Thyroid
© Mary Ann Liebert, Inc.
DOI: 10.1089/thy.2019.0353

Standardized Map of Iodine Status in Europe

Till Ittermann[1], Diana Albrecht[1, 31], Petra Arohonka[2, 32], Radovan Bilek[26], Joao J. de Castro[3], Lisbeth Dahl[4], Helena Filipsson Nystrom[5, 30], Simona Gaberscek[6], Eduardo Garcia-Fuentes[18], Monica L Gheorghiu[7, 27], Alicja Hubalewska-Dydejczyk[8], Sandra Hunziker[9], Tomislav Jukic[10], Borislav Karanfilski[11], Seppo Koskinen[32], Zvonko Kusic[10], Venjamin Majstorov[12], Konstantinos C Makris[13], Kostas B Markou[14], Christa Meisinger[15, 28], Neda Milevska Kostova[11], Karen R Mullen[29], Endre V. Nagy[16], Valdis Pirags[17], Gemma Rojo-Martinez[18], Mira Samardzic[19], Ljiljana Saranac[20], Ieva Strele[17], Michael Thamm[21], Işık Top[22], Malgorzata Trofimiuk-Müldner[8], Belgin Ünal[22], Seppo Koskinen[32], Lluis Vila[23], Paolo Vitti[24], Benjamin Winter[1], Jayne V. Woodside[25], Katja Zaletel[6], Vaclav Zamrazil[26†], Michael Zimmermann[9], Iris Erlund[2, 32]*, Henry Völzke[1]*

*Contributed equally

†in memoriam

[1]Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany

[2] Department of Government Services, Finnish Institute for Health and Welfare, Helsinki, Finland

[3]Department of Endocrinology, Hospital das Forças Armadas, Lisbon, Portugal

[4]Food security and nutrition, Institute of Marine Research (IMR), Bergen, Norway

[5]Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[6]Department of Nuclear Medicine, University Medical Centre, Ljubljana, Slovenia

[7]Carol Davila University of Medicine and Pharmacy, Bucharest, Romania.

[8]Department of Endocrinology, Jagiellonian University Medical College, Krakow, Poland

[9]ETH, Department of Health Sciences and Technology, Zürich, Switzerland

[10]University of Zagreb, School of Medicine, Department of Oncology and Nuclear Medicine, University Hospital Centre Sestre Milosrdnice, Zagreb, Croatia

[11]Centre for Regional Policy Research and Cooperation "Studiorum", Skopje, North Macedonia

[12]Institute of Pathophysiology and Nuclear Medicine, Ss.Cyril and Methodius University, Skopje, Former Yougoslavian Rebublic of Macedonia

[13]Cyprus International Institute for Environmental and Public Health, Cyprus University of Technology, Limassol, Cyprus

[14]Department of Endocrinology, Institute University of Patras Medical School, Patras, Greece

[15]Chair of Epidemiology, Ludwig-Maximilians Universität Munich, UNIKA-T Augsburg, Augsburg, Germany

[16]Division of Endocrinology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

[17]Department of Internal Medicine, University of Latvia, Riga, Latvia

[18]Department of Endocrinology and Nutrition, Hospital Regional Universitario de Málaga, IBIMA, Málaga, Spain

[19]Institute for Sick Children, Podgorica, Montenegro

[20]Department of Pediatrics, Faculty of Medicine, University of Niš, Niš, Serbia

[21]Department of Epidemiology and Health Monitoring, Robert Koch Institute, Berlin, Germany

[22]Dokuz Eylul University Medical Faculty, Department of Public Health, İzmir

[23]Department of Endocrinology and Nutrition, Hospital de Sant Joan Despi Moisès Broggi, Barcelona, Spain

[24]Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

[25]Centre for Public Health,Queen's University Belfast, Belfast, UK

[26]Institute of Endocrinology, Prague, Czech Republic

[27]C.I. Parhon National Institute of Endocrinology, Bucharest, Romania

[28]Independent Research Group Clinical Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany

[29]Belfast Health and Social Care Trust, Belfast, UK

[30]Department of Endocrinology, Sahlgrenska University Hospital, Göteborg, Sweden

[31]Leibniz Institute for Plasma Science and Technology (INP), Greifswald, Germany

[32]Department of Public Health Solutions, Finnish Institute for Health and Welfare, Helsinki, Finland

Address for correspondence:

Till Ittermann, Dr. rer. med.
Institute for Community Medicine
Ernst Moritz Arndt University
Walther Rathenau Str. 48
D-17487 Greifswald; Germany
Phone: ++49 - 3834 – 867552; FAX: ++49 - 3834 - 866684
e-mail: till.ittermann@uni-greifswald.de

Short title: Standardized Map of Iodine Status

Keywords: iodine, iodine supply, epidemiology, method comparison

E-mail addresses:

diana.albrecht@inp-greifswald.de, petra.arohonka@thl.fi , rbilek@endo.cz, joao.castro@defesa.pt , Lisbeth.Dahl@hi.no , helena.filipsson@medic.gu.se , simona.gaberscek@kclj.si , edugf1@gmail.com, monicagheorghiu@yahoo.com , alahub@cm-uj.krakow.pl , sandra.hunziker@hest.ethz.ch , tomislav.jukic@kbcsm.hr , karanfilski@hotmail.com , seppo.koskinen@thl.fi, zvonko.kusic@zg.t-com.hr , venjamin.majstorov@gmail.com , konstantinos.makris@cut.ac.cy , markoukonst@upatras.gr , christa.meisinger@helmholtz-muenchen.de , nmilevska@studiorum.org.mk , Karen.Mullan@belfasttrust.hscni.net , nagy@internal.med.unideb.hu , pirags@latnet.lv , gemma.rojo.exts@juntadeandalucia.es , samardzic@t-com.me , endoljilja@yahoo.com , ievastrele@inbox.lv, isikt0@gmail.com, ThammM@rki.de, mtrofimiuk@gmail.com, belgin.unal@deu.edu.tr , liisa.valsta@thl.fi, Lluis.Vila@sanitatintegral.org , paolo.vitti@med.unipi.it , winterb@uni-greifswald.de , j.woodside@qub.ac.uk , katja.zaletel@kclj.si, vzamrazil@endo.cz , michael.zimmermann@hest.ethz.ch , iris.erlund@thl.fi , voelzke@uni-greifswald.de

Abstract

Background

Knowledge about the population's iodine status is important, because it allows adjustment of iodine supply and prevention of iodine deficiency. The validity and comparability of iodine related population studies can be improved by standardization, which was one of the goals of the EUthyroid project. The aim of this study was to establish the first standardized map of iodine status in Europe by using standardized UIC data.

Methods

We established a gold-standard laboratory in Helsinki measuring UIC by inductively-coupled plasma-mass spectrometry. A total of 40 studies from 23 European countries provided 75 urine samples covering the whole range of concentrations. Conversion formulas for UIC derived from the gold-standard values were established by linear regression models and were used to post-harmonize the studies by standardizing the UIC data of the individual studies.

Results

In comparison to the EUthyroid gold-standard, mean UIC measurements were higher in 11 laboratories and lower in 10 laboratories. The mean differences ranged from -36.6% to 49.5%.

Of the 40 post-harmonized studies providing data for the standardization, 16 were conducted in schoolchildren, 13 in adults and 11 in pregnant women. Median standardized UIC was < 100 µg/L in 1 out of 16 (6.3%) studies in schoolchildren, while in adults 7 out of 13 (53.8%) studies had a median standardized UIC < 100 µg/L. Seven out of 11 (63.6%) studies in pregnant women revealed a median UIC < 150 µg/L.

Conclusions

We demonstrate that iodine deficiency is still present in Europe, using standardized data from a large number of studies. Adults and pregnant women, particularly, are at risk for iodine deficiency, which calls for action. For instance, a more uniform European legislation

on iodine fortification is warranted to ensure that non-iodized salt is replaced by iodized salt more often. In addition, further efforts should be put on harmonizing iodine related studies and iodine measurements to improve the validity and comparability of results.

Introduction

The iodine status of regions is assessed by median urinary iodine concentrations (UIC) determined in representative samples of populations. National iodine fortification programs are initiated and modified based on such studies. According to the World Health Organization (WHO), a region is iodine sufficient if the median UIC is ≥ 100 µg/L in non-pregnant populations (1). Based on this criterion, worldwide maps of country-specific iodine status are drawn (2, 3). Laboratory methods for measuring UIC, however, are heterogeneous, hampering the comparability of iodine monitoring studies (1). In a recent ring trial in Germany consisting of 300 samples, variations of up to 50% were observed between different UIC laboratory methods. These findings emphasize the need for standardization of iodine monitoring status as well as UIC measurements ensuring valid estimates of the iodine status in populations (4).

Besides the standardization of iodine monitoring studies, it will be necessary to harmonize fortification programs. In Europe, iodine fortification programs differ according to type of regulations (mandatory vs. voluntary iodine fortification), amount of iodine used, and chemical form (iodine vs. iodate) (5, 6). The variety of iodine fortification programs within Europe is a challenge for companies acting on the global market. In consequence, large parts of Europe can be seen as mildly to moderately iodine deficient with only 27% of European households having access to iodized salt (7). Around 350 million citizens are exposed to iodine deficiency being at higher risk for developing neurodevelopmental anomalies, since iodine deficiency remains as an important yet preventable cause of brain damage (7). In contrast, the “Global Scorecard of Iodine Nutrition 2017” provided by the Iodine Global Network (IGN) shows that large parts of Europe are adequately supplied by iodine (2). This discrepancy may be explained by a lack of standardization of iodine measurements used for the IGN scorecard. Furthermore, iodine status is reported at the national level in the IGN map, but, particularly in countries with voluntary iodine supply, median iodine levels may differ substantially between subpopulations and regions within the respective country. Therefore, harmonized monitoring studies and UIC measurements as well as the consideration of regional and population differences, are of great importance when evaluating and monitoring the effectiveness of fortification programs. In our study, we aimed to standardize European iodine monitoring studies with respect to these considerations in order to establish a valid map of the iodine status in European populations.

Material and Methods

Within the framework of the EUthyroid consortium, we collected data on iodine status from 48 European studies using the EUthyroid data exchange system (8). Information on data owner, study design (population-based, volunteers or patients), study population (children, adults or pregnant women), year of data collection, blood sampling, urine collection, and laboratory methods were collected from each study. Details of the included studies can be found in Supplementary Table 1. The maximum number of studies, for which UIC were analyzed in one laboratory, was three. The study region was assessed using the EU-recommended “Nomenclature of Territorial Units for Statistics” (NUTS) system, which classifies each European country by five hierarchical levels (9). For each study participating in the cross-lab comparison, the relevant ethics approval was obtained and each study followed the declaration of Helsinki.

The individual studies were post-harmonized by standardizing the UIC data. For this purpose, we established a gold-standard EUthyroid laboratory at THL in Helsinki, where UIC was measured with inductively coupled plasma – mass spectrometry (ICP-MS) using an Agilent 7800 ICP-MS system (Agilent Technologies Inc., Santa Clara, CA, USA). One-hundred µl of urine was extracted using ammonium hydroxide solution. Iodine was scanned on m/z = 127 and tellurium was used as internal standard. The National Institute of Standards and Technology (NIST) reference standard materials SRM2670a (with certified mass concentration value) and SRM3668 Level 1 and Level 2 were used to ensure accuracy of urinary iodine determinations. Coefficient of variation (CV) of control samples was 2.9% ±0.8 during the course of the study. The laboratory participates regularly successfully in the external quality assessment scheme “Ensuring the Quality of Urinary Iodine Procedures” (EQUIP) organized by the Centers for Disease Control and Prevention.

For standardization of the UIC data from the individual studies, each partner was asked to send 75 spot urine samples to the EUthyroid gold standard laboratory. This number was a priori determined by a power analysis, accounting for the variation of UIC measurements. Since the distribution of UIC varies according to current iodine supply of the respective study region, it is not useful to determine one strict cut-off to define these marginal areas. Instead the cut-offs should be determined study-specific based on distributional characteristics. To detect deviations at either end of the UIC distribution, the low and the high end were oversampled. Thus, samples were selected the following way:

- Between 0 – 5th percentile – 12 samples
- Between 5th percentile – 25th percentile – 13 samples
- Between 25th percentile – 50th percentile – 13 samples
- Between 50th percentile – 75th percentile -13 samples
- Between 75th percentile – 95th percentile – 13 samples
- Between 95th percentile – 100th percentile – 11 samples

Based on the comparisons, we calculated mean deviations ± 1.96 standard deviations in % by Bland & Altman plots. Correlations between two laboratory methods were assessed by linear regression (10). Conversions formulas derived from linear regression models were established and applied to the original studies. We also re-calculated formulas using Passing-Bablok regression for all laboratories and found no substantial differences to our findings when applying these formulas to the study data (data not shown).

Out of the 48 studies, eight studies were not able to submit samples to the EUthyroid laboratory resulting in a total number of 40 standardized studies from 23 European countries. Standardized UIC were calculated as median for each of the studies and plotted on the European map. Data analyses were conducted using Stata 15.1 (Stata Corporation, College Station, TX, USA). Maps were generated in ArcGIS (Environmental Systems Research Institute (ESRI), ArcGIS Release 10.3.1, Redlands, CA, USA).

Results

In comparison to the gold-standard EUthyroid laboratory, UIC measurements were on average higher in 11 laboratories and lower in 10 laboratories (Table 1). The mean differences ranged from -36.6% to 49.5%. Correlations of UIC to the gold-standard EUthyroid laboratory were ≥0.9 for 9 laboratories (42.9%), 0.8 – 0.9 for 5 laboratories (23.8%), 0.7 – 0.8 for 3 laboratories (14.3%), and <0.7 for 4 laboratories (19.0%). Conversion formulas used for generating standardized UIC values are given in Table 1.

Of the 40 standardized studies from 23 countries, 16 (40.0%) were conducted in schoolchildren, 13 (32.5%) in adults, and 11 (27.5%) in pregnant women. Table 2 shows the median standardized UIC for all 40 studies and in Figure 1 the median standardized UIC are printed on the European map. Studies are presented depending on the exact study region (status is not extrapolated to the national level) and very small study regions are highlighted by circles for better visibility. In population monitoring of iodine status using UIC, schoolchildren have been least impacted by thyroid medication (11), therefore preference has been given to studies carried out in schoolchildren. Thus, the UIC data have been selected for each country in the following order of priority: data from the most recent nationally representative survey carried out in (i) schoolchildren, (ii) adults, (iii) pregnant women. In the absence of recent national surveys, subnational data were used in the same order of priority.

European maps of standardized UIC in school children, adults and pregnant women are displayed in Figures 2 – 4 at the country level. Median standardized UIC was < 100 µg/L in 1 out 16 (6.3%) studies in schoolchildren, while in adults 7 out 13 (53.8%) studies had a median standardized UIC < 100 µg/L. In tendency, countries from Eastern Europe were better supplied by iodine than Northern and Western European countries. Seven out of eleven (63.6%) studies in pregnant women revealed a median standardized UIC < 150 µg/L. In some countries median UIC differed strongly across subpopulations. Especially in Latvia, but also in Germany, Switzerland, Spain, Czech Republic, and Macedonia schoolchildren had higher median UIC than adults.

Discussion

We observed substantial differences in UIC measurements between different laboratories. These results show that standardizing UIC measurements is important when comparing results. Looking for example at the population-based German adults studies DEGS (nationwide, 2011), SHIP-Trend (North-East Germany, 2012), and KORA (South Germany, 2008), the range of non- standardized median UIC varied substantially and were between 44 µg/L and 158 µg/L. Even though voluntary iodine fortification in Germany can lead to regional differences in iodine status, such large differences were not expected and do not seem plausible. However, different laboratories were responsible for the UIC measurements in the latter studies and we previously demonstrated larger differences in UIC measurements across these laboratories (4). While UIC measurements by Sandell-Kolthoff reaction were quite comparable to UIC measurements by the gold-standard ICP-MS for one laboratory, there were substantial differences in UIC for the other two laboratories using the Sandell-Kolthoff reaction compared to the ICP-MS method (4). Thus, we believe that a potential explanation for the differences across the laboratories is the use of different digestion methods (4). Particularly, an insufficient amount of the oxidizing digestion acid may result in elevated UIC measurements. After standardizing data from the European studies using the gold-standard EUthyroid laboratory, the median UIC were less variable, ranging between 51 µg/L and 93 µg/L, which indicates that Germany is currently mild to moderately iodine deficient.

Our standardized UIC data shows that mild-to-moderate iodine deficiency is still common in the adult population and in pregnant women in Europe, according to WHO criteria (1). Schoolchildren, on the other hand, are mostly iodine-sufficient, according to this study. Compared to children and adolescents, adults are likely to obtain less iodine from the diet because of lower consumption of milk products, the main source of dietary iodine in many countries (12-14). This, together with larger urine volumes in adults compared to schoolchildren (15) or amount of liquids consumed, may explain the higher frequency of adult studies with median UIC <100 µg/L compared to studies in schoolchildren.

Pregnant women represent a specific subgroup of the general population. During pregnancy, iodine demand is higher and iodine clearance in the kidney increases, which is taken into account in the WHO pregnancy population cut-off for sufficient iodine supply (150 µg/L) in UIC (1). Pregnant women are recommended to take iodine supplementation in some countries (16), which hampers the comparison between iodine status in pregnant women and other populations in a study region. Furthermore, physiological changes during pregnancy and the fact that sample collection from pregnant women is sometimes performed in conjunction with ultrasound measurements, when they are advised to drink more water, leads to a higher dilution of the urine samples and in consequence to lower UIC (17). For these reasons, monitoring studies in pregnant women should not be used to characterize the iodine status of the general population and should be assessed separately from monitoring studies in children and adults. Our data demonstrates that pregnant women are particularly affected by iodine deficiency in Europe, emphasizing the importance of monitoring studies and an improved iodine status in this vulnerable subgroup.

Our standardized UIC data shows iodine deficiency in 53.8% of all adult studies, but iodine deficiency in only 6.3% of studies in schoolchildren. The 2017 iodine scorecard of the IGN indicates only two European countries as iodine deficient, but in the IGN scorecard, the iodine status of all countries with data is based on studies in schoolchildren, with the exception of Finland (2). WHO recommends monitoring of UIC in school-age children as a proxy for the general population (1). Although WHO also defines adequate iodine intake in adults as a median UIC value ≥ 100 µg/L (1), the scientific basis for this threshold is weak (18). Future research to define a functional UIC cut-off value for adults indicating iodine deficiency would be valuable.

For the IGN scorecard, studies were not standardized, which may also be an explanation for the differences to our map. Another potential source of variation when comparing iodine surveys is the use of iodine-creatinine ratios (ICR). ICR has the advantage that UIC measurements are standardized to dilution of the urine samples, but the measurement error of ICR is larger than for UIC, because two biomarkers are set into context. In large populations the effect of the dilution of urine samples should cancel out. In a recent study it was reported that a study size of 500 individuals is needed to determine the iodine level of a population with a precision of 5% (19). Thus, we recommend to analyze UIC instead of the ICR in larger population studies. In pregnant women, however, ICR data is useful, because of the large variation in the dilution of urine during pregnancy.

Iodine supply appears to be better in Eastern European countries compared to Western or Northern European countries. This may be due to the fact, that in Eastern Europe iodine fortification programs are obligatory and well monitored, whereas in the rest of Europe iodine fortification programs are mostly voluntary (6).

The major strength of our study is that we present, for the first time, standardized data on iodine status for Europe. For standardization of each laboratory we used a sufficient number of samples (n=75) covering the whole range of UIC. The standardization approach was not ideal, because it was based on post-harmonization of data from existing studies. However, it yields a general view of the current iodine status across Europe, and indicates that pre-harmonized studies are needed, as well as actions to improve iodine intake in certain population groups. The main limitations imitations of our study arise from differences of the monitoring studies included, for example in recruitment procedures (population-based or not), size of study (ranging from 74 to 14,641 study participants), or timing of sample collection. Furthermore, subnational UIC surveys should be interpreted with caution. These surveys are commonly carried out to provide a rapid assessment of population iodine status, but due to a lack of sampling rigor, they may over- or underestimate the iodine status at the national level. Even though schoolchildren are the ideal population, they are not representative for adult populations, because adolescents and adults are expected to have a lower UIC due to differences in diet. Particularly, the consumption of milk varies significantly between these subpopulations.

In the EUthyroid project we standardized the data from European iodine monitoring studies and demonstrated that iodine status is generally adequate in schoolchildren but iodine deficiency may still present in adults and pregnant women. An improvement of the iodine supply in Europe is hampered by different national legislations leading to a disproportionate use of iodized salt in processed food production (6). Therefore, a more uniform European legislation on iodine fortification is required. The standardized European map of UIC is an important milestone to provide robust evidence to encourage stakeholders to improve and harmonize legislations towards Europe and beyond. In future studies, much more effort should be put on harmonizing the procedures used in iodine monitoring studies, beginning from the planning phase and including sample collection procedures and UIC measurements, to improve the validity and comparability of iodine studies.

Funding

The EUthyroid project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement number 634453.

Disclosure Statement

No competing financial interests exist

Literature

1. World Health Organization 2007 Assessment of Iodine Deficiency Disorders and Monitoring their Elimination. A Guide for Programme Managers (Third edition).

2. Iodine Global Network. Global map of iodine nutrition (http://www.ign.org/scorecard.htm). (Last accessed on 2018/09/12, 2018).

3. Zimmermann MB, Andersson M 2012 Update on iodine status worldwide. Curr Opin Endocrinol Diabetes Obes **19**:382-387.

4. Ittermann T, Johner S, Below H, Leiterer M, Thamm M, Remer T, Volzke H 2017 Interlaboratory variability of urinary iodine measurements. Clin Chem Lab Med.

5. Nystrom HF, Brantsaeter AL, Erlund I, Gunnarsdottir I, Hulthen L, Laurberg P, Mattisson I, Rasmussen LB, Virtanen S, Meltzer HM 2016 Iodine status in the Nordic countries - past and present. Food Nutr Res **60**:31969.

6. Volzke H, Caron P, Dahl L, de Castro JJ, Erlund I, Gaberscek S, Gunnarsdottir I, Hubalewska-Dydejczyk A, Ittermann T, Ivanova L, Karanfilski B, Khattak RM, Kusic Z, Laurberg P, Lazarus JH, Markou KB, Moreno-Reyes R, Nagy EV, Peeters RP, Pirags V, Podoba J, Rayman MP, Rochau U, Siebert U, Smyth PP, Thuesen BH, Troen A, Vila L, Vitti P, Zamrazil V, Zimmermann MB 2016 Ensuring Effective Prevention of Iodine Deficiency Disorders. Thyroid **26**:189-196.

7. Lazarus JH 2014 Iodine status in europe in 2014. Eur Thyroid J **3**:3-6.

8. The EUthyroid Consortium. EUthyroid Data Exchange System (https://dex.euthyroid.medizin.uni-greifswald.de/dex/). (Last accessed on 2018-09-12, 2018).

9. Eurostat. 2007 Regions in the European Union. Nomenclature of territorial units for statistics – NUTS 2006/EU-27. Office for Official Publications of the European Communities, Luxembourg.

10. Cashman KD, Dowling KG, Skrabakova Z, Kiely M, Lamberg-Allardt C, Durazo-Arvizu RA, Sempos CT, Koskinen S, Lundqvist A, Sundvall J, Linneberg A, Thuesen B, Husemoen LL, Meyer HE, Holvik K, Gronborg IM, Tetens I, Andersen R 2015 Standardizing serum 25-hydroxyvitamin D data from four Nordic population samples using the Vitamin D Standardization Program protocols: Shedding new light on vitamin D status in Nordic individuals. Scand J Clin Lab Invest **75**:549-561.

11. Diaz A, Lipman Diaz EG 2014 Hypothyroidism. Pediatr Rev **35**:336-347; quiz 348-339.

12. Rasmussen LB, Ovesen L, Bulow I, Jorgensen T, Knudsen N, Laurberg P, Pertild H 2002 Dietary iodine intake and urinary iodine excretion in a Danish population: effect of geography, supplements and food choice. Br J Nutr **87**:61-69.

13. Thamm M, Ellert U, Thierfelder W, Liesenkotter KP, Volzke H 2007 [Iodine intake in Germany. Results of iodine monitoring in the German Health Interview and Examination Survey for Children and Adolescents (KiGGS)]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz **50**:744-749.

14. Dahl L, Opsahl JA, Meltzer HM, Julshamn K 2003 Iodine concentration in Norwegian milk and dairy products. Br J Nutr **90**:679-685.

15. Johner SA, Shi L, Remer T 2010 Higher urine volume results in additional renal iodine loss. Thyroid **20**:1391-1397.

16. Ittermann T, Volzke H, Krey A, Remer T, Heckmann M, Lange A, Kramer A, Below H 2018 Median urinary iodine concentration reflected sufficient iodine supply in neonates from Northeast Germany in 2005-2006. Eur J Nutr.

17. Bath SC, Rayman MP 2015 A review of the iodine status of UK pregnant women and its implications for the offspring. Environ Geochem Health **37**:619-629.

18. Zimmermann MB, Andersson M 2012 Assessment of iodine nutrition in populations: past, present, and future. Nutr Rev **70**:553-570.

19. Andersen S, Karmisholt J, Pedersen KM, Laurberg P 2008 Reliability of studies of iodine intake and recommendations for number of samples in groups and in individuals. Br J Nutr **99**:813-818.

Table 1. Laboratory comparisons to the EUthyroid central lab for urinary iodine concentrations (UIC)

Laboratory	Difference in UIC; % Mean (1.96*SD)	Correlation	p_{int}	p_{slope}	Conversion formula
1	-0.1 (14.7)	0.99	0.925	0.356	-0.23 + 1.01*UIC
2	-18.2 (53.2)	0.98	0.667	<0.001	-0.90 + 1.16*UIC
3	-15.5 (75.8)	0.98	0.022	0.458	17.44 + 0.98*UIC
4	13.0 (27.0)	0.97	<0.001	0.040	-29.2 + 1.04*UIC
5	-2.6 (49.7)	0.95	0.836	0.225	-1.05 + 1.04*UIC
6	32.3 (32.9)	0.95	0.074	<0.001	15.71 + 0.66*UIC
7	3.4 (37.2)	0.95	0.892	0.179	0.91 + 0.97*UIC
8	5.5 (79.2)	0.93	0.287	0.972	-5.65 + 1.00*UIC
9	14.5 (27.3)	0.92	0.693	<0.001	2.39 + 0.86*UIC
10	12.4 (44.4)	0.89	0.363	<0.001	5.02 + 0.83*UIC
11	-15.9 (143.9)	0.87	0.337	0.124	9.48 + 0.93*UIC
12	34.7 (89.9)	0.83	<0.001	<0.001	-67.37 + 1.54*UIC
13	49.5 (63.1)	0.82	0.163	<0.001	-6.61 + 0.63*UIC
14	30.0 (51.1)	0.82	0.096	0.161	-27.27 + 0.93*UIC
15	10.9 (83.2)	0.77	0.824	0.723	-6.39 + 0.98*UIC
16	-25.4 (74.3)	0.76	0.017	0.938	-89.08 + 1.92*UIC

17	-36.4 (62.0)	0.76	0.952	<0.001	-0.91 + 1.51*UIC
18	-18.4 (101.9)	0.68	<0.001	<0.001	68.21 + 0.63*UIC
19	4.4 (83.7)	0.62	0.042	0.009	20.94 + 0.80*UIC
20	-36.6 (131.8)	0.57	<0.001	<0.001	80.08 + 0.59*UIC
21	-16.5 (139.7)	0.50	<0.001	<0.001	49.23 + 0.53*UIC

Mean and standard deviations (SD) derived from Bland & Altman plots; correlations and conversion formulas from linear regression models; p_{int} and p_{slope} are the p-values derived from the regression model for the intercept = 0 and the slope = 1. $p<0.05$ indicates significant difference.

Table 2. Standardized median urinary iodine concentrations (UIC) in European monitoring studies

Country	Year	Number of individuals	Standardized median UIC in µg/L (95%-CI)	Standardized inter-quartile-range of UIC
Studies in school children				
Croatia	2016	200	222 (209; 235)	179 – 282
Czech Republic	2006	302	210 (194; 225)	103 – 294
Germany	2006	14641	113 (111; 115)	61 – 169
Hungary	2018	110	254 (231; 276)	163 – 337
Northern Ireland and Republic of Ireland	2015	901	110 (104; 116)	71 – 162
Italy	2016	100	134 (126; 143)	114 – 162
Latvia	2011	915	102 (93; 111)	34 – 194
North Macedonia	2016	1167	216 (208; 224)	149 – 291
Montenegro	2016	406	181 (168; 193)	124 – 248
Norway	2015	457	98 (93; 103)	69 – 135
Poland	2017	1000	121 (116; 126)	82 – 168
Portugal	2011	4390	107 (106; 108)	94 – 156
Serbia	2018	74	187 (170; 204)	132 – 239
Spain	2011	1750	179 (174; 184)	121 – 246
Sweden	2007	866	127 (122; 132)	95 – 166
Switzerland	2016	727	152 (146; 158)	115 – 201

Country	Year	Number of individuals	Standardized median UIC in µg/L (95%-CI)	Standardized inter-quartile-range of UIC
Studies in adults				
Croatia	2016	227	178 (163; 193)	111 – 222
Cyprus	2014	121	99 (87; 111)	71 – 150
Czech Republic	2006	288	105 (101; 108)	83 – 191
Finland	2017	1542	96 (93; 100)	62 – 146
Germany	2012	4287	65 (63; 66)	36 – 103
	2011	7022	51 (49; 52)	26 – 82
	2008	2999	93 (90; 96)	58 – 136
	2001	4260	72 (70; 73)	41 – 107
Slovenia	2017	292	73 (63; 83)	38 – 151
Spain	2010	4383	121 (118; 124)	79 – 179
Sweden	2001	565	132 (123; 140)	71 – 204
Switzerland	2016	345	103 (87; 120)	63 – 184
Turkey	2017	165	116 (110; 121)	89 – 145
Studies in pregnant women				
Croatia	2016	202	157 (147; 167)	114 – 196
Greece	2015	1135	118 (114; 123)	79 – 180
Hungary	2016	190	144 (126; 161)	89 – 276
Latvia	2013	743	39 (35; 44)	16 – 75
North Macedonia	2017	593	177 (161; 192)	90 – 265
Poland	2017	300	113 (101; 126)	64 – 188

Country	Year	Number of individuals	Standardized median UIC in µg/L (95%-CI)	Standardized inter-quartile-range of UIC
Portugal	2011	4107	104 (103; 105)	65 – 155
Romania	2016	317	159 (142; 177)	99 – 243
Sweden	2007	459	114 (105; 123)	73 – 162
Switzerland	2016	358	156 (135; 177)	81 – 325
Northern Ireland (UK)	2015	240	66 (54; 79)	32 – 113

CI = confidence interval calculated by bootstrapping with 500 repetitions

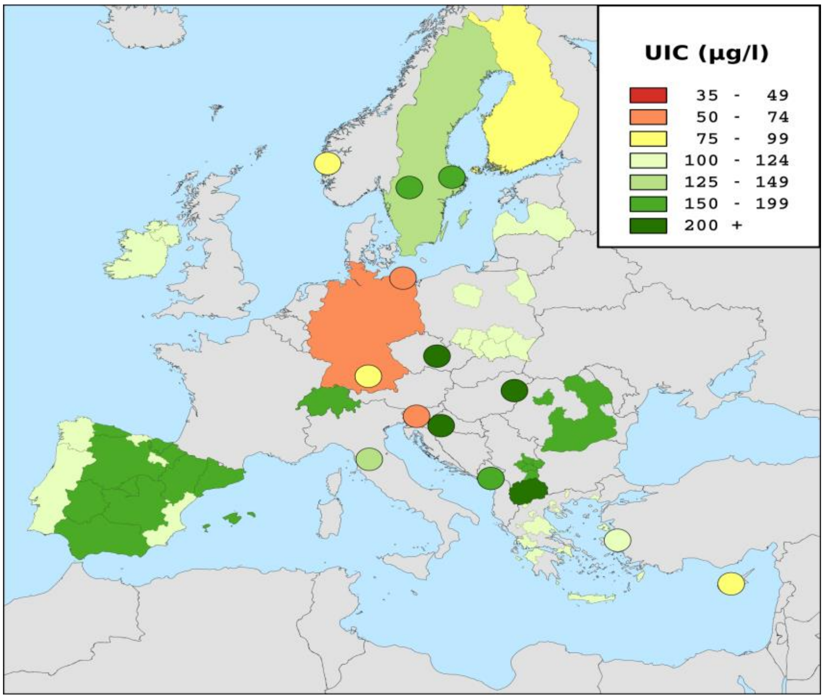


Figure 1. Standardized European map of median urinary iodine concentrations (UIC); studies have been selected for each country in the following order of priority: most recent study in (i) schoolchildren, (ii) adults, (iii) pregnant women; grey shadings indicate "no data available"

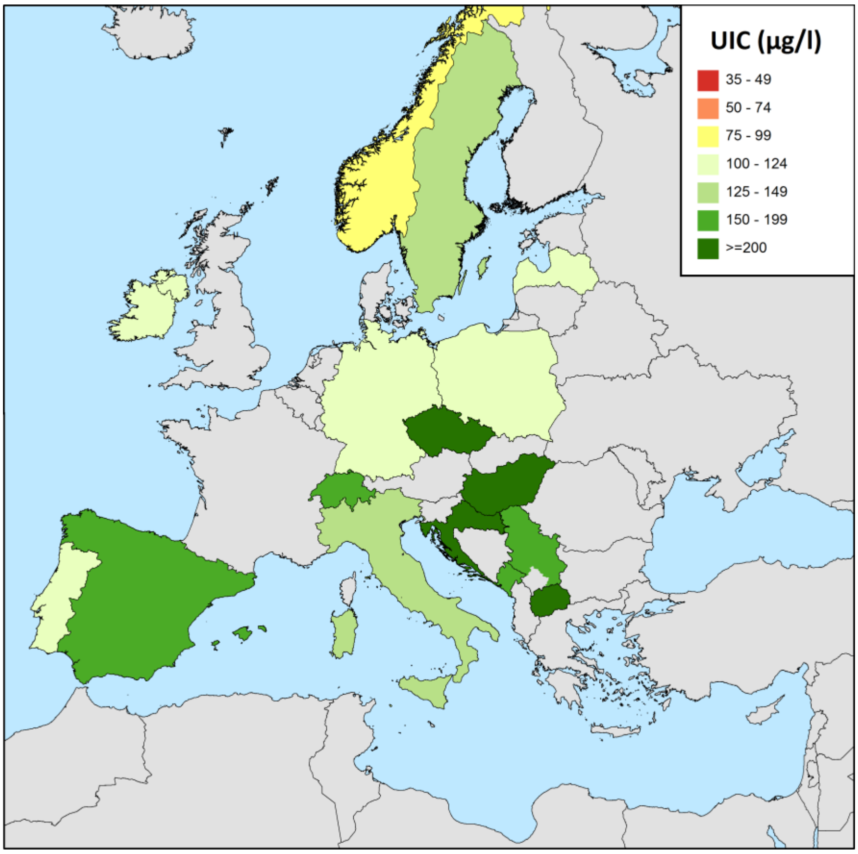


Figure 2. Standardized European map of median urinary iodine concentrations (UIC) in school children; grey shadings indicate “no data available”

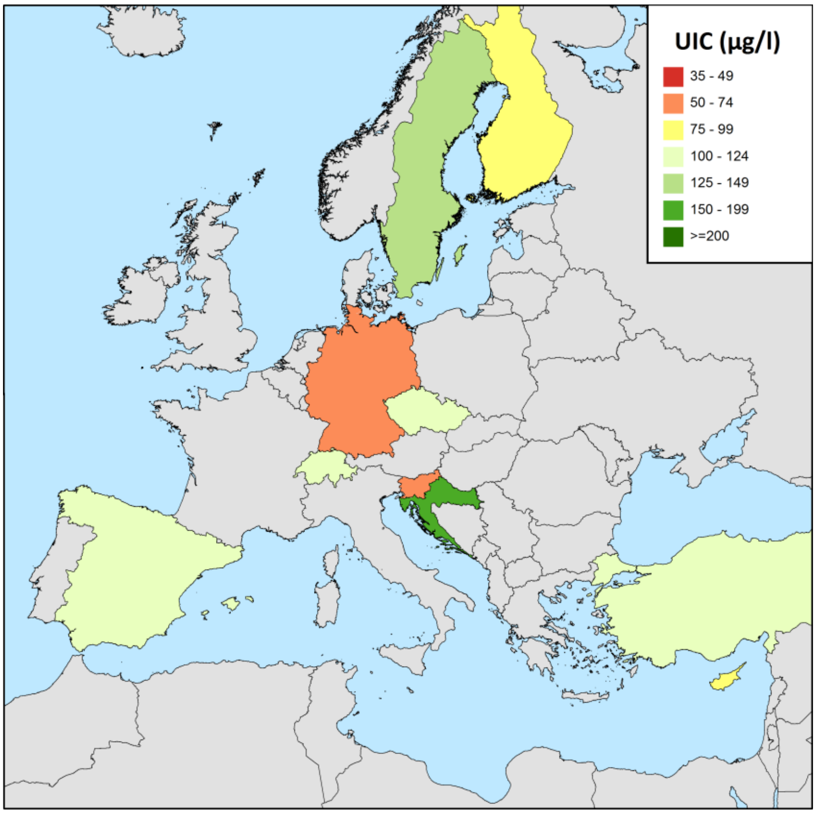
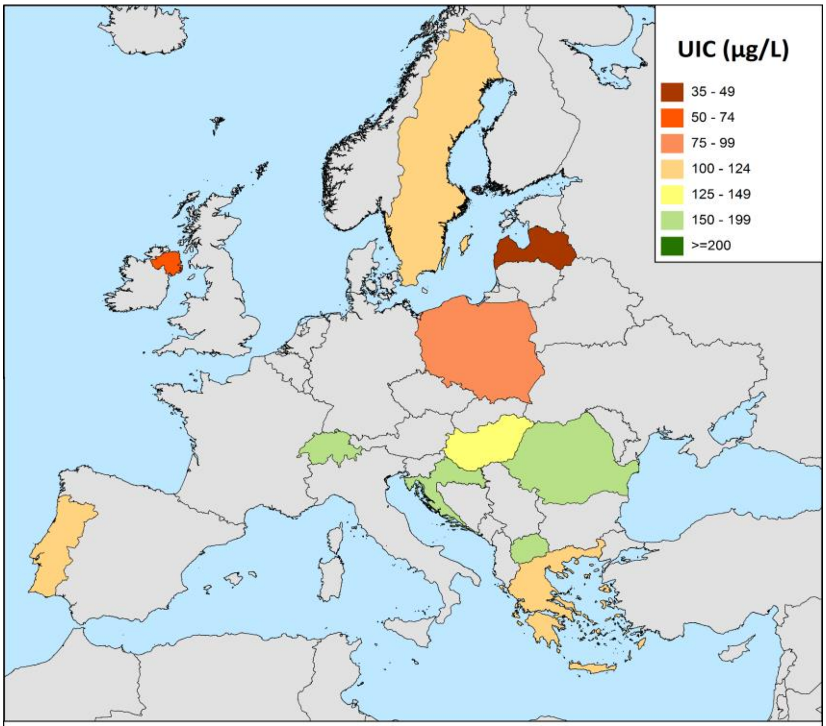


Figure 3. Standardized European map of median urinary iodine concentrations (UIC) in adults; grey shadings indicate “no data available”



Legend reflects adequate iodine intake in pregnant women with a median UIC of 150–249 µg/l as recommended by the World Health Organization (WHO).

Figure 4. Standardized European map of median urinary iodine concentrations (UIC) in pregnant women; grey shadings indicate "no data available"

Supplementary Table 1. Description of the involved studies

Country	Year	Study population	Iodine measurement	Reference
Croatia	2014 – 2016	Simplify study – population-based sample of 200 children, 227 adults and 202 pregnant women	Sandell-Kolthoff reaction (Wawschinek modification)	(1)
Cyprus	2014	Sample of 121 adults recruited from hospitals and advertisements	ICP-MS	
Czech Republic	2006	Study in Zdar nad Sazavou – population-based sample of 302 children and 288 adults	Sandell-Kolthoff reaction subsequent to dry alkaline	(2)
Finland	2017	FinHealth 2017 Study – Nationally representative survey, subsample with 1542 adults (Findiet 2017 Survey)	ICP-MS	
Germany	2003 – 2006	KiGGS study – nationwide population-based study in 14,641 children and adolescents	Sandell-Kolthoff reaction with ammonium persulfate digestion	(3)
Germany	2008 - 2012	SHIP-Trend – population-based study in 4287 adults	Sandell-Kolthoff reaction (Wawschinek modification)	(4)
Germany	2008 – 2011	DEGS – nation-wide population-based study in	Sandell-Kolthoff reaction with ammonium	(5)

Country	Year	Study population	Iodine measurement	Reference
		7022 adults	persulfate digestion	
Germany	2006 – 2008	KORA-F4 – Population-based study in 2999 adults	Sandell-Kolthoff reaction (Wawschinek modification)	(6)
Germany	1997 – 2001	SHIP-0 – population-based study in 4260 adults	Sandell-Kolthoff reaction (Wawschinek modification)	(7)
Greece	2012 – 2015	Representative sample of 1135 pregnant women	Sandell-Kolthoff reaction with ammonium persulfate digestion	(8)
Hungary	2018	One randomly-selected school including 110 children	Sandell-Kolthoff method adopted to microplate	
Hungary	2016	GS16 – 190 randomly selected pregnant women in week 16 of pregnancy	Sandell-Kolthoff method adopted to microplate	
Northern Ireland and Republic of Ireland	2014 – 2015	901 schoolgirls aged 14-15 years	Sandell-Kolthoff reaction with multiplate persulphate digestion	(9)
Northern Ireland (UK)	2014 – 2015	240 pregnant women recruited from maternity hospital	Sandell-Kolthoff reaction with multiplate persulphate digestion	(10)
Italy	2016	100 school children from Tuscany	ICP-MS	
Latvia	2010 –	Study of 915 school	Sandell-Kolthoff reaction	(11)

Country	Year	Study population	Iodine measurement	Reference
	2011	children from 46 randomly-selected schools	with ammonium persulfate digestion	
Latvia	2013 – 2014	Study of 743 pregnant women recruited by gynecologists from all regions	Sandell-Kolthoff reaction with ammonium persulfate digestion	(12)
North Macedonia	2016	Population-based sample of 1167 school children aged 8 – 10 years	Sandell-Kolthoff reaction with ammonium persulfate digestion	
North Macedonia	2017	Sample of 593 pregnant women recruited by advertisement	ICP-MS	
Montenegro	2016	Population-based sample of 406 school children	Sandell-Kolthoff reaction with ammonium persulfate digestion	
Norway	2015	FINS-TEENS –Randomized study of 457 adolescents aged 14 – 15 years from 8 secondary schools	ICP-MS	(13)
Poland	2017	Survey on iodine nutrition within the the National Health Programme including 1000 schoolchildren and 300 pregnant recruited on a voluntary basis	Sandell-Kolthoff reaction	
Portugal	2010 –	Sample of 4390 school	Colorimetric method	

Country	**Year**	**Study population**	**Iodine measurement**	**Reference**
	2011	children and 4107 pregnant women recruited voluntarily		
Romania	2015 – 2016	Sample of 317 pregnant women recruited from ambulatory care	Sandell-Kolthoff reaction with ammonium persulfate digestion	
Serbia	2018	74 children with thyroid disease recruited from ambulatory care	Chemiluminescent microparticule immunoassay	
Slovenia	2017	Sample of 292 women of reproductive age	Sandell-Kolthoff reaction with ammonium persulfate digestion adopted to microplate	
Spain	2010 – 2011	Tirokid study – Population-based sample of 1750 children	Sandell-Kolthoff reaction (Benotti & Benotti modification) with chloric acid digestion	(14)
Spain	2008 – 2010	Di@bet.es – Population-based study in 4383 adults	Sandell-Kolthoff reaction (Benotti & Benotti modification) with chloric acid digestion	(15)
Sweden	2006 – 2007	National sample of 866 school-aged children	Sandell-Kolthoff reaction (Pino modification)	(16)
Sweden	1987 – 2001	Swedish Obese Subjects (SOS) Study – 565 obese subjects choosing bariatric	Sandell-Kolthoff reaction (Pino modification)	(17)

Country	Year	Study population	Iodine measurement	Reference
		surgery		
Sweden	2006 – 2011	Karlstad-Uppsala-Study – Population-based study in 459 pregnant women	Sandell-Kolthoff reaction (Pino modification)	(18)
Switzerland	2015 – 2016	National representative study in 727 school children, 345 women of reproductive age and 358 pregnant women	Sandell-Kolthoff reaction (Pino modification)	(19)
Turkey	2016 – 2017	Sample of 165 high school and vocational school students aged 15 – 22	Sandell-Kolthoff reaction with ammonium persulfate digestion	

References

1. Dold S, Zimmermann MB, Jukic T, Kusic Z, Jia Q, Sang Z, Quirino A, San Luis TOL, Fingerhut R, Kupka R, Timmer A, Garrett GS, Andersson M 2018 Universal Salt Iodization Provides Sufficient Dietary Iodine to Achieve Adequate Iodine Nutrition during the First 1000 Days: A Cross-Sectional Multicenter Study. J Nutr **148**:587-598.

2. Bilek R, Bednar J, Zamrazil V 2005 Spectrophotometric determination of urinary iodine by the Sandell-Kolthoff reaction subsequent to dry alkaline ashing. Results from the Czech Republic in the period 1994-2002. Clin Chem Lab Med **43**:573-580.

3. Thamm M, Ellert U, Thierfelder W, Liesenkotter KP, Volzke H 2007 [Iodine intake in Germany. Results of iodine monitoring in the German Health Interview and Examination Survey for Children and Adolescents (KiGGS)]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz **50**:744-749.

4. Khattak RM, Ittermann T, Nauck M, Below H, Volzke H 2016 Monitoring the prevalence of thyroid disorders in the adult population of Northeast Germany. Popul Health Metr **14**:39.

5. Scheidt-Nave C, Kamtsiuris P, Gosswald A, Holling H, Lange M, Busch MA, Dahm S, Dolle R, Ellert U, Fuchs J, Hapke U, Heidemann C, Knopf H, Laussmann D, Mensink GB, Neuhauser H, Richter A, Sass AC, Rosario AS, Stolzenberg H, Thamm M, Kurth BM 2012 German health interview and examination survey for adults (DEGS) - design, objectives and implementation of the first data collection wave. BMC Public Health **12**:730.

6. Meisinger C, Ittermann T, Wallaschofski H, Heier M, Below H, Kramer A, Doring A, Nauck M, Volzke H 2012 Geographic variations in the frequency of thyroid disorders and thyroid peroxidase antibodies in persons without former thyroid disease within Germany. Eur J Endocrinol **167**:363-371.

7. Volzke H, Ludemann J, Robinson DM, Spieker KW, Schwahn C, Kramer A, John U, Meng W 2003 The prevalence of undiagnosed thyroid disorders in a previously iodine-deficient area. Thyroid **13**:803-810.

8. Koukkou EG, Ilias I, Mamalis I, Markou KB 2017 Pregnant Greek Women May Have a Higher Prevalence of Iodine Deficiency than the General Greek Population. Eur Thyroid J **6**:26-30.

9. Mullan K, Hamill L, Doolan K, Young I, Smyth P, Flynn A, Walton J, Meharg AA, Carey M, McKernan C, Bell M, Black N, Graham U, McCance D, McHugh C, McMullan P, McQuaid S, O'Loughlin A, Tuthill A, Bath SC, Rayman M, Woodside JV 2019 Iodine status of teenage girls on the island of Ireland. Eur J Nutr.

10. McMullan P, Hamill L, Doolan K, Hunter A, McCance D, Patterson C, Smyth P, Woodside JV, Mullan K 2019 Iodine deficiency among pregnant women living in Northern Ireland. Clin Endocrinol (Oxf).

11. Konrade I, Neimane L, Makrecka M, Strele I, Liepinsh E, Lejnieks A, Vevere P, Gruntmanis U, Pirags V, Dambrova M 2014 A cross-sectional survey of urinary iodine status in Latvia. Medicina (Kaunas) **50**:124-129.

12. Konrade I, Kalere I, Strele I, Makrecka-Kuka M, Jekabsone A, Tetere E, Veisa V, Gavars D, Rezeberga D, Pirags V, Lejnieks A, Dambrova M 2015 Iodine deficiency during pregnancy: a national cross-sectional survey in Latvia. Public Health Nutr **18**:2990-2997.

13. Skotheim S, Dahl L, Handeland K, Froyland L, Lie O, Oyen J, Kjellevold M, Stormark KM, Graff IE 2017 Design of the FINS-TEENS study: A randomized controlled trial assessing the impact of fatty fish on cognitive performance in adolescents. Scand J Public Health **45**:621-629.

14. Vila L, Donnay S, Arena J, Arrizabalaga JJ, Pineda J, Garcia-Fuentes E, Garcia-Rey C, Marin JL, Serra-Prat M, Velasco I, Lopez-Guzman A, Luengo LM, Villar A, Munoz Z, Bandres O, Guerrero E, Munoz JA, Moll G, Vich F, Menendez E, Riestra M, Torres Y, Beato-Vibora P, Aguirre M, Santiago P, Aranda J, Gutierrez-Repiso C 2016 Iodine status and thyroid function among Spanish schoolchildren aged 6-7 years: the Tirokid study. Br J Nutr **115**:1623-1631.

15. Soriguer F, Garcia-Fuentes E, Gutierrez-Repiso C, Rojo-Martinez G, Velasco I, Goday A, Bosch-Comas A, Bordiu E, Calle A, Carmena R, Casamitjana R, Castano L, Castell C, Catala M, Delgado E, Franch J, Gaztambide S, Girbes J, Gomis R, Gutierrez G, Lopez-Alba A, Martinez-Larrad MT, Menendez E, Mora-Peces I, Ortega E, Pascual-Manich G, Serrano-Rios M, Valdes S, Vazquez JA, Vendrell J 2012 Iodine intake in the adult population. Di@bet.es study. Clin Nutr **31**:882-888.

16. Andersson M, Berg G, Eggertsen R, Filipsson H, Gramatkovski E, Hansson M, Hulthen L, Milakovic M, Nystrom E 2009 Adequate iodine nutrition in Sweden: a cross-sectional national study of urinary iodine concentration in school-age children. Eur J Clin Nutr **63**:828-834.

17. Manousou S, Carlsson LMS, Eggertsen R, Hulthen L, Jacobson P, Landin-Wilhelmsen K, Trimpou P, Svensson PA, Nystrom HF 2018 Iodine Status After Bariatric Surgery-a Prospective 10-Year Report from the Swedish Obese Subjects (SOS) Study. Obes Surg **28**:349-357.

18. Granfors M, Andersson M, Stinca S, Akerud H, Skalkidou A, Poromaa IS, Wikstrom AK, Nystrom HF 2015 Iodine deficiency in a study population of pregnant women in Sweden. Acta Obstet Gynecol Scand **94**:1168-1174.

19. Andersson M, Hunziker S, Fingerhut R, Zimmermann MB, Herter-Aeberli I 2019 Effectiveness of increased salt iodine concentration on iodine status: trend analysis of cross-sectional national studies in Switzerland. Eur J Nutr.