:10.1002/pds.4355
40. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data resource profile: the Danish National Prescription Registry. *Int J Epidemiol*. 2017;46(3):798-798f. doi:10.1093/ije/dyw213
41. Bliddal M, Liew Z, Pottegård A, Kirkegaard H, Olsen J, Nohr EA. Examining nonparticipation in the maternal follow-up within the Danish National Birth Cohort. *Am J Epidemiol*. 2018;187(7):1511-1519. doi:10.1093/aje/kwy002
42. Black E, Khor KE, Kennedy D, et al. Medication use and pain management in pregnancy: a critical review. *Pain Pract*. 2019;19(8):875-899. doi:10.1111/papr.12814
43. Hegaard HK, Hedegaard M, Damm P, Ottesen B, Petersson K, Henriksen TB. Leisure time physical activity is associated with a reduced risk of preterm delivery. *Am J Obstet Gynecol*. 2008;198(2):180.e1-180.e5. doi:10.1016/j.ajog.2007.08.038

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Taagaard M, Rode L, de Wolff MG, et al. Paracetamol use prior to and in early pregnancy: Prevalence and patterns among women with and without chronic medical diseases. *Br J Clin Pharmacol*. 2023;89(8):2582-2591. doi:10.1111/bcp.15732