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This is an **author produced version** of a paper published in:

American Journal of Clinical Nutrition 118.1 (2023): 34-40

DOI: <https://doi.org/10.1016/j.ajcnut.2023.05.008>

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Dietary micronutrient adequacy and risk of multimorbidity in community-dwelling older adults

Running title: Micronutrient adequacy and risk of multimorbidity.

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Sources of support

This work was supported by grants from the Instituto de Salud Carlos III, State Secretary of R+D+I of Spain ERDF/ESF (European Regional Development Fund/ European Social Fund) (FIS 20/1040, 19/319) and the REACT EU Program, Comunidad de Madrid and the European Regional Development Fund (ERDF), European Union (FACINGLCOVID-CM project). VVC holds a “Training of university professors - FPU” grant (FPU19/06572) from the Spanish Ministry for Universities. EAS holds a Juan de la Cierva-Incorporación contract (IJC2018-035370-I) from Spanish Ministry of Science and Innovation. The funding agencies had no role in study design, data collection and analysis, interpretation of results, manuscript preparation or the decision to submit this manuscript for publication.

Conflict of interest

None of the authors has a conflict of interest related to this work.

Data sharing

Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval.

Abbreviations

MET: metabolic equivalent; RDA: Recommended Dietary Allowance

Abstract

Background: Multimorbidity refers to the coexistence of multiple chronic health conditions. The effect of nutritional adequacy on multimorbidity is mostly unknown.

Objective: The aim of this study was to assess the prospective association between dietary micronutrient adequacy and multimorbidity among community-dwelling older adults.

Methods: This cohort study included 1461 adults aged ≥ 65 years from the Seniors-ENRICA II cohort. Habitual diet was assessed at baseline (2015 to 2017) with a validated computerized diet history. Intake of 10 micronutrients (calcium, magnesium, potassium, vitamins A, C, D, E, zinc, iodine, and folate) was expressed as a percentage relative to dietary reference intakes, with higher scores indicating greater adequacy. Dietary micronutrient adequacy was computed as the average of all the nutrient scores. Information on medical diagnosis was obtained from the electronic health records up to December 2021. Conditions were grouped into a comprehensive list of 60 categories and occurrence of multimorbidity was defined as having ≥ 6 chronic conditions. Analyses were conducted using Cox proportional hazard models adjusted for relevant confounders.

Results: The mean age was 71.0 (SD: 4.2) years and 57.8% of participants were males. During a median follow-up of 4.79 years, we documented 561 incident cases of multimorbidity. Participants in the highest (85.8-97.7%) versus the lowest tertile (40.1-78.7%) of dietary micronutrient adequacy had a lower risk of multimorbidity [fully adjusted hazard ratio (95% confidence interval): 0.75 (0.59-0.95); p trend: 0.02]. A 1-SD increment in minerals adequacy and in vitamins adequacy were associated with lower risk of multimorbidity, although estimates were attenuated after additional

25 adjustment for the opposite subindex [minerals subindex: 0.86 (0.74-1.00); vitamins
26 subindex: 0.89 (0.76-1.04)]. No differences were observed by strata of
27 sociodemographic and lifestyle factors.

28 **Conclusion:** A higher micronutrient index score was associated with lower risk of
29 multimorbidity. Improving the dietary micronutrient adequacy could prevent
30 multimorbidity among older adults.

31 **Clinical Trial Registry:** ClinicalTrials.gov NCT03541135.

32 **Keywords:** Micronutrients, Diet Quality, Minerals, Vitamins, Multimorbidity, Chronic
33 Disease, Older Adults.

Introduction

Multimorbidity is the coexistence of multiple chronic health conditions in an individual [1]. Cardiovascular disease, cancer, chronic respiratory disease, musculoskeletal disease, and neurological disorders account for most of the global disease burden in the older population [2]. Increase in life expectancy and improved survival for these and other chronic conditions may partly explain the rising trend of multimorbidity [3], becoming a public health concern worldwide [4]. Multimorbidity increases with age, affecting around two-thirds of people aged 65 years and older, and is associated with reduced functional status, impaired quality of life, disability, and mortality [2,5]. Older adults with multiple conditions also require greater use of health care services [2]; moreover, it poses a challenge for usually single disease focused clinical practice [6], potentially leading to polypharmacy and fragmentation of care [7].

The study of modifiable lifestyle factors as determinants of multimorbidity is scarce [4]. Engaging in overall unhealthy lifestyle behaviors, including poor diet, smoking, alcohol consumption, insufficient physical activity, and high body mass index (BMI), has been associated with multimorbidity [8–10]. However, the independent impact of nutrition on multimorbidity remains an important evidence gap [11]. A recent longitudinal found that adherence to a Western diet pattern and higher consumption of processed meat and poultry were associated with increased risk of multimorbidity, while a Prudent diet pattern and higher consumption of fish, fruits and cereal were inversely associated with multimorbidity [12]. Another study in a smaller population found that consumption of fruits, vegetables and whole grain products, and intakes of some micronutrients, including magnesium, phosphorous, iron, selenium, and vitamin C, delayed the evolution of multimorbidity [13].

Recently, a dietary nutrient-based quality index was developed to capture micronutrient exposure relative to nutrient references intakes [14,15]. This is particularly important in older adults, where age-related physiological changes can lead to micronutrient deficiencies and, ultimately, malnutrition, which is frequently overlooked and poses a higher morbidity burden [16,17]. Thus, in this prospective study we aimed to examine the association between overall nutritional adequacy evaluated by a micronutrient-based diet quality index and risk of multimorbidity in community-dwelling older adults.

Methods

Study design and participants

We used data from the Seniors-ENRICA 2 cohort, an ongoing prospective study of 3273 adults aged ≥ 65 years. Participants were recruited between December 2015 and June 2017 by stratified random sampling of community-dwelling individuals living in the city of Madrid (Spain) and four nearby towns and holding a national healthcare card. Instruments and methods used for data collection were equivalent to those used in Seniors-ENRICA 1 cohort [18]. Briefly, information on sociodemographic factors, lifestyle, and health status were collected through a computer-assisted telephone interview by trained research staff. Additionally, two subsequent home visits were conducted to collect biological samples, perform a physical examination, and record habitual diet. Written informed consent was provided by all study participants and the Clinical Research Ethics Committee of *La Paz* University Hospital in Madrid approved the study protocol (PI-1793, PI-3554). The Research Central Commission of Madrid Regional Health Service (SERMAS), Primary Health Care, granted permission to access to computerized clinical records of primary health care.

Study variables

Diet and micronutrient index

Information on habitual food and beverage consumption in the preceding year was collected with a validated computer-assisted face-to-face dietary history, developed from the instrument used in the EPIC-cohort study in Spain [19]. This diet history recorded the consumption of more than 800 foods and beverages considering different cooking methods, seasonal variation in food consumption and portion sizes. Energy and nutrient intakes were estimated using standard food composition tables from Spain [20–24]. In the validation study, diet intake was measured with two repeated diet histories and compared against seven 24-hour recalls over a one-year period. Estimated Pearson's correlation coefficients (r) for micronutrients were as follows: $r=0.50$ for calcium, $r=0.43$ for potassium, $r=0.46$ for magnesium, $r=0.55$ for zinc, $r=0.47$ for iodine, $r=0.26$ for vitamin A, $r=0.66$ for vitamin C, $r=0.30$ for vitamin D, $r=0.52$ for vitamin E, and $r=0.46$ for folic acid [19].

Nutrient exposure was measured by a micronutrient-based diet quality index, that considers usual intake of eight micronutrients, previously identified as under-consumed among US adults: calcium, magnesium, potassium, choline, vitamin A, vitamin C, vitamin D, and vitamin E [14,15]. We expanded the index to include additional micronutrients relevant for older adults in Spain, including zinc, iodine, and folate [25,26]; of note, we excluded choline as we lacked information on its intake in our cohort. Each micronutrient is expressed as a percentage relative to the Recommended Dietary Allowance (RDA) proposed by the Spanish Agency for Food Safety and Nutrition (AESAN) [27], and truncated at 100% (i.e., intakes \geq RDA are scored a maximum of 100), with higher scores meaning better accordance to recommendations. The overall dietary micronutrient adequacy index is the average of the 10 scores for the

micronutrients considered and ranges from 0 to 100% [14,15]. Scoring details are described in **Supplementary Table 1**.

Chronic disease assessment

Information on chronic diseases was obtained through electronic health records from primary health care using the *International Classification of Primary Care* (ICPC-2). A condition was considered a chronic disease if it had a prolonged duration and a) left residual disability or worsening quality of life, or b) required a long period of care, treatment, or rehabilitation [28]. These conditions were grouped following the comprehensive list of 60 categories proposed by Calderón-Larrañaga et al. [28], based on a consensus among an international team of geriatricians, general practitioners, and epidemiologists. The full list of ICPC-2 codes used is included in **Supplementary Table 2**. Available data from electronic medical records from January 1, 1980, to December 31, 2021, were used for the study. Given their chronicity, any condition detected during that time was considered permanent. Conditions diagnosed prior the date of the study entry were defined as prevalent. The median number of prevalent chronic diseases in this population was 5; thus, the occurrence of multimorbidity was defined as the presence of ≥ 6 chronic diseases.

Covariates

We collected information on sociodemographic variables, health behaviors, and anthropometry. Participants reported their age, sex, educational level (primary or less, secondary, and university studies), and tobacco smoking (never, former, or current smoker). Weight and height were measured under standardized conditions and BMI was calculated as weight (kg) divided by height squared (m^2). Leisure-time physical activity, including time spent in walking, cycling, gardening, playing sports and housework, was

ascertained with the EPIC-cohort questionnaire validated in Spain and measured in metabolic equivalents hours per week (METs-h/week) [29]. During a home-visit, information on the medications currently used was collected by a trained nurse. All-cause mortality was ascertained by a computerized search of the National Death Index, which contains information on the vital status of all residents in Spain, up to the end of the study follow-up.

Statistical analysis

From the original study population at baseline, 483 individuals were excluded from the analyses because they lacked information on diet and another 6 participants were excluded because they did not provide their healthcare card information to access their clinical data. Excluded participants with missing information were older, more frequently females, had lower educational level, and were less often tobacco smokers. Since the cutoff point to define multimorbidity was having 6 or more chronic diseases, we excluded 1323 individuals with ≥ 6 chronic conditions at baseline to be able to assess the risk of incident multimorbidity among those without it at the beginning of the study. Thus, analyses were performed among 1461 participants (**Supplementary Figure 1**).

Participants were classified into tertiles of micronutrient adequacy and differences in subject characteristics across tertiles were assessed by analysis of variance (ANOVA), for continuous variables, and the Chi-Square test, for categorical variables. Person-years of follow-up were calculated from the date of the study entry to the date of occurrence of multimorbidity, death, or end of the study (December 31, 2021), whichever came first. Cox proportional hazard models were used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for the association between dietary micronutrient adequacy and risk of multimorbidity during follow-up; the lowest tertile was used as reference. Three sequential models were built: 1) adjusted for sex, age, educational

level, and number of chronic diseases at date of study entry (as a continuous variable); 2) additionally adjusting for tobacco smoking, physical activity (tertiles of METs-h/wk), BMI, energy intake (tertiles of g/d), alcohol consumption (tertiles of g/d) and number of medications, as a proxy for morbidity severity [30]; and 3) further adjusting for added sugars and consumption of processed meat, including bacon, ham, sausages, and salami, (both in tertiles of g/d), as a measure of poor diet quality. Linear trends were evaluated by modeling the tertiles median values of the dietary micronutrient adequacy index as a continuous variable. Also, analyses were performed per 1-SD theoretical increment of the index (8.52 percentage points). Additionally, we explored the association considering separately total minerals and total vitamins adequacy; models for the minerals' subindex were adjusted for the vitamins' subindex and vice versa.

We also assessed the association for each individual micronutrient. Participants were classified into two groups according to their adherence to the RDA: <RDA (i.e., score <100), as reference group, and \geq RDA (score = 100). Since vitamin D intake was low in this population, very few participants reached the RDA, thus, we used the median intake value to categorize the participants into two comparison groups.

To evaluate possible differences in the association between dietary micronutrient adequacy and multimorbidity risk, we stratified the analyses by sex, age (<70, \geq 70 years), education level (\leq primary, >primary studies), BMI (<30, \geq 30 kg/m²), energy intake (<median, \geq median of kcal/d), and physical activity (<median, \geq median of METs-h/wk). To test for interactions, we used likelihood-ratio tests to compare models with and without an interaction term, defined as the cross-product of the micronutrient index (as continuous variable) and the stratification variable.

Statistical significance was set at two-tailed $p < 0.05$. Analyses were performed using the SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina).

Results

Sociodemographic factors, lifestyle behaviors and morbidity of study participants are presented in **Table 1**. The mean age was 71.0 years (\pm 4.17) and 57.8 % of them were male. The most prevalent conditions at baseline were dyslipidemia (48.9%), hypertension (42.6%), ‘other musculoskeletal and joint diseases’ (25.7%), osteoarthritis (18.9%), osteoporosis (14.9%), and cataract (14.4%). Compared to participants in the first tertile of dietary micronutrient adequacy (range: 40.1-78.7%), those in the third tertile (range: 85.8-97.7%) were younger, less likely to be current smokers, had a higher BMI, spent more time on physical activities, and reported higher energy intake. They also had a lower prevalence of cataract and diabetes, and a higher prevalence of obesity at baseline.

During a median follow-up of 4.79 years, we identified 561 incident cases of multimorbidity. The condition which prevalence increased the most was ‘other metabolic diseases’ (20.5% increase), which included those with a diagnosis of vitamin/nutritional deficiency, followed by having cataract (13.7%), independently of subsequent surgery, ‘other musculoskeletal and joint diseases’ (11.0%), solid neoplasm (7.9%) and hypertension (7.9%) (**Supplementary Table 3**). Among participants who were identified as cases of multimorbidity, 19.8% developed one new chronic condition during follow-up, 35.8% developed two new chronic conditions, 22.8% three new chronic conditions, and 21.6% developed four or more new chronic conditions (**Supplementary Table 4**).

Participants with higher dietary micronutrient adequacy had a lower risk of developing multimorbidity compared to those with lower adequacy, after adjusting for sociodemographic factors and number of chronic diseases at baseline [model 1, HR (95% CI) for tertile 3 vs. 1: 0.79 (0.64-0.97); *p* trend 0.03]. This association remained statistically significant after adjusting for health behaviors, number of medications, and

205 dietary factors [model 3, HR (95% CI) for tertile 3 vs. 1: 0.75 (0.59-0.95); *p* trend 0.02].

206 When considering micronutrient adequacy as a continuous variable, a 1-SD increment
207 was associated with 14% (95% CI: 4 to 23%) lower risk of multimorbidity in fully
208 adjusted analysis (**Table 2**). Regarding the micronutrient subindices, we found a
209 significant association between a 1-SD increment in the mineral and vitamin subindices
210 and lower risk of multimorbidity, that were attenuated after additional adjustment for
211 the opposite subindex [model 4; minerals subindex: HR (95% CI): 0.86 (0.74-1.00);
212 vitamins subindex: 0.89 (0.76-1.04)] (**Table 2**).

213 Mean scores for minerals adequacy ranged from 83.3 to 92.7%, while for vitamins
214 ranged from 22.7 to 96.6% (**Supplementary Table 5**). Magnesium was the mineral
215 with the highest proportion of participants with maximum score (49.6% participants),
216 and calcium was the one with the lowest score (24.9%). For vitamins, vitamin C had the
217 highest proportion of participants with maximum score (86.2%), while for vitamin D,
218 only a 0.14% of them met the reference intake. When we assessed the association for
219 each micronutrient in the index, using non-adherence to the RDA as reference, we
220 found no statistically significant associations with multimorbidity for any of the
221 component scores (**Supplementary Table 6**). Lastly, in subgroup analyses, no
222 significant interactions were found for micronutrient adequacy and any of the
223 stratification variables (*p* for interactions >0.05 in all cases) (**Table 3**).

224 Discussion

225 In this prospective study, higher dietary micronutrient adequacy was associated with
226 lower risk of multimorbidity. This association was independent of health behaviors,
227 number of chronic conditions at baseline and use of medications, and consistent across
228 categories of sociodemographic and lifestyle variables. Adequacy of minerals intake, and
229 of vitamins intake, were also associated with multimorbidity. These results suggest that

improving nutritional adequacy of diet could prevent multimorbidity among community-dwelling older adults.

Previous evidence on the association between dietary indices and multimorbidity is scarce. In a longitudinal analysis of the UK Biobank cohort (participants mean age: 55 ± 8.1 y), three dietary patterns were derived by exploratory factor analysis; a “Western Pattern”, rich in red meat and processed meat, was associated with increased risk of multimorbidity, while for a “White meat pattern”, predominantly fish and poultry, and for a “Prudent pattern”, rich in vegetables, fruits, and cereal, with low consumption of processed meat, higher adherence was inversely associated with multimorbidity [12]. A cross-sectional study among middle-aged females in an Australian population, found that diet quality, measured with different indices including the Mediterranean Diet Score (MDS) and the Alternative Healthy Eating Index-2010 (AHEI-2010), was associated with lower multimorbidity [31]. Similarly, higher adherence to a Mediterranean diet ascertained with the Med Diet Score in a Cyprus population (mean age: 41 ± 17 years), was cross-sectionally associated with lower multimorbidity [32]. In a cross-sectional study with the Lifelines Cohort in the Netherlands, higher adherence to a “meat, alcohol and potato pattern” was related to higher prevalence of cardio-metabolic multimorbidity [33]. There is also some research on the association between food groups consumption and multimorbidity. Higher consumption of fruits, vegetables, whole grains, and fish have inversely been associated with multimorbidity [13, 34], while higher consumption of processed meat, poultry and soft drinks have directly been associated with multimorbidity [12, 35, 36].

Few studies have investigated the association between micronutrient intake and multimorbidity. In a study among Chinese adults (mean age: 49 ± 13 y) [13], higher intakes of several micronutrients, including magnesium, phosphorous, and iron, were

associated with less development of multimorbidity, and lower intakes of selenium and vitamin C were associated with more development, after a 5-year follow-up. In another cross-sectional study, intakes of calcium and potassium, but not sodium, were inversely associated with a cardiometabolic multimorbidity pattern [34]. Since minerals and vitamins are consumed in combination through different food sources, overall dietary micronutrient adequacy may better characterize the combined effect of bioactive components with anti-inflammatory and antioxidant activity relevant for preventing chronic diseases [37]. Micronutrients are involved in major biochemical and physiological pathways as cofactors and coenzymes for the maintenance of intermediary metabolism, the modulation of genetic transcription and the antioxidant response [38]. Thus, micronutrient inadequacy could lead to impaired biochemical functions, cellular senescence, and the acceleration of the ageing process [38,39].

There is currently no consensus for a standard definition of multimorbidity [4]. Issues concerning the list of conditions to operationalize multimorbidity, how diseases or group of conditions should be characterized, and cutoff to define multimorbidity originate a substantial heterogeneity in the literature [40]. We used a measure of multimorbidity based on a comprehensive list of chronic conditions categories constructed specifically for older adults [32], suitable for our study population. Although the most common definition is the coexistence of two or more conditions, we use a criterion based on having six or more to increase specificity and to allow for a greater differentiation between older adults with complex multimorbidity and those with lower number of morbidities [40].

Strengths of the study include its prospective design, the measurement of habitual food consumption with a validated diet history, the use of specific food composition tables to estimate nutrient intakes, and of coded data from primary care medical records, which may increase the reliability of the diagnoses. In addition, stratification analyses by

socioeconomic and lifestyle variables were robust. Several limitations should be acknowledged. Diet was measured only at baseline, which may entail some misclassification since participants may have changed dietary habits during the follow-up. In addition, some recall bias in food consumption may exist. We lacked information about the use of specific micronutrient supplements; however, only a few participants in our study were regular dietary supplements users (3%). It is possible that the questionnaire used to estimate the intake of supplements had methodological limitations and this intake was underestimated. Whereas choline was not included in the micronutrient index, choline concentration and intake have inconsistently been associated with several chronic diseases [41–43]. Despite the prospective nature of the study, reverse causality cannot completely be ruled out, since participants might have first experienced a deterioration in their general health due to multimorbidity and later, a decrease in their capacity to buy and cook a healthy diet with the appropriate amount of micronutrients. We did not examine the effect of micronutrient adequacy and interactions on specific clusters of multimorbidity. Also, any observational study, some residual confounding may persist despite adjustment for relevant confounders. Finally, due to the characteristics of the analytical sample and the inclusion of relevant micronutrients for non-institutionalized older adults from Spain, results can be applied only to this population.

In conclusion, a higher dietary micronutrient adequacy was associated with lower risk of multimorbidity in older adults. Though future studies should confirm these results in other populations, they suggest that improving nutritional adequacy through nutrient-dense healthy diets could prevent multimorbidity in this population.

ACKNOWLEDGMENTS

Authors' contributions

The authors' contributions were as follows: VVC, EAS and ELG designed the research; VVC performed the statistical analyses; VVC, EAS and ELG drafted the manuscript; ELG supervised the conduct of research; VVC and ELG had primary responsibility for final content; and all authors: reviewed the manuscript for important intellectual content and read and approved the final manuscript.

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Table 1. Baseline characteristics of study participants ($n=1461$)¹.

	Total study participants	Dietary Micronutrient Adequacy		
		Tertile 1	Tertile 2	Tertile 3
<i>n</i>	1461	487	487	487
Tertile median	NA	72.9	82.5	89.1
Tertile range	NA	40.1 – 78.7	78.8 – 85.7	85.8 – 97.7
Males, %	57.8	58.5	58.1	56.9
Age, y	71.0 ± 4.17	71.5 ± 4.42	70.9 ± 3.80	70.5 ± 4.21*
Education level, %				
Primary	58.7	61.4	55.2	59.3
Secondary	19.9	17.3	22.8	19.7
University	21.4	21.4	22.0	20.9
Tobacco smoking, %				
Current smoker	11.2	15.4	10.7	7.60*
Former smoker	41.8	37.4	42.5	45.6
Never smoker	47.0	47.2	46.8	46.8
BMI, kg/m ²	27.1 ± 3.98	26.7 ± 3.82	27.0 ± 3.93	27.5 ± 4.16*
Physical activity, METs-h/wk	66.9 ± 35.5	64.3 ± 36.9	66.0 ± 34.4	70.3 ± 35.0*
Energy intake, kcal/d	1988 ± 362	1798 ± 299	1978 ± 289	2189 ± 380*
Alcohol consumption, kcal/d	10.8 ± 14.3	10.9 ± 13.5	10.2 ± 14.4	11.2 ± 15.0
Added sugars consumption, g/d	20.3 ± 17.5	21.7 ± 19.9	20.1 ± 16.4	19.0 ± 15.7
Processed meat consumption, g/d	41.3 ± 38.4	38.5 ± 35.4	42.3 ± 38.6	43.2 ± 40.9

Number of medications	2.47 ± 2.13	2.54 ± 2.13	2.44 ± 2.08	2.43 ± 2.18
Number of prevalent conditions at baseline	3.40 ± 1.38	3.35 ± 1.37	3.40 ± 1.41	3.44 ± 1.36
Most prevalent conditions at baseline, %				
Cataract	14.4	12.7	18.5	11.9*
Dyslipidemia	48.9	49.5	48.3	49.0
Hypertension	42.6	44.2	42.9	40.9
Osteoarthritis and other degenerative joint diseases	18.9	18.5	19.3	18.9
Osteoporosis	14.9	13.4	15.0	16.4
Other musculoskeletal and joint diseases ²	25.7	26.3	22.8	27.9
Sleep disorder	13.9	11.7	16.2	13.8
Thyroid disease	12.5	12.7	11.9	12.7

BMI, body mass index; MET, metabolic equivalent; y, years.

¹Values are means ± SD or percentages unless otherwise indicated. *P* values based on Chi-Square test for categorical variables and ANOVA test for continuous variables: **p*<0.05.

²Including unspecified bursitis/tendinitis/synovitis, acquired spinal deformity and osteochondrosis.

Table 2. Hazard ratios (95% confidence interval) for the association between tertiles of dietary micronutrient adequacy and risk of multimorbidity during a median follow-up of 4.79 years ($n=1461$).

	Tertile 1	Tertile 2	Tertile 3	<i>P</i> trend	Per 1- <i>SD</i> increment
Micronutrient adequacy					
Person-years	1918	1920	2012		5850
Cases	196	192	173		561
Model 1	1.00	0.94 (0.77 – 1.15)	0.79 (0.64 – 0.97)	0.03	0.91 (0.84 – 0.98)
Model 2	1.00	0.92 (0.74 – 1.13)	0.76 (0.60 – 0.96)	0.03	0.88 (0.81 – 0.97)
Model 3	1.00	0.91 (0.74 – 1.13)	0.75 (0.59 – 0.95)	0.02	0.88 (0.80 – 0.97)
Minerals adequacy					
Range	45.2 – 84.6	84.7 – 93.2	93.3 – 100		42.2 – 100
Cases	200	192	169		561
Model 1	1.00	0.95 (0.78 – 1.16)	0.80 (0.66 – 0.99)	0.04	0.90 (0.82 – 0.98)
Model 2	1.00	0.93 (0.75 – 1.14)	0.76 (0.60 – 0.96)	0.03	0.87 (0.79 – 0.97)
Model 3	1.00	0.93 (0.75 – 1.15)	0.76 (0.60 – 0.96)	0.03	0.87 (0.78 – 0.97)
Model 4	1.00	0.96 (0.78 – 1.20)	0.79 (0.61 – 1.02)	0.08	0.86 (0.74 – 1.00)
Vitamins adequacy					
Range	27.0 – 71.0	71.1 – 79.9	80.0 – 99.8		27.0 – 99.8
Cases	198	175	188		561
Model 1	1.00	0.75 (0.61 – 0.92)	0.86 (0.70 – 1.05)	0.08	0.89 (0.81 – 0.98)
Model 2	1.00	0.77 (0.62 – 0.95)	0.87 (0.70 – 1.08)	0.12	0.87 (0.78 – 0.97)
Model 3	1.00	0.76 (0.61 – 0.93)	0.86 (0.69 – 1.07)	0.11	0.86 (0.77 – 0.97)

Model 4	1.00	0.79 (0.63 – 0.98)	0.92 (0.73 – 1.17)	0.35	0.89 (0.76 – 1.04)
Model 1: Cox proportional hazard model adjusted for age, sex, and educational level (\leq primary, secondary, university), and number of chronic conditions at baseline.					
Model 2: adjusted as Model 1 and for smoking status (never-, former-, current-smoker), BMI (<25 , $25\text{--}29.9$, ≥ 30 kg/m ²), energy intake (tertiles of kcal/d), alcohol consumption (tertiles of g/d), physical activity (tertiles of METs-h/wk), and number of medications.					
Model 3: adjusted as Model 2 and for added sugars (tertiles of g/d) and consumption of processed meat (tertiles of g/d).					
Model 4: adjusted as Model 3 and mineral subindex is additionally adjusted for vitamins subindex and vice versa.					

Table 3. Hazard ratios (95% confidence interval) for the association between dietary micronutrient adequacy and risk of multimorbidity, stratified by sociodemographic and lifestyle factors.

	<i>n</i>	Cases	Per 1-SD increment	<i>P</i> for interaction
Sex				
Male	845	300	0.90 (0.78 – 1.04)	0.69
Female	616	261	0.87 (0.76 – 1.00)	
Age				
<70 years	626	209	0.94 (0.80 – 1.10)	0.80
≥70 years	835	352	0.86 (0.76 – 0.97)	
Education level				
Primary	857	362	0.88 (0.78 – 1.00)	0.81
>Primary	604	199	0.88 (0.75 – 1.04)	
BMI				
<30 kg/m ²	440	143	0.86 (0.70 – 1.05)	0.67
≥30 kg/m ²	1021	418	0.89 (0.80 – 0.99)	
Energy intake ¹				
<median	731	289	0.88 (0.79 – 0.99)	0.71
≥median	730	272	0.89 (0.77 – 1.04)	
Alcohol consumption ²				
<median	730	292	0.81 (0.71 – 0.92)	0.19
≥median	731	269	0.98 (0.85 – 1.13)	
Physical activity ³				

<median	726	274	0.88 (0.77 – 1.01)	0.64
≥median	735	287	0.87 (0.76 – 1.00)	

BMI, body mass index; MET, metabolic equivalent.

Multivariable model: Cox proportional hazard model adjusted for age, sex, educational level (\leq primary, secondary, university), number of chronic conditions at baseline, smoking status (never-, former-, current-smoker), BMI (<25 , $25\text{--}29.9$, ≥ 30 kg/m²), energy intake (tertiles of kcal/d), alcohol consumption (tertiles of g/d), physical activity (tertiles of METs-h/wk), number of medications, consumption of added sugars (tertiles of g/d) and processed meat (tertiles of g/d), except for the stratification variable.

¹ Median: 1940 kcal/d

² Median: 4.60 g/d

³ Median: 61.2 METs-h/wk