British Journal of Nutrition (2021), 125, 260–265 doi:10.1017/S0007114520001592

Long-term iodine nutrition is associated with longevity in older adults: a 20 years' follow-up of the Randers–Skagen study

Johannes Riis[1,2]*, Klaus M. Pedersen[3], Mathias B. Danielsen[1,2], Gustav V. B. Sørensen[1,2], Martin G. Jørgensen[1], Stine L. Andersen[4], Allan Carlé[5], Inge B. Pedersen[5], Christian Torp-Pedersen[6,7] and Stig Andersen[1,2]

[1]*Department of Geriatric Medicine, Aalborg University Hospital, 9000 Aalborg, Denmark*
[2]*Department of Clinical Medicine, Aalborg University, 9000 Aalborg, Denmark*
[3]*Department of Internal Medicine, Vejle Hospital, 7100 Vejle, Denmark*
[4]*Department of Clinical Biochemistry, Aalborg University Hospital, 9000 Aalborg, Denmark*
[5]*Department of Endocrinology, Aalborg University Hospital, 9000 Aalborg, Denmark*
[6]*Department of Cardiology and Clinical Investigation, Nordsjaellands Hospital, 3400 Hillerød, Denmark*
[7]*Department of Cardiology, Aalborg University Hospital, 9000 Aalborg, Denmark*

(Submitted 20 December 2019 – Final revision received 15 March 2020 – Accepted 23 April 2020 – First published online 7 May 2020)

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 years' 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 31 December 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 with Randers was associated with a lower hazard ratio (HR) of death in both age- and sex-adjusted analyses (HR 0·60, 95 % CI 0·41, 0·87, $P = 0·006$), but also after adjustment for age, sex, number of drugs, Charlson co-morbidity 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 with residency in an iodine-deficient environment.

Key words: **Iodine nutrition: Longevity: Thyroid function: Older adults: Tap water**

Iodine deficiency is a global health issue and the main cause of preventable brain damage[1]. The WHO recommends iodine fortification to achieve sufficient iodine intake (150 μg/d in non-pregnant adults)[1]. In Denmark, iodine fortification was cautiously implemented in two steps[2]: voluntary iodine fortification (8 parts per million to salt) in June 1998 and mandatory iodine fortification (13 parts per million to salt) from July 2000. Iodine fortification has been accompanied by a monitoring programme of the incidence of overt thyroid dysfunction[2]. This monitoring programme 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 with 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

* **Corresponding author:** Johannes Riis, fax +45 97664192, email johannes0408@live.dk

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 with 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 years' follow-up on older adults aged 75–80 years.

Methods

Setting

Randers and Skagen are separated by only 140 km on the peninsula Jutland in Denmark. Iodine content in ground water differs due to differences in aquifer source rock as Skagen is based on raised 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 with 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, co-morbidity categorised according to Charlson co-morbidity index[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 co-morbidities. 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 31 December 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 ranges due to non-normal distributions. To compare variables between groups, χ^2 and Mann–Whitney U tests were used. 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, Charlson co-morbidity index 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 five knots at the 5th, 25th, 50th, 75th and 95th 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 multi-collinearity with age likely due to sampling methods. Therefore, sub-group 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 Charlson co-morbidity index (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 (Fig. 1), and 88 % of participants in Skagen died during follow-up compared with 95 % of

Table 1. Baseline characteristics by residency
(Median values and interquartile ranges (IQR); numbers and percentages)

	Iodine-deficient Randers (*n* 210)		Iodine-replete Skagen (*n* 218)		
	n	%	*n*	%	*P*
Urinary iodine concentration (μg/l)					
Median	55		160		<0·001
IQR	37–97		126–228		
UIE* (μg/d)					
Median	74		184		<0·001
IQR	45–118		144–246		
Female sex	128	61·0	134	61·5	0·91
Age (years)					
Median	78		76		<0·001
IQR	78–78		75–78		
Years of residence in city					
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	0·92		1		<0·001
IQR	0·82–1·15		0·91–1·26		
Alcohol					
None	23	11·3	43	20·1	0·043
0–10 units	148	72·9	137	64·0	
10–20 units	32	15·8	34	15·9	
Missing	7		4		
Smoking					
Never	74	35·4	75	34·7	0·44
Current	81	38·8	95	44·0	
Prior	54	25·8	46	21·3	
Missing	1		2		
Charlson co-morbidity index					
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	

UIE, urinary iodine excretion.
* UIE corrected for age- and sex-specific creatinine excretions (men 0·95 g/l; women 0·7 g/l).
† Income is indexed to median level in Skagen.

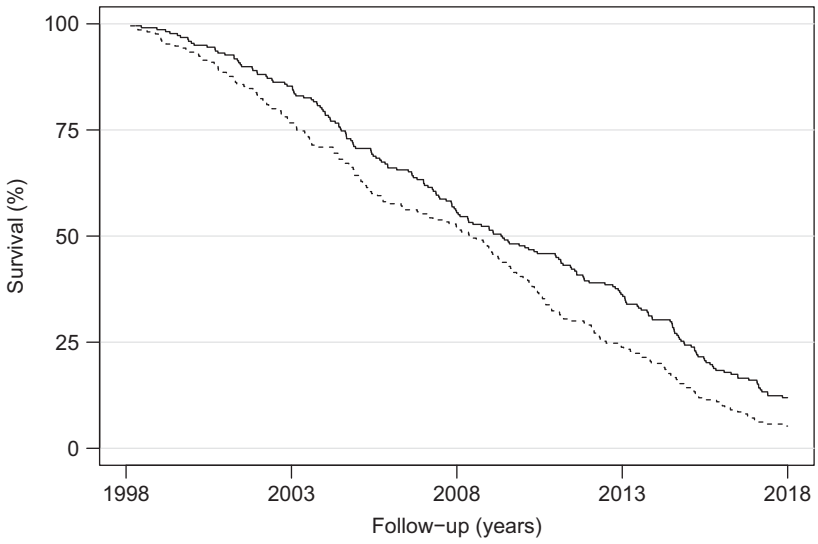

Fig. 1. Kaplan–Meier survival curve by residency in iodine-replete Skagen or iodine-deficient Randers. ——, Skagen; - - - -, Randers.

Table 2. Twenty years' follow-up of older Randers and Skagen residents in 1998
(Median values and interquartile ranges; hazard ratios (HR) and 95 % confidence intervals)

		Follow-up time (years)		Model 1*			Model 2†		
	Deaths/total	Median	Interquartile range	HR	95 % CI	*P*	HR	95 % CI	*P*
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
Sub-group aged 78 years 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 co-morbidity index and income.

participants in Randers. Thus, Skagen dwellers were followed for 11·5 (interquartile range 6·8, 17·0) years, while Randers dwellers were followed for a median of 10·1 (interquartile range 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 co-morbidity 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 % CI 0·41, 0·87) in favour of Skagen residency. The sub-group 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 years' follow-up in older adults. This is consistent with findings that longevity in older adults is associated with higher thyroid-stimulating hormone (TSH)[16,17], as higher iodine intake levels in a population raise the average TSH 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 with 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 difference in 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 programme was implemented during follow-up, and the monitoring programme (DanThyr) showed an approximately 50 µg/24 h 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 National Health and Nutritional Examination Survey population showed no association between iodine intake levels and CVD 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 National Health and Nutritional Examination Survey, 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 includes follow-up on thyroid function. Furthermore, the National Health and Nutritional Examination Survey stems 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 socio-economic 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 years' 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 was sponsored by the Department of Geriatric Medicine, Aalborg University Hospital, Aalborg, Denmark. C. T.-P. has received a research grant from BIOTRONIK and a research grant as wells as advisory board honoraria from Bayer.

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. B. S., M. G. J., S. L. A., A. C., I. B. P., C. T.-P. and S. A. interpreted the results. J. R. wrote the manuscript and all other authors critically revised the manuscript. All authors read and approved the final version of the manuscript.

The authors declare that there are no conflicts of interest.

References

1. World Health Organization/International Council for the Control of the Iodine Deficiency Disorders/United Nations Childrens Fund (WHO/ICCIDD/UNICEF) (2007) *Assessment of Iodine Deficiency Disorders and Monitoring Their Elimination*, 3rd ed. Geneva: WHO. https://apps.who.int/iris/bitstream/handle/10665/43781/9789241595827_eng.pdf;jsessionid=AC7324E67BDD0C22AC3F158ABE518F89?sequence=1
2. Laurberg P, Jørgensen T, Perrild H, *et al.* (2006) The Danish investigation on iodine intake and thyroid disease, DanThyr: status and perspectives. *Eur J Endocrinol* **155**, 219–228.
3. Carlé A, Pedersen IB, Knudsen N, *et al.* (2011) Epidemiology of subtypes of hyperthyroidism in Denmark: a population-based study. *Eur J Endocrinol* **164**, 801–809.
4. Petersen M, Knudsen N, Carlé A, *et al.* (2018) Thyrotoxicosis after iodine fortification. A 21-year Danish population-based study. *Clin Endocrinol* **89**, 360–366.
5. Andersen S, Iversen F, Terpling S, *et al.* (2009) More hypothyroidism and less hyperthyroidism with sufficient iodine nutrition compared to mild iodine deficiency–a comparative population-based study of older people. *Maturitas* **64**, 126–131.
6. Laurberg P, Pedersen KM, Hreidarsson A, *et al.* (1998) Iodine intake and the pattern of thyroid disorders: a comparative epidemiological study of thyroid abnormalities in the elderly in Iceland and in Jutland, Denmark. *J Clin Endocrinol Metab* **83**, 765–769.
7. Petersen M, Knudsen N, Carlé A, *et al.* (2019) Increased incidence rate of hypothyroidism after iodine fortification in Denmark. A 20 year prospective population-based study. *J Clin Endocrinol Metab* **104**, 1833–1840.
8. Selmer C, Olesen JB, Hansen ML, *et al.* (2012) The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. *BMJ* **345**, e7895.
9. Blum MR, Bauer DC, Collet T-H, *et al.* (2015) Subclinical Thyroid Dysfunction and Fracture Risk. *JAMA* **313**, 2055.
10. Gencer B, Collet T-H, Virgini V, *et al.* (2012) Subclinical thyroid dysfunction and the risk of heart failure events. *Circulation* **126**, 1040–1049.
11. Andersen S, Pedersen KM, Iversen F, *et al.* (2008) Naturally occurring iodine in humic substances in drinking water in Denmark is bioavailable and determines population iodine intake. *Br J Nutr* **99**, 319–325.
12. Rasmussen LB, Larsen EH & Ovesen L (2000) Iodine content in drinking water and other beverages in Denmark. *Eur J Clin Nutr* **54**, 57–60.
13. Andersen S, Petersen SB & Laurberg P (2002) Iodine in drinking water in Denmark is bound in humic substances. *Eur J Endocrinol* **147**, 663–670.
14. Charlson ME, Pompei P, Ales KL, *et al.* (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* **40**, 373–383.
15. Andersen S, Karmisholt J, Pedersen KM, *et al.* (2008) Reliability of studies of iodine intake and recommendations for number of samples in groups and in individuals. *Br J Nutr* **99**, 813–818.
16. Jansen SW, Roelfsema F, van der Spoel E, *et al.* (2015) Familial longevity is associated with higher TSH secretion and strong TSH-fT3 relationship. *J Clin Endocrinol Metab* **100**, 3806–3813.
17. Gussekloo J, van Exel E, de Craen AJM, *et al.* (2004) Thyroid status, disability and cognitive function, and survival in old age. *JAMA* **292**, 2591.
18. Hollowell JG, Staehling NW, Flanders WD, *et al.* (2002) Serum TSH, T sub4/sub, and thyroid antibodies in the United States Population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab* **87**, 489–499.
19. Bjergved L, Jørgensen T, Perrild H, *et al.* (2012) Predictors of change in serum TSH after iodine fortification: an 11-year follow-up to the DanThyr Study. *J Clin Endocrinol Metab* **97**, 4022–4029.
20. Laurberg P, Cerqueira C, Ovesen L, *et al.* (2010) Iodine intake as a determinant of thyroid disorders in populations. *Best Pract Res Clin Endocrinol Metab* **24**, 13–27.
21. Pedersen KM, Laurberg P, Nøhr S, *et al.* (1999) Iodine in drinking water varies by more than 100-fold in Denmark. Importance for iodine content of infant formulas. *Eur J Endocrinol* **140**, 400–403.
22. Andersen S & Laurberg P (2009) The nature of iodine in drinking water. In *Comprehensive Handbook of Iodine*, pp. 125–134. Cambridge, MA: Academic Press, Elsevier Inc.
23. Rasmussen LB, Carlé A, Jørgensen T, *et al.* (2008) Iodine intake before and after mandatory iodization in Denmark: results from the Danish Investigation of Iodine Intake and Thyroid Diseases (DanThyr) study. *Br J Nutr* **100**, 166–173.

British Journal of Nutrition

24. Inoue K, Leung AM, Sugiyama T, *et al.* (2018) Urinary iodine concentration and mortality among U.S. adults. *Thyroid* **28**, 913–920.
25. Lee KW, Cho MS, Shin D, *et al.* (2016) Changes in iodine status among US adults, 2001–2012. *Int J Food Sci Nutr* **67**, 184–194.
26. Knudsen N, Christiansen E, Brandt-Christensen M, *et al.* (2000) Age- and sex-adjusted iodine/creatinine ratio. A new standard in epidemiological surveys? Evaluation of three different estimates of iodine excretion based on casual urine samples and comparison to 24 h values. *Eur J Clin Nutr* **54**, 361–363.
27. Tran HV, Erskine NA, Kiefe CI, *et al.* (2017) Is low iodine a risk factor for cardiovascular disease in Americans without thyroid dysfunction? Findings from NHANES. *Nutr Metab Cardiovasc Dis* **27**, 651–656.
28. Andersen S, Pedersen KM, Pedersen IB, *et al.* (2001) Variations in urinary iodine excretion and thyroid function. A 1-year study in healthy men. *Eur J Endocrinol* **144**, 461–465.
29. Helweg-Larsen K (2011) The Danish register of causes of death. *Scand J Public Health* **39**, 26–29.

British Journal of Nutrition