Iodine deficiency among Italian children and adolescents assessed through 24-hour urinary iodine excretion

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ABSTRACT

Background: Iodine is an essential micronutrient for intellectual development in children. Information on iodine intakes based on 24-h urinary iodine excretion (UIE) is scant, because iodine status is only assessed by the measurement of urinary iodine concentration (UIC) in spot urine samples.

Objectives: The aim of our study was to evaluate the iodine intake of school-age children and adolescents, using UIE measurement in 24-h urine collections.

Methods: The study population included 1270 healthy subjects (677 boys, 593 girls) aged 6–18 y (mean age ± SD: 10.3 ± 2.9) from 10 Italian regions. Daily iodine intake was estimated as UIE/0.92, based on the notion that ~92% of the dietary iodine intake is absorbed. The adequacy of intakes was assessed according to the Dietary Reference Values for iodine of the European Food Safety Authority (EFSA). Body mass index (BMI) and UIC were also measured for each subject.

Results: Based on the scientific opinion of EFSA, 600 of 1270 subjects (47.2%) had a lower than adequate iodine intake, with a higher prevalence among girls (54.6%) compared with boys (40.2%) ($P < 0.001$). Although UIE and 24-h urinary volumes increased with age ($P < 0.001$), a progressive decrease in the percentage of subjects with iodine excretion <100 μg/24 h ($P < 0.001$) was observed, without any significant difference in the percentage of subjects with UIC <100 μg/L. No significant association was detected between BMI *z*-score and UIE ($P = 0.603$) or UIC ($P = 0.869$).

Conclusions: A sizable proportion of our population, especially girls, appeared to be at risk of iodine inadequacy. The simple measurement of UIC could lead to underestimation of the occurrence of iodine deficiency in younger children, because of the age-related smaller urine volumes producing spuriously higher iodine concentrations. *Am J Clin Nutr* 2019;109:1080–1087.

Keywords: nutrition, iodine intake, urinary iodine concentration, urinary iodine excretion, children, adolescents

Introduction

Iodine is an essential micronutrient for thyroid function, growth, and intellectual development. Children are particularly vulnerable to the effects of deficient iodine intake, which is a recognized risk factor for neurodevelopmental and cognitive disorders in this age group. Indeed, it has been reported that even mild iodine deficiency can impair cognition in children, and that moderate to severe iodine deficiency significantly reduces a child's intelligence quotient (1). Thus, monitoring

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Abbreviations used: AI, adequate intake; DII, daily iodine intake; EFSA, European Food Safety Authority; UIC, urinary iodine concentration; UIE, urinary iodine excretion.

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the iodine status of pediatric populations is crucial. Despite recommendations for increasing iodine intake through diet, iodization of drinking water or irrigation water (2, 3), and/or salt iodization (4) to prevent iodine deficiency, the WHO estimates that 241 million school-age children worldwide have iodine deficiency (5).

Iodine is almost completely absorbed by the small intestine, with an absorption efficiency of 92%, as reported by the US Institute of Medicine of the National Academy of Sciences. Because most of the iodine absorbed is eliminated with the urine (6, 7), 24-h urinary iodine excretion (UIE, measured in micrograms per day) is considered a sensitive indicator of recent iodine intake and, therefore, a good predictor of dietary iodine consumption at the population level. Iodine in urine can also be expressed as urinary iodine concentration (UIC, measured in micrograms per liter) and in relation to creatinine excretion (micrograms iodine per gram creatinine) (5). Because 24-h collections are bothersome to most people, single-spot urinary samples are generally preferred to 24-h urine collections in population studies; hence, daily iodine intakes have been estimated accordingly.

Age-specific adequate intakes (AIs) of iodine have been proposed in Europe by the European Food Safety Authority (EFSA), given the insufficient evidence to derive an average requirement and a population reference intake (8). The proposed AIs range between 70 μg/24 h for children and 150 μg/24 h at the end of adolescence. These values were based on iodine intakes ensuring a UIC ($\geq$100 μg/L) associated with the lowest prevalence of goiter in school-aged children. Age-specific urinary volumes and absorption efficiency of dietary iodine were taken into account to calculate the AIs, whereas it was considered unnecessary to give sex-specific values. (8).

Because information about dietary iodine intake assessed through 24-h UIE is scarce, our aim was to measure 24-h UIE in a large sample of school-age children and adolescents from 10 Italian regions and to evaluate its relationship with UIC in different age and nutritional categories.

Methods

As part of the MINISAL-GIRCSI (9)—a program supported by the Italian Ministry of Health—dietary iodine intake was assessed in a national sample of Italian children and adolescents recruited with the collaboration of the Italian Society for Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP), using 24-h urine collections (10).

The study was commissioned by the Center for Disease Control of the Italian Ministry of Health and complied with its ethical issues.

Study population

A total of 1625 healthy subjects aged 6–18 y were recruited (86.1% of those invited) in 10 Italian regions (northern Italy: Piemonte, Lombardia, Emilia Romagna; central Italy: Toscana, Umbria, Marche, Lazio; southern Italy: Puglia, Campania, Calabria).

Recruitment was organized by the regional coordinators of the SIGENP and undertaken by the pediatricians and the general practitioners of the Italian National Health Service (NHS) in charge, respectively, of subjects aged <14 y and of those aged 15–18 y. Pediatricians and general practitioners were thoroughly informed of the project and were specifically asked to consecutively recruit, among their patients, healthy subjects aged 6–18 y who would be willing to go through the study procedures. Recruits agreed to participate in the study, and written informed consent was obtained from their parents or legal guardians.

Study procedures

Participants underwent a standard physical examination and anthropometric evaluation. Height and weight were measured applying standard measurement techniques: standing height was measured to the nearest 0.5 cm on a standardized wall-mounted height board; weight was measured under the same conditions (undressed, after voiding) and was determined to the nearest 0.1 kg by a physician's scale. The body mass index (BMI) and BMI z-score were calculated for each subject, according to Centers for Disease Control and prevention (CDC) growth charts (http://www.cdc.gov/nchs/data/series/sr_11/sr11_246.pdf).

At the end of the visit, the participants (or their caregivers, in case of younger children) received a plastic container for the 24-h urine collection, together with detailed instructions on how to collect complete 24-h urine samples. Recommendations were made to void in the morning after rising and to discard urine from the first micturition completely, noting the time of voiding as the start time of the urine collection, and to collect all the urine produced during the following 24 h, including the first void of the following morning. Once the collection was returned, the total volume of the urine was recorded and 2 samples were extracted after shaking. The samples were immediately stored in plastic containers and frozen at −30°C for later analyses. Iodine and creatinine measurements were carried out, respectively, at the Departments of Clinical Medicine and Surgery and of Translational Medical Science, at Federico II University of Naples Medical School.

Urine iodine levels were analyzed with an automated system (Autoanalyzer 3 system; Bran + Luebbe GmbH), using the ceric-arsenious acid reaction and a modified digestion method, with the conventional acid digestion replaced by ultraviolet irradiation (11). Calibration of the analyzer was performed according to the manufacturer's instructions, using standard potassium iodide solutions with low, medium, and high concentrations of iodine, in triplicate in each assay.

Urinary creatinine—measured by the kinetic Jaffé reaction using an ABX Pentra 400 apparatus (HORIBA ABX)—was used as an indicator to assess the adequacy of the 24-h collection. Participants were excluded from the analysis if they reported not having provided complete urine collections or presented a urinary creatinine excretion <0.1 mmol/kg body weight, corresponding to the fifth percentile of the 24-h urinary creatinine distribution in a population of healthy individuals aged 3 to 18 y (12, 13). Quality controls were performed using the low and high Urichem Gold Standards from Bio Development s.r.l.

UIE was expressed as micrograms per 24 h. Daily iodine intake (DII) was estimated as UIE/0.92 (assuming 92% of iodine bioavailability), and the prevalence of adequate intake in the studied population was estimated according to the Dietary

Reference Values for iodine of the EFSA (8); UIC was expressed as micrograms per liter.

Statistical analysis

Data were entered into an electronic file and analyzed using the Statistical Package for the Social Sciences Software Version 22 (SPSS v.22; IBM). Separate analyses were conducted for boys and girls. Moreover, statistical analyses were performed upon stratification of the study population based on age (quartiles) and BMI *z*-score.

Results were expressed as means ± SD for continuous variables, and as frequencies for categorical variables. The Kolmogorov–Smirnov goodness-of-fit test was used for assessing the hypothesis of normal data distribution. Because most variables did not have a Gaussian distribution, median values and IQRs were calculated and nonparametric tests were used for group comparisons (the Mann–Whitney *U* test and Kruskal–Wallis test). The Spearman rank correlation coefficient was used to define associations between variables, and the χ^2 test to investigate differences in the frequencies of categorical variables. The Jonckheere–Terpstra test was used to analyze statistical trends between variables. The level of significance was set at $\alpha = 0.05$, 2-sided level.

Results

General features of the study population

As reported in **Figure 1**, 201 subjects were excluded from the analysis because of suspected incomplete 24-h urine collection, based on the criteria indicated in Methods. A further 130 subjects were excluded because their UIC was below the analytical sensitivity of the method (5 μg/L), and 24 subjects were excluded because their UIC was >400 μg/L, presumably ascribable to extradietary iodine intakes (14).

The analysis was eventually performed on 1270 subjects having a mean age (± SD) of 10.3 ± 2.9 y (range: 6–18 y), of whom 677 (53.3%) were boys (mean age: 10.2 ± 2.9 y) and 593 (46.7%) were girls (mean age: 10.4 ± 2.9 y, $P = 0.273$ vs. boys).

The population was stratified by quartiles of age, the first quartile including 322 children aged <7.8 y, the second quartile 315 children aged 7.8–10 y, the third quartile 326 subjects aged >10 to 12.5 y, and the fourth quartile 307 participants aged > 12.5 y.

The mean BMI *z*-score of the population as a whole was 0.6 ± 1.1 (range: −3.7 to 2.9). Forty subjects (3.1%) were underweight, 739 (58.2%) had a normal nutritional status, 261 (20.6%) were overweight, and 230 (18.1%) were obese. The distribution of BMI *z*-scores was not statistically different between boys and girls ($P = 0.078$) and fitted with the BMI *z*-score distribution already reported for a younger-age Italian population (15).

Population iodine status according to 24-h UIE

The UIE (mean: 114.8 ± 78.4 μg/24 h; range: 2.5–458.8 μg/24 h) was not normally distributed in the study population. Medians were 100.4 μg/24 h (IQR: 57.99–154.1) for the whole population, 108.7 μg/24 h (IQR: 65.6–164.2) for boys, and 89.04 μg/24-h (IQR: 49.2–139.1) for girls ($P < 0.001$ vs. boys).

As reported in **Table 1**, there was a significant increasing trend in UIE medians from the first to fourth quartiles of age ($P < 0.001$), a progressive decrease in the percentage of subjects with UIE <100 μg/24 h ($P < 0.001$), without any significant difference in the percentage of subjects with UIC <100 μg/L across quartiles ($P = 0.116$). There was a progressive increase in 24-h urine volume with age ($P < 0.001$).

Although **Table 2** shows a moderate increase in the estimated daily iodine intake (μg/d) with age ($P < 0.001$), the proportion of subjects with iodine intakes below the age-specific AI was not significantly different across quartiles of age. As shown in **Table 3**, the percentage of subjects with lower than adequate iodine intake was higher for girls than for boys ($P < 0.001$).

Figure 2 compares the percentage of subjects having a UIC <100 μg/L with the percentage of subjects having lower than adequate DII (according to the EFSA). Within the first quartile of age, the proportion of subjects with lower than adequate iodine intake was significantly higher than the percentage of those with a UIC <100 μg/L (the value most commonly used to assess nutritional iodine status).

Finally, an analysis of UIE and UIC was carried out by classifying the subjects according to their BMI *z*-score. As reported in **Figure 3**, no statistically significant association was detected between BMI *z*-score and either UIE ($P = 0.603$) or

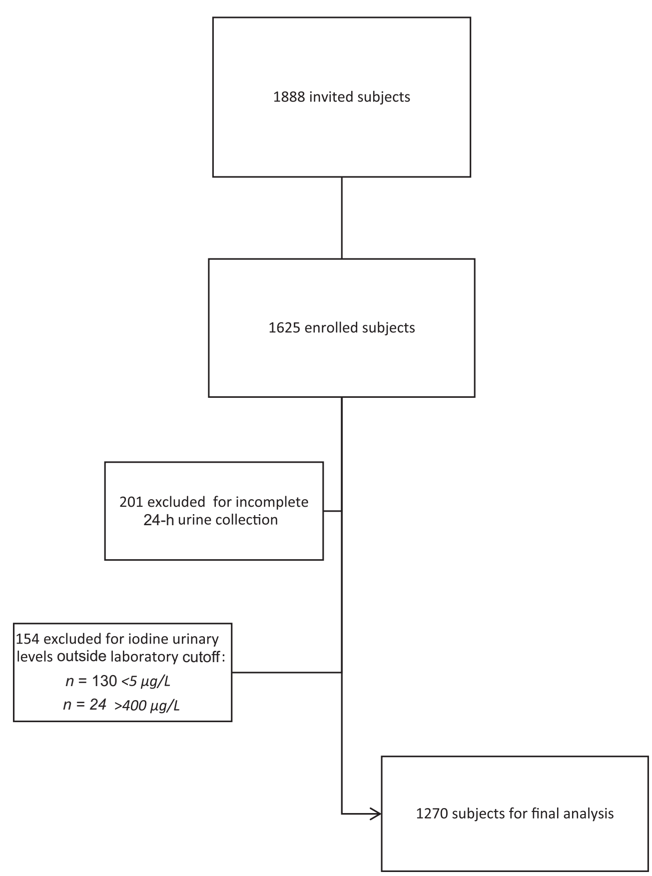

FIGURE 1 Flowchart of the study population.

TABLE 1 Medians (IQRs) of urinary iodine excretion (UIE), urine 24-h volume, and urinary iodine concentration (UIC) in the study population divided into quartiles of age[1]

	First quartile (n = 322)	Second quartile (n = 315)	Third quartile (n = 326)	Fourth quartile (n = 307)	P-trend
Median UIE, μg/24 h	88 (55.7–144.9)	93.8 (51.6–137.5)	107.5 (66.1–154.6)	112.3 (63.8–170.9)	<0.001
Subjects with UIE <100 μg/24 h, n (%)	186 of 322 (57.8)	168 of 315 (53.3)	148 of 326 (45.4)	128 of 307 (41.7)	<0.001
Median 24-h urine volume, mL	800 (600–963.7)	850 (650–1150)	1000 (750–1335)	1100 (850–1490)	<0.001
Subjects with UIC <100 μg/L, n (%)	130 of 322 (40.4)	141 of 315 (44.8)	143 of 326 (43.9)	145 of 307 (47.2)	0.116

[1]First quartile, 322 children aged <7.8 y; second quartile, 315 children aged 7.8–10 y; third quartile, 326 subjects aged >10 to 12.5 y; fourth quartile, 307 subjects >12.5 y. Data were analyzed using Jonckheere–Terpstra and Kruskal–Wallis tests for independent samples.

UIC (P = 0.591). Likewise, the proportion of subjects with lower than adequate DII was not statistically different between underweight, normal-weight, overweight, and obese children within each quartile of age (**Figure 4**).

Discussion

The present study is, to our knowledge, the first national survey assessing the habitual iodine intake in an Italian pediatric population, using 24-h urinary collections. Our data show that >40% of the population studied presented an iodine intake—estimated through 24-h UIE—lower than the age-specific AI proposed by the EFSA (8). This percentage was significantly higher for girls than for boys, a finding in line with a previous report by Ovadia et al. (16).

Our study was also able to compare the differences observed when using UIE or UIC values to assess the population's nutritional iodine status.

With increasing age, we observed a significant progressive increase in UIE and, consequently, a parallel decrease in the proportion of subjects with UIE <100 μg/24 h, but no significant change in the percentage of subjects with UIC <100 μg/L—the threshold used to identify school-age children and adolescent populations at higher risk of goiter (8). Notably, Figure 2 shows that in the first quartile of age, the proportion of subjects with inadequate DII was significantly higher than the percentage of those with UIC <100 μg/L. This can be explained by the lower urine volumes produced by younger children, leading to a higher UIC at any given level of 24-h urinary iodine excretion. Thus, in this age group the use of UIC could lead to underestimation of the degree of inadequacy of iodine intake at the population level.

Iodine status by overweight/obesity

No significant correlations were detected between body mass and nutritional iodine status, independently of the way the latter was assessed. Moreover, the proportion of subjects with lower than adequate iodine intake was not different between normal-weight and overweight or obese individuals.

It is intriguing that the same Italian study population presented, instead, a significant positive association between salt intake (also measured through 24-h urinary excretion) and BMI z-score (9). This would lead one to expect a similar association between BMI z-score and iodine intake, should mainly iodized salt be consumed. In fact, our data suggest that this is not really the case and that a large part of the salt consumed in Italy is not iodinated. This conclusion is consistent with recent data by Olivieri et al. showing that iodized salt represents only 55% of the salt sales in Italy and that the use of iodized salt by the food industry remains very low (17).

Methodological issues in the assessment of iodine status

Currently, the recommended and most widely used method to estimate iodine status in a given population is the measurement of UIC in spot urine samples. However, UIC is determined not only by the subject's iodine intake but also by his or her hydration status (18). Our observations indicate that in healthy children and adolescents, urinary volume can significantly influence UIC. For this reason, the measurement of 24-h urinary excretion is believed to provide a more accurate assessment of iodine status, especially in younger children, who tend to have a lower water intake and, consequently, a smaller urine volume. It has been proposed that UIC and 24-h UIE can be used interchangeably if the average daily urine volume approximates to 1 L, as is often (but not always) the case for older schoolchildren and adolescents (18, 19). Our data are in accord with these observations. Indeed, the major discrepancies between UIE and UIC were observed in the first and second quartiles of age, where the average 24-h urinary volume was <1 L.

The 24-h UIE should be taken as the best proxy for recent iodine intake (6, 19) and as the only parameter allowing a

TABLE 2 Daily iodine intake (DII) along age quartiles: medians (IQRs)[1]

	First quartile (<7.8 y; n = 322)	Second quartile (7.8–10 y; n = 315)	Third quartile (>10 to 12.5 y; n = 326)	Fourth quartile (>12.5 y; n = 307)	Total (N = 1270)	P value
Median DII, μg/d	95.7 (60.6–157.5)	101.9 (56.1–149.5)	116.8 (71.9–168.1)	122.1 (69.3–185.8)	109.1 (63–167.5)	<0.001
Number (%) of subjects with inadequate intake	156 of 322 (48.4)	141 of 315 (44.8)	145 of 326 (44.5)	158 of 307 (51.5)	600 of 1270 (47.2)	0.245

[1]Estimated iodine intake shows an increase with age (Jonckheere–Terpstra test: $z = 4.2$, $P < 0.001$, $r = 0.12$). The percentage of subjects with iodine intakes below the adequate intake was not significantly different across quartiles of age ($\chi^2_{(3)} = 4.161$, $P = 0.245$).

TABLE 3 Estimated daily iodine intake in boys and girls[1]

	Adequate intake		
	No	Yes	Total
Boys			
Number	276	401	677
%	40.8%	59.2%	100.0%
Girls			
Number	324	269	593
%	54.6%	45.4%	100.0%
Total			
Number	600	670	1270
%	47.2%	52.8%	100.0%

[1]The percentage of subjects with lower than adequate iodine intake was significantly higher in girls (54.6%) than in boys (40.8%) ($\chi^2_{(1)} = 24.397$, $P < 0.001$).

reasonably accurate estimate of the average habitual iodine intake for a given population. It is also amenable for monitoring the changes in habitual iodine intake occurring prospectively in a given population. This notwithstanding, most epidemiological surveys have relied only on the measurement of UIC (μg/L) in spot urine samples because of the inconvenience of collecting and handling 24-h collections (20, 21). Although this approach remains limited, it could be acceptable provided that a "sufficiently" large number of spot urine samples are made available from every participant, to overcome the confounding effects of intraindividual day-to-day variations of dietary iodine intake and volume of fluid ingestion (18, 22, 23).

Strengths and limitations

Major strengths of the current study are the use of 24-h urine samples to objectively measure iodine intake, the relatively large size of our study population, and its widespread distribution across the Italian territory.

A recent systematic review of the studies comparing spot and 24-h urine samples for the assessment of a population's iodine intake concluded that there is currently insufficient evidence to determine whether UIC estimated from spot urine samples provides an accurate reflection of 24-h urinary excretion (19). Although 24-h UIE provides the most reliable estimate of recent iodine intake (24), it has been suggested that, for epidemiological studies not aiming to assess individual intakes, there might be no need for the more troublesome 24-h urine collection, provided the sample size is large enough (24).

Another strength of our study is that all the participants were Caucasian, healthy and without restrictions, thus minimizing the risk that any disease state could have influenced their iodine intake.

By contrast, 2 main limitations of the study should be noted. The first is the lack of information about the use of iodized salt in the participants' family environment. This information would

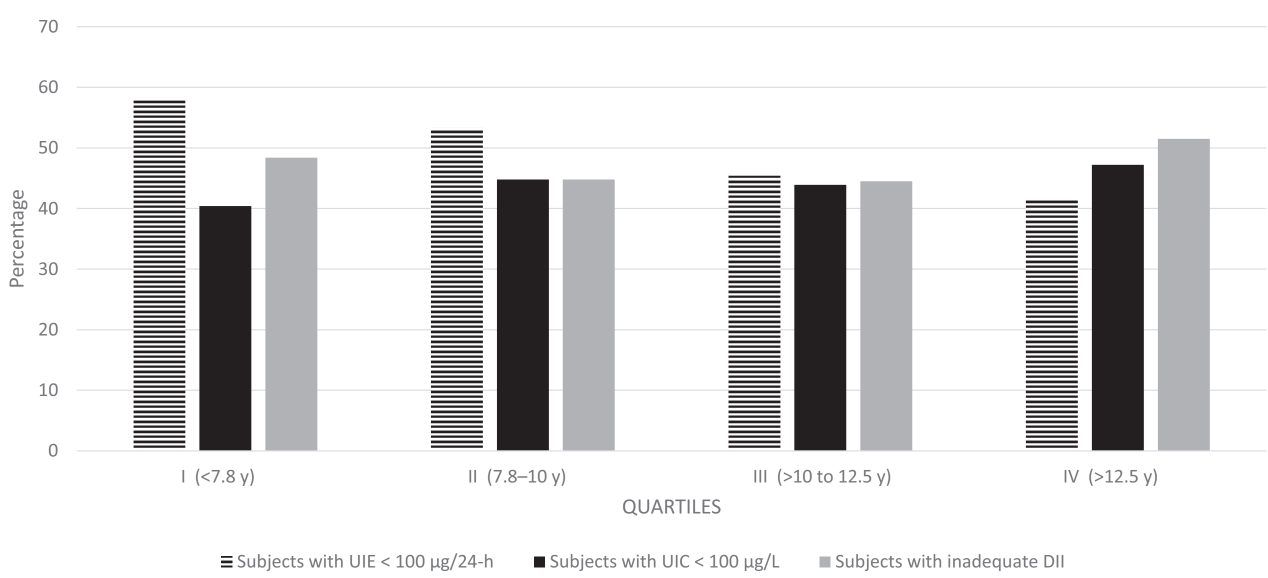

FIGURE 2 Comparison between the percentage of subjects with urinary iodine excretion (UIE) <100 μg/24 h, the percentage of subjects with urinary iodine concentration (UIC) <100 μg/L, and the percentage of subjects with inadequate daily iodine intake (DII) in the study population divided according to quartiles of age. First quartile ($n = 322$): 186 subjects (57.8%) had UIE <100 μg/24 h, 130 (40.4%) subjects had UIC <100 μg/L, and 156 subjects (48.4%) had inadequate DII. Second quartile ($n = 315$): 168 subjects (53.3%) had UIE <100 μg/24 h, 141 subjects (44.8%) had UIC <100 μg/L, and 141 subjects (44.8%) had inadequate DII. Third quartile ($n = 326$): 148 subjects (45.4%) had UIE <100 μg/24 h, 143 subjects (43.9%) had UIC <100 μg/L, and 145 subjects (44.5%) had inadequate DII. In the fourth quartile group ($n = 307$): 128 (41.7%) subjects had UIE <100 μg/24 h, 145 subjects (47.2%) had UIE <100 μg/L, and 158 (51.5%) subjects had inadequate DII. Statistical analysis, performed using a χ^2 test, showed significant differences between: percentage of subjects with UIE <100 μg/24 h and percentage of subjects with UIC <100 μg/L in the first quartile (57.8% vs. 40.4%, $P < 0.001$) and in the second quartile (53.3% vs. 44.8%, $P < 0.05$); percentage of children with UIE <100 μg/24 h and percentage of subjects with inadequate DII in the first quartile (57.8% vs. 48.4%, $P < 0.05$) and in the second quartile (53.3% vs. 44.8%, $P < 0.05$); percentage of children with UIC <100 μg/L and inadequate DII only in the first quartile (40.4% vs. 48.4%, $P < 0.05$). No statistical differences were recorded in comparing older groups.

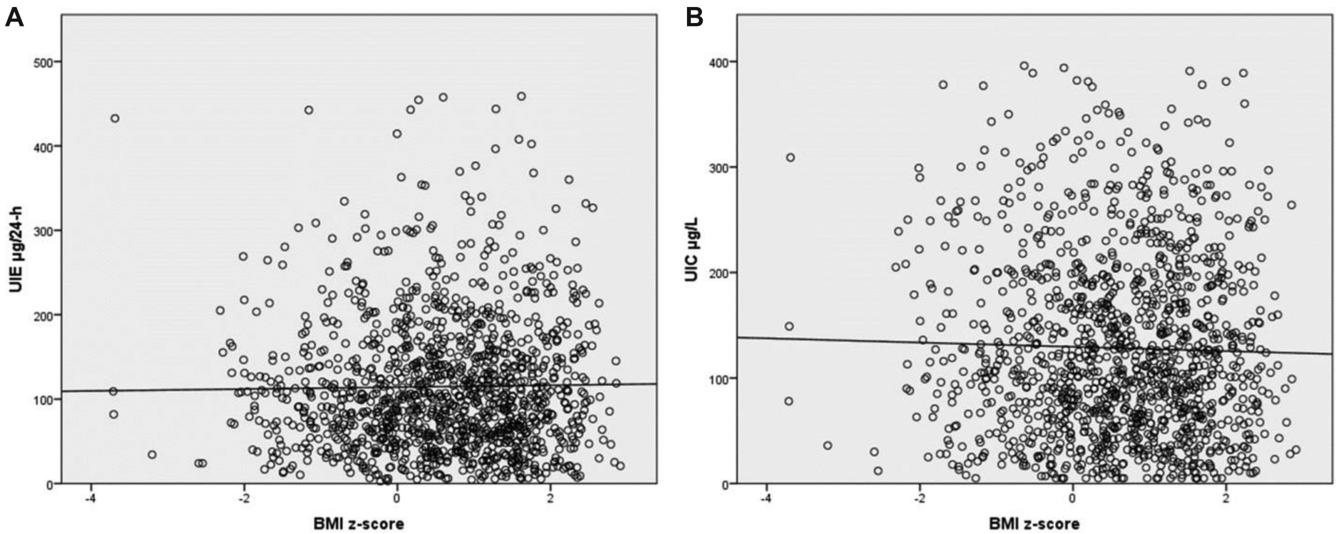

FIGURE 3 Association between urinary iodine and nutritional status. (A) Urinary iodine excretion (UIE, µg/24 h) and BMI *z*-score (Spearman's rank correlation: $\rho = 0.015$, $P = 0.603$). (B) Urinary iodine concentration (UIC, µg/L) and BMI *z*-score (Spearman's rank correlation: $\rho = -0.015$, $P = 0.591$).

have been useful to confirm the relationship between the regular use of iodized salt and adequate iodine status.

The second limitation is the use of a single urine collection to measure UIE rather than repeat measures followed by statistical modeling to remove/reduce within-individual variation. Unfortunately, as reported by König et al., at least 10 urine samples (whether spot or 24-h collection) would be necessary to estimate an individual's habitual iodine intake with 20% accuracy (25).

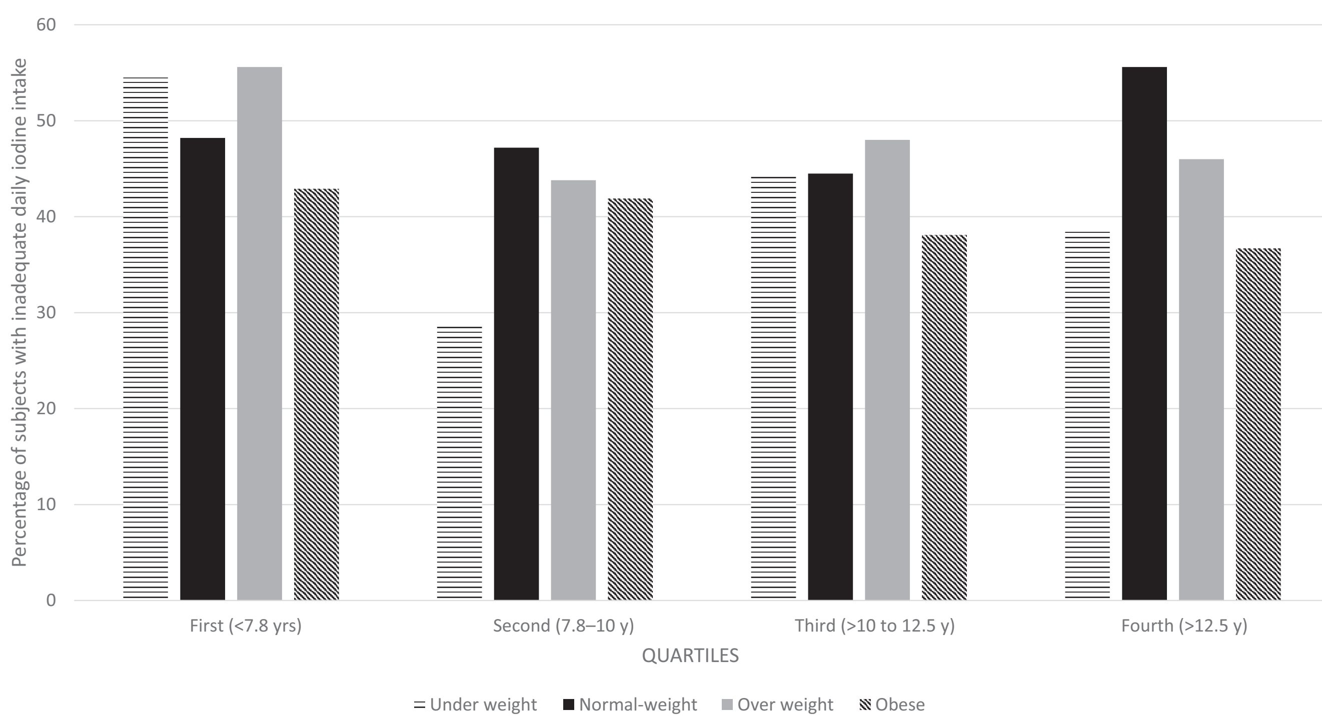

FIGURE 4 Percentage of subjects with inadequate daily iodine intake (DII) according to nutritional status in the different quartiles of age. In the first quartile ($n = 322$): 54.5% (6 of 11) of underweight children, 48.2% (79 of 164) of normal weight, 55.6% (35 of 63) of overweight, and 42.9% (36 of 84) of obese children had inadequate DII ($\chi^2_{(3)}$: 2.494, $P = 0.476$). In the second quartile ($n = 315$): 28.6% (2 of 7) of underweight, 47.2% (76 of 161) of normal weight, 43.8% (32 of 73) of overweight, and 41.9% (31 of 74) of obese children had inadequate DII ($\chi^2_{(3)}$: 1.4, $P = 0.705$). In the third quartile ($n = 326$): 44.4% (4 of 9) of underweight, 44.5% (89 of 200) of normal weight, 48% (36 of 75) of overweight, and 38.1% (16 of 42) of obese children presented with inadequate DII ($\chi^2_{(3)}$: 1.07, $P = 0.784$). In the fourth quartile ($n = 307$): 38.5% (5 of 13) of underweight, 55.6% (119 of 214) of normal weight, 46% (23 of 50) of overweight, and 36.7% (11 of 30) of obese subjects had inadequate DII ($\chi^2_{(3)}$: 5.578, $P = 0.134$).

Conclusions

To our knowledge, this is the first study to assess dietary iodine intake in a national sample of Italian schoolchildren and adolescents using 24-h urine collections. It shows that a sizable proportion of this young population, especially girls, has a lower than adequate iodine intake. Our study also suggests that the use of UIC could lead to underestimation of the occurrence and level of iodine deficiency in younger subjects because of the age-related smaller urine volumes producing spuriously higher iodine concentrations.

Furthermore, our results provide indirect evidence of the limited use of iodized salt by the Italian young population. These results are of concern because, as dietary habits tend to track into adulthood, low iodine intake during childhood will conceivably lead women to face a possible pregnancy with a suboptimal iodine status. Continued monitoring of iodine intakes of pediatric subjects, possibly using 24-h urine collections, is warranted in order to properly document changes in iodine intake, according to EFSA recommendations.

Campaigns to highlight the importance of iodine intake in growth and development and, therefore, on foods naturally rich in or supplemented with iodine, have clearly not yet had the desired effect. Special efforts should be made to promote such campaigns.

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