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Health and economic gain attributable to the introduction of the World Health Organization's drinking water standard on arsenic level in Hungary: A nationwide retrospective study on cancer occurrence and ischemic heart disease mortality

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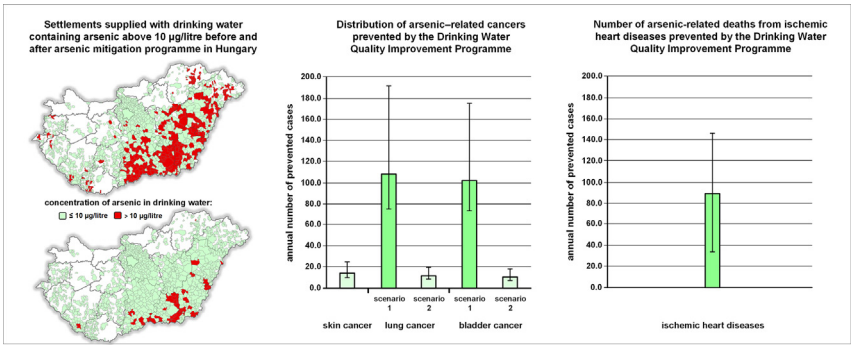
HIGHLIGHTS

- Exposure to arsenic in drinking water is a public health concern worldwide.
- Arsenic mitigation is the most effective way to prevent arsenic-related cancers.
- Cancer risk was estimated before and after a Hungarian arsenic mitigation programme.
- Arsenic mitigation resulted in a significant decrease in lifetime excess cancer risk.
- The health and economic benefits outweighed the cost of the arsenic mitigation.

GRAPHICAL ABSTRACT



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ABSTRACT

The World Health Organization (WHO) estimates that 140 million individuals are at risk from consumption of drinking water containing arsenic at concentrations above the WHO guideline value of 10 µg/l. Arsenic mitigation is considered to be the most effective way to prevent arsenic related diseases. After joining the European Union, Hungary implemented a Drinking Water Quality Improvement Programme (DWQIP) to reduce levels of arsenic in drinking water below the WHO guideline value. But what impact did this have on health? We estimated the change in lifetime excess skin, lung, and bladder cancer risks and mortality from ischaemic heart disease (IHD) associated with chronic arsenic intake among those exposed before (2004–2007) and after (2014–2017) the implementation of DWQIP. A population-based risk assessment approach was used to assess lifetime excess cancer risk applying two scenarios for lung and bladder cancers. The economic benefits of the DWQIP were estimated by the combination of cost of illness and value per statistical life methods. Compared to the period before the DWQIP, its implementation was associated with a significant reduction in arsenic in drinking water [median: 3.0 µg/l interquartile range (IQR): 1.5–12.0 µg/l to median: 2.15 µg/l IQR: 1.0–5.79 µg/l]. The two scenarios were estimated to be associated with 225.2 and 35.9 fewer cancer cases each year. The number of annually prevented IHD deaths was estimated to be 88.9. It was estimated that the benefits of the DWQIP will outweigh its costs. We conclude that reducing arsenic levels in drinking water to 10.0 µg/l

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resulted in significant health and economic benefits. Our study goes beyond the existing research, offering both new insights into the impact of arsenic mitigation and providing a methodological template for similar studies in the many parts of the world that have yet to reduce arsenic exposure.

1. Introduction

Ever since 1992, when it was enshrined in the Maastricht Treaty, the European Union (EU) has been required to ensure a "high level of human health protection" in all its policies. There are many examples of policies that have done so, either directly, such as the creation of the European Centre for Disease Prevention and Control or measures against tobacco, or indirectly, for example through regional development policies (López-Nicolás and Stoklosa, 2019). However, despite calls for assessments of the health impact of these policies, relatively few exist (Lock et al., 2003; Wright et al., 2005). There is, however, considerable and so far underexploited potential to take advantage of natural experiments associated with the implementation of EU policies, one of which, the reduction of arsenic in drinking water in Hungary, we now report.

When Hungary was preparing to join the EU in 2004, it progressively adopted the Acquis Communautaire, the accumulated body of European legislation. This included the 1998 Directive on the quality of water intended for human consumption, incorporated into Hungarian law in 2001 (The Council of the European Union, 1998; The Hungarian Government, 2001). Among its many consequences was a reduction in permitted levels of arsenic, a known cardiovascular toxicant and carcinogen linked to cancers of the skin, bladder, lung, liver, and prostate, from the value of ≤ 50 μg/l to the level of ≤ 10 μg/l recommended by the World Health Organization (Argos et al., 2010; Chappells et al., 2014; Chen et al., 2011; Palma-Lara et al., 2020; Rahaman et al., 2021). This was achieved, in large part, by a Drinking Water Quality Improvement Programme (DWQIP), financed mainly by the EU, which began in 2007. The main objective of this programme was to reduce the concentration of chemical contaminants of geological origin in drinking water, including arsenic, boron and fluoride of which, according to the number of affected population and health risk, arsenic was the most significant (Leonardi et al., 2012; National Public Health Centre, 2016; Vargha et al., 2019). The financial support provided by the DWQIP enabled the local suppliers of drinking water to affected municipalities to introduce new water treatment technologies to remove arsenic. The project accelerated after 2012 and most technological developments were completed by the mid-2010s. The programme resulted in a significant improvement in drinking water quality in Hungary. Previously, drinking water supplied to an estimated 1,680,000 Hungarian residents (approximately 15 % of the population) contained arsenic above the WHO standard but this had fallen to 44,512 by 2017 (calculated from data published by the National Institute of Public Health) (Dura et al., 2014; National Institute of Public Health, 2017). But what impact did this have on health?

There is little research from elsewhere to inform this assessment. Although cancer risk from exposure to arsenic in drinking water has been estimated in many epidemiological studies, only one assessed the health benefits of a nationwide arsenic mitigation programme (Nigra et al., 2017). Nigra et al. (2017) estimated the lifetime excess cancer risk (LECR) before and after the US Environmental Protection Agency also reduced the maximum permitted level of arsenic to 10 μg/l (Nigra et al., 2017). The authors used urinary concentrations of arsenic and its main metabolite (dimethylarsinate) in a representative population sample as measures of exposure (Nigra et al., 2017). Although this is an elegant approach and they considered the impact of food and tobacco smoke on urinary arsenic and its metabolite levels, these biomarkers can be subject to residual confounding (Joseph et al., 2015; Tsuji et al., 2019). These can be eliminated by using the arsenic concentration of drinking water consumed as the measure of exposure. In addition, it provided a point estimate of LECR and did not take into account the diversity of risk arising from differences in sex, patterns of drinking water consumption, and distribution of body weight in the population (Nigra et al., 2017). Besides malignant tumours, consuming arsenic contaminated drinking water can increase mortality from cardiovascular diseases (Argos et al., 2010; Chen et al., 2011). Therefore, to obtain a full picture of the health and economic impacts of a nationwide arsenic mitigation programme, mortality from cardiovascular diseases should also be investigated. We are able to complement the existing methodology using a comprehensive risk assessment approach in which we estimate not only the number of avoided cases of skin, lung, and bladder cancers but also avoided deaths from ischemic heart disease (IHD) associated with the reduction of chronic exposure to arsenic in drinking water. We applied a probabilistic, population-based Monte Carlo simulation that accounted for the population-level distribution of body weight, sex, and drinking water consumption levels to estimate the expected number of cancer cases avoided. In addition, we used age and sex specific mortality data to assess the number of deaths from IHD prevented by the DWQIP. This also allows us to estimate the health and economic benefits of the DWQIP, finding that it resulted in a significant decrease in LECR and mortality from IHD due to exposure to arsenic in drinking water and yielded considerable public health and economic benefits to the Hungarian population.

2. Data and methods

2.1. Water supply and monitoring of drinking water quality

In the vast majority of Hungarian settlements, drinking water is provided by a single water supply system that serves the entire municipality but some water supply systems serve the population of more than one settlement. Thus, the ratio of water supply systems to municipalities is 0.46 overall, calculated from the number of settlements (3155) and water supply systems (1462) (Hungarian Central Statistical Office, 2022; Vargha et al., 2019). Thus, we can assume that the inhabitants of each settlement consume drinking water containing identical arsenic levels. The monitoring of drinking water quality in Hungary is regulated by a Government Decree 201/2001. (X. 25.) in accordance with the European Union Drinking Water Directive 98/83/EC (The Council of the European Union, 1998; The Hungarian Government, 2001). This decree requires monitoring of the drinking water supplied to the consumers' taps. The decree applies to both public and private suppliers. However, drinking water produced by individuals for their own consumption (private wells) is exempt from monitoring requirements. The minimum sampling frequency for chemical contaminants, including arsenic, depends on the volume of drinking water produced per day by the suppliers but it is independent of the type of water source. If the volume of drinking water produced per day is <100 m^3 the number of required samples is determined by local public health authorities. At least one sample per year is required to be analysed when the volume of drinking water produced per day is between 100 and 1000 m^3. The sampling frequency increases gradually to 10 per year if the volume of drinking water produced per day is 100,000 m^3 and with 1 extra sample for each additional 25,000 m^3 per day. All samples are analysed in accredited laboratories.

2.2. Data sources

Water quality data, including arsenic concentration, are required to be submitted directly by the water quality monitoring laboratories to the

Information System on Water for Human Use (National Public Health Centre, 2016; Vargha et al., 2019). This information system is operated by the National Public Health Centre of Hungary [(NPHCH), National Public Health Centre, 2016; Vargha et al., 2019]. Data on the concentration of arsenic in drinking water in Hungarian settlements were provided by the NPHCH. All samples were collected at consumers' taps so they reflect arsenic concentrations after water treatment (The Council of the European Union, 1998; The Hungarian Government, 2001). Data on male and female population living in Hungarian settlements were obtained from the Hungarian Central Statistical Office (Hungarian Central Statistical Office, 2022). Sex–specific reference values for per capita drinking water intake from infancy to adulthood and life–stage specific body weights separately for males and females were retrieved from the European Food Safety Authority [(EFSA), European Food Safety Authority, 2010; European Food Safety Authority, 2012]. These data are reported in Table 1. Oral cancer slope factors (CSFs) for skin cancer used to calculate LECRs were taken from the United States Environmental Protection Agency [(US EPA), United States Environmental Protection Agency, 2017]. Cancer slope factors proposed for lung and bladder cancer were from the US EPA and United States Food and Drug Administration [(US FDA), Food and Drug Administration, 2016; United States Environmental Protection Agency, 2010].

2.3. Database development

The original dataset provided by NPHCH included 101,961 records on concentrations of arsenic in drinking water samples collected from 3047 Hungarian settlements. These had an average population of 9,927,000 between 2004 and 2017. First, arsenic concentrations were considered to be equal to the limit of detection (LOD) of 1.0 μg/l when levels were below the LOD. Second, the periods before and after arsenic mitigation were defined as 2004–2007 and 2014–2017, respectively. The number of records evaluated were 15,280 and 33,154 in the periods 2004–2007 and 2014–2017, respectively. This provided 48,434 data points with arsenic concentration for further analysis. The mean numbers of records per municipal drinking water systems were 13.4 and 29.2 in the periods 2004–2007 and 2014–2017, respectively. Our study included those municipalities from which the reports on arsenic concentration contained at least 3 records from both of the periods, before and after arsenic mitigation. There are thousands of small settlements in Hungary where the volume of drinking water supplied is <100 m^3 per day. According to the Government Decree, the local public health authorities regulate the sampling frequency in these municipalities (The Hungarian Government, 2001) so we lacked consistent annual data from them. Following exclusion of these settlements, our analysis included 1137 municipalities (37 % of the total) covering 7,206,029 people (72.6 % of the total population) and 7,145,963 people (71.9 % of the total population) in the periods 2004–2007 and 2014–2017, respectively. Third, the median arsenic level measured in each municipality was calculated for both periods. The Shapiro–Wilk test showed that the calculated median values were non–normally distributed so differences in the concentrations of arsenic in drinking water in the selected settlements before and after the DWQIP were determined by Mann–Whitney *U* tests. Fourth, the size of male and female populations was assigned to each municipality. Statistical analyses were carried out using IBM SPSS statistics 28.0 software (IBM Inc., Armonk, New York, USA). Values of $p < 0.05$ were considered statistically significant. The flow chart of the database development is reported in Fig. 1.

Table 1
Sex–specific reference values used to estimate arsenic–related lifetime excess cancer risks.

Life stage	Body weight [kg]		Drinking water consumption/capita [litre/day]	
	Male	Female	Male	Female
0–0.5 year[a]	5.8 (3.2–8.5)	5.8 (3.2–8.5)	0.1–0.19[b]	0.1–0.19[b]
0.5–1.0 year	8.7 (7.0–11.0)	8.7 (7.0–11.0)	0.8–1.0	0.8–1.0
1.0–3.0 years	11.6 (8.7–15.9)	11.6 (8.7–15.9)	1.1–1.3	1.1–1.3
3.0–10.0 years	21.7 (14.0–37.0)	21.7 (14.0–37.0)	1.6–2.1	1.3–1.9
10.0–14.0 years	42.0 (29.4–62.0)	42.0 (29.4–62.0)	2.1	1.9
14.0–18.0 years	60.0 (45.0–83.0)	60.0 (45.0–83.0)	2.5–4.0	2.0–3.1
18.0–65.0 years	82.0 (63.0–105.0)	66.0 (50.0–90.7)	2.5–4.0	2.0–3.1
Males: 65.0–72.5 years	82.5 (65.0–102.0)	–	2.5–4.0	–
Females: 65.0–79.3 years	–	71.0 (53.0–92.0)	–	2.0–3.1

Data on sex–specific body weight and per capita drinking water consumption were obtained from the European Food Safety Authority (European Food Safety Authority, 2010; European Food Safety Authority, 2012).

[a] This was obtained by combination of life–stage categories of 0–0.25 year and 0.25–0.5 year.

[b] Expressed in litre/body weight kg/day.

2.4. Estimation of arsenic-related lifetime excess cancer risks

To estimate risks of skin, lung, and bladder cancer from chronic exposure to arsenic in drinking water separately for the male and female population of each settlement in our database, we estimated LECRs using @Risk for Excel software, version 8.1 (Palisade Corporation, Ithaca, NY, USA) in combination with probabilistic Monte Carlo simulations with 10,000 iterations, Latin Hypercube sampling, and the Mersenne Twister random number generator (Bujdosó et al., 2019). LECRs were estimated for both 2004–2007 (before arsenic mitigation) and 2014–2017 (after arsenic mitigation). First, the distributions of bodyweight–adjusted daily arsenic intakes (BWDAIs) were determined separately for males and females using the life–stage categories reported in Table 1. Considering the average life expectancy at birth in Hungary in 2017, at 72.5 years for males, 79.3 years for females, separate life–stages were defined for males and females aged 65–72.5 years and 65–79.3 years, respectively. The distributions of BWDAIs were calculated by the following formula (Nigra et al., 2017):

$$BWDAI = \frac{C_{As} x\ WIx\ EF\ x\ ED}{BW\ x\ AT}$$

where, C_{As} is the median concentration of arsenic in drinking water (mg/l), WI is the distribution of life–stage and sex–specific daily water intake (litre/day, see data in Table 1), assuming a uniform distribution, EF is the exposure frequency (365 days), ED is the exposure duration, calculated as the number of years spent in each life–stage (years), BW is the distribution of life–stage and sex specific body weight (kg, see data in Table 1) supposing a truncated normal distribution, AT is the averaging time (365 days × number of years spent in the specific life–stage). Second, to take into account variations in water consumption, body weight, and duration of exposure in different life–stages, the share of years spent in each life–stage (SYSLS) within the lifetime was determined. SYSLS was calculated by dividing the number of years spent in each life–stage with the sex specific life expectancy at birth in Hungary in 2017 (see above). To assess the life–stage weighted distributions of BWDAIs, the values of SYSLS were multiplied by the distributions of BWDAIs. Subsequently, to determine the distribution of the lifetime daily dose of arsenic (LDDA), the distributions of the life–stage weighted BWDAIs were summed. Third, to obtain settlement specific distributions of skin, lung, and bladder LECRs, the distributions of LDDA were multiplied by the disease specific oral CSFs of inorganic arsenic. The CSF method of estimating excess skin cancer risk was published by the US EPA (United States Environmental Protection Agency, 2017). Two scenarios were used to estimate lung and bladder LECRs. Scenario 1 used CSFs proposed for lung and bladder cancers by the US EPA for estimation of excess cancer risks (United States Environmental Protection Agency, 2010). Scenario 2 used CSFs for lung and bladder cancers proposed by the US FDA (Food and Drug Administration, 2016). The CSFs are shown in Table 2. The results were expressed in LECR/1,000,000 population. Fourth,

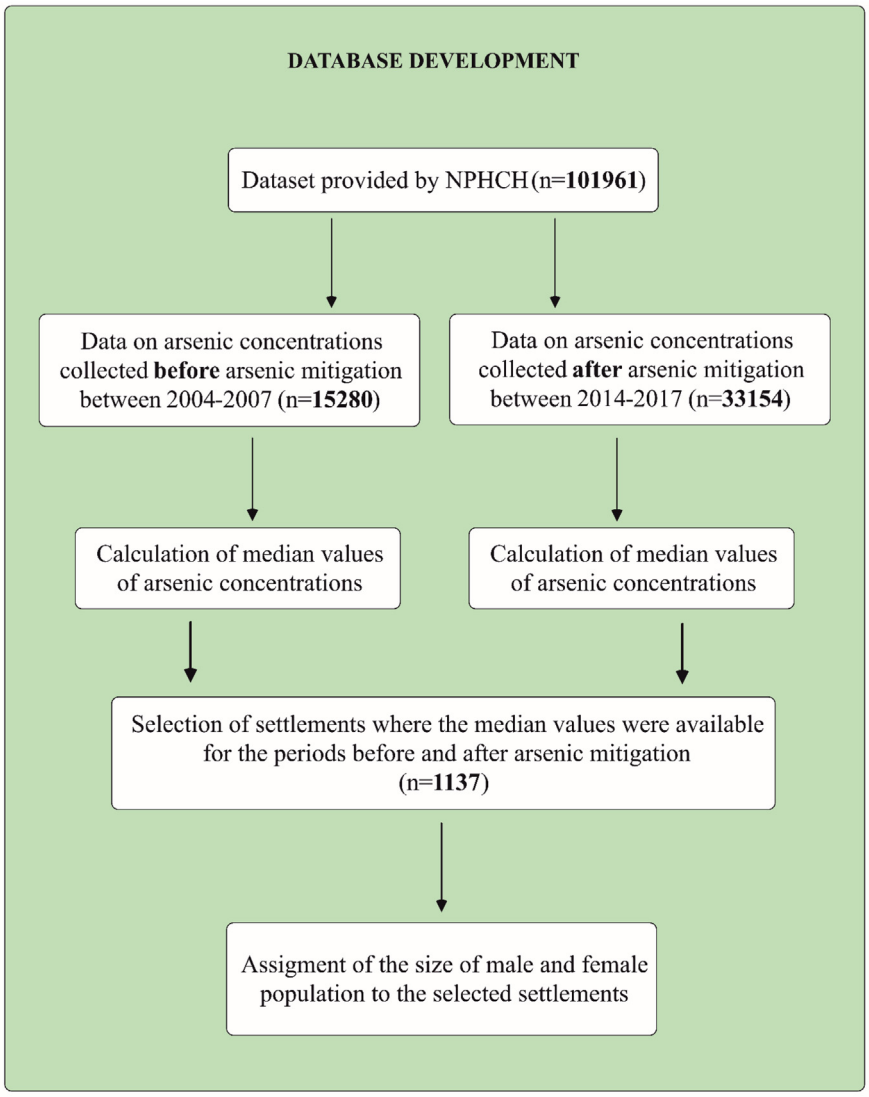

Fig. 1. Flowchart of database development; NPHCH: National Public Health Centre of Hungary

the distributions of skin, lung, and bladder LECRs for the population of all 1137 settlements were determined. The proportion of male and female population living in each settlement was obtained by dividing the number of male or female inhabitants by the total population of the selected municipalities. Then, the resulting proportions were multiplied with the sex- and settlement specific LECRs separately for each municipality. Finally, the distributions obtained for sex- and settlement specific LECRs estimated before and after arsenic mitigation were summed separately for males and females. The distributions of the corresponding skin, lung, and bladder LECR values before and after arsenic mitigation were compared using the Kruskal–Wallis test with the Dunn–Bonferroni post hoc method. Values of $p < 0.05$ were considered statistically significant.

Table 2
Cancer slope factors used to estimate arsenic–related lifetime excess cancer risks.

Cancer slope factor									
Skin cancer		Lung cancer scenario 1		Lung cancer scenario 2		Bladder cancer scenario 1		Bladder cancer scenario 2	
Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
1.5	1.5	6.7	16.6	0.96	1.36	11.2	10.5	0.89	1.39

Cancer slope factors were used to estimate arsenic–related lifetime excess skin, lung and bladder cancer risks. The cancer slope factor used to estimate excess skin cancer risk was published by the United States Environmental Protection Agency (2017). Different cancer slope factors reported by the United States Environmental Protection Agency (2010) and United States Food and Drug Administration (2016) were used to estimate excess lung and bladder cancer risks. Using cancer slope factors proposed for lung and bladder cancers by the United States Environmental Protection Agency for estimation of excess cancer risks was defined as "scenario 1". Using cancer slope factors suggested for lung and bladder cancers by the United States Food and Drug Administration for estimation of excess cancer risks was defined as "scenario 2".

2.5. Estimation of arsenic-related mortality risk from ischemic heart disease

The cardiovascular risk coefficient (β) used to estimate arsenic-related mortality from IHD was calculated from the hazard ratio (HR) of 1.29 (95 % CI: 1.10–1.52) per 115 μg/l change in the arsenic concentration of water consumed (Chen et al., 2011). First, β was calculated by the following formula (Greco et al., 2019):

$$\beta = \frac{ln\,(HR)}{\Delta C}$$

Table 3
Values used to estimate the economic benefit of Drinking Water Quality Improvement Programme.

Disease	Cost of illness [euro]	Value per statistical life [million euro]	5 year relative survival males [%]	5 year relative survival females [%]
Skin cancer	2262.0	4.3	91.6	91.6
Lung cancer	2694.0	4.3	9.4	14.8
Bladder cancer	4599.0	4.3	64.3	68.1
Ischemic heart disease	–	4.3	–	–

Cost of illness values were published by Brodszky et al., 2019 and Marcellusi et al., 2020. Data on value per statistical life were described by Viscusi, 2019. Data on 5 year relative survival were reported by the European Cancer Information System, 2022 and Gatta et al., 2011.

where, ΔC is 115 μg/l change in arsenic concentration, HR is 1.29. In addition, both the lower (1.10) and upper (1.52) border of confidence interval (CI) of the HR were used to consider the uncertainty of risk estimation. In this manner we obtained three β values for HR (2.21×10^{-3} per μg/l), lower border of CI of HR (8.3×10^{-3} per μg/l), and upper border of CI of HR (3.6×10^{-3} per μg/l). Second, we used the following formula to determine the annual mortality risk (AMR) from IHD attributable to arsenic exposure:

$$AMR = 1 - e^{-\beta\Delta C}$$

where, ΔC is 1 μg/l change in arsenic concentration, β is the cardiovascular risk coefficient. To calculate AMR and its uncertainty, we used each beta values obtained separately.

Third, to estimate the AMR for the Hungarian male and female population, we used the sex-specific death rates from IHD causes showing the closest association with arsenic exposure (National Research Council, 2013), coded as I20-I25 in the International Classification of Diseases (World Health Organization, 1990, International Classification of Diseases 10th Revision). We assumed that arsenic-related IHD mortality risk would be lower following the DWQIP so we took IHD death rates in 2019 as a baseline. Forth, we multiplied the AMR values with the baseline IHD mortality of 77.6/100,000 population and 1605.7/100,000 population for males aged 0–64 years and 65 years and older, respectively. Similarly, we multiplied the AMR values with the baseline cardiovascular mortality of 24.8/100,000 population and 1373.6/100,000 population for females aged 0–64 years and 65 years and older, respectively.

2.6. Estimation of prevented cancer cases and avoided mortality from ischemic heart disease due to the Drinking Water Quality Improvement Programme

The average number of men and women living in the selected municipalities between 2004 and 2007 was calculated separately. To determine the distributions of excess skin, lung and bladder cancer cases in males and females in each settlement, the averages obtained were multiplied by the distributions LECRs. Subsequently, to estimate the distributions of excess cancer cases in the selected municipalities ($n = 1137$) in the period between 2004 and 2007, settlement specific distributions of excess skin, lung and bladder cancer cases were summed separately. The distributions of excess cancer cases in the selected municipalities in the period between 2014 and 2017 were determined in the same manner. To estimate the distributions of cancer cases prevented due to the DWQIP, the distributions of sex specific excess skin, lung and bladder cancer cases in the period between 2014 and 2017 (henceforth excess cancer cases between 2014 and 2017) were subtracted from those between 2004 and 2007 (henceforth excess cancer cases between 2004 and 2007). To determine the distributions of skin, lung and bladder cancer cases prevented annually, their distributions were divided separately by the sex specific life expectancy at birth in Hungary in 2017. The distributions of these type of cancers for both sexes were assessed by summing the number of sex specific cancer cases prevented annually.

We also estimated the settlement-specific number of arsenic-related IHD deaths among males at ages 0–64 and 65–72.5 years. To obtain these data, we multiplied the AMR values for the Hungarian male population with the median arsenic concentration recorded at each municipality and weighted by the share of years spent in the life-stages defined above. Then, the resulting life-stage weighted AMR values were summed and multiplied by the number of males living in each settlement. The settlement-specific number of IHD deaths attributable to arsenic exposure among females at ages 0–64 and 65–79.3 years was calculated in the same manner. Subsequently, to assess the sex-specific number of excess arsenic-related IHD deaths in the selected municipalities in the period between 2004 and 2007, the settlement-specific number of arsenic-related IHD deaths among males and females were summed separately. The sex-specific number of excess arsenic-related IHD deaths in the selected municipalities in the period between 2014 and 2017 was determined in the same way. To estimate the number of avoided deaths from IHD associated with the DWQIP, the sex-specific number of excess arsenic-related IHD deaths in the period between 2014 and 2017 (henceforth IHD deaths between 2014 and 2017) was subtracted from that between 2004 and 2007 (henceforth IHD deaths between 2004 and 2007).

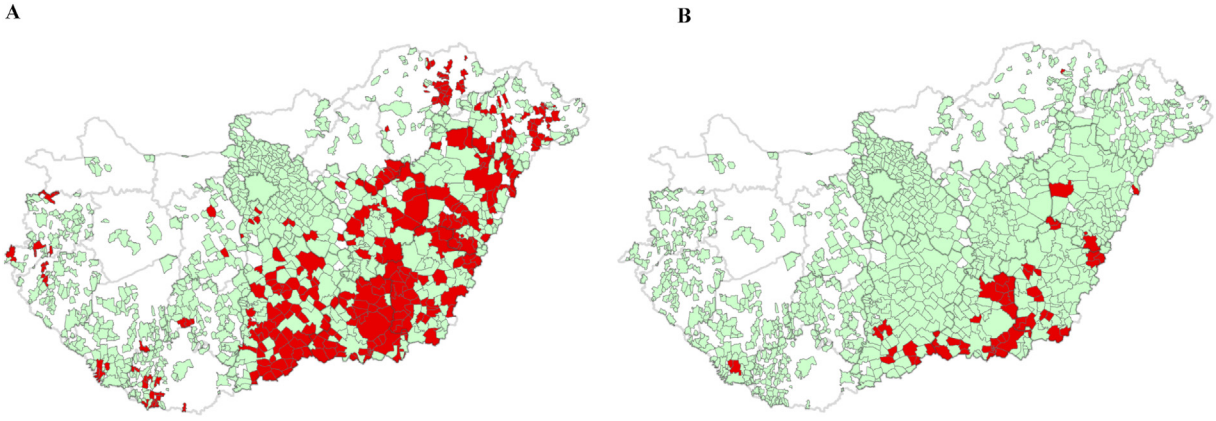

Fig. 2. Settlements supplied with drinking water containing arsenic above 10 μg/l before and after arsenic mitigation. The map shows all 1137 municipalities from which the reports on arsenic concentration contained at least 3 records from both of the periods before (2004–2007) and after arsenic mitigation (2014–2017). The white areas include those municipalities where data on arsenic concentration did not meet these criteria. The green and red areas indicate the administrative zones of the settlements supplied with drinking water containing arsenic below and above 10 μg/l, respectively. Panel A: before arsenic mitigation (2004–2007), panel B: after arsenic mitigation (2014–2017).

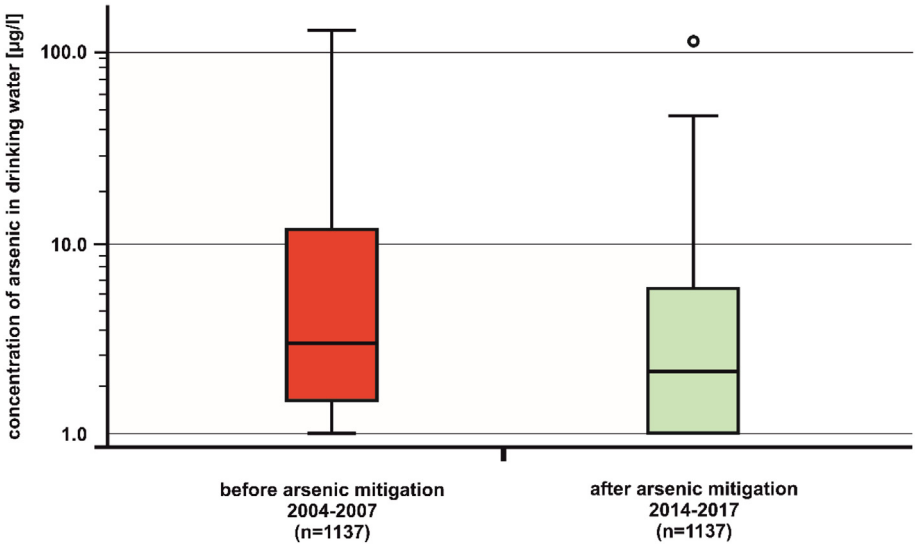

Fig. 3. Arsenic concentration in drinking water before and after arsenic mitigation. The medians of arsenic levels measured in 1137 municipalities were calculated for both the periods before (2004–2007) and after (2014–2017) arsenic mitigation. Differences in the concentrations of arsenic in drinking water before and after the drinking water quality improvement programme were determined by Mann–Whitney *U* tests. Values of $p < 0.05$ were considered statistically significant. Median concentrations, their interquartile ranges, and 1st and 99th percentiles are shown.

2.7. Estimation of the proportion of prevented cancer cases and avoided mortality from ischemic heart disease due to the Drinking Water Quality Improvement Programme

The number of new skin, lung, and bladder cancer cases/year for the period between 2004 and 2007 was obtained from the database of the Hungarian National Cancer Registry (Hungarian Cancer Registry, 2022). From these data the 4–year average was calculated for each cancer separately. Next, the distributions of skin, lung, and bladder cancer cases prevented annually (excess cancer cases between 2004 and 2007 minus excess cancer cases between 2014 and 2017) were divided by the 4–year average of the same cancer type registered in Hungary between 2004 and 2007. The resulting quotients were multiplied by 100 to obtain the proportion of new skin, lung, and bladder cancer cases prevented by the DWQIP.

The number of IHD deaths between 2004 and 2007 was obtained from the database of the statistical office of the European Union (European Commission, 2022. Eurostat Database. European Statistical Office). Next, the number of IHD deaths prevented annually (number of IHD deaths between 2004 and 2007 minus number of IHD deaths between 2014 and 2017) was divided by the average number of IHD deaths in Hungary between 2004 and 2007 separately for males and females. Subsequently, the total number of IHD deaths prevented annually (total number of IHD deaths between 2004 and 2007 minus total number of IHD deaths between 2014 and 2017) was divided by the average number of IHD deaths in Hungary between 2004 and 2007. The resulting quotients were multiplied by 100 to obtain the proportion of IHD deaths prevented by the DWQIP.

2.8. Estimation of the economic benefits of Drinking Water Quality Improvement Programme

To estimate the economic benefits of arsenic mitigation due to decreases in cancer morbidity and mortality we applied the combination of cost of illness (COI) and value of a statistical life (VSL) methods (Greco et al., 2019). In this case, median values, 1st and 99th percentiles of distributions were obtained. COI estimates the reduction in the economic burden of a disease/prevented case of the same disorder (Greco et al., 2019). To determine the economic benefit due to decreased cancer morbidity, the distributions of annually prevented skin, lung and bladder cancer cases were multiplied by the 5 year relative survival, the proportion of cancer patients survived 5 years after their disease was diagnosed, and the disease specific

Table 4
Distribution of arsenic–related lifetime excess cancer risks before and after the Drinking Water Quality Improvement Programme.

	LECR+ from skin cancer/1 million persons	Scenario 1		Scenario 2	
		LECR from lung cancer/1 million persons	LECR form bladder cancer/ 1 million persons	LECR from lung cancer/1 million persons	LECR from bladder cancer/ 1 million persons
Male, before arsenic mitigation	371.3 (289.8–521.6)	1657.6 (1306.5–2332.0)	2769.8 (2183.1–3896.6)	237.4 (187.1–334.0)	220.2 (173.5–309.7)
Male, after arsenic mitigation	212.2* (166.3–301.6)	946.9* (736.7–1342.4)	1582.85* (1231.5–2244.0)	135.7* (105.6–192.4)	125.8* (97.9–178.4)
Female, before arsenic mitigation	325.48 (254.52–464.99)	3608.3 (2809.1–5196.4)	2282.3 (1776.8–3286.9)	295.6 (230.1–425.7)	302.1 (235.2–435.1)
Female, after arsenic mitigation	187.7* (146.2–271.6)	2081.2* (1621.8–2983.1)	1316.4* (1025.9–1886.9)	170.5* (132.9–244.4)	174.3* (135.8–249.8)

Cancer slope factors were used to estimate arsenic–related lifetime excess skin, lung and bladder cancer risks. The cancer slope factor used to estimate lifetime excess skin cancer risk was published by the United States Environmental Protection Agency (2017). Using cancer slope factors proposed for lung and bladder cancers by the United States Environmental Protection Agency (2010) for estimation of excess cancer risks was defined as "scenario 1". Using cancer slope factors suggested for lung and bladder cancers by the United States Food and Drug Administration (2016) for estimation of excess cancer risks was defined as "scenario 2". The distributions of the corresponding LECR values before and after arsenic mitigation were compared using the Kruskal–Wallis test with the Dunn–Bonferroni post hoc method. The periods before and after arsenic mitigation were defined as 2004–2007 and 2014–2017, respectively. Median values, 1st and 99th percentiles (in brackets) are shown. +LECR: lifetime excess cancer risk.
* $p < 0.001$.

Table 5
Distribution of arsenic–related cancers prevented by the Drinking Water Quality Improvement Programme.

	Number of prevented skin cancer cases	Scenario 1		Scenario 2	
		Number of prevented lung cancer cases	Number of prevented bladder cancer cases	Number of prevented lung cancer cases	Number of prevented bladder cancer cases
Male	7.5 (1.8–14.9)	33.4 (8.2–66.4)	55.7 (13.7–111.0)	4.8 (1.2–9.5)	4.4 (1.1–8.8)
Female	6.6 (1.4–13.6)	73.5 (16.4–151.4)	46.5 (10.4–95.8)	6.0 (1.3–12.4)	6.2 (1.4–12.7)
Total	14.3 (6.6–24.3)	107.6 (44.1–191.4)	103.3 (46.9–175.8)	10.9 (4.8–18.7)	10.7 (4.7–18.4)

The distributions of arsenic–related cancers prevented by the Drinking Water Quality Improvement Programme were calculated from lifetime excess cancer risks. The cancer slope factor used to estimate lifetime excess skin cancer risk was published by the United States Environmental Protection Agency (2017). Using cancer slope factors proposed for lung and bladder cancers by the United States Environmental Protection Agency (2010) for estimation of excess cancer risks was defined as "scenario 1". Using cancer slope factors suggested for lung and bladder cancers by the United States Food and Drug Administration (2016) for estimation of excess cancer risks was defined as "scenario 2". Median values, 1st and 99th percentiles (in brackets) are presented.

COI. Data published on cancer specific COIs, VSL, and 5 year relative survival are presented in Table 3 (Brodszky et al., 2019; European Cancer Information System, 2022; Gatta et al., 2011; Marcellusi et al., 2020; Viscusi, 2019).

Costs saved by reduced mortality were determined for each cancer type separately using the VSL approach. By definition, VSL is the amount of money that a population in a country is collectively willing to pay to avoid one statistical case of premature death from a disease associated with environmental pollution (Viscusi, 2019). The VSL related to the Hungarian population was multiplied by the distributions of skin, lung, and bladder cancer cases prevented annually and the proportion of cancer patients who died within 5 years after their disease was diagnosed.

To calculate the economic gain due to prevention of arsenic-related mortality from IHD, we used only the VSL method. The reason for this was that mortality data are not suitable to obtain the COI values for IHD. In contrast to arsenic-related cancers, a large proportion of IHD is confirmed only by autopsy following the patients' death (Grey et al., 2017; Mehta et al., 1997). Most of these deaths have been reported to be sudden therefore, they are not included in the incidence of IHD which is necessary to estimate the COI (Grey et al., 2017; Mehta et al., 1997). Considering the VSL (4.3 million euros/death), the economic burden of arsenic-related mortality from IHD is substantially larger than that of the annual treatment of a patient with this disease (25,000 euros/patient), we used mortality data to avoid the underestimation of the economic benefits of the arsenic mitigation programme (Viscusi, 2019; Wilkins et al., 2017). The economic benefit due to a decrease in IHD mortality was estimated by multiplying the number of annually prevented IHD deaths by the VSL related to the Hungarian population. In this case, a point estimate and its uncertainty interval were obtained.

The total economic benefit of the DWQIP was calculated by summing the costs saved due to decreases in cancer morbidity and mortality estimated according to scenario 1 and 2 as well as death from IHDs. (See the definition of these scenarios in Section 2.4) The total economic benefit of the DWQIP was the sum of median and point estimate values. Finally, to calculate the return period for the amount of money invested in the DWQIP, the financial support of the EU was divided by the total economic benefit of the programme. All monetary values were adjusted for inflation and expressed in 2021 euro exchange rate.

3. Results

As shown in Fig. 2, the number of settlements supplied with drinking water containing arsenic above 10 μg/l decreased from 307 to 55 between 2004 and 2007 and 2014–2017, respectively (panels A and B). Considering all of the 1137 municipalities included in our study, the distribution of median arsenic concentration in drinking water before (median: 3.0 μg/l IQR: 1.5–12.0 μg/l) and after the DWQIP (median: 2.15 μg/l IQR: 1.0–5.79 μg/l) differed significantly (Fig. 3). Table 4 shows how skin, lung, and bladder LECR values for males and females fell significantly between 2004 and 2007 and 2014–2017. Table 5 presents the distributions of skin, lung, and bladder cancer cases prevented by the DWQIP for males and females. Table 6 demonstrates the proportion of skin, lung, and bladder cancer cases prevented by the DWQIP for males and females.

The number and proportions of arsenic–related IHD deaths prevented by the DWQIP are reported in Table 7. Compared to males, the number and proportions of IHD deaths avoided were higher among females (Table 7). Table 8 reports the estimated economic benefits derived from the prevention of arsenic–related skin, lung, and bladder cancers. Using COI, the greatest economic benefit derived from the prevention of arsenic–related bladder cancer morbidity while the lowest was from that of lung cancer in both scenarios. Using the VSL, with scenarios 1 and 2 the greatest economic benefit derived from the prevention of arsenic–related lung cancer mortality whereas the lowest was from that of skin cancer. The total estimated economic benefits of the DWQIP are shown in Table 9.

Table 6
Proportions of arsenic–related cancers prevented by the Drinking Water Quality Improvement Programme.

	Proportion of prevented skin cancer cases [%]	Scenario 1		Scenario 2	
		Proportion of prevented lung cancer cases [%]	Proportion of prevented bladder cancer cases [%]	Proportion of prevented lung cancer cases [%]	Proportion of prevented bladder cancer cases [%]
Male	0.1 (0.0–0.3)	0.5 (0.1–0.9)	2.9 (0.7–5.8)	0.1 (0.0–0.1)	0.2 (0.1–0.5)
Female	0.1 (0.0–0.2)	1.9 (0.4–4.0)	5.7 (1.3–11.8)	0.2 (0.0–0.3)	0.8 (0.2–1.6)

The distributions of proportions of arsenic–related cancers prevented by the Drinking Water Quality Improvement Programme were calculated from the distributions of the avoided arsenic-related cancer cases. The distributions of arsenic–related cancers prevented by the Drinking Water Quality Improvement Programme were calculated from lifetime excess cancer risks. The cancer slope factor used to estimate lifetime excess skin cancer risk was published by the United States Environmental Protection Agency (2017). Using cancer slope factors proposed for lung and bladder cancers by the United States Environmental Protection Agency (2010) for estimation of excess cancer risks was defined as "scenario 1". Using cancer slope factors suggested for lung and bladder cancers by the United States Food and Drug Administration (2016) for estimation of excess cancer risks was defined as "scenario 2". Median values, 1st and 99th percentiles (in brackets) are demonstrated.

Table 7
Number and proportions of arsenic–related deaths from ischemic heart diseases prevented by the Drinking Water Quality Improvement Programme.

	Number of prevented IHD deaths	Proportion of prevented IHD deaths [%]
Male	39.6 (14.8–65)	0.2 (0.1–0.4)
Female	48.3 (18.1–79.3)	0.3 (0.1–0.4)
Total	88.9 (33.3–146.1)	0.3 (0.1–0.4)

The number of arsenic-related deaths from ischemic heart diseases (IHDs) prevented by the Drinking Water Quality Improvement Programme (DWQIP) was calculated by subtracting the sex-specific number of excess arsenic-related IHD deaths in the period between 2014 and 2017 from that between 2004 and 2007. The proportion of arsenic-related IHD deaths prevented by the DWQIP was calculated by dividing the number of arsenic-related IHD deaths prevented annually with the average number of IHD deaths in Hungary between 2004 and 2007 separately for males and females. Subsequently, the total number of IHD deaths prevented annually (total number of IHD deaths between 2004 and 2007 minus total number of IHD deaths between 2014 and 2017) was divided by the average number of IHD deaths in Hungary between 2004 and 2007. The point estimates and lower and upper borders of their uncertainty interval are shown. They were determined by using the hazard ratio and its 95 % confidence interval as reported by Chen et al. (2011).

4. Discussion

From a public health perspective, the case for reducing arsenic levels in drinking water should be obvious. Yet, when the first proposals to reduce it to the current levels emerged they were attacked by some water companies who complained about the high cost they would incur while, in their estimation, the health benefits would be slight and "most of the cancers [avoided] … would be curable" (WaterWorlds eNewsletters, 2000).

While this is not the first study to show significant health benefits, it does go beyond the existing research, offering both new insights into the impact of arsenic mitigation and providing a methodological template for similar studies in many parts of the world lacking effective mechanisms to reduce exposure. The few previous studies of the effectiveness of an implemented arsenic mitigation programme (Nigra et al., 2017; Smith et al., 2018) used different approaches to assess the effect of reduction in arsenic exposure on associated disease burden. In an ecological study, 40 years after intervention the mortality rates from lung, bladder, and kidney cancers and acute myocardial infarction in a region of Chile affected by arsenic exposure were compared with those of in all the rest of this country (Smith et al., 2018). This intervention was associated with a decrease in the average concentration of arsenic in drinking water from 193.3 μg/l to 19.6 μg/l between 1971 and 1977 and 2005–2010, while arsenic concentrations met the threshold value of 10 μg/l in some cities between 2005 and 2010 (Smith et al., 2018). However, 32.2 % of the population in the affected area was still consuming drinking water containing arsenic above the standard in the same period (Smith et al., 2018). They concluded that the mortality risk from arsenic-related cancers can remain elevated 40 years after arsenic mitigation (Smith et al., 2018). Earlier, the same research group found that mortality from acute myocardial infarction associated with arsenic exposure reduced to the level found among those consuming drinking water below arsenic threshold value 10 years after arsenic mitigation (Yuan et al., 2007). Given that the interval between exposure and development of lung, bladder and kidney cancers can be up to 40 years, the full benefits can only be estimated by considering a period of decades after the implementation of arsenic mitigation.

Assuming that individuals in the affected population consume drinking water containing arsenic at the same concentration over their lifetime, a better approach is the comparison of changes in arsenic–related LECRs and AMR from IHDs, thereby, assessing the number of cancers and IHD deaths prevented annually. This methodology was used by Nigra et al. (2017) to estimate the number of avoided cancers. They found that introducing a maximum contaminant level for arsenic in drinking water in the United States was associated with prevention of 50 cases of skin and 200–900 cases of lung and bladder cancers combined annually (Nigra et al., 2017). However, the authors did not examine systematically the economic benefits of reducing arsenic exposure.

Instead of applying a single value to characterise LECR, it is better to assess its distribution in the population, while taking into account the variability and uncertainty of the parameters used to calculate cancer risk. This is why we used a probabilistic population–based Monte Carlo

Table 8
Estimated economic benefit derived from the prevention of arsenic–related skin, lung, and bladder cancers due to the Drinking Water Quality Improvement Programme.

Type of cancer	Cost of illness saved/year [million euro]	Value per statistical life saved/year [million euro]	Total economic benefit [million euro]
Skin cancer	0.03 (0.01–0.05)	5.15 (2.40–8.77)	5.18 (2.41–8.82)
Lung cancer, scenario 1	0.04 (0.01–0.07)	402.74 (166.08–712.42)	402.78 (166.09–712.49)
Bladder cancer, scenario 1	0.31 (0.14–0.53)	151.09 (68.26–257.18)	151.41 (68.41–257.71)
Sum of economic benefits for skin, lung and bladder cancers, scenario 1	0.38 (0.19–0.61)	562.94 (280.41–875.89)	563.92 (268.43–870.96)
Skin cancer	0.03 (0.01–0.05)	5.15 (2.40–8.77)	5.18 (2.41–8.82)
Lung cancer, scenario 2	0.004 (0.002–0.006)	41.13 (18.58–70.67)	41.14 (18.58–70.68)
Bladder cancer, scenario 2	0.03 (0.01–0.06)	15.42 (6.86–26.45)	15.45 (6.88–26.50)
Sum of economic benefits for skin, lung and bladder cancers, scenario 2	0.06 (0.04–0.10)	62.03 (34.22–92.02)	62.22 (34.88–92.58)

To estimate the economic benefits of arsenic mitigation, decreases in cancer morbidity and mortality were assessed by combining cost of illness (COI) and value of a statistical life (VSL) methods (Greco et al., 2019). Costs saved by reduced mortality were evaluated for each cancer type separately using the VSL approach. The VSL is the amount of money that a population in a country is collectively willing to pay to avoid one statistical case of premature death from a disease associated with environmental pollution (Viscusi, 2019). The VSL to the Hungarian population was multiplied by the distributions of skin, lung, and bladder cancer cases prevented annually and the proportion of cancer patients who died within 5 years after their disease was diagnosed. The distributions of COI and VSL were derived from the reduction in lifetime excess cancer risks due to the Drinking Water Quality Improvement Programme. Using cancer slope factors proposed for lung and bladder cancers by the United States Environmental Protection Agency (2010) for estimation of excess cancer risks was defined as "scenario 1". Using cancer slope factors suggested for lung and bladder cancers by the United States Food and Drug Administration (2016) for estimation of excess cancer risks was defined as "scenario 2". The sum of economic benefit derived from the prevention of arsenic–related skin, lung, and bladder cancers was calculated for both scenarios by summing the corresponding COI values and VSL. All monetary values were adjusted for inflation and expressed in 2021 euro exchange rate. Median values, 1st and 99th percentiles (in brackets) are demonstrated.

Table 9
Estimated total economic benefit of the Drinking Water Quality Improvement Programme.

Disease	Cost of illness saved/year [million euro]	Value per statistical life saved/year [million euro]	Total economic benefit [million euro]
Sum of economic benefits for skin, lung and bladder cancers, scenario 1	0.38 (0.19–0.61)	562.94 (280.41–875.89)	563.92 (268.43–870.96)
Ischemic heart disease	–	382.8 (143.4–629.0)	382.8 (143.4–629.0)
Total economic benefits for skin, lung and bladder cancers, scenario 1 and ischemic heart disease[a]	0.38	945.74	946.72
Sum of economic benefits for skin, lung and bladder cancers, scenario 2	0.06 (0.04–0.10)	62.03 (34.22–92.02)	62.22 (34.88–92.58)
Ischemic heart disease	–	382.8 (143.4–629.0)	382.8 (143.4–629.0)
Total economic benefits for skin, lung and bladder cancers, scenario 2 and ischemic heart disease[a]	0.06	444.83	445.02

The sum of economic benefit derived from the prevention of arsenic–related skin, lung, and bladder cancers was calculated for both scenarios by summing the corresponding COI values and VSL. In this case, median values, 1st and 99th percentiles (in brackets) are demonstrated. The economic benefit due to a decrease in mortality from ischemic heart disease (IHD) was estimated by multiplying the number of annually prevented IHD deaths with the VSL related to the Hungarian population. In this case, point estimate and lower and upper borders of its uncertainty interval (in brackets) are shown. The total economic benefit of the DWQIP was calculated by summing the costs saved due to decreases in cancer morbidity and mortality estimated according to scenario 1 and 2 as well as death from IHDs. All monetary values were adjusted for inflation and expressed in 2021 euro exchange rate. COI values for IHD are not shown, as explained in the Section 2.8, we were able to use only the VSL method to estimate the economic gain due to prevention of arsenic-related mortality from IHD.

[a] Sum of medians and point estimates.

simulation to estimate LECR and applied it in our evaluation of the benefits of the Hungarian DWQIP. We showed that the DWQIP would be expected to prevent a median number of 14.3 (1st and 99th percentiles: 6.6–24.3) skin cancers/year. The corresponding figures for lung and bladder cancers varied according to which scenario was used, with scenario 1 estimating that the DWQIP prevented a median of 107.6 (1st and 99th percentiles: 44.1–191.4) and 103.3 (1st and 99th percentiles: 46.9–175.8) cases of lung and bladder cancers/year, respectively. Based on scenario 2, a median number of 10.9 (1st and 99th percentiles: 4.8–18.7) lung and 10.7 (1st and 99th percentiles: 4.7–18.4) bladder cancers is being avoided annually by the DWQIP.

Cardiovascular diseases have been recognised as the main fatal outcome of chronic arsenic exposure (Argos et al., 2010; Chen et al., 2011; Interim report National Research Council, 2013). Given that IHD has been reported as the most important arsenic-related cardiovascular disease, the effect of DWQIP on mortality from these group of causes was also investigated. We found that 88.9 (uncertainty interval: 33.3–146.1) IHD deaths/year can be avoided by the DWQIP. This implies that the arsenic mitigation programme can prevent 0.3 % of total IHD deaths per year in Hungary.

Also two scenarios were applied to estimate the economic benefit due to supplying drinking water meeting the EU standard. Summing the COIs and VSLs of skin, lung, and bladder cancers and VSL of IHD, the total economic benefit was estimated to be €946.7 and €445.0 million/year in scenario 1 and 2, respectively. When the €784.2 million financial support provided by the EU is compared with the median total economic benefit, it is expected that the economic benefits of the DWQIP will outweigh the cost of the programme within 0.8 and 1.8 years based on scenario 1 and 2, respectively (European Court of Auditors, 2017).

The research presented in this paper is relevant beyond Hungary. Exposure to arsenic in drinking water remains a significant public health concern in many countries, including certain regions of Argentina, Bangladesh, Chile, China, India, Mexico, Taiwan, the United States of America, and Vietnam [Liang et al., 2016; World Health Organization, 2018]. Although it has been reported that an estimated 140 million individuals may be at risk from consumption of drinking water containing arsenic at concentrations above the WHO guideline value of 10 μg/l, policy makers and water suppliers in the countries concerned may be reluctant to introduce arsenic removal programmes (World Health Organization, 2018; WaterWorlds eNewsletters, 2000). The possible reasons for their hesitation include the high cost of arsenic mitigation and limited evidence on the health and economic return of the investments. To convince decision makers and water companies of the effectiveness of a drinking water quality improvement programme, including arsenic mitigation, public health professionals should provide strong evidence of its health and economic benefits. Therefore, it would be advantageous to prepare cost–benefit analyses before the implementation of interventions. To our knowledge, however, such preliminary studies have not been performed even in those EU countries that have high levels of arsenic in their water supply, such as Italy, and some parts of Romania, Slovakia, as well as Serbia, a candidate country for the EU membership (Leonardi et al., 2012; Lindberg et al., 2006). Cost-effectiveness studies are good practice when considering any public health intervention and our study offers a template for those considering drinking water quality improvement programmes.

5. Strengths and limitations

Our study is the first to estimate both the health and economic benefits of a nationwide DWQIP implemented in an EU Member State. This is also the first research that considered the variability and uncertainty of the parameters used to calculate LECR before and after arsenic mitigation. To demonstrate the health and economic benefit of the DWQIP more comprehensively, we went beyond morbidity and mortality from arsenic-related cancers to include mortality from IHD associated with arsenic exposure. To our knowledge, our study is also the first to provide evidence that the economic benefits of arsenic mitigation can outweigh the costs of a nationwide drinking water quality improvement programme. Data on arsenic concentration in drinking water were obtained from 1137 municipalities covering more than two–thirds of the Hungarian population. A limitation is the assumption that all residents of the municipalities included in our study consumed drinking water from public water suppliers. It has been estimated that 200,000 people use drinking water from individual wells in Hungary (Vargha et al., 2019). The average concentration of arsenic in these water sources has been reported to vary between 20 μg/l ± 20 μg/l and 100 μg/l ± 40 μg/l (Varsányi and Kovács, 2006). However, data on the arsenic levels in individual wells and number of persons consuming drinking water from their own water sources were not available at settlement level. In addition, some arsenic can remain in certain foodstuffs during cooking (Arcella et al., 2021; Cheyns et al., 2017). However, the level of arsenic exposure resulting from this practice is not known in the population included in our study. Therefore, it was not possible to consider the exposure to arsenic in drinking water from individual wells and foodstuffs when estimating the distributions of LECRs and AMR from IHDs. Although socioeconomic status has been shown to influence the risk of arsenic related diseases, the relationship between the level of exposure to arsenic in drinking water and frequency of associated diseases in populations with different socioeconomic status has not been investigated in Hungary (Argos et al.,

2007; Eick et al., 2019). Thus, we could not take account of this consideration in our study. The data used to estimate the COI were not specific to the Hungarian population, so the actual economic benefits of DWQIP may differ from our assessment. As explained in Section 2.8, we were able to use only the VSL method to estimate the economic gain due to prevention of arsenic-related mortality from IHD. Finally, we will have underestimated the total health benefit as we only included skin, lung, and bladder cancers as well as IHDs in our risk estimates.

6. Conclusions

The results presented in this paper provide evidence that the implementation of the WHO standard for arsenic concentration in drinking water in Hungary resulted in a significant decrease in LECR and yielded considerable health and economic benefits. Our study goes beyond the existing research, offering both new insights into the impact of arsenic mitigation and providing a methodological template for similar studies in the many parts of the world lacking effective mechanisms to reduce arsenic exposure. Our study also provides evidence that the economic benefits of arsenic mitigation can outweigh the costs of a nationwide drinking water quality improvement programme.

CRediT authorship contribution statement

László Pál: conceptualization, investigation, supervision, writing – original draft; **Tibor Jenei:** data curation, visualization, database development; **Martin McKee**: writing – review & editing; **Nóra Kovács:** database development, writing – review & editing; **Márta Vargha:** collection of data for database development; **Zsuzsanna Bufa–Dőrr:** collection of data for database development; **Teuta Muhollari:** visualization; **Marozsán Orsolya Bujdosó:** contribution to database development; **János Sándor:** conceptualization, resources, writing – review & editing; **Sándor Szűcs:** conceptualization, investigation, supervision, writing – original draft.

All authors contributed to the interpretation of data, and read and approved the final manuscript.

Data sharing

The aggregated data are accessible to researchers upon reasonable request for data sharing to the corresponding author. Requests for data require approval by National Public Health Centre, Budapest, Hungary.

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Data availability

Data will be made available on request.

Declaration of competing interest

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

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