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Environmental Pollution Effects on Mortality in an Industrial and a Non-industrial Municipality, in Voiotia Prefecture, Greece

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Abstract

In the Oinofita region, there was strong evidence of air pollution and hexavalent chromium (Cr(VI))-contaminated drinking water due to the increased number of industries, in contrast to the closely-located region of Arachova, which served as a control. To examine the health effects of environmental pollution, we performed an ecological study to compare the all-cause and cause-specific mortality. We considered the registered citizens of both study areas during an 11-year period (1999-2009) and we used the direct method of standardization to calculate the age, gender and period standardized rates (ASRs) and the standardized rate ratios (SRRs), using the greater Prefecture of Voiotia as the standard population. Statistically significantly higher rates of all-cause mortality (SRR = 1.22, 95% confidence intervals (CI) 1.1-1.4), cardiovascular (SRR = 1.36, 95% CI 1.1-1.7) and cerebrovascular diseases (SRR = 2.93, 95% CI 1.8-4.8) were identified for Oinofita compared to Arachova. Furthermore, suggestive results were found for cardiopulmonary diseases among males (SRR = 1.52, 95% CI 1.0-2.4) and leukaemias (SRR = 4.65, 95% CI 0.9-25.3). Elevated SRRs, not statistically significant though, were also observed for respiratory diseases, all cancers and specific cancer sites (lip, oral cavity and pharynx, liver, stomach, pancreas, lung, prostate, colon and kidney and other genitourinary organs among females). Increased mortality rates in the Oinofita region support the hypothesis of adverse health effects association with air pollution and Cr(VI)-contaminated drinking water. Further studies are needed to determine if this association is causal and to establish preventive guidelines and public health recommendations.

Keywords: contaminated sites, hexavalent chromium, industrial pollution, industrial waste, long-term exposure, mortality

1. Introduction

It is generally recognized that human mortality increases in industrialized areas due to the hazardous waste released into soil, groundwater and air (Mudu, Terracini, & Martuzzi, 2014). This study was focused on the municipality of Oinofita, one of the rare areas worldwide, where population has been exposed to hexavalent chromium Cr(VI) through drinking water due to dense industrial activity (Linos et al., 2011). In addition, the levels of air pollution have been increased, a fact that has recently given rise to concerns for adverse effects on public health and especially children (Papadimitriou, Riza, Pililitsis, Petralias, & Linos, 2012). To investigate the potential health effects of such an environmental pollution, we decided to compare the cause-specific mortality rates of the municipality of Oinofita to those of the municipality of Arachova, an environmentally clean area in the same prefecture and with similar demographic and socioeconomic characteristics with Oinofita.

Several epidemiological studies examined the relationship between residential proximity either to industrial plants or hazardous waste sites and all-cause mortality, cardiovascular diseases, respiratory diseases and specific cancer sites such as lung and leukaemias. It was shown that populations residing in industrialized areas had significantly increased mortality from lung cancer compared to populations residing in non-industrialized areas although their similar socioeconomic characteristics (Biggeri, Barbone, Lagazio, Bovenzi, & Stanta, 1996; Edwards et al., 2006;

Fano et al., 2006; Fantini et al., 2012; Parodi et al., 2004; Pless-Mulloli et al., 1998). Also, excesses risks of mortality due to leukaemias in populations residing in areas with metal production and processing installations have been reported by Garcia-Perez et al. (2010). More recently, a follow-up study by Pirastu et al. (2013) evaluated the mortality of individuals residing in districts near various industrial sources to identify an excess risk for all causes of death, all cancers, lung cancer, cardiovascular and respiratory diseases. Same health risk had been identified by the ecological study of Ruiz-Rudolph et al. (2016) that focused on communes near large industrial facilities. In addition, Parodi et al. (2015) conducted a population-based case-control study to suggest a possible etiological role of residential air pollution from industrial sites on the risk of developing leukaemias.

Although numerous studies have revealed the health consequences of the residential proximity to air polluted industries, little is yet known regarding the adverse effects on ingestion of Cr(VI)-contaminated drinking water. Furthermore, although Cr(VI) has been long recognized as a human carcinogen through inhalation (International Agency for Research on Cancer [IARC], 1990), there is still significant debate on the carcinogenicity of Cr(VI) when it is orally ingested. Cr(VI) at the cellular level is a highly active carcinogen (Costa, 1997; Proctor et al., 2002). It is not clear, though, whether Cr(VI) ingested through the oral route, converts to trivalent chromium Cr(III) (which does not easily cross the cell membrane) before entering a living cell (Costa, 2003). On the other hand, the U.S. National Toxicology Program (NTP, 2008) reported that rats and mice exposed to Cr(VI)-contaminated drinking water developed gastrointestinal abnormalities, including oral and intestinal tumors. In addition, toxicokinetic and genotoxicity studies in animals indicated that a portion of orally ingested Cr(VI) evades reduction in the stomach, enters into multiple tissues, causes DNA damage and appears to pose a carcinogenic risk (Chiu et al., 2010; Sedman et al., 2006; Sun, Brocato & Costa, 2015). In view of the NTP studies, Stern (2010) identified Cr(VI) as 'likely to be carcinogen to humans' when it is orally ingested with an estimate of the cancer potency equal to 0.5 $(mg/kg/day)^{-1}$.

Regarding human populations, Zhang and Li (1987) analyzed the effects of oral exposure to Cr(VI) on cancer mortality rates to note elevated deaths from total cancer, lung cancer and stomach cancer. These data were re-analyzed and re-evaluated by Beaumont et al. (2008) to support the conclusions of the original study. However, when Kerger, Butler, Paunstenbach, Zhang and Li (2009) compared the Cr(VI)-exposed population with demographically similar populations, concluded that there was no significant risk of human mortality from all cancers attributed to Cr(VI) exposure. More recently, Linos et al. (2011) performed an ecological study focusing on the municipality of Oinofita, where residents were exposed to Cr(VI)-contaminated drinking water. Their results indicated that there was a statistically significant increase in mortality from primary liver cancer, lung cancer and cancer of the kidney and other genitourinary organs among women, in Oinofita compared to the population of the surrounding prefecture. Furthermore, Karagiannis et al. (2015) performed a morbidity cohort study in the municipality of Oinofita to identify an increasing trend for malignant and non-malignant urologic diseases in the population with long-term exposure to Cr(VI) via the oral route.

In consideration of the relevant literature, this study evaluated the potential health effects of industrial pollution, by performing mortality comparisons between an environmentally polluted and an unpolluted study area in Greece. More specifically, we were interested in examining whether there was an increased mortality from all-cause, specific cancer sites, respiratory and cardiovascular diseases due to the residential proximity to air polluted industries. Furthermore, we wanted to examine whether there was an increased gastrointestinal and urologic cancer mortality, because of the oral exposure to elevated levels of Cr(VI).

2. Material and Methods

2.1 Study Area

Our interest was these areas to have similar demographic and socioeconomic characteristics and different environmental profiles and exposure risks. The first study area (Figure 1) was the municipality of Oinofita which had a dense industrial activity and high levels of environmental pollution, e.g. the levels of particulate matter (PM_{10}) for the year 2008 exceeded the national safety levels 56 times, with a maximum observed value of 98 $\mu g/m^3$ (Ministry of Environment and Energy, 2009). Municipality of Oinofita served as the study area with the industrial profile. The second study area was chosen from the same prefecture (Voiotia Prefecture) in order to have similar demographic and socioeconomic characteristics, but different environmental profiles and exposure risks. We chose the municipality of Arachova in Voiotia Prefecture (Figure 1), which was a popular touristic winter resort in Greece, built on the southern slopes of Mount Parnassus at an altitude of 968 meters and situated 170 kilometers north of the capital of Athens. Given the complete lack of industrial activities in the municipality of Arachova, we considered that this study area had a non-industrial environmental profile. The next paragraphs describe the main key features of the environmental profile of the municipality of Oinofita, based on its location and contemporary history.

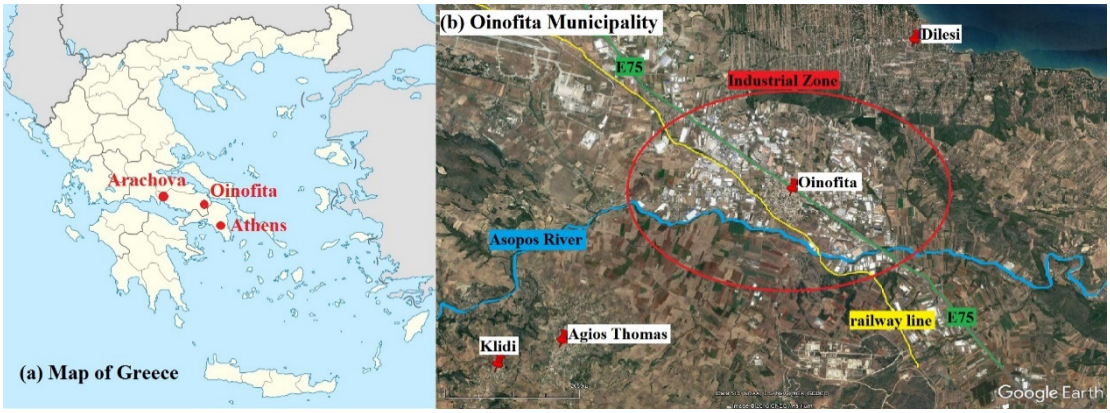


Figure 1. Map showing the (a) Physical locations of the considered study-areas of Oinofita and Arachova municipalities in Voiotia Prefecture, Greece and (b) Industrial zone of Oinofita region

The municipality of Oinofita was located 50 kilometers north from the capital of Athens and it was comprised of four villages (Klidi, Agios Thomas, Oinofita and Dilesi). National road, national railway line and Asopos River were running through the Oinofita region (Figure 1). Notably, although Asopos River was the main source of drinking water for the municipality of Oinofita, in 1969 the river started to be contaminated because a ministerial decision permitted industries to deposit processed waste into the river (registered as Γ1/1806/7.3.1969). In 1979 another presidential decree allowed the disposal of processed liquid waste into the river with only requirement the control of chromium-total concentrations (registered as No.19649/1979). With respect to these two permissions and in view of the short distance between the municipality of Oinofita and the capital of Athens, where industrial establishments have been restricted since 1984 (presidential decree No.33/A/21-3-84), the first key feature is that the last decades the industrial zone of the area has expanded, releasing even more hazardous waste into soil, groundwater and air. The National Technical University of Athens (Loizidou, 1998) reported that in 1998, 281 industries were operating in the area producing 9.500 m^3/day total waste, where 57%, 34% and 6% were coming from textile, food and metalworking, respectively.

The Technical Chamber of Greece (2009) reported that in 2009 more than 700 industries were operating in the Oinofita region, where 500 and 50 establishments were generating liquid waste and toxic substances, respectively. In 2010 according to the Registry of Industries of Oinofita's Municipal Office, various types of manufacturing activities were hosted in the industrial zone of the municipality such as metal, steel, dye and textile processing, production of detergents, cosmetics, fertilizers, pesticides, pharmaceuticals, pulp, paper, plastics and other chemicals, food, fodders, concrete, tanneries, foundries. Moreover, there was an extended agricultural activity throughout the region which coexisted with the dense industrial deployment.

The second key feature is that the industrial activities in the municipality of Oinofita, not only polluted the soil, groundwater and air but there is certain evidence for pollution in drinking water too, and particularly for Cr(VI)-contamination. Such evidence has been collected since 2007 through measurements in wells and public drinking water supply, made by three independent sources: the Institute of Geology and Mineral Exploration (Giannoulopoulos, 2008), the Economic Geology and Geochemistry Department of the University of Athens (Vasilatos, Megremi, Economou-Eliopoulos & Mitsis, 2008) and Oinofita's Municipal Office (Linos et al., 2011). During 2007-2008, all independent sources detected high Cr(VI) concentrations, ranged from 8.3 to 156 μg/l (Linos et al., 2011). Also, in early 2009 the main drinking water supply was diverted from Asopos River to Mornos Lake (reservoir), which is part of the drinking water supply network of Athens. More recent measurements made between June 2009-June 2010 by the Oinofita's Municipal Office recorded relatively lower levels of Cr(VI) (<0.01-1.53 μg/l), proving that the drinking water in the area was Cr(VI)-contaminated due to the industrial pollution of Asopos River.

To date, no regulation regarding the Cr(VI) concentration in drinking water has been set by any international body. Yet, the California Environmental Protection Agency proposed the Public Health Goal of 0.02 μg of Cr(VI) per liter of drinking water (Office of Environmental Health Hazard Assessment [OEHHA], 2011). Such threshold was relied on the study of Linos et al. (2011), which supported the hypothesis of Cr(VI) carcinogenicity via the oral ingestion pathway of exposure.

It should be finally noted that in contrast to Oinofita, drinking water in the municipality of Arachova was considered as particularly clean because it was derived from natural sources, which gushed straight out of the top of the Mount Parnassus.

2.2 Study Population

We examined the validity of all the available data among records for registered citizens of the municipality of Oinofita provided by the Municipal Office. Particularly, we collected all available records (13 582 in total) of the registered citizens in the municipality within the period 1895-2010. Since the Local Vital Statistics Registry maintained sufficient data of death certificates from 1/1/1999, we chose to survey records within the follow up period 01/01/1999-31/12/2009. From the total records gathered, 3989 and 2679 records were excluded due to duplications and redundant (e.g. not officially registered) cases respectively, leaving us a total of 6914 registered citizens.

The start-date of the follow up period for each person was set as either a) 1/1/1999 for individuals registered in the municipality before 1999 or b) the registration date in the municipality's records for individuals registered after 1999. The end-date of the follow up period for each person was set as either a) the date of death, or the date of deletion from the records due to moving to other municipality before 2009 or b) the date 31/12/2009, which was the default end-date of our study. The date of death for each individual was cross-checked with the corresponding death certificates provided by the Local Vital Statistics Registry within the follow up period. From our cross-checking we identified that during the follow up period 495 registered persons died from the total of 6914 records available.

Similarly, we examined the validity of all the available data among records for registered citizens of the municipality of Arachova. In this case, the original file included a total of 13 867 records, where 9403 records were redundant and excluded. The resulted cohort identified 4464 registered citizens, of which 399 persons died during the follow up period.

Finally, we generated a joint database to include all the authenticated information for both the municipalities of Oinofita and Arachova. In our joint database we encoded all deaths for both areas using the classification system of the International Classification of Diseases, 9th Revision (ICD-9, 2009) based on the underlying cause reported in death certificates and the same physician.

2.3 Statistical Analysis

We compared the risk of death between citizens of the municipalities of Oinofita and Arachova, over the 11-year follow up period using the direct method of standardization (Boyle & Parkin, 1991). Specifically, we accounted for the total number of registered citizens to compute the all-cause and cause-specific age-standardized rates (ASRs) and the standardized rate ratios (SRRs), stratified by age (five-year categories), gender and calendar year (one-year categories). SRR was defined as the quotient of the ASR of the municipality of Oinofita divided by the ASR of the municipality of Arachova per 10^5 population (Boyle & Parkin, 1991), i.e.,

$$SRR=10^5 x(ASR_{Oinofita}/ASR_{Arachova}) \quad (1)$$

Each ASR in (1) was expressed as the quotient of the aggregate age-adjusted death rate (AADR) divided by the aggregate standard weight (WI), i.e.,

$$ASR=\Sigma(AADR)/\Sigma WI \quad (2)$$

AADR in (2) was figured as the aggregate product of each age-specific mortality rate (AI) of the observed population and the corresponding WI, i.e.,

$$AADR=\Sigma(AIxWI) \quad (3)$$

Also, each AI in (3) was computed as the quotient of the observed deaths that occur in a specified age group divided by the corresponding person-years of the study population, i.e.,

$$AI=observed\ deaths/person\text{-}years \quad (4)$$

The observed deaths and the person-years were stratified by age, gender and calendar year, with the person-years to be calculated as the aggregated years that correspond to each person within the follow up period. WI in (2) and (3) was used to express the proportion of population in each stratum, defined as the quotient of the size of the standard population in the specific age group divided by the total standard population for all ages, i.e.,

$$WI=population\ size/total\ standard\ population \quad (5)$$

For the expression of WI in (5) the standard population was defined considering the entire Voiotia Prefecture, in which the municipalities of Oinofita and Arachova belong to. This is because the population of Voiotia Prefecture has homogeneous geographical, density, socioeconomic and ethnic origin characteristics. The population statistics regarding Voiotia Prefecture were provided by the Hellenic Statistical Authority (EL.STAT.) and they referred to the estimated population at the mid-point of each calendar year.

Furthermore, we utilized the Poisson method (Boyle & Parkin, 1991; Klein & Schoenborn, 2001) to compute the variance, the standard error and 95% confidence intervals (CI) of all ASRs. Similarly, we used the normal distribution (Boyle & Parkin, 1991) to compute the 95% CI and the corresponding p-values of each SRR.

Also, we analyzed the general trend of mortality for the 11-year follow up period (1999-2009). The analysis was performed by calculating the all-cause and all cancers ASRs per 100 000 (standard: Voiotia Prefecture population) together with their 95% CI, adjusted for age and gender, for each region and calendar year. The reason was to use years of follow up as a proxy to exposure level. The statistical analysis was performed using the SPSS statistical software and p-values less than 0.05 were considered statistically significant. Furthermore, 0.05<p-values<0.10 were considered suggestive results.

3. Results

Figures 2 to 6 present the descriptive statistics for the characteristics of the study populations regarding the number of total deaths, cancer deaths, person-years (total and within 20 year-age group) and the average age of death. From Figure 2 we observe that 132 from the 495 deaths and 92 from the 399 deaths that occurred in the municipality of Oinofita and Arachova, respectively, were cancer related. More than 50% of the calculated person-years corresponded to age groups under 40 years of age and above 40 years of age, in Oinofita and Arachova municipality, respectively (Figure 3). Figure 4 shows, that within the 11-year follow up period, there was a decrease of 659 person-years and an increase of 252 person-years for the municipality of Oinofita and Arachova, respectively. That means that in contrast to Arachova, the rate of individuals in Oinofita that exit the cohort (i.e. 31/12/2009) was higher than the corresponding rate of entry (i.e. 01/01/1999). Furthermore, Arachova had a higher percentage of elders compared to the municipality of Oinofita. This justifies the significant difference of 4.3 years in average age of death (73.7 *vs.* 78) between the two study areas (Figure 5). As shown in Figure 6, there were no differences between males and females regarding the age-distribution of person-years.

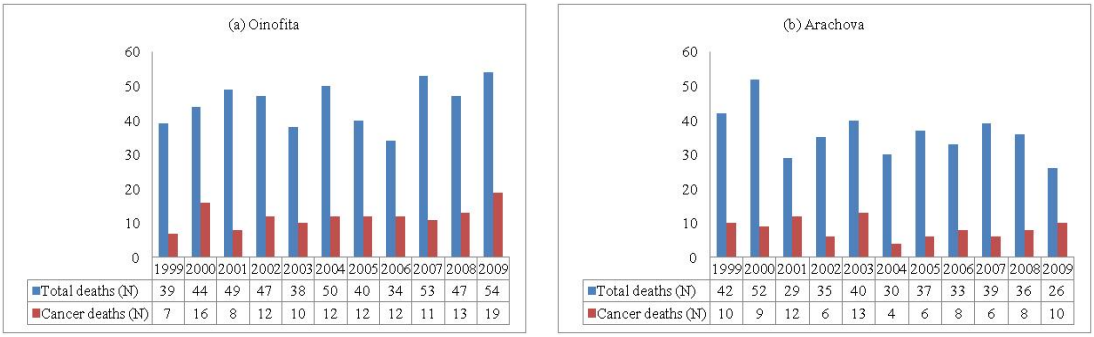


Figure 2. Total deaths and cancer deaths by calendar year for (a) Oinofita and (b) Arachova

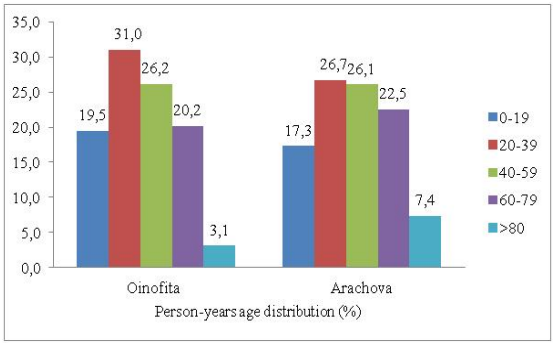


Figure 3. Person-years age distribution by region

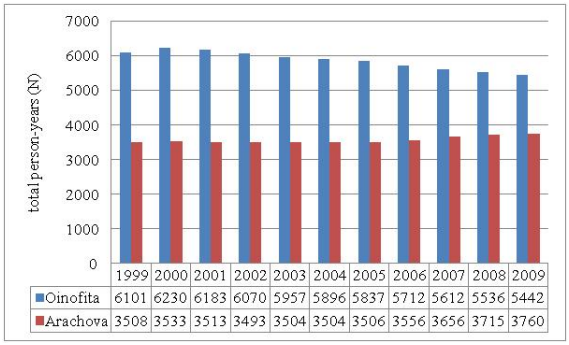
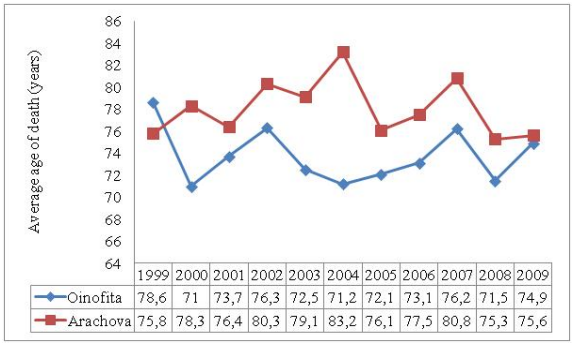


Figure 4. Total person-years by region and calendar year



	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Oinofita	78,6	71	73,7	76,3	72,5	71,2	72,1	73,1	76,2	71,5	74,9
Arachova	75,8	78,3	76,4	80,3	79,1	83,2	76,1	77,5	80,8	75,3	75,6

Figure 5. Average age of death by region and calendar year

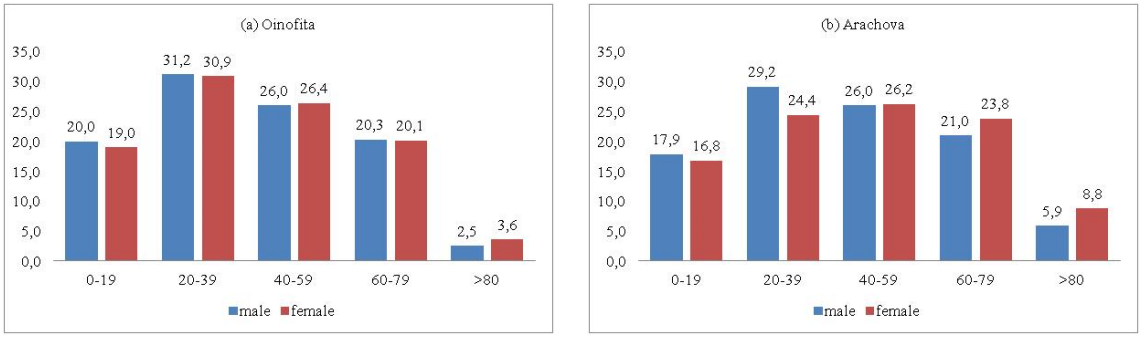


Figure 6. Person-years age distribution (%) by gender for (a) Oinofita and (b) Arachova

Tables 1 and 2 present the results of our statistical analysis in terms of the ASRs and SRRs with the corresponding p-values and 95% CI, stratified by gender, towards comparing the deaths from a) all-cause, b) specific-cause other than cancer, c) all cancers and d) specific cancer sites between the two study areas. Specifically, Table 1 shows the results of the mortality analysis regarding deaths from a) all-cause and b) specific-cause other than cancer. The all-cause risk of death in the municipality of Oinofita (ICD-9 range: 001-999) was 22% higher than the municipality of Arachova and statistically significant (SRR = 1.22, 95% CI 1.1-1.4, p-value = 0.004). In terms of gender, the all-cause risk of death between the two municipalities was statistically significant only between females (SRR = 1.09, 95% CI 0.9-1.3 for males and SRR = 1.37, 95% CI 1.1-1.7 for females). Similar results were observed for deaths from natural causes excluding the deaths from accidents (ICD-9 range: 001-799) (SRR = 1.22, 95% CI 1.1-1.4, p-value = 0.005).

With respect to specific-cause other than cancer, the risk of death from cardiovascular diseases (ICD-9 range: 390-459) in the municipality of Oinofita was 36% higher than the municipality of Arachova and statistically significant (SRR = 1.36, 95% CI 1.1-1.7, p-value = 0.003) for both males and females. Interestingly, the risk of death from cerebrovascular diseases (ICD-9 range: 430-438) in the municipality of Oinofita was three-fold higher than the municipality of Arachova and statistically significant (SRR = 2.93, 95% CI 1.8-4.8, p-value < 0.001) for both males and females. Also, the mortality from cardiopulmonary diseases (ICD-9 range: 415-429) in the municipality of Oinofita was 28% higher than the municipality of Arachova (SRR = 1.28, 95% CI 0.9-1.7), but this was a suggestive result only among males (SRR = 1.52, 95% CI 1.0-2.4, p-value = 0.062 for males and SRR = 1.06, 95% CI 0.7-1.6 for females). Increased SRRs were also observed for several other causes of death, including diseases of the respiratory system (ICD-9 range: 460-519) (SRR = 1.22, 95% CI 0.8-1.9), diseases of the nervous system (ICD-9 range: 320-359) (SRR = 2.28, 95% CI 0.5-11.1) and renal diseases among females (ICD-9 range: 580-629) (SRR = 1.90, 95% CI 0.3-10.9), but were not statistical significant. Note, that the risk of death from chronic airway obstruction and extrinsic allergic alveolitis (ICD-9 495,496) in the municipality of Oinofita was four-fold higher compared to the municipality of Arachova among females (SRR = 4.10, 95% CI 0.6-26.9). In contrast to the case of Oinofita, no deaths were observed in the case of Arachova for diseases of skin and subcutaneous tissue (ICD-9 range: 680-709) hence, the corresponding SRR could not be computed (Table 1).

Table 1. ASRs, SRRs (per 100 000 person-years) with 95% CI and p-values, stratified by gender and specific cause (other than cancer); Oinofita vs. Arachova: 1999-2009

Cause of death	ICD-9 Range[a]	ASR Oin	ASR Arach	SRR	95%CI (LL-UL)	p-value
TOTAL						
All causes	1-999	845.1	690.5	1.22*	1.1-1.4	0.004
Natural deaths	1-799	795.4	650.0	1.22*	1.1-1.4	0.005
Diseases of the nervous system	320-359	8.3	3.7	2.28	0.5-11.1	0.310
Cardiovascular diseases	390-459	392.3	288.4	1.36*	1.1-1.7	0.003
Hypertensive disease	401-405	6.2	4.8	1.29	0.3-5.9	0.745
Ischemic heart disease	410-414	100.7	107.6	0.94	0.6-1.3	0.722
Cardiopulmonary diseases	415-429	165.5	129.2	1.28	0.9-1.7	0.107
Cerebrovascular diseases	430-438	103.0	35.1	2.93*	1.8-4.8	<0.001
Arteries, arterioles, capillaries and veins, lymphatics and other diseases of circulatory system	440-459	16.9	11.6	1.45	0.5-4.1	0.478
Respiratory diseases	460-519	77.4	63.6	1.22	0.8-1.9	0.386
Pneumonia	480-486	24.8	20.7	1.20	0.6-2.5	0.637
Bronchitis, emphysema, asthma	490-493	0	2.7	-	-	-
Chronic airway obstruction, extrinsic allergic alveolitis	495,496	14.8	8.9	1.66	0.6-5.0	0.367
Pneumoconioses and other lung diseases	500-508	5.4	13.4	0.40	0.1-1.5	0.183
Other diseases of the respiratory system	488-489, 497-499, 509-510, 512-519	32.4	17.8	1.82	0.8-3.9	0.128
Diseases of the digestive system	520-579	12.0	13.9	0.86	0.3-2.5	0.787
Renal diseases	580-599	8.1	11.9	0.68	0.2-1.9	0.472
Diseases of skin and subcutaneous tissue	680-709	2.5	0	-	-	-
MALE						
All causes	1-999	961.7	882.7	1.09	0.9-1.3	0.357
Natural deaths	1-799	893.5	819.7	1.09	0.9-1.3	0.372
Diseases of the nervous system	320-359	0	0	-	-	-
Cardiovascular diseases	390-459	450.4	336.4	1.34*	1.01-1.8	0.043
Hypertensive disease	401-405	4.7	11.6	0.40	0.1-2.9	0.371
Ischemic heart disease	410-414	138.0	147.9	0.93	0.6-1.5	0.767
Cardiopulmonary diseases	415-429	194.3	127.5	1.52**	1.0-2.4	0.062
Cerebrovascular diseases	430-438	96.5	38.2	2.52*	1.2-5.3	0.015
Arteries, arterioles, capillaries and veins, lymphatics and other diseases of circulatory system	440-459	16.9	11.1	1.53	0.3-7.6	0.604
Respiratory diseases	460-519	70.5	71.3	1.00	0.5-1.9	0.972
Pneumonia	480-486	19.8	15.3	1.29	0.4-4.3	0.680
Bronchitis, emphysema, asthma	490-493	0	5.4	-	-	-
Chronic airway obstruction, extrinsic allergic alveolitis	495,496	12.5	16.4	0.76	0.2-3.2	0.706
Pneumoconioses and other lung diseases	500-508	7.6	17.0	0.45	0.1-2.5	0.357
Other diseases of the respiratory system	488-489, 497-499, 509-510, 512-519	30.7	17.2	1.79	0.6-5.4	0.302
Diseases of the digestive system	520-579	7.2	10.2	0.71	0.1-4.7	0.719
Renal diseases	580-599	5.7	18.9	0.30	0.1-1.3	0.112
Diseases of skin and subcutaneous tissue	680-709	5.6	0	-	-	-
FEMALE						
All causes	1-999	718.0	524.6	1.37*	1.1-1.7	0.003
Natural deaths	1-799	689.5	506.3	1.36*	1.1-1.7	0.004

Diseases of the nervous system	320-359	16.4	6.3	2.61	0.5-13.1	0.244
Cardiovascular diseases	390-459	335.3	246.8	1.36*	1.01-1.8	0.042
Hypertensive disease	401-405	6.7	0	-	-	-
Ischemic heart disease	410-414	64.3	69.7	0.92	0.5-1.7	0.796
Cardiopulmonary diseases	415-429	140.4	133.1	1.06	0.7-1.6	0.804
Cerebrovascular diseases	430-438	107.3	32.3	3.32*	1.7-6.6	0.001
Arteries, arterioles, capillaries and veins, lymphatics and other diseases of circulatory system	440-459	16.6	11.7	1.42	0.4-5.5	0.610
Respiratory diseases	460-519	75.0	55.4	1.35	0.7-2.5	0.337
Pneumonia	480-486	26.8	26.6	1.01	0.4-2.6	0.987
Bronchitis, emphysema, asthma	490-493	0	0	-	-	-
Chronic airway obstruction, extrinsic allergic alveolitis	495,496	15.9	3.9	4.10	0.6-26.9	0.141
Pneumoconioses and other lung diseases	500-508	2.6	8.6	0.30	0.0-2.2	0.238
Other diseases of the respiratory system	488-489, 497-499, 509-510, 512-519	29.7	16.4	1.81	0.6-5.3	0.280
Diseases of the digestive system	520-579	16.1	15.9	1.01	0.3-3.7	0.988
Renal diseases	580-599	11.3	5.9	1.91	0.3-10.9	0.468
Diseases of skin and subcutaneous tissue	680-709	0	0	-	-	-

Note. CI=confidence interval; LL=lower limit, UL=upper limit. * Statistically significant at 5% level. ** Suggestive results: 0.05<p-values<0.10. [a] Specific cause of death is classified according to the ICD-9.

Table 2 describes results for deaths from c) all cancers and d) specific cancer sites. The risk of death from all cancers (ICD-9 range: 140-239), combined over all 11 years of the follow up period, was increased in the municipality of Oinofita compared to the municipality of Arachova, but not statistically significant (SRR = 1.18, 95% CI 0.9-1.5). With respect to specific cancer sites, the risk of death from leukaemias (ICD-9 range: 204-208) in the municipality of Oinofita was almost five-fold higher than the municipality of Arachova and that was a suggestive result (SRR = 4.65, 95% CI 0.9-25.3, p-value = 0.075). Moreover, the risk of death from lung, trachea and bronchus cancer (ICD-9 162) in the municipality of Oinofita was higher compared to the municipality of Arachova (SRR = 1.58, 95% CI 0.9-2.8), but not statistical significant. The risk of death from leukaemias and lung, trachea and bronchus cancer among females was not evaluable since no deaths from these cancers were caused in the municipality of Arachova and thus, the corresponding SRRs could not be computed. Elevated SRRs with no statistical significance were further noted for the municipality of Oinofita regarding several other cancer sites, including cancers of lip, oral cavity and pharynx (ICD-9 range: 140-149) (SRR = 3.13, 95% CI 0.4-28.0), stomach (ICD-9 151) (SRR = 1.32, 95% CI 0.3-5.1), primary liver (ICD-9 155.0) (SRR = 1.91, 95% CI 0.5-7.6), pancreas (ICD-9 157) (SRR = 1.47, 95% CI 0.5-4.8), colon among females (ICD-9 153) (SRR = 2.00, 95% CI 0.5-8.4), female breast (ICD-9 174) (SRR = 1.37, 95% CI 0.5-4.1), prostate (ICD-9 185) (SRR = 1.20, 95% CI 0.4-3.6), kidney and other genitourinary organs among females (ICD-9 184,187,189) (SRR = 3.01, 95% CI 0.5-18.0) and brain (ICD-9 191) (SRR = 1.43, 95% CI 0.3-7.6). Finally, from Table 2 we noticed that in contrast to the municipality of Oinofita, no deaths were observed in the municipality of Arachova for the other respiratory cancers (ICD-9 160,163-165), malignant melanoma of skin (ICD-9 172), cancer of cervix uteri (ICD-9 180) and testis (ICD-9 186).

Time trends for mortality from all causes and all cancers are presented in Figure 7 and Figure 8, respectively. Mortality trends from all causes in the municipality of Oinofita appeared to rise in the last three-year period, while in the municipality of Arachova the trend has been decreasing for the same period. Furthermore, mortality from all causes was higher in Oinofita than that in Arachova throughout the study period. Mortality from cancer (all sites) has been increasing in Oinofita municipality in the last two-year period, while in Arachova municipality remained stable for the same period. Since 2004, mortality rates from all cancers in the Oinofita municipality were higher compared to those in Arachova municipality.

Table 2. ASRs, SRRs (per 100 000 person-years) with 95% CI and p-values, stratified by gender and cancer site; Oinofita vs. Arachova: 1999-2009

Cause of death	ICD-9 Range[a]	ASR Oin	ASR Arach	SRR	95%CI (LL-UL)	p-value
TOTAL						
All cancers	140-239	214.2	182.1	1.18	0.9-1.5	0.242
Lip, oral cavity, pharynx	140-149	4.6	1.5	3.13	0.4-28.0	0.307
Stomach	151	8.8	6.6	1.32	0.3-5.1	0.688
Colon	153	11.0	19.4	0.57	0.2-1.6	0.276
Rectum	154	1.9	3.6	0.53	0.1-5.5	0.598
Liver primary	155.0	10.5	5.5	1.91	0.5-7.6	0.355
Pancreas	157	13.8	9.4	1.47	0.5-4.8	0.525
Gallbladder and other digestive organs and peritoneum	155.1, 155.2, 156, 158-159	7.0	12.3	0.57	0.2-2.0	0.379
Lung, trachea and bronchus	162	53.3	33.7	1.58	0.9-2.8	0.117
Other respiratory organs and intrathoracic organs	160, 163-165	3.0	0	-	-	-
Bone and articular cartilage	170	1.4	2.7	0.54	0.0-10.7	0.686
Skin melanoma	172	1.7	0	-	-	-
Female breast	174	16.4	11.7	1.40	0.5-4.1	0.543
Uterus, cervix	180	1.7	0	-	-	-
Uterus, body	179,182	0	3.5	-	-	-
Ovary	183	1.5	6.7	0.22	0.0-1.9	0.172
Prostate	185	13.4	11.0	1.21	0.4-3.6	0.725
Testis	186	1.4	0	-	-	-
Bladder	188	5.7	6.8	0.84	0.2-3.9	0.820
Kidney and other genitourinary organs	184,187, 189	9.7	9.4	1.03	0.3-3.7	0.966
Brain	191	6.5	4.6	1.43	0.3-7.6	0.675
Other and unspecified malignant neoplasm	190, 192-199	18.0	15.7	1.14	0.5-2.8	0.787
Leukaemias	204-208	10.7	2.3	4.65**	0.9-25.3	0.075
Other lymphoid and hematopoietic tissue	200, 202-203	4.2	15.1	0.28	0.1-1.3	0.100
Uncertain/unspecified nature	235-239	7.9	6.1	1.30	0.3-5.0	0.698
MALE						
All cancers	140-239	258.3	256.8	1.01	0.7-1.4	0.974
Lip, oral cavity, pharynx	140-149	8.6	3.6	2.42	0.3-20.0	0.412
Stomach	151	10.5	4.3	2.42	0.3-16.7	0.370
Colon	153	2.4	27.5	0.09	0.0-0.7	0.024
Rectum	154	4.0	8.6	0.46	0.0-5.0	0.527
Liver primary	155.0	11.5	7.9	1.46	0.3-7.7	0.658
Pancreas	157	14.8	13.7	1.08	0.2-5.1	0.920
Gallbladder and other digestive organs and peritoneum	155.1, 155.2, 156, 158-159	7.4	11.2	0.66	0.1-4.0	0.650
Lung, trachea and bronchus	162	84.0	69.7	1.21	0.7-2.2	0.545
Other respiratory organs and intrathoracic organs	160, 163-165	4.9	0	-	-	-
Bone and articular cartilage	170	2.6	0	-	-	-
Skin melanoma	172	3.2	0	-	-	-
Prostate	185	29.1	24.3	1.20	0.4-3.6	0.753
Testis	186	3.1	0	-	-	-
Bladder	188	9.3	16.7	0.56	0.1-3.1	0.507
Kidney and other genitourinary organs	184,187, 189	3.0	13.5	0.22	0.0-2.3	0.207
Brain	191	9.2	5.7	1.62	0.2-13.9	0.660
Other and unspecified malignant neoplasm	190, 192-199	15.4	26.9	0.57	0.2-2.0	0.382
Leukaemias	204-208	13.8	4.1	3.39	0.5-21.8	0.198
Other lymphoid and hematopoietic tissue	200, 202-203	8.2	18.7	0.44	0.1-2.5	0.352
Uncertain/unspecified nature	235-239	13.5	8.7	1.55	0.3-7.2	0.577

FEMALE						
All cancers	140-239	166.5	121.9	1.37	0.8-2.2	0.188
Lip, oral cavity, pharynx	140-149	0	0	-	-	-
Stomach	151	6.2	9.0	0.69	0.1-5.4	0.728
Colon	153	19.7	9.9	2.00	0.5-8.4	0.344
Rectum	154	0	0	-	-	-
Liver primary	155.0	8.4	3.1	2.71	0.2-32.1	0.429
Pancreas	157	12.2	5.0	2.45	0.4-16.7	0.360
Gallbladder and other digestive organs and peritoneum	155.1, 155.2, 156, 158-159	6.1	15.4	0.40	0.1-2.5	0.323
Lung, trachea and bronchus	162	16.7	0	-	-	-
Other respiratory organs and intrathoracic organs	160, 163-165	0	0	-	-	-
Bone and articular cartilage	170	0	5.6	-	-	-
Skin melanoma	172	0	0	-	-	-
Female breast	174	33.6	24.5	1.37	0.5-4.1	0.567
Uterus, cervix	180	3.3	0	-	-	-
Uterus, body	179,182	0	6.9	-	-	-
Ovary	183	3.6	12.6	0.28	0.0-2.3	0.235
Bladder	188	3.7	0	-	-	-
Kidney and other genitourinary organs	184,187, 189	16.3	5.4	3.01	0.5-18.3	0.232
Brain	191	4.3	3.2	1.35	0.1-22.6	0.836
Other and unspecified malignant neoplasm	190, 192-199	21.8	8.4	2.58	0.6-11.8	0.221
Leukaemias	204-208	7.7	0	-	-	-
Other lymphoid and hematopoietic tissue	200, 202-203	0	12.9	-	-	-
Uncertain/unspecified nature	235-239	2.8	4.4	0.62	0.0-11.3	0.749

Note. CI=confidence interval; LL=lower limit, UL=upper limit. ** Suggestive results: 0.05<p-values<0.10. [a] Cancer sites are classified according to the ICD-9.

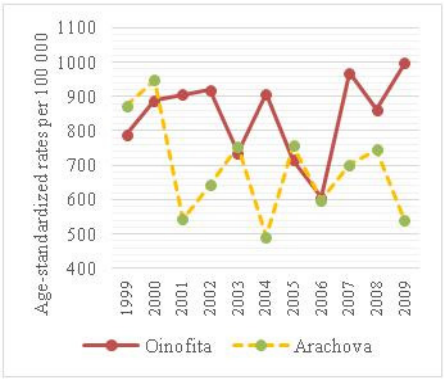


Figure 7. Overall mortality. Trends in age-standardized rates per 100 000, by region and calendar year

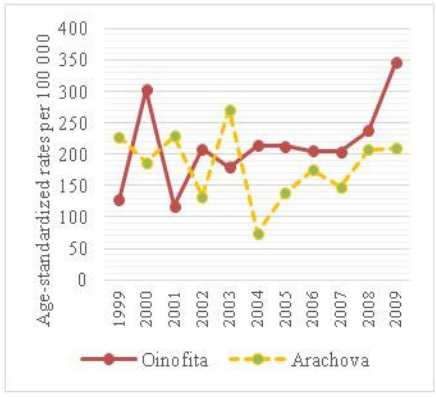


Figure 8. All cancers. Trends in age-standardized rates per 100 000, by region and calendar year

4. Discussion

In this paper, we evaluated the potential health effects of industrial pollution, by performing mortality comparisons between Oinofita and Arachova, an environmentally polluted and an unpolluted study area, respectively. Both areas belonged to the Voiotia Prefecture, Greece and the follow-up period was 1999-2009. We were interested in examining whether there was an increased mortality from all-cause, specific cancer sites, respiratory and cardiovascular diseases due to the residential proximity to air polluted industries as well as whether there was an increased gastrointestinal and urologic cancer mortality, because of the oral exposure to elevated levels of Cr(VI) through drinking water. We found that citizens residing in the industrial area of Oinofita had significantly increased risk of death from all-cause (SRR = 1.22, 95% CI 1.1-1.4), natural cause excluding accidents (SRR = 1.22, 95%

CI 1.1-1.4), cardiovascular (SRR = 1.36, 95% CI 1.1-1.7) and cerebrovascular diseases (SRR = 2.93, 95% CI 1.8-4.8) compared to the non-industrial area of Arachova. For the citizens of Oinofita we further observed suggestive results for cardiopulmonary diseases among males (SRR = 1.52, 95% CI 1.0-2.4) and leukaemias (SRR = 4.65, 95% CI 0.9-25.3). Also, in Oinofita municipality higher mortality rates, not statistically significant though, were observed for respiratory diseases (SRR = 1.22, 95% CI 0.8-1.9) and lung cancer (SRR = 1.58, 95% CI 0.9-2.8). Furthermore, citizens of Oinofita had increased risk of death from several oral, gastrointestinal and urologic cancers, e.g., cancers of lip, oral cavity and pharynx (SRR = 3.13, 95% CI 0.4-28.0), stomach (SRR = 1.32, 95% CI 0.3-5.1), liver (SRR = 1.91, 95% CI 0.5-7.6), pancreas (SRR = 1.47, 95% CI 0.5-4.8), colon among females (SRR = 2.00, 95% CI 0.5-8.4), prostate (SRR = 1.20, 95% CI 0.4-3.6), kidney and other genitourinary organs among females (SRR = 3.01, 95% CI 0.5-18.0).

While a direct comparison with other results is difficult because of the different statistical analysis methods utilized, our outcomes regarding the increased mortality from all-cause, specific cancer sites, respiratory and cardiovascular diseases are in agreement with those reported by studies focused on the residential exposure to air polluted industries (Edwards et al., 2006; Garcia-Perez et al., 2010; Parodi et al., 2015; Pirastu et al., 2013; Ruiz-Rudolph et al., 2016). For example, Pirastu et al. (2013) showed that within the period 2003-2009, citizens residing in a municipality which was polluted by a number of industrial sources (e.g. large steel plant, refinery, harbor, controlled and illegal waste dumps) had consistently excess risk of death from all-cause (males: SMR = 114, 90% CI 111-117, females: SMR = 108, 90% CI 105-110), lung cancer (males: SMR = 133, 90% CI 124-143, females: SMR = 130, 90% CI 109-153), cardiovascular (males: SMR = 114, 90% CI 109-119, females: SMR = 104, 90% CI 100-108) and respiratory diseases (males: SMR = 117, 90% CI 108-126, females: SMR = 104, 90% CI 94-115). Also, Ruiz-Rudolph et al. (2016) investigated communes near large industrial facilities to observe increased mortality from all-cause (males: RR = 1.17, 95% CI 1.03-1.33, females: RR = 1.09, 95% CI 0.98-1.20), cardiovascular diseases (males: RR = 1.15, 95% CI 1.01-1.31, females: RR = 1.16, 95% CI 1.02-1.33), respiratory diseases (males: RR = 1.26, 95% CI 1.06-1.52, females: RR = 1.09, 95% CI 0.93-1.28) and lung cancer (males: RR = 1.03, 95% CI 0.81-1.29, females: RR = 1.11, 95% CI 0.88-1.40) for communes with smelters. In addition, Edwards et al. (2006) found a modestly raised risk of lung cancer (OR = 1.83, 95% CI 0.82-4.08) with prolonged residence close to heavy industry, although the confidence intervals were wide. Similar to Ruiz-Rudolph et al. (2016) and Edwards et al. (2006), we also observed increased risk of lung cancer (SRR = 1.58, 95% CI 0.9-2.8), which however, did not reach statistical significance. Regarding leukaemias most studies, indicated suggestive results, which match with our findings (SRR = 4.65, 95% CI 0.9-25.3, p-value = 0.075). For instance, Garcia-Perez et al. (2010) suggested an association between leukemia-related mortality and proximity to Spanish metal industries revealing that during the period 1994–2003, excess mortality was detected in the vicinity of pre-1990 installations (males: RR = 1.07, 95% CI 1.02-1.13, females: RR = 1.05, 95% CI 1.00-1.11), with this being more elevated in the case of installations that released pollution to air versus water. Also, Parodi et al. (2015) observed higher risk from leukaemias for subjects living in heavily polluted zones (fossil fuel power plant, coke oven, chemical industry) compared to subjects living in moderately polluted zones, but statistical significance was not reached (OR = 1.56 and OR = 1.11, respectively, p-value = 0.190).

In addition, our results regarding increased mortality from all cancers and specific cancer sites including lip, oral cavity and pharynx, liver, stomach, pancreas, prostate, colon and kidney and other genitourinary organs among females are in consistence with relevant epidemiological and animal studies, which indicated carcinogenesis after long-term consumption of drinking water contaminated with Cr(VI) (Beaumont et al., 2008; Linos et al., 2011; NTP, 2008). Similar to our outcomes, Linos et al. (2011) showed that citizens residing in the industrial area of Oinofita were more likely to have higher mortality rates from primary liver (SMR = 1104.2, 95% CI 405.2-2403.3) and lung cancers (SMR = 145.1, 95% CI 100.5-202.8) in both males and females as well as kidney and other genitourinary organs among females (SMR = 367.8, 95% CI 119.4-858.3) compared to the population of the surrounding prefecture. Also, Beaumont et al. (2008) reported that mortality rates for all cancers (RR = 1.23, 95% CI 0.97-1.53), stomach cancer (RR = 1.69, 95% CI 1.12-2.44), and lung cancer (RR = 1.78, 95% CI 1.03-2.87) in 1970-1978 were higher in villages in Liaoning Province, China with Cr(VI)-contaminated drinking water than in the general population. The NTP (2008) results further revealed that rats and mice exposed to Cr(VI)-contaminated drinking water developed oral cavity neoplasms, small intestine neoplasms and hyperplasia, while displaying a significant increase in histiocytic cell infiltration in the duodenum, jejunum and liver. Interestingly, although such cancers are considered as particularly rare sites, we observed that mortality from such cancer sites had been unusually increased in Oinofita. According to the literature, this increase is mostly associated with the long-term contamination with Cr(VI) without however, excluding the impact of other contaminants in drinking water. Nevertheless, in the available samples there were no other water contaminants that exceeded the national safety

levels. Although these results were not statistically significant due to the small number of observed deaths, we indicated higher risk of death from several oral, gastrointestinal and urologic cancers.

Furthermore, we observed a considerable increase in lung cancer mortality for the citizens in Oinofita compared to Arachova. Besides the risk factor of air pollution due to industries, the increase in lung cancer mortality in Oinofita may be fostered due to the inhalation of Cr(VI) which occurs during showering. This is because the inhalation of the water droplets generated during showering can occur due to the movement of the agent from water into indoor air (OEHHA, 2011), whereas inhaled Cr(VI) is known to cause lung cancer to humans (IARC, 1990).

A limitation of our study was the fact that some citizens, although they were registered in the municipality of Oinofita were not permanent residents or consumed tap water for the follow up period. Hence, some small percentage of the population of Oinofita may not had been actually exposed to either environmental pollution in general or in Cr(VI) polluted water, which would in turn have underestimated the real risk of all causes of death.

Another limitation of our study, which is common in ecologic studies (Santos-Silva, 1999), was that no individual exposure (e.g. levels of Cr(VI) in drinking water) or confounder (e.g. smoking, diet) data were available. Therefore, we accounted for all available risk factors by calculating the cause-specific mortality rates stratified by gender, age and calendar year. Moreover, Karagiannis et al. (2015) and the National Health Survey of EL.STAT. (2011) reported that the percentage of smokers in Oinofita was even lower than the corresponding percentage in Greece (i.e. 26.3% and 37.9% in 2011 and 2009, respectively). Therefore, we considered that the percentage of smokers in Oinofita could not be higher than the percentage in Arachova and assumed that our results were not confounded by smoking. In the opposite case, (if more smokers were situated in Oinofita than Arachova) we would have expected increased mortality rates from all causes of death in the municipality of Oinofita which however, was not observed. Undoubtedly, further research is warranted as long as individual data on potential confounding factors will be officially available.

An additional potential problem would be the misclassification of the cause of death. Specifically, assigning deaths to a disease, while the real underlying cause of death was a different disease, often suggests systematic differences in diagnosis patterns across the regions. To eliminate this potential bias we used data for both study areas coded by the same physician. That way, we selected the underlying cause as the final cause of death by reviewing all original death certificates and in turn, we encoded the causes of death using the ICD-9 classification system. As result, any potential misclassification was random and could not overestimate the real risk of death.

A significant strength of our study was the large number of the accounted cases to estimate the mortality rates, considering the whole population of the registered citizens in both study areas. An additional strength was the considered reference population which facilitated appropriate comparisons between populations with different environmental exposures and similar demographic and socioeconomic characteristics. In these regards, large sample size along with accurate mortality data helped to assess the fundamental causes of our objective and gain integrated insights on evaluating health risks of the study-populations. It should be also noted that SRRs can effectively eliminate the age-gender differences due to the homogeneous standard weights employed on the observed age-gender-specific rates hence, they are generally considered as reliable mortality rates for comparisons between different areas, as done in this study (Bains, 2009; Breslow & Day, 1987).

To the best of our knowledge, it is the first ecological mortality study in Greece to compare two closely located residential areas towards evaluating the impact of their different environmental profiles on cause-specific mortality rates.

5. Conclusion

Air pollution has been well-associated with increased risk of death from all-cause, cardiovascular and respiratory diseases. Also, water contaminated with Cr(VI) has been suggested as a potential carcinogen in humans through the oral route. This study provides further evidence of these two associations. In light of the potentially widespread health implications of such pollutions, further studies, with individual exposures and risk factor information, are warranted to explore the possible causal link between exposure to environmental pollution of air and water and mortality risk. Such evidence is needed to establish guidelines for the prevention of air and water contamination from industrial pollution and formulate public health recommendations.

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