Propositions

I

Iodine concentrations above 300 μg/L in drinking water or 800 μg/L in the urine of adults represent a public health risk (this thesis).

II

Exposure to high iodine intakes is related to a small but significant decline in IQ of schoolchildren (this thesis).

III

A change in the source of drinking water can not only control cholera (John Snow, 1813- 1858), but also reduce thyroid size and partially normalize thyroid function (this thesis).

IV

Close monitoring of iodine concentration in salt and in drinking water is essential for elimination of adverse effects of both iodine deficiency and iodine excess.

V

Epidemiology is the study of counting and comparing.

VI

To learn without thinking is useless, to think without learning is dangerous (Confucius, 551-479 BC).

VII

Knowing is not enough; we must apply. Willingness is not enough; we must do (Goethe, 1749-1832).

VIII

The denser the population, the more bikes.

Propositions pertaining to the thesis of Jinkou Zhao entitled "Iodine deficiency and iodine excess in Jiangsu Province, China".

Wageningen University, The Netherlands, 4 September 2001.

Iodine Deficiency and Iodine Excess in Jiangsu Province, China

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Iodine Deficiency and Iodine Excess in Jiangsu Province, China

Jinkou Zhao

Proefschrift

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To my mother:
Wang Qiaoying
and my motherland:
The People's Republic of China

Abstract

Iodine deficiency and iodine excess in Jiangsu Province, China

PhD thesis by Jinkou Zhao, Division of Human Nutrition and Epidemiology, Wageningen University, The Netherlands, 4 September, 2001.

Endemic goiter can be caused both by iodine deficiency and iodine excess. Iodine deficiency was a public health problem in Jiangsu Province, China and has been eliminated through salt iodization in a majority of counties in Jiangsu. In Feng, Pei and Tongshan Counties in Xuzhou Municipality, endemic goiter has been found to be associated with iodine excess. This thesis describes the relationship of iodine intakes ranging from normal to excessive with thyroid size, thyroid function, goiter prevalence, intellectual development, physical development and hearing capacity, and the efficacy and effectiveness of iodine intervention programs in schoolchildren.

An ecological relationship of iodine intakes ranging from normal to excessive with an enlarged thyroid size, an increased prevalence of goiter and a perturbed thyroid function has been found in three counties in Xuzhou Municipality. A negative relationship of iodine intake from normal to excessive with intellectual quotient (IQ) in schoolchildren aged >11 y indicates that excessive iodine intake is associated with a decline in IQ. This was supported by the results of a meta-analysis of 16 studies where iodine excess was found to be related to a small but significant deficit in intellectual attainment of schoolchildren. Reduction of iodine intake from excessive to normal is accompanied by a reduction in thyroid size, a decreased urinary iodine concentration and a partial normalization of thyroid function. It is now estimated that iodine excess is a public health risk for nearly 16 million people in 92 counties of 10 provinces in China.

Comparison of thyroid volumes collected from schoolchildren in the US and in Bangladesh with those in Europe found that the new WHO reference for the upper limit of normal thyroid volume is not applicable worldwide. A randomized trial in an iodine deficient area showed that it takes 12 months for enlarged thyroid glands to reduce to normal if iodine supply is consistently adequate. This period is longer if the iodine supply fluctuates. An evaluation of the effectiveness of iodine intervention programs in 9 counties of Jiangsu Province indicated that iodine deficiency has been eliminated in these counties.

Based on the evidence from the work described in this thesis, a maximum allowable iodine concentration can be set at 300 μg/L in drinking water or at 800 μg/L in urine of adults. Iodine concentrations above these levels should be regarded as a public health risk.

Contents

Chapter I

General introduction

Iodine is essential for human health as it is a constituent of thyroid hormones, which play an important role in physical and mental development. Like other trace elements, iodine intake should be within a normal range, otherwise either deficiency or excess will cause health problems. The adverse consequences of iodine deficiency on growth and development are collectively known as iodine deficiency disorders (IDD; Hetzel, 1983). Excessive iodine intake may also induce goiter in certain subjects and is associated with an increase in hypothyroidism, hyperthyroidism, and other thyroid abnormalities (Suzuki, 1980; WHO, 1994).

Metabolism of iodine and daily requirements

Through geological time, the trace element iodine has been leached from the soil and carried into the sea (Hetzel & Maberly, 1986). Generally, drinking water is a minor source of dietary iodine with most dietary iodine coming from food. The iodine content of foods and of total diets differs appreciably and is influenced by geochemical, soil and cultural conditions, which modify the iodine uptake of crops and animals.

To ensure an adequate supply of thyroid hormones, the thyroid must trap about 60 μg iodine per day (Underwood, 1977). Most of the iodine in the human body enters the circulation as iodide, where it becomes part of the iodine pool, which comprises 15-20 mg iodine (Underwood, 1981). About 70-80% of iodine in healthy adult humans is in the thyroid gland, which weighs only 15-25 g.

The daily requirement of iodine is equal to the amount of hormone released by the thyroid gland and subsequently degraded on a daily basis. This is sufficient to maintain normal thyroid function essential for normal growth and development. The recommended iodine intake is 100-150 μg/day (WHO/UNICEF /ICCIDD, 1997). In the presence of goitrogens in the diet, intake needs to be increased to 200-300 μg/day. Iodine in excess of requirements is mostly excreted by the kidneys. Thus the level of excretion correlates well with the level of intake so that urinary iodine excretion can be used to assess the level of iodine intake (Vought et al. 1963). Dietary Reference Intakes (DRIs) of iodine differ among life stage groups. The Food and Nutrition Board of the Institute of Medicine of the National Academy Sciences in the United States recommended DRIs, including estimated average requirement (EAR) and recommended dietary allowance (RDA) as shown in Table 1 (Institute of Medicine, 2000).

The safe upper limit of iodine intake is less well established than iodine requirements. Suggested upper limits range from 100 to 2000 μg/day. Iodine intakes of less than 100 μg/day pose no risk for patients with autonomous thyroid tissue

Table 1. Criteria and dietary reference intake values and tolerable upper intake levels for iodine by life stage group (Institute of Medicine, 2000)

Life stage group	Criterion	Intake (µg/day)					
		EAR [a]		RDA [b]		AI [c]	UL [d]
		Male	Female	Male	Female		
0-6 months	Iodine content of human milk					110	ND [e]
7-12 months	Extrapolation from AI, 0-6 months					130	ND
1-3 years	Balance data on children	65	65	90	90		200
4-8 years	Balance data on children	65	65	90	90		300
9-13 years	Extrapolation from EAR, 19-50 years	73	73	120	120		600
14-18 years	Extrapolation from EAR, 19-50 years	95	95	150	150		900
19-50 years	Iodine turnover	95	95	150	150		1100
> 50 years	Extrapolation of iodine turnover studies, 19-30 years	95	95	150	150		1100
Pregnancy							
≤18 years	Balance data during pregnancy		160		220		900
19-50 years	Balance data during pregnancy		160		220		1100
Lactation							
≤18 years	EAR, 14-18 years plus average iodine content of human milk		209		290		900
19-50 years	EAR, 19-50 years plus average iodine content of human milk		209		290		1100

[a] EAR = Estimated Average Requirement. The intake that meets the estimated iodine needs of half of the individuals in a group.

[b] RDA = Recommended Dietary Allowance. The intake that meets the iodine need of almost all (97-98%) of individuals in a group.

[c] AI = Adequate Intake. The observed average or experimentally determined intake by a defined population or subgroup that appears to sustain a defined nutritional status, such as growth rate, normal circulating iodine values, or the other functional indicators of health. AI is used if sufficient scientific evidence is not available to derive an EAR. For healthy infants receiving human milk, AI is the mean intake. The AI is not equivalent to an RDA.

[d] UL = Tolerable Upper Intake Level. The highest level of daily iodine intake that is likely to pose no risk of adverse health effects to almost all dividuals in the general population. As intake increases above the UL, the risk of adverse effects increases. Unless specified otherwise, the UL represents total iodine intake from food, water and supplements.

[e] ND = Not determinable due to lack of data of adverse effects in this age group and concern about lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

caused by previous deficiency (Bourdoux et al. 1978). For such subjects the critical iodine intake probably lies between 100-200 μg/day (Joseph, 1980). The iodization of bread in Tasmania resulted in thyrotoxicosis for some individuals at levels of iodine intake of about 200 μg/day (Stuart et al. 1971). Iodized bread in the Netherlands contributed an additional 120-160 μg of iodine per day and increased the incidence of thyrotoxicosis (Stanbury, et al. 1998). A Spring-Summer peak of thyrotoxicosis attributed to higher iodine levels in milk has been reported from England, corresponding to iodine intakes of 236 μg/day in women and 306 μg/day in men (Nelson & Philips, 1985). Patients with endemic iodide goiter arising from iodine intakes of several milligrams per day are, generally speaking, clinically and biochemically euthyroid (Suzuki, 1980). Wolff (1969) suggested that intakes > 2000 μg of iodine/day in humans should be regarded as excessive or potentially harmful. The Tolerable Upper Intake Levels (Uls) recommended recently by the Institute of Medicine (2000) for different life stages are shown in Table 1.

Iodine excess

General description

Most people are very tolerant to excessive iodine intake from food (Pennington, 1990). Certain subgroups, such as those with autoimmune thyroid disease and iodine deficiency, respond adversely to intakes considered safe for the general population. For the general population, high iodine intakes from food, water or supplements have been associated with thyroiditis, goiter, hypothyroidism, hyperthyroidism, sensitivity reactions, thyroid papillary cancer, and acute responses in some individuals (Table 2).

Table 2 Consequences of iodine excess

Populations groups	Effects
All	Acute effects (iodine poisoning), iodermia
Fetal to infantile	Goiter
Schoolchildren	Goiter, hypothyroidism, elevated TSH, possible impaired cognitive development, hyperthyroidism
Adults	Goiter, hyperthyroidism, hypothyroidism, thyroid papillary cancer
Those with autoimmune thyroid disease	Hyperthyroidism, hypothyroidism, lymphocytic thyroiditis, positive antibodies

There is no generally accepted definition of iodine excess. Suzuki (1980) once defined iodine excess as that resulting from intakes exceeding the requirements for normal thyroid hormone synthesis. Iodine excess is relative. At the population level,

whether or not iodine excess occurs depends on the usual or baseline iodine level. Thus, in severe iodine deficient areas, a small increase in iodine intake may cause health problems while in populations with very high iodine intakes, no overt adverse health effects may be observed.

Iodine toxicity has been studied extensively in laboratory animals such as poultry, pigs and cattle, and in human being. Although results and conclusions are controversial, Wolff (1969) has defined four degrees of iodine excess in humans, as follows:

a. A relative modest excess, promoting temporary increases in the absolute uptake of iodine by the thyroid and the formation of organic iodine, but without inhibiting the capacity to release iodine in response to physiological demand.
b. A large excess, which can inhibit iodine release from the thyrotoxic human thyroid or from thyroids in which iodine release has been accelerated by an increased concentration of TSH.
c. A slightly greater intake, which inhibits organic iodine formation and which probably causes iodide goiter (the so-called Wolff-Chaikoff effect).
d. Very high levels of iodine, which saturate the active transport mechanism for this ion. The acute pharmacological effects of iodine can usually be demonstrated before saturation becomes significant.

Normal diets composed of natural foods are unlikely to supply very high levels of iodine and the most would supply < 1000 μg of iodine/day. Exceptions occur when diets are exceptionally high in marine fish or seaweed, or where foods are contaminated with iodine from adventitious sources, or where drinking water is highly rich in iodine.

Epidemiology of iodine excess

Iodine-induced hyperthyroidism (IIH): Administration of iodine in almost any chemical form may induce an episode of IIH (Stanbury et al. 1998). IIH was first reported in Tasmania in the 1960s when the iodine content in bread increased (Steward et al. 1971; Vidor et al. 1973). From 1964 to 1967, a sharp increase in the incidence of hyperthyroidism was observed. This increased incidence subsided afterwards, and completely disappeared in 1975 (Marins et al. 1989). It affected only people aged > 40 years. Similar studies in South America (Guatemala and Brazil) and Europe (England and The Netherlands) reported small increases of IIH in older people in the later 1950s after the introduction of iodized salt or iodized bread (Stanbury et al. 1998). Recently, a multi-center study in Africa found that there has been an increase in the number of adults affected by symptomatic and asymptomatic hyperthyroidism attending health care facilities during the past few years, shortly following the introduction of iodized salt, some of which were over-iodized in order

to compensate for possible losses during storage and food preparation (WHO/UNICEF/ICCIDD, 1997).

Based on studies up until now, it is generally accepted that independent of the actual iodine intake, IIH can occur at iodine intakes necessary for physiological thyroid function, but may not occur at iodine intakes 100 times normal. Thus, there is no strict correlation between urinary iodine concentration and the incidence of IIH. IIH is usually found in previously iodine deficient or sufficient areas (Stanbury et al. 1998). It occurs when subjects are exposed to increased iodine intake, usually resulting from an iodine supplemental program for the control of iodine deficiency. It would therefore seem to be an inevitable consequence of iodine supplemental programs.

Iodine excess caused by medications and water purification: Medications and purifying tablets used to purify (sterilize) water which contain large quantities of iodine may increase iodine levels in the human body shortly after administration, and cause transient thyroid abnormalities. Such cases are sporadic (Suzuki, 1980; Wolff, 1969). Under certain circumstances, thyroid abnormalities may become endemic, even epidemic, when these drugs or water-purifying agents were applied to a population on a large scale. Thyroid abnormalities related to iodine excess from water purification units were reported among Peace Corps volunteers in Niger, West Africa (Khan et al. 1998). Of 144 volunteers, 66 (46%) had enlarged thyroids (goiter). Of 96 volunteers in whom thyroid function was examined, 33 (34%) had thyroid dysfunction: both hypothyroidism (serum TSH concentration $\geq$ 4.2 mU/L, n = 29) and hyperthyroidism (serum TSH concentration $\leq$ 0.4 mU/L, n = 4). The mean concentration of iodine in drinking water was 10 mg/L. Because of the hot arid environment, most Peace Corps volunteers reported consuming at least 5 L of water daily, which led to an intake of at least 50 mg iodine per day through the drinking water. This is over 330 times the recommended dietary allowance of 150 µg iodine and led to mean urinary iodine concentration of 11 mg/L which is extremely high.

Iodine excess originating from iodine-rich drinking water: Iodine-induced goiter has been reported from many areas in China where average water iodine concentrations were > 300 µg/L or the median urinary iodine concentrations were > 800 µg/L. Goiter rates were all above 10% and thyroid functions were generally normal (Zhao et al. 2000).

Iodine excess originating from iodine-rich food: Seafood is generally rich in iodine. People in coastal areas of Japan and China obtain large quantity of iodine by eating seafood such as seaweed (Suzuki, 1980; Ma et al. 1982).

In 1965, it was reported from Japan that in Hidaka, on the southern coast of the Island of Hokkaido and on Rishiri Island, that goiter prevalences among schoolchildren were 9.0% and 2.6% respectively, compared with a prevalence of only 1.3% among schoolchildren in the inland town of Sapporo (Suzuki et al. 1965). The population of Hidaka and Rishiri consumed about 10-50 g of dry seaweed (kelp) per day, while the people of Sapporo, far from the coast, did not eat any kelp. The iodine content in kelp is 0.8-4.5 g/kg. Goitrous individuals were euthyroid although urinary iodine excretions were up to 20 mg per day.

There have been reports from China of iodine excess of food origin (Yu at al. 1987; Zhao & He 1997). Population in four counties of Shangdong and Hebei Provinces consumed kelp salt containing as much as 440-1080 mg/kg of iodine. This led to urinary iodine excretions of 1423-2007 µg/day in local residents.

It is still not well documented if iodine excess, like iodine deficiency (Bleichrodt et al. 1989), has any adverse effect on intellectual and physical development. Only a few studies have been carried out. Some studies (Sun et al. 1985; Xie et al. 1987; Ma et al. 1991; Hu et al. 1994) found iodine excess may impair cognitive function in schoolchildren while many (Li et al. 1987; Jupp et al. 1988; Wang et al. 1987; Ling, 1993; Wang et al. 1993; Yang et al. 1994) indicated it did not. All these studies on iodine excess were carried out comparing one group with excessive iodine intake with another group consuming a normal amount of iodine. All studies were conducted in different areas with different educational background, using different intelligence tests, even using different definitions of iodine excess. Because these studies gave different results, it is hard to answer the question as to whether iodine excess causes reduction in mental performance. No data were available dealing with the consequences of excessive iodine intake on hearing capacity.

It is biologically plausible that, in an iodine excess area, reduction of iodine intake will reduce thyroid size, urinary iodine excretion, and eliminate thyroid abnormalities if any. But it is generally unclear whether thyroid size decreases as a result of reducing iodine intake and how long it takes for enlarged thyroids to reduce to normal size. It is also unknown if reduction of iodine intake to within the normal range has any effects on thyroid function. Experimental evidence from Japan (Namba et al. 1993) shows that enlarged thyroids resulting from an acute increase of iodine intake returned to baseline size within 28 days after discontinuation of the high iodine supply. Whether long term chronic excessive exposure to iodine will affect the speed of normalization of thyroid size or reversibility of perturbed thyroid function remains unclear.

Iodine excess in Jiangsu Province

Jiangsu Province is in the eastern part of China, with a population of 72 million (1999) in 75 counties in an area of 102,600 km^2. Jiangsu is also one of the most developed parts in China, with a gross domestic product (GDP) of 1300 USD per head in 1999. Although 70% of the population live in rural areas, industrialization is proceeding at a rapid pace not only in the cities but also down to the village level. Industries include iron and steel, and the production of automobiles, textiles and electronics. Many foreign companies such as Philips have joint ventures in the province. The health system is highly developed ranging from large modern hospitals to village clinics. Much emphasis is given to disease prevention within the health system.

An investigation of endemic goiter about 15 years ago found that high goiter rates were accompanied by high iodine concentrations in urine and in water in certain townships in Xuzhou Municipality (Zheng & Yang, 1986). In 1995, before the universal salt iodization program was launched in the province, a pilot study (Zhao et al. 1997) in two townships and subsequent epidemiological studies in Xuzhou found that goiter among schoolchildren was endemic. Studies revealed that excessive iodine in the drinking water from shallow or deep wells is the primary causative factor of goiter (Zhao, 1997; Zhao et al. 2000). Iodine excess exists in at least 67 townships of 5 counties in Xuzhou, with a population of about 2.9 million. No iodine prophylaxis programs have been implemented in these areas.

Iodine deficiency

The most common cause of iodine deficiency is inadequate iodine in the diet resulting from a lack of this element in the environment. It usually coexists with poverty and remoteness, where foods from the outside world are out of reach of the local people. Poverty, poor sanitation and malnutrition are among the contributing factors to the etiology of iodine deficiency.

General description

The effects of iodine deficiency are seen at all stages of human development (Table 3), particularly in the fetus and in the neonate and infants, that is, in the period of rapid growth (Delange, 1994). Fetal survival and development are both sensitive to iodine deficiency. Development of the brain in the fetus and neonate is particularly affected. The effects form a continuum with the severity of the consequences increasing as the severity of iodine deficiency increases. The consequences resulted from the influence of a low maternal thyroxine level on the fetus associated with

iodine intakes < 25% of normal. Intakes < 50% of normal are associated with goiter. Data indicating that goitrous children have poor school performance have been reported. All these effects are fully preventable if the iodine deficiency is corrected before pregnancy (Hetzel & Maberly, 1986).

Table 3. The spectrum of iodine deficiency disorders (IDD)

Life span	Disorders
Fetus	Abortions, stillbirths, congenital anomalies
	Increased perinatal and infant mortality
	Neurological cretinism
	(mental deficiency, deaf mutism, spastic diplegia, squint)
	Myxoedematous cretinism *(dwarfism, mental deficiency)*
	Psychomotor defects
	Increased susceptibility to the consequences of nuclear fallout
Neonate	Neonatal goiter
	Neonatal hypothyroidism
	Increased susceptibility to the consequences of nuclear fallout
Child and	Goiter
adolescent	Juvenile hypothyroidism
	Impaired mental function
	Retarded physical development
	Increased susceptibility to the consequences of nuclear fallout
Adult	Goiter with its complications
	Hypothyroidism
	Impaired mental function
	Iodine induced hyperthyroidism
	Increased susceptibility to the consequences of nuclear fallout

Iodine deficiency is the leading preventable cause of brain damage and mental retardation worldwide. It has been a significant public health problem in more than 118 countries with about 1.6 billion population at risk globally (WHO, 1991). Most of populations at risk of IDD are concentrated in Asia, Africa, Latin America and South America. The elimination of IDD was determined to be a global public health priority at the World Summit for Children in 1990 (UNICEF, 1990). Over last decade, the elimination of iodine deficiency through national salt iodization programs has been a global development priority and much progress has been made. Estimates by UNICEF (Mason et al. 2001) revealed that about two thirds of all edible salt has been iodized in the world by the year of 1998. Many developing countries have achieved the goal of

eliminating IDD. Thus the number of people worldwide at risk of IDD is now less than 0.5 billion.

The primary intervention used to prevent IDD has been the iodization of salt, which has been proven effective in eliminating IDD in a number of countries. WHO (1997) recommends that salt be iodized in the range of 20-40 mg/kg at the point of production in order to assure that median urinary iodine levels are in the range of 100-200 μg/L.

There has been little information on how long it takes for thyroids, which increase in size as a consequence of the deficiency, to return to normal size following the introduction of iodized salt into iodine deficient population. This is an important question is because the prevalences of goiter and abnormal thyroid volumes in schoolchildren are used as an indicator of the magnitude of IDD. Many countries observed persistence of goiter in schoolchildren despite salt iodization which appears to be almost universal.

Iodine deficiency in Jiangsu Province

In China, IDD was a large public health problem, with approximately 725 million population at risk of iodine deficiency according to a national survey in 1995. The prevalence of goiter among schoolchildren was found to be > 10% in 27 of 30 provinces. In Jiangsu Province, endemic goiter and mental retardation have long been recognized as a public health problem. Provincial surveys of iodine deficiency indicators during the early 1980s showed that on average the prevalence of goiter among schoolchildren aged 7-14 years was 25% and the mean concentration of iodine in urine was 76 μg/L.

Since 1993, when the Chinese government proclaimed the national goal of elimination of IDD by the year 2000, substantial human and financial resources have been mobilized throughout the country. Universal salt iodization was started in Jiangsu province in 1995. Before iodine interventions, a provincial survey based on population proportionate sampling (PPS) found a total goiter rate in schoolchildren of 17% and median urinary iodine concentration of 85 μg/L. In 1997, after two years of implementation of universal salt iodization, a similar PPS survey found that total goiter rates had been reduced to 8.8% and median urinary iodine concentrations had increased to 300 μg/L. Another PPS survey was conducted in 1999 to measure effectiveness of the salt iodization program. Total goiter rates had decreased further to 4.4% and median urinary iodine concentrations had risen to 406 μg/L, indicating that IDD had been eliminated from this province.

Indicators for assessing iodine status: iodine deficiency and iodine excess

Indicators are essential for measuring the extent of iodine deficiency and excess, whether and which intervention is necessary, and for evaluating program implementation and impact. Indicators can be classified as outcome indicators (thyroid size, urinary iodine excretion) and process indicators (water iodine concentration or salt iodine content). A summary of outcome indicators for IDD and criteria for classifying the severity of IDD as a public health problem are given in Table 4. There are no generally agreed cut-off points for iodine excess. Usually, a prevalence of iodide goiter above 5% or urinary iodine concentration greater than 800 μg/L poses a public health problem (Zhao, 1997).

Table 4. Summary of outcome indicators for IDD and criteria for classifying the severity of IDD as a public health problem (WHO/UNICEF/ICCIDD, 1994)

Indicators	Target population	Classification of IDD severity			
		None	Low	Intermediate	High
Goiter, grade 1 and 2 * (%)	School-aged children	< 5	5-19.9	20-29.9	≥ 30
Thyroid volume > 97th percentile by ultrasound (%)	School-aged children	< 5	5-19.9	20-29.9	≥ 30
Median urinary iodine (μg/L)	School-aged children	≥ 100	50-99	20-49	< 20
TSH > 5mU/L whole blood (%)	Neonates	< 3	3-19.9	20-39.9	≥ 40

* See Table 5.

Thyroid size

The size of the thyroid gland changes in response to alteration in iodine intake. 'Goiter' has been used for many years to describe enlargement of the thyroid gland due to both iodine deficiency and iodine excess. Prevalence of goiter is the most commonly used indicator to assess severity of both iodine deficiency and excess, and to monitor intervention programs. Thyroid size can be determined by palpation and ultrasonography. The classification of goiter by palpation is shown in Table 5 and the criteria for classifying the severity of IDD are given in Table 4.

Palpation is quantitative only in the crude sense. It is a technique that requires no instruments, is relatively easy to conduct, can reach large number of subjects in a short period of time, is not invasive, and needs relatively limited skills of observers.

Total goiter rate describes the proportion of goiter of grade 1 and 2 in the population observed.

Table 5. Simplified classification of goiter (WHO/UNICEF/ICCIDD, 1994)

Grade 0:	No palpable or visible goiter.
Grade 1:	A mass in the neck that is consistent with an enlarged thyroid that is palpable but not visible when the neck is in the normal position. It moves upward in the neck as the subject swallows. Nodular alteration(s) can occur even when the thyroid is not visibly enlarged.
Grade 2:	A swelling in the neck that is visible when the neck is in a normal position and is consistent with an enlarged thyroid when the neck is palpated.

Ultrasonography is a safe, non-invasive specialized technique, which should be performed by trained operators who can perform up to 200 examinations per day. The degree of subjectivity in assessing results, however, points up the importance of developing standardized interpretation criteria (Delange et al. 1997; Hess & Zimmermann, 2000). Thyroid volume can be easily calculated using a calculator or a microcomputer during data entry. Ultrasonography provides a more precise measurement of thyroid volume compared with palpation. This becomes especially significant when the prevalence of visible goiters is small, and in monitoring iodine control programs where thyroid volumes are expected to decrease over time.

Normative thyroid volume size data from ultrasound on iodine-replete children in Europe and in China are depicted in Table 6 and criteria for classifying the severity of IDD are given in Table 4.

For each thyroid lobe, the depth (d), width (w) and length (l) are measured in mm. The volume of each lobe (mL) is calculated as $0.479 \times d \times w \times l$ /1000 and the thyroid volume is the sum of the lobes. As described by Dubois and Dubois (1916), body surface area (BSA, m^2) can be calculated as follows:

$$BSA = wt^{0.425} \times ht^{0.725} \times 0.007184$$

where wt = weight in kg and

ht = height in cm.

From Table 6, it can be seen that the age-specific upper limits derived from European schoolchildren are distinctively greater than those from China, which are similar to those obtained in a study in German children by Gutekunst and Martin-Teichert (1993), which were used as the WHO reference before the data from several countries in Europe (Delange et al. 1997) were published. As the US population has been iodine sufficient for

decades, it would be interesting to compare the US data on thyroid volume with those collected in Europe.

Table 6. Standards for upper limit of normal thyroid volume (ml) (> 97th percentile) based on measurements in iodine-replete children in Europe and China (China National Committee of Experts on Iodine, 1994; Delange et al. 1997)

By age				By body surface area (BSA)		
Age (year)	Upper limit of thyroid volume (mL)			BSA (m^2)	Upper limit of thyroid volume (mL)	
	Europe		China		Boys (Europe)	Girls (Europe)
	Boys	Girls				
6.0-6.9	5.4	5.0	3.5	0.75-0.84	4.7	4.8
7.0-7.9	5.7	5.9	4.0	0.85-0.94	5.3	5.9
8.0-8.9	6.1	6.9	4.5	0.95-1.04	6.0	7.1
9.0-9.9	6.8	8.0	5.0	1.05-1.14	7.0	8.3
10.0-10.9	7.8	9.2	6.0	1.15-1.24	8.0	9.5
11.0-11.9	9.0	10.4	7.0	1.25-1.34	9.3	10.7
12.0-12.9	10.4	11.7	8.0	1.35-1.44	10.7	11.9
13.0-13.9	12.0	13.1	9.0	1.45-1.54	12.2	13.1
14.0-14.9	13.9	14.6	10.5	1.55-1.64	14.0	14.3
15.0-15.9	16.0	16.1	12.0	1.65-1.74	15.8	15.6

Urinary iodine excretion

The concentration of iodine in urine is currently the most widely used biochemical marker of iodine intake. Usually > 90% iodine ingested is excreted in urine. Thus, the iodine level in urine reflects the subject's iodine intake. Urine is easy to obtain in the field, in contrast to serum. Iodine in urine is stable and can withstand collection and transport under field conditions (Dunn et al. 1993). Criteria for classifying the severity of IDD based on urinary iodine excretion are given in Table 4.

Objectives of the study and outline of the thesis

Jiangsu Province has not only the problem of iodine deficiency but also the problem of iodine excess. This situation provides the opportunity to conduct research on both of the problems. To address the problems, goiter prevalence has been used as an indicator and much attention has been paid to the use of ultrasonography for measurement of thyroid volume. Normative reference values are important for classification of thyroid volume. In order to validate the WHO reference for upper limits of normal thyroid volume, research was conducted in the US and Bangladesh.

The US is regarded as being iodine replete for many decades while Bangladesh still has a severe problem of iodine deficiency.

The objectives of the studies, mostly carried out between 1995 and 2000 are as follows,

1. To investigate the possible contribution of high iodine intakes to endemic goiter and their relationship with iodine concentrations in urine as well as their effects on thyroid function (Chapter II).
2. To demonstrate the magnitude of the problem of iodine excess and to examine the relationship of normal to excessive iodine intake with intellectual development, physical development and hearing capacity in Chinese school children using cross-sectional and ecological approaches (Chapters III and IV).
3. To compare the efficacy of reduction of iodine intake from excessive to normal on thyroid size and thyroid function (Chapter V).
4. To examine the efficacy and effectiveness of iodine intervention programs (Chapters VI and VII).
5. To validate the WHO reference for normal thyroid volume based on ultrasonic measurement of thyroid volume of schoolchildren in the United States and in Bangladesh (Chapter VIII).

Thus the outline of the remainder of this thesis is as follows.

Chapter II describes the ecology of high iodine intakes and endemic goiter in three counties of Jiangsu Province, China (Objective 1).

Chapter III describes the relationship of normal to excessive iodine intake with intellectual development, physical development and hearing capacity (Objective 2).

Chapter IV describes the magnitude of the problem of iodine excess and its possible relationship with cognitive development in schoolchildren (Objective 2).

Chapter V describes how reduction of iodine intake from excessive to normal counteracts enlarged thyroid glands and thyroid dysfunction caused by iodine excess (Objective 3).

Chapter VI compares the efficacy of three iodine intervention methods on thyroid size, goiter prevalence and urinary iodine concentrations (Objective 4).

Chapter VII describes the effectiveness of universal salt iodization in 9 counties of Jiangsu Province (Objective 4).

Chapter VIII describes the thyroid volumes measured by ultrasonography in US and Bangladeshi schoolchildren and compares these with European schoolchildren (Objective 5).

Chapter IX discusses the most important findings arising from the work carried out and provides recommendations for public health practice and future research.

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Chapter II

Endemic goiter associated with high iodine intake

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Abstract

In order to investigate the possible contribution of high iodine intake to goiter and its effect on iodine concentration in urine and on thyroid function, the concentration of iodine in drinking water was determined in 65 townships in three counties in Jiangsu Province, China. Indicators of iodine status in schoolchildren and adults were also assessed. The water iodine content in the townships ranged from 0.003 to 22.1 μmol/L, with a median of 4.3 μmol/L. Of the townships investigated, 59 (90.2%) had median water iodine concentrations between 1.6 and 9.5 μmol/L. Iodine concentrations in the urine of adults varied between 0.5 μmol/L and 54.8 μmol/L (median 8.3 μmol/L) and goiter prevalence measured by ultrasound in schoolchildren ranged from 5.3 to 16.8%, with a mean of 12.8%. In adults from townships with the highest water iodine content, thyroid function was perturbed as evidenced by elevated serum concentration of TSH[1]. Goiter prevalence in schoolchildren was positively correlated with iodine concentrations in drinking water and in urine across townships. Endemic goiter in this area is most probably due to excessive iodine intake from drinking water. It is proposed that the maximum allowable concentration of iodine in drinking water be set at 2.4 μmol/L (300 μg/L) and of iodine in urine at 6.3 μmol/L (800 μg/L) because above these levels, prevalence of goiter measured by ultrasound is > 5%.

Key words: • iodine excess • iodine intake • endemic goiter • thyroid function • iodized salt

1Abbreviation used: IDD, iodine deficiency disorders; IRMA, immunoradio monoclonal assay; RIA, radioimmunoassay; SD, standard deviation; T_4, thyroxine; T_3, triiodothyronine; TSH, thyroid stimulating hormone; WHO, World Health Organization.

Endemic goiter has been defined by WHO to occur in populations when total goiter rates are ≥ 5% in primary schoolchildren (1). The principal cause of endemic goiter is iodine deficiency, which may be exacerbated by the consumption of goitrogens (2). Because iodine deficiency is of a major public health concern, food-grade salt is being iodized in most countries (3). Iodine excess has been also reported to be a cause of endemic goiter in a number of geographically defined areas where drinking water, seafood, and medications are the most common sources of high iodine intake (2).

Iodine deficiency disorders (IDD) are a problem of serious public health significance in Jiangsu Province in China, as evident from surveys conducted in 1995 based on goiter prevalence and urinary iodine excretion patterns (4). In response to this situation, the provincial government developed plans to eliminate IDD throughout the province through salt iodization. An exception was made for three counties in Xuzhou Municipality where the cause of endemic goiter was not clear.

Xuzhou Municipality lies in the northwestern part of Jiangsu Province. It comprises six counties, amongst which Feng, Pei and Tongshan Counties are located to the west of Xuzhou City. These counties comprise a 4,000 km^2 plain formed by flooding in the past of the old Yellow River. The population of 2.4 million people in these three counties obtain their drinking water mainly from shallow wells 7-12 m deep, and occasionally from deep wells with depths of over 60 m. There are few central water supply systems in these counties. Surface drinking water is scarce and rainfall is low.

Surveys in the early 1980s indicated that goiter was endemic in Xuzhou Municipality (5). The overall prevalence of goiter among schoolchildren aged 7-14 y was 25%, varying from 18 to 36% among townships. Follow-up studies during 1986-1992 suggested that iodine deficiency was not the only cause of endemic goiter. Iodine concentrations in drinking water samples ranged from 0.15 μmol/L to 9.5 μmol/L, with a median of 1.8 μmol/L (4, 6). Urinary iodine concentrations among adults varied greatly from 0.36 to 9.8 μmol/g creatinine in different townships, with a median of 6.8 μmol/g creatinine (6). This was confirmed again in a study carried out in 1995, which identified iodine excess as the major cause of endemic goiter in two townships in Feng and Pei Counties (7). Yu et al (1987) and Zhao et al (1997) reported that iodine concentrations ≥ 2.36 μmol/L in drinking water or iodine concentrations in urine ≥ 6.30 μmol/L were associated with endemic goiter in a population (8, 9).

The objective of the present study was to examine the relationship among iodine intake, thyroid size and thyroid function. The study was conducted in Feng, Pei and

Tongshan Counties of Xuzhou Municipality where the iodine content of well water was expected to be high. Investigations in the other 3 counties (Pizhou, Shuining and Xinyi) of Xuzhou Municipality showed normal iodine status in most people, with median urinary iodine concentrations in the townships varying from 1.58 to 2.76 μmol/L (5, 10).

Methods

Study design

The present study was conducted in 65 townships in Feng, Pei and Tongshan Counties of Xuzhou Municipality (about 500 km northwest of Shanghai), Jiangsu Province, China. The study proceeded in two phases. The first phase conducted in 1996 assessed the iodine concentration in drinking water in all the townships, and the second phase conducted in 1997-1998 investigated the relationship between iodine intake and indicators of iodine status in selected townships.

For the first phase, each township was divided into five geographic locations. In each location, one village was identified by convenience for the collection of water samples from at least 3 shallow wells as well as from all wells > 60 m deep. During the second phase, based on the observed median iodine concentration in water collected during the first phase, townships were grouped into the following categories according to the median iodine concentrations in water: < 2.36, 2.36-3.93, 3.94-5.50, 5.51-7.08, and ≥ 7.09 μmol/L. Two or three townships, which were easily accessible by road from each group, were identified for further investigation. In selected townships, the thyroid size in all pupils in grades 2-4 (aged 8-10 y) from the central elementary school was estimated by palpation. In one township in each group, thyroid volume was measured by ultrasonography in children whose thyroid size was measured by palpation. A reference group was chosen from Jurong County in Jiangsu Province where salt iodization had been in place for > 10 y and iodine intake was known to be sufficient but not excessive (11). The reference group was investigated using the same protocol.

The research protocol including ethical clearance, was approved by the Scientific Research Committee of Jiangsu Provincial Center for Disease Control and Prevention, Nanjing, China. All procedures were carefully explained to all subjects who agreed to participate in the study.

From 50 healthy adults in each of the townships investigated, casual urine samples were collected and handled according to a standard protocol provided by the Chinese Institute for Iodine Deficiency Disorders in Harbin. Samples of urine were not collected from two subjects who possibly consumed seafood, which is possibly rich in

iodine, during the previous week. Samples of urine were collected in bottles tightly sealed and refrigerated at 4°C until laboratory analysis. Finally, from among the 50 adults in each of the two townships with the highest median water iodine concentrations, non-fasting blood samples were obtained from 30 and 32 subjects respectively who agreed to provide blood samples. There was strong superstition in the population about the harmful effects of providing blood. Serum was prepared by centrifugation within 2 h of blood collection and frozen at –20°C until analysis of thyroid hormones. After collection of blood samples, 2 μCi ^{131}I was administered orally to the subjects who agreed to provide not only blood but also to participate in this procedure. The uptake of ^{131}I by the thyroid was measured 24 h later using standard methods (12).

Thyroid size estimation

The thyroid of each pupil was palpated and classified according to the WHO guidelines (13). Thyroid volume was measured with a portable ultrasound unit equipped with a standard 7.5 MHz linear array transducer (AKHO, Inc, Canada). The depth (d), width (w) and length (l) of each lobe in millimeters were read from longitudinal and transverse scans, and the volume of the lobe was calculated by the formula V (mL) = $0.479 \times d \times w \times l \times 10^{-3}$ (14). The thyroid volume was obtained as the sum of the volumes of both lobes without including the volume of isthmus. Thyroid volume was classified as normal or abnormally large according to the China National Reference based on age (15), which is very similar to that proposed by Gutekunst and Martin-Teichert (16).

Laboratory analysis

Urinary iodine was analyzed using the acid-digestion method described by Dunn et al (17). Water iodine was determined using Barker's modified incineration technique and catalytic reduction of ceric ion by arsenate salt (18). All iodine analyses were conducted in Xuzhou Municipal Laboratory, which is accredited by the provincial iodine laboratory. Urinary iodine analysis of 18 blind control samples at three concentrations by the municipal laboratory did not demonstrate any bias compared to the results from the Chinese Institute for Iodine Deficiency Disorders in Harbin.

Serum T_3 and T_4 were measured by radioimmunoassay, TSH by IRMA using kits obtained from the Chinese Academy of Atomic Energy in Beijing and a gamma counter (Model: Cap RIA-16, Capintec Instruments, Inc, Ramsey, NJ, USA).

Data analysis

Data were analyzed with Epi Info 6.04 (CDC, Atlanta, GA, USA) and SAS 6.12. (SAS Institute, Cary, NC, USA). Goiter prevalence by palpation was calculated as the proportion of pupils with grade 1 or grade 2 goiter. Goiter prevalence by ultrasound was calculated as the proportion of pupils with thyroid volume above the age-specific reference. Because of their skewed distributions, the median was used to measure the central tendency of urinary iodine and water iodine concentrations. The median water iodine content in each township was calculated to express the typical level of iodine concentration in drinking water. It proved not possible to normalize data on iodine concentrations in water and urine. Thus, nonparametric Spearman rank correlation (19) was used to examine associations of iodine concentrations in water and urine with goiter prevalence.

Results

Iodine concentrations in water and urine

During the first phase of this study, a total of 1,151 samples of water in wells were collected from 65 townships, with approximately 4% of the samples from deep wells. The iodine content of water in wells ranged from 0.003 to 22.1 μmol/L, with a median of 4.3 μmol/L. Overall, 76% of the samples had an iodine content > 2.36 μmol/L. Fifty-two (80%) of the 65 townships had a median water iodine concentration > 2.36 μmol/L. The concentration of 2.36 μmol/L corresponds to the level, above which a high prevalence of goiter has been reported previously (8, 9). The distribution of water iodine concentration among townships is shown in **Fig. 1**. Water from both deep and shallow wells contained high iodine concentrations although shallow wells had a higher ($P < 0.05$) concentration (4.63, 2.44-7.20 μmol/L; median, 25-75 percentile) than deep wells (2.98, 2.10-4.59 μmol/L).

During the second phase of the study in which data were collected on indicators of iodine status in 12 townships, the median urinary iodine concentration from 607 adults was 8.3 μmol/L (range, 0.46-54.8 μmol/L). In 61.9% of the subjects, urinary iodine concentrations were > 6.30 μmol/L, which is the level above which endemic goiter has been reported previously (8, 9).

Goiter prevalence

In 12 selected townships, the prevalence of goiter as measured by palpation among 2,371 schoolchildren aged 6-15 y was 22.4%. Goiter prevalence measured by ultrasonography in 849 of the above children was 12.8%. When measured by either palpation or ultrasound, there was no difference in goiter prevalence between boys and girls, but prevalence did increase with age (data not shown).

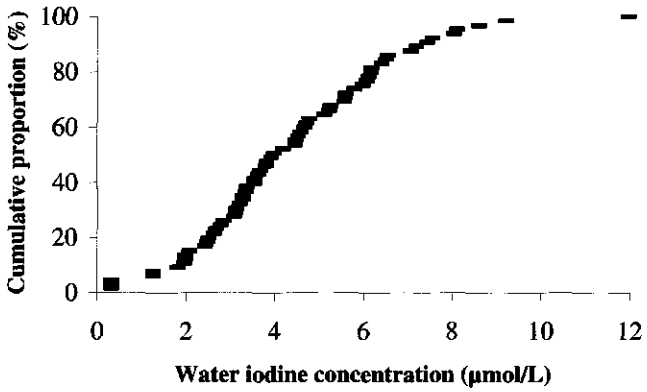

Figure 1. Distribution of median iodine concentration in drinking water from wells in 65 townships in Feng, Pei and Tongshan Counties. Concentrations are medians of the values measured in each township.

Relationships among water iodine, urinary iodine, and goiter prevalence

The relationship of the iodine concentration in urine with that in well water in 13 townships is shown in **Fig. 2.** The median iodine concentrations in water varied from 1.47 to 9.02 μmol/L, the corresponding iodine concentrations in the urine of adults ranged from 4.1 to 15.5 μmol/L, the values were highly correlated. Likewise, as shown in **Fig. 3** and **Fig. 4**, goiter prevalence measured by palpation and by ultrasound in schoolchildren was positively correlated to median iodine concentrations in water and in urine.

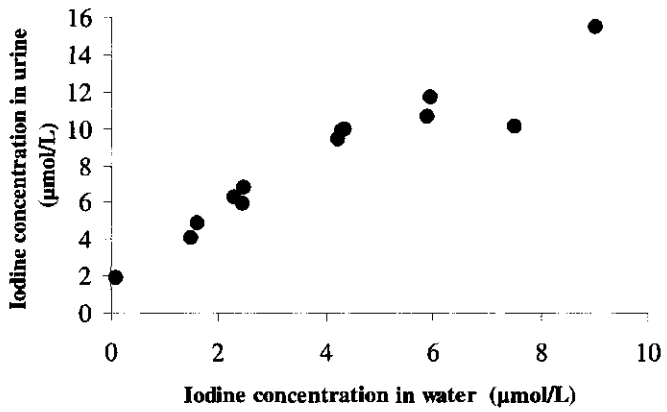

Figure 2. Relationship between median iodine concentration in drinking water from wells and those in urine of adults in 13 townships in Jiangsu Province, China. For Spearman rank correlation, the township with the lowest iodine concentration in water was excluded because this township was supplied with iodized salt. (Coefficient $r_s = 0.95$; $P = 0.0001$).

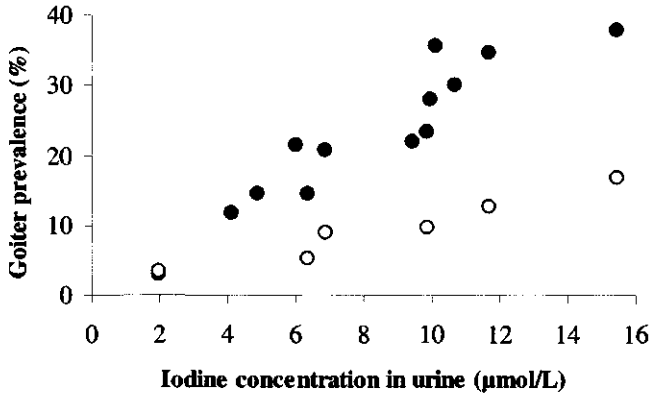

Figure 3. Relationship of goiter prevalence measured by palpation and ultrasound with median iodine concentration in drinking water from wells in 13 townships of Jiangsu Province, China (o = goiter prevalence by ultrasound, • = goiter prevalence by palpation). Spearman rank correlation: by ultrasound, $r_s = 0.97$, $P = 0.001$; by palpation, $r_s = 0.95$, $P = 0.0001$.

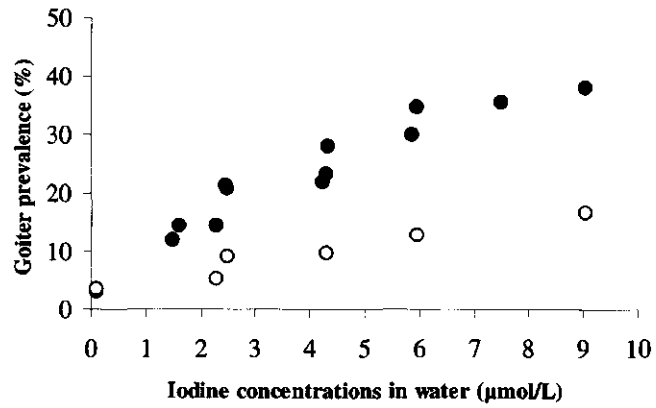

Figure 4. Relationship of goiter prevalence measured by palpation and ultrasound with median iodine concentration in urine of adults in 13 townships of Jiangsu Province, China (o = goiter prevalence by ultrasound, • = goiter prevalence by palpation). Spearman rank correlation: by ultrasound, $r_s = 0.97$, $P = 0.001$; by palpation, $r_s = 0.94$, $P = 0.0001$.

Thyroid function

Of the 62 adults from the two townships with the highest water iodine contents, 32 (52%) had an elevated serum TSH concentration (normal range according to the manufacture 0.4-3.6 mU/L). The concentration of TSH (median, 25-75 percentile) in serum was 5.60 (3.04-11.30) mU/L. The median serum T_4 concentration was 119 (106-135) nmol/L, with two cases above the normal range. The median serum T_3 was 1.08 (0.95-1.42) nmol/L, all within the normal range. The 24-h thyroid ^{131}I uptake was 4.6 ± 0.3% (mean ± SD; range 0.2-15.8%), which is significantly lower than the normal range of 10-30% in populations with normal iodine intake (20).

Discussion

In this study, goiter prevalence is clearly associated with high iodine intake from drinking water. Goiter prevalence assessed both by palpation and by ultrasound is positively associated with iodine concentrations in well water and in the urine of adults. Water from the wells appears to be the most important source of iodine because there is a strong relationship across townships of the median concentration of iodine in urine with that in drinking water. It would be expected that the concentration of iodine in well water would be affected in the food chain. However, an early study in this area (7) and studies in other provinces in China (21-23) with elevated concentration of iodine in well water were not accompanied by elevated iodine concentrations in soil or in grain, flour, fruits, and vegetables grown in the area. Although genetic factors and goitrogens may have played some role, endemic goiter observed in these three counties is most likely caused by excessive iodine in drinking water.

In general, it is thought goiter is caused by low iodine intake (24). However, there were very few adults (2/607) with urinary iodine concentrations < 0.8 μmol/L, indicating that there is no iodine deficiency. Goiter in this study population is associated with high iodine intake. This is supported by the low 24-h uptake of ^{131}I by adults in the two townships with the highest iodine concentration in water. This indicates that the thyroid gland in these subjects is relatively saturated with iodine.

Endemic goiter associated with iodine excess has been reported in other locations (21-23, 25, 26). But all the reports thus far were of studies of only small areas or populations. The present study covered a 4,000 km^2 area with a population of 2.4 million, the largest affected population or area ever reported.

In this study, concentrations of TSH in serum were elevated while concentrations of T_4 and T_3 were generally in the normal range. Similar results have been reported in China and in U.S. Peace Corps Volunteers working in Niger consuming disinfected

water from a filter with an iodine resin (26). In Japan, elevated serum TSH levels were reported from an area with iodine excess (25). A large single dose of iodide has been shown to inhibit thyroid hormone synthesis (27). Slightly elevated serum T_4 levels, normal serum T_3 levels, but raised serum TSH levels in adults from the townships with the highest water iodine in this study imply that with a chronic high intake of iodide, the population fails to maintain euthyroid status.

The thyroid gland in iodide goiter is exclusively diffuse. No nodular goiter was seen in iodine excess subjects, as is the case for severe iodine deficiency. In the thyroid gland of animals fed excessive iodine and of goitrous human subjects (28-31), the follicles are filled with colloid and the epithelial cells are flattened. This is different to the situation in iodine deficiency where parenchymal cells are abundant, follicular epithelial cells are thicker with papillary infolding and there is very little colloid. The thyroid gland of subjects with a grade I iodide goiter is firm, easily palpated, and has a pronounced boundary, as compared with a grade I goiter induced by iodine deficiency. Using ultrasound, the thyroid gland in iodide goiter is distinct from neighboring tissues with a clear boundary while the gland itself appears rough and uneven. This compares with the consistent distribution of the thyroid echogram seen in goiter caused by iodine deficiency. Because ultrasound apparatus used in this study was not fitted with a camera, no photographs are available.

At which level should iodine intake be considered excessive? Suzuki defined iodine excess as the amount of iodide beyond the physiological requirement for adequate thyroid hormone synthesis (2). For maintaining the intrathyroidal iodine concentration needed for normal thyroid hormone secretion in adults, a daily supply of between 0.4 and 3.9 μmol iodine should suffice (32). Other reports suggest, however, that iodine intake up to 15.8 μmol/day causes no adverse physiological reactions in healthy adults, and 7.9 μmol/day produces no physiological abnormalities in children (33). In our study, thyroid function appears to be perturbed in populations with a median iodine concentration in urine of 10.1 μmol/L or in drinking water of 7.5 μmol/L. The safe maximum allowable iodine concentrations should therefore be below these levels. Findings in this study show that when iodine concentrations reach 2.4 μmol/L in drinking water or 6.3 μmol/L in urine of adults, goiter prevalence measured by ultrasound becomes > 5%. This seems to support a maximum allowable iodine concentration of 6.3 μmol/L in urine or of 2.4 μmol/L in drinking water. This is consistent with other studies in China (8, 9, 34). Thus, iodine concentrations above these levels should be considered as a public health risk. However, further studies at lower iodine concentrations are still needed.

In this study, there is a substantial difference between goiter prevalence assessed by palpation and by ultrasound. The likely explanation is that the goiter caused by

iodine excess is firm and inconsistent in texture, which may lead to an overestimate by palpation of the prevalence. Assessment of thyroid enlargement by ultrasound is regarded as more precise than assessment by palpation (13).

In conclusion, endemic goiter in this area is most probably caused by excessive iodine intake from drinking water. When the iodine concentration is > 10.1 μmol/L in urine of adults or > 7.5 μmol/L in drinking water, thyroid function of adults appears to be perturbed. Maximum allowable iodine concentrations may be set at 6.3 μmol/L in the urine of adults or 2.4 μmol/L in drinking water if goiter prevalence ≥ 5% is defined as a public health problem. The results of this study also demonstrate that in the assessment of iodine status of a population, the collection of information on goiter or thyroid volume alone is not sufficient to characterize iodine status. Information on urinary iodine concentrations and the status of an iodine intervention program should also be collected. There are national policies for universal salt iodization in many countries to eliminate IDD. Populations in areas with iodine excess will not derive benefit from increased iodine intake from iodized salt or any other source. Measures should be taken to bring urinary iodine concentrations within the range of 0.8-1.6 μmol/L, as recommended by WHO (35), to minimize the hazards associated with either iodine deficiency or iodine excess.

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Chapter III

The relation between normal to excessive iodine intake and mental development, physical development and hearing capacity in Chinese schoolchildren

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Submitted

Abstract

To describe the relationship of normal to excessive iodine intake with intellectual development, physical development and hearing capacity in schoolchildren, iodine concentrations in drinking water and in urine were assessed in 13 townships in Jiangsu province, China. Based on the median iodine concentration in drinking water, the townships were divided into six groups (A to F), varying from normal (group A, 0.32 μmol/l) to very high iodine concentration in drinking water (group F, 8.58 μmol/l). A total of 2013 schoolchildren aged 8 to 15 years were selected. Height and weight were assessed and IQ was measured with a Combined Raven test. Hearing capacity of both ears was assessed with pure-tone audiometer at 1 kHz, 2 kHz and 4 kHz. For children aged > 11 years, the mean IQ scores of group D (105.5), group E (105.2) and group F (102.3) were significantly lower ($P < 0.01$) than the mean IQ score of group A (108.9). In these children, IQ was related negatively to concentration of iodine in drinking water and in the urine of adults ($\beta = -0.803$, $\beta = -0.546$ respectively). The IQ of children aged ≤ 11 years in group F was also lower than their counterparts in group A. There was no clear evidence that various degrees of iodine excess in the children could affect their physical development or hearing capacity. These results support the premise that the maximum allowable iodine concentration in drinking water should be set at 2.4 μmol/l (300 μg/l) or in adult urine of 6.3 μmol/l (800 μg/l).

Iodine excess: IQ: Physical development: Hearing capacity

Iodine deficiency disorders (IDD) are a worldwide health problem (UNICEF, 1998). IDD includes brain damage and mental retardation in human beings (Querido *et al.* 1978; Bleichrodt *et al.* 1980; Hetzel, 1983; Bleichrodt & Resing, 1994; Tiwari *et al.* 1996). Findings from animal studies have suggested that severe maternal and foetal iodine deficiency is associated with impaired maturation of the cerebral cortex and the cerebellum (Hetzel *et al.* 1989). In addition to impaired intellectual development, IDD also includes growth retardation (Mannar & Dunn, 1995) and hearing loss (Wang & Yang, 1985a; Wang & Yang, 1985b; Valeix *et al.* 1994; Azizi *et al.* 1995).

In some countries, people suffer from iodine excess, although no clear definition of iodine excess exists. Suzuki (1980) has defined iodine excess as the amount of iodine in excess of physiological requirements for thyroid hormone synthesis. According to Chinese researchers a situation of iodine excess poses a physical health problem if the median iodine concentration in drinking water is > 2.4 µmol/l or if the median urinary iodine concentration of the population is > 6.3 µmol/l. In both conditions the goitre prevalence of the population is > 5 %, indicating a public health problem (Zhao, 1997). This definition of iodine excess was used for this study, although it is not applied worldwide. Based on this definition, iodine excess has been reported in numerous locations in China, especially in the lower coastal provinces where large quantities of seafood and deep or shallow well water, rich in iodine, are consumed (Ma *et al.* 1982; Li *et al.* 1987; Zhao *et al.* 1998).

It is still not well documented if iodine excess, like iodine deficiency, has any adverse effect on intellectual and physical development. Only few studies have been carried out. Sun *et al.* (1985) reported that schoolchildren with a normal iodine intake had a higher mean IQ than those with excessive or deficient iodine intake. Similar results were found in other studies (Xie *et al.* 1987; Ma *et al.* 1991; Hu *et al.* 1994). In contrast, Jupp *et al.* (1988) concluded from a cross-sectional study among schoolchildren that iodine excess had no effect on growth and intellectual performance. Li *et al.* (1987) found similar results. In addition, other studies also found no effect of excessive iodine on IQ (Wang *et al.* 1987; Ling *et al.* 1993; Wang *et al.* 1993). Until now, no data on the consequences of excessive iodine intake on hearing capacity were available.

All previous studies on iodine excess have compared one group with an excessive iodine intake with another group with a normal iodine intake. All studies used different definitions of iodine excess. Therefore, in this study six different level of iodine intakes from normal to excessive were studied to measure effects of iodine excess over a greater range. The objective of this study is to describe the relationship between iodine intake, ranging from normal to excessive, with intellectual development, physical development and hearing capacity in schoolchildren.

Methods

Population and study design

The present study was conducted in 13 townships in Feng, Pei and Tongshan counties (about 500 km northwest of Shanghai) of the Jiangsu province in China. In a previous study (Zhao *et al.* 2000), the iodine concentration in drinking water was assessed in five villages of each township. In the 13 townships the median iodine concentrations in drinking water ranged from 0.32 to 9.02 μmol/l. Based on the median iodine concentrations in drinking water, the 13 townships were divided into six groups: <0.79, 0.79-2.35, 2.36-3.93, 3.94-5.51, 5.52-7.08, and ≥ 7.09 μg/L. This resulted in one group with normal iodine intake, one group with iodine intake more than adequate and four groups with iodine intake excessive to a different extent. The median urinary iodine concentrations of the adults ranged from 2.17 to 14.79 μmol/l. Sample size was estimated using Epi Info 6.04b (CDC, Atlanta, GA, USA) based on the following conditions: a prevalence of mentally retarded children in the normal group (group A) of 2.25% according to the Chinese IQ norm, a 5 times higher than expected prevalence (i.e. 11.25%) in the group with the highest iodine intake (group F), an α-value of 0.05 and a power of 90%. Given these conditions, 183 children in each group would be required. Sample size was increased in this study since the prevalence of mental retardation was not known. One to three townships were selected for each group to meet sample size requirements. In the central elementary school in each township, all children in grades 2-4 present on the day of study were selected. The children (2068 of the 2085 enrolled) were aged 8-15 years. Height was recorded to the nearest 0.1 cm with a calibrated SECA (Seca, CA, USA) and weight was measured to the nearest 0.5 kg on a calibrated digital scale. Hearing capacity was assessed in a sub-population of 1 township selected at random from each of the six groups. The township with the lowest iodine intake (Township One) was regarded as the normal reference. Approximately 110 schoolchildren were selected in each township with a total of 628.

Research protocols including ethical clearance, were approved by the Scientific Research Committee of Jiangsu Provincial Centre for Disease Control and Prevention, China. All research protocols were carefully explained to and an oral consent for voluntary participation obtained from all participants.

Urinary iodine concentration

In each school, approximately one third of selected children were randomly chosen for the collection of casual urine samples. All the urine collected was stored in plastic screw-topped collection bottles and refrigerated at 4°C until laboratory analysis within one week. Urinary iodine was analysed using an acid-digestion method (Dunn *et al.* 1993). The iodine concentration in drinking water was determined using Barker's modified incineration

technique and catalytic reduction of ceric ion by arsenate salt (Li et el. 1984). All iodine analyses were conducted in Xuzhou municipal laboratory, which is accredited by the provincial laboratory. Urinary iodine analysis of 18 blind control samples at three concentration levels, conducted by the municipal laboratory, demonstrated negligible bias (< 5%) compared to the China National Institute of IDD and to the China National Reference Laboratory.

Intelligence Quotient

A Combined Raven test adapted for use in rural areas of China was used to measure IQ. This test is suitable for group measurement and is less likely to be affected by environment, culture, and acquired knowledge (Bleichrodt & Born, 1994). The Chinese norm (Wang *et al.* 1999) was applied to calculate the age-adjusted IQ value for each child.

Hearing capacity

Hearing capacity of both ears was measured in the selected townships with pure-tone audiometer at 1 kHz, 2 kHz and 4 kHz (Model 60, Eckstein Bros., Inc. Los Angeles, CA, USA). Data from children with ear disorders were excluded from analyses, resulting in a population of 530 children.

Data analysis

Data were entered using Epi Info 6.04b and a check-file was used to eliminate errors. Variables that were not normally distributed were expressed as median. Children were divided into IQ groups based on the 25th (low IQ) and 75th (high IQ) percentiles of the IQ distribution. Shrestha *et al.* (1994) found that the effect of iodine deficiency might be different in different age groups. Therefore, IQ analyses were conducted separately for children aged ≤ 11 years and children aged > 11 years. To assess the number of children with impaired physical development, Z-scores (height for age, HAZ; weight for age, WAZ and weight for height, WHZ) were calculated, using Chinese standards for height and weight (Chang, 1992). When a child's HAZ, WAZ or WHZ was ≤ –2, the child was considered to be stunted, underweight or wasted, respectively. For each child the hearing threshold of the better ear was used for analysis. Analyses were carried out for speech frequencies (1 kHz and 2 kHz) and for 4 kHz (Niskar et al. 1998). Differences in IQ scores and in the prevalence of low and high IQ among groups were tested with ANOVA and Chi-square. Student's t-test and Chi-square were used to test differences in IQ scores and the proportions of low and high IQ between each excessive group and the normal group. Chi-square and Fisher's exact test were used to test differences in Z-scores. The relationships between urinary and water iodine concentrations and IQ were calculated with Spearman's rank correlation and linear regression. The median test was used for testing differences in

hearing threshold among the six townships and also between the townships with Township One as reference. Differences in proportions children with hearing loss between and among groups were tested with Chi-square. Data were analysed with Epi Info 6.04b and SAS 6.12 (SAS Institute, Cary, NC, USA).

Results

Demographic and anthropometric data

Data are only presented for children for whom a complete data set was available. The five groups were comparable with respect to age, height and sex distribution (Table 1). Weight slightly differed among the groups. The proportion of stunted, underweight and wasted children was 2.03 %, 0.19 % and 0.44 % respectively. The four groups with excessive iodine intake did not show different proportions of stunted, underweight or wasted children compared to the normal group (data not shown).

Urinary iodine concentration

The median urinary iodine concentrations of the children in the 6 groups ranged from 2.34 to 8.27 μmol/l (Table 1). The median concentrations of iodine in the urine of the children in each group measured in the present study were lower (Wilcoxon, $P = 0.012$) than that measured in adults previously (Zhao et al. 2000). This may have been the result of changes in the source of drinking water.

Intelligence Quotient

Of the selected children, 55 did not participate in the test. Individual IQ scores for the 2013 children studied ranged from 54 to 141. Overall, mean IQ was significantly higher for boys than for girls, 106.5 and 104.4 respectively ($P = 0.00091$).

There was a substantial difference of mean IQ among groups ($P < 0.0001$). For all children as a whole, a lower mean IQ was observed in groups D, E, and F, as compared to group A ($P = 0.02$, $P = 0.001$ and $P = 0.001$, respectively; data not shown).

For children aged > 11 years, the mean IQ and the proportion with a low or high IQ were significantly different among the groups ($P = 0.0001$, $P = 0.02$ and $P = 0.001$, respectively; Table 2). Groups D, E and F had significantly lower mean IQs compared to group A ($P = 0.00957$, $P = 0.01766$ and $P = 0.000174$, respectively). In addition, groups C and E had a significantly lower proportion of children high IQ than group A. These differences are confirmed in the significance of trends observed for children aged > 11 years. Although for children aged ≤ 11 years the mean IQ and the proportion low IQ were significantly different among the groups ($P = 0.008$ and $P = 0.04$, respectively), no significant trends were observed.

Table 1. Basic characteristics of the six groups in the study population

	Group A	Group B	Group C	Group D	Group E	Group F
Boys/girls	150/145	217/217	145/144	196/190	143/143	149/149
Age * (y)	11.9 ± 1.9	12.0 ± 1.6	11.8 ± 1.5	11.7 ± 1.5	11.9 ± 1.2	11.9 ± 1.4
Height * (m)	1.48 ± 0.12	1.49 ± 0.11	1.49 ± 0.10	1.47 ± 0.10	1.48 ± 0.09	1.48 ± 0.09
Weight * (kg)	42.3 ± 9.6	41.1 ± 9.8	43.3 ± 8.5	40.5 ± 8.5	42.6 ± 9.1	42.0 ± 8.4
Iodine concentration (μmol/l) †						
Drinking water‡†	0.32	1.68	2.44	4.26	5.91	8.58
Adults' urine‡†	2.17	4.76	6.56	9.50	10.97	14.79
Children's urine¶	2.34 (1.61, 2.99)	3.09 (1.91, 4.62)	4.44 (3.03, 6.39)	8.27 (4.59, 10.77)	6.44 (2.98, 10.04)	4.76 (3.20, 6.27)

*Mean ± SD

†1 μmol iodine/l = 126.9 μg iodine/l

‡Median values based on data presented in Zhao *et al.* (2000)

¶Median values with 25 th and 75 th percentiles in parenthes

Table 2. IQ of children exposed to different levels of iodine in drinking water*

	Group A	Group B	Group C	Group D	Group E	Group F
Mean IQ ± SD (n)						
≤ 11 y	105.7 ± 15.2 (127)	102.1 ± 15.0 (181)	105.7 ± 15.6 (98)	105.8 ± 14.5 (177)	104.9 ± 13.8 (101)	100.4 ± 15.9† (120)
> 11 y	108.9 ± 11.7 (168)	108.8 ± 11.7 (253)	107.7 ± 13.2 (191)	105.4 ± 11.4‡ (209)	105.3 ± 14.6‡ (185)	102.5 ± 14.9‡ (178)
Proportion of children with IQ ≤ 98 (n)						
≤ 11 y§	33.9 (57)	33.7 (61)	21.4† (21)	26.0 (46)	31.7 (32)	38.3 (46)
> 11 y§	20.5 (26)	20.6 (52)	16.8 (32)	27.8 (58)	28.1 (52)	27.5 (49)
Proportion of children with IQ ≥ 114 (n)						
≤ 11 y#	32.5 (35)	22.7 (41)	30.6 (30)	32.2† (57)	27.7 (28)	19.2 (23)
> 11 y¶	32.3 (41)	34.8 (88)	28.3 (54)	23.4‡ (49)	28.1 52)	16.9‡ (30)

*See Table 1 for iodine concentrations in water and urine.

Compared with Group A: †$P < 0.05$, ‡$P < 0.01$.

Significance for trend: §$P < 0.05$, ¶$P < 0.01$, #$P > 0.05$.

In order to quantify the effect of iodine intake on IQ, regression analyses was performed. For children aged > 11 years, the regression coefficients on IQ for iodine concentrations in drinking water and in adults' urine were -0.00423 (SE=0.0005) and -0.00635 (SE=0.00134), respectively (Fig. 1). Mean IQ of these children was not related to the median concentration of iodine in urine measured in the present study. No relation between iodine concentration in adults' urine and the proportion of these children with a high IQ was observed. For children aged ≤ 11 years, IQ was not related to any of iodine concentrations measured, except that group F had a lower mean IQ as compared to group A ($P < 0.01$; Table 2).

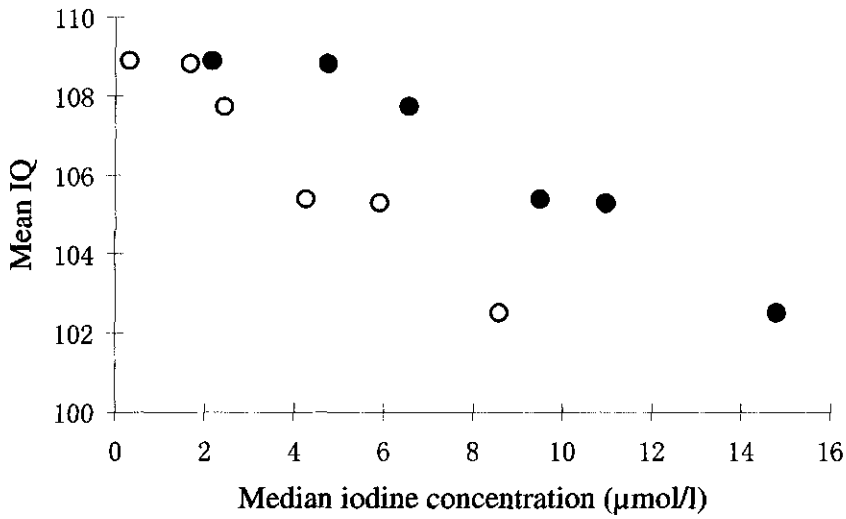

Fig. 1. Mean IQ of children aged > 11 years plotted against median iodine concentration in drinking water and in adults' urine (o = median iodine concentration in drinking water for groups, • = median iodine concentration in adults' urine for groups). For median iodine concentration in drinking water, $\beta = -0.807$ (SE = 0.086) and in adults' urine, $\beta = -0.536$ (SE = 0.059).

Hearing capacity

The six townships in the sub-population on which hearing capacity was measured were comparable with respect to mean age, height, weight and sex distribution (data not shown). There was a significant difference among the six townships in hearing capacity only for speech frequencies ($P = 0.021$). Townships Two and Three had a higher hearing threshold and a higher proportion of hearing loss at speech frequencies than the normal township, Township One (Table 3). At 4 kHz there was no significant difference in hearing threshold or proportion of hearing loss among townships except that Township Six had a lower

Table 3. Iodine values, hearing threshold and proportion of hearing loss at speech frequencies and at 4 kHz for each township

	Townships					
	One	Two	Three	Four	Five	Six
Iodine concentrations (μmol/l)						
Drinking water[†]	0.32	1.47	4.23	5.94	7.5	9.02
Adults' urine[†]	2.17	4.10	9.41	11.69	10.10	15.45
Children's urine[‡]	2.34 (1.61, 2.99)	2.81 (1.68, 3.76)	8.41 (4.28, 10.90)	9.33 (6.78, 11.27)	3.59 (2.77, 5.56)	5.88 (3.94, 8.57)
Hearing threshold (dB)						
Speech frequencies[‡]	15 (12.5, 17.5)	17.5 (15, 22.5) *	17.5 (12.5, 22.5) *	15 (12.5, 17.5)	15 (12.5, 17.5)	15 (12.5, 17.5)
4 kHz[‡]	10 (5, 15)	10 (10, 15)	10 (10, 15)	10 (5, 10)	10 (5, 15)	10 (5, 15)
Proportion of children with hearing loss[§] (n)						
Speech frequencies[‡]	33.0 (32)	53.4 (39) *	52.9 (46) *	38.5 (42)	36.6 (26)	39.0 (30)
4 kHz[‡]	10.3 (10)	13.7 (10)	13.8 (12)	9.2 (10)	7.0 (5)	5.2 (4) *

* $P < 0.05$, compared to Township One.

[†]Median values based on data presented in Zhao et al. (2000)

[‡]Median values with 25th and 75th percentiles in parentheses. Speech frequency indicates 1 and 2 kHz.

[§]Hearing threshold > 15 dB (Niskar et al., 1998).

proportion of hearing loss than Township One. Although the results in Table 3 indicate a negative trend, no significant relationship was found between hearing capacity and iodine concentration in drinking water or in adults' urine both for speech frequencies and for 4 kHz. Analyses were also performed for children aged > 11 years and ≤ 11 years separately but no relationships were found between iodine concentrations in water or urine and hearing (data not shown).

Discussion

This study demonstrates that excessive iodine intake in the past reduces mental performance but not physical development or hearing capacity in children. Thus for children aged > 11 years, the IQ was lower in those children who had access to water with high iodine concentration. Such an effect was also demonstrated in children aged ≤ 11 years exposed to extremely high iodine intake. Because iodine concentrations in the children at the time of the study were lower than that measured two years previously, it would appear that the source of iodine had changed during this period.

The significant negative relation for children aged > 11 years between IQ and iodine concentration in drinking water as well as in adults' urine, suggest a relationship between excessive iodine intake and intellectual development. Based on the regression analysis of data from children aged > 11 years, the level of excessive iodine from where IQ is significantly lower could be set at a median iodine concentration in drinking water of 2.4 µmol/l to 4 µmol/l or in adults' urine of 6.6 µmol/l to 9.5 µmol/l. The significant decreasing trend of IQ as a result of iodine excess was only present for children aged > 11 years. This is consistent with the results of studies in which IQ has been measured in children after iodine supplementation. Positive results have only been seen in studies with children < 10 years of age (Shrestha *et al.*, 1994) but not in those in older children (Bautista et al. 1982). For children age ≤ 11 years, we found a lower IQ in group F, where the iodine concentration in water or adults' urine was 8.6 µmol/l or 14.8 µmol/l (Table 2). It is possible that the IQ of all children has been affected by reduction of iodine concentrations in drinking water. Our results would suggest that reversal of IQ impairment due to excessive iodine occurs slower or to a lesser extent when children are older or when the iodine excess is more severe. The maximum allowable iodine concentration in drinking water or in the urine of adults which should be recommended are likely to be lower than the ranges suggested above. In our previous studies before interventions were implemented a median iodine concentration of 2.4 µmol/l in drinking water and of 6.3 µmol/l in urine were found to pose a public health problem, as evidenced by elevated prevalences (> 5%) of goitre (Zhao, 1997). Studies conducted in populations with lower iodine concentrations in water and

urine (water iodine ranging from 2.4 µmol/l to 3.6 µmol/l; urinary iodine ranging from 4.4 µmol/l to 9.7 µmol/l; Wang *et al.* 1987; Li *et al.*, 1987; Jupp *et al.*, 1988) than those where adverse effects on IQ were found in the present study, failed to find adverse effects of excessive iodine on IQ. These results are in favour of maximum allowable iodine concentrations between 2.4 and 4 µmol/l in water or between 6.3 and 9.5 µmol/l in the urine. To ensure a wide range of safety, our previous recommendations for maximum allowable iodine concentrations in water or urine of 2.4 µmol/l (300 µg/l) in drinking water or 6.3 µmol/l (800 µg/l) in the urine are applicable to this situation.

In agreement with the present study, some studies reported a lower IQ for children living in an iodine excessive area compared to children living in an iodine normal area (Xie *et al.*, 1987; Ma *et al.*, 1991; Hu *et al.*, 1994). However, other studies did not find a significant difference in IQ between children with normal and children with excessive iodine intake (Wang *et al.* 1987; Li *et al.*, 1987; Jupp *et al.*, 1988; Ling *et al.*, 1993). Explanations for these conflicting results could be the extent of iodine excess and the different intelligence tests used by various investigators.

For this study the Combined Raven test which had no verbal subtests was chosen. In contrary to other tests, this test can be used with groups and is suitable for children aged 5-15 years. In addition, there is a well-established Chinese version of the Combined Raven test, which has been standardised according to Chinese cultural and social environment (Wang *et al.*, 1999). Many factors may affect IQ such as heredity, infection, malnutrition, endocrinological disorders, but in this study these factors were similar for each group. The higher IQ observed in boys had no effect on the results, since both boys and girls were equally represented among the groups. Therefore, the differences in IQ are most likely to be caused by differences in iodine intake. Still, the results should be interpreted carefully since the researchers were not blinded as to the iodine concentration in drinking water at township level during IQ testing.

In this study, urinary iodine concentrations from a previous study conducted in the same area were also used for analyses (Zhao *et al.*, 2000). These concentrations were obtained from adults instead of children. Studies on iodine deficiency have demonstrated that iodine deficiency affects the intellectual development of children mainly during the early foetal period (DeLong, 1993; Cao *et al.*, 1994; Delange, 2000). Immaturity of the organic binding mechanism may account for the susceptibility of the foetal and neonatal thyroid to iodine (Woeber, 1991). Both deficient and excessive iodine status may then result in hypothyroidism (Woeber, 1991; Clark, 1990). As brain development requires thyroid hormones (Bleichrodt *et al.*, 1987), the lack of thyroid hormones can cause impaired intellectual development in these children. Since iodine status of the foetus depends on the iodine intake of the mother during pregnancy, the adults' current exposure to iodine is thought to be more related to the children's intellectual development, assuming the iodine

intake of adults has not changed over years.

In this study there was no evidence that various degrees of iodine excess could affect the physical development of children. This is in agreement with other studies on iodine excess (Jupp *et al.*, 1988; Li *et al.*, 1987).

Hearing loss is more severe (Valeix *et al.*, 1994) and more frequent (Azizi *et al.*, 1995) in areas with iodine deficiency than in those areas with normal iodine. Since iodine excess and iodine deficiency may have similar effects on health, lower hearing capacity was expected in those townships with a high iodine intake. However, in this study no clear relation was found between iodine intake from normal to excessive and hearing capacity.

The main conclusion of this study is that the IQ of children was impaired by excessive iodine intake. Based on the results of this and other studies, the maximum allowable iodine concentrations can be set at 2.4 μmol/l in drinking water or 6.3 μmol/l in adults' urine. In many countries salt iodisation programs have been developed to eliminate iodine deficiency. Over-consumption of iodised salt could occasionally result in excessive iodine intake (World Health Organisation/United Nations International Children's Emergency Fund/International Council for Control of Iodine Deficiency Disorders, 1997; Stanbury *et al.*, 1998). Thus, care should be taken to ensure the iodine consumption from iodised salt is not excessive in iodine deplete and replete areas and salt iodisation do not extend to areas with more than adequate natural iodine intake.

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Chapter IV

Iodine excess and its relation to cognitive development: epidemiological evidence from China

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Submitted

Abstract

To demonstrate the magnitude of the problem of iodine excess and the possible relation to cognitive development in schoolchildren, the distribution of iodine excess in China was described and data from 16 studies relating IQ to excessive intake of iodine in China were analysed. Based on the Chinese definition of iodine excess (water iodine concentration > 2.36 μmol/l or urinary iodine concentration > 6.30 μmol/l), iodine excess was found to exist in 92 counties of 10 provinces of China. Of 16 studies included, 5 found that excessive iodine intake reduced IQ. A meta-analysis indicated that IQ of children in areas with excessive iodine intake, based on urinary iodine concentration, was 3.24 points lower than that of children in areas where iodine intake was normal. The effect was even greater with an IQ shift of 3.74 points in areas with extremely high iodine intake, as compared with areas with normal iodine intake. It implies that high iodine exposure is related to a decline in IQ and strengthens the importance of intervention to normalise iodine intake.

Iodine excess: IQ: Epidemiology: Meta-analysis

Iodine sufficiency is attained when the median concentration of iodine in urine is between 0.79 and 2.36 μmol/l while a urinary iodine concentration > 2.36 μmol/l is regarded as 'above adequate' (World Health Organisation /United Nations Children's Fund /International Council for Control of Iodine Deficiency Disorders, 1997). There is no clear definition of excessive iodine intake. Studies in China have revealed that excessive iodine intake poses a health problem if the iodine concentration in urine of adults or in drinking water is > 6.30 μmol/l or > 2.36 μmol/l, respectively (Zhao et al. 1997). Both these conditions give rise to a problem of public health importance as they result in goitre prevalences ≥ 5% (World Health Organisation /United Nations Children's Fund /International Council for Control of Iodine Deficiency Disorders, 1994). The definition of excessive iodine intake based on urinary iodine concentration is in line with the tolerable upper intake level (UL) for iodine recommended recently by the US Institute of Medicine (2000), which defined UL for iodine intake for adults at 8.67 μmol/day. A daily intake of 8.67 μmol iodine corresponds to approximately 6.22 μmol/l in urine for a 60 kg person.

It is known that iodine deficiency can lead to brain damage and mental retardation in human beings (Querido et al. 1978; Bleichrodt et al. 1980; Bleichrodt & Resing, 1994; Tiwari et al. 1996). However, iodine excess can also cause health-related disorders. Iodine excess was first reported in the coastal areas of Hokkaido of Japan where goitre is endemic and the intake of iodine is extraordinarily high (Suzuki, et al. 1965). Reports on iodide goitre have appeared over the last 20 years in inland areas in China, especially in the lower coastal provinces where large quantities of seafood and shallow or deep well water, rich in iodine, are consumed (Ma et al. 1982; Li et al. 1987; Zhao et al. 1998).

Studies on iodine deficiency have demonstrated that iodine deficiency affects the intellectual development of children mainly during the early fetal period (Fierro-Benitez et al. 1972; Cahouki & Benmiloud, 1994; Pharoah, 1993; Cao et al. 1994). Immaturity of the organic binding mechanism may account for the susceptibility of the fetal and neonatal thyroid to iodine, with hypothyroidism as the end result (Woeber, 1991). As brain development requires thyroid hormones (Hetzel, 1983), the lack of thyroid hormones can cause impaired intellectual development in these children. Since excessive consumption of iodine may also result in a state of hypothyroidism (Begg & Hall, 1963; Clark, 1990; Konno et al. 1994), the mechanism could be the same for iodine excess. Thus, the question arises as to whether iodine excess may also play a causative role, at least partly, in human mental development, as iodine deficiency does. The objective of the present paper is to examine the relationship of iodine intake above the normal range with cognitive development. We

have conducted a meta-analysis of available data relating excessive iodine intake with intellectual quotient (IQ) is conducted. In order to address the magnitude of the problem, those areas with excessive iodine intake were first located.

Methods

Inclusion criteria

For this paper, the Chinese definitions of markers for excessive iodine intake were used, thus studies reporting iodine concentrations > 2.36 μmol/l in drinking water or > 6.30 μmol/l in urine were included.

Selection of studies

We screened MEDLINE (National Library of Medicine, Bethesda, MD, USA) and China Medical and Biological Literature (China Academy of Medicine, Beijing, China) for papers published up until 2001. The search was carried out using the following parameters: (*'iodine excess' or 'high iodine intake' or 'excessive iodine intake' or 'iodine-rich food' or 'iodine-rich water'*) to locate the counties where iodine excess was reported. Then this was combined with (*'IQ' or 'intellectual development' or 'cognitive development'*) to collect information on iodine excess related to intellectual development. In addition, all references found in the selected papers and in reviews (Yu, 1997; National Committee of Experts on Iodine, 1997; Zhao et al, 2000) were examined. An attempt was also made to collect unpublished data. Data were included when intellectual development in an area of excess iodine intake was compared with that in an area of normal iodine intake.

Analysis of data

The association of iodine excess with IQ was examined using meta-analysis procedures. For the overall estimate, Cohen's *d*-value (Cohen, 1988) was used to measure the standardised differences (weighed for sample size) in means of IQ between experimental and control groups in all studies. Cohen classified d-values into small effect size ($d = 0.2$), medium effect size ($d = 0.5$) and large effect size ($d = 0.8$).

Results

Distribution of areas with iodine excess in China

Before 1965, there were no reports of iodine excess. Searches found two reports of iodine excess originating from iodine-rich food (Suzuki et al. 1965; Lu et al. 1984) while most reported iodine excess originated from iodine-rich drinking water. All reports were from China, where iodine excess areas were reported in 92 counties in 10 provinces, with a total population of nearly 16 million (Table 1).

Iodine-rich drinking water is found exclusively underground. All areas with reported excessive iodine are on the plain, rather than in hilly or mountainous regions where iodine deficiency is found. Among the reported areas in China with excessive iodine, two large areas, which involve at least 15 counties, were nearby the Yellow River. One area (northern area: 300-600 km south of Beijing) is located north of the Yellow River, south of the Ziya river, and near the coast of the Yellow Sea, with an area of about 8,500 km^2 and a population of 4.5 million in 10 counties of Hebei and Shandong Provinces. In this area, iodine-rich water is found only in deep wells with a depth of 150-700 m. The other area (southern area: 500-700 km northwest of Shanghai) is located between the Old Yellow River and the Yellow River, with an area of about 9,000 km^2 and a population of approximately 6.4 million in some 9 counties of Jiangsu and Shandong Provinces. Over thousands of years, the Yellow River has shifted north from the Old Yellow River to its current location by flooding, leaving a flood plain between the previous and new locations of the Yellow River. In this area, iodine-rich water generally comes from shallow wells with a few exceptions from deep wells in some villages. Other areas, which are located in suburban Beijing and in the Provinces of Fujian, Hebei, Inner Mongolia, Shandong, Shanxi and Xinjiang, affect some 5 million people. Iodine-rich water is from either shallow wells or deep wells (Zhao et al. 2000).

Description of studies relating IQ to iodine excess

There are 16 epidemiological studies on the relationship of excessive iodine intake with cognitive development, all of which were conducted in China. Table 2 describes the general characteristics of these 16 studies. The studies were conducted in different locations of China, where educational level, living habits and culture were different, although all subjects had the Chinese nationality. IQ was measured using different tests, which were all 'Western' tests modified to Chinese culture. The total number of subjects involved in the 16 studies was 5425, ranging from 60 to 1274 per study. All studies were carried out in schoolchildren aged between 7 and 15 years. Average urinary iodine concentration ranged from 4.4 to 530 µmol/l (n=13). Most of studies (11/13) were conducted in population with an average iodine level in urine > 6.30 µmol/l. The average iodine level in drinking water ranged from 1.68 to 15.9 µmol/l (n=13).

Meta-analysis of data from selected studies

In undertaking a formal meta-analysis it is important to note the substantial heterogeneity of design. The 16 studies selected formed a heterogeneous group. The effect sizes (Cohen's *d*-value) of the individual studies ranged from -0.05 (study 15)

to -0.85 (study 6) and the mean effect size was –0.22, corresponding to a difference in IQ of 3.2 points (Fig. 1).

Table 1. Counties in which iodine excess* has been reported in China

Provinces	Counties
Northern area:	
Hebei	Baxian, Changxian, Dacheng, Damin, Dongguang, Guan, Guangzhong, Guantao, Haixing, Huanghua, Jinxian, Jingxiang, Langfang, Lingxi, Lingzhang, Mengcun, Nangong, Nanpi, Qiuxian, Qugao, Qinxian, Renqiu, Shuning, Waixian, Weixian, Wuqiao, Xiangang, Xianxian, Xincheng, Xiongxian, Yanshan, Yongqin, Zhongjie
Shangdong	Bingxian, Boxing, Dezhou, Gaoqing, Guanglao, Huimin, Jiyang, Kengli, Leling, Lijing, Lingxian, Lingyi, Linjing, Piyuan, Qinyun, Shanghe, Wucheng, Wutai, Xiajing, Yangxin, Zhanhua
Southern area:	
Anhui	Xiaoshan
Henan	Taiqian
Jiangsu	Fengxian, Peixian, Pizhou, Shuining, Tongshan
Shandong	Caoxian, Chenwu, Dingtao, Dongming, Hezhe, Jiaxiang, Jiling, Jushu, Liangshan, Jinxiang, Nianzhou, Qufu, Shanxian, Sishui, Tancheng, Tengxian, Weishan, Wenshang, Yuncheng, Yutai, Zaoauan, Zhouxian
Other areas:	
Beijing	Daxing
Fujian	Tongan
Hebei	Dachang, Leting, Tangshan
Inner Mongolia	Baodou
Shandong	Rizhao
Shanxi	Xiaoyi
Xinjiang	Kuitun

*Iodine excess is defined as an iodine concentration > 6.30 μmol/l in urine or >2.36 μmol/l in drinking water.

Table 2. General description of studies on iodine excess and cognitive development in schoolchildren in China

No	Authors	Study area	Sample size	Intelligence test	Age group	Water iodine (median or mean) (μmol/l)	Water iodine (median or mean) (μmol/gcr or μmol/l)	IQ (Mean ± SD)	significance	*d*
1	Sun et al. 1985	Rizao, Shandong	N: 480 E: 480	Binet	7-14	N/A	N: 1.32 ± 0.73 E: 529.94	N: 102 ± 14.79 E: 99 ± 13.55	P < 0.01	-0.212
2	Xie et al. 1987	Zanhua, Shandong	N: 92 E: 121	Binet	7-14	N: 0.79 E: 15.92	N: N/A E: 30.18	N: 87 ± 9.50 E: 84 ± 14.17	P < 0.005	-0.242
3	Wang et al. 1987	Huanghua, Hebei	N: 47 E: 47	Binet	8-9	N: 1.30 E: 3.40	N: 1.79 E: 4.40	N: 88.3 ± 8.8 E: 87.5 ± 9.2	NS (P > 0.05)	-0.089
4	Li et al. 1987	Gaojiabu and Huanglou, Shanxi	N: 51 E:120	Hiskey-Nebraska	7-15	N: 0.43 E: 3.64	N: 3.38 ± 0.03 E: 9.74 ± 0.01	N: 85 ± 17 E: 84 ± 16	NS (P > 0.05)	-0.061
5	Jupp et al. 1988	Gaojiabu and Huanglou, Shanxi	N: 51 E: 96	Hiskey-Nebraska	7-15	N: 0.43 E: 3.64	N: 3.38 ± 0.03 E: 9.74 ± 0.01	N: 85.79 ± 16.79 E: 77.54 ± 22.61	NS (P > 0.05)	-0.397
6	Ma et al. 1991	Qinyun, Shandong	N: 60 E: 31	Binet	7-12	N: 0.82-1.17 E: 8.67	N: 1.67 ± 0.02 E: 7.96 ± 0.01	N: 83.83 ± 9.3 E: 76.32 ± 7.85	P < 0.01	-0.850
7	Dong et al. 1991(Study I)	Sijiazuang, Hebei	N: 110 E: 99	Raven	8-12	N/A	N/A	N: 106.71 ± 13.03 E: 104.75 ± 16.83	NS (P > 0.05)	-0.131
8	Dong et al. 1991(Study II)	Sijiazuang, Hebei	N: 55 E: 60	Binet	8-9	N/A	N/A	N: 86 ± 7.13 E: 83.1 ± 9.25	NS (P > 0.05)	-0.349
9	Ling et al. 1993 (Study I)	Huanghua, Shandong	N: 55 E: 60	Binet	8-9	N: 1.30 E: 5.21 ± 0.14	N: 3.95 ± 1.47 E: 10.78 ± 3.58	N: 82.93 ± 6.78 E: 81.63 ± 8.35	NS (P > 0.05)	-0.170
10	Ling et al. 1993 (Study II)	Huanghua, Shandong	N: 119 E: 115	Binet	8-9	N: 1.52 E: 5.34 ± 0.75	N: 4.11 ± 0.31 E: 20.17 ± 2.60	N: 106.61 ± 12.88 E: 103.9 ± 16.43	NS (P > 0.05)	-0.184

Table 2. General description of studies on iodine excess and cognitive development in schoolchildren in China (continued)

No	Authors	Study area	Sample size	Intelligence test	Age group	Water iodine (median or mean) (μmol/l)	Water iodine (median or mean) (μmol/gcr or μmol/l)	IQ (Mean ± SD)	significance	*d*
11	Wang et al. 1993	Wutai, Shandong	N: 129 E1: 53 E2: 80	Binet	8-9	N: 0.39-1.46 E1: 11.98 E2: 7.09-8.35	N: 1.25 ± 0.02 E1: 21.04 ± 0.02 E2: 9.20 ± 0.01	N: 83.93 ± 9.30 E1: 84.03 ± 10.42 E2: 81.38 ± 7.98	NS (P > 0.05)	-0.163
12	Hu et al. 1994	Baodou, Inner Mongolia	N: 100 E: 105	Wechseler	> 7	N: 0.58 E: 6.84	N: N/A E: 9.08	N: 80.3 ± 11.83 E: 73.07 ± 10.75	P < 0.01	-0.640
13	Yang et al. 1994	Qinyun, Shandong	N: 30 E: 30	Binet	8-14	N: 1.01 E: 8.67	N: 1.67 E: 6.43	N: 81.67 ± 11.97 E: 76.67 ± 7.75	NS (P > 0.05)	-0.496
14	Wang et al. 2001	Pingying, Jiaxiang, Liangsan, Shandong	N: 130 E:110	Raven	7-14	N: 0.32-0.99 E: 7.64-8.20	N/A	N: 93.5 ± 8.93 E: 90.05 ± 9.22	NS (P > 0.05)	-0.380
15	Zhao et al. 2001	Feng and Pei, Jiangsu	N: 295 E: 732	Raven	8-15	N: 0.32 E: 1.98	N: 2.17 E: 5.47	N: 107.1 ± 13.9 E: 106.0 ± 13.0	NS (P > 0.05)	-0.052
16	Zhao et al. 2001	Feng and Pei, Jiangsu	N: 295 E: 987	Raven	8-15	N: 0.32 E: 6.06	N: 2.17 E: 11.55	N: 107.1 ± 13.9 E: 104.2 ± 14.3	P < 0.001	-0.216

N/A = not available; N = normal iodine intake; E = excessive iodine intake; NS = not significant; *d* = Cohen's d-value.

In order to examine whether the degree of iodine excess would affect the difference, the studies were splitted into two: those from areas in which urinary iodine concentrations were > 6.30 μmol/l (9 studies) and those in which urinary iodine concentrations were around or < 6.30 μmol/l (4 studies). For the first group, the effect size was 0.25 corresponding to an IQ difference of 3.7 points. For the second group, the effect size was 0.09 (NS) corresponding to an IQ difference of 1.4 points.

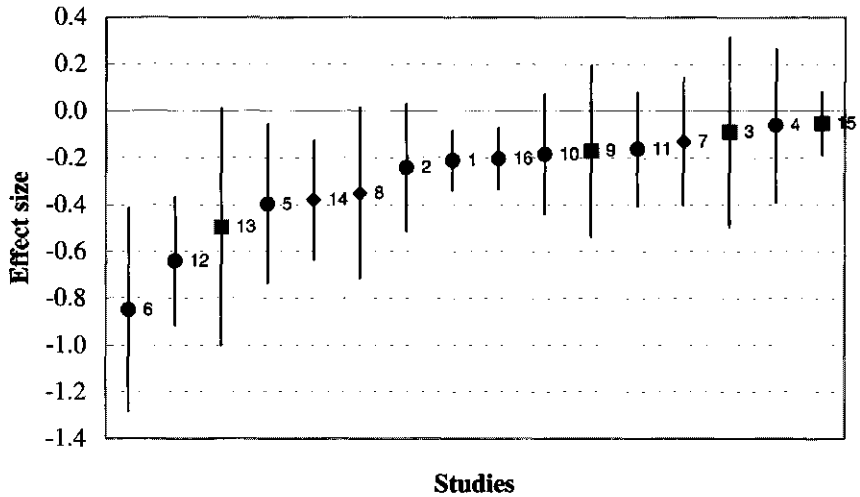

Fig. 1. Display of effect size and confidence intervals concerning general intelligence and iodine excess: •, studies with average urinary iodine concentrations far above 6.30 μmol/l; ■, studies with average urinary iodine concentrations around or below 6.30 μmol/l;◆, data on urinary iodine not available. The numbers correspond to those in Table 1.

Discussion

This paper provides information on the distribution of iodine excess in China and on the magnitude of the relationship between iodine excess and the intellectual performance of schoolchildren. The available epidemiological results provide evidence that iodine excess is a problem of public health significance in certain areas in China, and that excessive intake of iodine in children causes small but significant deficits in intellectual attainment.

The public health implications of exposure of children to high iodine intakes are probably not just limited to China. Excessive iodine intake can come from a number of sources. Many countries have developed salt iodisation programmes recently to

eliminate iodine deficiency. Over-consumption of iodised salt could occasionally result in a state of iodine excess (World Health Organisation /United Nations Children's Fund /International Council for Control of Iodine Deficiency Disorders, 1997). A decline in IQ as a result of salt iodisation is likely, if an extremely high intake of iodine from iodised salt occurs over a long period. This strengthens the importance of routine monitoring of the iodine content of salt to ensure urinary iodine concentrations of the population are kept within the normal range of 0.79 to 2.36 μmol/l (World Health Organisation /United Nations Children's Fund /International Council for Control of Iodine Deficiency Disorders, 1997).

The strength of a meta-analysis is that it is possible to gain useful and statistically significant information by combining studies, some of which may not have had sufficient power to obtain a significant result. There was a significant effect of iodine excess on intellectual development in only 6 of the 16 studies. However, when all 16 studies were combined, the effect of iodine excess was significant, corresponding to an IQ difference of 3.2. The difference in IQ increased to 3.7 points when the analysis was restricted to those studies in which urinary iodine concentrations were > 6.30 μmol/l.

Meta-analyses are prone to a number of limitations These include the inability to identify all studies which may introduce bias, the lack of detail provided on the study design and analysis, differences in definition of excessive iodine intake, and differences in the intelligence tests used. Because of our contacts within China, we think that nearly all important studies have been identified. Sufficient details of the design of the studies as well as on iodine concentration in urine and/or in drinking water were available. With respect to the intelligence tests, four different tests were used, of which three (Binet, Hiskey-Nebraska and Wechseler) have verbal subtests, which were developed for use in 'Western' cultures. Four of the five studies, where significant differences were found between experimental and control groups, used intelligence tests with verbal subtests. The researchers had made a big effort to modify them to the Chinese culture. Thus, we feel that the conclusions reached from our study are justified.

In 6 of the 9 studies where no significant difference in IQ was found, the water iodine level in the excessive areas did not exceed 6.0 μmol/l while in the other 4 studies the water iodine level in the excessive areas was above 6.0 μmol/l (studies 2, 6, 12, 16 in Table 2). Studies where a significant difference was found generally had higher iodine concentrations in urine than those where no significant difference was found. The results reported in this paper are in line with those reported from a recent study (Zhao et al. submitted for publication), in which the IQ of children < 11years of age was found increased when iodine intake from drinking water was reduced.

Reduction of iodine intake from excessive to normal may reverse the hypothyroidism induced by iodine excess (Tajiri et al. 1986). Hypothyroidism as a result of iodine deficiency has long been regarded as an important etiological factor in mental retardation (Hetzel, 1983; Delange, 1994). Hypothyroidism has been reported in many iodine excess environments where thyroglobulin in the thyroid gland incorporates more iodine with an increase in the diiodototyrosine (DIT) to monoiodotyrosine (MIT) ratio leading to increased T_4 production, relative to T_3, which is consistent with that iodide goitre is "colloid" predominant (Suzuki, 1985). Iodine excess may also inhibit the conversion of T_4 to T_3, leading to a rise in serum TSH (Li et al. 1987). Hypothyroidism may result thus leading to a decline in IQ of children exposed to high iodine intakes. The negative effect on cognitive development of iodine excess is much less than that of iodine deficiency. Up until now, no cases of cretinism have been reported from iodine excess areas.

In conclusion, iodine excess could appear to cause a small but significant decline in IQ of children. Thus, attention should be paid to areas where iodine concentrations in drinking water are very high (> 2.36 µmol/l) or to other circumstances when iodine intake is extremely high (iodine concentration in urine of adults > 6.30 µmol/l).

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Chapter V

Reduction of iodine intake from excessive to normal reduces thyroid size, partially normalizes thyroid function

Jinkou Zhao, Xiaoshu Hu, Qinlan Zhang, Li Shang, Clive E. West & Joseph G.A.J. Hautvast

Submitted

Abstract

To compare the efficacy of reduction of iodine intake on thyroid size and thyroid function in previously moderately and highly iodine excess areas, townships with water iodine concentrations of approximately 1000 μg/L and 400 μg/L were selected. Water iodine concentration was reduced in two townships to approximately 100 μg/L while another two townships served as controls. Thyroid size by palpation and ultrasound, and the concentration of iodine in urine and drinking water were measured at baseline, after 2 weeks and periodically between 1 and 12 months. Serum concentrations of thyrotropin (TSH), thyroxine (T_4) and triiodothyroxine (T_3) were measured at baseline and after 12 months. Urinary iodine concentration fell promptly after intervention started in the intervention townships. After three months, enlarged thyroids returned to normal volume. Elevated serum concentrations of TSH at baseline were lower at the end of study. Indicators of iodine status and thyroid function in the control townships remained unchanged throughout the study. In conclusion, urinary iodine concentration returned to normal quickly after reduction in iodine content of drinking water but thyroid volumes normalized after 3 months. After 12 months, initial elevated thyrotropin was reduced to normal in most but not all subjects.

While iodine deficiency is a global public health problem (1), iodine excess does pose a significant problem in certain areas in the world (2-4). Recent reports have revealed (4) that there are nearly 16 million people threatened by iodine excess in some 92 counties in 10 provinces of China. Iodine excess is associated not only with hyperthyroidism but also with hypothyroidism, goiter (5), and possible impairment of intellectual development (4).

Iodine deficiency was a significant public health problem in Jiangsu, which is a province located in the eastern part of China. Accordingly, universal salt iodization has been implemented in all counties except Feng, Pei and Tongshan counties in Xuzhou Municipality, where iodine excess exists. For more than a decade, residents in these three counties generally dig shallow wells to pump water for their use, because surface water is rare and rainfall is low. Seafood consumption of local residents is negligible because of its limited availability. In the 1980s, a few central water supply systems were established by combining household wells. From 1997 onwards, provincial and local governments launched 'safe water' projects to control water-borne infectious diseases.

Previous studies (6-7) in these three counties have revealed goiter was endemic and associated with high iodine intake in schoolchildren. Excessive iodine was mainly from drinking water. Thyroid function in adults appeared to be perturbed in two townships with extremely high iodine concentrations in drinking water (6).

It is unclear whether thyroid size decreases when iodine intake is reduced from excessive to normal and how long it takes for enlarged thyroids to become normal. Thyroid function is perturbed when iodine intake is excessive (6) but it is not known whether reduction of iodine intake to within the normal range will normalize thyroid function. In Japan adult male volunteers were given a daily oral dose of 27 mg of iodine (as lecithin-bound iodine) for 4 weeks (8). Thyroid volume as measured by ultrasound increased during the period when iodine intake was elevated but normalized within 28 days of iodine intake returning to normal. In those areas of China where populations are exposed to chronic excessive iodine intake, there are few data on the rate at which thyroid size and function become normal.

Therefore, the aim of this study was to compare the efficacy of reducing iodine intake to normal on goiter prevalence, thyroid volume, urinary iodine concentration and thyroid function in townships with moderately and highly excessive concentrations of iodine in drinking water.

Materials and Methods

Study site

Four townships in Feng and Pei counties, Jiangsu province, China were selected by convenience. Two pairs of townships were matched based on baseline iodine concentrations in drinking water. The high township pair (high townships; Tanglou and Mengzuan in Pei County) had median iodine concentrations in drinking water of about 1000 μg/L, while the low township pair (low townships; Zhaozuan in Feng County and Huxi in Pei County) of about 400 μg/L.

Study population

Schoolchildren aged 8-10 years attending the central elementary school in each township were chosen randomly for measurement of urinary iodine excretion, thyroid size, and the serum concentration of thyroid hormones over a one-year period. Measurements of thyroid size, thyroid hormones, and the concentration of iodine in urine and in drinking water were performed blind. Research protocols were explained carefully to all participants who agreed to participate voluntarily. Research protocols including ethical clearance were approved by the Scientific Research Committee of Jiangsu Provincial Center for Disease Control and Prevention.

Interventions

In each pair of townships, one was chosen for intervention and the other as a control. Intervention was carried out in Tanglou and Mengzuan, which are thus referred to as "high-intervention township" and "low-intervention township" respectively. There was no intervention in Zhaozuan and Huxi, which are thus referred to as "high-control township" and "low-control township" respectively. Deep wells were dug in the two intervention townships with the aim of reducing iodine content in drinking water to approximately 100 μg/L. Impermeable materials were used during construction of wells to ensure stability of iodine concentrations in drinking water during the study period.

Iodine concentration in drinking water

At least three water samples from different parts of water supply system (1 from source of water, and 2 from household outlets) were collected before, 2 weeks after the study began and every month thereafter in both intervention and control townships. Water iodine concentrations were determined using Barker's modified incineration technique based on catalytic reduction of ceric ion by arsenate salt (9).

Thyroid size

Thyroid size was assessed among 150 randomly selected schoolchildren in each township by experienced physicians both by palpation (10) and using real-time ultrasonography at baseline and 2 weeks, 1, 3, 6, 9, 12 months after baseline. Longitudinal and transverse scans were performed using portable ultrasound equipment with a 7.5 MHz linear array transducer (AKHO, Inc, Canada), allowing the measurement of depth (d), width (w) and length (l) of each lobe in millimeters. The volume of each lobe was calculated by the formula: volume (mL) = $0.479 \times d \times w \times l \times 1^{-3}$ and the thyroid volume estimated as the sum of both lobes (11). Thyroid volume was classified as normal or abnormal using the age-specific thyroid volume reference (12).

Estimation of sample size was based on the following assumptions: thyroid volumes are normally distributed; reduction in thyroid volume in both intervention townships of 1.4 ± 0.82 mL; and no change in thyroid volume in the control townships. The following equation was used (13):

$$N \geq (Z_{2\alpha} + Z_{\beta})^2 \frac{\sigma_1^2 + \sigma_2^2}{(\delta_1 - \delta_2)^2}$$

where $(Z_{2\alpha} + Z_{\beta})$ is 7.9 if $\alpha = 0.05$, $\beta = 0.80$, σ_1 and σ_2 are standard deviations for intervention and control townships, δ_1 and δ_2 are the mean reductions of thyroid volume in intervention and control townships (expected to be zero), the sample size is estimated to be 43 for each group. Thus the sample size chosen of 150 per township was regarded to be sufficient.

Iodine concentration in urine

Casual urine samples were collected from all children for thyroid size estimation in each township at baseline and 2 weeks and 1, 3, 6, 9 and 12 months after baseline. Standardized acid digestion method was used for detection of iodine (14). All sampling bottles were processed with mineral acid prior to sample collection to avoid any possible iodine contamination. Sample size was estimated based on the following equation (15):

$$N = M(\alpha, \beta) \frac{2(\sigma_1^2 + \sigma_2^2)}{(\mu_1 + \mu_2)^2} = M(\alpha, \beta) \frac{2(\sigma_1^2 + \sigma_2^2)}{[\ln(Y_{11}/Y_{12}) - \ln(Y_{21}/Y_{22})]^2}$$

where Y_{11} and Y_{21}, Y_{12} and Y_{22} are individual urinary iodine concentrations at baseline and at the end of study for the intervention and control townships respectively; σ_1 and σ_2 are the standard deviations of differences of urinary iodine concentration between baseline and the end of study. Given $\alpha = 0.05$, $\beta = 0.80$ and assuming that at baseline, urinary iodine concentrations will be 1400 μg/L in the high township pair and reduce to 200 μg/L at the end of study in the high-intervention township, urinary iodine concentration will be 800 μg/L in the low township pair and

reduce to 200 μg/L in the low-intervention township, sample size will be 25 and 21 per township for the high- and low-township pair respectively. The sample size chosen of 150 per township was regarded to be sufficient.

Thyroid functions

Blood samples (n = 25) were obtained at baseline and 12 months after intervention in each of the four townships from apparently healthy schoolchildren without any overt thyroid abnormalities. Sera were stored at –20 °C until analysis. Reagents for measurement of total T_4 (RIA) and total T_3 (RIA) and sTSH (IRMA) were from commercial sources (Diagnostic Product Corporation, Tianjin, China). Reference ranges for T_4, T_3 and sTSH were 6-12 μg/dL, 1.2-3.4 nmol/L and 0.3-5 μIU/mL, respectively. The sensitivity for sTSH was 0.03 μIU/mL.

Data analysis

All data were double entered using Epi Info's validate duplicate entry module. Data were analyzed with Epi Info 6.04b (CDC, Atlanta, GA, USA) and SAS 6.12 (SAS Institute, Cary, NC, USA). Medians were used to describe the central tendency of iodine concentrations in urine and in drinking water. The Kruskal-Wallis method was used to test the differences in ranking of iodine concentrations in drinking water and in urine. One way ANOVA was applied for comparison of mean thyroid volume, mean height and weight. Chi square test was used to compare prevalence of goiter and the proportion of children with high or low thyroid hormone concentrations before and after intervention within each pair and between pairs.

Results

Description of the study population at baseline

The four townships did not differ at baseline in mean age, sex proportion, mean height and mean weight (Table 1). Prevalence of goiter by palpation and ultrasound, iodine concentrations in drinking water and in urine were similar within each pair, but differed between pairs. Thyroid volume was similar among the four townships. Girls tended to have larger thyroid volumes than boys (4.59 mL vs 4.45mL; $P > 0.2$). Serum concentrations of TSH, T_3 and T_4 values were not different statistically between pairs and within each pair except the high township pair had lower serum T_3 concentration than the low township pair (1.22 vs1.44, $P = 0.02$).

Iodine concentration in drinking water

Table 1. Baseline data for the four townships

	Townships*					
	High-control	High-intervention	P values†	Low-control	Low-intervention	P values†
Water iodine concentration (μg/l)	1092 (n = 32) (708, 1204)	984 (n = 28) (518, 1164)	0.07	484 (n = 30) (392, 733)	394 (n = 29) (248, 524)	0.08
Boys/girls	75/75	75/75		75/75	76/76	
Age (mean ±SD, years)	8.34 ± 0.86	8.44 ± 0.79	0.29	8.55 ± 0.93	8.43 ± 0.90	0.25
Height (mean ±SD, cm)	126.74 ± 6.95	128.06 ± 6.38	0.08	127.75 ± 6.31	127.05 ± 5.78	0.68
Weight (mean ±SD, kg)	26.45 ± 4.43	27.27 ± 4.56	0.11	26.99 ± 5.11	26.39 ± 3.22	0.21
Urinary iodine (median, μg/l)	1293.6	1353.6	0.07	834.3	847.1	0.30
Thyroid volume (mean ±SD. Ml)	4.46 ± 1.38	4.77 ± 1.57	0.06	4.38 ± 1.14	4.47 ± 1.56	0.62
Prevalence of goiter (%) palpation	46.7	45.3	0.82	32.0	30.9	0.84
ultrasound	32.7	32.0	0.90	18.7	22.4	0.43

* The high township pair includes high-intervention and high-control townships while the low township pair includes low-intervention and low-control townships. Iodine concentration in water was reduced in high- and low-intervention townships while high- and low-control townships served as controls.

† Chi-square test was used for comparison of prevalence of goiter; One-way ANOVA was used for comparison for the mean weight, mean height and mean thyroid volume; The kruskal-Wallis method was used to compare the median iodine concentrations in urine and in drinking water.

A total of 1679 samples of drinking water were collected (Fig. 1). At baseline, water iodine concentrations differed between pairs ($P < 0.01$), but did not within each pair ($P > 0.05$). Beginning at 2 weeks after baseline, iodine concentrations in drinking water dropped substantially to around 100 μg/L and remained relatively stable within the range of 82-165 μg/L in the two intervention townships. Iodine concentrations in the control townships did not change during the study period, ranging from 395 to 501 μg/L and from 978 to 1102 μg/L for low- and high-control townships respectively.

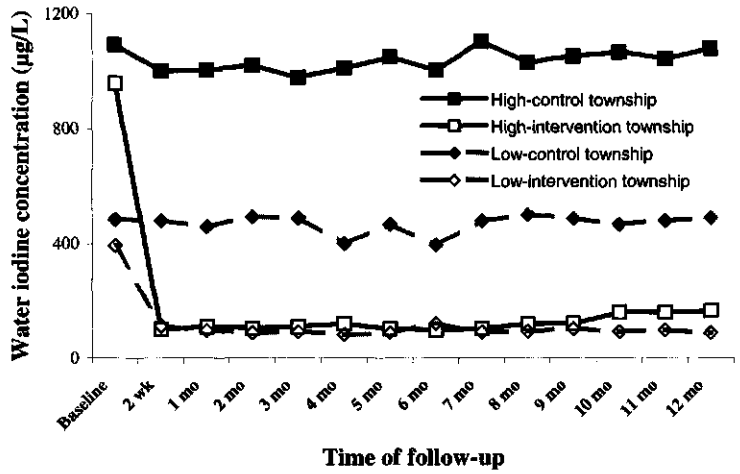

Fig.1 Median iodine concentrations in drinking water over the study period (N=1679). High-intervention and high-control townships are the high township pair with iodine concentrations of around 1000 μg/L while low-intervention and low-control townships in the low township pair have iodine concentrations of about 400 μg/L.

Iodine concentration in urine

Median urinary iodine concentrations in the four townships are shown in Fig. 2. At baseline, iodine concentrations in urine among schoolchildren differed between pairs ($P < 0.01$), being about 800 μg/L for the low townships and around 1300 μg/L in the high townships. Median iodine concentrations in urine in the intervention townships were significantly decreased 2 weeks after the intervention began compared with those in the control townships ($P < 0.01$), as were iodine concentrations in drinking water. After 2 weeks, urinary iodine concentrations remained around 250 μg/L throughout the whole study period in both high- and low-intervention townships. For the control townships, iodine concentrations in urine remained at their initial high levels with few changes. Boys tended to have higher median urinary iodine concentrations than girls at baseline and at each follow-up measurement ($P > 0.05$; data not shown).

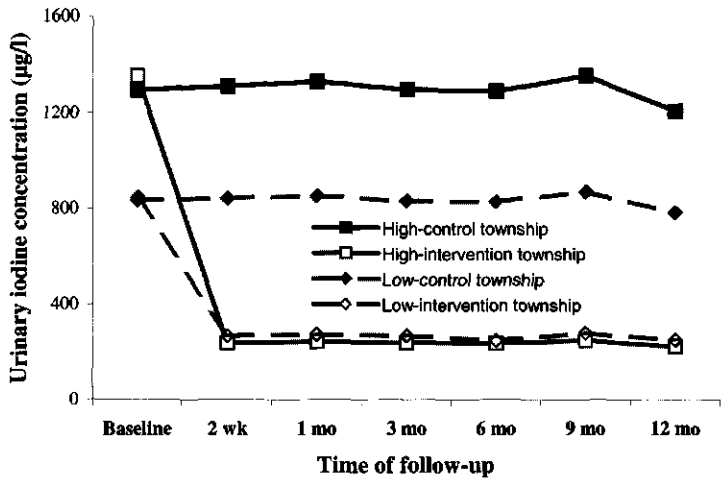

Fig. 2 Median iodine concentrations in urine over the study period (N=4205).

Thyroid size

At baseline, prevalence of goiter measured by palpation for each township was different between pairs but not within each pair. In the control townships, prevalence of goiter measured both by palpation and ultrasonography at each follow-up measurement did not differ from baseline values ($P > 0.2$), except that in the high-control township prevalence of goiter measured by palpation was lower than the baseline value at the end of study ($P < 0.05$) (Fig. 3). In the intervention townships, prevalences of goiter measured by ultrasound decreased significantly at 3 months ($P < 0.01$) while those measured by palpation shown difference at 9 months ($P < 0.05$). In the intervention townships, mean thyroid volume, observed after 3-month follow-up, was already significantly lower than at baseline ($P < 0.01$) with 32.7% and 48.5% reduction for the high- and low-intervention townships respectively (Fig. 3). After 3 months, there was little further change in thyroid volume in the intervention townships while in the control townships thyroid volume remained enlarged throughout the study. The prevalence of goiter in girls tended to be higher than that in boys ($P > 0.05$; data not shown).

Thyroid hormones

Over the one-year intervention period, a reduction of 0.42 μIU/mL in serum concentration of TSH was observed in the high-intervention township, which is significantly greater ($P = 0.003$) than that (0.02 μIU/mL) in the high-control township (Table 2). Also the reduction in TSH was larger in the low-intervention township than in the low-control township (0.48 vs 0.04 μIU/mL, $P = 0.002$). At baseline, high TSH

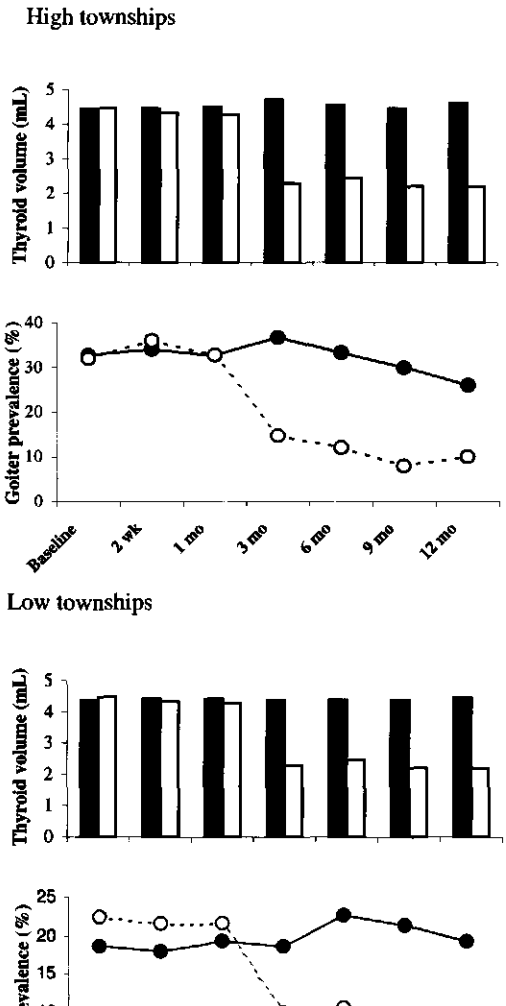

Fig.3 Thyroid volume and goiter prevalence in townships with initially moderately and highly excessive iodine in drinking water. Solid lines and circles refer to the control townships while open lines and circles refer to the intervention townships. For description of intervention, see text.

Table 2. Thyroid function in four townships in China before and after intervention

	Time after baseline	Townships*																			
		High-control					High-intervention					Low-control					Low-intervention				
		N	Mean (SE)	L†	W	H	N	Mean (SE)	L	W	H	N	Mean (SE)	L	W	H	N	Mean (SE)	L	W	H
T4	Baseline	25	8.68 (0.17)		25		25	8.96 (0.22)		25		25	8.16 (0.35)	2	25		25	9.04 (0.17)		25	
	12 m	25	8.28 (0.31)	2	23		25	8.80 (0.22)		25		25	9.48 (0.31) ‡,§		25		26	8.77 (0.23)		26	
T3	Baseline	25	1.16 (0.08)	21	4		25	1.28 (0.09)	18	7		23	1.30 (0.10)	16	7		25	1.56 (0.10)	11	14	
	12 m	25	1.12 (0.07)	22	23		25	1.40 (0.10) §	15	10		25	1.56 (0.10)	11‡	14		26	1.62 (0.10)	10	16	
TSH	Baseline	24	4.96 (0.41)		18	6	25	4.40 (0.37)		17	8	22	4.05 (0.57)		19	3	25	3.84 (0.31)		22	3
	12 m	25	4.95 (0.35)		19	6	25	4.08 (0.24) §		23	2‡	23	4.00 (0.24)		20	3	26	3.35 (0.24) §		25	1

*Refer to the footnotes of Table 1.

† L, W and H: lower, within and higher than the reference range, respectively.

‡ $P < 0.01$ as compared with baseline values.

§ $P < 0.05$ as compared with respective values in the control townships.

values were more common in the high township pair than in the low township pair (28.6% vs 12.8%, $P = 0.057$). After intervention, the proportion of children with high TSH values was reduced from 47.1% to 8.7% ($P = 0.033$) in the high-intervention township with a 81.5% reduction, which is relatively more ($P < 0.0001$) than the reduction (5.3%) observed in the high-control township. Similarly, the reduction in the proportion of children with high TSH values was higher in the low-intervention township than that in the low-control township (70.5% vs 5.0%; $P < 0.0001$).

Serum concentrations of T_3 were higher in the low township pair than in the high township pair (1.44 vs 1.22, $P = 0.02$) at the beginning. Elevated concentrations of T_3 were observed in the high-intervention township at the end of study, which are significantly higher than respective values in the high-control township ($P = 0.023$). The increase in T_3 was not significantly different between the high-intervention and high-control townships or between the low-intervention and low-control townships. The high township pair had a higher proportion of lower T_3 values than the low township pair (78.0% vs 56.3%, $P = 0.02$ at baseline, 74.0% vs 41.2%, $P = 0.0009$ after 12 months).

Changes of T_4 values were not significant among townships, between baseline and at the end of the intervention, nor was the increase in T_4 over the intervention period within each pair ($P < 0.05$).

Discussion

The present study clearly shows that enlarged thyroid volumes, elevated serum concentrations of TSH and elevated urinary iodine concentrations decreased significantly in response to reduction in iodine intake from drinking water. Urinary iodine concentrations dropped dramatically after reducing the concentration of iodine in drinking water. This prompt response in the intervention townships and lack of response in the control townships implies that the high iodine concentration in drinking water was responsible for the high iodine intake, as reflected in urinary iodine concentrations. Thyroid gland volume decreased by 30-50% three months after the intervention commenced. This confirms the hypotheses arising from our previous studies (6, 7) that endemic goiter in this area is due to iodine excess rather than iodine deficiency.

Although there was a marked reduction in thyroid volume measured by ultrasound, the reduction took 3 months which is contrast to the prompt decline in the concentrations of iodine in urine. In iodine deficiency, it takes even longer for enlarged thyroids to reduce to normal size after iodine intake becomes normal (16-18). This difference may be attributable to the different mechanisms by which iodine excess and iodine deficiency produce goiter. For iodide goiter, the follicles are filled

with colloid and the epithelial cells are flattened (3, 19, 20), while for goiter due to iodine deficiency, more pathological changes are found, where parenchymal cells are abundant, follicular epithelial cells are thicker with papillary infolding and there is very little colloid (21).

Limited experimental studies (8, 22, 23) on iodine excess have indicated that the extent and length of exposure to excessive iodine may be among those factors to affect the speed of normalization of thyroid volume, and of reduction in prevalence of goiter. Two similar studies have been carried out in China previously in which only goiter prevalence by palpation was measured (22, 23). In one study (22), the level of iodine in drinking water was reduced from 801 μg/L to123 μg/L and the prevalence of goiter was reduced from 35% prior to the intervention to 23%, 20% and 18% after 1, 2 and 3 years respectively. In the other study (23), the level of iodine in drinking water was reduced from 559 μg/L to 44 μg/L and the prevalence of goiter was reduced from 29% to 15% within 3 months. In an experimental study in Japan (8) in which subjects received 27 mg iodine as iodized lecithin for 4 weeks, thyroid volume reduced to normal one month after iodine intake returned to normal.

When thyroid volumes decline, it would be expected that prevalence of goiter would decline to the same extent. However, while most enlarged thyroids were reduced in volume in response to the decreased iodine intake, the thyroids of some subjects remained large or were reduced in size but remained abnormal based on the age-specific thyroid volume reference (12). There appears to be marked individual sensitivity, implying pre-existing underlying thyroid abnormalities in those subjects. This is consistent with other studies (8, 22) indicating persistence of large goiters for a prolonged period of time after normalization of iodine intake. Fine needle biopsy of these large goiters would be necessary to explore the pathological or histological alterations of thyroid gland.

There is a substantial difference in prevalence of goiter measured by palpation and by ultrasound. Possible reasons could be that iodide goiter is firm and consistent, which may lead to an overestimate of the true prevalence by palpation. Another explanation could be that the Chinese age-specific thyroid volume reference is too high so that estimates of goiter prevalence were lower than those obtained by palpation. The difference by the two methods became even larger when the reference value based on body surface area (11) was applied to this population (data not shown). There is a need for further standardization of thyroid volume by ultrasound in areas with different iodine intakes.

As the reduction in thyroid size lags behind the reduction in urinary iodine concentration, it is important not just to measure thyroid size but also other

parameters when monitoring changes due to the iodine supply or to other interventions which may affect iodine status of the population.

Thyroid function in the population living in these four townships appeared to be perturbed, as evidenced by the high proportion of children with elevated serum TSH concentrations. Other reports (24-29) on iodine excess have found similar results. At the end of this study, when intakes of iodine were normal for one year, decreased mean serum TSH concentration and the proportion of children with high TSH levels, and increased serum concentrations of T_3 were observed in the intervention townships. It can be reasonably inferred that perturbed thyroid function could possibly be reversed if exposure to excessive iodine ceases.

High TSH values are observed in some individuals when iodine intake had been normal for one year. This is consistent with the results from another study (22) in China, which did not find any decrease in serum TSH concentration after a high iodine intake had been reduced for 2 years. This is contrast to the study in Japan referred above in which the subjects were exposed acutely to excess iodine. The elevated TSH levels returned to normal within a month after cessation of the excess iodide supply (8). It may even take longer for biochemical and pathological dysfunctional thyroid glands to become normal in those members of the population chronically exposed to excess iodine as were the subjects described in this study. Our findings seem to support those of Tajiri et al (30) who described an irreversible type of hypothyroidism not sensitive to iodine restriction.

Up until now, there is no agreed definition of iodine excess. Our previous studies (6, 31) led us to set the maximum allowable concentration in urine at 800 μg/L. In this study, the proportion of children with high serum TSH concentrations in the high township pair was higher than the low township pair but similar to that in another study (28) where mean urinary iodine concentrations were 1104 ± 1914 μg/dL. In this study, thyroid volume values were not different between two pairs at baseline. Reduction in thyroid volume observed in two intervention townships was not statistically significant between pairs. It appears to support a threshold of maximum allowable concentration for iodine excess below 830 μg/L in urine or 400 μg/L in drinking water.

In conclusion, as iodine concentration in drinking water decreases from excessive levels, there is a prompt reduction in iodine intake as reflected in urinary iodine concentration. It took three months for the volume of thyroid glands to become normal after iodine intake was normalized. Thyroid function became normal in most but not all subjects as indicated by the reduction of mean serum TSH concentration and the decrease in the proportion of children with high TSH values. Based on the

evidence in this study, a maximum allowable concentration of iodine lies below 830 μg/L in urine or 400 μg/L in drinking water.

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Chapter VI

Randomized clinical trial comparing different iodine interventions in school children

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Abstract

Objective: the purpose of this trial was to compare three different iodine interventions.
Design: School children aged 8-10 years were randomized into one of three groups: group A was provided with iodized salt by researchers with an iodine concentration of 25 ppm; group B purchased iodized salt from the market; and group C was similar to group B with the exception that they were given iodized oil capsules containing 400 mg iodine at the beginning of the study. Salt iodine content was measured bimonthly for 18 months and indicators of iodine deficiency were measured at baseline and 6, 9, 12 and 18 months after randomization.
Results: The prevalence of abnormal thyroid volumes, based on the World Health Organization (WHO) body surface area reference >97th percentile, was 18% at baseline and declined to less than 5% by 12 month in groups A and C, and to 9% after 18 months in group B. Results for goitre by palpation were similar. The median urinary iodine was 94 µg/L at baseline and increased in all groups to > 200 µg/L at the 6-month follow-up.
Conclusions: In this population of school children with initially a low to moderate level of iodine deficiency, the group receiving salt with 25 ppm (group A) was not iodine deficient on all indicators after 18 months of study. When the iodine content of the salt varied, such as in group B, by 18 months thyroid sizes had not yet achieved normal status.

Key words: Iodine deficiency disorders, Randomized trial, Intervention, Iodized salt, Iodized oil, Goitre, Thyroid volume

Iodine deficiency is the leading preventable cause of brain damage and mental retardation worldwide[1]. The consequences of iodine deficiency, collectively referred to as iodine deficiency disorders (IDD), include cretinism, mental retardation, goitre, abortion, stillbirths, congenital anomalies and low birth weight[2]. In 1990 it was estimated that 655 million people worldwide had goitre and 1.6 billion are at risk of IDD[1]. The elimination of IDD by the year 2000 was determined to be a global public health priority at 'World Summit for Children' in 1990[3]. Over this decade, the elimination of iodine deficiency through national salt iodization programs has been a global development priority. Most national programs use the prevalence of goitre in school children as their main indicator to evaluate program success. The prevalence of goitre has not declined as rapidly as expected in some areas and sometimes it is inconsistent with urinary iodine results.

IDD is a significant public health problem in China[1]. A national survey in 1995 found the prevalence of goitre among school children to be ≥10% in 27 of 30 provinces[4]. The present study was performed in Jiangsu Province which was classified in 1995 as having a mild level of IDD[5] according to WHO/UNICEF/ICCIDD criteria with a total goitre rate (TGR) in school children of 17% and median urinary iodine levels of 85 μg/L.

The primary intervention used to prevent IDD has been the iodization of salt, which has been associated with the successful elimination of IDD in a number of countries[6]. Currently it is recommended that salt be iodized in the range of 20-40 ppm at the point of production in order to assure that median urinary iodine levels are in the 100-200 μg/L range. UNICEF estimates that nearly 60% of all edible salt in the world is currently iodized[8]. If iodized salt is not available in an iodine-deficient area, iodized oil capsules are frequently distributed. An oral dose of 400 mg iodized oil may maintain a median level of iodine in the urine of >100 μg/L for 12 months[9, 10].

Following the introduction of iodized salt into iodine deficient population, there has been little information on how long it takes for thyroids, which increase in size as a consequence of the deficiency, to return to normal size. The importance of this question is because the prevalence of goitre and abnormal thyroid volumes in school children are used as an indicator of the magnitude of IDD. Many countries are now observing a persistence of goitre in school children despite apparent successful implementation of near universal iodized salt consumption. This randomized clinical trial was performed to determine the impact of iodized salt and iodized oil on thyroid size and urinary iodine in school children in a remote population during an 18-month period.

Methods

Study population

This study was performed on Baguanzhou Island, Jiangsu Province, China. This island, located on the Yangzi River with a ferry connection to the mainland, has a population of 30,000 and covers an area of approximately 47.8 km^2. Agriculture is the principal occupation and the most foods consumed are grown locally. Prior to the present study there were no data on the iodine status of the population nor had an iodine prophylaxis program been initiated on this island. Salt distributed in the area had not been iodized prior to the present study.

Sample size was estimated based on the following conditions: the prevalence of goitre or abnormal thyroid volume at baseline would be 25% and after 18 months, would be 5%; an alpha value of 0.05; and a power of 80%. Given these conditions, 60 children in each group would be required. The sample size was increased to allow for loss to follow-up and because the prevalence at baseline was not known with accuracy.

Households of pupils in grades 2-4 in Baguanzhou Elementary School were invited to participate voluntarily in the study. Pupils who were less than 8 years of age were excluded from the study.

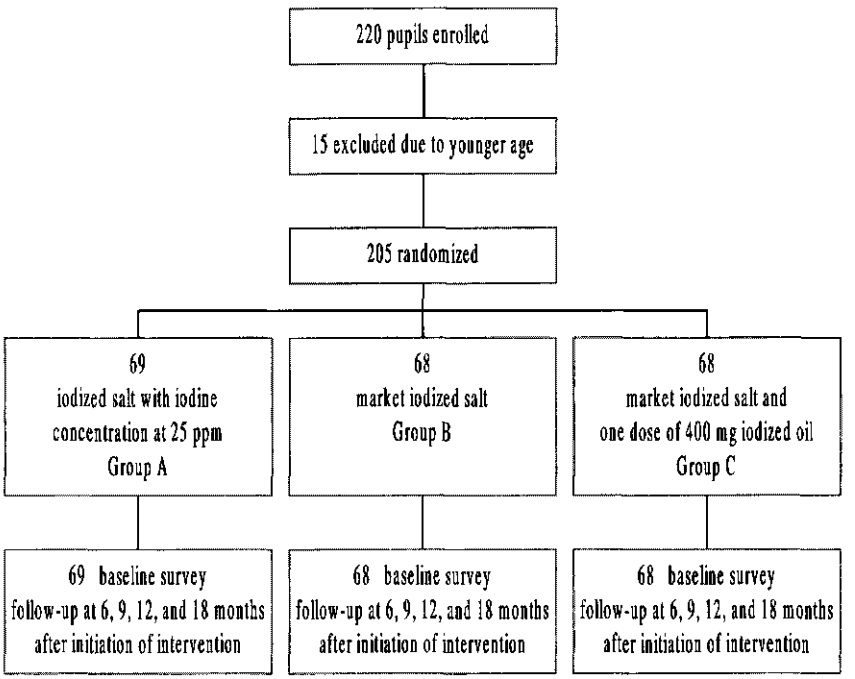
Intervention and outcome measures

Pupils were allocated into one of three groups using systematic block randomization based on age and sex (Fig. 1): pupils in group A were provided with iodized salt specifically produced to contain 25 ppm (42.25 g of potassium iodate per kilogram of salt). Homogeneity, consistency and precise iodine concentration of the salt were achieved by thorough mixing and close laboratory monitoring. Every 2 months, researchers distributed the iodized salt to their households immediately after production and collected salt left over from the previous distribution. Pupils in group B purchased commercially available salt in the market. Pupils in group C were similar to group B except that they receive four capsules of iodized oil, each containing 100 mg iodine, at the start of the study. The iodized oil used in this trial was provided by Wuhan Fourth Pharmaceuticals Factory (Wuhan, China), in which iodine was bound to unsaturated fatty acids from poppy seed oil[11]. All salt used for the study, both the specifically prepared salt for group A and the salt commercially available in the market, was supplied by one producer (Xiaguan Salt Company, Nanjing, China).

The three populations were followed for 18 months. Salt samples were tested for their iodine content using the titration method described by Sullivan et al.[12]. Starting at the second month of the study, every 2 months until the end of study, pupils brought salt samples from their homes for iodine detection. At baseline and 6, 9, 12 and 18 months after randomization, palpation and thyroid ultrasonography were performed

and height, weight and urine samples were obtained. Thyroid volume was measured using real-time ultrasonography, which was performed by one experienced physician using portable ultrasound equipment with a 7.5 MHz linear array transducer (AKHO, Inc, Canada). Longitudinal and transverse scans were performed allowing the measurement of the depth (d), the width (w) and the length (l) of each lobe in centimeters. The volume of each lobe was calculated by the formula: volume (ml)=0.479×d×w×l and the thyroid volume estimated as the sum of both lobes. Thyroid volume was classified as normal or abnormal using the thyroid volume for body surface area (BSA) reference described by Delange et al.[13]. BSA was calculated by using the formula: BSA (m^2)=$W^{0.425}\times H^{0.725}\times 71.84\times 10^{-4}$ where W is the child's weight in kilograms and H is the child's height in centimeters[14]. The prevalence of abnormal thyroid volume (ATV) was calculated as the number of children with a volume above the upper limit (>97th percentile) divided by the total number of children measured.

Fig. 1 Trial profile



Casual urine samples were collected using bottles processed with heavy acids and washed with demineralized water several times before collecting urine samples to avoid contamination. The urinary iodine concentrations were analyzed within 24 hours using a modified acid-digestion method in the Jiangsu Province iodine laboratory[15], which is under regular quality control by the Chinese National Institute of IDD. Urinary iodine analysis of 6 blind quality assurance samples at three levels by the Jiangsu Province laboratory did not demonstrate bias compared to the true values (P = 0.14). The precision of these determinations is 2.4%. (Laboratory quality assurance results can be found in the Appendix.)

All laboratory tests (salt titration and urinary iodine analyses) and thyroid size determinations (palpation and ultrasonography) were performed without knowledge into which group the pupils had been randomized.

Data analysis

Criteria by WHO/UNICEF/ICCIDD were used to classify the severity of IDD in the population[16]. For thyroid volumes and goitre, the classification is based on the prevalence of the condition: mild, 5-19.9%; moderate, 20-29.9%; and severe, ≥30%. For the median urinary iodine, the classification is: mild, 50-99 μg/L; moderate, 20-49 μg/L; severe, <20 μg/L.

Data were analyzed with Epi Info 6.04 and SAS 6.12. Confidence intervals for median values were calculated as described by Campbell and Gardner[17]. Confidence intervals for the prevalence of ATV and TGR are based on the exact binomial method. The differences in ranking of the urinary iodine distributions were tested using the Kruskal-Wallis method. Chi-square tests were applied to compare the TGR and the prevalence of ATV over time among groups.

Results

Of the 220 pupils enrolled in grade 2-4, 205 were 8-10 years of age and were randomized into one of three groups (Fig. 1). All households agreed to voluntarily participate in the study and there were no withdrawals during the 18-month study period. The number of urinary iodine results available varied at each follow-up visit, from 130 (63%) to 149 (73%) out of the 205 pupils followed. The three groups did not differ in age, sex, weight, height, BSA, TGR, prevalence of ATV, or median urinary iodine at baseline (Table 1). Approximately half of the pupils were male, TGR was 27%, the prevalence of ATV 18%, and the median urinary iodine in all three

groups was <100 μg/L. Using the WHO/UNICEF/ICCIDD classifications[16], the TGR would classify the area as having a moderate level of IDD, and the levels of prevalence of ATV and median urinary iodine would classify the area as having a mild level of IDD.

Table 1 Comparison of general variables among three groups at the beginning of the study

Variables	Group A	Group B	Group C	P value*
Number of pupils				
aged 8 years	23	22	23	
aged 9 years	23	24	22	
aged 10 years	23	22	23	0.996
total	69	68	68	
Sex: male (%)	50.7	50.0	50.0	0.995
Weight (mean, kg)	28.0	28.1	28.0	0.990
Height (mean, cm)	129.3	129.1	129.2	0.983
Body surface area (mean, m^2)	1.002	1.004	1.003	0.959
Total goitre rate (%)	26.1	26.5	26.5	0.998
Prevalence of abnormal thyroid volume (%)	17.4	17.7	17.7	0.999
Median urinary iodine (μg/L)	92.4	95.0	94.2	0.828

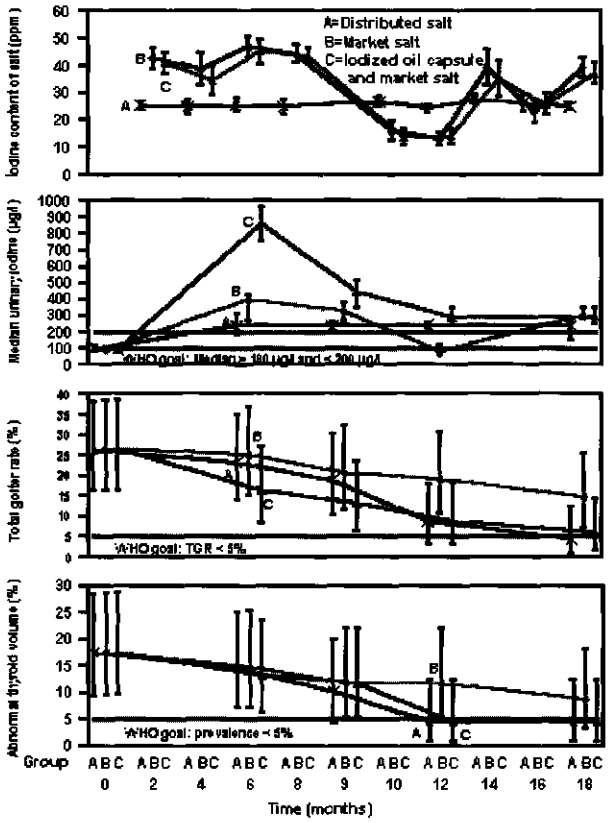
*Chi-square test was used for comparison for proportion of age, sex, total goitre rate and the prevalence of abnormal thyroid volume.

One-way ANOVA was used for comparison for the mean weight, mean height, mean body surface area and mean thyroid volume.

The Kruskal-Wallis method was used to compare the median urinary iodine concentration.

The salt iodine content in group A was stable with mean values ranging from 24 to 28 ppm during the study period. For groups B and C, the iodine concentrations in the salt varied, with mean values from 13 to 47 ppm (Fig. 2). No significant difference in mean salt iodine concentrations was found between groups B and C ($P > 0.05$), but the mean salt iodine content in group A differed significantly from groups B and C ($P < 0.01$). At baseline all three groups had a median urinary iodine <100 μg/L and at all subsequent visits the urinary iodine was >200 μg/L with one exception (Fig. 2). In group B the urinary iodine fell below 100 μg/L at the 12-month follow-up, which corresponds to the time when the iodine content of the market salt fell below 16 ppm (months 10, and 12). After the iodine content of the market salt remained > 23 ppm at months 14-18, the median urinary iodine level increased in group B. When the iodine content of the market salt was >25 ppm, group B had a higher median urinary iodine level than group A; when the iodine content of the market salt fell below 25 ppm,

Fig. 2 Iodine content of salt, median urinary iodine levels, total goitre rate and the prevalence of abnormal thyroid volume by group over time. Error bars represent 95% confidence intervals.



group A had higher urinary iodine level than group B. As would be expected, the median urinary iodine at month 6 was the greatest in pupils who received the iodized oil capsules. Significant differences in median urinary iodine levels were found among the three groups ($P < 0.001$) at 6, 9, 12, and 18 months.

In all three groups, the prevalence of ATV and TGR declined during the study period (Fig. 2). By the 12th month, groups A and C had a prevalence of ATV <5%, and a TGR near 5% by the 18th month. For group B, the prevalence of ATV declined similarly to groups A and C until between months 9 and 12, where there was little decline. This corresponds to the same time when the iodine content of the market salt fell below 16 ppm.

Discussion

Based on the results in group A, one of the main findings in this study was that consumption of salt with a uniform iodine content of 25 ppm maintained a urinary iodine level >100 μg/L and reduced thyroid sizes to normal levels after 12-18 months. In a population where the salt iodine concentration is not consistently maintained to at least 20 ppm in the household, it may take longer for thyroid sizes to return to normal, as with group B. The latter situation is more likely to be found in the real world, as many salt producers have not established stringent quality assurance to guarantee a uniform and standard concentration of iodine at the household level. In group C, the addition of iodized oil capsules as well as iodized salt from the market gave similar beneficial results to those seen in group A after 12-18 months. In populations with severe level of IDD, it is likely that the prevalence of ATV and TGR may take longer to become normal.

In the study population, the severity of IDD based on the WHO/UNICEF/ ICCIDD criteria for urinary iodine, goitre and ATV indicated a mild or moderate level of IDD prior to intervention[16]. Six months after initiation of the study, for group A the urinary iodine values indicated no IDD whereas goitre and thyroid ultrasound still indicated a mild to moderate level of IDD. It is biologically plausible that as the iodine intake increases, this will be reflected within days in the excretion of urine, but it takes months, and perhaps years, for thyroid size to return to normal, at least in an initially mildly to moderately deficient population. After 18 months, in groups A and C, all three IDD indicators were in agreement in indicating no IDD. In group B, after 18 months the urinary iodine indicated no IDD while the TGR and the prevalence of ATV indicated mild IDD. When there are inconsistencies between different indicators of IDD, where frequently urinary iodine is normal but thyroid size indicates IDD, this may be due to an inadequate amount of time allowed for the population to attain a low prevalence of goitre after initiation of the intervention. Another possible explanation for differences between indicators could be the accuracy of urinary iodine analyses and the assessment of thyroid size.

A concern with the introduction of iodized salt into populations with moderate to severe levels of IDD is the potential for the occurrence of iodine-induced hyperthyroidism (IIH) [18]. To minimize the potential of IIH, it has been recommended that the iodine content of salt be set at the minimal level to result in median urinary iodine levels in the 100-200 μg/L range. In group A, it appears that the iodine content of the salt could be decreased slightly while still ensuring iodine sufficiency. In group B, the iodine content of the salt varied widely during the study period indicating

potentially poor quality control by the producer. When the iodine content of the salt in the household in group B was >38 ppm the urinary iodine levels were much higher than 200 μg/L, and when the iodine content was <15 ppm the urinary iodine level fell below 100 μg/L.

Because of the limited sample size, the power to detect some difference between groups was not high. While the confidence intervals around the salt iodine content and urinary iodine levels were relatively narrow, the confidence intervals around the prevalence of ATV and TGR were wide.

At baseline, the median urinary iodine level and ATV indicated 'mild' IDD while the TGR indicated 'moderate' IDD. The WHO/UNICEF/ICCIDD cut-offs are not exact, the slight discrepancies may be expected. Other possible explanations for the slight differences include that the individual performing the palpation may have overestimated the prevalence or that the urinary iodine results may be higher than in other laboratories. Concerning the comparison of ATV and TGR, the WHO thyroid volume for BSA reference is relatively new and, as of this writing, there was no published literature comparing these two methods.

Compared to group B, the urinary iodine concentration in group C was about 450 μg/L higher, which is consistent with results of studies using the same iodized oil capsules[11], and remained higher until 12 months. This indicates that oral administration of 400 mg of iodized oil can be effective for the first 12 months. This result is similar to a number of studies [9, 10, 19-21], and in contrast with others[22, 23]. A literature review failed to find any studies reporting the simultaneous effects of iodized salt and iodized oil. The raised median urinary iodine concentration in group C in the first 12 months could be the combined effects of iodized oil and iodized salt.

It is recommended that all salt for human and animal consumption be adequately iodized to eliminate IDD. The iodine content of the salt should ideally result in urinary iodine levels in the 100-200 μg/L level[7]. In may situations this requires iodizing the salt between 20 and 40 ppm at the factory. The exact level at which to iodize salt depends on a number of factors, including the amount of iodine from other sources, the average salt consumption per person per day, the methods used to add iodine to salt, and other factors that lead to iodine loss between production and consumption. It is important for salt producers and public health officials to work together to ensure that iodized salt is produced with high and consistent quality and that its impact on the production is monitored to ensure that iodine intake of the population is neither too low nor too high.

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Appendix

All quality assurance specimens were tested three times with the results shown below.

No. of Specimen	True value (µg/L)	Mean of measured values (µg/L)*
1	76.3	79.4 (78.9, 79.7, 79.6)
2	153.9	159.1 (157.6, 158.6, 161.2)
3	296.3	294.4 (295.4, 296.8, 300.1)
I1	89.4	91.1 (89.8, 91.6, 92.0)
I2	133.0	132.7 (131.9, 132.8, 133.4)
I3	184.9	192.7 (193.6, 191.4, 193.1)

*Numbers in parentheses are measured values

Chapter VII

Virtual elimination of iodine-deficiency disorders achieved in nine counties of Jiangsu Province, China

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Food and Nutrition Bulletin **1998; 19: 347-352.**

Abstract

To assess the iodine-deficiency disorder status in nine counties of Jiangsu Province, China, where salt iodization was initiated in 1985, a special verification survey was conducted in 1997 by a provincial multisectoral team. Results obtained by regular monitoring of counties indicated that the goiter rate in schoolchildren had progressively decreased from 41.9% in 1983 to 3.9% in 1997, while the median urinary iodine concentrations of the population had remained above 100 μg/L since 1985. More than 90% of the edible salt supplied to households had been iodized at ≥ 20 mg I/kg during the previous five years. The data obtained by the provincial verification confirmed the county findings of ≥ 90% adequate iodized salt in households, < 5% goiter rate in schoolchildren, and adequate urinary iodine excretions. The provincial team also considered the established mechanisms for salt iodization and supply and iodine information management potentially sustainable. The high variability of the iodine content of household salt indicates that improved quality assurance of iodized salt at production and continued monitoring of population iodine indicators are needed.

Introduction

Iodine deficiency is the leading cause of preventable intellectual deficit worldwide, with 1.6 billion people globally at risk [1]. The prevention of iodine-deficiency disorders received a major impetus at the 1990 United Nations Global Summit for Children from the call by world leaders for its virtual elimination by the year 2000 [2]. Following recommended policy [3], salt iodization has been started in many countries, and almost all have passed legislation to assure its implementation. UNICEF estimates that by 1997 nearly 60% of all the edible salt produced in the world was iodized [4].

In Jiangsu, a province in China with 70 million inhabitants, endemic goiter and mental retardation have long been recognized as a public health problem. Provincial surveys of iodine-deficiency indicators during the early 1980s showed an average prevalence of goiter of 25.5% among 7- to 14-year-old schoolchildren, a mean urinary iodine concentration in the population of 76 μg/L, and an average drinking water iodine content of 6.6 μg/L [5]. Nine of the 75 counties of the province, Gaoqun, Jiangning, Jiangpu, Jintan, Jurong, Lishui, Liyang, Luhe, and Xuyi, were most severely affected, with an overall total goiter prevalence of 41.9% in schoolchildren in 1983. In 1985, before its introduction throughout the province, salt iodization was initiated in these counties, and by 1997 the policy had been in place for more than 10 years.

Since 1993, when the Chinese government proclaimed the national goal of elimination of iodine-deficiency disorders by the year 2000, a substantial amount of human and financial resources has been mobilized throughout the country. Universal salt iodization, requiring 50 mg I/kg salt at production, was started in Jiangsu Province in 1995. The supply and quality of iodized salt have been improved continually by the salt industry, and provincial data indicate that 90% or more of the population have had access to iodized salt since 1996 [6].

To follow the progress being made towards elimination of iodine-deficiency disorders in all the counties of Jiangsu Province, a surveillance system was devised based on provincial investigation of iodine-deficiency disorder indicators every two years and continuous monitoring of the iodine content in salt. According to national guidelines, all counties collect 25 salt samples for titration monthly from salt factories and households, and quarterly from retail outlets. Each month the iodine content of salt samples obtained at the factory, retail, and household levels is checked using rapid test kits.

In 1997 government officials and management personnel from the provincial health and salt sectors formed a special evaluation team to assess the salt and iodine status of the population in the nine counties of Jiangsu Province most at risk. The overall aim

was to determine whether there was sufficient evidence that virtual elimination of iodine-deficiency disorders had been achieved in these nine counties, based on criteria recommended by the World Health Organization/UNICEF/International Council for the Control of Iodine-Deficiency Disorders [7].

Methods

Review of existing data

The provincial team inspected the monitoring records from each county and reviewed the data on total goiter rates and urinary iodine concentrations among schoolchildren and salt iodine contents at salt factories, retailers, and households for the previous five years.

Self-evaluation by county

County officials divided each township into five areas that served as primary sampling units. The population of each primary sampling unit was listed alphabetically, and 30 clusters were selected proportionately to population size [7]. One elementary school was randomly selected per cluster, and in each school, 40 pupils aged 8 to 10 years were selected at random from the attendance roster for palpation of thyroid size, 25 pupils for collection of salt samples brought from home, and 12 pupils for casual collection of urine samples.

Verification by the provincial team

Each county was divided into five areas of approximately equal size, and two elementary schools were randomly selected in each area. In each school, 40 pupils aged 8 to 10 years were selected at random from the attendance roster for palpation of thyroid size and ultrasonography, and 12 pupils for casual collection of urine samples. In each area, 25 pupils were selected to bring a salt sample from home for iodine titration.

Thyroid size determination

County health professionals palpated the thyroid gland and classified the grade of goiter according to the WHO/UNICEF/ICCIDD description [7]. For verification, an experienced physician obtained an ultrasonogram of the thyroid gland with a portable ultrasound unit equipped with a 7.5-MHz linear array transducer (AKHO, Canada).

The depth (d), width (w), and length (l) of each lobe in millimeters were obtained from longitudinal and transverse scans, and the volume of the lobe was calculated by the formula [8]:

$$V\ (ml) = 0.479 \times d \times w \times l \times 1/1{,}000$$

The thyroid volume was the sum of the volumes of both lobes without including the volume of the isthmus. Thyroid size was classified according to age standards [10].

Laboratory methods

Urinary iodine was analysed by the acid-digestion method [9]. The iodine content in salt samples was obtained by titration [10]. The urine and salt samples from the county self-evaluation surveys were analysed in county laboratories, which are accredited by the provincial laboratory. All iodine analyses for the verification survey were done by the provincial laboratory, which is under regular quality surveillance by the Chinese Academy of Preventive Medicine in Beijing and the National Institute of Iodine-Deficiency Disorders in Harbin. Urinary iodine analysis of 18 blind control samples at three levels by the provincial laboratory did not demonstrate bias compared with the results from the reference laboratories. The precision of these determinations was 2.4%.

Data analysis

All field survey and laboratory data were analysed with Epi Info 6.04. The total goiter rate according to palpation was calculated as the proportion of pupils with grade 1 or 2 goiter. The total goiter rate according to ultrasonography was calculated as the proportion of pupils with thyroid volume above the age-specific reference [11]. Because of their skewed distributions, the median was used to measure the central tendency of urinary iodine concentrations.

A county was declared to be free of iodine-deficiency disorders if ≥ 90% of households had access to adequately iodized salt during the last five years; the median urinary iodine concentration of the population was above 100 μg/L; and a sustainable mechanism for monitoring salt iodine content and iodine-deficiency disorders has been established. For the purpose of this survey, salt samples from household with an iodine content above 20 mg/kg were classified as adequate.

Results

County monitoring records

Figure 1 shows the percentage of household salt samples containing adequate iodine from 1993 to 1997, obtained from review of county monitoring records. In 2 of 45 possible occurrences (once each in 1993 and 1994), the adequacy was below 90%. Overall, however, in each county ≥90% of the household salt samples had adequate iodine according to titration during the five-year period.

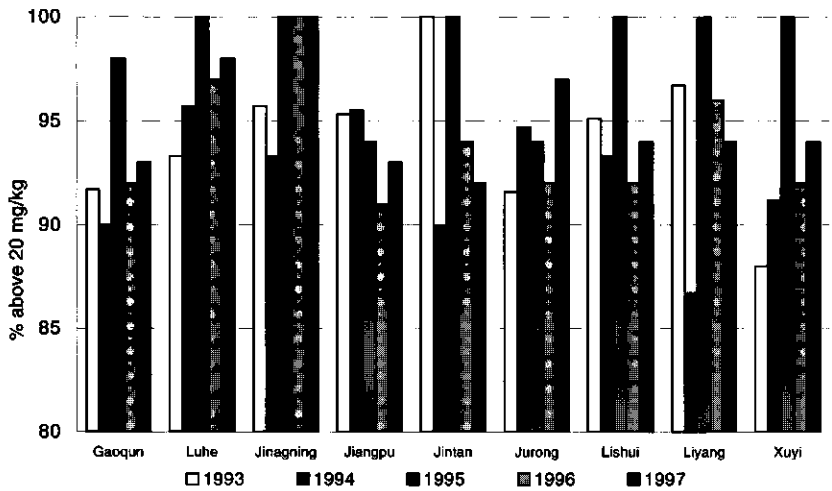

Figure 1 Adequacy of iodized salt in households in nine counties during 1993-97.

The results obtained by provincial review of the county's urinary iodine and total goiter monitoring since 1983 are shown in Table 1. The median urinary iodine concentrations exceeded 100 μg/L in all counties from 1985 onwards, and the total goiter rate declined to below 20% in 1988-1989, below 10% in 1995, and below 5% in 1997 (Figure 2).

County self-evaluation

The self-evaluation results obtained by the counties are presented in Table 2. The total goiter rate according to palpation ranged from 2.4% in Luhe to 5.1 % in Xuyi, and the median urinary iodine concentrations were above 250 μg/L in all counties. The frequency distribution of iodine contents in 6,897 household salt samples analysed by titration is presented in Figure 3. Almost 60% of salt iodine concentrations were between 20 and 40 mg/kg, and the large majority is between 20 and 70 mg/kg.

Table 1. Median urinary iodine (UI, μg/L) and total goiter rate (TGR, %) during 1983-1997 in the nine counties of Jiangsu, China

County	1983 [a]		1985 [a]		1988-89 [a]		1992 [b]		1995 [b]		1997 [b]	
	UI	TGR	UI	TGR	UI	TGR	UI	TGR	UI	TGR	UI	TGR
Gaoqun	65	37.1	102	35.7	168	18.5	251	13.6	463	8.2	670	2.6
Jiangning	79	45.3	126	42.2	245	19.7	324	15.4	268	9.7	322	2.8
Jiangpu	69	39.8	106	39.5	236	18.6	220	14.5	196	8.6	358	4.7
Jintan	80	40.4	143	39.9	255	17.6	216	13.3	327	7.5	339	4.5
Jurong	69	42.4	104	41.5	174	19.2	169	15.3	362	9.4	257	3.8
Lishui	68	38.2	96	37.5	196	18.5	263	14.2	330	8.6	318	4.9
Liyang	64	45.8	155	44.5	357	19.8	452	15.6	362	9.3	346	4.8
Luhe	69	41.4	99	39.7	216	17.6	224	14.4	241	9.4	363	2.4
Xuyi	65	43.9	89	44.3	152	20.3	152	18.7	415	10.3	420	5.1

a. UI measured in healthy adults, TGR in children aged 7-14 years.

b. UI measured in schoolchildren. TGR in children aged 8-10years.

Table 2. Salt iodine and population indicators of iodine-deficiency disorders in nine counties of Jiangsu Province, 1997: Results of counties' self-evaluation

County	TGR (%)		UI (μg/L)			Salt iodine adequacy	
	n	Palpation	n	Median	Range	n	% adequacy
Gaoqun	1,200	2.6	360	670	100-2,500	750	94
Jiangning	1,200	2.8	360	322	25-3,881	897	94
Jiangpu	1,200	4.7	360	358	103-712	750	93
Jintan	1,200	4.5	360	339	60-1,540	750	94
Jurong	1,200	3.8	360	257	65-3,083	750	99
Lishui	1,200	4.9	360	318	130-701	750	100
Liyang	1,200	4.8	361	346	34-2,729	750	100
Luhe	1,200	2.4	360	363	81-801	750	100
Xuyi	1,200	5.1	360	420	24-992	750	93

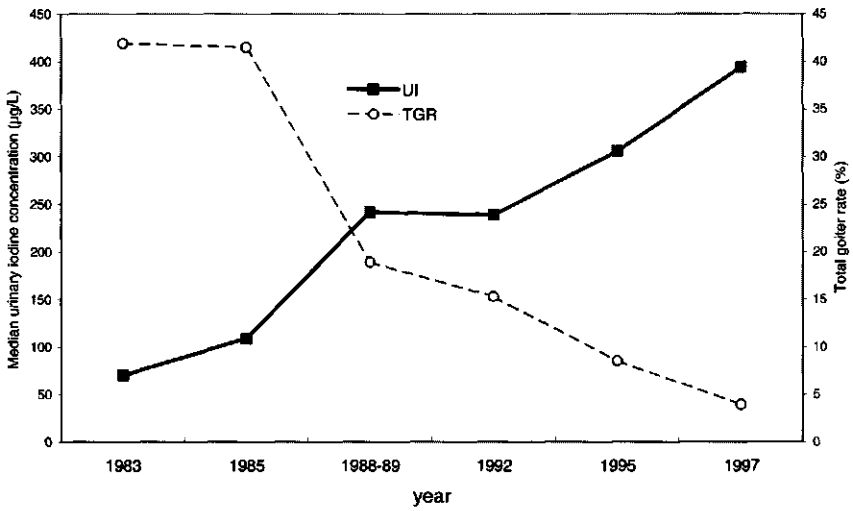

Figure 2. Median urinary iodine concentration (UI) and total goiter rate (TGR) in nine counties during 1983-1997

Table 3. Salt iodine and population indicators of iodine-deficiency disorders in nine counties of Jiangsu Province, China: Results of provincial verification

County	TGR (%)			UI (μg/L)			Salt iodine adequacy	
	n	Palpation	Ultrasound	n	median	range	n	% adequacy
Gaoqun	400	3.0	3.0	120	630	100-1,030	124	96
Jiangning	400	3.3	4.5	124	436	25-3,881	322	91
Jiangpu	400	2.8	3.3	120	358	101- 708	125	98
Jintan	400	3.3	3.5	120	739	39-1,244	129	100
Jurong	400	3.0	3.5	118	246	60- 809	125	100
Lishui	400	3.3	5.0	120	309	128- 578	125	100
Liyang	400	3.5	4.0	120	290	23-3,879	125	96
Luhe	400	3.0	4.5	121	525	86-1,028	127	94
Xuyi	400	5.0	6.3	120	427	40- 976	122	99

Provincial verification

Table 3 shows the results obtained by the provincial verification team. The total goiter rate according to ultrasonography ranged from 3.0% in Gaoqun to 6.3% in Xuyi, with an average of 3.6%. The urinary iodine concentration of 246 μg/L found in Jurong was the lowest median value, whereas in the other counties the urinary iodine was above 250 μg/L. The proportion of adequate salt iodine level was above 90% in all counties.

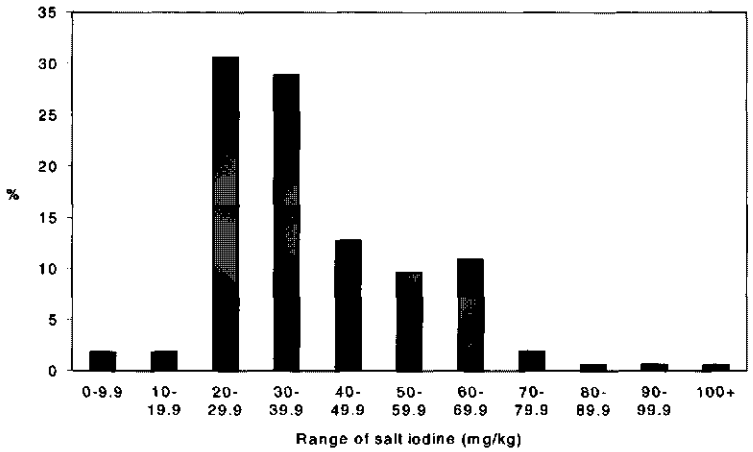

Figure 3. Salt iodine contents in 6,897 households in nine counties in 1997

Discussion

In Jiangsu Province, as in other areas of China and the world, iodization of food-grade salt is the main measure to prevent the public health consequences of iodine deficiency. As evident from the prevalence of goiter in more than 25% of the schoolchildren during surveys in the early 1980s, the proportion did not obtain sufficient iodine from foods grown indigenously. The low iodine content in drinking water indicated that the iodine deficit was of environmental origin. It also appeared that the nine counties presently under review were the most severely affected. If elimination of iodine-deficiency disorders by salt iodization could be accomplished in these counties, its achievement in other parts of the province, where iodine deficiency was milder, was considered to be less problematic.

The combined population of the nine counties is 5 million, and the geography is hilly and mountainous. Since 1985 the salt-iodization efforts by counties have formed part of an overall strategy to ameliorate iodine deficiency in the population, and prior to 1997 oral iodized oil was distributed annually by health workers to high–risk groups of schoolchildren and women of child-bearing age. Public health surveillance

of salt iodine levels and population indicators of iodine-deficiency disorders was also part of the programme from its inception.

The results from the province- and county-based surveillance system indicated that nine counties have made progress continuously during the past 12 years in supplying iodized salt and reducing iodine-deficiency disorders. The median urinary iodine concentration of the population had remained above 100 μg/L in each county since 1985, and the total goiter rate decrease steadily from above 40% in 1983 to below 5% in 1997. Although the use of iodized oil may have contributed to the urinary iodine improvement, the extent of its contribution is unknown. From the observation it is clear, however, that the use of iodized oil should be discontinued.

An effort was made in 1997 by county and provincial authorities to verify the results obtained from surveillance, including the collection of evidence about whether iodine-deficiency disorders had been eliminated in these counties. The design included the collection of salt iodine and population indicators of iodine-deficiency disorders by county officials, complemented by special independent verification of the data by a multisectoral provincial team. Overall, the results obtained by the counties and the provincial team satisfy the criteria recommended by an international expert group [7]. At least 90% of the household salt brought from home for testing at school by a random selection of schoolchildren had ≥ 20 mg/kg iodine, and the total goiter rate in schoolchildren according to palpation was 3.9% for all counties combined. The total goiter rate according to ultrasound was 3.6% on average for all counties. The true prevalence is probably less, however, because the early study [11] is now known to have overestimated goiter status [12]. It is concluded, therefore, that iodine-deficiency disorders in the nine counties of Jiangsu have been eliminated as a public health problem. This means that the consequences of iodine deficiency, such as new cases of endemic cretinism and mental retardation due to iodine deficiency in utero, are extremely rare or nonexistent.

The provincial team concluded from their review of salt production and supply and iodine information management systems that mechanism of salt iodization, distribution, and monitoring established in the nine counties was potentially sustainable. At the same time, it must be understood that the iodine deficiency of the environment will not be improved by introducing iodine into the food supply. It should be kept in mind that in some countries, after iodine deficiency had been controlled, iodine-deficiency disorders re-emerged when governmental, industrial, and popular support for the programme decreased [13]. It was recommended, therefore, that the efforts to maintain regular monitoring of iodized salt and surveillance of the prevalence of iodine-deficiency disorders should be continued.

Salt iodization is a successful measure to eliminate iodine-deficiency disorders, and since its introduction in 1985, iodized salt has been the main food source of iodine in these nine counties. As shown in Figure 3, the salt iodine content observed in households in 1997 was very variable, and 40% of the samples had iodine contents outside the expected range of 20 to 40 mg/kg. This indicates the need to improve quality assurance at the production sites. Also, although the median urinary iodine concentrations in the population of the counties were ≥ 250μg/L, urinary iodine concentrations above 800 μg/L or below 100 μg/L were observed in individuals in casual samples. Thus, a certain proportion of the population may have had a very high or a very low iodine intake, due to variability in salt intake or iodine content. Hyperthyroidism from high salt iodine intake has been reported in a number of countries [14], while on the other hand, low iodine intake may continue to impair children's normal brain development. It is necessary to strengthen quality assurance of salt production and reassess the assumption of iodine loss during supply to ensure that the urinary iodine concentrations of the population fall between 100 and 200 μg/L, as recommended by WHO [15].

The elimination of iodine-deficiency disorders from nine counties in Jiangsu Province is a small initial success in accomplishing the national mission launched in 1993 to eliminate iodine-deficiency disorders in China. The approach and methodology applied in this survey may serve as an example for other parts of China as to how the status of iodine-deficiency disorders in a population could be assessed and conclusions drawn to preserve the success of iodine-deficiency disorders elimination, once achieved.

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Chapter VIII

Thyroid volumes in US and Bangladeshi schoolchildren: comparison with European schoolchildren

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European Journal of Endocrinology **1999; 140: 498-504.**

Abstract

Objective The World Health Organization (WHO) recently adopted thyroid volume ultrasonography results from European schoolchildren as the international reference for assessing iodine deficiency disorders. Our objective study was to describe thyroid volumes measured by ultrasonography in US and Bangladeshi schoolchildren and compare these with European schoolchildren.

Methods Cross-sectional studies were performed in schoolchildren in the US (n = 302) and Bangladesh (n = 398). Data were collected on the following: thyroid size by palpation and ultrasonography; urinary iodine; age; sex; weight; and height.

Results Applying the new WHO thyroid volume references to the Bangladeshi children resulted in prevalence estimates of enlarged thyroid of 26% based on body surface area (BSA) and 7% based on age. In contrast, in the US children, the prevalence estimates were less than 1% for each reference. In the US children, the best single predictor of thyroid volume was BSA ($R^2 = 0.32$), followed by weight ($R^2 = 0.31$). Using linear regression, upper normal limits (97th percentile) of thyroid volume from US children were calculated for BSA, weight and age, and were found to be lower than the corresponding references based on BSA and age from European schoolchildren.

Conclusions In areas with malnutrition, such as Bangladesh, the BSA reference should be preferred to the reference based on age. Results from the US children indicated that a thyroid volume reference based on weight alone would perform as well as the one based on BSA. European schoolchildren had larger thyroids than US children, perhaps due to a residual effect of iodine deficiency in the recent past in some areas in Europe.

Introduction

Iodine deficiency is a major public health problem and is the leading preventable cause of mental impairment worldwide (1). The most apparent manifestation of iodine deficiency is goiter, an enlargement of the thyroid gland, and one method for determining the severity of iodine deficiency in a population is by estimating the proportion of children with enlarged thyroid volumes based on ultrasonography. Correct interpretation of ultrasonography results depends upon the availability of a valid reference. Recently the World Health Organization (WHO) has adopted a new thyroid volume reference (2). This reference is based on 3474 European schoolchildren living in areas with a median urinary iodine (UI) level greater than 100 µg/l from four countries: The Netherlands, the Slovak Republic, Austria, and France. Sex-specific upper normal limits of thyroid volume (the 97th percentile) were provided based on age and BSA (3).

We performed similar studies in the United States (US) and Bangladesh in 1996. The US population has been iodine sufficient for decades as evidenced by iodine excretion data from NHANES I and NHANES III surveys, whereas Bangladesh has historically had endemic iodine deficiency disorders (IDD) (4, 5). Recent surveys in Bangladesh have estimated the national prevalence of goiter in schoolchildren to be 50% and only 44% of households consume iodized salt (6). The objective of this study was to describe thyroid volumes measured by ultrasonography in US and Bangladeshi schoolchildren and compare these with European schoolchildren.

Subjects and methods

Subjects

Schoolchildren from the US and Bangladesh were studied using the same research protocol approved by Emory University Human Investigation Committee; written consent was obtained in the US and verbal consent was obtained in Bangladesh. In the US, 303 schoolchildren, 7-12 years of age, were studied from seven schools in the Atlanta metropolitan area. One individual was excluded because of cystic lesions on the thyroid gland. In Bangladesh, 400 schoolchildren, 7-10 years of age, from three schools in Saver, located approximately 50 kilometers northwest of Dhaka, were studied. Two subjects were excluded due to missing values on weight or thyroid volume, leaving a sample of 398. Information on age, sex, height, weight, thyroid volume estimated by ultrasonography, goiter by palpation, and urine samples for UI were collected.

Age

In the US data, exact age was calculated from the date of birth and date of survey. In Bangladesh, a stated age was used. For the calculation of age-based anthropometry, for US children the calculated age in months was used and for the Bangladeshi school children the stated age in years plus 6 months was used. The addition of 6 months was to correct for the usual rounding down of age.

Thyroid volume

Ultrasound volume was measured according to Brunn *et al.* (7) using Philips portable ultrasound units (Philips SDR 1200) with a standard 5.0 MHz transducer. The volume of each lobe was calculated by the formula: V (ml) = 0.000479 × length × width × thickness (mm). The thyroid volume was the sum of the volumes of both lobes. The volume of the isthmus was not included. Thyroid glands were classified into "normal" or "enlarged" using the Gutekunst reference (thyroid volume-for-age) and the new WHO references (thyroid volume-for-age and thyroid volume-for-BSA) (2, 8). Thyroid volumes greater than the 97th percentile were considered abnormally large and those less than or equal to the 97th percentile as normal.

Urinary iodine

Casual urine samples were collected, packed and transported according to a standard protocol provided by the Program Against Micronutrient Malnutrition (PAMM) laboratory at the Centers for Disease Control and Prevention (CDC). Collection and transport containers were provided by PAMM laboratory to avoid sample contamination or leakage. For the US study, all UI tests were performed by the PAMM laboratory. In Bangladesh, all UI tests were performed by the Institute of Nutrition and Food Science (INFS) at the University of Dhaka, which participated in a UI laboratory quality assurance program by the PAMM laboratory. UI analysis used a modified acid-digestion method, based on the catalytic effect of iodine on the reaction between cerium IV and arsenic III (Sandell-Kolthoff reaction) (9, 10). One hundred urine specimens from Bangladesh were also tested by the PAMM laboratory and a high correlation was found (Spearman rank correlation = 0.91, $P < 0.001$). Results of analysis in Bangladesh had a higher median than the PAMM laboratory (60.3 vs. 50.0, Wilcoxon signed rank test $p<0.001$) but there was no statistically significant difference in classifying children as having low UI (< 10 vs > 10μg/dl, exact sign test $P = 0.13$).

Anthropometry

Weights and standing heights were collected. The BSA (m^2) was calculated by using the formula: BSA = Weight (kg) $^{0.425}$ × Height (cm) $^{0.725}$ × 71.84 × 10^{-4} (11). Based on the WHO/CDC growth reference, z-scores were calculated for height-for-age (HAZ), weight-for-age (WAZ), and weight-for-height (WHZ) using the Epi Info software (12). Low HAZ was defined as HAZ < -2 S.D., low WAZ as WAZ < -2 S.D., and low WHZ as WHZ < -2 S.D.

Statistical methods

Statistical analyses were performed using SAS Version 6.12. The logarithmic transformation was used to normalize the distribution of thyroid volume. The Shapiro-Wilk test was applied to check normality before linear regression was done (13). In the US children, polynomial regressions were used to fit the relation between thyroid volume and various predictors at the normal and natural-log scale. Confidence intervals (CI) for proportions were calculated using Fisher's exact method (14), and CI values for median values were calculated using the method described by Gardner and Altman (15).

The WHO/UNICEF/ICCIDD (1994) (16) criteria were used to classify a population's severity of IDD based on school-aged children. For UI, the criteria are as follows: mild, 50-99 µg/l; moderate, 20-49 µg/l; severe, < 20 µg/l. For the prevalence of goiter and the prevalence of thyroid volume > 97th percentile are as follows: mild, 5-19.9%; moderate, 20-29.9%; and severe, ≥ 30%.

Results

The mean age of the US schoolchildren was 9.2 years and that of the Bangladeshi children was 8.8 years. Approximately half of the children at each site were male. US children were, on average, taller and heavier than the WHO/CDC growth reference, while Bangladeshi children had a high prevalence of low HAZ (34%) and low WAZ (54%) (Table 1).

The median UI level in US children was 282 µg/l and the prevalence of goiter by palpation 2%. The prevalence of enlarged thyroid was 6% when the Gutekunst reference was applied to the US children. When the new WHO thyroid volume references were applied to the US children the prevalence of enlarged thyroid was 0.3% based on age and 0.0% based on BSA (Table 1). Since the US population is an iodine-sufficient population, we would expect the prevalence of enlarged thyroid around 3% when the new WHO thyroid volume references are applied to the US sample (because the reference cutoffs were the 97th percentiles). The probability of observing a prevalence of 0.3% or 0.0% in the US sample in our study is less than

0.002 assuming the "true" prevalence to be 3%. Based on the criteria for IDD by WHO/UNICEF/ICCIDD, the US children would be classified as having no IDD for all criteria except the Gutekunst reference where the US children would be classified as having mild IDD.

Table 1 Descriptive Statistics of US and Bangladeshi schoolchildren

	US	Bangladesh
Sample size	302	398
Age in years		
Mean	9.2	8.8
Range	7-12	7-10
Male %	47	53
Anthropometry		
Prevalence of low HAZ (95% CI)	0.3% (0, 1)	34% (29, 39)
Prevalence of low WAZ (95% CI)	0% (0, 1)	54% (49, 59)
Prevalence of low WHZ (95% CI)	0% (0, 2)	24% (20, 29)
BSA: mean (95% CI)	1.20 (1.18, 1.22)	0.86 (0.85, 0.87)
Median UI level: µg/l (95% CI)	282 (253, 308)	73 (66, 81)
Prevalence of goiter by palpation (95% CI)	2% (1, 5)	27% (23, 32)
Prevalence of enlarged thyroid		
New WHO reference by age (95% CI)	0.3 (0, 2)	7% (4, 10)
New WHO reference by BSA (95% CI)	0% (0, 1)	26% (21, 31)
Gutekunst reference by age (95% CI)	6% (4, 10)	32% (28, 37)

The prevalence of low anthropometry defined as a z-score < -2 S.D.; due to WHO/CDC growth limitations, WHZ could not be calculated on 134 of the US children or 57 Bangladeshi children; UI results in US were not available for 20 children; the prevalence of enlarged thyroid based on the WHO reference for BSA was assessed on only 297 children whose BSA were within the reference BSA range and on 352 Bangladeshi children for the same reason. Enlarged thyroid volume is defined as > 97th percentile.

For the 398 Bangladesh children the median UI was 73 µg/l and the prevalence of goiter by palpation 27% (Table 1). The prevalence of enlarged thyroid was 32% based on the Gutekunst's reference, 7% based on the WHO for-age reference, and 26% based on the WHO for-BSA reference. Note that for the WHO reference for BSA, the lowest value of BSA was 0.75, of which 12% children in Bangladesh were below. The median UI and the WHO thyroid volume-for-age would classify the Bangladeshi children as having mild IDD, the prevalence of goiter and the new WHO thyroid volume-for-BSA as moderate, and the Gutekunst's reference as severe.

Based on the US children, the R^2 values for different predictors of thyroid volume and the natural log (ln) of thyroid volume were determined (Table 2). The ln of thyroid volume was analyzed because of skewness; after the transformation, the ln of

thyroid volume was found to be normally distributed (Shapiro-Wilk p = 0.82). BSA (R^2 = 0.32) and weight (R^2 = 0.29) were the best predictors of ln thyroid volume, followed by height (R^2 = 0.26) and age (R^2 = 0.20); similar results were found in Bangladeshi children, in whom BSA (R^2 = 0.12) predicted better than age (R^2 = 0.07).

Table 2 Relation of several factors with thyroid volume in US schoolchildren

	n	Thyroid volume R^2	Ln (thyroid volume) R^2
BSA (m^2)	301	0.33	0.32
Ln (BSA)	301	0.32	0.32
Weight (kg)	301	0.30	0.29
Ln (weight)	301	0.31	0.31
Height (cm)	302	0.26	0.26
Ln (height)	302	0.25	0.26
Age (months)	302	0.20	0.20

*P<0.008 for all predictors.

Various multiple linear regression models were estimated to determine how well multiple variables predicted the ln of the thyroid volume. The full model (a model using weight, age, BSA and sex as predictors) had a R^2 near 0.35. Sex became insignificant ($P > 0.05$) once age and weight, or height, or BSA were included in the model. A simple linear model was chosen because none of higher order terms was significant. References of upper limits of normal were derived from the US children for thyroid volume-for-weight, BSA, and age, where references (the 97th percentiles) were lines in parallel with the linear regression lines with the intercept increased by 1.881 times the square root of the mean square error of the regression. Regression equations for the 97th, 50th, and 3rd percentiles are given in Table 3. Scatter plots for each of the references with the percentile lines are shown in Fig. 1 and appear to fit the data well--about 3% of individuals have thyroid volumes beyond the 3rd or 97th percentiles for each predictor.

Comparisons of the various thyroid volume references by age and BSA are shown in Fig. 2. The 97th percentiles for BSA and age from the US were estimated using the equations in Table 3 and then converted back to normal scale. To account for the rounding down in reporting age, 0.5 was added to the age in years. The 97th percentiles were then estimated by multiplying the corrected age (in years) with 12 before plugging into the equation using age in months. The 97th percentiles from the US are lower than the new WHO reference from the study by Delange *et al* (3). For thyroid volume-for-age, the US references are intermediate between references by Delange *et al.* (3) and Gutekunst *et al.* (8)

Table 3 Regression Equations for Predicting Thyroid Volume (TV) in US Children.

Predictor	Regression equation
BSA (m^2)	97^{th}: ln (TV) = 1.565 + 1.010 ln (BSA)
Range: 0.8 – 1.8 m^2	50^{th}: ln (TV) = 1.132 + 1.010 ln (BSA)
	3^{rd}: ln (TV) = 0.698 + 1.010 ln (BSA)
Weight (kg)	97^{th}: ln (TV) = -0.305 + 0.570 ln (weight)
Range: 20- 90 kg	50^{th}: ln (TV) = -0.743 + 0.570 ln (weight)
	3^{rd}: ln (TV) = -1.181 + 0.570 ln (weight)
Age (months)	97^{th}: ln (TV) = 0.749 + 0.009 age
Range: 90-155 month	50^{th}: ln (TV) = 0.277 + 0.009 age
	3^{rd}: ln (TV) = -0.195 + 0.009 age

When the US references were applied to the Bangladeshi children, the prevalence of enlarged thyroid was 17%, 56% and 54% based on references on age, BSA and weight respectively (Table 1). Compared with the WHO references, the US references indicate a higher prevalence of enlarged thyroid. References based on BSA and weight yielded a similar prevalence of enlarged thyroid, with both references identifying virtually the same children; the concordant rate based on the two references was 98.5% in Bangladesh and 99.3% in US.

Discussion

We found that US children had significantly smaller thyroids than European children. It has been previously reported that iodine deficiency existed in the majority of European countries up to 1992 (17, 18). The study by Aghini-Lombardi *et al.* (19) showed that thyroid size in children exposed to iodine deficiency in the first years of life might fail to regress completely when the intervention is via iodized salt. In that study, thyroid volume in children born prior to iodine prophylaxis was still larger than that in children in an iodine-sufficient comparison area 10 years after the introduction of iodized salt. A recent study from China found that under optimal iodized salt intervention conditions, it took 12 months for the prevalence of abnormally large thyroids in schoolchildren with mild to moderate IDD to fall below 5% (J Zhao, unpublished data). The difference in thyroid volume between the US and European children increased with age or BSA (Fig. 2). A similar pattern was also observed by Aghini-Lombardi *et al* (19) in comparing thyroid volume in children from borderline iodine-deficient area (median UI = 98 μg/L) with iodine-sufficient area (median UI = 110 μg/L). These findings suggest that the larger thyroids in European schoolchildren may result from the residual effect of IDD in the recent past in some European areas,

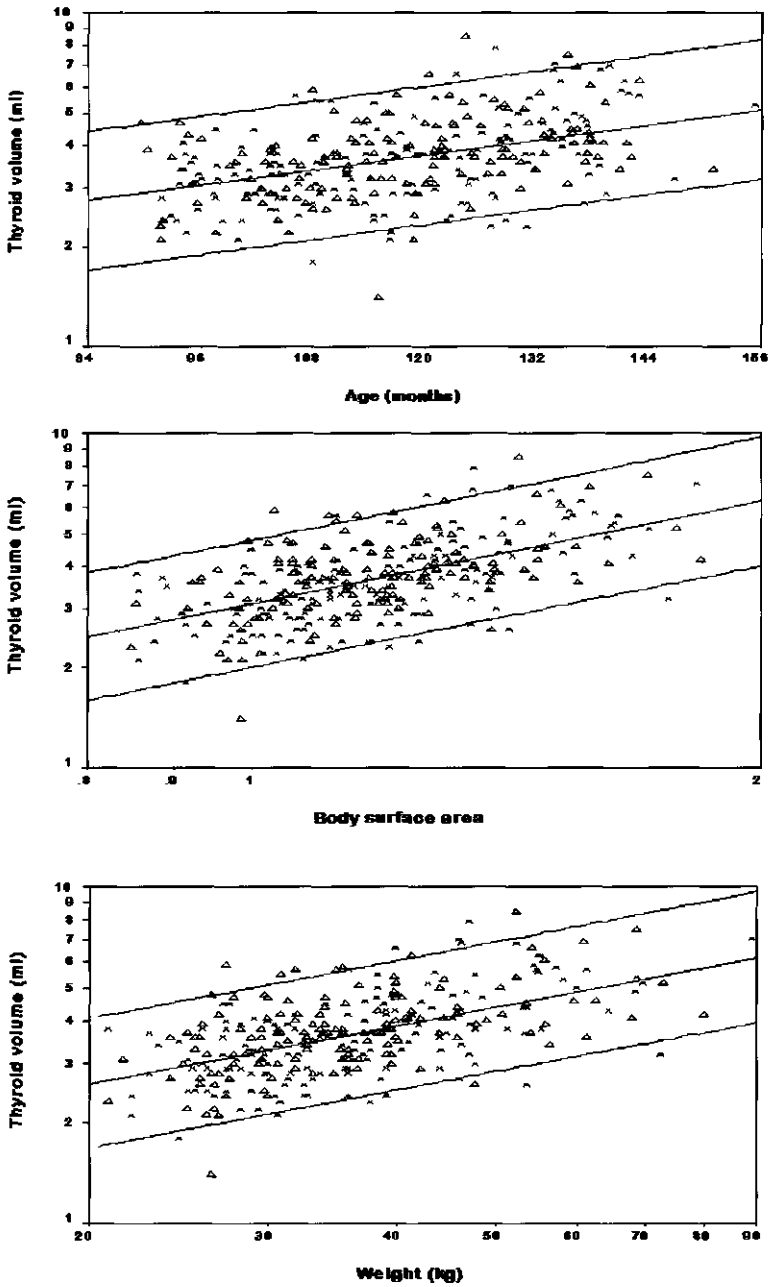

Figure 1 Scatter plots and the estimated lines of 97th, 50th and 3rd percentiles of thyroid volume versus age, BSA and weight. Boys (△); girls (×).

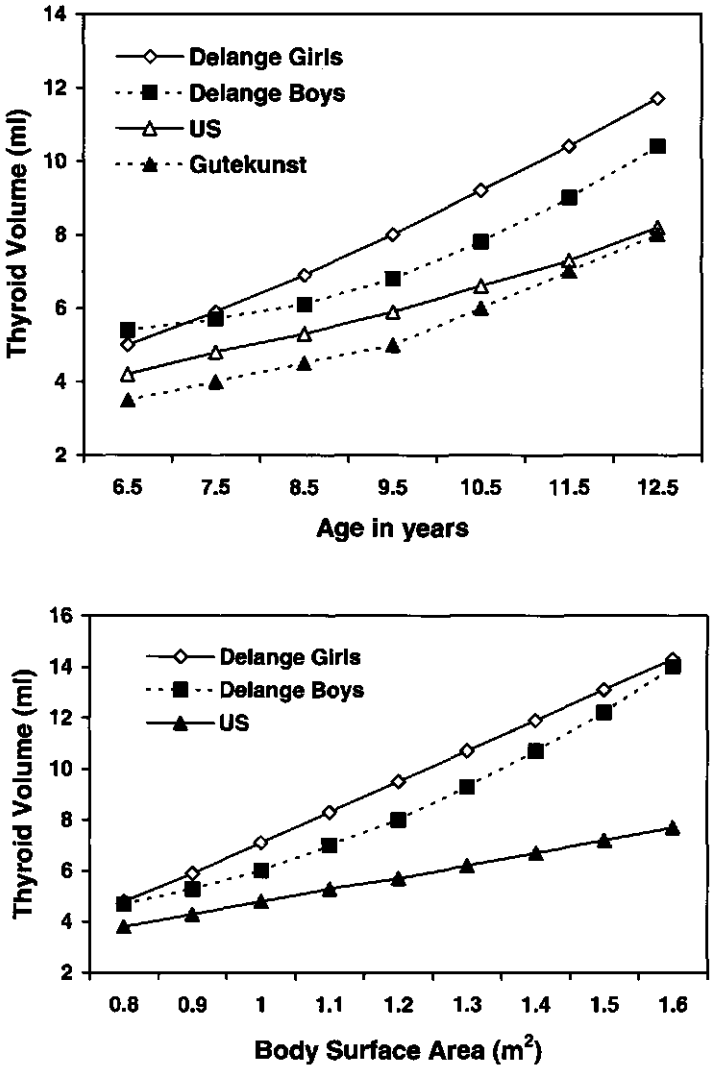

Figure 2 Comparison of the new WHO reference with 97th percentiles of thyroid volume from the US population by age and BSA.

although the difference in dietary factors such as the intake of goitrogens cannot be ruled out.

Another factor that might account for differences between the European and US schoolchildren is the differences in ultrasonography, such as use of different ultrasound equipment and different observers. Note that a 7.5 MHz transducer was used for European children in the study by Delange *et al.* (3) To our knowledge, no

quantitative data comparing different ultrasound units, especially equipment with different transducers, are available, but our experience with ultrasound units with 5 MHz and 7.5 MHz transducers in measuring thyroid size suggests that the impact of difference in the frequency of transducers may be trivial in schoolchildren. In general, the interobserver variation in thyroid ultrasonography is thought to be small and unlikely to account for the large differences in thyroid volumes between the European and US children (20).

In the present study, no difference in thyroid volumes was found between males and females. A number of other studies based on ultrasonography in iodine-sufficient areas have also found no difference by sex (8, 20-22). Two reasons may account for the larger thyroid volume in girls in European children: first, borderline iodine deficiency affects girls more; and secondly, enlarged thyroid regresses less quickly in girls after iodine intervention.

In this study, a linear relation assumption between thyroid volume and BSA at the natural log-log scale, and between age in months and log thyroid volume was made, and thereafter, the 97th percentiles were estimated accordingly. Although the model appears to fit the data well, we may fail to recognize more complicated patterns due to the small sample size.

Based on US schoolchildren, no important differences were found in the prevalence of enlarged thyroid based on BSA versus weight. For survey purposes, it would be simpler to use a reference based on weight rather than BSA because the latter requires the collection of weight and height and the use of a complex formula. We would agree with Delange *et al.* (3) that the thyroid volume based on BSA should be used in areas with a high prevalence of malnutrition. Given that BSA is a better predictor of thyroid volume, at least in the US children and Bangladeshi children, we would recommend that it should always be used, regardless of the nutritional status of the population when both weight and height are available.

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Chapter IX

General discussion

The primary aim of this thesis was to examine the relationship of iodine intake ranging from normal to excessive with thyroid size, thyroid function, goiter prevalence, intellectual and physical development, and hearing capacity in schoolchildren in China. To define the causative factors of endemic goiter in three counties of Jiangsu Province, an ecological study was conducted in 65 townships (Chapter II). Excessive iodine in drinking water was found to be responsible for the elevated iodine concentrations in urine of adults and the increased goiter prevalence. This was confirmed by evidence from an experimental study (Chapter V) where reduction in iodine concentration of drinking water was accompanied by a reduction in thyroid size and a decrease in goiter prevalence. As iodine intake increased from normal to extremely excessive, a decreasing trend in mean IQ was observed in schoolchildren aged >11 years (Chapter III). A meta-analysis of available data (Chapter IV) revealed that iodine excess causes a small but significant deficit in intellectual attainment of schoolchildren. Thyroid function appeared to be perturbed in subjects exposed to high iodine intakes (Chapters II and V), but reversed to normal in most of the subjects 12 months after normalization of iodine intake (Chapter V). There is no clear evidence on the association of excessive iodine intake with impaired physical development and hearing capacity.

Further aims of this thesis were to examine the efficacy and effectiveness of iodine intervention programs and to validate the WHO reference for upper limits of normal thyroid volumes in schoolchildren. Stable iodine supply to an iodine deficient population can normalize the enlarged thyroid within 12-18 months (Chapter VI) although fluctuations in iodine supply may slow down the speed of such a normalization (Chapters VI and VII). US children have smaller thyroid volume than European children included in the study by Delange et al (1997), perhaps due to a residual effect of iodine deficiency in the recent past in some European areas. Body surface area or weight predicts thyroid volume better than age in both iodine sufficient and iodine deficient children. Hence, reference for normal thyroid volumes should always be based on body surface area.

In this chapter, the research described in this thesis will be presented in the context of the knowledge on iodine deficiency and iodine excess. In addition, the strengths and limitations of the methods used will be discussed.

Selection of study subjects

WHO/UNICEF/ICCIDD (1994) recommended that the primary target group for iodine deficiency surveillance should be schoolchildren aged 6-12 years, or ideally 8-10 years. In iodine deficiency populations, thyroid size increases with age. As puberty

can also play a role in determining thyroid size, children aged > 12 years are not included. School-based surveys also have the advantage that children in schools are readily accessible although sick children and others such as cretins were not seen in schools. School-based prevalence surveys can be performed in a relatively short period of time by collecting data on thyroid size and collecting samples of urine for subsequent iodine analysis. One concern with school-based surveys in areas where school attendance is low is that children attending the schools may not be representative of all children at the same age in the same area. This was not the case in the studies described in this thesis. School attendance for all children aged ≥ 7 years is mandatory by Chinese Education Law. There are very few children attending special education schools due to physical or mental disabilities. Children enrolled in the school should represent all children in the study area. Thus, schoolchildren were chosen for all studies in this thesis.

In Xuzhou, where the studies described in Chapters II, III and V were conducted, some children had access to iodine supplements. After an advocacy meeting of the Chinese government in 1993 aimed at eliminating IDD in China by the year of 2000, many people in the population tried to obtain iodine supplements, such as iodized oil for their children. This was even though such supplements were only being provided to a few schoolchildren in Xuzhou Municipality. To minimize confusing the population on this matter, urine samples were collected from adults rather than from schoolchildren in areas with iodine excess (Chapter II). The research project started in 1995 before universal salt iodization had been implemented in Jiangsu Province. To increase the internal validity of the study (Chapter II) relating iodine levels of the water to iodine levels in the urine, two adults who had consumed seafood in the week before urine collection were excluded. The exclusion of these individuals would have a minimal effect on potential selection bias for the overall study (Chapter II). Few of selected pupils failed to participate in the measurement of IQ, weight, height and hearing capacity. Thus, such dropout would not bias the results to any great extent.

Although researchers were aware which township had access to water of a known iodine content, those involved in making measurements such as laboratory analysis, were blinded with respect to the origin of samples. Thus, this would unlikely be a cause of bias. In the studies described in Chapters II and III researchers were not blind to grouping and townships were not selected randomly, the occurrence of bias cannot be excluded. In addition, in Chapters II, III and V iodine status was determined by measuring the concentration of iodine in urine of adults while other indicators were measured among schoolchildren. However, measurement of the concentration of iodine in urine samples collected from adults gives similar results to that obtained among children in defining the iodine status of a population.

Etiology of goiter

Goiter is simply an enlargement of the thyroid gland, which can be caused both by iodine deficiency and iodine excess. Goiter may present in the following conditions: hyperthyroidism, hypothyroidism, Hashimoto's thyroiditis; subacute thyroiditis; painless/postpartum thyroiditis and malignancy (Siminoski, 1995).

Goiter has been reported as a consequence of iodine excess in numerous locations in China and other countries (Suzuki, 1980; Zhao et al. 2001). As iodine concentration in drinking water, and thereby in urine increases to excessive levels, thyroid volume becomes larger, and therefore the goiter prevalence becomes higher (Chapter II). This process is reversible when iodine intake from drinking water is reduced to the normal range (Chapter V). Goiter in the study area reported upon in the thesis is most probably caused by iodine excess rather than iodine deficiency, and excessive iodine is mainly from drinking water although other factors such as goitrogens, selenium deficiency and genetic factors may also play some role in the etiology.

Table 1. Distinctions between iodide goiter and diffuse goiter caused by iodine deficiency

		Iodide goiter	Iodine deficient goiter
Palpation	Texture	Firm, easily palpable	Soft, less distinctive from surrounding tissues
	Boundary	Smooth and clear	Less clear
Inspection		Visible with rough edge of gland at grade I*	Visible at grade II
Ultrasonography		Clear boundary, rough and uneven echogram	Obscure boundary, even, consistent echogram

*Because the boundary is pronounced, thyroid glands can already be observed at a size which would remain undetected if caused by iodine deficiency.

Distinctions between iodide goiter and diffuse goiter caused by iodine deficiency are depicted in Table 1. For iodine deficient goiter, the parenchyma is abundant, the follicular epithelium is thick with papillary infolding, and colloid is rare. Autoregulatory enhancement of the growth response to TSH may account for this TSH-dependent hyperplasia (Delange, 1994). In contrast, excessive iodine intake decreases the release of T_3 and T_4 and colloid is common in iodide goiter. Animal and human studies have found that the follicular lumen of an enlarged thyroid, under the conditions of iodine excess, is full of colloid which is comprised of thyroglobulin. The dominant type of endemic coast goiter in Japan is "colloid" goiter. In "iodide

goiter" there is no histological evidence of thyroiditis, as shown by observational studies (Shimpo, et al. 1943; Suzuki, et al. 1965) and in an experimental study (Many et al. 1986).

The iodide goiter seen in the excess iodine study areas is exclusively diffuse and no nodular goiter is found. This is consistent with other studies in iodine excess areas (Fang, 1988; Zhu et al. 1988; Wu et al. 1989; Yang et al. 1989). It differs from diffuse goiter caused by iodine deficiency.

Thyroid function

Iodine is an essential component of thyroid hormones. A change in iodine intake may affect the synthesis of thyroid hormones. Excessive iodine intake can induce either hypothyroidism or hyperthyroidism. Hypothyroidism results from abnormalities that lead to insufficient synthesis of thyroid hormone and is characterized by increased serum concentrations of TSH, decreased concentration of T_4 and normal or decreased T_3. On the other hand, hyperthyroidism denotes the clinical, physiological and biochemical findings that result when the tissues are exposed, and respond to, excess thyroid hormone. In a state of hyperthyroidism, the serum concentration of TSH is very low or undetectable while serum concentrations of T_3 and T_4 are increased.

Increased serum concentrations of TSH has been reported from many studies following consumption of iodine-rich food, water or iodinated water (Begg & Hall, 1963; Li et al. 1987; Konno et al. 1994; Matsubayashi et al. 1998). As elevated serum concentrations of TSH and normal serum concentrations of T_3 and T_4 were found in children and adults included in the present study (Chapters II and V), it would appear that subclinical hypothyroidism is the main thyroid dysfunction in populations exposed to high iodine intakes (Begg & Hall, 1963; Clark, 1990; Chen, et al. 1991; Konno et al. 1994; Chapters II and V).

There have been reports of an increased incidence of hyperthyroidism in iodine excess areas (Zhang et al. 1980; Fang. 1988; Zhao et al. 1994) but this was not found in the present study (Chapter II) or in an area with high iodine intakes in Japan (Suzuki et al. 1965). After normalization of iodine intakes, serum concentrations of TSH reduce to normal in most but not all subjects (Chapter V). This is consistent with the findings from several studies in Japan (Suzuki 1980; Yoshinari et al. 1983; Tajiri et al. 1986). Tajiri et al (1986) reported that there is a reversible type of hypothyroidism sensitive to iodine restriction and characterized by relatively minor changes in lymphocytic thyroiditis. For this type of hypothyroidism, thyroid function may revert to normal with iodine restriction alone. At the end of the present study (Chapter V), there were still some subjects with elevated concentrations of TSH and

normal concentrations of T_3 and T_4. This raises the possibility of the existence of an irreversible type of hypothyroidism. Subjects with this condition may have undergone destruction of thyroid tissue during the period of exposure to excess iodine or may have had autoimmunity prior to exposure to excess iodine. This type of hypothyroidism cannot be reversed through iodine restriction alone.

In some studies, differences have been noticed in thyroid function resulting from acute and chronic exposure to excess iodine intake. Serum TSH levels increased into the abnormal range with 2 to 4 weeks in five of six euthyroid subjects receiving 5 drops of potassium iodine solution, and promptly returned to normal when the administration of iodide was discontinued (Clark, 1990). Similar results in an experimental study by Namba et al (1993) found that elevated serum concentrations of TSH returned to baseline levels 2 weeks after cessation of excessive iodide supply. Also, spontaneous improvement was observed in about one-half of patients with primary hypothyroidism living in an iodine-sufficient area of Japan. A substantial reduction of mean concentration of TSH from 1.38 μU/mL to 0.52 μU/mL was found in a study in China where iodine concentration in drinking water remained normal for three years (Wang et al. 1994).

Cognitive and physical development, and hearing capacity

Iodine deficiency has been recognized as the leading cause of mental retardation worldwide, it is also a cause of growth retardation and hearing loss (Delange, 1994). Whether or not iodine excess has similar effects has been less documented.

The role of iodine in brain development is mediated through thyroid hormones. Hypothyroidism produced by iodine deficiency thus forms the basis of the hypothesis that iodine deficiency causes a reduction in mental performance. As mentioned above, iodine excess also causes hypothyroidism. Thus it is feasible that iodine excess may play a role in the etiology of mental retardation. More than 10 studies have been carried out previously in iodine excess areas of China in attempting to establish the relationship of iodine excess with mental performance. In these studies, various intelligence tests were used in a variety of populations. In the present study (Chapter III), a uniform intelligence test was used for children in one area exposed to different levels of iodine intake from normal to excessive while adjustment was made for confounding factors. By comparing the mean IQ and the proportion of children with high or low IQ among comparable groups, it could be concluded that iodine excess does impair mental performance. These conclusions are consistent with the results of 5 previous studies (Sun et al. 1985; Xie et al. 1987; Ma et al. 1991; Hu et al. 1994, Zhao et al. 2001) and are supported by the results of a meta-analysis of available studies (Chapter VII) where a small but significant negative effect of high iodine

intake on cognitive development in schoolchildren was found.

Prior to the time when the present study (Chapter III) was conducted, there was no information on the reversibility of intellectual impairment due to excessive intake of iodine. Studies have been carried out to explore the reversibility of impaired cognitive performance as a result of iodine deficiency. Iodine supplementation prior to pregnancy can effectively prevent iodine deficiency disorders. Some studies have found that mental performance can be improved if the intervention starts during childhood (Bautista et al. 1982; Shrestha et al. 1994) while others have not (Huda et al. 2001). During the time in which a cross-sectional study reported in this thesis was being carried out (Chapter III), source of drinking water changed leading to a reduction in iodine intake. In this study, when iodine intakes based on the original concentrations in urine of adults, increased from normal to excessive, a trend of decreasing IQ was noticed in children aged > 11 years but for children aged <11 years, a decline in IQ was found only in the group with the highest iodine concentrations in drinking water. This suggests that impairment of IQ due to excessive iodine intake could be reversed but that this occurs slower or to a lesser extent in children who are older or when the iodine excess is more severe.

The present study found no evidence that various degrees of iodine excess could affect the physical development of children (Chapter III). This is in agreement with cross-sectional studies among schoolchildren by Jupp et al. (1988) and Li et al. (1987), who failed to find any effect on growth of iodine excess. It appears that iodine excess has no effect on physical growth, at least at levels of iodine intakes examined.

Studies up until now on the relationship between iodine intake and hearing capacity have been confined to iodine deficiency. Severe hearing loss is common in iodine deficient areas (Valeix et al. 1994; Azizi et al. 1995). It was hypothesized that hearing capacity would be lower in those townships exposed to high iodine intakes, assuming that iodine excess and iodine deficiency have similar effects on health. However, no clear relation was found between iodine intakes from normal to excessive and hearing capacity (Chapter III).

Normal thyroid volume

Ultrasonography makes it possible to obtain an accurate measurement of thyroid volume, and therefore to provide an estimate of the proportion of children with enlarged thyroid glands. Correct interpretation of the results of thyroid ultrasonography depends on the availability of a valid reference and feasible and uniform guidelines. In 1997, WHO/UNICEF (1997) adopted a new thyroid volume reference. Before that, results of the study by Gutekunst and Martin-Teichert (1993) were used as an international reference. In order to evaluate the performance of the

new WHO reference, data on thyroid volume were collected in US and in Bangladesh (Chapter VIII).

The new WHO reference was derived from clusters of European children having median urinary iodine concentrations ≥ 100 μg/L and was age-specific and body surface area specific. When this reference was applied to Bangladeshi children who were iodine deficient, the prevalence of goiter based on the body surface area specific reference was much higher than that based on the age-specific reference. In contrast, the prevalences were similar when two specific references were applied to US children who were iodine replete. The prevalences of goiter based on the new WHO reference were systematically lower than those based on the old international reference.

Significantly smaller thyroids have been found in US children than European children (Chapter VIII). The US has long been believed to be iodine replete as evidenced by iodine excretion data from the NHANES I and NHANES III surveys (Hollowell et al. 1998) while it has been previously reported that iodine deficiency existed in the majority of European countries up until 1992 (Delange et al. 1993; Gutekunst & Delange, 1994). The effect of this iodine deficiency in the recent past in some European areas was still evident. Zimmermann et al (2001) reported recently that the observer who generated the thyroid volume data that form the basis for the current WHO normative thyroid volumes systematically assessed thyroid volumes to be larger than did other observers. Thus the values for the new WHO reference would appear to be too high and should not be applied as the international reference. The results reported in this thesis (Chapter VIII) are similar to those of a number of other studies (Foo et al. 1999; Langer, 1999; Djokomoeljanto et al. 2001; Zhang et al. 2001; Zimmermann et al. 2001) in which the new WHO reference values were found to be inapplicable in certain populations. It is also necessary to carry out further work following standard procedures to standardize ultrasound measurement of the upper limits of normal thyroid volumes in populations with various ethnic backgrounds in areas with different nutritional status.

Usually a reference for the upper limit of normal thyroid volume is based on some growth variables of children. Age and body surface area have been used as the growth variables. The cutoff values between normal and enlarged thyroid size have been traditionally set at the 97th percentiles of thyroid volumes in an iodine-replete population. As US children were iodine sufficient, and on average taller and heavier than the WHO/CDC growth reference, attempts were made to explore the best predictor of thyroid volume. Body surface area and weight were found to be the best predictors, followed by height and age. Similarly, body surface area predicts thyroid volume better than age in iodine deficient Bangladeshi children. Thus, thyroid volume

based on body surface area should always be used regardless of the nutritional status of the population.

Goiter prevalence measured by palpation and by ultrasound

The prevalence of goiter can be determined by palpation and by ultrasound. By palpation, goiter has been defined as 'a thyroid gland whose lateral lobes have a volume greater than the terminal phalanges of the thumbs of the person examined' (Perez, et al. 1960). Using ultrasound, goiter is defined as a thyroid gland with a volume > upper limit of normal thyroid volume. Age-specific or body surface area specific upper limits have been proposed based on studies in various areas (Gutekunst & Martin-Teichert, 1993; Delange et al. 1997; Foo et al. 1999).

In areas with excessive iodine intakes, prevalence of goiter measured by palpation is generally higher than when measured by ultrasonography (Chapters II, IV, V, and VI; Table 2). This might be because that the enlarged thyroid glands are harder and firmer in conditions of iodine excess than in conditions of iodine deficiency.

Table 2. Goiter prevalence by palpation and by ultrasound in this thesis

Chapter		Goiter prevalence (%)	
		By palpation	By ultrasonography
II		22.4	12.8*
V	Baseline	30.9~46.7	18.7~32.7*
	End of study	19.7~48.0	7.9~26.0*
VI	Baseline	26.1~26.5	17.4~17.7†
	End of study	4.3~14.7	4.3~8.8†
VII		3.0~5.0	3.0~6.3*
VIII	Bangladesh	27	7-32‡
	US	2	0-6‡

* Based on age-specific reference.

† Based on body surface area specific reference.

‡ Based on body surface area and age specific references.

In iodine deficient areas, intra-observer and inter-observer variation in the estimation of thyroid size has been reported to be high. The specificity and sensitivity of palpation are low for grade I goiter due to high inter-observer variation as compared with the results obtained by ultrasonography. Among experienced examiners, misclassification can be as high as 40% (WHO/UNICEF/ICCIDD, 1994). Intra-observer variation measurement of thyroid volume was 8.4%. Inter-observer

variation was 13.3%. As reported by Ozgen et al. (1999), the widest inter-observer variation is encountered in determining the craniocaudal diameter of the thyroid gland.

Thyroid size after normalization of iodine intakes

Prior to the work described in this thesis being carried out, many studies had been conducted to measure thyroid volume after iodine supplementation in iodine deficient areas (Delange, et al. 1997; Foo et al. 1999). However no studies have measured thyroid volume by ultrasound in areas where exposure to excessive iodine was reduced to normal.

As with mild to moderate iodine deficiency, as described in Chapter VI, enlarged thyroid volume returned to normal in 12 months when a stable iodine supply was guaranteed (Guaranteed iodized salt group and Market salt + iodized oil group, Chapter VI). It took years when the supply of iodine through iodized salt fluctuated (Market salt group of Chapter VI, Chapter VII). But enlarged thyroid glands caused by excessive iodine intakes could be reduced to normal size within 3 months (Chapter V). The different rates of normalization may be attributable to the different etiologies of the two types of goiter. As iodine intake reduces from excessive to normal, T_4 is released and the T_4-containing thyroglobulin of the colloid disappears, thus reducing the size of the thyroid. As iodine intake increases from deficient to normal, serum concentrations of T_4 increase and those of TSH decrease. Thus TSH-dependent hyperplasia disappears, albeit gradually, and thyroid size reduces to normal more slowly than in iodide goiter.

Normalized thyroid volumes ranged from 2.4 to 3.7 mL (Chapters II, IV, V and VI, data not shown for all chapters) for prepubertal schoolchildren. These values are similar to the results of a few studies where iodine status was normal (Liesenkotter, et al, 1997; Erdogan, et al, 2000), but smaller than all reported upper limits of normal thyroid volumes in Europe (Gutekunst & Martin-Teichert, 1993; Delange, et al. 1997), in Asia (Foo et al. 1999) and US (Chapter VIII).

Maximum allowable iodine concentrations

Like that for other essential trace elements, iodine intake should be kept within a reasonable range. An intake either above or below this range may cause adverse effects to the human body. Practically all efforts up until now have been towards trying to understand the functional consequences of iodine deficiency. These efforts have led to the establishment of the lower limit of normal iodine intake. However, the upper limit of the normal has not yet been established.

Previously, a few studies (Bourdoux et al. 1978; Yu et el. 1987; FAO/WHO, 1996; Zhao, 1997; Institute of Medicine, 2000) tried to establish an upper limit for normal iodine intake. The suggested upper limits range from 100 to 2,000 μg/day. From the work described in this thesis, based on the relationship of iodine exposure with indicators on thyroid size, function and cognitive function, maximum allowable iodine concentrations of 800 μg/L in urine of adults and of 300 μg/L in drinking water are proposed.

Three steps were undertaken in order to establish the maximum allowable concentrations in drinking water or in urine (National Research Council, 1993):

Step 1, Identification of hazard evidence pertaining to the adverse effects of excessive iodine intake;

Step 2, Examining the dose response in order to identify the highest level of iodine that is likely to pose no risk of adverse health effects for almost all individuals in the general population;

Step 3, Drawing conclusions.

During step 1, hazards of high iodine intake were identified. High iodine intake is associated with enlargement of thyroid size, increased prevalence of goiter (Suzuki et al. 1980; Chapters II and V), increased prevalence of hypothyroidism or other thyroid dysfunction (Nagataki et al. 1964; Yu et al. 1987; Suzuki, 1980; McMonigal et al. 2000; Chapters II and V) and increased prevalence of impaired intellectual function in schoolchildren (Chapters III and IV).

During step 2, a strong relationship of iodine concentration in drinking water with those in urine of adults was found across townships and a strong association of goiter prevalence with iodine concentrations in drinking water or in urine was also observed.

The lowest-observed-adverse-effect level (LOAEL) is the highest intake of iodine at which no adverse effects have been observed in the individuals studied. The no-observed-adverse effect level (NOAEL) is the lowest intake at which an adverse effect has been identified. Whenever possible, the upper limit is based on a NOAEL. If there is no adequate data demonstrating a NOAEL, the LOAEL may be used (Zielhuis et al. 1979). Based on the findings in this thesis, the NOAEL and LOAEL for iodine concentrations in urine and in drinking water are summarized in Table 3.

From Table 3, LOAEL of iodine for goiter prevalence (> 5%) is 800 μg/L in urine of adults or 290 μg/L in drinking water (Chapter II) while for thyroid function, LOAEL of iodine is 830 μg/L (Chapter V) to 1280 μg/L (Chapter II) in urine or 400 μg/L (Chapter V) to 950 μg/L (Chapter II) in drinking water. As one of the most important findings in the present thesis is that excessive iodine intake may impair cognitive development (Chapter III). Much emphasis is placed on this parameter for determining the maximum permissible intake of iodine, fortunately data for both

LOAEL and NOAEL are available for cognitive development. The LOAEL is 540 μg/L in drinking water or 1210 μg/L in urine of adults, and NOAEL is 832 μg/L in the urine of adults or 310 μg/L in drinking water (Chapter III).

Table 3. NOAEL and LOAEL for iodine concentrations in urine and in drinking water.

Chapter	Indicator	Iodine concentrations (μg/L)			
		Urine		Drinking water	
		NOAEL	LOAEL	NOAEL	LOAEL
II	Goiter prevalence		802		290
	Thyroid function		1280		950
III	IQ	832	1206	310	540
V	Thyroid function		830		400

In step 3, before drawing conclusions, uncertainties should be assessed. Usually, the greater the uncertainty, the smaller the maximum allowable iodine concentrations. In this thesis, factor, such as nutrient-nutrient interactions, which may result in these uncertainties, are not known. Duration of exposure is also important. Because the magnitude, duration, and frequency of exposure can vary considerably in different situations, consideration needs to be given to the type of the exposure (chronic daily vs short term) to dietary intakes by human populations.

To leave a margin of safety, NOAEL is used for the extrapolation of maximum allowable concentrations. Thus, the maximum allowable concentrations should therefore be set at 800 μg/L in urine of adults or at 300 μg/L in drinking water.

Maximum allowable concentrations in urine and drinking water in this thesis refer to the highest concentrations that are likely, on a chronic daily basis, to pose no risk of adverse health effects to general population, at least to the population included in this study, under conditions that other potential contributing factors involved are not clear. As iodine concentrations increase beyond the maximum allowable concentrations, the risk of adverse effects increases. When iodine concentrations reach these levels, close monitoring, even intervention should be launched to minimize the adverse effects associated with high iodine intake. However, further research on measurable indicators under difference levels of exposure to iodine, and their interaction with other nutrients, such as fluoride, selenium and zinc, is still encouraged.

Conclusions

Based on the work described in this thesis, the following conclusions can be drawn:

a. Excessive iodine in drinking water is responsible for endemic goiter in Feng, Pei and Tongshan Counties in Jiangsu Province, China.
b. Iodine excess causes enlargement of the thyroid gland which can return to normal within 3 months after iodine intake becomes normal.
c. Iodine excess causes a decline in IQ in schoolchildren: such an effect seems to be reversed by the reduction in iodine intake from drinking water.
d. In areas with excessive iodine intakes, elevated serum concentration of TSH and normal serum concentrations of T_3 and T_4 indicated the existence of subclinical hypothyroidism in adults and children, which is partially reversible by reducing iodine intakes from excessive to normal.
e. Iodine concentration > 800 μg/L in urine of adults or > 300 μg/L in drinking water should be regarded as a public health risk.
f. Salt in which the iodine content is guaranteed and stable can normalize the size of thyroid glands which have been enlarged by mild to moderate iodine deficiency within 12-18 months: fluctuation in iodine supply may slow down this normalization process.
h. The current WHO reference for upper limits of normal thyroid volume should not be adopted as the international reference because thyroid volumes are smaller in US children where iodine status has been replete for decades than European children where the effect of past iodine deficiency is still evident.

Recommendations for public health practice and for future research

Recommendations for public health practice are as follows:

a. As many nations achieved the goal of eliminating IDD through universal salt iodization, regular monitoring of salt iodine content should be emphasized to ensure that urinary iodine concentrations in the population are within the range of 100 to 300 μg/L.
b. When the iodine concentration in drinking water reaches 300 μg/L or in urine reaches 800 μg/L in a population, intervention program should be launched to bring median urinary iodine concentration within the range of 100 to 300 μg/L.
c. Although palpation can roughly estimate thyroid size, ultrasound is strongly recommended to measure thyroid volume accurately. For better interpretation of data on thyroid volume, upper limits for normal thyroid volume based on body surface area and not age should be used for classification of thyroid volume.
d. Data on thyroid size alone are not enough to assess the iodine status in a population. Data on iodine concentration in urine and in drinking water, and information about on-going iodine intervention programs should also be collected.

Recommendations for future research are as follows:

a. The current WHO reference for upper limits of normal thyroid volumes cannot assess the problem of iodine status in a population accurately. As racial and nutritional differences exist, upper limits for normal thyroid volumes could be further standardized in different areas and in populations differing in nutritional status. As there is large inter-observer variation, guidelines for performing ultrasonography for measurement of thyroid volume are needed.
b. Like iodine, other micronutrients such as iron and zinc may also affect intellectual development. Thus research on the interaction of iodine with other micronutrients could give a better insight into the adverse effects of different levels of iodine intakes on human health and facilitate the formulation of comprehensive intervention strategies.
c. Because hypothyroidism and goiter due to excessive iodine intakes can disappear spontaneously, it is necessary to explore the natural clinical course of this process.
d. After correction of deficient or excessive iodine intakes, enlarged thyroid glands persist in a small proportion of subjects (usually < 5%), therefore it is necessary to examine in well-designed studies why such thyroid glands remain enlarged.

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Summary

Iodine is an essential element for human health. Like other trace elements, iodine intake should be kept within a normal range as iodine intakes either above or below this range may cause adverse effects on human health. Jiangsu is a province located in the eastern part of China. Iodine deficiency was a significant public health problem and has been eliminated with universal salt iodization in most counties in this province. In Feng, Pei and Tongshan Counties in Xuzhou Municipality, endemic goiter has been found to be associated with iodine excess. This thesis presents the findings of studies conducted in Jiangsu Province on the magnitude of the problems of iodine excess and iodine deficiency, interventions to overcome these problems, and adverse effects of iodine excess.

The relationship of iodine concentrations in drinking water in Feng, Pei and Tongshan Counties with iodine concentration in urine of adults, goiter prevalence in schoolchildren and thyroid function of adults was examined. Iodine concentrations in drinking water of townships ranging from 190 to 1150 μg/L were accompanied by an increase in iodine concentrations in the urine of adults from 520 to 1960 μg/L and by an increase in goiter prevalence measured by ultrasound in schoolchildren from 5.3 to 16.8%. Thyroid function appeared to be perturbed in adults from townships with the highest iodine concentrations in drinking water. Endemic goiter in this area is most probably due to excessive iodine intake from drinking water. Goiter associated with iodine excess is found to be diffuse and "colloid", which is different from goiter as a result of iodine deficiency.

The relationship of iodine intakes, ranging from normal to excessive, with intellectual development, physical development and hearing capacity in schoolchildren was described in 13 townships of the three counties of Xuzhou. For children aged > 11 years, IQ was related negatively to the concentrations of iodine in drinking water and in urine of adults while for children aged ≤ 11 years, a lower IQ was found only in the group with the highest iodine concentration in drinking water. Impaired cognitive development appears to be reversed by the reduction of iodine intake, suggesting partial reversibility of impaired intellectual development due to excessive iodine intakes if normalization of iodine intakes starts during childhood. No clear evidence exists for the relation of various degrees of iodine excess with the physical development or hearing capacity in schoolchildren.

Based on the published data, the magnitude of the problem of iodine excess was determined and, in a meta-analysis, its possible relation to cognitive development in schoolchildren was demonstrated. Iodine excess has been shown to be a public health problem in 92 counties of 10 provinces in China, affecting nearly 16 million people.

The IQ of children in areas with excessive iodine intakes was 3.2 points lower than that of children in areas where iodine intakes were normal. The effect was even greater with an IQ shift of 3.7 points in areas when iodine intake become extremely high, as compared with areas with normal iodine intake. These findings strengthen the importance of intervention to normalize iodine intakes.

Thyroid size and function were measured and compared in two pairs of townships with moderately and highly excessive iodine concentrations in drinking water where the iodine concentrations in drinking water were reduced from excessive to normal in one township of each pair. Thyroid volume reduced to normal size within 3 months after normalization of iodine intakes from drinking water. Thyroid function became normal in most but not all subjects at the end of the study, suggesting there are two types of hypothyroidism due to high iodine intakes, one is reversible and sensitive to iodine restriction and the other is not.

A randomized clinical trial was conducted to compare three iodine interventions (Guaranteed iodized salt, Market salt, and Market salt + iodized oil). When adequate iodine supply was constantly guaranteed, enlarged thyroids returned to normal within 12-18 months in a population with initially mild to moderate degree of iodine deficiency such as in the Guaranteed iodized salt group and in the Market salt + iodized oil group, while normal status of thyroid size was not achieved when iodine content in salt fluctuated, such as in the Market salt group.

A multisectoral evaluation of effectiveness of iodine intervention programs was conducted in 1997 in 9 counties where iodized salt has been available for 12 years. It was established that these 9 counties have achieved their goals of eliminating iodine deficiency. Urinary iodine concentrations have been above 100 μg/L since 1985. Goiter prevalence in schoolchildren progressively decreased from 42% in 1983 to 4% in 1997. More than 90% of the salt for human consumption become adequately iodized during the period from 1991 to 1996. Sustainable mechanisms for salt iodization and iodine information management have been established in these 9 counties. The methodology and approach used in this evaluation has become an example for other parts of China to assess the iodine status and the progress of iodine intervention programs.

To validate the new WHO reference of upper limits of normal thyroid volume, thyroid volumes of schoolchildren in US and in Bangladesh were compared with those in Europe. US children had significantly smaller thyroid volumes than European children did. The difference could be attributable to the residual effects of iodine deficiency in some European areas. The new WHO reference for upper limits of normal thyroid volumes should not be adopted as an international reference. Reference of thyroid volume based on body surface area should always be used regardless of the nutritional status of the population because body surface area

predicts the thyroid volume better than age both in iodine sufficient US children and in iodine deficient Bangladeshi children.

Based on the concentrations of iodine in drinking water or in urine where adverse effects, such as a decline in IQ, an increase in goiter prevalence and perturbation of thyroid function were detected, maximum allowable iodine concentrations can be set at 300 μg/L in drinking water or at 800 μg/L in urine of adults. Iodine concentrations in urine or in drinking water exceeding these levels should be regarded as a public health risk and interventions should be launched to normalize the iodine intakes. When assessing the iodine status of a population, goiter prevalence alone is not enough to characterize the iodine status. Information on urinary iodine concentrations and the status of an iodine intervention program should also be collected. Close monitoring on iodine status is necessary to minimize the adverse effects associated with either iodine excess or iodine deficiency.

Samenvatting

Jodium is een essentieel spoorelement voor de gezondheid van mensen. Evenals bij andere spoorelementen moet de hoeveelheid jodium die opgenomen wordt in het menselijk lichaam tussen bepaalde grenzen blijven; een lagere of hogere jodiuminname kan negatieve gezondheidseffecten veroorzaken.

Jiangsu is een provincie gelegen in het oosten van China. In deze provincie is jodiumtekort lange tijd een groot probleem voor de volksgezondheid geweest, maar door effectieve zout-joderingsprogramma's is dit probleem tegenwoordig grotendeels verdwenen. In de streken Feng, Pei en Tongshan, alle behorende bij de gemeente Xuzhou, is het endemisch voorkomen van krop (struma, schildkliervergroting) juist geassocieerd met een overmatige jodiuminname. Dit proefschrift presenteert de resultaten van een aantal studies, uitgevoerd in de Jiangsu provincie, naar de omvang van de problemen die ontstaan als gevolg van jodiumtekort en jodiumovermaat, naar interventies die deze problemen moeten oplossen en naar de negatieve effecten van een overmatige jodiuminname.

In dit onderzoek is de relatie tussen de jodiumconcentraties in het drinkwater in Feng, Pei en Tongshan en de jodiumconcentratie in de urine van volwassenen, de prevalentie van krop bij kinderen en de schildklierfunctie van volwassenen onderzocht. Een verschil in de jodiumconcentratie van het drinkwater van 190 tot 1150 µg/L ging gepaard met een jodiumconcentratie van 520 tot 1960 µg/L in de urine van volwassenen en met prevalenties van krop bij schoolkinderen, gemeten met behulp van ultrasound, van 5,3 tot 16,8%. De schildklierfunctie bleek verstoord bij volwassen die in de gebieden woonden waar de hoogste jodiumconcentraties in het drinkwater werden gevonden. Het endemisch voorkomen van krop in deze gebieden wordt waarschijnlijk veroorzaakt door een overmatige jodiuminname uit het drinkwater. De krop welke in verband gebracht kan worden met een overmatige jodiuminname is diffuus en colloïdaal, wat verschilt van de krop veroorzaakt door een te lage inname van jodium.

De relatie tussen jodiuminname, variërend van normaal tot overmatig, en mentale ontwikkeling, lichamelijke ontwikkeling en gehoorvermogen is beschreven aan de hand van gegevens verzameld in 13 dorpen in de drie streken in Xuzhou. Er werd een negatieve relatie gevonden tussen zowel de concentraties jodium in het drinkwater en het IQ van kinderen ouder dan elf jaar, als tussen de concentraties in de urine van volwassenen en het IQ van deze kinderen. Voor kinderen van elf jaar en jonger werd alleen een lager IQ gevonden in de groep met de hoogste jodiumconcentratie in het drinkwater. Dit wijst erop dat er een gedeeltelijke reversibiliteit bestaat van een verstoorde mentale ontwikkeling als gevolg van een overmatige jodiuminname, mits

reeds op jonge leeftijd begonnen wordt met het normaliseren van de jodiuminname. Er is geen duidelijk bewijs gevonden voor een relatie tussen verschillende gradaties van overmatige jodiuminname en de lichamelijke ontwikkeling of het gehoorvermogen van schoolkinderen.

De omvang van het probleem van overmatige jodiuminname is vastgesteld op grond van gepubliceerde data en met behulp van een meta-analyse is de mogelijke relatie tussen overmatige jodiuminname en cognitieve ontwikkeling van schoolkinderen aangetoond. Overmatige jodiuminname blijkt een probleem voor de volksgezondheid te zijn in 92 gemeenten in tien provincies in China. In totaal betreft het zo'n zestien miljoen mensen. Het IQ van kinderen in gebieden waar een overmatige jodiuminname is geconstateerd, was 3.2 punten lager dan bij kinderen die uit gebieden kwamen waar de jodiuminname normaal was. In gebieden waar de jodiuminname extreem hoog was, was het IQ zelfs 3.7 punten lager dan in gebieden met een normale jodiuminname. Deze bevindingen versterken het belang van interventies die de jodiuminname moeten normaliseren.

De schildkliergrootte en de schildklierfunctie werd gemeten en vergeleken in vier dorpen, verdeeld over twee paren, met gemiddelde tot hoge jodiumconcentratie in het drinkwater. De jodiumconcentratie in het drinkwater werd verlaagd in één van de dorpen van elk paar. Het schildkliervolume nam een normale waarde aan binnen drie maanden na normalisatie van de jodiuminname via het drinkwater. Voor de meeste, maar niet voor alle kinderen was de schildklierfunctie normaal aan het einde van het onderzoek. Dit doet vermoeden dat door overmatige jodiuminname twee soorten hypothyroïdie kunnen ontstaan: een reversibele, welke gevoelig is voor jodiumbeperking, en één die dat niet is.

Met behulp van een gerandomiseerde trial zijn drie jodiuminterventies met elkaar vergeleken (gegarandeerd gejodeerd zout, marktzout en marktzout+ gejodeerde olie). Bij een gegarandeerde adequate jodiumvoorziening werd een vergrote schildklier binnen 12-18 maanden teruggebracht tot een normaal volume in een populatie met aanvankelijk een milde tot matige vorm van jodiumtekort, zoals in de 'gegarandeerd gejodeerd zout' groep en in de 'marktzout + gejodeerde olie' groep, terwijl een normale schildkliergrootte niet gerealiseerd werd in een groep waarin de jodiumvoorziening fluctueerde, zoals in de 'marktzout' groep.

In 1997 werd een multisectorale evaluatie uitgevoerd naar de effectiviteit van jodiuminterventie programma's in 9 gebieden waar gejodeerd zout al gedurende twaalf jaar beschikbaar was. Er kon worden geconstateerd dat jodiumdeficiëntie in deze gebieden niet meer voorkwam. Sinds 1985 zijn de jodiumconcentraties in de urine boven de 100 µg/L. De prevalentie van krop bij schoolkinderen nam af van 42% in 1983 tot 4% in 1997. Meer dan 90% van het consumptiezout was voldoende

gejodeerd in de periode 1991-1996. In deze gebieden zijn duurzame mechanismen ontwikkeld voor de jodering van zout en voor de voorlichting omtrent jodium die de jodering van zout moeten handhaven. De methodologie en benadering, welke in deze evaluatie zijn gebruikt, hebben tot een voorbeeld gediend voor het vaststellen van jodiumstatus en de voortgang van interventieprogramma's in andere delen van China.

De volumes van de schildklier van schoolkinderen in de VS en in Bangladesh zijn vergeleken met die in Europa om de nieuwe referentiewaarde van de WHO voor de bovenste grens van een normaal schildkliervolume te testen. Amerikaanse schoolkinderen hadden een significant kleiner schildkliervolume dan Europese kinderen. Dit verschil kon worden toegeschreven aan de overblijvende effecten van jodiumtekort in het verleden in enkele Europese gebieden. De nieuwe referentiewaarde van de WHO is niet universeel bruikbaar als referentiewaarde. Voor zowel Amerikaanse schoolkinderen met een adequate jodiumstatus als voor jodiumdefieciënte schoolkinderen in Bangladesh kon het schildkliervolume beter voorspeld worden op basis van het lichaamsoppervlak dan op basis van leeftijd. De referentiewaarde voor het schildkliervolume bepaald aan de hand van het lichaamsoppervlak is dan ook beter bruikbaar, ongeacht de voedingsstatus van de populatie.

Op basis van de jodiumconcentratie in het drinkwater of in de urine waarbij negatieve effecten werden geconstateerd, zoals afname van het IQ, toename van de incidentie van krop en een verstoring van de schildklierwerking, kan de maximaal toegelaten jodiumconcentratie vastgesteld worden op 300 µg/L in het drinkwater en op 800 µg/L in de urine van volwassenen. Jodiumconcentraties boven deze waarden moeten worden beschouwd als een risico voor de volksgezondheid en als een indicatie voor het opzetten van interventieprogramma's om de jodiuminname te normaliseren. Bij het vaststellen van de jodiumstatus van een populatie is het bepalen van de prevalentie van krop niet voldoende. Er moet ook informatie verzameld worden over de jodiumconcentraties in de urine en de stand van zaken van een eventueel aanwezig interventieprogramma. Nauwkeurige monitoring van de jodiumstatus is noodzakelijk om de negatieve effecten gepaard gaande met enerzijds overmatige jodiuminname en anderzijds jodiumtekort te minimaliseren.

碘缺乏、碘过多及其干预
（概述）

碘是人体必需的微量元素之一。与其他微量元素一样，碘的摄入量必须保持在一个“正常”范围内，高于或低于这个范围均会对人体健康造成危害。人们对正常碘摄入量的下限已经有了较清楚的认识,对其上限的认识则不够清晰。碘缺乏病在江苏省是一个重要的公共卫生问题，通过1995年以来的全民食盐加碘，该病的危害在全省大部分县已得到消除，但在徐州市的部分县，如丰县、沛县及铜山县的部分乡（镇），地方性甲状腺肿与碘摄入量过高有关。本书描述的是在江苏省进行的研究结果，包括碘缺乏和碘过多问题的严重性、解决这些问题的方法以及高碘对人体健康的危害。本书第一章为引言,第九章为讨论。其余各章节内容概述如下。

第二章描述了丰县、沛县和铜山县饮水碘含量与学生甲状腺肿大率、成人尿碘水平及成人甲状腺功能的关系。随着水碘含量由190微克/升增至1150微克/升，成人尿碘水平由520微克/升增至1960微克/升，B超法学生甲状腺肿大率由5.3%升至16.8%，在水碘水平最高的两个乡镇，成人甲状腺功能受到抑制。故该地区的地方性甲状腺肿主要由饮水中碘含量过高所致，高碘甲状腺肿为弥漫“胶质”型，明显不同于缺碘造成的甲状腺肿。

第三章叙述了上述三个县十三个乡（镇）正常至过高碘摄入量与儿童智力发育、体格发育及听力的关系。对11岁以上的儿童，智商与饮水碘含量及成人尿碘水平呈显著负相关，而对11岁及11岁以下儿童，仅在水碘水平最高的乡发现儿童智商低于正常。在研究期间因饮水结构发生了变化，学生的智力水平已经受到影响，提示如果在儿童期将碘摄入量降至正常，学生智力发育落后状况存在一定的可逆性。对于不同高碘水平是否会造成体格发育落后或对听力产生影响，研究未发现明显证据。

第四章对中国现有研究数据进行了综述和Meta分析。据文献报道，高碘甲状腺肿存在于中国10个省、市、自治区约92个县，影响人口约1600万。Meta分析发现高碘地区儿童智商比碘摄入量正常地区儿童的智商低3.24点，当碘摄入量非常高时，智商差异增至3.74点。研究结果提示采取措施使碘摄入量正常化的重要性。

第五章比较了两对高碘乡（镇）学生甲状腺大小和甲状腺功能。对每对乡（镇）中的一个乡（镇）实施改水，将水碘水平降至正常，另一乡（镇）则维持现状作为对照。从碘摄入量降至正常的3个月，甲状腺容积即降至正常大小。研究结束时，大部分儿童甲状腺功能转为正常，提示高碘造成的甲状腺功能低下症存在两种类型，一种为可逆型，对碘限制饮食敏感，另一种则相反，为不可逆型，需临床治疗。

第六章为人群随机化实验，比较了三种不同的补碘措施：特制碘盐、市场供应碘盐、市场供应碘盐+碘油丸。在起始状态为轻度至中等程度碘缺乏的人群

中，如果碘的供给使人群碘摄入量持续稳定，甲状腺肿会在12至18个月内消失，如特制碘盐组和市场供应碘盐+碘油丸组；如果碘的供给使碘摄入量出现波动，18个月时甲状腺肿大率仍未降至正常，如市场供应碘盐组。

第七章对江苏省原十个碘缺乏病重点县中九个县的碘缺乏病防治效果进行了评估。在这九个县全民供应碘盐12年后，省政府组织多部门评估组进行的评估发现，1985年以来这九个县的尿碘水平一直保持在100微克/升以上，儿童甲状腺肿大率由1983年的42%逐步降至1997年的4%，1991至1997年间居民户碘盐合格率均在90%以上，同时这九个县均已建立可持续的碘缺乏病防制、管理机制，这九个县实现了消除碘缺乏病的目标。该评估所使用的方法成为中国其他地区评估碘缺乏病防制效果及评价补碘措施进程的范例。

第八章论证了新的WHO甲状腺容积正常值，对美国和孟加拉国儿童甲状腺容积进行了测量并与欧洲儿童进行了比较。美国儿童的甲状腺容积显著小于欧洲儿童，这一差异可能是由于欧洲一些地区近年来还存在碘缺乏的残余影响。基于欧洲儿童的新的WHO甲状腺容积正常值不能作为国际标准。不管营养状况如何，应始终使用以体表面积校正的甲状腺容积正常值，因为无论对碘充足的美国儿童还是对碘缺乏的孟加拉国儿童体表面积的预测性均优于年龄。

依据人体危害指标，如智力水平降低、甲状腺肿大率升高、甲状腺功能受到抑制等，检出时的水碘水平或尿碘水平，最大可允许碘浓度可定为：饮水，300微克/升、成人尿样，800微克/升，高于此浓度应被视为公共卫生危害，必须采取适当措施使碘摄入量降至正常。甲状腺肿大率一项指标不足以评价一个人群的碘营养状况，必须同时收集尿碘水平、正在实施的补碘或降碘措施等有关信息。对碘营养状况进行定期监测是将碘缺乏或碘过多危害降至最低程度的重要保证。

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Jinkou (Button) Zhao was born in Gaoyou County, Jiangsu Province, China, on February 23, 1965. He completed his high school education in Linzhe township in the countryside of Gaoyou County, Jiangsu Province, China. Afterwards, he studied in the School of Medicine, Yangzhou University, China. After graduation in August 1986 as Doctor of Medicine, he started his career in public health in the Department of Endemic Disease, Jiangsu Provincial Center for Public Health and Disease Control. In July 1995, he was appointed as Deputy Director of the Department of Endemic Disease. In 1996, he enrolled for a MSc degree in Epidemiology and Biostatistics in Nanjing University of Medical Sciences. From January 1998 to February 1999, he studied and worked in the Departments of Epidemiology and International Health of the Rollins School of Public Health at Emory University in Atlanta with a WHO fellowship. In February 1999, he was appointed as Director of the Department of Chronic and Endemic Disease of Jiangsu Provincial Center for Public Health and Disease Control. In May 1999, he obtained his MSc degree from Nanjing University of Medical Sciences. In the same month, Button started his PhD program in the Division of Human Nutrition and Epidemiology at Wageningen University. In December 1999, he was elected to the Board of the China National Committee of Experts on Iodine Nutrition. From 1995 to 2000, he carried out the research work described in this thesis. After graduation, he will resume his position in Jiangsu.

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Front cover: Pump used by local residents to draw water from a shallow well for domestic purposes. Water from shallow wells have very high concentrations of iodine.

Back cover: Upper, area of iodine excess where studies described in Chapters II, III and V were conducted; Lower, areas in China where iodine excess has been reported.