| **מספר המחקר במשרד להגנת הסביבה:****180-1-1** |
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| **כותרת המחקר בעברית:** הקשר בין עומס חלקיקי וסיכונים בריאותיים במפרץ חיפה בהשוואה לגוש דן |
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| **כותרת המחקר באנגלית:**The Association between Particulate Matter (PM) Burden and Health Hazards in the Haifa Bay Area Compared to the Tel Aviv Area |
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| **שנת המחקר** שלישית |

**מוגש ללשכת המדענית הראשית המשרד להגנת הסביבה**

| תאריך הגשה: 25.9.2022 |
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\*תודות:

ד"ר אמיליה חרדק- מנהלת מכון ריאות ב"יח בני ציון

ד"ר שושן ולארי – רופאה ראשית משטרת ישראל

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**תקציר בעברית**

*רקע*: חלק גדול מהמחקרים הסביבתיים נעשים ע"פ נתונים של תחנות ניטור (ניטור סביבתי).

תחנות אלו מודדות רמות של תרכובות אורגניות נדיפות, תחמוצות חנקן, גופרית דו-חמצנית, פחמן חד-חמצני וזיהום חלקיקי. הקשר לחולי נעשה רק באמצעות כלים אפידמיולוגים.

לעומת זאת, ניטור ביולוגי מאפשר מדידה של חשיפה כוללת (ספיגה דרך העור וחשיפה של דרכי הנשימה). בסוף חודש דצמבר 2018, המשרד להגנת הסביבה אישר מימון להצעה זו.

*מטרת המחקר*: לזהות מדדים ביולוגיים, אשר באמצעותם ניתן למדוד חשיפה שונה בין תל אביב לבין חיפה ואשר ישמשו בעתיד לניטור יעיל יותר מאשר הניטור הסביבתי הקיים כיום.

*שיטות ואוכלוסיית המחקר*: אוכלוסיית המחקר כללה 100 אנשי צוות רפואי והייתה אמורה לכלול 100 שוטרי סיור (כאשר בכל אוכלוסייה תהיה חלוקה ל-50 מגוש דן ו-50 ממפרץ חיפה). חשיפה של שוטרי הסיור ייצגה את הזיהום הסביבתי החיצוני ובעיקר התחבורתי וצוות רפואי את הזיהום הסביבתי ללא תוספת תחבורתי.

במשך שנת 2019 גויסו 39 שוטרים , אך בפרוץ מגפת הקורונה שונה פרוטוקול המחקר ובהמשך המחקר גויסו רק אנשי צוות רפואי, כאשר 50 מהם עובדים במרכז הרפואי ע"ש סוראסקי בתל אביב ו-50 מהם עובדים במרכז הרפואי בני ציון בחיפה.

שיטות המחקר בפרוטוקול המחקר המקורי כללו בדיקת ספירומטריה (תפקודי ריאות), בדיקת כיח מגורה ובדיקת עיבוי נשימתי (Exhaled Breath Condensate, EBC). דגימת עיבוי נשימתי משקפת את הנוזל הנימצא מעל שכבת האפיטליום העליון (Epithelial Lining Fluid). על פני נוזל זה מצטברים חלקיקי הנשאבים לתוך דרכי הנשימה, שאותם ניתן לזהות ולספור. כמו כן מילוי שאלון לגבי מצב סוציואקונומי ובריאותי.

היות ובדיקת כיח מגורה יוצרת אירוסולים – דבר שנאסר בזמן מגפת הקורונה, פרוטוקול המחקר שונה ובמקום כיח מגורה בוצעו בדיקת FeNO (Fractional Nitric Oxide) ואיסוף דגימת רוק. יתר הבדיקות נותרו ללא שינוי.

מדידת חלקיקי ננו ומיקרו מטר נבדקו בדגימות הביולוגיות שנאספו וכן מתכות, מינרלים וספירת תאים. בשיטות הסטטיסטיות נעשתה אנליזה באמצעות Latent Class Analysis (=LCA) בכדי לזהות קבוצות הומוגניות לגבי מדדים חשובים מבחינה ביולוגית ובהם נמצאו הבדלים שונים.

*תוצאות*: בחלק הראשון של דוח זה, נעשתה השוואה בין אוכלוסיית השוטרים בתל אביב ובחיפה (n=39, כולם גברים גיל ממוצע של שוטרים בחיפה± 5.7 30.6 ובתל אביב 11.2± 36.6 הגיוס הופסק בגלל מגפת הקורונה). לא נמצאו הבדלים משמעותיים סטטיסטית בין אוכלוסיות השוטרים בפרמטרים הדמוגרפים וכן בכל הפרמטרים של תפקודי ריאות, גודל חלקיקים ב-EBC ובכיח, כימות מינרלים ב-EBC ואף לא מבחינת ספירת תאים דיפרנציאלית בכיח.

בחלק השני של הדוח, מוצגות תוצאות ההשוואה בין אוכלוסיית צוות רפואי בתל אביב ובחיפה.

לאחר פרוץ מגפת הקורונה, גויסו 49 אנשי צוות רפואי בתל אביב (27.1% מהם גברים, כאשר אחת מהמגויסות נפסלה מהמחקר בשל רקע של השתלת כליה) ו-50 אנשי צוות רפואי בחיפה (34% מהם גברים). הגיל הממוצע של הצוות הרפואי בתל אביב הוא 37.92 ± 8.92 שנים ובחיפה 40.98 ± 7.11 שנים. (טבלה 6).

לאחר שנה, בוצע מפגש מעקב בו נבדקו אותם המדדים בשנית.

לא נמצאו הבדלים משמעותיים סטטיסטית בין הקבוצות של אנשי צוות רפואי בנתונים הדמוגרפים וכן בתפקודי הריאות וה-FeNO, בשני המפגשים (ספירומטריה, כיח מגורה, עיבוי נשימתי ומילוי שאלון).

מבחינת האנליזה של חלקיקים בגודל ננומטרי ב-EBC, נמצאו מספר הבדלים משמעותיים באופן

סטטיסטי במפגש הראשון: בצוות הרפואי בתל אביב גודל החלקיקים הממוצע הוא 166.99 ± 60.22nm, לעומת 231.75 ± 60.19nm בחיפה (p<0.001), וכן האנליזה של החלקיקים המצטברים עד 90,50,10% בכלל תכולת החלקיקים שונה באופן משמעותי (D10, D50, D90, p<0.001). לא נמצא הבדל משמעותי בריכוז החלקיקים במפגש הראשון.(טבלה 9 )

כמו כן, נמצאו הבדלים משמעותיים סטטיסטית בריכוז מתכות ב-EBC. כאשר ריכוז מתכות כמו מוליבדנום ((Mo, ניוביום (Nb (וזירקוניום ((Zi היה גבוה יותר בקרב צוות רפואי בחיפה (p<0.001), ואילו ריכוז מתכות כמו קדמיום ((Cd ופלדיום ((Pd היה גבוה יותר בקרב צוות רפואי בתל אביב (p<0.001 ו-p<0.05, בהתאמה).

במפגש השני, נמצאה ירידה משמעותית סטטיסטית בכל המדדים של גודל החלקיקים הננומטרים בצוות הרפואי בחיפה- כך למשל, נמצאה ירידה משמעותית בגודל החלקיקים הממוצע (231.75 ± 60.19nm במפגש הראשון לעומת 181.57 ± 28.81nm במפגש השני, p<0.001) ואף בריכוז החלקיקים (5.44 ± 3.48 108 particles/ml במפגש הראשון לעומת 2.93 ± 1.98 108 particles/ml במפגש השני, p<0.001) (טבלה 12).

בצוות הרפואי התבצעה ספירת תאים דיפרנציאלית ואנליזת חלקיקים בגודל מיקרומטרי בדגימות רוק. כצפוי רוב התאים ברוק היו תאי אפיתל (81.6 ± 15.9% בתל אביב ו-79.8 ± 13.3% בחיפה), ללא שינוי משמעותי בביקור השני וללא הבדלים משמעותיים בין הקבוצות.

לא נמצאו הבדלים משמעותיים סטטיסטית באנליזת חלקיקים בגודל מיקרומטרי בין הקבוצות, אך בשתי הקבוצות נצפתה עלייה משמעותית בגודל המיקרו-חלקיקים במפגש השני, כאשר בצוות הרפואי בתל אביב חלה עלייה מ2.34 ± 1.4µm במפגש הראשון ל- 6.26 ± 3.9µm במפגש השני (p<0.001), ובצוות הרפואי בחיפה חלה עלייה מ2.32 ± 1.1µm במפגש הראשון ל- 6.07 ± 3.5µm במפגש השני (p<0.001) (טבלה 13).

במפגש הראשון והשני נמצאו הבדלים משמעותיים סטטיסטית בריכוז ה-Blood Urea Nitrogen (BUN) שהיה גבוה יותר בצוות הרפואי בחיפה (p<0.05). הבדל נוסף נמצא בריכוז ה-lactate dehydrogenase (LDH) ברוק במפגש השני, שהיה גבוה יותר בצוות הרפואי בחיפה (616.02 ± 537.6 U\L בחיפה, לעומת 310.44 ± 195.6 U\L בתל אביב, p<0.001). (טבלה13).

בניתוח הסתברותי בשיטת LCA אופיינה תת קבוצה אשר היה להם BMI גבוה, ריכוז גבוה של חלקיקים קטנים בגודל ננומטרי, ריכוז גבוה של LDH ואחוז גבוה של לימפוציטים ברוק. בנוסף הם היו גם יותר אטופיים. בקבוצה זו היו באופן משמעותי יותר תושבי חיפה מאשר תושבים תל אביב.

*סכום ומסקנות*:

* עבודות רבות נעשו על זיהום האוויר בעיר חיפה באמצעות נתונים אשר מתקבלים מניטור סביבתי מתחנות ניטור הכולל מזהמים שונים לרבות חלקיקים. המחקר הנוכחי הוא הראשון מסוגו אשר חוקר את זיהום אוויר בעיר חיפה באמצעות ניטור ביולוגי בנוזלי גוף שטרם נבדקו.
* קבוצת הנבדקים עם ריכוזים גבוהים של חלקיקים בגודל ננומטרי בדגימות EBC, ריכוז גבוה של LDH וקלציום ברוק היו תושבי חיפה. ממצאים אלו היו עם קורלציה חיובית ישירה עם מדדים דלקתיים (לימפוציטים ברוק ותסמינים הקשורים למחלות *אטופיות.*

*המלצות:*

* קיימת חשיבות מרבית בהתמקדות בנושא חלקיקים בגודל ננומטרי אשר מתקבלים באמצעות בדיקות ביולוגיות. תחנות הניטור הסביבתיות נכון להיום, אינן מותאמות למדידה של חלקיקים בגודל זה. יש להיערך ולמקד את התיכנון העתידי בכיוון זה.
* מומלץ לבנות מודל הכולל מדדים ביולוגים המשקפים את התמונה הדלקתית הנגרמת כתוצאה מזיהום האוויר.

***English Abstract***

*Background:* Most of the epidemiological studies carried out to date had been done using data recovered from environmental monitoring. While it provides data for evaluating pollution control, but it is a poor surrogate measure of the extent of the adverse effects of particulate matter and volatile organic compounds to the human health. Only biological monitoring of the internal dose takes into account the route of exposure (e.g., inhalation or dermal absorption).

On December 2018, the Ministry of Environmental Protection decided to fund the present research.

*Aim of the study:* The objective of the proposed research is to biologically monitor the effects of exposure to toxic particles by measuring the load of micro-, ultrafine, and nanoparticles in biological samples and combine those findings with the results of functional and inflammatory parameters and clinically established adverse health effects.

*Study Population and Methods*: The study population includes 100 (Haifa: Tel Aviv, 50:50) healthy medical staff and 39 (16:23) policemen from the Haifa Bay area and Gush Dan. The police population represents the traffic pollution, while the medical staff population represents the environmental pollution.

During 2019, we recruited 39 policemen, but with the spread of Covid-19 pandemic, we further recruited medical staff only.

The original methods proposed in this study were spirometry, induced sputum (IS) and exhaled breath condensate (EBC), as well as the filling in of a questionnaire on the socioeconomic and health state of the participants.

Since induced sputum generates aerosols, we were obliged to restrict the study protocol during the year of 2020 to include fractional exhaled nitric oxide (FeNo) and saliva collection, instead of IS. No other test was changed. Micro- and nanoparticles were measured in these samples.

*Results*: In the first part of the present report, we compared the police populations in Tel Aviv (TLV) and Haifa (n=39 in total. The recruitment was interrupted due to the Covid-19 pandemic). There were no statistical differences between the demographic, functional, inflammatory and nano- and microparticle size distributions between the groups (Table 1-4).

In the second part of this report, we present the results of 49 medical staff from Tel Aviv Sourasky Medical Center representing Gush Dan (one of the 50 participants was disqualified due to kidney transplantation) compared to 50 medical staff from Bnai Zion Medical Center representing the Haifa Bay area.

These groups had a follow-up of one year following the first session (Table 5).

No differences were found in the demographic and functional parameters of the medical staff population between the groups and between the two sessions (Table 6) Table 7 display the result of the questionnaire.

The main difference between the medical staff groups was in the nano-particle analysis, in which the mean particle size in Haifa was 231.75 ± 60.19 nm compared to 166.99 ± 60.22 nm in Tel Aviv, p<0.001 (Table 8). At the second session, the mean particle size in Haifa decreased to 181.57 ± 28.81 nm (p<0.001 vs. Haifa 1st session) (Table 12).

The mean nano-sized particle concentration in Haifa was 5.44± 3.48 108 particles/ml, and it decreased to 2.93 ± 1.98 108 particles/ml at the 2nd session (p=0.034) while the Tel Aviv concentration was unchanged at around 5.06 108 particles/ml in both sessions (p<0.001 vs. Haifa 2nd session). (Table12)

Moreover, statistically significant different metal concentrations were found in the EBC samples at the 1st session. Metals like molybdenum, niobium and zirconium were at significantly higher levels among the Haifa medical staff (p<0.001 vs. Tel Aviv medical staff), while metals like cadmium and palladium were significantly higher among the Tel Aviv medical staff (p<0.001 and <0.05, respectively, vs. Haifa medical staff) (Table 12)

Differential cell count and micro-particles analysis of the medical staff were performed in saliva samples. Expectedly, most of the saliva comprised of epithelial cells (81.6±15.9% in Tel Aviv, and 79.8±13.3% in Haifa), with no statistical difference between the groups or sessions (Table10).

No differences were found in the micro-particles analysis between the groups. However, in both of the groups a significant elevation in the mean size of micro-particles size was observed between the two sessions (2.34±1.4 µm in the 1st session to 6.26 ± 3.9µm in the 2nd session in Tel Aviv, p<0.001; and 2.32 ± 1.1µm in the 1st session to 6.07 ± 3.5µm in the 2nd session in Haifa, p<0.001) (Table13).

Additionally, significant differences were found in the biochemical analysis of the saliva. Higher levels of Blood Urea Nitrogen (BUN) were found in Haifa medical staff in both sessions (p<0.05, vs Tel Aviv). Higher levels of Lactate dehydrogenase (LDH) were found Haifa medical staff in both sessions, but was statistically significant only on the 2nd session (616.02 ± 537.6 U\L in Haifa vs 310.44 ± 195.6 U\L in Tel Aviv, p<0.001) (Table10).

We ran latent class analysis (LCA) to identify the number of homogenous subgroups according to selected measurements within the overall sample: FEV1, FeNO, UFP mean size, BUN, LDH, pH, Cadmium, Palladium, Molybdenum, Niobium and Zirconium. Once the ideal number of classes was determined, individuals were assigned to their most likely class and were compared between the classes on demographical, clinical and biological variables using univariate analysis.

*Summery and Conclusion*s:

* Environmental monitoring is used in most of the epidemiological studies but are poor surrogate to measure the extent of direct adverse effects to human health. The internal dose measured by biological monitoring takes into account route of exposure both inhalation or dermal absorption.
* In the cluster with higher BMI, higher concentrations of UFP in EBC and LDH- calcium in saliva, are from the Haifa group. Those have more lymphocytes in saliva, presenting more atopic symptoms.

 *Recommendations*

* There is a crucial point that must be taken in account when monitoring particulate pollution in the big cities (i.e Haifa and Tel Aviv). The environmental stations should be adapted to measure particles in the nanosize.
* The result of this analysis showed that in order to show the deleterious effect of the environment on Haifa population health there is an urgent need to build a model that include measurement of ultrafine particles in air and biological samples including metals levels, biochemical parameters and inflammatory index (i.e. FeNO).

**ביצוע מול תכנון**

|  |  |  |
| --- | --- | --- |
| תאריך | יעד | ביצוע |
| 11.11.2013 | קול קורא של איגוד הערים | מחקר על זיהום אוויר במפרץ חיפה |
| 24.3.2015 | אוניברסיטת חיפה זכתה במכרז | תחילת מחקר על זיהום אוויר במפרץ חיפה |
| 5.1.2016 | משרד הבריאות בקשה להשעות את ביצוע המחקר | נפסלו כל הקבוצות פרט לקבוצה שלנובנושא ניטור ביולוגי |
| 31.12.2018 | המחקר הועבר למשרד להגנת הסביבה | מטרה זהה למחקר הקודם |
| 1.1.2019-1.1.2020 | בדיקת שוטרי סיור במרחב חיפה ובתל אביב | גויסו 23 שוטרים בתל אביב ו16 בחיפה |
| 1.2020 | תחילת מגפת הקורונה | עצירה של המחקר |
| 1.11.2020 | תחילת גיוס צוות רפואי תל אביב | המשך ביצוע המחקר עם שינוי בפרוטוקול (ללא ביצוע כיח מגורה) \* |
| 3.2021 | תחילת גיוס צוות רפואי חיפה | המשך ביצוע המחקר עם שינוי בפרוטוקול (ללא ביצוע כיח מגורה) \* |
| 20.5.2021 | סיום גיוס צוות רפואי | עיבוד נתונים של מפגש ראשון |
| 20.5.2021 | ניסיון לחדש מחקר במשטרה | העברנו בקשה להסתפק בנתונים הקיימים |
| 19.10.2021 |  | תחילת מעקב צוות רפואי תל אביב |
| 2.2022 |  | תחילת מעקב צוות רפואי חיפה |
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**מילות מפתח**

ניטור ביולוגי, זיהום חלקיקי, מיקרו חלקיקים, ננו חלקיקים.

Biological Monitoring, Particulate Matter, Nano-sized Particle, Micro-sized Particle.

**סקר ספרות וחדשנות**

Epidemiologic studies have established an association between mortality and morbidity and exposure to airborne particles at concentrations currently found in major metropolitan areas worldwide [1,2]. Ambient airborne particulate matter (PM) is ubiquitously distributed, although the concentrations, particle sizes, and chemical characteristics of PM vary widely in space and time [3]. A useful way to characterize particle size is by its “aerodynamic” diameter, which is defined as the diameter of a spherical particle with a density of 1 g/cm3 with the same settling velocity as the particle that is being measured [4]. Such quantification is used to group exposures: PM in the aerodynamic diameter range <10 µm (PM10) is further categorized into coarse, fine, and ultrafine particles (UFP) based on aerodynamic diameter ranges between 2.5-10 µm (coarse), <2.5 µm (fine or PM2.5), and <0.1 µm (ultrafine 100 nm; UFP or PM0.1), respectively.

Most of the studies had been done using data recovered from environmental monitoring that provide an excellent approach for evaluating regulatory compliance in terms of pollution control, but they are a poor surrogate measure of the extent of the adverse effects of particulate matter upon the human respiratory system. Measurements of a pollutant’s internal dose take into account route of exposure (e.g., inhalation, dermal absorption) and variation in delivered dose at the individual level [5]. This internal dose metric can be assessed accurately solely by biological monitoring. In this context, volatile materials were recently bio monitored using urine samples in residents living near gas stations [6]. Blood and hair samples were used to detect metals in an occupationally unexposed population residing in polluted areas of East Kazakhstan and Pavlodar regions [7]. Biomonitoring of radioactive contamination of the Yenisei River was measured using aquatic plants [8]. Biomonitoring of particulate matter and polycyclic aromatic hydrocarbon (PAH) was performed in children attending schools in polluted urban and industrial areas that are exposed to higher levels of PM and PAHs with increased concentrations of urinary PAH metabolites in comparison with children from rural areas [9].

Assessments of particulate burden in the lung can be done by combinations of fiberoptic bronchoscopy and bronchoalveolar lavage (BAL). The relative invasiveness of this technique, however, has hampered its application as a practical tool for screening programs, for evaluating levels of exposure, and for repeated follow-up tests in large populations. The ongoing search for noninvasive techniques has led to the development of the analysis of exhaled breath condensate (EBC) and the examination of cells, mediators and particulate matter in samples of induced sputum (IS).

Over the past few years, we have focused our IS and EBC research on occupational and environmental exposure exclusively using micron-sized air-borne particles (Eyetech Laser Analyzer, Ankersmid, Israel). To the best of our knowledge, there are no reports of direct biomonitoring of PM in airways using similarly advanced methods. We studied several populations: a. workers exposed to hazardous dust in Israel [10-11] b. World Trade Center dust‑exposed firefighters in the USA [12] and c. asthmatic children in the Tel-Aviv area [13]. We have recently carried out ongoing complementary measurements on nano-particulate matter (NanoSight LTD, London, UK) in IS samples from patients with various pulmonary diseases referred to us for diagnostic purposes [14-15].

The original protocol included the performance of sputum induction, but this procedure was considered as an aerosol-generating procedure (AGP) that is more likely to generate higher concentrations of infectious respiratory aerosols than coughing, sneezing, talking, or breathing. AGPs potentially put healthcare personnel and others at an increased risk for pathogen exposure and infection [16].

As a surrogate to IS, we proposed the measurement of fractional exhaled nitric oxide (FeNO) and metabolome measurement in saliva.

Epidemiological and toxicological research support a link between air pollution and an increased incidence and/or severity of airway inflammation. FeNO is a simple, safe and noninvasive method to detect airway inflammation. It is also correlated well with eosinophil count and eosinophil cationic protein in IS and a widely used metric for the evaluation and management of airway inflammation with the sensitivity and specificity 0.846 and 0.817 when the cutoff value is 31.5 ppb [17].

Increasing evidence shows that environmental, rather than genetic, factors are the major causes of most chronic diseases. By measuring entire classes of chemicals in archived biospecimens, exposome-wide association studies (EWAS) are being conducted to investigate associations between a myriad of exposures during life and chronic diseases. Saliva offers many advantages over other bio fluids: it can be collected safely and non-invasively with minimal training and it is rich in biological information. Saliva (also referred as oral fluid) is a natural filtrate of blood that contains omics features (small molecules, metals, proteins, and DNA) worthy of interrogation via EWAS. Because saliva collection is “stress-free,” repeated specimens of saliva are routinely obtained for determination of steroid hormones in psychobiological studies [18].

**מטרות העבודה**

Adverse health effects on the pulmonary system (reduced worker productivity, hospital admissions, pulmonary infections, asthma and chronic obstructive pulmonary disease exacerbations) are responsible for a considerable economic and social burden. The results of consolidating the evidence from the biological monitoring of injury to the respiratory system will provide indisputable proof that there is a pressing need to change current policies for regulating sources of particulate pollution.

The objectives of the proposed research are:

1. To biologically monitor the effects of exposure to particles by measuring the load of micro-, ultrafine particles in Saliva and EBC samples.
2. To combine those findings with the results of functional and inflammatory parameters and clinically established adverse health effects.
3. To find a model combining biological and environmental parameters to indicate polluted areas in the Haifa districts to avoid decremental health

**תיאור העבודה**

During 2016 we collected data from 13 policemen in Tel Aviv and 13 in Haifa;

This study was funded by 'Igud Arim Haifa' and interrupted by the Ministry of Health.

On December 2018 the Ministry for Environmental Protection decided finally to fund the above mention research again.

During 2019 we recruited 39 policemen in total. Regretfully the study was interrupted when the World Health Organization (WHO) declared the spread of COVID-19 to be a [Public Health Emergency of International Concern](https://www.who.int/dg/speeches/detail/who-director-general-s-statement-on-ihr-emergency-committee-on-novel-coronavirus-%282019-ncov%29) (PHEIC) on January 30 this year and later [characterized it as a pandemic on March 11](https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020).

The original protocol included the performance of sputum induction but this procedure was considered as an Aerosol-Generating Procedures (AGP) and are more likely to generate higher concentrations of infectious respiratory aerosols than coughing, sneezing, talking, or breathing. AGPs potentially put healthcare personnel and others at an increased risk for pathogen exposure and infection

(<https://www.cdc.gov/coronavirus/2019-ncov/hcp/non-us-settings/overview/index.html#standard-based-precautions>

The police departments in Tel Aviv and in Haifa were unable to offer us the facilities to test individuals in an open space with adequate ventilation in order to avoid Corona virus infection among the recruited population and our staff.

In this context we decided to change the original protocol using methods and procedures that can be a surrogate for sputum induction without the generation of aerosols

The results from 2016are presented in pages 56-70.

**שיטות**

***Ethical Conduct of the Study:*** The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice and applicable regulatory requirements. The study was approved by the local Ethics Committees (IRB number 0731-14-TLV in the Tel Aviv Sourasky Medical Center and 0114-20-BNZ in the Bnai Zion Medical Center). All participants provided informed consent.

***Study population and research methodology:***The study population was changed to healthy medical staff members. Fifty healthy medical staff members working in Bnai Zion Hospital and 49 working in Tel Aviv Medical Center were recruited. 16 healthy policemen from the Haifa Bay area, and 23 healthy policemen from Gush Dan were enrolled as well in the first part of this study. They were required to fulfill the following criteria: **a.** No chronic respiratory symptoms. **b.** No atopic symptoms, such as allergic rhinitis, atopic dermatitis or food allergies. **c.** No exposure to environmental tobacco smoke. **d**. No respiratory infection during the 4 weeks prior to recruitment and testing.

They were asked to complete a questionnaire on their respiratory symptoms as well as on selected socioeconomic factors and general health profile.

The study included the following tests

* ***Pulmonary Function Tests (PFT):*** These measurements were performed according to standard protocols of the ARS/ERS guidelines and by means of Koko Legend Spirometers (nSpire Health Inc.). The parameters that were collected were: **FEV1**, Forced Expiratory Volume in the 1st second (% of predictive values); **FVC**, Forced Vital Capacity, (% of predictive values); **FEV1 /FVC**, the ratio between the two parameters; **FEF25-75**, Forced Expiratory Flow at 25–75% of FVC (% of predictive values). Values of 100 ± 20% of predictive values are usually considered as normal values.
* ***Exhaled breath condensate (EBC) collection:*** Exhaled breath was condensed by a TURBO-DECCS condenser (Medivac, Parma, Italy). The condenser has a refrigerating system (TURBO) that thermostatically controls the working temperature, and a disposable respiratory system (DECCS) that consists of a mouthpiece connected to a one-way aspiration valve and an EBC collection test tube at the end. Subjects were asked to perform normal tidal breathing into the mouthpiece for 10 minutes at an initial condenser temperature of −4°C to collect 1-2ml samples which reflect the composition of the airway lining fluid of the lungs. The EBC samples were then analyzed with Nanosight and XRF as described below.
* ***Sputum induction and processing:*** Induced sputum (IS) was carried out by conventional methods only in the police population prior the pandemia of Covid-19.Briefly, the subjects were asked to inhale nebulized 3% saline through an ultrasonic nebulizer (U-22 Micro Air; Omron Health Care) for 15 minutes, which allowed secretions from the lower airways to be sampled. Selected sputum plugs were treated with 0.1% dithiothreitol (Sputolysin; Calbiochem Corp., CA, USA). The cell suspension was filtered through a nylon mesh filter. The filtered cell suspension was centrifuged at 1200 rpm for 10 minutes. The supernatants were stored at -200C for further tests. Cell pellets were resuspended in complete cell medium (RPMI 1640, 10% fetal bovine serum, 1% L-glutamine, 1% penicillin–streptomycin-nystatin; Biological Industries Beit HaEmek, Israel) and were prepared for differential cell count using 2 drops on a slide and then cytocentrifuged (5 minutes at 1000 rpm). A total of 400 non-squamous cells were differentially counted on Giemsa-stained (Merck, USA) cytopreps with a light microscope.
* ***Saliva collection and processing:*** Subjects were asked to refrain from eating and drinking 1 hour before the session. They were then asked to rinse their mouths with water 5 minutes before spontaneous saliva was collected in a sterile tube placed on ice. The saliva samples were centrifuged at 4°C, 13000 rpm for 30 minutes. The supernatants were removed and stored at -200C and later analyzed for chemical composition as described below. The cell fraction of the saliva samples was suspended with complete cell medium and cytospins were prepared. A total of 200 cells were differentially counted on Giemsa-stained cytopreps with a light microscope.
* ***Fractional exhaled Nitric Oxide (FeNO) measurement:*** FeNO is measured using NIOX VERO (Circassia, UK), in which subjects breathe into the device and the FeNO result is returned in ppb. Values lower than 25 ppb are considered normal and higher indicate inflammation of airways
* ***Micro particle size distribution (PSD):*** The size distribution of the particles (particulate matter, PM) was assessed from the rich cell fraction of the processed plugs in IS samples or from the saliva samples by means of a Dipa 2000 Analyzer (Donners Technology, Israel) and an Eyetech Analyzer by conventional methods. Briefly, 3 drops of sputum or saliva cells or supernatant suspensions were introduced into a quartz cuvette that contained 3ml of double distilled water and that were stirred during the analysis. A helium-neon laser beam crossed the particles in suspension, and the signal was registered by a photodiode placed directly behind the suspension.

PSD included the following parameters:

* PM2.5: fine inhalable particles, with diameters of 2.5 micrometers and smaller.
* PM5: inhalable particles, with diameters of 5 micrometers and smaller.
* PM10: coarse inhalable particles, with diameters of 10 micrometers and smaller.
* Mean size (micrometers).
* ***Nano-sized particle measurement:*** The size of the ultrafine particles (UFP, PM0.1: with diameters of 0.1 micrometers and smaller) was assessed in the EBC samples by means of Nanosight NS300 (Malvern Panalytical, UK) and the Nanoparticle Tracking Analysis software (NTA, version 3.4, NanoSight Ltd., Salisbury, UK). Approximately 250 µl of EBC samples were inserted into the sample chamber.

The NTA software then utilized the properties of both light scattering and Brownian motion in order to obtain the size distribution and concentration measurement of the particles in the sample. A 450 nm laser beam was passed through the sample chamber, and the particles' scatter light was visualized via a 20x magnification microscope and a camera. The camera operates at 30 frames per second, capturing a video file of the particles moving under Brownian motion (i.e., the smaller the particle, the faster and further it moves). The software tracks many particles individually and calculates their hydrodynamic diameters by means of the Stokes-Einstein equation. Each sample was recorded three times at different positions for average calculation. The parameters that were obtained are: mean particle size (nm); D10, the diameter of 10% of total UFP (nm); D50, the diameter of 50% of total UFP (nm); D90, the diameter of 90% of total UFP (nm); particles concentration (108 particles/ml).

* ***X-ray Fluorescence (XRF):*** The mineral content of the EBC samples was analyzed with a Thermo Scientific Niton XL3t GOLDD+® XRF analyzer.

Each EBC sample was scanned thrice by XRF and an average was calculated. Briefly, the instrument was fitted with an X-ray tube with an Ag anode target excitation source (operating at voltages up to 50 kV and at beam currents up to 200 μA), and a geometrically optimized large area drift detector. A helium purge technique was employed for enhanced light element analysis. A charged coupled device camera stored sample images, and the data were transferred via Thermo Scientific Niton data transfer PC software (Thermo Niton Analyzers LLC, version NDT\_REL\_8.2.1). Calibration was performed each morning before measurements (using control samples: 180-706pp USGS SdAr-M2; NIST 2709a PP 180-649) according to the manufacturer's instructions.

A total of 200 µl of EBC were placed in the center of a 4 μm polypropylene film over a 3 mm small-spot collimator above the detector. Each measurement took 240 seconds, and spectra up to 40 keV were quantified with a factory-installed algorithm (fundamental parameters calibration) for a “mining” mode that yielded elemental concentrations in parts per million (ppm, μg/ml) with an error of 2*σ* or 95% confidence.

* ***Chemical composition measurement*:** Saliva supernatant chemical composition measurements were performed with the Avdia 2400 Siemens clinical chemistry system (Siemens Healthineers) in the Biochemistry Laboratory of Tel Aviv Sourasky Medical Center. The parameters that were analyzed are: **BUN**, Blood Urea Nitrogen (mg/dL using Nirtogen Urease). **K**, Potassium (mmol/L). **CL**, Chloride (mmol/L). **CA**, Calcium (mg/dL). **Phos**, Phosphorus (mg/dL). **LDH**, Lactate Dehydrogenase (U/L using Lactate Dehidrogenase).

A **follow-up** including the same above-mentioned methods (except for completing a questionnaire) was performed one year later in order to validate the results of the first session. Each participant was asked whether they had recovered from COVID-19 during the past year.

**Statistical analyses** were performed using the SPSS® statistics software, version 27.0 for Windows (IBM® corporation).

Results are given in mean ± standard deviation (SD), unless indicated otherwise. Differences between continuous parameters were compared by the *t*-test, and differences between categorical parameters were compared by the *x2 test*. The *Mann-Whitney U non-parametric test* was used to calculate the differences between small cohorts**.** Differences between paired observations were calculated with a *paired t-test* or the *Wilcoxon signed rank test*. Pearson correlation coefficients (*r*) were used to correlate between clinical and functional parameters and particles size and other characteristics in biological samples. Ap value (p) below 0.05 was considered statistically significant.

LCA is used to detect latent (or unobserved) heterogeneity in samples [19] The assumption underlying LCA is that membership in unobserved classes can cause or explain patterns of scores across survey questions, assessment indicators, or scales B. [20] We ran latent class analysis (LCA) to identify the number of homogenous subgroups according to selected measurements within the overall sample. A 1 to 3 classes were constructed, and we used three criteria to determine which solution was the best.

The first criterion was whether there was a sufficient number of participants in each latent class to allow for comparison between classes such that if a class had fewer than 17 participants (20% of the sample), a solution with fewer latent classes was analyzed.

The second criterion was whether the class model solutions is theoretically relevant.

The third criterion was the best fitting model. Better model fit was suggested by a lower Akaike information criterion (AIC) [19]; a lower Bayesian information criterion (BIC) [22]; a significant Lo-Mendell-Rubin likelihood ratio test, suggesting the more complex model (i.e., model with more classes) fits the data better than the model with fewer classes [23]; and entropy, the estimate of certainty of classification (ranging from 0 to 1).

Indicators of the LCA were the following measurements: FEV1, FeNO, UFP mean size, BUN, LDH, pH, Cadmium, Palladium, Molybdenum, Niobium and Zirconium.

Once the ideal number of classes was determined, individuals were assigned to their most likely class and were compared between the classes on demographical, clinical and biological variables using univariate analysis.

All analyses related to class formation were conducted using Mplus v8.3 (Muthen &Muthen).

**תוצאות**

The results will be presented as follows:

* The results of 23 policemen from the Tel-Aviv area compared to 16 policemen from the Haifa Bay area and their follow-up results after one year.
* The results of 49 medical staff members from Tel-Aviv compared to 50 medical staff members from Haifa and their follow-up results after one year.
* The baseline results of each medical staff group compared with their own follow-up results one year later.

**Results of the Police populations**

**Table 1. Comparison between Demographic Data in the Tel Aviv and Haifa Police Populations**

|  |  |  |
| --- | --- | --- |
|  | **TLV police** **(N=23)** | **Haifa police** **(N=16)** |
| **Age, years (mean ± SD)** | 30.6±5.7 | 36.6±11.2 |
| **Male, *n* (%)** | 21 (91.3) | 14 (87.5) |
| **Height, cm (mean ± SD)**  | 173.9±12.5 | 175.1±7.8 |
| **Weight, kg (mean ± SD)**  | 75.5±15.3 | 81.4±14.3 |
| **Smoking, *n* (%)** |  |  |
| **Active** | 6 (26.1) | 7 (43.8) |
| **Passive** | 16 (69.6) | 8 (50) |
|  |  |  |

The p value was calculated with an independent t-test for continuous variables and the *X*2 test for categorical variables.It was non-significant in all comparisons.

No differences were found between the demographic data and smoking habits between policemen in Tel Aviv and Haifa areas (Table 1).

**Table 2. Comparison between Pulmonary function test (PFT) Findings in the Tel Aviv and Haifa Police Populations**

|  |  |  |
| --- | --- | --- |
|  | **TLV police** **(N=22)** (missing=1) | **Haifa police** **(N=16)** |
| **FEV1%**  | 92.4±9.2 | 88.4±9.2 |
| **FVC%**  | 93.4±9.2 | 87.7±8.7 |
| **FEV1/FVC%** | 99.2±4.9 | 100.4±4.7 |
| **FEF25-75%** | 92.2±19.5 | 92.2±17.7 |

Results are given in mean ± SD.Thep value was calculated with an independent t-test and it wasis non-significant in all comparisons.

**FEV1**, Forced Expiratory Volume in one second, percent of predictive values. **FVC**, Forced Vital Capacity, percent of predictive values. **FEF25-75**, Forced Expiratory Flow at 25–75% of FVC, percent of predictive values.

No differences were found between the PFT results of the Haifa and Tel Aviv police groups (Table 2).

**Table 3. Comparison between Ultrafine Particles (UFP) and X-ray Fluorescence (XRF) Data Measured in Exhaled Breath Condensate (EBC) in the Tel Aviv and Haifa Police Populations**

|  |  |  |
| --- | --- | --- |
|  | **TLV Police** **(N=21)**(missing=2) | **Haifa Police** **(N=16)** |
| **UFP**  | **Mean size, nm** | 204.4±44.7 | 199.5±34.3 |
| **D10, nm** | 116.9±34.8 | 100.9±40.8 |
| **D50, nm** | 194.3±49.8 | 187.6±39.1 |
| **D90, nm** | 293.9±67.5 | 317.6±74 |
| **Concentration,** **108 particles/ml** | 5.14 ± 3.27 | 5.22± 3.12 |
| **XRF**  | **Stibnite** | 6.9±0.8 | 6.8±1.8 |
| **Silver** | 6.5±0.4 | 6.6±0.7 |
| **Molybdenum** | 23.1±0.8 | 22.6±1.8 |
| **Niobium** | 23.7±1 | 23.6±1 |
| **Zirconium** | 20±0.9 | 19.6±1 |
| **Strontium** | 5.6±0.4 | 5.6±0.4 |
| **Vanadium** | 16.8±2.8 | 15.3±2.5 |

Results are given in mean ± SD. The p value was calculated with an independent t-test, and it was non-significant in all comparisons.

**D10**, the diameter of 10% of total UFP; **D50**, the diameter of 50% of total UFP; **D90**, the diameter of 90% of total UFP.

No differences were found in EBC mineral content (XRF analysis) and UFP load between the police groups (Table 3).

**Table 4. Comparison between sputum data in the Tel Aviv and Haifa Police Populations**

|  |  |  |
| --- | --- | --- |
|  | **TLV police** **(N=12)**(missing=11) | **Haifa police** **(N=8)**(missing=8) |
| **DCC** | **%Neutrophils** | 35.1±31 | 39.3±28 |
| **%Lymphocytes**  | 4.52±3.9 | 5.8±4.1 |
| **%Macrophages**  | 55.9±30 | 45.1±23.3 |
| **%Eosinophils**  | 4.4±11.9 | 9.66±18.2 |
| **PM** **(Sputum Supernatant)** | **<2.5μm %**  | 68.3±15.6 | 58.4±13.4 |
| **<5μm %**  | 81.5±12.9 | 75.5±10.2 |
| **<10μm %**  | 92.2±6.7 | 88.8±5.9 |
| **Size, μm** | 3.1±0.3 | 3.3±0.3 |

Results are given in mean ± SD. The *P* value was calculated with the Mann-Whitney U-test, and it was non-significant in all comparisons.

**DCC**, Differential Cell Count. **PM**, Particulate Matter expressed as % of accumulated particles in the different sizes.

Differential cell count was performed in sputum samples of the police populations prior to the COVID-19 pandemic. No differences were found between the DCC and the PM size distribution of the Haifa and Tel Aviv police groups (Table 4).

**Results of the Medical Staff Population**

This part of the report is describing the use of **saliva and FeNO** as surrogate for induced sputum in the evaluation of the medical staffs in Tel Aviv and Haifa during the COVID-19 pandemic.

49 members of the Tel-Aviv medical staff and 50 from the Haifa medical staff were recruited to the study (1st session). 43 participants of each group attended the follow-up session one year later (2nd session).

**Table 5. Participation Dates of the Medical Staffs**

|  |  |  |
| --- | --- | --- |
|  | **TLV****Medical Staff** | **Haifa****Medical Staff** |
| **1st session** | 10 participants: 8.202039 participants: 10.2020-11.2020 | 50 participants: 3.2021-5.2021 |
| **2nd session** | 43 participants: 10.2021-11.2021 | 43 participants: 2.2022-4.2022 |

COVID-19 Lockdown dates:

1. 25.3.2020-4.5.2020
2. 18.9.2020-17.10.2020
3. 27.12.2020-7.2.2021

Keynotes for Table 5

* Most of the participants of the first session in Tel Aviv were done after the second lockdown.
* Participants of the first session in Haifa were done after the third lockdown.
* The second sessions of both Tel Aviv and Haifa were done without any lockdown.

**Table 6. Comparison between Demographic Data of the Tel Aviv and Haifa Medical Staffs**

|  |  |  |
| --- | --- | --- |
|  | **1st session** | **2nd session** |
|  | **TLV****Medical Staff (N=49)** | **Haifa** **Medical Staff (N=50)**  | **TLV****Medical Staff (N=43)** | **Haifa** **Medical Staff (N=43)**  |
| **Age, years**  | 37.92 ± 8.92 | 40.98 ± 7.11 | 37.98 ± 9.19 | 41.21 ± 6.6 |
| **Male, *n* (%)** | 13 (26.5) | 17 (34) | 11 (25.6) | 15 (34.9) |
| **Height, cm**  | 165.52 ± 8.13 | 167.64 ± 10.41 | 165.16 ± 8.14 | 167.7 ± 10.88 |
| **Weight, kg**  | 68.56 ± 14.2 | 73.18 ± 18.3 | 68.07 ± 14.6 | 73.93 ± 18.8 |
| **Smoking, *n* (%)** |  |  |  |  |
|  **Active** | 3 (6.1) | 1 (2) | 2 (4.7) | 1 (2.3) |
|  **Passive** | 12 (24.5) | 15 (30) | 9 (20.9) | 14 (32.6) |
| **Post-COVID-19, *n* (%)** |  |  | 21 (42.9) | 23 (46) |

The p value was calculated with an independent t-test for continuous variables and the *X*2 test for categorical variables and found to be non-significant in all comparisons. Values are given as mean ± standard deviation.

No differences were found in the demographic data and smoking habits between the medical staffs in Tel Aviv and Haifa (Table 6). There also was no difference in the COVID-19 recovery rates between the two groups at follow-up.

**Table 7. Comparison between questionnaire Data of the Tel Aviv and Haifa Medical Staffs#**

|  |  |  |
| --- | --- | --- |
|  | **TLV****Medical Staff (N=49)** | **Haifa** **Medical Staff (N=50)**  |
| **Indoor Parameters** |  |  |
|  Home with balcony or yard | 31 (63.3) | 29 (58) |
|  Home facing street | 26 (53.1) | 31 (62) |
|  Frequent barbeque  | 7 (14.3) | 14 (28.6) |
|  House heating with fireplace | 2 (4.1) | 1 (2) |
|  House with moisture or mold | 13 (26.5) | 14 (28.6) |
|  Home furnishings (carpets, curtains, etc.) | 25 (56.8) | 10 (24.4)\* |
|  Pets at home | 16 (34) | 19 (38) |
| **Outdoor Parameters** |  |  |
|  Routine Outdoor Exercise | 30 (61.2) | 24 (48) |
|  *Neighborhood Characteristics:* |  |  |  |
|  Traffic | 30 (61.2) | 21 (42) |
|  Noise | 25 (51) | 18 (36) |
|  Garbage | 14 (28.6) | 10 (20) |
|  Unpleasant odors | 6 (12.2) | 8 (16) |
|  Smoke | 4 (8.2) | 5 (10) |
|  Exposure during military service | 7 (14.3) | 6 (12) |
| **Clinical Parameters** |  |  |
|  Cough during Sickness | 4 (8.2) | 13 (26)\* |
|  Sputum during Sickness | 9 (18.4) | 23 (46)\* |
|  Sensitivity to Odors | 4 (8.2) | 3 (6) |
|  History of atopy | 34 (69.4) | 11 (22)\*\* |

#Responses to the questionnaire in the first session were validated during the second session.

Results represent the number of 'yes' answers, n (%). The p value was calculated with the *X*2 test.

*\**p<0.05, \*\*p<0.001

The data obtained from the questionnaire revealed significantly higher levels of clinical parameters such as atopy (p<0.001), sputum and cough during sickness (p<0.05) among the Haifa medical staff compared to the Tel Aviv medical staff (Table 7).

**Table 8.** **Comparison of the Pulmonary function test (PFT) Results and Fractional Nitric Oxide (FeNO ) Data between the Tel Aviv and Haifa Medical**

 **Staffs**

|  |  |  |
| --- | --- | --- |
|  | **1st session** | **2nd session** |
| **TLV****Medical Staff (N=49)** | **Haifa** **Medical Staff (N=50)**  | **TLV****Medical Staff (N=43)** | **Haifa** **Medical Staff (N=43)**  |
| **PFT** | **FEV1%**  | 92.87± 17.55 | 97.20 ± 10.58 | 92.49 ± 12.53 | 96.65 ± 11.12 |
| **FVC%**  | 95.97 ± 12.57 | 97.94 ± 11.19 | 92.98 ± 12.75 | 97.09 ± 11.43 |
| **FEV1/FVC%** | 99.00 ± 6.66 | 99.20 ± 8.16 | 99.23 ± 6.36 | 99.40 ± 8.39 |
| **FEF25-75%** | 96.62 ± 22.74 | 99.64 ± 28.59 | 92.56 ± 22.3 | 98.81 ± 29.9 |
| **FeNO** | **FeNO, ppb**  | 16.92 ± 10.5 | 19.7 ± 20  | 14.41 ± 12.7 | 15.6 ± 14.5  |

Results are given as mean ± SD. Thep value was calculated with an independent t-test, and all values were non-significant.

**FEV1**, forced expiratory volume in one second, percent of predictive values. **FVC**, forced vital capacity, percent of predictive values. **FEF25-75**, forced expiratory flow at 25–75% of FVC, percent of predictive values. **ppb**, parts per billion.

There were no significant differences in the PFT results of the Haifa and Tel Aviv medical staffs (Table 8). A nonsignificant increase in the inflammatory parameter (FeNO) was recorded for both groups during the second session.

**Table 9.** **Comparison between Ultrafine Particles (UFP), X-ray Fluorescence (XRF) and PH Data Measured in Exhaled Breath Condensate (EBC) of Tel Aviv and Haifa Medical Staffs**

|  |  |  |
| --- | --- | --- |
|  | **1st session** | **2nd session** |
| **TLV****Medical Staff (N=49)** | **Haifa** **Medical Staff (N=50)**  | **TLV****Medical Staff (N=43)** | **Haifa** **Medical Staff (N=43)**  |
| **UFP**  | **Mean size, nm** | 166.99 ± 60.22 | 231.75 ± 60.19\*\* | 184.38 ± 36.1 | 181.57 ± 28.81 |
| **D10, nm** | 88.8 ± 30.63 | 123.57 ± 36.76\*\* | 102.60 ± 18.5 | 94.18 ± 16.44\* |
| **D50, nm** | 139.63 ± 57.49 | 207.5 ± 63.71\*\* | 163.28 ± 36.08 | 160.1 ± 27.27 |
| **D90, nm** | 281.35 ± 102.27 | 371.63 ± 92.17\*\* | 297.28 ± 63.6 | 301.39 ± 65.08 |
| **Concentration,** **108 particles/ml** | 5.06 ± 4.86 | 5.44± 3.48 | 5.06 ± 6.02 | 2.93 ± 1.98\* |
| **XRF**  | **Cadmium** | 27.1 ± 1.9 | 25.5 ± 1.1\*\* | 25.13 ± 0.73 | 25.42 ± 0.72 |
| **Palladium** | 10.3 ± 0.63 | 9.99 ± 0.64\* | 10.13 ± 0.41 | 10.12 ± 0.4 |
| **Silver** | 6.64 ± 1.1 | 6.4 ± 0.42 | 6.39 ± 0.4 | 6.47 ± 0.54 |
| **Molybdenum** | 18.67 ± 3.5 | 21.9 ± 2.5\*\* | 22.44 ± 1.1 | 22.56 ± 0.82 |
| **Niobium** | 21.3 ± 2 | 22.74 ± 1.63\*\* | 22.86 ± 1.07 | 22.92 ± 0.88 |
| **Zirconium** | 17.8 ± 0.3 | 19.05 ± 1.3\*\* | 19.13 ± 0.93 | 19.20 ± 0.78 |
| **Strontium** | 5.2 ± 0.5 | 5.3 ± 0.7 | 5.16 ± 0.46 | 5.20 ± 0.38 |
| **Tungsten** | 81.5 ± 17.5 | 82.4 ± 40.8 | 81.34 ± 18.5 | 77.73 ± 13.4 |
| **pH**  | **Before DA** | 7.24 ± 0.17 | 7.21 ± 0.16 | 7.18 ± 0.1 | 7.15 ± 0.06 |
| **After DA** | 7.71 ± 0.27 | 7.65 ± 0.27 | 7.79 ± 0.25 | 7.72 ± 0.2 |

Results are given in mean ± SD. The p value was calculated with an independent t-test.

\*p<0.05, \*\*p<0.001

**D10**, the diameter of 10% of total UFP; **D50**, the diameter of 50% of total UFP; **D90**, the diameter of 90% of total UFP. **UPF,** ultrafine particles; **DA**, de-aeration.

The analysis of **EBC** samples is shown in Table 9.

Significant differences were found in EBC UFP size between the medical staffs. The mean size was larger in Haifa (231.75 ± 60.19nm) than in Tel Aviv (166.99 ± 60.22nm) in the 1st session (p<0.001) but not in the second session. In addition, the concentration was significantly lower in Haifa in the 2nd session (2.93 ± 1.98 108 particles/ml vs 5.06 ± 6.02 108particles/ml in Tel Aviv, p<0.05).

There were also significant differences in the mineral content (XRF analysis) between the two groups only during the first session. The levels of the metals molybdenum, niobium and zirconium were significantly higher for the Haifa medical staff (p=0.001 vs. Tel Aviv medical staff), while the cadmium and palladium levels were significantly lower for the Tel Aviv medical staff (p<0.001 and <0.05, respectively, vs. Haifa medical staff). There were no comparable differences during the second session. No differences were found in the EBC pH levels between the two groups in both sessions.

**Table 10.** **Comparison between saliva data of the Tel Aviv and Haifa Medical Staffs First and Second Sessions.**

|  |  |  |
| --- | --- | --- |
|  | **1st session** | **2nd session** |
| **TLV****Medical Staff (N=49)** | **Haifa** **Medical Staff (N=50)**  | **TLV****Medical Staff (N=43)** | **Haifa** **Medical Staff (N=43)**  |
| **DCC#**  | **%Epithelial cells**  | 81.6 ± 15.9 | 79.8 ± 13.3 | 73 ± 22.6 | 79.9 ± 14.9 |
| **%Neutrophils**  | 18.95 ± 16.3 | 18.2 ± 12.6 | 25 ± 21.6 | 21.7 ± 13.9 |
| **%Lymphocytes**  | 1.91 ± 1.8 | 2.32 ± 1.5 | 4.12 ± 3.7 | 2.46 ± 2.3 |
| **PM** **(Saliva cell fraction)** | **<2.5μm %**  | 86.13 ± 9.5 | 85.45 ± 10.1 | 82.65 ± 11.17 | 82.15 ± 10.3 |
| **<5μm %**  | 93.34 ± 5.8 | 93.2 ± 6.3 | 91.09 ± 8 | 91.03 ± 7.33 |
| **<10μm %**  | 97.7 ± 2.4 | 97.62 ± 2.7 | 96.43 ± 3.93 | 96.39 ± 3.31 |
| **Size, μm** | 1.92 ± 0.7 | 1.98 ± 0.9 | 2.26 ± 1.1 | 2.34 ± 0.98 |
| **PM +****(Saliva supernatant)** | **<2.5μm %**  | 80.88 ± 13.9 | 77.05 ± 14.6 | 52.60 ± 22.3 | 51.33 ± 22.12 |
| **<5μm %**  | 90.6 ± 9.8 | 90.57 ± 8.5 | 67.37 ± 20.7 | 68.33 ± 18.5 |
| **<10μm %**  | 96.66 ± 4.7 | 97.6 ± 3.8 | 81.40 ± 16.2 | 83.98 ± 13.1 |
| **Size, μm** | 2.34 ± 1.4 | 2.32 ± 1.1 | 6.26 ± 3.9 | 6.07 ± 3.5 |
| **Chemistry (Saliva supernatant)** | **BUN, mg/dL** | 13.1 ± 4 | 15.5 ± 5.4\* | 11.76 ± 3.6 | 15.65 ± 7.9\* |
| **K, mmol/L** | 19.2 ± 3.5 | 19.9 ± 4.7 | 19.60 ± 3.3 | 21.22 ± 5.5 |
| **CL, mmol/L** | 21.0 ± 4.5 | 23.4 ± 7.2 | 22.32 ± 6.8 | 26.98 ± 9.7\* |
| **CA, mg/dL** | 4.2 ± 1.5 | 5.1 ± 0.9\*\* | 4.80 ± 0.9 | 5.12 ± 1.08 |
| **PHOS, mg/dL** | 16.3 ± 3.9 | 16.9 ± 5.8 | 16.78 ± 4.4 | 17.77 ± 6.86 |
| **LDH, U/L** | 412.1 ± 420 | 606.6 ± 609\* | 310.44 ± 195.6 | 616.02 ± 537.6\*\* |

Results are given in mean ± SD. The p value was calculated with an independent t-test.

\*p <0.05, \*\*p <0.001

**DCC**, differential cell count; **PM**, particulate matter; **BUN**, blood urea nitrogen; **K**, potassium; **CL**, chloride; **CA**, calcium; **Phos**, phosphorus; **LDH**, lactate dehydrogenase.

**#DCC:** 1st session: 0.5-3% macrophages were counted in 12 samples; 2% eosinophils were counted in 2 samples. 2nd session: 1-4% macrophages were counted in 8 samples; 1% eosinophils were counted in 2 samples.

+ % accumulation of particles in the different sizes (<2.5un;<5um;<10um)

The analysis of saliva samples is shown in Table 10.

Differential cell count (DCC) analyses were performed in the saliva samples of the medical staff following the COVID-19 pandemic, and there were no significant group differences in any of the DCC parameters.

The biochemical analysis of the saliva samples showed higher levels in all parameters tested in both Tel Aviv and Haifa during the second session, but the increase in both sessions were significant only in blood urea nitrogen (BUN) and lactate dehydrogenase (LDH).

Table 11. Comparison between the Pulmonary function test (PFT) Results and the fractional nitric oxide (FeNO) Data of the Two Groups at the First and Second Sessions inside the two groups

|  |  |  |
| --- | --- | --- |
|  | TLV Medical Staff | HAIFA Medical Staff |
| **1st session** **(N=49)** | **2nd session (N=43)**  | **1st session** **(N=50)** | **2nd session** **(N=43)**  |
| **PFT** | **FEV1%**  | 92.87 ± 17.55 | 92.49 ± 12.53 | 97.20 ± 10.58 | 96.65 ± 11.12 |
| **FVC%**  | 95.97 ± 12.57 | 92.98 ± 12.75 | 97.94 ± 11.19 | 97.09 ± 11.43 |
| **FEV1/FVC%** | 99.00 ± 6.66 | 99.23 ± 6.36 | 99.20 ± 8.16 | 99.40 ± 8.39 |
| **FEF25-75%** | 96.62 ± 22.74 | 92.56 ± 22.3 | 99.64 ± 28.59 | 98.81 ± 29.9 |
| **FeNO** | **FeNO, ppb**  | 16.92 ± 10.5 | 14.41 ± 12.7 | 19.7 ± 20 | 15.6 ± 14.5  |

Results are given in mean ± SD. The p value was calculated with the independent t-test and it was non-significant for all comparisons.

**FEV1**, Forced Expiratory Volume in one second, percent of predictive values; **FVC**, Forced Vital Capacity, percent of predictive values; **FEF25-75**, Forced Expiratory Flow at 25–75% of FVC, percent of predictive values; **FeNO**, fractional exhaled nitric oxide.

**ppb part** per billion**.**

The PFT and FeNO results were similar for the two sessions for both study groups (Table 11).

**Table 12. Comparison between the-Ultrafine Particles (UFP), X-ray Fluorescence (XRF) and PH Data Measured in Exhaled Breath Condensate (EBC) of the Two Groups at the First and Second Sessions inside the two groups**

|  |  |  |
| --- | --- | --- |
|  | **TLV Medical Staff** | **HAIFA Medical Staff** |
| **1st session** **(N=49)** | **2nd session** **(N=43)**  | **1st session** **(N=50)** | **2nd session** **(N=43)**  |
| **UFP**  | **Mean size, nm** | 166.99 ± 60.22 | 184.38 ± 36.1 | 231.75 ± 60.19 | 181.57 ± 28.81\*\* |
| **D10, nm** | 88.8 ± 30.63 | 102.60 ± 18.5\* | 123.57 ± 36.76 | 94.18 ± 16.44\*\* |
| **D50, nm** | 139.63 ± 57.49 | 163.28 ± 36.08 | 207.5 ± 63.71 | 160.1 ± 27.27\*\* |
| **D90, nm** | 281.35 ± 102.27 | 297.28 ± 63.6 | 371.63 ± 92.17 | 301.39 ± 65.08\*\* |
| **Concentration,** **108 particles/ml** | 5.06 ± 4.86 | 5.06 ± 6.02 | 5.44 ± 3.48 | 2.93 ± 1.98\*\* |
| **XRF**  | **Cadmium** | 27.1 ± 1.9 | 25.13 ± 0.73\*\* | 25.5 ± 1.1 | 25.42 ± 0.72 |
| **Palladium** | 10.3 ± 0.63 | 10.13 ± 0.41 | 9.99 ± 0.64 | 10.12 ± 0.4 |
| **Silver** | 6.64 ± 1.1 | 6.39 ± 0.4 | 6.4 ± 0.42 | 6.47 ± 0.54 |
| **Molybdenum** | 18.67 ± 3.5 | 22.44 ± 1.1\*\* | 21.9 ± 2.5 | 22.56 ± 0.82\* |
| **Niobium** | 21.3 ± 2 | 22.86 ± 1.07\*\* | 22.74 ± 1.63 | 22.92 ± 0.88 |
| **Zirconium** | 17.8 ± 0.3 | 19.13 ± 0.93\*\* | 19.05 ± 1.3 | 19.20 ± 0.78 |
| **Strontium** | 5.2 ± 0.5 | 5.16 ± 0.46 | 5.3 ± 0.7 | 5.20 ± 0.38 |
| **Tungsten** | 81.5 ± 17.5 | 81.34 ± 18.5 | 82.4 ± 40.8 | 77.73 ± 13.4 |
| **pH**  | **Before DA** | 7.24 ± 0.17 | 7.18 ± 0.1 | 7.21 ± 0.16 | 7.15 ± 0.06 |
| **After DA** | 7.71 ± 0.27 | 7.79 ± 0.25 | 7.65 ± 0.27 | 7.72 ± 0.2 |

Results are given in mean ± SD. The p value was calculated with an independent t-test.

\*p<0.05, \*\*p<0.001.

**UFP**, ultrafine particles; **D10**, the diameter of 10% of total UFP; **D50**, the diameter of 50% of total UFP; **D90**, the diameter of 90% of total UFP; **XRF,** X-ray fluorescence.

The differences in the analysis of EBC samples between the two sessions are shown in Table 12.

Significant differences were found in the EBC UFP size between the two sessions for the Haifa medical staff: the mean size was 231.75 ± 60.19nm in the 1st session and decreased to 181.57 ± 28.81nm in the 2nd session (p<0.001). The concentration was also significantly lower in the 2nd session (2.93 ± 1.98 108particles/ml vs 5.44 ± 3.48 108particles/ml in the 2nd session, p<0.001).

There were significant differences in the mineral content analysis (XRF) between the two sessions for the Tel Aviv medical staff. The metals molybdenum, niobium and zirconium had significantly higher levels at the 2nd session (p<0.001 vs. 1st session), while cadmium was significantly lower (p<0.001, 1st vs. 2nd session). In the second session group in Haifa the Molybdenum was significant high than in the first session.

No differences were found in the EBC pH levels between the two sessions in both groups.

**Table 13. Comparison between saliva data in the first and second session inside the two groups**

|  |  |  |
| --- | --- | --- |
|  | **TLV Medical Staff** | **HAIFA Medical Staff** |
| **1st session** **(N=49)** | **2nd session** **(N=43)**  | **1st session** **(N=50)** | **2nd session** **(N=43)**  |
| **DCC#**  | **%Epithelial cells**  | 81.6 ± 15.9 | 73 ± 22.6 | 79.8 ± 13.3 | 79.9 ± 14.9 |
| **%Neutrophils**  | 18.95 ± 16.3 | 25 ± 21.6 | 18.2 ± 12.6 | 21.7 ± 13.9 |
| **%Lymphocytes**  | 1.91 ± 1.8 | 4.12 ± 3.7 | 2.32 ± 1.5 | 2.46 ± 2.3 |
| **PM +****(Saliva cell fraction)** | **<2.5μm %**  | 86.13 ± 9.5 | 82.65 ± 11.17 | 85.45 ± 10.1 | 82.15 ± 10.3 |
| **<5μm %**  | 93.34 ± 5.8 | 91.09 ± 8 | 93.2 ± 6.3 | 91.03 ± 7.33 |
| **<10μm %**  | 97.7 ± 2.4 | 96.43 ± 3.93 | 97.62 ± 2.7 | 96.39 ± 3.31 |
| **Size, μm (mean)** | 1.92 ± 0.7 | 2.26 ± 1.1 | 1.98 ± 0.9 | 2.34 ± 0.98 |
| **PM +****(Saliva supernatant)** | **<2.5μm %**  | 80.88 ± 13.9 | 52.60 ± 22.3\*\* | 77.05 ± 14.6 | 51.33 ± 22.12\*\* |
| **<5μm %**  | 90.6 ± 9.8 | 67.37 ± 20.7\*\* | 90.57 ± 8.5 | 68.33 ± 18.5\*\* |
| **<10μm %**  | 96.66 ± 4.7 | 81.40 ± 16.2\*\* | 97.6 ± 3.8 | 83.98 ± 13.1\*\* |
| **Size, μm (mean)** | 2.34 ± 1.4 | 6.26 ± 3.9\*\* | 2.32 ± 1.1 | 6.07 ± 3.5\*\* |
| **Chemistry (Saliva supernatant)** | **BUN, mg/dL** | 13.1 ± 4 | 11.76 ± 3.6 | 15.5 ± 5.4 | 15.65 ± 7.9 |
| **K, mmol/L** | 19.2 ± 3.5 | 19.60 ± 3.3 | 19.9 ± 4.7 | 21.22 ± 5.5\* |
| **CL, mmol/L** | 21.0 ± 4.5 | 22.32 ± 6.8 | 23.4 ± 7.2 | 26.98 ± 9.7\* |
| **CA, mg/dL** | 4.2 ± 1.5 | 4.80 ± 0.9 | 5.1 ± 0.9 | 5.12 ± 1.08 |
| **PHOS, mg/dL** | 16.3 ± 3.9 | 16.78 ± 4.4 | 16.9 ± 5.8 | 17.77 ± 6.86 |
| **LDH, U/L** | 412.1 ± 420 | 310.44 ± 195.6 | 606.6 ± 609 | 616.02 ± 537.6 |

Results are given in mean ± SD. The p value was calculated with an independent t-test.

\*p <0.05, \*\*p <0.001

+ % accumulation of particles <2.5um;5um;10mu

**PM** particulate matter; **BUN**, blood urea nitrogen; **K**, potassium; **CL**, chloride; **CA**, calcium; **Phos**, phosphorus; **LDH**, lactate dehydrogenase.

The results for differences in the analysis of saliva samples inside the sessions of each city are shown in Table 13.

There were no differences in the DCC between the two sessions.

The PM size distribution of the saliva supernatant was significantly different between the two sessions in both groups, with a larger microparticle size measured at the 2nd session (p<0.001, 1st vs 2nd session). The mean size of the particles in the saliva supernatant was significantly lower (p<0.001) in the first session in Tel Aviv and Haifa groups.

The only differences in the biochemical analysis of the saliva between the two sessions were the higher levels of potassium and chloride in the 2nd session in Haifa (p<0.05, vs the 1st Haifa session).

**Table 14. Comparison between UFP in EBC and PM in saliva Mean Size**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **EBC** | **Saliva Cell Fraction** | **Saliva Supernatant** |
| **Particles, mean size (um)** |  0.1997 ± 0.068\* (199.7 ± 68.16 nm) | 1.95 ± 0.8 | 2.32 ± 1.2 |

Results are given in mean ± SD. p value was calculated with ANOVA.

\*p <0.001: EBC vs saliva cell fraction and vs saliva supernatant.

um, micrometer; nm, nanometer

Table 14 details a comparison between the mean size of the particles in saliva and EBC.

The EBC is seen to be recovered from middle airways while saliva is retrieved from a compartment that is anatomically high above the bronchus. In this context the mean size of particles is significantly larger than the mean size in the EBC.

**Table 15. Pearson Correlation coefficient (*r*) between Forced Vital Capacity (FVC) and Particulate Matter (PM) Size in the Saliva Supernatant**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **PM<2.5µm** | **PM<5µm** | **PM<10µm** |
| **FVC%** |  |  |  |
| *r* | -0.372\* | -0.456**\*** | -0.398\* |

\*p value <0.001

**PM**, Particulate Matter; **FVC**, Forced Vital Capacity, percent of predictive values.

**Table 16. Comparison of the Pearson Correlation Coefficient (*r*) between Functional Parameters and Particulate Matter (PM) Size in the Saliva Supernatant between the Tel Aviv and Haifa Groups**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **TLV** | **Haifa**  | **TLV**  | **Haifa**  | **TLV**  | **Haifa**  |
| **FEV1%** | ***PM<2.5µm*** | ***PM<5µm*** | NS |
| *r* | NS | -0.301\* | NS | -0.383\* |  |  |
| **FVC%** | ***PM<2.5µm*** | ***PM<5µm*** | ***PM<10µm*** |
| *r**p* value | NS | -0.388\* | -0.389\* | -0.526\* | -0.421\* | -0.401\* |
|  |  |  |  |  |  |  |

\*p value <0.05 NS, not significant.

**PM**, particulate Matter; **FEV1**, Forced Expiratory Volume in one second, percent of predictive

Values; **FVC**, Forced Vital Capacity, percent of predictive values.

**Table 17. Comparison of the Pearson Correlation Coefficient (*r*) between Functional Parameters and PH of Exhaled Breath Condensate between the Tel Aviv and Haifa Groups**

|  |
| --- |
|  **pH After De-aeration** |
|  | **TLV** | **Haifa** |
| **FEV1%** |  |
| *r* | NS | 0.289\* |
| **FVC%** |  |
| *r* | NS | 0.457\* |

\*p value <0.05 NS, not significant.

**FEV1**, Forced Expiratory Volume in one second, percent of predictive values.

**FVC**, Forced Vital Capacity, percent of predictive values.

**Table 18. Pearson Correlation coefficient (*r*) between Fractional exhaled Nitric Oxide (FeNO) and Ultrafine Particle (UFP) Size in Exhaled Breath Condensate (EBC)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Mean Particles Size (nm)** | **D10 (nm)** | **D50 (nm)** | **D90 (nm)** |
| **FeNO (ppb)** |  |  |  |  |
| *r* | 0.265\* | 0.235\* | 0.285\* | 0.220\* |

\*p value <0.05

**ppb**, parts per billion; **nm**, nanometer; **D10**, the diameter of 10% of total UFP; **D50**, the diameter of 50% of total UFP; **D90**, the diameter of 90% of total UFP.

**Table 19. Comparison of the Pearson Correlation Coefficient (*r*) between Fractional exhaled Nitric Oxide (FeNO) and Ultrafine Particle Size (UFP) in Exhaled Breath Condensate (EBC) between the Tel Aviv and Haifa Groups**

|  |  |  |
| --- | --- | --- |
|  | **Mean Particles Size (nm)** | **D50 (nm)** |
|  | **TLV** | **Haifa** | **TLV** | **Haifa** |
| **FeNO (ppb)** |  |  |
| *r**p* value | NS | 0.299\* | NS | 0.302\* |

\*p value <0.05 NS, not significant

**D50**, the diameter of 50% of total UFP

**Table 20. Pearson Correlation coefficient (*r*) between Mineral Content by Xray Fluorescence (XRF) and Ultra Fine Particles (UFP) size and concentration in Exhaled Breath Condensate (EBC)**

|  |  |  |
| --- | --- | --- |
|  | **UFP Mean Particles Size (nm)** | **Concentration** **(108 particles/ml)** |
| **Cadmium (ppm)** |  |  |
| *r* | -0.362\*\* | -0.235\* |
| **Palladium (ppm)** |  |  |
| *r* | -0.335\*\* |  |
| **Silver (ppm)** |  |  |
| *r* | -0.300\*\* |  |
| **Molybdenum (ppm)** |  |  |
| *r* | 0.475\*\* | 0.348\*\* |
| **Niobium (ppm)** |  |  |
| *r* | 0.359\*\* | 0.366\*\* |
| **Zirconium (ppm)** |  |  |
| *r* | 0.392\*\* | 0.397\*\* |
| **Strontium (ppm)** |  |  |
| *r* | *NS* | 0.344\*\* |
| **Tungsten (ppm)** |  |  |
| *r* | *NS* | 0.298\*\* |

\*p<0.05, \*\*p<0.001nm, nanometer; ppm, parts per million

**Meaningful Associations in the Medical Staff Groups**

Table 15 displays the negative significant association between the accumulation of particles <2.5 µm, <5 µm and <10 µm in the saliva supernatant and a functional parameter (FVC), indicating that the greater the accumulation of particles, the lower the functional parameters. Testing the association of particle accumulation with functional parameters (FVC and FEV1) in Tel Aviv and Haifa groups separately indicates that some of the associations lose their significance in the TLV group but not in the Haifa group.

The acidification of airways was measured by pH in EBC. There was a positive significant association of PH with functional parameters (FVC and FEV1) in the Haifa group, indicating that a low pH is associated with low functional parameters (Table 17).

Inflammation in airways was measured by FeNO, and positive significant associations between FeNO and UFP size distribution and between FeNO and mean size were revealed, indicating that UFP of all sizes induce elevated values of FeNO (Table 18). These associations remained significant only in the Haifa group when the associations in were tested separately in each group (Table 19).

The levels of the metals (cadmium. palladium and silver) were negatively correlated to the mean size of the UFP and positively correlated to the others (molybdenum, niobium and zirconium). The concentration of UFP correlated positively with the levels of molybdenum, niobium, zirconium, strontium and tungsten. This suggests that major toxic effects of inhaled UFP are related to their large surface area and concentration, which enable transmission and absorption of hazardous materials, such as heavy metals (Table 20)

**Sample Profiles**

Table 21a presents the fit indicators of the LCA procedure. The first criterion for a minimum of 20 participants in class ruled out the 3-Class solution.

2 Class solution has a lower AIC and BIC than the 1 Class solution and a significant Lo-Mendell-Rubin likelihood ratio test, therefore we identified the 2 Class model as optimal. The first class consisted of 34 subjects and the second class consisted of 65 subjects (Table 21b).

**Table 21a. Latent Class Analysis Model estimation fit indices, N=99**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Minimal no. of participants in each class** | **Entropy (0-1)** | **LMRT (p<.05)** | **BIC↓** | **AIC↓** | **Class** |
| 99 |  |  | 6715.605 | 6653.322 | **1** |
| 34 | 1.00 | 0.0271 | 6316.983 | 6220.964 | **2** |
| 5 | 0.996 | 0.5754 | 6304.223 | 6174.467 | **3** |

**LMRT**, Lo-Mendell-Rubin Test; **AIC**, Akaike information criterion; **BIC**, Bayesian information criterion.

**Table 21b. Latent Class Analysis of the Medical Staff**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Cluster 1 (N=34)** | **Cluster 2 (N=65)** |  |
| **FEV1, %** | 94.5 (20.6) | 95.4 (10.3) |  |
| **FENO, ppb** | 17.0 (13.3) | 19.0 (17.3) |  |
| **EBC UFP Mean Size, nm** | 151 (64.6)  | 225 (55.2) \*\* |  |
| **Saliva BUN, mg/dL** | 13.2 (3.90) | 14.8 (5.30) |  |
| **Saliva LDH, U/L** |  361 (488)  |  581 (541)  |  |
| **PH before de-aeration** | 7.24 (0.19) | 7.21 (0.16) |  |
| **PH after de-aeration** | 7.75 (0.28) | 7.64 (0.26)\* |  |
| **XRF Cadmium, ppm** | 28.2 (1.41) | 25.3 (0.73) |  |
| **XRF Palladium, ppm** | 10.3 (0.97) | 10.1 (0.40) |  |
| **XRF Molybdenum, ppm** | 15.8 (0.99) | 22.6 (1.19)\*\* |  |
| **XRF Nibium, ppm** | 19.8 (0.93) | 23.2 (1.25)\*\* |  |
| **XRF Zirconium, ppm** | 16.5 (0.79) | 19.4 (1.08)\*\* |  |

\*p<0.05, \*\*p <0.001; nm, nanometer; ppm, part per million

As seen in Table 21b, Cluster 2 was characterized as having:

* A higher mean UFP size in EBC.
* A higher LDH level in saliva.
* Lower PH levels in EBC (airway acidosis).
* Higher levels of molybdenum, niobium, and zirconium, and lower levels of cadmium in EBC.

These results indicate two homogeneous clusters. The profile of the subjects in cluster 2 had clear and defined parameters that could be used in the future to form more homogeneous groups in order to show the biological effects of pollution in their airways.

**Table 22. Latent Class Analysis of the Medical Staffs – Further Analysis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **Cluster 1 (N=34)** | **Cluster 2 (N=65)** |  |
| **Study Group** | **TLV**  |  30 (88.2%)  |  19 (29.2%)\*  |  |
| **Haifa**  |  4 (11.8%)  |  46 (70.8%)  |  |
| **Sex** | **Male** |  8 (23.5%)  |  22 (33.8%)  |  |
| **Female** |  26 (76.5%)  |  43 (66.2%)  |  |
| **BMI** |  23.9 (4.66)  |  26.1 (4.65)\*  |  |
| **EBC** | **UFP mean size, nm** |  151 (64.6)  |  225 (55.2)\*\*  |  |
| **UFP D10, nm** |  83.3 (36.9)  |  118 (32.8)\*\*  |  |
| **UFP D50, nm** |  125 (60.3)  |  199 (59.9)\*\*  |  |
| **UFP D90, nm** |  252 (106)  |  366 (85.1)\*\*  |  |
| **UFP concentration, 108/ml** |  3.56 (2.47) |  6.13 (4.65)\*\*  |  |
| **XRF Cd, ppm** |  28.2 (1.41)  |  25.3 (0.73)\*\*  |  |
| **XRF Pd, ppm** |  10.3 (0.97)  |  10.1 (0.40)  |  |
| **XRF Ag, ppm** |  8.63 (1.70)  |  6.39 (0.43)  |  |
| **XRF Mo, ppm** |  15.8 (0.99)  |  22.6 (1.19)\*\*  |  |
| **XRF Nb, ppm** |  19.8 (0.93)  |  23.2 (1.25)\*\*  |  |
| **XRF Zr, ppm** |  16.5 (0.79)  |  19.4 (1.08)\*\*  |  |
| **XRF Sr, ppm** |  5.03 (0.44)  |  5.33 (0.66)\*  |  |
| **XRF W, ppm** |  77.8 (17.3)  |  83.6 (36.6)  |  |
| **PH before de-aeration** |  7.24 (0.19)  |  7.21 (0.16)  |  |
| **PH after de-aeration** |  7.75 (0.28)  |  7.64 (0.26)\*  |  |
| **Saliva** | **BUN, mg/dL** |  13.2 (3.90)  |  14.8 (5.30)  |  |
| **CA, mg/dL** |  3.75 (1.50)  |  5.04 (0.92)\*  |  |
| **LDH, U/L** |  361 (488)  |  581 (541)  |  |
|  **LDH<=330 U/L** |  20 (69.0%)  |  23 (35.9%)\*  |  |
|  **LDH>330 U/L** |  9 (31.0%)  |  41 (64.1%)  |
| **Saliva %Neutrophils** |  20.2 (18.3)  |  17.6 (12.1)  |  |
| **Saliva %Lymphocytes** |  1.29 (0.95)  |  2.43 (1.65)\*  |  |
| **Saliva %Epithelial cells** |  79.4 (18.8)  |  81.7 (11.6)  |  |
| **Questionnaire** | **Atopic**  **No** |  13 (38.2%)  |  41(63.1%)\*  |  |
|  | **Yes** |  21 (61.8%)  |  24(36/9%) |
| **Cough during sickness**  |   |  |  |
|  | **No** |  13 (38.2%)  |  50 (76.9%)  | ***0.061*** |
|  | **Yes** |  21 (61.8%)  |  15 (23.1%)  |
| **Sputum during sickness**  |   |  |  |
|  | **No** |  26 (76.5%)  |  41 (63.1%)  |  |
|  | **Yes** |  8 (23.5%)  |  24 (36.9%)  |

\*p<0.05, \*\*p <0.001; nm, nanometer; ppm, part per million

We further analyzed the association between the clusters and the demographic and clinical parameters (Table 22), and found that cluster 2 was characterized as having:

* Greater proportion of the Haifa population.
* Higher BMI levels.
* Higher UFP concentrations in EBC.
* Higher levels of calcium and LDH (above 330U/L) in saliva.
* Higher percent of lymphocytes in saliva.
* More atopic symptoms.

This cluster included more Haifa individuals with high concentrations of UFP in EBC. The biochemical analysis of the saliva showed high concentrations of LDH (as a marker of degradation). The inflammatory effect of the higher concentration of UFP was depicted by symptoms of atopy and high percentages of lymphocytes in saliva.

**דיון ומסקנות**

The samples of the police populations taken during 2019-2020 are presented in pages 20-23 (n=39). Spread of the pandemic in 2020 interrupted the study on this population. The results from other police group during 2016 (n=26) are presented in the appendix. In spite of the small samples, small non-significant differences could be detected in each parameter tested.

The population studies in Medical Staff in Tel Aviv and Haifa displayed the same Pulmonary Function Tests values and showed no differences between them when compared individually in the first and second session (Table 8 and Table 11). These results confirmed those of our earlier studies on other worker populations compared to normal populations [24-25]. PFT values are not sufficiently sensitive to serve as a tool for biological monitoring.

The original protocol had included the performance of sputum induction but it was considered as an aerosol-generating procedure (AGP) and one more likely to generate higher concentrations of infectious respiratory aerosols than coughing, sneezing, talking, or breathing. AGPs potentially put healthcare personnel and others at an increased risk for pathogen exposure and infection.

We therefore collected saliva as the less biologically invasive tool as a surrogate for induced sputum.

Saliva (also referred to as oral fluid) is a natural filtrate of blood that contains omics features (small molecules, metals, proteins, and DNA). It offers many advantages compared to other bio fluids since it can be collected safely and noninvasively with minimal training, in addition to being rich in biological information [18]. The multiple functions provided by saliva are essential for proper protection and functioning of the body as a whole as well as for general health. With the spread of the COVID pandemic, the saliva-based molecular tests have shown a similar sensitivity and specificity compared to nasopharyngeal tests for SARS-CoV-2 [26-27]. The use of saliva in other pathological conditions, such cancer [28], autoimmune disease [29] and Alzheimer disease [30] have also been reported.

In our current investigation, we demonstrated the validity of our methods using samples of saliva to measure the mean size of particulate matter in the airways. It is known that iinhaled particles distribute in the airways according to their size and become smaller the deeper the site in the bronchial tree [31]. It emerged that the mean size of particles in saliva were significantly larger than those measured in EBC (Table 14) since the saliva sample was recovered from an upper airway compartment. These results are in agreement with those shown by us in a previous study where we showed that particles recovered from bronchioalveolar lavage are smaller than those recovered from induced sputum [32].

The particulate matter measured in the saliva in the Tel Aviv group was not different from the results from the Haifa group in the first and second sessions (Table 10). Looking at the results within each city, however, revealed a uniform significant decrease in mean size of the particulate matter (Table 13). This can be explained by some atmospheric disturbance affecting the entire geographic area during this period of time.

We performed biochemical analyses in the saliva samples. We were mainly interested in the LDH content, but other biochemical parameters were tested as well. The results of all of the biochemical parameters were consistently higher in Haifa compared to Tel Aviv in both the first and second session (Table 10), but significant for two of them (LDH and BUN). We were especially interested in the LDH levels, since this metabolite had been found to be suggestive of disturbances of the cellular integrity and a marker of lung and pulmonary endothelial cell injury [33]. This marker had also been tested for tuberculosis [34], breast carcinoma [35], and buccal fibrosis [36].

Blood urea nitrogen (BUN) is a serum byproduct of protein metabolism. It is one of the oldest prognostic biomarkers of heart failure. Urea is formed by the liver and carried by the blood to the kidneys for excretion, and may be used as a marker for predicting renal disease [37]. The data in a recently published paper showed that UFP particles are excreted in urine [38].

Exhaled Breath condensate (EBC) samples were used to measure the mean size and the levels of metals in UFP particles. The mean size of UFP particles was significantly larger for each percentage of accumulated particles in the Haifa population in the first session but not in the second (Table 9). In the second session, the concentration of UFP particles decreased by almost one-half in the Haifa population compared to the Tel Aviv group and also compared to the Haifa group in the first session (Table 9 and Table 12).

The comparison of these very significant changes in the size of UFP particles between the two populations at two periods of time (first and second session Table 9 and 12) may indicate that this parameter can be very sensitive to some unpredictable atmospheric changes like those resulting from lockdown that can act as a confounder. This was demonstrated in a very recent observational study that showed that reduced levels of air pollution during the COVID-19 lockdown in Israel were reflected in increased levels of UFP airway contents [39].

Interestingly, the large size of particles in Haifa and the high concentration of UFP particles occurred in parallel with high levels of metals during the first session (Table 9). During the second sessions the size decreased and the level of concentration lowered by almost one-half (5.06 ± 6.02 vs 2.93± 1.98). This may be explained due to the fact that the metals which are attached to the surface of particles, increase due to their small dimension.

In this context, we looked at associations between the levels of metals with size and concentration of UFP in both cities and during two sessions. It emerged that the mean size and concentration were associated to the levels of metal in EBC (Table 20). This suggests that major toxic effects of inhaled UFP are related to their large surface area and concentration which enable transmission and absorption of hazardous materials, such as heavy metals [40-42].

Interesting associations are shown in Table 15-19. Accumulation of PM in saliva samples (PM 2.5um, PM 5um, and PM 10um) were negatively associated to PFT parameters (FVC and FEV1), indicating that the higher the accumulation of this fraction of PM the worse will be the PFT parameters. This correlation remained significant only in the Haifa population when the two urban populations were compared. The fact that inhaled particles correlated with worse PFT results had already been reported in an elderly [42] and in a pediatric population [43]. While those studies used measurements in the environment PM, however, to the best of our knowledge ours is the first report on PM findings in saliva.

A negative association was found between pH and PFT, demonstrating that acidification of the airways (i.e., lower pH) was correlated to worse PFT results (Table 17), supporting our earlier findings [44].

Feno was used in this study as a surrogate for eosinophils in IS and its concentration was shown to be positively associated to the accumulation of UFP. This was significant only in the Haifa study population. These results may indicate that small particle accumulation in the airways as measured in EBC caused high inflammatory values of Feno in the Haifa population.

Epidemiological and toxicological research support a link between air pollution and an increased incidence and/or severity of airway inflammation. Feno is a simple, safe and noninvasive method to detect airway inflammation. It is also correlated well with eosinophil count and eosinophil cationic protein in induced sputum, and serves as a widely used metric for the evaluation and management of airway inflammation [43-47].

**The present study represents a first attempt to find a profile of tests that can be used to build a future model to bio monitor the Haifa city health population and define which of them will be useful in showing the deleterious effect of this specific pollution**

In this context toward this end, we performed a latent class analysis (LCA) to identify the number of homogenous subgroups according to selected measurements within the overall sample (detailed in the Statistical Methods section). Once the ideal number of classes had been determined, individuals were assigned to their most likely class and compared between the classes based upon demographic, clinical, and biological variables by means of a univariate analysis.

The results yielded two homogeneous clusters. The measurements chosen as indicators of the LCA were: FEV1(the only physiological parameter) , FeNO, UFP (very small particles mean size) pH, cadmium, palladium, molybdenum, niobium and zirconium in EB, BUN, LDH (Table 21a and 21b) in saliva. These markers were selected according to the parameters that had been shown to be with significant differences and sensitive all over the study performed.

 Cluster 2 (Table 22) included more Haifa individuals who had high concentrations of UFP in EBC. The biochemical analysis of the saliva showed high concentrations of calcium and LDH (as a marker of degradation). The inflammatory effect of the higher concentration of UFP was reflected by symptoms of atopy and high percentages of lymphocytes in saliva.

Recommendations

The deleterious effect of air pollution on the health of the Haifa population cannot be identified only by the currently employed environmental measurements. The parameters that should be used to build a model which include biological parameters for this purpose are:

* PFT
* FeNO,
* UFP (very small particles mean size) in EBC.
* pH in EBC.
* Cadmium, palladium, molybdenum, niobium and zirconium in EBC.
* BUN, LDH and lymphocytes in saliva.
* Atopy symptoms

This model and parameters should be validated by association to environmental measurements.

Recommendations to the Ministry of Environmental Protection and its practical applications

The Ministry of Environmental Protection should fund a follow-up with a larger and well-defined population in order to study the deleterious effect of atmospheric pollution on the health and wellbeing of Haifa inhabitants **using the model proposed in this study.**

Limitations of the study

* Our study was done during the COVID-19 pandemic. We faced a lot of practical problems due to the lockdowns and post covid healthy volunteers' diseases. Although we were unable to find any differences between the COVID and non-COVID groups in the demographic and smoking parameters (Table 6) or in any other parameters tested here (data not shown), we nevertheless believe that pandemic did have some deleterious influence on the environment that affected airway conditions of the urban residents.
* Due to the fact that the study sample remain small additional multivariate analysis was not done.
* Due to the Covid 19 Pandemia the study methods were changed and recruitment population begins again during 2020 using saliva samples instead of induced sputum.
* Environmental monitoring was not measured here as it was not included in our proposal.

**רשימת ספרות**

1. Schraufnagel DE, Balmes JR, De Matteis S, Hoffman B, Kim WJ, Perez-Padilla R, et al. Health Benefits of Air Pollution Reduction. Ann Am Thorac Soc. 2019 Dec;16(12):1478-148.
2. Pryor JT, Cowley LO, Simonds SE. [The Physiological Effects of Air Pollution: Particulate Matter, Physiology and Disease.](https://pubmed.ncbi.nlm.nih.gov/35910891/) Front Public Health. 2022 Jul 14.
3. Rana S, Saxena MR, Maurya RK. [A review on morphology, nanostructure, chemical composition, and number concentration of diesel particulate emissions.](https://pubmed.ncbi.nlm.nih.gov/34997510/) Environ Sci Pollut Res Int. 2022 Mar;29(11):15432-15489.
4. Schraufnagel DE, Balmes JR, Cowl CT, De Matteis S, Jung SH, Mortimer K, et al. [Air Pollution and Noncommunicable Diseases: A Review by the Forum of International Respiratory Societies' Environmental Committee, Part 2: Air Pollution and Organ Systems.](https://pubmed.ncbi.nlm.nih.gov/30419237/) Chest. 2019 Feb;155(2):417-426.
5. Sarigiannis DA, Karakitsios S, Dominguez-Romero E, Papadaki K, Brochot C, Kumar V, et al. [Physiology-based toxico kinetic modelling in the frame of the European Human Biomonitoring Initiative.](https://pubmed.ncbi.nlm.nih.gov/30818231/) 2019.

https://hero.epa.gov/hero/index.cfm/reference/details/reference\_id/5741266

1. [Nelson Barros](https://pubmed.ncbi.nlm.nih.gov/?term=Barros+N&cauthor_id=31266404)E, [Márcia Carvalho](https://pubmed.ncbi.nlm.nih.gov/?term=Carvalho+M&cauthor_id=31266404) CS, [Fontes](https://pubmed.ncbi.nlm.nih.gov/?term=Fontes+T&cauthor_id=31266404)T,  [Prata](https://pubmed.ncbi.nlm.nih.gov/?term=Prata+JC&cauthor_id=31266404) JC, [André Sousa](https://pubmed.ncbi.nlm.nih.gov/?term=Sousa+A&cauthor_id=31266404) A, Conceição M. Environmental and biological monitoring of benzene, toluene, ethylbenzene and xylene (BTEX) exposure in residents living near gas stations. Toxically Environ Health A. 2019;82(9):550-563.
2. Semenova Y, Zhunussov Y, Pivina L, Abisheva A, Tinkov A, Belikhina T, et al. [Trace element biomonitoring in hair and blood of occupationally unexposed population residing in polluted areas of East Kazakhstan and Pavlodar regions.](https://pubmed.ncbi.nlm.nih.gov/31442951/) Trace Elem Med Biol. 2019 Dec;56:31-37.
3. [Bolsunovsky](https://pubmed.ncbi.nlm.nih.gov/?term=Bolsunovsky+A&cauthor_id=31739227) A, [Dementyev](https://pubmed.ncbi.nlm.nih.gov/?term=Dementyev+D&cauthor_id=31739227) D, [Trofimova](https://pubmed.ncbi.nlm.nih.gov/?term=Trofimova+E&cauthor_id=31739227) E. Biomonitoring of radioactive contamination of the Yenisei River using aquatic plants. J Environ Radioact. 2020 Jan; 211:106100.
4. [Oliveira](https://pubmed.ncbi.nlm.nih.gov/?term=Oliveira+M&cauthor_id=30654326)M, [Slezakova](https://pubmed.ncbi.nlm.nih.gov/?term=Slezakova+K&cauthor_id=30654326) K, [Delerue-Matos](https://pubmed.ncbi.nlm.nih.gov/?term=Delerue-Matos+C&cauthor_id=30654326) C, [Maria Carmo Pereira](https://pubmed.ncbi.nlm.nih.gov/?term=Pereira+MC&cauthor_id=30654326) M, S. Children environmental exposure to particulate matter and polycyclic aromatic hydrocarbons and biomonitoring in school environments: A review on indoor and outdoor exposure levels, major sources and health impacts. Environ Int. 2019 Mar; 124:180-204.
5. Fireman E, Lerman Y, Stark M, Schwartz Y, Ganor E, Grinberg N, et al. Detection of occult lung impairment in welders by induced sputum particles and breath oxidation. Am J Ind Med. 2008 Jul;51(7):503-11.
6. Fireman E, Mazor O, Kramer M, Priel I, Lerman Y. Non-invasive diagnosis of chronic beryllium disease in workers exposed to hazardous dust in Israel. Occup Environ Med. 2010 Sep;67(9):631-5.
7. Fireman EM, Lerman Y, Ganor E, Greif J, Fireman-Shoresh S, Lioy PJ, et al. Induced sputum assessment in New York City firefighters exposed to World Trade Center dust. Environ Health Perspect. 2004 Nov;112(15):1564-9.
8. Fireman E, Bliznuk D, Schwarz Y, Soferman R, Kivity S. Health Biological monitoring of particulate matter accumulated in the lungs of urban asthmatic children in the Tel-Aviv area. Int Arch Occup Environ Health. 2015 May;88(4):443-449.
9. Ophir N, Bar Shai A, Korenstein R, Kramer MR, Fireman E [Functional, inflammatory and interstitial impairment due to artificial stone dust ultrafine particles exposure.](https://pubmed.ncbi.nlm.nih.gov/31562234/).Occup Environ Med. 2019 Dec;76(12):875-879.
10. Fireman E, Edelheit R, Stark M, Shai AB [Differential pattern of deposition of nanoparticles in the airways of exposed workers.](https://pubmed.ncbi.nlm.nih.gov/28163602/).J Nanopart Res. 2017;19(2):30
11. [https://www.cdc.gov/coronavirus/2019-ncov/hcp/non-us settings/overview/index.html#standard-based-precautions](https://www.cdc.gov/coronavirus/2019-ncov/hcp/non-us%20settings/overview/index.html#standard-based-precautions).
12. Khatri SB, Iaccarino JM, Barochia A, Soghier I, Akuthota P, Brady A, et al.  [Use of Fractional Exhaled Nitric Oxide to Guide the Treatment of Asthma: An Official American Thoracic Society Clinical Practice Guideline.](https://pubmed.ncbi.nlm.nih.gov/34779751/) American Thoracic Society Assembly on Allergy, Immunology, and Inflammation. Am J Respir Crit Care Med. 2021 Nov 15;204(10).
13. Bessonneau V, Pawliszyn J, Rappaport SM. The Saliva Exposome for Monitoring of Individuals' Health Trajectories Health Perspec. 2017 Jul 20;125(7):077014.
14. [JA Hagenaars](https://scholar.google.co.il/citations?user=D5DWuccAAAAJ&hl=iw&oi=sra), [AL McCutcheon](https://scholar.google.co.il/citations?user=xLPsxpwAAAAJ&hl=iw&oi=sra) Applied latent class analysis2002‏ - books.google.co
15. Bridget E. Weller1 , Natasha K. Bowen2, and Sarah J. Faubert3 Latent Class Analysis: A Guide to Best Practice Journal of Black Psychology 2020, Vol. 46(4) 287–311
16. Akaike H. Factor analysis and AIC. Psychometrika. 1987; 52:317–32.
17. Sclove L. Application of model-selection criteria to some problems in multivariate analysis. Psychometrika. 1987; 52:333–43.
18. Nylund KL, Asparouhov T, Muthen B. Deciding on the number of classes in latent class analysis and growth mixture modeling: a Monte Carlo simulation study. Struct Equ Model: Multidiscip J. 2007; 14:535–69.
19. Ophir N, Shai AB, Alkalay Y, Israeli S, Korenstein R, Kramer MR, Fireman E**.** [Artificial stone dust-induced functional and inflammatory abnormalities in exposed workers monitored quantitatively by biometrics.](https://pubmed.ncbi.nlm.nih.gov/27730180/) 2022 ERJ Open Res. 2016 Mar 17;2
20. Fireman E, Lerman Y, Stark M, Schwartz Y, Ganor E, Grinberg N, Frimer R, Landau DA, Zilberberg M, Barenboim E, Jacovovitz R [Detection of occult lung impairment in welders by induced sputum particles and breath oxidation.](https://pubmed.ncbi.nlm.nih.gov/18459140/) .Am J Ind Med. 2008 Jul;51(7):503-11
21. Parodi C, Ottaviano E, Cocco N, Ancona S, Bianchi S, Massa V, Bartolotti R, Pezzoni B, Giuliani R, Borghi E, Ranieri R.Front. [Feasibility and acceptability of saliva-based testing for the screening of SARS-CoV-2 infection in prison..](https://pubmed.ncbi.nlm.nih.gov/36033789/)Public Health. 2022 Aug 11;10.
22. Jo SJ, Kim J, Kim S, Kim J, Kwon H, Kwon Y, Kim H, Kim HH, Lee H, Kim SW, Yeo CD, Lee SH, Lee J [Simple Saliva Sample Collection for the Detection of SARS-CoV-2 Variants Compared to Nasopharyngeal Swab Sample.](https://pubmed.ncbi.nlm.nih.gov/36026554/) Arch Pathol Lab Med. 2022 Aug 26.
23. Waniczek D, Świętochowska E, Śnietura M, Kiczmer P, Lorenc Z, Muc-Wierzgoń M.Metabolites. 2022 Jul 28;12(8):704[Salivary Concentrations of Chemerin, α-Defensin 1, and TNF-α as Potential Biomarkers in the Early Diagnosis of Colorectal Cancer.](https://pubmed.ncbi.nlm.nih.gov/36005576/)
24. Sciascia S, Bentow C, Radin M, Barinotti A, Cecchi I, Foddai S, Roccatello D, Mahler M.Diagnostics (Basel). 2022 Aug 22[Detection of Autoantibodies in Saliva as New Avenue for the Diagnosis and Management of Autoimmune Patients.](https://pubmed.ncbi.nlm.nih.gov/36010376/)
25. Gong X, Zhang H, Liu X, Liu Y, Liu J, Fapohunda FO, Lü P, Wang K, Tang M. I[s liquid biopsy matures enough for the diagnosis of Alzheimer's disease?](https://pubmed.ncbi.nlm.nih.gov/35992602/)

Front Aging Neurosci. 2022 Aug 5:14.

1. Thiago C. Carvalhoa, Jay I. Peters b, Robert O. Williams III a Influence of particle size on regional lung deposition – What evidence is there? International Journal of Pharmaceutics 406 (2011) 1–10.
2. Fireman E, Topilsky I, Greif J, Lerman Y, Schwarz Y, Man A, Topilsky M.Respir Med. 1999 Nov;93(11):827-34 Induced sputum compared to bronchoalveolar lavage for evaluating patients with sarcoidosis and non-granulomatous interstitial lung disease.
3. M.Drent, N.A.N Cobben, R.F. Henderson, E.F.M Wouters, M. van dieijen-Visser, Usefulness of lactate dehydrogenase and its isoenzyms as indicators of lung damage or inflammation. *Eur Respir J*. 1996;9 :1736-1742.
4. Sharma PR, Jain S, Bamezai RN, Tiwari PK. Utility of serum LDH isoforms in the assessment of mycobacterium tuberculosis induced pathology in TB patients of Sahariya tribe*. Indian J Clin Biochem* 2010, Jan;(1):57-63.
5. Agrawal A, Gandhe MB, Gupta D, Reddy MV. Preliminary Study on Serum Lactate Dehydrogenase (LDH) – Prognostic Biomarker in Carcinoma Breast. *J Clin. Diagn Res*. 2016 Mar; 10(3) BC06-8.
6. Mishra S, Kritika C, Bajoria AA, Choudhury P, Sahoo Sk, Sangamesh NC.

 Estimation of salivary and a serum Lactate Dehydrogenase in oral submucous fibrosis. J Int Prev Community Dent. 2018 Jul-Aug;8(4):289-295.

1. Makiko Seki , Masaru Nakayama, Teppei Sakoh , Ryota Yoshitomi , Akiko Fukui , Eisuke Katafuchi , Susumu Tsuda , Toshiaki Nakano, Kazuhiko Tsuruya Takanari Kitazono Blood urea nitrogen is independently associated with renal outcomes in Japanese patients with stage 3–5 chronic kidney disease: a prospective observational study BMC Nephrology (2019) 20:115
2. Fireman Klein E, Klein I, Ephrat O, Dekel Y, Kessel A, Adir Y. [Trajectory of inhaled cadmium ultrafine particles in smokers.](https://pubmed.ncbi.nlm.nih.gov/34845007/)

BMJ Open Respir Res. 2021 Nov;8

1. Fireman Klein E, Elimeleh Y, Adir Y, Majdoub L, Shteinberg M, Kessel A. [COVID-19 Lockdown in Israel: The Environmental Effect on Ultrafine Particle Content in the Airway.](https://pubmed.ncbi.nlm.nih.gov/35564902/) Int J Environ Res Public Health. 2022 May 1;19(9):5507
2. Li N, Georas S, Alexis N, [Fritz](https://pubmed.ncbi.nlm.nih.gov/?sort=date&term=Fritz+P&cauthor_id=27130856),P,  [Xia](https://pubmed.ncbi.nlm.nih.gov/?sort=date&term=Xia+T&cauthor_id=27130856) T, [Williams](https://pubmed.ncbi.nlm.nih.gov/?sort=date&term=Williams+MA&cauthor_id=27130856) MA, [Horner](https://pubmed.ncbi.nlm.nih.gov/?sort=date&term=Horner+E&cauthor_id=27130856)E, [Nel](https://pubmed.ncbi.nlm.nih.gov/?sort=date&term=Nel+A&cauthor_id=27130856) A A work group report on ultrafine particles (American Academy of Allergy, Asthma & Immunology): why ambient ultrafine and engineered nanoparticles should receive special attention for possible adverse health outcomes in human subjects. J Allergy Clin Immunol 2016; 138: 386–396.
3. Brown DM, Wilson MR., MacNee, W.. Stone V, and. Donaldson K Size-Dependent Proinflammatory Effects of Ultrafine Polystyrene Particles: A Role for Surface Area and Oxidative Stress in the Enhanced Activity of Ultrafines Toxicology and Applied Pharmacology 2001.175, 191–199.
4. [Chi-Hsien Chen](https://pubmed.ncbi.nlm.nih.gov/?term=Chen+CH&cauthor_id=31616001), [Chih-Da Wu](https://pubmed.ncbi.nlm.nih.gov/?term=Wu+CD&cauthor_id=31616001) [Hung-Che Chiang](https://pubmed.ncbi.nlm.nih.gov/?term=Chiang+HC&cauthor_id=31616001) [Dachen Chu](https://pubmed.ncbi.nlm.nih.gov/?term=Chu+D&cauthor_id=31616001), [Kang-Yun Lee](https://pubmed.ncbi.nlm.nih.gov/?term=Lee+KY&cauthor_id=31616001), [Wen-Yi Lin](https://pubmed.ncbi.nlm.nih.gov/?term=Lin+WY&cauthor_id=31616001), [Jih-I Yeh](https://pubmed.ncbi.nlm.nih.gov/?term=Yeh+JI&cauthor_id=31616001), [Kun-Wei Tsai](https://pubmed.ncbi.nlm.nih.gov/?term=Tsai+KW&cauthor_id=31616001), [Yue-Liang Leon Guo](https://pubmed.ncbi.nlm.nih.gov/?term=Guo+YL&cauthor_id=31616001) The effects of fine and coarse particulate matter on lung function among the elderly. Sci Rep2019 Oct 15;9(1):14790.
5. [Acute Effects of Individual Exposure to Fine Particulate Matter on Pulmonary Function in Schoolchildren.](https://pubmed.ncbi.nlm.nih.gov/33106210/) Yang XY, Wen B, Han F, Wang C, Zhang SP, Wang J, Xu DQ, Wang Q. Biomed Environ Sci. 2020 Sep 20;33(9):647-659
6. Fireman E, Lerman Y, Stark M, Schwartz Y, Ganor E, Grinberg N, Frimer R, Landau DA, Zilberberg M, Barenboim E, Jacovovitz R. Detection of occult lung impairment in welders by induced sputum particles and breath oxidation

 Am J Ind Med. 2008 Jul;51(7):503-11

1. Zheng Zhu, Yanqing Xie, Weijie Guan, Yi Gao, Shu Xia, Nanshan Zhong, and Jinping Zheng FeNO for detecting lower airway involvement in patients with allergic rhinitis Exp Ther Med. 2016 Oct; 12(4): 2336–2340.
2. Sivan Y, Gadish T, Fireman E, Soferman R [The use of exhaled nitric oxide in the diagnosis of asthma in school children.](https://pubmed.ncbi.nlm.nih.gov/19394049/) .J Pediatr. 2009 Aug;155(2):211-6.
3. Gadish T, Soferman R, Merimovitch T, Fireman E, Sivan Y. Arch Pediatr Adolesc Med [Exhaled nitric oxide in acute respiratory syncytial virus bronchiolitis.](https://pubmed.ncbi.nlm.nih.gov/20679163/) 2010 Aug;164(8):727-31

**נספחים**

During 2016 we collected data from 13 policemen in Tel Aviv and 13 in Haifa;

This study was funded by 'Igud Arim Haifa' and interrupted by the Ministry of Health.

On December 2018 the Ministry for Environmental Protection decided finally to fund the above mention research.

During 2019 we recruited 44 policemen. Regretfully the study was interrupted when the World Health Organization (WHO) declared the spread of COVID-19 to be a [Public Health Emergency of International Concern](https://www.who.int/dg/speeches/detail/who-director-general-s-statement-on-ihr-emergency-committee-on-novel-coronavirus-%282019-ncov%29) (PHEIC) on January 30 this year and later [characterized it as a pandemic on March 11](https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020).

The original protocol included the performance of sputum induction but this procedure was considered as an Aerosol-Generating Procedures (AGP) and are more likely to generate higher concentrations of infectious respiratory aerosols than coughing, sneezing, talking, or breathing. AGPs potentially put healthcare personnel and others at an increased risk for pathogen exposure and infection

(<https://www.cdc.gov/coronavirus/2019-ncov/hcp/non-us-settings/overview/index.html#standard-based-precautions>

The police departments in Tel Aviv and in Haifa were unable to offer us the facilities to test individuals in an open space with adequate ventilation in order to avoid Corona virus infection among the recruited population and our staff.

In this context we decided to change the original protocol using methods and procedures that can be a surrogate for sputum induction without the generation of aerosols

The results from 2016are presented in pages 55-57.

**Data from 2016**

**Table 23. Comparison between DEMOGRAPHICS DATA in Tel Aviv and Haifa Police Populations - 2016**

|  |  |  |
| --- | --- | --- |
|  | **TLV police (n=13)** | **Haifa police (n=13)** |
| **Age, years (mean ± SD)** | 29.2±4 | 29.2±5 |
| **Male, *n* (%)** | 12(85.7) | 8(57.1) |
| **Smoking, *n* (%)** |  |  |
| **Active** | 1(7.1) | 2(8.3) |
| **Passive** | 9(64.3) | 8(57.1) |

*P* value was calculated Mann-Whitney U test for continuous variables and *X*2 for categorical variables. *PV* is non-significant in all comparisons.

**Table 24. Comparison between Pulmonary function tests (PFT) Data in Tel Aviv and Haifa Police Populations - 2016**

|  |  |  |
| --- | --- | --- |
|  | **TLV police** **(N=12)** | **Haifa police (n=13)** |
| **FEV1%**  | 96.8±10 | 96.1±9.4 |
| **FVC%**  | 97.2±10.4 | 94.9±9.8 |
| **FEV1/FVC%** | 100.1±7.1 | 102.1±4.3 |
| **FEF25-75%** | 93.2±19.1 | 102.4±17.4 |

Results are given in mean ± SD. *P* value was calculated Mann-Whitney U test.

*PV* is non-significant in all comparisons.

**FEV1**, Forced Expiratory Volume in one second, percent of predictive values. **FVC**, Forced Vital Capacity, percent of predictive values. **FEF25-75**, Forced Expiratory Flow at 25–75% of FVC, percent of predictive values.

**Table 25. Comparison BETWEEN ULTRAFINE PARTICLES (UFP) and X-ray Fluorescence (XRF) Data measured in Exhaled Breath Condensate (EBC) in Tel Aviv and Haifa Police Populations - 2016**

|  |  |  |
| --- | --- | --- |
|  | **TLV police** **(n=13)** | **Haifa police** **(n=13)** |
| **UFP**  | **Mean Size, nm** | 196.4±65 | 222.3±68 |
| **D10, nm** | 114.4±64 | 114.3±16 |
| **D50, nm** | 186.6±56 | 213.3±67 |
| **D90, nm** | 285.8±101 | 332.7±130 |
| **XRF**  | **Silica** | 672±218 | 558±190 |
| **Sulfur** | 743±221 | 861±213 |
| **Chlorine** | 9261±8462 | 9930±3043 |
| **Silicon** | 314±102 | 260±89 |
| **Phosphorus** | 714±102 | 894±194 |
| **Copper** | 9±22 | 30±30 |
| **Tungsten** | 81±89 | 83±107 |

Results are given in mean ± SD. *P* value was calculated Mann-Whitney U test.

*PV* is non-significant in all comparisons.

**D10**, the diameter of 10% of total UFP; **D50**, the diameter of 50% of total UFP;

**D90**, the diameter of 90% of total UFP.

**Table 26. Comparison BETWEEN SPUTUM data in Tel Aviv and Haifa Police Populations - 2016**

|  |  |  |
| --- | --- | --- |
|  | **TLV police** **(N=12)**(missing=1) | **Haifa police** **(N=12)**(missing=1) |
| **DCC** | **%Neutrophils** | 22.6±17 | 45.2±30 |
| **%Lymphocytes**  | 6±3.7 | 4.7±4.2 |
| **%Macrophages**  | 69.6±17 | 47.5±30 |
| **%Eosinophils**  | 1.8±3.7 | 1.8±3.5 |
| **PM** **(Sputum Supernatant)** | **<2.5μm %**  | 79.2±5.6 | 76.1±5.1 |
| **<5μm %**  | 98.1±1.4 | 97.0±2 |
| **<10μm %**  | 99.7±0.4 | 99.6±0.5 |
| **Size, μm** | 4.27±0.76 | 4.57±1.1 |

Results are given in mean ± SD. *P* value was calculated with Mann-Whitney U-test.

*PV* is non-significant in all comparisons.

**DCC**, Differential Cell Count. **PM**, Particulate Matter.

**Table 1 (2019) and Table 23 (2016):** There were no significant differences between demographic and smoking habits between policemen in Tel Aviv and Haifa.

**Table 2 (2019) and Table 24 (2016):** There were no significant differences between Pulmonary Function Testing between policemen in Tel Aviv and Haifa**.**

**Table 3 (2019) and Table 25 (2016):** There were no significant differences between Ultra Fine Particles load and metals analysis in EBC between policemen in Tel Aviv and Haifa**.**

**Table 4 (2019) and Table 26 (2016):** There were no significant differences between DCC and PM size distribution of induced sputum between policemen in Tel Aviv and Haifa**.**

**Conclusion**: Taking into consideration that we did not find differences between the tested police population recruited in 2016 and 2019, we continued only with the Tel Aviv and Haifa medical staff populations following COVID-19 pandemia.

**שאלון בריאות-מבוגרים**

תאריך מילוי השאלון |\_|\_|/|\_|\_|/|\_|\_| מס' סידורי|\_|\_|\_| טלפון |\_|\_|\_|\_|\_|\_|\_|\_|\_|

 נייד |\_|\_|\_|\_|\_|\_|\_|-|\_|\_|\_|

**פרטים אישיים**

**1.** שם פרטי : \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**2.** שם משפחה: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**3.** מין: 1.זכר 2. נקבה

**4.** מצב משפחתי: 1.רווק/ה 2.נשוי/ה 3.אלמן /ה 4.גרוש /ה 8.אחר \_\_\_\_\_\_\_\_\_\_

**5.** שנת לידה: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**6**. ארץ לידה: \_\_\_\_\_\_\_\_\_\_\_\_\_\_

**7**. ארץ לידת האב: \_\_\_\_\_\_\_\_\_\_\_\_\_\_

**8**. ארץ לידת האם: \_\_\_\_\_\_\_\_\_\_\_\_\_\_

**9.** שנת עליה­­­­­­­­­­: \_\_\_\_\_\_\_\_\_\_­\_\_\_\_\_\_\_\_

**10.** דת: 1.יהודי/ה 2. נוצרי/ה 3.ערבי /ה מוסלמי/ת 4 .ערבי/ה נוצרי /ת 5.דרוזי /ת 6 .אחר \_\_\_\_\_\_\_\_

**11.** מקום מגורים נוכחי (כתובת מלאה): **\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

 מס' סידורי|\_|\_|\_|

**פרטים סביבתיים**

**12.** מספר שנים בו את/ה גר בבית הנוכחי: 1-שנה 2. שנתיים 3- לפחות שלוש שנים

**13**. האם לדירה או בית בו אתה מתגורר יש מרפסת פתוחה או חצר

 1. כן 2. לא

**14**. האם הבית/דירה ממוקמת:

 1. חזית 2. עורף

**15.** האם אתה נוהג לעשות מנגל?

 1. כן 2. לא

**16.**  אם כן, באיזו תדירות?

 1. פעם בשבוע 2. פעם בחודש 3.פעם בשנה 4. אחר \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**17.**  איך אתה מחמם את הבית?

 1. מזגן 2. רדיאטור 3. תנור חשמלי 4. חימום מרכזי 5. תנור נפט 6. תנור גז 7. קמין 8. אח 9. אחר\_\_\_\_\_\_

**18**. אנא ציין את סוג הבנייה בה אתה מתגורר (ניתן לסמן יותר מאחד):

 1. בניית איטונג 2. חלונות כפולים 3. בנייה ירוקה 4. אחר \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**19**. איך אתה מקרר את הבית?

 1.מזגן 2. מאוורר 3. אחר \_\_\_\_\_\_\_\_\_\_\_

**20**. האם בביתך בעיות של עובש ולחות?

 1.כן 2. לא 3. לא יודע

**21**. האם בביתך אחד או יותר מהבאים (ניתן לסמן יותר מאחד):

 1. קרדית האבק 2. רהיטי עץ חדשים 3. שימוש בנפטלין 4. גגות אסבסט 5. צבע קירות עם עופרת

 6. שימוש בחומרי הדברה 7. חומרי ניקוי חומציים 8. שטיחים 9. וילונות 10. שכנים המשפצים את דירתם

 (כולל תמ"ה 38, פינוי בינוי) 11. אחר \_\_\_\_\_\_\_\_\_\_

 מס' סידורי|\_|\_|\_|

**22.** מקומות מגורים קודמים

|  |  |  |
| --- | --- | --- |
|  | כתובת | שנים |
| 1. |  |  |
| 2. |  |  |
| 3. |  |  |
| 4. |  |  |
| 5. |  |  |
| 6. |  |  |
| 7. |  |  |

 **השכלה**

**23.** מה ההשכלה שלך?

 1.יסודי 2.חטיבה 3.תיכון חלקי 4.תיכון מלא 5.לימודים מקצועיים על תיכוניים 6.השכלה אקדמית 7.אחר\_\_\_\_

**שירות צבאי**

**24.** האם שרתת בצבא ? 1-לא 2-כן 3-בחו"ל

**25.** האם אתה משרת במילואים? 1-לא 2-כן

**26.** האם שרתת במילואים? 1-לא 2-כן 3-בחו"ל

**27.** אם שרתת בצבא פרט:

חיל תפקיד חשיפה אפשרית החומרים משנה עד שנה סה"כ שנים

\_\_\_\_ \_\_\_\_\_\_ 1-לא 2-כן \_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_

\_\_\_\_ \_\_\_\_\_\_\_ 1-לא 2-כן \_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_

**28**. זמן חשיפה אפשרי במהלך השירות (סה"כ שנים):

 1. פחות משנה 2. שנה עד שנתיים 3. שנתיים עד שלוש 4.שלוש שנים ויותר.

**תעסוקה**

**29.** מה המקצוע/עיסוק שלך?\_\_\_\_\_\_\_\_\_\_\_\_\_

**30.** מה המקצוע/עיסוק של בן/בת הזוג?\_\_\_\_\_\_\_\_\_\_\_\_

 מס' סידורי|\_|\_|\_|

**31.** מקום עבודה בהווה ובעבר לפי סדר כרונולוגי כולל עבודה עונתית או בחופשה:

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| שם מפעל/חברה. | ענף | תפקיד | משנה עד שנה. | סה"כ שנים. | סוג משרה | חשיפה לחומרים | אלו חומרים |
|  |  |  |  |  |  | 1-לא 2-כן |  |
|  |  |  |  |  |  | 1-לא 2-כן |  |
|  |  |  |  |  |  | 1-לא2-כן |  |
|  |  |  |  |  |  | 1-לא 2-כן |  |
|  |  |  |  |  |  | 1-לא2-כן |  |
|  |  |  |  |  |  | 1-לא2-כן |  |

אחוז משרה: 1-פחות מחצי משרה 2-חצי משרה ויותר 3-משרה מלאה 4-יותר ממשרה 8-אחר

**32**. אם אתה שוטר תנועה, כמה שעות ביום אתה מבלה בכביש? \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**33**. אם אתה שוטר תנועה, באיזה אזור אתה עובד? \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**34.** אם נחשפת לחומרים כימיים אנא ציין:

בתדירות חשיפה, נא ציין מספר: 1-מס' פעמים בשנה. 2-מס' פעמים בחודש.

3-מס' פעמים בשבוע. 4 –מס' פעמים ביום. 5-אחר. 6-לא זוכר

 מס' סידורי|\_|\_|\_|

|  |  |  |
| --- | --- | --- |
| שם החומר | תדירות חשיפה | משך חשיפה |
|  |  | 1-פחות משנה 2.שנה ויותר |
|  |  | 1-פחות משנה 2.שנה ויותר |
|  |  | 1-פחות משנה 2.שנה ויותר |
|  |  | 1-פחות משנה 2.שנה ויותר |
|  |  | 1-פחות משנה 2.שנה ויותר |
|  |  | 1-פחות משנה 2.שנה ויותר |
|  |  | 1-פחות משנה 2.שנה ויותר |

**35.** האם יש לך תחביבים?

 1-לא 2-כן 8-בעבר

**36.** האם ההתעסקות בתחביב מחייב מגע עם חומרים כלשהם לדוגמא: חמר, צבע , חומרים ממיסים חומר אחר פרט:\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**37.** מס שנים בהם אתה עוסק בתחביב:

1-פחות משנה. 2-שנה עד שנתיים. 3- שנתיים ויותר.

**38.** תדירות עיסוק בתחביב:\_\_\_\_\_\_\_\_\_\_\_\_\_

1-כל יום. 2-פעם בשבוע או יותר. 3-פעם בחודש או יותר

**39**. האם אתה משתמש באמצעי מיגון?

 1. כן 2. לא

**הרגלים**

**40.** האם אתה מעשן סיגריות /נרגילה 1-לא 2-כן

**41**. אם כן, כמה שנים אתה מעשן? \_\_\_\_\_\_\_\_\_\_\_\_\_\_

**42.** אם כן, איזו כמות של סיגריות ביום? \_\_\_\_\_\_\_\_\_\_\_\_\_

**43**. האם עישנת בעבר? 1 - לא 2 – כן

 מס' סידורי|\_|\_|\_|

**44**. אם כן, מתי הפסקת?

 1- פחות משנה. 2-שנה עד שנתיים. 3- שנתיים ויותר

**45.** האם בן/בת הזוג מעשן/ת סיגריות/נרגילה 1-לא 2-כן

**46.** האם יש בקרבתך מעשנים כגון בני משפחה /חברים קרובים: 1-לא 2-כן

**47**. מה סוג הלבוש שאתה לרוב נוהג ללבוש בקיץ:

 א. שרוולים: 1. ארוכים 2. קצרים

 ב. מכנסיים: 1. ארוכים 2. קצרים

**מחלות ריאה מאובחנות:**

**48.** האם אבחנת בהווה/עבר באחת מהמחלות הבאות:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **שם המחלה** | **1-לא 2-כן** | **מס שנים חולה** | **זקוק לטיפול תרופתי** | **שם התרופה/ות** |
| אמפיזמה | 1-לא 2-כן | 1-שנה ופחות2-מעל שנה | 1-לא  2-כן |  |
| אסתמה | 1-לא  2-כן | 1-שנה ופחות2-מעל שנה | 1-לא 2-כן |  |
| COPD  | 1-לא  2-כן | 1-שנה ופחות2-מעל שנה | 1-לא  2-כן |  |
| אלרגיה | 1-לא 2-כן | 1-שנה ופחות2-מעל שנה | 1-לא 2-כן |  |
| מחלת ריאות אחרת | 1-לא 2-כן | 1-שנה ופחות2-מעל שנה  | 1-לא 2-כן |  |

**49.** האם אחד מבני משפחתך אובחן /חולה במחלת ריאה ? 1-לא 2-כן

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **שם המחלה**  | **חולה/לא חולה** | **מס שנים חולה** | **זקוק לטיפול תרופתי** | **שם התרופה/ות** |
| אמפיזמה | 1-לא  2-כן | 1-שנה ופחות2-מעל שנה | 1-לא 2-כן |  |
| אסתמה | 1-לא  2-כן | 1-שנה ופחות2-מעל שנה | 1-לא 2-כן |  |
| COPD | 1-לא 2-כן | 1-שנה ופחות2-מעל שנה | 1-לא 2-כן |  |
| אלרגיה | 1-לא  2-כן | 1-שנה ופחות2-מעל שנה | 1-לא 2-כן |  |
| מחלת ריאות אחרת | 1-לא  2-כן | 1-שנה ופחות2-מעל שנה | 1-לא 2-כן |  |

 מס' סידורי|\_|\_|\_|

**50.** האם ידוע לך על עובדים אחרים במקום עבודתך החולים במחלות ריאה?

1-לא 2-כן

**51**. האם ידוע לך על עובדים שבעבר חלו במחלות ריאה?

 1-לא 2-כן

**גורמי סיכון:**

שיעול:

**52.** האם הנך סובל משיעול כאשר אתה מצונן?

 1-לא 2-כן 3-לפעמים 8-לא יודע/זוכר

**53.** האם הנך סובל משיעול כאשר אתה לא מצונן?

 1-לא 2-כן 3-לפעמים 8-לא יודע/זוכר

**54.** אם אתה סובל משיעול ללא צינון משך כמה זמן אתה כבר משתעל? 1–פחות משנה 2-מעל שנה

**55**. האם אתה סובל מבעיות נשימתיות כשאתה נחשף לריחות חזקים, עשן סיגריות או בושם?

1-לא 2-כן 3-לפעמים 8-לא יודע/זוכר

**56**. האם בגלל בעיות נשימתיות אתה מרגיש שאינך יכול ליהנות מחייך במלואם?

1-לא 2-כן 3-לפעמים 8-לא יודע/זוכר

**57**. האם בגלל קוצר נשימה אינך יכול למלא את כל הפעילויות בעבודתך?

1-לא 2-כן 3-לפעמים 8-לא יודע/זוכר

**58**. האם בגלל בעיות נשימתיות אתה מרגיש קושי נשימה בעליות?

1-לא 2-כן 3-לפעמים 8-לא יודע/זוכר

**כיח (הפרשת ליחה)**

**59.** האם אתה מעלה כיח כאשר הנך מצונן? 1-לא 2-כן 3-לפעמים 8-לא יודע/זוכר

**60.** מה הוא משך הזמן בו הנך מכייח? 1-חלק מהזמן שאני חולה. 2-כל זמן שאני חולה

**61.** האם אתה מעלה כיח כאשר אתה לא מצונן? 1-לא 2-כן 3-לפעמים 8-לא יודע/זוכר

 מס' סידורי|\_|\_|\_|

**62.** מה משך הזמן בו הנך מכייח: 1-מידי פעם 2-כל יום 8-לא זוכר

**63.** האם הנך מעלה כיח רוב הימים במשך שלושה חודשים בשנה לפחות 1-לא 2-כן 8-לא יודע/זוכר

**64.** האם סבלת מהתקף של שיעול מוגבר והעלאת כיח מוגברת שארכו שבוע או יותר במהלך השנה

 1-לא 2-כן 8-לא זוכר

**65.** כמה פעמים את/ה מצונן בשנה? 1-לא מצונן. 2-פעם עד פעמיים בשנה. 3-מעל שלוש פעמים בשנה.

**צפצופים בנשימה**

**66.** האם נשימתך נשמעת מצפצפת או שורקת?

1. כאשר אתה מצונן: 1-לא 2-כן 3-לפעמים 8-לא יודע
2. בלי קשר לצינון: 1-לא 2-כן 3-לפעמים 8-לא יודע
3. בשעות השינה: 1-לא 2-כן 3-לפעמים 8-לא יודע
4. רוב הימים: 1-לא 2-כן 3-לפעמים 8-לא יודע

**67.** האם סבלת פעם מהתקף של נשימה מצפצפת אשר גרם לך לקוצר נשימה?

 1-לא 2-כן 3-לפעמים 8-לא יודע/זוכר.

**68.** האם אתה סובל מהתקף כזה אחרי פעילות מאומצת או עליה במדרגות?

 1-לא 2-כן 3-לפעמים 8-לא יודע /זוכר.

**69.** אם כן היה/יש התקף כזה האם הנך זקוק לטיפול תרופתי?

 1-לא 2-כן 3-לפעמים 8-לא יודע/זוכר

**70.** מה שם/ות התרופה/ות אותן אתה לוקח/ת בעת התקף?\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**71.** תדירות התרופה: 1.רק בזמן התקף. 2.פעם ביום. 3.יותר מפעם ביום .

**72.** האם הנך מוגבל בפעילות יום יומית עקב סימפטומים אלו ?

 1-לא 2-כן 3-לפעמים 8-לא יודע/זוכר

**73.** האם הנך נמצא/ת במעקב רפואי עקב מחלת אסתמה או ברונכית ספסטית?

 1-לא 2-כן

**מחלות דרכי הנשימה**

**74.** האם סבלת/סובל בארבעה שבועות אחרונים ממחלה נשימתית?

1-לא 2-כן 8-לא יודע/זוכר

 מס' סידורי|\_|\_|\_|

**75.** שם המחלה:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

תרופה:1-לא 2-כן שם התרופה/ות\_\_\_\_\_\_\_\_\_\_\_\_\_

**76.** האם כאשר היית חולה העלית כיח? 1-לא 2-כן 3-לפעמים 8-לא יודע /זוכר

**77.** האם היו בעבר או בהווה אחת מהמחלות הבאות?

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **שם המחלה** | **כן/לא** | **באיזה גיל** | **תרופה כן/לא** | **שם התרופות** |
| דלקת ריאות | 1-לא 2-כן |  | 1-לא 2-כן |  |
| קדחת השחת | 1-לא 2-כן |  | 1-לא 2-כן |  |
| ברונכית ספסטית/אסתמה | 1-לא 2-כן |  | 1-לא 2-כן |  |
| בעיות סינוסים | 1-לא 2-כן |  | 1-לא 2-כן |  |
| ציסטיק פיברוזיס | 1-לא 2-כן |  | 1-לא 2-כן |  |
| אלרגיות של העור | 1-לא 2-כן |  | 1-לא 2-כן |  |
| נזלת אלרגית | 1-לא 2-כן |  | 1-לא 2-כן |  |
|  | 1-לא 2-כן |  | 1-לא 2-כן |  |
| ניתוח שקדים או פוליפים | 1-לא 2-כן |  | 1-לא 2-כן |  |
| נחירות לילה | 1-לא 2-כן |  | 1-לא 2-כן |  |

**אלרגיות**

**78.** האם הנך רגיש לאחד מהחומרים הבאים? פרט:

|  |  |  |
| --- | --- | --- |
| תרופה | 1-לא 2-כן |  |
| מזון | 1-לא 2-כן |  |
| בע"ח | 1-לא 2-כן |  |
| צמחים | 1-לא 2-כן |  |
| חומרי ניקויי | 1-לא 2-כן |  |
| עובש | 1-לא 2-כן |  |
| אחר | 1-לא 2-כן |  |

 מס' סידורי|\_|\_|\_|

**גידול בעלי חיים**

**79.** האם הנך מגדל בע"ח כל-שהוא בביתך? 1-לא 2-כן

**80.** סוג בע"ח אותו הנך מגדל­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­­

**81**. האם אתה חבר במועדון ספורט?

1. כן 2. לא

**82**. אם כן, האם אתה משתמש:

1. בריכה מקורה 2. סאונה 3. ג'קוזי

**83**. האם אתה נוהג לבצע פעילות גופנית בחוץ?

 1.כן 2. לא

**84**. אם כן, באיזו תדירות?

 1. פעם ביום 2. שלוש פעמים בשבוע 3. פעם בשבוע 4. אחר \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**85**. כמה זמן בכל פעם?

 1. חצי שעה 2. שעה 3. אחר \_\_\_\_\_\_\_\_\_\_\_\_

**86**. כשאתה חושב על השכונה בה אתה מתגורר, כמה מההיבטים הבאים הוא לדעתך בעיה. אנא ציין כל אחד במספרים מ-0 עד 5. 0: אין בעייה 5: בעיה חמורה

1. יותר מדי תחבורה 1 2 3 4 5

2. יותר מדי רעש 1 2 3 4 5

3. אשפה ולכלוך 1 2 3 4 5

4. ריחות לא נעימים ממפעלים 1 2 3 4 5

5. עשן מבעירה 1 2 3 4 5

**87**. באופן כללי איך היית מגדיר את בריאותך

1. מעולה

2. טובה מאוד

3. טובה

4. סבירה

5. ניתנת לשיפור