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ORIGINAL ARTICLE

Prevalence of low dietary zinc intake in women and pregnant women in Ireland

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Abstract

Background In humans, zinc is involved in many biological functions acting as signaling ion, neurotransmitter, structural component of proteins, and cofactor for many enzymes and, through this, is an important regulator of the immune and nervous system. Food supplies zinc to the human body, but a high prevalence of inadequate dietary zinc intake has been reported worldwide.

Aims The objective of this study was to investigate the zinc intake and bioavailability of over 250 women (pregnant and non-pregnant) based in Ireland, in order to evaluate the dietary inadequacy of zinc.

Methodology We used a food frequency questionnaire designed to assess the zinc intake and bioavailability of the participants.

Results Our results show that 58% of participants are at risk of inadequate zinc intake and that 29% may be zinc deficient. The prevalence of inadequate zinc intake was lower for pregnant women (zinc deficient 9%, at risk 38%) than for non-pregnant women due to more frequent consumption of supplements. Low zinc intake was not correlated with the age of participants and resulted from a combination of inadequate intake of zinc-rich food and relatively higher intake of food items rich in phytate, a major zinc uptake inhibitor.

Conclusions We conclude that at present, low zinc intake may be prevalent in as much as 87% of women, including 47% of pregnant women. Therefore, zinc status needs to be considered as a factor impacting the health of women, and in particular pregnant women, also in industrialized and developed countries such as Ireland.

Keywords Diet · Food frequency questionnaire · Nutrition · Phytates · Zinc

Introduction

The divalent cation zinc plays a vital role in a large number of biological functions. Free zinc is an intracellular signaling ion and neurotransmitter [1, 2], and with its ability to bind to almost 10% of proteins in the human proteome [3], protein-bound zinc has essential protein regulatory functions. For example, it is a cofactor for over 300 enzymes [4]. Besides, zinc is required for the function and the activity of over 2000 transcription factors. Through this plethora of interactions, it has neuroprotective and anti-inflammatory properties [5]. In particular, in humans, zinc is involved in the healthy development of the brain and the coordination of brain functions. In the central nervous system (CNS), zinc is responsible for neurogenesis, synaptic plasticity, neuronal migration and differentiation, and ion signaling and acts as a modulator of neurotransmission [6].

At least two pools of zinc are found in the human body. The first zinc pool is comprised of slow-exchanging zinc, which is mainly located in muscle and bone. This pool represents the majority of zinc in the body. The other pool (10% of the body's zinc) is a rapid-exchanging zinc pool and is located mainly in the blood and also the gastrointestinal tract, the liver, and other internal organs [7, 8]. The two pools can play different roles. In particular, the rapid-exchange zinc pool is most reactive to the amount of zinc

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absorbed from food and is also the pool that is most relevant for the physiological role of zinc. Consequently, this pool is susceptible to zinc intake. Especially in the case of zinc deficiency, this pool is the first to be depleted through low dietary zinc intake [9].

The average human body contains 2.3 g of zinc. However, zinc requirements are different for each individual due to factors such as age, lifestyle, and health. In 1996, the World Health Organization (WHO) suggested values for the recommended daily intake of zinc, considering the different needs between men and women and different age groups and considering the bioavailability of zinc in the diet (categorized as low, medium, and high). For an adult female, the recommended daily intake of zinc, based on a high, medium, and low zinc bioavailability, was 6 mg, 10 mg, and 20 mg, respectively. During pregnancy, the daily zinc requirement was estimated based on calculating the rate of tissue weight gain and the zinc concentration found in these tissues. The recommended zinc requirements are different for each phase of the pregnancy: in the first quarter of pregnancy, the additional absorption of 0.08 mg/day, 0.24 mg/day in the second quarter, 0.53 mg/day in the third quarter, and 0.73 mg/day in the final quarter has been deemed necessary [10]. This additional demand can be covered by an additional 5–10 mg zinc intake per day by pregnant (and lactating) women.

Zinc is naturally present in many categories of food. However, throughout the world, major shifts in dietary patterns are occurring recently [11]. Therefore, here, we performed a current assessment of the zinc intake of women and pregnant women based in Ireland. The food items representing the richest sources and high bioavailability in zinc are fish and shellfish (especially oysters and mollusks), beef, and other types of red meats, poultry, eggs, milk, and some products derived from milk such as hard cheese and yogurt. In addition to this, legumes, nuts, and whole grain are good zinc sources [12]. In contrast, the bioavailability of zinc is low in a mainly plant-based diet, where high levels of the leading known inhibitor of zinc absorption, phytic acid, are found. Phytate within food is composed of a mixture of various phosphorylated forms of inositol phosphate (for the majority represented by hexaphosphates and also pentaphosphates, tetraphosphates, and triphosphates) [13]. The molar ratios of phytate:zinc can predict the inhibitory effects of phytic acid on zinc in the diet with molar ratios of more than around 18:1 significantly inhibiting zinc absorption [9]. Thus, in this study, we utilize an evaluation method that accounts for the presence of phytic acid and its levels in the diet and therefore considers the bioavailability of zinc rather than the pure zinc concentration in the diet.

The most commonly used method to determine zinc status is to measure zinc concentrations in blood serum. However, several studies have shown that using blood serum as a biomarker is unsuitable for assessing mild (subclinical) zinc deficiency and zinc deficiency during pregnancy. On the one hand, serum zinc levels only provide a snapshot of the zinc status in an individual as the serum zinc concentrations can fluctuate naturally greatly throughout the day by as much as 20% [7]. On the other hand, during pregnancy, zinc is redistributed from blood to other tissues. Thus, pregnancy significantly affects serum zinc levels making the application of standard serum zinc parameters to detect low zinc status ambiguously [7, 14]. Therefore, mild zinc deficiency in humans may be relatively overlooked, especially during pregnancy, where an increased demand puts women at high risk for low zinc status, which ultimately will affect fetal development.

For example, numerous studies using serum, nail, hair, teeth, or cerebrospinal fluid, and meta-analyses, have reported a strong association between early life zinc deficiency and neurodevelopmental disorders in humans [15–17] that show increasing incidence rates in industrialized nations [18]. In addition, low zinc status may increase the likelihood for infections, including SARS-CoV-2 [19].

Zinc levels can also be assessed indirectly by using food frequency questionnaires (FFQ). In a study published in 2018 by Trame et al. [20], a biochemically validated questionnaire was developed that allows predicting the zinc status of an individual reliably. The FFQ was used to calculate the average zinc and phytate diet scores of each individual within the study assessing the diet of individuals over 6 months. The final zinc scores that are corrected for the presence of phytates in the diet were then associated with zinc status by measuring zinc in the blood serum of the participants, and a significant correlation between zinc scores and serum zinc levels was confirmed. The participants in the study were also based in Europe (Germany). Thus, the FFQ is a valuable method to detect individuals with low body zinc levels reliably and has been adapted for this study.

Material and methods

Study design and population

All participants provided written informed consent before filling out the questionnaires. The confidentiality of the participants was ensured. The study was approved by the Faculty for Science and Engineering ethics committee, University of Limerick, Ireland, ID: 2018_05_03_S&E. The inclusion criteria for participation were 18–65 years of age, including both pregnant and non-pregnant women. Participants aged over 65 were excluded ($n = 10$). Only pregnancies less than 10 years ago were considered for the evaluation. No pregnancies with twins were included in the study. Only pregnancies of participants based in Ireland during pregnancy were included. For each mother, we considered only the last two trimesters of pregnancy for a data consistency reason with the non-pregnant participants. The sample size with over 250 participants has sufficient statistical power for validation of food frequency questionnaires which is reached by 134 participants and is in line with published studies [21]. Nine participants with a total of 11 children with neurodevelopmental disorder were included. The participants were recruited using public advertisements/word of mouth and from across the Republic of Ireland, and participants were from nine Irish counties (Clare, Cork, Donegal, Dublin, Galway, Kerry, Limerick, Mayo, and Tipperary) and recruited for the study in the years 2018–2021.

The minimum sample size was calculated using the formula for a cross-sectional study for estimating prevalence in a population: $n \geq Z^2 \times p(1-p) / d^2$, where n is the sample size, and Z is the value of standard normal deviation corresponding to the level of confidence. The value was set at 1.96 for a 95% confidence level. p is the expected prevalence expressed in proportion. The value is taken from published studies that report an estimated 9.6% of the population with inadequate zinc intake in Central and Eastern Europe [22]. It was therefore set at 0.096. d is the margin of error and was set at 5%. Thus, the minimum sample size is calculated as $n \geq (1.96)^2 \times 0.096\ (1-0.096) / 0.05^2$; $n \geq 134$.

Dietary intake assessment

The assessment of food intake, which served as the basis for the estimation of dietary zinc intake, was performed using the FFQ [20] that allowed calculating average zinc and phytate diet scores (see supplementary information 1). It includes questions about the consumption of 18 food items: meat (3 products including red and white meat and lunchmeat), fish (2 products including fresh and canned fish, shellfishes, and crustacea), milk and dairy products (3 products), breads and cereals (3 products), egg, grouped nuts and peanuts, seeds and bran, legumes and their products, corn and its products, snacks and fast food items (2 products). The questionnaires assessed the frequency and servings and portion sizes of different food categories. Besides, the participant needed to indicate whether any nutritional supplements were taken and, if known, the concentration of zinc in the supplement.

To that end, the FFQ showed rows to indicate (1) food item, (2) the food frequency, (3) type and number of portions, and (4) amount of a portion. "Food frequency" was categorized as "1 × daily," "2–4 × weekly," "1 × weekly," "2–3 × monthly," or "less than 1 × monthly/never." For "type and number of portion," examples were given such as "1 cup/ 2 slices/ 3 tablespoons/ 1 teaspoon/ amount in g/ 1 bar/ 2 pieces,". For the "amount of portion," a selection between "small," "medium," or "large" should be made.

An FFQ was filled out by each participant listing the diet of the last 6 months and the diet during pregnancy (or multiple pregnancies), if applicable. In addition, the FFQ assessed data such as age, whether the individual was in Ireland during the pregnancy, and whether the child resulting from pregnancy is diagnosed with a neurodevelopmental disorder.

The Irish Food Portion Sizes Database by Lyons [23] was used in order to look at the median portion weights (g) and interquartile ranges (IQR) of a variety of foods consumed by men and women aged 18–64 years. The median scores for women were the values used as this study was based on women in Ireland. The zinc scores obtained from supplemental zinc were calculated the same way as the calculation of zinc from food sources. The scores from supplementation were then added to the zinc scores from food sources.

Zinc and phytate scores were calculated based on published data [24] using a validated equation multiplying the following elements: frequency index quantity index zinc or phytate content expressed in mg. In addition to this, to estimate the zinc and the phytate contents, the tables developed by Elmadfa et al. [25] and Schlemmer et al. [26] were used. According to the FFQ developed and validated by Trame et al. [20], the 18 food items listed have different zinc bioavailability, depending on whether they are animal food products or vegetable food products. In particular, vegetable foods have less bioavailable zinc due to their phytate and fiber contents [14]. For this reason, the food items categorized as vegetable foods such as vegetables, fruits, and potatoes were assigned a modified score, obtained by dividing the primary score by the factor 1.1 and subtracting it from the total zinc diet score. Another category in the list of food items is represented by nuts, seeds, legumes, bread, pasta/rice, sweet corn, oatmeal/cereal, and pseudocereal. While this food group is a good zinc source, it also contains less bioavailable zinc because of the phytate and fiber contents. Also, in this case, the primary score is modified. It is divided by the factor 2 before subtraction from the total zinc diet score. In addition, zinc and phytate diet score values of items with the frequency "less than 1 time monthly or never" were not included in the calculation of the final score. The last modification of the total zinc score results from supplemented zinc; the value for supplemented zinc is calculated by multiplying frequency index quantity index set as 2 (= medium) elementary zinc content expressed in mg. This zinc supplementation score is added to the zinc scores from food sources.

The same evaluation method was also applied to the period of pregnancy for which participants filled out the FFQ for the months in which they were pregnant. This was completed for all pregnancies of a participant.

According to Trame et al. [20], zinc scores were translated into serum zinc levels and adjusted for increased demand for zinc during pregnancy (Table 1).

Table 1 Clinical interpretation of zinc diet scores to serum zinc values (modified from Trame et al., 2018)

Non-pregnant		Pregnant		
Zinc diet score	**Equivalent serum zinc (µg/dl)**	**Zinc diet score**	**Equivalent serum zinc (µg/dl)**	**Clinical interpretation**
> 437	> 160	> 553	> 160	Zinc intoxication
351–437	121–160	442–553	121–160	At risk of oversupply
113–350	85–120	141–441	85–120	Normal
51–112	60–84	63–140	60–84	At risk of marginal zinc deficiency
< 51	< 60	< 63	< 60	Zinc deficiency

Statistics

Normal distribution was analyzed using the Shapiro–Wilk test. Data are presented as average ± SEM or as frequencies (%). One-way ANOVA and Tukey's multiple comparison test were used to compare characteristics in the analyzed cohort of non-pregnant participants and the cohort of pregnant participants. The evaluation was performed with Microsoft Excel for Mac Version 16.30 and GraphPad Prism Version 8.4.1 (460). Statistical tests used are mentioned in the figure legends. Statistically significant differences are indicated in the figures by * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, and **** $p \leq 0.0001$. Values are shown as mean ± SEM.

Results

To understand the frequency of low zinc intake in women and pregnant women, 258 study participants were handed out food frequency questionnaires. The characteristics of the studied population are shown in Table 2 and Supplementary Fig. S1.

The youngest participant in this study was aged 18, and the oldest was 62. The age range reflects the inclusion criteria described in the "Material and methods" part (18–65 years). The average age of the participants is 32.24 ± 0.8135 years.

The FFQ was completed by women that had at least one pregnancy and participants without any pregnancy. The study analyzed 115 participants with pregnancy and 143 participants without pregnancy. Of the 115 participants with pregnancy, several had multiple pregnancies. The minimum number of pregnancies in our pregnant study population is 1. The maximum number of pregnancies per participant analyzed was 5, with an average number of children per participant of 2.104 ± 0.09517. Due to multiple pregnancies, a total of 237 pregnancies were analyzed.

The average zinc score calculated for the participants for the pregnancies with children later diagnosed with a neurodevelopmental disorder was 197.221 ± 24.75 ($n = 10$), which was not significantly different from the average zinc score of pregnant women without neurodevelopmental disorders (177.361 ± 4.29 ($n = 227$)).

The majority of participants are at risk of inadequate zinc intake

In our first set of analyses, to establish if the zinc intake of women participating in the study is adequate in their diet, we analyzed the zinc intake of all our participants ($n = 258$) in the last 6 months. The average zinc score was 74.86 ± 2.983 (Fig. 1A). According to Table 1, the clinical interpretation of the zinc diet score in our non-pregnant participants shows that, on average, participants are at risk of marginal zinc deficiency. Zinc diet scores were heterogeneous, showing a

Table 2 Study population characteristics ($n = 258$). Averages are shown as mean ± SEM; the number of participants is shown as percent of total participants in brackets

Population characteristics	
Average age (all participants) (y)	32.24 ± 0.8135
Participants with pregnancy	115 (44.57%)
Average age of participants with pregnancy	31.83 ± 0.39
Participants without pregnancy	143 (55.42%)
The average number of children per participant with pregnancy	2.104 ± 0.09517
Number of participants with children with autism spectrum disorder	8 (6.956%)
Number of participants with children with other neurodevelopmental disorder	1 (0.8695%)
Number of vegetarian participants	9 (3.488%)
Number of participants consuming predominantly fast food	1 (0.387%)

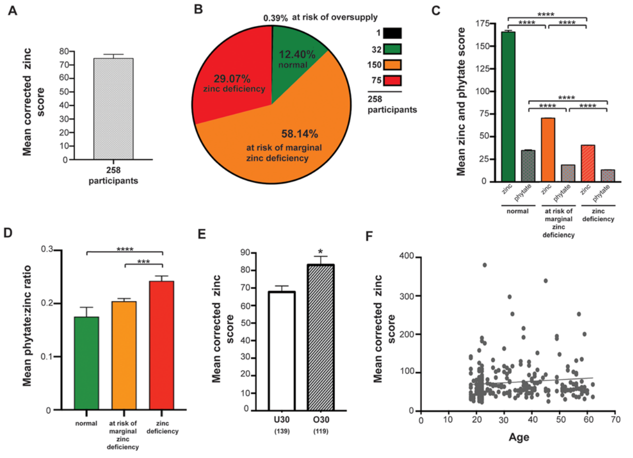

Fig. 1 Dietary zinc intake characteristics of non-pregnant participants. **A** Average corrected zinc score calculated for all participants ($n = 258$). The average zinc score was 74.86 ± 2.983 (average ± SEM). **B** Participants were classified using their zinc scores. A total of 0.39% of the studied population ($n = 1$) was in the "at risk of zinc oversupply" category, 12.40% ($n = 32$) in the "normal zinc" category, 58.14% of the population ($n = 150$) were classified in the "at risk of marginal zinc deficiency category," and 29.07% of the participants ($n = 75$) were in the "zinc-deficient" category. **C** Comparison between average non-corrected zinc score and phytate zinc score of all the participants in each category. A significant difference was found (one-way ANOVA, $p < 0.0001$). Post hoc tests (Tukey's multiple comparison test) revealed the following significances: average zinc score in the "normal zinc" category vs. average zinc score in the "at risk of marginal zinc deficiency" ($p < 0.0001$); average zinc score in the "normal zinc" category vs. average zinc score in the "zinc-deficient" category ($p < 0.0001$); average zinc score in the "at risk of marginal zinc deficiency" category vs. average zinc score in the "zinc-deficient" category ($p < 0.0001$); average phytate score in the "normal zinc" category vs. average phytate score in the "at risk of marginal zinc deficiency" ($p < 0.0001$); average phytate score in the "normal zinc" category vs. average phytate score in the "zinc-deficient" category ($p < 0.0001$); average phytate score in the "at risk of marginal zinc deficiency" category vs. average phytate score in the "zinc-deficient" category ($p < 0.0001$). **D** The mean phytate:zinc ratios derived from zinc and phytate scores of participants are significantly different (one-way ANOVA, $p < 0.0001$). Post hoc tests (Tukey's multiple comparison test) revealed the following significances: average phytate:zinc score in the "normal zinc" category vs. "zinc-deficient" category ($p < 0.0001$); average phytate:zinc score in the "at risk of marginal zinc deficiency" category vs. "zinc-deficient" category ($p = 0.0007$). **E** The average zinc score of participants under 30 years old (U30, $n = 139$) (67.79 ± 3.45) and over 30 years old (O30, $n = 119$) (83.11 ± 4.96) of non-pregnant participants (143 non-pregnant, and 115 with previous pregnancy, but currently non-pregnant) showed a significant difference between the two groups (t-test, $p = 0.0102$). **F** Correlation between the mean zinc scores and the age of the non-pregnant participants. A linear regression analysis did not show any statistical significance: ($p = 0.0873$); $y = 0.3911{*}x + 62.25$. **A**–**E** All data are shown as average ± SEM

fluctuation of the values between the highest zinc diet score found (380) and the lowest score (23.50) (Fig. 1A). The diet zinc score was later translated into serum zinc equivalents. The study population was divided into four different zinc categories with the following percentage: 0.39% (1 participant) is at risk of zinc oversupply, 12.40% of the participants (32 participants) are in the "normal zinc" category, 58.14% (150 participants) are "at risk of marginal zinc deficiency," and 29.07% (75 participants) were classified in the "zinc-deficient category" (Fig. 1B). Thus, our results showed that only a small proportion of the population represented by 32 participants out of 258 was found to have zinc intake that correlates with normal serum zinc levels.

Multiple factors affect the zinc score of the participants

To understand the possible factors that contribute to the low zinc scores that classified the majority of women in the study to be at risk of inadequate zinc intake or likely zinc deficient, we analyzed the role of diet style of our participants (Table 2). In particular, we considered the impact of a vegetarian diet, typically characterized by the absence of animal tissue, the richest bioavailable source of zinc. Nine participants were classified as vegetarians, representing 3.488% of the study population analyzed. All were ranked in the categories "at risk of marginal zinc deficiency" or "zinc-deficient." In parallel, we also investigated the role of a fast food-based diet (defined by daily consumption of fast food). Only 1 participant (0.387% of the total population, $n = 258$) indicated daily fast food consumption. She was classified as "at risk of marginal zinc deficiency."

Another factor that we considered impacting the zinc diet score is nutritional zinc supplementation in the investigated population. A total of 22 participants (8.527%) analyzed included zinc supplements in their diet. Twelve of these were found in the "marginal zinc deficiency" category, 8 in the "normal zinc" category, and one in the "zinc-deficient" category and "at risk of oversupply." Thus, with 25% of participants in the "normal zinc" category, but only 8% and 1.3% in the "marginal zinc deficiency" and "zinc-deficient" category, respectively, taking a zinc supplement, zinc supplementation may be a key contributor for participants to reach normal zinc intake.

In addition to this, we considered the possible inhibition of the zinc absorption caused by phytate within the diet (Fig. 1C). Therefore, we analyzed the phytate score in relation to the zinc scores in each category: normal, at risk of zinc deficiency, and zinc-deficient (Fig. 1C). The mean zinc score in the normal zinc level category was 165.74 ± 9.929 ($n = 32$), and the associated phytate score was 34.842 ± 4.188 ($n = 32$); the mean zinc score found in the category at risk of zinc deficiency was 70.581 ± 1.34 ($n = 150$), and the associated phytate score was 18.728 ± 0.779 ($n = 150$). In the zinc-deficient category, the average zinc score was 40.57 ± 0.795 ($n = 75$), with a mean phytate score of 13.37 ± 0.677 ($n = 75$). The statistical analysis showed significant differences between the phytate scores of the "normal" category and the phytate score of the participants "at risk of zinc deficiency" ($p < 0.0001$), the phytate score of the "normal" category and the phytate score in the category of "zinc deficiency" ($p < 0.0001$), and the phytate score in the "at-risk of zinc deficiency" category and the phytate score in the "zinc deficiency" category ($p < 0.0001$). Thus, phytate scores are not higher in the groups with low zinc status. However, considering the significantly reduced zinc intake between the groups, the phytate:zinc ratio significantly increases in the "at risk of zinc deficiency" category and further increases in the "zinc deficiency" category (Fig. 1D). Lower zinc scores of participants in the "at risk of zinc deficiency" and "zinc deficiency" category are, therefore, a result of both significantly lower zinc intake and less pronounced decreased phytate intake.

To understand whether age could be a factor that impacts the zinc score, we compared the mean zinc score of non-pregnant participants under 30 years old (U30) and participants over 30 years old (O30). We used the data of 258 participants (143 without pregnancy and 115 with prior pregnancy, but currently non-pregnant). According to our results, participants U30 had an average zinc score of 67.79 ± 3.45 ($n = 139$), and participants O30 had a higher average zinc score of 83.11 ± 4.96 ($n = 119$). The p-value calculated with a t-test analysis was statistically significant: $p = 0.0102$ (Fig. 1E). However, correlating age and zinc score with a Spearman's correlation analysis, we found no statistically significant relationship ($p = 0.08$) (Fig. 1F).

Pregnant participants frequently show inadequate zinc intake or are at risk of inadequate zinc intake

In the second part of the study, we focused our attention on the physiological zinc status of women during pregnancy. We analyzed the FFQ of $n = 237$ pregnancies of 115 participants. We found that the average zinc score was 178.586 ± 4.236, with fluctuation of the values between the highest zinc diet score detected (339.053) and the lowest score (32.652). The zinc score of women during pregnancy was significantly higher ($p < 0.0001$) than the mean zinc score obtained from the data analysis based on non-pregnant participants that was 74.86 ± 2.98 ($n = 258$) (Fig. 2A). However, often, the higher mean zinc score of pregnant participants is not pronounced enough to compensate for the higher zinc demand during pregnancy. Consequently, despite 124 pregnancies representing 52.32% of the pregnant study population falling into the "normal" zinc intake category, 113 pregnancies (47.68%) were in low zinc categories (91 pregnancies (38.39%)) were in the "at-risk of zinc deficiency" category and 22 pregnancies (9.28%) were in the "zinc-deficient" category) (Fig. 2B). Mostly, dietary habits of pregnant women are unchanged between the first and subsequent pregnancies, resulting in similar overall categorical distributions if comparing the second, third, or fourth pregnancy (Supplementary Fig. 1B). A total of 28.75% of participants with multiple pregnancies changed their categories. The majority of these (82.60%) transitioned from the "normal zinc" category to the "at-risk of zinc deficiency" category (4.37% changed from the "zinc-deficient" category

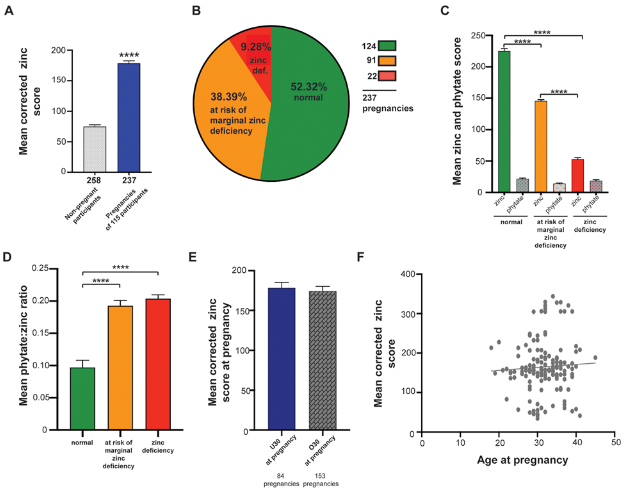

Fig. 2 Dietary zinc intake characteristics of pregnant participants. **A** Comparison between the average corrected zinc score calculated for all non-pregnant participants ($n = 258$) (74.86 ± 2.983) and the average corrected zinc score calculated for all the pregnancies ($n = 237$) of the 115 participants with pregnancy (178.6 ± 4.236). A significant difference between the two groups was found (t-test, $p < 0.0001$). **B** Distribution of pregnancies: % and number of pregnancies for each category are shown. For 124 pregnancies (52.32%), the participants were in the "normal" zinc intake category, in 91 pregnancies (38.39%), the participants were in the "at-risk of zinc deficiency" category, and 9.28% (22 pregnancies) were in the "zinc-deficient" category. **C** Comparison between average non-corrected zinc score and phytate zinc score of all the pregnancies reported by the participants. The mean zinc and phytate scores are given for each category. A one-way ANOVA revealed significant differences ($p < 0.0001$). Post hoc tests (Tukey's multiple comparison test) showed the following significant differences: average zinc score in the "normal zinc" category vs. average zinc score in the "at risk of marginal zinc deficiency" ($p < 0.0001$); average zinc score in the "normal zinc" category vs. average zinc score in the "zinc-deficient" category ($p < 0.0001$); average zinc score in the "at risk of marginal zinc deficiency" category vs. average zinc score in the "zinc-deficient" category ($p < 0.0001$); no significant differences were detected for phytate scores. **D** The mean phytate:zinc ratios derived from zinc and phytate scores of participants are significantly different (one-way ANOVA, $p < 0.0001$). Post hoc tests (Tukey's multiple comparison test) revealed the following significances: average phytate:zinc score in the "normal zinc" category vs. "at risk of marginal zinc deficiency" category ($p < 0.0001$); average phytate:zinc score in the "normal" category vs. "zinc-deficient" category ($p < 0.0001$). **E** The mean zinc score of pregnancies of participants under 30 years old (U30, 178.275 ± 6.926 ($n = 84$)) and pregnancies of participants at over 30 years of age (O30, 174.456 ± 5.76 ($n = 153$)) was significantly different (t-test, $p = 0.6822$). **F** Correlation analysis of the mean zinc scores and the age of the pregnant participants: A linear regression analysis shows no statistically significant correlation ($p = 0.5088$). **A**–**E** All data are shown as average ± SEM

to the “at-risk” category and 8.69% from the “at risk of zinc deficiency” category to the “zinc-deficient” category). Only 1 participant with multiple pregnancies changed more than one category across all pregnancies.

To find a possible explanation for the low zinc scores, we again studied the diet style of the participants. In detail, we found that during pregnancy, the participants in our study are more prone to consume mainly all the 18 food items in their diet, without showing any particular preference to a vegetarian-based style diet. No participant was identified as a vegetarian in the analyzed population during pregnancy.

As described in the first part of this study, we also examined how a fast food-based diet can affect physiological zinc intake. However, no participant had daily consumption of fast food. Interestingly, pregnant participants indicated less fast food consumption in general.

Therefore, we focused again on the possible influence of phytate on zinc absorption within the diet (Fig. 2C), comparing the mean uncorrected zinc scores with the mean phytate scores in each group. The mean zinc score in the “normal” zinc level category was 225.027 ± 4.064, and the associated phytate score was 21.715 ± 1.285 ($n=124$); the mean zinc score found in the category “at risk of zinc deficiency” was 145.712 ± 2.175, and the associated phytate score was 14.31 ± 0.835 ($n=91$). In the “zinc-deficient” category, the average zinc score was 52.987 ± 2.506, with a mean phytate score of 18.418 ± 1.836 ($n=22$). One-way ANOVA analysis showed significant differences among means ($p<0.0001$). In detail, post hoc tests found significant differences between the zinc score in the “normal” category and the “at-risk of zinc deficiency” category ($p<0.0001$), as well as the “zinc-deficient” category ($p<0.0001$). However, no significant differences were found between the groups with respect to their phytate scores (Fig. 2C). Therefore, as in non-pregnant women, a decrease in zinc intake from sources with low phytate content results in zinc scores that more significantly decrease in categories associated with low zinc intake. In contrast, phytate levels remain relatively stable, leading to an overall significant increase in phytate:zinc ratios. Significantly higher phytate:zinc ratios were detected comparing the value of the “normal” category to the “at risk of zinc deficiency” and “zinc deficiency” categories ($p<0.0001$) (Fig. 2D).

We also considered age as a factor that could impact zinc intake/dietary habits during pregnancy. To this aim, we calculated the mean age of the participants 31.83 ± 0.39 ($n=149$) when pregnant (considering all pregnancies of a woman) (Supplementary Fig. 1C). The average age increases with the number of pregnancies: for the first pregnancies of our population, the average age was 31.15 ± 0.61 ($n=73$), the mean age for the second pregnancies was 31.73 ± 0.68 ($n=45$), the average age for the third pregnancies was 32.65 ± 0.65 ($n=23$), and the mean age for the fourth pregnancies was 36.37 ± 1.23 ($n=8$). Only one participant reported a fifth pregnancy, but did not specify her age at the time of pregnancy.

In addition to this, we compared the mean zinc score of pregnant women U30 and pregnant participants O30 at the time of pregnancy (Fig. 2E). Pregnant participant U30 had an average zinc score of 178.275 ± 6.926 ($n=84$) that is not significantly different compared to pregnant participants O30 that had an average zinc score of 174.456 ± 5.76 ($n=153$) ($p=0.6822$). Accordingly, a correlation analysis does not reveal any significant correlation between age at pregnancy and zinc score using linear regression analysis ($p=0.5088$) (Fig. 2F).

Compared to non-pregnant women, pregnant women less frequently scored in the low-zinc categories. A major contributing factor to this was more frequent nutritional supplementation. We analyzed nutritional zinc supplementation in the population during the gestation period. While 85.21% of pregnant women in this study ($n=98$) took folic acid supplements, a number of participants (98 out of 115, representing 85.21% of the population analyzed) also took zinc supplements. A further 42.60% ($n=49$) took other mineral/vitamin supplements that, however, did not contain zinc (Fig. 3A). The most used preparations and their zinc content (as indicated by participants) were Zinc gluconate tablets (15 mg), Forever Daily™ Multivitamin (5 mg), Nourishing Pregnancy Multivitamin (15 mg) (Mayfair Nutrition), Pocket Multivit-10G tablet (15 mg) and Zinc sulfate tablets (15 mg), Vitabiotics Pregnacare® (with 15 mg Zn) and Vitabiotics Feroglobin capsules (Fe 17 mg, Zn 12 mg, and Cu 1 mg, plus folic acid and vitamin B12 and B6). Among non-zinc-containing supplements were, for example, iron supplements, such as Ferrograd® tablets (325 mg Fe).

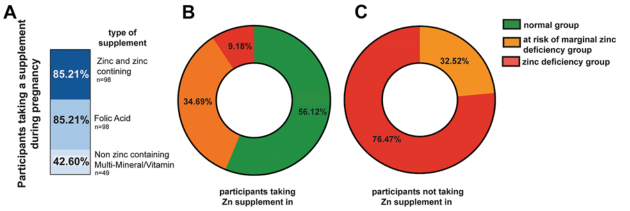

Fig. 3 Zinc supplementation during pregnancy. **A)** Overview of the supplements taken by pregnant participants. 85.21% ($n=98$) of participants took Folic Acid. 85.21% took a zinc or zinc containing supplement ($n=98$) and 42.6% ($n=49$) of the participants used a multi-mineral / Vitamin supplement that did not contain zinc. **B)** Distribution of the participants that took zinc supplements per risk category: 56.12% were in the “normal,” 34.69% were included in the “at marginal risk of zinc deficiency” category, and the 9.18% were in the “zinc-deficient” category. **C)** Distribution of the participants that did not take zinc supplements per risk category: 0% were in the “normal” ($n=0$), 23.52% ($n=4$) were included in the “at marginal risk of zinc deficiency” category, and the 76.47% were in the “zinc-deficient” category

The majority of participants taking zinc-containing supplements scored in the "normal" category (56.12%), 34.69% of participants that took zinc supplements classified in the "at-risk of zinc deficiency" category, and 9.18% in the "zinc-deficient" category indicated the consumption of zinc supplements (Fig. 3B). In contrast, the distribution of the participants not taking any zinc supplements was distributed in the following way: 0% participants not taking zinc supplement scored in the "normal" category, 23.52% in the "at-risk of zinc deficiency" category, and 76.47% in the "zinc-deficient" category (Fig. 3C).

Discussion and conclusion

Zinc is an essential trace element for humans. It is the 2nd most abundant trace metal in the body, taking part in several crucial biological processes. It is an essential part of the development and function of various organ systems such as the intestinal system and CNS. The levels of zinc required by the body vary depending on biological demand (i.e., physical activity), age, and the physiological state of an individual. In Ireland, the dietary reference value for zinc has been set to 10 mg/d. However, the levels of zinc required almost double during pregnancy. To maintain adequate zinc levels, it may be vital for pregnant women to increase their dietary zinc intake.

Here, we aimed to answer the questions whether women in industrialized nations such as Ireland are at risk of inadequate zinc intake and whether pregnant women are particularly vulnerable to developing zinc deficiency. We considered zinc bioavailability rather than zinc intake alone, which allows us to predict the body's zinc status reliably. The main findings indicate that 58.14% of women and 38.39% of pregnant women participating in the study are at risk of inadequate zinc intake, and 29.07% of women and 9.28% of pregnant women may be considered zinc-deficient due to dietary inadequacy, based on their intake of bioavailable zinc. Thus, about 88% of women and 48% of pregnant women have suboptimal zinc supply. These findings are consistent with the results from other studies that showed that zinc intake in Ireland and other countries around Europe is generally below the recommended daily amount (RDA) [27–32]. These studies were carried out in cohorts with a similar age range (18–62) and indicated that the mean zinc intake for women within the populations surveyed was slightly below the recommended amount. In particular, Ireland was reported with a mean intake of 8.5 mg/d, which is below the RDA of 10 mg/d [27].

We also investigated possible explanations and implications of the results. The zinc intake of participants was not correlated to their age. Although studies report a decreased zinc intake due to less intake of meat and meat products in aging, this has been mainly observed for individuals over 60 years of age, which were not included in our data [29, 33]. However, all participants whose FFQ indicated a vegetarian diet were in the "at-risk" and "zinc-deficient" categories. While a plant-based diet has health benefits, such as reducing heart disease, high blood pressure, stroke, and type 2 diabetes [34, 35], vegetarian diets may not provide enough bioavailable zinc due to the lack of zinc-rich foods, e.g., red meat, white meat and fish, and the presence of high phytate levels. Zinc absorption in vegetarian diets is between 15 and 26% instead of 33 and 35% in omnivorous diets [36, 37] since a diet high in phytates can inhibit zinc absorption in the small intestine [38]. However, the consumption of foods high in phytic acids was not solely responsible for participants to be in the "at-risk" or "zinc-deficient" category. Our data show that a combination of reduced intake of food items with high zinc content (predominantly meat) with no concurrent reduction in food items rich in phytates results in increased phytate:zinc ratios that ultimately lead to low zinc bioavailability. While no data is available for Ireland, data from the UK National Diet and Nutrition Survey indicates that women aged 19 to 64 years ate, on average, 47 g of red and processed meat a day in years 5 and 6 of the study, which was lower than the 58 g per day recorded for the first and second years [39], indicating a decrease in meat consumption of women in this age-range in recent years.

A limitation of our study is that the evaluation does not include other variables such as ethnicity, education level, and income that may further identify underlying factors of the low zinc status of participants. In addition, participants for this study were recruited through public advertisement and word of mouth. Thus, despite reaching an adequate sample size, we cannot draw final conclusions on whether this sample is a representation of Irish women in general, although a wide age and regional distribution was achieved. Finally, while for current intakes, the last 6 months needed to be recalled, pregnancies may have been several years in the past, and recalls may be less reliable.

Zinc supplementation is a handy tool to combat low zinc intake levels. Participants in the "normal" category were 3.1 times more likely to regularly take a zinc supplement compared to participants in the "at-risk" group and 19.2 times more likely than participants in the "zinc-deficient" group. During pregnancy, zinc was supplemented more frequently, although often not specifically but as part of a multi-mineral and vitamin supplement. The higher rate of participants taking a zinc or zinc-containing supplement (8.53% of non-pregnant vs. 85.21% of pregnant women) is a key factor for the comparably less pregnant participants in low-zinc categories in this study, reflected by the significantly higher average bioavailable zinc levels of pregnant compared non-pregnant women in this study. Still, the increased demand during pregnancy means that as much as 9.28% of pregnant women in Ireland may fall into the zinc-deficient category, and another 38.39% of pregnant women may be considered “at-risk” for zinc deficiency. These numbers likely are underestimating the population with low zinc intake since the full amount of zinc contained in a supplement was added to the zinc score in this study. However, multi-mineral supplements also contain high levels of copper, calcium, and iron that were shown to inhibit zinc uptake [40]. More importantly, 85% of pregnant women indicated taking a folic acid supplement. Folic acid supplementation is highly encouraged for pregnant women by health authorities in several countries. Folic acid is another inhibitor of zinc absorption [40, 41]. The effects of folic acid and the inhibitory effects of other divalent ions in mineral supplements have not been considered for the calculation of zinc bioavailability. Therefore, the bioavailability of zinc for pregnant women in this study may be an overestimation.

For both non-pregnant participants and pregnant participants, no age effect was seen. Like non-pregnant women, a combination of reduced intake of zinc-rich foods with relatively less reduction of intake in phytate-rich foods results in increased dietary phytate:zinc ratios lowering zinc bioavailability.

The International Zinc Nutrition Consultative Group (IZiNCG) considers zinc deficiency a public health concern when the prevalence of low serum zinc concentrations exceeds 20% [42]. Although our study only indirectly assessed serum zinc concentrations, we can interpret the serum equivalents through our zinc scores, illustrating that more than 20% of the female population may have low serum zinc concentrations. Low zinc levels may impact several health aspects of women in Ireland. According to a report published by the Organization for Economic Cooperation and Development (OECD, Health at a Glance), with 18.5%, Ireland has one of the highest rates of mental illness in Europe. Among these, high levels of depression have been reported [43]. Low zinc status has been linked to depression in humans [44], and the beneficial effects of zinc for reducing depressive symptoms were demonstrated [45]. In addition, it is known from the literature that maternal zinc deficiency is a risk factor for neurodevelopmental diseases such as autism spectrum disorders (ASDs) [46–48]. Although this study does not have the statistical power to make correlations between children with neurodevelopmental diseases and the zinc status of mothers during pregnancies, it should be noted that Ireland has a comparably high rate of autism [49].

Taken together, in this study that considered zinc bioavailability rather than intake, we detected a high prevalence of low-zinc status among women and pregnant women using a sample size with sufficient statistical power (the number of participants required for validation of a food frequency questionnaire is 110 [21] and comparable to many similar studies in the field). Although supplementation with folic acid during pregnancy is widely accepted due to the associated health benefits, and vitamin D supplements and fortified foods are considered a suitable public health approach to increasing vitamin D intakes in Ireland [50], little attention is paid to zinc supplementation so far. However, zinc status may be essential for the immune processes that, among others, mediate antiviral immunity [51] and mental health [52]. In the future, it will be necessary to ensure adequate zinc intake through the use of existing and new supplements and novel approaches such as exploring prebiotics and probiotics as an indirect option to influence trace metal uptake. In particular, more research is needed to understand the impacts of low zinc status and the benefits of normalizing zinc levels on a population level.

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Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Faculty for Science and Engineering ethics committee, University of Limerick, Ireland, ID: 2018_05_03_S&E.

Informed consent Informed consent was obtained from all individual participants included in the study. The confidentiality of the participants was ensured.

Conflict of interest The authors declare no competing interests.

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