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Re-exploration of dietary iodine intake in Chinese adult males using a modified iodine balance study

Xiaobing Liu[1,2]†, Jun Wang[3]†, Yajie Li[4]†, Hongxing Tan[2], Xiuwei Li[5], Deqian Mao[1], Yanyan Liu[2], Weidong Li[1], Wei Yu[2], Jiaxi Lu[1], Junan Yan[2], Jianhua Piao[1], Lichen Yang[1], Chongzheng Guo[4]*, Xiaoli Liu[2]* and Xiaoguang Yang[1,2]*

[1]*Chinese Center for Disease Control and Prevention, National Institute for Nutrition and Health, Beijing 100050, People's Republic of China*

[2]*Shenzhen Center for Chronic Disease Control, Shenzhen, Guangdong 518020, People's Republic of China*

[3]*Shenzhen Polytechnic, School of Food and Drug, Shenzhen, Guangdong 518055, People's Republic of China*

[4]*Changzhi Medical College, Changzhi, Shanxi 046000, People's Republic of China*

[5]*Chinese Center for Disease Control and Prevention, National Reference Laboratory for Iodine Deficiency Disorders, Beijing 100050, People's Republic of China*

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Abstract

There is still controversy about optimal dietary iodine intake as the Universal Salt Iodization policy enforcement in China. A modified iodine balance study was thus conducted to explore the suitable iodine intake in Chinese adult males using the iodine overflow hypothesis. In this study, thirty-eight apparently healthy males (19·1 (SD 0·6) years) were recruited and provided with designed diets. After the 14-d iodine depletion, daily iodine intake gradually increased in the 30-d iodine supplementation, consisting of six stages and each of 5 d. All foods and excreta (urine, faeces) were collected to examine daily iodine intake, iodine excretion and the changes of iodine increment in relation to those values at stage 1. The dose–response associations of iodine intake increment with excretion increment were fitted by the mixed effects models, as well as with retention increment. Daily iodine intake and excretion were 16·3 and 54·3 μg/d at stage 1, and iodine intake increment increased from 11·2 μg/d at stage 2 to 118·0 μg/d at stage 6, while excretion increment elevated from 21·5 to 95·0 μg/d. A zero iodine balance was dynamically achieved as 48·0 μg/d of iodine intake. The estimated average requirement and recommended nutrient intake were severally 48·0 and 67·2 μg/d, which could be corresponded to a daily iodine intake of 0·74 and 1·04 μg/kg per d. The results of our study indicate that roughly half of current iodine intakes recommendation could be enough in Chinese adult males, which would be beneficial for the revision of dietary reference intakes.

Key words: Iodine requirement: Zero iodine balance: Iodine overflow hypothesis: Dietary reference intakes: Mixed effects models

Iodine is one of the essential elements required for normal body functioning, and it is an intrinsic constituent of thyroid hormones, including thyroxine (T4) and triiodothyronine (T3), that are important regulators of multiple biological process and metabolism[1,2]. So far, accumulating adverse consequences in populations with iodine deficiency has been documented, such as goitre, lower intelligence quotient, growth retardation and reproductive health problems[3,4]. However, as is the case for virtually all essential nutrients, long-term inadequate or excessive iodine intake will potentially cause thyroid dysfunctions[5].

Iodine deficiency is a serious public health problem, and its prevalence is considerably high in China compared with that in other countries. Approximately 425 million Chinese people living in iodine-deficient areas are affected, and nearly 35 million cases of goitre have been reported before 1995[6]. Fortunately, the status quo of iodine deficiency had been greatly improved as the implementation of Universal Salt Iodization policy[7]. Yet, numerous potential threats probably due to excessive iodine intake have gradually attracted more attention, although its health association has not well understood[8,9]. Excessive iodine intake can increase the risk of clinical hypothyroidism,

Abbreviations: EAR, estimated average requirement; MEM, mixed effects model; RNI, recommended nutrient intake.

* **Corresponding authors:** Xiaoguang Yang, email xgyangcdc@163.com; Xiaoli Liu, email liuxl36@126.com; Chongzheng Guo, email gczmed@126.com

† These authors equally contributed to this work

which has been reported in the Chinese populations[10]. The U-shaped curve relationship has also been observed between urinary iodine concentration and the prevalence of thyroid nodules[11]. Thus, a rigorous problem is repeatedly mentioned, that is, whether the current dietary iodine intake is much higher than that required for a certain population.

To date, the WHO, the United Nations International Children's Emergency Fund (UNICEF) and the International Council for Control of Iodine Deficiency Disorders (ICCIDD) had jointly recommended iodine intakes of 120 μg/d for schoolchildren, 150 μg/d for adolescents and adults and 250 μg/d for pregnant and lactating women[12]. The Chinese Nutrition Society also suggested that the dietary iodine intake was calculated by the adjustment of adult body weight in the data from other countries' studies. In theory, the dietary reference intakes should be set according to the physiological requirement of certain population in the traditional balance study[13,14]. Regrettably, only a few relevant studies have been conducted[13,15,16]. The issue on whether superfluous iodine is stored in the thyroid is mentioned in current China, and the traditional balance study may no longer be suitable for the individuals with iodine over-nutrition. The iodine overflow hypothesis was thus proposed in order to avoid the interferences, and that had been validated by recent studies in the south and north China[17,18]. However, some points should be noted that the smaller iodine intake range and sex difference, especially female menstrual cycle, can affect the collection of urine specimens.

Therefore, to avoid the known interferences, this study aimed to examine the iodine dynamic changes and to explore the iodine requirement in Chinese adult males based on a modified iodine balance study using the iodine overflow hypothesis; furthermore, it aimed to provide the data reference to the new Chinese iodine dietary reference intakes, such as the estimated average requirement (EAR) and recommended nutrient intake (RNI).

Methods

Participants

Participants were recruited in Changzhi Medical College, located in northern China; participants were required of 18–21 years; with a BMI of 18·5–27; with no thyroid, liver and kidney dysfunction; with no infection and inflammatory condition; with no overt constipation and who were not exposed to iodine-containing drugs and iodinated contrast media within the previous 6 months. The sample size of participant was estimated using the software of G × Power (version 3.1.9). As this study was a self-control study, it was estimated that thirty-four participants would be required for a paired t test to detect a medium effect size (F = 0·5) with a statistical power (1–β error probability) of 80 % and an α of 0·05. Thus, the sample size of 38 was adequate.

Iodine overflow hypothesis

The hypothesis demonstrated that the ingested iodine could be effectively absorbed and utilised only before or only when thyroid hormone biosynthesis and necessary for storage *in vivo* are adequate; meanwhile, the remaining iodine will be totally excreted from the body. The increment (Δ) iodine excretion will increase as the Δ iodine intake increases until a certain threshold (i.e. Δ iodine excretion = Δ iodine intake) after a short-term iodine depletion following a long-term superfluous status. A zero iodine balance will dynamically arrive to a similar iodine imminent 'overflow' in the human body. In this case, the iodine intake was exactly regarded as the basic iodine requirement of the individuals.

Study design

As shown in Fig. 1, this study was carried out for 44 d. The former 14 d was set as the depletion period to reduce the supersaturated iodine level in the thyroid. The later 30 d was set as the supplementation period to increase the iodine intake by stages, which involved the provision of milk or eggs based on the participants' daily diet; the 30 d was divided into six stages, and each stage lasted for 5 d. Physical examination was arranged at baseline day (Day_0) before iodine depletion, at start day (Day_{start}) and at end day (Day_{end}) for iodine supplementation. The weight and height of participants were measured by calibrated instruments, and blood samples were together collected through venous puncture after fasting for 8 h. Serum thyroid-stimulating hormone, free thyroxine, free triiodothyronine, alanine transaminase and aspartate aminotransferase levels were measured. The study protocol was conducted according to the guidelines of the Declaration of Helsinki of the World Medical Association[19] and approved by the Ethics Committee of National Institute of Nutrition and Health of Chinese Center for Disease Control and Prevention. Signed informed consent was obtained from all participants after explaining the nature of the study. This study was registered in medresman.org (ChiCTR1800016184).

Diet preparation, sample collection and determination

The iodine contents of raw materials such as rice, flour and other food items and the compound condiments were measured in advance. Diet plans were then carefully designed by a professional dietician based on balanced meals to avoid the use of condiments and foods with high iodine content, including kelp, seaweed and marine products and uniformly prepared with non-iodised salt. Details of the recipe used in preparing a typical daily meal are provided in Table 1. In this study, serving foods and drinking water were restrictively monitored and provided to all participants at the college canteen. The amounts of daily consumed foods were weighed and recorded. All foods were collected by duplicate portion method and stored in a cryogenic refrigerator at −20°C. The 24-h urine specimens were collected and weighed upon delivery at baseline and the whole study, and the estimated amount of missed urine was accordingly recorded. To ensure the integrity of the faecal sample collection, all participants were asked to take a carmine capsule to visually label the faeces at the onset of each stage and at the end of the 6th stage. The faecal samples were subsequently collected and homogenised at each stage according to the labelled red pigmentation; a portion was proportionally taken, lyophilised and stored at −20°C. After this study, all specimens were sent to the National Institute of Nutrition and Health in Chinese Center for Disease Control and Prevention for analysis. The

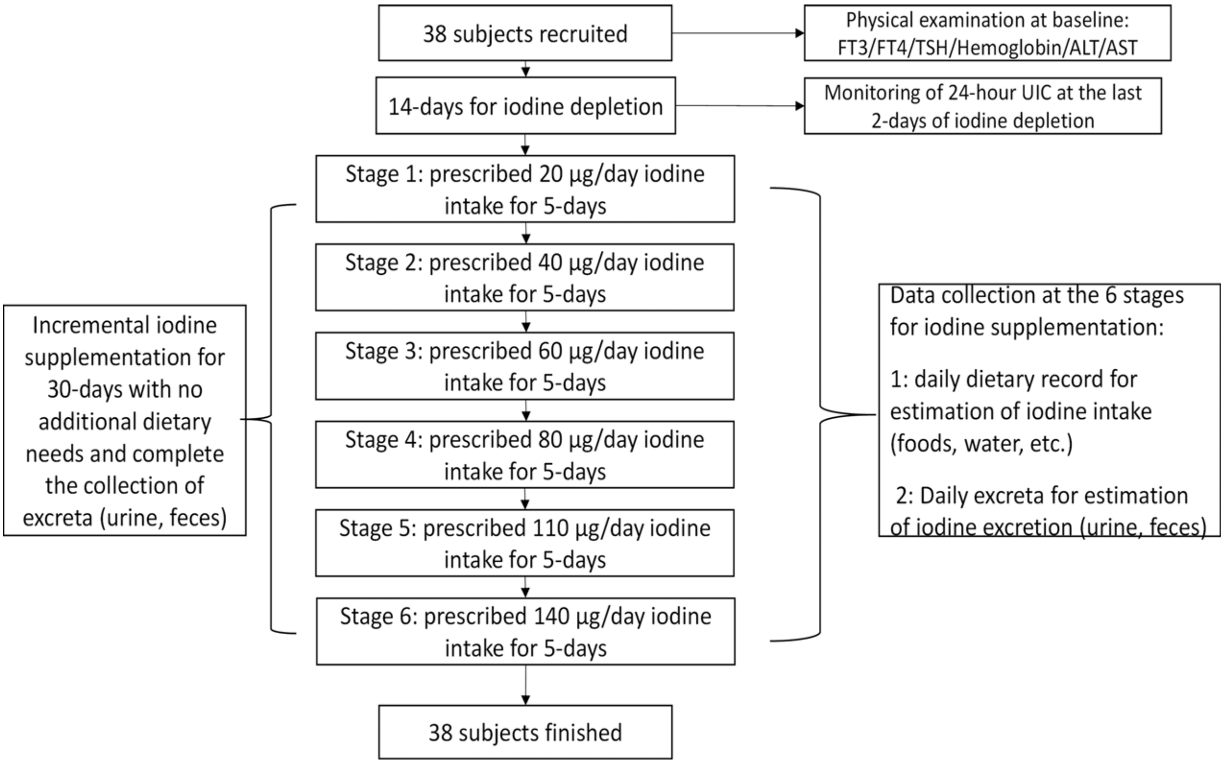

Fig. 1. Flow chart of iodine balance study in Chinese adult males.

Table 1. Typical daily meal plan

	Diet	Dietary component
Breakfast	Rice, steamed bread, oil-fried vegetables such as cabbage, spinach and pumpkin	Rice 100 g, flour 100 g, salad oil 5–10 g, green vegetables 100–150 g
Lunch	Rice, steamed bread, oil-fried vegetables such as cabbage, celery, green pepper, tomato and pork or chicken	Rice 100 g, flour 100 g, salad oil 15–20 g, vegetables 150–300 g, pork 100 g or chicken 100 g
Supper	Rice, steamed bread, oil-fried vegetables such as cabbage, celery, green pepper, tomato and pork or chicken	Rice 100 g, flour 100 g, salad oil 15 g, vegetable 150–300 g, pork 100 g or chicken 100 g
Fruit	Apple, banana, pear, peach	Apple 100–150 g, or banana 100 g, or pear 100–150 g, or peach 100–150 g

iodine contents in urine specimens, faecal samples from all six stages and foods were determined using inductively coupled plasma MS and the Sandell–Kolthoff method after acid wet washing[20]. The urinary creatinine level was measured by kinetic calorimetric assay[21]. The quality control samples were analysed in each assay. The recovery of measurement was between 92·3 and 106·7 %. The intra-day and inter-day precision for urinary indicators ranged from 2·1 % to 5·7 %.

Quality control

All exogenous sources of iodine were determined to eliminate unknown food sources of iodine or iodine-containing drugs. In addition, the excreta sample was deemed incomplete or invalid if any one of the following occurred: (1) the urinary creatinine concentration was < 0·1 mmol/kg per d, (2) the 24-h urine volume was < 500 ml and (3) no red pigmentation was observed in staged faeces.

Statistical analysis

All analyses were performed in the SAS 9.3 (SAS Institute) and R statistical software (version 3.5.1) using the nlme and ggplot 2 packages for data processing and statistical analyses. The Shapiro–Wilk test was used to evaluate the distribution of data, while the Mauchly's test was used to assess whether the assumption of sphericity was met or not. The differences in height, weight, urinary electrolytes excretion, alanine transaminase, aspartate aminotransferase, and serum thyroid-stimulating hormone, free triiodothyronine and free thyroxine were compared using ANOVA with Bonferroni correction or Kruskal–Wallis test for multiple comparisons. *P* value < 0·05 was considered significant.

The data on iodine intake and urinary and faecal iodine excretion per stage in each participant were provided. Iodine intake, iodine excretion and iodine retention were expressed in micrograms per day (μg/d) and in micrograms per kilogram

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of body weight per day (μg/kg per d) in order to obtain a clearer illustration. According to the iodine overflow hypothesis, the Δ iodine intake was calculated by subtracting the corresponding iodine intake at stage 1 of each participant from the daily iodine intake from stage 2 to stage 6; meanwhile, the Δ iodine excretion was calculated by subtracting the corresponding excretion at stage 1 from the iodine excretion from stage 2 to stage 6. Lastly, the Δ iodine retention was calculated by subtracting the Δ iodine excretion from the Δ iodine intake.

In this study, 1140 data points for iodine intake and iodine excretion were collected, while 1031 data points were originally retained through the data screening for the incomplete collection. Data on the Δ iodine intake and the Δ iodine excretion were further removed as outliers for triple standard difference method, leaving 985 data for statistical analysis. The association of the Δ iodine intake and the Δ iodine excretion was assessed using the mixed effects models (MEM) for micrograms per day and micrograms per kilogram of body weight per day, with the Δ iodine intake of the individuals as fixed factor and the participants as random factor compared with those used in previous literature[14]. The selection of predicted function was determined based on the Akaike information criterion and evaluated using goodness-of-fit plots. In addition, a linear regression function was built to determine the association between the Δ iodine intake and the Δ iodine excretion, as well as between the Δ iodine intake and the Δ iodine retention. The predicted Δ iodine excretion and predicted Δ iodine retention increment based on the actual Δ iodine intake of each participant were obtained. The association between measured and predicted values of the Δ iodine excretion and the Δ iodine retention was further evaluated using Pearson's correlation coefficient (*r*). The dynamic zero iodine balance (Δ iodine intake = Δ iodine excretion, Δ iodine retention = 0 μg/d) was obtained from the MEM of the Δ iodine intake compared with the Δ iodine retention per day or per kilogram of body weight per day, with the former used to estimate the proposed EAR. In addition, a 20 % variable coefficient (CV) of the EAR is more inclined to suggest the estimation of iodine RNI, rather than the 10 % CV if considering a relative variation in populations according to previous studies[22]. In this case, the current iodine RNI was calculated as equal to the EAR plus twice the CV (i.e. 1·4 times the EAR) to satisfy the requirement among the majority of individuals.

Results

Participants' characteristic

The baseline characteristics of all participants are shown in Table 2. In total, thirty-eight healthy male adults aged 19·1 (SD 0·6) years were enrolled and finished the modified iodine balance study. The mean 24-h urinary iodine concentration was 237·7 μg/l at baseline (Day_0), initially decreased to 30·9 μg/l at the Day_{start}, and then eventually increased to 88·8 μg/l at the Day_{end}. Significant differences were found in the 24-h urinary iodine concentration, 24-h urinary iodine excretion, alanine transaminase, aspartate aminotransferase, urea, creatinine, uric acid and thyroid-stimulating hormone ($P < 0·05$), but no significant differences were observed in other indicators, including weight, 24-h urine volume, Hb, free triiodothyronine and free thyroxine ($P > 0·05$).

Table 2. Baseline characteristics of thirty-eight Chinese adult males (Mean values and standard deviations)

	Day_0		Day_{start}		Day_{end}	
Variables	Mean	SD	Mean	SD	Mean	SD
Age (years)	19·1	0·6	19·1	0·6	19·1	0·6
Height (cm)	171·9	6·7	173·3	7·1	172·5	8·2
Weight (kg)	64·6	11·0	64·7	10·3	63·6	9·8
24-h UIC (μg/l)	237·7	67·5 ᵃ	30·9	13·4 ᵇ	88·8	35·8 ᶜ
Urine Volume (L)	1·0	0·4 ᵃ	1·8	0·6 ᵇ	1·7	0·8 ᵇ
24-h UIE (μg/day)	213·8	39·0 ᵃ	49·5	12·4 ᵇ	134·9	30·1 ᶜ
ALT (U/L)	12·5	6·3 ᵃ	17·8	8·1 ᵇ	17·6	7·9 ᵇ
AST (U/L)	16·2	3·5 ᵃ	19·0	4·6 ᵇ	19·2	3·7 ᵇ
Hb (g/L)	164·7	8·6	162·0	8·4	161·0	7·9
Urea (mmol/l)	4·8	1·1 ᵃ	4·4	0·8 ᵃ	5·7	0·9 ᵇ
Creatinine (μmol/L)	86·7	13·4 ᵃ	75·0	8·3 ᵇ	81·3	9·5 ᵃ
Uric acid (mmol/L)	442·2	74·6 ᵃ	378·5	57·1 ᵇ	350·5	51·1 ᵇ
TSH (uIU/ml)	2·4	0·7 ᵃ	1·4	0·4 ᵇ	1·9	0·7 ᶜ
FT4 (pmol/l)	18·5	2·1	18·6	2·2	18·3	1·7
FT3 (pmol/l)	5·6	0·5	6·0	0·4	5·9	0·3

Day_0, means the day at baseline; Day_{start} and Day_{end}, mean the start and the end day for iodine supplementation; 24-h UIC, 24-h urinary iodine concentration; 24-h UIE, 24-h urinary iodine excretion; ALT, alanine transaminase; AST, aspartate aminotransferase; TSH, thyroid-stimulating hormone; FT4, free thyroxine; FT3, free triiodothyronine and other values are expressed as mean values and standard deviations. Differences are examined by repeated-measures ANOVA by use of Bonferroni correction for multiple comparisons. Values with different superscript letters (a, b, c) are significantly different ($P < 0·05$).

Iodine intake and excretion

Iodine status of participants was assessed using WHO/UNICEF/ICCIDD references ranges[23], as shown in Table 3; the majority of participants had more than adequate iodine levels at baseline, while the urinary iodine levels were distinctly changed to induce iodine depletion. The median 24-h urinary iodine concentration immediately decreased from 256·1–205·5 μg/l to 28·7–28·8 μg/l, whilst the median 24-h urinary iodine excretion decreased from 197·0–198·6 μg/d to 47·7–50·0 μg/d at the end of iodine depletion.

The dynamic changes in iodine balance are shown in Table 4. The iodine excretion and iodine retention increased with the iodine intake increased; the Δ iodine excretion and the Δ iodine retention also increased with iodine supplementation. Significant differences were found in the iodine intake, iodine excretion, iodine retention, and the Δ iodine intake, the Δ iodine excretion and the Δ iodine retention among all stages ($P < 0·001$ for all comparisons). In this study, the dose–response relationship between the Δ iodine intake and the Δ iodine excretion was investigated based on the MEM estimate each day, as well as that between the Δ iodine intake and the Δ iodine retention according to the data distribution. We fitted the linear function for the Δ iodine excretion or the Δ iodine retention along with the Δ iodine intake per kilogram of body weight to intuitively understand the correlation; these predicted formulas were expressed as follows:

Table 3. Comparison of 24-h UIC and 24-h UIE at baseline and last 2 d of iodine depletion for thirty-eight Chinese adult males
(Median values and inter-quartile ranges)

	Urinary iodine at baseline				Last 2-d data of iodine depletion			
	Day 1		Day 2		Day 1		Day 2	
Variables*	Median (M$_0$)	Interquartile (P$_{25}$, P$_{75}$)	Median (M$_0$)	Interquartile (P$_{25}$, P$_{75}$)	Median (M$_0$)	Interquartile (P$_{25}$, P$_{75}$)	Median (M$_0$)	Interquartile (P$_{25}$, P$_{75}$)
24-h UIC, μg/l	256·1	201·5, 295·2	205·5	158·8, 265·5	28·7	21·5, 41·8	28·8	22·2, 40·5
24-h UIE, μg/d	197·0	151·0, 277·3	198·6	155·4, 225·1	47·7	41·6, 58·6	50·0	41·2, 57·0

* Values are expressed as median (M$_0$) and interquartile (P$_{25}$, P$_{75}$); 24-h UIC, 24-h urinary iodine concentration; 24-h UIE, 24-h urinary iodine excretion.

Table 4. Iodine intake, excretion, retention and Δ iodine intake, Δ excretion and Δ retention for thirty-eight Chinese adult males among the six stages of iodine supplementation*
(Mean values and standard deviations)

	Stage 1		Stage 2		Stage 3		Stage 4		Stage 5		Stage 6	
Variables	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Observed (μg/d)												
Iodine intake	16·3	6·2^{a}	28·7	7·4^{b}	55·3	7·3^{c}	78·8	5·3^{d}	108·6	9·3^{e}	134·2	9·1^{f}
Iodine excretion	54·3	19·1^{a}	65·7	21·2^{a}	84·3	20·1^{b}	107·0	20·1^{c}	126·9	25·0^{d}	154·5	30·6^{e}
Iodine retention	–38·0	21·7^{a}	–37·0	24·2^{ab}	–29·0	20·6^{bc}	–28·2	21·5^{bc}	–18·4	26·8^{d}	–20·3	29·7^{d}
Δ Observed (μg/d)												
Δ Iodine intake	——		11·8	4·7^{a}	37·6	7·4^{b}	62·5	5·2^{c}	92·2	6·9^{d}	118·1	8·3^{e}
Δ Iodine excretion	——		18·1	14·8^{a}	35·2	18·5^{b}	53·4	20·2^{c}	72·7	26·7^{d}	99·8	29·3^{e}
Δ Iodine retention	——		–6·3	16·3^{a}	2·4	20·3^{ab}	9·1	21·7^{b}	19·5	27·7^{c}	18·3	30·0^{c}
Δ Predicted† (μg/d)												
Iodine intake†	——		n. a.		n. a.		n. a.		n. a.		n. a.	
Iodine excretion†	——		17·2	4·1^{a}	36·0	5·9^{b}	54·3	4·5^{c}	76·2	5·6^{d}	95·1	6·5^{e}
Iodine retention†	——		–5·3	2·9^{a}	1·7	3·5^{ab}	8·2	3·2^{bc}	16·0	3·3^{cd}	22·8	3·5^{d}
Observed (μg/kg per d)												
Iodine intake	0·26	0·10^{a}	0·46	0·13^{b}	0·87	0·17^{c}	1·25	0·20^{d}	1·73	0·29^{e}	2·14	0·35^{f}
Iodine excretion	0·86	0·31^{a}	1·06	0·37^{b}	1·33	0·36^{c}	1·70	0·40^{d}	2·02	0·46^{e}	2·47	0·61^{f}
Iodine retention	–0·60	0·35^{a}	–0·60	0·40^{ab}	–0·45	0·33^{bc}	–0·45	0·35^{bc}	–0·29	0·43^{d}	–0·32	0·48^{d}
Δ Observed (μg/kg per d)												
Δ Iodine intake	——		0·19	0·08^{a}	0·59	0·14^{b}	1·00	0·18^{c}	1·47	0·25^{d}	1·89	0·33^{e}
Δ Iodine excretion	——		0·29	0·25^{a}	0·56	0·31^{b}	0·85	0·35^{c}	1·16	0·47^{d}	1·60	0·55^{e}
Δ Iodine retention	——		–0·10	0·27^{a}	0·03	0·32^{ab}	0·14	0·34^{b}	0·31	0·46^{c}	0·29	0·49^{c}
Δ Predicted‡ (μg/kg per d)												
Iodine intake‡	——		n. a.		n. a.		n. a.		n. a.		n. a.	
Iodine excretion‡	——		0·24	0·07^{a}	0·53	0·11^{b}	0·83	0·13^{c}	1·18	0·19^{d}	1·49	0·24^{e}
Iodine retention‡	——		–0·02	0·05^{a}	–0·09	0·06^{ab}	0·20	0·07^{bc}	0·32	0·08^{cd}	0·43	0·10^{d}

* Values are expressed as mean values and standard deviations. Difference of iodine intake and excretion is evaluated using repeated-measures ANOVA with Bonferroni correlation. Values with different superscript letters (a, b, c, d, e) are significantly different ($P < 0·05$); n. a., not applicable.

† Predicted excretions are calculated from observed intake by use of MEM: Δ iodine excretion (μg/d) = 0·736 × Δ iodine intake (μg/d) + 8·359; predicted Δ iodine retention is calculated from observed Δ iodine intake by use of MEM: Δ iodine retention (μg/d) = 0·262 × Δ iodine intake (μg/d) – 8·216.

‡ Predicted Δ iodine excretions is calculated from observed Δ iodine intake by use of MEM: Δ iodine excretion (μg/kg per d) = 0·738 × Δ iodine intake (μg/kg per d) + 0·134; predicted Δ iodine retention is calculated from observed Δ iodine intake by use of MEM: Δ iodine retention (μg/kg per d) = 0·259 × Δ iodine intake (μg/kg per d) – 0·129.

Δ iodine excretion (μg/d) = 0·736 × Δ iodine intake (μg/d) + 8·359

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Δ iodine excretion (μg/kg per d) = 0·738 × Δ iodine intake (μg/kg per d) + 0·134

Δ iodine retention (μg/kg per d) = 0·259 × Δ iodine intake (μg/kg per d) – 0·129

The graphical demonstration showed that the dose–response association of the Δ iodine excretion and the Δ iodine intake obtained from the MEM agreed well with the measured data, as well as the Δ iodine retention and the Δ iodine intake. As shown in Figs. 2 and 3, the locally weighted scatter plot smoothing lines were comparable with the predicted function obtained from the MEM analysis. Furthermore, a distinct correlation was observed between the measured and predicted data for iodine excretion ($r = 0·749$, $P = 0·0001$, for μg/d) and iodine retention ($r = 0·392$, $P = 0·0001$, for μg/d) and that between iodine excretion ($r = 0·766$, $P = 0·0001$, for μg/kg per d) and iodine retention ($r = 0·387$, $P = 0·0001$, for μg/kg per d). In this study, the dynamic zero iodine balance (Δ iodine intake = Δ iodine excretion, Δ iodine retention = 0 μg/d) was obtained using the MEM based on the incremental change and achieved at a transient Δ iodine intake of 31·7 μg/d. Therefore, an iodine intake of 48·0 μg/d was precisely suitable when the dynamic zero iodine balance was reached in the body. As shown in Figs. 2 and 3, the use of a linear regression function also yielded a similar estimation of the Δ

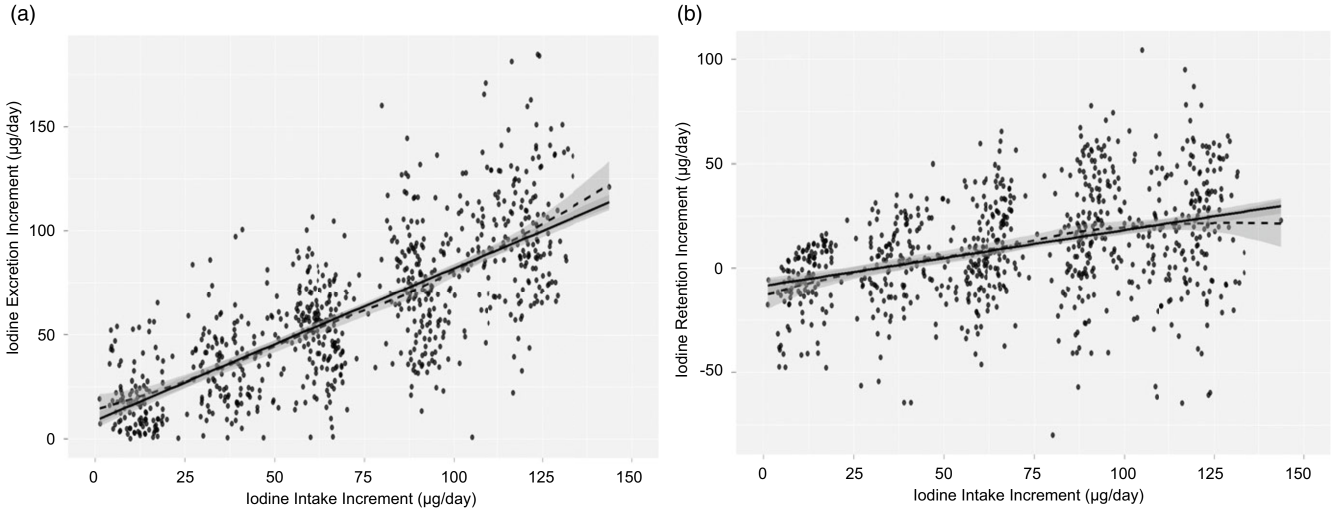

Fig. 2. Dose–response relationship of the increment (Δ) of iodine intake and the Δ iodine excretion (a), together with the Δ iodine retention (b) by the mixed effects model (dashed) and linear regression function (solid) for iodine supplementation.

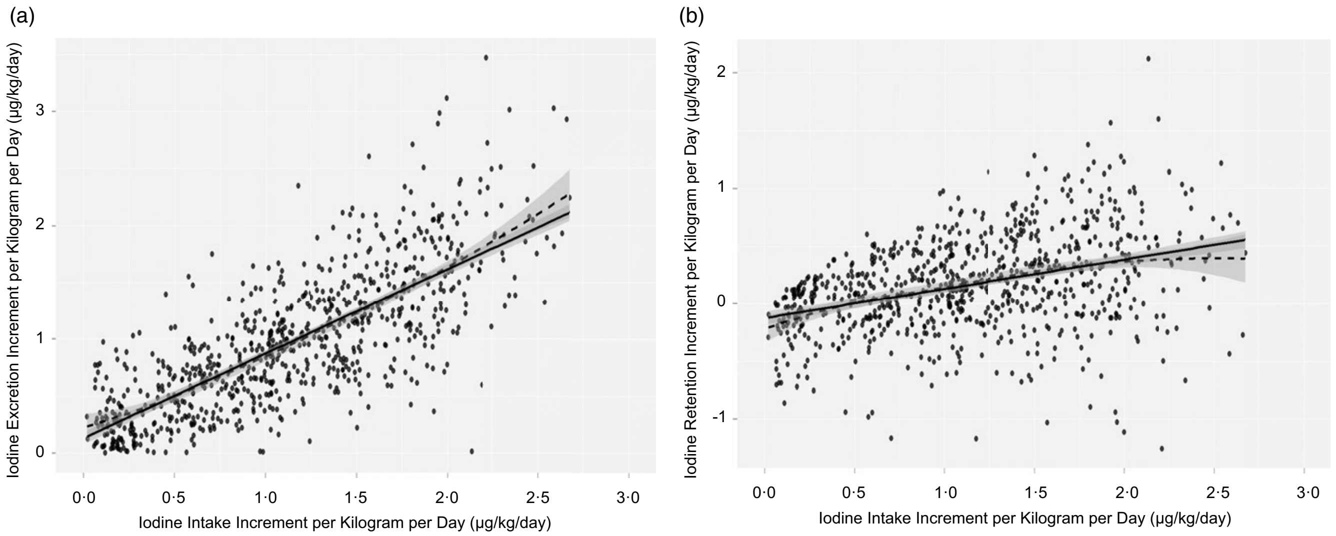

Fig. 3. Dose–response relationship of the increment (Δ) of iodine intake per kilogram of body weight and the Δ iodine excretion per kilogram of body weight (a), together with the Δ iodine retention per kilogram of body weight (b) by the mixed effects model (dashed) and linear regression function (solid) for iodine supplementation.

iodine intake at null balance as the MEM but did not change the data interpretation for the association.

Discussion

This was a modified iodine balance study, which was performed on a group of Chinese adult males according to our suggested iodine overflow hypothesis. In this study, the dose–response functions were consecutively established between the Δ iodine intake and the Δ iodine excretion using the MEM and linear regression analysis, as well as between the Δ iodine intake and the Δ iodine retention. Through these formulas derived from the available data, the estimates of dietary iodine intake were considered as appropriate for 48·0 μg/d of EAR and 67·2 μg/d of RNI. These values further corresponded to daily iodine intakes of 0·74 μg/kg per d and 1·04 μg/kg per d.

Given that the enforcement of Universal Salt Iodization policy in China over 20 years, it had probably induced the iodine over-saturation in the most individuals[24,25], particularly those living in areas whose drinking water contains high iodine levels[26]. Furthermore, daily consumption of salt and iodine is usually higher in male than that in female. In our study, the majority of participants were more than adequate iodine levels at baseline; this finding is slightly higher as compared with the results of a national survey, which reported that nearly 42 % of the population had more than adequate and excess iodine intake[7]. In this case, the traditional balance study could no longer be used, as previously mentioned[17,18]. With regard to the dilemma, our iodine overflow hypothesis could accurately simulate the iodine dynamic change *in vivo*; moreover, iodine depletion was only required within a short period of time in those individuals with excess iodine exposure. Noteworthy, after iodine supplementation, the Δ iodine excretion gradually increased with the Δ iodine intake increased until the iodine 'overflow' threshold was reached, following the excretion of excess iodine.

In line with previous studies[15,27], negative iodine balance without exception occurred in the participants following a low iodine supplementation (from 16·3 to 134·2 μg/d). In our opinion, it is only a short-term adaptation to the changes of iodine intake levels rather than a long-term change in the body, considering that the thyroid hormone levels remained normal if the absence of iodine recycling and depletion of iodine storage in the thyroid for over 3 months. This might be attributed to the excessive amounts of iodine administered previously or the delayed response in iodine insufficiency. By contrast, a recent iodine balance study reported that there was no negative iodine balance in Chinese women[28]. It was believed to be due to the high iodine intake (194·8–487·1 μg/d), that is, the administrative iodine intake far exceeds its metabolic absorption and redundant iodine be then excreted.

In our study, the proposed EAR was 48·0 μg/d, and the RNI was 67·2 μg/d based on an EAR of 1·4 times in view of the characteristics and complexity of the balance study design in the population[22]. These estimates of iodine requirement are relatively consistent with those of previous studies reported[18,27,29,30], but significantly lower than the recommended iodine intake of adults, based on the new EAR (85 μg/d) and RNI (120 μg/d)[31]. In addition, the USA and Canada used an iodine intake of 90 μg/d as a safe EAR limit for adults[29], while Australia and New Zealand suggested an EAR of 100 μg/d and RNI of 150 μg/d[32,33]. The European Scientific Committee for Food recommended 100 and 130 μg/d[34], while Chinese women suggested 110 and 155 μg/d as the EAR and RNI of iodine, respectively[28]. The values reported in the current study are almost one-half of the current recommended iodine intakes.

When interpreting our findings, some advantages and limitations should be noted. First, the iodine contents in foods and excreta (urine and faeces) were extremely low to measure the dynamic change in iodine intake and the amounts of urine and faeces excreted were smaller during the depletion and supplementation stages, resulting in the uncertainty of the actual iodine contents. The application of inductively coupled plasma MS has resolved the difficulty in analysing low iodine levels, and the obtained results were relatively reliable. Second, the daily iodine intake and excretion are well controlled throughout the study, although it is fairly low and easily disrupted by exogenous factors. However, the amount of iodine excreted might be underestimated as the iodine loss from sweat or other sources was not measured. Third, the current study was only conducted on a group of Chinese adult males, so the generalisability of the results might have some practical difficulties in the general population. Thus, many factors should be taken into account in the following studies, such as sex or age or geographical location.

In summary, this modified iodine balance study was conducted in Chinese adult males using our suggested iodine overflow hypothesis and provided a reliable experimental data on the iodine metabolic balance of individuals with superfluous iodine status. The findings of our study indicated that rough half of the current dietary iodine intake recommendation is enough as an iodine requirement for Chinese male adults, which would be beneficial for the revision of iodine dietary reference intakes in China.

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All authors declare that they have no competing financial interests.

References

1. Zimmermann MB (2011) The role of iodine in human growth and development. *Semin Cell Dev Biol* **22**, 645–652.
2. Lazarus JH (2015) The importance of iodine in public health. *Environ Geochem Health* **37**, 605–618.
3. Zimmermann MB (2009) Iodine deficiency. *Endocr Rev* **30**, 376–408.
4. Patriota ESO, Lima ICC, Nilson EAF, *et al.* (2021) Prevalence of insufficient iodine intake in pregnancy worldwide: a systematic review and meta-analysis. *Eur J Clin Nutr* **76**, 703–715.
5. Pearce EN, Lazarus JH, Moreno-Reyes R, *et al.* (2016) Consequences of iodine deficiency and excess in pregnant women: an overview of current knowns and unknowns. *Am J Clin Nutr* **104**, 918S–923S.
6. Liu L, Liu P, Lin Q, *et al.* (2021) Iodine nutrition status of women after 10 years of Lipiodol supplementation: a cross-sectional study in Xinjiang, China. *Br J Nutr* **126**, 9–21.
7. Li Y, Teng D, Ba J, *et al.* (2020) Efficacy and safety of long-term universal salt iodization on thyroid disorders: epidemiological evidence from 31 Provinces of Mainland China. *Thyroid* **30**, 568–579.
8. Du Y, Gao Y, Meng F, *et al.* (2014) Iodine deficiency and excess coexist in China and induce thyroid dysfunction and disease: a cross-sectional study. *PLoS One* **9**, e111937.
9. Farebrother J, Zimmermann MB & Andersson M (2019) Excess iodine intake: sources, assessment, and effects on thyroid function. *Ann N Y Acad Sci* **1446**, 44–65.
10. Teng W, Shan Z, Teng X, *et al.* (2006) Effect of iodine intake on thyroid diseases in China. *N Engl J Med* **354**, 2783–2793.
11. Song J, Zou SR, Guo CY, *et al.* (2016) Prevalence of thyroid nodules and its relationship with iodine status in shanghai: a population-based study. *Biomed Environ Sci* **29**, 398–407.
12. Karwowska P & Breda J (2017) The role of the World Health Organization in eliminating iodine deficiency worldwide. *Recent Pat Endocr Metab Immune Drug Discov* **10**, 138–142.

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13. Costa A, Bacci R, Campagnoli C, *et al.* (1969) Iodine balance studies in pregnancy. *Folia Endocrinol* **22**, 364–372.
14. Dold S, Zimmermann MB, Baumgartner J, *et al.* (2016) A dose-response crossover iodine balance study to determine iodine requirements in early infancy. *Am J Clin Nutr* **104**, 620–628.
15. Vought RL & London WT (1967) Iodine intake, excretion and thyroidal accumulation in healthy subjects. *J Clin Endocrinol Metab* **27**, 913–919.
16. Hays MT (2001) Estimation of total body iodine content in normal young men. *Thyroid* **11**, 671–675.
17. Wang J, Zhang H, Mao D, *et al.* (2022) Exploration of the lower threshold of iodine intake in Southern Chinese young adults based on 'overflow theory' in an iodine balance study. *Nutr J* **21**, 35.
18. Yang L, Wang J, Yang J, *et al.* (2020) An iodine balance study to explore the recommended nutrient intake of iodine in Chinese young adults. *Br J Nutr* **124**, 1156–1165.
19. World Medical A (2013) World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* **310**, 2191–2194.
20. Machado A, Lima L, Mesquita RBR, *et al.* (2017) Improvement of the Sandell-Kolthoff reaction method (ammonium persulfate digestion) for the determination of iodine in urine samples. *Clin Chem Lab Med* **55**, e206–e208.
21. Chromy V, Rozkosna K & Sedlak P (2008) Determination of serum creatinine by Jaffe method and how to calibrate to eliminate matrix interference problems. *Clin Chem Lab Med* **46**, 1127–1133.
22. Medicine Io (2001) *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Washington, DC: National Academies Press (US).
23. WHO/UNICEF/ICCIDD (2007) *Assessment of Iodine Deficiency Disorders and Monitoring their Elimination: a Guide for Programme Managers*, 3rd ed. Geneva: WHO.
24. Liu T, Li Y, Teng D, *et al.* (2021) The characteristics of iodine nutrition status in China after 20 years of universal salt iodization: an epidemiology study covering 31 provinces. *Thyroid* **31**, 1858–1867.
25. Shan Z, Chen L, Lian X, *et al.* (2016) Iodine status and prevalence of thyroid disorders after introduction of mandatory universal salt iodization for 16 years in China: a cross-sectional study in 10 cities. *Thyroid* **26**, 1125–1130.
26. Yao J, Zhang W, Wang J, *et al.* (2022) The status of iodine nutrition after removing iodized salt in high water iodine regions: a cross-sectional study in China. *Biol Trace Elem Res* **200**, 1020–1031.
27. Malvaux P, Beckers C & De Visscher M (1969) Iodine balance studies in nongoitrous children and in adolescents on low iodine intake. *J Clin Endocrinol Metab* **29**, 79–84.
28. Tan L, Tian X, Wang W, *et al.* (2019) Exploration of the appropriate recommended nutrient intake of iodine in healthy Chinese women: an iodine balance experiment. *Br J Nutr* **121**, 519–528.
29. Harrison MT (1968) Iodine balance in man. *Postgrad Med J* **44**, 69–71.
30. Ingenbleek Y & Malvaux P (1974) Iodine balance studies in protein-calorie malnutrition. *Arch Dis Child* **49**, 305–309.
31. Society CN (2013) *Chinese DRIs Handbook*. Beijing: Standards Press of China.
32. Thomson CD (2004) Selenium and iodine intakes and status in New Zealand and Australia. *Br J Nutr* **91**, 661–672.
33. Mackerras DE & Eastman CJ (2012) Estimating the iodine supplementation level to recommend for pregnant and breastfeeding women in Australia. *Med J Aust* **197**, 238–242.
34. Zimmermann M & Delange F (2004) Iodine supplementation of pregnant women in Europe: a review and recommendations. *Eur J Clin Nutr* **58**, 979–984.