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# Long-term mortality patterns in a residential cohort exposed to inorganic selenium in drinking water

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ABSTRACT

Selenium (Se) is a metalloid of considerable nutritional and toxicological importance in humans. To date, limited epidemiologic evidence exists about the health effects of exposure to this trace element in drinking water. We investigated the relationship between Se levels in water and mortality in the municipality of Reggio Emilia, Italy, where high levels of Se were previously observed in drinking water. From 1974 to 1985, 2065 residents consumed drinking water with Se levels close to the European standard of 10 μg/l, in its inorganic hexavalent form (selenate). Follow-up was conducted for the years 1986–2012 in Reggio Emilia and a lesser exposed comparison group of around 100,000 municipal residents, with comparable socio-demographic characteristics. Overall mortality from all causes, cardiovascular disease and cancer showed little evidence of differences. However, excess rate ratios were seen for some site specific cancers such as neoplasms of buccal cavity and pharynx, urinary tract, lymphohematopoietic tissue, melanoma, and two neurodegenerative diseases, Parkinson's disease and amyotrophic lateral sclerosis. Excess mortality in the exposed cohort for specific outcomes was concentrated in the first period of follow-up (1986–1997), and waned starting 10 years after the high exposure ended. We also found lower mortality from breast cancer in females during the first period of follow-up. When we extended the analysis to include residents who had been consuming the high-selenium drinking water for a shorter period, mortality rate ratios were also increased, but to a lesser extent. Overall, we found that the mortality patterns related to long-term exposure to inorganic hexavalent selenium through drinking water were elevated for several site-specific cancers and neurodegenerative disease.


## 1. Introduction

The trace element selenium (Se) in its various chemical species continues to attract strong interest in environmental health, due to the broad and varying effects suggested by laboratory studies, ranging from toxic to beneficial (Jablonska and Vinceti, 2015; Misra et al., 2015; Vinceti et al., in press), and to the intriguing effects on several human diseases suggested by epidemiologic investigations (Vinceti et al., in press) (Table 1). Mainly based on observational studies, Se has been hypothesized to have some beneficial effects in the prevention of cancer and cardiovascular disease (Vinceti et al., 2014a; Zhang et al., 2016). However, recent randomized controlled trials (RCTs) did not show decreases in cancer and cardiovascular rates in subjects taking organic Se supplements, but instead showed some evidence of increased risk of advanced prostate cancer, diabetes and skin cancer (Vinceti et al., in press). These observations have raised concern about the safe range of Se intake. On the converse, very little is known about inorganic Se effects on human health, although the results of most, but not all, laboratory studies suggest it is more toxic than organic Se compounds found in foods (Nogueira and Rocha, 2011; Weekley and Harris, 2013; Vinceti et al., 2014b, 2015; Dolgova et al., 2016), and it also appears to have peculiar metabolic pathways (Jager et al., 2016). Inorganic Se forms tend to occur in occupational environments, outdoor air in polluted areas, and drinking water (Fan and Vinceti, 2015). In drinking water, Se is generally present as inorganic hexavalent, selenate, and sometimes approaches the European Union (EU) standard of 10 μg/l even outside known seleniferous areas (Vinceti et al., 2013a; Yu et al., 2015). The lack of

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adequate information on Se toxicity is also recognized by WHO (2011b), and concern has been recently given to the adequacy of current standards and guidelines (Vinceti et al., 2013a; Frisbie et al., 2015), especially considering the higher toxicity of inorganic Se species compared with the organic forms in several laboratory models (Tsunoda et al., 2000; Maraldi et al., 2011; Benko et al., 2012; Peyroche et al., 2012). These concerns highlight the need for further research on the health effects of this chemical in human populations.

In the present study, we took advantage of a unique 'natural experiment' which allowed the distribution of drinking water with high Se levels or geologic origin for over 15 years, to assess the long-term effects of Se in drinking water on mortality from chronic disease. In order to evaluate causal inference and other factors we also compared the association of selected causes of death and exposure to Se stratifying by length of exposure and time elapsed from exposure cessation.

## 2. Methods

### 2.1. Study setting and population

With the approval of the Reggio Emilia Ethics Committee, we performed a historical cohort study on consumers of high-Se drinking water using methods similar to those already adopted in previous investigations (Fig. 1) (Vinceti et al., 1995, 1996, 1998, 2000). Briefly, in the municipality of Reggio Emilia (a Northern Italy community with a population over 150,000) we identified a unique environmental situation which led to consumption of municipal tap water with unusually high Se content. This unique situation began in September 1972 when technical difficulties prevented the pumping of drinking water from the main water supply for the municipality to Rivalta, a small village in the southern part of the municipality. Because of these difficulties, residents of Rivalta began obtaining their tap water exclusively from two local underground sources, a well named 'Pozzo del Prete', owned by the local parish, and a few years later a second well located few meters away. The Rivalta population consumed very little bottled water, as ascertained through a postal survey we carried out in a randomly selected group of residents (Vinceti et al., 2000). Based on information we systematically ascertained from the local Public Health Department and the Municipal Water Authority, the quality and chemical composition of the tap water used in Rivalta, other than elevated Se, was similar to that distributed to the rest of the municipality and complied with national and European regulations. The chemicals which were investigated in routine mandatory surveillance efforts in both Rivalta and the remaining Reggio Emilia tapwater were volatile solvents, trihalomethanes, pesticides, and other 41 chemicals including all recognized toxic elements. Additional investigation for radon content was conducted during the 1990s, which failed to identify high levels in either the two Rivalta wells or the low-Se drinking water supplied to the rest of the municipality (Vinceti et al., 1998).

Testing for Se began during the 1980s, and Se levels in the tapwater distributed in Rivalta averaged 8 μg/l and in some cases approached the 10 μg/l European Union standard. Such a high Se content was confirmed in the water supplied by both the 'Pozzo del Prete' well and the nearby well (Vinceti et al., 1998). After extensive investigation, the origin of these high Se levels in the water from these two wells and consequently in tapwater distributed in Rivalta was found to be geologic, and not associated to any possible anthropogenic source. In the main municipality tapwater supply, Se levels were always very low (0.6 μg/l). Based on concerns regarding the potential health effects of the elevated Se in Rivalta, the municipality began pumping water from other municipal supplies into local aquifers near Rivalta from 1986 to 1988, and then closed the two high Se wells entirely in September 1988. Overall, this resulted in a dramatic lowering of Se concentration in Rivalta to the same levels of those in the main municipal water supply system.

In previous analyses done in the 1990s, we selected two residential cohorts who consumed the high-Se tapwater in Rivalta for different lengths of time, based on the oldest reliable data sources available. Computerized records of all residents living in the study area were available from the Municipal Registry Office beginning on December 1, 1980, and death certificate directory information was available from the Department of Public Health of the Local Health Authority beginning on January 1, 1986. Based on this, the 5182 subjects who had been continuatively and officially residing in Rivalta from December 31, 1980 through December 31, 1985, and whose addresses were listed in the Water Supply

**Table 1**
Summary of evidence[a] from observational cohort studies and from randomized controlled trials on the association between Se exposure and chronic disease risk[b].

| Disease | Observational cohort studies | Randomized controlled trials |
|---|---|---|
| Cancer | ↔ | ↔ |
| Buccal cavity and pharynx | ↗ | . |
| Stomach | ↓ | . |
| Colon-rectum | ↓ | ↔ |
| Pancreas | ↔ | . |
| Lung | ↔ | ↗ |
| Melanoma & other skin cancers | ↑ | ↑ |
| Breast | ↔ | ↗ |
| Prostate | ↓ | ↔ |
| Bladder | ↓ | ↗ |
| Kidney | ↓ | . |
| Lymphoid malignancies | ↔ | ↗ |
| Cardiovascular diseases | ↘ | ↔ |
| Parkinson's disease | . | . |
| Motor neuron diseases | . | . |

[a] ↑, direct association; ↔, no substantial association; ↓, inverse association; ↗, weak and statistically unstable tendency towards direct association; ↘, weak and statistically unstable tendency towards inverse association;., no evidence available.
[b] Rees et al., 2013; Vinceti et al., 2014a, 2016; Zhang et al., 2016.

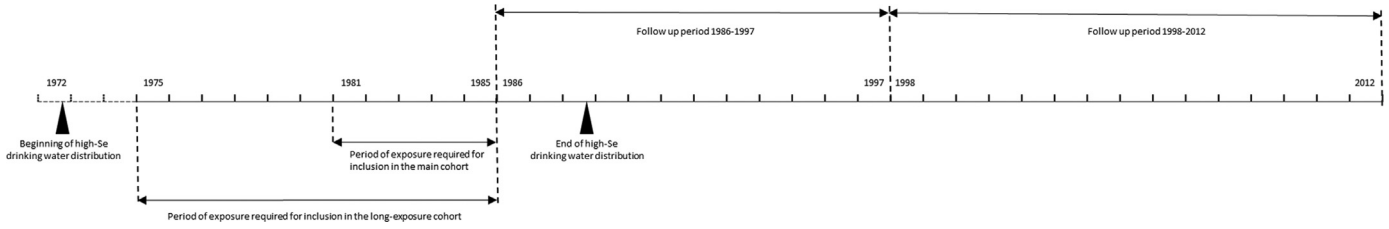


**Fig. 1.** Chart of the methodology for selection and follow-up of the cohorts exposed to inorganic selenium via drinking water since 1972 through 1988 in the Reggio Emilia municipality, Northern Italy.