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RESEARCH PAPER

Reduced interleukin-2 production and increased CREMα protein expression in vegetarians and vegans due to zinc deficiency

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Abstract

Nutrition is a key determinant of health and may be regarded as a form of preventive medicine, as an adequate supply of vitamins, fats, proteins, and trace elements is essential for proper immune function. In recent decades, vegetarian and vegan diets have become increasingly popular but may increase the risk of trace element deficiencies if not carefully planned. Zinc deficiency can impair immune responses and reduce resistance to infections. While previous research has mainly focused on animal models or elderly populations, little is known about younger adults. Thus, we investigated the impact of zinc intake through different diets (omnivorous, vegetarian, and vegan) on immune function in healthy young volunteers aged 19–33 years. We identified zinc deficiency to be prominent in young, healthy individuals adhering to plant-based diets (vegetarian and vegan) compared with omnivorous individuals of the same age. This was associated with impaired immune function, as indicated by reduced IL-2 cytokine production, which was linked to zinc deficiency-dependent overexpression of CREMα. Furthermore, we validated the applicability of our recently established food frequency questionnaire (FFQ) in this cohort. Individuals adhering to plant-based diets are at considerable risk of developing zinc deficiency. Zinc deficiency, regardless of diet, provokes immune system dysfunction by impairing IL-2 production, a consequence of zinc deficiency-dependent overexpression of CREMα. These results underscore the critical importance of ensuring adequate zinc intake among young individuals following plant-based diets to prevent severe immune dysfunction.
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Keywords: Trace elements; Zinc deficiency; Plant-based diet; Interleukin-2; CREMα-expression.

1. Introduction

Nutrition is a key determinant of health and of a well-functioning immune system. In recent decades, dietary habits have changed for multiple reasons, including concerns about sustainability, animal rights and welfare, ethical considerations, and carbon dioxide emissions [1,2]. In addition, general health considerations and prevailing food trends frequently contribute to such changes.

Over the past decades, two dietary patterns in particular have gained increasing prominence: (1) vegan diets, which are entirely plant-based, and (2) vegetarian diets, which exclude fish and meat as well as fish- and meat-derived products. The prevalence of these dietary approaches has grown markedly [3,4]. In contemporary societies, the reduction or complete avoidance of meat and other animal-derived products constitutes a continuously expanding trend, most notably within industrialized nations. Globally, about one billion people refer themselves as vegetarians and about 500 million people adhere to a vegan diet [4,5].

During the last few decades, the number of individuals adhering to vegetarian and vegan diets has increased [6–9].

Vegetarian and vegan lifestyles are particularly prevalent among younger generations [10]. There is scientific evidence that reducing meat consumption or abstaining from meat may improve gut health and lower the risk of certain kinds of cancer [11,12]. Moreover, a vegan diet may reduce the risk of chronic diseases, such as type 2 diabetes, cardiovascular disease, arteriosclerosis, and hypertension, and may prevent obesity [2,13–15].

Although vegetarian and vegan diets offer a myriad of essential nutrients [2,16], special attention must be paid to certain key components that may be more difficult to obtain solely from plant-based sources. To prevent deficiencies, particular attention must be paid to nutrients such as iron, zinc, vitamin B12, vitamin D, and omega-3 fatty acids [11].

Zinc bioavailability is classified by the World Health Organization according to the molar ratio of phytic acid to zinc, to provide a framework for determining appropriate zinc intake levels across different population groups [17–19].

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Zinc intake—that is, the total amount of zinc consumed through food—zinc uptake—that is, the proportion of zinc taken up by the cells—and zinc bioavailability—that is, the proportion of zinc available at the site of action—heavily depend on the composition of the diet. The absorption and bioavailability of zinc from plant-based food is markedly lower than from animal-derived products, which typically account for approximately half of total zinc intake. Major plant sources of zinc include whole-meal bread, peas, nuts, carrots, whole grains, wheat germ, soybeans, cabbage, radish, watercress, and legumes [3,11]. The principal inhibitor of intestinal zinc absorption is phytic acid (phytate), present in unrefined cereals, pulses, oilseeds, and nuts. Zinc bioavailability in plant-based food therefore depends on the phytate level of the diet. In addition, other dietary ingredients can also lower intestinal zinc absorption, thus reducing its bioavailability, such as polyphenols, fiber, oxalate, phosphate, tannin, and lignin, which are present in, for example, berries, herbs, nuts, flaxseeds, vegetables, coffee, and tea [20,21].

Vegan dietary patterns are generally classified as having moderate zinc bioavailability, as they typically do not rely exclusively on unrefined, unfermented, or ungerminated cereal grains, nor on high-extraction-rate flours [19]. Supplementation or the consumption of fortified breakfast cereals and other enriched foods may be essential to ensure adequate zinc intake among individuals following a plant-based diet [22].

Zinc deficiency is recognized as the fifth most significant health risk factor in developing countries and the eleventh globally [18,21]. In Western nations, the elderly population has historically been the most affected [23,24]; however, due to shifts in dietary patterns toward plant-based diets, the prevalence of zinc deficiency may be higher than previously assumed.

Studies have shown that individuals adhering to a vegan diet exhibit the lowest zinc intake and are more affected by zinc deficiency [2,17,20].

Regarding zinc deficiency, the occurrence of metabolic and chronic diseases is reported, including diabetes mellitus, allergic conditions, neurodegenerative diseases, and cancer [12,25–27]. Furthermore, zinc deficiency has been shown to heighten susceptibility to infectious diseases [28], as it disrupts T cell activation and T cell-dependent cytokine production. Studies have demonstrated that pro-inflammatory cytokines, such as interleukin (IL)-6 and interferon (IFN)-γ, are elevated, while immunomodulatory cytokines, such as IL-2, and specific cell populations are reduced or dysregulated [28–33]. The production of the immunomodulatory cytokine IL-2 is known to decrease markedly during zinc deficiency, particularly in elderly individuals, and is crucial for cell proliferation and function [23]. The molecular mechanisms underlying this process are highly complex and not fully understood; however, the expression of cAMP-responsive element modulator alpha (CREMα) appears to be a key modulator in this context [23,34,35]. Recently, Baarz et al. demonstrated that inhibition of IL-2 is associated with an altered signaling pathway involving the transcription factor CREMα in elderly hospitalized patients suffering from zinc deficiency. Short-term zinc supplementation led to increased IL-2 production, indicating a restoration of immune function. Comparable findings were reported in *in vitro* studies and animal experiments following zinc supplementation [23,34]. It is already known that vegans and vegetarians show a reduced IFN-α production due to a lack of IRF3, and that the expression of IRF correlates with the serum zinc status [36]. However, zinc supplementation in zinc-deficient vegetarians and vegans enhances NK cell cytotoxicity [37].

However, little is known about the IL-2 expression in zinc-deficient young individuals. Therefore, in this study, we investigated the impact of zinc intake through different diets (omnivorous, vegetarian, and vegan) on immune function in healthy young volunteers aged 19 to 33 years.

2. Materials and methods

2.1. Subject recruitment and study design

This study was conducted from April to September 2022. The study design was reviewed and accepted by the institutional ethics committee of the Medical Faculty of RWTH Aachen University (EK 23/234). The research complies with the principles of the Declaration of Helsinki. All participants provided written informed consent prior to enrollment and sample collection. Eligible participants were healthy young adults aged 18–35 years and were recruited through a public call for participation issued by the local medical faculty. Exclusion criteria comprised acute or severe infection requiring antimicrobial therapy, autoimmune diseases requiring immunosuppressive treatment, and any diagnostically confirmed progressive malignancy.

In total, 95 healthy volunteers aged 19–33 years were included in the study. Participants were stratified according to dietary pattern into omnivores ($n = 28$), vegetarians ($n = 33$), and vegans ($n = 34$). The dietary pattern was based on self-report with participants following their diet for at least 3 months. The sexes were equally distributed among the formed groups. Zinc deficiency was defined as a serum zinc concentration <70 μg/dL and/or an adjusted dietary zinc score <113 points.

2.2. Blood collection and isolation of peripheral blood mononuclear cells

After overnight fasting, 25 mL of blood was collected in heparinized 50 mL tubes (Sarstedt, Nürnbrecht, Germany) by venipuncture. Peripheral blood mononuclear cell (PBMC) isolation was performed by using Biocoll Separating Solution 1.077 g/mL (Biochrom, Berlin, Germany) as described elsewhere (Maywald et al.). Finally, cells were adjusted to a concentration of 2×10^6 cells/mL in Roswell Park Memorial Institute (RPMI) cell culture medium, containing 10% fetal calf serum (FCS, Capricorn, Ebsdorfergrund, Germany), 2 mM L-glutamine, 100 U/mL potassium penicillin, and 100 U/mL streptomycin sulfate (all Sigma-Aldrich, Steinheim, Germany). All incubation steps were carried out in a humidified 5% CO_2 atmosphere at 37°C.

2.3. Dietary zinc uptake assessment via nutrition questionnaire

On the same day as the blood sample collection, the dietary zinc uptake was assessed by using an established 18-item food frequency questionnaire (FFQ) (https://www.zink-app.de) specialized on zinc [38]. According to the questionnaire's instructions, a phytate-corrected zinc diet score was calculated. Because phytates are zinc chelators that decrease intestinal zinc absorption despite adequate amounts of zinc contained in the diet, we decided to calculate this adjusted zinc diet score to estimate net zinc uptake. Food frequency, serving types, and quantity were inquired. Additionally, the intake of supplementary zinc products was evaluated. According to the information provided in the FFQ, an adjusted zinc diet score of less than 113 points was considered zinc deficient [38].

2.4. Serum zinc measurement

Serum samples were collected in 2.7 mL serum monovettes suitable for zinc measurement (Sarstedt, Nürnbrecht, Germany) and were allowed to clot for at least 30 min at room temperature.

Subsequently, samples were centrifuged for 10 min at 1,841 × *g*, serum was collected and stored at −20°C. The analysis was performed using an Agilent 8,900 inductively coupled plasma triple quadrupole mass spectrometer system (Agilent, Darmstadt, Germany). The samples were diluted 1:50 with Millipore water, acidified with 20 µL of 65% nitric acid, and mixed with 300 µL of a 10% Triton X solution. A 100 µL volume of rhodium (1 mg/L) was used as an internal standard. The analysis was performed in the single quadrupole Helium mode. The limit of detection was 0.01 g/L. The limit of quantification was 0.03 g/L. The calibration curve ranged from 20 to 7,000 ng/L using dotted blood samples and blank solutions [39]. In accordance with comparable studies, serum zinc concentrations below 70 µg/dL were considered zinc deficient [40,41].

2.5. Cytokine quantification

After PBMC isolation, 2 × 10^6 cells/mL were stimulated with 2.5 µg/mL PHA-L (Pan-Biotech, Aidenbach, Germany) for 48 h at 37°C. For IL-2 determination, supernatants were harvested and stored at −20°C. IL-2 and IFN-γ protein concentrations were determined by OptEIA ELISA (BD, Heidelberg, Germany) according to the manufacturer's instructions with a detection limit of 7.8 pg/mL. The intra and interassay coefficients of variability were calculated to be 4.5% and 8.8%, respectively. Each sample was investigated in duplicate. The absorption was measured using a Spark well plate reader (Tecan, Crailsheim, Germany).

2.6. Western blotting

PBMCs (2 × 10^6 PBMC per sample) were prepared for protein detection and quantification by Western blot analysis as previously described [34]. For weight determination, 5 µL colored prestained standard (New England BioLabs, Frankfurt a.M., Germany) was applied to every gel respectively. The primary antibody CREM C-2 (Santa Cruz Biotechnology, Heidelberg, Germany) and the housekeeping gene β-actin (Cell Signaling Technology, Frankfurt a.M., Germany) were used. Antibodies were diluted 1:1000 in tris-buffered saline (TBS: 20 mM Tris–HCl, 136 mM NaCl (Applichem, Darmstadt, Germany)), supplemented with 0.1% Tween 20 (Sigma-Aldrich) containing 5% bovine serum albumin (BSA, AppliChem). Incubation of the primary antibody was performed at 4°C overnight. The second day, membranes were washed three times with TBS-T before incubation in the secondary antibody. Each secondary antibody, an HRP-coupled antimouse IgG for CREM C-2 and antirabbit IgG for β-actin (all from Cell Signaling Technology, Frankfurt a.M., Germany), was diluted 1:2000 in TBS-T containing 5% powdered milk, and membranes were incubated for 3 h at room temperature. LumiGlo reagent (Cell Signaling Technology, Frankfurt a. M., Germany) was used for visualization of the protein bands. Luminescence was analyzed by using an LAS 3000 (Fujifilm Lifescience, Düsseldorf, Germany) and quantified with ImageJ (NIH, USA). To provide comparability between the different blots, the relative protein expression of each sample was normalized to a corresponding loading control standard administered at every gel.

2.7. Quantitative real-time polymerase chain reaction

Following PBMC isolation, 2 × 10^6 cells were centrifuged (300 × *g*, 5 min). The cell pellet was lysed in 1 mL EXTRAzol Reagent (Blirt, Danzing, Polen) and stored at −80°C. mRNA was isolated according to the manufacturer's instructions and measured with a Nanodrop 2000 (Fisher Scientific, Schwerte, Germany). Transcription into cDNA was performed with the qScript cDNA Synthesis Kit (Quantabio, Darmstadt, Germany) following the manufacturerś instructions.

Quantitative real-time PCR (qRT-PCR) was performed using fluorescent SYBR green on a QuantStudio3 Real-Time PCR System (Applied Biosystems, Darmstadt, Germany). The following primers were used: CREMα (forward primer: TCG CGA ACT TGG GAC GA, reverse primer: GCT GGG GTG TTG AAG GT), and porphobilinogen deaminase (PBGD) (forward primer: ACG ATC CCG AGA CTC TGC TTC, reverse primer: GCA CGG CTA CTG GCA CAC T) [34]. Reaction conditions were initial 95°C for 10 min, followed by 40 cycles of 95°C for 15 s and 60°C for 60 s. Each sample was analyzed in duplicate. Aqua ad injectabilia (Braun, Melsungen, Germany) in the equivalent volume to DNA functioned as a no-template control. For quality control, every PCR was completed by a melt curve stage (95°C 15 s, 60°C 1 min, 95°C 15 s). With the use of the $\Delta\Delta C_T$ method, CREMα expression was first normalized to the expression of the housekeeping gene PBGD and then normalized to a standard sample administered at every PCR plate.

2.8. Statistics

Statistical analysis was performed using GraphPad Prism (version 9.1). Values were considered significant at $P < .05$. For column statistics, one-way ANOVA followed by Tukey's *post hoc* test and unpaired Student's *t*-test were performed. Correlation was determined by the Spearman correlation coefficient. Mean values were specified + SEM. In the figure legends, results are indicated with the applied statistical method.

3. Results

3.1. Zinc levels decrease in individuals adhering to a plant-based diet

Between April and September 2022, a total of 95 young healthy volunteers (aged 19–33 years) were included in this study. The average zinc uptake of omnivores, vegetarians, and vegans was determined using an FFQ for zinc, implemented as a smartphone application (Zinc-APP), and an adjusted zinc diet score (adj. zinc diet score; phytate-corrected [38]) was calculated to indicate the individual's zinc status. Additionally, we measured the individual's serum zinc by using Inductively Coupled Plasma-Mass Spectrometry (ICP-MS). Zinc deficiency was defined as a zinc concentration below 113 points (FFQ) or below 70 µg/dL (ICP-MS).

When comparing the adjusted zinc diet scores of omnivores, vegetarians, and vegans, the zinc intake of vegetarians and vegans was significantly lower compared to omnivores, and even lower in vegans compared to vegetarians (Fig. 1A). Accordingly, serum zinc levels were also significantly decreased in vegetarians and vegans (Fig. 1D). However, no difference was found between those two groups. Similar effects were uncovered when gender-separated evaluation was done for adjusted zinc diet score (Fig. 1B and C) and serum zinc (Fig. 1E and F). Moreover, zinc deficiency was statistically significantly more prevalent in the vegetarian and vegan cohorts than in the omnivorous cohort (Fig. 1G). Overall, serum zinc and the adjusted zinc diet score correlated significantly (Fig. 1H). These results indicate that subjects adhering to plant-based diets have a significantly lowered daily zinc in- and uptake, which might result in immune function dysregulation.

Several publications indicate that the copper-zinc ratio plays an important role in proper immune function; an imbalance may lead to immune dysregulation and, ultimately, to an increased risk of cancer development, metabolic disorders, and inflammatory diseases [42–46].

In line with that we uncovered an elevated copper-zinc ratio in vegetarians and vegans compared to omnivores (Fig. 2A and B) pointing to a dysbalanced copper-zinc ratio due to plant-based diets. Interestingly, there was a significantly higher copper-zinc ratio

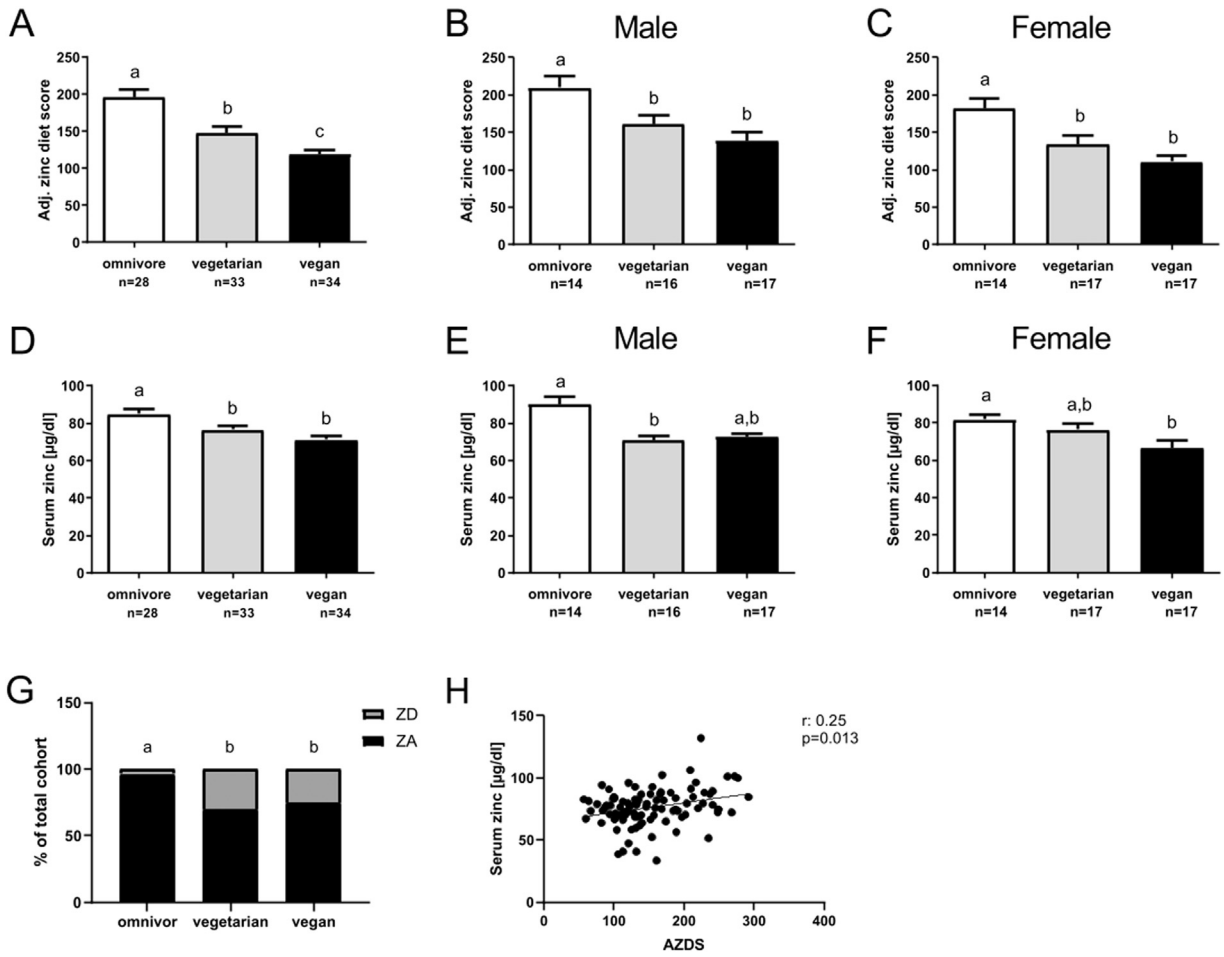


Fig. 1. Zinc levels decrease in individuals adhering to a plant–based diet. Adjusted zinc diet score and serum zinc levels of omnivores, vegetarians, and vegans. (A–C) The adjusted zinc diet score was determined by Zinc-APP via a food frequency questionnaire (FFQ) for a total of 95 young volunteers (omnivorous n = 28, vegetarians n = 33, vegans n = 34), with separate analyses conducted by gender in male (B) and female (C) cohorts. (D–F) Serum zinc levels in the same group (omnivore n = 28, vegetarian n = 33, vegan n = 34) were analyzed by using ICP-MS, with separate analyses conducted by sex in male (D) and female (F) cohorts. (G) The percentage of zinc-deficient and zinc-adequate volunteers within each group (omnivorous, vegetarians, vegans) was analyzed. (H) Correlation between adjusted zinc diet score and serum zinc level. All data are considered as unpaired variables and presented as the mean + SEM. Statistical significance was determined using one-way ANOVA followed by Tukey's *post hoc* test. Correlations were determined by the Spearman rank correlation coefficient (r, $P < .05$). Fisher's exact test was used to investigate the statistical significance of the percentage of zinc-deficient and zinc-adequate volunteers within each group. Statistical significance ($P < .05$) is indicated by different letters (a–c).

in females than in males in omnivores and vegetarians, whereas these gender differences were not significant in vegans (Fig. 2C–E).

3.2. Zinc deficiency diminished IL-2 cytokine expression in vegetarians and vegans

Zinc deficiency is known to affect immune function, resulting in an altered cytokine expression profile, which in turn increases susceptibility to infections or the development of autoimmune conditions [2,17,25]. This is primarily due to changes in T cell differentiation, which disrupt the T helper (Th) cell Th1/Th2 balance [30,47], as well as modifications in cytokine production, such as an increased release of pro-inflammatory cytokines [31]. Additionally, zinc deficiency can lead to altered IL-2 signaling through active gene silencing, a process driven by enhanced CREMα expression in T cells [34]. This mechanism is well described for cultivated T cells *in vitro* or elderly individuals, especially nursing home or hospitalized elderly, suffering of zinc deficiency [23,34,40,48].

In this study, we observed a similar effect in young healthy volunteers adhering to plant-based diets (vegetarian and vegan) compared with omnivorous controls. IL-2 cytokine expression of isolated primary human PBMCs was significantly reduced in vegetarians and vegans following cellular activation by mitogenic stimulation (Fig. 3A). This effect was more pronounced in male than in female participants, the latter showing the same trend but not statistically significant (Fig. 3B and C). Within the diet groups, gender had no significant effect on IL-2 production (Fig. 3D–F). Moreover, we observed that zinc deficiency itself without regard to the specific diet, reduces IL-2 production (Fig. 3G). In addition, we investigated IFN-γ expression after stimulation via PHA. There were no significant changes observed between zinc-deficient and zinc-adequate participants (Fig. 3H).

3.3. Zinc levels determine CREMα mRNA expression in vegetarians and vegans

To investigate the impact of differences in zinc status on the expression of the IL-2 gene-regulating transcription factor CREMα, we compared CREMα mRNA expression levels in isolated PBMCs from omnivores, vegetarians, and vegans.

Consistent with previous findings, CREMα mRNA expression was significantly elevated in volunteers adhering to plant-based diets (vegetarians and vegans) than in omnivores. This effect was also observed when the analysis was performed

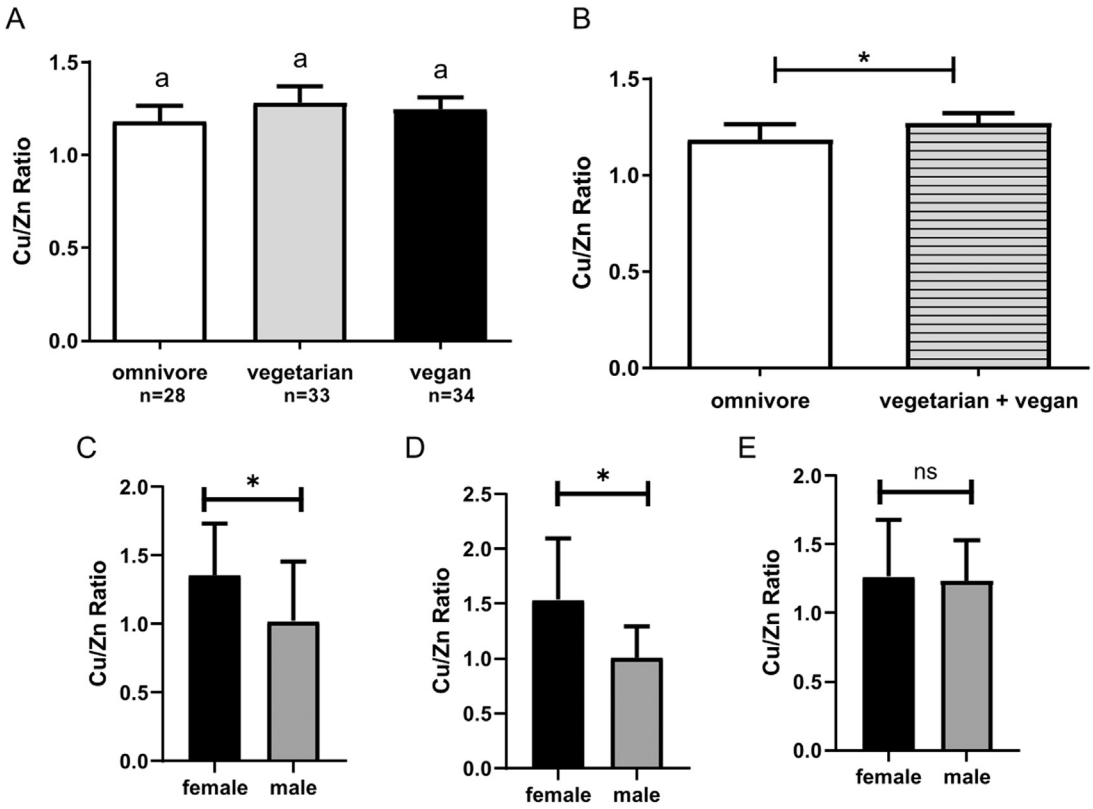


Fig. 2. Copper-zinc ratio of omnivores, vegetarians, and vegans. (A) Serum zinc levels and copper-zinc levels for a total of 95 young volunteers (omnivorous n = 28, vegetarian n = 33, vegan n = 34) were analyzed by using ICP-MS, and the copper-zinc ratio (Cu/Zn) was calculated. (B) Pooled analysis was performed for vegetarians and vegans (n = 67) compared to omnivores. (C–E) Copper-zinc ratio by gender of omnivorous (C), vegetarians (D), and vegans (E) was analyzed. All data are considered as unpaired variables and presented as the mean + SEM. Statistical significance was determined using one-way ANOVA followed by Tukey's *post hoc* test or unpaired Student's *t*-test. Statistical significance ($P < .05$) is indicated by different letters (one-way ANOVA followed by Tukey's *post hoc*), or marked with * (unpaired *t*-test). The Mann–Whitney test was performed to investigate the gender differences between male and female volunteers in each diet group.

gender-separated in both male (Fig. 4B) and female cohorts (Fig. 4C). While the effect was significant in the female cohort, the male cohort showed a clear, but not significant trend. Elevated CREMα expression ultimately resulted in reduced IL-2 cytokine production, as shown in Figure 3A–C, and could be associated with altered immune function in individuals adhering to plant-based diets or to zinc deficiency. Within the diet groups, gender had no significant effect on CREMα mRNA expression (Fig. 4D–F).

3.4. Zinc levels determine CREMα protein expression in vegetarians and vegans

In line with the results shown in Figure 4, CREMα protein expression was significantly elevated in vegetarians and vegans compared to individuals adhering to an omnivorous diet (Fig. 5B). A similar pattern was observed when the analysis was performed gender-separated in both male (Fig. 5C) and female cohorts (Fig. 5D). However, in the male cohort, only vegetarians exhibited a statistically significant increase in CREMα protein expression, whereas in the female cohort, a significant increase was observed only in vegans. These findings may be attributable to the smaller number of study participants in the sex-stratified analyses, as the overall trend was consistent with that observed in the combined analysis shown in Figure 5B. Additionally, CREMα protein expression was significantly higher in zinc-deficient participants than in zinc-adequate ones regardless of their diet (Fig. 5E).

3.5. CREMα protein expression and IL-2 cytokine expression correlate with zinc status in healthy young volunteers adhering to different diets

To test the hypothesis that CREMα protein expression is strongly regulated by zinc status, we plotted CREMα protein expression for each participant against the corresponding dietary zinc score assessed by the FFQ and against serum zinc (Fig. 6A and C). In addition, the association between zinc status and IL-2 cytokine expression was evaluated for each participant (Fig. 6B and D). Consistent with earlier findings, in this study, correlation analyses revealed a statistically significant inverse association between CREMα protein expression and zinc status (Fig. 6A and C), as well as a statistically significant positive association between zinc status and IL-2 cytokine expression (Fig. 6B), but not between the adjusted zinc score and IL-2 cytokine expression (Fig. 6D). CREMα protein expression and IL-2 cytokine expression did not correlate significantly (Fig. 6E). This points to a zinc-dependent CREMα-mediated IL-2 gene silencing in young people adhering to plant-based diets, having a lower zinc intake and resorption due to chelating effects by phytates and other plant components.

4. Discussion

For decades, it has been known that zinc deficiency is associated with reduced IL-2 cytokine production, as well as altered T cell maturation, differentiation, and function [26,28,30–32,48]. To date, this phenomenon has been predominantly investigated

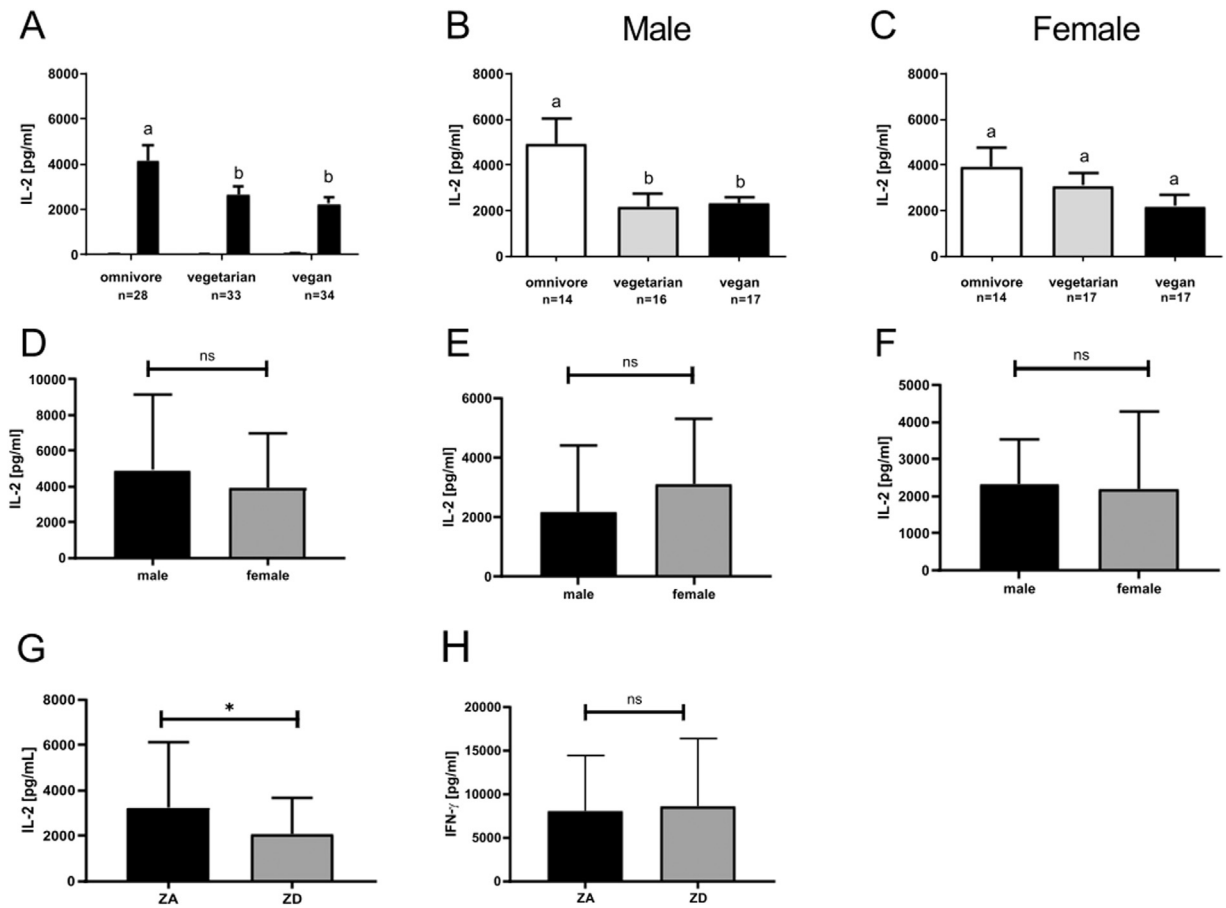


Fig. 3. Zinc deficiency diminished IL–2 cytokine expression in vegetarians and vegans. IL-2 cytokine expression in omnivores, vegetarians, and vegans. (A) IL-2 cytokine expression was measured in isolated PBMC of n = 95 healthy volunteers following different diets (omnivorous n = 28, vegetarian n = 33, vegan n = 34), without (white bars) or with mitogen stimulation (black bars) for 48 h (PHA 2.5 μg/mL). Separate analyses conducted by sex in male (B) and female (C) cohorts were performed. Additionally, gender differences in omnivorous (D), vegetarians (E), and vegans (F) were analyzed. Moreover, IL-2 expression and interferon gamma production after stimulation were analyzed regarding the zinc status independently of the diet (G and H). All data are considered as unpaired variables and presented as the mean + SEM. Statistical significance was determined using one-way ANOVA followed by Tukey's *post hoc* test. To investigate gender differences in diet groups and zinc status, the Mann–Whitney test was used. Statistical significance ($P < .05$) is indicated by different letters (a, b).

in *in vitro* studies and in elderly populations [23,24,34,35,40,47–49]. Since more recent studies have demonstrated that individuals adhering to plant-based diets, particularly vegan diets, exhibit the lowest zinc intake and seem to be more likely to suffer from zinc deficiency compared with those following other dietary patterns [2,17,50], we investigated zinc status and associated immune function in young, healthy volunteers adhering to plant-based diets compared with omnivorous individuals of the same age. We found a zinc deficiency prevalence of 56.7% among subjects adhering to plant-based diets, with the highest prevalence among vegans (64.7%) and lower prevalence among vegetarians (48.5%). In omnivores, only two participants were found to be zinc deficient (7.1%). In line with that, former studies uncovered a prevalence of about 68% among elderly hospitalized subjects, which exceeded the values described in other studies (25–35%) [41,51,52]. Comparable prevalences are described for vegetarians (33.3%) and vegans (42.5%) by Klein et al. [53].

To date, the most commonly used method for assessing zinc status is the measurement of zinc levels in blood serum [54]. However, several studies have demonstrated that serum zinc is an unsuitable biomarker for the reliable detection of mild zinc deficiency, as serum zinc concentrations provide only a transient snapshot of an individual's zinc status because of fluctuations over the course of the day, by as much as 20% [55]. In addition, the biologically relevant zinc pool—the rapidly exchangeable zinc pool in the blood—accounts for only approximately 0.1% of total body zinc, as the majority is located in muscle and bone [28,56]. Consequently, zinc deficiency in humans may frequently remain undetected when assessed solely by serum measurements. Moreover, a substantial interlaboratory variability in zinc measurements exists [57,58].

To evaluate the phytate-corrected average zinc uptake, we developed a food frequency questionnaire in former studies (FFQ) [38,59]. The use of serum zinc and the FFQ in combination allows a better estimation of the actual zinc status.

In this study, we used both measurements, serum zinc and FFQ, to determine the individual's zinc status. We uncovered a significantly reduced serum zinc concentration in study participants adhering to plant-based diets compared to omnivores (Fig. 1A–C), which is in line with former investigations [36,60–62]. The adjusted zinc diet score of vegetarians and vegans, measured by FFQ, was significantly lower compared to omnivores, and even lower in vegans compared to vegetarians (Fig. 1D and E). Studies implicated a vegan diet as having the lowest zinc intake compared to other dietary patterns [2,17], leading to zinc deficiency more often [50]. This is due to high amounts of zinc chelating components (like phytates, polyphenols, fiber, oxalate, phosphates, tannin, and lignin) mainly present in unrefined cereals, pulses, oilseeds,

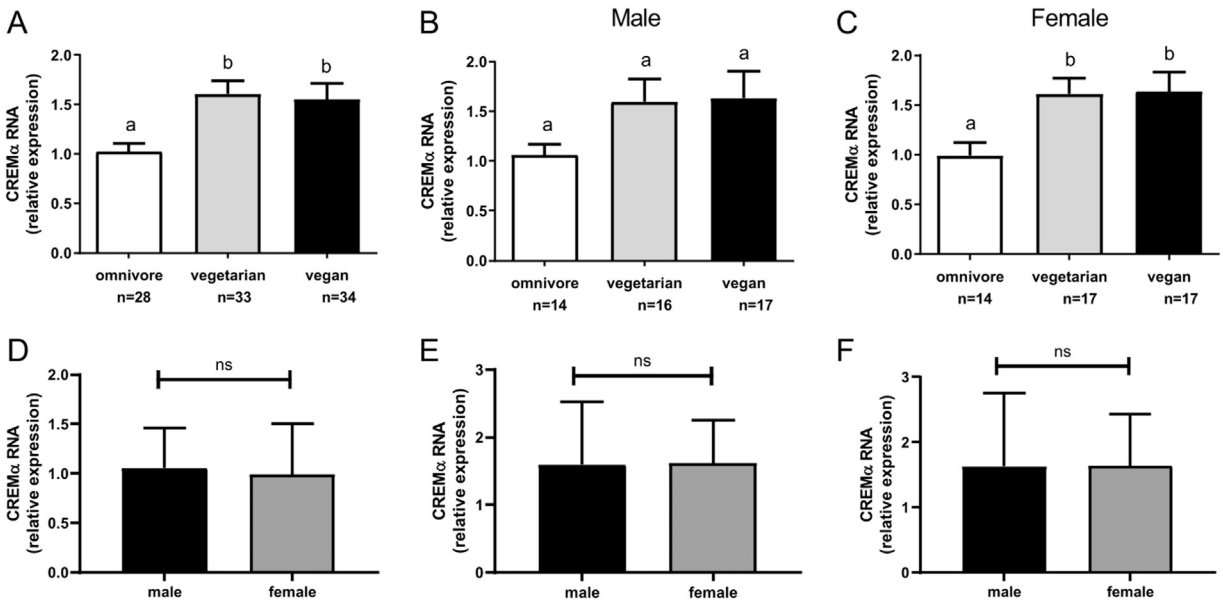


Fig. 4. Zinc status influences expression of CREMα mRNA in omnivores, vegetarians, and vegans. (A) mRNA expression of CREMα was in PBMC of n = 95 healthy volunteers adhering to different diets (omnivorous n = 28, vegetarian n = 33, vegan n = 34). Separate analyses conducted by sex in male (B) and female (C) cohorts were performed. Additionally, gender differences in omnivorous (D), vegetarians (E), and vegans (F) were analyzed. CREMα mRNA expression analysis by RT-PCR was normalized to the housekeeping gene PBGD. All data are considered as unpaired variables and presented as the mean + SEM. Statistical significance was determined using one-way ANOVA followed by Tukey's *post hoc* test. To investigate gender differences in diet groups, the Mann–Whitney test was used. Statistical significance ($P < .05$) is indicated by different letters (a, b).

berries, herbs, nuts, flaxseeds, and vegetables [11,20,21], making zinc supplementation or consumption of enriched foods or fortified breakfast cereals essential for vegetarians and vegans. Zinc deficiency can have far-reaching consequences for immune function, ultimately predisposing individuals to a range of metabolic, chronic, and infectious diseases [12,25–28]. Overall, low levels of serum zinc and low score in the adjusted zinc diet score correlated with each other (Fig. 1H) underlining their shared validity to estimate zinc deficiency.

Our results indicate an elevated copper-zinc ratio in vegetarians and vegans compared to omnivores (Fig. 2) pointing to a dysbalanced copper-zinc ratio due to plant-based diets. Several publications describe the copper-zinc ratio as well-established biomarkers for inflammatory and infectious diseases, metabolic diseases, and cancer development [42–46], since changes in copper-zinc ratios are often more reliable risk predictors for diseases than single trace element concentrations [58]. In contrast, other studies did not discover a significant difference in copper-zinc ratios due to different diets [53,61,63], which might be due to different study setups. Moreover, it is well established that copper and zinc are tightly connected in terms of absorption and that the copper bioavailability might also be reduced by fiber comparable to zinc. Besides, the tight homeostatic regulation of trace elements, nondietary factors such as infections, inflammations, hormonal status, aging, and the use of medications influence the concentrations of trace elements as well [58]. Interestingly, we found that female participants in the omnivorous and vegetarian cohorts had significantly higher copper-zinc ratios than their male counterparts (Fig. 2C and D). This might be due to a relatively small cohort size but further investigations on the impact of a disturbed copper-zinc ratio in females and males could elaborate whether these differences go along with other gender-specific immunological reactions regarding infection and inflammation.

On the molecular level, we showed for the first time a significantly decreased IL-2 cytokine production due to zinc deficiency triggered by plant-based diets in otherwise healthy young adults (Fig. 3). This effect was more pronounced in male than in female cohorts (compare Fig. 3B and C), which may be attributable to hormone-related variation in women, such as the effects of the sex steroid estrogen or menstrual cycle-dependent fluctuations in luteinizing hormone-releasing hormone, both of which influence IL-2 expression and IL-2 receptor activity [64–66]. Moreover, the standard deviation was higher in the female cohort, which might explain the clear trend but lack of significance. Gender differences within each diet group had no significant influence on IL-2 cytokine production (Fig. 3D–F). On the other hand, zinc deficiency, regardless of the diet, significantly reduced IL-2 cytokine production, which highlights the significance of zinc in this context (Fig. 3G). Former studies indicate a lower IL-2 cytokine production due to zinc deficiency, particularly seen in *in vitro* examinations [34,35,49] and in the context of immunosenescence [23]. Moreover, an altered T cell differentiation, maturation, and function, seen *e.g.*, by Th1/Th2 disbalances has been described, as well as an impairment of essential transcription factors and hormones like thymulin [28,29,47,67,68] influencing immune function. No significant differences between zinc-deficient and zinc-adequate participants were observed in the production of IFN-γ following stimulation through PHA. This might be due to our relatively small cohort size, but further investigation is needed to illuminate whether this result is consistent with other findings. Furthermore, it would be interesting to investigate whether IL-2 production and cell proliferation correlate with each other in the context of zinc deficiency.

The expression of cAMP-responsive element modulator alpha (CREMα) appears to be a key modulator in IL-2 gene regulation and cytokine production [34,49]. Recently, Baarz et al. revealed that inhibition of IL-2 cytokine production is linked to an altered signaling pathway involving the transcription factor CREMα in elderly hospitalized patients suffering from zinc deficiency [23]. In line with that, similar results were uncovered for proton-pump-inhibitor-treated PBMCs *ex vivo* and in human T cell lines *in*

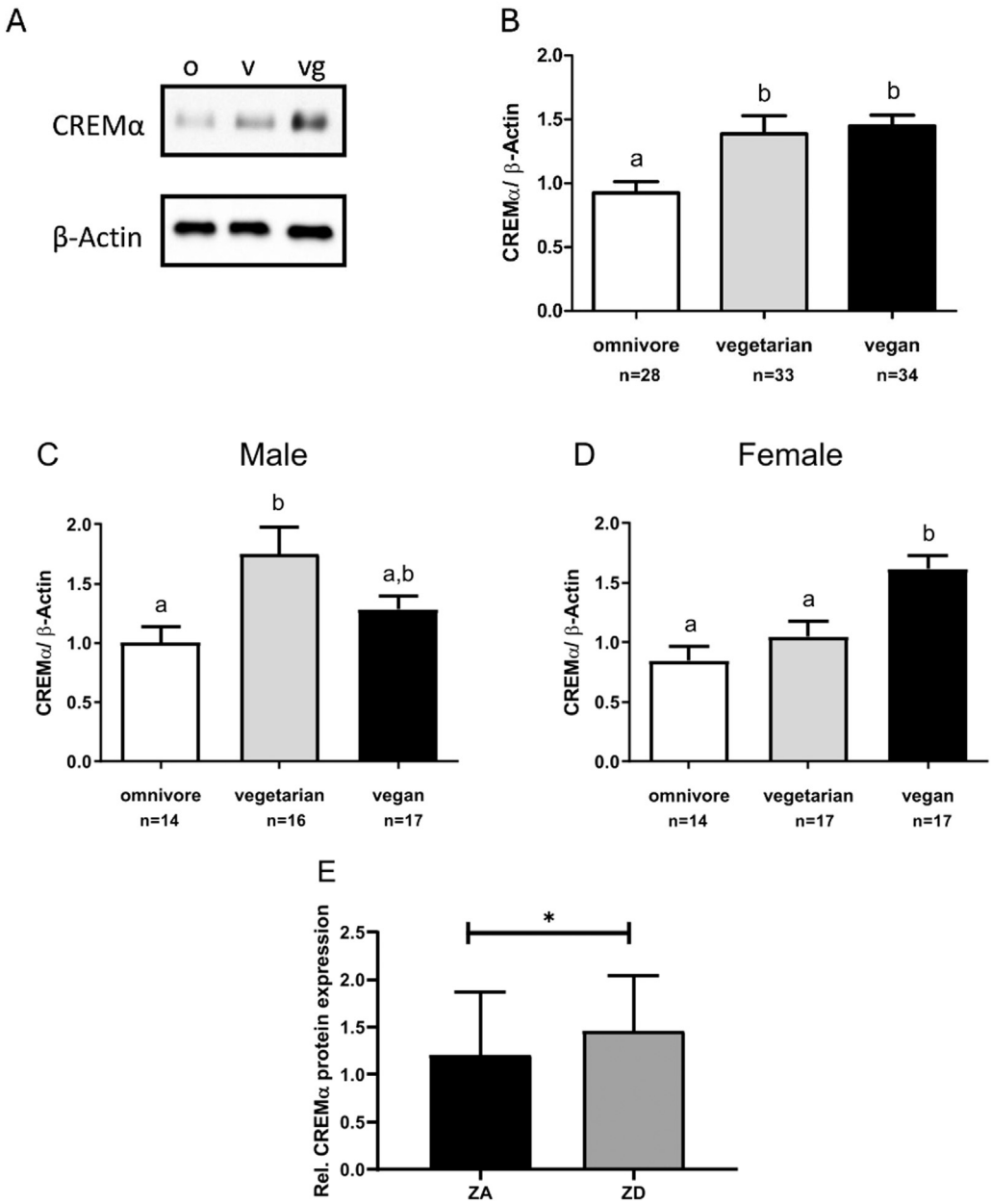


Fig. 5. Zinc levels determine CREMα mRNA expression in vegetarians and vegans. Zinc status influences CREMα protein expression in omnivores, vegetarians, and vegans. CREMα protein expression was analyzed in PBMCs of n = 95 healthy volunteers following different diets (omnivorous n = 28, vegetarian (v) n = 33, vegan (vg) n = 34). (A) One representative Western Blot is shown, and (B) analysis of the whole cohort. Separate analyses conducted by gender in male (C) and female (D) cohorts were performed. Additionally, the influence of zinc deficiency on CREMα protein expression was analyzed (E). CREMα protein expression was normalized to the housekeeping gene β-actin. All data are considered as unpaired variables and presented as the mean + SEM. Statistical significance was determined using the Mann–Whitney test and one-way ANOVA followed by Tukey's *post hoc* test. Statistical significance ($P < .05$) is indicated by different letters (a, b).

vitro [35]. In accordance, we found a zinc deficiency-dependent CREMα overexpression in vegetarians and vegans (Figs. 4 and 5), leading to cellular hypo-responsiveness upon mitogen exposure (Fig. 3). Comparing gender differences and zinc-deficiency over all diet groups, zinc-deficiency was shown to be the main influencing factor of CREMα protein expression (Fig. 5). Our correlation analyses revealed a statistically significant inverse association between CREMα protein expression and the individual's zinc status, as well as a positive association between zinc status and IL-2 cytokine expression (Fig. 6), underlining the zinc-dependent CREMα-mediated IL-2 gene silencing in young people adhering to plant-based diets. Only the correlation between the adjusted zinc diet score and IL-2 cytokine expression was not statistically significant, probably due to a higher variety and self-reported diet in the adjusted zinc score compared to serum zinc. Interestingly, we did not observe a correlation between CREMα protein expression and IL-2 cytokine expression. However, this might be the byproduct of a small sample size. The resulting immune dysfunction may impair the body's ability to mount an effective response to infectious pathogens. In line with that, Vallböhmer et al. recently showed an impaired antiviral immune response in vegetarians and vegans due to zinc deficiency by negatively influencing IFN-α and IRF3 expression [36]. Moreover, studies suggest that the overexpression of CREMα plays a crucial role in autoimmune diseases such as systemic lupus ery-

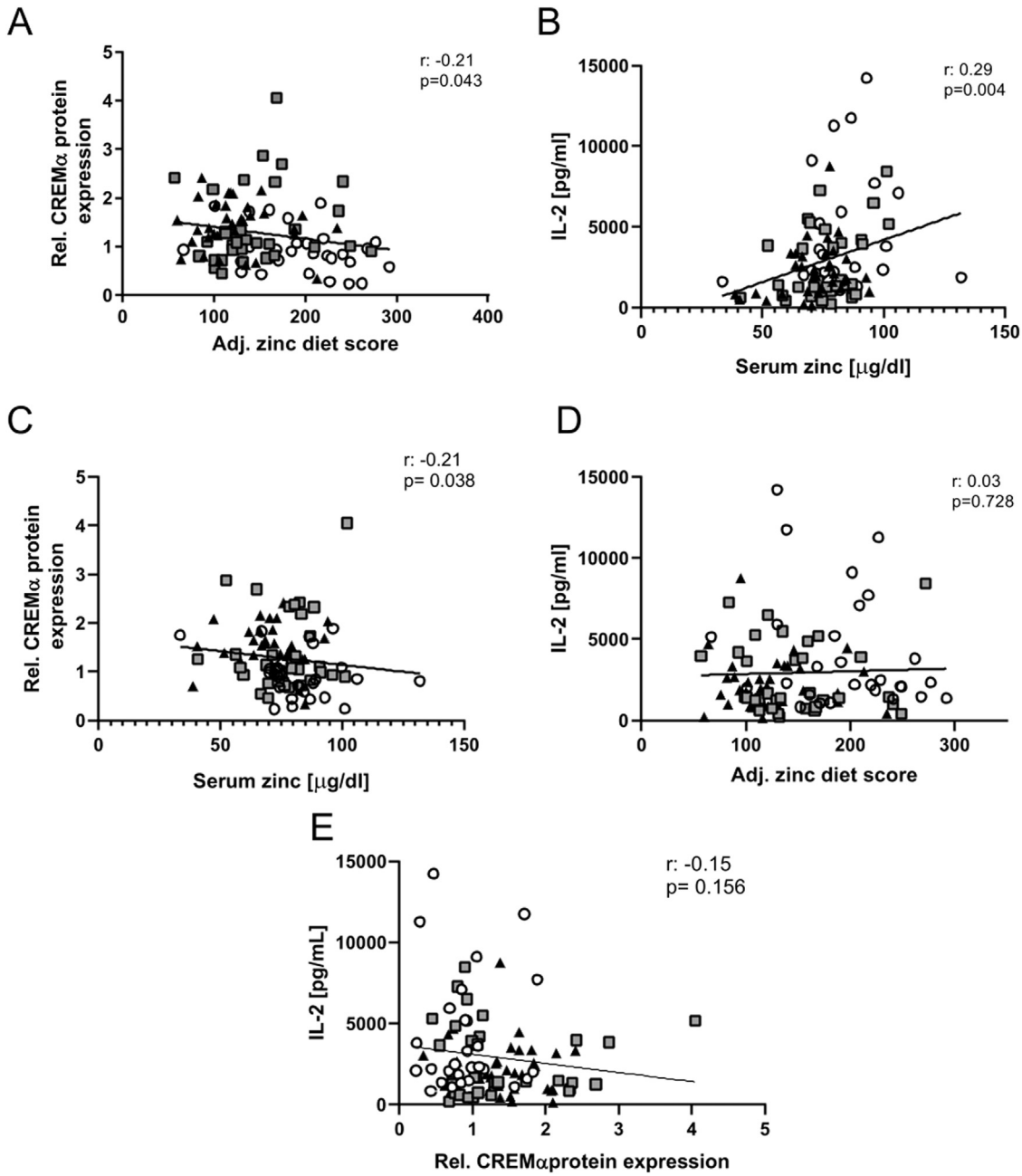


Fig. 6. CREMα protein expression and IL–2 cytokine expression correlate with zinc status in healthy young volunteers adhering to different diets. Correlation of CREMα protein expression and IL-2 cytokine expression to zinc status of omnivorous, vegetarian, and vegan study participants. (A) CREMα protein expression was plotted against the adjusted zinc diet score assessed by FFQ for each study participant (n = 95 XY pairs), as well as (B) IL-2 cytokine expression was plotted against serum zinc levels of each study participant (n = 95 XY pairs). Additionally, CREMα protein expression was plotted against serum zinc levels (C), and IL-2 cytokine expression was plotted against the adjusted zinc diet score (D). CREMα protein expression was plotted against IL-2 cytokine expression (E). Correlations were determined by the Spearman rank correlation coefficient (r, $P < .05$).

thematosus [69,70] highlighting the importance of an adequate dietary intake of trace elements for the maintenance of proper immune function.

The average age of our participants was low therefore it would be interesting to investigate how a vegetarian or vegan diet influences the immune system in a middle-aged population. Thus, further investigations regarding zinc deficiency and its effects on IL-2 and CREMα are important. Moreover, the self-reported diet could be a source of error.

Since studies uncovered a positive effect of zinc supplementation in zinc-deficient elderly individuals, animal experiments, and human T cell lines *in vitro*, which resulted in reduced CREMα expression levels and normalized IL-2 transcription [23,34], further investigations might be useful to evaluate zinc supplementation in healthy young people adhering to plant-based diets.

5. Conclusion

Individuals adhering to plant-based diets are at considerable risk of developing zinc deficiency as evidenced by reduced serum zinc concentrations and lower zinc scores assessed via FFQ. Zinc deficiency has been associated with an increased in-

cidence of metabolic and chronic diseases, as well as heightened susceptibility to infectious diseases. This increased vulnerability is attributable to altered IL-2 cytokine production, which results from zinc deficiency-dependent overexpression of CREMα. Consequently, our findings underscore the critical importance of ensuring adequate zinc intake, even among healthy young individuals following plant-based diets, to prevent severe immune dysfunction.

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Declaration of Generative AI and AI-assisted technologies in the writing process

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Declaration of competing interest

The authors declare that there are no conflicts of interest.

CRediT authorship contribution statement

Martina Maywald: Writing – original draft, Visualization, Validation, Project administration, Investigation, Formal analysis, Data curation. **Klara Marie Schmitt:** Validation, Visualization, Writing – review & editing. **Jens Bertram:** Writing – review & editing, Investigation. **Lothar Rink:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Conceptualization.

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