Health Consequences of Disinfection Against SARS-CoV-2: Results of a Biomonitoring Approach

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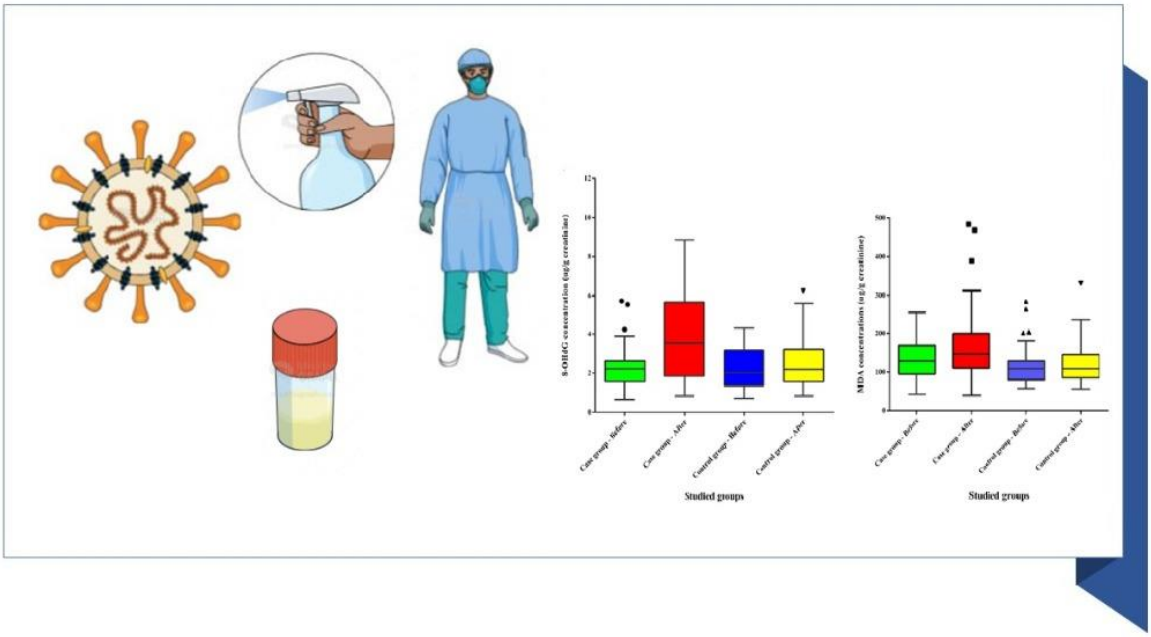
Abstract

We aimed to assess the health effects of exposure to disinfectants during the COVID-19 pandemic by measuring DNA oxidative damage markers. 75 operators engaged in disinfection of public places were recruited as the case group, and 60 individuals who were not exposed to disinfectant were chosen as the control group. Spot urine samples were collected before (BE) and after exposure (AE) to disinfectants in the case group. Likewise, controls provided two spot urine samples in the same way as the case group. 270 urine samples were gathered, including 150 samples from the case group and 120 samples from the controls. Urinary malondialdehyde (MDA) levels were quantified from the formation of thiobarbituric acid reactive substances in the urine. Besides, an ELISA kit was used to determine the concentration of 8-hydroxy-2′-deoxyguanosine (8-OHdG) in the urine. Results showed significant differences in the urinary levels of DNA oxidative damage markers, where median 8-OHdG and MDA levels in case group AE samples were 1.55 and 1.35-time higher than the control group AE samples ($P<0.05$), respectively. Besides, urinary levels of DNA oxidative damage markers in AE samples of the case group were significantly higher than BE samples ($P<0.05$). Our results reflect that exposure to disinfectants is associated with increased concentration of DNA oxidative damage markers in disinfection operators. Regression analysis identified the use of gloves and the volume of disinfectant used as predictors of oxidative damage. With this in mind, implementing robust protective measures, such as specific respirators, is crucial to reduce the health burdens of exposure to disinfectant.

Keywords: Biomonitoring, COVID-19, Disinfectants, DNA oxidative damage, Urinary biomarkers.

Impact statement: Our work presents the first biomonitoring study to address health consequences of disinfection against SARS-CoV-2.



1. Introduction

COVID-19, a disease caused by the severe acute respiratory syndrome 2 (SARS-CoV-2) virus, was first reported in late 2019 in Wuhan, China, and then rapidly spread to other countries worldwide. The new coronavirus showed higher transmissibility potential than SARS-CoV and MERS-CoV [1]. With this in mind and because of its rapid spread, the World Health Organization (WHO) declared this viral outbreak a pandemic on March 11, 2020 [2]. In addition, according to the WHO situation report, there have been over 65.8 million confirmed cases and over 1.5 million deaths reported around the world, with over one million confirmed cases and over 50,000 deaths in Iran (as of December 7, 2020) [2].

To date, studies reported that SARS-CoV-2 could be transmitted to humans through person-to-person contact, fomites, aerosol, and droplets [3-5]. Likewise, studies reported that 1 ml of an infected individual's sputum contains 108 viral copies [6]. COVID-19 infection symptoms have been mainly reported as cough, fever, fatigue, and dyspnea [7]. According to Johns Hopkins University's coronavirus resource center, the average case fatality rate of SARS-CoV-2 is 2.2%, with the highest (29.1%) and lowest (0.2%) reported in

Belgium and Vietnam, respectively [8]. In most cases, the disease onset could be mild; however, the infection could cause severe illness such as Acute Respiratory Distress Syndrome (ARDS) and even death in individuals over 70 years old and those with immunodeficiency [9].

Contamination of frequently touched surfaces in public places is one of the potential sources of SARS-CoV-2 transmission. With this in mind, WHO recommends consistent and proper environmental cleaning and disinfection procedures to ensure that frequently touched surfaces are free from SARS-CoV-2 [2]. Studies recently reported the effectiveness of various disinfectants such as ethanol (78-95%), isopropanol (70-100%), formaldehyde (0.7-1%) and other available disinfectants against the inactivation of SARS-CoV-2 [10, 11]. However, various disinfectants require different concentrations in order to be effective against SARS-CoV-2. For instance, hydrogen peroxide could inactivate SARS-CoV-2 with a concentration of 0.5%, while other disinfectants like sodium hypochlorite need a concentration of at least 0.21% to inactivate the SARS-CoV-2 [11].

Individuals who get involved in disinfection procedures of public settings can be potentially exposed to significant levels of disinfectant chemicals through inhalation and dermal contact, which could cause adverse effects on their health. Adverse health effects such as asthma, inflammatory reactions in the airways, decreased lung function, and eye irritation have been correlated with exposure to disinfectants and cleaning products [12]. In addition, Vizcaya, Mirabelli *et al* [13]) found a significant correlation between the use of cleaning sprays and lower forced expiratory volume (FEV1) in cleaning workers. Likewise, a significant association between occupational exposure to disinfectant and increased risk of chronic obstructive pulmonary disease (COPD) was reported among nurses who had worked in different hospitals across the United States [14].

Human biomonitoring (HBM) is a reliable complementary approach in exposure assessment and has been used widely for many years to characterize environmental and occupational exposure to different contaminants and chemicals in the general population and various occupational settings [15-18].

Considering the increasing use of disinfectants during the COVID-19 pandemic and the lack of scientific-based evidence regarding the health consequences of disinfectant exposure in those engaged in disinfection

of public places against SARS-CoV-2, this study aims to fill that gap. With this in mind, a biomonitoring approach was used to assess the health effects of exposure to disinfectants among individuals involved in the disinfection against SARS-CoV-2 during the COVID-19 pandemic. DNA oxidative damage markers, including malondialdehyde (MDA) and 8-hydroxy-2′-deoxyguanosine (8-OHdG), were measured.

2. Materials and methods

2-1. Study area and selection of the participants

We collected urine samples from two groups of subjects according to their known occupational exposure to disinfectants. The exposed group were individuals involved in the disinfection process of various big grocery stores across Tehran, Iran's capital, with a population of over 10 million inhabitants.

Since this is the first study to evaluate oxidative damage related to the use of disinfectants, no power calculation could be done to determine the number of samples. Instead, scientific judgement and professional expertise were used to decide an optimal size group of 75 operators who were healthy and engaged in public places' disinfection to be recruited as the case group. Besides, the non-exposed group consisted of 60 healthy individuals who were not exposed to disinfectant exposure, either from occupational or environmental exposure.

Several inclusion criteria were set for both the case and control subjects. Recruitment of the case participants into the study was subjected to the following inclusion criteria:

1. Individual must have engaged in public places disinfection process as an operator;
2. Participation in the study should be voluntary;
3. Participation restricted to non-smokers, to capture the effect of exposure to disinfectant only;
4. Healthy individuals with no background disease;

5. No occupational exposure to disinfectants; and

6. Individuals not exposed to high levels of occupational stressors, such as high temperature and humidity, and higher levels of chemical pollutants in their working environment.

Subjects who could not satisfy the case inclusion criteria mentioned above were excluded from the study.

In addition, the inclusion criteria for subjects in the control group were:

1. Individuals not occupationally exposed to disinfectants.

2. Participation in the study should be voluntary;

3. Not using sodium hypochlorite for disinfecting their living environment;

4. Healthy individuals with no background disease;

Any subjects who could not satisfy the inclusion criteria for the control group mentioned above were excluded from the study. Subjects in the control group were asked to minimize their hand sanitizer usage and wash their hands with soaps instead. In addition, all subjects filled out a questionnaire including socio-demographic information and information about respiratory and cardiovascular impairments such as asthma and high blood pressure. All subjects in the case group used hypochlorite sodium as the disinfectant in the course of performing their operations. The Ethical aspects of the present study were approved by the National Institute for Medical Research Development (NIMAD) of Iran, under ethic no. IR.NIMAD.REC.1399.085.

2-2. Urine sampling

Urine samples from subjects in the case group were collected twice: the first urine sample was collected before the disinfection process, considered the before exposure (BE) sample hereafter. In addition, a second urine sample was collected after the disinfection process completion, considered the after exposure (AE) sample. The whole disinfection process lasted two hours. Likewise, participants in the control group provided two spot urine samples in the same way as the case group. In total, 270 urine samples were collected, including 150 samples from the case group and 120 samples from the control subjects. Urine samples were collected into 60mL polypropylene vials, labelled, and transferred to the laboratory using a portable fridge 4 °C.

2-3. Identification of urinary MDA and 8-OHdG

The urinary MDA levels were quantified from the formation of thiobarbituric acid reactive substances in the urine based on the method described elsewhere [19]. Briefly, 500 µL of urine were exposed to phorbol-myristate acetate (PMA) (10 µgmL-1). In the next step, samples were centrifuged at 1200 rpm for 10 minutes at 4 °C and the supernatant was collected. After vortexing for 5 s, butylated hydroxytoluene (BHT) was added at a concentration of 0.02% to prevent further lipid peroxidation. Finally, samples were incubated at 90-100 °C for 15 min and cooled at room temperature, centrifuged at 10,000 rpm for 10 min, and finally measured spectrophotometrically at a wavelength of 535 nm.

DNA Oxidative Damage ELISA kit (Zell Bio, GmbH., Germany) was used to determine the concentration of 8-OHdG in the urine based on the method described elsewhere [20]. In brief, 100 µL of conjugate 8-OHdG/ bovine serum albumin (BSA) were added to each of the 96-well plates of the ELISA kit and incubated overnight at 4 °C and washed with water, followed by 200 µL blocking buffer and incubated for 1 hour at room temperature. 50 µL of samples of 8-OHdG standards were added, and after 10 minutes of incubation, 100 µL of monoclonal anti-8-OHdG was added and incubated for 1 hour at room temperature, then washed three times by the addition of secondary antibody conjugated to 100 µL of horseradish peroxidase, followed by 1-hour incubation at room temperature. Next, 100 µL of substrate for peroxidase was added to the plate and incubated for 20 minutes. Then, 100 µL of reaction stop solution was added. Absorbance was spectrophotometrically measured at a wavelength of 450 nm. The amount of 8-OHdG was calculated by comparison with a standard curve determined from standards treated similarly to the samples. In addition, both MDA and 8-OHdG were corrected for creatinine, determined by the Jaffé reaction method [21].

2-4. Statistical approach

In the present study, SPSS 21.0 package software (SPSS Inc. Chicago, IL) and Graph Pad Prism software 8.0 were used to perform statistical analysis on oxidative stress markers in urine samples. The normality of the data distribution was checked using the Kolmogorov–Smirnov test. Since data was not normally distributed, Mann–Whitney U test was employed to assess differences in urinary levels of MDA and 8-

OHdG among studied groups. Multiple linear regression analysis was applied to evaluate the association between concentrations of oxidative stress biomarkers and variables describing use of disinfectants, use of personal protective equipment and covariate factors, including age, BMI.

3. Results and Discussion

3.1. General characterizations of the participants

Table 1 represents the socio-demographic characteristics and health status of the participants. No significant differences were observed between cases and controls in terms of age and BMI ($P>0.05$). There was a significant difference between studied groups in regarding education ($P<0.05$). Subjects in the case group had used significantly higher hand sanitizers than controls ($P<0.05$). In addition, subjects in the case group used significantly higher volumes of disinfectants than controls ($P<0.05$). According to information obtained by the questionnaire and personal interviews, almost half of the subjects in the case group reported skin and eye irritation after using disinfectants, a frequency significantly higher than reported by participants in the control group ($P<0.05$).

Table 1. Socio-demographic characteristics and health status of the participants

Variables	Case (n=75)	Control (n=60)
Age (years)	39 ± 9	41 ± 10
Height (cm)	177 ± 5	175 ± 4
Weight (kg**)**	78 ± 11	75 ± 9
BMI (kg/m^2)	27 ± 4	25 ± 5
Education (%)		
High school Diploma	55	10
Bachelor	45	50
Master	-	40
Using hand sanitizers per day (%)		
Up to-3 times/day (Low)	44	95
3-6 times/day (Medium)	26	5
More than 6 times/day (High)	30	-
Volume of disinfectants usage per week (%)		

Less than 20 cc	-	55
21-35 cc	29	35
36-50 cc	38	10
More than 50 cc	33	-
Using disinfectants to disinfect surfaces per day (%)		
Up to-3 times/day (Low)	38	100
3-6 times/day (Medium)	35	-
More than 6 times/day (High)	27	-
Skin irritation after using disinfectants (%)		
Yes	46	34
No	54	66
Eyes irritation after using disinfectants (%)		
Yes	48	25
No	52	75

3.2. Urinary profile of MDA and 8-OHdG

Results of DNA oxidative damage urinary biomarkers are presented in Table 2 and Figure 1. Concentrations of 8-OHdG in the present study (arithmetic means ranging between 2.27 and 3.84 µg/g creatinine) are similar to those reported for garage and waste collection workers exposed to traffic emissions in Finland [22]; workers exposed to TiO_2, SiO_2 and indium tin oxide nanomaterials in Taiwan [23]; and waste collectors exposed to polycyclic aromatic hydrocarbons in China [24], with 8-OHdG concentrations in the range of 3.28 and 3.65 µg/g creatinine. Similar concentrations were measured in control groups in occupational exposure studies in China [24, 25], Taiwan [26, 27] and Finland [22], with 8-OHdG concentrations ranging 2.86-4.10 µg/g creatinine. Very few occupational exposure studies reported lower concentrations than those measured in the present study, such as those reported for farmers exposed to pesticides [28] in South Korea and concentrations in the control group in Taiwan [23, 29], which range 0.9-1.84 µg/g creatinine. On the contrary, most occupational exposure studies report 8-OHdG concentrations higher than those measured in the present study. Workers exposed to organic compounds, such as spray painters exposed to ethylbenzene [30], pharmacy technicians exposed to antineoplastic drugs [31] or plastic recycling workers exposed to di-(2-ethylhexyl) phthalate [32] reported higher 8-OHdG concentrations, in the range of 15 to 30 µg/g creatinine. Larger concentrations than those measured in this study were also reported in occupationally exposed workers to heavy metals. 8-OHdG concentrations ranged 5.0-7.8 µg/g creatinine for foundry plant worker [29], aluminium smelter workers [33] and electroplaters [26], whilst the largest were recorded for lead-zinc and

steel-iron mining and smelting workers, with mean 8-OHdG concentrations ranging 92.7-103.40 μg/g creatinine. Concentrations were also higher than current levels for workers exposed to combustion emissions, such as cooks in India [34] and China [25], highway toll station workers in China [35](7.56 - 14.47 μg/g creatinine), as well as firefighters in the USA (70 ± 90 μg/g creatinine) [36].

The concentrations of MDA in workers involved in disinfectant jobs to eliminate SARS-CoV-2 from surfaces in Iran (169 ± 89 μg/g creatinine) are similar to concentrations measured for cooks in Taiwan exposed to cooking fumes [25, 37], electroplating workers exposed to hexavalent chromium [26, 38] and miners exposed to elemental mercury [39], with concentrations of MDA ranging between 152 and 199 μg/g creatinine. Similarly, the MDA concentrations measured in the control groups are within the same range of concentrations (102-135 μg/g creatinine) than those measured in the control group in the present study (129 ± 52 μg/g creatinine). On the other hand, lower MDA concentrations were reported for wildland firefighters exposed to woodsmoke (68.4 ±21.6 μg/g creatinine) [36], rural population in the north of China exposed to e-waste PAH emissions (ranging 44.2–132 μg/g creatinine) [40] or farmers exposed to pesticide (9.58 ± 5.04 μg/g creatinine) [28].

Significant differences were observed in urinary 8-OHdG levels between studied groups, where the median 8-OHdG levels in case group AE samples were 1.55-time higher than control group AE samples ($P<0.05$). Likewise, the urinary median 8-OHdG level in case group AE samples was 1.21-fold higher than BE samples ($P<0.05$). On the other hand, no significant differences were observed for median urinary 8-OHdG levels between case group BE samples and control group BE samples ($P>0.05$). In addition, there were no significant differences for median urinary 8-OHdG levels between case group BE samples and control group AE samples ($P>0.05$).

In terms of MDA, significant differences were observed between studied groups, where the median urinary MDA levels of case group AE samples were 1.15-fold higher than BE samples ($P<0.05$). Likewise, the median MDA levels in case group AE samples were 1.35-time higher than the corresponding values in control group AE samples ($P<0.05$). No significant differences were observed for median urinary MDA levels between case group BE samples and control group AE samples ($P>0.05$). In addition, there were no

significant differences between control group BE and AE samples in terms of median urinary MDA levels ($P>0.05$).

The comparative analysis results between the DNA and lipid oxidative damage markers suggest that the use of sodium hypochlorite as a disinfectant produces oxidative damage in the workers. This is consistent with information extracted from the Hazardous Substances Data Bank (HSDB), which reports that sodium hypochlorite is a strong oxidizing agent [41, 42]. Hawkins and Davies (1998) reported that hypochlorite damages proteins by reaction with amino acid side-chains or backbone cleavage producing high- and low-molecular-mass nitrogen-centred protein-derived radicals. In their experiment, these radicals reacted with ascorbate, glutathione, and synthetic vitamin E [43]. This suggests that hypochlorite exposure may produce hypochlorite-derived radicals leading to oxidative stress, which could overwhelm the antioxidant capacity leading to oxidative DNA and lipid damage. Hypochlorite can also directly react with a large number of biomolecules, including proteins, lipids and DNA [44-47], which could also explain the increase in DNA and lipid oxidative damage markers measured in the exposed workers.

Table 2. Urinary levels (µg/g creatinine) of DNA oxidative damage markers in the studied groups

Markers	Case group – before exposure (BE)		Case group – after exposure (AE)		Control group – morning (equivalent to BE)		Control group – afternoon (equivalent to AE)	
	Mean ± S.D (Min-Max)	Geo mean	Mean ± S.D (Min-Max)	Geo mean	Mean ± S.D (Min-Max)	Geo mean	Mean ± S.D (Min-Max)	Geo mean
8-OHdG	3.40 ± 1.95 (0.7-9.8)	2.89	3.84 ± 2.89 (0.85-8.81)	3.2	2.27 ± 1.02 (0.76-4.3)	2.04	2.54 ± 1.21 (0.86-6.24)	2.29
MDA	136 ± 51.3 (43.2-255)	127	169 ± 89 (40.6-509)	152	115 ± 46 (59-284)	108	121 ± 47 (57-331)	113

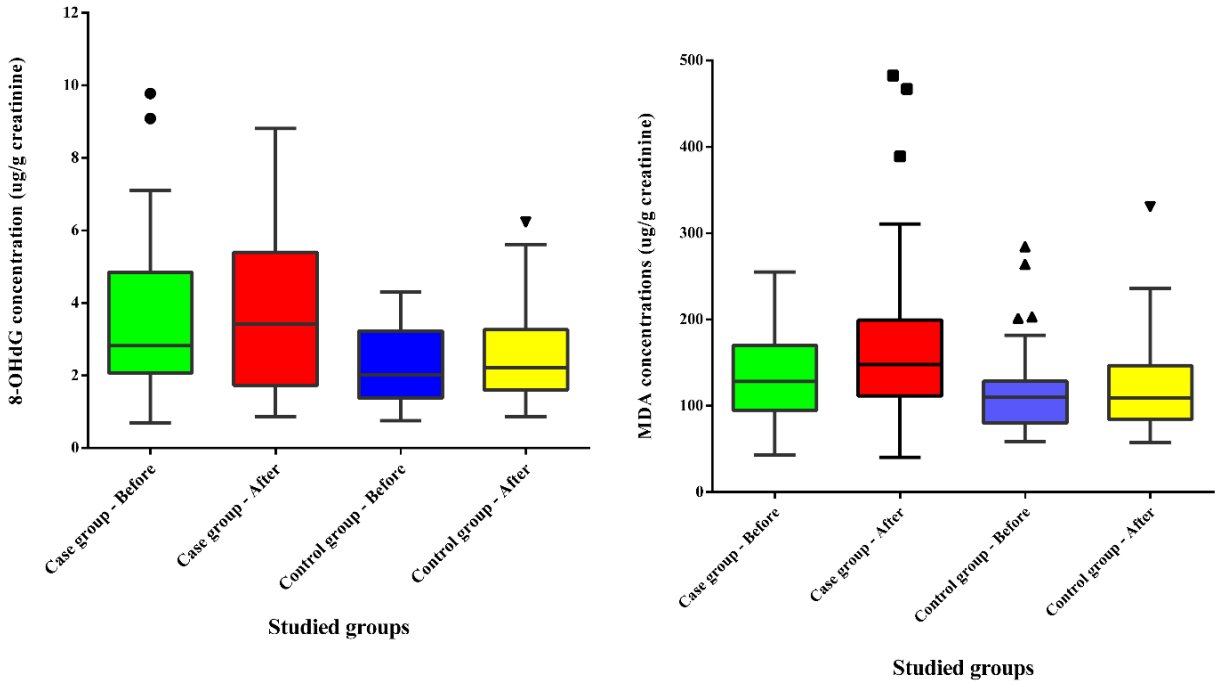


Figure 1. Urinary MDA and 8-OHdG levels in studied groups

3.3. Multivariate regression analysis

Results of the multivariate regression analysis are provided in Table 3. Using gloves and the volume of disinfectants used were highlighted as the predictor factors affecting the urinary concentrations of MDA and 8-OHdG in the studied groups. The fact that the volume of disinfectant used is a predictor of the concentration of MDA and 8-OHdG urinary concentrations strengthens the suggestion that exposure to sodium hypochlorite is associated with DNA and lipid oxidative damage. The analysis presented in Table 3 also provides insights into the possible routes of exposure to sodium hypochlorite. On one hand, exposed subjects report a larger frequency of skin irritation (Table 1). In addition, according to Table 3, those who did not use gloves reported concentrations of MDA 0.402 µmol/mol creatinine (95% CI: 0.396, 2.008 µmol/mol creatinine) higher and concentrations of 8-OHdG 0.382 ng/mmol creatinine (95% CI: 0.154, 0.542 ng/mmol creatinine) higher than those who do use gloves. These results are highly suggestive that

dermal contact might be an important route of exposure to sodium hypochlorite, leading to increased levels of DNA and lipid oxidative damage in the workers in charge of disinfecting surfaces with sodium hypochlorite as a preventative measure against COVID-19 transmission. Likewise, Table 1 shows that workers using sodium hypochlorite to disinfect surfaces reported eye irritation more frequently ($p<0.05$). This is suggestive that vapours associated with the use of sodium hypochlorite might causing the eye irritation. However, under normal conditions, chlorine gas is not released by bleach solutions and hence inhalation of sodium hypochlorite vapours is very rare [48]. On the other hand, mixing bleach with acids, like acidic cleaning agents, releases highly irritant gases [48, 49]. The large frequency of workers reporting eye irritation suggests that this might have been a common practice undertaken during their job chores in the population under study.

Table 3. Association between oxidative stress biomarkers concentrations and exposure to disinfectants and other potential confounders

MM Levels and covariates	MDA (µmol/mol creatinine)			8-OHdG (ng/mmol creatinine)		
	Estimate	[95% Conf. Interval]		Estimate	[95% Conf. Interval]	
Age	-0.100	-4.573	1.715	-0.212	-4.790	0.653
BMI	0.018	-0.269	0.087	0.022	-0.172	0.094
Education	0.024	-0.069	0.094	-0.030	-0.134	0.086
Using gloves (reference: yes)	0.402	0.396	2.008	0.382	0.154	0.542
Using hand sanitizer (reference: no)	0.063	-0.169	0.194	0.041	-0.372	0.092
Volume of disinfectants	0.314	0.117	2.859	0.281	0.182	0.908

Green cells represent regression coefficients with p-value <0.05.

The main limitation of the study is that no information is available on other exposures that could have lead to increase levels of DNA and lipid oxidative damage in the population under study. This might could have also been associated with exposure to traffic emissions [50, 51], cooking fumes [25, 52, 53], per- and polyfluoroalkyl substances [54, 55], heavy metals [56-60], VOCs [30, 61, 62] and pesticides [28, 63]. On the other hand, it has adequately controlled for the smoking-associated DNA and lipid oxidation damage by recruiting non-smokers only,

with similar anthropometric measures (age, height, weight, BMI), which also may affect oxidative biomarker concentrations [64-67].

4. Conclusions

To the best of our knowledge, this is the first study to examine the association between the use of sodium hypochlorite as a disinfectant against SARS-CoV-2 and its health effects associated with oxidative damage, using biomarkers of DNA and lipid peroxidation. A simple protective measure, such as the use of gloves, was identified as an effective way of reducing exposure to sodium hypochlorite and its associated DNA and lipid oxidation damage. In addition, a large proportion of workers frequently reported eye irritation. Since sodium hypochlorite is extensively used to clean surfaces as a preventative measure against COVID-19 transmission, it is recommended that workers handling sodium hypochlorite use gloves, suitable respirators, and safety goggles to reduce health effects associated with its handling.

Data availability: Additional data can be found in supplementary section.

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Competing interests:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.