Health risks related to polyurethane foam degradation in CPAP devices used for sleep apnoea treatment

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To the Editor:

A recent medical device recall notification from Philips Respironics reported on risk for degradation of polyurethane foam (PUF) in continuous positive airway pressure (CPAP) devices used for obstructive sleep apnoea (OSA) treatment [1]. The degraded foam particles may cause airway irritation, and the volatile gas products (diethylene glycol, toluene di-isocyanate isomers, toluene diamine isomers) released during the degradation process may also have cyto- and genotoxic effects [1]. Kendzerska *et al*. [2] reported no increase in cancer incidence in 1220 patients using PUF devices over a mean observation time of 7.5 years. However, studies assessing airway symptoms and health outcomes other than cancer are lacking. Airway irritation from degraded foam particles may be particularly harmful for patients with pre-existing obstructive lung disease (OLD). This study aimed to evaluate the association between PUF-CPAP use and adverse health outcomes in OSA patients with/without comorbid OLD.

This was a longitudinal analysis of the national, population-based DISCOVERY cohort of OSA patients aged ⩾16 years starting CPAP treatment from July 2010 to March 2018 in Sweden [3]. The brands of CPAP devices included in the recent medical device recall notification were defined as PUF-CPAP and CPAP devices of other brands were defined as non-PUF-CPAP. Counties prescribing PUF-CPAP (⩾80% PUF-CPAP prescribed) and non-PUF-CPAP (<10% PUF-CPAP) could be identified. Remaining counties (10% to <80% PUF-CPAP) were excluded from subsequent analyses. Data were crosslinked with mandatory governmental registries, as follows. 1) The Swedish Prescribed Drug Registry using anatomical therapeutic chemical (ATC) codes) [4]. Comorbid OLD was defined as at least two collections of anti-obstructive medication (ATC code R03) during the 12 months before baseline; deteriorated airway obstruction was defined as collection of ⩾3 short-acting β-agonists (SABA; R03AC02) or oral corticosteroids (OCS; H02AB) during the first year or during any 1-year timespan of the study. Incident OLD after starting CPAP was defined as collection of two or more anti-obstructive medications within a window of consecutive 365 days after starting CPAP in patients without OLD at baseline. 2) The National Patient Register for hospitalisations using ICD-10 codes [5] for defining comorbid heart failure (ICD-10 codes I11, I42 and I50) and ischaemic heart disease (I20–25) 5 years before CPAP start and for identifying hospitalisation due to OLD during follow-up (primary diagnosis J44–46). 3) The National Cancer Registry [6]. 4) The Cause of Death Registry [7]. Patients with PUF-CPAP *versus* non-PUF-CPAP were compared using propensity score matching, accounting for age, sex, body mass index (BMI), apnoea–hypopnoea index, heart failure, ischaemic heart disease, and study observation time. Sensitivity analyses were performed: 1) excluding the county of Skåne, a county known for a slightly high smoking rate [8]; 2) clustering the regression models by county; and 3) adjusted for anthropometric data and comorbidities instead of propensity score matching using multivariable logistic and Cox regression models. Analyses were conducted using Stata version 16.0 (StataCorp LP; College Station, TX, USA). The study was approved by the Ethics Committee at Medical Faculty, Lund University, log number 2018/51 (amendments 2020-02721, 2021-04984).

We included 18 561 individuals in four PUF-CPAP dominated counties (27.2% females, mean±SD age 57.8±12.4 years, median (interquartile range (IQR)) BMI 31 (28–35) kg·m^{-2}, OLD at baseline 13.4%, mean±SD nocturnal CPAP use 6.0±1.6 h, median (IQR) observation time 2.6 (1.1–4.7) years), and 29 830 individuals from 10 non-PUF-CPAP counties (30.2% females, mean±SD age 56.9±12.6 years, median

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Patients with PUF-CPAP and especially those with pre-existing obstructive lung disease had increased use of anti-obstructive medication but there were no differences in hospitalisations and mortality, and data on cancer were inconclusive https://bit.ly/3uVIzXG

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(IQR) BMI 31 (28–36) kg·m^{-2}, OLD at baseline 12.2%, mean±SD nocturnal CPAP use 5.6±2.0 h, median (IQR) observation time 2.3 (0.9–4.6) years). The cohort was followed for a total of 139 056 person-years. Deteriorated airway obstruction in the first year after CPAP initiation was more frequent in the PUF-CPAP group (table 1). Deteriorated airway obstruction anytime during follow-up was also more frequent in the PUF-CPAP group (SABA use 9.4% *versus* 8.8%, p=0.047; and OCS use 19.7% *versus* 17.3%, p<0.001) in matched groups (table 1).

In patients with OLD at baseline, use of PUF-CPAP devices was associated with increased SABA use (22.4% *versus* 18.2%, p<0.001) and OCS use (26.0% *versus* 23.2%, p=0.027) during the first year after CPAP initiation. For the entire observation period, a total of 2797 OLD patients (38.5%) collected OCS, and PUF-CPAP was associated with an increased risk of OCS collection (41.7% *versus* 36.8%, p<0.001). SABA use for the entire observation period was comparable in the PUF-CPAP (47.0%) and non-PUF-CPAP groups (44.6%).

All-cause cancer and lung cancer incidence was higher in the PUF-CPAP group (4.5% *versus* 4.1%, p=0.045; and 0.3% *versus* 0.1%, p<0.001, respectively). However, in the sensitivity analysis excluding the county Skåne with known higher smoking rates [8], the associations between PUF-CPAP exposure and incident cancer disappeared (cancer: 3.6% in PUF-CPAP *versus* 4.0% in non-PUF-CPAP, p=0.29; lung cancer: 0.21% in PUF-CPAP *versus* 0.15% in non-PUF-CPAP, p=0.491). Hospitalisation due to OLD and mortality did not differ between groups (table 1). The results from the adjusted logistic and Cox regression models did not differ significantly from the propensity score matched analyses (data not shown).

In this nationwide study of patients with OSA, PUF-CPAP use was associated with mild deterioration of OLD control during a median follow-up of 2.4 years. However, severe OLD exacerbations requiring hospitalisation or increased OLD incidence were not observed. Further, we identified signals of increased lung cancer incidence in the PUF-CPAP group, but this finding needs further confirmation in other studies, as it was not robust in sensitivity analyses and may be related to regional differences in lung cancer risk factors.

Hazardous effects of PUF-CPAP devices have only recently been reported [1]. Experimental data simulating the 6–8 h daily PUF-CPAP user pattern of OSA patients do not exist yet. The lack of a firm association between use of PUF-CPAP devices and overall cancer incidence is consistent with a recent

TABLE 1 Outcomes in all patients and in patients with obstructive lung disease (OLD)

	Unmatched analysis			Matched analysis		
	Non-PUF-CPAP	PUF-CPAP	p-value	Non-PUF-CPAP	PUF-CPAP	p-value
Outcomes in all patients	n=29 830	n=18 561		n=17 310	n=17 310	
Collection of SABA ⩾3 times in first year	785 (2.6%)	616 (3.3%)	<0.001	470 (2.7%)	573 (3.3%)	0.001
Collection of SABA ⩾3 times any year	2591 (8.7%)	1765 (9.5%)	0.002	1516 (8.8%)	1622 (9.4%)	0.047
Prescription of OCS in first year	2697 (9.0%)	1923 (10.4%)	<0.001	1579 (9.1%)	1775 (10.3%)	<0.001
Prescription of OCS during follow-up	4957 (16.6%)	3651 (19.7%)	<0.001	2990 (17.3%)	3405 (19.7%)	<0.001
Hospitalisation due to OLD	153 (0.5%)	114 (0.6%)	0.14	102 (0.6%)	100 (0.6%)	0.89
Incident OLD	2025 (6.8%)	1296 (7.0%)	0.41	1184 (6.8%)	1197 (6.9%)	0.78
Incident cancer (except skin cancer)	1183 (4.0%)	838 (4.5%)	0.003	711 (4.1%)	787 (4.5%)	0.045
Incident lung cancer	47 (0.16%)	58 (0.31%)	<0.001	24 (0.14%)	56 (0.32%)	<0.001
Mortality during follow-up	712 (2.4%)	490 (2.6%)	0.082	406 (2.3%)	441 (2.5%)	0.22
Outcomes in patients with OLD	n=3640	n=2492		n=2213	n=2294	
Collection of SABA ⩾3 times in first year	668 (18.4%)	552 (22.2%)	<0.001	403 (18.2%)	514 (22.4%)	<0.001
Collection of SABA ⩾3 times in a 1-year timespan	1632 (44.8%)	1165 (46.7%)	0.14	988 (44.6%)	1079 (47.0%)	0.11
Prescription of OCS in first year	858 (23.6%)	654 (26.2%)	0.017	513 (23.2%)	597 (26.0%)	0.027
Prescription of OCS	1325 (36.4%)	1037 (41.6%)	<0.001	815 (36.8%)	957 (41.7%)	<0.001
Hospitalisation due to OLD	122 (3.4%)	93 (3.7%)	0.43	79 (3.6%)	80 (3.5%)	0.88
Incident cancer (except skin cancer)	174 (4.8%)	120 (4.8%)	0.95	108 (4.9%)	107 (4.7%)	0.73
Incident lung cancer	13 (0.36%)	13 (0.52%)	0.33	9 (0.41%)	13 (0.57%)	0.44
Mortality during follow-up	159 (4.4%)	115 (4.6%)	0.65	101 (4.6%)	99 (4.3%)	0.69

Data are presented as n (%) for categorical measures. Outcomes were compared between groups unmatched (crude) and after propensity score matching, accounting for sex, age, body mass index, apnoea–hypopnea index, presence of OLD at baseline, ischaemic heart disease, heart failure and observation time. CPAP: continuous positive airway pressure; OCS: oral corticosteroids; PUF: polyurethane foam; SABA: short-acting β-agonist.

report [2]. Strengths of the present study include the unselected national cohort of OSA patients, which increases precision, validity and generalisability of results, and permits identification of rare outcomes [9]. No patients were lost to follow-up due to cross-linkage with mandatory national registries. A key advantage of the design is that the choice of CPAP device (and hence PUF-CPAP exposure) was made centrally on the sleep unit level and was not based on individual patient characteristics or preferences. This could be considered to approach an "instrumental variable" or "quasi-randomised" design, as suggested by the fact that characteristics were similar between the treatment groups. Several limitations need to be acknowledged. PUF-CPAF use was categorised retrospectively by the responsible staff for each sleep unit. To limit misclassification, only counties with very high (⩾80%) or very low (<10%) PUF-CPAF prescription were compared. This design still enabled us to include most CPAP patients in Sweden in the analyses (74.4% of Swedevox patients). It cannot be excluded that some individuals changed the device category during follow-up. However, this misclassification would align the treatment groups and, if anything, underestimate any influence of PUF-CPAP on patient outcomes. Data were lacking on smoking, but this is unlikely to bias the findings as PUF-CPAP use was decided at the county level independent of smoking status. Finally, mean exposure time of PUF-CPAP was rather short to evaluate any risk estimate on cancer incidence.

In conclusion, PUF-CPAP associates with increased use of anti-obstructive medication after CPAP initiation, particularly in people with underlying OLD. PUF in CPAP may contribute to increased airway symptoms and OLD exacerbations. For cancer incidence the results were less conclusive and further studies are urgently needed.

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