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Residential exposure to air pollution and incidence of leukaemia in the industrial area of Viadana, Northern Italy

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ABSTRACT

Background: Exposure to air pollution has been proposed as one of the potential risk factors for leukaemia. Work-related formaldehyde exposure is suspected to cause leukaemia.

Methods: We conducted a nested register-based case-control study on leukaemia incidence in the Viadana district, an industrial area for particleboard production in Northern Italy. We recruited 115 cases and 496 controls, frequency-matched by age, between 1999 and 2014. We assigned estimated exposures to particulate matter (PM_{10}, $PM_{2.5}$), nitrogen dioxide (NO_2), and formaldehyde at residential addresses, averaged over the susceptibility window 3rd to 10th year prior to the index date. We considered potential confounding by sex, age, nationality, socio-economic status, occupational exposures to benzene and formaldehyde, and prior cancer diagnoses.

Results: There was no association of exposures to PM_{10}, $PM_{2.5}$, and NO_2 with leukaemia incidence. However, an indication of increased risk emerged for formaldehyde, despite wide statistical uncertainty (OR 1.46, 95%CI 0.65–3.25 per IQR-difference of 1.2 μg/m^3). Estimated associations for formaldehyde were higher for acute (OR 2.07, 95%CI 0.70–6.12) and myeloid subtypes (OR 1.79, 95%CI 0.64–5.01), and in the 4-km buffer around the industrial facilities (OR 2.78, 95%CI 0.48–16.13), although they remained uncertain.

Conclusions: This was the first study investigating the link between ambient formaldehyde exposure and leukaemia incidence in the general population. The evidence presented suggests an association, although it remains inconclusive, and a potential significance of emissions related to industrial activities in the district. Further research is warranted in larger populations incorporating data on other potential risk factors.

Abbreviations: BC, black carbon; CH_2O, formaldehyde; ELAPSE, Effects of Low-Level Air Pollution: A study in Europe; EPISAT, Dati satellitari ed uso del territorio per la stima delle esposizioni a livello nazionale; LUR, land use regression; NO_2, nitrogen dioxide; PM, particulate matter; PM_{10}, particulate matter with an aerodynamic diameter of 10 μm or less; $PM_{2.5}$, particulate matter with an aerodynamic diameter of 2.5 μm or less.

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1. Introduction

Outdoor air pollution is a major concern due to its adverse effects on human health (European Environmental Agency, 2022). Human exposure to air pollutants induces inflammation, oxidative stress, and DNA damage (Møller et al., 2014), which can lead to the development of respiratory, cardiovascular, metabolic diseases, and cancer (IARC, 2016; Kampa and Castanas, 2008).

Air pollution may be associated with an increased risk of leukaemia, a type of blood cancer that affects both children and adults (Raaschou-Nielsen et al., 2016). Leukaemia is characterized by the abnormal proliferation of white blood cells, interfering with the body's capacity to fight infections. Although the exact causes of leukaemia are not fully understood, environmental factors such as exposure to chemicals and radiation have been linked to an increased risk of developing this disease (Bispo et al., 2020; Poynter et al., 2017).

Formaldehyde (CH_2O) is among the suspected air pollutants associated with leukaemia incidence (IARC, 2006; Kang et al., 2021). It is emitted into the atmosphere from natural processes, as well as from human activities including industrial processes, fossil fuel combustion, and vehicular emissions (WHO, 2010). Its release occurs both through direct emission and by secondary formation from precursor gases, such as volatile organic compounds and NOx, under the influence of sunlight and other environmental factors (Bastien et al., 2019). Formaldehyde is released indoors from various household products, such as chipboard furniture, adhesives, coatings, and cleaning agents (Nielsen et al., 2013).

Industrial wood manufacturing and chipboard production generate a range of air pollutants that can pose risks to the health of workers

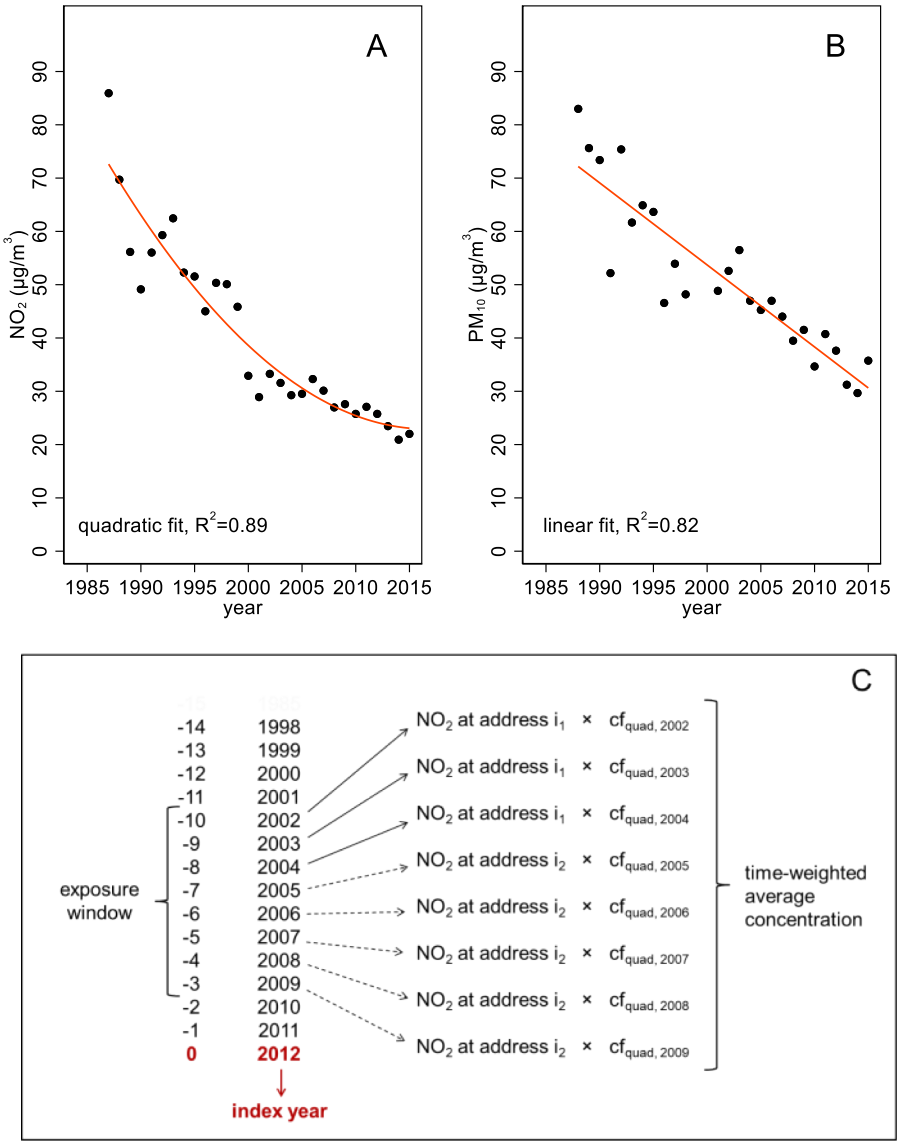

Fig. 1. Time trends in NO_2 and PM_{10} concentrations during the study period (panels A and B, respectively),[a] and illustration of the exposure assignment strategy over the susceptibility window from the 3rd to the 10th year before the index year (panel C).[b]

a data source: "Rapporto sulla qualità dell'aria della provincia di Mantova, anno 2015. ARPA Lombardia"; for 1988–1998, TSP concentrations were converted to PM_{10} concentrations, assuming that PM_{10} equals 80% of TSP;

b Steps of the procedure: 1) identification of index year for participant i; 2) reconstruction of relevant residential address history over 15 years (e.g., participant lived at addresses i1 and i2); 3) assignment of pollutant concentrations to geocoded addresses; 4) back-extrapolation of pollutant concentrations to relevant years using year-specific correction factors; 5) calculation of the time-weighted average concentration over the susceptibility window

(Scarselli et al., 2022) and nearby inhabitants (Dahlgren et al., 2003; de Marco et al., 2010); formaldehyde, utilised in the resins used to bond wood particles, is one such pollutant. While the majority of studies have focused on the health impact of indoor exposure, particularly in occupational settings, there is limited research on the effects of outdoor exposure to formaldehyde.

Italy's largest production site for chipboard is in the health district of Viadana, Lombardia administrative region, which is part of the Po plain (northern Italy), one of the most polluted areas of Europe (Larsen et al., 2012; Stafoggia et al., 2017). The district, in the province of Mantova, is part of the Health Protection Agency "Agenzia di Tutela della Salute (ATS) della Val Padana". It includes Viadana and 9 other smaller municipalities and counts a population of 47,701 inhabitants over 363 km^2 (year 2018, http://demo.istat.it). Plants for the synthesis of urea-formaldehyde resins, small incinerators, and facilities for chipboard production and storage are mainly located in the southern part of the district (municipalities of Viadana and Pomponesco), as shown in Fig. 1 of Marcon et al. (2014).

People living closer to the industrial plants in the Viadana district are exposed to higher levels of air pollutants (Marcon et al., 2014, 2021). Proximity to chipboard industries in the district has been linked to several health effects in the paediatric population, including respiratory and irritation symptoms and hospital admissions for respiratory diseases (de Marco et al., 2010; Girardi et al., 2012; Marchetti et al., 2014; Panunzi et al., 2023; Rava et al., 2011). Notably, higher exposures to NO_2 and formaldehyde have been associated with increased genotoxicity damage in mouth mucosa cells of children living in the district (Marcon et al., 2014). The above evidence implies that individuals residing in the district who are chronically exposed to elevated levels of air pollution may face an augmented risk of developing cancer (Bonassi et al., 2011).

The aim of this study was to investigate the association between residential exposure to air pollution and the risk of developing leukaemia in the Viadana district. For this purpose, we first described leukaemia incidence at the municipality level. Then, we conducted a nested case-control study including all incident cases of leukaemia retrieved from the local cancer registry and a random sample of controls, frequency-matched by age, assigning individual estimates of residential exposure to air pollution derived from available models.

2. Methods

2.1. Data collection

We obtained data from the cancer registry of the province of Mantova, which is accredited by the International Agency for Research on Cancer (IARC) and the Italian association of cancer registries (AIRTUM, Associazione Italiana Registri Tumori). We used the International Classification of Diseases for Oncology 3rd revision (ICDO3) coding system to define cancer topology (T) and morphology (M). We identified the following cancer diagnoses: all cancers (ICDO3T: C*), hemolymphopoietic cancers (ICDO3T: C42 and C77), and leukaemia (ICDO3T: C42 and ICDO3M: M980-M994). Among cases with leukaemia, we further identified acute leukaemia (ICD03M: 98353, 98363, 98613, 98663, 98723, 98913); chronic leukaemia (ICD03M: 98233, 98633, 99403, 99453 and restriction to age $\geq$35 years); lymphoid leukaemia (ICD03M: 98203, 98233, 98353, 98363, 99403); and myeloid leukaemia (ICD03M: 98613, 98633, 98663, 98723, 98913, 99453).

We used Stata statistical software, release 17.1 (College Station, TX: StataCorp LLC).

2.2. Study design

We conducted a descriptive analysis of cancer incidence in the 10 municipalities of the Viadana district during 1999–2014 (Supplementary analysis S1). We then conducted a nested register-based case-control study. This implied retrospectively following, between 1999 and 2014, all the residents in the district using the health registry of the ATS Val Padana, and identifying all the cases of incident leukaemia using the cancer registry for each year, along with a random sample of controls among the population members at risk for leukaemia during the same year. This procedure is called incidence density sampling (Richardson, 2004). We applied a 1 to 4 case/control ratio and frequency-matching by age in order to increase statistical efficiency (Rose and Laan, 2009). Cases and controls were required to be living in the district during the index year (30 June), i.e., the year of diagnosis for cases and the year of sampling for controls, and to have lived in the district for at least 1 year.

2.3. Exposure assignment

We traced the residential addresses of cases and controls living in the district over the 15 years leading up to the index year, spanning from 1984 to 2014, utilizing the civil registries of the 10 municipalities. We geocoded all retrieved addresses in two stages, as described in Appendix 1 of Marcon et al. (2021). At each residential address, we derived concentrations of outdoor air pollution by applying exposure models available from three projects, as described elsewhere (Marcon et al., 2021; Panunzi et al., 2023).

In brief, the "Viadana II" study provided NO_2 and formaldehyde concentrations for 2010 by spatial interpolation, applying ordinary kriging to passive sampling data (Marcon et al., 2014). Root mean square errors (RMSE) from leave-one-out cross-validation were 11.997 and 0.089 $\mu g/m^3$, respectively. The ELAPSE (Effects of Low-level Air Pollution: a study in Europe) study provided NO_2, $PM_{2.5}$, and black carbon (BC) concentrations for 2010 (de Hoogh et al., 2018). In ELAPSE, land use regression models were estimated for Western Europe using annual mean concentrations calculated from routine air quality measurements for $PM_{2.5}$ and NO_2; annual mean concentrations of BC were obtained as $PM_{2.5}$ absorbance based on reflectance measurement of the filters collected in the European Study of Cohorts for Air Pollution Effects. RMSE from five hold-out validations (each holding 80% sites for model training and 20% for validation) were 9.51 $\mu g/m^3$ ($PM_{2.5}$), 2.97 $\mu g/m^3$ (NO_2), and 0.58 10^{-5} m^{-1} (BC). The EPISAT study ("Dati satellitari ed uso del territorio per la stima delle esposizioni a livello nazionale") provided PM_{10} concentrations for 2012 and $PM_{2.5}$ concentrations for 2013, estimated by spatiotemporal land use regression models using data from routine air quality stations in Italy in combination with spatial and temporal predictor variables (Stafoggia et al., 2017, 2019). Co-authors MS and CB optimised exposure models for the study area aimed to capture PM variation due to very local sources, according to stage 4 modelling in Stafoggia et al. (2017, 2019). RMSE computed on held-out monitoring stations were 8.0 $\mu g/m^3$ for PM_{10} (year 2012) and 6.6 $\mu g/m^3$ for $PM_{2.5}$ (year 2013).

To adjust for the declining trend in air pollution concentrations throughout the study period (Fig. 1, panels A and B), we conducted back-extrapolation of exposure estimates for each year of residence for every participant within the observation period. We carried out back-extrapolation using the "ratio method" as follows (see an illustration of the procedure in Fig. 1, panel C). First, we retrieved available time series of annual concentrations from air quality stations in Mantova province for NO_2 (1987–2015), total suspended particulate (1988–1998) and PM_{10} (2001–2015) (Rapporto sulla qualità dell'aria della provincia di Mantova, anno 2015. ARPA Lombardia). By assuming that PM_{10} is around 80% of total suspended particulate, we derived a single time series for PM_{10} (1988–2015). Second, we modelled the temporal trends of NO_2 and PM_{10} annual concentrations using linear (year) and quadratic polynomial regression (year + $year^2$) and used likelihood ratio tests to select the best fitting model. The quadratic and linear relationships resulted to be the best fitting for NO_2 and PM_{10}, respectively (Fig. 1, panels A and B). Third, we calculated correction factors for quadratic and linear relationships (cf_{quad} and cf_{lin}) for every year in the period (1984–2014) as the ratio of concentrations predicted

from the regression model for each year and for the reference year (i.e., the year when concentrations were available from the exposure models). For instance, for pollutants derived from the Viadana II model (reference year 2010) cf_{quad} was:

$$cf_{quad,\ year} = predicted_{year}/predicted_{2010}$$

Fourth, for each address and participant, we computed back-extrapolated air pollutant concentrations by multiplying the relevant correction factor with the modelled concentration. We decided *a priori* to use the quadratic correction factor for the pollutants that are known to have local dispersion patterns (NO_2, formaldehyde, and BC), and the linear correction factor for regional pollutants (PM_{10} and $PM_{2.5}$). Finally, we obtained the exposure variable as a time-weighted average of back-extrapolated concentrations over an 8-year period from the 3rd to the 10th year before the index date (main susceptibility window), with weights proportional to the duration of residence at each address. This susceptibility window was selected to downplay recent exposures, which are less likely to be causally related to blood cancer due to a too short latency period, but also to downplay less recent exposures, which might be more affected by the uncertainty due to the back-extrapolation to distant time points in our study.

For sensitivity analysis, we also calculated average concentrations over whichever period of residence over the 15-year period (i.e., we retained all subjects in the analysis regardless the residence duration) and over the exact 15-year period (i.e., we excluded subjects with residence duration <15 years).

We calculated distance to the closest industrial emission source in the district for each address of each participant using GIS. Then, we calculated time-weighted average distances to the closest chipboard industry and wood factory of any type. Based on these distances, we defined the following proximity indicators: the minimum distance to chipboard industries in km; a categorical indicator: no wood factories in a 2 km buffer (reference group), ≥1 small wood factory (but no chipboard industries) in a 2 km buffer, one chipboard industry in a 2 km buffer.

2.4. Potential confounders

We derived sociodemographic information (sex, age, nationality) from the health registry of the ATS Val Padana for both cases and controls. Nationality was coded as Italian vs non-Italian. We linked residential addresses to census blocks (number inhabitants: mean = 208, SD = 245), and for each census block we obtained the deprivation index, a measure of the socio-economic disadvantage at the "micro-ecological" level. The index was calculated as the sum of 5 standardized indicators of poverty derived from the 2001 Italian population census data: percentage of the population with a low education level, percentage of unemployed, percentage of houses not owned, percentage of single-parent families with children, and number of people per 100 m^2 (Caranci et al., 2010). The index was recalibrated for the Lombardia region and categorized according to its population quartiles, from highest (index = 1) to lowest socio-economic status (index = 4).

We reconstructed occupational histories using the records from the Italian social security institute (INPS). The goal was to identify participants with a possible exposure to known or suspected work-related risk factors for leukaemia. Utilizing ATECO coding, a classification system for economic activities by the Italian Institute for Statistics (ISTAT), we defined possible work-related exposure to benzene and formaldehyde based on employment for any duration in specific industries during the 15-year period. These were leather tanning, woodworking, fuel manufacturing, chemical industry, rubber or plastics industry, and furniture manufacturing (ATECO codes: 19, 20, 23, 24, 25, and 361, respectively). Furthermore, we considered individuals potentially exposed if they were employed in the packaging industry, paper industry, and hospitals (ATECO codes: 174 and 18, 21 and 22, and 8511, respectively) before 1995, a period when exposure to formaldehyde in these sectors is believed to have ceased based on authors' knowledge.

We obtained information about prior diagnoses of cancer other than leukaemia from the data available in the cancer registry.

2.5. Statistical analysis

We presented quantitative variables using mean (SD) and median (Q1-Q3), for symmetrical and asymmetrical distributions, respectively, and categorical variables using relative frequency (%). We calculated pairwise correlations between pollutants' concentrations using Pearson's r correlation coefficients.

We analysed associations between exposures to pollutants (or proximity indicators) and leukaemia incidence using conditional logistic regression models adjusted for sex, age, age^2 (included to allow for non-linearity), and deprivation index (categorized by quartiles), with index year as the stratum variable. We conducted the following sensitivity analyses: 1) excluding participants aged <18 years to focus on adult-onset leukaemia, since paediatric cases were a minority; 2) excluding non-Italian participants (nationality was not included in the models due to very small numbers of foreign participants); 3) excluding participants with a possible occupational exposure to formaldehyde and/or benzene; 4) excluding participants with cancer diagnoses prior to the index year, to rule out previous chemotherapy or radiotherapy as causes of leukaemia; 5) excluding participants living at ≥4 km to the chipboard industries, to gain a deeper understanding of the impact of emissions associated with industrial activities; 6) performing the main analysis and the analysis at point 5 using air pollution concentrations estimated by the exposure models without applying backextrapolation, to understand the impact of such procedure.

Finally, we repeated the main analysis for acute, chronic (among cases and controls aged ≥35 years), lymphoid, and myeloid leukaemia.

For air pollutants, we represented associations using odds ratios (ORs) per 1-interquartile range (IQR) difference in exposure. The IQR values were computed for the main analysis and maintained constant across all the analyses conducted, since they showed negligible variation. They were (in $\mu g/m^3$): Viadana II model NO_2 7.9, formaldehyde 1.2; ELAPSE model NO_2 13.5, $PM_{2.5}$ 7.4, BC 0.9; EPISAT model $PM_{2.5}$ 8.4, PM_{10}, 11.2. As an example, in the analysis restricted to the 4-km buffers they were: Viadana II model NO_2 8.4, formaldehyde 1.2; ELAPSE model NO_2 14.0, $PM_{2.5}$ 7.3, BC 0.9; EPISAT model $PM_{2.5}$ 9.3, PM_{10}, 11.2. An exception was the analysis without backextrapolation (point 6 above), where we utilised recalculated IQR values since these were much lower: Viadana II model NO_2 2.9, formaldehyde 0.3; ELAPSE model NO_2 3.9, $PM_{2.5}$ 2.9, BC 0.2; EPISAT model $PM_{2.5}$ 2.1, PM_{10}, 4.2.

3. Results

No discernible differences in the incidence of all cancers, hemolymphopoietic cancers, and leukaemia were identified in the Viadana district that could be plausibly attributed to the proximity of chipboard industrial facilities (Table 1 and Supplementary analysis 1).

In the case-control study, we originally identified 126 cases of leukaemia and 504 controls. Nine cases were excluded after an internal review of the cancer registry determined that they did not meet the criteria for incident leukaemia. Two cases and 6 controls were excluded since they did not reside in the Viadana district for at least 1 year during 1999–2014. Two controls were excluded because of insufficient geocoding quality. Finally, 115 cases and 496 controls were retained. The characteristics of this sample of cases and controls, the largest across the analyses conducted, are described in Table 2.

Cases of leukaemia were older compared to controls: mean ages at index date were 66.7 and 63.1 years, respectively (Table 2). Cases were less likely to have been exposed to formaldehyde or benzene in the workplace (2.6 vs 4.0%) and more likely to have a past cancer diagnosis (6.1 vs 3.6%). Both cases and controls spent an average of 13.8 years in

Table 1
Standardized incidence rates (SIR) with 95%CI for all cancers, hemolymphopoietic cancers, and leukaemia by municipality (Viadana district, 1999–2014).[a]

Municipality	All cancers		Hemolymphopoietic cancers		Leukaemia	
	n	SIR (95%CI)	n	SIR (95%CI)	n	SIR (95%CI)
Viadana	1766	0.99 (0.94; 1.03)	136	1.01 (0.85; 1.20)	41	1.01 (0.72; 1.36)
Pomponesco	155	0.86 (0.73; 1.00)	10	0.74 (0.36; 1.36)	5	1.20 (0.39; 2.81)
Bozzolo	427	0.96 (0.87; 1.05)	38	1.15 (0.81; 1.58)	14	1.39 (0.76; 2.34)
Commessaggio	141	1.03 (0.87; 1.22)	17	1.68 (0.98; 2.69)	6	1.95 (0.72; 4.25)
Dosolo	323	0.90 (0.80; 1.00)	22	0.82 (0.52; 1.25)	4	0.49 (0.13; 1.26)
Gazzuolo	317	1.08 (0.96; 1.20)	24	1.10 (0.70; 1.64)	9	1.35 (0.62; 2.57)
Marcaria	751	0.98 (0.91; 1.05)	48	0.84 (0.62; 1.11)	14	0.80 (0.44; 1.35)
Rivarolo Mantovano	342	1.15 (1.03; 1.28)	22	0.99 (0.62; 1.49)	7	1.02 (0.41; 2.10)
Sabbioneta	439	0.90 (0.81; 0.98)	33	0.91 (0.63; 1.28)	15	1.36 (0.76; 2.25)
San Martino dell'Argine	213	0.99 (0.86; 1.13)	16	1.02 (0.58; 1.65)	2	0.42 (0.05; 1.50)

[a] Indirect standardization. Reference population: province of Mantova (1999–2014). The chipboard industrial facilities are located in Viadana and Pomponesco.

Table 2
Characteristics of cases and controls (n = 611).

	Cases (n = 115)	Control (n = 496)
Female sex, n (%)	66 (57.4%)	283 (57.1)
Age in years, mean (SD)	66.7 (20.4)	63.1 (17.9)
Foreign nationality, n (%)	3 (2.6%)	19 (3.8%)
Deprivation index, median (Q1-Q3)	−0.6 (−0.9; −0.2)	−0.4 (−0.9; 0.1)
Deprivation index by quartiles, n (%)	25 (22.3)	124 (25.2)
1 (least deprived)	38 (33.9)	110 (22.4)
2	28 (25.0)	127 (25.8)
3	21 (18.8)	131 (26.6)
4 (most deprived)	3	4
Missing values		
Possible occupational exposure to formaldehyde or benzene, n (%)	3 (2.6)	20 (4.0)
Prior cancer diagnosis, n (%)	7 (6.1)	18 (3.6)
Residential period in years, mean (SD)	13.8 (3.3)	13.8 (3.3)
Residential period of 15 years, n (%)	99 (86.1)	425 (85.7)
Changes of residential address within the district area, n (%) none	95 (82.6)	381 (76.8)
one	17 (14.8)	92 (18.6)
two or more	3 (2.6)	23 (4.6)

the Viadana district, and 86% spent the whole 15-year period considered for exposure assignment in the district. During 1999–2014, 17.4% of cases and 23.2% of controls moved their residential address inside the district, and therefore had 2 or more addresses considered for exposure assignment.

Correlations between exposures to air pollutants estimated at residential addresses of the 611 participants prior to the back-extrapolation procedure ranged from low (Pearson's r = 0.17 for $PM_{2.5}$ EPISAT vs NO_2 Viadana II) to high (r = 0.78 NO_2 ELAPSE vs BC ELAPSE) (Supplementary Table S1). Correlations for pollutants estimated from the same model were higher compared to correlations for the same pollutant estimated using different models (e.g., NO_2 Viadana II vs ELAPSE r = 0.34). The back-extrapolation procedure shifted correlations towards high values (Supplementary Table S2).

The main analysis considered the 113 cases and 483 controls living in the district for the full 8-year period from the 3rd to the 10th year before the index date. Average exposures to air pollutants were highly correlated, as indicated by Pearson's correlation coefficients between 0.72 (PM_{10} EPISAT vs NO_2 Viadana II) and 0.95 (NO_2 ELAPSE vs BC ELAPSE) (Table 3).

Average exposures to air pollutants and distances were similar between cases and controls (Table 4). Results for the main analysis of association, adjusted for sex, age, age^2, and census-block deprivation index, are illustrated in Fig. 2 (panel A). ORs for exposures to air pollutants ranged from 0.51 (95%CI 0.17–1.56) for BC to 1.46 (95%CI 0.65–3.25) for formaldehyde (per IQR-difference in exposure). Distance to chipboard industries was not associated with leukaemia incidence (OR 1.00, 95%CI 0.97–1.03 per 1 km increase). The odds of leukaemia was estimated to be 17% higher among people living at ≤2 km from the chipboard industries, compared to having no factories in a 2 km radius around home, but the estimate was characterized by wide uncertainty (OR 1.17, 95%CI 0.69–1.96).

The analysis considering the individuals who resided in the district during the full 15-year period before the index date (Fig. 2, panel B), provided association estimates consistent with the main analysis, except for BC exposure whose association shifted toward a protective effect (OR 0.29, 95%CI 0.08–0.98). When including all the individuals who lived at least one year in the district (Fig. 2, panel C), the results were similar to the main analysis (panel A), except for the association for ELAPSE pollutants, which shifted to the null, and for formaldehyde, which shifted away from the null (OR 1.60, 95%CI 0.84–3.02).

Table 3
Pearson's r coefficients for the correlation between time-weighted average back-extrapolated exposures to air pollutants of 596 participants included in the main analysis (susceptibility window 3rd to 10th year before the index date).*

		Viadana II (2010)		ELAPSE (2010)			EPISAT	
		NO_2	CH_2O	NO_2	$PM_{2.5}$	BC	$PM_{2.5}$ (2013)	PM_{10} (2012)
Viadana II (2010)	NO_2	1						
	CH_2O	0.84	1					
ELAPSE (2010)	NO_2	0.82	0.88	1				
	$PM_{2.5}$	0.85	0.89	0.93	1			
	BC	0.85	0.92	0.95	0.94	1		
EPISAT	$PM_{2.5}$ (2013)	0.77	0.86	0.86	0.86	0.87	1	
	PM_{10} (2012)	0.72	0.78	0.79	0.78	0.80	0.88	1

* CH2O, formaldehyde.

Table 4
Distribution of time-weighted average back-extrapolated exposures to air pollutants and distance to chipboard industries for participants included in the main analysis (susceptibility window 3rd to 10th year before the index date).*

		Cases	Controls	
		n = 113 Median (IQR)	n = 483 Median (IQR)	p-value
Viadana II	NO_2 (μg/m^3)	23.2 (8.1)	23.0 (7.8)	0.757
	CH_2O (μg/m^3)	3.6 (1.3)	3.6 (1.2)	0.720
ELAPSE	NO_2 (μg/m^3)	39.2 (14.9)	38.6 (13.4)	0.187
	$PM_{2.5}$ (μg/m^3)	33.9 (6.8)	33.6 (7.5)	0.434
	BC (μg/m^3)	2.8 (0.9)	2.8 (1.0)	0.095
EPISAT	$PM_{2.5}$ (μg/m^3)	38.5 (8.3)	38.4 (8.5)	0.930
	PM_{10} (μg/m^3)	53.5 (9.6)	53.0 (11.5)	0.360
Distance to chipboard industries (km)		8.8 (15.1)	9.3 (14.7)	0.513

* CH2O, formaldehyde.

When excluding children, foreign participants, participants with a possible occupational exposure to formaldehyde or benzene, or those with a previous diagnosis of cancer, the results remained consistent with the main analysis (Table 5). When restricting the main analysis to the participants living in the 4-km buffers around the chipboard industries (38 cases and 157 controls in the complete-case analysis), all associations shifted towards non-significant protective estimates (OR <1), with the exception of formaldehyde, which shifted away from the null towards an indication of stronger association, despite wide statistical uncertainty (OR 2.78, 95%CI 0.48–16.13). Even when using non-backextrapolated estimates of air pollutant exposure, we observed higher association estimates for formaldehyde, albeit these were attenuated (Table S3).

Fig. 3 reports the results from the analyses of leukaemia risk by clinical and histological subtype for the susceptibility window considered in the main analysis (3rd to 10th year before the index year). In the case of acute leukaemia (panel A), the association estimated for formaldehyde shifted away from the null, towards an indication of greater risk (OR 2.07, 95%CI 0.70–6.12), as did the association estimated for participants living close to the chipboard industries (OR 1.69, 95%CI 0.84–3.39). A similar pattern of associations was observed for myeloid leukaemia (OR 1.79, 95%CI 0.64–5.01 for formaldehyde and OR 1.82, 95%CI 0.95–3.47 for proximity to the chipboard industries, panel D). Chronic and lymphoid leukaemia did not show any pattern of association with the exposure indicators (panels B and C, respectively).

4. Discussion

Using a nested case-control design, we investigated the relationship between long-term residential exposure to outdoor air pollution and incidence of leukaemia in the population living in a chipboard industrial area in Northern Italy. We used incidence data from an accredited cancer registry and reconstructed residential histories of cases and controls over 15 years through consultation of municipal registries.

We estimated air pollutant exposures using three available models. The EPISAT and ELAPSE models were developed from comprehensive input data on spatial and spatiotemporal predictors using well validated LUR approaches; however, they did not incorporate local air pollution data and the predictors used for model training may not be optimal for capturing variability in industrial pollution. On the other hand, the Viadana II model relied on extensive data from air quality monitoring campaigns in the district but generated low-resolution maps through interpolation, which could inadequately represent local emission sources such as streets. As previously documented and discussed (Marcon et al., 2021), we could not postulate *a priori* which of the modelled pollutants was the primary contributor to leukaemia risk. Moreover, none of the exposure assessment method can be deemed a "gold standard" *a priori*; each of the indicators utilised in the analysis would capture some of the variability in the exposure of study participants to the complex air pollution mixture, as also implied by moderate correlations across pollutants.

We observed no difference in leukaemia incidence between municipalities with operating chipboard facilities and those without, nor we found evidence of association of particulate matter, BC, and NO_2 exposures with the risk of leukaemia. However, we observed an indication of risk for formaldehyde exposure, which was consistent across most of the sensitivity analyses. Nonetheless, we acknowledge that the analyses employing different susceptibility windows gave conflicting results and that our findings were likely affected by random fluctuations due to the small number of cases. Our study suggests that more data are needed to elucidate the possible link between outdoor formaldehyde exposure and the development of lymphohaematopoietic pathologies in the general population.

The peculiar orographic conditions of the Po Basin, restricting the dispersion of air pollutants, coupled with extensive urbanization and industrialization in the studied area, lead to residents being exposed to elevated air pollution concentrations. In the area, PM_{10}, $PM_{2.5}$, and NO_2 concentrations exceed the limit values established by European regulations and WHO guidelines for a significant portion of the year. Unlike the other examined pollutants, there are no regulatory limits for the atmospheric concentration of formaldehyde and BC. Consequently, assessing whether these exposures were low or high in our study is more

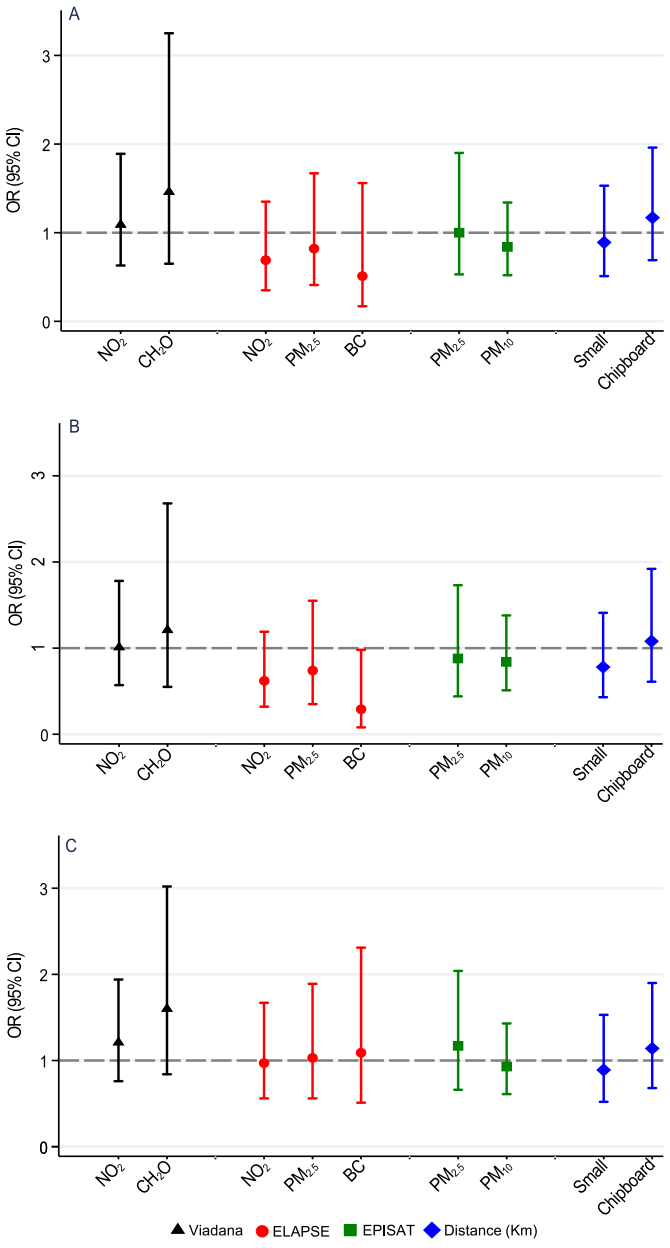

Fig. 2. Estimated associations between exposure indicators and incidence of leukaemia.*

* CH_2O, formaldehyde. Adjusted for sex, age, age^2, census-block deprivation index (by quartiles), and conditioned on the index year. ORs for air pollutant' exposures are per 1-IQR difference. Panel A: susceptibility window 3rd to 10th years before the index date (main analysis, overall n = 589, cases/controls n = 110/479; panel B: 15-year susceptibility window before the index date (overall n = 517, cases/controls n = 96/421); panel C: at least 1 year in the district (overall n = 604, cases/controls n = 112/492)

challenging. This is also due to the scarcity of studies having measured formaldehyde outdoors, as we discussed elsewhere (Marcon et al., 2021). In fact, most studies focused on indoor exposure, especially in occupational settings where formaldehyde levels tend to be elevated (Liu et al., 2019). Because of the near absence of studies on outdoor exposure, there was no research encompassing populations across all age groups prior to the present study, including individuals who are frail and potentially more vulnerable to the effects of prolonged formaldehyde exposure. Hence, we emphasize a strength of our study, which is the first on the association between outdoor formaldehyde exposure and incidence of leukaemia in the general population to the best of our knowledge.

Several studies have reported that traffic-related exposure to air pollution, especially benzene, $PM_{2.5}$, BC, NO_2, and ammonium (NH_4), is associated with an increased risk of developing leukaemia in both children and adults (Boothe et al., 2014; Taj et al., 2021; Zhong et al., 2023). While the precise mechanisms through which traffic pollution contributes to the development of leukaemia are not fully understood, several have been proposed, including the induction of DNA damage, alterations in gene expression, modulation of the immune system, and disruption of normal haematopoiesis (Bispo et al., 2020). Notably, not all the literature is coherent regarding the impact of outdoor air pollution on leukaemia (Raaschou-Nielsen et al., 2011). Probably due to low statistical power, our study also failed to detect an association of $PM_{2.5}$, PM_{10}, BC, and NO_2 with leukaemia risk. In fact, there were only 113 cases of leukaemia in the main analysis and exposure contrasts were small compared to multicentre studies. Published studies investigating the impact of outdoor air pollution on leukaemia involved larger areas and populations and longer times of observation, with a number of cases ranging between ~2000 and 15,000 (Puett et al., 2020; Raaschou-Nielsen et al., 2016).

Formaldehyde is currently classified as "carcinogenic to humans" (Group 1) by the International Agency for Research on Cancer, although to date evidence is considered to be strong but not sufficient to claim its causal link with human leukaemia (Bachand et al., 2010; Goldstein, 2011; IARC, 2006; Protano et al., 2021). A positive association between formaldehyde exposure in the workplace and leukaemia has been observed in several studies (Beane Freeman et al., 2009; Hauptmann et al., 2003, 2009; Zhang et al., 2009, 2010). The mechanisms underlying the potential carcinogenic effects of formaldehyde on human health are not completely understood. Formaldehyde can bind to DNA, inducing DNA-DNA as well as DNA-protein crosslinks (Allegra et al., 2019). Formaldehyde exposure has been shown to alter immune function in animals, which may contribute to the development of leukaemia (Golalipour et al., 2008). Epigenome-wide association studies have also linked occupational exposures with changes in DNA methylation (Phillips et al., 2022). Notably, recent literature appears to challenge the hypothesis that occupational exposure to formaldehyde may have a leukaemogenic effect on humans (Allegra et al., 2019; Gentry et al., 2020), at least when concentrations fall within the limits set by current regulations (Tupper and Garg, 2023). This is why we highlight that studies on outdoor exposures considering large and heterogenous populations are warranted.

The latency period for leukaemias is not clear. For acute myeloid leukaemia, it is usually being given between 2 and 15 years (Goldstein, 2011). In the main analysis, we considered exposures occurring between the 3rd and the 10th year before the index year. In a sensitivity analysis we documented similar associations when considering any year of exposure during the 15 years prior to the index date. This scenario has the advantage of increasing sample size, since there is no need to exclude participants living for ≤15 years in the district. However, we obtained conflicting results when considering the subset of participants living for the whole 15-year period in the district, since a paradoxical protective association emerged for BC. We can speculate that this association may have occurred by chance (potentially influenced by a further restriction in sample size) or to bias induced by the back-extrapolation procedure (based on unverifiable assumptions regarding past trends in BC concentrations).

Foreigners were a minority among study participants, and exclusion of these did not materially affect the association estimates. Results were also consistent when excluding the participants with suspected occupational exposures to benzene and formaldehyde, and those with a prior diagnosis of cancer, an indicator of a possible treatment with leukaemogenic cancer therapies (Morton et al., 2019). Interestingly, our study found stronger associations in the 4-km buffers around the chipboard industrial facilities for formaldehyde, but not for the other examined pollutants. The 4-km buffers are a smaller district area where unmeasured confounding and misclassification of exposures related to industrial emissions are expected to be reduced. Fig. S1 compares the results

Table 5
Estimated associations between exposure indicators and incidence of leukaemia: sensitivity analyses.

		Excluding subjects aged <18 years	Non-Italian participants excluded	Participants with occupational exposures to formaldehyde or benzene excluded	Participants with prior cancer diagnoses excluded	Participants living at ≥4 km from the chipboard industries excluded
	N. participants (cases/controls)	580 (109/471)	579 (111/468)	573 (110/463)	571 (106/465)	207 (42/165)
	N. participants (cases/controls, complete-case analysis)	573 (106/467)	572 (108/464)	566 (107/459)	564 (103/461)	195 (38/157)
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Viadana II	NO_2 (7.9 μg/m^3)	1.02 (0.58; 1.80)	1.08 (0.62; 1.87)	1.13 (0.65; 1.97)	1.11 (0.64; 1.92)	0.99 (0.3; 3.21)
	Formaldehyde (1.2 μg/m^3)	1.46 (0.64; 3.29)	1.39 (0.62; 3.14)	1.51 (0.67; 3.41)	1.33 (0.59; 3.00)	2.78 (0.48; 16.13)
ELAPSE	NO_2 (13.5 μg/m^3)	0.63 (0.32; 1.24)	0.64 (0.32; 1.26)	0.72 (0.36; 1.41)	0.62 (0.31; 1.22)	0.31 (0.07; 1.49)
	$PM_{2.5}$ (7.4 μg/m^3)	0.74 (0.36; 1.52)	0.78 (0.38; 1.60)	0.90 (0.44; 1.84)	0.75 (0.36; 1.54)	0.43 (0.05; 3.63)
	BC (0.9 μg/m^3)	0.43 (0.14; 1.38)	0.42 (0.13; 1.35)	0.55 (0.18; 1.70)	0.42 (0.14; 1.31)	0.54 (0.04; 7.48)
EPISAT	$PM_{2.5}$ (8.4 μg/m^3)	0.96 (0.50; 1.87)	0.94 (0.50; 1.80)	0.95 (0.49; 1.81)	0.84 (0.43; 1.61)	0.69 (0.17; 2.79)
	PM_{10} (11.2 μg/m^3)	0.79 (0.49; 1.29)	0.82 (0.51; 1.32)	0.80 (0.49; 1.29)	0.77 (0.47; 1.24)	0.45 (0.17; 1.22)
Distance	≥2 km any factory	1	1	1	1	–
	<2 km small factories	0.86 (0.49; 1.51)	0.89 (0.51; 1.55)	0.92 (0.53; 1.62)	0.96 (0.55; 1.68)	–
	<2 km chipboard industries	1.16 (0.68; 1.97)	1.17 (0.69; 1.97)	1.28 (0.75; 2.17)	1.18 (0.69; 2.03)	–
Distance to chipboard industries (km)		1.00 (0.97; 1.03)	0.99 (0.96; 1.03)	0.99 (0.96; 1.02)	0.99 (0.96; 1.03)	0.78 (0.49; 1.25)

[a]Adjusted for sex, age, age^2, census-block deprivation index (by quartiles), and conditioned on the index year. ORs for air pollutant' exposures are per 1-IQR difference.

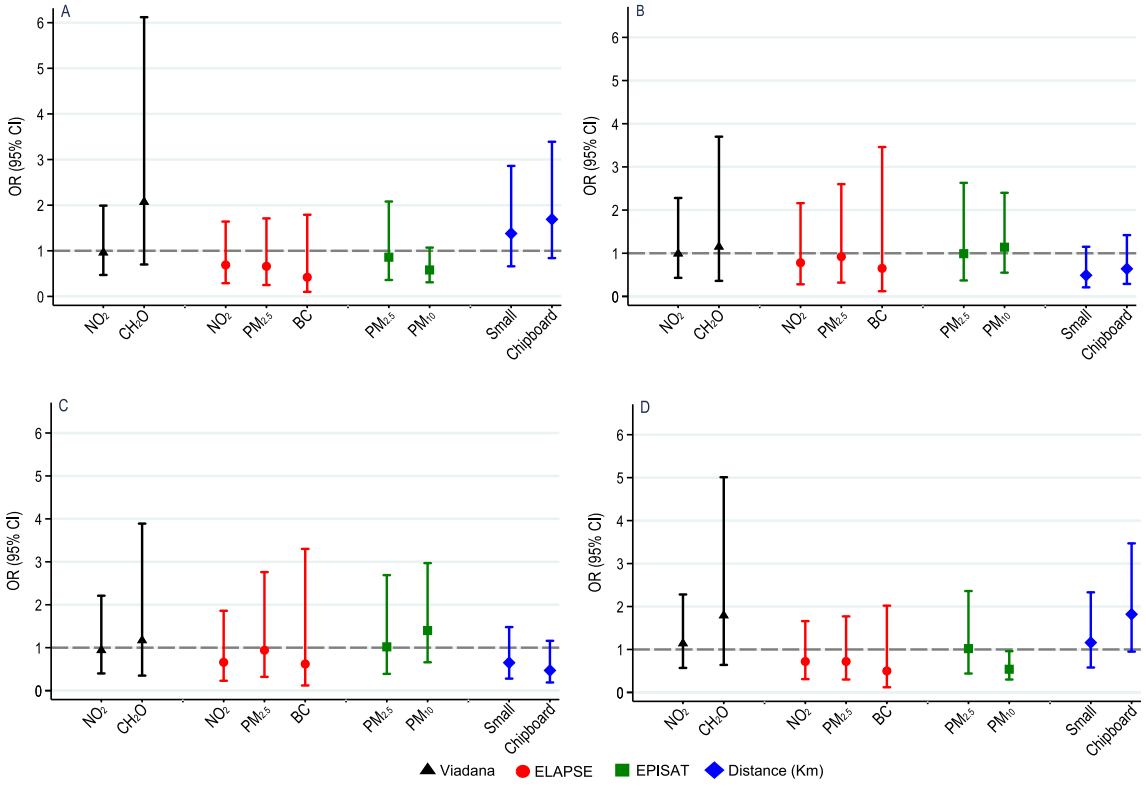

Fig. 3. Estimated associations between exposure indicators and incidence of leukaemia subtypes.*
* Susceptibility window 3rd to 10th year before the index date. CH_2O, formaldehyde. Adjusted for sex, age, age^2, census-block deprivation index (by quartiles), and conditioned on the index year. ORs for air pollutant' exposures are per 1-IQR difference. Panel A: acute leukaemia (overall n = 526, cases/controls n = 55/471); panel B: chronic leukaemia, among participants ≥35 years of age (overall n = 477, cases/controls n = 48/429); panel C: lymphoid leukaemia (overall n = 472, cases/controls n = 44/428); panel D: myeloid leukaemia (overall n = 541, cases/controls n = 62/479)

from the main and sensitivity analysis in the 4-km buffers using p-value functions (Infanger and Schmidt-Trucksäss, 2019). This analysis suggests that, in the 4-km buffers, there was the same level of statistical confidence for the null hypothesis of no formaldehyde effect and for an 8-fold increase in the odds of leukaemia, strengthening the plausibility that formaldehyde emissions related to the industrial activities may indeed play a role in increasing the risk of leukaemia in the district.

Among the considered disease subtypes, acute and myeloid leukaemias showed an association trend with formaldehyde exposure, as well as with proximity to chipboard industries. These results are consistent with numerous studies that found such lymphohematopoietic cancers to be more likely to be associated not only with exposure to formaldehyde (Meyers et al., 2013; Zhang et al., 2009, 2010), but also with exposure to traffic-related air pollution (Raaschou-Nielsen et al., 2016).

One strength of our study is that we were able to retrieve annual residential addresses of participants from civil registries. One limitation is that we assigned residential exposures retrospectively based on a limited data set on historical trends for some air pollutants (but not formaldehyde), under assumptions that cannot be validated due to the lack of data. The analysis using non-backextrapolated exposures was consistent with the main analysis, although associations for formaldehyde were attenuated. Moreover, we had no data on indoor exposures and time-activity patterns. Data on some confounders were not available. We adjusted for a micro-area indicator of socioeconomic status based on census data, since individual data was not available. We also lacked data on smoking habits. Nonetheless, using data from the Viadana I survey, we found that exposures to NO_2 and formaldehyde were not associated with smoking habits in the adult population living in the district (Supplementary analysis 2). This indirectly indicates that active smoking is unlikely to have acted as a confounder in our study, although we acknowledge that this evidence comes from a younger population overrepresenting parents.

5. Conclusions

Formaldehyde is typically considered an indoor air toxic and is not routinely monitored outdoors (Liu et al., 2019). The Viadana study is one of the few that raised attention towards the potential health risks of outdoor formaldehyde exposure in the general population. We found an indication that higher long-term exposure to outdoor formaldehyde may be associated with a higher incidence of leukaemia in the Viadana district, suggesting a possible role for emissions related to industrial activities. However, the number of cases was limited due to the small size of the target population, and exposure contrasts were limited, which made association estimates uncertain. These results are widely consistent with large part of the literature, albeit not unanimous on the subject, including the higher risk observed for acute and myeloid leukaemias, and with previous evidence, in the district, of a link between formaldehyde exposure and genotoxicity biomarkers, a possible mediator of increased cancer risk (Marcon et al., 2014). Further research is warranted, especially in larger populations, incorporating data on other risk factors such as lifestyles, as well as investigations to gain a more comprehensive understanding of the possible underlying mechanisms.

Ethical approval

The Viadana III study has been approved by the Comitato Etico Val Padana (Prot. n. 4813, February 12, 2019).

Funding

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Consent to participate

The need for a consent to participate was waived for individuals identified through electronic health records since data were anonymized.

CRediT authorship contribution statement

Francesca Locatelli: Writing – review & editing, Visualization, Methodology, Formal analysis, Data curation. **Luigi Martinelli:** Writing – review & editing, Writing – original draft, Investigation. **Pierpaolo Marchetti:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Gulser Caliskan:** Writing – review & editing, Investigation. **Chiara Badaloni:** Writing – review & editing, Resources, Methodology, Data curation. **Nicola Caranci:** Writing – review & editing, Resources, Data curation. **Kees de Hoogh:** Writing – review & editing, Resources, Data curation. **Luciana Gatti:** Writing – review & editing, Resources. **Paolo Giorgi Rossi:** Writing – review & editing, Methodology. **Linda Guarda:** Writing – review & editing, Resources, Data curation. **Marta Ottone:** Writing – review & editing. **Silvia Panunzi:** Writing – review & editing, Formal analysis, Data curation. **Massimo Stafoggia:** Writing – review & editing, Resources, Data curation. **Caterina Silocchi:** Writing – review & editing, Resources. **Paolo Ricci:** Writing – review & editing, Resources, Methodology, Investigation, Funding acquisition, Conceptualization. **Alessandro Marcon:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT 3.5 in order to improve language and readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Alessandro Marcon reports financial support was provided by ATS della Val Padana. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2024.119120.

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