Long-term Iodine nutrition is associated with longevity in older adults

A 20-year follow-up of the Randers-Skagen study

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Published in:
British Journal of Nutrition

DOI (link to publication from Publisher):
10.1017/S0007114520001592

Publication date:
2021

Document Version
Accepted author manuscript, peer reviewed version

Title: Long-term Iodine nutrition is associated with longevity in older adults: a 20-year follow-up of the Randers-Skagen study.

Short title: Long-term iodine intake and longevity

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Keywords: Iodine nutrition; longevity; thyroid function; older adults; tap water.

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This peer-reviewed article has been accepted for publication but not yet copyedited or typeset, and so may be subject to change during the production process. The article is considered published and may be cited using its DOI
10.1017/S0007114520001592
The British Journal of Nutrition is published by Cambridge University Press on behalf of The Nutrition Society

Abstract

Iodine intake affects the occurrence of thyroid disorders. However, the association of iodine intake with longevity remains to be described. This led us to perform a 20-year follow-up on participants from the Randers-Skagen (RaSk) study. Residents in Randers born in 1920 (n=210) and Skagen born in 1918-1923 (n=218) were included in a clinical study in 1997-1998. Mean iodine content in drinking water was 2 µg/L in Randers and 139 µg/L in Skagen. We collected baseline data through questionnaires, performed physical examinations, and measured iodine concentrations in spot urine samples. Income data were retrieved from Danish registries. We performed follow-up on mortality until 12-12-2017 using Danish registries. Complete follow-up data were available on 428 out of 430 of participants (99.5%). At baseline, the median urinary iodine concentration was 55 µg/L in Randers and 160 µg/L in Skagen residents. Participants were long-term residents with 72.8% and 92.7% residing for more than 25 years in Randers and Skagen, respectively. Cox regression showed that living in Skagen compared to Randers was associated with lower hazard ratio (HR) of death in both age- and sex-adjusted analysis (HR 0.60, 95% CI: 0.41-0.87, *P = 0.006*), but also after adjustment for age, sex, number of drugs, Charlson Comorbidity Index, smoking, alcohol, and income (HR 0.60, 95% CI: 0.41-0.87, *P = 0.008*). Residing in iodine replete Skagen was associated with increased longevity. This indicates, that long-term residency in an iodine replete environment may be associated with increased longevity compared to residency in an iodine deficient environment.

Introduction

Iodine deficiency is a global health issue and the main cause of preventable brain damage[1]. The World Health Organization (WHO) recommends iodine fortification to achieve sufficient iodine intake (150 µg/day in non-pregnant adults) [1]. In Denmark, iodine fortification was cautiously implemented in two steps[2]; voluntary iodine fortification (8 ppm. to salt) in June 1998 and mandatory iodine fortification (13 ppm. to salt) from July 2000. Iodine fortification has been accompanied by a monitoring program of the incidence of overt thyroid dysfunction[2]. This monitoring program has shown that the iodine fortification in Denmark was followed by a transient rise in the occurrence of hyperthyroidism, which was more marked in older adults compared to younger adults [3,4].

Iodine nutrition has an impact on the occurrence of thyroid dysfunction. Hyperthyroidism is more frequent in mild and moderate iodine deficient populations, whereas iodine replete populations may have a higher occurrence of hypothyroidism[4–7]. Hyperthyroidism can lead to complications such as atrial fibrillation, heart failure and increased fracture risk. These complications are associated with increased mortality, especially in vulnerable groups such as older adults[8–10]. However, the association between long-term iodine intake level and longevity remains to be described.

We performed a follow-up on a previous cross-sectional study of two groups of older adults in Denmark conducted in 1997-1998[5,11]. One group lived in the iodine replete city of Skagen and the other in the moderately iodine deficient city of Randers. The prevalence of thyroid dysfunction was markedly different with 26% of participants in the iodine deficient city having hyperthyroidism compared to 6% among the iodine replete[5]. Our follow-up aimed to assess the association between long-term residency in an iodine replete environment and longevity with a 20-year follow-up on older adults aged 75-80-years.

Methods

Setting

Randers and Skagen are separated by only 140 kilometres on the peninsula Jutland in Denmark. Iodine content in ground water differs due to differences in aquifer source rock as Skagen is based on sea bottom. Previous investigations found mean drinking water iodine concentrations of 2 µg/L in Randers and 139 µg/L in Skagen without dispersion between samples taken at different time points[11–13]. Furthermore, the clinical investigations in 1997-1998 found markedly different iodine intake levels between the two populations with a median urinary iodine concentration of 55 µg/L in Randers, suggesting mild to moderate iodine deficiency, compared to 160 µg/L in Skagen confirming that this population was iodine replete[1,11,12].

Baseline

Invited participants in Randers were all residents born in 1920 and those in Skagen were all residents born in 1918-1923. They were investigated in late 1997 and 1998 as described in detail previously[5]. The wider age range in Skagen was to ensure equal sample sizes. Participation rate was 47%[5]. Ten percent of non-responders were previously selected at random for a telephone interview. There were no differences in sex, smoking, alcohol intake, comorbidity categorised according to Charlson Comorbidity Index (CCI)[14], or known thyroid disease between responders and non-responders[5]. Participants in both cities completed a questionnaire about previous or current thyroid disease and treatment, smoking, alcohol, and comorbidities. Data on income for the year of 1996 were gathered from the Danish Registry of Income Statistics and indexed to one at the median level of Skagen. Spot urine samples were analysed for creatinine using a kinetic Jaffé method, and iodine concentrations were determined by the Sandell-Kolthoff reaction modified after Wilson and van Zyl as described previously [11,15].

Follow-up

Participants were followed until death, emigration, or end of study by the 31st of December in 2017. Data on mortality were collected from the Registry of Causes of Death. Data on emigration were collected from the Central Persons Registry.

Statistical analyses

Categorical variables are presented as numbers and percentages. Continuous variables, age and income, are given with medians and interquartile range due to non-normal distributions. Chi-square and Mann-Whitney U tests were used to compare variables between groups. Kaplan-Meier curves of survival probability are presented.

The association between residency and death during follow-up was analysed using multivariate Cox proportional hazards model with calendar year as the time scale. All associations were tested using two models. First, a basic model included age and sex as covariates. Second, an advanced model included age, sex, smoking, alcohol consumption, CCI, and income.

Proportional hazards assumptions were checked by inspecting cumulative Martingale residual plots, and they were met. Interaction terms between place of residency and all covariates were tested using likelihood ratio tests. Inspection of Martingale residuals revealed that income was non-linear and was modelled accordingly as a restricted cubic spline with 5 knots at the 5^{th},25^{th}, 50^{th}, 75^{th} and 95^{th} percentiles. Age was recorded as a discrete variable and was modelled as such in the analysis.

The variation inflation factor for the residency variable was 3.35 with age in the model and 1.14 without. This suggested multicollinearity with age likely due to sampling methods. Therefore, subgroup analysis on participants aged 78 years was performed.

The sample size of 428 participants with an event rate of 91% in two similar sized groups gave us a minimally detectable hazard ratio of 0.76 at 80% power and 5% significance level.

All analyses were performed as complete-case analyses as there were few missing data. All analyses were performed using R statistical software version 3.5.1 (R Core Team 2018).

Ethics

Ethical approval was granted by the Regional Research Ethics Committees of Northern Jutland and Viborg County[5]. Approval for registry follow-up was granted by the Danish Data Protection Agency (P-2019-191).

Results

In the original clinical study, there were 430 participants. Of these, two participants were excluded due to insufficient record linkage. One emigrated during follow-up and was censored at the date of emigration.

Baseline characteristics

Participants from Randers and Skagen had similar sex distributions, smoking habits, and CCI (Table 1), whereas differences in alcohol consumption (primarily occasional use) and income were seen. As expected according to the inclusion, there were also differences in urinary iodine concentration, age, and length of residency.

Survival analyses

Overall, survival was higher in Skagen than in Randers for 20 years follow-up (Figure 1, and 88% of participants in Skagen died during follow-up compared to 95% of participants in Randers. Thus, Skagen dwellers were followed for 11.5 (IQR: 6.8-17.0) years while Randers dwellers were followed for a median of 10.1 (IQR: 4.8-14.1) years.

Cox regression conducted both adjusted for sex and age (basic model) and with additional adjustment for smoking, alcohol consumption, Charlson Comorbidity Index, and income (advanced model) provide strong statistical support for an association between residency and longevity (Table 2). The hazard ratio for death was 0.60 (95% confidence interval (CI): 0.41-0.87) in favour of Skagen residency. The subgroup analysis of 78-year-olds showed similar trends as the primary analysis.

Discussion

We found that long-term residency in an iodine replete environment is associated with lower mortality during 20-year follow-up in older adults. This is consistent with findings that longevity in older adults is associated with higher TSH[16,17], as higher iodine intake levels in a population raises the average TSH values with age[18,19].

The influence of iodine nutrition on morbidity has been studied extensively[2,4–7,20]. Specifically, iodine nutrition is a pivotal determinant of thyroid dysfunction, and this influence is strengthened with advancing age[20]. Iodine deficiency is known to be associated with an increased occurrence of hyperthyroidism. In our baseline study, 26% of participants from the moderately iodine-deficient Randers residents had hyperthyroidism compared to 6% among the iodine replete Skagen residents as published previously[5]. Even slight thyroid dysfunction may influence mortality, and hyperthyroidism increases the risk of complications such as atrial fibrillation, heart failure, and fractures[8–10]. Thus, the difference in the prevalence of hyperthyroidism could explain some of the differences in longevity between the two cities.

Long-term iodine intake influences the occurrence of thyroid disorders as discussed above. The iodine intake level in these populations was determined by the iodine content of tap water [11,21]. Tap water iodine was documented to be stable for decades prior the baseline examination[22]. An iodine fortification program was implemented during follow-up and the monitoring program (DanThyr) showed an approximately 50 µg/24h rise in urinary iodine excretion[23]. A raised iodine intake was followed by a transient increase in hyperthyroidism in a formerly iodine deficient population parallel to the population in Randers[4] and hence the differences in the present report could be strengthened. Still, for participants not taking iodine supplements the anticipated population iodine intake level would remain within the recommended level in Skagen and mild iodine deficiency to recommended intake would be anticipated in Randers[11].

Data on the association between iodine nutrition and mortality are scarce. Only one study aimed to assess the relationship between a single spot urine iodine concentration measurement and mortality based on a sample of the National Health and Nutritional Examination Survey III (NHANES)[24]. They did not find that iodine deficiency was related to increased mortality in conflict with our results. However, the population included was iodine replete[25] without the same large span of iodine intake levels as found in the present study. Furthermore, the study excluded participants with known thyroid dysfunction and thus prevented for any effect of iodine deficiency mediated through thyroid disease. Additionally, they based their analysis on a single urine sample which potentially

could lead to misclassification of iodine nutritional status on the individual level and provides very limited information about long-term iodine intake[26].

An additional report based on the NHANES population showed no association between iodine intake levels and cardiovascular disease after the exclusion of individuals with abnormal thyroid function[27]. Their study used the age- and sex-adjusted iodine/creatinine ratio, which has been shown to give a more accurate assessment of iodine nutrition status than urinary iodine concentration[26,28]. Their cut-off score for low iodine levels was based on quartiles, which complicates the determination of iodine nutritional status of subjects in the lowest quartile of iodine intake. These two studies, based on the NHANES, in conjunction with our study, suggests that any association between iodine nutrition and mortality may be mediated by thyroid function. However, this needs confirmation in studies using appropriate statistical methods and include follow-up on thyroid function. Furthermore, the NHANES stem from an iodine replete population. Thus, further studies are needed to rule out non-thyroidal effects in iodine deficiency.

Our study also had some limitations. Importantly, there may be unknown and residual confounders including socioeconomic status and other unmeasured differences between the two cities, which could influence our results and thus needs further exploration in prospective cohorts. Our study would have been strengthened by the addition of a city with mild iodine deficiency to explore a potential dose-response relationship. Furthermore, we did not perform follow-up on thyroid function or iodine intake in our participants, and any potential thyroidal or non-thyroidal effects cannot be evaluated. Finally, we chose not to analyse causes of death, as systematic validation of the Causes of Death Registry is lacking, the autopsy rate is low and there are indications of misclassification in the registry[29]. Additionally, we were concerned that geographical variations in coding practices could severely confound any findings from analysis of causes of death.

Conclusion

Long-term residency in an iodine replete environment is associated with increased longevity as evaluated from 20-year follow-up in older adults.

Acknowledgements

The authors would like to thank the late Professor Peter Laurberg for his invaluable contribution to design, planning, and Steen Terpling and Finn Iversen for the execution of the Randers-Skagen study.

The work is sponsored by the Department of Geriatric Medicine, Aalborg University Hospital, Aalborg, Denmark.

J.R. and S.A. designed the study. K.M.P., and S.A. conducted the initial clinical study and C.T.-P acquired follow-up data. J.R., C.T.-P, and S.A. designed and performed the statistical analysis. J.R., M.B.D., G.V.S., M.G.J., S.L.A, A.C., I.B.P., C.T.-P, and S.A. interpreted the results. JR wrote the manuscript and all other authors critically revised the manuscript. All authors read and approved the final version of the manuscript.

C.T.-P. has received a research grant from BIOTRONIK and a research grant as wells as advisory board honoraria from Bayer. The authors report no further conflicts of interest.

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Tables

Table 1. Baseline characteristics by residency

	Iodine deficient Randers (n = 210)	**Iodine replete Skagen (n = 218)**	**p-value**
UIC – median (IQR)	55 (37-97)	160 (126-228)	<0.001
UIE – median (IQR)	74 (45-118)	184 (144-246)	<0.001
Female sex – n (%)	128 (61.0%)	134 (61.5%)	0.91
Age – median (IQR)	78 (78-78)	76 (75-78)	<0.001
Years of residence in city – n (%)			
25 years or more	150 (72.8%)	202 (92.7%)	<0.001
40 years or more	131 (63.6%)	189 (86.7%)	<0.001
Missing	*4*	*0*	
Income* – median (IQR)	0.92 (0.82-1.15)	1 (0.91-1.26)	<0.001
Alcohol – n (%)			0.043
None	23 (11.3%)	43 (20.1%)	
0-10 units	148 (72.9%)	137 (64.0%)	
10-20 units	32 (15.8%)	34 (15.9%)	
Missing	*7*	*4*	
Smoking – n (%)			0.44
Never	74 (35.4%)	75 (34.7%)	
Current	81 (38.8%)	95 (44.0%)	
Prior	54 (25.8%)	46 (21.3%)	
Missing	*1*	*2*	
CCI – n (%)			
0	122 (58.1%)	109 (50.0%)	0.13
1	56 (26.7%)	81 (37.2%)	
2	20 (9.5%)	19 (8.7%)	
3	12 (5.7%)	9 (4.1%)	

* income is indexed to median level in Skagen. Abbreviations; UIC: urinary iodine concentration, UIE: urinary iodine excretion corrected for age and sex specific creatinine excretions (men 0.95 g/l; women 0.7 g/l), CCI: Charlson Comorbidity Index.

Table 2. 20-years follow-up of older Randers and Skagen residents in 1998

	Death/ total	Follow-up time (median, IQR)	Model 1*			Model 2**		
			HR	95% CI	p-value	HR	95% CI	p-value
Randers	199/210	10.1 (4.8 – 14.1)	Reference			Reference		
Skagen	192/218	11.5 (6.8 – 17.0)	0.60	0.41-0.87	0.006	0.60	0.41-0.87	0.008
Subgroup aged 78 at inclusion (n = 225, 52.5%)								
Randers	185/196	10.2 (4.8 – 14.5)	Reference			Reference		
Skagen	25/29	11.1 (8.8 – 17.0)	0.67	0.44-1.03	0.07	0.65	0.41-1.04	0.07

*Adjusted for age and sex. **Adjusted for age, sex, smoking, alcohol consumption, Charlson Comorbidity Index, and income. Abbreviations: IQR, interquartile range; HR, Hazard ratio; CI, Confidence Interval.

Figure caption/legend

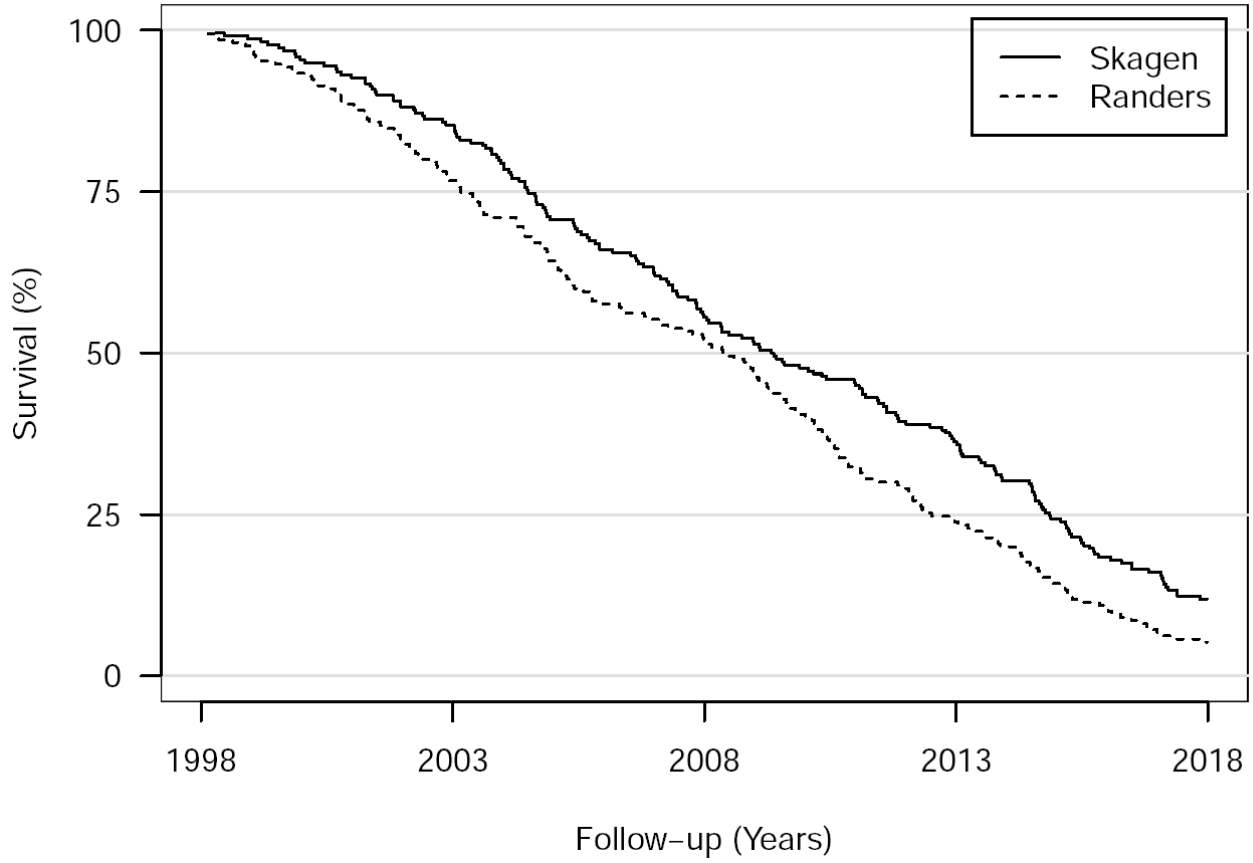

Figure 1. Kaplan-Meier survival curve by residency in iodine replete Skagen or iodine deficient Randers.