Water desalination, serum magnesium and dementia: a population-based study

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ABSTRACT

Although dementia affects roughly 50 million people worldwide, its etiology is largely unknown. Recent studies have found a link between hypermagnesemia, hypomagnesemia, and increased risk of dementia. In this study, we explore the link between serum magnesium levels and the prevalence of dementia following the adoption of desalinated water (DSW) in Israel. DSW contains no magnesium, and relying on it for drinking water can lead to an increased incidence of hypomagnesia. Our objective was to analyze in a treat-control context how the switch to desalinated drinking water affected serum magnesium concentrations and the prevalence of dementia. We selected two cities which differed in terms of their access to underground aquifers but were otherwise similar. Rehovot has no underground water and uses over 90% DSW, whereas Kfar Saba relies almost entirely on its own aquifers. The cities are otherwise relatively similar in terms of their demographic composition. Using medical records for all subjects insured by the Maccabi Health Services in Rehovot ($n = 23{,}991$) and Kfar Saba ($n = 20{,}541$), we examined mean serum concentrations of Mg in the period prior to desalination (2001–2006) and post-desalination (2007–2018). Dementia prevalence is taken from 2007 to 2020 for the same coverage population. Serum magnesium levels were significantly lower in Rehovot following the switch to DSW (2.067 ± 0.21 pre-desalination and 2.059 ± 0.216 post-desalination, $p < 0.01$). In contrast, serum magnesium levels increased in Kfar Saba, which continued to rely on groundwater (2.008 ± 0.179 vs. 2.067 ± 0.206, $p < 0.01$). The prevalence of dementia was similar in the two cities (488/20,541, 2.37% in Rehovot and 613/23,991, 2.55% in Kfar Saba). In this ecological study, the adoption of DSW was associated with a significant decrease in serum magnesium concentrations. However, this change was not associated with a higher prevalence of dementia. While this association study cannot rule out some effect of hypomagnesemia on dementia morbidity, it suggests that the effect, if it exists, is relatively small.

Key words | Alzheimer, dementia, hypomagnesemia, magnesium, water desalination

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HIGHLIGHTS

- Magnesium insufficiency has been suggested as a cause of dementia.
- Water desalination causes the decrease in population serum magnesium levels.
- The decrease in serum mean magnesium was not associated with increase prevalence of dementia.

INTRODUCTION

Magnesium is the fourth most abundant mineral in the human body after calcium, potassium, and sodium (Caspi *et al.* 2018). It is essential for the stability of cell function, RNA and DNA synthesis and cell repair, and for the maintenance of the antioxidant status of the cell. Magnesium is also an important cofactor for many biological processes and the activation of a wide range of transporters and enzymes (Swaminathan 2003; Tong & Rude 2005) Furthermore, magnesium plays a critical role in nerve transmission, cardiac excitability, neuromuscular conduction, muscular contraction, blood pressure and glucose, and insulin metabolism. Magnesium plays a critical role in disease prevention and overall health maintenance (Kirkland *et al.* 2018).

The recommended daily allowance (RDA) for magnesium intake is a matter of academic debate (Gröber *et al.* 2015). The Institute of Medicine (1997) recommends 310–320 and 400–420 mg/day for women and men, respectively, whereas the European Food Safety Authority recommends 300 and 350 mg/day for women and men, respectively. Nearly two-thirds of the population in the western world suffer from magnesium deficiency, as a result of inadequate dietary intake, reduced absorption, or increased excretion of magnesium (Institute of Medicine 1997). Hypomagnesemia is a serious health risk, as low levels of magnesium have been associated with a number of chronic diseases, including migraine headaches, stroke, hypertension, cardiovascular disease, type II diabetes mellitus, and Alzheimer's disease (Gröber *et al.* 2015).

Alzheimer's disease (ICD-9 code 331.0) is the most common form of dementia (ICD-9 code 294.20). Research has found an association between the illness and several environmental risk factors, including nutrition, vitamins, and other elements (Ozturk & Cillier 2006). Differentiation of Alzheimer's from other forms of dementia is important in order to implement an appropriate treatment plan and to provide prognostic information for the patients. Criteria for distinguishing types of dementia include demographics, risk factors, clinical treatment course, examination features, and laboratory findings (Camicioli 2004). Vascular dementia (VaD) (ICD-9 code 290.42), dementia caused by cerebrovascular disease, is the second most common form of dementia. Cerebrovascular disease is a risk factor for Alzheimer's disease but can also coexist with Alzheimer's disease, hence creating a form of 'mixed' dementia.

There are several potential mechanisms for magnesium to affect the risk of dementia. First, magnesium can prevent neuronal destruction associated with N-methyl-D-aspartate (NMDA) toxicity (Vyklicky *et al.* 2014). Second, serum magnesium can influence dementia through its potential to mitigate oxidative stress. Magnesium deficiency has been found to stimulate the secretion of inflammatory mediators like interleukins, tumor necrosis factors, and nitric oxide. These mediators are thought to stimulate atherosclerosis and thereby increase the risk of dementia (Kieboom *et al.* 2017).

Although dementia affects roughly 50 million people worldwide, its etiology is largely unknown. Recently, several studies have suggested that the risk of dementia is increased by having serum magnesium levels that are either higher or lower than the ideal range (Kieboom *et al.* 2017; Lo *et al.* 2019). Hypomagnesia was found in tissues of patients with Alzheimer's disease in clinical, experimental, and autopsy studies (Barbagallo *et al.* 2011). A reduction in the frequency of intracellular magnesium deposits in the neurons of Alzheimer's patients was observed when compared with those without the disease. The decrease in Mg, K, and glutamic acid have been shown in the hippocampal tissue of Alzheimer's patients (Durlach 1990). There are also some studies reporting a positive effect of magnesium in the treatment of various degenerative illnesses. An improvement in memory and other symptoms was reported with nutritional magnesium support in patients with dementia (Slutsky *et al.* 2010). Higher self-reported dietary intake of magnesium was found to be associated with a decreased risk of dementia (Mekonnen & Hoekstra 2016). Kieboom *et al.* (2017) found that both low and high serum magnesium levels were associated with an increased risk of Alzheimer's disease and mixed dementia.

The lack of a consensus regarding the role of magnesium levels in the incidence of dementia suggests that further research is warranted, especially in light of the recent trend toward increased use of desalinated water (DSW).

Worldwide, two-thirds of the global population lives under conditions of severe water scarcity at least 1 month of the year (Mekonnen & Hoekstra 2016), and the emerging solution is desalination. In 2018, over 18,000 desalination plants were in operation in 150 countries, producing 87 million cubic meters of clean water each day and supplying drinking water to over 300 million people. Today, Israel relies on DSW for 75% of its drinking water, and the health consequences of this shift are a major concern, as DSW has no magnesium or iodine (Koren *et al.* 2017; Boroje *et al.* 2018).

The study had two objectives:

1. To examine whether the switch to DSW led to lower serum concentrations as compared with the period prior to desalination.
2. To examine whether a community which begins to rely on DSW exhibits a higher prevalence of dementia.

SUBJECTS AND METHODS

We selected two cities residing in the central region of Israel (Figure 1).

Rehovot, a city which has relied almost entirely on DSW since 2007 and Kfar Saba, which experienced no change. These cities are of similar sizes and comparable demographics (Table 1). The study population was comprised of all inhabitants of these two cities who had chosen Maccabi Health Service as their health provider. This generated a sample of 20,541 in Rehovot and 23,991 in Kfar Saba. Maccabi Healthcare Service (MHS) maintains a central computerized database that contains demographic and medical data, including diagnoses, drug purchases (all prescription drugs and some over-the-counter drugs), laboratory data, hospitalizations, and physician visits. The study was approved by Maccabi Health Services Research Ethics Board.

For our study, we designated the first quarter of 2007 as the beginning of the 'post-desalination' period since this was when the switch to DSW in Rehovot took place.

From the patients' electronic chart, we identified members who were diagnosed with dementia and Alzheimer based on ICD9 codes between 2007 and 2019. Alzheimer's disease (ICD-9 codes 331.0) is the most common form of

dementia (ICD-9 code 294.20). Vascular dementia carries ICD-9 code 290.42. Cerebrovascular disease is a risk factor for Alzheimer's disease but can also coexist with Alzheimer's disease, hence creating a form of 'mixed' dementia. We combined for this analysis all forms of dementia.

For each subject, where Mg levels were available, we calculated her/his mean Mg levels from 2001 to 2007 and from 2008 to 2017 and compared these two periods in each city by Student's *t* test for unpaired results.

The prevalence of dementia between the two cities was compared using the chi-square test.

Body mass index (BMI) was calculated from the most recent weight and height measurements. Socioeconomic status was calculated using economic features of the individual (such as salary and car ownership) available in the Maccabi health service database.

RESULTS

The demographics of MHS members in the two cities are presented in Table 1, showing no significant differences. Serum magnesium significantly decreased following initiation of desalination in the desalinated city (2.067 ± 0.21 pre- and 2.059 ± 0.216 post-desalination, $p < 0.01$), and increased in the city which did not use DSW (2.008 ± 0.179 vs. 2.067 ± 0.206, $p < 0.01$) (Table 2). The prevalence of dementia was not different between the two cities (436/20,541, 2.12% in the desalinated city and 563/23,991, 2.34% in the un-desalinated city). Mean Mg concentration in the groundwater was 5.4 mg/L in the DSW community as compared with 25.2 mg/L in the non-desalinated community. The prevalence of dementia was not different between 2001–2007 and 2001–2020 (Table 3), and these figures in the two communities were in line with the prevalence in Israel.

DISCUSSION

This study examined the effect of the initiation of water desalination on serum magnesium levels and the prevalence of dementia by comparing two cities that were relatively similar, except that one community began to rely on DSW and the other continued to rely almost exclusively on
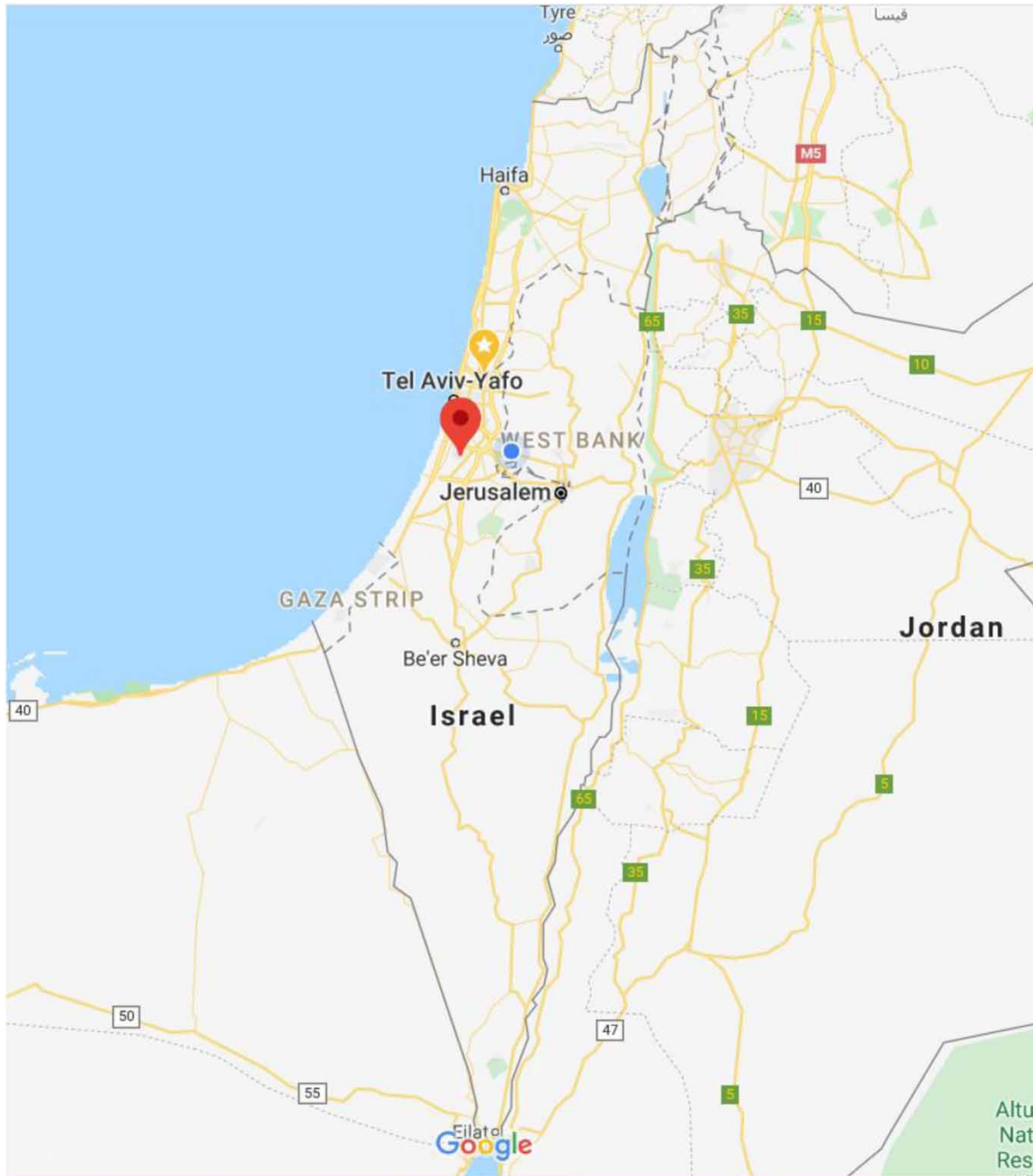
Figure 1 | The locations of Rehovot (red circle) and Kfar Saba (yellow atar) in Israel. Please refer to the online version of this paper to see this figure in colour: http://dx.doi.org/10.2166/wh.2020.132.

groundwater. Our results indicate that switching to DSW resulted in a statistically significant decrease in serum magnesium levels.

The research design enabled us to compare two populations with relatively similar characteristics but very different reliance on DSW. Unlike other studies that paid little attention to potential confounding from other variables associated with DSW use, this study relied on two populations that differed primarily in their distance from Israel's national water carrier, rather than other factors.

Table 1 │ Demographics of the subjects in the two cities

Demographics	Rehovot (desalination) (*n* = 20,541)	Kfar Saba (no desalination) (*n* = 23,991)
Age	38.6(23.9)	34(23.7)
SES (1–19)	12.7(5.32)	13.3(3.10)
BMI	22.9(5.9)	23.1(6.1)
No. of Mg prescriptions (per 10,000)	7.9(0.6)	10.4(0.77)

Note: Data were taken from 57,424 members of the Maccabi Health Services living in Rehovot and Kfar Saba. Magnesium mean concentrations are reported for all tests administered to the coverage population.
SES, socioeconomic status; BMI, body mass index.

The results of the present study indicate a statistically significant effect of DSW exposure on serum magnesium levels, but without evidence that these changes had affected the prevalence of dementia. These results of magnesium levels agree with a previous study conducted by us (Koren *et al.* 2017), although this time the methodology has substantially improved: Because the Israeli water authorities tend to mix DSW with well water, for many jurisdictions, the actual levels of magnesium would change daily. The present study is unique in identifying two cities where the use/or lack of DSW was constant over the period of 2007–2020, after a baseline period with no DSW between 2001 and 2007.

The growing global water stress, which is predicted to increase desalination significantly in the following decades, highlights, even more, the need for research on the health effects of DSW consumption.

Natural water contains around 10 mg of Mg per liter. If the typical personal water consumption is 1.5 L/d, then DSW would lead to a 15 mg Mg deficit per day, which constitutes only 3–5% of the typical RDA (Institute of Medicine 1997), while our study could detect this shortage in mean Mg serum level, it did not translate to a toxic effect as far as dementia. However, this does not rule out adverse effects on other systems, such as the cardiovascular system. In

Table 3 │ Prevalence of dementia in a desalinated city (Rehovot) vs. non-desalinated city (Kfar Saba)

Dementia cases 2007–2020	REHOVOT (*n* = 20,541) (desalinated)	KFAR SABA (non-desalinated) (*n* = 23,991)
Total no.	488	613
Overall prevalence of dementia (%)	2.37*	2.55*

*P = chi-square non-significant.

addition, one may argue that a follow up of 14 years may not be sufficiently long to see an effect on the prevalence of dementia.

Several recent studies have suggested an association between low or high magnesium intake and the prevalence of dementia (Kieboom *et al.* 2017; Lo *et al.* 2019). However, opposing and inconclusive results make it difficult to drive at conclusions toward identifying preventative measures. While this association study cannot rule out the effect of hypomagnesemia on dementia morbidity in some patients, it suggests that overall such effect, if they exist, is marginal.

Several potential challenges of the present study need to be acknowledged.

We did not address potential effects of water quality with measurements of metals such as aluminum, lead, arsenic, tetrachlorobenzene, and other organic pollutants; however, overall the water quality in these townships is high and all these contaminants have been substantially lower than the WHO guidelines. We did not collect data on dietary magnesium; however, supplementary magnesium prescriptions were recorded and they did not differ between the two cities.

CONCLUSIONS

In conclusion, we have found a statistically significant decrease in magnesium serum concentrations in a city that

Table 2 │ Mean serum magnesium (Mg) levels (mEq/L) before and after desalination

	REHOVOT	KFAR SABA	SIGNIFICANCE
Mean serum Mg prior to desalination (2002–2007)	2.067(0.210)	2.008(0.179)	<0.01
Mean serum Mg after desalination (2008–2017)	2.059(0216)	2.067(0.206)	<0.01
Changes	00008(0.004) $P < 0.01$	−0.059(0.009) $P < 0.01$	<0.01

Note: Data were taken from 17,533 magnesium blood test results of Maccabi Health Services membership in the cities of Rehovot and Kfar Saba.

turned to water desalination, but the lack of effect on dementia suggests that, at least for dementia, these changes in serum magnesium may be statistically significant, but not clinically significant.

DATA AVAILABILITY STATEMENT

All relevant data are included in the paper or its Supplementary Information.

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