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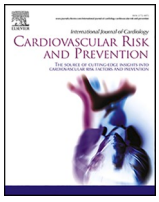

The adverse association of animal zinc intake with cardio-cerebrovascular and metabolic risk factors

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ABSTRACT

Background: The effect of zinc intake on cardio-cerebrovascular and metabolic diseases has always been controversial.
Aims: We hoped to evaluate the associations of the daily dietary estimate (DDE) of zinc intake with cardio-cerebrovascular and metabolic risk factors.
Methods: Baseline data from the Study of Women's Health Across the Nation (SWAN) were obtained. Multivariable linear regression analysis was used to examine associations of the DDE of zinc intake with cardio-cerebrovascular and metabolic risk factors.
Results: The smooth curve demonstrated positive associations of the DDE of animal zinc intake with low-density lipoprotein-cholesterol (LDL-C), triglycerides, total cholesterol, fasting blood glucose, insulin, systolic blood pressure (BP) and diastolic BP and an inverse association of the DDE of animal zinc intake with high-density lipoprotein-cholesterol (HDL-C). Consistently, multivariable linear regression models also showed that an increased DDE of animal zinc intake was closely related to a higher risk of cardio-cerebrovascular and metabolic risk factors [systolic BP: 0.37 (0.13, 0.61); diastolic BP: 0.17 (0.02, 0.33); fasting blood glucose: 1.13 (0.67, 1.59); insulin: 0.26 (0.05, 0.47); LDL-C: 0.82 (0.34, 1.29), triglycerides: 1.65 (0.75, 2.55), total cholesterol: 0.91 (0.38, 1.43) and HDL-C: −0.24 (−0.45, −0.03)] when age, race/ethnicity, total family income, smoking status, alcohol consumption and menopausal status were controlled for. Importantly, stratified analysis supported that the independent associations between the DDE of animal zinc intake and risk factors for cardio-cerebrovascular and metabolic diseases were hardly affected by age and body mass index (BMI).
Conclusion: We found that an increased DDE of animal zinc intake was associated with higher cardiovascular and metabolic risks among middle-aged women, which did not support the benefit of zinc intake in reducing cardiovascular and metabolic risks. The association seems to be incongruous with the anti-inflammation and antioxidation physiological functions of zinc. Thus, additional well-designed and prospective studies are needed to confirm this association.

1. Introduction

Cardio-cerebrovascular and metabolic diseases, such as hypertension, coronary heart disease, diabetes mellitus and dyslipidemia, are the largest contributors to morbidity and mortality in most countries [1,2]. Improved nutrition and dietary habits are very important strategies to prevent these chronic diseases [3,4]. Considering the existing evidence that mineral substances play a very important role in regulating various functions within the body and maintaining general health [5,6], zinc is particularly important in this context because of its major role in cell metabolism [7]. Zinc deficiency might weaken immunity and hinder the development of the body in children, and it is associated with the pathophysiology of cardiovascular diseases (CVDs) and type 2 diabetes (T2D) in adults [8–12]. However, the impacts of supplemental or dietary

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zinc intake on the risk for cardio-cerebrovascular and metabolic diseases have always been controversial.

For instance, studies about whether zinc intake affects blood pressure (BP) have been conflicting. Some studies have reported a negative association between zinc supplementation and hypertension [13,14], but other studies have reported a direct association between the two variables [15,16]. Although mechanistic research has confirmed that zinc is related to hypertension, including zinc's role in the NO pathway and ATP-dependent calcium pumps [17,18], the association of zinc with BP is not entirely certain. Moreover, some recent meta-analyses also reported inconsistent conclusions by analyzing the association of zinc supplementation with risk factors of CVDs and T2D [19–23]. Several recent studies concluded that zinc supplementation (supplementation trials) had beneficial effects on risk factors for CVDs and T2D, such as glycemic control and lipid metabolism [19–21], but other observational studies found that an increased zinc intake was related to a higher CVD risk and all-cause mortality [22,23]. However, the latest meta-analysis reported that low-dose, long-duration zinc intake from supplements can benefit risk factors for CVDs and T2D [24].

Therefore, considering the current controversy and the impacts of supplemental or dietary intake of zinc on CVD- and T2D-related health, large and well-designed clinical investigations are necessary to better confirm the effects of zinc intake on risk factors for cardio-cerebrovascular and metabolic diseases among various general populations. Here, we retrospectively analyzed the baseline data from the Study of Women's Health Across the Nation (SWAN) and evaluated the associations of the daily dietary estimate (DDE) of zinc intake with systolic BP, diastolic BP, fasting blood glucose, insulin, low-density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), triglycerides and total cholesterol in a population of middle-aged women.

2. Materials and methods

2.1. Study population

The SWAN study is a community-based, multiethnic, longitudinal study of the natural history of late midlife women who were enrolled at 7 field sites in the United States as previously described [25]. A total of 3302 female participants were enrolled at baseline between 1995 and 1997 by telephone interview to determine individual eligibility. For the purpose of our cross-sectional analysis, we chose the baseline data [(SWAN): Baseline Dataset, United States, 1996–1997 (ICPSR 28762)] of the study to analyze the association of animal zinc intake with cardio-cerebrovascular and metabolic risk factors. All of the included women were aged 42–53 years. They did not use reproductive hormone therapy in the past three months and had at least 1 menstrual period, and had an intact uterus with at least 1 ovary. The SWAN study provided detailed information on ethnic groups, health information, lifestyle, physicals, cardiovascular-related risk factors and blood indicators. We obtained data based on the baseline data, and female subjects with missing important data were excluded (Fig. 1). Finally, 2689 female participants were included in our analysis. The study protocol was approved by The Institutional Review Board (IRB) at each SWAN site, and written informed consent was obtained from all included individuals.

3. Cardiovascular and metabolic risk factors

All SWAN subjects completed interviewer-administered questionnaires at baseline to obtain smoking status, drinking status, physical measures and other health information. Measured values of metabolic and cardio-cerebrovascular risk factors were collected from these data. Information on BP and blood biomarker measurements was obtained from visits to SWAN sites. After at least a 5-min rest, systolic and diastolic BP were measured in a seated position. The average values of two

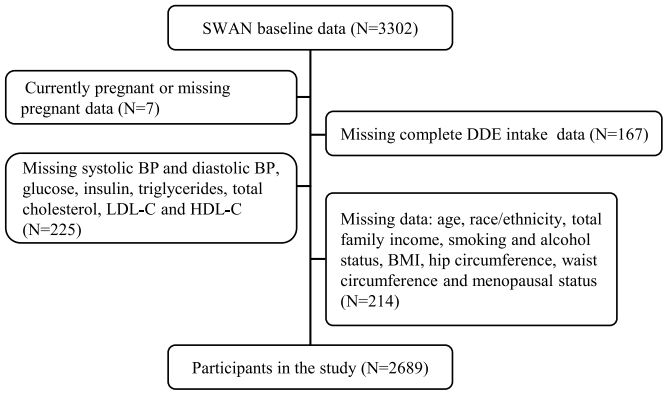

Fig. 1. Flow chart for participant inclusion.

BP readings were used for analyses. Direct LDL-C, HDL-C, triglyceride and total cholesterol were tested by coupled enzymatic methods. Blood glucose was tested by using a 2-step enzymatic reaction, and insulin was tested by a 2-site sandwich immunoassay. Blood insulin, glucose and lipid profile assays were performed by a Siemens ADVIA 2400 automated chemistry analyzer.

3.1. DDE of zinc

The DDE intake was obtained by a modified 1995 Block Food Frequency Questionnaire (FFQ) with 103 food items [26,27] based on Caucasians and African Americans in the Second National Health and Nutrition Examination Survey (NHANES) [28,29]. Nutrient intake (the DDE of zinc and the DDE of animal zinc) was estimated by food composition according to the United States Department of Agriculture data (USDA), taking into account the frequency with which the foods were consumed [30].

3.2. Covariates

Included population characteristics included age, ethnicity (Black/African American, Japanese/Japanese American, Chinese/Chinese American, Caucasian/Non-Hispanic White and Hispanic), total family income, smoking status, alcohol consumption, menopausal status and body mass index (BMI). Cardiovascular and metabolic risk factors included HDL-C, LDL-C, triglycerides, total cholesterol, fasting blood glucose, insulin, systolic BP and diastolic BP. Age was based on the self-reported date of birth. Race/ethnicity was self-reported at the SWAN baseline. Alcohol consumption was categorized as having consumed alcohol in the last 24 h (yes or no). Smoking status was classified as having ever smoked regularly (yes or no) based on self-reported smoking status. Menopausal status was categorized as early peri- or premenopausal. Height and weight were measured using standardized protocols [31], and then BMI (kg/m^2) was calculated via weight divided by height squared. Covariates were added into the reported associations between independent variables (the DDE of zinc intake and the DDE of animal zinc intake) and dependent variables (systolic BP, diastolic BP, fasting blood glucose, insulin, LDL-C, HDL-C, triglycerides and total cholesterol).

3.3. Statistical analysis

Each continuous variable was tested for normality, and descriptive statistics (continuous variables described as the mean or median values and categorical variables described as percentages) were performed to describe subject characteristics or cardiovascular and metabolic risk factors. Multivariable linear regression models were used to explore trends of associations between zinc intake (the DDE of zinc and the DDE of animal zinc intakes) and cardio-cerebrovascular and metabolic risk

factors (systolic BP, diastolic BP, fasting blood glucose, insulin, LDL-C, HDL-C, triglycerides and total cholesterol). These regression models were performed with systolic BP, diastolic BP, fasting blood glucose, insulin, LDL-C, HDL-C, triglycerides and total cholesterol as the dependent variables in separate models with the DDE of zinc and the DDE of animal zinc intakes as predictors. Model 1 adjusted for age and race ethnicity, Model 2 added covariates for total family income and smoking status, and Model 3 added dichotomous (yes/no) alcohol consumption status in the last 24 h and menopausal status as covariates. Subgroup analysis was also used to examine these associations. EmpowerStats 4.1 was used for all analyses. A *P* value of <0.05 was considered to indicate statistical significance.

4. Results

4.1. Characteristics of participants

Baseline data from 2689 participants from the SWAN study were analyzed (Table 1). The median age of all included participants was 46 years. The median systolic and diastolic BP values were 115 mmHg and 75 mmHg, respectively. The median intake levels of the DDE of zinc and the DDE of animal zinc in these participants were 8.30 mg and 4.66 mg, respectively. Cardio-cerebrovascular and metabolic risk factors, including fasting blood glucose, insulin, LDL-C, HDL-C, triglycerides and total cholesterol, were 91 mg/dl, 8.50 μIU/ml, 114.00 mg/dl, 54.00 mg/dl, 90.00 mg/dl and 191.00 mg/dl, respectively. Furthermore, the smooth curve showed that the DDE of animal zinc intake, as well as the DDE of zinc intake, has a gradual upward association with systolic BP, diastolic BP, fasting blood glucose, insulin, LDL-C, triglycerides and total cholesterol and a gradual downward association trend with HDL-C (Fig. 2).

Table 1
Characteristics of participants.

Variables	Mean or median or n (%)
Age (year)	46 (44–48)
BMI (kg/m^2)	26.48 (22.80–31.95)
Hip circumference (cm)	103.60 (96.00–114.50)
Waist circumference (cm)	82.50 (74.00–95.00)
Systolic BP (mmHg)	115 (106–126)
Diastolic BP (mmHg)	75 (69–81)
Blood indicators	
Glucose (mg/dl)	91 (86–98)
Insulin (uIU/ml)	8.50 (6.10–12.90)
Triglycerides (mg/dl)	90.00 (67.00–129.00)
Total cholesterol (mg/dl)	191.00 (171.00–214.00)
LDL-C (mg/dl)	114.00 (95.00–135.00)
HDL-C (mg/dl)	54.00 (46.00–64.00)
Race ethnicity	
Black/African American	716 (26.63 %)
Chinese/Chinese American	211 (7.85 %)
Japanese/Japanese American	220 (8.18 %)
Caucasian/White Non-Hispanic	1335 (49.65 %)
Hispanic	207 (7.70 %)
Total family income	
Less Than $19,999	365 (13.57 %)
$20,000 to $49,999	907 (33.73 %)
$50,000 to $99,999	1011 (37.60 %)
$100,000 or More	406 (15.10 %)
Ever smoked regularly	
No	1542 (57.34 %)
Yes	1147 (42.66 %)
Alcohol in last 24 h	
No	2336 (86.87 %)
Yes	353 (13.13 %)
Menopausal status	
Early peri	1212 (45.07 %)
Pre-menopausal	1477 (54.93 %)
DDE zinc (mg)	8.30 (6.47–10.68)
DDE animal zinc (mg)	4.66 (3.34–6.32)

BMI: body mass index; BP: blood pressure; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; DDE: daily dietary estimate.

Linear regression analysis showed a positive association of a higher DDE of animal zinc intake with increased cardio-cerebrovascular and metabolic risk.

After adjusting for age and race ethnicity, multivariate linear regression supported positive associations of the DDE of animal zinc intake with systolic BP [correlation coefficient = 0.41, 95 % CI (0.17, 0.65), P = 0.001], diastolic BP [correlation coefficient = 0.18, 95 % CI (0.02, 0.33), P = 0.024], fasting blood glucose [correlation coefficient = 1.21, 95 % CI (0.75, 1.66), P < 0.001], insulin [correlation coefficient = 0.28, 95 % CI (0.07, 0.49), P = 0.009], LDL-C [correlation coefficient = 0.86, 95 % CI (0.39, 1.34), P < 0.001], total cholesterol [correlation coefficient = 0.98, 95 % CI (0.46, 1.51), P < 0.001] and triglycerides [correlation coefficient = 1.95, 95 % CI (1.05, 2.85), P < 0.001], and there was an inverse association with HDL-C [correlation coefficient = −0.27, 95 % CI (−0.49, −0.05), P = 0.017] in Model 1 (Tables 2, 3 and Supplementary Material Tables). After adding covariates for total family income, smoking status, alcohol consumption in the last 24 h and menopausal status, independent associations of the DDE of animal zinc intake with BP, fasting blood glucose, insulin and blood lipids still changed slightly. However, in addition to the lipid profile and glucose values, the DDE of zinc intake did not have any association with these cardiovascular and metabolic risk factors after adjusting for these covariates (see Tables 2, 3 and Supplementary Material Tables).

Stratified analysis still showed a positive association of a higher DDE of animal zinc intake with increased cardio-cerebrovascular and metabolic risk.

Furthermore, associations of the DDE of animal zinc intake with BP, fasting blood glucose, insulin and blood lipids were performed by stratified analysis using “age” and “BMI” as covariates (Tables 4 and 5 and Supplementary Material Tables). We observed that a high DDE of animal zinc intake significantly contributed to higher blood glucose in subjects with BMI≥24 [correlation coefficient = 1.44, 95 % CI (0.82, 2.07), P < 0.001] but not in those subjects with BMI<24 [correlation coefficient = -0.37, 95 % CI (-0.87, 0.14), P = 1.55]. The interaction-P for the two subgroups was 0.001 (Table 5). In addition, high the DDE of animal zinc intake was significantly associated with higher diastolic BP in subjects aged ≥46 years [correlation coefficient = 0.35, 95 % CI (0.12, 0.57), P = 0.002] but not in subjects aged <46 years [correlation coefficient = −0.00, 95 % CI (−0.22, 0.22), P = 0.984], with an interaction-P value of 0.028 (Table 4). Additionally, “age” and “BMI” did not affect independent associations between the DDE of animal zinc intake and other cardio-cerebrovascular and metabolic risks, and their interaction-P values for the subgroup analysis were >0.05 (Tables 4 and 5 and Supplementary Material Tables).

5. Discussion

In the present study, we included a total of 2689 female subjects who were 42–53 years old from the baseline data of the SWAN study for analysis. We investigated the associations of the DDE of animal zinc intake and the DDE of zinc intake with cardio-cerebrovascular and metabolic risk factors (systolic BP, diastolic BP, fasting blood glucose, insulin, LDL-C, HDL-C, triglycerides and total cholesterol). We found that a high DDE of animal zinc intake, rather than the DDE of zinc intake, was significantly and positively associated with these cardio-cerebrovascular and metabolic risk factors after adjusting for potential confounders. This may provide new evidence that a higher intake of zinc from animal meat did not contribute risk-lowering benefits for cardio-cerebrovascular and metabolic diseases.

Considering that zinc can play important roles in the physiological process of lipid metabolism and insulin homeostasis, it can alter the risk of cardiovascular and metabolic diseases by antioxidant and anti-inflammatory effects, impacting insulin sensitivity and resistance, and other mechanisms [32]. Therefore, it is undoubtedly logical that some

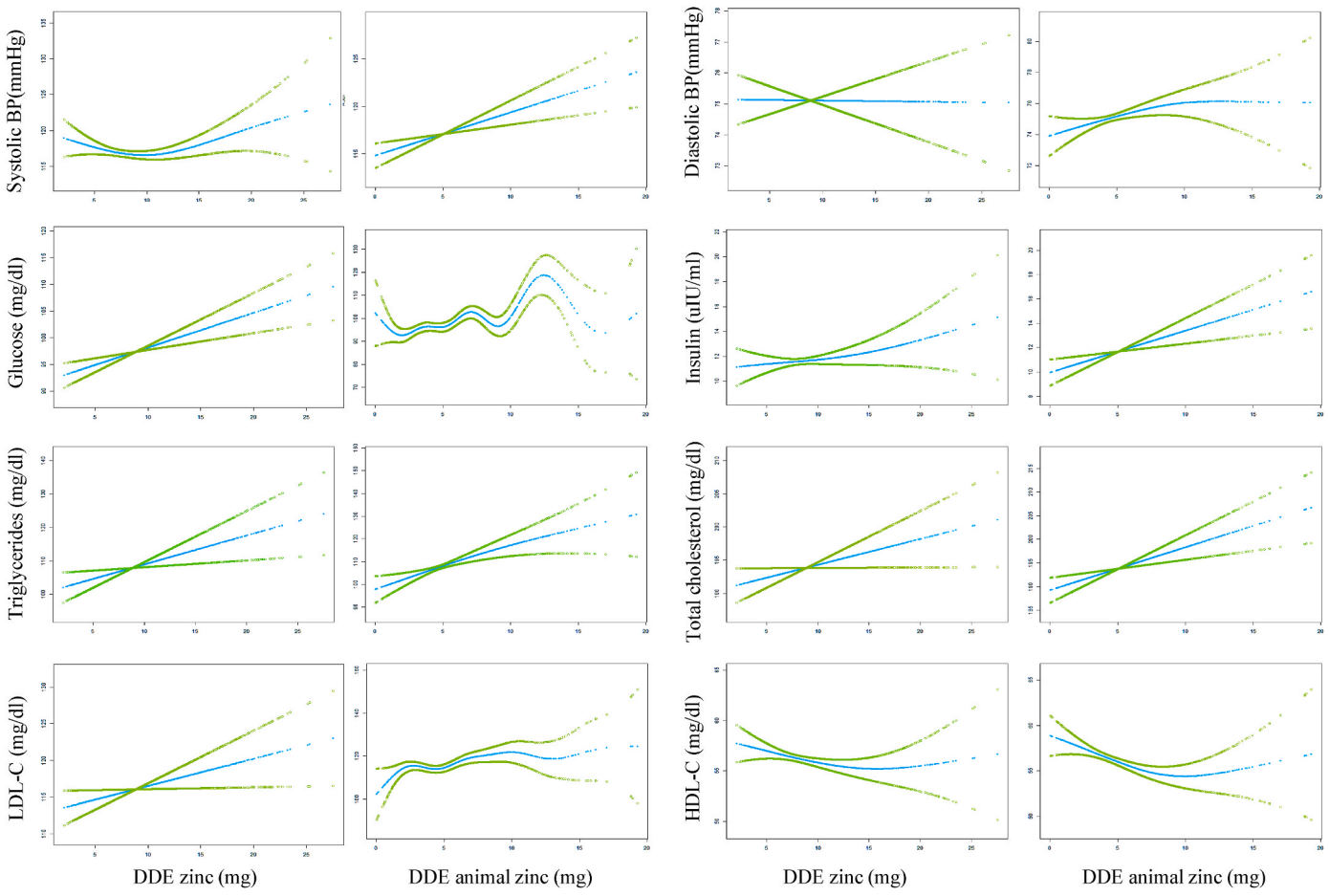

Fig. 2. Associations of zinc intake (the DDE of zinc and the DDE of animal zinc) with cardio-cerebrovascular and metabolic risk factors, including low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), triglycerides, total cholesterol, fasting blood glucose, insulin, systolic blood pressure (BP) and diastolic BP.

Table 2
Multivariable linear regression analysis for association between zinc and BP.

	Systolic BP (mmHg)		Diastolic BP (mmHg)	
	Correlation coefficient (95%CI)	*P*-value	Correlation coefficient (95%CI)	*P*-value
Model 1				
DDE zinc (mg)	0.17 (−0.00, 0.35)	0.054	0.05 (−0.07, 0.16)	0.428
DDE animal zinc (mg)	0.41 (0.17, 0.65)	0.001	0.18 (0.02, 0.33)	0.024
Model 2				
DDE zinc (mg)	0.15 (−0.03, 0.32)	0.103	0.04 (−0.07, 0.15)	0.505
DDE animal zinc (mg)	0.36 (0.12, 0.60)	0.003	0.17 (0.01, 0.32)	0.037
Model 3				
DDE zinc (mg)	0.15 (−0.03, 0.32)	0.096	0.04 (−0.07, 0.16)	0.466
DDE animal zinc (mg)	0.37 (0.13, 0.61)	0.003	0.17 (0.02, 0.33)	0.030

Model 1: Adjusted for age and race ethnicity.
Model 2: Adjusted for age, race ethnicity, total family income and ever smoked regularly.
Model 3: Adjusted for age, race ethnicity, total family income, ever smoked regularly, alcohol in last 24 h and menopausal status.
BP: blood pressure; DDE: daily dietary estimate.

Table 3
Multivariable linear regression analysis for association between zinc and glucose and insulin.

	Glucose (mg/dl)		Insulin (uIU/ml)	
	Correlation coefficient (95%CI)	*P*-value	Correlation coefficient (95%CI)	*P*-value
Model 1				
DDE zinc (mg)	0.74 (0.40, 1.07)	<0.001	0.13 (−0.02, 0.29)	0.085
DDE animal zinc (mg)	1.21 (0.75, 1.66)	<0.001	0.28 (0.07, 0.49)	0.009
Model 2				
DDE zinc (mg)	0.71 (0.37, 1.04)	<0.001	0.13 (−0.03, 0.28)	0.105
DDE animal zinc (mg)	1.14 (0.68, 1.60)	<0.001	0.27 (0.05, 0.48)	0.014
Model 3				
DDE zinc, (mg)	0.69 (0.36, 1.03)	<0.001	0.12 (−0.03, 0.27)	0.128
DDE animal zinc (mg)	1.13 (0.67, 1.59)	<0.001	0.26 (0.05, 0.47)	0.016

Model 1: Adjusted for age and race ethnicity.
Model 2: Adjusted for age, race ethnicity, total family income and ever smoked regularly.
Model 3: Adjusted for age, race ethnicity, total family income, ever smoked regularly, alcohol in last 24 h and menopausal status.
DDE: daily dietary estimate.

Table 4
Stratification analysis for association between zinc and BP.

	Systolic BP (mmHg)			Diastolic BP (mmHg)		
	Correlation coefficient (95 % CI)	*P*-vale	Interaction-P	Correlation coefficient (95 % CI)	*P*-value	Interaction-P
DDE zinc (mg)						
Age < 46 (years)	0.08 (−0.16, 0.31)	0.531	0.402	−0.08 (−0.24, 0.08)	0.349	0.037
Age≥46 (years)	0.23 (−0.03, 0.49)	0.086		0.17 (0.00, 0.33)	0.044	
BMI < 24 (kg/m^2)	−0.07 (−0.36, 0.22)	0.625	0.267	−0.06 (−0.26, 0.14)	0.528	0.386
BMI≥24 (kg/m^2)	0.14 (−0.07, 0.36)	0.194		0.04 (−0.09, 0.18)	0.520	
DDE animal zinc (mg)						
Age < 46 (years)	0.29 (−0.03, 0.62)	0.079	0.583	−0.00 (−0.22, 0.22)	0.984	0.028
Age≥46 (years)	0.43 (0.07, 0.79)	0.019		0.35 (0.12, 0.57)	0.002	
BMI < 24 (kg/m^2)	0.23 (−0.18, 0.64)	0.267	0.936	0.10 (−0.18, 0.38)	0.485	0.862
BMI≥24 (kg/m^2)	0.25 (−0.04, 0.55)	0.095		0.13 (−0.06, 0.32)	0.171	

Adjusted for age, race ethnicity, total family income, ever smoked regularly, alcohol in last 24 h and menopausal status.
BMI: body mass index; BP: blood pressure; DDE: daily dietary estimate.

Table 5
Stratification analysis for association between DDE zinc and glucose and insulin.

	Glucose (mg/dl)			Insulin (uIU/ml)		
	Correlation coefficient (95%CI)	*P*-value	Interaction-P	Correlation coefficient (95%CI)	*P*-value	Interaction-P
DDE zinc (mg)						
Age < 46 (years)	0.57 (0.12, 1.03)	0.014	0.492	0.11 (−0.08, 0.29)	0.261	0.891
Age≥46 (years)	0.80 (0.32, 1.29)	0.001		0.13 (−0.11, 0.37)	0.299	
BMI < 24 (kg/m^2)	−0.22 (−0.58, 0.14)	0.228	0.002	−0.10 (−0.21, 0.01)	0.063	0.170
BMI≥24 (kg/m^2)	0.92 (0.46, 1.37)	<0.001		0.13 (−0.09, 0.34)	0.238	
DDE animal zinc (mg)						
Age < 46 (years)	0.82 (0.20, 1.45)	0.010	0.211	0.28 (0.02, 0.53)	0.035	0.867
Age≥46 (years)	1.41 (0.73, 2.08)	<0.001		0.24 (−0.10, 0.57)	0.163	
BMI < 24 (kg/m^2)	−0.37 (−0.87, 0.14)	0.155	0.001	−0.07 (−0.23, 0.08)	0.352	0.190
BMI≥24 (kg/m^2)	1.44 (0.82, 2.07)	<0.001		0.24 (−0.06, 0.53)	0.114	

Adjusted for age, race ethnicity, total family income, ever smoked regularly, alcohol in last 24 h and menopausal status.
BMI: body mass index; BP: blood pressure; DDE: daily dietary estimate.

previous studies have reported that zinc supplementation had beneficial impacts on lowering the risk of CVDs and T2D [32–34]. Wang et al. even observed that increased supplementation with zinc can promote the expression of metallothionein and lower the risk of vascular complications induced by diabetes [35]. Consistently, Khazdouz et al. conducted a recent meta-analysis which showed that zinc supplementation improves HbA1c and fasting blood glucose, very low-density lipoprotein-cholesterol, triglycerides and total cholesterol concentrations but had no effect on homeostasis model assessment-insulin resistance (HOMA-IR), systolic BP or diastolic BP [33]. Similar results were also found in a recent meta-analysis in which zinc supplementation improved HbA1c and fasting blood glucose, triglycerides and total cholesterol concentrations but not systolic or diastolic BP [24]. However, that study also reported that zinc supplementation had a beneficial effect on improved HOMA-IR [24], which is inconsistent with the results of the above studies. It is also markedly inconsistent with previous studies that our study reported a positive association of a higher DDE of animal zinc intake with cardiovascular and metabolic risk, which seems to indicate that the DDE of animal zinc intake has no benefit or even an adverse effect on cardio-cerebrovascular and metabolic risk. In addition to our results, some other studies also reported that an increased zinc intake was associated with an increased risk of chronic diseases [22,23]. There are some reasons to possibly explain these completely opposite conclusions. For example, an increased zinc intake from animal sources means that the person has a higher meat intake. Excessive intake of meat, especially meat containing saturated fat, may potentially increase cardiovascular, obesity and death risks [36–38]. As far as we know, those previous studies only explored the total intake of zinc and did not specify the source of intake, which probably partly explains why an increased DDE of animal zinc intake, but not the DDE of non-animal zinc intake,

was associated with higher cardio-cerebrovascular and metabolic risks. Moreover, these discrepancies may be closely related to the different selection of the included population, the analysis of the included variables and other factors. For instance, Khazdouz et al. only included study subjects with obesity, CVDs or T2D. Conversely, Laura M. Pompano et al. analyzed all study participants without considering their health status at baseline [24], which is consistent with our population of 2689 female subjects, for whom health status was not considered. Additionally, the types and definitions of covariates included in the multivariate analysis in various studies are also different.

Importantly, there was evidence supporting the observation that populations with health problems such as CVDs and T2D have been found to obtain a greater risk-lowering benefit for cardiovascular and metabolic diseases from dietary and/or supplemental zinc than those who did not have those chronic diseases [10], but that does not mean that the individuals without those health problems could not benefit from zinc-related interventions. In particular, a large number of individuals in rural areas or in areas with low resources in developing or poor countries might still benefit greatly from increased dietary zinc or zinc supplementation because many developing or poor countries with malnutrition burdens tend to have populations with insufficient zinc intakes, which increases their risk for zinc deficiency [39,40]. Fernández-Cao et al. performed a meta-analysis reporting a significant beneficial effect of a high dietary zinc intake in rural areas, whereas the effect was nonsignificant or much smaller in urban areas [12], which is similar to our results that the DDE of zinc intake is not associated with cardiovascular and metabolic risk factors. This study suggested that improved zinc intake in rural areas might be especially important for reducing risk factors for CVDs and T2D. In our stratified analysis, we found that a high DDE of animal zinc intake contributed to an increased risk for high blood glucose in subjects with a BMI$\geq$24 but not in those subjects with a BMI<24. It might be easy to explain that excessive intake of meat or animal viscera with high zinc content easily leads to obesity and diabetes. Although aging, lifestyle and menopause are closely related to changes in immunity, metabolism and the endocrine system in the human body, our results showed that covariates including “alcohol consumption”, “smoking status” and “menopausal status” did not significantly affect the association between the DDE of zinc intake and cardiovascular and metabolic risk (data not shown), even if zinc plays an important role in cellular metabolism and physiological processes.

The present study has several advantages that should be emphasized. The first advantage was that we used data from the SWAN study, which contained a large-sample, community-based female population (N = 2689) who were middle-aged, to examine the associations of the DDE of animal zinc intake with cardio-cerebrovascular and metabolic risk factors. Another advantage is that our study subjects were from a multiethnic population in the US, thereby increasing the generalizability of the results to various races. Furthermore, confounding variables such as age, race ethnicity, total family income, smoking status and drinking status were adjusted for these independent associations, which further contributed more reliability to our conclusions compared with some previous studies. The present study also had several limitations. First, unfortunately, male participants were not included in our analysis due to inherent limitations in the SWAN study. It is not known whether there is a sex difference in the independent relationship of the DDE of animal zinc intake with cardio-cerebrovascular and metabolic risk factors. Our results are also not generalizable to women who are younger or older than the age range of our participants. Second, the intake of animal zinc was calculated by a Food Frequency Questionnaire, which is not completely equal to the amount absorbed in the body due to individual differences in gastrointestinal digestion ability and various living habits. This may affect the detection of the actual association of zinc in the body with cardiovascular and metabolic risk factors to some extent in real-world conditions. Third, all included samples in our analysis were based on the community population, ignoring their health status or disease history, which may partly explain why our research results are not completely consistent with other conclusions from previous studies. Fourth, although the SWAN study is a longitudinal cohort study, we only analyzed the baseline data (cross-sectional analysis). Thus, we cannot determine temporal or causal relationships of the DDE of animal zinc intake with cardio-cerebrovascular and metabolic risk factors.

6. In conclusion

We observed an association of higher intakes of animal zinc with higher cardio-cerebrovascular and metabolic risk among middle-aged women. Although this seems surprising that it is consistent with many previous studies reporting a negative impact of zinc on the risk for chronic diseases, more well-designed research is needed to confirm this hypothesis.

Ethics approval

The study protocol was approved by The Institutional Review Board (IRB) at each SWAN site, and informed consent was obtained from all included individuals.

Authors’ contributions

Shu Feng Zou completed the first draft; Bixia Jiang completed data collation and validation; Rong Wan and Ying Huang revised the final draft and supervised it. All authors reviewed the manuscript.

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Availability of data and materials

Our study data in this retrospective analysis are mainly from the ICPSR public database (https://www.icpsr.umich.edu/web/ICPSR/search/studies?q=SWAN). The public-use data files in this collection are available for access by the general public. Access does not require affiliation with an ICPSR member institution.

Consent for publication

This paper is new, and neither the entire paper nor any part of its content has been published or accepted elsewhere. All authors agree to submit manuscripts to this journal.

Declaration of competing interest

There is no conflict of interest to be clarified.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcrp.2023.200231.

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