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Is selenate a diabetogenic form of selenium? Evidence from a natural experiment in Northern Italy

Marco Vinceti [a,b,*], Massimo Vicentini [c], Marta Ottone [c], Lauren A. Wise [b], Francesca Leoni [c,d], Marcella Malavolti [a], Cinzia Gentile [e], Paolo Giorgi Rossi [c], Tommaso Filippini [a,f]

[a] CREAGEN - Environmental, Genetic and Nutritional Epidemiology Research Center, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy
[b] Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA
[c] Interinstitutional Epidemiology Unit, Local Health Authority, Reggio Emilia and Arcispedale S. Maria Nuova, IRCCS, Reggio Emilia, Italy
[d] Centre for Biostatistics, Epidemiology, and Public Health, Department of Clinical and Biological Sciences, University of Turin, Orbassano, Turin, Italy
[e] Health Directorate, Local Health Authority, Reggio Emilia, Italy
[f] School of Public Health, University of California Berkeley, Berkeley, CA, USA

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ABSTRACT

Background: Consistent evidence from randomized controlled trials has shown that overexposure to selenium induces type 2 diabetes. However, uncertainties remain about the specific species and doses of selenium that trigger such diabetogenic effect.
Methods: We investigated the long-term effects of selenium exposure on diabetes risk using data from a natural experiment in Northern Italy. During 1974–1985, a small cohort of residents had been consuming drinking water with an unusually high content of inorganic hexavalent selenium, selenate (8–10 μg/L), close to the standard of the European Union and other countries of 10 μg/L. Using data from a population-based registry, we compared the prevalence of type 2 diabetes in 2013 in selenate-exposed (n = 1310) and unexposed residents (n = 56,251).
Results: In December 2013, the prevalence of diabetes in exposed and unexposed cohorts was 9.85 % and 10.29 %, respectively, with a multivariable-adjusted prevalence ratio of 0.95 (95 % confidence interval 0.81–1.12). Results were similar after stratifying by sex, age, and country of birth.
Conclusions: Overall, these results do not support the hypothesis that consumption of water with inorganic hexavalent selenium levels close to the European limit increases the risk of type 2 diabetes. Null results could be due to non-differential outcome misclassification, other sources of bias, or the fact that selenate is a non-diabetogenic selenium species or that the dose of exposure was too low to elicit an adverse effect.

1. Introduction

A research landmark about the essential trace element selenium was the observation of an excess risk of type 2 diabetes within the Nutritional Prevention of Cancer trials, following long-term supplementation with 200 μg/day of selenium in yeast, expected to be largely or entirely in the organic form [1]. Following this unexpected adverse effect, diabetes was included among the safety endpoints by the subsequent randomized controlled trials (RCTs) with selenium. These RCTs have subsequently confirmed the adverse effect of daily administration of 200 μg/day, added to the background daily intake of the element (likely in the 50–100 μg/day range) [2], thus showing a diabetogenic effect of selenium. Concerns about excess diabetes risk contributed to the early termination of the largest and most informative selenium trial, SELECT [3], and to the understanding of the overall safety profile of the element [4]. Following these observations from experimental human studies, several cohort or cross-sectional studies [5–11] and Mendelian randomization studies [12–16] have been performed, largely replicating the findings of the trials. These studies also suggested a threshold of exposure for such effects slightly above the 55 μg/day of recommended dietary allowance set by the US Institute of Medicine in 2000 [17] and the 26–34 μg/day recommended selenium intake proposed by Food and Agriculture Organization & World Health Organization for females and males, respectively [18]. The toxicological mechanisms underpinning

* Correspondence to: Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Via Campi 287, Modena 41125, Italia.
E-mail address: marco.vinceti@unimore.it (M. Vinceti).

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the diabetogenic effect of selenium have been extensively investigated [19–25].

Uncertainties, however, remain about the exact amount of exposure involved in such diabetogenic effect of selenium, also given the many uncertainties still existing about its safety profile, and about the specific selenium species having a diabetogenic effect, considering the key relevance of its chemical species in determining both nutritional and toxicological properties [4,26,27]. In particular, inorganic selenium species are considered more toxic than the organic compounds based on most, though not all, laboratory and animal studies [25,28–35]. Inorganic Se forms tend to occur in drinking water [36], where they are generally found in the inorganic hexavalent form, selenate, whose safety profile is not well elucidated [37,38]. Furthermore, there is evidence of effects of sex and age in modulating the diabetogenic properties of selenium, but this issue has not been well studied [1,5,39,40].

We investigated the long-term effects of selenium exposure on diabetes risk using data from a natural experiment in Northern Italy. During 1974–1985, a small cohort of residents had been consuming drinking water with an unusually high content of inorganic selenium content (selenate), close to the drinking water limit. Using 2013 data from a population-based registry, we evaluated the prevalence of type 2 diabetes in selenate-exposed and unexposed residents.

2. Methods

The natural experiment occurred in the municipality of Reggio Emilia, Northern Italy (population around 150,000) has already been described in detail [41–45]. In Rivalta—one of the smallest and highest areas of the municipality—an unusual environmental and technical situation led residents to use tap water from two local wells between 1972 and 1988, owing to difficulties in pumping water from the main municipal supply up to this neighborhood. Tap water supplied in Rivalta was entirely similar to tap water distributed in the remaining municipal territory in terms of chemical and physical characteristics (including volatile solvents, trihalomethanes, pesticides, 41 inorganic chemicals, and radon [46]), apart from selenium. Testing for this element initiated during the 1980s, with selenium levels later identified as the inorganic hexavalent species i.e. selenate, averaged 8–10 μg/L, approaching the European Union standard of 10 μg/L, a value much higher than the < 1 μg/L characterizing the remaining municipal territory. This high selenium content was not known to the Water Municipal Authority or any residents, and led to the progressive reduction and final cessation of use of the two Rivalta wells in September 1988, and connection of the Rivalta aqueduct with the main municipal one.

In previous cohort studies conducted in that study area, we selected two residential cohorts: one of Rivalta residents also listed as municipal Water Supply Authority subscribers since December 31, 1974 through December 31, 1985 (n = 2065), and the remaining unexposed 95,715 residents in the Reggio Emilia municipality in the same time period who never resided in Rivalta from 1974 to 1980. We retrospectively carried out a cross-sectional analysis of these two cohorts at December 31, 2013, provided that cohort members were still alive and residing in the Reggio Emilia province at that date. We ascertained the vital status and residential address of cohort members by accessing administrative population data of the Reggio Emilia municipality and the Local Health Authority. Data on educational attainment and occupational status of exposed and unexposed cohort members, made available at the beginning of the follow-up by Reggio Emilia municipality, indicated that they were similar with respect to baseline characteristics [42,43,46,47].

The outcome of interest was type 2 diabetes prevalence, based on matches between the two cohorts of residents with the population-based Diabetes Registry, which collected data on all incident and prevalent cases of type 1 and type 2 diabetes since 2010 in the Reggio Emilia province [48]. The Diabetes Registry ascertained disease cases through the use of an *ad hoc* algorithm and six routinely collected data sources, including hospital discharges, drug dispensation directory, biochemistry laboratory file, disease-specific payment exemption, diabetes outpatient clinics, and mortality directory. We focused on disease prevalence at December 31, 2013, since at that date coverage and reliability of the population-based diabetes registry in the Reggio Emilia province was considered to be satisfactory.

We compared the crude prevalence of diabetes between exposed and unexposed cohorts overall and stratifying by sex, age, and country of immigration. We also ran multivariable log-binomial regression models, adjusting for sex (in overall analyses) and age, computing prevalence ratios (PRs) for type 2 diabetes according to exposure status, alongside their 95 % confidence intervals (CIs), in the overall population and in selected subgroups.

The study was approved by the Reggio Emilia Province Ethics Committee (authorization no. 29362/2015).

3. Results

As of December 31, 2013, there were 1310 exposed cohort members and 56,251 unexposed cohort members still alive and residing in the Reggio Emilia province, who were eligible for participation in the present study. From these cohorts, we removed members affected at that date by type 1 diabetes (83 in the unexposed group, none in the exposed one).

In the unexposed cohort, there were 5791 prevalent cases of type 2 diabetes in December 31, 2013, with a disease prevalence of 10.29 %, while the corresponding figure in the exposed cohort was 129, yielding a prevalence of 9.85 %. Prevalence ratio by comparing the selenium-exposed cohort with the unexposed one was 0.95 (95 % confidence interval 0.81–1.12).

In sex-stratified analysis, little difference emerged between the two cohorts (Table 1). In both cohorts, higher prevalence can be noted for males compared with females, with a slightly lower prevalence in the exposed cohort (prevalence ratio 0.90, 95 % confidence interval 0.73–1.13).

There were some differences in age, as shown in Fig. 1, with higher prevalence in older individuals, and slightly higher prevalence in exposed subjects aged 51–60 and 91–110 years, while the opposite was true for age categories 39–50 and 71–80.

When analyses were stratified according to country of birth, there was an excess risk among those who were born abroad, but numbers of subjects were small (Table 1).

4. Discussion

In a natural experiment occurring in an Italian municipality where some residents unknowingly consumed drinking water with high amounts of selenium, we did not identify meaningful changes in long-term diabetes prevalence across exposure groups. Null associations were also observed in analyses stratified by potential effect modifiers such as sex, age, and country of birth. We therefore conclude that additional daily exposure to around 20 μg of inorganic hexavalent selenium, selenate, assuming a daily consumption up to 2.5 L of drinking water [49], does not appreciably increase the risk of type 2 diabetes, contrary to what was demonstrated for organic selenium by the experimental studies [2]. This finding must be viewed against an average background intake of this Italian population of approximately 60–90 μg/day [30,50], largely in the organic forms expected from diet [26,51] apart from individuals with very high fish intake [52]. This additional intake of 20 μg/day of selenate certainly induced a marked difference in exposure to this inorganic selenium species (one of the less common composing the human diet) between exposed and unexposed cohorts, though the overall intake of total selenium in the two study cohorts remained limited (around 110 vs. 90 μg/day). Fortunately, such a naturally occurring increase was unknown to residents and also occurred in a subgroup comparable to the remaining municipal population, thus reducing the risk of bias. However, evidence from RCTs

Table 1
Association between exposure to selenium-contaminated drinking water and diabetes risk, overall and by sex, age and country of birth, adjusting for the remaining variables.

	Exposed		Unexposed			
	Total	Cases of diabetes N (%)	Total	Cases of diabetes N (%)	Prevalence ratio	95 % CI
Overall subjects	1310	129 (9.8)	56251	5791 (10.3)	0.95	0.81–1.12
Sex						
Males	636	69 (10.8)	25993	3102 (11.9)	0.90	0.73–1.13
Females	674	60 (8.9)	30258	2689 (8.9)	1.01	0.80–1.28
Age range (at Dec 31, 2013)						
39–50	394	2 (0.5)	14631	204 (1.4)	0.36	0.09–1.42
51–60	184	14 (7.6)	10366	522 (5.0)	1.44	0.86–2.39
61–70	200	25 (12.5)	11457	1459 (12.7)	1.00	0.70–1.45
71–80	351	53 (15.1)	11387	2032 (17.8)	0.84	0.65–1.08
81–90	158	30 (19.0)	7016	1346 (19.2)	0.97	0.70–1.35
91–110	23	5 (21.7)	1394	228 (16.4)	1.33	0.61–2.92
Country of birth						
Italy	536	50 (9.3)	55688	5741 (10.3)	0.94	0.80–1.11
Abroad	12	2 (16.7)	1298	127 (9.8)	1.35	0.36–5.09

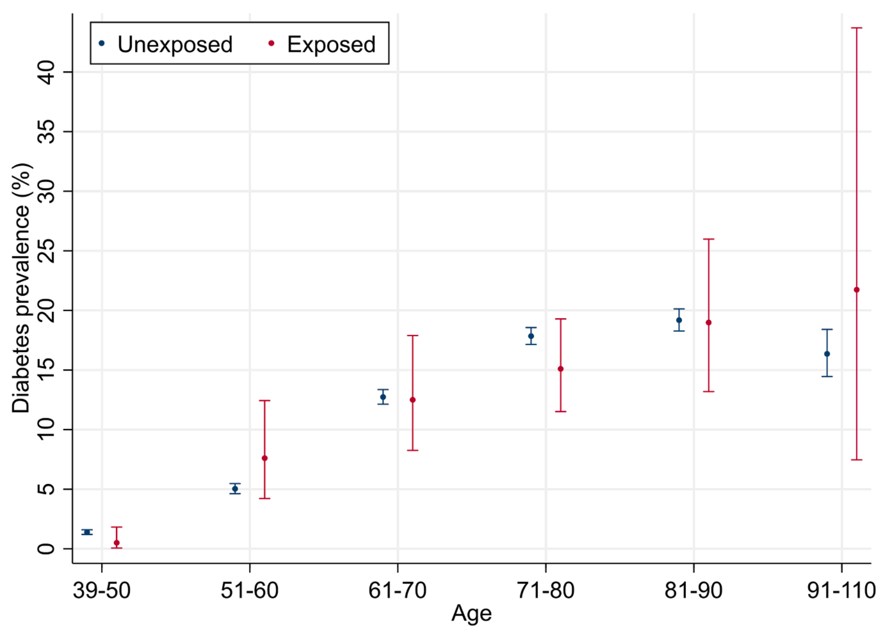

Fig. 1. Age-specific diabetes prevalence in the selenium-exposed and unexposed cohort in the Northern Italy Reggio Emilia municipality at Dec 31, 2013. Dots represent the prevalence (%) and vertical spikes the corresponding 95 % confidence intervals.

indicated a diabetogenic effect of 200 µg/day of supplemental (organic) selenium in addition to background intakes of around 50–100 µg/day [2]. Therefore, either the difference in the amount of intake between our exposed and unexposed cohorts was not large enough to affect diabetes occurrence, or selenate is less likely to induce diabetes compared with organic or other inorganic species.

Some *caveats* must be considered when assessing study results. First, we used prevalence data at around 25 years after the end of the exposure period, and therefore our ascertainment of the outcome, though based on a population-based registry, could not use incidence data and was not further extended in time. We must therefore assume that the induction and latent period of diabetes was not longer than the one considered in this study, and that selenium exposure did not influence diabetes-related mortality. Should the latter assumption not be tenable, i.e. should a higher (or lower) mortality from diabetes have occurred in the exposed cohort (due to diabetes and other chronic diseases), our reliance on prevalence data at a specific time period could have biased the detection of the actual relation between exposure and outcome. Unfortunately, in a mortality analysis previously performed in the study area, deaths from diabetes as primary cause were too few to yield meaningful risk estimates [43]. In addition, we could not follow up cohort members who emigrated outside the province, though this loss was likely unrelated to the exposure status and therefore is not expected to have introduced systematic bias.

We must also temper our conclusion about the absence of a diabetogenic effect by noting that it applies only to the specific chemical form and exposure level present in the study area. For instance, the diabetogenic properties of selenium have been demonstrated in humans in association with administration of organic (or by far mainly organic) selenium, as occurred in all RCTs [2], and therefore this could explain the different findings. Though inorganic selenium forms are generally more toxic than the organic forms, and some animal studies indicated a detrimental effect [24,25,53], this may not hold true for selenium effects on type 2 diabetes in humans. In fact, almost all the laboratory evidence about the adverse effects of selenium on metabolic disease and glycemic control are not related to selenate, but to inorganic tetravalent selenium (selenite) or more frequently to organic selenium forms, such as selenomethionine and the selenoproteins glutathione peroxidase and selenoprotein P [22,23,54–60], selenium compounds able to determine insulin resistance, hyperglycemia and oxidative stress among other effects. In addition, the amount of exposure to selenate in the study area may have been insufficient to elicit a diabetogenic response, and more than around 20 μg/day may be needed to induce adverse effects, an observation of relevance for regulatory purposes [38].

In conclusion, this study suggests that, despite the established capacity of selenium to increase risk of type 2 diabetes at slightly supranutritional levels in randomized trials, such effect may not occur following exposure to selenate, an inorganic selenium species, through drinking water at concentrations close to the European Union 10 μg/L limit.

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Declaration of Competing Interest

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

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