Dietary iodine exposure and brain structures and cognition in older people. Exploratory analysis in the Lothian Birth Cohort 1936

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Authors:

Maria del C. Valdés Hernández[1,2]†, Janet Kyle[3], Julia Allan[4], Michael Allerhand[1], Heather Clark[3], Susana Muñoz Maniega[1,2], Natalie A. Royle[1,2], Alan J Gow[1,5], Alison Pattie[1,6], Janie Corley[1,6], Mark E. Bastin[1,2], John M. Starr[1], Joanna M. Wardlaw[1,2], Ian J. Deary[1,6] and Emilie Combet [7]†

Author Affiliations:

[1]Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK

[2]Department of Neuroimaging Sciences, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK

[3]Department of Nutrition, University of Aberdeen, Aberdeen, UK

[4]Department of Psychology, University of Aberdeen, Aberdeen, UK

[5]Department of Psychology, Heriot-Watt University, Edinburgh, UK

[6]Department of Psychology, University of Edinburgh, Edinburgh, UK

[7]Human Nutrition, School of Medicine, College of Medical, Veterinary and Lifesciences, University of Glasgow, Glasgow, UK

†Both authors equally contributed to this work

Correspondence: Dr. Maria C. Valdés Hernández, Department of Neuroimaging Sciences, Centre for Clinical Brain Sciences, University of Edinburgh, 49 Little France Crescent, Chancellor's Building, Edinburgh, EH16 4SB, UK. Telephone: +44-131-4659527, Fax: +44-131-3325150, E-mail: M.Valdes-Hernan@ed.ac.uk

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Abstract

Background: Iodine deficiency is one of the three key micronutrient deficiencies highlighted as major public health issues by the World Health Organisation. Iodine deficiency is known to cause brain structural alterations likely to affect cognition. However, it is not known whether or how different (lifelong) levels of exposure to dietary iodine influences brain health and cognitive functions.

Methods: From 1091 participants initially enrolled in The Lothian Birth Cohort Study 1936, we obtained whole diet data from 882. Three years later, from 866 participants (mean age 72 yrs, SD ±0.8), we obtained cognitive information and ventricular, hippocampal and normal and abnormal tissue volumes from brain structural magnetic resonance imaging scans (n=700). We studied the brain structure and cognitive abilities of iodine-rich food avoiders/low consumers versus those with a high intake in iodine-rich foods (namely dairy and fish).

Results: We identified individuals (n=189) with contrasting diets, i) belonging to the lowest quintiles for dairy and fish consumption, ii) milk avoiders, iii) belonging to the middle quintiles for dairy and fish consumption, and iv) belonging to the middle quintiles for dairy and fish consumption. Iodine intake was secured mostly though the diet (n=10 supplement users) and was sufficient for most (75.1%, median 193 μg/day). In individuals from these groups, brain lateral ventricular volume was positively associated with fat, energy and protein intake. The associations between iodine intake and brain ventricular volume and between consumption of fish products (including fish cakes and fish-containing pasties) and white matter hyperintensities (p=0.03) the latest being compounded by sodium, proteins and saturated fats, disappeared after type 1 error correction.

Conclusion: In this large Scottish older cohort, the proportion of individuals reporting extreme (low vs. high)/medium iodine consumption is small. In these individuals, low iodine-rich food intake was associated with increased brain volume shrinkage, raising an important hypothesis worth being explored for designing appropriate guidelines.

Keywords

Ageing, iodine, brain, MRI

1. Introduction

Iodine is one of the three key micronutrient for which deficiency is highlighted as a major public health issue by the World Health Organisation, and the most preventable cause of mental retardation and brain damage (1). While the role of iodine in neurodevelopment has become better understood in early life, there is little evidence available regarding the lifelong impact of iodine on brain function. European countries are usually assumed to have sufficient dietary iodine intake, but the UK has been classified as insufficient (2,3). This is a particular threat to pregnant women and their offspring, since insufficient early exposure to iodine leads to blunted mental capacity. Indeed, the offspring of mothers taking part in the ALSPAC study (www.bristol.ac.uk/alspac/) had lower IQ at age 8 if maternal iodine in pregnancy had been in the lowest quartile (4). Childhood IQ is known to be one of the key determinants of later life cognition and wellbeing, and is associated with mortality, morbidity and frailty in old age (5).

Iodine is obtained mainly through the diet, with no ongoing iodine-fortification programme in the UK. The main sources of iodine in the British diet are milk and dairy products, as well as fish and seafood. While cross-sectional surveys revealed mild insufficiency in the population (1), recent studies have highlighted that most women struggle to reach the recommended iodine daily intake (150 µg/day), a recommended intake that increases during pregnancy to 250 µg/day (6).

Iodine deficiency, mainly in children and young adults, has been suggested to cause certain brain proteins to be down-regulated in particular brain regions, anterior commissure axons and mRNA expression to be reduced, and dendrite size to be altered resulting in potential premature cell apoptosis. Additionally, iodine deficiency may cause a reduction in cerebellar cell size and decreased myelination throughout the central nervous system (7), and, therefore, may be related to brain atrophy and brain white matter damage. Altogether, such changes are likely to affect cognitive functions. Preservation of mental / cognitive capacities is key in having a healthy long life, as well as enabling society to achieve its full productivity potential. However, it is not known how different exposures to dietary iodine throughout life influences brain health and cognition in the elderly.

Here, we investigate the link between estimated dietary iodine intake, brain structural measurements from magnetic resonance imaging (MRI) and cognitive abilities in the Lothian Birth Cohort 1936 (LBC1936) (8) with the hypothesis that individuals most likely to have a sustained sufficient intake of iodine-rich foods in their diets have better preserved brain health in late adulthood and, consequently, better cognitive performance. This study aims to estimate whether very low or high iodine intake throughout life is associated with cognitive abilities and brain health in later life. Acknowledging the difficulties in assessing lifelong exposure to nutrients, the analysis is carried out by relating dietary

measures based on iodine-rich food intake from individuals with specific dietary patterns more likely to be sustained through longer periods of time: fish/dairy avoiders and low consumers, versus groups with medium (sufficient) intake and high consumers) to measures of cognitive function, brain atrophy and brain white matter damage in later life. We also explored whether childhood intelligence (IQ) is associated with iodine consumption levels in late adulthood, thus, enabling to inform the development of evidence-based recommendations for the design and targeting of dietary interventions. Finally, since iodine is a critical component of the thyroid hormones, we analyse the stability of the thyroid functioning across the three years elapsed from the collection of the dietary data and the cognitive and brain imaging data, through the analysis of relevant laboratory data obtained at both time points.

2. Materials and Methods

2.1 Participants

From the LBC1936, which comprises community-dwelling surviving members of the Scottish Mental Survey of 1947(8), 1091 individuals (548 men and 543 women) with an average age of 69.5 (SD=0.8) years completed cognitive tests, and provided personality, demographic, health, lifestyle, habitual diet information (participants completed a 165 item Food Frequency Questionnaire) and blood samples on a first wave of data collection, between 2004 and 2007. On a second wave of data collection, 866 participants (mean age 72.7 years, SD 0.8 years) repeated almost all assessments from wave 1 with the exception of the dietary questionnaire, and a subgroup (n=700) had an MRI brain scan. The main causes for withdrawal at wave 2, as reported elsewhere(9), were: death (n=19), lost contact (n=20), health reasons (n=64), dementia (n=7), care roles (n=13) and lack of time (n=17). This study uses dietary information (wave 1), laboratory data obtained from the analyses of the blood samples (waves 1 and 2), and cognitive and imaging data (wave 2). The research was carried out in compliance with the Helsinki Declaration. Written informed consent was obtained from all participants under protocols approved by the Lothian (REC 07/MRE00/58) and Scottish Multicentre (MREC/01/0/56) Research Ethics Committees.

2.2 MRI acquisition and processing

MRI scans were acquired using a 1.5T GE Signa Horizon HDxt clinical scanner (General Electric, Milwaukee, WI, USA) operating in research mode and using a self-shielding gradient set with maximum gradient of 33 mT/m, and an 8-channel phased-array head coil. The imaging acquisition and processing protocol is fully described in(10). For this particular study, we used hippocampal, ventricular, subarachnoid space, cerebellar and white matter hyperintensity volumes, all adjusted for

intracranial volume, as it has been reported that these brain imaging parameters could be influenced by deficient iodine intake(7). They were obtained from a high resolution T1-weighted (T1W), and whole brain T2- (T2W), T2*- (T2*W) and fluid attenuated inversion recovery (FLAIR)-weighted MRI sequences.

Briefly, brain ventricular boundaries were semi-automatically delineated from the T1W volume scan using a region-growing thresholding method from the Region of Interest tool in Analyze 9.0™ (AnalyzeDirect, Mayo Clinic) software. Hippocampi were also segmented from the high-resolution T1W volume scan using an automatic atlas-based segmentation pipeline that uses FSL tools: SUSAN(11), FLIRT(12) and FIRST(13), followed by manual editing when required. Intracranial volume was obtained semi-automatically from thresholding the T2*W sequence using the Object Extraction tool in Analyze 9.0™, followed by manual removal of erroneously included structures and rectification of the inferior limit at the level of the odontoid peg. A validated multispectral image segmentation method: MCMxxxVI(14) implemented on a freely available tool: bric1936 (www.sourceforge.net/projects/bric1936), was used to extract white matter hyperintensities (WMH) and cerebrospinal fluid from the colour data fusion of co-registered T2*W and FLAIR images. Superficial subarachnoid space (SSS, the space between the inner edge of the dura and the brain cortical surface) volume was calculated as the difference between the total cerebrospinal fluid and the ventricular volumes. Finally, cerebellar white matter and cortical volumes were obtained automatically using FreeSurfer (http://freesurfer.net/).

2.3 Cognitive testing

For this study, we used cognitive measures obtained at the time of the MRI scan / wave 2 (mean age 72.7, SD 0.8 years). These cognitive variables, described in (8), were: a general cognitive factor (g), general processing speed (g-speed) and general memory (g-memory). These cognitive ability measures (i.e. g, g-speed and g-memory) were generated using principal component analysis from batteries of well-validated cognitive tests. To derive g, six subtests of the WAIS-III^{UK} (15) (Digit Symbol, Digit Span Backward, Symbol Search, Letter-Number Sequencing, Block Design & Matrix Reasoning) were used. g-memory was derived from five subtests from the WMS-III^{UK} (16) (Logical Memory Total Immediate & Delayed Recall, Verbal Paired Associates Immediate & Delayed Recall, & Spatial Span Total Score) and two subtests from the WAIS-III^{UK} (Letter-Number Sequencing & Digit Span Backward). g-speed was obtained from two reaction time tests (Simple Reaction Time & Choice Reaction Time), an Inspection Time test(8), and two WAIS-III^{UK} subtests (Digit Symbol & Symbol Search). Childhood intelligence was derived from scores on the Moray House test taken by the participants at age 11 years(8).

2.4 Diet

All study participants (n=1091) were asked to complete the Scottish Collaborative Group Food Frequency Questionnaire (SCG-FFQ) at home and return it by post. Of these, 98 were not returned, 26 were returned blank, and 39 had more than 10 missing items and were therefore excluded from the analyses. Individuals with extreme energy intakes (<2.5th or >97.5th centile, n=46) were also excluded to obtain the most reliable food frequency data(17). The SCG-FFQ is a self-report instrument validated for older adults(17), where respondents rate the frequency of consumption of standard portions of 175 different foods and drinks over the last 2-3 months (rarely/never, 1-3 per month, 1 per week, 2-3 per week, 4-6 per week, 1 per day, 2-3 per day, 4-6 per day or 7+ per day) and responses are used to estimate typical micro and macro nutrient intakes. For this study, consumption (g/day) of specific foods with high iodine content was extracted (i.e. milk, other dairy, fish (white, oily, canned and fish products), shellfish), and the habitual daily intake of iodine was calculated. Intake of dietary supplements was also reported. To assess the ability of the SCG-FFQ in estimating iodine intake, a separate dietary assessment was carried out: iodine intakes estimated after 50 Scottish participants completed the SCG FFQ were compared with 4-day diet records and excretion of iodine in 24 hour urine samples. Urinary iodine was calculated employing a ISO9000 accredited laboratory and mass spectrometry. There was moderate / fair agreement between the SCG FFQ and dietary records (r_s=0.488, k_w=0.222, with low (16%) gross misclassification to the opposite tertile). The agreement between SCG FFQ and urinary excretion was weaker (r_s=0.329, with low (18%) gross misclassification to the opposite tertile).

With the assumption that extreme, or very specific, consumption patterns are likely to express a trait possibly reflecting the long term intake of specific nutrients, we specifically focus on groups representing opposite ends of the iodine intake spectrum: low iodine consumers (those with low intakes of dairy foods and fish, and dairy avoiders) and moderate-high iodine consumers (those with medium or high intakes of dairy foods and fish).

For the purpose of the analyses, the following contrasting groups were formed:

i) Group A (low intake of dairy and fish): Those in the lowest quintile for dairy consumption (less than 151 gram per day) and the lowest two quintiles for fish consumption (less than 37 g per day)

ii) Group B (dairy avoiders): Those never consuming any milk, and not belonging to group A, C or D.

iii) Group C (medium intake of dairy and fish): Those in the middle quintile for dairy consumption (204 to 320 g per day) and quintiles 3 and 4 for fish consumption (37 to 50 g per day)

iv) Group D (high intake of dairy and fish): Those in the highest quintile for dairy and fish consumption (over 432 g and 50 g per day, respectively)

For these individuals, energy (KJ/day), fat (g/day), proteins (g/day), cholesterol (g/day), saturated fats (g/day) and sodium (mg/day) were derived from the food frequency questionnaire, in addition to the daily intake of iodine.

2.5 Thyroid function

Thyroid stimulating hormone (TSH) and free thyroxine (free T4) were measured as described in (18). Briefly, analysis were carried out using a two-step immunoassay. The laboratory reference range for TSH was 0.2 to 4.5 mU/l, with coefficients of variability ranging from 3.0% to 3.5%, and for free T4 it was 9 to 21 pmol/L, with coefficients of variability ranging from 5.1% to 8.9%.

2.6 Statistical analysis

In all analyses, volumetric MRI data were standardised by head size (i.e. expressed in percentage with respect to the intracranial volume) and adjusted by age in days at the time of the MRI scan. To examine the associations between diet and cognition and brain health related indicators at older age, and the associations between the haematological parameters that relate to the thyroid function in waves 1 and 2 (i.e. acquired 3 years apart), we applied robust univariate regression analysis using iteratively reweighted least squares with a bisquare weighting function from MATLAB R2014a Statistical Toolbox and an adding bootstrap, and repeated the analyses without excluding outliers (ANOVA). False Discovery Rate (FDR) was applied to adjust for multiple comparisons. Kruskal-Wallis and Mood's Median tests were used to evaluate differences in the cognitive and imaging parameters between the four groups with extreme/middle levels of iodine consumption. To explore whether childhood intelligence was associated with dietary iodine consumption at age 72 years we used a general linear model with age 11 IQ as predictor and iodine (extracted from the SCG-FFQ) as the response. Gender at each data collection wave was used as covariate in all analyses. All our results were corroborated using IBM-SPSS Statistics 21.

3. Results

3.1 Sample characteristics

3.1.1 Imaging and cognition

Valid imaging data were available for 61-64% of the participants classified according to their iodine consumption. As Table 1 shows, the descriptive values of the imaging variables for the subsample with extreme/middle iodine intake/avoidance (n=189, 87 men and 102 women) are similar to those from the whole sample (n=1091). The subtle inter-hemispheral differences on the hippocampal, cerebellar cortex and ventricular volumes in the subsample follow the same pattern of the whole sample: slightly more atrophy (i.e. reduced volume) in the left hemisphere compared to the right, but this difference was not significant (previously reported (19)). The median and distribution of the imaging and cognitive measures did not significantly differ between the four iodine consumption groups: low intake of dairy and fish (Group A, n=63), dairy avoiders (Group B, n=22), medium intake of dairy and fish (Group C, n=76) and high intake of dairy and fish (Group D, n=28).

Table 1. Descriptive statistics of the imaging and cognitive variables in the whole sample (n=1091) and in the subsample with extreme/middle iodine intake/avoidance (n=189). For variables normally distributed (†), the mean and standard deviation (SD) are given. For not normally distributed variables, median and interquartile range (IQR) are given instead.

Imaging variables		Full Cohort (n=1091)		Present Subsample (n=189)	
		Valid data (n)	Mean (SD)or Median (IQR)	Valid data (n)	Mean (SD)or Median (IQR)
Brain ventricular volume (ml)	Lateral right	671/1091 (62%)	13.93 (9.30)	117 / 189 (62%)	14.44 (8.46)
	Lateral left		15.26 (10.70)		15.10 (10.73)
	Third		1.74 (0.90)		1.79 (0.88)
	Fourth		0.27 (0.25)		0.30 (0.24)
Subarachnoid space volume (ml)		669/1091 (61%)	189.59 (75.25)	117 / 189 (62%)	190.83 (66.28)
Hippocampal volume (ml) (†)	Right hippocampus	660/1091 (60%)	3.33 (0.46)	117 / 189 (62%)	3.34 (0.68)
	Left hippocampus		3.09 (0.46)		3.06 (0.56)

White matter hyperintensity volume (ml)		678/1091 (62%)	7.70 (13.20)	120 / 189 (64%)	6.44 (14.98)
Cerebellar volume (ml) (†)	White matter right	647/1091 (59%)	11.36 (1.64)	115 / 189 (61%)	11.51 (1.68)
	Cortex right		43.13 (4.78)		43.65 (4.95)
	White matter left		11.32 (1.68)		11.44 (1.72)
	Cortex left		42.40 (4.70)		42.50 (4.88)
Cognitive variables					
g		856/1091 (78%)	0.04 (1.29)	151/189 (80%)	0.07 (0.96) (†)
g-speed		838/1091 (77%)	0.11 (1.26)	147/189 (78%)	0.08 (0.93) (†)
g-memory		840/1091 (77%)	0.13 (1.34)	148/189 (78%)	0.03 (0.89) (†)
Age 11 IQ (†)		1028/1091 (94%)	100.00 (14.99)	183/189 (7%)	102.26 (13.62)

Note: (†) refers to normally distributed variable data

3.1.2 Iodine-rich foods and iodine intake

Total fish and dairy intake for the whole cohort is shown in Table 2. There was a broad range of intakes for most iodine-rich food groups, except shellfish, canned fish and fish-products (such as fish cakes and fish-containing pasties), which were consumed at a lower level, and avoided by a large proportion of the population under consideration (n=882).

Table 2. Distribution of iodine-rich food intake in the LBC36 cohort sample (n=882)

	Fish (g/day)						Dairy (g/day)		
	White fish	**Oily fish**	**shellfish**	**fish pro-ducts**	**Can-ned fish**	**Total fish intake**	**Milk**	**other dairy**	**All dairy**
Complete data	*n=870*	*n=864*	*n=872*	*n=877*	*n=874*	*n=849*	*n=869*	*n=873*	*n=862*
Non-consumers (0g / day)	**n=35**	**n=105**	**n=488**	**n=558**	**n=369**	**n=12**	**n=33**	**n=26**	**n=3**
Median (g/day)	**17.6**	**13.7**	**0.0**	**0.0**	**3.2**	**43.2**	**146.0**	**50.0**	**250.6**

Percentiles (g/day)	*Min*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*	*0.0*
	20th	*9.6*	*6.5*	*0.0*	*0.0*	*0.0*	*26.0*	*103.7*	*12.2*	*151.2*
	40th	*16.1*	*12.4*	*0.0*	*0.0*	*0.0*	*36.9*	*146.0*	*30.9*	*203.9*
	60th	*21.7*	*18.8*	*2.6*	*0.0*	*3.2*	*49.9*	*156.2*	*64.8*	*319.7*
	80th	*29.7*	*30.0*	*4.9*	*4.9*	*6.3*	*69.0*	*365.0*	*125.0*	*431.6*
	Max	*88.2*	*231.3*	*31.6*	*44.4*	*225.0*	*477.3*	*1460.2*	*692.7*	*1550.5*

Iodine-rich food avoiders were a minority, with 3.8% never consuming milk, 1.4% never consuming fish, 1.7% consuming low amounts of fish and dairy (less than 200g fish per week, less than 200g dairy per day, of which less than 100g should be milk). Furthermore, 0.2% combined low dairy consumption with no fish at all, and 0.8% avoided both dairy and fish totally.

In the subsample with extreme/middle iodine intake/avoidance no overlap was observed between the individuals (n=189) categorised under the four groups with patterns of iodine intake representative of a trait (Table 3).

Table 3. Iodine-rich food intake of the four groups with extreme/middle iodine intake/avoidance (n=189)

	Group A Low intake of dairy and fish (n=63)	**Group B Dairy avoiders (n=22)**	**Group C Medium intake of dairy and fish (n=76)**	**Group D High intake of dairy and fish (n=28)**
White fish (g/day)	16.1 (11.9)	16.1 (18.8)	20.0 (9.6)	29.7 (25.4)
Oily fish (g/day)	6.5 (12.1)	31.8 (30.1)	18.7 (13.3)	40.2 (35.6)
Shellfish (g/day)	0.0 (2.5)	0.0 (5.1)	0.0 (2.6)	2.6 (5.1)
Fish products (g/day)	0.0 (0.0)	0.0 (5.4)	0.0 (4.9)	1.0 (6.9)
Canned fish (g/day)	0.0 (3.2)	3.2 (6.3)	3.2 (6.3)	6.3 (6.3)
Total fish intake (g/day)	**25.9 (11.0)**	**67.3 (27.5)**	**48.2 (15.1)**	**86.2 (32.5)**
Milk (g/day)	51.1 (83.2)	0.0 (0.0)	146.0 (10.0)	365.0 (161.3)
Other dairy (g/day)	8.8 (17.5)	72.7 (137.9)	104.6 (60.3)	96.6 (58.4)
Total dairy (g/day)	**107.2 (86.3)**	**72.7 (137.9)**	**250.3 (57.9)**	**489.4 (146.0)**

Iodine-rich food intake was not normally distributed. Therefore, the values given are Median (IQR). Comparison of intake between groups, done with the Kruskall Wallis and Mood's Median tests showed significant differences for all parameters ($p<0.001$) between groups.

On this subsample, intake of iodine containing nutritional supplements was reported by 10 participants (n=4 in group A, n=2 in group B, n=2 in group C and n=2 in group D). In general, reported iodine intake was sufficient (median 193 µg/day), IQR 109.3, as per the UKs recommended diary iodine intake(20) of 140µg/day, ranging from 61.6 µg to 524.4 µg per day. A quarter (n=47, 24.9%) had an iodine intake below the reference nutrient intake for iodine (140 µg/day). The median (IQR) total

iodine intake µg/day was 120.0 µg/day (59.7) for Group A, 169.8 µg/day (56) for Group B, 207.4 µg/day (63.9) for Group C and 352.7 µg/day (128.3) for Group D.

3.1.3 Thyroid function

The thyroid function of euthyroid subjects (i.e. having normal thyroid gland function) are reported in(18), along with associations with cognition. The haematological parameters related to the thyroid function at old age, measured 3 years apart, were strongly and significantly associated (standardised $\beta = 0.55$ (TSH) and 0.51 (free T4), $p<0.0001$) indicating high stability of these measures over time. Specifically for the subsample studied, very few cases of overt hypothyroidism were reported. The distribution of cases of subclinical hypothyroidism did not significantly differ between the four groups. The median levels of TSH and T4 and distributions did not differ between groups (Table 4).

Table 4: Thyroid function in the selected subsample

		Group A Low intake of dairy and fish (n=63)	Group B Dairy avoiders (n=22)	Group C Medium intake of dairy and fish (n=76)	Group D High intake of dairy and fish (n=28)
Wave 1	**TSH**	N=63/63	N=22/22	N=72/76	N=26/28
	mU/L (median, IQR)	1.74 (1.02–3.07)	1.70 (0.85–2.27)	1.72 (1.29-2.88)	2.04 (1.28-2.08)
	free T4	N=63/63	N=21/22	N=72/76	N=26/28
	pmol/L (median, IQR)	16.0 (13.0–17.0)	15.0 (15.0–17.0)	15.0 (14.0-17.0)	15.0 (14.0-17.2)
	Overt hypothyroidism	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Subclinical hypothyroidism	6 (9.5%)	2 (9.5%)	5 (6.9%)	1 (3.8%)
Wave 2	**TSH**	N=49/63	N=17/22	N=63/63	N=22/22
	mU/L (median, IQR)	1.50 (1.04–2.30)	1.50 (1.15 – 2.05)	1.40 (0.97-2.30)	1.65 (1.00-1.90)
	free T4	N=49/63	N=17/22	N=63/63	N=22/22
	pmol/L (median, IQR)	13.0 (12.0–14.0)	13.0 (12.0-14.5)	13.0 (12.0-14.0)	12.5 (11-14.25)
	Overt hypothyroidism† n(%)	0 (0%)	0 (0%)	0 (0%)	1 (3.8%)
	Subclinical hypothyroidism‡ n(%)	1 (2%)	0 (0%)	2 (3.2%)	0 (0%)

† TSH>4.5mU/L, T4<9pmol/L; ‡ TSH>4.5mU/L, T4>9pmol/L

3.2 Associations between dietary sources of iodine and volumetric brain structural data

Table 5 shows the associations between reported dietary iodine intake (including and excluding iodine supplementary intake) and dietary sources of iodine and the volumetric brain structural parameters that can be affected by extreme iodine intake. Of the subsample studied, only the size of the brain lateral ventricles was positively associated with iodine intake (β=0.2, p≤0.01), indicating that the consumption of iodine, likely to indicate long exposure to this nutrient, mainly due to the consumption of dairy products (β=0.21, p=0.02) may have an influence in inner brain atrophy at older age. Results from the robust regression with bootstrap did not differ substantially from those presented in Table 5. As expected, the burden of white matter damage, represented by the volume of white matter hyperintensities, was associated with the intake of fish products (β=0.28, p=0.002), rich in fats and saturated fats (see Table 6) in this subsample.

3.3 Associations between general dietary variables and volumetric brain structural data

In the subsample representative of a trait of iodine consumption, high calorie, fat, cholesterol, protein and sodium intake (present in dairy and fish products) were significantly associated with lateral and third ventricular enlargement and the percentage of white matter hyperintensity volume in ICV at old age (Table 6). However, after adjusting for multiple comparisons, only the associations between energy, fat and proteins with lateral and third ventricular enlargements remained significant. Interestingly, sodium intake was negatively associated with the percentage of subarachnoid space occupied in ICV, but this association disappeared after FDR correction.

3.4 Dietary iodine and cognition

Initial tests showed a positive association between the general cognitive factor at older age and the intake of dairy products excluding milk and shell fish (before excluding outliers β=0.19, p=0.02 and after β=0.16, p=0.01). However, the effect was no longer statistically significant following post-hoc adjustments for multiple comparisons. Only the association between general memory (g-memory) at age 72.7 years and the intake of canned fish in this subsample with extreme/medium intake of iodine remained significant (before excluding outliers β=0.23, p=0.005 and after β=0.2, p=0.003) (Table 5).

Childhood intelligence did not predict iodine intake levels at old age in the whole sample (p=0.29) or in the reduced sample with known iodine consumption levels (p=0.32).

Table 5. Results of the associations between dietary variables that relate to iodine and imaging and cognitive variables in the subsample with extreme/middle iodine intake/avoidance, before FDR correction. Given: standardised coefficient β (p-value)

Imaging variables (% volume in ICV)	Iodine (ug/day)	Iodine + supplements (ug/day)	Milk (g/day)	Other dairy (g/day)	All dairy (g/day)	White fish (g/day)	Oily fish (g/day)	Shell fish (g/day)	Fish products (g/day)	Fish canned (g/day)
Cerebellum WM_R	0.04 (0.69)	0.04 (0.63)	0.02 (0.81)	-0.07 (0.47)	0.02 (0.83)	-0.06 (0.48)	0.07 (0.44)	-0.03 (0.73)	-0.02 (0.83)	0.08 (0.41)
Cerebellum Cortex_R	0.05 (0.62)	0.05 (0.59)	-0.04 (0.66)	0.002 (0.98)	0.01 (0.92)	-0.03 (0.77)	0.03 (0.75)	-0.11 (0.23)	-0.004 (0.96)	0.04 (0.66)
Cerebellum WM_L	-0.02 (0.86)	0.025 (0.79)	0.02 (0.82)	-0.1 (0.29)	-0.02 (0.79)	-0.11 (0.22)	0.02 (0.84)	-0.07 (0.47)	-0.07 (0.47)	-0.004 (0.97)
Cerebellum Cortex_L	0.06 (0.55)	0.06 (0.54)	-0.03 (0.74)	-0.01 (0.88)	0.03 (0.77)	0.001 (0.99)	0.06 (0.56)	-0.11 (0.24)	-0.04 (0.65)	0.04 (0.64)
Lateral Ventricle_R	**0.24 (0.008)***	**0.24 (0.01)***	0.12 (0.18)	0.14 (0.13)	**0.21 (0.02)***	0.04 (0.63)	0.16 (0.08)	-0.05 (0.59)	0.06 (0.53)	-0.08 (0.37)
Lateral Ventricle_L	**0.29 (0.002)***	**0.30 (0.001)** **	0.08 (0.38)	0.14 (0.14)	**0.21 (0.02)***	0.05 (0.56)	**0.20 (0.03)*†**	-0.03 (0.73)	0.007 (0.94)	-0.05 (0.60)
3rd Ventricle	0.17 (0.07)	0.12 (0.18)	0.009 (0.92)	0.02 (0.78)	0.05 (0.55)	0.1 (0.29)	0.11 (0.22)	-0.11 (0.23)	-0.004 (0.97)	-0.05 (0.60)
4th Ventricle	0.12 (0.20)	0.13 (0.16)	0.08 (0.37)	0.10 (0.29)	0.05 (0.63)	0.03 (0.78)	0.01 (0.90)	0.02 (0.88)	-0.09 (0.32)	-0.05 (0.56)
Sub-arachnoid space	-0.07 (0.43)	-0.055 (0.56)	-0.12 (0.19)	**-0.19 (0.04)***	-0.14 (0.12)	0.06 (0.48)	0.03 (0.75)	0.03 (0.77)	-0.06 (0.5)	-0.14 (0.14)
Hippo-campus R	-0.005 (0.96)	0.025 (0.79)	-0.04 (0.65)	0.06 (0.52)	0.03 (0.77)	0.07 (0.45)	0.008 (0.93)	-0.13 (0.15)	0.03 (0.72)	-0.11 (0.26)
Hippo-campus L	0.007 (0.94)	-0.008 (0.94)	0.008 (0.93)	0.08 (0.42)	0.07 (0.47)	0.07 (0.47)	0.03 (0.77)	-0.10 (0.30)	0.08 (0.39)	-0.04 (0.63)
WMH	0.12 (0.21)	0.09 (0.33)	0.07 (0.48)	-0.05 (0.61)	0.07 (0.48)	0.13 (0.16)	0.005 (0.96)	-0.03 (0.73)	**0.28 (0.002)***	-0.06 (0.51)
Cognition at mean age 72.7 years										
g	0.03 (0.74)	0.04 (0.65)	0.07 (0.37)	0.11 (0.18)	0.07 (0.41)	-0.06 (0.50)	0.12 (0.17)	**0.19 (0.02)***	-0.08 (0.35)	0.13 (0.12)

g_speed	-0.02 (0.79)	-0.04 (0.64)	0.07 (0.42)	0.05 (0.53)	0.01 (0.87)	-0.06 (0.49)	-0.02 (0.84)	0.13 (0.13)	0.05 (0.58)	0.09 (0.30)
g_memory	0.04 (0.63)	0.06 (0.47)	0.05 (0.59)	0.04 (0.60)	0.08 (0.34)	-0.05 (0.52)	0.10 (0.23)	0.06 (0.46)	0.06 (0.45)	**0.23 (0.005)***

Note: L and R refer to the Right and Left brain hemispheres respectively

† Became non-significant when outliers were excluded (robust regression with bootstrap)

Table 6. Results of the robust associations between general dietary variables and imaging and cognitive variables in the subsample with extreme/middle iodine intake/avoidance, before FDR correction. Given: standardised coefficient β (p-value)

Imaging variables (% volume in ICV)	KJ	Fat	Proteins	Cholesterol	Saturated fats	Sodium
Cerebellum WM_R	0.70 (0.45)	0.04 (0.70)	0.06 (0.49)	0.09 (0.31)	0.04 (0.66)	0.03 (0.75)
Cerebellum Cortex_R	0.15 (0.10)	0.16 (0.08)	0.09 (0.34)	0.14 (0.14)	0.17 (0.07)	0.14 (0.14)
Cerebellum WM_L	0.09 (0.32)	0.06 (0.54)	0.07 (0.42)	0.12 (0.19)	0.07 (0.48)	0.05 (0.63)
Cerebellum Cortex_L	0.13 (0.15)	0.16 (0.09)	0.08 (0.37)	0.11 (0.22)	0.17 (0.07)	0.10 (0.27)
Lateral Ventricle_R	**0.32 (<0.001)****	**0.31 (0.001)****	**0.31 (0.001)****	**0.26 (0.005)***	**0.28 (0.002)***	**0.27 (0.003)***
Lateral Ventricle_L	**0.34 (<0.001)****	**0.32 (0.001)****	**0.35 (<0.001)****	**0.29 (0.002)***	**0.24 (0.009)***	**0.26 (0.004)***
3rd Ventricle	**0.26 (0.004)***	**0.21 (0.02)***	**0.24 (0.009)***	**0.19 (0.04)***	0.16 (0.09)	**0.23 (0.01)***
4th Ventricle	0.11 (0.23)	0.02 (0.79)	0.10 (0.29)	0.14 (0.12)	0.04 (0.64)	0.02 (0.80)
Subarachnoid space	-0.14 (0.14)	-0.14 (0.13)	-0.17 (0.06)	-0.15 (0.11)	-0.14 (0.14)	**-0.19 (0.04)***
Hippocampus R	-0.08 (0.40)	-0.12 (0.21)	-0.07 (0.47)	-0.02 (0.81)	-0.10 (0.29)	-0.06 (0.47)
Hippocampus L	-0.08 (0.40)	-0.10 (0.27)	-0.07 (0.46)	-0.07 (0.44)	-0.08 (0.37)	-0.05 (0.59)
WMH	0.17 (0.06)	**0.18 (0.05)***	**0.20 (0.03)***	0.16 (0.07)	**0.24 (0.009)***	**0.19 (0.04)***
Cognition at mean age 72.7 years						
g	-0.08 (0.22)	-0.11 (0.11)	-0.01 (0.82)	-0.05 (0.40)	-0.11 (0.10)	-0.05 (0.56)

g_speed	-0.08 (0.28)	-0.08 (0.26)	-0.06 (0.40)	-0.09 (0.23)	-0.04 (0.55)	-0.08 (0.33)
g_memory	0.04 (0.56)	0.004 (0.95)	0.07 (0.34)	0.03 (0.70)	-0.008 (0.92)	0.09 (0.29)

4 Discussion

Iodine intake is key for the formation of thyroid hormones, and for neurodevelopment. While the critical role of nutrition is becoming better understood at important developmental stages, limited data exist on iodine intake in the elderly(21), and much less is known regarding its impact throughout the lifespan. With the assumption that extreme, or very specific, consumption patterns are likely to remain relatively stable throughout life; that is, that dairy or fish avoiders in later life will have been likely to have acquired such specific dietary habits earlier in life, we identified four groups with contrasting intake of iodine-rich products in a well characterised large birth cohort of elderly adults. Contrary to our hypothesis, we did not observe any difference in cognition or brain atrophy/white matter damage between groups with marked differences in iodine consumption. In the small subsample of individuals with dietary habits suggesting a sustained trait of iodine consumption, low animal fat intake and, in general, a low calorie-and-salt diet were associated with preserved lateral brain ventricular size, indicative of reduced or absent brain atrophy. This result is confirmatory of those from a study on 674 non-demented older adults from a multi-ethnic cohort in Manhattan, which concluded that higher fish (iodine-rich, but also a source of other nutrients) and lower meat (energy and protein-rich) intake were the key two elements contributing to the association of the Mediterranean diet with less brain atrophy(22). It also confirms results from another study on 52 individuals cognitively normal but at risk for Alzheimer's disease (AD), which also assessed brain atrophy from brain MRI and found that the nutrient combination identified as "AD-protective" (i.e. that was associated with reduced brain atrophy) was linked to higher intake of fish and low-fat dairy products and lower intake of high-fat dairies, processed meat and butter(23).

It is of course difficult to disentangle the absolute effect of iodine as it is one of several nutrients supporting brain health, in particular long chain polyunsaturated fatty acids (LC PUFA). Several fatty acid desaturase genotypes have been found associated with erythrocyte membrane LC PUFA levels in patients with mild cognitive impairment(24). On the other hand, the subsample analysed represents

only 21.4% of the total number of study participants that provided dietary data, not being representative of the whole cohort. Nevertheless, by analysing only the subsample indicative of a stable trait on iodine consumption, this study partly overcomes the measurement error resulting from self-rated dietary information known to be sub-optimally associated with iodine sufficiency. The cohort reported rather homogeneous, high iodine intake compared to that of younger British women(6), and contemporaries in Brazil(21).

A key challenge is the characterisation of lifelong exposure to iodine as a nutrient, since most retrospective dietary assessment tools will provide insight only on the preceding few months of intake, like the one used in this study. To the best of our knowledge, there are only two dietary questionnaires focusing on iodine intake specifically, one developed in younger UK female adults(25), and the other in older Australian adults(26). They also provide insight on the intake only on the months preceding their application, rather than intake throughout life. While sea fish would have always represented a rich source of iodine, the same cannot be said for dairy. Dairy iodine levels have fluctuated over the years, depending mostly on farming practice – initially very low, levels steadily increased from the late 1920s to the late 1990s (through cattle feeds and iodophores usage in the milking industry), before introduction of regulatory changes stemming the use of iodophores(27). The reported three-fold increase in iodine intake between 1952 and 1982, from 80ug/day to 255ug/day(27) would have been relevant to this cohort, making the lifelong estimation of iodine intake even more challenging. The time between the collection of the dietary data and the MRI scans and cognitive tests (3 years) would have been a limitation of the study. However, like in previous analyses on this cohort (9), strong and significant associations between haematological parameters measured at both waves, known to be related to the dietary parameters analysed (i.e. iodine intake levels in this case), were observed suggesting the key measures were stable over time.

Lifelong cognitive abilities could potentially influence errors in dietary data, with implications for epidemiological methodology in diet assessment and analysis methods (28). Childhood IQ was not found to predict iodine intake levels at late adulthood in this cohort. However, in a cohort of more than 8000 individuals(29), childhood IQ was associated with healthier dietary habits at mean age 30 years (e.g. consumption of fruit, vegetables (cooked and raw), wholemeal bread, poultry, fish, and foods fried in vegetable oil), indicating that perhaps the learning and reasoning abilities captured by the IQ tests could be important in the successful management of individuals' dietary behaviour(29). In term of iodine nutrition, a sizeable contribution to childhood IQ (which influences later life cognition), happens in the womb. This could not be evaluated in this population. In the subsample

described, most were euthyroid with very few cases of subclinical hypothyroidism. As described by Booth et al, thyroid function in euthyroid subjects was not associated with cognition in this group of older adults(18), with associations between cognition and thyroid function previously established at clinical level of thyroid dysfunction(30,31), and not at subclinical level(32).

This study has several strengths, starting with a very well described birth cohort of elderly adults with detailed brain imaging volumetric measurements. Drop-outs at second wave are not thought to affect or bias the results of our analyses in the context of "healthy ageing"(33). Our approach focused on specific dietary patterns, and should be replicated in cohorts with more heterogeneous dietary profiles. While studying the relationship between lifelong dietary patterns, brain structure and cognition will remain challenging when using retrospective approaches to define the diet and lifestyle, there is scope to set-up well defined prospective studies following individuals through life, in order to draw more definitive answers. This study has found an interesting link between low iodine intake and inner brain atrophy, represented by large ventricular sizes – this is particularly important for studies of aging and AD and warrant further studies. At present, our results raise an important hypothesis between brain atrophy and iodine-product consumption, which ought to be better defined with a view to design appropriate guidelines.

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