Nutrition, Metabolism & Cardiovascular Diseases (2010) xx, 1–8

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/nmcd

Nutrition, Metabolism & Cardiovascular Diseases

Gender differences in copper, zinc and selenium status in diabetic-free metabolic syndrome European population – The IMMIDIET study

J. Arnaud [a,b,*], M. de Lorgeril [c], T. Akbaraly [d,e], P. Salen [c], J. Arnout [f], F.P. Cappuccio [g], M.C.J.M. van Dongen [h], M.B. Donati [i], V. Krogh [j], A. Siani [k], L. Iacoviello [i], on behalf of the European Collaborative Group of the IMMIDIET Project [1]

[a] *Inserm, U 884, Bioénergétique Fondamentale et Appliquée, BP 53X, Grenoble Cedex 9, F38041 France*
[b] *Département de Biochimie, Toxicologie et Pharmacologie, Pôle de Biologie, CHU de Grenoble, BP 217, 38043 Grenoble Cedex 9, France*
[c] *Laboratoire Cœur et Nutrition, TIMC-IMAG-CNRS UMR 5525, Faculté de médecine, Domaine de la Merci, 38710 La Tronche, France*
[d] *Inserm, U 888, Pathologies du système nerveux: recherche épidémiologique et clinique; Université Montpellier I. Hôpital La Colombière, 39 avenue Charles Flahault, BP 34493, Montpellier Cedex 5, F34093, France*
[e] *Department of Epidemiology and Public Health, University College London, WC1E 6BT, United Kingdom*
[f] *Centre for Molecular and Vascular Biology, Katholieke Universiteit Leuven, O&N I Herestraat 49, 3000 Leuven, Belgium*
[g] *Clinical Sciences Research Institute, Warwick Medical School, The University of Warwick, Coventry CV4 7AL, United Kingdom*
[h] *Department of Epidemiology, Maastricht University, P.O. Box 616, 6200 MD Maastricht, The Netherlands*
[i] *Catholic University, Laboratory of Genetic and Environmental Epidemiology, Research Laboratories, 'John Paul II' Centre for High Technology Research and Education in Biomedical Sciences, Largo Gemelli 1, 86100 Campobasso, Italy*
[j] *Nutritional Epidemiology Unit, National Cancer Institute, Via Venezian, 1, 20133 Milan, Italy*
[k] *Unit of Epidemiology & Population Genetics, Institute of Food Sciences CNR, Via Roma 64, 83100 Avellino, Italy*

Received 22 March 2010; received in revised form 18 September 2010; accepted 20 September 2010

KEYWORDS
Metabolic syndrome;
Copper;
Zinc;

Abstract *Background and aims:* The European 'IMMIDIET' study was designed to evaluate the effect of genetic and dietary habit interactions on cardiovascular disease risk factors in non-diabetic subjects. Copper, zinc and selenium are involved in redox balance and modifications of their homeostasis could be associated with metabolic syndrome. Because few studies have

* Corresponding author. Département de Biochimie, Toxicologie et Pharmacologie, Pôle de Biologie, CHU de Grenoble, BP 217, 38043 Grenoble Cedex 9, France. Tel.: +33 4 76 76 54 84; fax: +33 4 76 76 56 64.
E-mail addresses: JArnaud@chu-grenoble.fr (J. Arnaud), michel.delorgeril@ujf-grenoble.fr (M. de Lorgeril), tasnime.akbaraly@inserm.fr (T. Akbaraly), patricia.salen@ujf-grenoble.fr (P. Salen), jef.arnout@med.kuleuven.be (J. Arnout), f.p.cappuccio@warwick.ac.uk (F.P. Cappuccio), MCJM.vanDongen@EPID.unimaas.nl (M.C.J.M. van Dongen), mbdonati@rm.unicatt.it (M.B. Donati), krogh@istitutotumori.mi.it (V. Krogh), asiani@isa.cnr.it (A. Siani), licia.iacoviello@rm.unicatt.it (L. Iacoviello).
[1] The European Collaborative Group of the *IMMIDIET* Project is listed in the Appendix.

0939-4753/$ - see front matter
doi:10.1016/j.numecd.2010.09.005

Please cite this article in press as: Arnaud J, et al., Gender differences in copper, zinc and selenium status in diabetic-free metabolic syndrome European population – The IMMIDIET study, Nutrition, Metabolism & Cardiovascular Diseases (2010), doi:10.1016/j.numecd.2010.09.005

Selenium;
Cardiovascular disease;
Europe

dealt with trace element status in metabolic syndrome with conflicting results, we aimed at investigating the relationships between plasma copper, zinc and selenium concentrations and metabolic syndrome in the IMMIDIET population.

Methods and results: Male–female couples born and living in Abruzzo, Italy ($n = 271$); Limburg, Belgium ($n = 267$), southwest part of London, England ($n = 263$) and 205 Italian–Belgian mixed couples living in Belgium were enrolled. Data on medical history, hypertension and blood lipid profile, medication use, smoking and alcohol habits, physical activity and socioeconomic status were collected using a standardised questionnaire. Anthropometric, blood pressure, glucose, insulin, lipid profile and copper, zinc and selenium measurements were performed. Participants were classified in two groups according to the presence of metabolic syndrome (Yes/No).

Comparison between these two groups, performed separately in men and women, indicated no association in men whereas, in women, metabolic syndrome was associated with higher plasma selenium concentrations (odds ratio (OR) = 1.55(1.28–1.89)); this association remained significant after adjustment for age, group, social status, physical activity, energy intake, alcohol consumption, smoking and hormonal status (OR = 1.33 (1.06–1.67)).

Conclusion: Our results indicate gender differences in the association between plasma selenium concentration and metabolic syndrome without diabetes and may suggest a sub-clinical deleterious effect of high selenium status in women.

Metabolic syndrome is defined as a cluster of risk factors which may predispose an individual to diabetes and cardiovascular diseases [1]. It has been hypothesised that oxidative stress represents a central mechanism of the metabolic syndrome because redox imbalance is at the crossroads of all risk factors involved in the syndrome [2,3]. According to this hypothesis, whether disturbances in copper, zinc and selenium homeostasis would be related to the metabolic syndrome is worth investigating, as these three trace elements are co-factors of antioxidant enzymes such as superoxide dismutase and glutathione peroxidases [4]. However, the few studies that compared these trace element concentrations in people with or without metabolic syndrome [5–8] in different countries led to conflicting results. The risk of developing cardiovascular diseases varies significantly across Europe [9], and according to age and gender [10]. Several factors may explain the European North–South and West–East gradients such as genetics, dietary and lifestyle habits.

The IMMIDIET study, designed to examine the impact of the interaction between dietary and genetic factors on cardiovascular risk profile in non-diabetic couples from different European countries, offered the opportunity of investigating the relationships between plasma copper, zinc and selenium concentrations and metabolic syndrome separately in both genders.

Methods

Study population

The IMMIDIET study was a cross-sectional study designed to investigate gene–environment interactions in relation to cardiovascular risk in apparently healthy couples or partners living together from Italy, Belgium and England. Details are available at http://www.moli-sani.org/immidiet_site/welcome.html. Briefly, the couples were randomly recruited from general practice in southeast London, England ($n = 263$), the Flemish territory of Belgium ($n = 267$) and the Abruzzo region of Italy ($n = 271$). The parents of these couples lived for at least two generations in the country of enrolment. The influence of cross-cultural changes was evaluated by including mixed couples ($n = 205$), formed by Italian migrants of the second generation, and native Belgians, living in the Flemish territory of Belgium. Exclusion criteria for all groups were history of cardiovascular disease (acute myocardial infarction, stable and unstable angina, stroke, transient ischemic attack and peripheral arterial disease), known diabetes (types 1 and 2), familial hypercholesterolaemia, malignancies, chronic diseases such as heart, liver or renal failure, defined coagulation deficiency, hypo- and hyperthyroidism and epilepsy.

The study was approved by the ethics committees of all participating institutions. All study participants gave their written informed consent.

Questionnaires

Data were collected using a well-standardised questionnaire that included items on medical history, hypertension and dyslipidaemia, family history of myocardial infarction, use of any medication, cigarette smoking and socioeconomic status defined as a score based on education, job and housing. Physical activity was estimated from the reported daily number of stairs climbed, time spent on walking or bicycling, frequency of housework, gardening, farming, lifting heavy materials and sports during the past year. Energy intakes were evaluated by semi-quantitative food frequency questionnaires [11,12].

Physical examination

Participating couples attended their general practitioner's clinic for the screening visit performed by trained physicians and nurses of the IMMIDIET staff. Blood pressure was

Please cite this article in press as: Arnaud J, et al., Gender differences in copper, zinc and selenium status in diabetic-free metabolic syndrome European population — The IMMIDIET study, Nutrition, Metabolism & Cardiovascular Diseases (2010), doi:10.1016/j.numecd.2010.09.005

measured with an automatic device (OMRON-HEM-705CP; Omron Health Care, Inc., Bannockburn, IL, USA) after the subject had been resting in the seated position for 10 min, and before blood sampling. Systolic and diastolic blood pressure was taken three times, with 2-min intervals between measurements and the average of the last two readings was used for the analyses. Body weight and height were measured on a standard beam balance scale with an attached ruler, with subjects wearing no shoes and only light indoor clothing. The body mass index (BMI) was calculated as weight in kilograms divided by the square of height in metres (kgm^{-2}). Waist circumference (WC) was measured according to the National Institutes of Health, National Heart, Lung and Blood Institute guidelines. In practice, with the subject standing erect with the abdomen relaxed, the arm at the sides and the feet together, WC was measured, to the nearest 0.1 cm, at a midway level between the lower rib margin and iliac crest with the tape all around the body in the horizontal position. The measurements were performed with a flexible inextensible plastic tape whose length was checked before starting the survey and once per month during the survey.

Biological analyses

Blood samples were obtained from participants after overnight fasting. The measurements of serum lipids and blood glucose were performed on automated analyser (Cobas-Mira-Plus; Roche, Milan, Italy). Plasma insulin was determined by enzyme-linked immunosorbent assay (ELISA) kit (DAKO Insulin, DAKO, Ely, UK) using a completely automated ELISA analyser (ETI-STAR, DiaSorin S.p.A, Saluggia, Italy). Plasma copper and zinc were determined by flame atomic absorption spectrometry (Perkin Elmer 560, Norwalk, CT, USA), and selenium by Zeeman electrothermal atomic absorption spectrometry (Perkin Elmer 4100, Norwalk, CT, USA). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as follows: ((glucose in $mmoll^{-1}$ $\times$ insulin in mUl^{-1})/22.5).

Metabolic syndrome definition

Metabolic syndrome was defined according to the revised criteria of International Diabetic Federation (IDF) and American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) [13], based on the presence of at least three of the following factors: waist circumference $>$102 cm in men and $>$88 cm in women; serum triglycerides $\geq$1.7 $mmoll^{-1}$ or specific treatment for this lipid abnormality; high-density lipoprotein (HDL) cholesterol $<$1 $mmoll^{-1}$ in men and $<$1.3 $mmoll^{-1}$ in women or specific treatment for this lipid abnormality; systolic blood pressure 130 mmHg or diastolic blood pressure $\geq$85 mmHg or treatment of previously diagnosed hypertension; fasting plasma glucose $\geq$5.5 $mmoll^{-1}$. The last criterion originally included a previous diagnosis of type 2 diabetes, but was not applied to IMMIDIET population as known diabetes (types 1 and 2) subject was a study exclusion criterion. However, 5.7% of the participants exhibited fasting blood glucose higher than 5.5 $mmoll^{-1}$.

Statistical analyses

Statistical analyses were performed separately in men and women as the criteria used for the definition of metabolic syndrome depend on gender. In addition, all interactions between plasma copper, zinc or selenium concentrations and other variables were tested, and we found a significant interaction between plasma selenium concentration and gender ($P = 0.0004$). Descriptive analysis results are presented as frequency or mean $\pm$ standard deviation (SD), according to the qualitative or quantitative nature of the variable. Characteristics of participants according to metabolic syndrome status were compared using the Student's *t*-test for continuous variables and the Mantel–Haenszel chi-square test for categorical variables. Furthermore, analysis of variance (ANOVA) was used to compare plasma trace element concentrations in the different groups. Logistic regression models were performed to examine the association between *z*-scores of plasma copper, zinc or selenium concentrations (analysed as continuous variables) and metabolic syndrome (model 1); after adjusting for age, national origin or mixed couple group, social status, physical activity, dietary energy intake, smoking habits and alcohol intake (model 2). Further adjustment for menopausal status and the use of oral contraceptive pills and hormone replacement therapy (HRT) were introduced in analyses carried out on women (model 3). Logistic regressions were performed simultaneously for copper and zinc as their metabolisms are intimately related. Association between each element concentration and metabolic syndrome was expressed by odds ratio (OR) with its confidence interval for each increase of one standard deviation of the component considered. *P* values $<$0.05 were considered statistically significant. Statistical analyses were performed with the SAS statistical software, Ver. 8.2 (SAS Institute Inc., Cary, NC, USA).

Results

The present study was carried on the 1902 non-diabetic participants (942 men and 960 women) with complete data on metabolic syndrome, plasma copper, zinc and selenium concentrations and without missing data for other co-variates. As many as 293 participants presented metabolic syndrome (15.4%), with a doubled prevalence of metabolic syndrome in men (20.6%) compared with women (10.3%). For each gender separately, characteristics of the IMMIDIET population as a function of metabolic syndrome status are described in Tables 1 and 2. Participants with metabolic syndrome were more likely to be older and overweight (both genders), to drink more alcohol and practice less physical activity (men only) and to consume a lower-energy diet (women only), compared with participants without metabolic syndrome. No significant difference was observed regarding social status and smoking habits between metabolic syndrome and non-metabolic syndrome groups. Expectedly, all the components contributing to metabolic syndrome as well as insulin and HOMA-IR were significantly different in participants with metabolic syndrome compared with participants without metabolic syndrome. Nevertheless, in

Please cite this article in press as: Arnaud J, et al., Gender differences in copper, zinc and selenium status in diabetic-free metabolic syndrome European population — The IMMIDIET study, Nutrition, Metabolism & Cardiovascular Diseases (2010), doi:10.1016/j.numecd.2010.09.005

Table 1 Socio-demographic status, lifestyle and anthropometric characteristics of the individuals with and without metabolic syndrome (MS) in both genders in the 1902 IMMIDIET participants with complete set of data. Results expressed as mean (standard deviation (SD)) or percentages.

		Men (n = 942)		p	Women (n = 960)		p
		Non MS (n = 748)	MS (n = 194)		Non MS (n = 861)	MS (n = 99)	
		Mean (SD) or %	Mean (SD) or %		Mean (SD) or %	Mean (SD) or %	
Age, years		46.2 (7.9)	49.1 (7.5)	<0.0001	43.9 (7.8)	49.4 (7.2)	<0.0001
Social Status Score	0	0.80	2.1	0.39	0.8	2.0	0.14
	1	13.0	10.3		13.4	19.2	
	2	31.7	29.9		27.3	33.3	
	3	24.7	27.8		30.8	21.2	
	4	26.9	28.4		25.6	23.2	
Tobacco consumption	Never smoker	72.1	66.5	0.17	78.3	74.7	0.87
	Former smoker	2.0	1.0		1.0	1.0	
	Smoker 0–9 cigd^{-1}	3.6	6.2		5.7	7.1	
	Heavy smokers ≥10 cigd^{-1}	22.3	26.3		15.0	17.2	
Alcohol consumption, gd^{-1}		24.2 (26.6)	29.9 (31.7)	0.02	8.5 (11.6)	8.1 (13.6)	0.79
Physical activity score		18.0 (7.1)	16.1 (6.8)	0.001	17.5 (6.1)	16.7 (5.6)	0.20
Energy intake, kJd^{-1}		2842 (874)	2910 (1086)	0.41	2319 (716)	2169 (716)	0.05
Waist circumference, cm		93.4 (9.2)	103.7 (10.2)	<0.0001	83.2 (10.6)	96.0 (9.3)	<0.0001
Body Mass Index, kgm^{-2}		26.6 (3.4)	29.9 (4.0)	<0.0001	25.2 (4.5)	29.9 (5.0)	<0.0001

participants with metabolic syndrome, the average values of fasting blood glucose in both genders, HDL cholesterol in men and diastolic blood pressure in women were in the 'not at risk' range. In addition, body mass index mean values indicated a high prevalence of overweight in the non-metabolic syndrome population.

Prevalence of metabolic syndrome differed significantly according to country groups, with the highest in Italy and the lowest in the mixed Belgian–Italian couples (Table 3). Plasma copper and selenium concentrations were the highest in Italians and the lowest in the mixed couples (Table 3). However, country group did not interact in the relationships between trace elements and metabolic syndrome (results not shown).

Plasma selenium concentrations were significantly higher in women with metabolic syndrome compared with women without metabolic syndrome (Table 2). Results of logistic regression models showed that women with high plasma selenium concentrations were more likely to have metabolic

Table 2 Medication and biological characteristics of the individuals with and without metabolic syndrome (MS) in both sexes in the 1902 IMMIDIET participants with complete set of data. Results expressed as mean (standard deviation (SD)) or percentages.

	Men (n = 942)		p	Women (n = 960)		p
	Non MS (n = 748)	MS (n = 194)		Non MS (n = 861)	MS (n = 99)	
	Mean (SD) or %	Mean (SD) or %		Mean (SD) or %	Mean (SD) or %	
Triglycerides, mmoll^{-1}	1.57 (0.86)	2.52 (0.16)	<0.0001	0.95 (0.41)	1.90 (0.79)	<0.0001
HDL cholesterol, mmoll^{-1}	1.32 (0.33)	1.10 (0.29)	<0.0001	1.54 (0.36)	1.32 (0.35)	<0.0001
Lipid lowering drugs, %	4.1	34.0	<0.0001	2.4	41.4	<0.0001
Systolic Blood pressure, mmHg	125.6 (14.5)	137.8 (15.5)	<0.0001	114.6 (15.5)	130.1 (20.3)	<0.0001
Diastolic blood pressure, mmHg	79.8 (9.4)	87.4 (8.9)	<0.0001	73.6 (9.1)	81.6 (10.7)	<0.0001
Anti hypertensive drugs, %	6.7	22.7	<0.0001	5.9	31.3	<0.0001
Fasting blood glucose, mmoll^{-1}	4.5 (0.6)	5.1 (1.5)	<0.0001	4.3 (0.6)	4.8 (1.6)	0.0009
Insulin, pmoll^{-1}	39.3 (25.6)	61.6 (39.5)	<0.0001	35.7 (23.2)	58.2 (32.6)	<0.0001
HOMA-IR	1.15 (0.81)	2.02 (1.39)	<0.0001	1.01 (0.75)	1.85 (1.27)	<0.0001
Oral contraceptive pills, %				71.7[a]	59.6[a]	0.01
Menopause, %				23.8[a]	45.5[a]	<0.0001
Hormonal replacement therapy, %				19.4[a]	29.7[a]	0.02
Copper, μmoll^{-1}	15.2 (2.4)	15.4 (2.3)	0.45	19.5 (5.3)	20.0 (4.8)	0.41
Zinc, μmoll^{-1}	13.1 (1.8)	13.2 (2.3)	0.15	12.5 (1.7)	12.8 (1.3)	0.02
Selenium, μmoll^{-1}	1.24 (0.23)	1.24 (0.23)	0.84	1.21 (0.23)	1.32 (0.28)	0.0002

[a] Information for oral contraceptive pills, menopause and hormonal replacement therapy were available for respectively 954 (no MS: 855; MS: 99), 948 (no MS: 849; MS: 99), and 814 (no MS: 723; MS: 91) women.

Please cite this article in press as: Arnaud J, et al., Gender differences in copper, zinc and selenium status in diabetic-free metabolic syndrome European population — The IMMIDIET study, Nutrition, Metabolism & Cardiovascular Diseases (2010), doi:10.1016/j.numecd.2010.09.005

Table 3 Plasma trace element concentrations, expressed as mean (standard deviation) and frequency of metabolic syndrome in men and women from the four population groups.

	Men (n = 942)				P	Women (n = 960)				P
	England	Italy	Belgium	Mixed[a]		England	Italy	Belgium	Mixed[a]	
n	247	240	258	197		254	246	260	200	
Metabolic syndrome, %	23.9	21.7	20.5	15.2	0.15	10.6	12.2	10.8	7.0	0.33
Copper, μmol^{-1}	15.1 (2.3)	16.0 (2.5)	15.0 (2.3)	14.7 (2.1)	<0.0001	18.9 (4.6)	20.3 (5.6)	20.1 (5.7)	18.8 (5.0)	0.002
Zinc, μmol^{-1}	13.3 (2.4)	12.8 (1.6)	13.0 (1.6)	13.2 (1.8)	0.05	12.6 (1.9)	12.1 (1.5)	12.8 (1.6)	12.5 (1.6)	<0.0001
Selenium, μmol^{-1}	1.19 (0.20)	1.40 (0.23)	1.20 (0.21)	1.16 (0.19)	<0.0001	1.18 (0.24)	1.33 (0.23)	1.22 (0.23)	1.13 (0.20)	<0.0001

[a] Mixed = cross-cultural change group formed by marriages between Italian migrants at the first or second generation, and native Belgian, living in the Flemish territory of Belgium.

syndrome (Table 4, Model 1). This positive association remained significant after adjustments (Table 4, Models 2 and 3). No significant association was found in men.

Plasma copper and zinc concentrations were not associated with metabolic syndrome in both genders in either univariate or multivariate models (Table 4).

Discussion

The present finding provides evidence that selenium is positively associated with a higher odd of metabolic syndrome in women but not in men in this population without diabetes. By contrast, no significant association was found between copper or zinc and metabolic syndrome.

With regard to zinc, the lack of association between zinc and metabolic syndrome in both genders in the IMMIDIET population is in agreement with the results of the study conducted in Iran [8]. By contrast, in the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX) trial [5], the occurrence of metabolic syndrome during the 7.5-year follow-up rose with increasing baseline zinc concentrations despite no significant impact of multi-antioxidant supplementation (β-carotene, vitamin C and E, zinc and selenium) over the 7.5-year intervention on occurrence of metabolic syndrome was found. However, we cannot compare our results to those of SU.VI.MAX trial due to the huge differences in study design, that is, lack of metabolic syndrome at baseline and multi-antioxidant supplement administration.

With regard to copper, the lack of association reported here is in accordance with the results reported in Iran [8].

With regard to selenium, we found increased plasma selenium concentrations in women with metabolic syndrome and the association remained significant after adjustments, suggesting but not demonstrating a cause–effect relationship. No significant association was found in men. Several factors may contribute to the selenium–gender interaction. Among them, sex hormones, use of tobacco and alcohol, hypertension, glucose intolerance,

Table 4 Association between copper, zinc or selenium (as continuous variable) and metabolic syndrome in men and women.

		Men				Women			
		n	OR[c]	95%CI	p	n	OR[c]	95%CI	p
Copper (by increase of 1 SD)	Model 1	942	1.12	0.96–1.30	0.15	960	1.09	0.89–1.33	0.41
	Model 2[a]	942	1.07	0.91–1.26	0.42	960	1.13	0.80–1.42	0.30
	Model 3[a]	_	–	–	–	810	1.13	0.88–1.44	0.35
Zinc (by increase of 1 SD)	Model 1	942	1.07	0.92–1.25	0.39	960	1.21	0.99–1.48	0.06
	Model 2[b]	942	1.14	0.98–1.34	0.09	960	1.19	0.96–1.48	0.11
	Model 3[b]	_	–	–	–	810	1.21	0.95–1.53	0.12
Selenium (by increase of 1 SD)	Model 1	942	0.98	0.84–1.15	0.84	960	1.55	1.28–1.89	<0.0001
	Model 2	942	0.97	0.81–1.16	0.75	960	1.42	1.15–1.77	0.001
	Model 3	_	–	–	–	810	1.33	1.06–1.67	0.01

Model 1: unadjusted association.
Model 2: adjustment for age, country group, social status, physical activity, energy intake, alcohol consumption and smoking.
Model 3: further adjusted for menopausal status, uses of oral contraceptive pills or hormonal replacement therapy.
[a] In these models plasma zinc was further included as a covariate.
[b] In these models plasma copper was further included as a covariate.
[c] Odd ratio associated with and increase in one SD of plasma trace element concentrations [copper (men: SD = 2.38 μmol^{-1}, women: SD = 5.29 μmol^{-1}) zinc (men: SD = 1.93 μmol^{-1}, women: SD = 1.67 μmol^{-1}) and selenium (men: SD = 0.23 μmol^{-1}, women: SD = 0.24 μmol^{-1})].

Please cite this article in press as: Arnaud J, et al., Gender differences in copper, zinc and selenium status in diabetic-free metabolic syndrome European population – The IMMIDIET study, Nutrition, Metabolism & Cardiovascular Diseases (2010), doi:10.1016/j.numecd.2010.09.005

dyslipidaemia, obesity, diet and lifestyle are the most well known [14—16]. In addition, biosynthesis of selenoenzymes and selenoproteins displays sex-specific differences in a dose-dependant manner [17]. Finally, it has been reported that variation in the selenoprotein S 1 gene locus contributes to the cardiovascular risk only in females [18]. Nevertheless, our results contrast with those of previous studies. In the Third National Health and Nutrition Examination Survey, similar serum selenium concentrations in people with or without metabolic syndrome were observed [6]. In the SU.VI.M.AX trial [5], serum selenium concentrations were not associated to metabolic syndrome but, as indicated above, the study design does not allow comparison with our findings. In addition, in these two large-scale studies [5,6], the analyses were not performed separately for men and women, which is a limitation in comparison with IMMIDIET results. Nonetheless, in the United Kingdom, among patients attending a cardiovascular risk-management clinic, serum selenium levels and glutathione peroxidase activity were similar in patients with and without metabolic syndrome in both genders [7]. Interestingly, in this study, serum selenium concentrations significantly decreased with increasing features of the metabolic syndrome in women but not in men [7]. This observation corroborates a potential gender effect, although opposite to our findings; and suggests that the association between selenium and the metabolic syndrome depends on the cumulative number of metabolic disturbances. Nonetheless, this negative association was not found in the Third National Health and Nutrition Examination Survey [6]. The impact of selenium in cardiovascular diseases remains inconclusive, due partly to the threshold in the protective effect of selenium [19], and depends on the type of cardiac diseases. The moderate inverse relationship between plasma or serum selenium concentrations and coronary heart diseases is observed in populations with low intakes but not in those with high intakes [19]. On the contrary, there is some evidence that selenium deficiency may lead to chronic heart failure [20]. Regarding specific association between serum selenium concentrations and each component of the metabolic syndrome, opposite effects of selenium on the different components of the metabolic syndrome (negative associations between serum selenium concentrations and abdominal obesity or HDL cholesterol and positive associations between serum selenium concentrations and triglycerides concentrations or blood pressure) have been reported in the United States [6,16]. These opposite relationships may explain the lack of association between selenium and metabolic syndrome reported in this population [6]. Other recent epidemiological reports and intervention trials [15,21—24] suggest that high concentrations of blood selenium may have adverse effects on metabolic cardiovascular risk factors such as glucose intolerance and dyslipidaemia by different potential mechanisms implying the mevalonate pathway, which is involved in selenoprotein and cholesterol synthesis; the regulation of lipoprotein synthesis by selenoprotein P; the effect of selenium compounds; and, particularly, glutathione peroxidase 1 on protein tyrosine phosphatase 1B [23—25]. However, selenium deficiency is also associated with diabetes [25], suggesting a nonlinear association between plasma (or serum) selenium concentrations and insulin resistance. In addition, the same dose of selenium may exert deleterious effects on diabetes and a protective effect against cancer [25,26].

Differences in study designs, population characteristics, cut-off points for classification and the weight of each component of the metabolic syndrome proposed by different consensus conferences, together with the complex interplay between trace elements and cardiometabolic risk contribute to discrepancies between IMMIDIET and previous reports [5—8] and may disclose some limitation of the concept of metabolic syndrome.

Our study presents limitations. First, IMMIDIET is a cross-sectional study that does not allow us to assess whether higher plasma selenium concentration in women with metabolic syndrome is a cause or a consequence of the metabolic disturbances. The interpretation of the association between trace elements and metabolic syndrome remains complex as the relationship between selenium — but also copper and zinc — and each component of the metabolic syndrome may manifest in opposite directions and are dose dependent [6,25]. Second, the IMMIDIET population might not be representative of metabolic syndrome as known diabetes was an excluding factor in IMMIDIET. Third, while plasma (or serum) selenium concentration is a good index of selenium status, plasma (or serum) copper and zinc have been criticised as indices of status [27,28]. However, in epidemiological studies [29,30] conducted in healthy populations such as in IMMIDIET, blood trace element concentrations remain the more usual way to assess trace elements status. Four, the participants included in IMMIDIET are obviously not representative of the whole European population, which limits the generalisation of our findings. Finally, the statistical power of IMMIDIET is not sufficient for analysing the association between trace element and metabolic syndrome in each country group. Despite these limitations, our results, combined to those reported in other studies, clearly underline that the full understanding of the relationships between trace element concentrations, metabolic syndrome and related cardiovascular diseases need further investigations in which gender need to be taken into account.

Acknowledgements

The IMMIDIET Project was supported by European Union grant No. QLK1-2000-00100. TNA was supported by the BUPA Foundation (UK).

Appendix

European Collaborative Group of the *IMMIDIET* Project
Project Co-ordinator: Licia Iacoviello
Scientific Committee: Jef Arnout, Frank Buntinx, Francesco P. Cappuccio, Pieter C. Dagnelie, Maria Benedetta Donati, Michel de Lorgeril, Vittorio Krogh, Alfonso Siani
Co-ordinating secretariat: Carla Dirckx
Data management and statistics: Augusto Di Castelnuovo
Dietary assessment and analysis: Martien CJM van Dongen, Vittorio Krogh
Communication and dissemination: Americo Bonanni

Please cite this article in press as: Arnaud J, et al., Gender differences in copper, zinc and selenium status in diabetic-free metabolic syndrome European population — The IMMIDIET study, Nutrition, Metabolism & Cardiovascular Diseases (2010), doi:10.1016/j.numecd.2010.09.005

Recruitment: Carla Dirckx, Pit Rink, Branislav Vohnout, Francesco Zito
External advisory committee: Mario Mancini, Napoli, Italy; Antonia Trichopoulou, Athens, Greece
The *IMMIDIET* group, collaborative centres and associated investigators
Research Laboratories, Centre for High Technology Research and Education in Biomedical Sciences, Catholic University, 86100 Campobasso, Italy (Licia Iacoviello, Francesco Zito, Augusto Di Castelnuovo, Romina di Giuseppe, Americo Bonanni, Branislav Vohnout, Marco Olivieri, Amalia De Curtis, Maria Benedetta Donati, Giovanni de Gaetano)
Centre for Molecular and Vascular Biology, Katholieke Universiteit Leuven, Leuven, Belgium (Jef Arnout, Carla Dirckx, Ward Achten)
Academic Centre for General Practice, Leuven, Belgium (Frank Buntinx, Carla Dirckx, Jan Heyrman)
Clinical Sciences Research Institute, Warwick Medical School, Coventry, United Kingdom (Francesco P. Cappuccio, Michelle A Miller)
Division of Community Health Sciences, St George's, University of London, United Kingdom (Pit Rink, Sally C Dean, Clare Harper)
Department of Epidemiology, Maastricht University, Maastricht, The Netherlands (Pieter C Dagnelie, Martien CJM van Dongen, Dirk Lemaître)
Laboratoire TIMC-IMAG, UFR de Médecine, Domaine de la Merci, 38710 La Tronche, France (Michel de Lorgeril)
Nutritional Epidemiology Unit, National Cancer Institute, Milan, Italy (Vittorio Krogh, Sabrina Sieri, Manuela Bellegotti, Daniela Del Sette Cerulli)
Unit of Epidemiogy & Population Genetics, Institute of Food Sciences CNR, Avellino, Italy (Alfonso Siani, Gianvincenzo Barba, Paola Russo, Antonella Venezia).

References

[1] Day C. Metabolic syndrome, or what you will: definitions and epidemiology. Diab Vasc Dis Res 2007;4:32—8.
[2] Roberts CK, Sindhu KK. Oxidative stress and metabolic syndrome. Life Sci 2009;84:705—12.
[3] Grattagliano I, Palmieri VO, Portincasa P, Moschetta A, Palasciano G. Oxidative stress-induced risk factors associated with the metabolic syndrome: a unifying hypothesis. J Nutr Biochem 2008;19:491—504.
[4] Klotz LO, Kroncke KD, Buchczyk DP, Sies H. Role of copper, zinc, selenium and tellurium in the cellular defense against oxidative and nitrosative stress. J Nutr 2003;133: 1448S—51S.
[5] Czernichow S, Vergnaud AC, Galan P, Arnaud J, Favier A, Faure H, et al. Effects of long-term antioxidant supplementation and association of serum antioxidant concentrations with risk of metabolic syndrome in adults. Am J Clin Nutr 2009;90:329—35.
[6] Ford ES, Mokdad AH, Giles WH, Brown DW. The metabolic syndrome and antioxidant concentrations: findings from the Third National Health and Nutrition Examination Survey. Diabetes 2003;52:2346—52.
[7] Ghayour-Mobarhan M, Taylor A, Lanham-New S, Lamb DJ, Azimi-Nezhad M, Kazemi-Bajestani SMR, et al. Serum selenium and glutathione peroxidase in patients with obesity and metabolic syndrome. Pakistan J Nutr 2008;7:112—7.
[8] Ghayour-Mobarhan M, Shapouri-Moghaddam A, Azimi-Nezhad M, Esmaeili H, Parizadeh SM, Safarian M, et al. The relationship between established coronary risk factors and serum copper and zinc concentrations in a large Persian cohort. J Trace Elem Med Biol 2009;23:167—75.
[9] Kromhout D. Epidemiology of cardiovascular diseases in Europe. Public Health Nutr 2001;4:441—57.
[10] Pilote L, Dasgupta K, Guru V, Humphries KH, McGrath J, Norris C, et al. A comprehensive view of sex-specific issues related to cardiovascular disease. CMAJ 2007;176:S1—44.
[11] Pisani P, Faggiano F, Krogh V, Palli D, Vineis P, Berrino F. Relative validity and reproducibility of a food frequency dietary questionnaire for use in the Italian EPIC centres. Int J Epidemiol 1997;26:S152—60.
[12] Bingham SA, Gill C, Welch A, Cassidy A, Runswick SA, Oakes S, et al. Validation of dietary assessment methods in the UK arm of EPIC using weighed records, and 24-hour urinary nitrogen and potassium and serum vitamin C and carotenoids as biomarkers. Int J Epidemiol 1997;26(Suppl. 1):S137—51.
[13] Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640—5.
[14] Ren J. Cardiac health and diabetes mellitus in women: problems and prospects. Minerva Cardioangiol 2006;54:289—309.
[15] Yang KC, Lee LT, Lee YS, Huang HY, Chen CY, Huang KC. Serum selenium concentration is associated with metabolic factors in the elderly: a cross-sectional study. Nutr Metab 2010;7:38.
[16] Laclaustra M, Navas-Acien A, Stranges S, Ordovas JM, Guallar E. Serum selenium concentrations and hypertension in the US population. Circ Cardiovasc Qual Outcomes 2009;2: 369—76.
[17] Schomburg L. Selene, the goddess of the moon: does she shine on men only? Eur Heart J 2007;28:2043—4.
[18] Alanne M, Kristiansson K, Auro K, Silander K, Kuulasmaa K, Peltonen L, et al. Variation in the selenoprotein S gene locus is associated with coronary heart disease and ischemic stroke in two independent Finnish cohorts. Hum Genet 2007;122: 355—65.
[19] Navas-Acien A, Bleys J, Guallar E. Selenium intake and cardiovascular risk: what is new? Curr Opin Lipidol 2008;19: 43—9.
[20] de Lorgeril M, Salen P. Selenium and antioxidant defenses as major mediators in the development of chronic heart failure. Heart Fail Rev 2006;11:13—7.
[21] Bleys J, Navas-Acien A, Guallar E. Selenium and diabetes: more bad news for supplements. Ann Intern Med 2007;147: 271—2.
[22] Bleys J, Navas-Acien A, Stranges S, Menke A, Miller 3rd ER, Guallar E. Serum selenium and serum lipids in US adults. Am J Clin Nutr 2008;88:416—23.
[23] Stranges S, Laclaustra M, Ji C, Cappuccio FP, Navas-Acien A, Ordovas JM, et al. Higher selenium status is associated with adverse blood lipid profile in British adults. J Nutr 2010;140: 81—7.
[24] Stranges S, Marshall JR, Natarajan R, Donahue RP, Trevisan M, Combs GF, et al. Effects of long-term selenium supplementation on the incidence of type 2 diabetes: a randomized trial. Ann Intern Med 2007;147:217—23.
[25] Mueller AS, Mueller K, Wolf NM, Pallauf J. Selenium and diabetes: an enigma? Free Radic Res; 2009:1—31.
[26] Bleys J, Navas-Acien A, Guallar E. Serum selenium levels and all-cause, cancer, and cardiovascular mortality among US adults. Arch Intern Med 2008;168:404—10.

Please cite this article in press as: Arnaud J, et al., Gender differences in copper, zinc and selenium status in diabetic-free metabolic syndrome European population — The IMMIDIET study, Nutrition, Metabolism & Cardiovascular Diseases (2010), doi:10.1016/j.numecd.2010.09.005

[27] Milne DB. Assessment of copper nutritional status. Clin Chem 1994;40:1479–84.
[28] Arnaud J, Chappuis P, Jaudon MC, Bellanger J. Nutritional biological markers of deficiencies of zinc, copper and selenium. Ann Biol Clin (Paris) 1993;51:589–604.
[29] Ford ES. Serum copper concentration and coronary heart disease among US adults. Am J Epidemiol 2000;151:1182–8.
[30] Hess SY, Peerson JM, King JC, Brown KH. Use of serum zinc concentration as an indicator of population zinc status. Food Nutr Bull 2007;28:S403–29.

Please cite this article in press as: Arnaud J, et al., Gender differences in copper, zinc and selenium status in diabetic-free metabolic syndrome European population — The IMMIDIET study, Nutrition, Metabolism & Cardiovascular Diseases (2010), doi:10.1016/j.numecd.2010.09.005