Journal of Health Care Communications
ISSN: 2472-1654

Open access Research Article

E-cigarette/Vaping Associated Lung Injury (EVALI) Severity Correlates with Reduced Diffusing Capacity, Need for Lung Biopsy, and Deposition of Titanium in Lung Tissue

Andrew Weber[1,2], Vicken Khazar[2,3], Samuel Escobar[3,4], Robert Promisloff[5], Keely Cheslack-Postava[6], Juergen Thieme[7,8], Mary Lee-Wong[9,10], Anthony M Szema[2,3,11,12,13,14*]

[1]Mather Pulmonary and Sleep Associates, Port Jefferson, USA
[2]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell Health, USA
[3]Three Village Allergy and Asthma, South Setauket, USA
[4]Warren Alpert Medical School at Brown University, Providence, USA
[5]Drexel University College of Medicine, Philadelphia, USA
[6]Department of Psychiatry, Columbia University Global Psychiatric Epidemiology Group, NYSPI Columbia University, USA
[7]Brookhaven National Laboratory's National Synchrotron Light Source II Beam Line ID-5, Upton, USA
[8]Institute for X-Ray Physics, University of Goettingen, Germany
[9]Icahn School of Medicine at Mount Sinai, New York City, USA
[10]Maimonides Medical Center, New York City, USA
[11]Department of Pulmonary and Critical Care and Division of Allergy/Immunology, Northwell Health, USA
[12]Department of Occupational Medicine, Epidemiology and Prevention, International Center of Excellence in Deployment Health and Medical Geosciences, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, USA
[13]Department of Technology and Society, College of Engineering and Applied Sciences, Stony Brook University, USA
[14]RDS2 Solutions Inc., Stony Brook, NY, USA

ABSTRACT

Originally marketed as a safer tool for cigarette smoking cessation, electronic cigarettes (e-cigarettes) and vaping devices have now been associated with e-cigarette/vaping associated lung injury (EVALI). Examination of lung tissue from these patients is infrequent. We now report a cohort of 19 vaping adults hospitalized with EVALI (IRB 20-0094 Feinstein Institutes of Medical Research, Northwell Health). 8 patients were biopsied and one patient's lung tissue was examined at Brookhaven National Laboratory's National Synchrotron Light Source II Beam Line ID-5 for the presence of metals. This sample contained abundant amounts of titanium and small amounts of chromium, iron, zinc, calcium, and copper. Vaping coils contain titanium, which is heated via a battery and aerosolized in the inhaled plume. Titanium is pro-inflammatory and may induce lung scarring. Subjects who vaped more frequently and for a longer duration had a lower DLCO, increased necessity of undergoing a lung biopsy, and a longer duration of hospitalization. Lung volumes and spirometry were normal in all patients. Concurrent cannabis use was self-reported in 95% of subjects, while concurrent tobacco use was 32%. 26% were diagnosed with COVID-19 pneumonia during their hospitalization.

EVALI may result in hospitalization and respiratory failure. An etiology for EVALI is not yet determined. We report, for the first time, titanium, among other metals, in the biopsy of a patient with EVALI. Titanium may induce lung injury

Received:	27-September-2023	**Manuscript No:**	IPJHCC-23-17841
Editor assigned:	29-September-2023	**PreQC No:**	IPJHCC-23-17841 (PQ)
Reviewed:	13-October-2023	**QC No:**	IPJHCC-23-17841
Revised:	18-October-2023	**Manuscript No:**	IPJHCC-23-17841 (R)
Published:	25-October-2023	**DOI:**	10.36846/2472-1654-8.5.8049

Corresponding author Anthony Szema, Department of Pulmonary and Critical Care and Division of Allergy/Immunology, Northwell Health, USA, E-mail: aszema@northwell.edu

Citation Weber A, Khazar V, Escobar S, Promisloff R, Cheslack-Postava K, et al. (2023) E-cigarette/Vaping Associated Lung Injury (EVALI) Severity Correlates with Reduced Diffusing Capacity, Need for Lung Biopsy, and Deposition of Titanium in Lung Tissue. J Healthc Commun. 8:8049.

among the 2.55 million adolescents who vape regularly. We earlier reported oxidized titanium in lung tissue of soldiers exposed to burn pits in Iraq and Afghanistan with Iraq Afghanistan War Lung Injury (IAW-LI). Those samples also indicate titanium was burned before inhalation. The role of titanium in both these inhalational lung injuries requires further investigation.

Keywords: Vaping; E-cigarette; Titanium; EVALI; Lung biopsy; Diffusing capacity for carbon monoxide; Marijuana/Cannabis; Tobacco

INTRODUCTION

According to the 2022 National Youth Tobacco Survey (NYTS), more than 2.55 million (9.4%) high school and middle school students in the United States use e-cigarettes [1,2]. E-cigarette use (vaping) has previously been marketed as healthier, as well as a safe cessation tool for cigarette smoking [3]. However, vaping has been associated with EVALI since August 2019, in a Wisconsin cohort [4]. Further, the CDC reports 2,807 cases of EVALI and 68 associated deaths as of February 2020 [5,6]. In 2016, other investigators found that 75% of electronic-liquids (e-liquid), the substance in e-cigarettes that is aerosolized and inhaled, contained diacetyl and 94% of bronchoalveolar lavage (BAL) samples from e-cigarette users contained vitamin E acetate [7,8]. Diacetyl was previously associated with bronchiolitis obliterans, initially described as "popcorn lung," which is a form of severe obstructive lung disease of the small airways [9,10]. The role of vitamin E acetate has not been further elucidated. Thus, many researchers and health officials largely associated the negative health effects of vaping with these ingredients [11]. Diacetyl was originally banned from e-cigarette products by the European Union in 2016, and the UK followed suit in 2019 [12]. Furthermore, diacetyl and vitamin E acetate are now undetectable in regulated e-cigarettes in the US, including brands JUUL, King Louis, and Crazy 8 products, although they are not formally banned [13]. However, despite an undetectable amount of diacetyl and Vitamin E acetate in e-liquids, cases of EVALI, although fewer than in past years, have still been reported [14].

Given recent EVALI cases despite the absence of diacetyl and vitamin E acetate, it is reasonable to pursue an alternative cause of EVALI. We hypothesize that fragments of metal from the e-cigarette coil are being aerosolized when heated by the battery and inhaled by the user, causing an accumulation of metals, such as titanium, chromium, calcium, iron, nickel, and copper, in the lungs. Inhalation exposure to titanium causes pulmonary inflammation and may lead to fibrosis in the lungs [15]. We hypothesized that pulmonary function testing with spirometry and lung volumes is not sensitive enough to detect EVALI, and that DLCO should be included in evaluations. For our cohort, we investigated contributory factors for morbidity due to EVALI. These factors included frequency and duration of vaping, concurrent tobacco and marijuana smoking with vaping, as well as rates of COVID-19 pneumonia.

METHODS

Study Design

This study was approved by the Feinstein Institutes of Medical Research, Northwell Health (IRB 20-0094). We retrospectively examined a database consisting of an anonymously coded, de-identified cohort of 19 patients who were hospitalized at either North Shore University Hospital or Long Island Jewish Medical Center with new-onset respiratory symptoms and diagnosed with e-cigarette/vaping associated lung injury (EVALI). We also reviewed patient-demographics, including: Age, sex, tobacco and marijuana smoking status, duration of hospitalization, and vaping status. All patients underwent extensive pulmonary workup, and clinical indices included:

- Spirometry
- Lung biopsy when applicable
- Lung volumes
- Diffusing capacity for carbon monoxide (DLCO)

Venovenous extracorporeal membrane oxygenation (VV-ECMO) was employed for one patient who experienced severe refractory respiratory failure. 7 patients had transbronchial lung biopsies, while one had a thoracoscopic lung biopsy performed. All patients were tested for COVID-19 via polymerase chain reaction (PCR) during hospitalization. Patients who had a positive COVID-19 PCR result and abnormal chest X-ray were diagnosed with COVID-19 pneumonia by a pulmonologist.

Pulmonary Function Testing

Within 6 weeks of discharge from the hospital, we conducted spirometry, lung volumes, and DLCO, according to American Thoracic Society guidelines. Findings were interpreted using the standards of Crapo and colleagues [16-18].

Procurement and Pathological Analysis of Lung Tissue

Subjects underwent lung biopsy when clinically indicated. 7 subjects received transbronchial lung biopsies, and one subject underwent a thoracoscopic lung biopsy. Lung tissue from one patient was examined for metals, including titanium, zinc, calcium, iron, chromium, and copper at Brookhaven National Laboratory's National Synchrotron Light Source II Beam ID-5.

National Synchrotron Light Source II Beam ID-5

Samples were thin sections prepared by our team:

- Sample is a biopsy of a subject's lung
- The biopsy sample was embedded in paraffin; thin sections were taken for these studies
- Sections were mounted on a polymeric microscopy slide (Ted Pella Corporation) for support during the measurements

- The physicists at NSLS-II were blinded to the identity of the sample

PyXRF and Athena software were utilized. Both software packages are open-source and can be found on github.

- http://nsls-ii.github.io/PyXRF/
- https://bruceravel.github.io/demeter/

There is no written permission necessary as this is open-source [19,20].

X-ray fluorescence (XRF) mapping and X-ray absorption near-edge fine structure (XANES) spectroscopy are techniques available at beamline 5-ID, the Sub-micron Resolution X-ray spectroscopy (SRX) beamline, of NSLS-II [20,21]. This lung biopsy sample was prepared as a thin section on a polymeric microscopy slide. The slide was mounted into the beamline for XRF mapping. The optical system of beamline 5-ID allows for focusing X-rays to a spot of about 0.5 µm diameter through which the samples were raster-scanned. The interaction of X-rays with the elements within the sample causes XRF radiation which is collected with an energy dispersive silicon drift detector. Thus, a full XRF spectrum for each individual scan point is created. To identify individual elements, the XRF spectra are fitted using the software PyXRF [19]. With this method, maps showing the distribution of elements were created. Using these maps, hotspots of Ti and Cr within the more abundant Fe have been identified.

Retrospective Chart Review

We retrospectively examined medical records for: Demographic information, vaping device-type, vaping frequency and duration, length of hospitalization, tobacco and marijuana smoking status, radiologic imaging and non-invasive pulmonary function testing, using the American Thoracic Society (ATS) standard interpretation based on Crapo et al., and for a limited cohort, lung biopsy data.

Statistical Analysis

Characteristics and demographic information of the patients were tabulated and the means and standard deviations of pulmonary function testing were calculated. These means were compared to those derived from predictions based on each patient's height, weight, sex, and race as described by the American Thoracic Society [23]. All statistical testing was done at a 95% confidence interval.

Ethics Approval

All methods were carried out in accordance with guidelines and regulations. All experimental protocols were approved by Feinstein Institutes for Medical Research IRB Institutional Review Board Northwell IRB: 20-0094 Feinstein Institute for Medical Research.

RESULTS

Our cohort was separated into groups based on whether the subject had a lung biopsy performed (group 1) or did not (group 2). 42% of subjects presented with symptom severity that warranted lung biopsy analysis, based on physician evaluation. The average ages of group 1 and group 2 were statistically similar (p=0.76). Subjects in group 1 vaped for an average of 1.2 hours per day more than those in group 2 (p=0.02). Similarly, subjects in group 1 vaped for an average of 1.4 years longer than those in group 2 (p=0.006). Both groups had similar rates of COVID-19 pneumonia (p=0.74), concurrent marijuana smoking (p=0.23), and concurrent tobacco smoking (p=0.65). Subjects in group 1 were hospitalized for an average of 1.7 days longer than those in group 2 (p=0.36). Subjects who vaped more frequently and for a longer duration had a lower DLCO (p=0.02), increased necessity of undergoing a lung biopsy, and a longer duration of hospitalization (**Table 1**).

Table 1: Self-reported demographic information and pertinent medical/social history. One subject in group 1 and three subjects in group 2 were lost to follow up

Variable	Group 1 (biopsy)	Group 2 (no biopsy)	P-value	Between-group difference
N (subjects)	7	8	N/A	N/A
Age (years)	34.5 ± 15.9	36.9 ± 17.9	0.76	-2.4
Vaping frequency (hrs/day)	4.1 ± 0.6	2.9 ± 1.0	0.02*	1.2
Vaping duration (years)	4.5 ± 0.9	3.1 ± 0.7	0.006*	1.4
E-cigarette brands	JUUL, King Louis, Crazy-8	JUUL, Crazy-8	N/A	N/A
Length of hospitalization (days)	8.3 ± 4.5	6.6 ± 2.9	0.36	1.7
Concurrent marijuana smoking (%)	88	100	0.23	-12
Strain of marijuana consumption	Delta-9-THC; Delta-8-THC	Delta-9-THC; Delta-8-THC	N/A	N/A
Concurrent tobacco smoking (%)	25	18	0.65	7
COVID-19 pneumonia (%)	25	27	0.74	-2

Note: *denotes statistically significant p-value at 95% confidence interval

All spirometry and lung volume measurements were normal. Diffusing capacity for carbon monoxide was decreased in all subjects. However, DLCO was worse in subjects who underwent biopsy (53%), compared to those who did not (71%) (p=0.02) (**Table 2**).

Table 2: Pulmonary function testing results conducted within 6 weeks after hospital discharge. Two subjects in group 1 and four subjects in group 2 were lost to follow up

Pulmonary Function Testing	Group 1 (biopsy)	Group 2 (no biopsy)	P-value	Between-group difference
N (subjects)	6	7	N/A	N/A
FVC (% predicted)	79.7 ± 42.4	92.4 ± 16.1	0.51	12.7
FEV1 (% predicted)	82.5 ± 42.3	91.4 ± 9.5	0.64	8.9
FEV1/FVC (% predicted)	86.0 ± 3.7	82.0 ± 10.3	0.37	4
TLC (% predicted)	94.5 ± 23.6	93.6 ± 12.9	0.93	0.9
DLCO (% predicted)	53.8 ± 12.4	71.9 ± 9.0	0.02*	-18
ERV (% predicted)	73.8 ± 11.8	84.7 ± 39.6	0.51	-10.9
RV (% predicted)	86.2 ± 29.7	91.1 ± 14.6	0.72	-4.9

Note: *denotes statistically significant p-value at 95% confidence interval

Lung tissue from one subject was examined at Brookhaven National Laboratory's National Synchrotron Light Source II Beam ID-5 for the presence of metals, including titanium. This sample contained titanium, and small amounts of chromium, zinc, iron, calcium, and copper were detected (**Figures 1 and 2**).

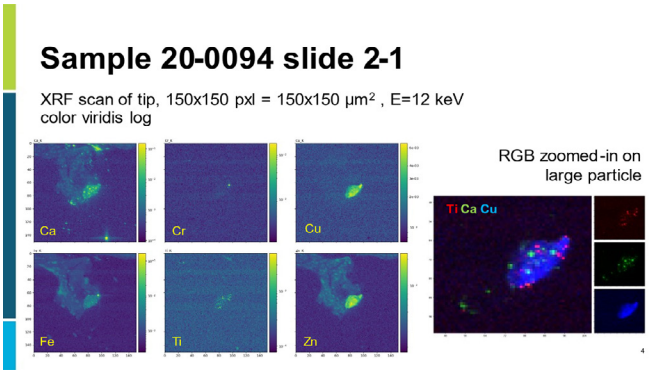

Figure 1: Lung biopsy sample from one subject. Titanium is shown in red and calcium in green in a metal particle mostly consisting of copper, shown in blue. This particle was detected in lung tissue from a patient with EVALI.

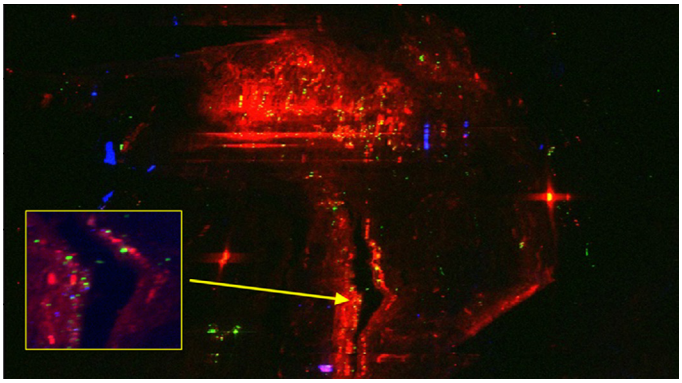

Figure 2: Lung biopsy sample from one subject. Here, titanium is shown as green dots on the background of abundant iron in red in the tissue. The large picture is 800 × 500 pixels with 1 μm pixel size. The blue dots represent calcium. The yellow-framed inset depicts a scan of a smaller area with 0.5 μm pixel size and 160 × 160 pixel. Here, titanium is again visible in green, but as well chromium is apparent in blue. Both elements are known to cause lung diseases, and both metals are constituents of a vaping device. The lung tissue originates from a patient with EVALI. X-ray energy=12 keV, dwell time 0.2 sec/pxl

DISCUSSION

Titanium and chromium, among other metals, were detected in the lung tissue of a subject with EVALI, which was identified by analyzing this tissue at Brookhaven National Laboratory's National Synchrotron Light Source II beamline ID-5. The accumulation of titanium and chromium suggests that both metals from the e-cigarette coils were burned and aerosolized prior to inhalation. Thus, we present a previously undescribed mechanism for EVALI. A similar finding of inhalation related lung injury was observed in Iraq-Afghanistan War Veterans diagnosed with Iraq Afghanistan War Lung Injury (IAW-LI), who were exposed to burn pit plumes and found to have oxidized titanium in lung tissue [24]. Subjects who vaped more frequently and for a longer duration had a lower DLCO, increased necessity of undergoing a lung biopsy, and a longer duration of hospitalization. Spirometry and lung volumes were not sensitive enough to detect EVALI. However, DLCO was reduced in all subjects and worse in those who vaped more frequently and for a longer duration. These subjects were more likely to have undergone a lung biopsy [25].

CONCLUSION

Vaping is not safe and may result in respiratory failure and hospitalization. To date, the mechanism of lung injury associated with EVALI is incompletely understood. However, we have detected an association between EVALI and deposition of metals in the lungs. The severity of EVALI appears to correlate with more frequent and longer duration of vaping and lower DLCO. We believe it is necessary to conduct serial DLCO testing to determine if these changes are acute or chronic in nature.

Although the percentage of cigarette smokers in the US has declined to <12% of the population, the use of e-cigarettes has increased. Considering the rapid increase in popularity of vaping, especially among adolescents with developing lungs, there is notable concern for a future epidemic of vaping-related lung injury. At risk individuals warrant earlier identification and

serial monitoring.

ACKNOWLEDGEMENT

Financial Disclosures

Anthony M. Szema, MD has the following grants to disclose:

1. 2022 Site PI and co-investigator CDMRP Congressionally Directed Medical Research Program DOD Department of Defense Peer Reviewed Medical Research Program (PRMRP) PR211133-"A Wearable Device for Airborne Hazard and Burn Pit Exposure Monitoring" Goal is to test a wearable sensor in simulated burn pit vs. animal and human pathology and physiology.
2. 2021-Present Principal Investigator, New York State A Manufacturing and Technology Resource Consortium (MTRC) Supplemental Award Agreement MTRC Project No. 20211012.1605 Goal is to develop a pulmonary fibrosis drug and medicine for Iraq Afghanistan War Lung Injury (IAW-LI).
3. 2021 U01 OH012264-01 Longitudinal Follow-Up of 9/11 Directly Exposed Children in their Age of Transition: Independence, Occupation and Morbidity (Hoven PI) co-investigator
4. 2020-2024 Consultant, NIH R01 HL152385, Hoven, Amsel (MPIs) 05/01/20-04/30/24, "Childhood Mass Trauma Exposure, Inflammatory Programming, and Psychopathology in Young Adulthood" Goal is to examine blood samples taken from children exposed to the World Trade Center disaster.
5. 2020-Present Principal Investigator, Butterfly Ultrasound Unlimited Cloud Storage Grant for Resource Limited Studies Goal is to save data from ultrasounds of returning soldiers from Iraq and Afghanistan
6. 2018-Present Site Principal Investigator and Co-Investigator Centers for Disease Control Grant CDC NIOSH U01 OH011308 "9/11 Trauma and Toxicity in Childhood: Longitudinal Health and Behavioral Outcomes" Goal is to assess lung and immune function from children who were exposed to the World Trade Center disaster.

CONFLICT OF INTEREST

The authors declare there are no competing interests.

REFERENCES

1. New data show more than 2.5 million us youth currently use e-Cigarettes (2022) U.S. Food and Drug Administration (FDA).
2. Cooper M, Park-Lee E, Ren C, Cornelius M, Jamal A, et al. (2022) Notes from the field: E-cigarette use among middle and high school students-United States, 2022. MMWR Morb Mortal Wkly Rep. 71(40):1283-1285.
3. Zhu SH, Sun JY, Bonnevie E, Cummins SE, Gamst A, et al. (2014) Four hundred and sixty brands of e-cigarettes and counting: Implications for product regulation. Tob Control. 23(Suppl 3):iii3-iii9.
4. King BA, Jones CM, Baldwin GT, Briss PA (2020) The EVALI and youth vaping epidemics-implications for public health. N Engl J Med. 382(8):689-691.
5. Perrine CG, Pickens CM, Boehmer TK, King BA, Jones CM, et al. (2019) Characteristics of a multistate outbreak of lung injury associated with e-cigarette use, or vaping-United States, 2019. MMWR Morb Mortal Wkly Rep. 68(39):860-864.
6. Ellington S, Salvatore PP, Ko J, Danielson M, Kim L, et al. (2020) Update: Product, substance-use, and demographic characteristics of hospitalized patients in a nationwide outbreak of e-cigarette, or vaping, product use-associated lung injury-United States, august 2019-january 2020. MMWR Morb Mortal Wkly Rep. 69(2):44-49.
7. Allen JG, Flanigan SS, LeBlanc M, Vallarino J, MacNaughton P (2016) Flavoring chemicals in e-cigarettes: Diacetyl, 2,3-pentanedione, and acetoin in a sample of 51 products, including fruit, candy, and cocktail-flavored e-cigarettes. Environ Health Perspect. 124(6):733–739.
8. Blount BC, Karwowski MP, Shields PG, Morel-Espinosa M, Valentin-Blasini L, et al. (2020) Vitamin E acetate in bronchoalveolar-lavage fluid associated with EVALI. N Engl J Med. 382(8):697-705.
9. Barrington-Trimis JL, Samet JM, McConnell R (2014) Flavorings in electronic cigarettes: An unrecognized respiratory health hazard? JAMA. 312(23):2493-2494.
10. Boudi F, Patel S, Boudi A, Chan C (2019) Vitamin E acetate as a plausible cause of acute vaping-related illness. Cureus. 11(12):e6350.
11. White AV, Wambui DW, Pokhrel LR (2021) Risk assessment of inhaled diacetyl from electronic cigarette use among teens and adults. Sci Total Environ. 772:145486.
12. Diacetyl-Health risks & illnesses associated with Diacetyl (2023)LawFirm.com
13. Bickford J (2022) Juul ingredients-everything about Juul Pod Ingredients+Mythbusting. Vaping Daily.
14. Vaping Associated Lung Injury (EVALI) (2020) Department of public health. Center for healthy communities.
15. Świdwińska-Gajewska AM, Czerczak S (2014) Titanium dioxide nanoparticles-biological effects. Med Pr. 65(5):651-656.
16. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper B, et al. (2019) Standardization of spirometry 2019 update. An official American thoracic society and European respiratory society technical statement. Am J Respir Crit Care Med. 200(8):e70-e88.
17. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, et al. (2005) Interpretative strategies for lung function tests. Eur Respir J. 26(5):948-968.
18. Crapo RO, Morris AH, Gardner RM (1981) Reference spirometric values using techniques and equipment that meet ATS recommendations. Am Rev Respir Dis. 123:659-664.

19. Li L, Yan H, Xu W, Yu D, Heroux A, et al. (2017) PyXRF: Python-based X-ray fluorescence analysis package. X-Ray Nanoimaging Instrum Methods. 3:103890U.

20. Nazaretski E, Xu W, Yan H, Huang X, Xu W, et al. (2021) Recent advances in nano-scale spatial resolution x-ray microscopy instrumentation at NSLS-II, Proc SPIE 11839. X-ray Nanoimaging Instrum Methods. 5:1183903.

21. Chen-Wiegart YCK, Williams G, Zhao C, Jiang H, Li L, et al. (2016) Early science commissioning results of the sub-micron resolution X-ray spectroscopy beamline (SRX) in the field of materials science and engineering. AIP Conf Proc. 1764:030004.

22. Ferrari AC, Robertson J (2000) Interpretation of Raman spectra of disordered and amorphous carbon. Phys Rev B. 61(20):14095.

23. Culver BH, Graham BL, Coates AL, Wanger J, Berry CE, et al. (2017) Recommendations for a standardized pulmonary function report. An official American thoracic society technical statement. Am J Respir Crit Care Med. 196(11):1463-1472.

24. Olsen T, Caruana D, Cheslack-Postava K, Szema A, Thieme J, et al. (2022) Iraq/Afghanistan war lung injury reflects burn pits exposure. Sci Rep. 12(1):14671.

25. Current cigarette smoking among adults in the United States (2023) Centers for Disease Control and Prevention.