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Association between exposure to desalinated sea water and ischemic heart disease, diabetes mellitus and colorectal cancer; A population-based study in Israel

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ABSTRACT

Background: Drinking water (DW) is an important dietary source of magnesium. Recently, Israel has increased its use of desalinated seawater (DSW) as DW country-wide. Its negligible magnesium content, however, raises concern that consumption of DSW may be associated with hypomagnesemia and increase the risk of ischemic heart disease (IHD), diabetes mellitus (DM), and colorectal cancer (CRC).

Objectives: We tested whether there was a change in incidence of negative health outcomes (IHD, DM, and CRC) following the introduction of DSW supply in a population-based ecologic study in Israel.

Methods: A historical prospective analysis was applied to members aged 25–76 during 2004–2013 of Clalit Health Services (Clalit), the largest healthcare provider in Israel, using its electronic medical record database. Multivariable analyses were adjusted for age, sex, socioeconomic status, smoking status, and body mass index.

Results: An increased odds ratio was found for IHD (0.96, 95% CI 0.93–0.99 at baseline and 1.06, 95% CI 1.02–1.11 at the end of the follow-up period), but no time trend was observed.

Conclusions: We found that the risk for IHD increased during the study period. The risks for DM and CRC were unchanged. Long term studies are needed for assessing the risk for CRC due to the long latency. The higher risk for IHD has practical public health implications and raise the need to add magnesium to DSW.

1. Introduction

The availability worldwide of fresh water sources is rapidly diminishing due to climate change and global warming. The perpetually increasing global population combined with a parallel decrease in precipitations jointly deepen the need for fresh water supply. As a form of compensation, desalinated sea water (DSW) has steadily gained credence. In 2015, 150 countries were reported to have operated over 17,000 desalination facilities, daily generating a total of over 80 million cubic meters of drinking water (DW) upon which 300 million people relied (International Desalination Association, 2015).

During the past decade, Israel has massively accelerated the production of DSW. Today, over 50% of Israeli tap water comprises DSW (Koren et al., 2017). It follows, then, that a large Israeli population is exposed to any health effects potentially incurred by DSW (Spungen et al., 2013), specifically with respect to loss of calcium and magnesium. Since both are vital for human health (World Health Organization (WHO), 2005), the WHO recommended in its 2011 report that "in circumstances where a supply is moving from a source that has significant levels of calcium and magnesium to low-mineral desalinated water, it would be appropriate to consider remineralizing with calcium and magnesium salts" (World Health Organization, 2011, p. 25).

Consequently, in Israel, an expert committee recommends adding calcium to DW and advocates monitoring the long-term effects of magnesium absence in DSW on cardiovascular disease (CVD) (Adin Committee, 2007), which is the major health hazard of magnesium deficiency in developed countries (Ferrandiz et al., 2004). Subsequently, calcium has been added to DSW in Israel, but magnesium has

Abbreviations: DSW, desalinated sea water; DW, drinking water; IHD, ischemic heart disease; DM, diabetes mellitus; CRC, colorectal cancer; CVD, cardiovascular disease; AMI, acute myocardial infarction; BMI, body mass index; SES, socioeconomic status; WHO, World Health Organization; Clalit, Clalit Health Services

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not been added. Magnesium is essential for over 300 metabolic processes, including energy production, protein and nucleic acid synthesis, regulation of vascular tone, and insulin sensitivity (Guerrera et al., 2009). Magnesium deficiency may result in hypertension, cardiac arrhythmia, atherosclerosis, diabetes mellitus (DM), and increased risk for colorectal cancer (CRC) (Markovits et al., 2016; Rasic-Milutinovic et al., 2012; Rosanoff et al., 2012). A recent study has shown a significant increase in all-cause mortality in hospitalized patients in Israel suffering from acute myocardial infarction (AMI), who were living in regions where DSW is the main source of DW (Shlezinger et al., 2016). Due to their researched prevalence, three of these phenomena are further elaborated here: CVD, DM, and CRC.

In a 1992 retrospective review of studies that span a period of 30 years Eisenberg established an association between magnesium deficiency and sudden death (Eisenberg, 1992). The studies were epidemiological and clinical by nature and included human and animal autopsies. Eisenberg suggested a regular supply of magnesium as a possible mean to mitigate the risk of sudden death. Some resolutions to combat this risk included population-level education on the benefits of a magnesium-rich diet, taking magnesium supplements, and enriching DW and food with magnesium.

Numerous reports have demonstrated an inverse association between CVD-related morbidity and mortality and water hardness (e.g., Ferrandiz et al., 2004; Knezović et al., 2014; Kousa et al., 2004, 2006; Luoma et al., 1983; Marque et al., 2003; Punsar and Karvonen, 1979; Rubenowitz et al., 1996, 2000; Rylander et al., 1991; Sauvant and Pepin, 2000; Yang et al., 2006). Of note, Catling and others have calculated a pooled OR of 0.75 for an inverse association between magnesium levels in DW and CVD mortality (95% CI 0.68–0.82; $p < 0.001$). The effect of calcium, however, remained inconclusive (Catling et al., 2008). Additional studies also render controversial the relationship between magnesium and calcium content and CVD risk (Leurs et al., 2010; Maheswaran et al., 1999; Miyake and Iki, 2004; Morris et al., 2008; Rosenlund et al., 2005).

Poor magnesium content in modern processed food further emphasizes the potential benefits of magnesium in DW, especially in areas where prevalent nutritional habits rely mainly on a magnesium-poor diet. Rosanoff (2013) estimated that global consumption of DW and beverages containing moderate to high levels of magnesium (10–100 ppm) would have the power to prevent as much as 4.5 million heart diseases and stroke deaths per year. Indeed, Gharedaghi et al. (2014) showed a marked reduction in CVD morbidity in an Iranian province after increasing the magnesium content in DW for one year. Similarly, a recent meta-analysis of case-control studies showed a protective effect of magnesium in DW for CVD, with an effect size of 0.75 (95% CI 0.66–0.86; $p = 0.000$) (Gianfredi et al., 2017). However, high heterogeneity and certain publication bias limit the robustness and generalizability of these findings. A large-scale Japanese study showed an inverse association between magnesium intake and mortality from hemorrhagic stroke in men and ischemic strokes, coronary heart disease, heart failure, and total CVD in women (Zhang et al., 2012). A multivariable hazard ratio of 0.49 (95% CI 0.26–0.95) was found for the highest vs. lowest quintiles of magnesium intake, after adjusting for CVD risk factors and sodium intake.

Another disease that seems to be influenced by magnesium intake is DM. A case-control study (Yang et al., 1999), which had a heavy impact on the Taiwanese water industry and human health, showed magnesium intake provided an important protective effect against DM mortality. Similarly, Longstreet et al. (2007) studied magnesium as a candidate contributor to DM in Australian Aboriginals and Torres Strait Islanders based on magnesium content of DW and diet. They explored additional climate and socioeconomic status (SES) properties potentially influencing properties on magnesium intake, such as temperature, rainfall, education, employment, and income. They reported a strong correlation between the magnesium content of DW and DM-related mortality, supporting their hypothesis that low magnesium dietary intake, characterized by low DW magnesium content, can elevate DM-mortality risk in the endemic population of Queensland. In contrast, a register-based Finnish study (Kousa et al., 2011) did not conclusively demonstrate an association of well water magnesium content with the geographical variation of DM while an earlier study (Joslyn et al., 1990) has altogether failed to find a direct effect of magnesium in DW on DM.

The relationship between DSW and cancer was studied extensively. In their recent review, Nriagu et al. (2016) focused on the Arabian Gulf region population, which relies on DSW as its primary source of DW. The authors comment on the potential risk for cancer development from consuming DSW, proposing that DSW can critically upset the body's electrolyte balance due to its low concentrations of calcium, sodium, potassium, and magnesium, ultimately leading to tumorigenesis and full-fledged cancer. The direct causal relation linking DSW and cancer, however, is yet to be proven. More specifically, in a Taiwanese case-control study on CRC (Yang et al., 1997) no evidence was found for a significant relationship between magnesium levels in DW and CRC whereas calcium intake from DW showed a significant protective effect. Further evidence suggests the presence of other substances is required in order to observe the influence of magnesium on CRC. For example, data of a case-control study based on Taiwanese death certificates across a 5-year period (from 2003 to 2007) shows that low magnesium in DW is associated with CRC-related deaths when nitrate content is high in DW (Chiu et al., 2010). Similarly, Kuo et al. (2010), who have gathered data from 53 municipalities in Taiwan, concluded that while trihalomethanes alone did not influence the risk of CRC-related death, their combination with lower magnesium levels in DW evidently works in favor of CRC development.

Despite the vast research demonstrating various adverse health effects of low magnesium and calcium content in DW and the sharp increase in the utilization of DSW globally, only a few studies were conducted exploring the association between DSW and health outcomes. The impact of exposure to DSW on the incidence of ischemic heart disease (IHD), DM, and CRC morbidity is as yet under-explored; this, together with the inconclusive results of previous studies on poor magnesium content in DW and diet, prompted us to investigate changes in incidence of IHD, DM, or CRC among a population residing in a region where DSW is the main source of DW.

2. Methods

2.1. Study area and population

This is a large historical prospective cohort study conducted on data from 2004 to 2013 that was extracted from the electronic medical record database of Clalit Health Services (Clalit), the largest health fund in Israel. Members of Clalit represent a geographically and socioeconomically diverse population of over 4 million patients, both inpatients and outpatients, with less than 1% attrition per year (Shmueli et al., 2007). Furthermore, Clalit has a single, comprehensive, universally adopted electronic medical record system in which all members' health care data is compiled into a single data warehouse, including diagnoses, laboratory measurements, and medication usage. This system thus provides an opportunity to capture incidence of new diseases at the population level.

450,174 members were included in the cohort if they were 25–74 years of age (inclusive) as of index date and had been members in Clalit for at least two consecutive years prior, to increase the completeness of the dataset, the final model includes only those members with available smoking, body mass index (BMI) and demographic data (Fig. 1). Members whose primary care clinic changed to a region of a different type of water supply during the course of the study were excluded. This study was approved by Clalit's ethical review committee.

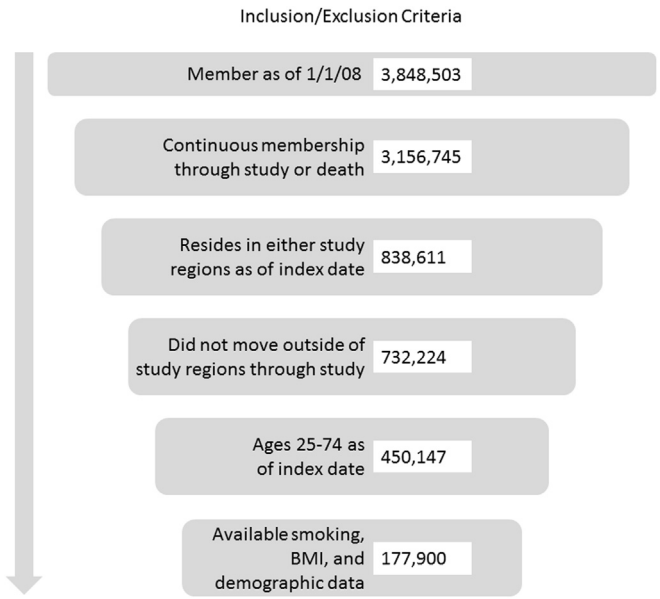

Fig. 1. Flow-chart of members met Inclusion Criteria.

2.2. Desalinated sea water exposure status

The introduction of DSW occurred in September 2005 (Lahav and Birnhack, 2006) in the cities of Be'er Sheva, Ofakim, Sderot, and Qiryat Gat (Exposed Region 1) and during 2007 (Hermony et al., 2015) in the cities of Holon, Bat Yam, Rishon Lezion, Rehovot, and Nes Ziona (Exposed Region 2). The designated index dates were set on the first day of January in 2006 and 2008 in those regions, respectively. The data among those exposed was combined into a single region (exposed), disregarding the calendar year, but rather tracking the number of years following the introduction to exposure. A third unexposed region to which DSW was not introduced prior to 2013 was included in the study from 2008, comprising the cities of Nahariya, Akko, Zefat, Kiryat Shmonah, Nazareth Illit, Jerusalem, and Haifa, in which water was supplied from an assortment of natural sources. No region was included in this study if DSW was introduced after 2008.

2.3. Primary outcomes

The primary outcomes of this study were incidence cases of IHD, DM and CRC. The follow up period was for six years, each exposed areas is measured for a total for six years, from 2006 to 2011 and from 2008 to 2013, respectively, or until death.

DM was defined using a combination of laboratory testing and medication dispensing, consistent with an internal algorithm built to identify DM, the results and validation of which appear in previous publications (Karppanen et al., 1978; Karpati et al., 2014).

IHD was defined by the first incidence of any one of the following diagnoses in the inpatient or outpatient records according International Classification of Disease (ICD) 9 codes 40[1-5]% (Hypertensive Disease), 41[0-4]% (Ischemic Heart Disease), 42[0-9]% (Other Forms of Heart Disease), 44[0-8]% (Diseases of Arteries, Arterioles, and Capillaries), excluding nevus (448.1) and septic arterial embolism (449), or associated free text validation. CRC was defined using a combination of the Israeli National Cancer Registry, the Clalit Chronic Registry, and any single occurrence of ICD9 codes 153% or their associated free text validation.

Date of death was determined using validated records from the Ministry of Interior.

2.4. Covariates

We additionally controlled for multiple sociodemographic and clinical variables in our multivariable models. Age in years was as of index date, and the value for each of all other covariates (sex, ethnicity, immigrant status, smoking status and BMI category) was the value closest to the index date, with a lookback period as far back as 1 January 2004, as some variables were not available on the exact index date. Variables included: age in years (categorized as 25–35, 36–50, 51–74), sex, ethnicity (Jewish or Arab, as based on the predominant ethnicity in the catchment area for the patient's chosen primary care clinic), SES (low, medium, or high, as based on the predominant status in the catchment area for the patient's chosen primary care clinic), and immigrant status (born in Israel or elsewhere). We also controlled for smoking status (current, former, or never) as well as BMI category (underweight BMI < 18.5, normal weight $18.5 \leq$ BMI < 25, overweight $25 \leq$ BMI < 30, and obese $30 \leq$ BMI). These measures were introduced in 2008 as part of the national quality indicator program and have near universal compliance as of 2009.

2.5. Analysis

Demographic and clinical descriptive data are presented for three regions: Exposed Region 1, Exposed Region 2, and Unexposed Region. Additionally, all Exposed Region 1 and Exposed Region 2 were combined into a single cohort named Total Exposed. Baseline prevalence of each disease of interest was determined in all regions as were annual and cumulative incidence for each disease of interest.

Each outcome was studied independently and not as a composite outcome. We used Cox proportional hazard modeling of the survival of outcome free status. We also created an adjusted model using descriptive statistics to detect outliers and unite categories with low prevalence of the covariates. We then removed variables with no univariate influence on the outcome. Cases with missing values were removed and no imputation was performed. Due to the small group size of the Arab population in the exposed regions, this group was excluded from the final model.

We tested significant covariates for collinearity by variance inflation factor and excluded variables scoring above 4, thereby removing variables that showed lower predetermined clinical importance. The remaining covariates were used in a backwards stepwise Cox regression optimized using Bayesian information criterion. This process was performed for each outcome separately. We additionally tested whether the differential hazard began immediately at the intervention or whether any impact was amplified over time. Moreover, we tested the interaction between time and intervention in a linear model for rates. We further compared the post intervention incidence with the pre-intervention baseline rate for the three diseases. We also tested whether a clustering effect could be observed between sub-regions and age groups. Finally, we sought second order interactions as well as splines of the continuous variables. Model validity was tested by Martingale, Cox-Snell, and Schoenfeld residuals as well as by log ($-$ log) plots to validate that proportional hazard assumptions were met.

3. Results

A total of 450,147 members met inclusion criteria (Fig. 1). The demographic data per region is presented in Table 1. Among those exposed to DSW, Exposed Region 1 appears to comprise younger individuals than other regions, and has a higher percent of individuals born in foreign countries and lower rates of current smokers and obesity. Additionally, we note that in all regions data was missing for smoking and BMI at index date, ranging from approximately 30% in Exposed Region 2 to over 70% in Exposed Region 1. Demographic characteristics of the final cohort which contains members who did not have missing historical data (BMI, smoking status and demographic

Tablee 1
Baseline characteristics among all residents as of index date, by exposed and unexposed regions[a].

Characteristic	Exposed Region 1 (1/1/06) *n* = 72,840 (%)	Exposed Region 2 (1/1/08) *n* = 141,206 (%)	Total exposed *n* = 214,046 (%)	Unexposed *n* = 236,101 (%)	Total *n* = 450,147 (%)
Age, years					
25–35	16,017 (21.99)	27,232 (19.29)	43,249 (20.21)	54,680 (23.16)	97,929 (21.75)
36–50	24,216 (33.25)	34,112 (24.16)	58,328 (27.25)	67,431 (28.56)	125,759 (27.94)
51–74	32,607 (44.77)	79,862 (56.56)	112,469 (52.54)	113,990 (48.28)	226,459 (50.31)
Sex					
Male	33,701 (46.27)	65,368 (46.29)	99,069 (46.28)	110,504 (46.80)	209,573 (46.56)
Female	39,139 (53.73)	75,838 (53.71)	114,977 (53.72)	125,597 (53.20)	240,574 (53.44)
Ethnicity					
Jewish	70,182 (96.35)	141,171 (99.98)	211,353 (98.74)	183,932 (77.90)	395,285 (87.81)
Non-Jewish	2658 (3.65)	35 (0.02)	2693 (1.26)	52,169 (22.10)	54,862 (12.19)
Immigrant					
No	25,805 (35.43)	72,625 (51.43)	98,430 (45.99)	142,199 (60.23)	240,629 (53.46)
Yes	47,035 (64.57)	68,581 (48.57)	115,616 (54.01)	93,902 (39.77)	209,518 (46.54)
SES[b]					
Low	35,420 (48.63)	21,842 (15.47)	57,262 (26.75)	83,884 (35.53)	141,146 (31.36)
Medium	33,574 (46.09)	82,025 (58.09)	115,599 (54.01)	126,724 (53.67)	242,323 (53.83)
High	3381 (4.64)	36,222 (25.65)	39,603 (18.50)	25,363 (10.74)	64,966 (14.43)
Missing	465 (0.64)	1117 (0.79)	1582 (0.74)	130 (0.06)	1712 (0.38)
Smoking status					
Never	8641 (11.86)	67,575 (47.86)	76,216 (35.61)	112,932 (47.83)	189,148 (42.02)
Current	8134 (11.17)	23,677 (16.77)	31,811 (14.86)	39,017 (16.53)	70,828 (15.73)
Former	603 (0.83)	11,817 (8.37)	12,420 (5.80)	15,336 (6.50)	27,756 (6.17)
Missing	55,462 (76.14)	38,137 (27.01)	93,599 (43.73)	68,816 (29.15)	162,415 (36.08)
BMI					
Underweight	294 (0.40)	1595 (1.13)	1889 (0.88)	1600 (0.68)	3489 (0.78)
Normal	3786 (5.20)	29,994 (21.24)	33,780 (15.78)	32,710 (13.85)	66,490 (14.77)
Overweight	7196 (9.88)	36,852 (26.10)	44,048 (20.58)	47,535 (20.13)	91,583 (20.35)
Obese	9003 (12.36)	24,921 (17.65)	33,924 (15.85)	42,606 (18.05)	76,530 (17.00)
Missing	52,561 (72.16)	47,844 (33.88)	100,405 (46.91)	111,650 (47.29)	212,055 (47.11)
Prevalence[b]					
IHD	5868 (8.06)	13,278 (9.40)	19,146 (8.94)	21,092 (8.93)	40,238 (8.94)
DM	8018 (11.01)	18,261 (12.93)	26,279 (12.28)	29,638 (12.55)	55,917 (12.42)
CRC	457 (0.63)	985 (0.70)	1442 (0.67)	1408 (0.60)	2850 (0.63)

[a] All values are presented as n (%).
[b] SES, socioeconomic status; BMI, body mass index; IHD, ischemic heart disease; DM, diabetes mellitus; CRC, colorectal cancer.

data) are described in Table 2. The proportion in the lower SES group appears to differ: 33.86% within the unexposed region and 18.45% within the exposed region. However, the baseline prevalence of diseases differs by type of exposure.

In Table 3, we present the annual and cumulative incidences of the different health outcomes. Incidence of CRC, DM and IHD was slightly higher in the populations exposed to DSW. However, when the cohort is limited to members who were ultimately included in the model (members who did not have missing historical data for BMI, smoking status and demographic data) (Table 4), the group exposed to DSW appears to have similar risk for IHD and higher risk for DM whereas the group unexposed to DSW appears to be at greater risk for CRC.

In Table 5 we present the odds ratio, unadjusted and adjusted for each disease's prevalence prior to the intervention in the areas that were exposed to DSW compared with unexposed areas. The risks for IHD, DM, and CRC were all significantly different between the regions, even after adjusting for sex, age, BMI, smoking status, and SES. The adjusted odds ratio shows in the region exposed to DSW lower prevalence rates at baseline for IHD (OR: 0.96, 95% CI 0.93–0.99) and CRC (OR: 0.86, 95% CI 0.79–0.93) and higher prevalence at baseline for DM (OR: 1.10, 95% CI 1.03–1.19).

In Table 6, we present the hazard ratios for incident disease during follow-up. Hazard ratios for IHD and DM were higher in the group exposed to DSW (HR: 1.06, 95% CI 1.02–1.11 and HR: 1.10, 95% CI 1.06–1.14, respectively) whereas no significant difference was found for CRC. Change over time in hazard ratio was insignificant (p value > 0.05 for all diseases).

4. Discussion

DSW is consumed by over 300 million people globally; it contains virtually no magnesium, an essential ion for cardiovascular health. Despite the sharp increase in consuming DSW, there is very limited research on adverse effects from lack of magnesium from consumption of DSW. On the other hand, many studies have shown that reduced water hardness, and specifically reduced magnesium concentrations in DW from natural sources had adverse health effects such as IHD, other CVD and stroke, as well as DM (see Jiang et al., 2016 for a list of such studies). The evidence for increased risk of CRC due to reduced magnesium in DW is less compelling as it is based on only two studies (Chiu et al., 2010; Kuo et al., 2010).

Low serum magnesium concentrations were found to predict cardiovascular and all-cause mortality (Reffelmann et al., 2011). Kanadhia et al. (2014) indicate that lower magnesium concentrations in DW correlate with low serum magnesium in consumers. Similarly, focusing on heart diseases, both Rosanoff (2013) and Zhang et al. (2012) have shown an inverse relation between heart diseases and water hardness, and multiple other studies have proposed an inverse correlation between water hardness and CVD-related death (Ferrandiz et al., 2004; Knezović et al., 2014; Kousa et al., 2004, 2006; Luoma et al., 1983; Marque et al., 2003; Monarca et al., 2006; Punsar and Karvonen, 1979; Rubenowitz et al., 1996, 2000; Rylander et al., 1991; Sauvant and Pepin, 2000; Yang et al., 2006). Similarly, lower concentrations of magnesium are associated with an increased risk of coronary heart disease (CHD) mortality and sudden cardiac death (Kieboom et al., 2016; Peacock et al., 2010). In contrast, a 2005 report dismissed the hypothesis of a protective effect of hard water on myocardial infarction (Rosenlund et al., 2005), and a wide range cohort study from 2007

Table 2
Baseline characteristics of among residents included in the final model[a] as of index date, by exposed and unexposed regions[b].

Characteristic	Exposed Region 1 (1/1/06) *n* = 6265 (%)	Exposed Region 2 (1/1/08) *n* = 80,934 (%)	Total exposed *n* = 87,199 (%)	Unexposed *n* = 90,701 (%)	Total *n* = 177,900 (%)
Age, years					
25–35	540 (8.62)	8398 (10.38)	8938 (10.25)	8355 (9.21)	17,293 (9.72)
36–50	1499 (23.93)	15,327 (18.94)	16,826 (19.30)	17,744 (19.56)	34,570 (19.43)
51–74	4226 (67.45)	57,209 (70.69)	61,435 (70.45)	64,602 (71.23)	126,037 (70.85)
Sex					
Male	2930 (46.77)	34,789 (42.98)	37,719 (43.26)	38,727 (42.70)	76,446 (42.97)
Female	3335 (53.23)	46,145 (57.02)	49,480 (56.74)	51,974 (57.30)	101,454 (57.03)
Ethnicity					
Jewish	6265 (100.00)	80,934 (100.00)	87,199 (100.00)	90,701 (100.00)	177,900 (100.00)
Immigrant					
No	1409 (22.49)	36,099 (44.60)	37,508 (43.01)	41,054 (45.26)	78,562 (44.16)
Yes	4856 (77.51)	44,835 (55.40)	49,691 (56.99)	49,647 (54.74)	99,338 (55.84)
SES[c]					
Low	3033 (48.41)	13,056 (16.13)	16,089 (18.45)	30,710 (33.86)	46,799 (26.31)
Medium	3016 (48.14)	48,280 (59.65)	51,296 (58.83)	48,645 (53.63)	99,941 (56.18)
High	216 (3.45)	19,598 (24.21)	19,814 (22.72)	11,346 (12.51)	31,160 (17.52)
Smoking status					
Never	3253 (51.92)	52,645 (65.05)	55,898 (64.10)	60,175 (66.34)	116,073 (65.25)
Current	2708 (43.22)	17,706 (21.88)	20,414 (23.41)	19,169 (21.13)	39,583 (22.25)
Former	304 (4.85)	10,583 (13.08)	10,887 (12.49)	11,357 (12.52)	22,244 (12.50)
BMI[c]					
Underweight	90 (1.44)	1302 (1.61)	1392 (1.60)	1184 (1.31)	2576 (1.45)
Normal	1239 (19.78)	25,496 (31.50)	26,735 (30.66)	24,978 (27.54)	51,713 (29.07)
Overweight	2242 (35.79)	32,124 (39.69)	34,366 (39.41)	35,535 (39.18)	69,901 (39.29)
Obese	2694 (43.00)	22,012 (27.20)	24,706 (28.33)	29,004 (31.98)	53,710 (30.19)
Prevalence[c]					
IHD	1429 (22.81)	10,890 (13.46)	12,319 (14.13)	13,742 (15.15)	26,061 (14.65)
DM	65 (1.04)	999 (1.23)	1064 (1.22)	1298 (1.43)	2362 (1.33)
CRC	103 (1.64)	1445 (1.79)	1548 (1.78)	1553 (1.71)	3101 (1.74)

[a] Data on only those members who did not have missing historical data (BMI[c],smoking status and demographic data).
[b] All values are presented as n (%).
[c] SES, socioeconomic status; BMI, body mass index; IHD, ischemic heart disease; DM, diabetes mellitus; CRC, colorectal cancer.

suggests that neither high water hardness nor high calcium or magnesium dietary intake confer protection from CVD (Morris et al., 2008). However, a recent meta-analysis (Jiang et al., 2016) of pooled published results from various seminal databases regarding the relationship between DW with low magnesium content and CHD has shown a significant inverse association between magnesium levels in DW and CHD mortality.

DSW as a main source of DW is a special case of low magnesium consumption that to date has received only little attention in the literature. In measurement of magnesium in residential 53 tap water samples from communities consuming DSW and non-DSW during 2016, we have found substantial differences in mean magnesium level in DW (5.4 mg/l and 25.1 mg/l, respectively). We are aware of only three studies pointing at the important potential of such a study trajectory. Evidence for increased risk of all-cause mortality was recently reported by us among hospitalized patients with AMI who are living in regions where DSW is the primary source of DW (Shlezinger et al., 2016). In addition to the direct effect of reduced magnesium intake resulting from the consumption of DSW as a substantial source of DW, consumption of crops irrigated by DSW may also contribute to hypomagnesemia. Yermiyahu et al. (2007) showed that crops such as tomatoes, basil, and edible flowers had shown symptoms of magnesium deficiency when irrigated by DSW. In a recent study a decrease of 30% in magnesium was found in the leaves of citrus trees in Israel during 2008–2016, in parallel to the increased use of DSW for irrigation. Also, the magnesium concentration in fruits and vegetables grown in Israel in 2017 were universally lower compared to the levels in similar products in the US (Raveh and Ben-Gal, 2018).

Our study focused on the effect of low magnesium content in DSW as DW in Israel as observed in a large population, prospective cohort study. Although Israeli DSW is enriched with calcium, it lacks any enrichment with magnesium. As a result, a large part of the Israeli

Table 3
Incidence of outcomes by year among all residents at risk at Index date, by exposed and unexposed regions[a].

Year following index date	IHD[b]		DM[b]		CRC[b]	
	Exposed *n* = 194,900 (%)	Unexposed *n* = 215,009 (%)	Exposed *n* = 187,767 (%)	Unexposed *n* = 206,463 (%)	Exposed *n* = 212,604 (%)	Unexposed *n* = 234,693 (%)
Year 1	1485 (0.76)	1478 (0.69)	2720 (1.45)	2987 (1.45)	306 (0.14)	343 (0.15)
Year 2	1472 (0.76)	1397 (0.66)	2720 (1.48)	2648 (1.31)	277 (0.13)	296 (0.13)
Year 3	1402 (0.74)	1425 (0.68)	2456 (1.36)	2796 (1.41)	347 (0.17)	317 (0.14)
Year 4	1283 (0.68)	1428 (0.69)	2488 (1.41)	2823 (1.46)	305 (0.15)	310 (0.14)
Year 5	1314 (0.71)	1417 (0.70)	2134 (1.24)	2257 (1.19)	275 (0.13)	307 (0.14)
Year 6	1399 (0.77)	1411 (0.71)	2471 (1.46)	2242 (1.21)	281 (0.14)	292 (0.13)
Cumulative Incidence	8355 (4.29)	8556 (3.98)	14,989 (7.98)	15,753 (7.63)	1791 (0.84)	1865 (0.79)

[a] All values are presented as n (%).
[b] IHD, ischemic heart disease; DM, diabetes mellitus; CRC, colorectal cancer.

Table 4
Incidence of outcomes by year among all residents at risk at index date included in the final model[a], by exposed and unexposed regions[b].

Year following index date	IHD[c]		DM[c]		CRC[c]	
	Exposed *n* = 74,880 (%)	Unexposed *n* = 76,959 (%)	Exposed *n* = 85,651 (%)	Unexposed *n* = 89,148 (%)	Exposed *n* = 86,135 (%)	Unexposed *n* = 89,403 (%)
Year 1	772 (1.03)	798 (1.04)	1354 (1.58)	1352 (1.52)	202 (0.23)	206 (0.23)
Year 2	739 (1.01)	754 (1.00)	1337 (1.60)	1258 (1.44)	154 (0.18)	189 (0.21)
Year 3	709 (0.99)	734 (1.00)	1215 (1.49)	1347 (1.59)	167 (0.20)	200 (0.23)
Year 4	641 (0.91)	703 (0.97)	1268 (1.59)	1262 (1.53)	148 (0.18)	175 (0.20)
Year 5	712 (1.03)	694 (0.98)	1017 (1.31)	967 (1.20)	133 (0.16)	172 (0.20)
Year 6	727 (1.08)	717 (1.04)	918 (1.22)	996 (1.27)	164 (0.20)	154 (0.18)
Cumulative Incidence	4300 (5.74)	4400 (5.72)	7109 (8.30)	7182 (8.06)	968 (1.12)	1096 (1.23)

[a] Data on only those members who did not have missing historical data (BMI, smoking status and demographic data).
[b] All values are presented as n (%).
[c] IHD, ischemic heart disease; DM, diabetes mellitus; CRC, colorectal cancer; BMI, body mass index.

Table 5
Odds ratio of outcomes (prevalent cases) prior to the index date of areas subsequently introduced to DSW[a,b,c].

Outcome	Unadjusted	Unadjusted (*n* as in model)	Adjusted
IHD[c]	0.97 (0.95, 0.99)	0.92 (0.90, 0.95)	0.96 (0.93, 0.99)
DM[c]	1.13 (1.06, 1.20)	1.04 (0.97, 1.11)	1.10 (1.03, 1.19)
CRC[c]	0.94 (0.88, 1.00)	0.85 (0.78, 0.92)	0.86 (0.79, 0.93)

[a] Variables included in the final models were region, sex, age, BMI[c], smoking status, SES[c].
[b] All values are presented as OR (95% CI), unless stated otherwise.
[c] DSW, desalinated sea water; IHD, ischemic heart disease; DM, diabetes mellitus; CRC, colorectal cancer; BMI, body mass index; SES, socioeconomic status.

population consumes DW with low magnesium content. This prompted us to study the health implications of low magnesium intake that accompany seawater desalination, an endeavor that, to the best of our knowledge, has not been attempted before. Similar to previous studies, our study found inconsistent associations between exposure to DSW and adverse health outcomes over time.

Our population-based model demonstrated that areas receiving DSW had an increased risk of IHD which was statistically significant after adjusting for age, sex, SES, and immigrant status represented by place of birth. Our data did not demonstrate that this risk increased over time, suggesting that continuous exposure to DSW did not result in progressive increased disease burden. No evidence was found for an effect of DSW on the risk for DM, as the hazard ratio was elevated at baseline and remained so during the period after DSW supply had begun. We also found no association between exposure to DSW and CRC. Furthermore, we found that at baseline (prior to the exposure), the risks for IHD, DM, and CRC were all significantly different between the regions, even after adjusting for sex, age, BMI, smoking status, and SES. This suggests that in this natural experiment, we are unable to adequately control for baseline differences between the regions that are subsequently exposed to DSW.

There is no a clearly defined latency period of magnesium-deficiency related to IHD and to DM. Certain authors (Rubenowitz et al., 1996) mentioned exposure period of 1-year as sufficient to produce observable effects of magnesium deficiency (for the group with the highest levels of magnesium in DW, the odds ratio for death from AMI adjusted for age and calcium level was 0.65 (95% CI 0.50–0.84)). Shlezinger et al. (2016) has shown a significant decrease in admission serum magnesium levels in patients from DSW regions and significant increase in 1-year all-cause mortality in AMI patients, in the DSW regions (HR:1.87, 95% CI 1.32–2.63, $p < 0.0001$), In meta-analysis of cohort studies with 313,041 subjects, circulating magnesium (per 0.48 mg/dL increment) was associated with a 30% lower risk of CVD (RR: 0.70, 95% CI 0.56–0.88) and in AMI mortality (RR: 0.61, 95% CI 0.37–1.00) during 4–30 follow-up years.(Del Gobbo et al., 2013).

A recent meta-analysis of prospective cohort studies (Wu et al., 2017) concluded 4 studies on the association between circulation magnesium and incidence of DM. By comparing the highest to the lowest category of circulating magnesium concentration, the relative risk for DM was 0.64 (95% CI 0.5–0.81) during an 8.8-year follow-up; Béjar et al. (2009) suggest a minimal latency period of 10–15 years for CRC. The lack of association with CRC risk in our study could therefore be expected as the longest exposure period for DSW was six years.

The scientific advisory report of the Dietary Guidelines Advisory Committee (DGAC), submitted to the US Secretary of Health and Human Services and the Secretary of Agriculture, has suggested that the US population should increase consumption of foods rich in magnesium. This recommendation was made following an observation among a representative sample of the US population aged 2 years or more that the consumption of magnesium (as well vitamins A, D, E, C, folate and calcium) falls short of the recommended acceptable daily intake. Daily magnesium intake is also inadequate compared to the benchmark set by the WHO at 420 and 320 mg for adult men and women, respectively (World Health Organization, 2005). In Israel, for example, the average consumption amounted to 228–270 mg magnesium daily, less than 70% of the recommended daily dose for men, even before the large scale use of DSW (World Health Organization, 2009).

Table 6
Hazard ratios of outcomes (incident cases) during the six-year follow up period of areas receiving DSW[a,b,c].

Outcome	Unadjusted	Unadjusted (*n* as in model)	Adjusted	Interaction of region and time *p*-value
IHD[c]	1.05 (1.01, 1.08)	1.02 (0.97, 1.06)	1.06 (1.02, 1.11)	0.955
DM[c]	1.09 (1.06, 1.11)	1.03 (1.00, 1.07)	1.10 (1.06, 1.14)	0.107
CRC[c]	0.97 (0.91, 1.03)	0.92 (0.84, 1.00)	0.93 (0.86, 1.02)	0.946

[a] Variables included in the final models were region, sex, age, BMI[c], smoking status, SES[c].
[b] All values are presented as HR (95% CI), unless stated otherwise.
[c] DSW, desalinated sea water; IHD, ischemic heart disease; DM, diabetes mellitus; CRC, colorectal cancer; BMI, body mass index; SES, socioeconomic status.

In a study conducted by one of us (MS) during 2015–2016 in 250 AMI patients from DSW (exposed) regions and 130 AMI patients from non-DSW (unexposed) regions, magnesium intake from diet, beverages and supplements was assessed, based on previously described questionnaires (Spungen et al., 2013; Seelig and Rosanoff, 2003). Intake of magnesium supplements was reported only by 7% of the patients in both regions, no differences were found between magnesium intakes from food. In addition, the proportions of the intake of tap or filtered water vs. bottled water were similar in both regions: about 40% of the weekly beverages consumption was reported for tap or filtered water, 10% for bottled water and 50% for other beverages Other beverages included soda/carbonated water, fruit juice and fruit nectar, soft drink, regular and diet, carbonated and non-carbonated, syrup-based drink, water-based soup, tea and coffee. Milk was not included in the list of beverages but was classified as food. In this study, the estimated mean daily magnesium intake from DW was significantly lower in AMI patients from DSW regions, compared with those living in non-DSW regions (29 mg/day and 86 mg/day respectively, $p < 0.001$)

The WHO recommends that in regular climatic conditions and effort, the daily water intake for children, adult women, and men should be 1, 2.2, and 2.9 l respectively while under conditions of warm climate and intensive labor the recommended daily water consumption is 4.5 l. At normal rates of DW consumption, natural resources of DW in Israel supply approximately 20% of recommended daily magnesium intake for adults whereas DSW supplies very little magnesium or not at all (Yermiyahu et al., 2007). In Spain, too, the supply of DSW as a primary source of DW would devoid the population of the 7.5–17% of the recommended daily magnesium intake for adults that natural DW supplies (Maraver et al., 2015). Thus, supply of DSW as the main source of DW clearly aggravates magnesium deficiency. Moreover, the increased daily requirement of DW in subjects living in warm climate or under conditions of strenuous physical activity, could further aggravate magnesium deficiency from the consumption of DSW.

A report by the Israeli Ministry of Health (Ginsberg, 2010) estimated that "DW supply with deficient magnesium in DSW is expected to result in excess mortality of about 250 Israelis from CVD, annually. If DSW is supplied to 27.3% of the population, annual AMI mortality will be expected to rise from 1417 to 1682. However, adding magnesium to DSW in concentrations of 10, 20 and 30 mg/l will reduce annual AMI mortality to 1507, 1464 and 1425 respectively". In reality, the fraction of the Israeli population that received DSW has dramatically increased since 2010, approaching over 50% in 2016 (Koren et al., 2017) to the extent that these estimates of CVD mortality related to the consumption of DSW should be scaled up by a factor of two. We thus call on researchers to continue this important trajectory of investigation.

4.1. Limitations

There are a number of significant limitations to this study. This is an ecological study conducted on population-level data. We thus have no data concerning individuals' exposure to DSW or any associated laboratory values to support the assumption that the effects of DSW are mediated by an insufficient consumption of minerals. Furthermore, we note that the populations in our study who were exposed to DSW differ significantly from those populations who were not exposed to DSW. Baseline demographic characteristics and risks for chronic disease of the two groups vary to such an extent that we are unable to adequately control for these differences in our analysis. Finally, this analysis is subject to the inherent limitations of observational studies using an electronic medical record database and we do not have the ability to validate whether cases were in fact incident cases. The strengths of this study include its significant population size, duration, and ability to track inpatient and outpatient diagnoses.

5. Conclusions

Our work is the first to report that in a population-based study among those exposed to DSW, there is an increased hazard ratio for IHD that does not change over time. However, given the ecological design, and inability to adequately control for baseline differences in the populations, our ability to interpret these findings is beyond the scope of this study. Further research is required to estimate the attributable burden of DSW consumption in Israel at the national level. It is also advisable to research data of a longer timeframe, accounting for the latency period of CRC (10–15 years; Béjar et al., 2009). The insights our present study offers may have potential impact on risk considerations and health implications as associated with global consumption of DSW.

Conflict of interest

The authors declare they have no actual or potential competing financial interests.

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