Trends in Iodine Deficiency Disorders from 1980 to 2010

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DEDICATION

I would like to dedicate this work to the members of my graduating MPH cohort: Stephanie Ahn, Kathryn Andrews, Laura Dwyer-Lindgren, Spencer James, Leslie Mallinger, Lisa Rosenfeld, and Sarah Wulf. Thank you for your unwavering support during our time together at IHME. I feel exceptionally honored to be graduating with such a talented, honest, and hardworking group of people, and I look forward to seeing how you will all make our world a better place.

Introduction

Iodine is an essential mineral necessary for normal thyroid function. Common sources of dietary iodine include seafood, dairy products, and food additives, such as calcium iodate and potassium iodate, which are commonly found in bread products [1]. The recommended daily intake of iodine is approximately 120 µg per day for school aged children (6-12 years) and 150 µg per day for adults, while 220 µg is recommended for pregnant women and 290 µg for breast feeding women [2]. Iodine deficiency can lead to an entire spectrum of conditions including goiter (thyroid enlargement), cognitive impairment (deficiency in children), and cretinism (deficiency in utero). Iodine deficiency is recognized as the leading cause of preventable cognitive impairment worldwide [3].

The assessment of iodine deficiency has seen measurable changes over time. Prior to the 2000s, the primary outcome of interest in population surveys was the prevalence of goiter. Goiter is typically measured by degree of palpation, as defined by the volume of the thyroid. Because thyroid enlargement is a long term condition, goiter prevalence rates are often difficult to interpret because the measurement captures both past and present iodine deficiency [4]. In addition, measurement of thyroid enlargement in mildly iodine deficient regions has been shown to have poor sensitivity and specificity, necessitating ultrasound diagnosis for better accuracy [5]. Cretinism prevalence, on the other hand, is responsive to acute changes in iodine intake, and declines in many regions have been correlated with the introduction of iodine interventions [6].

In 2004, the WHO revised their assessment of iodine deficiency to focus on urinary iodine concentration (UIC) [7]. A recent study published in 2012 by Andersson et al investigated the prevalence of school-aged children with severe, moderate, and mild iodine deficiency, as defined by UIC less than 20 µg/L, 20-49 µg/L, and 50-99 µg/L respectively. UIC is regarded as a better measure of current trends in iodine deficiency, since goiter captures residual iodine deficiency. However, data on UIC is limited pre-2003,

and there are few studies in the iodine literature that have analyzed the relationship between urinary iodine deficiency and goiter prevalence [8, 9].

Salt iodization is a low-cost intervention to provide populations with access to a sufficient and consistent daily intake of iodine, estimated to cost US$0.05 per person per year [10]. However, barriers to implementing iodized salt programs include difficulties in monitoring the import, production, and distribution of iodized salt. Incentives to producers are often necessary to guarantee access to high quality iodized salt, and marketing strategies are also important for promoting iodized salt consumption. According to UNICEF reports, approximately 90% of households in the Americas and the Western Pacific region have access to iodized salt, while less than 50% of countries in the Eastern Mediterranean have access [11]. In addition to challenges in monitoring iodized salt production and distribution, there is also poor coverage of population consumption of iodized salt many countries in Latin America and the Caribbean and West and Central Africa [12].

The goal of this study is to provide country-level estimates of the prevalence of goiter, cretinism, and household salt iodization for 187 countries from 1980 to 2010. Our study builds upon existing research by analyzing the relationship between UIC and prevalence of clinical outcomes for all ages using new modeling techniques. This approach maximizes existing data sources on UIC and prevalence and incidence of outcomes, and seeks to describe the relationship between different outcomes of iodine deficiency. From these results, we hope to provide a comprehensive picture of changes in the prevalence iodine deficiency disorders by country, age and sex.

Methods

Goiter

Data sources

The primary data source used in this analysis was the WHO Vitamin and Mineral Nutritional Information System (VMNIS) [13].This database provides data on the proportion of the population with severe, moderate, and mild iodine deficiency, median and mean UIC, and prevalence of grade 1, grade 2 and total goiter. WHO classifications of iodine deficiency are shown in Table 1 and the simplified classification of goiter grades is shown in Table 2 [14].

Table 1. WHO urinary iodine deficiency classification

Median UIC in SAC and adults (ug/L)	Iodine deficiency status
<20	Severe iodine deficiency
20-49	Moderate iodine deficiency
50-99	Mild iodine deficiency
100-199	Adequate iodine nutrition
200-299	More than adequate, slight risk of excessive iodine intake
>300	Excessive intake, risk of hyperthyroidism

Table 2. WHO simplified classification of goiter grades

Grade	Criteria
0	No goiter presence is found (thyroid impalpable and invisible)
1	Neck thickening is present result of enlarged thyroid, palpable, however, no visible in normal position of neck; the thickened mass moves upwards during swallowing. Grade 1 includes also nodular goiter if thyroid enlargement remains invisible.
2	Neck swelling, visible when the neck is in normal position, corresponding to enlarged thyroid – found in palpation.

This database is a compilation of country reports, and national and subnational surveys in 152 countries, primarily from school-based studies. Table 3 shows the number of site-years of data available for goiter prevalence and urinary iodine deficiency from 1980 to 1990, 1990 to 2000, and 2000 to 2010.

Table 3. VMNIS Database site years of data

IDD outcome	1980-1990	1990-2000	2000-2010
Total goiter	720	3,715	523
Grade 1 goiter	354	1,822	308
Grade 2 goiter	396	1,991	297
UIC < 20 μg/L	9	742	752
UIC 20-49 μg/L	8	703	720
UIC 50-99 μg/L	17	809	834
UIC < 100 μg/L	17	1,078	1,079
Median UIC	43	1,890	1,654
Mean UIC	53	818	394

The distribution of UIC and goiter data reflects the change in iodine deficiency measurement, as data on urinary iodine concentration is sparse prior to 1990, with only 9 site years of data for UIC < 20 μg/L from 1980 to 1990, compared to 752 site years of data from 2000 to 2010. Previous analyses by Andersson et al estimated the median urinary iodine concentration for missing data based on regressions of the median and mean UIC, and median and the percentage of the population (UIC <20, 20–49, 50–99, and ,100 μg/L) and vice versa [8].

Our approach focused on linking UIC to goiter prevalence and maximizing data sources over time. We examined the relationship between mild, moderate, and severe iodine deficiency with grade 1, grade 2 and total goiter prevalence in log space, as the data was nonlinear. The relationship between UIC under 20μg/L and grade 2 goiter was the most significant, as shown in Table 4. Given this relationship shown in the data, we elected to model goiter based on the prevalence of grade 2 goiter and UIC < 20 μg/L.

Table 4. Regression coefficients of log goiter prevalence vs log urinary iodine deficiency

Log UIC (µg/L)	Log Total (95% CI)	Log Grade 1 (95% CI)	Log Grade 2 Goiter (95% CI)
< 20	0.566 (0.398, 0.733) **	0.475 (0.287, 0.662) **	0.618 (0.511, 0.725) **
20-49	0.418 (0.312, 0.524) **	0.352 (0.235, 0.468) **	0.302 (0.221, 0.381) **
50-99	0.203 (0.127, 0.278)	0.175 (0.095, 0.254)	0.081 (0.022, 0.140)
< 100	0.317 (0.239, 0.395) **	0.254 (0.170, 0.339) **	0.199 (0.131, 0.267) **
Median	-0.158 (-0.273, -0.028)	-0.147 (-0.266, -0.028)	-0.144 (-0.240, -0.049)
Mean	-0.334 (-0.486, -0.182)	-0.325 (-0.509, -0.142)	-0.278 (-0.397, -0.159)

** Indicates a significance level at $p < 0.001$, based on linear regression of log UIC and log goiter prevalence

Because the majority of the data relies on school-based surveys, the data demonstrates a significant compositional bias by age. To overcome this compositional bias, we incorporated additional data from a national level clinical examination study from Iran in 1996. This study provided age and sex specific data on prevalence of grade 0, grade 1 and grade 2 goiter, and was used to inform the age and sex specific pattern of goiter, assuming that the age distribution does not vary significantly between regions. A limitation of this assumption is that the introduction of salt programs can impact the age distribution of goiter, leading to variation between regions. However, the effect of such an intervention is gradual since goiter is not responsive to acute changes in iodine intake.

The VMNIS database includes both national and subnational sources of varying sample sizes. We included an indicator for nationally representative studies and set these observations as a reference group in our models. We excluded all studies with a sample size less than 100 persons, and studies based in areas classified as “endemic locations”, as these studies are likely to introduce bias to our national estimates of level iodine deficiency.

Estimating goiter prevalence

We produced country-year-sex-age specific estimates of grade 2 goiter prevalence using DisMod 3, a compartmental model of disease progression with a mixed effects negative binomial model [15]. We utilized DisMod 3 without all parameters of the compartmental model (prevalence, incidence, remission and excess mortality) in order to estimate the prevalence parameter only. An important function of DisMod 3 is adjustment of input data through study level covariates. This approach allows us to model different outcomes and obtain coefficients from the regression to transform prevalence of one outcome to prevalence of another outcome. In modeling goiter, we input both prevalence of UIC < 20 μg/L and prevalence of grade 2 goiter, and included a study level covariate on grade 2 goiter. From the regression outputs, we took the coefficient on grade 2 goiter (0.427) and transformed the prevalence of UIC < 20 μg/L to the prevalence of UIC < 20 μg/L. This modeling strategy is a novel method for bridging the gap in information between urinary iodine level and goiter prevalence. Furthermore, we set national-level observations as a reference group, to up-weight nationally representative studies in our estimates. Our final model used fixed effects on sex, national observations, grade 2 goiter, and random effects on country and region.

Another application of DisMod 3 is the specification of heterogeneity of the age distribution across regions. In our model, we assumed that the age pattern of goiter would not vary considerably across regions. We acknowledge this assumption as a limitation of our model, given that the age distribution of goiter is affected by the long-term introduction of salt iodization. The model incorporated a linear spline with knots at ages 0, 10, 20, 45, 65 and 100 to represent a plausible age pattern of goiter. From this model, we produced country-sex-age-specific prevalence estimates at more refined 5-year age groups.

Household salt iodization

Data sources

In order to construct a time-series of household salt iodization use, we compiled data from the UNICEF State of the World's Children (SOWC) Reports from 1996 to 2012 [16]. The SOWC Statistical Annexes provide data on the proportion of households consuming adequately iodized salt in 152 countries, in four year time periods. Adequately iodized salt is defined as > 15ppm and is determined by rapid testing for salt iodization [17]. Iodized salt consumption data were gathered primarily from the Multiple Indicator Cluster Surveys (MICS), with additional data from UNICEF studies, Demographic and Health Surveys (DHS), PAHO, and national surveys and Ministry of Health databases. These data are current for all countries and have the added advantage of being subject to quality assessment. Figure 1 shows the global availability of iodized salt consumption data.

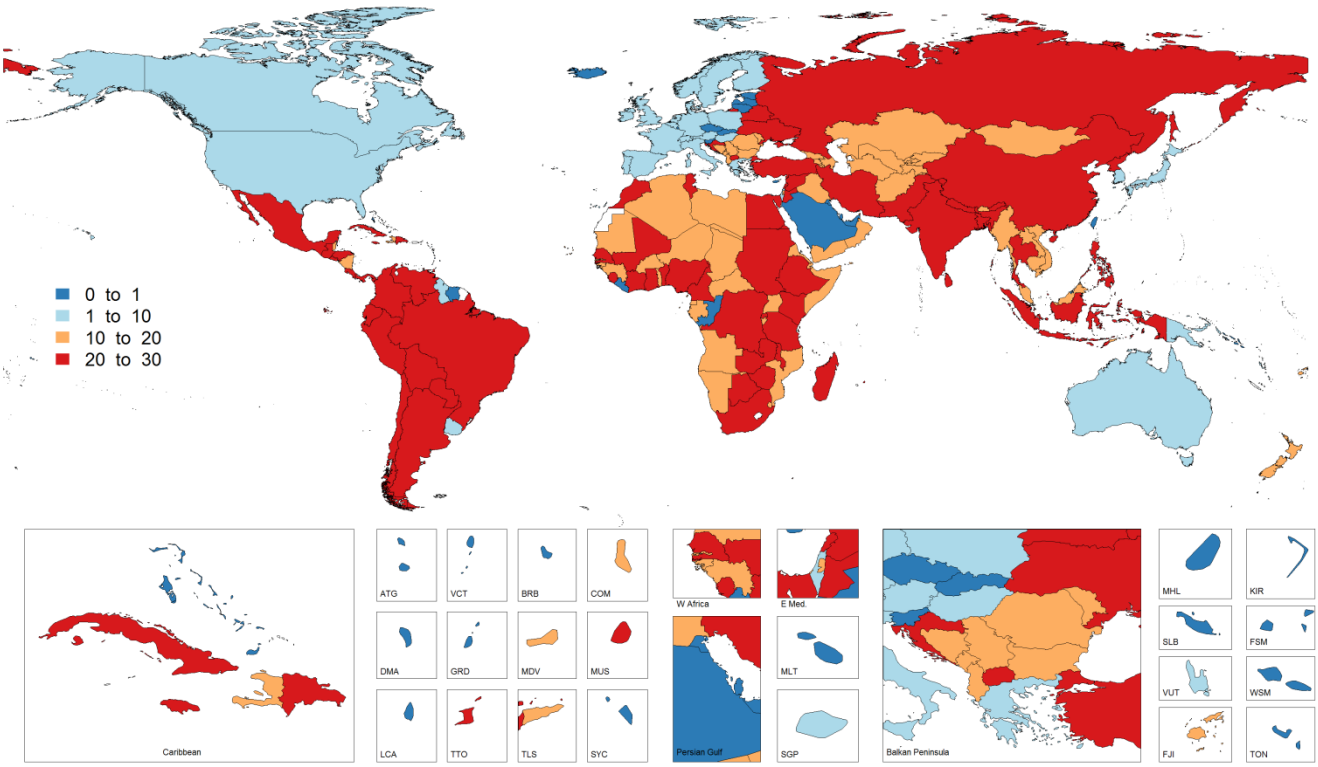

Figure 1. Country years of household iodized salt consumption data, UNICEF 1980-2011

Constructing a time series of household salt iodization

We ran the data available on the percent of households using iodized salt through a spatial-temporal smoothing model to generate a complete time series of household iodized salt consumption from 1980 to 2010 for 187 countries. In this two-step model, we first ran an ordinary least squares regression on available data to obtain residuals for each data point. In the second step, we ran regressions in two dimensions, by time and geographic region, such that observations in greater geographic and temporal proximity were weighted higher than those that were more distal. This method allows us to capture systematic variation that is explained by region and time. For countries with no data, we used residuals from corresponding region-time periods to predict household iodized salt consumption. Figure 2 shows how data points are smoothed to estimate household iodized consumption over time in Mongolia.

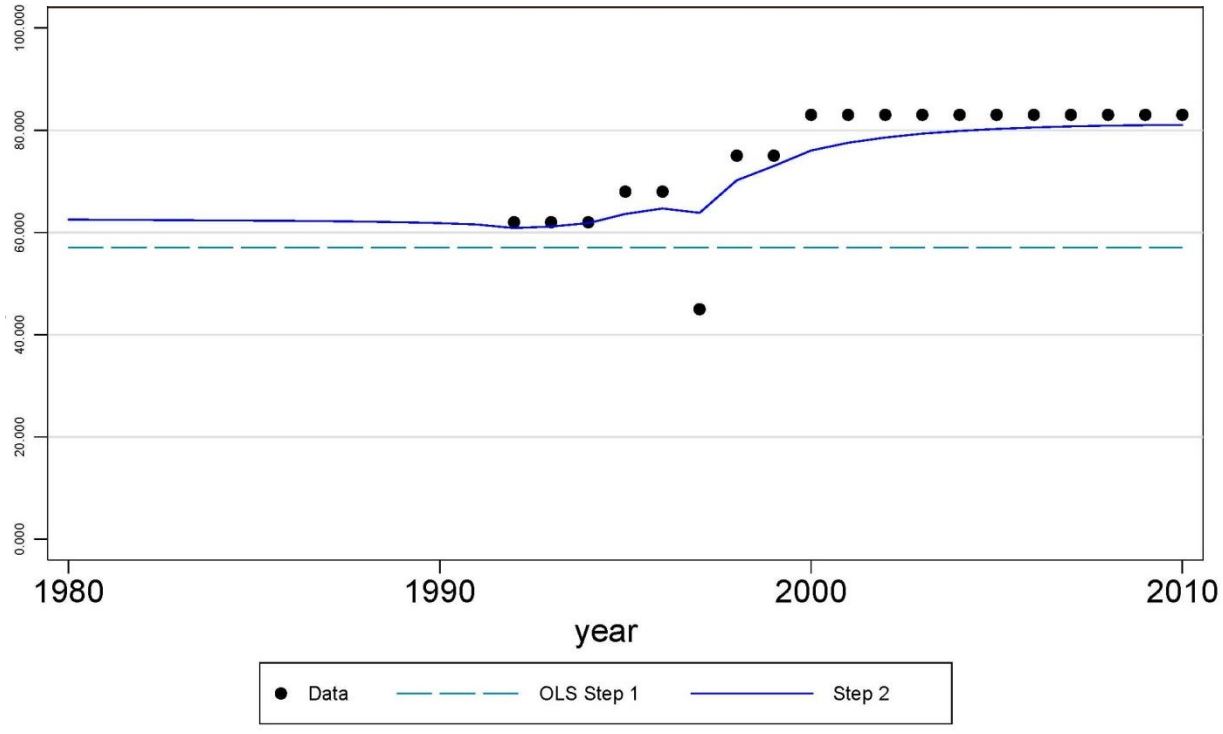

Figure 2. Spatial-temporal smoothing of household iodized salt consumption in Mongolia, 1980-2010

Cretinism

Data sources

A literature search was conducted to gather information on the relationship between cretinism prevalence, incidence and goiter prevalence. We used the search terms, “cretinism and goiter prevalence” and “cretinism incidence” in PubMed, resulting in 235 and 954 articles respectively. We excluded case control studies and studies with no measure of uncertainty around the point estimate. We also excluded studies on congenital hypothyroidism because of challenges in attributing congenital hypothyroidism exclusively to iodine deficiency in many countries [18]. Literature available on cretinism is limited and primarily dates to studies prior to 2000. Using these criteria and given these limitations, we obtained a total of 22 articles reporting both cretinism prevalence and goiter prevalence in the same population. These studies included national and subnational population-based surveys on iodine deficiency conducted in Sub Saharan Africa, Southeast Asia, Eastern Mediterranean, India, China, and Papua New Guinea. For studies that reported goiter prevalence as “visible goiter”, we assigned these cases to grade 2 goiter, based on WHO classifications of goiter grades [14].

Estimating cretinism prevalence

To estimate cretinism, we modeled the relationship between grade 2 goiter prevalence and cretinism prevalence, based on studies reporting both outcomes in the same sample population. We transformed cretinism prevalence and goiter prevalence to logit space to restrict our data to a zero-to-one scale, and ran a regression on the logit prevalence of grade 2 goiter and the logit prevalence of cretinism (Figure 3) We used the outputs of this regression to predict cretinism prevalence for all 187 countries based on prevalence generated from the grade 2 goiter model.

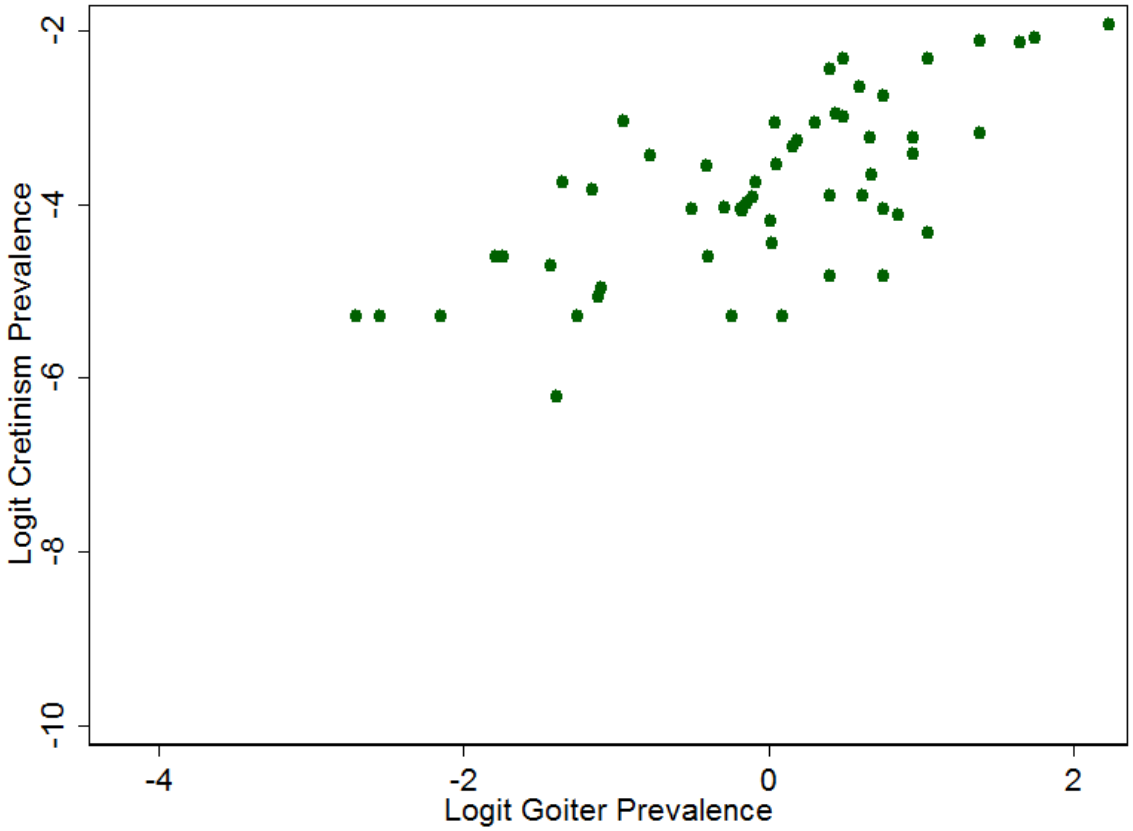

Figure 3. Logit grade 2 goiter prevalence versus logit cretinism prevalence

Following methods used by Rastogi and Mathers in the Global Burden of Disease 2000 estimates of iodine deficiency disorders, we assumed that the incidence of cretinism would be negligible in countries with greater than 90% household consumption of adequately iodized salt, and where the total goiter rate is under 20% [19, 20] We included observations in children aged 5 and under, and used these data as inputs into DisMod 3. In DisMod 3, we set remission to be zero because the disease is a lifelong condition, and set incidence to be zero after 5. We used a relative risk of 6.33 across all ages to capture the increased risk of death due to mental retardation. This relative risk was based on a meta-analysis by Harris and Barraclough, which found that the major causes of death in populations with mental retardation were infections, respiratory, and circulatory system disorders [21].

Results

Goiter prevalence

Global goiter prevalence has seen relatively little change over time, remaining at a global prevalence of 7.15%. We found modest reductions in the prevalence of goiter by region, with decreases in Sub-Saharan Africa from 14.6% to 14.2% and South Asia from 10.1% to 8.8% (Figure 4). Goiter prevalence increased in Eastern Europe and Central Asia, from 11.2% to 11.5%, while goiter prevalence remained unchanged in the North Africa/Middle East around 14.5% from 1990 to 2010. At the country level, Congo demonstrated the highest goiter prevalence at 34.7% in 1990, maintaining its high level at 34.3% in 2010. Countries showing the largest declines in goiter prevalence include Bangladesh, from 15.5% to 13.6%, India, from 8.8% to 7.7%, and Cameroon from 16.9% to 16.2%. Countries that experienced increases in goiter prevalence include Turkmenistan (13.9% to 14.3%) and Ukraine (12.8% to 13.2%) (Figure 5-6). We estimated a total of 180 million people with goiter in 2010, up from 139 million in 1990.

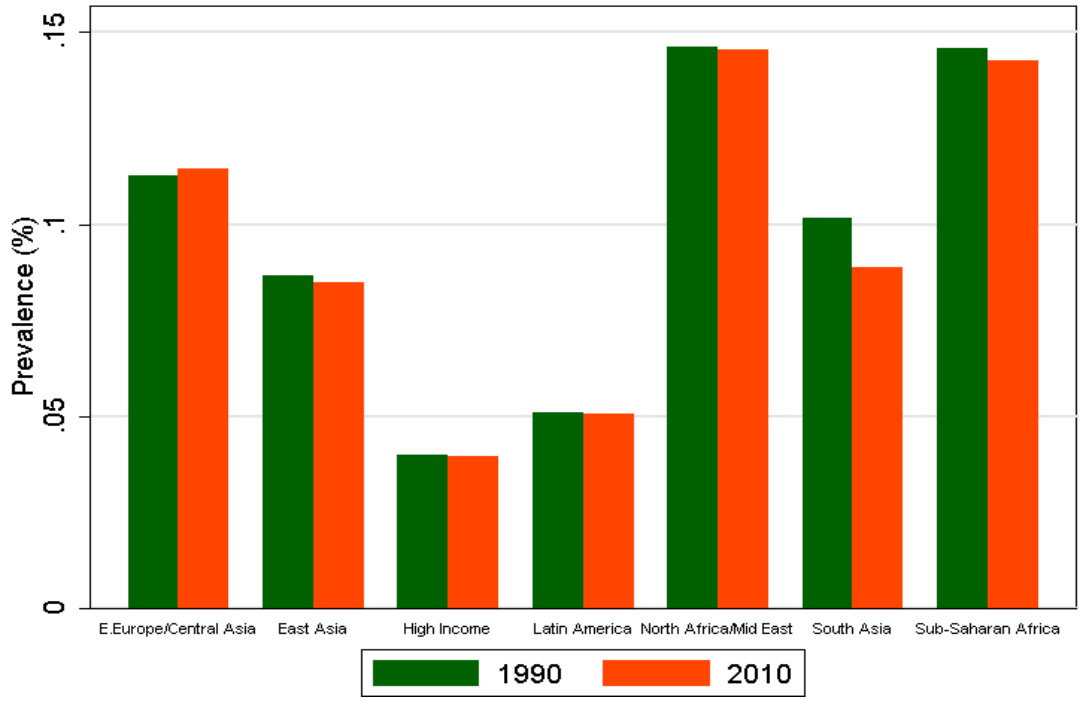

Figure 4. Goiter prevalence (%) by super region in 1990 and 2010

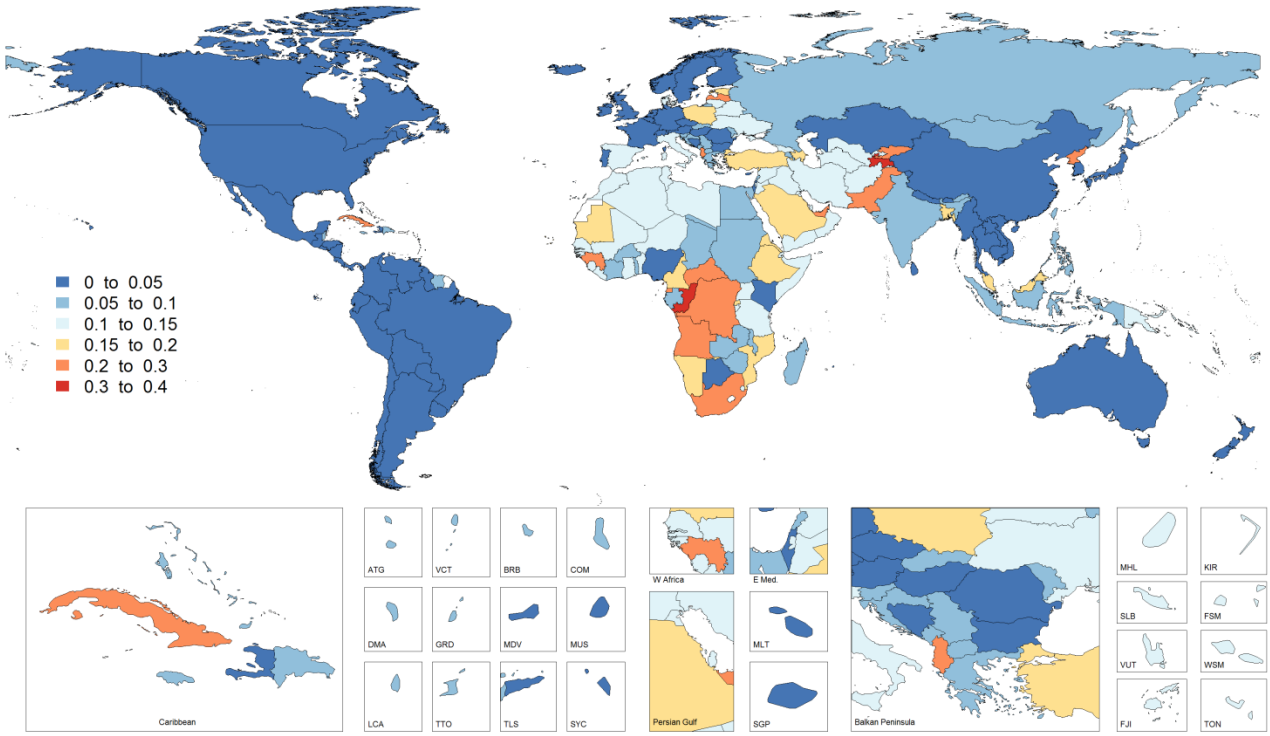

Figure 5. Global goiter prevalence (%), 1990

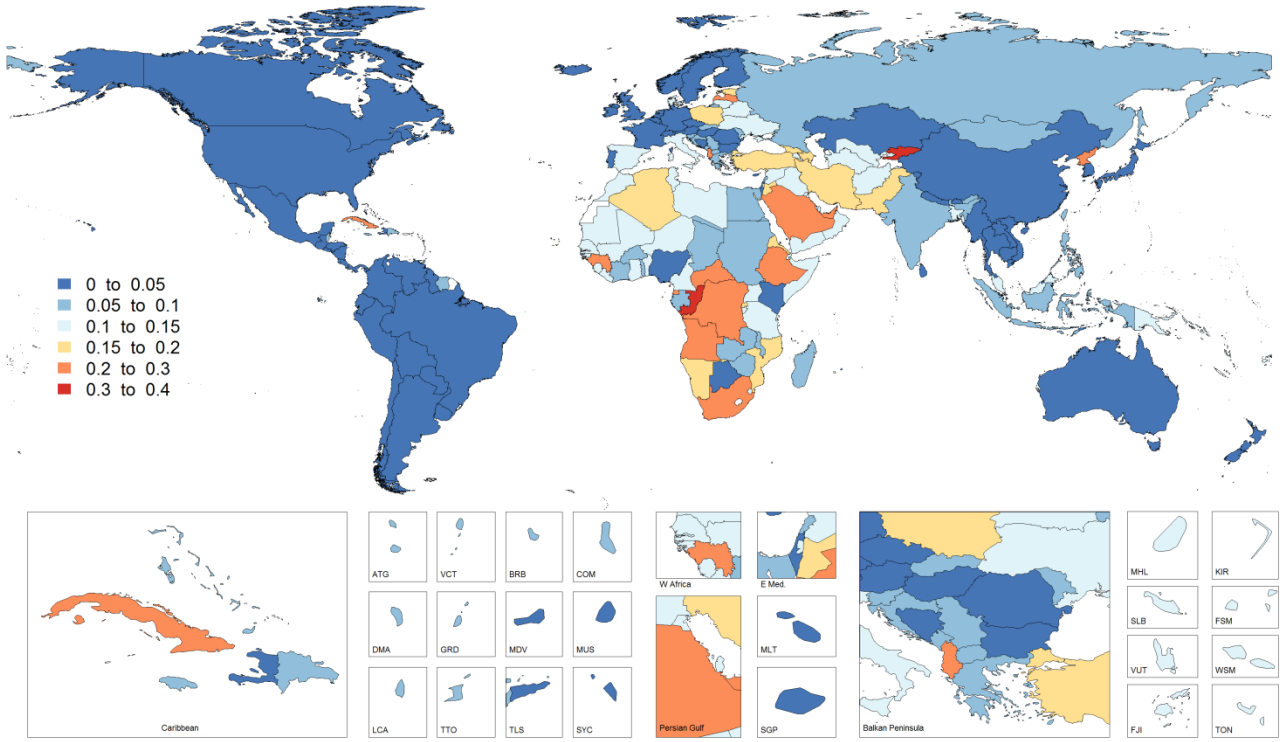

Figure 6. Global goiter prevalence (%), 2010

Household iodized salt consumption

Data on the proportion of households consuming adequately iodized salt was available for a total of 152 countries. We had no data for 35 countries, and used modeled estimates for these countries. Annex Table 2 shows the percent household consumption of iodized salt by country and year, indicating where estimated were based on raw or modeled data. As shown in Annex Table 2 and Figure 1, over 25 country years of data were available in China and South American countries, compared to less than 10 country years of data for each country in Western Europe.

Unlike goiter prevalence, the global trend in the consumption of adequately iodized salt has seen significant changes over time. Substantial progress has been made notably in China, where the percent consumption of household iodized salt rose from 73% to 97%, and throughout Latin America, where the percent consumption of household iodized salt rose from 77% to 96% in Brazil and 64% to 94% in Paraguay. 32 countries achieved the goal of universal household iodized salt consumption at 90% in 2010, compared to just 13 countries in 1990. Consumption of adequately iodized salt has shown a steady increase in the United States, growing from 35% to 88% in 2010. In contrast, the majority of countries in Western Europe saw little to no change in the percent household consumption of iodized salt (Figure 7-8). Furthermore, several countries saw a reduction in the percent consumption of adequately iodized salt including Serbia, decreasing from 64% to 32%, Croatia from 100% to 88%, and Eritrea from 76% to 68%.

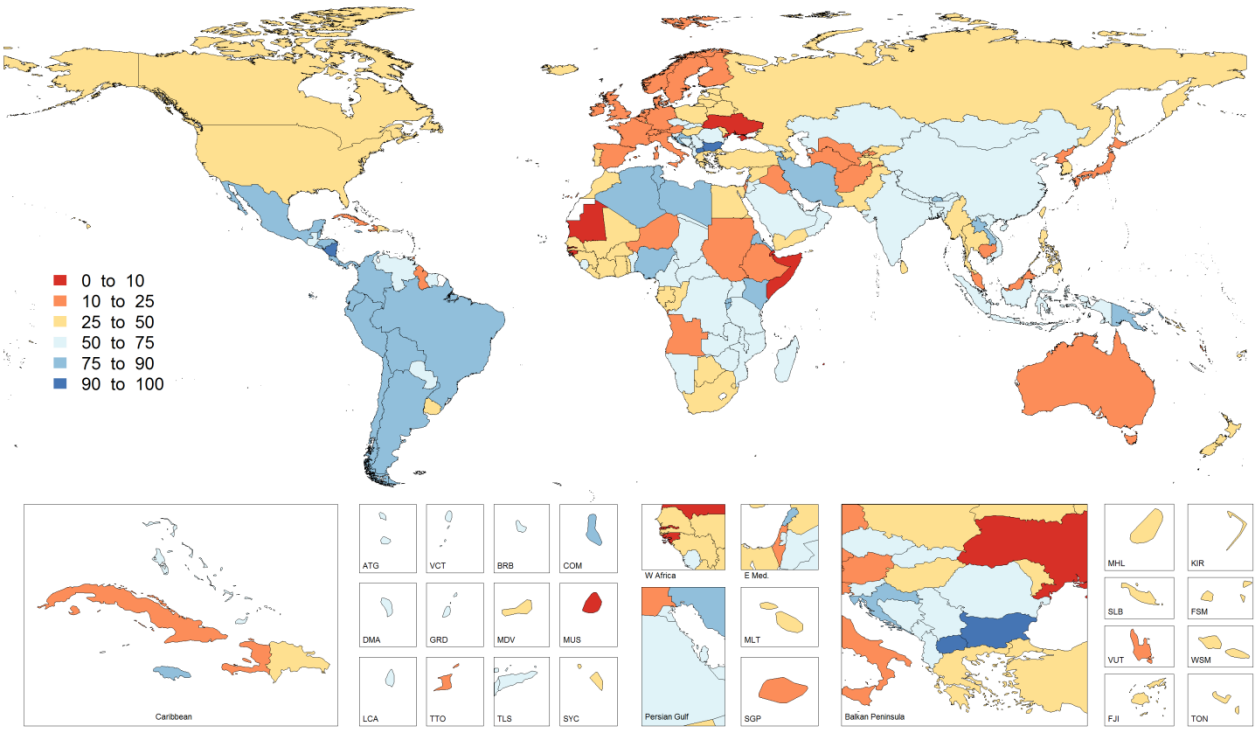

Figure 7. Percent household iodized salt consumption, 1990

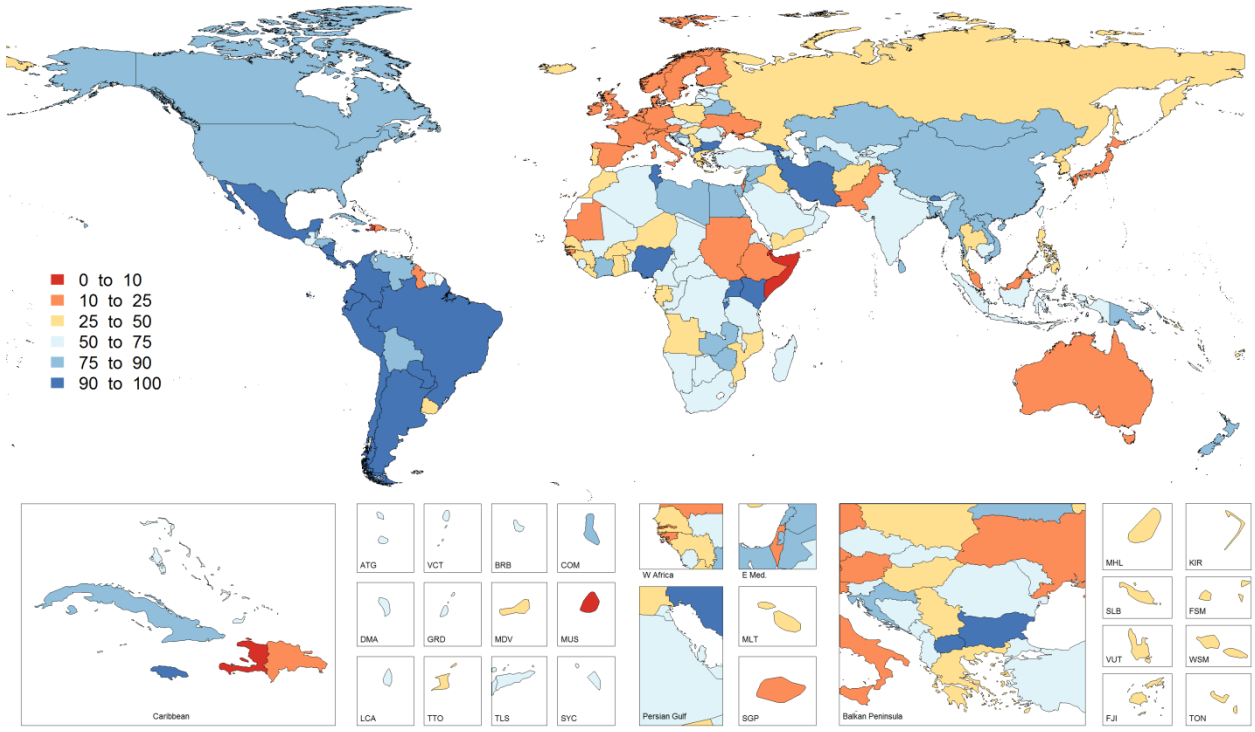

Figure 8. Percent household iodized salt consumption, 2010

Cretinism prevalence

The global prevalence of cretinism has declined from 22 per 100,000 in 1990 to 3 per 100,000 in 2010, representing an annual rate of decline of 8.8%. We estimated 819,188 cases in 2010, a decrease from 1.92 million cases in 1990. Declines were observed in all regions except South Asia, which saw an increase in cretinism prevalence from 15 per 100,000 to 17 per 100,000. Declines in regional prevalence were also observed in Eastern Europe and Central Asia, from 26 per 100,000 to 1 per 100,000, and in North Africa and the Middle East from 30 per 100,000 to 5 per 100,000. At the country level, substantial declines in cretinism prevalence were observed in Ghana, from 66 per 100,000 to 9 per 100,000 and Tanzania, from 59 per 100,000 to 1 per 100,000. No new cases of cretinism were estimated in China in 2010, a marked decrease from the 357,744 cases estimated in 1990, while cretinism cases rose in India from 405,635 cases 1990 to 498,898 cases in 2010. As shown in Figure 12, cretinism prevalence is the highest in children under five, and prevalence falls rapidly at older ages as the result of the high relative risk. In addition, we found that trends in cretinism prevalence were similar in males and females.

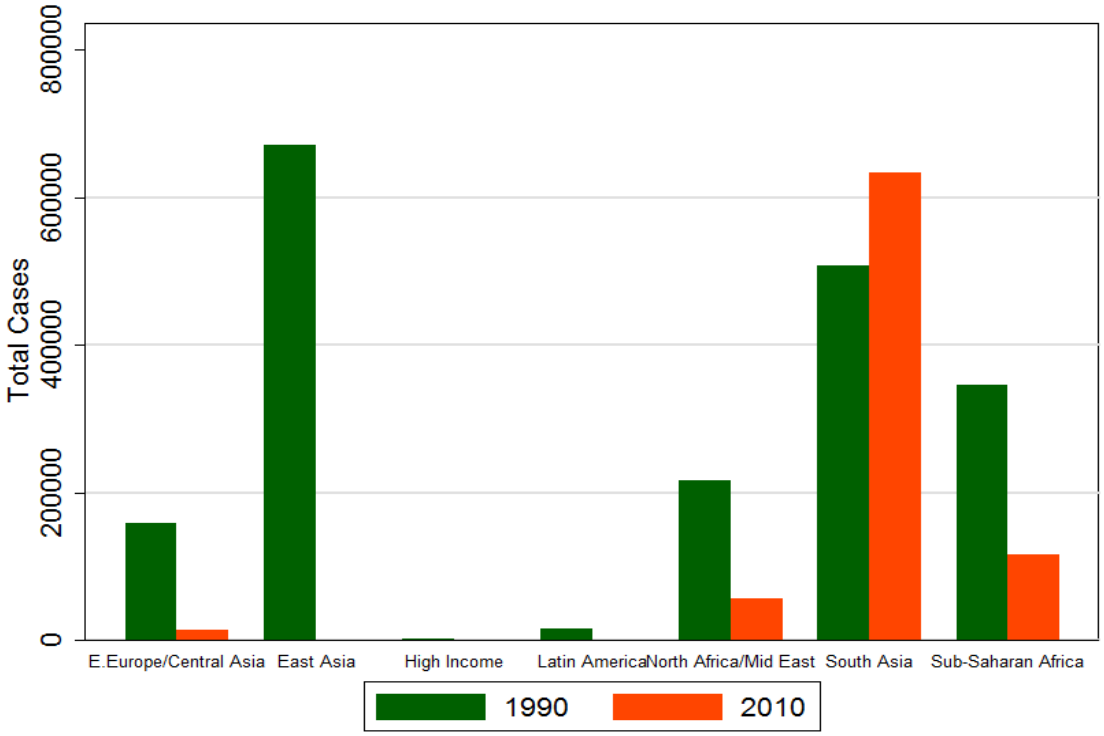

Figure 9. Total number of cretinism cases by region in 1990 and 2010

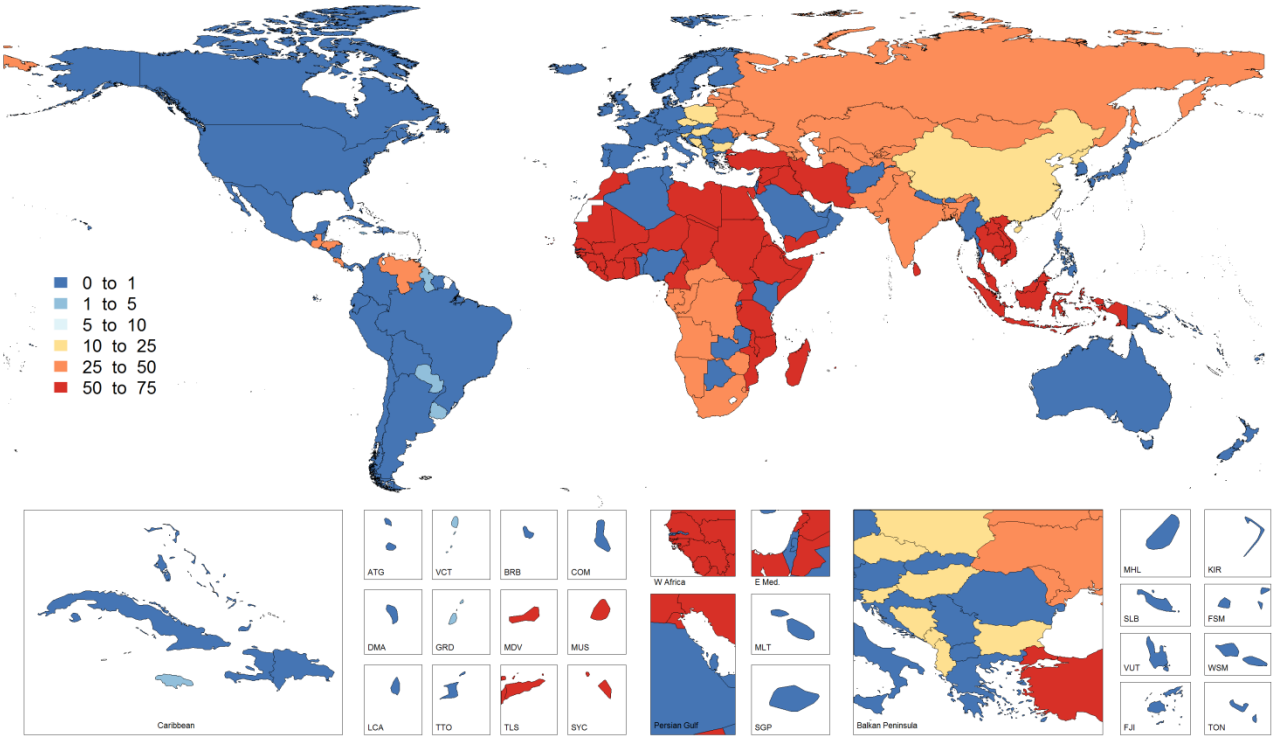

Figure 10. Global cretinism prevalence per 100,000 persons, 1990

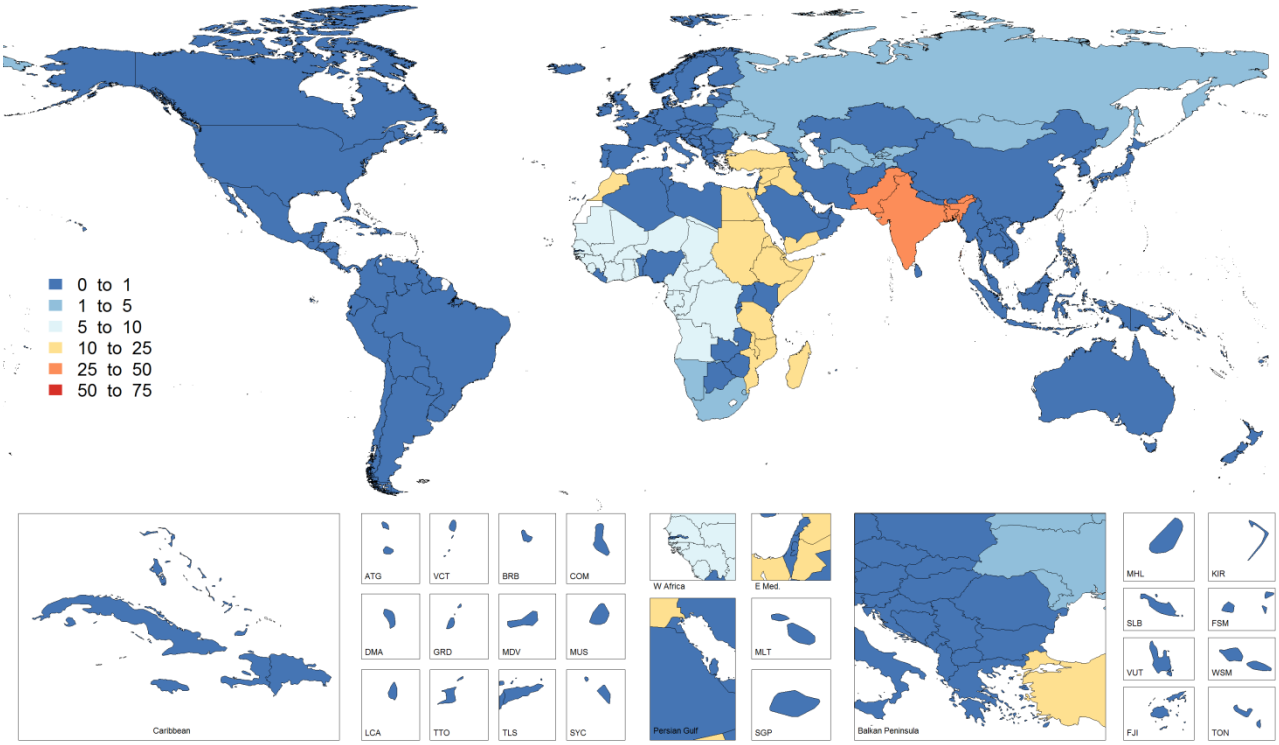

Figure 11. Global cretinism prevalence per 100,000 persons, 2010

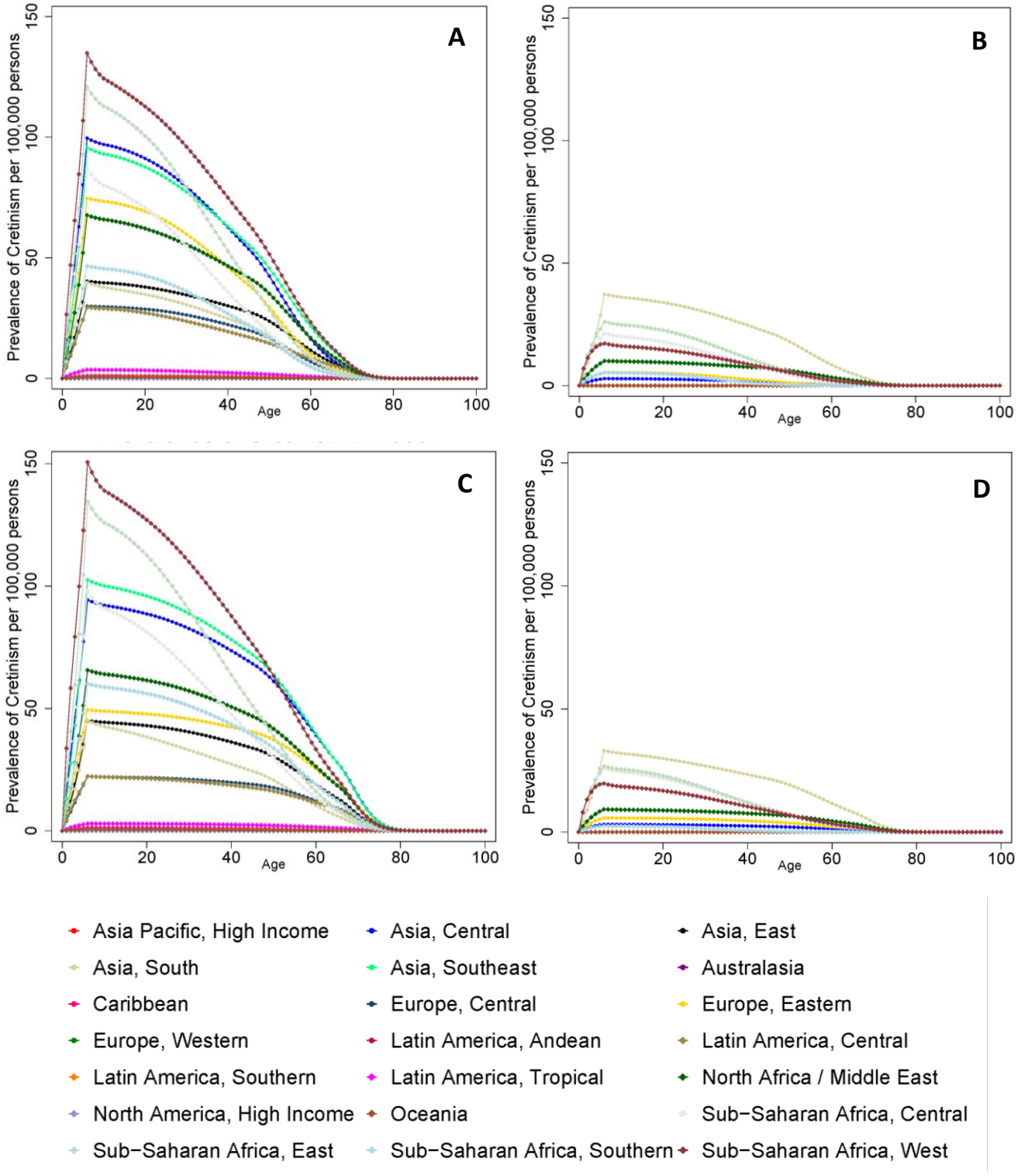

Figure 12. Cretinism prevalence per 100,000 persons, by GBD Region: (A) Males in 1990, (B) Males in 2010, (C) Females in 1990, (D) Females in 2010

Discussion

Summary of findings

Iodine deficiency indicators have seen major changes in their assessment over the past two decades. The shift from measuring goiter prevalence to urinary iodine concentration has led to large disparities in our knowledge of iodine deficiency disorders over time. Our study used novel modeling methods to integrate these disparate sources of information to estimate the prevalence of goiter and cretinism. Similarly, many gaps exist in our knowledge of household iodized salt consumption over time. Using available sources from UNICEF, we estimated the proportion of households consuming iodized salt for 187 countries from 1980 to 2010.

We found a significant relationship between grade 2 goiter prevalence and severe urinary iodine deficiency, defined by UIC < 20 µg/L. Previous work by Liu et al found a strong association between UIC < 20 µg/L and goiter prevalence in a nationally representative sample of Chinese children aged 8 to 10 years in 1999, 2002, and 2005, though notably, the association was found between UIC and total goiter prevalence [22]. Liu et al also noted that the relationship between UIC and goiter prevalence is sensitive to the long term adoption of salt iodization (approximately 10 years after the introduction of iodized salt), and will vary by region by region according to the consumption of adequately iodized salt.

Our findings show that the global trend in goiter has remained steady from 1990 to 2010, at a global prevalence of 7.15%. Despite progress in the implementation of salt iodization programs, goiter prevalence remains high in part due to the historical burden of goiter cases. Improvements in socioeconomic status, health outcomes and life expectancy in previously iodine-deficient nations may also be a contributing factor to the unwavering number of goiter cases worldwide [23]. At the global level, our results confirm that goiter prevalence is an inappropriate indicator of present iodine deficiency, given its slow response to iodization [24]. However, our country level findings indicate that

goiter burden is decreasing in countries such as India and Bangladesh, and increasing in countries such as Turkmenistan and Ukraine. Such findings highlight the positive impact of large scale iodization programs in countries like India, where the domestic salt refining capacity increased from 5% to 50% from 1990 to 2000, and where government regulation resulted in ban in the production and sales of non-iodized salt in 2005 [10, 25]. These findings also underscore the importance of targeting iodization programs in nations that demonstrate increases in goiter prevalence.

We found substantial declines in the global trend of cretinism, falling from 1.92 million cases in 1990 to 819,188 cases in 2010. Cretinism prevalence decreased in every region, with the largest declines in East Asia. In China, cretinism decreased from a total of 357,744 cases in 1990 to no cases of cretinism 2010. These results indicate remarkable progress in iodine deficiency control in the past two decades. In the early 1990s, iodine deficiency was recognized as a major public health threat in China, with more than 30% of the population deemed at risk for iodine deficiency [26]. In response, the State Council of China adopted universal salt iodization as a national policy in 1993, with the aim to eliminate iodine deficiency disorders by 2000 [27]. Additionally, a national monitoring system of biannual prevalence surveys and county-based iodine testing was established to monitor goiter prevalence, household iodized salt consumption and iodine status in school children [28, 29]. Our findings indicate that these concerted efforts in China have led to significant reductions in iodine deficiency disorders from 1990 to 2010.

In 2010, we found that 32 countries met the goal of universal salt iodization, compared to just 13 countries in 1990. Large gains were notably made in Latin America, where over 90% of households consume adequately iodized salt in 10 of the 29 countries. One limitation of data from Latin America and the Caribbean noted by UNICEF, however, is the low coverage of the population, at approximately 50% [17]. For this reason, our national estimates of household salt iodization may not entirely reflect the trends in iodized salt consumption in Latin America. Additionally, we need to consider that variation

within countries, particularly differences between rural and urban areas, contribute additional challenges to estimating national consumption of iodized salt. In India, the 2009 Coverage Evaluation Survey found that approximately 71% of households consume adequately iodized salt. However, this statistic masks the disparity between urban and rural household consumption patterns, where 83.2% of urban households consume adequately iodized salt, versus 66.1% of rural households [30].

We lack substantial knowledge about salt iodization and consumption in Western Europe, with less than 10 country-years of data available in most countries. This trend reflects an absence of salt monitoring combined with an absence of salt iodization mandates in Western Europe. According to a report by the European Commission, universal salt iodization remains voluntary in almost all Western European countries, with the exception of Denmark and Austria. In comparison, universal salt iodization is mandated in the majority of Central and Eastern European countries including Bosnia, Bulgaria, Croatia, the Czech Republic, Macedonia, Hungary, Romania, Poland, Slovakia and Slovenia. Although efforts have been put forth to increase iodized salt consumption in Western Europe, variation in policies pertaining to the production and trade of iodized food products within the European Union have been major obstacles to comprehensive regional regulation [31, 32]. As a result, many countries in Western Europe including Belgium, France and Spain are classified as “mildly iodine deficient”, with a population median UIC under 100 μg/L [33].

Our findings also indicate that household consumption of iodized salt in the Former Soviet Union and the Former Yugoslav Federation has been decreasing in the past decade. In Serbia, the proportion of households consuming iodized salt lingered around 73% in 2000, but fell to 32% between 2000 and 2010, while in the Ukraine, the proportion of households consuming adequately iodized salt fell from 32% in 1997 to 18% in 2010. These declines capture the impact of changes in the political landscape and the subsequent dissolution of iodization mandates and salt monitoring systems established in the Soviet

Union and Yugoslav Federation. Since 1956, salt iodization existed as a government ordinance in the Former Soviet Union, leading to a domestic salt production volume of around 1 million tons per year. By the 1990s, salt production had fallen to half of its original volume, coupled with a reduction in the quality of iodized salt. Thus, it is unsurprising that iodine deficiency disorders are increasing in Former Soviet Union, as indicated by rising goiter prevalence in the Ukraine and Turkmenistan [34].

In 2010, we estimated that 88% of American households consume adequately iodized salt. Our results found a steady increase in the proportion of households consuming adequately iodized salt at an annual rate of increase of 4.55% from 1990 to 2010. Salt producers have held a long standing relationship with public health authorities in the United States, ensuring that iodized and non-iodized salt are sold at the same price. Salt manufacturers have been iodizing salt since the 1920s, although iodization remains a voluntary program in the United States [35]. We should also note that the absence of regulation regarding salt in processed food, combined with an increase in processed food consumption has led to a decrease in daily iodine intake in the United States, from 250 μg/L to 150 μg/L per day [36].

Limitations

A major limitation of a time-series analysis of iodine deficiency is the disparity in indicators over time. Only 10% of the VMNIS database provides data on urinary iodine concentration from 1980 to 1990, while 45% of the database provides data on goiter prevalence from 2000 to 2010. We attempted to reconcile these disparate sources by estimating the relationship between goiter prevalence and urinary iodine concentration, and modeling both sources of data in DisMod 3. Our novel modeling strategy allows us to maximize both sources of data, but because few studies have examined the relationship between urinary iodine concentration and goiter prevalence at the global scale, there are challenges to fully evaluating our estimates. Furthermore, we assumed that the age distribution of goiter would be similar across regions in the goiter prevalence model. This is a limitation because the introduction of salt iodization impacts the age distribution of goiter, leading to variation in age by country and region. However, such interventions can take up to 10 years to have an effect, and the effect size will vary considerably between countries. In forthcoming analyses, we will incorporate years of salt iodization introduction as a covariate in the goiter prevalence models.

It is important to note that changes in the prevalence of iodine deficiency disorders not only reflect the impact of iodization interventions, but also general improvements in household income, education and nutrition [23]. We tested models using GDP, education and malnutrition (less than 2 SDs, weight for age) as covariates but dropped them from the final analysis, in part due to linearity with household iodized salt consumption. Additionally, we did not include other sources of dietary iodine in our analyses, such as dairy products, bread, and seafood. Consumption of seafood plays a major role in Scandinavian countries and Japan; where despite low household iodized salt consumption (around 20% in Japan and Norway in 2010) low prevalence of goiter (less than 1%) is observed [37]. Further analyses should consider using a composite measure of iodine intake, incorporating various sources of dietary iodine.

Recommendations

In our study, we estimated that over 180 million people worldwide suffer from goiter and cretinism in 2010. Household salt iodization has been shown to be a cost effective intervention for the control of iodine deficiency disorders, and increases in consumption of iodized salt have been linked to major declines in the prevalence of cretinism worldwide. In contrast, the breakdown of iodization systems in the former Soviet Union and former Yugoslav Republic have led to increases in the prevalence of goiter. This underscores the importance of implementing regulatory frameworks to monitor the production and distribution of iodized salt, in order to ensure that a population has access to high quality iodized salt, and highlights the need for surveillance systems that provide comprehensive coverage of household iodized salt consumption within country.

REFERENCES

1. Haldimann M, Alt A, Blanc A, Blondeau K. **Iodine content of food groups**. *J Food Comp Anal* 2005; 18: 461-471
2. Institute of Medicine. **Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Molybdenum, Nickel, Silicon, Vanadium and Zinc**. Food and Nutrition Board National Academy Press, Washington, DC (2001)
3. Zimmerman MB, Jooste P, Pandav CS. **Iodine-deficiency disorders**. *Lancet* 2008; 372: 1251-62
4. Zimmerman MB, Hess SY, Adou P, Torresani T, Wegmuller R, Hurrell RF. **Thyroid size and goiter prevalence after introduction of iodized salt: 5-yr prospective study in school children in Cote d'Ivoire**. *Am J Clin Nutr* 2003; 77: 663-67
5. Zimmerman MB, Saad A, Hess S, Torresani T, Chaouki N. **Thyroid ultrasound compared with World Health Organization 1960 and 1994 palpation criteria for determination of goiter prevalence in regions of mild and severe iodine deficiency**. *Eur J ENdocrinol* 2000; 143: 727-31
6. Pharoah POD, Hornabrook RW. **Endemic cretinism of recent onset in New Guinea**. *Lancet* 1974; 304: 1038-1040.
7. Li M, Eastman CJ. **The changing epidemiology of iodine deficiency**. *Nat Rev Endocrinol* (advanced online publication April 3 2012) doi 10.1038/nrendo.2012.43
8. Andersson M, Karumbunathan V, Zimmerman, M. **Global Iodine Status in 2011 and Trends over the Past Decade**. *J. Nutr* (advanced online publication February 29, 2012) doi: 10.3945/jn.111.149393
9. Benoist B, McLean E, Anderson M, Rogers L. **Iodine deficiency in 2007: Global progress since 2003**. *Food Nutr Bull* 2007; 29: 195-201
10. Mannar MG. **Iodized salt for the elimination of iodine deficiency disorders**. International Salt Consultants Training Workshop, Papendal, Netherlands June 1994.

11. UNICEF. **The State of the World's Children 2012: Children in an urban world**. http://www.unicef.org/sowc/files/SOWC_2012-Main_Report_EN_21Dec2011.pdf (accessed Apr 15, 2012)
12. UNICEF. **Iodine deficiency: Current Status**. http://www.childinfo.org/idd_status.html (accessed Jul 16, 2012)
13. World Health Organization. **Vitamin and Mineral Nutrition Information System** (VMNIS). http://www.who.int/vmnis/en/ (accessed Nov 1, 2011)
14. World Health Organization/UNICEF/International Council for the Control of Iodine Deficiency Disorders. **Assessment of iodine deficiency disorders and monitoring their elimination: A guide for programme managers**. (WHO/NHD/01.1). Geneva: WHO, 2001.
15. Flaxman AD, Vos T, Murray CJL (eds). *An Integrated Meta-Regression Framework for Descriptive Epidemiology*. University of Washington Press, manuscript in preparation
16. UNICEF. **The State of the World's Children**. Nutrition Annex Tables. http://www.unicef.org/sowc/ (accessed Nov 1, 2011)
17. UNICEF. **Iodized Salt Consumption**. Statistical Table. http://www.childinfo.org/idd_profiles.php (accessed Jul 16, 2012)
18. Moltz KC, Postellon DC. **Congenital hypothyroidism and mental development**. *Compr Ther* 1994; 20: 342–6
19. Clugson G, Dulberg EM, Pandav CS, Tilden RL. **Iodine deficiency disorders in South East Asia**. *The Prevention and Control of Iodine deficiency disorders*. Elsevier: Amsterdam 1987
20. Rastogi T, Mathers C. **Global burden of iodine deficiency disorders in the year 2000**. Unpublished draft 2002
21. Harris EC, Barraclough B. **Excess mortality of mental disorder**. *Br J Psychiatry* 1998; 173: 11-53

22. Liu P, Liu SJ, Su H, Zhang SB, Ji XH. **Relationship between urinary iodine and goiter prevalence: Results of the Chinese national iodine deficiency disorders survey**. *J. Endocrinol Invest* 2010; 33: 26-31

23. Dunn J. **Endemic goiter and cretinism: an update on iodine**. *J Pediatr Endocr Met* 2001; 14: 1469-73

24. Jooste PL, Weight ML, Lombard CJ. **Short-term effectiveness of mandatory iodization of table salt, at an elevated iodine concentration, on the iodine and goiter status of schoolchildren with endemic goiter**. *Am J Clin Nutr* 2000; 71: 75-80

25. Srivastav A and Naqvi S. India: Ban on production and sale of non-iodized salt will protect children. UNICEF India Newsline, July 6 2005 http://www.unicef.org/infobycountry/india_27575.html (Accessed July 16, 2012)

26. Endemic Disease Control Department, Ministry of Public Health, People's Republic of China. **Sounding an Alarm to Prevent Iodine Deficiency Disorders**. Beijing: China Population Publishing House, 1995.

27. Chen J, Wu H. **Fortification of salt with iodine**. *Food Nutr Bull* 1998; 19: 172-5

28. Ma X, ed. **1993-2003: ten years of remarkable progress on IDD control in China**. Beijing: Ministry of Health, People's Republic of China, 2003.

29. Zhao J, Xu F, Zhang Q, Shang L, Xu A, Gao Y, Chen Z, Sullivan KM, Maberly GF. **Randomized clinical trial comparing different iodine interventions in school children**. *Public Health Nutr* 1999; 2: 173-8

30. ICCIDD. IDD Newsletter India, May 2011 www.thyroid.org/professionals/.../IDD_NL_May11.pdf (Accessed July 16, 2012)

31. Arbeitskreis Jodmangel (AKJ). EU Commission. Discussion Paper on the setting of maximum and minimum amounts for vitamins and minerals in foodstuffs. http://ec.europa.eu/food/food/labellingnutrition/supplements/documents/akj_en.pdf (Accessed July 16, 2012)

32. Delange F, de Benoist B, Pretell E, Dunn JT. I**odine deficiency in the world: where do we stand at the turn of the Century?** *Thyroid* 2001; 11: 437-447

33. ICCIDD. CIDDS Database. Current IDD Status Database 2004 http://www.people.virginia.edu/~jtd/iccidd/mi/cidds.html (Accessed July 16, 2012)

34. UNICEF. Universal Salt Iodization in Central and Eastern Europe and the Commonwealth of Independent States: Experiences, achievements and lessons learned during the decade 2000-2009. http://www.unicef.org/ceecis/UNICEF_USI_Strategies_Report_summary_E_print.pdf (Accessed July 18, 2012)

35. Dasgupta PK, Liu Y, Dyke JV**. Iodine nutrition: iodine content of iodized salt in the United States**. *Environ Sci Technol* 2008; 42: 1315-1323

36. Salt Institute. Iodized Salt: Uses and Benefits. http://www.saltinstitute.org/Uses-benefits/Salt-in-Food/Essential-nutrient/Iodized-salt (Accessed July 16, 2012)

37. Ivengar GV, Kawamura H, Parr RM, Miah FK, Wang JX, Dang HS, Djojosubroto H, Cho SY, Akher P, Natera ES, Nguyen MS. **Dietary intake of essential minor and trace elements from Asian diets**. *Full Nutr Bull* 2002; 23: 124-8