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Biological monitoring and personal exposure to traffic-related air pollutants of elementary school-age children living in a metropolitan area

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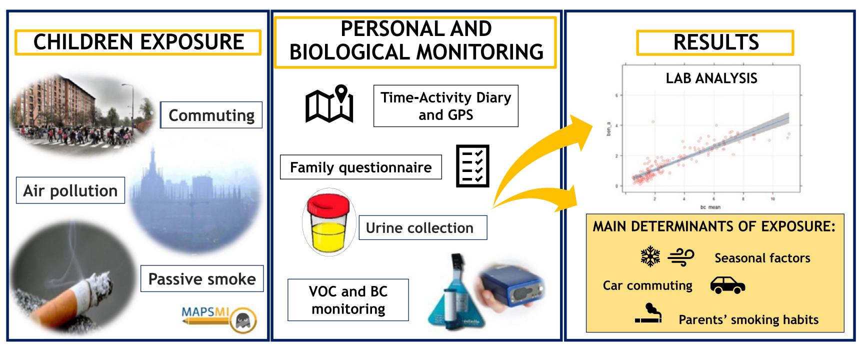
HIGHLIGHTS

- VOCs and eBC personal exposure was investigated in children.
- Biological monitoring was applied to assess urinary benzene and MTBE
- Determinants of exposure were related to meteorological information, traffic, mobility and passive smoking.
- Being transported by car affected air pollutants and urinary benzene.
- eBC and VOCs, as well as biomarkers, were well correlated.

GRAPHICAL ABSTRACT



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ABSTRACT

An ever-growing burden of scientific evidence links air pollution to different aspects of human health even at very low concentrations; the impact increases for those living in urban environments, especially the youngest and the elderly. This study investigated the exposure to air pollution of urban school children of Milan, Italy, by personal and biological monitoring, in the frame of the MAPS-MI project.

A total of 128 primary school children (7–11 years) were involved in a two-season monitoring campaign during spring 2018 and winter 2019. Personal exposure to airborne VOCs and eBC, and biological monitoring of urinary benzene (BEN-U) and methyl-tert-butyl ether (MTBE-U) were performed. Time-activity patterns, environmental tobacco smoke (ETS), spatial, and meteorological information were evaluated as determinants in mixed effects regression analysis.

Children personal exposure was mostly quantifiable with median (5th–95th percentile) levels 1.9 (0.8–7.5) μg/m^3 for eBC, and 1.1 (<0.6–3.4) and 0.8 (0.3–1.8) μg/m^3 for benzene and MTBE, respectively; with values 2–3-fold higher in winter than in spring. In urine, median (5th–95th) BEN-U and MTBE-U levels were 44.9 (25.7–98.6) and 11.5 (5.0–35.5) ng/L, respectively. Mixed effect regression models explained from 72 to 93 % of the total variability for air pollutants, and from 58 to 61 % for biomarkers. Major contributors of personal exposure were season, wind speed, mobility- or traffic-related variables; biomarkers were mostly predicted by airborne exposure and ETS.

Our results suggest that traffic-mitigation actions, together with parents' educational interventions on ETS and commuting mode, should be undertaken to lower children exposure to air pollution.

1. Introduction

An ever-growing body of scientific evidence links ambient and indoor air pollution to different aspects of human health (Dhital and Rupakheti, 2019; Sun and Zhu, 2019). The recent update of the World Health

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Organization's air quality guidelines remarks that the associations between exposure and all-cause or respiratory mortality and respiratory and cardiocirculatory hospital admissions are valid for different pollutants even at very low concentrations (WHO, 2021). The magnitude of this impact increases for those who spend their lifetime in polluted environments and for the susceptible individuals. The living environment may affect especially the youngest, who inhale in a lower breathing zone than adults, often closer to sources of pollution, and present faster metabolic rate and still immature and more fragile organs (Etzel, 2020). Natural barriers against exogenous stressors, such as nasal epitheliums and blood-brain barrier, have been shown to be altered in children living in a polluted urban environment (Calderón-Garcidueñas et al., 1999, 2015).

In metropolitan areas, air pollution is mainly driven by combustion processes linked to transportation and heating systems. In these environments, individuals are more likely to experience exposure peaks mainly influenced by the time spent in or nearby traffic (Dons et al., 2019; Boniardi et al., 2021a). Traffic-related air pollution (TRAP) is a peculiar mixture of both gaseous and particulate pollutants that mostly derives from the primary emissions of motor vehicles plus other non-combustion emissions (e.g. road and brakes dust). Among others, there are gaseous contaminants such as the volatile organic compounds (VOCs) benzene, toluene, ethylbenzene and xylene (BTEX), methyl-tert-butyl ether (MTBE), ethyl tert-butyl ether (ETBE) and tert-Amyl methyl ether (TAME). BTEX are well known aromatic compounds, present in gasoline, while MTBE, ETBE and TAME are oxygenated gasoline additives improving octane number; all are emitted with traffic exhausts. Among the particulate fraction, equivalent black carbon (eBC) represents fine and ultrafine particles strictly linked with fuel and biomass combustion. Numerous studies have shown significant associations between exposure to TRAP and negative outcomes for the respiratory system of children like asthma, reduced lung function, or cardiovascular endpoint (Khreis et al., 2017; Gehring et al., 2013; Provost et al., 2017; Pieters et al., 2015). Long-term exposure can be also associated with neurological and behavioral outcomes (Newman et al., 2013; Suglia et al., 2008). Moreover, Filippini et al. (2019) in a recent meta-analysis found an association between exposure to benzene and childhood acute myeloid leukaemia, with no indication of a threshold effect (Filippini et al., 2019). These epidemiological studies take advantage from a model-based exposure approach that helps to overcome the lack of information and resources when the aim is to assign exposure values to a high number of individuals. However, the lack of insights about time-activity patterns, contribution of indoor air pollution, and/or the use of aggregated data affects the accuracy of estimates by increasing exposure attribution bias (Sheppard et al., 2012). In the study of human exposure, the combination of environmental personal monitoring and time-activity analysis still represents the most accurate approach, offering the opportunity to study exposure determinants, and to promote possible mitigation interventions. Besides, biological monitoring allows the assessment of the internal dose of pollutants integrating all exposure sources and routes, taking into account the interaction between the individual and the environment (Fustinoni et al., 2010). In the last decades, personal exposure of school-age children has been the focus of numerous scientific contributions, however only a few of them simultaneously considered ambient and biological monitoring (Minoia et al., 1996; Park and Jo, 2004; Lagorio et al., 2013; Pilia et al., 2021). Nevertheless, none of these contributions reported information or analyzed the influence of children time-activity patterns on exposure.

Given this picture, this study aimed at taking a step forward in the knowledge of children exposure to traffic-related air pollution by involving 128 elementary school-age children (7–11 years) living in the city of Milan, Italy, in a two-season monitoring campaign during spring 2018 and winter 2019 in the frame of the project MAPS-MI ("Mapping Air Pollution in a School catchment area of Milan"). In this contribution, the focus is placed on personal exposure to airborne VOCs and eBC, and biological monitoring of urinary benzene and MTBE, taking into account the children's time-activity patterns.

2. Material and methods

2.1. Study design and study population

Subjects recruited for this study participated in the MAPS-MI project aimed to study the exposure to air pollution of schoolchildren in Milan, using spatial models, air pollutant personal monitoring, and biological monitoring techniques with a participatory approach (Boniardi et al., 2019a, b, 2021a, b). The study population consisted of 128 school-age children (7–11 years old) from a primary school in Milan, Italy, who were involved in two campaigns, Spring 2018 (20th April–8th June 2018) and Winter 2019 (8th January–13th March 2019). The study was approved by the school board and by the ethics committee of the University of Milan and all the participants, children and their parents, were informed about the aims and the contents of the research. The study has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. During the year, children and their teachers were involved in a series of educational activities on air pollution themes (including laboratories, frontal teaching, and experimental measures in the school neighborhood). After the first month of activities (Spring 2018), children and their family were invited to participate to the field study involving the personal environmental and biological monitoring of exposure to a panel of air pollutants. Through the school diary, an invitation letter was given, together with a leaflet illustrating the MAPS-MI project. Only parents answering positively to the invitation letter were telephonically contacted to arrange for an informative meeting at school and for the sampling day. During the first meeting, children and their parents were informed about the project and, as required by the General Data Protection Regulation of the European Union (EU) (2016), were asked to sign three forms: 1) an informed consent sheet about the project specifically prepared to be understood by children; 2) an informed consent sheet about the project for parents or legal guardians; and 3) a consent sheet to process personal data. The same procedure was repeated for the winter monitoring campaign. Participating children were asked: 1) to wear a GPS device, 2) to complete a time-activity diary (TAD) with the help of their parents to collect information on their activities and locations, and 3) to wear a shoulder bag equipped with a series of samplers among which a Radiello sampler to measure personal exposure to VOCs and a micro-aethalometer to measure eBC (Boniardi et al., 2019a, b). A brief training on how to handle the equipment during the personal monitoring was given as well, to both children and their parents: for instance, they were asked to wear the bag as long as possible during their activities, to leave it in their proximity if they were involved in outdoor activities or in the dressing room if they went swimming or performed other indoor sports, and to leave the bag near their bed during the night (all samplers were silent). Moreover, children were warned on the importance of leaving the equipment in an open environment (i.e. not locked in a wardrobe) and with the inlet tube free from obstruction. No formal protocol compliance data was collected, but children and parents were asked to report any inconveniences they had noticed. Finally, parents were asked to fill in a personal information questionnaire.

All the logistic operations linked to the monitoring campaign were carried out in the former infirmary room of the school. Starting on Monday afternoon and up to Thursday afternoon, each day, at 4 pm, a group of 4–5 children was enrolled in the study and wore the equipped shoulder bag; then, after the home-to-school commuting of the next day, from 8 to 9 am, children returned the shoulder bag and collected a spot urine sample.

2.2. Questionnaire, GPS and time-activity diary

A questionnaire was completed by children's parents to collect information on children personal and lifestyle characteristics, home characteristics, and parent smoking status, while a time-activity diary was completed by children and parents to describe the activities carried out by children during the monitored period. Data derived from the GPS device worn by children were manually checked and used to confirm TAD information.

Material and methods including the TAD are reported and described in more detail in Boniardi et al. (2021).

2.3. Personal air sampling and analysis

Personal exposure to airborne benzene (BEN-A), toluene (TOL-A), ethylbenzene (EtBEN-A), o-xylene (o-XYL-A), m + p-xylene (m + p-XYL-A) (all together BTEX-A), methyl tert-butyl ether (MTBE-A), ethyl tert-butyl ether (ETBE-A), and ter-amyl methyl ether (TAME-A) were monitored during a 16-h period (starting at 4:00–4:30 p.m. and ending the following morning at 8:00–9:00). Air was sampled using the passive sampler Radiello equipped with a 35–50 mesh charcoal cartridge (Supelco, Sigma-Aldrich, Milano, Italy). Children wore the sampler on their upper chest, near their respiratory zone. At the end of the sampling period, the cartridge was sealed in the proper glass tube, and kept in a clean box at room temperature until analysis, which occurred within 30 days from the collection, according to the manufacturer's instruction.

Airborne VOCs were measured by gas chromatography coupled to mass spectrometry (GC–MS) (Fustinoni et al., 2010; Cattaneo et al., 2021) Quantification limit (LOQ) was 8 μg/L for all analytes. Considering the average sampling time and the uptake rates of each analyte, this concentration was estimated to correspond to airborne levels of 0.2 $\mu g/m^3$ for MTBE-A, ETBE-A, TAME-A, TOL-A, EtBEN-A, o-XYL-A and LIM-A, 0.3 $\mu g/m^3$ for m + p-XYL-A, and 0.6 $\mu g/m^3$ for BEN-A.

Equivalent black carbon (eBC) levels were detected by means of micro-aethalometer AE51 (AethLabs, California, United States). Raw data were post-processed to smooth background noise (Hagler et al., 2011), to account for difference between the devices, and to correct the concentration underestimate linked with the loading effect of the particulate matter collected on the filter (Virkkula et al., 2007). The post processing method applied for this study is described in detail in Boniardi et al. (2021a).

2.4. Urine sample collection and analysis

Urine spot samples were collected in the morning within 10 min of the end of the air sampling. Urine was collected in disposable polyurethane bottles, and then, using a disposable syringe, a 7 mL aliquot was immediately poured into an 8-mL pre-evacuated storage vial for the determination of urinary VOC (Fustinoni et al., 2007). A 20 mL aliquot was stored in a polyethylene tube for creatinine analysis. After collection, the specimens were immediately stored at −20 °C and analyzed, according to their stability, within 60 days.

Urinary benzene (BEN-U) and methyl tert-butyl ether (MTBE-U) were determined by headspace solid-phase microextraction (HS-SPME) followed by GC–MS analysis according to published methods (Fustinoni et al., 1999, 2010; Scibetta et al., 2007) with some modifications (Fustinoni et al., 2010; Cattaneo et al., 2021). The LOQ was 10 ng/L.

The quality control of the method to quantify BEN-U is guaranteed by the successful participation twice a year to the German External Quality Assessment Scheme (G-EQUAS) for analyses in biological materials (G-EQUAS, 2009). To our knowledge, no external quality control for the analysis of MTBE-U is available.

Urinary creatinine (crt) was determined using Jaffe's colorimetric method (Kroll et al., 1986). No criteria of acceptability based on urine dilution was applied.

2.5. Statistical analysis

Statistical analysis and data treatment were performed by using R studio (Bates et al., 2015; R Core Team, 2013; Wickham et al., 2019). Descriptive analyses were used to obtain the medians, ranges, and percentiles of ambient and biological analytes. Additional statistical analysis was performed on decimal log-transformed data to obtain the normal distribution. The raw values calculated from the integration of analytical peaks were used unchanged instead of applying substitution methods (e.g. using fractions of the quantification limit) to avoid substantial bias by substitution (Helsel, 2006). Data with zero values were substituted with a value corresponding to the half of the lowest detectable values. Comparisons were performed by Student's *t*-test for independent or partially dependent samples, where required. Seasonal differences were investigated with Wilcoxon test. Pearson's correlations were used to measure the associations between quantitative variables. A *p*-value < 0.05 was considered statistically significant.

The main regression analysis reported in this contribution regards all the collected data pooled together. In this way, since data were clustered by days and id, multiple linear random intercept models were developed to investigate the association between ambient and biological markers (decimal log transformed mean values) and a set of possible explanatory variables. The latter are reported in the supplementary materials (Table S1) and can be classified in: socio-economic variables (e.g. scholar level of the parent who filled the questionnaire); personal characteristic of children (e.g. BMI); ETS information (e.g. urine cotinine levels); meteorological information (e.g. the average wind speed during the monitoring session); home features (e.g. type of cooking stoves, daily number of vehicles in a certain circular buffer); mobility habits (e.g. home to school transport mode, time spent being transported by cars); other microenvironments (e.g. time spent outdoor); and airborne analytes (only to explain the quantified levels of urinary analytes). These variables were collected from the TAD, the GPS device and the family questionnaires. Besides, wind speed values were obtained from the nearest (about 1 km from the school) air quality network station run by the Regional Environmental Protection Agency (ARPA), while the height of the mixed layer was estimated for the city of Milan by the Regional Environmental Protection Agency of Emilia Romagna (ARPAE). Finally, spatial variables (e.g. home-road distance) were elaborated by using Quantum GIS (QGIS Development Team, 2022) based on children's home address and traffic layers from the Municipality of Milan.

To develop the multiple regression, the first step was to check all the collected variables in a single-variable mixed-effect model controlled by the education level of the parent who filled in the questionnaire, the sex of the child, and the number of members of the family plus age, BMI, and creatinine levels for urinary markers. The use of creatinine as independent variable in the multiple regression model allows the urinary marker concentration to be adjusted appropriately for urinary creatinine and the statistical significance of other variables in the model to be independent of effects of creatinine concentration (Barr, Wilder et al. 2005). Only the predictors with *p*-value < 0.1 and having an expected direction of effect were selected. As a second step, we introduced the variables one by one in an empty new model, again controlled by the education level of the parent who filled in the questionnaire, the sex of the child, and the number of members of the family plus age, BMI, and creatinine levels for urinary markers. We started from the predictors with the lowest *p*-value. For each iteration, the new variable was retained if the related *p*-value was <0.1, and the Akaike Information Criterion (AIC) of the model decreased. The significance ($p < 0.1$) was tested by comparing the previous step model AIC with the new one, by means of Analysis of Variance (ANOVA) test. Whether this approach could not be used (e.g. different number of cases due to different variables retained), we selected the model with the highest coefficients of determination (R^2). Marginal and conditional coefficients of determination (R^2_m and R^2_c) were computed following Nakagawa and Schielzeth (2013). To give predictors rank of importance, the relative amount of explained variability was calculated separately for each fixed effect in single-predictor mixed-effect regression analysis. To identify the proportion of the total variability explained by the random effects, the Intra-Class Correlation coefficient (ICC) was computed as the ratio between the random effect variance and the total variance. Finally, to better understand the influence of seasons on predictors of exposure, the same explanatory variables selected in the main pooled data analysis were tested in new seasonal models. In particular, new mixed-effect regression models were developed for each analyte using separately spring and winter data. For this analysis, the “season” explanatory variable previously tested for the pooled data models was discarded and the date of monitoring remained as the only tested random effect.

3. Results

3.1. Study population

The main characteristics of the study population are given in Table 1. Out of invited children ($n = 128$), 85 (66 %) and 109 (85 %) expressed their interest to be involved in the Spring 2018 and Winter 2019 field campaigns, respectively. Three children in Spring 2018 and 11 in Winter 2019 did not confirm their participation (reasons: unavailability or illness), so the actual participants were 82 in Spring 2018 and 98 in Winter 2019. One participant from the Winter campaign was excluded from this analysis because the questionnaire was not complete, so the actual participants in this study were 82 and 97 during Spring 2018 and Winter 2019, respectively, 76 repeated in the two seasons. Not all the different kind of samples were available for each participant: urine samples and eBC measurements were available for 81 and 95 children, while VOC measurements for 82 and 89 children, in Spring 2018 and Winter 2019, respectively. Either way, females were the majority (55–52 %). On average, children lived in families composed of 4 members, in apartments at the second floor equipped with gas stoves (86 %), in urban areas with busy roads and <1 km far from school. Children living with parents who smoke or vape were 29 (36 %) in spring and 26 (27 %) in winter. While involved in the monitoring campaign, children spent most of their time at home, while only a few spent some time outdoor after school. Children spent on average 41 and 47 min commuting respectively during spring and winter, and those who were transported at least one time by car were 56 (68 %) and 57 (59 %).

3.2. Personal exposure to air pollutants

Descriptive statistics of the monitored air pollutants are reported in Table 2. Considering airborne particles, eBC personal concentrations were always detectable with values about 3 times higher in winter than in spring. For what concerns airborne VOCs, with the exception of ETBE-A and TAME-A, that were almost never detected in both seasons, the percentage of detection for airborne BTEX and MTBE-A was about 100 % in both seasons, with the notable exception of BEN-A, for which it was as low as 52 % in spring.

Except for TAME-A and ETBE-A, personal exposure to airborne VOCs was >2-fold higher in winter than in spring.

3.3. Urinary biomarkers of exposure

Urinary BEN-U and MTBE-U results are reported in Table 2. During both seasons, BEN-U was quantifiable in 100 % of the samples, while MTBE-U samples above the LOQ passed from 82 % in winter to 42 % in spring. Seasonal differences were found, with both BEN-U and MTBE-U higher in winter than in spring.

3.4. Correlation analysis

The two correlograms reported in Fig. 1 show p- and r values related to the Pearson's correlation tests performed between pollutants. All the airborne VOCs showed mid to strong positive correlations with each other with r values ranging from 0.63 (o-XYL-A vs. MTBE-A, $p < 0.001$) to 0.94

Table 1
Characteristics of the study participants, stratified by campaign (Spring 2018, Winter 2019).

Characteristics			Study campaign Spring (N = 82)	Study campaign Winter (N = 97)
Personal	Age (years), mean (min–max)		8 (7–10)	9 (7–11)
	Gender, N (%)	Males	37 (45 %)	47 (48 %)
		Females	45 (55 %)	51 (52 %)
	BMI (kg/m^2), median (25th–75th)		16.2 (15.0–17.2)	15.9 (15.0–17.7)
Family	Number of family members, mean (min–max)		4 (2–8)	4 (2–8)
	Number of children, mean (min–max)		2 (1–6)	2 (1–6)
	Questionnaire responder, N (%)	Mother	67 (82 %)	75 (77 %)
		Father	15 (18 %)	21 (22 %)
		Missing	/	1 (1 %)
	Responder education, N (%)	High school or less	22 (27 %)	29 (30 %)
		University or higher	60 (73 %)	67 (69 %)
		Missing	0	1 (1 %)
ETS exposure	Living with smokers or vapers, N (%)	Yes	29 (36 %)	26 (27 %)
		No	53 (64 %)	71 (73 %)
Home	Gas stoves, N (%)		74 (90 %)	77 (83 %)
	Internal fireplace, N (%)		1 (<1 %)	1 (<1 %)
	Internal boiler, N (%)		43 (52 %)	47 (48 %)
	Use of aroma burners (candles, incense), N (%)		1 (<1 %)	2 (<1 %)
	Home height, (m), median (25th–75th)		6 (3–12)	6 (3–15)
	Distance to school (meters), median (25th–75th)		690 (510–1045)	754 (520–1057)
	Distance to the first road (m)[1], median (25th–75th)		15 (11–24)	15 (11–25)
	Daily number of vehicles in a 50-m radius buffer around home, N median (25th–75th)		11,732 (1822–30,384)	11,712 (1560–28,649)
Time-activity information	Time at home (min), median (25th–75th)		806 (784–860)	828 (789–877)
	Time at home while cooking (minutes), median (25th–75th)		27 (0–36)	30 (12–40)
	Time at home while internal boiler working (min), median (25th–75th)		0 (0–0)	0 (0–15)
	Number of children commuting by car, N (%)		56 (68 %)	57 (59 %)
	Time commuting by car (min), median (25th–75th)		29 (15–45)	24 (15–44)
	Time walking (min), median (25th–75th)		20 (7–33)	24 (14–36)
	Total commuting (min), median (25th–75th)		41 (29–54)	47 (32–59)
	Number of children commuting from home to school, N (%)	On foot	39 (48 %)	53 (55 %)
		By car	33 (40 %)	29 (30 %)
		Other	10 (12 %)	15 (15 %)
Meteorological variables	Wind speed (m/s), median (25th–75th)		1.4 (1.2–1.7)	1.2 (1.1–1.6)

ETS = environmental tobacco smoke.
[1] The first road with >1000 Veh/day.

Table 2
Children personal exposure to eBC, airborne VOCs and VOC urinary levels stratified by campaign (Spring 2018, Winter 2019). Results are reported as median (5°–95° percentiles) of the mean personal exposure.

Personal exposure Median (5°–95°); % > LOQ[a]			
Airborne particles (μg/m^3)	**Spring (N = 81)**	**Winter (N = 95)**	**All (N = 176)**
eBC***	1.4 (0.7–2.3); 100	3.9 (1.1–8.7); 100	1.9 (0.8–7.5); 100
Airborne VOCs	**Spring (N = 82)**	**Winter (N = 89)**	**All (N = 176)**
BEN-A***	0.6 (<0.6–1.3); 52	1.9 (0.8–3.5); 98	1.1 (<0.6–3.4); 76
TOL-A***	4.3 (1.7–9.0); 100	9.9 (4.0–66.9); 100	5.9 (2.2–23.8); 100
EtBen-A***	0.7 (0.3–2.0); 100	1.6 (0.7–3.1); 100	1.0 (0.3–3.0); 100
m + p-XYL-A***	2.0 (0.8–6.2); 99	4.6 (2.3–10.8); 100	3.0 (1.0–8.4); 100
o-XYL-A***	0.8 (0.4–2.0); 99	1.6 (0.8–3.5); 100	1.2 (0.4–3.4); 100
MTBE-A***	0.5 (0.3–1.6); 99	1.1 (0.4–2.2); 100	0.8 (0.3–1.8); 100
ETBE-A	<0.2 (<0.2–0.2); 7	<0.2 (<0.2 to <0.2); 7	<0.2 (<0.2 to <0.2); 7
TAME-A	<0.2 (<0.2 to <0.2); 0	<0.2 (<0.2 to <0.2); 0	<0.2 (<0.2 to <0.2); 0
Urinary biomarkers (ng/L)	**Spring (N = 81)**	**Winter (N=95[1])**	**All (N = 176[2]*)**
BEN-U**	41.8 (24.4–73.0); 100	51.1 (27.9–113.1); 100	44.9 (25.7–98.6); 100
MTBE-U***	<10 (<10–18.8); 42	15.1 (<10–47.2); 82	11.5 (5.0–35.5); 37

Wilcoxon test Winter versus Spring.
[a] Limit of quantification.
[1] 94 urine samples were available for MTBE-U.
[2] 175 urine samples were available for MTBE-U.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

(o-XYL-A vs. m + p-XYL-A, $p < 0.001$). Considering also airborne particles, eBC was positively correlated with all VOCs with r values ranging from 0.62 (eBC vs. o-XYL-A, $p < 0.001$) to 0.86 (eBC vs. BEN-A, $p < 0.001$, Fig. S1).

For biomarkers, BEN-U showed a weak positive correlation with MTBE-U ($r = 0.19$, $p < 0.01$). Besides, BEN-U was positively correlated with all airborne pollutants with r values ranging from 0.17 (BEN-U vs. m + p-XYL-A, $p < 0.05$) to 0.35 (BEN-U vs. MTBE-A, $p < 0.05$); the correlation with EtBEN-A and o-XYL-A was not statistically significant ($p = 0.11$ and $p = 0.12$). The correlation between BEN-U and BEN-A was positive ($r = 0.31$, $p < 0.001$). Finally, MTBE-U was positively correlated with all the airborne contaminants with r values ranging from 0.44 (MTBE-U vs. o-XYL-A, $p < 0.001$) to 0.57 (MTBE-U vs. MTBE-A, $p < 0.001$). Both BEN-U and MTBE-U were also correlated with eBC, with r values 0.32 and 0.48 ($p < 0.001$), respectively.

3.5. Exposure covariates

3.5.1. Mixed-effect models for airborne VOCs and eBC

A summary of selected parameters for the mixed-effect models for airborne VOCs and eBC is reported in Table 3. Overall, the models explained from 72 % (o-XYL-A) to 93 % (eBC) of the total measured variability (R^2_c) of the personal exposure, while the marginal effects of the explanatory variables (R^2_m) explained from 24 % (o-XYL-A) to 64 % (BEN-A). According to the single-variable mixed-effect models reported in Table S2, the season of monitoring (Season) was the most predictive covariate for all the analytes, explaining from 19.3 % (MTBE-A) to 56.9 % (BEN-A) of the measured variability. The average wind speed during the day of monitoring (Wind speed), i.e., the second most predictive covariate, entered all the models but those for EtBEN-A and o-XYL-A, explaining from 12.4 %

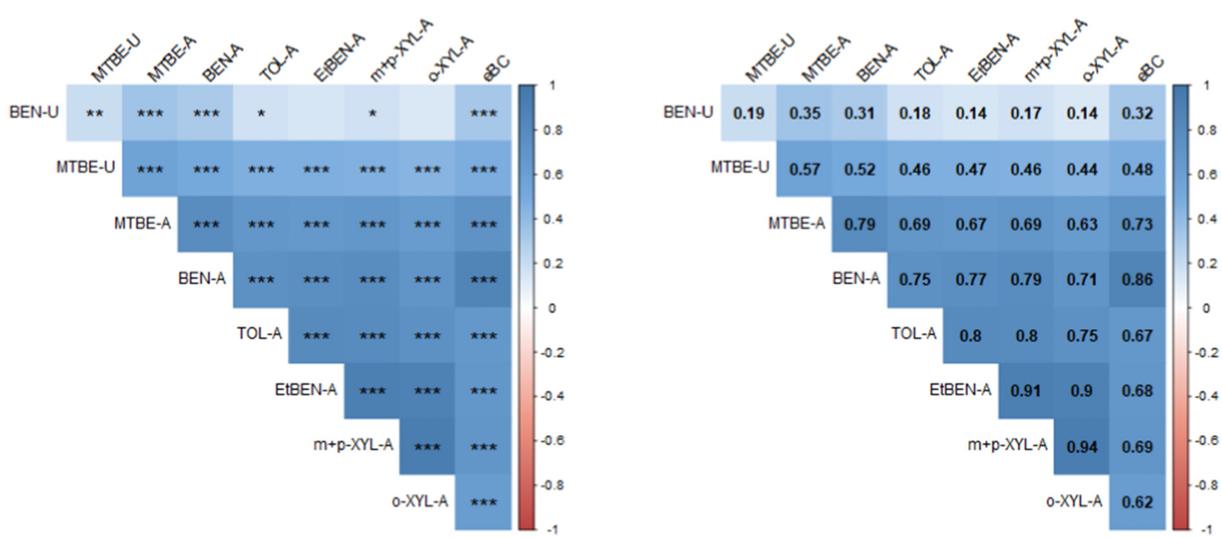

Fig. 1. Correlograms reporting *p*- and r values of the Pearson's correlation tests performed between pollutants.
Pearson's correlation *p*-values: *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

Table 3
Ambient mixed-effect random intercepts multiple regressions. All models were controlled by the education level of the parent who filled the questionnaire, the sex of the child, and the number of members of the family. Predictors are reported when $p < 0.1$.

	eBC	BEN-A	TOL-A	EtBen-A	m + p-XYL-A	o-XYL-A	MTBE-A
R^2_c [1]	0.93	0.91	0.85	0.74	0.75	0.72	0.77
R^2_m [1]	0.55	0.64	0.39	0.34	0.37	0.24	0.39
RMSE[1]	0.068	0.074	0.11	0.13	0.12	0.12	0.10
VIF[1]	1.14	1.13	1.06	1.02	1.08	1.02	1.12
All observations	174	171	169	171	171	171	169
All groups (date)	43	42	42	42	42	42	42
All groups (id)	98	99	97	99	99	99	97
ICC[1] (date)	0.80	0.60	0.68	0.45	0.39	0.45	0.18
ICC[1] (id)	0.034	0.16	0.078	0.15	0.21	0.18	0.45
	Estimate (95 % CI)	Estimate (95 % CI)	Estimate (95 % CI)	Estimate (95 % CI)	Estimate (95 % CI)	Estimate (95 % CI)	Estimate (95 % CI)
Intercept	3.17**	−0.31***	0.59***	−0.24*	0.32**	−0.13	−0.12
	(3.02; 3.31)	(−0.48; −0.14)	(0.36; 0.81)	(−0.44; −0.037)	(0.089; 0.54)	(−0.33; 0.081)	(−0.32; 0.08)
Season: winter	0.39***	0.52***	0.39***	0.36***	0.35***	0.28***	0.23***
ref: spring	(0.28; 0.51)	(0.42; 0.63)	(0.25; 0.54)	(0.24; 0.47)	(0.24; 0.46)	(0.17; 0.40)	(0.13; 0.33)
Wind speed (m/s)	−0.78**	−0.59**	−0.67*		−0.41		−0.89***
	(−1.19; −0.36)	(−1.01; −0.16)	(−1.27; −0.070)		(−0.86; 0.033)		(−1.31; −0.47)
Time in car (min)	0.0014**	0.0014**	0.0015*		0.0014*	0.0016*	0.0013*
	(7.50×10^{-4}; 0.0021)	(4.83×10^{-4}; 0.0023)	(2.95×10^{-4}; 0.0025)		(1.95×10^{-5}; 0.0026)	(3.01×10^{-4}; 0.0028)	(1.65×10^{-4}; 0.0024)
Parents who smoke: yes	0.065***	0.11***	0.0072*				
ref: no	(0.029; 0.100)	(0.058; 0.16)	(0.092; 0.13)				
Height of home (m)	−0.0031*		−0.0035				−0.0055*
	(−0.0053; -8.47×10^{-4})		(−0.074; 3.50×10^{-4})				(−0.0095; −0.0014)
Distance home-school (m)				6.83×10^{-5}*	5.54×10^{-5}		
				(1.35×10^{-5}; 1.25×10^{-4})	(-3.87×10^{-6}; 1.17×10^{-4})		
Distance home-road (m)	−0.0011*						
	(−0.0022; -8.27^{-4})						
Home-school mode: car		0.063*					0.073*
ref: walk		(0.010; 0.12)					(0.0061; 0.14)

[1] R^2_c = conditional R^2, R^2_f = marginal R^2, VIF = highest Variance Inflation Factor, RMSE = Root Mean Square Error, ICC = Interclass Correlation Coefficient.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

(TOL-A) to 21.7 % (MTBE-A). Other important covariates were: the total time spent in car during the day of monitoring (Time in car), that entered all the models, but EtBEN-A, explaining from 2.8 % (eBC) to 7.9 % (m + p-XYL-A) of the total measured variability; the presence of parents who smoke (Parents who smoke), that explained from 1.4 % (TOL-A and eBC) to 6.7 % (BEN-A); the height of children's dwellings (Height of home) that explained from 0.8 % (eBC) to 2.0 % (TOL-A); the distance from home to school (Distance home-school) that explained 9.8 % and 10.2 % for EtBEN-A and m + p-XYL-A, respectively; the distance of the first road to the children's dwellings (Distance home-road) that entered only the eBC model explaining 1.8 % of the measured variability; and the mode of transportation during home-school commuting (Home-school mode) that explained the 5.2 % and the 7.9 % for BEN-A and MTBE-A, respectively.

A summary of selected parameters (beta and *p*-value) of the explanatory variables reported as winter, spring, and pooled data models are reported in supplementary materials (Table S3). The direction of the effect was consistent between seasons, while the statistical significance of the variables was not always kept.

3.5.2. Mixed-effect models for urinary benzene and methyl tert-butyl ether

A summary of selected parameters for the mixed-effect models for BEN-U and MTBE-U is reported in Table 4. The models explained 61 % and 58 % of the total measured variability (R^2_c) respectively for BEN-U and MTBE-U, while the marginal effects of the explanatory variables (R^2_m) explained 27 % and 41 %. According to the single-variable mixed-effect models reported in Table S2, airborne benzene (BEN-A) and methyl tert-butyl ether (MTBE-A) were the most predictive variables, explaining 26.6 % and 34.9 % of the measured variability of BEN-U and MTBE-U. Other important covariates for BEN-U were the presence of parents who smoke (Parents who smoke) and whether children were transported by car during the day of monitoring (Transported by car) that explained respectively the 18.9 % and the 16.8 % of the measured variability. Important covariates for MTBE-U were the season of monitoring and the ratio between the daily estimated vehicles on the nearest road from children's dwellings and its distance (Traffic on nearest road/Distance home-road) that explained respectively 20.7 % and 2.2 % of the measured variability.

Table S3 reports a summary of parameters (beta and *p*-value) of the explanatory variables reported as winter, spring, and pooled data models. As observed for the airborne analytes, the direction of the effect was consistent between seasons, while the statistical significance of the variables was not always maintained.

4. Discussion

In this paper, the exposure to several traffic related pollutants was assessed by environmental and biological monitoring in a group of schoolchildren living in the city of Milan, Italy. Moreover, the determinants of exposure were studied, with a focus on traffic exposure and personal habits in commuting. The investigation of a typical weekday in two different periods of the year (spring and winter) allowed us obtaining the real-life exposure.

The levels of children personal exposure were generally low, in the range of some μg/m^3, but still mostly quantifiable and with higher values in winter than in spring. In particular, if considering airborne benzene, the overall median level was 1.1 μg/m^3, five times below the level enforced as a mean calendar year limit in the EU (5 μg/m^3). The levels here found for

Table 4
Urinary mixed-effect random intercepts multiple regressions. All models were controlled by the education level of the parent who filled the questionnaire, plus age, sex, BMI and creatinine levels of the child and finally the number of members of the family. Predictors are reported when $p < 0.1$.

	BEN-U	MTBE-U
R^2_c [1]	0.61	0.58
R^2_m [1]	0.27	0.41
RMSE[1]	0.10	0.18
VIF[1]	1.21	1.45
all observations	167	166
All groups (days)	42	42
All groups (id)	–	97
ICC[1] (date)	0.46	0.02
ICC[1] (id)	–	0.27
	Estimate (95 % CI)	Estimate (95 % CI)
Intercept	2.02*** (1.65; 2.39)	1.20*** (0.54; 1.86)
Sex: M ref: F	0.044* (0.0018; 0.086)	
Age	−0.039* (−0.075; −0.0033)	
Number of members of the family	−0.030* (−0.056; −0.0035)	
Creatinine	0.29*** (0.17; 0.41)	
Season: winter ref: spring		0.17*** (0.081; 0.26)
BEN-A	0.12** (0.027; 0.22)	
MTBE-A		0.54*** (0.40; 0.69)
Parents who smoke: yes ref: no	0.048* (0.044; 0.092)	
Transported by car: yes ref: no	0.060** (0.017; 0.10)	
Traffic on nearest road/distance home-road		9.91×10^{-6}* (1.81×10^{-6}; 1.78×10^{-5})

* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.
[1] R^2_c = conditional R^2, R^2_f = marginal R^2, VIF = highest Variance Inflation Factor, RMSE = Root Mean Square Error, ICC = Interclass Correlation Coefficient.

benzene are similar to those reported for children living in an industrial area in Sardinia (Italy) in 2016 (median 1.6 μg/m^3) (Pilia et al., 2021) and higher than those reported for children living in South Korea in 2008 (median 0.3 μg/m^3) (Byun et al., 2010). Children exposure to benzene and to the other studied VOCs was also similar to or lower than that observed in our previous study on adults living and working in Milan (median for BEN-A 2.3 μg/m^3) (Cattaneo et al., 2021). However, if we consider that benzene is a Group 1 carcinogen (IARC, 2018) which possibly affects health even at very low concentrations (Filippini et al., 2019), and that children are deemed to be among the most susceptible, our results stress the need for actions to lower their exposure in the city of Milan.

To the best of our knowledge, this is the first time that the personal exposure of children to oxygenated additives to fuels, such as MTBE, ETBE, and TAME, has been studied. Previous measures have been scarce and limited to occupational exposure (Vainiotalo et al., 2006; Campo et al., 2011, 2016a) or to adults (Cattaneo et al., 2021). Among airborne ethers, only MTBE was always quantifiable, showing a diffuse exposure for children, similar to that found in adults in the same city of Milan (median 0.8 μg/m^3) (Cattaneo et al., 2021).

Determinants of exposure to air pollutants in children were identified by using mixed effect regression models (Tables 3 and S2), that explained from 72 % (o-XYL-A) to 93 % (eBC) of the total measured variability of the personal exposure. Major contributions were given by the season, explaining up to 57 % of the variability, and the wind speed, explaining up to 22 % of the total variability. As regards the season, 2- to 3-fold higher values were observed for all analytes in winter than in spring, and for BEN-A also the percentage of positive samples doubled in winter. This is an expected pattern for the pollutant distribution in this area, as the season accounts for several meteorological variables and concomitant causes that can play a key role. Among the others, the lower mixing height in winter which hinders the dispersion of pollutants, and the lower outdoor temperature together with the lower photochemical activity which slows down the removal of chemicals from the atmosphere (Masiol et al., 2017). Moreover, some personal habits, such as the commuting mode, are affected by the season, with a higher number of vehicles in urban areas in the cold than in the warm season. At the same time, also indoor exposure should be considered, taking into account that study children spent most of the monitored time at home. For VOC in particular, higher levels are generally found indoor in the cold season, due to the reduced indoor ventilation and the consequent accumulation of pollutants.

The season may act as a modulator on the role of predictors in explaining personal exposure to air pollution. However, according to the seasonal beta values reported in Table S3, the direction of effect of the predictors were consistent in both spring and winter seasons, even if the statistical significance was not always maintained. This could be linked to the lower statistical power of the seasonal models due to the reduced amount of data.

As regards indoor pollution, the sources can be both external, such as road traffic, and internal, including smoking and cooking habits (Vardoulakis et al., 2020). However, in our study the variables related to cooking, such as the time spent at home while cooking, were not significant in single regression analysis and were not included in the final models. The lack of significance here found is consistent to what previously observed (Cattaneo et al., 2021). Besides, since the great majority of study households (86 %) hosted gas stoves, the influence of the type of stove could not be tested. The presence of an internal boiler and its use were not significant too. Finally, it was not possible to test the influence of other possible source of indoor pollution like the use of aroma burners (candles, incense) or internal fireplaces since these variables were under-represented.

Other significant determinants of exposure were related to the commuting mode of children, and in particular the use of car along the whole monitored period increased all analytes, but EtBEN-A, with an estimated increase of about 0.3 % for each minute spent in car. Even if the time dedicate to home-school commuting was very short in comparison with the total monitored time, as children mostly lived in the close proximity to the school (median home-school distance about 700 m), this had a great impact on children exposure, as walking instead of using car along this route decreased their exposure to BEN-A and MTBE-A by 16 and 18 %, respectively. In addition, a longer home-school distance resulted associated with a higher exposure to EtBEN-A and to m + p-XYL-A. These results were expected, since the morning rush hour in Milan is the most critical time-window of the day for traffic-related air pollution (Boniardi et al., 2019a, b).

In a recent paper, we highlighted the impact of environmental tobacco smoke (ETS) on children by quantifying cotinine in urine samples (Campo et al., 2021). In this contribution, we show that children exposure to ETS significantly affects their exposure to eBC and BEN-A, with respectively 16 % and 29 % higher values in children exposed than in those not exposed. As it is widely recognized, the exposure to ETS causes the exposure to a mixture of hundreds of chemicals, among which at least 70 carcinogenic substances (IARC, 2004), such as benzene. In children, ETS exposure has been associated with an increased risk of developing asthma, sudden infant death syndrome, ear and respiratory infections, neurodevelopment disorders, obesity, and premature atherosclerosis (IARC, 2009; WHO, 1999; U S Department of Health and Prevention, 2014; Braun et al., 2020).

Biological monitoring of VOC exposure of the general population and of children in particular has been very limited, maybe for the difficulties encountered in involving children in a biomonitoring study. In this sense, a significant result of this study is the relatively high participation rate, which benefited from the participatory approach of the study, as showed by the increased participation in the second campaign (Boniardi et al., 2021a). The overall BEN-U median level (44.9 ng/L) was similar to that reported for Italian children living in Central Italy in 2017 (winter mean 41.1 ng/L) (Antonucci et al., 2021), higher than in children living near or far from a petrochemical plant in Sardinia (Italy) in 2016 (10 ng/L) (Pilia et al., 2021), and much lower than in children living near or far from a petrochemical plant in Sicily in 2015 (Italy) (200 ng/L) (Andreoli et al., 2015), or in a urban area in Thailand in 2004 (70 ng/g creatinine) (Buthbumrung et al., 2008). BEN-U median levels were also slightly lower than in non-smoking adults in Milan (67 ng/L) (Cattaneo et al., 2021). As regards MTBE-U, overall median levels (11.5 ng/L) were much lower than data previously reported for children in Italy (70–800 ng/L) (Andreoli et al., 2015; Antonucci et al., 2021) and in a selected population of Milan policemen exposed to traffic during work shifts (147 ng/L) (Campo et al., 2011).

Both Pearson's correlation and mixed effect regression models showed that urinary biomarkers were significantly associated with their respective airborne levels, with $r = 0.31$ (BEN-U vs. BEN-A) and $r = 0.57$ (MTBE-U vs. MTBE-A) (Fig. 1). The correlation found for benzene is similar to that found in our previous studies in the general population (Fustinoni et al., 2010; Cattaneo et al., 2021). The relatively low correlation coefficients found are justified, considering that multiple confounders may affect the relationship between air and urinary analytes, also considering their low levels. Among the others, smoking is a relevant contributor to benzene intake. The regression models (Tables 4 and S2) highlighted indeed that living with smoking parents was the major determinant of BEN-U excretion, explaining 19 % of the total variability of BEN-U and with 12 % higher levels in exposed than in not exposed children.

The second major determinant to BEN-U was being transported by car, that contributed 17 % to the total BEN-U variability. This is in line with results for airborne benzene and confirms that BEN-U, although impacted by tobacco smoke exposure, is a reliable marker of exposure to traffic, as shown by a few previous studies showing associations between BEN-U and different surrogates of traffic exposure, such as using car for commuting (Cattaneo et al., 2021), time spent in urban traffic (Lovreglio et al., 2011), and residence in urban areas (Protano et al., 2010; Campagna et al., 2014). Also, this is in line with a recent study conducted in Milan which showed that the exposure to benzene is higher in car commuters if compared to other type of commuters (Boniardi et al., 2021b).

For MTBE-U, we previously reported an excellent association with MTBE-A in petrol station attendants (Campo et al., 2016b), while this is the first time that a significant correlation is reported in the general population. Moreover, MTBE-U was better associated to all airborne pollutants ($0.44 < r < 0.52$) than BEN-U ($0.14 < r < 0.35$), showing that this biomarker is useful to assess the exposure not only to MTBE, but also to other pollutants related with fuel emissions. A reason for the better association may be that MTBE-U, differently from BEN-U, is not affected by tobacco smoke exposure, as already observed in occupational scenarios (Campo et al., 2011, 2016a). Among the tested variables, only the season, the personal exposure to MTBE-A and, to a minor extent the ratio between the daily estimated vehicles on the nearest road from children's dwellings and its distance, were significant determinants for MTBE-U excretion.

To investigate the role of personal characteristics on biomarkers excretion, gender, age, BMI, and urinary creatinine were introduced in the regression models. As we previously observed, BEN-U was associated with creatinine and sex, while MTBE-U was not associated to any of these parameters (Cattaneo et al., 2021; Campo et al., 2011).

To the best of our knowledge, we report here for the first time significant correlations between personal eBC and VOC exposure, with the highest correlation coefficients with BEN-A ($r = 0.86$) and MTBE-A ($r = 0.73$). The high correlation found between eBC and BEN-A highlights their common sources, mainly represented, in the urban environment, by fuel combustion and tobacco smoke. The importance of traffic-related sources is confirmed by the high correlation between eBC and MTBE-A. These evidences are confirmed also by the significant correlations between eBC and urinary benzene and MTBE.

The main limitation of this study is the relatively low number of children and their recruitment on a voluntary base, which makes our results not generalizable to the entire population. However, the participatory approach allowed us obtaining a high participation rate, so it is likely that it is representative, at least, of the studied area. Besides, the low number of children hindered the investigation of some under-represented variables, mostly related to indoor sources of pollution. Another limitation is that the personal air monitoring had a relatively short duration and children spent most of the monitored time indoors. However, the study design was based on the reasonable assumption that children activities, and thus their exposure, is roughly constant along the days. Moreover, the investigated time-window included both the evening and morning rush hours, so allowed us to investigate these critical times of the day.

The investigation of general population exposure by using a combined approach of personal air monitoring and biological monitoring is very limited in the literature, especially if considering studies involving children. The main strength of this study is the investigation of such an expanded panel of pollutants in two different seasons by using a multidisciplinary approach that includes personal air monitoring, biological monitoring, and up-to-date statistical analysis. Moreover, the collection of information from different sources, including questionnaires, time-activity-diary, and spatial variables, allowed us to highlight the different factors contributing to children exposure.

In conclusion, this study investigated the exposure to several VOCs and eBC in school-age children living in Milan. The personal exposure was mainly related to meteorological and seasonality factors, but an important role was played also by traffic related variables and mobility habits, including the time spent in a car, the home-school mode, and the exposure to passive smoke. As regards biological monitoring, the internal dose of benzene was mainly determined by commuting by car and passive smoke exposure.

Our results have some implications for environmental epidemiology. The overall high correlation coefficients found among both VOCs, eBC, as well as biomarkers, suggests the importance of a multi-pollutant approach for a proper exposure assessment in the study of air pollution health effects (Dominici et al., 2010). Besides, the impact of mobility-related habits on exposure suggest the opportunity to incorporate such kind of variables in exposure assessment analysis (Khreis and Nieuwenhuijsen, 2017). Finally, from a public health perspective, the results of this study show that traffic-mitigation actions focused especially on morning rush hour and home-to school commuting paths, together with personal choices in commuting mode, could be effective in lowering the personal exposure of children to several air pollutants. At the same time, educational interventions aimed to make smoking parents aware of risks connected with passive smoking should be promoted.

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CRediT authorship contribution statement

Luca Boniardi: Conceptualization, Methodology, Formal analysis, Resources, Data curation, Writing – review & editing, Visualization, Project administration, Funding acquisition. **Laura Campo:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Luca Olgiati:** Investigation. **Francesca Longhi:** Investigation. **Chiara Scuffi:** Investigation. **Silvia Fustinoni:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Data availability

Data will be made available on request.

Declaration of competing interest

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

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Appendix A. Supplementary data

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