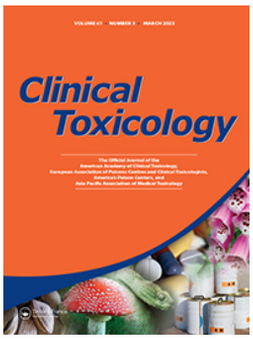

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Clinical characteristics of hospitalized patients with paracetamol poisoning before and after restrictions of over-the-counter sale of paracetamol

Charlotte Uggerhøj Andersen[a,b,c], Steffen Hansen[a], Kim Peder Dalhoff[d,e], Lars Peter Nielsen[a], Jørn Munkhof Møller[f] and Anne Estrup Olesen[a,b]

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ABSTRACT

Introduction: Paracetamol poisoning is a frequent cause of hospitalization in Denmark. On 30 September 2013, the Danish authorities restricted packages available without a prescription in pharmacy outlets to contain a maximum of 10 g of paracetamol. We aimed to investigate the effects of this regulation.

Methods: This was a cross-sectional study of two groups of patients admitted consecutively to a Danish University Hospital due to poisoning with paracetamol in 365 days in 2012–13 before 30 September 2013, and a corresponding 365-day period in 2017–18. Data were extracted from patient records.

Results: In 2012–2013 and 2017–18, 156 and 92 admissions in 127 and 78 unique patients, respectively, were identified. Ingestion of more than 20 g paracetamol occurred in a significantly higher proportion of cases in 2012–13 compared to 2017–18 (29% vs 13%, $P < 0.01$). In accordance, there were no cases of international normalized ratio >1.5 or alanine aminotransferase activity >1000 U/L in the post-legislation period, and seven and five cases in the pre-legislation period, respectively. Females accounted for 80% and 78% of patients in the two periods, respectively, and were considerably younger than males (median [interquartile range]: 22 [17–40] vs. 47 [30–56], $P < 0.01$ in 2012–13, and 23 [18–46] vs. 43 [27–49] years, $P = 0.02$ in 2017–18). Furthermore, in 2012-13, intentional poisonings occurred in a higher proportion of females than males 2012–13 (97% vs 85%, $P < 0.01$).

Conclusions: The present study demonstrated a lower number of paracetamol poisonings, a decreased proportion of poisonings involving ingestion of more than 20 g of paracetamol, and a lower occurrence of hepatotoxicity after the regulation. However, circumstances other than pack size restrictions, such as increased public awareness of the danger of paracetamol poisonings, may affect these associations. Furthermore, the study showed that females and males constitute two distinct groups in terms of age and intentional poisoning.

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Introduction

Paracetamol is the most frequent pharmaceutical involved in poisonings leading to contact with poison information centers [1] and hospitalization [2] in Denmark. An Irish study showed that the number of intentional overdoses with paracetamol increased from 2007–2018 [3], and similarly, a study from Canada showed a sharp increase in intentional overdoses with paracetamol from 2010 to 2015 in young people [4], indicating that paracetamol poisonings constitute an important health issue. Several European countries have implemented paracetamol pack size restrictions in pharmacies and non-pharmacy outlets to reduce harm related to paracetamol overdose [1], which can ultimately lead to fatal liver failure and death. A meta-analysis of the effect of paracetamol pack size restrictions introduced in the United Kingdom (UK) in 1998 showed some indications of reduced severity of paracetamol poisonings after the regulation [5]. In Denmark, the pack size restriction of paracetamol sale to patients without prescription was introduced on 30 September 2013 [6,7]. Before the regulation, people could purchase packages containing up to 300 tablets of 500 mg of paracetamol without a prescription in pharmacies, and packages with 10 tablets with 500 mg in non-pharmacy outlets [6]. With the pack-size restriction, only packages containing a maximum of 10 g of paracetamol could be purchased without a prescription in pharmacies. The restrictions concerned all types of paracetamol tablets, not mixtures or suppositories. The regulation only applied to pack size. More than one pack could still be bought at a time in pharmacies [8].

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A previous registry-based study covering the period 2010–2015 showed that after the regulation, the total number of patients treated for non-opioid analgesic poisonings in Denmark decreased, that the concentration of paracetamol in plasma was lower compared to before 2013 in patients admitted with non-opioid analgesic poisoning and that a lower proportion of patients treated for paracetamol poisoning had severely increased liver enzyme activities [6]. However, information on ingested doses, sex differences, and treatment was not reported [6]. The aim of the present study was to compare the characteristics of patients admitted with paracetamol poisoning at Aalborg University Hospital before and after the regulation in 2013. More specifically, we aimed to examine differences in the distribution of age, sex, and ingested dose of paracetamol, impact on plasma activities of liver enzymes, treatment, and duration of hospital stay.

Methods

The study was designed and reported according to the STROBE statement [9].

Design and identification of patients

This was a cross-sectional study including two groups of patients admitted consecutively to Aalborg University Hospital due to poisoning with paracetamol in 365 days in 2012–13 before 30 September 2013, and a corresponding 365-days period in 2017–18.

To include all cases in the defined period in 2012–13, we searched for patients admitted to all departments of Aalborg University Hospital with the ICD codes DT398A, DT399, DT398, and DT390 (Figure 1). Since 2014, all acute admissions to Aalborg University Hospital are received through the Acute and Trauma Center (A&E Department), except for children, who are admitted through the Pediatric Department. Thus, cases from 2017–2018 were identified by searching for admissions with ICD codes DT398A, DT399, DT398, and DT390 at the A&E Department and the Pediatric Department in the defined period (Figure 1). Some of the cases from 2017-18 were part of a previous study including all drug poisonings admitted to the A&E Department [2]. Translated from Danish, the ICD codes refer to the following: DT398A: poisoning with paracetamol, DT399: poisoning with unspecified weak analgesic DT398: poisoning with other weak analgesic, DT390: poisoning with weak analgesic of a known kind. The records of the resulting lists were reviewed and excluded as illustrated in Figure 1.

Data collection

Data extracted included patients' demographics, comorbidities, the total number of prescribed medications, initial laboratory values, intentional or unintentional overdose, and drugs or medication other than paracetamol contributing to the poisoning, including the total number of involved substances. Comorbidities were recorded by checking pre-specified diseases in the template for data collection shown in Figure S1 in the online supplement. Alcohol use disorder was assigned as a co-morbidity to a specific patient if alcohol use disorder was part of the patient's diagnoses in the patient record. Paracetamol doses ingested in grams based on patient information were also recorded. Initial laboratory values included alanine aminotransferase (ALT) activity, alkaline phosphatase activity, bilirubin concentration, and international normalized ratio (INR). The date of admission, date

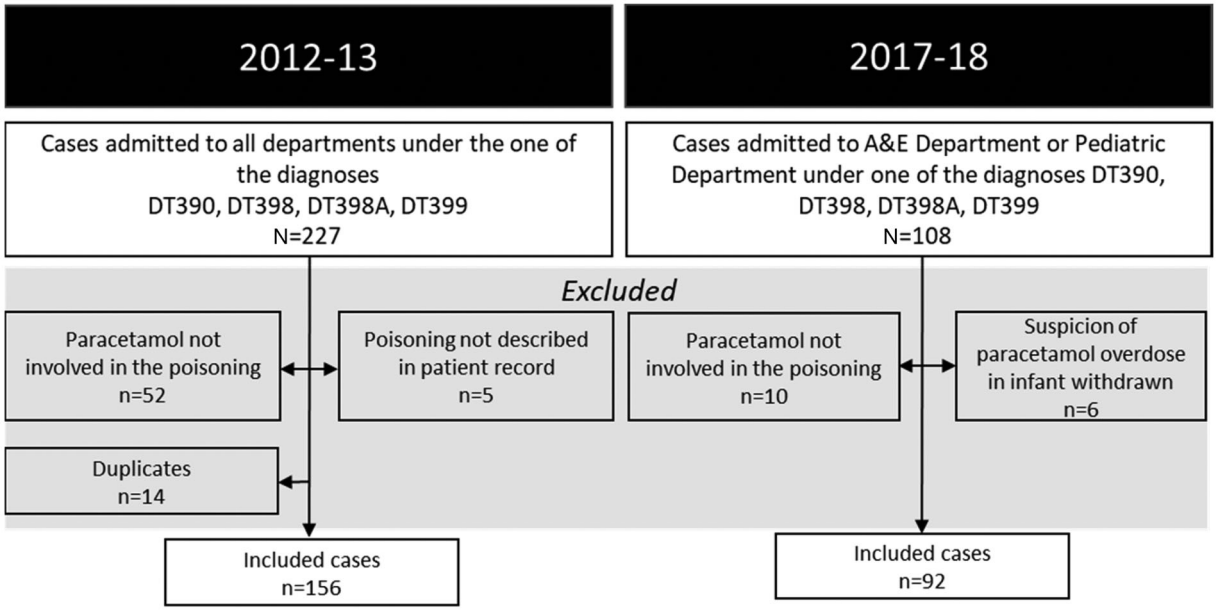

Figure 1. Flow chart of excluded and included cases. We searched the hospital's database for all patients admitted under one of the diagnoses DT390, DT398, DT398A, and DT399 during 365 days in 2012–13 at all departments. Since 2014, all acute admissions to the hospital enter through the Acute and Trauma Center (A&E Department), except for children. Thus, we performed a search in a corresponding 365-day period in 2017–18 at the Pediatric Department and the A&E Department for all patients admitted with ICD-codes DT390, DT398, DT398A, and DT399. Cases in which paracetamol was not involved, or cases appearing twice on the list of search results (duplicates) were excluded, as well as cases where a diagnosis code was used, but suspicion of overdose was withdrawn during the admission. This type of exclusion concerned six infants in 2017–18.

of discharge, and time from ingestion to admission to the hospital was recorded where possible, and the duration of the hospital stay was defined by subtracting the date of admission from the date of discharge. Plasma paracetamol concentration, and the treatment given to the patient (activated charcoal and/or acetylcysteine) were recorded. Of note, our guideline recommends measurement of paracetamol at admission and treatment with acetylcysteine if patient history or other circumstances point towards an ingestion greater than 6 g in general or an ingestion of >4 g in patients with alcohol use disorder or malnutrition [10]. Plasma paracetamol concentrations are reported in both μmol/L and mg/L, with a lower limit of quantification of 7.94 μmol/L (1.2 mg/L).

Data handling, statistical analysis, and reporting

Study data were entered in REDCap (Vanderbilt, USA) electronic data capture tools hosted at Aalborg University [11]. Data were exported in pseudonymized form for statistical analysis in STATA (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC). When the same patient was admitted more than once, each admission was registered as an individual case, because the paracetamol dose and character of the poisoning could differ in the same individual. Demographics of the patients were calculated using only unique cases.

A cut-off value of 20 g was used to define ingestion of a high dose of paracetamol and was based on the 75% percentile of ingested doses in all cases in both periods. Cut-off values for ALT activities were based on the previous study [6]. A cut-off value for an abnormally high INR of 1.5 was chosen as this level is regarded as clinically significant in terms of bleeding risk [12]. Patients using warfarin were excluded from the analysis of INR.

The distribution of variables was evaluated using histograms and Shapiro–Wilk test. None of the analyzed parameters were normally distributed. Non-parametric data were summarized and displayed by medians [inter quartile range]. Differences between groups were tested with Wilcoxon's signed rank test. Binary outcomes were compared by Chi^2-test and reported as a number of cases and percentage (*n* (%)). Missing data were not imputed. If data were not available for all patients in each parameter, the number of available observations is shown. A P-value less than 0.05 was considered statistically significant.

Ethics statement

The study was registered at the Danish Data Protection Agency. In accordance with Danish legislation (Act on Research Ethics Review of Health Research Projects § 14 stk. 2 dated 15 September 2017 and the Danish Health Act § 46 stk. 2 dated 2 November 2018), the Danish Patient Safety Authority approved the project, including the transmission of the data from the patient records. Data were handled in accordance with the General Data Protection Regulation (GDPR) and the Danish Data Protection Act.

Results

Demographics

In 2012–2013 and 2017–18, 156 and 92 admissions (cases) in 127 and 78 unique patients, respectively, were identified (Table 1). The median age was not significantly different between the two periods. The distribution of age is shown in Figure 2. All patients were aged 12 years or older. There was a tendency towards a lower proportion of patients less than 16 years of age in 2017-18, but it was not statistically significant ($P = 0.07$). Approximately half of the patients in both periods had a psychiatric comorbidity. The proportion of patients with multiple admissions during the two respective periods was similar in the two periods (Table 1).

Clinical characteristics

The median recorded ingested dose of paracetamol was equal in the two periods. However, the proportion of cases ingesting more than 20 g of paracetamol was higher in 2012–13 compared to 2017–18 ($P < 0.01$) (Table 2). The distribution of ingested doses is shown in Figure 3.

Table 1. Demographics for all unique patients before (2012–13) and after (2017–18) paracetamol pack size restriction.

		2012–13	2017–18
Unique patients		127	78
Age[a]	years	24 [18–45]	26 [18–48]
Age less than 16 years	*n* (%)	21 (17)	6 (8)
Female sex	*n* (%)	102 (80)	61 (78)
1 admission[b]	*n* (%)	109 (87)	68 (87)
2 admissions[b]	*n* (%)	10 (8)	7 (9)
≥3 admissions[b]	*n* (%)	7 (6)	3 (4)
Any co-morbidity	*n* (%)	70 (55)	54 (70)
Psychiatric comorbidity	*n* (%)	58 (46)	41 (53)
Depression	*n* (%)	25 (20)	12 (15)
Alcohol use disorder	*n* (%)	8 (6)	12 (15)
Personality disorder	*n* (%)	17 (13)	9 (12)
Cardiovascular disease	*n* (%)	5 (4)	8 (10)
Endocrine disease	*n* (%)	4 (3)	5 (6)
Respiratory disease	*n* (%)	7 (6)	7 (9)
Gastrointestinal disease	*n* (%)	5 (4)	8 (10)
Total number of prescribed medications[a]		1 [0–4][c]	2 [0–5][d]

[a]Median [Q_1 – Q_3]
[b]With paracetamol poisoning during the 365-day study period.
[c]Data obtained from n=120
[d]Data obtained from n=76

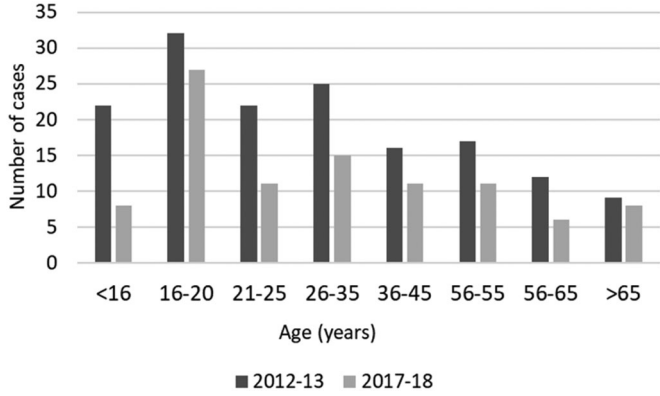

Figure 2. Age distribution among admissions before (2012–13) and after (2017–18) pack size restriction. All patients were aged 12 years or older.

Table 2. Characteristics of cases before (2012–13) and after (2017–18) pack size restriction.

		2012–13		2017–18	
			Data obtained from		Data obtained from
Number of cases		156		92	
Ingested dose of paracetamol[a]	g	12.5 [9–25]	$n = 139$	12.50 [8–17.5]	$n = 83$
Ingesting > 20 g	*n* (%)	40 (29)	$n = 139$	11 (13)	$n = 83$
Intentional overdose	*n* (%)	146 (95)	$n = 153$	87 (95)	$n = 92$
Time from ingestion to admission	h	3.5 [2–6]	$n = 111$	3.25 [2–5]	$n = 59$
Arriving more than 8 hours after ingestion	*n* (%)	20 (18)	$n = 111$	7 (12)	$n = 59$
Number of different drugs ingested[a]	*n*	1 [1–2]	$n = 156$	1 [1–2]	$n = 92$
ALT activity	U/L	19 [13–30]	$n = 156$	16 [12–25]	$n = 92$
ALT activity > 210 U/L	*n* (%)	6 (4)	$n = 156$	<3	$n = 92$
ALT activity > 1000 U/L	*n* (%)	5 (3)	$n = 156$	0 (0)	$n = 92$
INR> 1.5	*n* (%)	7 (5)	$n = 154$	0 (0)	$n = 91$
Alkaline phosphatase activity[a]	U/L	67 [54–91]	$n = 156$	73 [63–87]	$n = 82$
Bilirubin concentration[a]	µmol/L	5 [4–9]	$n = 156$	5 [3–8]	$n = 86$
Paracetamol concentration[a]	µmol/L	230 [0–740]	$n = 149$	430 [80–1100]	$n = 88$
Paracetamol concentration[a]	mg/L	34.8 [0–111.9]	$n = 149$	65.0 [12.1–166.2]	$n = 88$
Treated with acetylcysteine	*n* (%)	154 (99)	$n = 156$	87 (95)	$n = 92$
Treated with activated charcoal	*n* (%)	82 (53)	$n = 156$	51 (55)	$n = 92$
Duration of hospital stay[a]	days	2 [1–2]	$n = 156$	1 [1–1]	$n = 92$

Abbreviations: ALT: alanine aminotransferase (threshold value for males: >70 and for females: >45 U/L). INR: normalized international ratio.
[a]Median [Q_1 – Q_3].

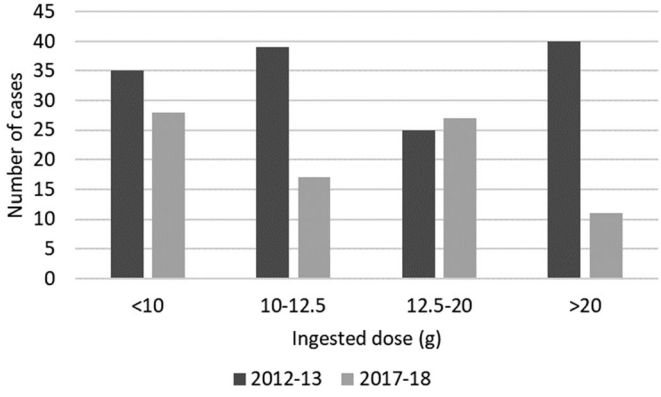

Figure 3. Distribution of ingested doses of paracetamol reported by the patient or relatives before (2012–13) and after (2017–18) pack size restriction. Information on ingested dose was available in 139 cases in 2012–13 and 83 cases in 2017–18.

Concentrations of paracetamol in plasma, the time from ingestion to admission, and the proportion of cases presenting at the hospital later than 8 h after ingestion did not differ significantly between the two periods ($P = 0.1$ $P = 0.8$, and $P = 0.4$, respectively) (Table 2). Cases with ALT activity higher than 1000 U/L and INR > 1.5 only occurred in 2012–13, not in 2017–18 ($P = 0.09$ and $P = 0.04$, respectively) (Table 2). No differences were seen in median ALT and alkaline phosphatase activities ($P = 0.4$ and 0.2, respectively) (Table 2).

The proportion of intentional poisonings was equal in the two periods, and we found no significant differences in the proportion of patients treated with acetylcysteine ($P = 0.06$) or activated charcoal ($P = 0.6$) (Table 2). However, the median duration of hospital stay was shorter in 2017–18 than in 2012–13 ($P < 0.001$) (Table 2). No deaths occurred.

Demographics and clinical characteristics according to sex

Females made up 80% and 78% of unique patients in the two periods, respectively. Unique male patients were older compared to females in both 2012–13 and 2017–18 ($P = 0.02$ and $P < 0.01$, respectively) (Table 3). In 2012–13, the median ingested dose of paracetamol was significantly higher in males compared to females ($P < 0.01$), and the proportion of intentional poisonings was lower in males than females ($P < 0.01$) (Table 3).

A higher proportion of cases ingesting more than 20 g paracetamol, and a longer hospital stay in 2012–13 compared to 2017–18 was observed both within the group of females and males (Table 3).

Discussion

In this retrospective review of paracetamol poisonings, the implementation of pack size restrictions in Denmark was associated with less hepatotoxicity and a lower proportion of patients ingesting > 20 g. Nevertheless, the median ingested dose remained unchanged. In the present study, paracetamol was involved in all included cases in contrast to a previous study concerning the effect of pack-size restrictions in Denmark on poisonings with non-opioid analgesics in general [6]. Additionally, it adds knowledge on ingested doses, treatment, and differences between females and males, which was not described previously [6].

The lower frequency of poisonings involving more than 20 g taken together with the median ingested dose higher than 10 g in 2017–18, may indicate that purchasing two packages of paracetamol may still be easy, whereas gathering more packages requires more effort. Hence, further restricting the number of available packages could be considered as a means of reducing harm.

Similar to the present study, the previous Danish study [6] found a decreased occurrence of severe liver damage after the regulation [6]. On the other hand, median paracetamol concentrations in plasma were not lower in 2017–18 than in 2012–13 in the present study in contrast to the findings by Morthorst et al. [6]. In Denmark, all paracetamol poisonings (> 6 g) are treated with acetylcysteine on arrival, in contrast

Table 3. Characteristics of cases by sex before (2012–13) and after (2017–18) paracetamol pack size restriction.

		Females				Males			
		2012–13		2017–18		2012–13		2017–18	
			Data obtained from		Data obtained from		Data obtained from		Data obtained from
Number of unique patients		**102**		**61**		**25**		**17**	
Age[a]	Years	22 [17–40]	$n = 102$	23 [18–46]	$n = 61$	47 [30–56]	$n = 25$	43 [27–49]	$n = 17$
Age less than 16 years	*n* (%)	21 (21)	$n = 102$	6 (10)	$n = 61$	0 (0)	$n = 25$	0 (0)	$n = 17$
Any comorbidity	*n* (%)	54 (53)	$n = 102$	40 (66)	$n = 61$	16 (64)	$n = 25$	14 (83)	$n = 17$
Psychiatric comorbidity	*n* (%)	46 (45)	$n = 102$	30 (49)	$n = 61$	12 (48)	$n = 25$	11 (65)	$n = 17$
Number of cases		**129**		**74**		**27**		**18**	
Ingested dose of paracetamol[a]	g	12.5 [9–20]	$n = 118$	11.5 [8–15]	$n = 68$	21 [12.5–50]	$n = 21$	13 [10–20]	$n = 15$
Ingested dose > 20 g	*n* (%)	29 (25)	$n = 118$	8 (12)	$n = 68$	11 (52)	$n = 21$	3 (20)	$n = 15$
Intentional overdose	*n* (%)	123 (98)	$n = 126$	71 (96)	$n = 74$	23 (85)	$n = 27$	16 (89)	$n = 18$
Time from ingestion to admission	hours	3 [2–6]	$n = 95$	3 [2–4]	$n = 48$	4.25 [4–8.5]	$n = 16$	4.5 [3–8.5]	$n = 11$
Number of different drugs ingested[a]	*n*	1 [1–2]	$n = 129$	1 [1–2]	$n = 74$	1 [1–2]	$n = 27$	1 [1–2]	$n = 18$
Co-ingestion of alcohol	*n* (%)	28 (23)	$n = 121$	15 (23)	$n = 64$	7 (26)	$n = 27$	9 (64)	$n = 14$
Paracetamol concentration[a]	μmol/L	230 [0–755]	$n = 123$	455 [140–1070]	$n = 74$	240 [0–640]	$n = 25$	210 [0–780]	$n = 18$
Paracetamol concentration[a]	mg/L	34.8 [0–114.1]	$n = 123$	68.8 [21.2–161.8]	$n = 74$	36.3 [0–96.8]	$n = 25$	31.8 [0–117.9]	$n = 18$
ALT activity	U/L	18 [11–28]	$n = 129$	16 [11–21]	$n = 74$	27 [15–50]	$n = 27$	29 [16–52]	$n = 18$
Duration of Hospital stay[a]	days	2 [1–2]	$n = 129$	1 [1–1]	$n = 74$	2 [1–3]	$n = 27$	1 [1–1]	$n = 18$

Demographic data (age and comorbidity) are shown for unique patients. Characteristics of the individual poisonings (dose, intention, time from ingestion, paracetamol concentration, liver enzymes, co-ingestion, and duration of stay are based on each admission (case). One unique patient could have more than one admission. Abbreviations: ALT: alanine aminotransferase (threshold value for males: >70 and for females: >45 UL/L).
[a]Median [Q_1 – Q_3].

to many other countries which utilize the paracetamol nomogram that requires an accurate time of ingestion to guide acetylcysteine treatment [13]. Thus, the time from ingestion to measurement may not be consistently stated in Danish patient records. In accordance, we did not obtain data on time from ingestion to measurement of paracetamol concentration, and moreover, data on time from ingestion to admission was not available in all cases. Thus, although the median recorded time from ingestion to admission was not significantly different in the two periods based on the available data, it cannot be excluded that the similar paracetamol concentrations in the two periods could be affected by more cases presenting earlier after the regulation. Furthermore, there was a trend towards more patients presenting within 8 h of paracetamol ingestion in the post-regulation period. As initiation of treatment after 8 h is an important prognostic factor [14], this may have played a role in terms of the lower proportion of cases experiencing hepatotoxicity. Further research is required to examine whether this trend of earlier presentation persists and why this has occurred. A possible explanation is that paracetamol sales restrictions resulted in increased public awareness of the dangers of paracetamol poisoning resulting in earlier presentations to hospitals.

We found considerably fewer cases of paracetamol poisoning in 2017–18, than in 2012–13. Still, we cannot conclude whether the rate of paracetamol poisonings requiring hospitalization per inhabitant in the area covered by Aalborg University Hospital was significantly lower in 2017–18 than in 2012–13, because the number of inhabitants covered by the hospital in the two periods was not available to us. However, in the first quarters of 2013 and 2018, the population in Aalborg counted 203,448 and 213,558 people, respectively [15], which speaks against a decreased population as the explanation of the lower number of poisonings in 2017–18 compared to 2012–13. Furthermore, the apparent decrease agrees with Morthorst et al. [6] who observed an instant reduction (18.5%) in admissions due to non-opioid analgesics per year in the entire Danish population after the pack size reduction. The shorter duration of the stay in hospital in 2017–18 compared to 2012–13 is most likely due to a change of guidelines for acetylcysteine treatment of paracetamol poisoning, which implied that the minimum length of treatment was reduced from 36 h to 20 h in 2013 [13].

In the present study, males had a considerably higher age than females. This finding seems to correspond well with a recent study from Algeria, in which the female sex was most pronouncedly overrepresented among cases admitted to hospital with paracetamol poisoning in the age group of 16–25 years [16]. Furthermore, in a Chilean study, the age of male and female cases with paracetamol poisoning differed significantly, but only by one year [17]. Besides a higher age, males seemed more likely to experience accidental poisonings due to uncontrolled pain, although the proportion in whom this type of poisoning occurred was small. Thus, our study suggests that male and female cases of paracetamol poisonings are two distinct groups, which should be considered in relation to future research and preventive efforts.

Our study comprises a comparison of cross-sectional studies performed in two different periods. Although the pack size restriction is a considerable change between the two periods, it is possible that other changes in society, culture, education, or other parameters over time have had an impact. On the other hand, it is difficult to perform studies to conclude beyond associations on this type of regulatory effort. Furthermore, there are several other limitations of the present study. First, it is a single-center study with a

relatively small sample size, and the organization of the hospital changed between the two investigated periods. However, our search should have identified all patients admitted with the concerned ICD diagnoses during the two periods. We know from our previous study [2] that a few poisonings with paracetamol may be coded under other codes such as DT509A"poisoning with medicine, unspecified". However, as paracetamol poisonings are frequent, we trust that the used diagnostic codes have a high sensitivity for identifying the patients. Furthermore, we did not include the diagnostic codes for self-harm with non-opioid analgesics (ICD-code DX60) as these cases may not represent poisonings and may concern other exposures than paracetamol. A supplementary search revealed that less than five patients per year were admitted to Aalborg University Hospital with ICD-code DX60, rendering the effect of omitting these negligible. The retrospective design precludes focused interviews and examinations, but may on the other hand lead to a completer and more representative sample of patients. The recorded doses of paracetamol were based on the information given by the patient and/or relatives and cannot be confirmed. Moreover, it is an important limitation that we do not have the time from ingestion to the measurement of paracetamol concentration as a variable. Finally, the fact that one unique patient could account for more than one case may bias the results, as well as the fact that complete data could not be obtained for all parameters.

Conclusion

The present study demonstrated a lower number of paracetamol poisonings, a decreased proportion of poisonings involving ingestion of more than 20 g of paracetamol, and a lower occurrence of severe hepatotoxicity after regulation of paracetamol pack size available in over-the-counter sale. Furthermore, the study showed that females and males constitute two distinct groups in terms of age and intentional poisoning. This should be considered in future research and public health prevention.

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Disclosure statement

The authors report there are no competing interests to declare.

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to restrictions on the transmission of personal data according to Danish legislation.

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