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This is the first study that reports measurements of biomarkers of exposure to disinfection by-products as surrogate markers of exposure to disinfectant use in healthcare facilities. Biomarker measurements are coupled with detailed job exposure matrix and job-task exposure matrix estimates that provide refined exposure estimates for occupational exposures of nurses and their possible metabolic health outcomes.

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Key terms: biomarker; Cyprus; diabetes; disinfectant; disinfection; exposure; healthcare; job exposure matrix; nurse; occupational exposure; pre-diabetes; trihalomethane

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Occupational exposures to disinfectants and pre-diabetes status among active nurses in Cyprus

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Objectives A cross-sectional study was designed in two hospitals of Cyprus to: (i) examine the possible association between exposure to disinfectants/trihalomethanes (THM) with point of care glycosylated hemoglobin (HbA1c) levels among active nurses, and (ii) identify the main determinants of pre-diabetes metabolic risk among active nurses in Cyprus.

Methods In total, 179 nurses from two public hospitals in Cyprus were recruited excluding pregnant or nurses working <5 years (participation rate ~25.6%). End-of-shift urine samples were used to measure exposures to THM, and questionnaire items were used to construct improved exposure classification matrices, ie, the job exposure matrix (JEM) and the job-task exposure matrix (JTEM).

Results Results showed associations between JEM- and JTEM-derived metrics of exposure and HbA1c for few disinfectants (eg, peracetic acid), but no consistent trends were derived. In multivariable models, adjusted for age, BMI, sex, smoking status and alcohol consumption, the number of night shifts per month, and (ln)chloroform (a THM compound) were associated with HbA1c levels [β 0.11 (95% confidence interval (CI) 0.05–0.17) and 0.05 (95% CI 0.00–0.11), respectively].

Conclusion A significant association between the number of monthly night shifts and HbA1c was observed, but no consistent associations were found between three exposure metrics of eleven different disinfectants, or urinary THM and point of care HbA1c levels in active nurses. Replication of the study findings in larger prospective sample is warranted. This is a novel occupational health dataset shedding light on the possible metabolic effects of exposures to disinfectants/by-products that have not been studied before.

Key terms biomarker; disinfection; healthcare; job exposure matrix; trihalomethane.

Disinfectants represent a class of biocides used to inactivate microorganisms present in various settings, including households, hospitals, and other healthcare facilities. The frequency of disinfection tasks in hospitals has been increasing as a measure against the transmission of hospital-associated infections (1). Nurses represent one of the largest occupational groups in the healthcare sector, worldwide, and they are systematically exposed to disinfectants and other cleaning-related chemicals. Disinfectants, when prepared or used, often react with naturally-occurring organic matter commonly found in water, surfaces, dust, and particulate matter, resulting in the instantaneous formation of disinfection by-products (DBP) (2). The most abundant class of DBP is the group of trihalomethanes (THM), which comprises of chloroform (TCM), bromodichloromethane (BDCM), dibromochloromethane (DBCM), and bromoform (TBM). THM are ubiquitous in drinking water and they are used as surrogate markers of exposure to DBP via ingestion (drinking water) and/or non-ingestion routes of exposure (ie, inhalation and/or dermal uptake during cleaning, washing, etc.) (3, 4). The release of THM indoors is quite common when disinfectants (eg, chlorine-based) are used for both bleaching processes or for disinfecting occupational areas/surfaces (5, 6).

Exposures to disinfectants or activities involving disinfectants (eg, cleaning) have been primarily linked with respiratory health outcomes, such as lung function

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decline and asthma at work (7). Exposures to DBP such as the THM have been primarily linked with bladder cancer occurrence in the general population (8). Additionally, in exploratory human studies or in animal studies, THM have been implicated with the manifestation of metabolic alterations, such as liver enzyme alterations and type 2 diabetes with mixed results (9, 10).

Exposure to household disinfectants was associated with higher body mass index (BMI) at age 3, mediated by gut microbial composition at age 3–4 months in the CHILD birth cohort (11). But the possible metabolic perturbations of disinfectant exposures have not been extensively studied in the adult general population and particularly in high risk groups, such as the highly exposed occupational group of nurses. Limited literature exists on respiratory health outcomes and exposures to disinfectants in nurses and other healthcare professionals (12). There is a plethora of disinfectants that are often used in combination during routine nurses' tasks. Simultaneously, there is a lack of established biomonitoring protocols for disinfectants. Thus, improved characterization of occupational exposures for nurses was set up, utilizing measurements of a biomarker of exposure to DBP (THM) as surrogate marker of exposure to disinfectants and coupled with detailed exposure questionnaires to quantify the use and exposure to disinfectants.

Given the frequent occupational exposure of nurses to disinfectants and the lack of clear evidence about the possible links of these exposures with possible metabolic alterations, the main objectives of this study were: (i) examine the possible association between exposure to disinfectants (THM) with point of care glycosylated hemoglobin (HbA1c) levels among active nurses, and (ii) identify the main determinants of pre-diabetes metabolic risk among active nurses in Cyprus.

Methods

Study design, recruitment, and data collection

A cross-sectional study was set up in two public hospitals in Cyprus. The recruitment took place in the summer of 2016. All registered nurses working in these hospitals were eligible to participate and were contacted during their shift. Pregnant and/or nurses working <5 years were excluded, according to the study bioethics protocol. More details of recruitment, samples/data collection and processing can be found in Ioannou et al (6) and they are briefly described below. All volunteers signed a written informed consent for study participation. All methods were performed in accordance with the relevant guidelines and regulations, and the Cyprus National Bioethics Committee (#ΕΕΒΚ/ΕΠ/2015/28), the Office of the Commissioner for Personal Data Protection (#3.28.375), and the Cyprus Ministry of Health (#0332/2015) approved the study.

All study participants completed questionnaires, adapted by the ones previously used in the US Occupational Survey for Nurses' Health study (approval for use obtained by Prof C Camargo, Harvard Medical School), about the routine use of disinfectants, the performance of specific tasks, and the use of disinfectants 24 hours before sampling. To assess the risk of diabetes development within the next ten years, the Finnish Diabetes Risk Score (FINDRISC) questionnaire was also administered (13). Briefly, the FINDRISC uses information on: age, BMI, physical activity, vegetable consumption, history of high blood pressure medication, history of elevated blood glucose levels, and family history. Each response was scored according to the type 2 diabetes risk assessment form of the Finnish Diabetes Association, (<7: low risk, 7–11: slightly elevated risk, 12–14: moderate risk, 15–20: high risk, >20: very high risk).

Anthropometric and clinical measurements

Anthropometric characteristics, such as waist, hip, height, and weight were measured at the end of the shift, following a standardized protocol. HbA1c was measured on the spot with a point-of-care Quo-Lab HbA1c portable device (Quo-Lab 0110-0061; IFU0110.EU-GR.02.01) provided by MedLab diagnostics, using capillary blood. Urine samples were collected at the end of the nurses' working shift, which typically are at 07:00, 13:00 or 19:00 in polypropylene vials without preservatives. All samples were transported to the lab on the same day in cool boxes.

Urine analyses

A liquid-liquid extraction protocol was used for the measurement of THM in urine, following the protocol by Charisiadis & Makris (14). Three mL urine (spiked with surrogate solution, 9 μL of 10 mg/L in n-propanol, at a final concentration of 30 μg/L) were mixed with 150 μL of n-propanol and 1 mL of pentane (extraction solvent), followed by the addition of 1.2 g of sodium sulfate, shaking for 10 minutes at 100 rpm and centrifuged for 1 minute at 2500 rpm. Half of the volume from the organic phase was transferred into a gas chromatography (GC) autosampler screw-top glass vial with blue PTFE/butyl rubber septa (Restek, USA), containing the internal standard solution, 10 μL of 10 μg/L in acetone, at final concentration of 200 μg/L. Finally, a 2 μL portion of sample was then injected. GC-MS spectra were recorded on an Agilent 7890A GC equipped with an Agilent 7000B triple quadrupole MS detector.

The THM compounds were separated on an Rxi-

5ms (5% diphenyl/95% dimethylpolysiloxane) column from Restek (30 m × 250 µm × 0.25 µm) and helium carrier gas (99.999%) flow was maintained at 1.0 mL/minutes. The inlet temperature was set at 140 °C for 0.1 minutes then ramped to 300 °C at a rate 300 °C min^{-1} where it was maintained. The oven was set to 30 °C for 5 minutes, ramped to 100 °C at a rate 50 °C min^{-1} where it was maintained for 2.4 minutes, then ramped to 260 °C at a rate 120 °C min^{-1} where it was maintained for 1.6 minutes followed by a post run period at 260 °C for 1 minute. The total run time was 11.5 minutes. The injection volume was 2 µL, and the injection syringe was washed three times with acetone before and after sample injection. MSD transfer line and MS source temperatures were held at 250 °C, while quadruples were held at 150 °C. Mass spectra were obtained using electron impact ionization (70 eV) in the multiple reaction monitoring mode, in three per second scanning cycles, with a solvent delay of 4.0 minutes. The software Mass Hunter Workstation (Agilent, rev. B.05.00) was used to control the system. Urinary creatinine levels were measured with the Jaffe method (15). Quality control and quality assurance schemes ensured the accuracy and reproducibility of the measurements. Sample order was randomized in different batches. Between and within batches reproducibility was always <8%. The quality control checks were within 80–120% of the spiked concentration value.

Job-exposure and job-task-exposure matrices

The job-exposure matrix (JEM) and job-task-exposure matrix (JTEM) were developed using self-reported information on: job type (department/unit), type of professional tasks, and self-reported frequency of use of disinfectants (16). The categorical variable of task as used in JTEM had three categories: (i) disinfecting materials/places and preparation/mixing of disinfectants; (ii) either of the tasks (disinfecting only materials/place or only preparation/mixing/filling disinfectants); and (iii) none of the above tasks. Ten hospital departments were included in the analysis, employing ≥10 study participants, namely, cardiology, emergency room (ER), gynecology, intensive care unit (ICU), nephrology, surgery, orthopedics, pathology, pediatrics, and other. The category other, included all departments with <10 study participants, such as administration, outpatient clinic or other smaller clinic/departments unique to each hospital.

Following the methodology developed by Quinot et al (16) and as previously described in Ioannou et al (6), two different methods were used to classify disinfectant exposures in the JEM and JTEM matrices. Method 1 was based on the percentage of participants reporting any exposure to disinfectants (exposure prevalence) in their respective department for the JEM approach, and stratification by department and task for the JTEM approach. Method 2 was based on a weighted score of the frequency of exposure to each disinfectant. The percentage of self-reported exposure was weighted by a factor of 2 for those reporting use of 1–3 days/week, or a factor of 5 for those reporting use of 4–7 day/week. The median of the exposure prevalence was used as the exposure cut-off for each disinfectant in method 1, or the median of the scores for method 2. Additional details about the JEM and JTEM methodology can be found in Quinot et al (16) and Ioannou et al (6).

Statistical analyses

BMI was calculated as weight (kg) divided by height squared (m^2) and waist-to-hip ratio (WHR) was calculated using measurements of waist (cm) divided by hip circumference (cm). Point of care HbA1c levels were used to stratify participants in two groups, namely, non-diabetics (<5.7%) and pre-diabetics (≥5.7%) that did not report having been diagnosed with diabetes. The category of pre-diabetics included also participants with HbA1c levels>6.4% which could be categorized as diabetics using the definition of the American Diabetes Association (17).

Total THM (TTHM) was defined as the sum of all four THM (TCM, BDCM, DBCM, and TBM) species and brominated THM (BrTHM) as the total of BDCM, DBCM, and TBM. Because of skewed distributions, all urinary THM were log transformed. Urinary concentrations below the method's limit of detection (LOD) were assigned to half the LOD and concentrations above the LOD and below the method's limit of quantification (LOQ) were assigned half the LOQ. LOD values for TCM, BDCM, DBCM, and TBM were 0.030, 0.017, 0.021, and 0.015 µg/L, respectively, and the respective LOQ values were 0.091, 0.052, 0.064, and 0.045 µg/L, respectively. Urinary creatinine values <0.1 g/L were excluded from the analysis as these were considered unacceptably low values for a healthy population (18). Median concentrations of TCM and BrTHM were compared to TTHM to identify the ratio of exposure.

The t-test was used to test mean differences in continuous variables (age, BMI, WHR, years working in a hospital, night shifts per month) between the two HbA1c groups and chi-squared tests were used for determining the difference in proportions for the categorical variables (sex, education, smoking status, hospital, sampling time, vegetable consumption, daily exercise, FINDRISC). For differences in the urinary THM concentrations between groups, the non-parametric Kruskal-Wallis test was used.

Associations between HbA1c and exposures (ie, disinfectants and DBP) were described using: (i) the self-reported last 24-hour exposure to any disinfectant from the questionnaire, (ii) the self-reported weekly

exposure to any disinfectant, (iii) the biomarkers of exposure to DBP (THM), and (iv) the exposure categories associated with either the JEM or JTEM. Linear multivariable regression analysis was conducted to describe the association between HbA1c levels and disinfectant (THM) exposure metrics adjusting for different covariates. In the first step, crude models were used to identify whether known predictors and/or confounders of HbA1c (eg, age, BMI, WHR, smoking) were supported by the data. Those that satisfied the criterion of statistical significance with P<0.05 were added in a model (full model) from which they were systematically removed until only predictors with P<0.1 remained (reduced model). The covariates selected following the aforementioned process were used as covariates in models adjusted for the different exposure metrics (ie, self-reported, JEM, JTEM, and THM levels). Sensitivity analyses were performed by removing the lowest and highest 2.5th percentiles of the distribution of HbA1c.

All tests were two-tailed with the level of nominal significance set at P<0.05. All statistical analyses were performed using R (version 3.4.0) and RStudio (version 1.0.143) using the packages: tableone, knitr, readr, readxl, plyr (19–27).

Results

Out of ~700 registered nurses in the two public hospitals, a total of 179 agreed to participate (25.6%). Six participants were excluded, because of urinary creatinine values being <0.1 ug/L. A total of 7 participants were self-reported diabetics (type 1 or type 2), while only 3 were classified as diabetics, according to the HbA1c test. The 4 that self-reported type 2 diabetes but were classi-

Table 1. Descriptive characteristics of the study population stratified by glycosylated hemoglobin (HbA1c) levels. [SD=standard deviation; FINDRISC= Finnish Diabetes Risk Score.]

	Overall		HbA1c<5.7		HbA1c≥5.7		P-value [a]
	N (%)	Mean (SD)	N (%)	Mean (SD)	N (%)	Mean (SD)	
Sex							0.96
Male	65 (38.5)		54 (38.0)		11 (40.7)		
Female	104 (61.5)		88 (62.0)		16 (59.3)		
Age	169 (100)	36.21 (8.53)	142 (84)	35.45 (7.97)	27 (16)	40.15 (10.26)	0.008
Body mass index	169 (100)	26.17 (5.24)	142 (84)	25.48 (4.53)	27 (16)	29.82 (7.05)	<0.001
Waist:hip ratio	169 (100)	0.86 (0.10)	142 (84)	0.86 (0.10)	27 (16)	0.89 (0.10)	0.162
Education (degree)							0.612
Non-university	4 (2.4)		4 (2.8)		0 (0.0)		
Postgraduate	42 (25)		36 (25.5)		6 (22.2)		
University	122 (72.6)		101 (71.6)		21 (77.8)		
Smoking status							0.412
Former smoker	17 (10.2)		13 (9.3)		4 (15.4)		
Non-smoker	102 (61.4)		85 (60.7)		17 (65.4)		
Smoker	47 (28.3)		42 (30.0)		5 (19.2)		
Years working in hospital	169 (100)	4.97 (5.04)	142 (84)	4.72 (4.62)	27 (16)	6.12 (6.64)	0.201
Night shifts per month	169 (100)	4.48 (1.82)	142 (84)	4.45 (1.88)	27 (16)	4.68 (1.42)	0.602
Hospital							0.536
Hospital 1	112 (66.3)		96 (67.6)		16 (59.3)		
Hospital 2	57 (33.7)		46 (32.4)		11 (40.7)		
Sampling time							0.008
Morning	68 (41.5)		37 (27.0)		2 (7.4)		
Noon	57 (34.8)		59 (43.1)		9 (33.3)		
Night	39 (23.8)		41 (29.9)		16 (59.3)		
Vegetable consumption							1
Everyday	114 (67.9)		96 (67.6)		18 (69.2)		
Not everyday	54 (32.1)		46 (32.4)		8 (30.8)		
Daily exercise							0.661
No	48 (28.6)		42 (29.6)		6 (23.1)		
Yes	120 (71.4)		100 (70.4)		20 (76.9)		
Alcohol (servings/per week)							0.352
0	73 (45.3)		58 (43.0)		15 (57.7)		
1	46 (28.6)		42 (31.1)		4 (15.4)		
2	16 (9.9)		14 (10.4)		2 (7.7)		
≥3	26 (16.1)		21 (15.6)		5 (19.2)		
FINDRISC							0.027
Low	86 (57.3)		79 (61.2)		7 (33.3)		
Slightly elevated	36 (24.0)		29 (22.5)		7 (33.3)		
Moderate	18 (12.0)		14 (10.9)		4 (19.0)		
High	9 (6.0)		7 (5.4)		2 (9.5)		
Very high	1 (0.7)		0 (0.0)		1 (4.8)		

[a] Comparisons for the difference in means between the two groups were made with t-test and chi-squared test for the difference in proportions.

fied as non-diabetics according to their HbA1c levels, were removed from the analyses. Of the remaining 169 participants, 142 (84%) had HbA1c levels <5.7%, and 27 (16%) had HbA1c levels ≥5.7% (table 1). Three participants were above the type 2 diabetes threshold (>6.4%).

Most nurses (61.5%) were females (mean age of 36 years) with the pre-diabetic group being significantly older (P=0.008) (table 1). BMI was significantly higher in the pre-diabetic group (P<0.001), but this was not the case for WHR. Other factors, such as education, smoking, years working in a hospital, frequency of vegetable consumption, and physical exercise did not significantly (P>0.05) differ between the two groups (table 1).

Overall, the median urinary TTHM levels (ng/g creatinine) were not significantly different (P=0.89) between the two groups (1037 versus 1027 ng/g creatinine in healthy and pre-diabetic groups, respectively) (table 2). TCM was the predominant THM compound measured among the four species in end-of-shift urine voids of prediabetics and healthy controls, accounting for approximately 70% of the total THM; the other 30% was attributed to the brominated fraction of TTHM.

The association between specific disinfectant exposures and HbA1c was investigated using linear regression models. Multivariate regression models of HbA1c for the exposure to peracetic acid, adjusted for age, BMI, and monthly frequency of night shifts, showed a borderline positive significant association (P<0.05) when exposure metrics relied upon the JEM (method 1: P=0.05; method 2: P<0.04) and JTEM (method 1: P<0.01) while there was no significant association (P>0.05) for the self-reported exposure metric (supplementary table S1, www.sjweh.fi/show_abstract.php?abstract_id=3804). A significant association was also observed between exposures to octenidine and HbA1c with method 1 JEM (P=0.02). Self-reported exposures to each disinfectant were not significant predictors of higher HbA1c in any of the models, besides for formaldehyde. Certain disinfectant exposures such as hydrogen peroxide and ammonia (for JEM) were significantly negatively associated with HbA1c (P=0.03), but no consistent trend in these associations could be derived (table S1).

Linear regression models of HbA1c with the biomarkers of exposure to THM showed a marginally significant (P=0.05) association of urinary TCM with HbA1c adjusted for age, BMI, sex, smoking status, and alcohol consumption (table 3). The number of night shifts per month was also significantly (P<0.001) associated with HbA1c when adjusted for the same covariates. Although the time of sample collection appeared to be positively associated with the levels of HbA1c, the effect was not present when adjusted for the full model (table 3).

In the sensitivity analyses [removing the lowest (<4.5%, N=3) and highest (>6.38%, N=5) 2.5th percentiles of the HbA1c distribution], the previously observed trends for TCM and the number of night shifts were not retained. Crude estimates for the time of sampling showed an increase of 0.2 (P=0.01) and 0.4 (P <0.001) for HbA1c levels for the noon and afternoon sampling times, respectively, with the morning time being the reference group, while for the adjusted model's respective effects were 0.12 (P=0.12) and 0.3 (P<0.001) (supplementary table S2, www.sjweh.fi/show_abstract.php?abstract_id=3804).

Table 2. Urinary concentrations of trihalomethanes (THM) for each HbA1c group, and overall. [HbA1c=glycosylated hemoglobin.]

Disinfection by-products (ng/g creatinine)	Overall				HbA1c <5.7%				HbA1c ≥5.7%				P-value
	N	Q1	Median	Q3	N	Q1	Median	Q3	N	Q1	Median	Q3	
Chloroform	169	214	673	1869	142	206	685	1804	27	308	673	2264	0.68
Bromodichloromethane	169	94	144	232	142	93	144	236	27	99	119	178	0.58
Dibromochloromethane	169	36	59	109	142	37	61	109	27	26	53	101	0.44
Bromoform	169	53	105	190	142	52	105	181	27	67	113	201	0.31
Brominated THM	169	210	341	505	142	207	343	547	27	238	323	458	0.87
Total THM	169	562	1027	2484	142	563	1037	2382	27	503	1027	2856	0.89

* For the differences between the two HbA1c groups, the non-parametric Kruskal -Wallis test was used.

Table 3. Crude and multivariate linear regression models of HbA1c levels with biomarkers of exposure to disinfection by-products and shift work.

Disinfection by-products (ng/g creatinine)	N	Crude			N	Adjusted [a]		
		β	95% CI	P-value		β	95% CI	P-value
Chloroform	169	0.04	-0.01–0.10	0.14	160	0.05	-0.00–0.11	0.05
Brominated trihalomethanes	169	-0.34	-0.72–0.04	0.08	160	-0.20	-0.58–0.18	0.3
Total trihalomethanes	169	0.08	-0.04–0.20	0.17	160	0.11	-0.01–0.22	0.08
Night shifts per month	146	0.07	0.01–0.13	0.03	139	0.11	0.05–0.17	<0.001
Sampling time (ref: morning)	164				155			
Noon		0.25	-0.01–0.51	0.05		0.15	-0.12–0.41	0.27
Afternoon		0.36	0.10–0.63	0.01		0.25	-0.03–0.52	0.08

[a] Adjusted for age, body mass index, sex, smoking status, and alcohol consumption.

Discussion

In this cross-sectional occupational study, we described associations between biomarkers of exposure to DBP/disinfectants and the levels of HbA1c in active nurses. We coupled metrics of exposure to disinfectants using both self-reported (questionnaires) information and biomarker measurements for nurses currently employed by two major public hospitals in Cyprus. Additionally, we included metrics of exposure classification using JEM and JTEM. The frequency of monthly night shifts was an important predictor of HbA1c levels among active nurses, along with TCM (biomarker of exposure to THM) and peracetic acid (common disinfectant). Exposures to other DBP did not show any statistically significant associations with HbA1c.

The association between the number of night shifts per month and HbA1c in nurses, shown by the data of our study, has been previously observed. It is well established that rotating night shift work may be associated with obesity, metabolic syndrome, and glucose dysregulation (28, 29). The duration of shift work was monotonically associated with higher type 2 diabetes risk in 6165 (NHS I) and 3961 (NHS II) incident cases (28). In Danish nurses, increased risk of type 2 diabetes was found for those nurses who worked at night [odds ratio (OR) 1.58, 95% confidence interval (CI) 1.25–1.99] or had evening shifts (OR 1.29, CI 1.04–1.59) (29). A randomized, cross-over study with healthy chronic shift workers showed that internal circadian time disturbed glucose tolerance mechanisms; circadian misalignment reduced glucose tolerance, increasing the risk of developing type 2 diabetes (30). A Japanese cohort study among workers documented the association between the type of job schedule and increase in HbA1c (31, 32). Evidence from a meta-analysis hinted that night shift work and irregular work schedule were associated with type 2 diabetes (33), while a higher risk for developing type 2 diabetes was presented for certain occupational types, such as nurses, due to their irregular work schedule (29, 33).

Higher exposure to disinfectants in this dataset was not found to be associated with HbA1c, except for peracetic acid where the strength of association remained using the JEM and JTEM exposure classification methods (JEM methods 1 & 2 and JTEM method 1). Eighteen nurses reported exposure to peracetic acid in this study working in six different departments (ER, gynecology, nephrology, surgery, pathology, and other). Of those, only the nurses of the ER and pathology were assigned to the higher exposure group (JEM method 1). Nurses in surgery reported use while doing one of the two tasks (high exposure) and nurses in pathology reported use of peracetic acid while doing both of the tasks and they were classified as highly exposed using JTEM method 1.

The urinary THM levels in the Cypriot nurses of this study were nearly double those previously reported for the general population of Cyprus (6). The significant association between urinary TCM (of the most abundant THM) and HbA1c, after adjusting for classical confounders warrants further investigation in a bigger sample. In our analysis, the fact that this association was shown only in the linear regression analysis and not when the two groups (HbA1c < and >5.7%) were compared, possibly indicates that the pathway between exposure and metabolic effect is complex and cannot be elucidated without more accurate measurement of exposures. A prospective analysis of exposures and outcomes is warranted, including the measurement of intermediate steps (eg, other biomarkers of effect) lying in the biological pathway. Our biomonitoring THM data for TCM were corroborated by earlier personal air measurements in healthcare facilities, where nurses were the single occupational group with the highest exposure to (semi) volatile organic compounds, including TCM, followed by cleaners and floor strippers/waxers (34).

Our results coincide with those of other studies in the general population that showed the association between THM and type 2 diabetes (9, 35). Participants in the upper tertile of urinary Br-THM levels had a higher risk for type 2 diabetes (OR 3.99, 95% CI 1.07, 19.7) when compared with the lower tertile participants (35). Non-drinkers with elevated alanine aminotransferase (ALT) activity (men: 40 IU/L and women: 30 IU/L) were 2.88 times more likely (95% CI 1.21, 6.81) to have higher circulating TBM levels (one of the Br-THM) after adjustment for potential confounders in the US NHANES dataset (1999–2006) (10). A case–control study (N=95) showed that THM could act as hepatic toxins that elevated liver enzyme ALT, potentially causing hepatic injury and thus, signaling that initiation of diabetogenic effects had occurred (9).

The use of JEM and JTEM in occupational health studies is a novel approach in better classifying the reported disinfectant exposures at work, taking the form of the overall reported exposure per job/department (JEM) and job-task (JTEM) activities. Such an approach appears to be suppressing the differential misclassification bias induced from studies that solely rely upon self-reported metrics of exposure (36–38). The JEM protocol assigned exposure by department, thus, assigning the same exposure to all nurses of the same department. As a further step, the JTEM protocol assigned exposure per task, thus taking into consideration the variability of exposure among departments, hence, further limiting this differential classification (16). In comparison with self-reported exposure metrics, the use of JEM/JTEM methods seemed to allocate exposure with higher specificity and sensitivity, at least for the higher exposure groups (16).

The HbA1c diagnostic test has been routinely used as an average measure of blood glucose levels over a period of up to three months, with little if any, within subject variability. A notable between-nurses variability of HbA1c levels was observed at different sampling times during the day where urine voids were always collected at the end of the shift work. Specifically, the morning urine HbA1c levels (at the end of the night shift) were lower in magnitude than those obtained at the noon or afternoon sampling times; this relationship did not hold when the crude effects were adjusted for the full model. Simulated night work including circadian misalignment or simulated day work including circadian alignment in a randomized cross-over trial showed that circadian misalignment significantly increased postprandial glucose by 5.6% (P=0.004) in healthy chronic shift workers (34).

In recent years, the gradual transition of higher type 2 diabetes and pre-diabetes incidence rates to younger ages has been documented (39). A population-based, cross-sectional study in England showed the increase in the percentage of pre-diabetic individuals with the prevalence rate of pre-diabetes increasing from 11.6% to 35.3% from 2003 to 2011 (39). Similar findings were reported for the Cypriot population, where ~60% of pre-diabetics fell <40 years of age (40). The prevalence of pre-diabetes in this study's relatively young nurses group (mean 36 years) was 16.0%, while the prevalence of type 2 diabetes and pre-diabetes for the general population of Cyprus were 9.2% and 16.3%, respectively, using the World Health Organization cut-offs (40).

The study had certain limitations. The participation rate was relatively low (25.6%), preventing us from extrapolating the results to the whole nurses population. Heavy workload resulted in low participation of nurses from a few departments of the two hospitals. The fact that end of shift information and urine sampling were required did not help in reducing attrition. Despite that both verbal and visual (pictures of common products containing the disinfectants) materials were used during the administration of the questionnaires, most nurses were not aware of the type of disinfectants they were using. It is possible that information and recall bias occurred, but not more than what occupational studies with disinfectants could typically face. Additionally, the sample size of the study is relatively small, and the number of tests was large. Since the number of significant associations was rather small and it did not highlight a trend between specific exposure metrics or specific disinfectants and the outcome. We opted not to perform a correction for multiple testing in order to use all available results to inform future studies. Considering these limitations, all associations should be interpreted with caution before they are replicated in larger studies.

Concluding remarks

In recent years, the use of disinfectants has come under scrutiny given the links between healthcare-associated infections and antimicrobial resistance. This cross-sectional occupational study presented possible associations between shift work and urinary biomarkers of exposure to DBP (ie, TCM) with HbA1c levels in active nurses. A significant association between the number of monthly night shifts and HbA1c was observed, but no consistent associations were found between three exposure metrics of 11 different disinfectants, or urinary THM and point of care HbA1c levels in active nurses. This is a novel dataset adding to the literature on the possible metabolic effects of disinfectants/DBP that have not been investigated before in an occupational setting. A larger prospective sample is warranted to infer whether human exposures to disinfectants are indeed associated with a higher risk of developing pre-diabetes.

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