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ORIGINAL ARTICLE

High dietary copper in cognitive impairment among North Indian females: findings from a population-based study

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Background Cognitive impairment (CI) is a pressing public health issue worldwide. Studies suggest a possible relationship between dietary intake of certain trace elements and cognitive functions. Therefore, it is pertinent to explore the status of dietary intake of trace elements and their impact on CI in populations with unique dietary patterns.

Aim To explore the relationship between dietary intake of selected trace elements (Zinc, Selenium, Copper, Chromium, and Manganese) with CI among adults of a lacto-vegetarian population.

Patients and Methods A total of 500 individuals aged 30–70 years belonging to a lacto-vegetarian community of North India were recruited. All the recruited individuals were screened for CI using mini-mental state examination. Those scoring below the standard cutoff were categorized as cases and others as controls. The data on dietary intake were collected using the Food frequency. food frequency questionnaire data were analyzed using Dietcal software. Statistical analysis was performed using Statistical Package for the Social Science.

Results Median copper intake was found to be significantly higher in the case group than in the control group. After stratification for sex, the difference remained significant only among females. Further, females in the fourth quartile of copper intake were found to be at a two-fold increased risk for CI against those in the first quartile. Differences in median intake of other studied trace elements between cases and controls were not found to be statistically significant.

Conclusions The present study suggests a possible role of high copper intake in the causation of CI among females in the studied population.

Keywords Cognitive impairment, Copper intake, Recommended dietary allowances, Trace elements, Vegetarian population.

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INTRODUCTION

With an increased average lifespan of humans worldwide, the size of the elderly population has expanded, which, in turn, has led to an increased burden of cognitive impairment (CI) in the last few decades. According to estimates, nearly 48 million people globally are currently suffering from dementia and the number is expected to increase to 131 million by 2050 (Wolters and Ikram, 2018). Moreover, the prevalence of mild CI has been reported to be between 5 and 36.7% across various populations worldwide (Sachdev *et al.,* 2015). The situation in India is no different. According to several population-based studies from India, the prevalence of CI ranges from 8.8 to 34.3% in various Indian populations (Khullar *et al.,* 2017; Kaur *et al.,* 2018; Verma *et al.,* 2020).

Although the precise aetiological pathways of most forms of CIs are poorly understood, studies have identified several environmental risk factors for CI (Killin *et al.,* 2016). Optimal dietary intake of certain trace elements, among other environmental risk factors, has been reported to play an important role in healthy cognitive functioning (Janka, 2019). Trace elements, like Chromium, Cobalt, Copper, Fluorine, Iodine, Iron, Manganese, Molybdenum, Selenium, and Zinc, play an important role in metabolic and redox reactions in the central nervous system (Janka, 2019). By implication, variation in dietary intake of trace elements is bound to influence cognitive functions. Again, dietary intake of trace elements varies across populations due to varied dietary patterns (Hunt, 2003; Weikert *et al.,* 2020). Therefore, it is important to explore the status of dietary intake of trace elements and its relationship with CI in populations with unique dietary patterns.

Studies exploring the relationship between dietary intake of trace elements and CI have predominantly been conducted in nonvegetarian populations (Li *et al.,* 2019; Gu *et al.,* 2021). The nutritional composition of nonvegetarian diets (in terms of both quantity and quality of trace elements as well as other nutrients, like vitamin B6, B12, folate, etc., that may influence the relationship between trace elements and CI) is essentially different from that of vegetarian diets (Gajski *et al.,* 2018). Further, a vast majority of these studies are hospital-based and are conducted on CI patients (Nascimento *et al.,* 2021; Socha *et al.,* 2021). The dietary patterns of diagnosed CI patients are likely to differ from their undiagnosed counterparts and also from the general population. Hence, the results from such studies may not fully apply to the general vegetarian populations. Therefore, the present population-based study attempted to explore the relationship between dietary intake of selected trace elements (Zinc, Selenium, Copper, Chromium, and Manganese) and CI among adults of a lacto-vegetarian population (Jats of Palwal district of Haryana). Further, studies have highlighted the importance of sex in influencing dietary patterns (D'Amico *et al.,* 2020); therefore, apart from overall analyses, separate analyses have been performed for males and females.

PATIENTS AND METHODS

Study area and participants

The present study is a population-based cross-sectional study conducted among a lacto-vegetarian population spread across 15 villages in Palwal District of Haryana, North India. A total of 500 apparently healthy (having no self-reported chronic illness like cardiovascular disorders, cancers, psychiatric disorders, etc.) adult individuals of either sex (202 males and 298 females) aged 30–75 years (mean age: 52.7±10.2 years) were recruited through household survey method. Those having any chronic physical or mental disease, pregnant and lactating women, and those on long-term medication of any kind were excluded from the study.

Data collection

From each participant, data about demographic variables like age, sex, education, occupation, socioeconomic status, and marital status were collected using a pretested interview schedule. Data pertaining to dietary intake of trace elements were collected by administering a food frequency questionnaire (FFQ), valid for the rural Haryana populations (Kapil *et al.,* 2004). FFQ is one of the most widely used nutritional assessment tools used in epidemiological studies across the world (Cade *et al.,* 2002). FFQ consists of a context/area-specific list of food and beverages along with a frequency response section to calculate the frequency and quantity of the consumed food items on a daily, weekly, monthly, and occasional basis (Cade *et al.,* 2002).

Cognitive assessment

Assessment of CI was done by administering the mini-mental state examination (MMSE) on all the recruited participants. MMSE is an extensively used 30-point questionnaire that measures CI (Folstein *et al.,* 1975). Study participants who score 24 or above were considered to have normal cognition (controls), while others who scored less than 24 were considered to have CI (cases) (Folstein *et al.,* 1975).

Data analysis

Data obtained by FFQ were analyzed by using Dietcal software to generate the nutrient profile of each participant (Kaur, 2015). Dietcal is a software tool that computes the nutritional composition of commonly consumed food products as per the Indian Dietetic Scenario (Gupta *et al.,* 2018). The adequacy of dietary intake of various trace elements being studied was determined by comparing the levels of dietary intake of the trace elements with recommended dietary allowance levels (FSSAI, 2020).

Statistical Analysis

Statistical analyses were done using SPSS, version 22 and MS Excel 2019. The normality of the continuous variables was determined using Kolmogorov–Smirnov normality test. Median values along with the respective interquartile ranges have been reported for nonnormally distributed variables. To determine the statistical significance of the observed difference in the median values of a nonnormally distributed continuous variable between the case and the control groups, the Mann–Whitney U test was used. To determine if the distributions of categorical variables were significantly different between the case and the control groups, the χ^2 test for independence was performed. Further, the participants were divided into quartiles based on the dietary intake of copper, and the prevalence of CI was determined in each quartile. Binary logistic regression was used to determine the odds ratio. Statistical tests computed in the present study were considered significant at a two-tailed P value less than 0.05.

Ethical approval

The study was approved by the departmental ethics committee, (Department of Anthropology, University of

Delhi) (reference number: Anth/2010/455/5). Informed written consent, typed in the local language, was obtained from each participant before their recruitment.

RESULTS

Sociodemographic profile of the participants

The numbers of individuals in the case and the control groups were not found to be significantly different for any of the studied sociodemographic variables, except educational status and employment, where the proportions of illiterate and agriculturist individuals were found to be significantly higher in the case group than in the control group (Table 1).

Median levels of trace elements intake among cases and controls

Overall, copper intake was significantly higher among cases (participants with CI) than in controls (participants without CI) (Table 2). In sexwise analysis (Table 2), the difference in copper intake between cases and controls remained significant only among females. Nonetheless, median copper intake among males with CI was higher than their normal counterparts (although statistically not significant). No such difference between cases and controls was observed with respect to the intake of any other studied trace element.

Distribution of participants with respect to consumption of adequate and inadequate levels of trace elements and cognitive impairment status

No significant difference in the distribution of participants consuming adequate and inadequate levels of studied trace elements (as per recommended dietary allowance) was found between cases and controls (Table 3). However, the number of females consuming adequate levels of copper was found to be relatively higher among cases than among controls (P= 0.07).

Distribution of cases and controls in various quartiles of copper intake and odds ratio analyses

Due to the observed significant difference in median copper intake between cases and controls, the distribution of cases and controls was further seen in various quartiles of copper intake (Table 4). This analysis revealed that the proportion of cases was the lowest in the first quartile and the highest in the fourth quartile. A sharp jump in the percentage of cases was observed from the first to the second quartile and from the third to the fourth quartile (~10 and 5%, respectively). Further, the difference in the distribution of cases and controls between quartile 1 and quartile 4 was found to be statistically significant. When stratified for sex, a similar trend was seen among females; however, among males, a rather gradual increase in the proportion of cases from quartile 1 to quartile 3 and a modest dip from quartile 3 to quartile 4 was observed (Table 4). Odds ratio analysis revealed that in overall participants and also among females (but not among males), those in the fourth quartile of copper intake were at a significantly increased risk of CI in reference to those in the first quartile (Fig. 1).

Table 1: Distribution of demographic variables among participants with (cases) and without (controls) cognitive impairment:

	Control (N=176) [n (%)]	Case (N=324) [n (%)]	P value
Age group (years)			
30–39	17 (9.7)	37 (11.4)	0.92
40–49	57 (32.4)	101 (31.2)	
50–59	48 (27.3)	84 (25.9)	
60 and above	54 (30.7)	102 (31.5)	
Sex			
Female	109 (61.9)	198 (61.1)	0.85
Male	67 (38.1)	126 (38.9)	
Educational status			
Literate	157 (89.2)	68 (21.0)	<0.001*
Illiterate	19 (10.8)	256 (79.0)	
Employment status			
Service	43 (24.4)	8 (2.5)	<0.001*
Agriculturist	133 (75.6)	316 (97.5)	
Marital status			
Married	163 (92.6)	296 (91.4)	0.96
Unmarried	1 (0.6)	4 (1.2)	
Widowed	12 (6.8)	24 (7.4)	

*P value less than 0.05, significant.

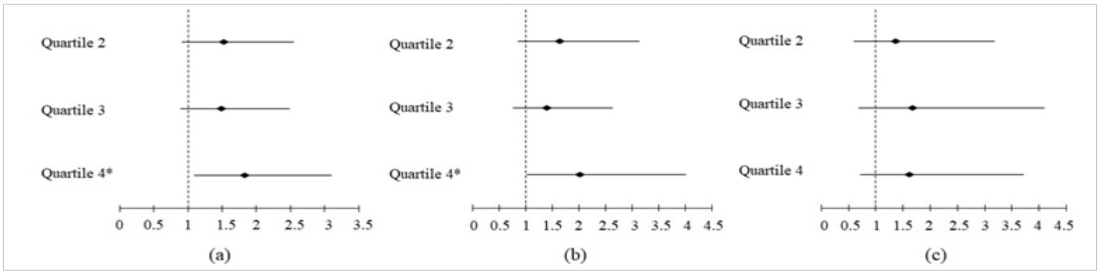

Figure 1: Forest plot showing odds ratio for cognitive impairment (CI) in various quartiles of copper intake (with the first quartile as the reference) among (a) overall participants, (b) females, and (c) males; *Significant at p-value <0.05.

Table 2: Overall and sexwise median intake levels of studied trace elements among participants with (cases) and without (controls) cognitive impairment:

	Zinc	Selenium	Copper	Chromium	Manganese
Overall					
Controls	5.78 (3.84–8.18)	65.99 (48.51–100.51)	1.01 (0.64–1.74)	0.04 (0.02–0.09)	4.05 (2.42–0.09)
Cases	5.86 (4.22–8.85)	65.73 (45.81–95.33)	1.18 (0.73–1.86)	0.05 (0.03–0.09)	4.26 (2.76–6.06)
P value	0.35	0.44	0.028**	0.47	0.46
Males					
Controls	5.73 (3.65–9.71)	65.51 (45.77–99.17)	1.06 (0.65–2.03)	0.04 (0.02–0.10)	4.32 (2.60–6.94)
Cases	5.61 (3.98–8.33)	65.65 (44.16–99.39)	1.22 (0.78–2.01)	0.04 (0.03–0.08)	4.20 (2.78–5.52)
P value	0.73	0.84	0.36	0.85	0.60
Females					
Controls	5.78 (4.14–476)	66.35 (48.87–100.96)	0.91 (0.64–1.68)	0.04 (0.02–0.08)	3.66 (2.37–5.71)
Cases	6.15 (4.36–9.26)	65.85 (46.68–94.66)	1.11 (0.71–1.85)	0.05 (0.03–0.10)	4.31 (2.70–6.10)
P value	0.09	0.40	0.032**	0.26	0.16

Mann–Whitney U test. ***P* value less than 0.05, significant.

Table 3: Overall and sexwise distribution of participants consuming adequate and inadequate levels of trace elements in case and control groups (with and without cognitive impairment, respectively):

Trace element	Intake level	Overall		*P* value	Males		*P* value	Females		*P* value
		Controls [*n* (%)]	Cases [*n* (%)]		Controls [*n* (%)]	Cases [*n* (%)]		Controls [*n* (%)]	Cases [*n* (%)]	
Zinc	Adequate	9 (5.1)	21 (6.5)	0.54	4 (5.6)	7 (5.4)	0.96	5 (4.9)	14 (7.3)	0.42
	Inadequate	166 (94.9)	301 (93.5)		68 (94.4)	123 (94.6)		98 (95.1)	178 (92.7)	
Selenium	Adequate	151 (86.3)	273 (84.8)	0.65	61 (84.7)	112 (86.2)	0.78	90 (87.4)	161 (83.9)	0.42
	Inadequate	24 (13.7)	49 (15.2)		11 (15.3)	18 (13.8)		13 (12.6)	31 (16.1)	
Copper	Adequate	47 (26.9)	108 (33.5)	0.12	22 (30.6)	42 (32.3)	0.80	25 (24.3)	66 (34.4)	0.07
	Inadequate	128 (73.1)	214 (66.5)		50 (69.4)	88 (67.7)		78 (75.7)	126 (65.6)	
Chromium	Adequate	0	0	–	0	0	–	0	0	–
	Inadequate	175 (100.0)	322 (100.0)		72 (100.0)	130 (100.0)		103 (100.0)	192 (100.0)	
Manganese	Adequate	88 (50.3)	173 (53.7)	0.46	39 (54.2)	70 (53.8)	0.97	49 (47.6)	103 (53.6)	0.32
	Inadequate	87 (49.7)	149 (46.3)		33 (45.8)	60 (46.2)		54 (52.4)	89 (46.4)	

χ^2, χ^2 test.

Table 4: Overall and sexwise distribution of participants with (cases) and without (controls) cognitive impairment in various quartiles of copper intake:

	Quartiles→ CI status↓	1 (≤0.7 mg) [*n* (%)]	2 (0.7–1.09 mg) [*n* (%)]	3 (1.09–1.83 mg) [*n* (%)]	4 (>1.83 mg) [*n* (%)]	*P* value$^{\alpha}$	*P* value$^{\beta}$	*P* value$^{\zeta}$
Overall	Controls	54 (43.5)	42 (33.6)	42 (34.1)	37 (29.6)	0.10	0.13	0.022*
	Cases	70 (56.5)	83 (66.8)	81 (65.9)	88 (70.4)			
Females	Controls	36 (43.9)	24 (32.4)	29 (35.8)	19 (27.9)	0.14	0.29	0.043*
	Cases	46 (56.1)	50 (67.6)	52 (64.2)	49 (72.1)			
Males	Controls	18 (42.9)	18 (35.3)	13 (31.0)	18 (31.6)	0.45	0.25	0.24
	Cases	24 (57.1)	33 (64.7)	29 (69.0)	39 (68.4)			

αQuartile 1 versus quartile 2. βQuartile 1 versus quartile 3. ζQuartile 1 versus quartile 4. **P* value less than 0.05, significant.

DISCUSSION

The present study attempted to explore the status of dietary intake of selected trace elements among cases and controls in a lacto-vegetarian population and further understand the relationship between dietary intake of these trace elements and CI. Several studies have explored the relationship between serum or plasma levels of trace elements and CI, however, only a few have focused on dietary intake of trace elements and CI (Li *et al.,* 2019). To the best of our knowledge, this is the first study that explores the relationship between dietary intake of trace elements and CI in a lacto-vegetarian population. Of all the studied trace elements, dietary intake of copper was found to be significantly higher among the cases than in the controls. However, after stratification for sex, the difference remained significant only among females. Further, females in the fourth quartile of copper intake were found to be at a two-fold increased risk for CI in reference to those in the first quartile ($P= 0.045$). These results partially confirm our hypothesis (among females) that imbalances in dietary intake of certain trace elements, unique to the lacto-vegetarian dietary pattern, could be a risk factor for CI.

Several other studies have reported high copper intake to be associated with CI (Wei *et al.,* 2022; Morris *et al.,* 2006). In fact, Shen *et al.* (2014) in their study found a positive association between copper concentration in soil and annual Alzheimer's disease mortality. However, contrary findings have also been reported (Li *et al.,* 2019). Possible reasons behind contradictory reports can be the modulating effect of other nutrients/dietary components and the nonlinear relationship between copper intake and CI. Dietary components like trans and saturated fats have been reported to play an important role in modulating the effect of dietary copper on CI (Morris *et al.,* 2006; Li *et al.,* 2019). Variations in levels of such modulating nutrients in different populations could be the factor behind contradictory observations. Further, a recent study reported a nonlinear relationship between copper intake and CI, where the increment in copper intake below a threshold (0.8 mg/day of Cu for the CERAD test) was found to be positively associated with cognitive functions, and increment beyond the threshold showed a negative trend (Wang *et al.,* 2021). The contradictory associations between copper intake and cognitive functions could also be due to the threshold effect, where populations with low average copper intake show a positive association and those with high average copper intake show a negative association between the two.

The precise mechanism behind the observed association between copper intake and CI is largely unknown (Li *et al.,* 2019). However, studies have suggested that high copper might be associated with higher oxidative stress in different brain regions resulting in cognitive disturbances (Squitti *et al.,* 2015). Animal model studies have revealed that in animals with a cholesterol-rich diet, high copper intake triggers the accumulation of beta-amyloid (Aβ), which forms amyloid plaques in the brain (associated with Alzheimer's disease) (Squitti *et al.,* 2015). Further, some studies have argued that high copper intake may be involved in increased levels of ceruloplasmin, which could, in turn, be associated with inflammation and CI (Park *et al.,* 2014; Squitti *et al.,* 2014).

In sexwise stratified analysis, this trend of higher copper intake among cases than controls remained significant among females but not among males. Few studies have suggested sex-specific associations between copper intake and cognitive functions, however, trends are inconsistent and contradictory (Gong *et al.,* 2022). Sex-specific role of copper intake in CI needs further investigation.

Differences in median dietary intake of other trace elements (Zn, Se, Cr, and Mn) between cases and controls were not found to be statistically significant. Scrutiny of published literature vis-a-vis intake of Zn and Se in CI gives an inconsistent picture. While some of the studies, similar to the trends observed in the present study, have reported no association between cognitive functions and intake/levels of Zn (Yaffe *et al.,* 2004) and Se (Cardoso *et al.,* 2018), others have reported positive or negative associations (Maylor *et al.,* 2006; Akbaraly *et al.,* 2007; Li *et al.,* 2019). Studies exploring the role of dietary intake of Cr and Mn are sparse. A study conducted by Krikorian *et al.,* (2010) reported a positive effect of Cr supplementation on cognitive functioning. Further, studies have suggested a negative impact of both high and low Mn exposure on cognitive functioning (U-shaped relationship) (Vollet *et al.,* 2016; Balachandran *et al.,* 2020). However, the role of dietary intake of Cr and Mn (as well as other trace elements) in CI has not been adequately explored and further population-based studies are warranted.

One of the limitations of the present study is that the study has been conducted among a single population and must be validated among other vegetarian populations for the generalization of results. Another limitation is that the screening for CI has been performed using MMSE. Although MMSE is a widely used and crossculturally validated tool for screening CI, it is not the gold standard method. A comprehensive neuropsychological assessment is considered the gold standard method for diagnosis of CI and should ideally be employed for confirmation of CI. However, time and cost considerations did not permit us to conduct comprehensive neuropsychological assessments in the present study. In resource-constrained setups, future population-based studies should use more rigorous tools for the assessment of cognitive function like the Montreal Cognitive Assessment test and the Wisconsin Card Sorting Test along with MMSE.

CONCLUSION

The present study shows that a higher dietary intake of copper can be a risk factor for CI, especially among females. Populations relying heavily on cereal (wheat)-based diets, which are usually rich in copper, can be at a greater risk for developing CI. Dietary diversification can help in optimizing the intake of various micronutrients including copper.

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The paper was presented as part at a meeting, the organization, place, and exact date on which it was read. A full statement to the editor about all submissions and previous reports that might be regarded as redundant publication of the same or very similar work. Any such work should be referred to specifically and referenced in the new paper.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

REFERENCE

Akbaraly TN, Hininger-Favier I, Carriere I, Arnaud J, Gourlet V, Roussel AM, *et al.* (2007). Plasma selenium over time and cognitive decline in the elderly. Epidemiology 18:52–8.

Balachandran RC, Mukhopadhyay S, McBride D, Veevers J, Harrison FE, Aschner M, *et al.* (2020). Brain manganese and the balance between essential roles and neurotoxicity. J Biol Chem 295:6312–29.

Cade J, Thompson R, Burley V, Warm D (2002). Development, validation and utilisation of food-frequency questionnaires – a review. Public Health Nutr 5:567–587.

Cardoso BR, Szymlek-Gay EA, Roberts BR, Formica M, Gianoudis J, O'connell S, *et al.* (2018). Selenium status is not associated with cognitive performance: a cross-sectional study in 154 older Australian adults. Nutrients 10:1847.

D'Amico D, Parrott MD, Greenwood CE, Ferland G, Gaudreau P, Belleville S, *et al.* (2020). Sex differences in the relationship between dietary pattern adherence and cognitive function among older adults: findings from the NuAge study. Nutr J 19:1–8.

Folstein MF, Folstein SE, McHugh PR (1975). 'Mini-mental state': a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–98.

FSSAI (2020). Recommended dietary allowance (RDA). Food safety and standard authorities of India. Available at: https://fssai.gov.in/upload/advisories/2021/07/60f1798019f94Direction_RDA_16_07_2021.pdf [Accessed March 1, 2022]

Gajski G, Gerić M, Lovrenčić MV, Božičević S, Rubelj I, Nanić L, *et al.* (2018). Analysis of health-related biomarkers between vegetarians and non-vegetarians: a multi-biomarker approach. J Funct Foods 48:643–53.

Gong Z, Song W, Gu M (2022). Serum copper and zinc concentrations and cognitive impairment in older adults aged 60 years and older. Biol Trace Elem Res 200:1495–1501.

Gu L, Yu J, Fan Y, Wang S, Yang L, Liu K, *et al.* (2021). The association between trace elements exposure and the cognition in the elderly in China. Biol Trace Elem Res 199:403–12.

Gupta A, Noronha JA, Garg M (2018). Dietary intake of macronutrients and micronutrients among adolescent girls: a cross sectional study. Clin. Epidemiology Glob Health 6:192–7.

Hunt JR (2003). Bioavailability of iron, zinc, and other trace minerals from vegetarian diets. Am J Clin Nutr 78:633S–9S.

Janka Z (2019). Tracing trace elements in mental functions. Ideggyogy Szle 72:367–79.

Kapil U, Singh P, Pathak P, Pradhan R (2004). Reproducibility and Validity of the Food Frequency Questionnaire in a Rural Block of Haryana, India. Pak J Nutr 3:35–37.

Kaur G (2015). Dietcal: a tool for dietary assessment & planning. Profound Tech Solutions. Department of Dietetics; AIIMS, New Delhi, India. Available at: http://dietcal.in/index.html. Accessed March 1, 2022.

Kaur G, Gaur R, Yadav S, Saraswathy KN (2018). Association of vitamin B12 mediated hyperhomocysteinemia and methylenetetrafolate reductase (C677T) gene polymorphism with cognitive impairment: a population based study from North India. Psychiatry Res 270:123–5.

Khullar S, Kaur G, Dhillon H, Sharma R, Mehta K, Singh M, *et al.* (2017). The prevalence and predictors of cognitive impairment in type 2 diabetic population of Punjab. India. J soc health diabetes 5:47–53.

Killin LO, Starr JM, Shiue IJ, Russ TC (2016). Environmental risk factors for dementia: a systematic review. BMC Geriatr 16:1–28.

Krikorian R, Eliassen JC, Boespflug EL, Nash TA, Shidler MD (2010). Improved cognitive-cerebral function in older adults with chromium supplementation. Nutr Neurosci 13:116–22.

Li S, Sun W, Zhang D (2019). Association of zinc, iron, copper, and selenium intakes with low cognitive performance in older adults: a cross-sectional study from National Health and Nutrition Examination Survey (NHANES). J Alzheimer's Dis 72:1145–57.

Maylor EA, Simpson EE, Secker DL, Meunier N, Andriollo-Sanchez M, Polito A, *et al.* (2006). Effects of zinc supplementation on cognitive function in healthy middle-aged and older adults: the ZENITH study. Br J Nutr 96:752–60.

Morris MC, Evans DA, Tangney CC, Bienias JL, Schneider JA, Wilson RS, *et al.* (2006). Dietary copper and high saturated and trans fat intakes associated with cognitive decline. Arch Neurol 63:1085–8.

Nascimento CQ, Barros-Neto JA, Vieira NF, Menezes-Filho JA, Neves SJ, Lima SO (2021). Selenium concentrations in elderly people with Alzheimer's disease: a cross-sectional study with control group. Rev Bras Enferm 74(Suppl 2):e20200984.

Park JH, Lee DW, Park KS (2014). Elevated serum copper and ceruloplasmin levels in Alzheimer's disease. Asia Pac Psychiatry 6:38–45.

Sachdev PS, Lipnicki DM, Kochan NA, Crawford JD, Thalamuthu A, Andrews G, *et al.* (2015). The prevalence of mild cognitive impairment in diverse geographical and ethnocultural regions: the COSMIC collaboration. PloS one 10:e0142388.

Shen XL, Yu JH, Zhang DF, Xie JX, Jiang H (2014). Positive relationship between mortality from Alzheimer's disease and soil metal concentration in mainland China. J Alzheimer's Dis 42:893–900.

Socha K, Klimiuk K, Naliwajko SK, Soroczyńska J, Puścion-Jakubik A, Markiewicz-Żukowska R, *et al.* (2021). Dietary habits, selenium, copper, zinc and total antioxidant status in serum in relation to cognitive functions of patients with Alzheimer's disease. Nutrients 13:287.

Squitti R, Simonelli I, Ventriglia M, Siotto M, Pasqualetti P, Rembach A, *et al.* (2014). Meta-analysis of serum non-ceruloplasmin copper in Alzheimer's disease. J Alzheimer's Dis 38:809–22.

Squitti R, Tecchio F, Ventriglia M (2015). The role of copper in human diet and risk of dementia. Curr Nutr Rep 4:114–25.

Verma M, Grover S, Singh T, Dahiya N, Nehra R (2020). Screening for cognitive impairment among the elderly attending the noncommunicable diseases clinics in a rural area of Punjab, North India. Asian J Psychiatr 50:102001.

Vollet K, Haynes EN, Dietrich KN (2016). Manganese exposure and cognition across the lifespan: contemporary review and argument for biphasic dose–response health effects. Curr Environ Health Rep 3:392–404.

Wang X, Li X, Xing Y, Wang W, Li S, Zhang D, *et al.* (2021). Threshold effects of total copper intake on cognitive function in US older adults and the moderating effect of fat and saturated fatty acid intake. J Acad Nutr Diet 121:2429–42.

Wei J, Gianattasio KZ, Bennett EE, Stewart JD, Xu X, Park ES, *et al.* (2022). The Associations of Dietary Copper With Cognitive Outcomes The ARIC Study. Am J Epidemiol 191:1202–1211.

Weikert C, Trefflich I, Menzel J, Obeid R, Longree A, Dierkes J, *et al.* (2020) Vitamin and mineral status in a vegan diet. Dtsch Arztebl Int 117:575.

Wolters FJ, Ikram MA (2018). Epidemiology of dementia: the burden on society, the challenges for research. In: Perneczky R, editor. Biomarkers for Alzheimer's Disease Drug Development. New York, NY: Humana Press. p. 3–14.

Yaffe K, Clemons TE, McBee WL, Lindblad AS (2004). Age-related eye disease study research group. Impact of antioxidants, zinc, and copper on cognition in the elderly: a randomized, controlled trial. Neurology 63:1705–7.