The Global Prevalence of Multiple Micronutrient Inadequacy by Age and Sex

Haley Lescinsky

A thesis

submitted in partial fulfillment of the

requirements for the degree of

Master of Public Health

University of Washington

2021

Committee:

Ashkan Afshin

Nicholas J Kassebaum

Program Authorized to Offer Degree:

Global Health

©Copyright 2021
Haley Lescinsky

University of Washington

Abstract

The Global Prevalence of Multiple Micronutrient Inadequacy by Age and Sex

Haley Lescinsky

Chair of the Supervisory Committee:

Ashkan Afshin

Department of Health Metrics Sciences

Micronutrient deficiency is one of the most recognized and critical forms of malnutrition. Generally, micronutrient deficiency is quantified by low levels of a micronutrient biomarker in the body, but key micronutrients often lack sensitive and specific biomarkers. Additionally, there is a shortage of data on micronutrient status, especially surveys that assess multiple biomarkers on the same population. To quantify multiple micronutrient inadequacy, and provide insights into micronutrient consumption patterns around the world, we estimate the prevalence of inadequate intake of iron, vitamin A and zinc, using a standardized set of nutrient requirement levels and a copula joint distribution approach. We found that a large proportion of the world is at risk of inadequate intake of key micronutrients, ranging from 60% of people in high-income locations to 94% of people in locations in South Asia. Globally, 5.9 billion people have dietary inadequacy of at least one of the three micronutrients examined. There is higher prevalence of inadequate intake of vitamin A and zinc than iron, likely because dietary recall surveys and requirement levels do not distinguish between the differential absorption of heme and non-heme iron. By assessing the prevalence of multiple micronutrient inadequacy rather than a single micronutrient, we revealed that a much higher number of people are at risk for micronutrient inadequacy than the 2 billion previously thought. Our findings highlight the need for better data on micronutrient status indicators across geographically diverse populations. Further research is warranted to define the relationship between inadequacy and deficiency, which has implications on the management and planning of nutrition interventions.

Introduction

In the year 2019, an estimated 3 million deaths and 295 million disability adjusted life years (DALYs) were attributed to child and maternal malnutrition and in children under 5 years old, malnutrition was responsible for 50% of total health burden faced by this age group[1]. Micronutrient deficiency is one of the most recognized and critical forms of malnutrition. Since micronutrients are necessary for healthy development, disease prevention, and general wellbeing, deficient levels of micronutrients in the body can lead to adverse health outcomes such as vision loss, goiter, or a weakened immune system.

Given the severe outcomes associated with it, micronutrient deficiency has been recognized as a major public health problem for several decades[2]. In that time, the field has witnessed advances in supplementation, biofortification, and micronutrient status indicators[3,4]. However, many challenges still remain and make comprehensive analysis of micronutrient status challenging. There is a lack of nationally representative data on micronutrient status, a lack of reliable biomarkers to reflect micronutrient deficiency, and a lack of scientific consensus on how to define micronutrient deficiency.

When it comes to defining micronutrient deficiency, micronutrient status can be assessed at any point along the causal pathway of micronutrient deficiency (Figure 1), which starts with micronutrient intake and ends with the clinical manifestations and death due to deficiency. Generally, micronutrient deficiency refers to low levels of a micronutrient in the body, detectable using biochemical indicators. However rarely do micronutrients have biomarkers with high sensitivity and specificity, especially in the presence of inflammation[5]. The biomarkers that do exist have different cutoff values for deficiency, with varying levels of severity[6]. Additionally, biomarker tests require a laboratory sample and are generally not included in national nutrition surveys, nor across a large population sample; many studies for example just assess biomarkers on young children. Collectively, these limitations lead to few studies that assess multiple biomarkers on the same population and limited confidence in comparing deficiency prevalence estimates across micronutrients.

Given the challenges associated with biomarker indicators and the lack of nationally representative data, the Global Burden of Disease study (GBD) has been unable to assess deficiency status using a biomarker indicator for three of the four micronutrients present in the GBD study: iron, zinc, and iodine, and has been unable to quantify multiple micronutrient deficiency.

Most nutritional intervention programs target the root cause of micronutrient deficiency, the inadequate intake of micronutrients. Understanding the extent to which different populations are not

meeting dietary intake recommendations is crucial to improving our ability to effectively plan and manage interventions. Data on dietary intake generally comes from self-reported surveys of varying quality. The 24-hour dietary recall survey has high intrapersonal variation but comes the closest to capturing true intake. Compared to food frequency questionnaires, it also has the highest amount of correlation with biological availability indicators[7]. While acknowledging that all nutrition status data is imperfect, with proper adjustment for biases, dietary recall can provide valuable information on the consumption patterns of populations. Although efforts exist to estimate micronutrient deficiency[8,9], we are unaware of a comprehensive effort to estimate micronutrient intake levels at a global scale[10].

In this paper, we calculate the prevalence of inadequate intake of three key micronutrients: zinc, iron, and vitamin A, using a standardized set of nutrient requirement levels to evaluate intake inadequacy. Our estimates leverage the high data coverage of a database on nutrient availability alongside individual level correlations from survey data to characterize the global distribution of micronutrient intake and the prevalence of multiple micronutrient inadequacy.

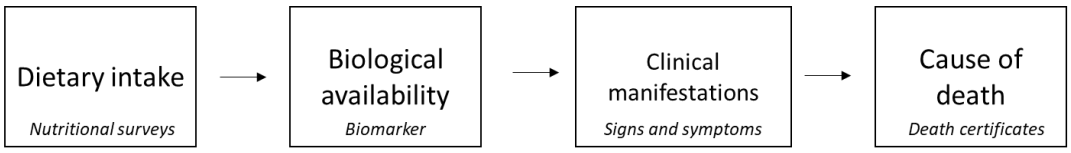

Figure 1. Causal pathway of micronutrient deficiency, along with data types and indicators that can be used to assess micronutrient status at that point. Micronutrient deficiency starts with inadequate intake which can lead to low levels of a micronutrient circulating in the body, detectable by biochemical indicators (biomarkers). Then, deficiency can manifest as various clinical outcomes and potentially cause death if severe.

Methods

Input data

This project uses two key types of data sources on micronutrient intake and availability. First, we use a dataset of 79 dietary recall surveys from 33 different countries that report individual level intake of zinc, vitamin A, or iron. These data sources were screened for and identified from the GHDx; a full list of sources used and demographics captured is available in Table S1. While a substantial portion of the data is from high-income countries and well-known survey series like the USA's National Health and Nutrition Examination Survey (NHANES), South Korea's KNHANES, and the UK's National Diet Nutrition Survey (NDNS), we have identified several surveys that provide intake estimates for low and middle

income countries. Out of the 7 GBD super regions, there is at least one survey covering all of them except North Africa and the Middle East.

Secondly, we use an updated version of the global nutrient database[11] which provides information on micronutrient availability for 190 countries from 1961-2017. The global nutrient database represents a collaboration between the GBD dietary risk factors team and the UN's Food and Agriculture Organization, leveraging administrative data on supply and utilization amounts of food commodities alongside nutrient composition tables from the USDA.

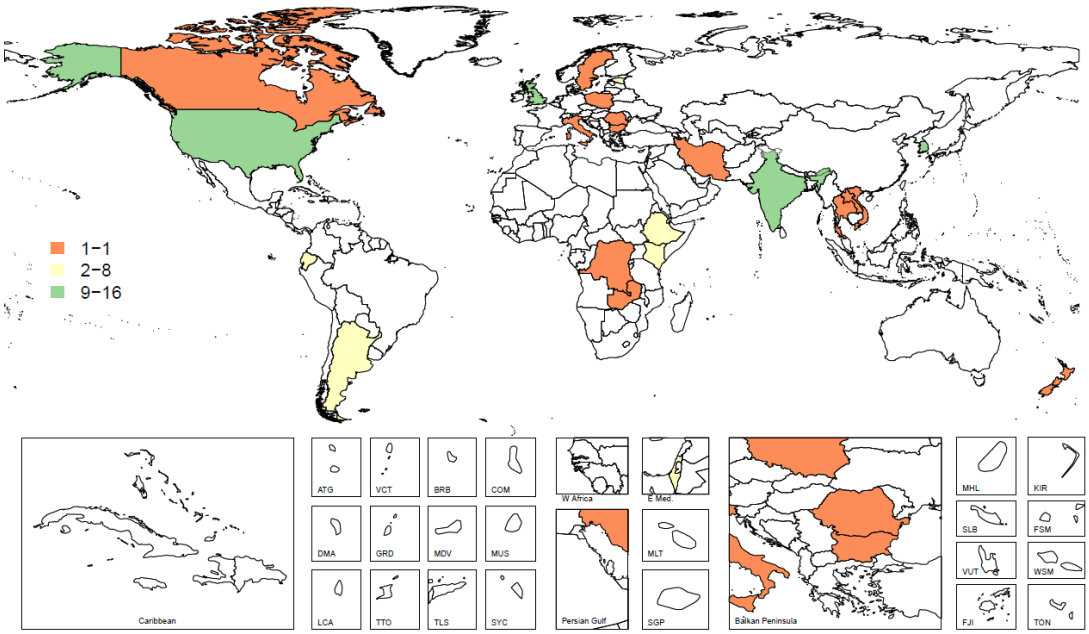

Figure 2. Map of dietary recall availability data coverage. Number indicates number of survey-years in that location. Details on the specific surveys can be found in Supplemental Table 1.

In order to get a smooth time trend of the availability data and generate estimates of micronutrient availability for the few countries that are not in the global nutrient database, we rely on IHME's Spatio-Temporal Gaussian Process Regression (ST-GPR)[1] for its imputation and time-space smoothing abilities. Then, to get estimates of age and sex-specific availability of micronutrients, we split the all-age both-sex availability estimates using the age and sex patterns of intake observed in the dietary recall surveys.

Specifically: $A_{asly} = A_{ly} * (I_{asly} / (I_{ly} / P_{ly}))$

Where A is availability, I is the intake from the age pattern, P is population, a is age-specific, s is sex-specific, l is location-specific and y is year-specific. In words, the all-age both-sex availability is multiplied

by the age-sex-specific intake estimate divided by the average intake per person across sex and age groups. The age and sex specific intake values are super-region specific and modeled in DisMod.

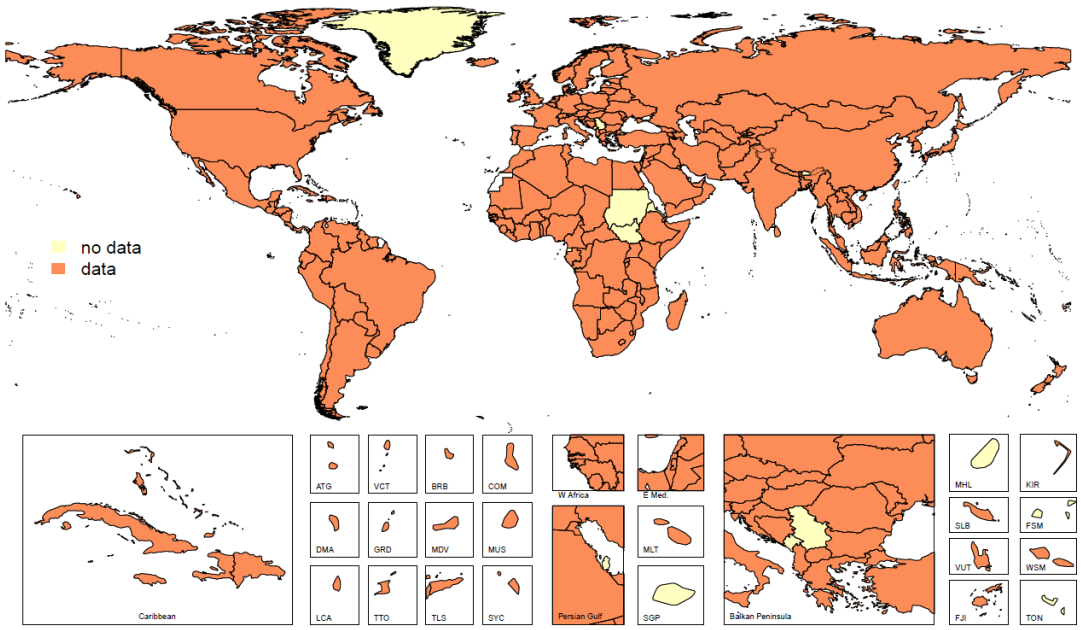

Figure 3. Map of FAO data coverage. Locations are orange if we have high-quality availability data for them, and light yellow if no data is included.

Estimating the mean intake

Given the vast data coverage provided by the global nutrient database, we incorporate the availability data in the estimates of micronutrient intake using an adjustment factor that accounts for systematic variation between availability and intake data sources. The adjustment factor is calculated by generating a set of matched data points for all locations, years, sexes and ages where both availability data and intake data is available and modeling the ratio of intake to availability in a network meta-regression; the regression coefficient is treated as the adjustment factor. Specifically, the regression is implemented in MR-BRT: Meta-Regression – Bayesian, Regularized, Trimmed although no trimming priors or covariates are included in the model. In the main analysis, a single global adjustment factor is used. However, we also report and provide the sensitivity results of super-region specific adjustment factors.

The transformed availability estimates and the survey intake data are combined into a final ST-GPR model that provides estimate of micronutrient intake for all locations by age, sex and year.

Characterizing the distribution of intake

To characterize the distribution of intake, estimates of the distribution shape and population standard deviation are needed.

We model the shape of the distribution using an ensemble of weighted distributions, fit by minimizing the KS statistic on the individual-level dietary intake data[1,12]. An ensemble distribution is fit to each most-detailed set of microdata, and then those weights are aggregated to determine the set of distribution weights for each micronutrient and age sex group.

The dietary recall microdata provides valuable information on the relationship between the mean and standard deviation of intake for each of the micronutrients. We modeled this relationship with a spline and linear regression and found the best fit with the linear regression. Then we used the regression equation to predict SDs for all of the modeled mean intake estimates. However, individuals experience high fluctuations in diet on a daily basis, so data from one day often poorly represents an individual's average intake. To account for this, we used a subset of dietary recall surveys (n = 11) that reported multiple days of intake and determine the SD reduction adjustment factor, which when applied to the distribution SD of a single-day of intake, can approximate usual intake instead. Results without applying the SD reduction factor are provided as a sensitivity analysis.

Determining the requirement level

In order to quantify inadequacy, we use dietary reference intakes to determine the nutrient requirement levels. The National Academy of Sciences has released several rounds of dietary reference intakes for US and Canadian populations that synthesize a tremendous amount of information on each micronutrient[13]. The Estimated Average Requirement (EAR) is defined as "the average daily nutrient intake level estimated to meet the requirement of half the healthy individuals in a particular life stage and gender group" and is recommended for population level nutrient adequacy inference[13]. The EARs are age and sex specific. Women who are pregnant or lactating have higher requirement levels, which we have adjusted for by using GBD estimates of pregnancy prevalence by location and taking an average of the two requirements using the prevalence of pregnant/not-pregnant women as weights. Unfortunately it is difficult to do an analogous adjustment for lactating women without proper estimates of the prevalence and duration of lactation, which are not available through the GBD study.

Table 1. EAR cutpoints for iron, vitamin A, and zinc[13].

Age group	Sex	Iron (mg/day)	Vitamin A (ug RAE/day)	Zinc (mg/day)
1-3 yrs	females	3	210	2.5
1-3 yrs	males	3	210	2.5
4-8 yrs	females	4.1	275	4
4-8 yrs	males	4.1	275	4
9-13 yrs	females	5.7	420	7
9-13 yrs	males	5.9	445	7
14-18 yrs	females	7.9	485	7.3
14-18 yrs	females (lactating)	7	885	10.9
14-18 yrs	females (pregnant)	23	530	10.5
14-18 yrs	males	7.7	630	8.5
19-30 yrs	females	8.1	500	6.8
19-30 yrs	females (lactating)	6.5	900	10.4
19-30 yrs	females (pregnant)	22	550	9.5
19-30 yrs	males	6	625	9.4
31-50 yrs	females	8.1	500	6.8
31-50 yrs	females (lactating)	6.5	900	10.4
31-50 yrs	females (pregnant)	22	550	9.5
31-50 yrs	males	6	625	9.4
51-70 yrs	females	5	500	6.8
51-70 yrs	males	6	625	9.4
70-125 yrs	females	5	500	6.8
70-125 yrs	males	6	625	9.4

Estimating the deficiency level

Using a joint distribution approach, we estimate the prevalence of inadequate intake for 204 countries by 5-year age groups and sex, for the years 2019. The inputs to the joint distribution are: estimates of intake, estimates of standard deviation, distribution shape, inadequacy threshold, and the copula correlation structure.

To calculate the prevalence of multiple micronutrient inadequacy, that is what proportion of the population has inadequate intake in any combination of vitamin A, zinc, or iron, the marginal distributions of vitamin A, zinc, and iron are linked using a copula. The copula is fit using the correlation structure observed in the dietary recall microdata. Then, the marginal distributions with the given correlation structure can be used to generate estimates of the proportion of a population that falls into each of the 8 mutually exclusive combinations for vitamin A, zinc, and iron: inadequate intake of all, none, vitamin A and zinc, vitamin A and iron, iron and zinc, vitamin A only, zinc only, iron only.

Sensitivity analyses

As an exploratory analysis, we tested for correlation between micronutrient intake and biological availability within the two surveys that reported intake and biomarker on the same population: USA NHANES and UK NDNS.

Results

Inadequate intake of iron

At the global level, iron intake was 12.3 mg/day (95%UI 10.9–13.8), with highest intakes observed in North Africa and the Middle East (17.3 mg/day, 95%UI 15.9 –18.8) and Eastern Europe (15.8 mg/day, 14.6–17.0), and Central Asia (15.4 mg/day, 14.1–16.7). At the country level, the highest all-age iron intakes were observed in Tunisa (20.9 mg/day, 19.4 – 22.4), Turkey (19.8 mg/day, 18.2–21.3), and Morocco (19.8 mg/day, 18.2 –21.3). The lowest iron intakes were in the DRC (5.0 mg/day, 3.9–6.1), Central African Republic (6.6 mg/day, 5.5–7.6), and Somalia (6.8 mg/day, 5.6–7.9).

There were generally low levels of iron inadequacy across the world. Globally, there was about 12% (95%UI: 11.5 – 12.4) prevalence of iron inadequacy across all ages, ranging from 3.4% (3.2–3.6) in adults aged 55 to 59 to 24.9% (24.2–25.6) in 15 to 19 year olds. Between sexes, iron inadequacy was highest in females (17.8%, 17.2–18.4) compared to males (6.1%, 5.8–6.4).

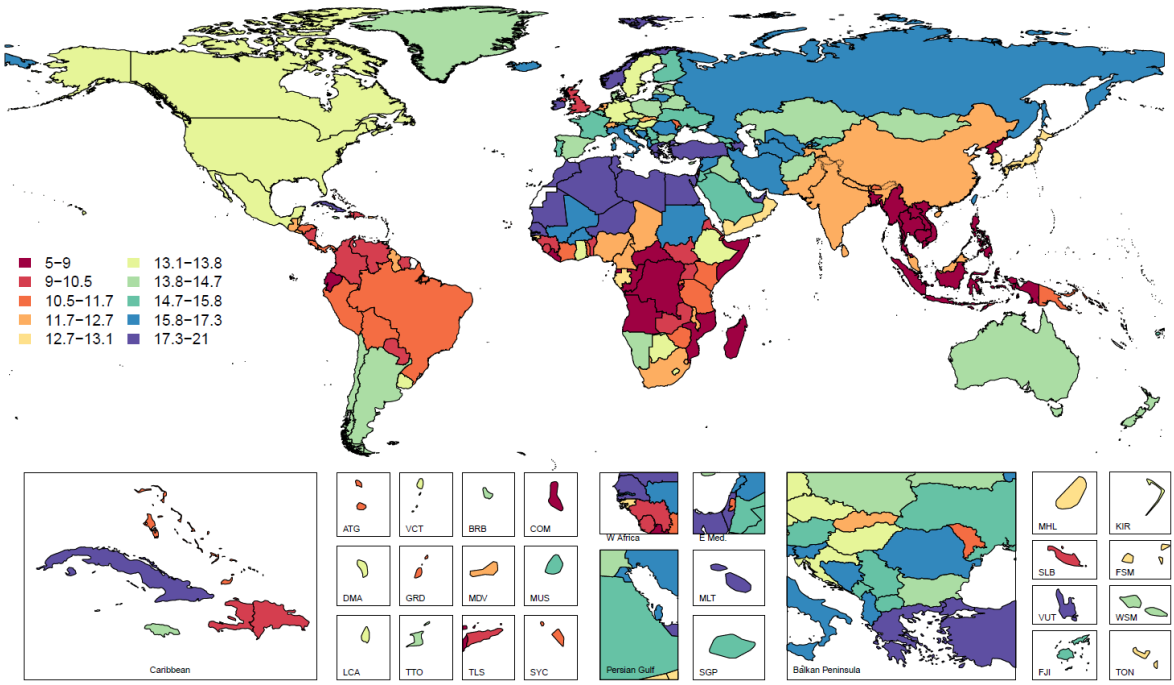

Figure 4 Map of mean iron intake (in mg/day) estimates for the year 2019. Color bins represent deciles of intake.

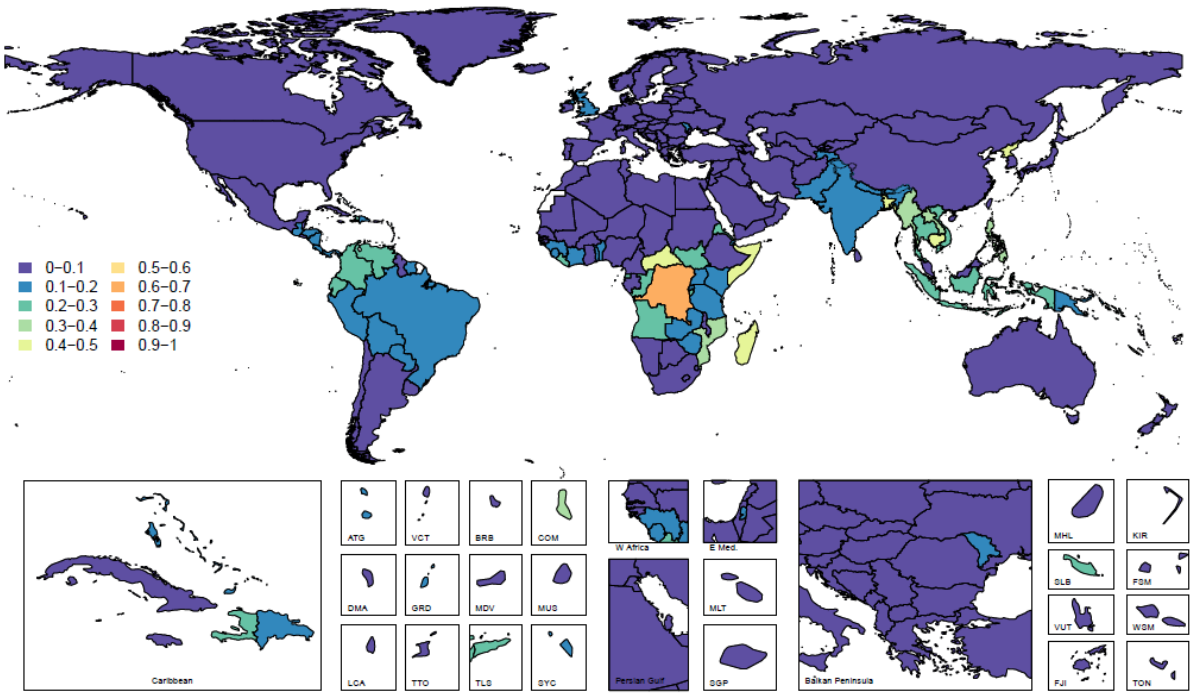

Figure 5 Map of mean prevalence of iron inadequacy in the year 2019, aggregated across all-ages and both-sexes.

The geographic pattern of iron inadequacy matches the pattern of iron intake estimates. The DRC, which had the lowest intake of iron, expectedly has the highest prevalence of iron inadequacy at 69.3% (95%UI 68.5– 70.1) for all-ages and both-sexes. The Central African Republic follows with 46.6% (45.5– 47.8) prevalence. The lowest prevalence was observed in Tunisia (0.8%, 0.7–0.9) and Senegal (1.0%, 0.8–1.1).

Inadequate intake of vitamin A

At the global level, vitamin A intake was 444 ug/day (95%UI 387–502 ug/day). There was high variation in intake across regions. Australiasia had the highest intake with 1286 ug/day (1222–1350) and South Asia had the lowest intake with 249 ug/day (178 –321). At the country level, the highest all-age vitamin A intakes were observed in the Solomon Islands (1773 ug/day, 95%UI 1701–1844), Australia (1315 ug/day, 1253–1377), and New Zealand (1148ug/day, 1073–1222) while the lowest were in Togo (117 ug/day, 91–144), Gambia (132 ug/day, 97–166), and Kiribati (136 ug/day, 961–75).

Over 65% of the world had inadequate vitamin A intake (66.7%, 95%UI 65.5–67.9), with males having a slightly higher prevalence (68.7%, 67.7–69.8) than females (64.8, 63.5–66.1). Young children aged 1 to 4 had the lowest global prevalence of iron inadequacy (35.4%, 34.5–36.2) while 15 to 19 year olds had the highest prevalence 76.0% (74.7–77.4).

Among regions, Australiasia had the lowest prevalence of inadequacy (8.4%, 95%UI 7.8–9.0) and South Asia had the highest (89.5%, 88.1%–90.8). In nine countries, the all-age and both-sex prevalence on vitamin A inadequacy was higher than 95%: Togo, Gambia, Sao Tome and Principle, Guinea-Bissau, Kiribati, Bangladesh, DRC, Zimbabwe, and North Korea. The highest prevalence estimate was in Togo at 99.3% (97.6–100%). The Solomon Islands, which had the highest intake of vitamin A had 1.5% (1.3–1.7) prevalence of dietary inadequacy.

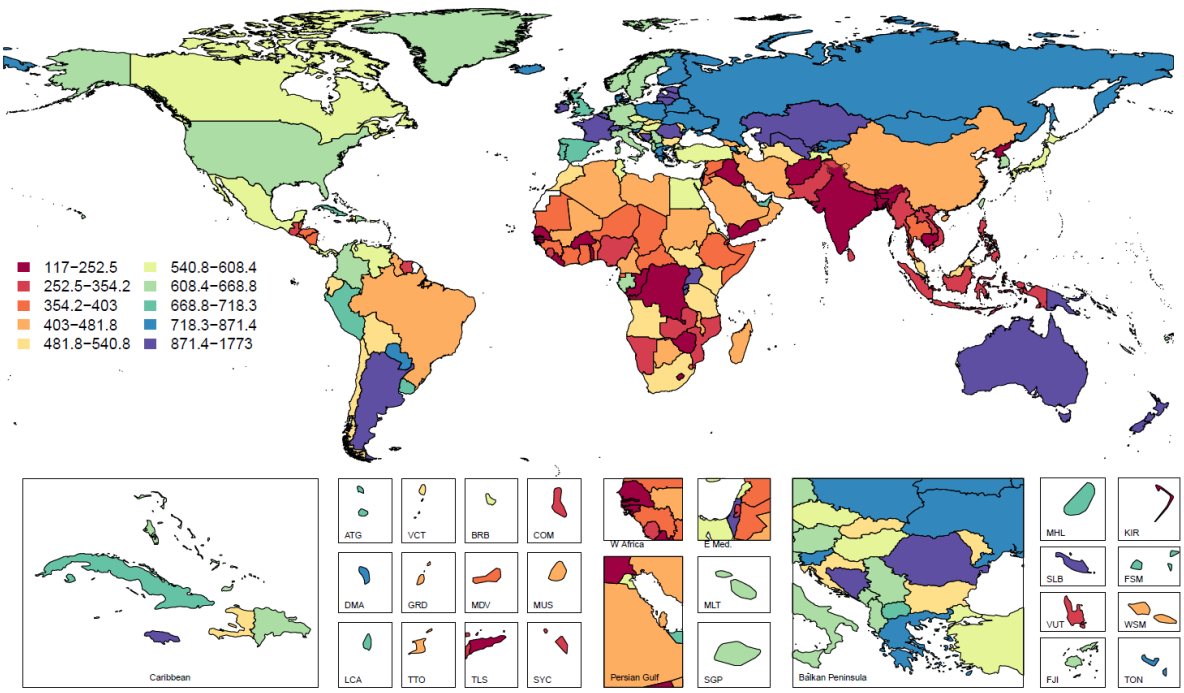

Figure 6 Map of mean vitamin A intake (in ug/day) estimates for the year 2019. Color bins represent deciles of intake.

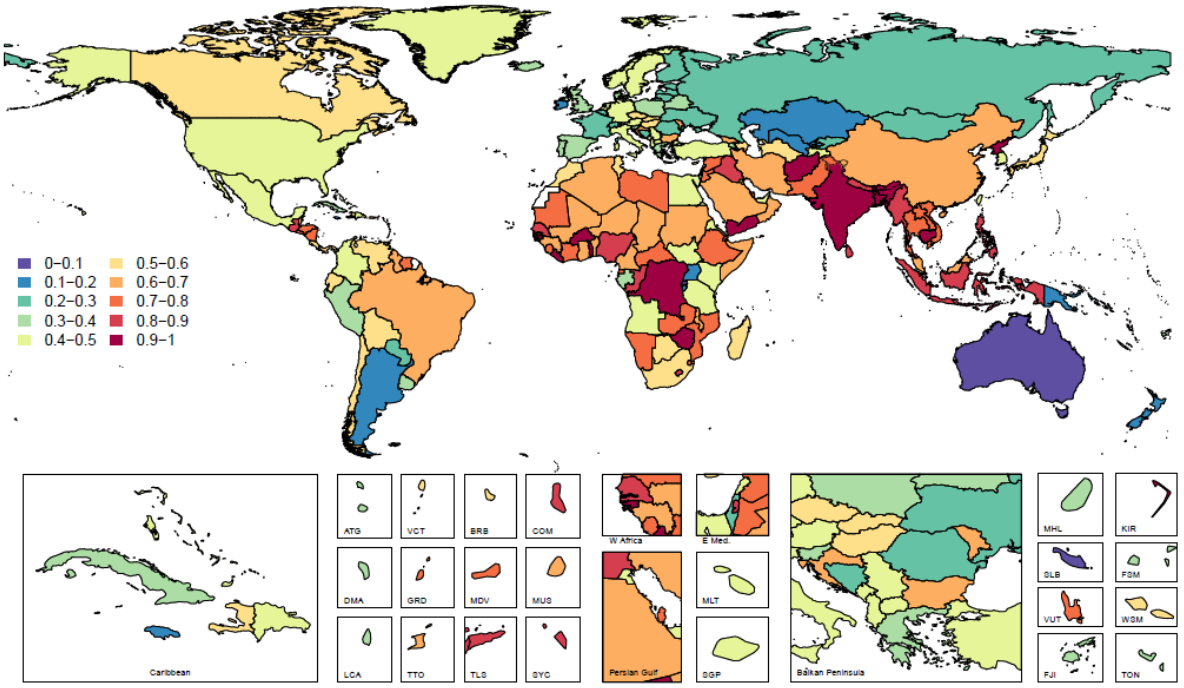

Figure 7 Map of mean prevalence of vitamin A inadequacy in the year 2019, aggregated across all-ages and both-sexes.

Inadequate intake of zinc

Globally, zinc intake was 7.0 mg/day (95%UI 6.3 – 7.7). Australiasia and High-income regions had the highest intakes of 10.1 mg/day (9.5–10.7) and 10.0 mg/day (9.3–10.7) respectively. The regions with the lowest levels of intake were Central Sub-Saharan Africa (3.8 mg/day, 3.22–4.4) and South Asia (5.5, 4.6 – 6.4). At the country level, the highest intakes of zinc were observed in Australia (10.4 mg/day, 9.7–11.0), Luxumberg (10.1 mg/day, 9.5–10.7), and the USA (10.1 mg/day, 9.4–10.8) while the lowest were in the DRC (3.1 mg/day, 2.5–3.7) ,Congo (4.0 mg/day, 3.5–4.5), and Tajikistan (4.3 mg/day, 3.8–4.8).

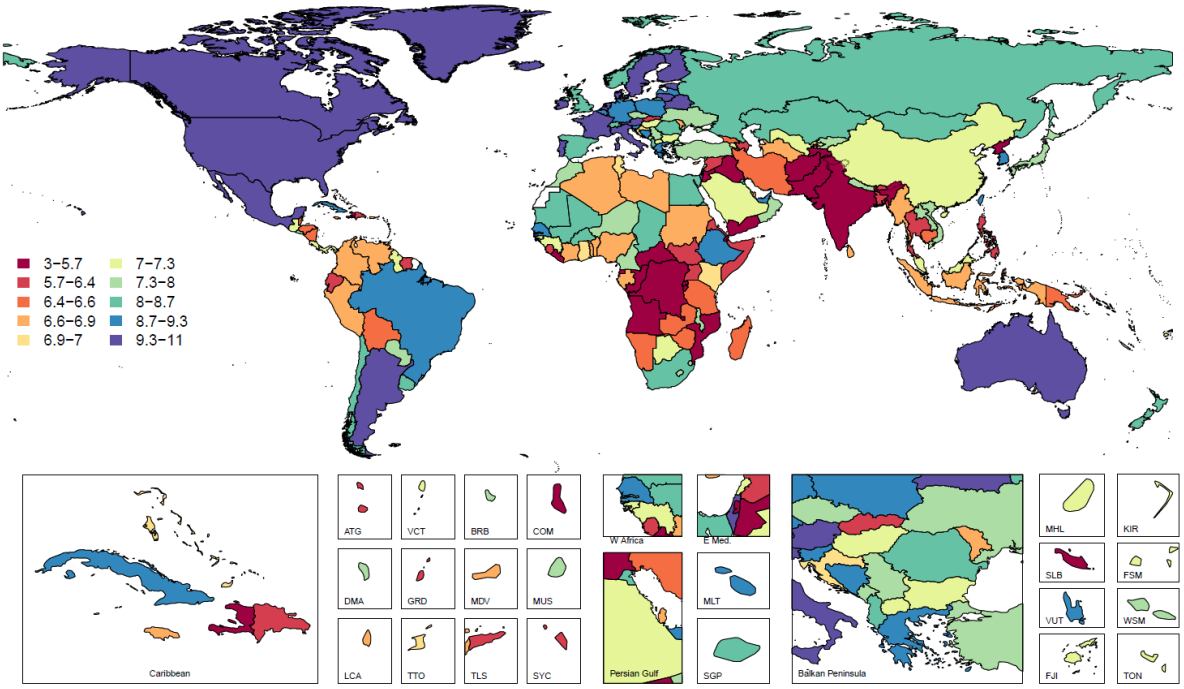

Figure 8 Map of mean zinc intake (in mg/day) estimates for the year 2019. Color bins represent deciles of intake.

The prevalence of zinc inadequacy showed high variation across geography and age. The global prevalence of zinc inadequacy was estimated to be 58.0% (95%UI: 56.9–59) across both-sexes, 59.5% (58.5–60.4) for males-only, and 56.4% (55.2–57.7) for females-only. As with vitamin A, children aged 1 to 4 had the lowest global prevalence of zinc inadequacy (8.5%, 8.0–8.9) and 15 to 19 year olds had the highest prevalence (68.8%, 67.5–70.0).

The geographic pattern of zinc inadequacy matches the pattern of iron intake estimates. The highest prevalence estimate was in the Democratic Republic of the Congo at 94.2% (92.9–95.5%) and the lowest was in Australia at 23.0% (21.9–24.0).

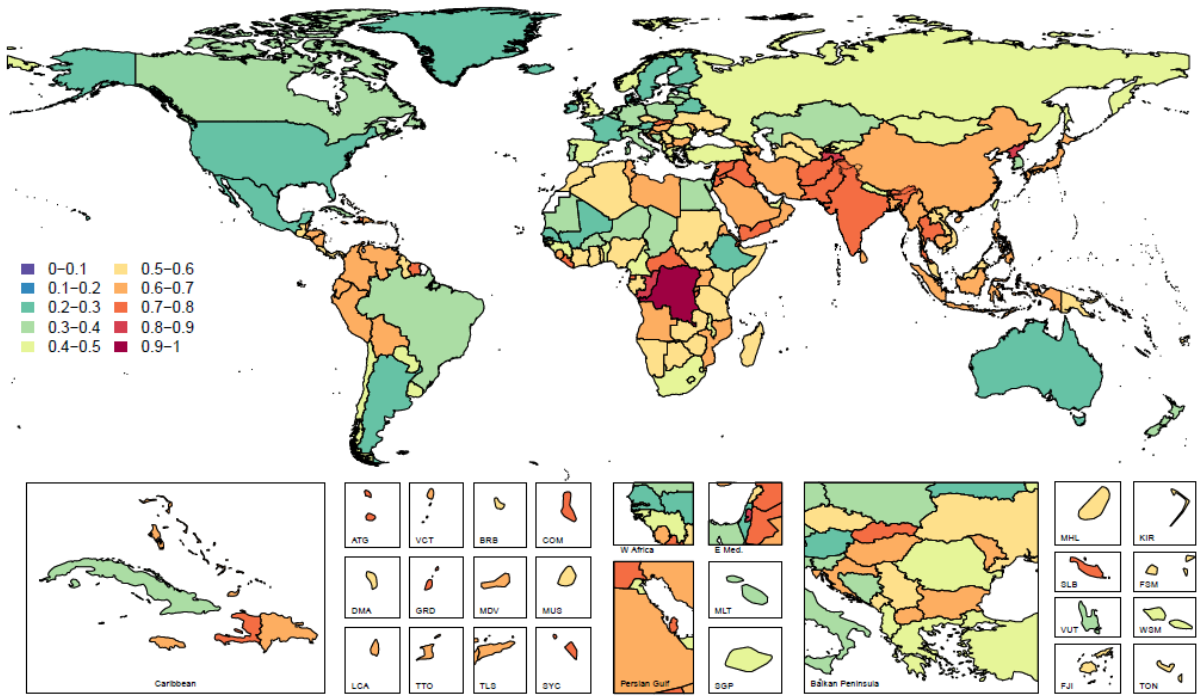

Figure 9 Map of mean prevalence of zinc inadequacy in the year 2019, aggregated across all-ages and both-sexes.

Inadequate intake of multiple micronutrients

The estimates of micronutrient inadequacy vary by age and sex. Globally, 78.0% (95%UI 77.6–78.4) of the population, 77.1% (76.6–77.5) of females, and 79.0% (78.6–79.3) of males, had estimated inadequate intake of at least one micronutrient. The prevalence of inadequate intake peaked in females and males aged 15 to 19 with prevalence of 87.2% (86.7–87.5) and 88.1% (87.7–88.5) respectively. Across sexes, higher proportions of the population have inadequate zinc or vitamin A consumption than iron, as indicated by the light blue, green, and pink bars in the figures. Globally, 44% (43.6–44.5) of males and 30.9% (30.4–31.3) of females have dietary inadequacy of both vitamin A and zinc, the largest category.

The age and sex trend of micronutrient inadequacy are noticeably influenced by the thresholds. The increase in iron inadequacy in women of child-bearing age is due to the pregnancy adjustment, that factors in the higher requirements for pregnant women. Referencing Table 1, the requirement for women aged 19-50 who are not pregnant nor lactating is 8.1 mg/day of iron, while the requirement for pregnant women aged 19-50 is 22 mg/day of iron. Lower prevalence of inadequacy is observed in young children as a result of the lower requirement levels but intake on-par with the rest of the age range.

Geographically, region-level estimates of any micronutrient inadequacy range from 55.4% (54.7–56.1) in high-income locations to 94.7% (94.4–94.9) in South Asia.

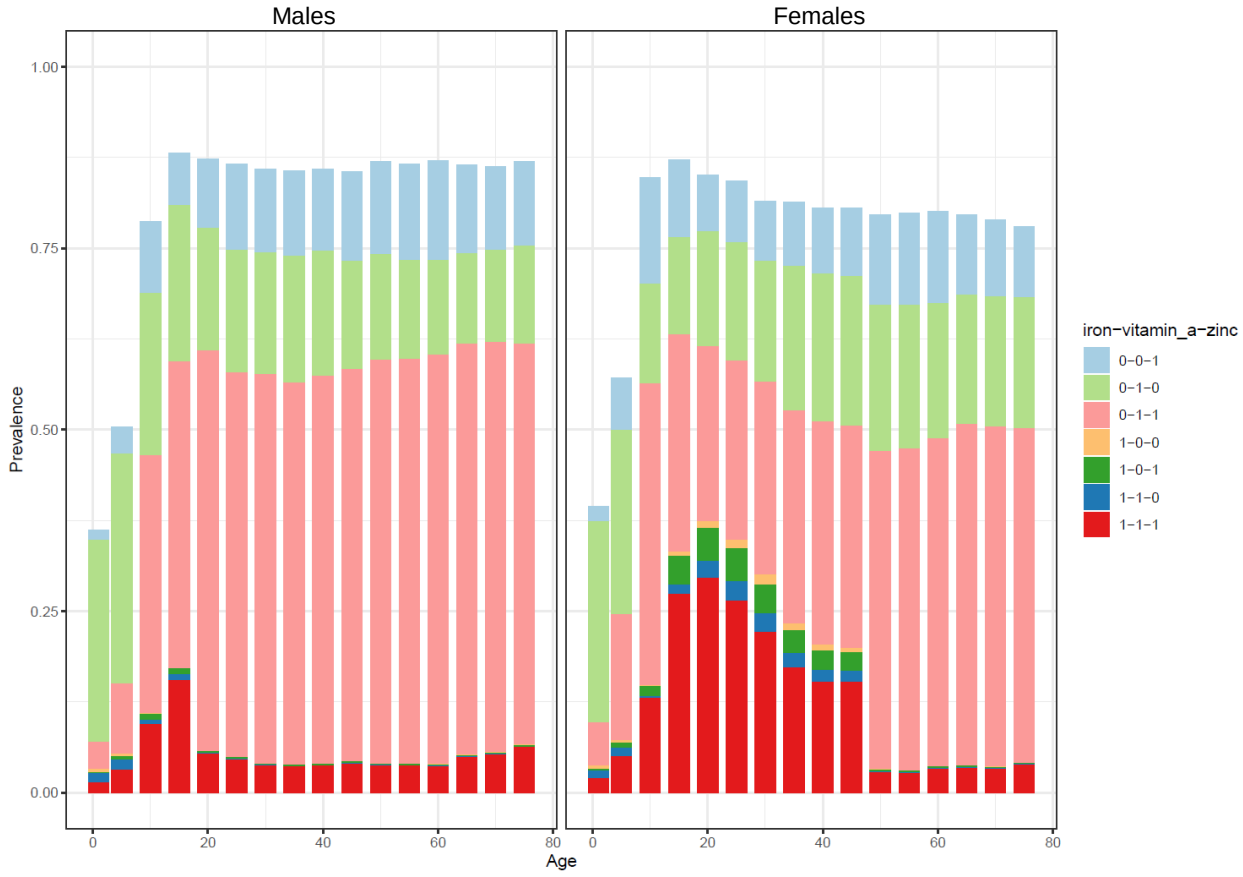

Figure 10. Proportion of the global population in each of the 8 mutually exclusive bins by age group and sex, with the empty space on top representing the proportion of individuals without any micronutrient inadequacies. The key has a 1 on the left if the group includes individuals who have iron inadequacy, a 1 in the middle for vitamin A, and a 1 on the right for zinc. For example the top color, light blue, is the proportion of people who have inadequate intake of only zinc, and the bottom color, red, is the proportion of people who have inadequate intake of iron, vitamin A and zinc.

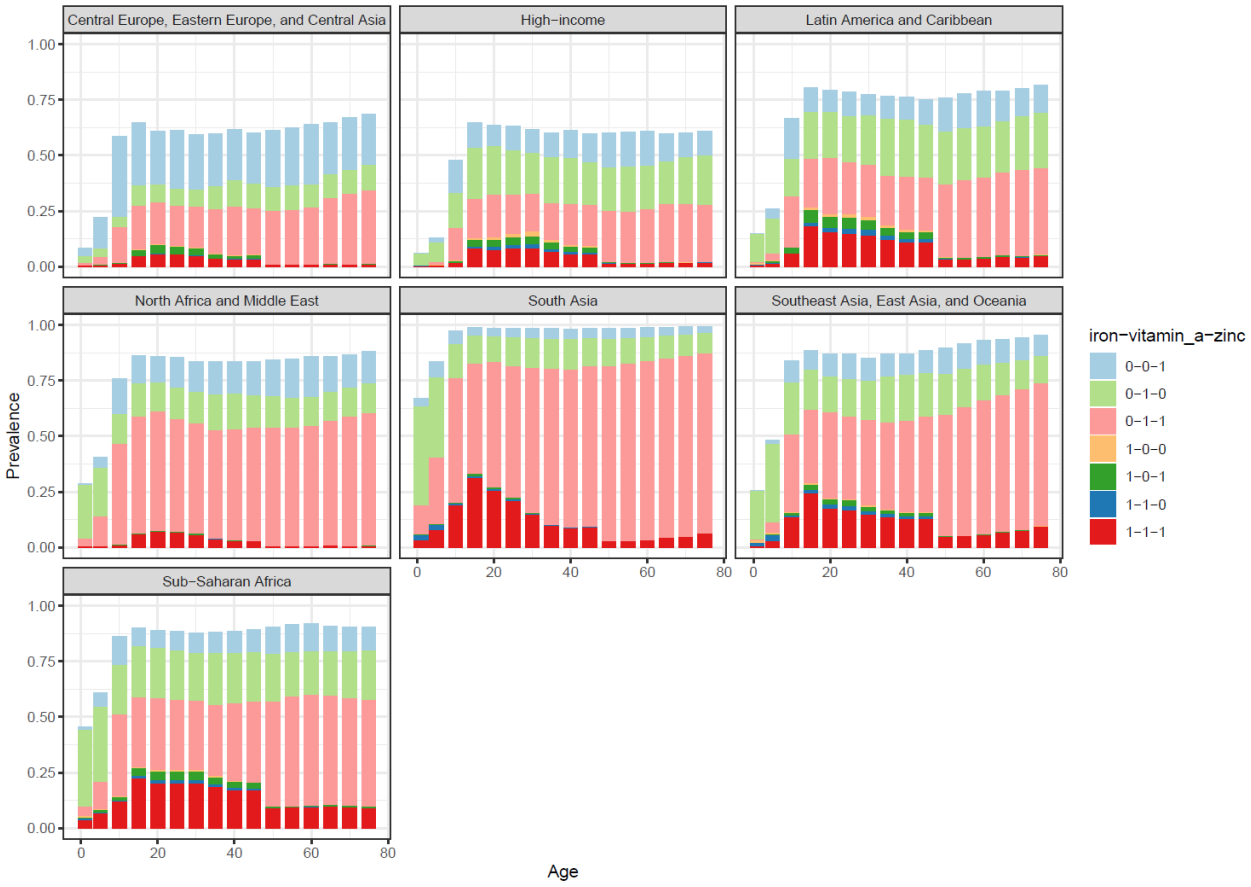

Figure 11. Proportion of the global population in each of the categories of micronutrient inadequacy, by super-region and age group.

By numbers, we estimate that 5.9 billion people in the world have inadequate intake of micronutrients, meeting that only 1.7 billion people are meeting the nutrient intake requirements for iron, vitamin A, and zinc (Table 2).

Table 2. Global population at risk of micronutrient inadequacy of iron, vitamin A, and zinc, or any combination of the three.

Inadequacy status	Mean (in millions)
none	1666 (1638-1701)
Zinc only	735 (715-755)
Vitamin A only	1435 (1405-1465)
Vitamin A, zinc	2843 (2810-2875)
Iron only	25 (23-27)
Iron, zinc	93 (88-99)

Iron, vitamin A	61 (58-64)
Iron, vitamin A, zinc	725 (705-748)

Sensitivity analyses

In the NHANES and NDNS studies that evaluated biomarkers and micronutrient intake on the same population, very little to no correlation was observed between indicators when assessed on the same individual. In this example that is representative of the rest of the demographic, survey, and indicator groups tested, the correlation between biomarker and intake values (left) was 0.12 and the correlation between biomarker and intake ranks (right) was 0.09.

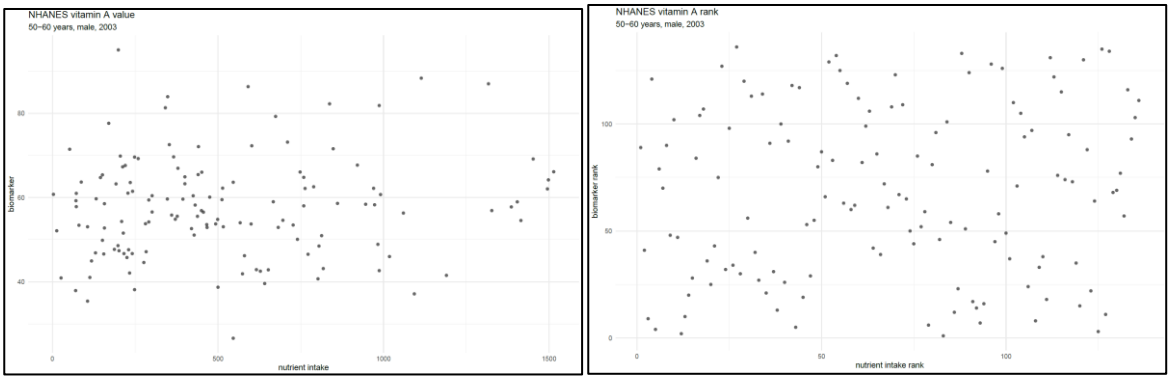

Figure 12. Visual correlation between individuals who had both vitamin A intake and a vitamin A biomarker (serum retinol) assessed. On the left, the raw values are plotted, vitamin A RAE intake in ug/day, and serum retinol assessment in ug/dL. On the right, the ranked values are plotted to examine whether the order of intake and biomarker values is preserved.

When removing the SD reduction to approximate the distribution that would exist under multiple days of recall, the prevalence of iron inadequacy decreased, shifting more of the global proportion into the vitamin A and zinc only bin, and lowering the amount of individuals with no inadequate intake of iron, vitamin A, or zinc. Since the iron means were relatively high compared to the requirement levels, reducing the standard deviation resulted in a lower proportion of the iron intake distribution that was below the intake requirement.

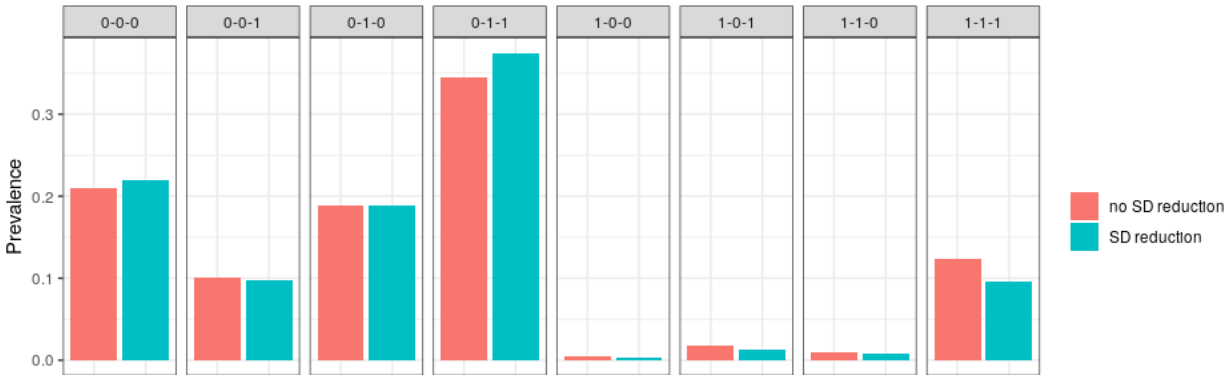

Figure 13. Comparison of the inadequacy prevalence results with the SD reduction in place (blue, the main result presented in this paper) and the prevalence results without the SD reduction. The facets illustrate the global prevalence in each category, labeled as iron-vitamin A-zinc with a "1" indicating inadequacy.

Discussion

In this study, for the first time to our knowledge, we systematically determined inadequate intake of multiple micronutrients: iron, vitamin A, and zinc for all countries in the world, by age and sex. These results show that a large proportion of the world is at risk of inadequate intake of key micronutrients, ranging from 60% of people in high-income locations to 94% of people in locations in South Asia. We observe higher prevalence of inadequate intake of vitamin A and zinc than iron, though women of reproductive age have higher iron inadequacy given the high iron intake requirements when pregnant. The prevalence of inadequacy is similar between sexes and across older age groups. Young children have lower prevalence since the intake requirements are substantially lower in children than adults compared to the estimates of intake.

These findings are sensitive to the intake requirements used. The estimated average requirement levels are set by the Institute of Medicine and in reference to USA and Canadian populations[13]. Recalling the earlier definition, the EARs are consumption levels that about half of the population is expected to obtain. We observe a similar finding in our work where 58% and 63% of the populations for USA and Canada, respectively, have any micronutrient inadequacy. The estimated average requirement levels are lower than the recommended dietary allowance, since they are aimed to be used at the individual level rather than for population risk assessment. Therefore, using recommended dietary allowances would result in even more extreme estimates of micronutrient inadequacy. Since the requirements are set with expected risk of inadequacy in mind, they are challenging to interpret biologically. Additional requirements exist and could provide good sensitivity analysis[14,15].

Of the three micronutrients we studied, inadequate intake of vitamin A and zinc is more prevalent than inadequate intake of iron. This could be because the intake requirements used in this analysis, while consistent with the intake and availability data, do not differentiate between heme and non-heme iron. Heme iron is known to be readily absorbed by the body while non-heme iron absorption can by inhibited by dietary components like phytates, tannins, and polyphenols.[16] Relying on total iron can mask the differential effects of heme vs non-heme consumption and lead to a biased, likely underestimate, of iron inadequacy. Recognizing that the intake requirements for micronutrients are affected by diet composition, some nutrient requirement recommendations differentiate between high-absorption and low-absorption micronutrient intakes[15]. However, in the absence of intake data specifying low vs high absorption or micronutrient source, it would be challenging to choose which requirement to use.

This work would be much stronger with a better data basis, particularly an increase of high-quality dietary recall surveys from low and middle-income areas which unfortunately does not exist. We rely on patterns observed in the microdata for most of the methodological assumptions: the age pattern, the mean-SD relationship, distribution shape, crosswalk ratio, and intake correlation structure. Although we have tested whether geographic variation exists in these steps and have implemented it where it seems fair, we aired on the side of using a global relationship given the relatively poor coverage and low data quality in many important geographic regions. This assumption has substantial impacts for the availability to intake data bias adjustment step. Since the adjustment factor is effectively approximating food waste, we are assuming that the proportion of food waste is constant throughout the world. We know this to not be true, as the FAO has documented that food loss varies by region[17]. However, the regional adjustment factors derived for a single nutrient span a much wider range than the differences in food loss (Appendix: Table S2), implying poor quality of the data informing those relationships.

Our work is also limited by its reliance on the 24-hour dietary recall to capture micronutrient intake. Dietary recall surveys are at risk of recall bias and under reporting of intake. Individuals experience high fluctuations in diet on a daily basis, so data from one day often poorly represents an individual's average intake. We have adjusted for this by reducing the standard deviation by a factor approximated from the excess SD regression, however ideally the data on intake would capture usual intake across many days of recall. Additionally, dietary recall surveys have different approaches for micronutrient composition or do not have an available food composition table, making micronutrient intakes sparse and inconsistent. The NHANES for example, assigns nutrient content from mixed food items to that nutrient intake, while

many other studies do not. Most studies also do not capture intake from fortification or supplementation, including all of those included in this analysis. Since most nutrition interventions target the diet, via diversification, fortification, or supplementation, it is very important to have a good knowledge basis of true intake levels in a population. However, intake levels from studies that are part of an intervention and therefore include fortification or supplementation, are not representative of the rest of the country. Without the data coverage to model intake at a granular, subnational, level, or to quantify the extent and impact of fortification and supplementation on the diet, we must rely on the limited pool of nationally representative nutrition surveys.

We chose to not adjust intake data for energy intake, since many of the studies did not report energy intake and we did not want to artificially increase micronutrient intake amounts in populations that had low overall energy intake. Also, the absolute intake on micronutrients is considered a more important indicator compared to relative intake (i.e., standardized to 2000Kcal)[18]. Often in dietary adequacy assessment work, it can be challenging to determine whether populations have inadequate intake because of diet quality (i.e. enough of a required nutrient) as opposed to diet quantity (i.e. enough food in general). Although we only look at three micronutrients here, the high global prevalence of multiple micronutrient inadequacy could be because of low nutrient intake across the board.

There has been limited work done validating the intake requirement thresholds alongside the cutpoints for deficiency. Generally the biomarker cutpoints for deficiency are more sensitive, identifying stages of clinical deficiency[19], while the population level requirements of intake are more liberal as we've seen with the EARs. For this reason, it is not surprising that population-level estimates of micronutrient deficiency prevalence do not correlate with micronutrient inadequacy, even when measured on the same population. However, as we have seen in this analysis, individual level measurements of nutrient consumption and biological availability have poor correlation. Other studies have identified modest to moderate correlations, depending on the ability to account for variations in absorption, metabolism, and excretion[20]. Two studies that looked at factors affecting serum retinol concentrations found that variables like gender, age, season, region, race, serum cholesterol and BMI affected concentration, alongside dietary intake[21,22]. Therefore while our results show that a large proportion of the world is at risk of micronutrient inadequacy, that risk depends on factors that are challenging to quantify, particularly at a global level.

Conclusion

From this research, it is clear that urgent work is needed to address the limitations in data coverage, both the number and geographic coverage of surveys and the number of indicators assessed on a population. Measuring multiple indicators on the same population can inform research on the relationship between inadequate intake and clinical deficiency, which is critically important for the implications of results such as those presented in this paper. Additionally, our findings question the reliability of current intake requirements levels, especially as validated against biomarker requirement levels, and urge for standardized and global thresholds to exist for quantifying both micronutrient inadequacy and deficiency. Finally, the copula method presents a useful way to model joint distributions, and though we have only applied it to iron, vitamin A, and zinc, this method could be extended for *n* micronutrients. The joint distribution offers unique insights into the correlation of poor micronutrient status throughout the world and by assessing the prevalence of multiple micronutrient inadequacy rather than a single micronutrient, we reveal that a much higher number of people are at risk for micronutrient inadequacy than the 2 billion previously thought.

Acknowledgements

I am very grateful for many people in helping this thesis come to fruition. The biggest thanks of all to Dr. Ashkan Afshin for his ever-patient guidance and mentorship, and for his expertise in nutrition research. I feel very lucky to have been able to work with you these past three years.

This project was made much better, and possible, by oversight and contributions from Dr. Josef Schmidhuber. It has been a joy working alongside you and tackling (some of) the questions that arose during this project. I'd also like to thank Dr. Nicholas Kassebaum for his insight, responsiveness, and helpful attitude, on this thesis and also during my time at IHME.

Several members of the diet and nutrition team at IHME were critical to this project: Molly Herbert and Giannina Ferrara for their data extraction efforts, Vinay Srinivasan for introducing me to the world of copulas, and Justin Lo for being a great teammate. Thank you also to Erin Mullany for overseeing much of this research and for helping to keep us on track.

Finally, I'd like to thank Sarah Dillard for being a tremendous graduate advisor, and my family, friends, and fellow PBFs for all of their support. I couldn't have done this without you.

References

1 Murray CJL, Aravkin AY, Zheng P, *et al.* Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet* 2020; **396**: 1223–49.

2 Howson CP, Kennedy ET, Horwitz A, *et al.* Prevention of micronutrient deficiencies: tools for policymakers and public health workers. Washington, D.C.: National Academy Press, 1998 http://site.ebrary.com/id/10055663 (accessed June 15, 2021).

3 Allen LH. Micronutrient Research, Programs, and Policy: From Meta-analyses to Metabolomics. *Advances in Nutrition* 2014; **5**: 344S-351S.

4 Hedrick VE, Dietrich AM, Estabrooks PA, Savla J, Serrano E, Davy BM. Dietary biomarkers: advances, limitations and future directions. *Nutrition Journal* 2012; **11**: 109.

5 Dignass A, Farrag K, Stein J. Limitations of Serum Ferritin in Diagnosing Iron Deficiency in Inflammatory Conditions. *International Journal of Chronic Diseases* 2018; **2018**: e9394060.

6 Raghavan R, Ashour FS, Bailey R. A Review of Cutoffs for Nutritional Biomarkers. *Advances in Nutrition* 2016; **7**: 112–20.

7 Freedman LS, Commins JM, Moler JE, *et al.* Pooled results from 5 validation studies of dietary self-report instruments using recovery biomarkers for energy and protein intake. *Am J Epidemiol* 2014; **180**: 172–88.

8 Ramakrishnan U. Prevalence of Micronutrient Malnutrition Worldwide. *Nutrition Reviews*; **60**: 7.

9 WHO. Global prevalence of vitamin A deficiency in populations at risk 1995–2005. WHO Global Database on Vitamin A Deficiency. Geneva: World Health Organization, 2009 https://apps.who.int/iris/bitstream/handle/10665/44110/9789241598019_eng.pdf.

10 Hess SY. National Risk of Zinc Deficiency as Estimated by National Surveys. *Food Nutr Bull* 2017; **38**: 3–17.

11 Schmidhuber J, Sur P, Fay K, *et al.* The Global Nutrient Database: availability of macronutrients and micronutrients in 195 countries from 1980 to 2013. *The Lancet Planetary Health* 2018; **2**: e353–68.

12 Massey FJ. The Kolmogorov-Smirnov Test for Goodness of Fit. *Journal of the American Statistical Association* 1951; **46**: 68–78.

13 Institute of Medicine (US) Panel on Micronutrients. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington (DC): National Academies Press (US), 2001 http://www.ncbi.nlm.nih.gov/books/NBK222310/ (accessed June 14, 2021).

14 European Food Safety Authority (EFSA). Dietary Reference Values for nutrients Summary report. *EFSA Supporting Publications* 2017; **14**: e15121E.

15 Allen LH, Carriquiry AL, Murphy SP. Perspective: Proposed Harmonized Nutrient Reference Values for Populations. *Advances in Nutrition* 2020; **11**: 469–83.

16 Anderson GJ, Frazer DM. Current understanding of iron homeostasis. *Am J Clin Nutr* 2017; **106**: 1559S-1566S.

17 FAO. Global food losses and food waste – Extent, causes and prevention. Rome, 2011.

18 Willett W. Nutritional Epidemiology. Oxford University Press, 2013.

19 Sezgin G, Monagle P, Loh TP, *et al.* Clinical thresholds for diagnosing iron deficiency: comparison of functional assessment of serum ferritin to population based centiles. *Sci Rep* 2020; **10**: 18233.

20 Knutsen SF, Fraser GE, Linsted KD, Beeson WL, Shavlik DJ. Comparing biological measurements of vitamin C, folate, alpha-tocopherol and carotene with 24-hour dietary recall information in nonhispanic blacks and whites. *Ann Epidemiol* 2001; **11**: 406–16.

21 Neuhouser ML, Rock CL, Eldridge AL, *et al.* Serum concentrations of retinol, alpha-tocopherol and the carotenoids are influenced by diet, race and obesity in a sample of healthy adolescents. *J Nutr* 2001; **131**: 2184–91.

22 Faure H, Preziosi P, Roussel A-M, *et al.* Factors influencing blood concentration of retinol, alpha-tocopherol, vitamin C, and beta-carotene in the French participants of the SU.VI.MAX trial. *Eur J Clin Nutr* 2006; **60**: 706–17.

Supplementary materials

Table S1: A list of all dietary recall data sources used in this project. Total sample size is aggregated across all years of the survey.

COUNTRY	SURVEY NAME	TOT. SAMPLE SIZE	YEARS OF SURVEY	YEAR RANGE	AGE RANGE	MICRO-NUTRIENTS
ARGENTINA	national survey nutrition health	19975	1	2004-2005	0-51 years	Zinc, vitamin A, iron
ARGENTINA	national status eating habits	1200	1	2012-2013	18-71 years	Zinc, vitamin A, iron
BULGARIA	national food intake nutritional status	1198	1	2004	16-95 years	Zinc, vitamin A, iron
CANADA	community health survey	20457	1	2015	1-95 years	Zinc, vitamin A, iron
DEMOCRATIC REPUBLIC OF THE CONGO	wild edible plants womens diet survey	488	1	2009	15-72 years	Zinc, vitamin A, iron
ECUADOR	baseline child nutritional status	716	1	2008	0-2 years	Zinc, iron
ECUADOR	baseline child nutritional status rural highland	347	1	2008	0-2 years	Zinc, iron
ESTONIA	national dietary survey	4906	2	1997-2015	11-75 years	Zinc, vitamin A, iron
ETHIOPIA (AMHARA)	gondar nutritional status dietary intake urban residents	353	1	2007	18-80 years	iron
ETHIOPIA (SOUTHERN NATIONS, NATIONALITIES, AND PEOPLES)	butajira dietary behavior women	318	1	2013	18-45 years	Zinc, vitamin A, iron
INDIA	multicentre urban survey	787	1	2008-2009	1-18 years	Zinc, iron
INDIA	survey diet and nutritional status	17849	6	1975-1980	0-99 years	vitamin A, iron
INDIA	urban children survey	937	1	2016	1-18 years	Zinc, iron
INDIA	urban school survey	608	1	2016	10-16 years	Zinc, iron
IRAN (FARS)	fluoride intake children	108	1	1995-1996	4-5 years	Zinc, vitamin A, iron
ISRAEL	national health nutrition survey	3813	2	1999-2004	12-64 years	Zinc, vitamin A, iron

ISRAEL	national health nutrition survey elderly	1784	1	2005-2006	65-96 years	Zinc, vitamin A, iron
ITALY	national survey food consumption	3305	1	2005-2006	0-97 years	vitamin A, iron
KENYA	biodiversity inula initiative	856	1	2012	0-65 years	Zinc, vitamin A, iron
KENYA (VIHIGA)	biodiversity landscapes baseline	740	1	2018	0-59 years	Zinc, vitamin A, iron
LAO PEOPLE'S DEMOCRATIC REPUBLIC	national food consumption survey	2008	1	2016-2017	0-89 years	vitamin A, iron
NEW ZEALAND	national children nutrition survey	3270	1	2002	5-15 years	Zinc, vitamin A, iron
POLAND	household consumption anthropometric survey	4127	1	2000	1-96 years	Zinc, vitamin A, iron
PUERTO RICO	oral health survey	790	1	2010	12 years	Zinc, vitamin A, iron
REPUBLIC OF KOREA	national health and nutrition examination survey knhanes	102092	13	1998-2018	1-103 years	vitamin A, iron
ROMANIA	dieta pilot survey	1379	1	2012	19-92 years	Zinc, vitamin A, iron
SWEDEN	national dietary survey	1795	1	2010-2011	18-80 years	Zinc, vitamin A, iron
THAILAND	food consumption survey	7272	1	2004-2005	18-103 years	Zinc, vitamin A, iron
UNITED KINGDOM	national diet nutrition survey	23911	14	1992-2017	1-104 years	Zinc, vitamin A, iron
UNITED STATES OF AMERICA	national health and nutrition examination survey	46543	9	1999-2016	0-85 years	Zinc, vitamin A, iron
UNITED STATES OF AMERICA	USDA continuing food intake and diet health knowledge survey	36705	7	1989-1998	0-102 years	Zinc, vitamin A, iron
VIET NAM	nutritional status lifestyles	1171	1	2006	15-20 years	Zinc, vitamin A, iron
ZAMBIA	food consumption vitamin a survey	1663	1	2009	0-70 years	Zinc, vitamin A, iron

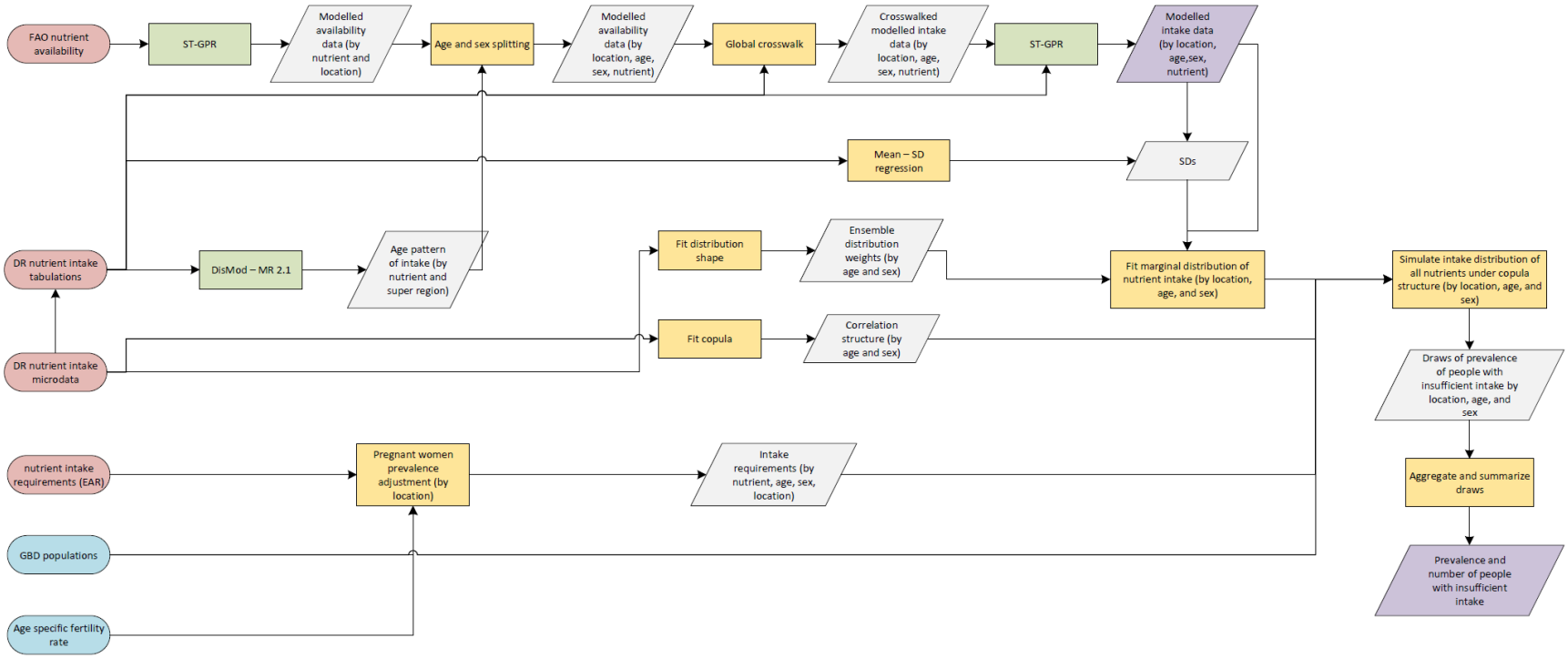

Figure S1. An overview of the steps and methods implemented in this project. An oval signifies input data, a rectangle signifies a process, and a parallelogram signifies results. Since this project builds off of inputs and modeling tools in the GBD study, custom inputs are red, GBD inputs are blue, custom methods are gold, and GBD central methods are green. Additionally, intermediate outputs are grey, while the final outputs are purple.

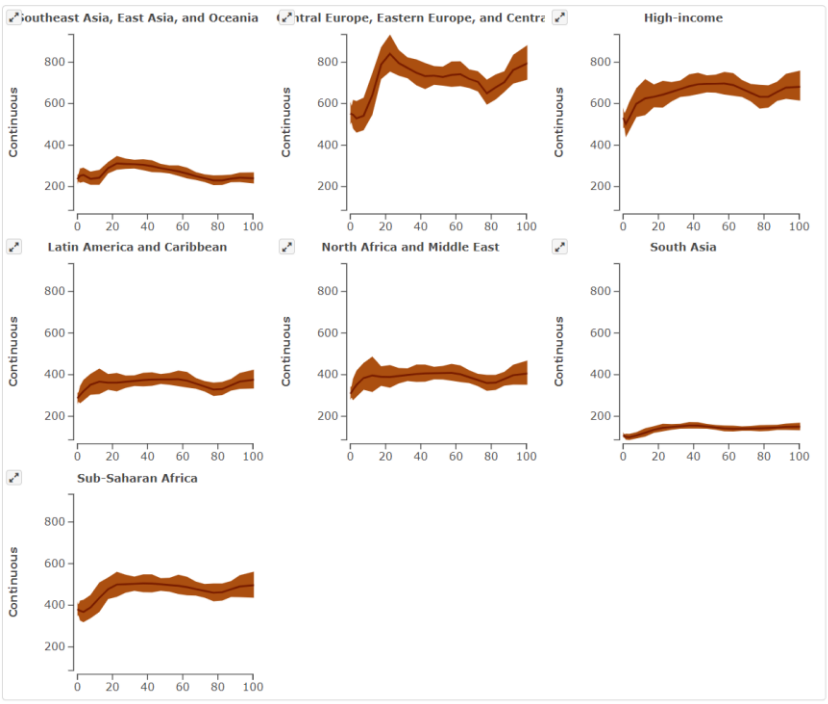

Figure S2. The GBD super-region specific age pattern for vitamin A intake. The x-axis is the age and y-axis the intake (in ug/day). Each curve was informed by available data in that region and in the absence of data, the curve was inferred from the global age pattern. Although the magnitude for some regions varies, the age pattern is only used to characterize differences in consumption across ages, and the value of the intake does not affect the age split.

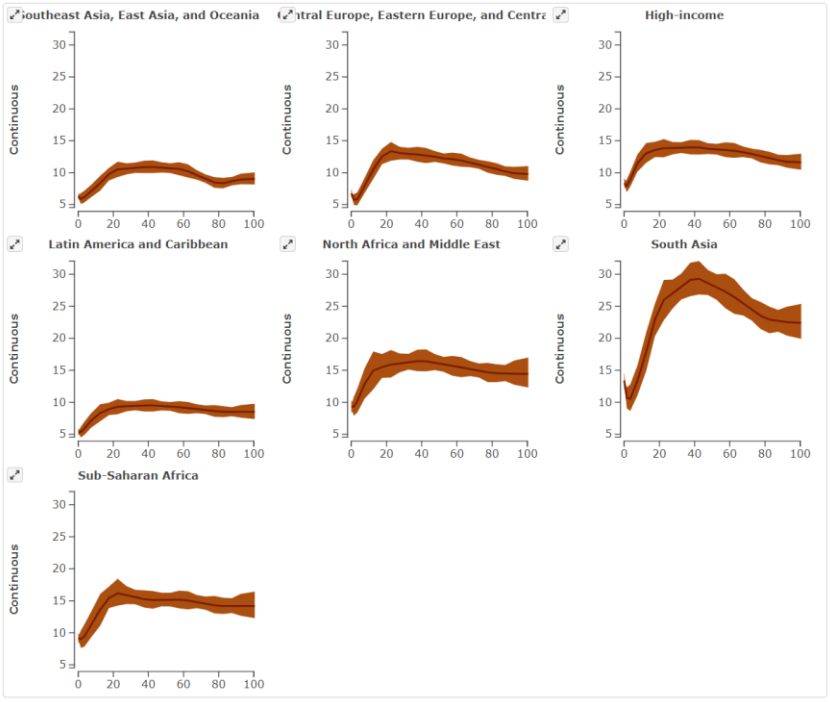

Figure S3. The GBD super-region specific age pattern for iron intake. The x-axis is the age and y-axis the intake (in ug/day). Each curve was informed by available data in that region and in the absence of data, the curve was inferred from the global age pattern.

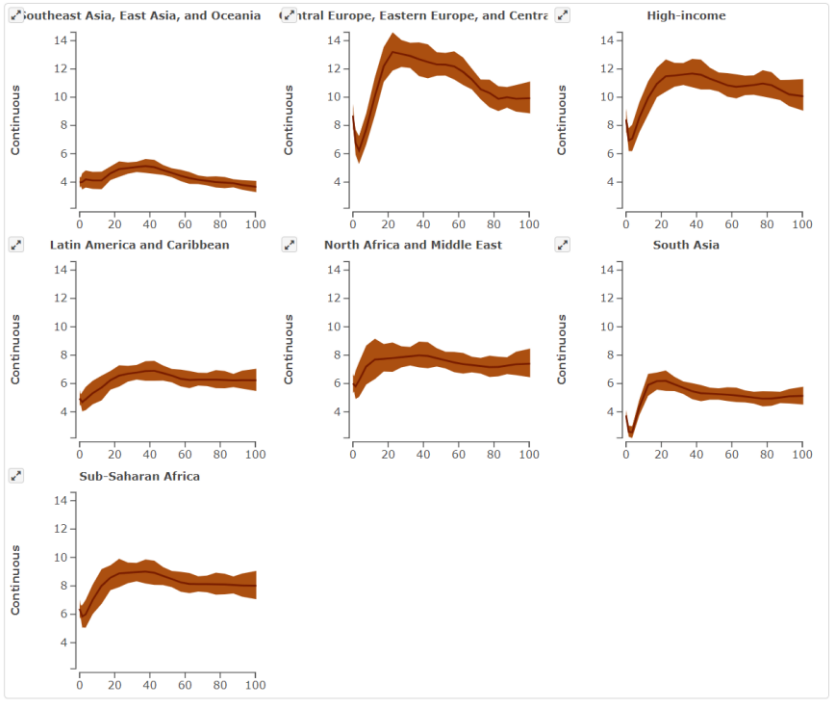

Figure S4. The GBD super-region specific age pattern for zinc intake. The x-axis is the age and y-axis the intake (in ug/day). Each curve was informed by available data in that region and in the absence of data, the curve was inferred from the global age pattern.

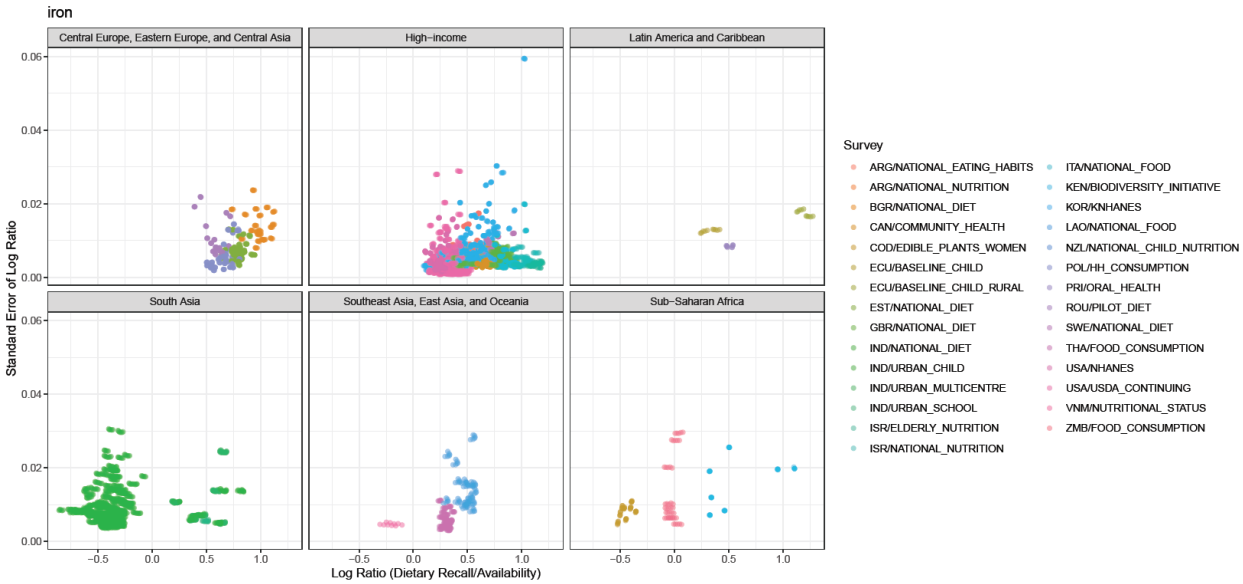

Figure S5. A visualization of the matched data set, by GBD super region, as used in the bias adjustment crosswalk for iron. The regression beta will fall along the middle of the data for the given region. Since the model was fit in log space and we discuss the adjustment factors in normal space, A = 1/exp(B) and B = -1*log(A) where B is the regression beta and A is the reported adjustment factor, since A communicates the multiplier to convert availability to dietary recall.

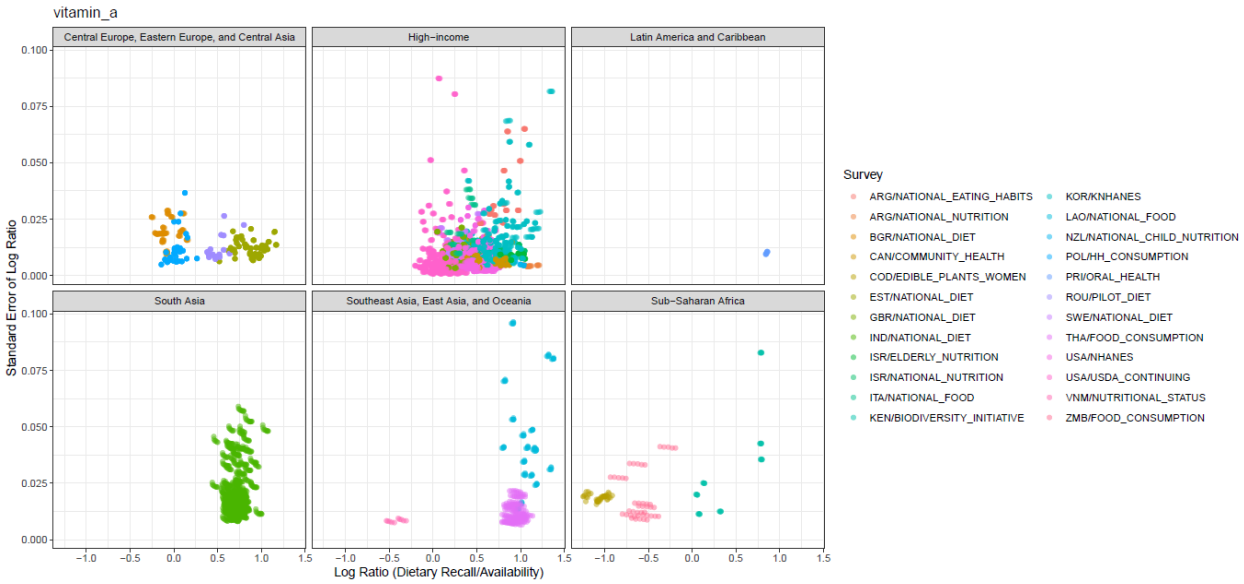

Figure S6. A visualization of the matched data set, by GBD super region, as used in the bias adjustment crosswalk for vitamin A. The regression beta will fall along the middle of the data for the given region.

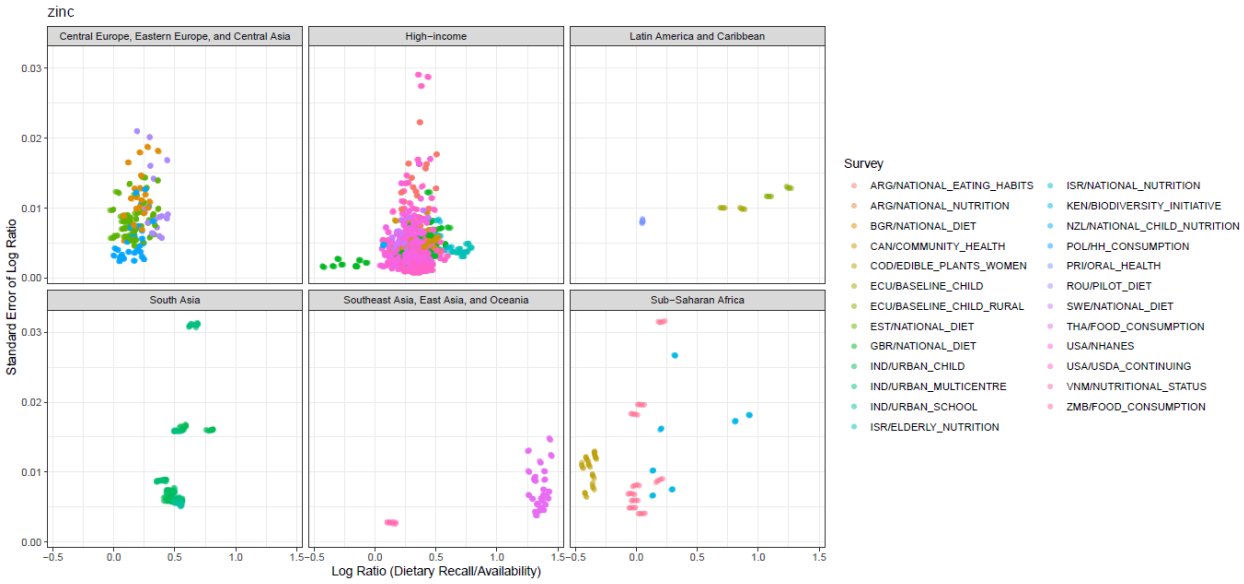

Figure S7. A visualization of the matched data set, by GBD super region, as used in the bias adjustment crosswalk for zinc. The regression beta will fall along the middle of the data for the given region.

Table S2: Adjustment factors from the crosswalk.

Region	Iron	Vitamin A	Zinc
Global	0.71	0.74	0.75

NHANES only (USA)	0.74	0.57	0.75
Southeast Asia, East Asia, and Oceania	0.83	0.57	0.45
Central Europe, Eastern Europe, and Central Asia	0.47	0.67	0.84
High-income	0.69	0.75	0.76
Latin America and Caribbean	0.51	0.43	0.51
South Asia	1.14	0.49	0.59
Sub-Saharan Africa	1.01	1.64	1.01

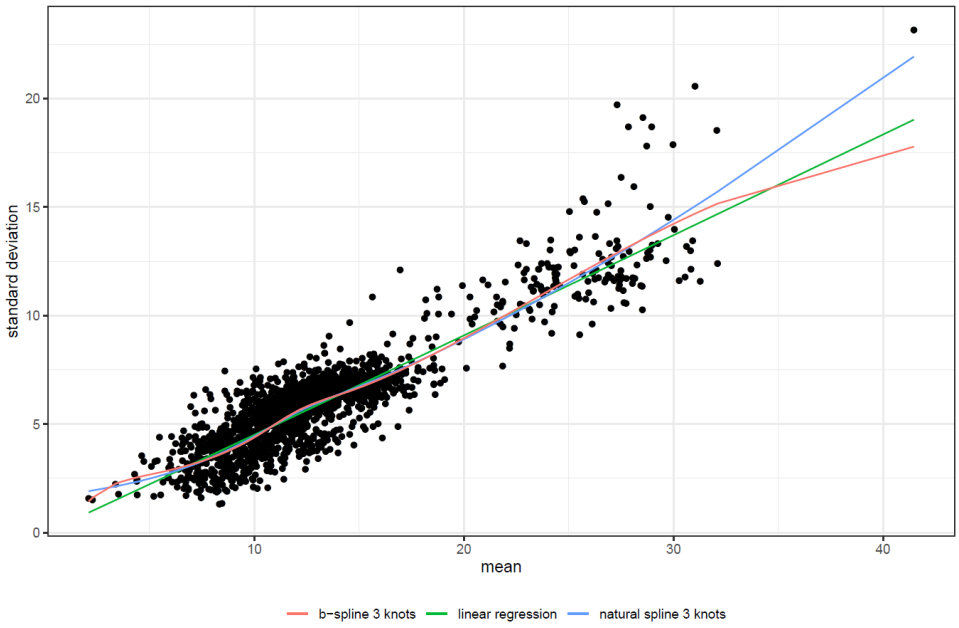

Figure S8. Visualization of dietary recall data mean-sd regression for iron

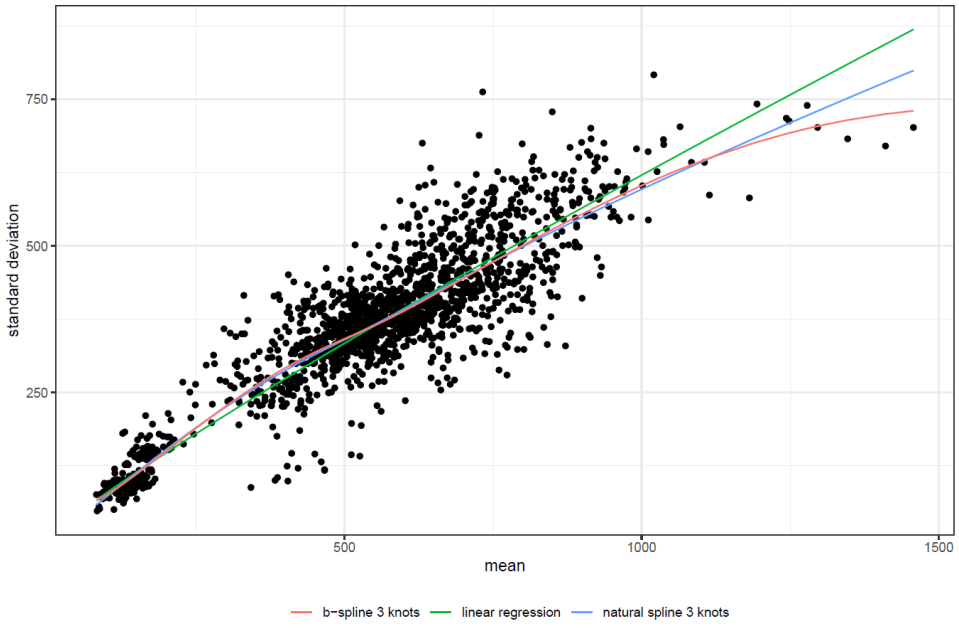

Figure S9. Visualization of dietary recall data mean-sd regression for vitamin A.

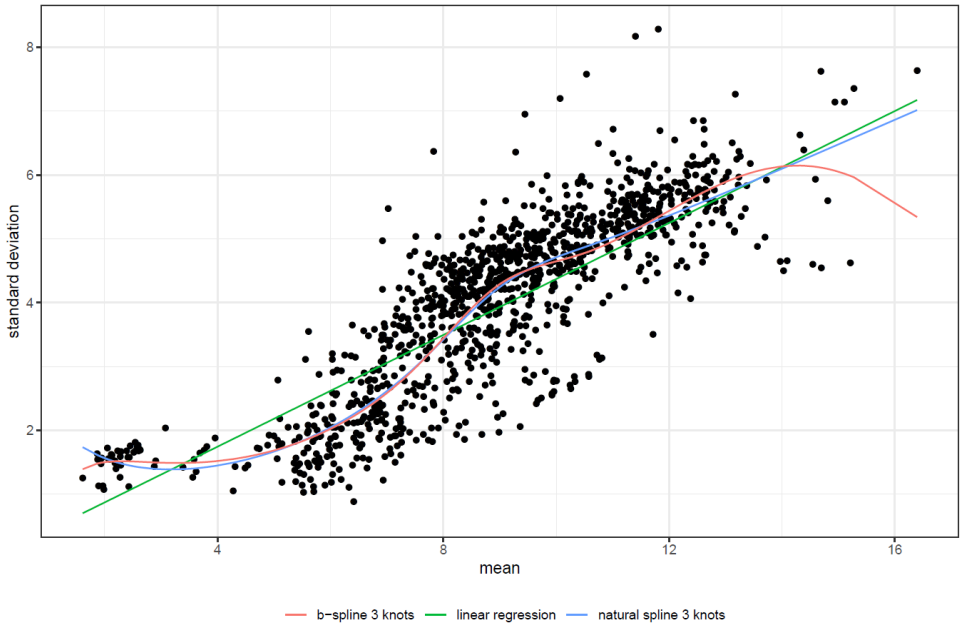

Figure S10. Visualization of dietary recall data mean-sd regression for zinc.

Table S3: SD reduction factors used to approximate usual intake

Micronutrient	SD reduction factor
iron	0.80
vitamin A	0.76
zinc	0.74

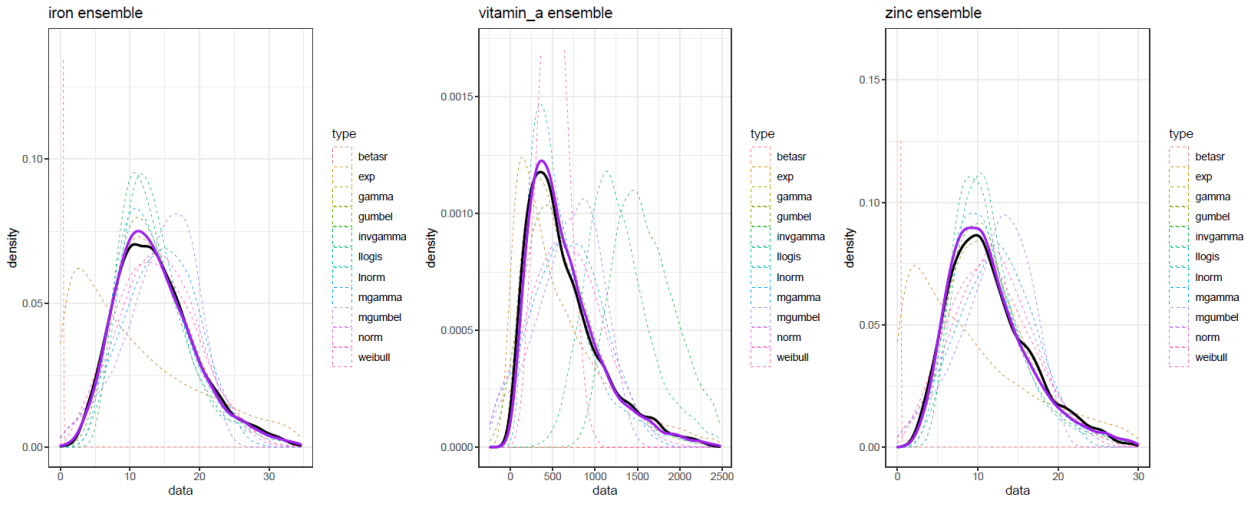

Figure S11. Example of global distribution fits for iron, vitamin A and zinc for males aged 25-30. The final distribution shape is a weighted ensemble of each of the 11 common distribution types, weights determined by fit to the microdata.

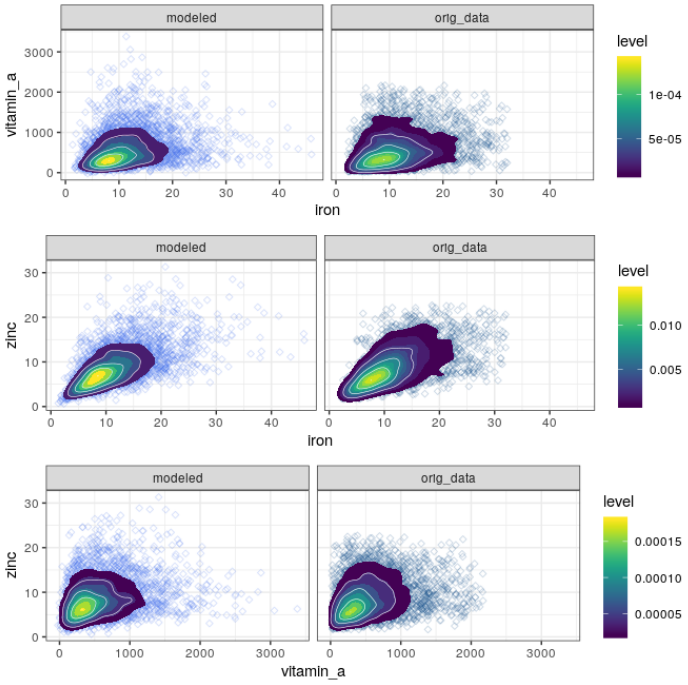

Figure S12. Example of copula correlation fits for the pairwise combinations of iron, vitamin A, and zinc. On the right the correlation structure as observed in the microdata is plotted as a 2D density, while the left shows the structure as modeled from the copula fit.