

MONITORING OF LIVER AND KIDNEY PROFILES IN ANESTHESIOLOGISTS WORKING IN A REGIONAL REFERENCE TEACHING HOSPITAL IN NORTHERN ITALY: ANALYSIS OF HEALTH SURVEILLANCE DATA USING A LINEAR MIXED MODEL

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Abstract

Objectives: Anesthesiologists represent an occupational group exposed to specific occupational hazards, including potential exposure to waste anesthetic gas released during medical procedures. In recent decades, halogenated anesthetic gases, such as desflurane and sevoflurane, have largely replaced nitrous oxide, due to better safety profiles and lower adverse health effects. However, possible long-term effects of low concentration exposures are unknown. A longitudinal analysis of health surveillance data was performed to test for possible changes over time in key markers of liver and kidney function. Moreover, the authors assessed the appropriateness of applying linear mixed models to occupational health data.

Material and Methods: A retrospective cohort study was conducted using health surveillance data from a cohort of anesthesiologists and a cohort of unexposed physicians working at the Polyclinic Hospital San Martino of Genoa, Italy, during 2016–2022. A 2-level linear mixed model with covariance structure of first order autoregressive model (AR(1)) type at the first level and unstructured type at the second level was applied. **Results:** One hundred seventy subjects were included in the analysis, equally divided between exposed and unexposed. At the first and last periodic examination, liver and kidney markers were not statistically different in the 2 cohorts. The only significant change found related to estimated glomerular filtrate, which was found at the last follow-up to be greater among the exposed ($M = 104.18$ vs. 90.07 , $p = 0.007$). The linear mixed model showed that anesthetic gas exposure was not associated with any of the outcomes. These results suggest the absence of increase in liver and kidney profile markers in the study population. **Conclusions:** Health surveillance data, aggregated and analyzed with appropriate statistical models, allow inferences to be made about potential health effects of workers due to uncontrolled exposures. To this end, the linear mixed model represents a powerful tool for longitudinal analysis of data derived from monitoring workers. *Int J Occup Med Environ Health.* 2024;37(5):557–68

Key words:

occupational health, risk assessment, multilevel model, waste anesthetic gas, subcritical effects, operation room risk

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INTRODUCTION

Since the discovery of the hypnotic and analgesic effects of nitrous oxide (N_2O) in the first half of the 19th century, general anesthesia emerged as an important part of clinical and surgical practice. Indeed, inhaled anesthetic gases have been widely used and developed since, mainly N_2O , ether, and chloroform, and after 1950, with the prevalent introduction of gas containing fluorine. This shift was due to improved safety, such as nonflammability, as well as greater chemical stability, and of no less importance lower toxicity. Advancing further in this direction, in the last few decades, in many developed countries, more toxic substances such as N_2O , chloroform and halothane have progressively been replaced with fully fluorinated gases, such as desflurane and sevoflurane, due to better safety profiles and lower risk of adverse health effects to patients [1].

Although extensive toxicological studies have been conducted on the clinical use of these latter substances in patients, demonstrating reduced reprotoxicity, cardiotoxicity and neurotoxicity compared to previous classes of inhaled anesthetics, the long-term effects of possible low-dose exposures on occupationally exposed populations are still an area of scientific research, particularly with regards to potential hepatotoxic and nephrotoxic effects [2–7]. Despite the fact that some studies have suggested an absence of such health risks, nonetheless, only few studies assessing longitudinal data obtained from occupationally exposed workers [8,9], and none specifically focusing on anesthesiologists, workers most closely implicated in inhaled gas anesthetic administration, are available.

Indeed, while many protective and preventive measures exist to eliminate or reduce exposures to workers during surgical operations, such as appropriate ventilation and effective scavenging systems, accidental and unplanned exposure could occur in the form of waste anesthetic gases (WAGs), which are small amounts of volatile anesthetic gases that escape from the patient's anesthetic breathing circuit into the air of operating rooms during anesthe-

sia administration [10–12]. While short-term acute exposure to high concentrations of WAGs is associated with immediately perceived negative health effects by the workers, such as headache, fatigue, drowsiness, on the other hand, chronic exposure to low-doses of WAGs could cause long-term effects such as reproductive and developmental effects, such as spontaneous abortion, birth defects, infertility, genotoxicity, as well as hepatotoxicity, and nephrotoxicity [13–15]. Indeed, while evidence is scarce for adverse effects of volatile anaesthetics at concentrations lower than air monitoring limit values, such as the U.S. National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit (REL) for halogenated waste anesthetic gas of 2 ppm in a 1-hour time period, innovative surveillance methods that include systematic data collection and analysis of clinical and exposure biomarkers are warranted to appropriately monitor the long-term health of exposed workers [15].

In consideration of the potential risk of unplanned exposure, in the case of faulty or ineffective control measures, in accordance with Article 41 of Legislative Decree 81/2008 [16], occupational health surveillance programs are activated for early identification of potential health effects of all exposed healthcare workers, at critical levels, manifesting clearly as signs or symptoms or target organ dysfunction, or at sub-critical level, showing non clinically significant but increasing and progressive alterations of biomarkers.

The objective of this study was to assess possible longitudinal sub-critical or critical alterations in renal and hepatic biochemical parameters of anesthesiologists working in a hospital where desflurane and sevoflurane are used for inhaled anesthesia, compared to a reference group of medical doctors not exposed to any chemical hazard. Furthermore, this study presents a case for the application of linear mixed model to real-world occupational health data collected during surveillance programs. This model allows longitudinal data of individual workers to be analyzed to explain the observed variance and to derive in-

ferences about populations of workers at different hierarchical levels (e.g., inferences about single worker, among different workers, among different groups of workers by department, type of operation, type of hospital). Indeed, the effective application of an appropriate method capable of analyzing aggregated longitudinal occupational health data, often characterized by limitations such as cluster-correlation and missing data which hinder analysis by means of traditional modelling, could result in a powerful tool for occupational physicians by providing useful insights for the overall improvement of occupational health and safety from a practical standpoint, but also enhancing the scientific understanding of subcritical and critical health risks caused by occupational exposures.

MATERIAL AND METHODS

An observational study, with a retrospective longitudinal design, with repeated measures on the same person at different time periods, was performed using occupational health surveillance data collected between 2016–2022. This data is gathered as part of occupational health surveillance programs performed by the Occupational Health Service (OHS) of the University of Genoa and Polyclinic Hospital San Martino of Genoa, Italy, the regional tertiary adult acute care reference hospital, in accordance with Italian Legislative Decree 81/2008.

In this study the authors aimed to evaluate variable's changes over time and factors influencing it. Two important groups of changes are to be observed: individual's changes over time and variations between individuals. The 2 groups of changes of interest define a hierarchical structure at 2 levels. Repeated measurements form the first level units, and the individuals form the second level units. As these observations are not independent, the authors applied the mixed model analysis of longitudinal data to infer repeated measures, taking into consideration the dependencies between observations. These models consider the random effects in modelling, account for individual

changes and render more accurate results. Since multilevel modeling does not require balanced data, there is no requirement for complete observations for each participant, and permits differences in the timing and spacing of the measurements across participants [17–20].

The general formula for a mixed model is:

$$y_i = X_i\beta + Z_i b_i + \epsilon_i \quad (1)$$

$$b_i \sim N_q(0, \Psi) \quad (2)$$

$$\epsilon_i \sim N_{n_i}(0, \sigma^2 \Lambda_i) \quad (3)$$

where:

y_i – the $n_i \times 1$ response vector for observations in the i th group,

X_i – the $n_i \times p$ model matrix for the fixed effects for observations in group i ,

β – the $p \times 1$ vector of fixed-effect coefficients,

Z_i – the $n_i \times q$ model matrix for the random effects for observations in group i ,

b_i – the $q \times 1$ vector of random-effect coefficients for group i ,

ϵ_i – the $n_i \times 1$ vector of errors for observations in group i ,

Ψ – the $q \times q$ covariance matrix for the random effects,

$\sigma^2 \Lambda_i$ – the $n_i \times n_i$ covariance matrix for the errors in group i .

The study population consisted of physicians and surgeons employed at Polyclinic Hospital San Martino of Genoa, Italy, the regional tertiary adult acute care reference hospital with a total workforce of over 977 employed medical doctors and 1056 resident doctors. In this hospital, desflurane and sevoflurane are currently used in anesthetic procedures that require inhaled gases. In the absence of precise measurements of exposures of anesthetic gases among different working groups, that would be required to create different levels, and with the aim of assessing the potential health effects of WAGs, the authors sampled 2 cohorts of workers, one comprising only of specialists and residents

in anesthesiology, the other comprising only of doctors not exposed to anesthetic gas and any other chemical hazards. To reduce confounding effects, these 2 equally distributed cohorts were selected randomly in order to have a not statistically significant difference in gender ($t = 1.08$, $p = 0.28$) and age ($U = 3099.5$, $p = 0.11$) since these variables are known physiological modifiers of hepatic and kidney biomarker levels. To be included in the study, the workers had to be free from any acute health condition and any known chronic hepatic or renal disease, and to have been visited at least 2 different times, which includes blood testing and physical examination among assessments, in the period of interest.

The following information was extracted from the electronic health files into a dataset: gender; age; years of work experience; for each repeated visit body mass index (BMI); *Alcohol Use Disorders Identification Test* (AUDIT) score; use of hepatotoxic drugs (classified according to Drug Induced Liver Injury Rank [DILIrank], dataset published by the U.S. Food and Drug Administration [FDA] [21]); use of nephrotoxic drugs (including angiotensin converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], nonsteroidal anti-inflammatory drugs [NSAIDs], thiazide diuretics), plasma urea in mg/dl, plasma creatinine in mg/dl, estimated glomerular filtration rate (eGFR) in ml/min/1.73 m², alanine transaminase (ALT) in unit/liter (U/l), and γ -glutamyl transferase (GGT) in U/l.

After reviewing the health records and applying the exclusion criteria, 170 workers were indicated as eligible to enter the analysis.

Descriptive statistics are reported as means with standard deviation (SD) for continuous variables, and as frequencies and percentages for categorical variables. To account for the longitudinal character of the data with repeated measurements over the follow-up period with intra-class correlation at the level of the individual workers, the authors analyzed trends in outcome parameters (ALT, GGT, urea, creatinine, eGFR) with linear mixed models. To assess the

individual variation over time, the measurements were numbered by the order and the date when they were performed, in order to take into account missed appointments.

Model fitting was performed stepwise, and the most adapted model was selected based on covariance structure and lowest information criteria, namely the -2 restricted log likelihood ($-2LL$) and the Akaike information criterion (AIC). Basic models included the outcome parameters as a function of time in random intercept, fixed slope models. As the best model allowed different baseline profiles and different line slopes for different workers, the random intercepts and slopes model were used. Indeed, in the authors' analysis, the individuals were considered as groups. The random intercept model takes into account that workers' hepatic or renal profiles at the onset are not assumed as average but different people are considered to have different profiles, while the random slope model allows different workers to have individual differences in increasing hepatic or renal markers affected by increase in work experience.

The authors calculated 2-tailed p values, with the statistical significance level set at $p < 0.05$. All computations were carried out with IBM SPSS Statistics, v. 26.0.

All the activities were performed in compliance with the Declaration of Helsinki and current healthcare standards according to the recommendations of the Italian Ministry of Health. All participants included in the study had signed a written informed consent according to routinely healthcare procedures of the Occupational Health Surveillance Program at the San Martino Polyclinic Hospital, Genoa, Italy.

RESULTS

A total of 170 workers participated in at least 2 occupational medical examinations between 2016–2022. Mean number of examinations per worker was 3.3; 18 workers had 5 examinations, 55 had 4 examinations, 60 had 3 visits, and 37 had 2 visits. Median follow-up was 2.9 years.

Table 1. Demographic characteristics of physicians and surgeons employed at Polyclinic Hospital San Martino of Genoa, Italy, using occupational health surveillance data collected between 2016–2022, stratified by exposure status to anesthetic gases

Variable	Participants (N = 170)		
	total	exposed (N = 85)	unexposed (N = 85)
Sex [n (%)]			
male	73 (42.9)	40 (47.1)	33 (38.8)
female	97 (57.1)	45 (52.9)	52 (61.2)
Age [years] (M±SD)	39.9±10.8	38.5±10.5	41.3±11.0
Job seniority before enrollment [years] (M±SD)	2.3±4.2	2.9±5.5	1.8±2.1

Table 2. Mean of independent repeated variables and values of the outcome parameters in physicians and surgeons during 5 consecutive time points obtained through periodic health surveillance visits, Polyclinic Hospital San Martino of Genoa, Italy, 2016–2022

Variable	Health surveillance visit				
	first (baseline) (N = 170)	second (N = 127)	third (N = 127)	fourth (N = 97)	fifth (N = 43)
BMI (M±SD)	22.9±3.8	22.7±3.5	22.8±3.6	23.8±4.2	23.9±4.2
Alcohol Use Disorders Identification Test (AUDIT) [pts] (M±SD)	1.5±0.9 (from 124 subjects)	1.6±1.1 (from 106 subjects)	1.5±0.9 (from 92 subjects)	1.4±1.0 (from 60 subjects)	1.4±1.0 (from 30 subjects)
Use of drug [n (%)]					
with hepatic toxicity	42 (24.7)	27 (21.3)	30 (23.6)	22 (22.7)	14 (32.6)
with renal toxicity	8 (4.7)	3 (2.4)	7 (5.5)	8 (8.2)	7 (16.3)
Urea [mg/dl] (M±SD)	31.7±8.2	31.1±9.6	31.8±9.3	32.3±9.3	33.0±10.5
Creatinine [mg/dl] (M±SD)	0.88±0.17	0.87±0.16	0.86±0.15	0.87±0.16	0.87±0.19
Estimated glomerular filtration rate (eGFR) [ml/min/1.73 m ²] (M±SD)	102.8±16.0	104.5±15.0	102.9±15.2	100.6±15.1	99.3±17.1
Alanine aminotransferase (ALT) [U/l] (M±SD)	19.9±12.2	17.8±9.2	17.8±9.4	18.8±9.2	20.3±11.4
Gamma-glutamyl transferase (GGT) [U/l] (M±SD)	21.4±29.8	20.8±28.1	19.3±22.5	22.4±27.7	25.5±26.9

All demographic characteristics are summarized in Table 1. Overall, 57.1% were female, and mean age was 39.9 years (SD = 10.8), and mean job seniority before the first examination was 2.3 years (SD = 4.2). Stratifying by exposure status, female gender resulted 52.9% and 61.2%, mean age of 38.5 years (SD = 10.5) and 41.3 years

(SD = 11.0), and mean seniority of 2.9 (SD = 5.5) and 1.8 (SD = 2.1), among anesthesiologists and other unexposed medical professionals, respectively.

The characteristics and mean values of hepatic and renal function parameters of the participants at baseline and successive examinations are summarized in Table 2.

At the time of their first medical examination, BMI was $M = 22.9$ (range: 16.0–39.5), 75.8% reported drinking alcohol (AUDIT score among drinkers of $M \pm SD 2 \pm 0.4$) and 24.7% reported using pharmaceuticals with possible liver toxicity (DILIRank score $M \pm SD 3.6 \pm 2.1$) while 4.7% reported using nephrotoxic drugs. Stratifying baseline values by exposure status it was found that mean BMI was 22.8 (range: 17.4–36.7) and 23.1 (range: 16.0–39.5), alcohol consumption prevalence was 81.8% (AUDIT score $M \pm SD 2 \pm 0.3$) and 67.3% (AUDIT score $M \pm SD 2.1 \pm 0.5$), use of pharmaceuticals with possible liver toxicity was 22.4% and 27.1%, and use of drugs with possible renal toxicity was 3.5% and 5.9%, respectively among anesthesiologists and the unexposed group.

Figure 1 shows each outcome parameter in each measurement time point, stratified by exposure status. Each dot represents the results of the measurement of 1 worker. Graphically, the regression lines for exposed and unexposed groups do not show an increase with time, and the latter cohort shows an overall higher value in both liver and renal function parameters. As detailed in Table 3, comparing baseline and final assessments between the 2 groups, showed a significant increase of estimated glomerular filtration among exposed subjects compared to unexposed individuals. However, in order to take into account the variability among individuals comprising each cohort, a model with 21 parameters was developed for each outcome of interest, with a first order autoregressive model (AR(1)) covariance type for repeated measurements and an unstructured type for random effects of time, intercept and subject. Analysis of the linear mixed model showed that variance between observations was explained for ALT by gender, BMI, use of medication, and exposure by years of seniority; for GGT by gender, AUDIT score, exposure by years of seniority; for urea by gender and age; for creatinine by gender, AUDIT score; and eGFR by gender, age, AUDIT score. Detailed information on statistics can be found in Table 4.

Assessing the resulting marginal mean estimate for each outcome variable based on exposure status and gender, the authors found mean ALT values among male unexposed subjects of 25.7 U/l (95% CI: 21.2–30.1 U/l), while among female workers 19.9 U/l (95% CI: 15.3–24.6 U/l), and among male exposed subjects of 25.5 U/l (95% CI: 21.2–29.9 U/l) while among female of 19.8 U/l (95% CI: 15.2–24.5 U/l), without any statistical difference at pairwise comparison ($p = 0.91$). The same comparisons were performed for GGT ($p = 0.27$), urea ($p = 0.64$), creatinine ($p = 0.68$), eGFR ($p = 0.61$), without any significant difference between groups.

DISCUSSION

In this longitudinal study, real-world occupational health data were analyzed retrospectively using an innovative methodological approach, the linear mixed model, in order to assess the potential effects of low-dose waste anesthetic gas exposure on anesthesiologists. The levels of exposure to WAGs depend on several parameters, including presence or absence of proper ventilation and scavenging systems in operating rooms, type of surgery, the extent of leaks from anesthesia face masks during the administration of the anesthetic gases to patients, leakage from machines, as well as length of operations and daily shifts. Indeed, although periodic environmental measurement of exposure to inhaled gas are performed in the surgical theatres to assess the effectiveness of scavenging systems, ventilation and other safety procedures, which successfully protect workers from high dose exposures and consequent acute effects, the possible chronic effects due to low-dose of gases on workers' health, are assessed by occupational physicians during yearly medical examinations. In this manner, occupational physicians can directly evaluate potential health effects at the individual worker level. The application of appropriate types of longitudinal epidemiologic studies can however expand the scope of this assessment to the whole exposed population. After a median follow-up of 2.9 years (max. 5 years) and accounting for age, gender,

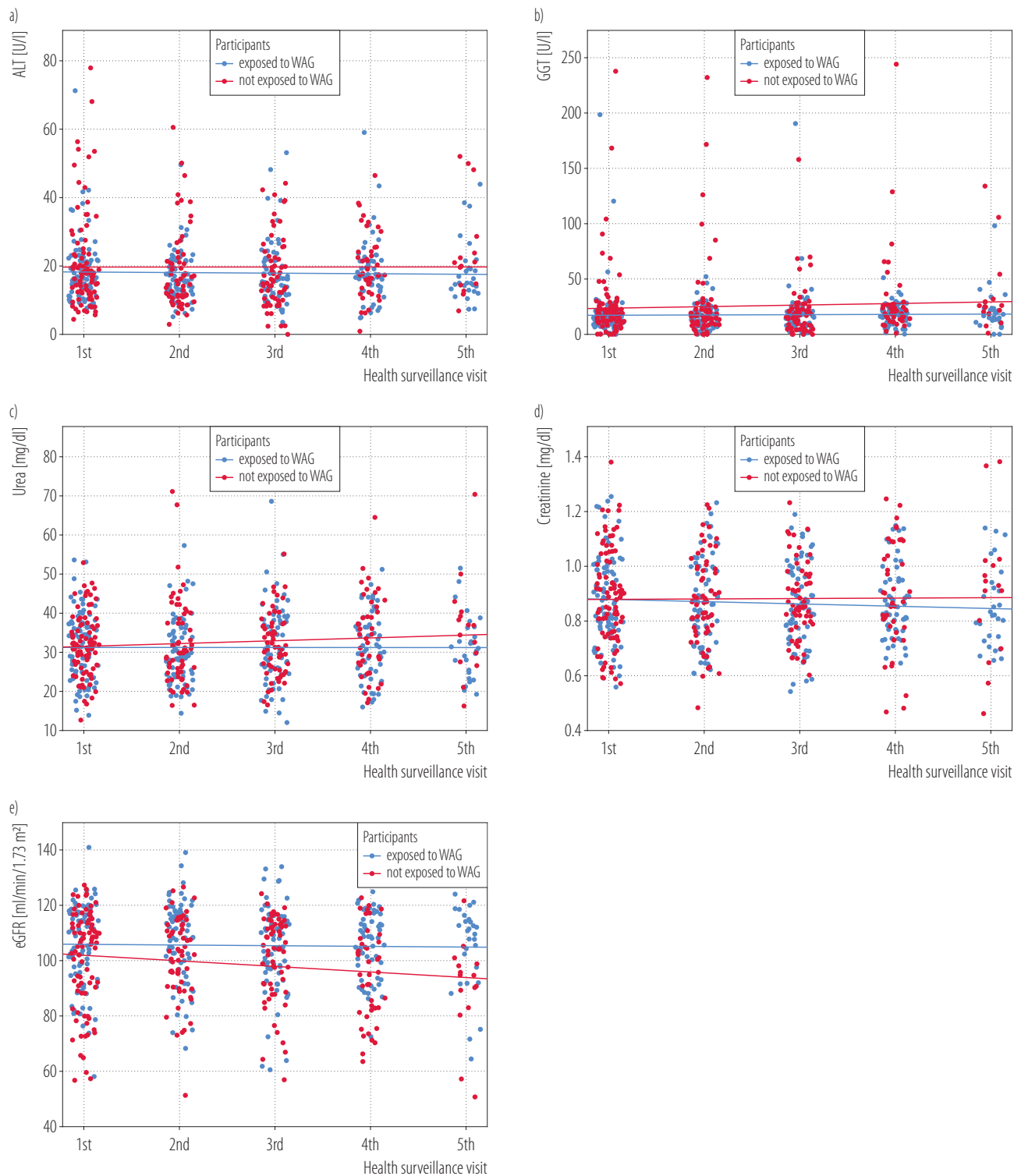


Figure 1. Scatter plots of hepatic and renal function parameters by waste anesthetic gas (WAG) exposure status during successive examinations of: a) alanine aminotransferase (ALT), b) γ -glutamyl transferase (GGT), c) urea, d) creatinine, e) estimated glomerular filtration rate (eGFR), in physicians and surgeons employed at Polyclinic Hospital San Martino of Genoa, Italy, 2016–2022

Table 3. Comparison of baseline and final examination values among exposed and unexposed groups of physicians and surgeons employed at Polyclinic Hospital San Martino of Genoa, Italy, 2016–2022

Parameter	M	SD	Mann-Whitney U	p
Baseline examination				
ALT [U/l]				
not exposed (N = 85)	20.86	14.491	3815.50	0.53
exposed (N = 85)	18.93	9.391		
GGT [U/l]				
not exposed (N = 85)	24.51	34.225	3311.50	0.35
exposed (N = 85)	18.19	24.373		
urea [mg/dl]				
not exposed (N = 85)	31.82	8.049	3679.00	0.84
exposed (N = 85)	31.64	8.440		
creatinine [mg/dl]				
not exposed (N = 85)	0.882	0.1781	3576.50	0.91
exposed (N = 85)	0.878	0.1538		
eGFR [ml/min/1.73 m ²]				
not exposed (N = 85)	100.42	17.040	4157.00	0.09
exposed (N = 85)	105.07	14.526		
Final examination				
ALT [U/l]				
not exposed (N = 15)	24.47	14.525	148.00	0.11
exposed (N = 28)	18.07	8.927		
GGT [U/l]				
not exposed (N = 15)	35.67	35.532	137.50	0.06
exposed (N = 28)	20.11	19.521		
urea [mg/dl]				
not exposed (N = 15)	36.20	13.327	157.00	0.18
exposed (N = 28)	31.25	8.444		
creatinine [mg/dl]				
not exposed (N = 15)	0.907	0.2576	176.50	0.39
exposed (N = 28)	0.843	0.1399		
eGFR [ml/min/1.73 m ²]				
not exposed (N = 15)	90.07	16.351	315.50	0.007
exposed (N = 28)	104.18	15.675		

ALT – alanine aminotransferase; eGFR – estimated glomerular filtration rate; GGT – γ -glutamyl transferase.
 Bolded are statistically significant results.

Table 4. Significant estimates of fixed effects in the linear mixed model analysis for each outcome, showing the effect on variability by independent variables among physicians and surgeons employed at Polyclinic Hospital San Martino of Genoa, Italy, 2016–2022

Parameter	Estimate	p	95% CI
ALT [U/l]			
male gender	5.72	0.000	3.29–8.15
no use of nephrotoxic drugs	−8.52	0.002	−13.90–(−3.13)
work seniority before enrollment	−0.50	0.011	−0.88–(−0.12)
BMI	0.63	0.000	0.31–0.95
GGT [U/l]			
male gender	8.68	0.035	0.60–16.76
frequent alcohol use (AUDIT = 3)	23.81	0.039	1.26–46.36
work seniority before enrollment in unexposed workers	5.79	0.000	2.65–8.93
Urea [mg/dl]			
male gender	5.45	0.000	3.06–7.84
age	0.28	0.001	0.12–0.43
Creatinine [mg/dl]			
male gender	0.17	0.000	0.13–0.22
frequent alcohol use (AUDIT = 4)	0.39	0.004	0.13–0.66
eGFR [ml/min/1.73 m²]			
male gender	−6.18	0.003	−10.29–(−2.07)
frequent alcohol use (AUDIT = 4)	−36.26	0.011	−64.29–(−8.24)
age	−0.67	0.000	−0.94–(−0.41)

AUDIT – *Alcohol Use Disorders Identification Test*.

Other abbreviations as in Table 3.

BMI, alcohol consumption and medication use, the authors found no alteration among exposed workers, as data variability was explained by other factors, particularly gender, BMI and aging, which are well-known factors in liver and renal function physiologic variability [22–24]. Based on these findings, the long-term effectiveness of appropriate control measures can be inferred. Previous studies, that had assessed effective exposure using both environmental and biological monitoring data, had found a significant subcritical prepathological health effect on liver and kidney function of exposed healthcare workers. However, the exposure included N₂O and isoflurane other than sevoflurane, 2 gases that are known to have increased toxic profiles on these organs. Moreover, although liver and kidney

function parameters were increased, they remained in the normal range [2]. While the NIOSH has recommended REL values of 2 ppm for all the halogenated agents [25], and biological exposure indices levels for these anesthetic gases have not been established by American Conference of Governmental Industrial Hygienists (ACGIH), however, some authors have reported biological equivalent limits on urine of 3.6 µg/l for sevoflurane [26].

This study was characterized by few limitations, including the lack of precise and timely exposure measurements for each gas, lack of information on the specific type of surgery and operation theatre location and the limited number of participants. Moreover, data collected during regular occupational health examinations are limited to

few general parameters, reducing the accuracy of possible harmful effects, particularly concerning reprotoxicity. Concerning the possible liver toxicity, several relevant hepatic and biliary function parameters were not available from health surveillance data, such as bilirubin and alkaline phosphatase [27]. The inclusion of these data in the multilevel hierarchical analysis could have improved the definition of exposure level and possible health effects. A further limitation was the relatively short duration of exposure and follow-up, as health effects could possibly take many more years of exposure to present. However, the study was strengthened by several aspects, thanks to the rigorous methodological approach of the linear mixed model which enables the analysis of occupational health data which is, by definition, comprised of data from a cohort during time. Indeed, the main goal of a longitudinal study is to describe changes over time and measure the individual influence of variables to explain these observed changes. However, many challenges and methodological issues make it difficult to analyze real-world longitudinal data. These analytical problems include the correlated structure of intra-individual data, irregular time-spaced measurements, non-linear patterns, latent constructs, as well as the combination of time-varying and static covariates [17]. In this perspective, this study represents a proof of concept that could be applied to all aspect of occupational health, and could improve the understanding of many potential subcritical health effects taking into account both intergroup differences at multiple levels, between individual analysis, but also within group and individual analysis.

CONCLUSIONS

This study shows that health surveillance data can be used not only to assess individual workers' health, but that, through appropriate analyses of aggregated occupational health data, could also monitor changes in groups of workers. This strategy could be of use as a separate integrative assessment in occupational health surveillance

programs, particularly where unplanned low-dose exposure could occur (e.g., chemical risks, physical risks), potentially enabling the rapid detection of alterations in biological parameters, even at subcritical levels. Indeed, the implementation of these powerful statistical tools in occupational health could further improve the verification of hazard control effectiveness, contributing to the exposure and risk assessment performed by means of environmental and personal monitoring.

Author contributions

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