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ABSTRACT

Introduction: Bisphenol A (BPA) is frequently used in the production of plastics. It is an endocrine disruptor, and BPA exposure in mice has been associated with reduced offspring growth due to insufficient milk production. However, human studies of associations between BPA exposure and duration of breastfeeding are sparse.
Methods: Pregnant women from the Odense Child Cohort (n = 725) donated a third trimester morning urine sample, which was analyzed for BPA by LC-MS/MS. Information about duration of exclusive and any breastfeeding was obtained through questionnaires three and 18 months postpartum, and a subgroup of women responded to weekly text messages about breastfeeding. Associations between pregnancy BPA exposure and duration of breastfeeding were analyzed using Cox regression adjusting for potential confounders.
Results: The median urine BPA concentration was 1.29 ng/mL. Compared to women within the lowest tertile of BPA exposure, women in the second and third tertile were slightly more likely to terminate breastfeeding at any given time; HRs (95% CI) were 1.05 (0.87; 1.26) and 1.06 (0.89; 1.27), respectively, and to terminate exclusive breastfeeding at any time up to 20 weeks after birth, HRs (95% CI) were 1.07 (0.88; 1.28) and 1.06 (0.88; 1.27), respectively. However, confidence intervals were also compatible with no effect or even a protective effect.
Discussion: This study indicated that high BPA exposure in pregnancy was associated with shorter duration of breastfeeding. Although our findings were not statistically significant, all estimates were above one suggesting increased risk of early breastfeeding termination with high exposure. Using a single spot morning urine sample to measure BPA has likely caused imprecision as it might not adequately reflect long term exposure. Future studies should consider measuring BPA more than once, including other timepoints during pregnancy and after birth.

1. Introduction

Breastfeeding has beneficial effects both for the mother and the child (Chung et al., 2007). It strengthens the immune system and protects the child against diarrhea, respiratory infections, otitis media, and sudden infant death syndrome (Chung et al., 2007; Hauck et al., 2011). In addition, breastfeeding is associated with reduced risk of breast and ovary cancer in the mother (Chowdhury et al., 2015). The World Health Organization (WHO) recommends exclusive breastfeeding for the first six months postpartum and partly breastfeeding for two years or more (World Health Organization, 2009), and the Danish Health Authorities recommends introduction of solid food at age 4–6 months (Sundhedsstyrelsen, 2018). However, only 61% of Danish mothers exclusively breastfed their child four month postpartum, and in the United States only 25.6% of mothers breastfed their children exclusively for six months (Center for Disease Control and Prevention, 2020; Pommerencke et al., 2020). Early weaning can be ascribed to biology, psychology, demography and social factors (Thulier and Mercer, 2009a), but

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several studies have shown that one of the most common reasons for cessation of breastfeeding is insufficient milk production (Ahluwalia et al., 2005; Li et al., 2008; Wambach et al., 2005). Sufficient milk supply depends on the development of the breast, which occurs from prenatal life throughout puberty, gestation and lactation (Barbieri, 2019; Perrot-Applanat et al., 2018). In utero and early post-natal life the ductal system is founded mostly independently of hormones, and the ducts are elongated and branches during puberty (Barbieri, 2019). During pregnancy further branching occurs and secretory cells are developed, and after giving birth the production and secretion of milk is initiated (Perrot-Applanat et al., 2018). The mammary gland development in puberty, gestation and lactation is regulated by hormones including estrogen (Barbieri, 2019; Watson and Khaled, 2008).

Bisphenol A (BPA) is a non-persistent chemical produced in large quantities worldwide to make polycarbonate plastics and epoxy resins (Rubin, 2011). It is found in a variety of consumer products including storage plastic containers, food can linings, thermal paper receipts, medical equipment, dental sealants and toys (Rubin, 2011). Humans are primarily exposed through diet (Geens et al., 2012; Rubin, 2011). BPA is an endocrine disruptor that can bind and activate estrogen receptors e.g. in the mammary glands (Perrot-Applanat et al., 2018; Vandenberg et al., 2007), although with much lower affinity than estradiol (Kuiper et al., 1998). BPA seems to affect mammary gland development in rodents (Criswell et al., 2020), and in mice, gestational exposure to BPA has been associated with reduced offspring growth after birth due to insufficient supply of breast milk (Matsumoto et al., 2004). In a small Mexican study (n = 218), no significant association was found between BPA exposure and breastfeeding, but women with higher BPA exposure during pregnancy had higher odds of having weaned one month postpartum (Kasper et al., 2016). The aim of the present study was therefore to investigate the association between BPA excretion in urine in gestational week 28 and duration of breastfeeding in a larger cohort of Danish women.

2. Methods

2.1. Study population

Between January 2010 and December 2012, all pregnant women living in the municipality of Odense were invited to participate in the Odense Child Cohort (OCC) before gestational week 16 (Kyhl et al., 2015). A total of 6707 pregnant women were eligible, and 2874 women (48%) agreed to participate (Kyhl et al., 2015). The women who participated were older, more often non-smokers and more educated than non-participants (Kyhl et al., 2015). In third trimester, the women were invited for an examination including donation of a urine sample. The examinations were performed in the morning, and the women were fasting from the night before. During pregnancy, the women answered two questionnaires, from which information about educational level, pre-pregnancy body mass index (BMI) and smoking during pregnancy was obtained. In addition, date of birth, and duration of gestation were obtained from medical records. Women giving birth to twins were excluded from the study, but 10 women were included twice with pairs of siblings.

2.2. Breastfeeding

All women were asked to complete questionnaires at three and 18 months postpartum including questions about duration of exclusive and any breastfeeding (Kyhl et al., 2015). Exclusive breastfeeding was defined as breastmilk being the only source of nutrition with the exception of formula in the first two weeks postpartum as well as once per week during the rest of the breastfeeding period. Duration of any breastfeeding was defined as the sum of time with breastfeeding, either exclusive or partial. Women who gave birth between April 2012 and October 2013 (N = 499) additionally responded to weekly text messages indicating whether they were still breastfeeding, and whether supplementary formula and solid foods were introduced (Bruun et al., 2016). The first text message was sent three days postpartum and the weekly text messages continued until the child was no longer breastfed (Bruun et al., 2017). The estimated duration of any breastfeeding based on questionnaires was fairly close to the estimated duration based on text messages, whereas the estimated duration of exclusive breastfeeding was longer when based on questionnaires compared to text messages (Bruun et al., 2017). Due to the timing and frequency of the text messages, we considered the answers from text messages to be more reliable than answers from the questionnaires. Thus, we used information about breastfeeding duration from the text messages when available and otherwise supplemented with information from the questionnaires. A total of 2222 women provided information about duration of exclusive breastfeeding (46% through text messages) and 1967 women provided information about duration of any breastfeeding (47% through text messages).

In Denmark, a health visitor routinely visits all families with newborns within the first two weeks after birth as well as approximately two, five and nine months postpartum, and additional visits are planned if required. The health visitor assesses and advise on child growth, breastfeeding, and general child health. To identify women who weaned early due to reasons other than insufficient milk supply, two of the authors (AM and LH) reviewed 180 health visitor records from women who weaned within 16 weeks postpartum. Reasons other than insufficient milk supply could be previous breast surgery or illness in the mother or child. For 14 women, the registered duration of exclusive and/or any breastfeeding was corrected due to discrepancies following the health visitor's information.

2.3. Bisphenol A

BPA was measured in 846 morning urine samples from gestational week 28 (median 28.2, range 26.4–34.0). The urine samples were deconjugated by enzymatic hydrolysis and the sum of deconjugated and free BPA content was measured using isotope dilution TurboFlow-LC-MS/MS as described in detail elsewhere (Frederiksen et al., 2013). All BPA result have previously been reported (Frederiksen et al., 2014). The measured BPA concentrations were adjusted for the osmolality of the urine: each BPA concentration was multiplied with the ratio of the median osmolality of all samples divided by the osmolality of the sample (Jensen et al., 2019). Osmolality of the urine samples was measured by the freezing point depression method using an automatic cryoscopic osmometer. The limit of detection (LOD) for BPA measured in urine was 0.12 ng/mL (Frederiksen et al., 2013). BPA concentrations under LOD were replaced by dividing LOD with the square root of 2.

2.4. Statistical analysis

The median, 25th and 75th percentile of BPA, exclusive- and any breastfeeding were compared across groups of maternal characteristics. Differences were tested using Kruskal-Wallis for characteristics with more than two categories and Wilcoxon Rank-sum test for characteristics with two categories. As 15.4% of the women had BPA concentrations below LOD, BPA was divided into tertiles. The associations between BPA exposure and duration of exclusive- and any breastfeeding were examined in Kaplan-Meier survival plots and using Cox regression. The underlying time variable was weeks from birth to weaning. For the women who breastfed for less than one week, the duration of breastfeeding was set to 0.01 week.

Using a directed acyclic graph (DAG) based on a priori knowledge (Fig. 1), age (continuous), educational level (≤high school, high school + 1–4 years, high school + >4 years), and BMI (≤18.4, 18.5–24.9, 25–29.9, ≥30) were identified as potential confounders, while preterm birth was identified as a mediator, and these four variables were included in the adjusted Cox model.

When examining associations with any breastfeeding, hazards were

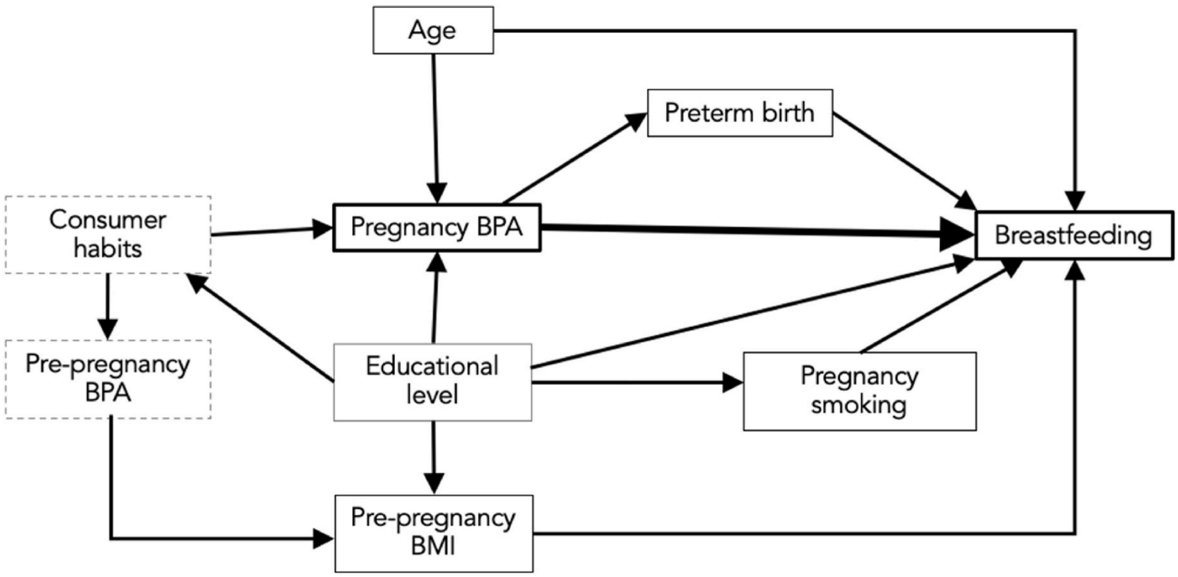

Fig. 1. Directed Acyclic Graph showing the hypothesized association between maternal BPA exposure, breastfeeding duration, and potential confounders. The association of interest in this study is marked with a fat arrow, and unmeasured variables are shown in dotted boxes.

non-proportional for educational level and BMI, and the adjusted cox models were therefore stratified based on educational level and BMI. Furthermore, non-proportional hazards were found for the third compared to the first tertile of BPA exposure in relation to exclusive breastfeeding, and consequently, these analyses were also performed examining breastfeeding up to 20 weeks only.

As the information about exclusive breastfeeding in OCC questionnaires have been shown to deviate from the information provided in text messages (Bruun et al., 2017), we also ran the analyses using information about duration of exclusive breastfeeding from text messages only. Finally, to minimize misclassification, we ran all analyses censoring women who weaned early due to reasons other than insufficient milk supply or if reasons for early weaning was not provided in the health visitor record. All regression analyses were performed with cluster-robust standard errors for dependence between women being included twice with siblings. All analyses were performed in STATA 16.1 (StataCorp, College Station, TX), using a significance level of 5%.

2.5. Ethics

The data from the OCC was collected in accordance with the Declaration of Helsinki II. The OCC has further been approved by the Regional Scientific Ethical Committee for Southern Denmark (application no. S-20090130). All the participating women gave written consent

Table 1
Participant characteristics according to median (25th – 75th percentile) BPA (ng/mL) and weeks of exclusive- and any breastfeeding.

Maternal characteristics	Maternal (BPA ng/mL[a])		Exclusive breastfeeding (weeks)		Any breastfeeding (weeks)	
	N	Median (25–75 percentile)	N	Median (25–75 percentile)	N	Median (25–75 percentile)
All	725	1.29 (0.52–2.33)	724	11 (2–19)	658	33 (17–47)
Age, years						
<25	91	1.29 (0.52–2.69)	91	9 (2–19)	77	26 (8–49)
25–34.9	530	1.26 (0.52–2.35)	529	11 (2–19)	489	33 (18–46)
≥35	104	1.39 (0.52–2.13)	104	10 (1–20)	92	35.5 (23–52)
p-value[b]		*0.92*		*0.77*		*0.07*
Education level						
≤ High school	203	1.40 (0.54–2.36)	203	8 (1–16)	179	26 (8–45)
High school + 1–4 years	374	1.26 (0.54–2.43)	373	11 (3–20)	340	34 (20–46)
High school + >4 years	148	1.25 (0.42–2.00)	148	12 (2–21)	139	36 (24–51)
p-value[b]		*0.43*		*<0.01*		*<0.01*
BMI, pre-pregnancy						
≤18.4	19	1.28 (0.44–1.74)	19	14 (9–20)	17	33 (33–49)
18.5–24.9	418	1.23 (0.43–2.22)	417	11 (3–20)	387	36 (20–49)
25–29.9	197	1.44 (0.66–2.43)	197	10 (2–19)	172	32 (15.5–43.5)
≥30	91	1.42 (0.62–2.76)	91	5 (0–13)	82	18 (4–39)
p-value[b]		*0.18*		*<0.01*		*<0.01*
Smoking during pregnancy						
Yes	26	1.25 (0.69–2.64)	26	3.5 (0–13)	24	17 (4–30.5)
No	699	1.29 (0.52–2.31)	698	11 (2–19)	634	34 (17–48)
p-value[b]		*0.54*		*0.017*		*<0.01*
Preterm birth						
Yes	33	1.13 (0.69–2.13)	33	10 (0–20)	32	23 (10–41)
No	692	1.29 (0.51–2.35)	691	11 (2–19)	626	34 (17–47)
p-value[b]		*0.90*		*0.76*		*0.055*

[a] Osmolality adjusted BPA measured in an overnight fasting morning spot urine sample from third trimester.
[b] P-value obtained using Wilcoxon Rank-sum test for characteristics with two categories and Kruskal-Wallis for characteristics with more than two categories.

after receiving oral and written information.

3. Results

Among the 2874 women, 725 had BPA measured in a morning spot urine sample and answered questions about duration of breastfeeding. The median BPA concentration in urine was 1.29 ng/mL, and the median duration of exclusive- and any breastfeeding was 11 and 33 weeks, respectively. Women who were non-smokers, had lower BMI, and longer education typically breastfed longer (Table 1).

3.1. *Any breastfeeding*

Women within the higher tertiles of BPA exposure were slightly more likely to terminate any breastfeeding at any given time (Fig. 2). After adjustment for age, educational level, pre-pregnancy BMI and preterm birth, women in the second and third tertile of BPA exposure had a 5% (95% CI: 13; 26%) and 6% (95% CI: 11; 27%), respectively, higher hazard of terminating any breastfeeding, compared to women with BPA concentrations in the lowest tertile (Table 2). Censoring of women (n = 105) who terminated breastfeeding due to reasons other than insufficient milk production, and women for whom reasons for termination were not provided, did not substantially change the findings (Table 2).

3.2. *Exclusive breastfeeding*

Overall, women with BPA concentrations in the second and third tertile were *less* likely to terminate exclusive breastfeeding at any time (Table 2). However, before 20 weeks of breastfeeding, women in the second and third tertile were slightly *more* likely to terminate exclusive breastfeeding (Fig. 3). After adjustment, women in the second and third tertile of BPA exposure had 7% (95% CI: 12; 28%) and 6% (95% CI: 12; 27%), respectively, higher hazard of terminating exclusive breastfeeding, compared to women with BPA concentrations in the lowest tertile (Table 2). In sensitivity analyses, higher hazards were found among women who reported duration of exclusive breastfeeding from the text messages only. However, none of the associations were statistically significant. Censoring of women who terminated breastfeeding due to reasons other than insufficient milk production, and women for whom reasons for termination were not provided, did not substantially change the findings (Table 2).

4. Discussion

Among 725 Danish women, BPA measured in a morning spot urine sample in third trimester of pregnancy was associated with a slightly increased risk of weaning at any given time, although not significant. To our knowledge, only one other study on BPA and breastfeeding has been published (Kasper et al., 2016). In accordance with our findings, third trimester urinary BPA in the second and third tertile was non-significantly associated with higher odds of having weaned one month postpartum among 216 Mexican women (Kasper et al., 2016).

In rodents, in utero BPA exposure has been associated with changes in mammary tissue (Markey et al., 2001; Vandenberg et al., 2007), and Kass et al. (2012) showed that the female offspring of Wistar rats exposed to high doses of BPA during gestation and lactation (perinatally) had lower production of milk (Kass et al., 2012). However, reduced production of milk was not seen at lower exposures (Lakind and Naiman, 2011), whereas the composition of the milk was affected even at low exposure (Kass et al., 2012). Likewise, Altamirano et al. (2015) found that perinatal BPA exposure of F0 rats modified milk quality among F1 females and growth among F2 pups (Altamirano et al., 2015). However, these rodents were exposed in utero when ducts are founded whereas we studied BPA exposure in adult life during pregnancy. To our knowledge, the effects of gestational BPA exposure on mammary gland development among the exposed animals have not been examined. However, high level BPA exposure in pregnant mice has been associated with reduced offspring growth, which was ascribed to insufficient supply of breast milk (Matsumoto et al., 2004), and other endocrine disrupting chemicals have been shown to affect mammary gland development in gestation (Criswell et al., 2020). BPA has long been known to have estrogenic properties as it can bind to and activate estrogen receptors (Rubin, 2011; Vom Saal and Vandenberg, 2021), and it is possible that BPA exposure in pregnancy could affect the hormonally regulated branching of the ductal system and development of secretory cells, but experimental studies are needed to examine the mechanisms by which gestational BPA exposure might affect lactation.

The median third trimester morning urine BPA concentration among

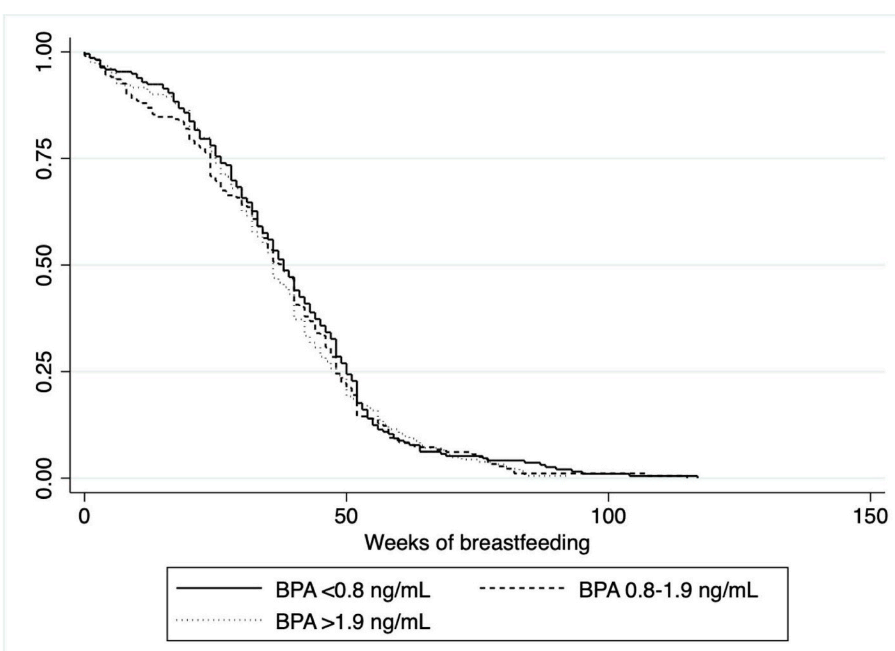

Fig. 2. Kaplan-Meier curve for any breastfeeding by BPA tertiles.

Table 2
Cox regression for the association between urinary BPA excretion in week 28 and breastfeeding duration.

	BPA concentration (ng/mL)	Exclusive breastfeeding HR (95% CI)	Exclusive breastfeeding up to 20 weeks HR (95% CI)	Exclusive breastfeeding up to 20 weeks, only SMS data HR (95% CI)	Any breastfeeding HR (95% CI)
		n = 724	n = 724	n = 282	n = 658
Crude	<0.79	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	0.79–1.87	0.98 (0.84; 1.15)	1.08 (0.90; 1.30)	1,24 (0.94; 1.65)	1.08 (0.90; 1.31)
	>1.87	0.96 (0.82; 1.13) [c]	1.05 (0.88; 1.27)	1.19 (0.87; 1.62)	1.09 (0.91; 1.31)
Adjusted[a]	<0.79	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	0.79–1.87	0.98 (0.83; 1.15)	1.07 (0.88; 1.28)	1.23 (0.92; 1.63)	1.05 (0.87; 1.26)
	>1.87	0.96 (0.82; 1.14)	1.06 (0.88; 1.27)	1.21 (0.89; 1.65)	1.06 (0.89; 1.27)
Censured[a,b]	<0.79	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	0.79–1.87	0.97 (0.82; 1.16)	1.08 (0.88; 1.33)	1.28 (0.93; 1.77)	1.05 (0.86; 1.28)
	>1.87	0.96 (0.80; 1.15) [c]	1.07 (0.87; 1.31)	1.13 (0.80; 1.60)	1.07 (0.89; 1.30)

[a] Adjusted for maternal age (continuous), educational level (≤high school, high school + 1–4 years, high school + >4 years), preterm birth (yes/no) and pre-pregnancy BMI (≤18.4 + 18.5–24.9 + 25–29.9 + ≥30).
[b] Women were censured at the time of termination if termination was due to reasons other than insufficient milk supply or when no reason for termination was given in the health visitor records.
[c] Hazards were non-proportional.

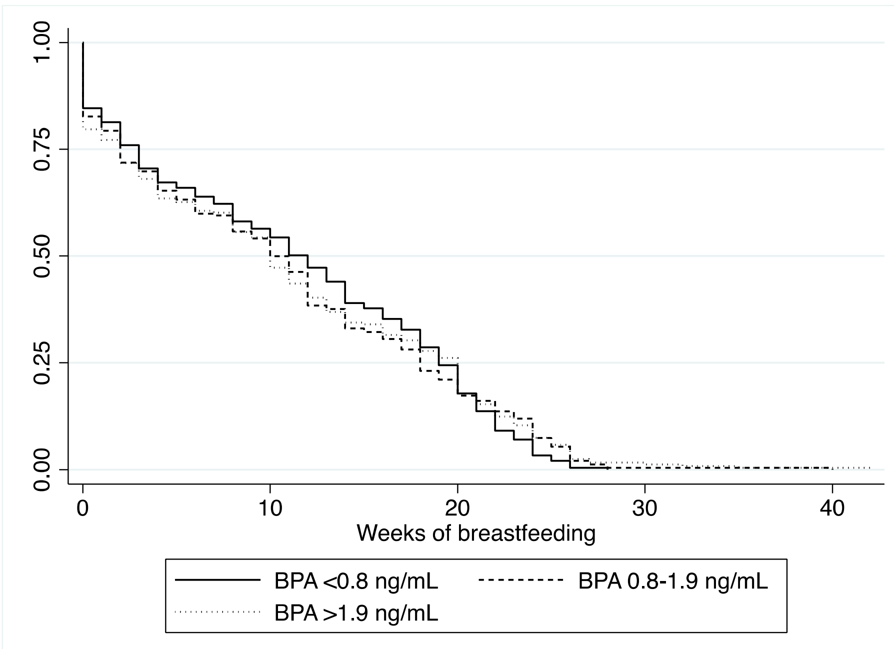

Fig. 3. Kaplan-Meier curve for exclusive breastfeeding by BPA tertiles.

the pregnant women in our study was 1.29 ng/mL, which is higher than the mean BPA concentration of 1.07 ng/mL among Mexican women who were breastfeeding one month postpartum but lower than the mean BPA concentration of 1.42 among Mexican women who were not breastfeeding one month postpartum (Kasper et al., 2016). Furthermore, BPA concentrations in our study were slightly lower than among 191 pregnant French women with a median urinary BPA concentration of 2.7 ng/mL (Philippat et al., 2012), and among 479 pregnant Spanish women with a median urinary BPA concentration of 1.8 ng/mL (Casas et al., 2013). In the French study, urine was collected once, whereas spot urine samples were collected twice in the Spanish study with no indication of time of the day. In the present study, BPA was measured in a fasting morning urine sample, which might partly explain the low exposure levels compared to other European women. The women in our study will not have been exposed to dietary BPA in the hours before sampling, and in third trimester of pregnancy it is not uncommon to urinate during the night, which will have lowered their BPA urine concentration in the morning.

Strengths of this study includes the prospective design, the large study population, and the precision of the breastfeeding measure was increased by obtaining weekly text messages from a subgroup of women. Furthermore, we had detailed information available about potential confounders including pre-pregnancy BMI, maternal age, and education which are known to be associated with breastfeeding (Thulier and Mercer, 2009b; Wojcicki, 2011). BPA exposure has been associated with preterm birth (Mustieles et al., 2020), which may act is a mediator between BPA exposure and breastfeeding, and models were therefore also adjusted for preterm birth to identify the direct effect of BPA on breastfeeding.

The study, however, also has limitations. BPA has a half-life between 5.4 and 21.4 h (Sasso et al., 2020; Völkel et al., 2002) and although we are continuously exposed, the exposure will vary over time. The within-person variability of BPA has previously been shown to be high (Lassen et al., 2013), meaning that BPA measured in a single urine sample might not adequately reflect long-term BPA exposure. Still, BPA measured in a single sample has some predictive value of exposure over time, since exposure patterns often stay the same. To increase the reliability, analyses of more than a one urine sample would have been preferable. Furthermore, we measured BPA during third trimester, and the most sensitive window of exposure could also be prenatally, during puberty, earlier in pregnancy or even after pregnancy when initiating and maintaining breastfeeding.

Among some of the women in our study, information about duration of breastfeeding was provided 18 months postpartum at which point, details about breastfeeding and introduction of supplementary formula or food might be difficult to recall. However, as the women were unaware of their BPA exposure, any misclassification is likely non-differential. Likewise, measuring BPA only once in a morning spot urine sample is likely to have caused non-differential misclassification of the BPA exposure. The non-differential misclassification could have led to bias towards the null and thus contributed to the non-significant findings.

The women in the OCC are better educated and less likely to smoke compared to the background population (Kyhl et al., 2015). However, we would not expect this selection to have affected the association between BPA exposure and breastfeeding duration.

Hazards of terminating exclusive breastfeeding were non-proportional, and the hazards crossed around 20 weeks, which is most likely because Danish women are encouraged to introduce solid foods, when the child is between four and six months old. Thus, when we examined the risk of terminating exclusive breastfeeding before 20 weeks only, we found associations similar to those seen for termination of any breastfeeding. Furthermore, median duration of exclusive breastfeeding in our cohort (11 weeks) was shorter than in Odense municipality in 2012 (17.6 weeks) (Esundhed, 2019), and information about exclusive breastfeeding based on questionnaires in the OCC have been shown to deviate from the information based on text messages (Bruun et al., 2017). These limitations of the questionnaire data might explain why we found stronger associations between BPA and duration of exclusive breastfeeding, when limiting the analyses to data from text messages.

5. Conclusion

In this cohort of 725 women, we found that pregnant women in third trimester with the highest BPA exposure had slightly increased risks of terminating exclusive breastfeeding at any time up to 20 weeks after birth and terminating any breastfeeding at any given time. The associations were, however, not statistically significant. Some imprecision is inevitable in observational studies, but despite the limitations, we need epidemiological studies to understand how environmental chemicals affect human health. By combining new knowledge from experimental animal studies and observational epidemiological studies, we can hope to fill the gaps in the current knowledge about endocrine disrupting chemicals and breastfeeding duration.

Future epidemiological studies should consider collecting more than one sample, including other timepoints during pregnancy and after birth, to obtain more reliable BPA measurements, and additionally measure BPA in breast milk.

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Authors' contributions

Agnethe Mehlsen: Data curation, Formal analysis, Writing – original draft, Lærke Høllund: Data curation, Formal analysis, Writing – original draft, Henriette Boye: Data curation, Writing – review and editing, Hanne Frederiksen: Methodology, Writing – review and editing, Anna-Maria Andersson: Methodology, Writing – review and editing, Signe Bruun: Data curation, Writing – review and editing, Steffen Husby: Funding acquisition, Writing – review and editing, Tina Kold Jensen: Funding acquisition, Writing – review and editing, Clara Amalie Gade Timmermann: Conceptualization, Data curation, Writing – review and editing.

Declaration of competing interest

The authors have no actual or potential competing financial interests.

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