

Original article

Association between nutrition and the evolution of multimorbidity: The importance of fruits and vegetables and whole grain products



Guillaume Ruel^{a,b,*}, Zumin Shi^{b,c}, Shiqi Zhen^c, Hui Zuo^c, Edeltraut Kröger^{a,d},
Caroline Sirois^{a,e}, Jean-Frédéric Lévesque^{a,f}, Anne W. Taylor^b

^a Institut national de santé publique du Québec, Québec, Canada

^b Population Research and Outcome Studies, University of Adelaide, South Australia, Australia

^c Department of Nutrition and Foodborne Disease Prevention, Jiangsu Provincial Center for Disease Control and Prevention, Nanjing, China

^d Centre d'excellence sur le vieillissement de Québec, Université Laval, Québec, Canada

^e Université du Québec à Rimouski, Canada

^f Centre de recherche du Centre hospitalier de l'Université de Montréal, Canada

ARTICLE INFO

Article history:

Received 3 April 2013

Accepted 10 July 2013

Keywords:

Nutrition

Multimorbidity

Comorbidity

Chronic diseases and fruits and vegetables

SUMMARY

Background & aims: Multimorbidity is a common health status. The impact of nutrition on the development of multimorbidity remains to be determined. The aim of this study is to determine the association between foods, macronutrients and micronutrients and the evolution of multimorbidity.

Methods: Data from 1020 Chinese who participated in the Jiangsu longitudinal Nutrition Study (JIN) were collected in 2002 (baseline) and 2007 (follow-up). Three-day weighted food records and status for 11 chronic diseases was determined using biomedical measures (hypertension, diabetes, hypercholesterolemia and anemia) or self-reports (coronary heart disease, asthma, stroke, cancer, fracture, arthritis and hepatitis). Participants were divided in six categories of stage of evolution of multimorbidity. Association of foods, macronutrients and micronutrients at baseline with stages in the evolution of multimorbidity were determined. Data were adjusted for age, sex, BMI, marital status, sedentary lifestyle, smoking status, annual income, education and energy intake.

Results: The prevalence of multimorbidity increased from 14% to 34%. A high consumption of fruit and vegetables ($p < 0.05$) and grain products other than rice and wheat ($p < 0.001$) were associated with healthier stages in the evolution of multimorbidity. The consumption of grain products other than rice and wheat was highly correlated with dietary fibers ($r = 0.77$, $p < 0.0001$), iron ($r = 0.46$, $p < 0.0001$), magnesium ($r = 0.49$, $p < 0.0001$) and phosphorus ($r = 0.57$, $p < 0.0001$) intake which were also associated with healthier stages.

Conclusion: This study provides the first evidence of an association between nutrition and evolution towards multimorbidity. More precisely, greater consumption of fruits and vegetable and whole grain products consumption appear to lower the risk of multimorbidity.

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1. Introduction

Multimorbidity, mainly defined as the presence of two or more medical conditions in an individual,¹ is common.^{2–4} Multimorbidity is part of a continuum which starts when a healthy individual develops a chronic disease. Thereafter, this patient lives

with the chronic disease and, in time, may develop other chronic disease(s). In the present paper, the term evolution of multimorbidity encompasses this continuum. This continuum implies transitions in chronic disease development stages that could be associated with an increased patient vulnerability but also periods of stability.

Some risk factors, such as smoking, physical activity and nutrition are known to modify the development of chronic disease. In this regard, malnutrition is consistently associated with increased multimorbidity and comorbidity rates^{5,6} leading to food consumption recommendations toward daily reference intakes for specific macronutrients and micronutrients.⁷ However, the impact of malnutrition on mortality in older and hospitalized populations

Non-standard abbreviations: FBG, fasting blood glucose; Hb, hemoglobin; JIN, Jiangsu longitudinal Nutrition Study.

* Corresponding author. Institut national de santé publique du Québec, 945, rue Wolfe, Québec G1V 5B3, Canada. Tel.: +1 418 650 5115x5716; fax: +1 418 643 5099.

E-mail address: guillaumeruel4@hotmail.com (G. Ruel).

seems to be secondary when compared to the impact of comorbidities.⁸ In this context the impact of nutrition on chronic disease development and treatment has increased. Studies on the impact of nutrition on chronic disease development are mainly undertaken for individual chronic disease. For example, numerous dietary approaches were developed to treat specific chronic disease including the Dietary Approach to Stop Hypertension (DASH),⁹ the Portfolio diet for hypercholesterolemia,¹⁰ the American Heart Association diet for cardiovascular disease.¹¹ General nutritional recommendations, such as those provided by food guides and the WHO/FAO consultation on the nutrition, diet and prevention of chronic disease, are mainly based on daily recommended intakes and on nutritional evidence for individual chronic disease. On the other hand, general approaches investigating the impact of nutrition on many chronic diseases simultaneously will provide an overview of the impact of nutrition on the large spectrum of chronic diseases in the general population and could be useful for food guide creation.

There are few studies investigating the evolution of multimorbidity, conceptualized as a gradual progression through different health stages. To the best of our knowledge, none have examined its relationship with nutrition. The main goal of this study was to determine the associations between nutrition and the evolution of multimorbidity. More specifically, the association of macronutrients, micronutrients and food categories with different steps of evolution of multimorbidity was assessed.

2. Materials and methods

2.1. Study design

The Jiangsu longitudinal Nutrition Study (JIN) is an ongoing cohort study investigating the relationship between nutrition and non-communicable chronic disease.¹² It uses the sub-sample from Jiangsu Province of the Chinese National Nutrition and Health Survey in 2002 as baseline. The rural sample was selected from six counties (Jiangyin, Taichang, Shuining, Jurong, Sihong and Haimen). From each of the six counties, three smaller towns were randomly selected. The urban sample was selected from the capital cities of the two prefectures, Nanjing and Xuzhou; and from each capital city three streets were randomly selected. The six counties and the two prefectures represented a geographically and economically diverse population. In each town/street, two villages/neighbourhoods were randomly selected, and ninety households were further selected randomly from each village/neighbourhood. All the members in the households were invited to take part in the study. In addition, one-third of the households gave dietary information, and all family members aged 20 years and older from these households were invited to give fasting blood samples. Flow chart has been described elsewhere.¹² Briefly, at baseline, complete dietary information was available for 2849 individuals. Of those, 1682 were identified for follow-up in 2007 and 1282 participated to the follow-up interview (76%). Among those, 1020 had complete information for every chronic disease status both at baseline and follow-up (80%) and were included in the present study. Individuals lost to follow-up were younger and had higher Body mass index (BMI) but no difference was found for energy intake and sex.¹³ The study was approved by the Jiangsu Provincial Center for Disease Control and Prevention. Written consents were obtained from all participants.

2.2. Physical and socio-demographic characteristics

Health professionals measured height, weight and waist circumference. Waist circumference was measured midway between the inferior margin of the last rib and the iliac crest in a

horizontal plane. Participants were interviewed by trained health workers using a pre-coded questionnaire. Interviews took approximately two hours to complete and included questions on socio-demographic information, medical history, cigarette smoking, physical activity and other lifestyle factors. Smoking was assessed by asking about the frequency of daily cigarette smoking. Household income was assessed by questions on family income and number of persons in the household. Education was based on six categories of education levels in the questionnaire. Occupational information was based on a question with twelve categories.

2.3. Chronic disease status assessments

Chronic disease status was determined at baseline and follow-up for the following 11 conditions: anemia, hypertension, hypercholesterolemia, diabetes, arthritis, hepatitis, coronary heart disease, asthma, stroke, fracture and cancer. Anemia, hypercholesterolemia and diabetes status were measured using overnight fasting blood samples collected from study participants. The blood samples were analyzed for fasting blood glucose (FBG), cholesterol and hemoglobin (Hb) in the local Centers for Disease Control and Prevention. FBG was measured using a hexokinase colorimetric test. Diabetes was defined by a FBG of above 7.0 mmol/l or the self-report use of glucose-lowering medication. Concentrations of total cholesterol were assessed enzymatically with commercially available reagents. Hypercholesterolemia was defined as a total cholesterol level of above 6.2 mmol/L or the self-report use of cholesterol-lowering medication.¹⁴ Hb was measured using the cyanmethaemoglobin method. Anemia was defined as Hb below 13 g/dl for men and 12 g/dl for women.¹⁵ Blood pressure was measured twice by mercury sphygmomanometer on the right upper arm of the participant, who was seated for five minutes before the measurement. The mean of these two measurements was used in the analyses. The cuff size was selected on the basis of the upper arm circumference to ensure that the cuff did not overlap. Hypertension was defined as systolic blood pressure above 140 mmHg and/or diastolic blood pressure above 90 mmHg, or the self-report use of antihypertensive drugs. Arthritis, hepatitis, coronary heart disease, asthma, stroke, fracture and cancer status were determined by participants' self-report of a medical diagnosis from a physician. Individuals with a positive status for a chronic disease at baseline were considered as having the chronic disease at follow-up. While some chronic diseases, such as anemia, could be considered as curable, those chronic diseases could exert some long term consequences on health that should be taken into account.¹⁶

2.4. Stages of evolution of multimorbidity

The present authors conceptualize the evolution of multimorbidity as a continuum including the stages leading to multimorbidity and those following its development. Participants were divided according to chronic disease status at baseline and chronic disease transition stages in 6 groups (Fig. 1, Panel A): healthy, healthy to a single chronic disease, stable with a single chronic disease, healthy to multimorbidity, stable multimorbidity, and increasing multimorbidity. Briefly, healthy individuals at baseline could stay the same (healthy), develop one chronic disease (healthy to a single chronic disease) or more chronic disease (healthy to multimorbidity) and were grouped accordingly. Other groups had one chronic disease (stable with one chronic disease) or more (stable multimorbidity) throughout the study. Finally, the increasing multimorbidity group had at least one chronic disease at baseline and developed at least another chronic disease.

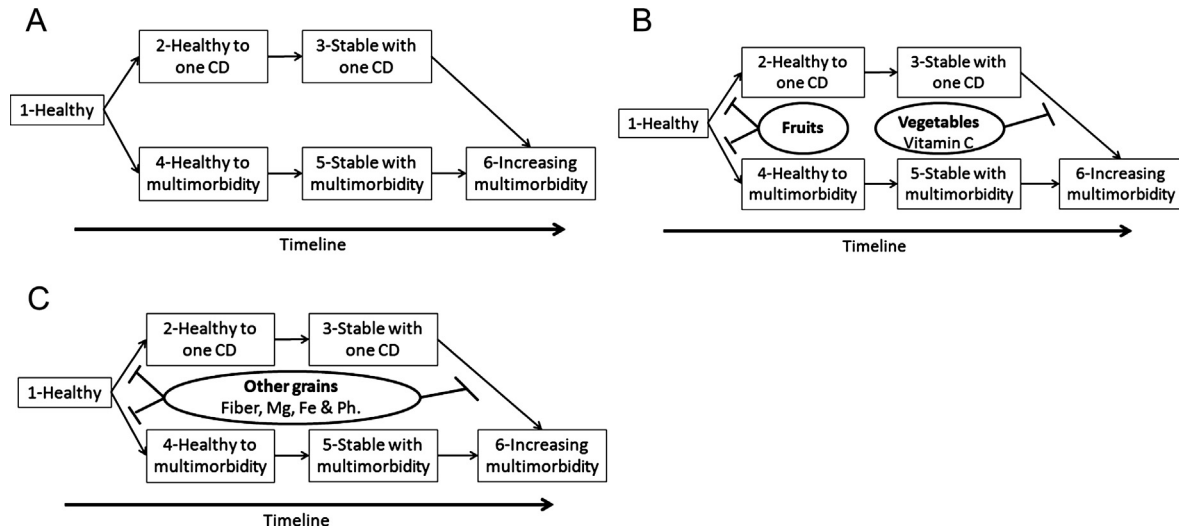


Fig. 1. Description of the different stages of evolution of multimorbidity (**panel A**) and the speculative impact of fruits and vegetables (**panel B**) and the grain products other than wheat and rice (**panel C**) on them.

2.5. Dietary measurements

At baseline, food intake was measured by three-day weighted food records. Participants were instructed to undertake this for three consecutive days including one weekend day. The food consumption data were analyzed for individual composition in macronutrients and micronutrients using the Chinese Food Composition Table.¹⁷

2.6. Statistical analyses

Paired *t* test was used to determine significant difference in the mean number of chronic disease between baseline and follow-up. Analysis of variance between groups (ANOVA) was used to determine significant differences in food categories, macronutrients and micronutrients between the study participants according to their evolution of multimorbidity stages. Those analyses were performed crude, adjusted for age group and sex and fully adjusted. The fully adjusted analysis including the following: age group, sex, BMI status, marital status, sedentary lifestyle, smoking status, annual income, educational attainment, and total caloric intake. When a significant difference in food category, macronutrients or micronutrients was observed between groups in the ANOVA crude analysis, a least square means analysis was used to determine significance between subgroups. Association between macronutrients and micronutrients significantly associated with stages of evolution of multimorbidity and foods category were determined using Pearson correlation coefficient. Unless stated otherwise, in the tables results are presented as crude data \pm SE while in the text the crude data \pm SD are used. In the text, the *p* values are from the fully adjusted model. All analyses were carried out using SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA) and a *p* < 0.05 was considered significant.

3. Results

Table 1 describes the baseline physical and socio-demographic characteristics of the cohort. Briefly, the cohort (mean age \pm SD, 49 \pm 13 years old) includes slightly more women (58%) than men and was mainly working (81%) and married (92%). At baseline, multimorbidity prevalence was 14%, and 58% of the population had at least one chronic disease. The number of individuals with

multimorbidity (two or more chronic diseases) increased from 139 to 346 which correspond to a significant increase in the mean number of chronic disease per person from 0.74 \pm 0.76 to 1.23 \pm 0.98 (*p* \leq 0.0001). More precisely, 627 individuals did not experience any change in chronic disease status while 296 and 97 individuals respectively gained either one or more chronic disease. For individual chronic disease status, the highest prevalence increase (18.9%) was noted for hypertension which increased from 31.6% in 2002 to 50.5% in 2007. Important increases were also noted for anemia (13.2%), hypercholesterolemia (7.7%) and diabetes (3.4%).

Association between evolution of multimorbidity and daily intake by food category as calculated from the three-day weighted food records at baseline is presented in Table 2. Healthy participants who developed a first chronic disease and those stable with one chronic disease had a higher total fruit and vegetable intake than those with either a stable or an increasing multimorbidity (*p* < 0.05). Fruits consumption was higher in the healthy group than in the other groups (*p* < 0.05). On the other hand, vegetables consumption (*p* < 0.05), mainly light vegetables (*p* < 0.01), was higher in individuals who developed a first chronic disease, those stable with one chronic disease and those healthy who developed multimorbidity than in those with a stable multimorbidity or those with an increasing multimorbidity. The groups stable with either one chronic disease or multimorbidity had higher salted vegetable consumption than the other groups (*p* < 0.005).

Difference between groups for total grain products and wheat were only significant in the crude model while those for rice and other type of grains were significant for every model. Total grain products consumption was lower in the stable with multimorbidity group than in any other group (*p* < 0.05). Wheat consumption was higher in the healthy and the healthy to first chronic disease groups than in both stable groups (*p* < 0.05). In the healthy group, the consumption of grain products other than wheat and rice was close to twice the intake of any other group (*p* < 0.05). The mean consumption of other grains was three time higher in the healthy to first chronic disease and the stable with one chronic disease groups than both the stable and the increasing multimorbidity groups (*p* < 0.05). Individuals who were healthy or developed their first chronic disease had a lower rice mean intake than those stable with one chronic disease, stable with multimorbidity and with increasing multimorbidity (*p* < 0.05).

Table 1
Baseline physical and socio-demographic characteristics for the 1020 participants.

Variable	N (%)
Age groups	
20–39	262 (26)
40–49	277 (27)
50–59	248 (24)
60+	233 (23)
Sex	
Male	430 (42)
Female	590 (58)
Education	
Illiterate	212 (21)
Primary school	317 (31)
Junior school	370 (36)
High school and over	121 (12)
Occupation	
Employed	
Farmers	295 (29)
Household work	214 (21)
Worker	176 (17)
Professional	49 (5)
Commercial service	47 (5)
Ordinal staff	25 (3)
Governmental employee	19 (2)
Unemployed	34 (3)
Retired	100 (10)
Others	61 (6)
Marital status	
Unmarried	12 (1)
Married & NR	939 (92)
Divorced	7 (1)
Widow	62 (6)
Annual income in yuan per person	
Under 800	88 (9)
800–1999	156 (15)
2000–4999	333 (33)
5000–9999	316 (31)
10 000–19 999	93 (9)
Over 20 000	29 (3)
NR	5 (1)
Number of person in family	
1	23 (2)
2	329 (33)
3	320 (31)
4	158 (16)
5 and more	190 (19)
Smoking status (1 cig per week)	
Yes	276 (27)
No	744 (73)

NR: Not reported.

In the meat and alternative food category, differences between groups were significant only in the fully adjusted model. In this model, total meat consumption was found to be higher in individuals stable with multimorbidity than in any other group except the increasing multimorbidity group ($p < 0.05$). Among meat and alternatives subcomponents, red meat intake was higher in both the stable and increasing multimorbidity groups than in the stable with one chronic disease and the healthy to multimorbidity groups ($p < 0.05$).

Difference between stages of evolution of multimorbidity and energy and macronutrients daily intake as calculated from three-day weighted food records at baseline are presented in Table 3. While total energy intake was not associated with the stages of evolution of multimorbidity, the increasing multimorbidity group had a lower mean energy density than the other groups ($p < 0.001$). Carbohydrate consumption was found to be lower in the stable with multimorbidity than in healthier groups ($p < 0.05$) and fat consumption was lower in the healthy to multimorbidity than the other groups ($p < 0.05$ in the fully adjusted model). In support, a

low proportion of energy from fat and a high from carbohydrate were associated with increased risk to develop multimorbidity (healthy to multimorbidity) as compared to the other groups ($p < 0.05$). Concerning fat sources, a highest proportion of fat from animal sources was observed in both the increasing and stable with multimorbidity groups as compared to the healthy, healthy to one chronic disease and the stable with one chronic disease groups ($p < 0.05$, in both adjusted model).

A high fiber intake was strongly associated with better health stages ($p < 0.001$). More precisely, the healthy group had a higher fiber intake than the stable with one chronic disease, stable with multimorbidity and the increasing multimorbidity groups. Also, those who developed a first chronic disease (healthy to one chronic disease) had higher fiber intake than those in either the stable and the increasing multimorbidity stages. Finally, those stable with one chronic disease had higher intake than those stable with multimorbidity ($p < 0.05$).

Table 4 presents the association between multimorbidity evolution stages and micronutrients. Among others, a high intake in iron, magnesium and phosphorus is associated with a healthier profile. More specifically, the daily intake in those micronutrients was higher in healthy individual than in those stable with one chronic disease, stable with multimorbidity or with increasing multimorbidity ($p < 0.05$). Magnesium and phosphorus daily intakes were also higher in the healthy to one chronic disease group than in both the stable and the increasing multimorbidity groups ($p < 0.05$). Those micronutrients were also higher in individuals stable with one chronic disease than in those in the stable with multimorbidity ($p < 0.05$). Concurrently, a low intake in selenium was found in the healthy to multimorbidity group ($p < 0.05$ vs. healthy, healthy to first chronic disease and increasing multimorbidity groups) while vitamin C was lower in those in the increasing multimorbidity group ($p < 0.05$ vs. healthy to first chronic disease, stable with one chronic disease and the healthy to multimorbidity groups). Potassium and vitamin B1 intake were higher in the healthy and the healthy to first chronic disease groups than in the stable with multimorbidity group ($p < 0.05$ only for crude data).

In order to establish potential associations between food sources and macronutrients and micronutrients, Pearson correlation coefficients were calculated (Table 5). Dietary fiber ($r = 0.77$, $p < 0.0001$), iron ($r = 0.46$, $p < 0.0001$), magnesium ($r = 0.49$, $p < 0.0001$) and phosphorus ($r = 0.57$, $p < 0.0001$) intakes were highly correlated with the consumption of grain products other than wheat and rice. Accordingly, correlations between daily intake in iron, magnesium, potassium and fibers were all between 0.65 and 0.92. Another pattern was observed for total cereal intake which was correlated with potassium ($r = 0.39$, $p < 0.0001$) and vitamin B1 ($r = 0.42$, $p < 0.0001$). Potassium and vitamin B1 were correlated ($r = 0.61$, $p < 0.0001$). Vitamin C intake was correlated with vegetable ($r = 0.70$, $p < 0.0001$) intake.

4. Discussion

To the best of our knowledge, this study provides the first evidence on the relationship between nutrition and evolution of multimorbidity. The present study reports a beneficial effect of the consumption of greater amounts of fruits and vegetables and grain products other than rice and wheat to prevent evolution of multimorbidity in a Chinese cohort. Those findings are in line with current food guides recommendations on fruits and vegetables and whole grain cereals.

The mean daily intake of fruits and vegetables is higher in the healthy, healthy to first chronic disease and the stable with one chronic disease groups than in the stable and increasing

Table 2

Association between stages of evolution of multimorbidity and food category as calculated from three-day food records in 2002 for the 1020 participants.

N	Stages of evolution of multimorbidity						Statistical models		
	Healthy	Healthy to first disease	Stable with one disease	Healthy to multimorbidity	Stable with multimorbidity	Increasing multimorbidity	Crude	Adjusted for age and sex	Adjusted for other risk factors ^a
	234	145	295	51	98	197			
Fruits & Vegetables (g/day)									
Total	377 ± 198 ^{e,f}	385 ± 204 ^{e,f}	374 ± 175 ^{e,f}	377 ± 170 ^e	316 ± 151	333 ± 152	≤0.005	≤0.05	≤0.05
Fruits	57 ± 103 ^{b,c,d,e,f}	36 ± 76	40 ± 91	24 ± 62	26 ± 55	34 ± 71	≤0.01	≤0.05	≤0.05
Vegetables									
Total	320 ± 164	349 ± 184 ^{e,f}	333 ± 155 ^{e,f}	353 ± 166 ^{e,f}	290 ± 132	298 ± 138	≤0.01	≤0.05	≤0.05
Dark	139 ± 124	151 ± 147	136 ± 113	160 ± 119	138 ± 96	137 ± 104	ns	ns	ns
Light	164 ± 114	183 ± 118 ^{e,f}	176 ± 125 ^{e,f}	182 ± 126 ^{e,f}	128 ± 99	146 ± 100	≤0.001	≤0.005	≤0.01
Salted	16 ± 24 ^{c,e}	15 ± 19 ^{c,e}	21 ± 29 ^{d,f}	11 ± 16 ^{e,f}	24 ± 30 ^f	15 ± 22	≤0.005	≤0.005	≤0.005
Meat & Alternatives (g/day)									
Total meat	96 ± 88 ^e	94 ± 79 ^e	90 ± 77 ^{e,f}	84 ± 67 ^e	101 ± 73	96 ± 77	ns	ns	≤0.05
Poultry	25 ± 45	25 ± 41	22 ± 39	32 ± 44	26 ± 38	21 ± 40	ns	ns	ns
Red meat	71 ± 68	69 ± 63	67 ± 66 ^{e,f}	52 ± 55 ^{e,f}	75 ± 60	76 ± 66	ns	ns	≤0.05
Pork	57 ± 58	57 ± 52	53 ± 56 ^f	47 ± 49 ^f	58 ± 54	65 ± 61	ns	ns	≤0.05
Substitutes									
Fish	59 ± 68	71 ± 80	58 ± 64	44 ± 55	53 ± 62	63 ± 71	ns	ns	ns
Offal	8 ± 24	6 ± 16	7 ± 20	3 ± 14	8 ± 25	5 ± 13	ns	ns	ns
Nuts	8 ± 24	7 ± 16	6 ± 22	7 ± 18	7 ± 18	6 ± 20	ns	ns	ns
Legume									
Fresh	15 ± 22	13 ± 18	15 ± 25	9 ± 14	15 ± 20	12 ± 18	ns	ns	ns
Dry	2.9 ± 12.2	4.0 ± 14.1	4.0 ± 22.6	3.8 ± 11.6	1.7 ± 5.5	5.4 ± 25.2	ns	ns	ns
Milk and alternatives (g/day)									
Dairy products	10 ± 43	5 ± 28	9 ± 36	4 ± 21	16 ± 50	10 ± 39	ns	ns	ns
Eggs	28 ± 34	29 ± 41	24 ± 26	25 ± 38	26 ± 32	30 ± 40	ns	ns	ns
Grain products									
Total	400 ± 142 ^e	401 ± 117 ^e	386 ± 124 ^e	423 ± 121 ^e	357 ± 106 ^f	382 ± 119	≤0.05	ns	ns
Wheat	99 ± 137 ^{c,e}	109 ± 141 ^{c,e,f}	70 ± 109	85 ± 140	65 ± 102	81 ± 122	≤0.01	ns	ns
Rice	251 ± 138 ^{c,d,e,f}	265 ± 146 ^{c,d,f}	296 ± 131	325 ± 156	289 ± 119	295 ± 131	≤0.001	≤0.001	≤0.001
Others	50 ± 112 ^{b,c,d,e,f}	27 ± 79 ^{e,f}	20 ± 78 ^{e,f}	13 ± 48	2 ± 10	6 ± 40	≤0.001	≤0.001	≤0.001
Cakes & Biscuits	5 ± 18	6 ± 19	11 ± 29	5 ± 13	9 ± 24	9 ± 23	ns	ns	ns

Data are presented as mean ± SD.

^a Includes age, sex, smoking status, annual income, marital status, education, BMI and sedentarity.^b Significantly different from the healthy to first disease group.^c Significantly different from the stable with one CD group.^d Significantly different from the healthy to multimorbidity group.^e Significantly different from the stable with multimorbidity group.^f Significantly different from the increasing multimorbidity group.

multimorbidity groups. The beneficial impact of fruits and vegetables on different chronic diseases has been recently reviewed.¹⁸ Boeing et al. concluded that the evidence of a beneficial impact of fruits and vegetables consumption on hypertension, coronary heart disease, diabetes and stroke are convincing while those for cancer, arthritis, fracture, asthma were either probable or possible.¹⁸ This review did not report on hypercholesterolemia, a prevalent chronic disease in the present study. While fruits are known to improve arterial stiffness¹⁹ and plasma high density lipoprotein cholesterol (HDL-C) concentration²⁰ their impact on hypercholesterolemia remains to be proven and is debatable.

In the present study, fruit consumption was higher in the healthy group than any other group while vegetable consumption was higher in the healthy to 1 chronic disease and the stable with 1 chronic disease groups. This is an important finding that suggest that fruit consumption may be an important factor in preventing the occurrence of a first chronic disease while vegetable consumption could delay the occurrence of later chronic disease (Fig. 1, Panel B). In support of this observation the consumption of fruits, but not vegetables, was shown to exert a beneficial impact on the 12.6 years development of hypertension,²¹ a chronic disease that could be hypothesized to develop in earlier step of the evolution of multimorbidity. Our results highlight the possible association between higher consumption of fruits and vegetables and a lower risk of multimorbidity.

Figure 1 (Panel C) presents important results on the beneficial impact of grain products other than rice and wheat to prevent

evolution of multimorbidity. The decrease in the mean intake of grain products is progressive and significant across evolution of multimorbidity stages starting from 50 g/day in healthy to 6 g/day in the increasing multimorbidity group. Grains other than rice and wheat such as oat, corn, sorghum, rye, barley, millet, quinoa are less likely to be refined and thus have the potential to contain more dietary fibers. In support of this hypothesis, 59% of the variance in fiber intake was explained by the consumption of cereals other than rice and wheat. The benefits associated with whole grain are well known and include, among others, a reduction in cardiovascular disease, diabetes and colorectal cancer risk.²² Also, a healthy diet pattern including a high consumption of whole grains was associated with a reduced risk of anemia in the present cohort.²³ Phytochemicals, namely phenolics (phenolic acids, alkylresorcinols and flavonoids), carotenoids, vitamin E, β-glucan and dietary fibers, and micronutrients (including magnesium, iron, selenium and potassium) are thought to play an important role in the benefits associated with whole grain consumption.²² In this regard, the consumption of grain products other than rice and wheat also accounted for over 24% of the magnesium, 32% of the phosphorus and 21% of the iron intake. In support, those micronutrients had a similar progressive decrease in their dietary intake through the evolution of multimorbidity stages. A high intake of magnesium is associated with a decreased risk of diabetes, hypertension, CVD and anemia.^{24,25} The identification of grain products as the main source of phosphorus as already been reported in the Japanese but evidences of the beneficial impact of phosphorus on chronic diseases

Table 3
Association between stages of evolution of multimorbidity and macronutrient and micronutrient intakes calculated from three-day food records in 2002 for the 1020 participants.

N	Stages of evolution of multimorbidity						Statistical models		
	Healthy	Healthy to first disease	Stable with one disease	Healthy to multimorbidity	Stable with multimorbidity	Increasing multimorbidity	Crude	Adjusted for age and sex	Adjusted for other risk factors ^a
	234	145	295	51	98	197			
Energy (Kcal/day)	2368 ± 679	2419 ± 647	2319 ± 664	2313 ± 665	2166 ± 571	2314 ± 632	ns	ns	ns
Energy density (J/Kgday) ^a	2.5 ± 0.9 ^e	2.5 ± 0.8 ^e	2.4 ± 0.8 ^e	2.5 ± 0.8 ^e	2.4 ± 0.9 ^e	2.2 ± 0.8	≤0.01	≤0.005	≤0.001
Daily intake (g/day)									
Carbohydrates	322 ± 111 ^d	324 ± 86 ^d	317 ± 101 ^d	343 ± 96 ^d	294 ± 87	310 ± 90	≤0.05	ns	≤0.01
Fiber	14 ± 12 ^{b,d,e}	12 ± 9 ^{d,e}	11 ± 9 ^d	12 ± 8	9 ± 4	10 ± 9	≤0.001	≤0.001	≤0.001
Sugar	5 ± 17	6 ± 17	5 ± 16	7 ± 17	5 ± 21	4 ± 12	ns	ns	ns
Fat	84 ± 40 ^c	86 ± 37 ^c	79 ± 34 ^e	72 ± 34 ^{d,e}	77 ± 33	83 ± 36	ns	ns	≤0.05
Protein	74 ± 22	74 ± 22	71 ± 21	69 ± 23	68 ± 20	72 ± 23	ns	ns	ns
Alcohol	1.6 ± 4.4	1.9 ± 5.4	1.9 ± 5.4	0.6 ± 2.5	1.4 ± 5.2	2.2 ± 6.2	ns	ns	ns
Proportion of energy (%)									
Carbohydrate	54 ± 11 ^c	55 ± 9 ^c	56 ± 10 ^c	59 ± 8 ^{d,e}	54 ± 9	54 ± 9	≤0.05	≤0.05	≤0.005
Fat Total	32 ± 10 ^c	32 ± 8 ^c	31 ± 9 ^c	28 ± 8 ^{d,e}	32 ± 9	32 ± 9	≤0.05	≤0.05	≤0.01
Animal	33 ± 22	32 ± 20	34 ± 22	34 ± 22	38 ± 20	37 ± 21	ns	≤0.05	≤0.05
Vegetable	67 ± 22	68 ± 20	66 ± 22	66 ± 22	62 ± 20	62 ± 21	ns	≤0.05	≤0.05
Protein	14 ± 3	14 ± 3	14 ± 3	13 ± 3	14 ± 3	13 ± 3	ns	ns	ns

Data are presented as mean ± SD.

^a Includes age, sex, smoking status, annual income, marital status, education, BMI and sedentarity.

^b Significantly different from the stable with one CD group.

^c Significantly different from the healthy to multimorbidity group.

^d Significantly different from the stable with multimorbidity group.

^e Significantly different from the increasing multimorbidity group.

is limited.²⁶ The negative association between iron intake and anemia is well known and has been previously reported in the present cohort.²⁵ Whole grains contain important quantities of non-hemic iron which has reduced bioavailability as compared to hemic iron. The high consumption of vitamin C in the healthy groups could have contributed to increasing its bioavailability and preventing anemia development. In the present cohort, a high iron intake was associated with an increased risk of diabetes except in those who also had a high magnesium consumption.¹² Overall, grain products other than rice and wheat, which are strongly

associated to fibers, magnesium, phosphorus and iron intake, are also associated with a progressive beneficial impact in the evolution of multimorbidity.

Rice consumption was significantly lower in the healthy than in the other groups. Its negative association with dietary fibers intake suggest that rice is mainly refined and deprived of the benefits associated with fibers and phytochemicals from whole grain.²⁷ Two prospective studies have shown that a high baseline consumption of rice was associated with an increased risk of developing hyperglycaemia¹³ and type 2 diabetes in women.²⁸

Table 4
Association between stages of evolution of multimorbidity and daily micronutrient intakes calculated from three-days food records in 2002 for the 1020 participants.

N	Stages of evolution of multimorbidity						Statistical models		
	Healthy	Healthy to first disease	Stable with one disease	Healthy to multimorbidity	Stable with multimorbidity	Increasing multimorbidity	Crude	Adjusted for age and sex	Adjusted for other risk factors ^a
	234	145	295	51	98	197			
Minerals									
Phosphorus (mg)	1119 ± 409 ^{b,c,d,e}	1092 ± 370 ^{b,d,e}	1012 ± 334 ^d	1002 ± 308	923 ± 234	987 ± 336	≤0.0001	≤0.005	≤0.001
Magnesium (mg)	343 ± 135 ^{b,d,e}	334 ± 121 ^{d,e}	318 ± 122 ^d	321 ± 121 ^d	280 ± 77	302 ± 127	≤0.001	≤0.05	≤0.005
Iron (mg)	27 ± 10 ^{b,d,e}	25 ± 9	25 ± 9	24 ± 8	23 ± 8	24 ± 9	≤0.01	ns	≤0.05
Calcium (mg)	427 ± 173	440 ± 176	441 ± 196	401 ± 191	417 ± 174	428 ± 216	ns	ns	ns
Copper (µg)	2.3 ± 1.0	2.3 ± 0.7	2.3 ± 1.0	2.3 ± 0.8	2.0 ± 0.7	2.2 ± 0.9	ns	ns	ns
Manganese (mg)	6.9 ± 2.5	7.0 ± 2.0	6.9 ± 2.5	7.4 ± 2.6	6.4 ± 2.0	6.8 ± 3.1	ns	ns	ns
Potassium (mg)	1712 ± 564 ^d	1761 ± 558 ^{c,d,e}	1683 ± 560	1578 ± 536	1554 ± 462	1633 ± 642	≤0.05	ns	ns
Sodium (mg)	6737 ± 4065	7118 ± 4263	6770 ± 4146	6278 ± 3289	5825 ± 2548	6406 ± 5440	ns	ns	ns
Selenium (µg)	44 ± 18 ^c	47 ± 21 ^{b,c,d}	42 ± 19 ^e	38 ± 17 ^e	41 ± 15	45 ± 20	≤0.05	≤0.05	≤0.01
Zinc (mg)	12 ± 4	12 ± 3	12 ± 3	12 ± 4	11 ± 3	12 ± 4	ns	ns	ns
Vitamin									
A (IU)	203 ± 489	237 ± 576	187 ± 461	372 ± 1030	216 ± 437	194 ± 533	ns	ns	ns
B1 (mg)	1.02 ± 0.43 ^d	1.04 ± 0.45 ^d	0.96 ± 0.43	0.91 ± 0.31	0.87 ± 0.36	0.95 ± 0.40	≤0.05	ns	ns
B2 (mg)	0.81 ± 0.36	0.82 ± 0.30	0.80 ± 0.32	0.78 ± 0.36	0.78 ± 0.27	0.79 ± 0.32	ns	ns	ns
C (mg)	66 ± 39 ^c	69 ± 36 ^c	68 ± 40 ^e	78 ± 46 ^{d,e}	61 ± 32	60 ± 33	≤0.05	≤0.05	≤0.05
E (mg)	37 ± 28	40 ± 25	34 ± 23	38 ± 26	33 ± 23	36 ± 33	ns	ns	ns

Data are presented as mean ± SD.

^a Includes age, sex, smoking status, annual income, marital status, education, BMI and sedentarity.

^b Significantly different from the stable with one CD group.

^c Significantly different from the healthy to multimorbidity group.

^d Significantly different from the stable with multimorbidity group.

^e Significantly different from the increasing multimorbidity group.

Table 5

Association between food categories and macronutrient and micronutrient significantly associated with evolution of multimorbidity for the 1020 participants.

	Energy density	Dietary fibers	Iron	Magnesium	Phosphorus	Vitamin C	Potassium	Vitamin B1	CHO (% of energy)	Fat (% of energy)	Selenium
Fruits and vegetables	0.14***	0.32***	0.31***	0.36***	0.30***	0.69***	0.53***	0.26***	0.13***	−0.14***	0.08*
Fruits	0.02	0.25***	0.11***	0.13***	0.14***	0.16***	0.22***	0.06	0.02	−0.03	0.11***
Vegetables											
Total	0.15***	0.23***	0.29***	0.39***	0.27***	0.70***	0.48***	0.26***	0.13***	−0.14***	0.03
Light	0.11***	0.19***	0.20***	0.27***	0.22***	0.43***	0.35***	0.24***	0.10***	−0.10***	0.02
Salted	0.11***	0.01	0.07*	0.04	0.01	0.07*	0.12***	0.00	0.11***	−0.00	0.00
Total meat	−0.01	−0.25***	0.07*	−0.09**	0.06*	0.03	0.18***	0.24***	−0.55***	0.48***	0.39***
Redmeat	0.03	−0.22***	0.05	−0.08*	0.07*	0.03	0.18***	0.28***	−0.50***	0.47***	0.35***
Pork	0.11***	−0.22***	−0.03	−0.10***	0.03	0.04	0.13***	0.21***	−0.48***	0.49***	0.26***
Cereals	0.32***	0.46***	0.54***	0.60***	0.62***	0.21***	0.39***	0.42***	0.46***	−0.38***	0.18***
Rice	0.12***	−0.32***	−0.01	−0.04	−0.42***	0.16***	0.16***	0.00	0.07*	−0.05	0.10**
Wheat	0.07*	0.32***	0.27***	0.33***	0.34***	0.03	0.14***	0.14***	0.20	−0.18***	0.12***
Other cereals	0.19***	0.77***	0.46***	0.49***	0.57***	0.01	0.12***	0.12***	0.28***	−0.22***	−0.06

*, $p < 0.05$; **, $p < 0.01$; ***, $p \leq 0.0001$.

Lower proportion of energy from fat was associated with an increased risk from healthy individual to develop multimorbidity. Among fat subtype, a lower percentage of energy from animal fat was found in healthier stages. Animal fat is rich in saturated fat, which is a type of fat known to be implicated in chronic disease development.^{11,29} Detailed fat subtypes information was not available in the present study and further investigations are needed in order to better understand the relationship between fat and evolution of multimorbidity.

This study presents some limitations. The present approach could favor dietary components which exert a beneficial impact toward chronic diseases with higher prevalence. Individual lost to follow-up for causes of death are not included in the present study and this could bring a 5-years survival bias. However, the general approach of the present study aims at evolution of multimorbidity in general population and not the impact of chronic disease on mortality. Also, the fully adjusted model accounts for numerous risk factors, other factors not available in the present study could modulate evolution of multimorbidity. While it would have been interesting to create other subgroups from the increasing multimorbidity groups based on the number of chronic disease at baseline and developed during follow-up, they were merged in order to ensure sufficient statistical power for analyses. The authors also suggest that the impact of nutrition could be more important in the initial steps of chronic disease development. Also, food measurement was only done at baseline and dietary habits could have changed during follow-up. Those changes could be important in the context of the evolution of multimorbidity, particularly to explain potential differences between the healthy to multimorbidity and the stable with multimorbidity groups. In this regard, the concurrent and longitudinal evolution of dietary habits and multimorbidity evolution stages should be the subject of future investigations.

The strengths of this study include the longitudinal study design, the biomedical chronic diseases diagnosis assessment and the use of a three-day weighted food records. Food frequency questionnaires (FFQ) are frequently used in large studies for their ease of administration and low cost³⁰ but the weighted three-day food record is often considered as the gold standard in nutrition assessment.

In summary, we report that fruits and vegetables and grain products other than rice and wheat could prevent evolution of multimorbidity in the Chinese. It is our understanding that the presence of phytochemicals and micronutrients such as dietary fibers, iron, vitamin C and magnesium in those products are responsible, at least partly, for those benefits. The use of multimorbidity instead of individual chronic disease produced findings

that could be relevant for food guide creation and that reinforces the notion that health benefits can be obtained from fruits and vegetables and whole grain products consumption. Clinical trials are needed in order to determine whether a dietary intervention including fruits, vegetables and whole grains consumption could exert beneficial impact on evolution of multimorbidity.

Funding

Guillaume Ruel is supported by “Le fond de recherche du Québec – Santé (FRQS)”.

Statement of authorship

Zumin Shi, Shiqi Zhen, Hui Zuo, designed and conducted research. Guillaume Ruel and Zumin Shi performed statistical analysis. Guillaume Ruel, Zumin Shi, Shiqi Zhen, Hui Zuo, Edeltraut Kröger, Caroline Sirois, Jean-Frédéric Lévesque and Anne W Taylor contributed to the writing of the paper. Guillaume Ruel, Jean-Frédéric Lévesque and Anne W. Taylor had primary responsibility for final contents. All the authors read and approved the final manuscript.

Conflict of interest

None of the authors have any financial or relationship conflicts of interest in presenting this paper.

References

- van den Akker M, Buntinx F, Knottnerus JA. Comorbidity or multimorbidity what's in a name? A review of literature. *Eur J Gen Pract* 1996;65–70.
- Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012;380(9836):37–43.
- Fortin M, Stewart M, Poitras ME, Almirall J, Maddocks H. A systematic review of prevalence studies on multimorbidity: toward a more uniform methodology. *Ann Fam Med* 2012;10(2):142–51.
- Taylor AW, Price K, Gill TK, Adams R, Pilkington R, Carrangis N, et al. Multimorbidity – not just an older person's issue. Results from an Australian biomedical study. *BMC Public Health* 2010;10:718.
- Marco J, Barba R, Zapatero A, Matia P, Plaza S, Losa JE, et al. Prevalence of the notification of malnutrition in the departments of internal medicine and its prognostic implications. *Clin Nutr* 2011;30(4):450–4.
- Koren-Hakim T, Weiss A, Hershkovitz A, Otrateni I, Grosman B, Frishman S, et al. The relationship between nutritional status of hip fracture operated elderly patients and their functioning, comorbidity and outcome. *Clin Nutr* 2012;31(6):917–21.
- Nishida C, Uauy R, Kumanyika S, Shetty P. The joint WHO/FAO expert consultation on diet, nutrition and the prevention of chronic diseases: process, product and policy implications. *Public Health Nutr* 2004;7(1A):245–50.

8. Vischer UM, Frangos E, Graf C, Gold G, Weiss L, Herrmann FR, et al. The prognostic significance of malnutrition as assessed by the Mini Nutritional Assessment (MNA) in older hospitalized patients with a heavy disease burden. *Clin Nutr* 2012;**31**(1):113–7.
9. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med* 1997;**336**(16):1117–24.
10. Jenkins DJ, Kendall CW, Faulkner D, Vidgen E, Trautwein EA, Parker TL, et al. A dietary portfolio approach to cholesterol reduction: combined effects of plant sterols, vegetable proteins, and viscous fibers in hypercholesterolemia. *Metabolism* 2002;**51**(12):1596–604.
11. Lichtenstein AH, Appel LJ, Brands M, Carnethon M, Daniels S, Franch HA, et al. Summary of American Heart Association Diet and Lifestyle Recommendations revision 2006. *Arterioscler Thromb Vasc Biol* 2006;**26**(10):2186–91.
12. Shi Z, Zhou M, Yuan B, Qi L, Dai Y, Luo Y, et al. Iron intake and body iron stores, anaemia and risk of hyperglycaemia among Chinese adults: the prospective Jiangsu Nutrition Study (JIN). *Public Health Nutr* 2010;**13**(9):1319–27.
13. Shi Z, Taylor AW, Hu G, Gill T, Wittert GA. Rice intake, weight change and risk of the metabolic syndrome development among Chinese adults: the Jiangsu Nutrition Study (JIN). *Asia Pac J Clin Nutr* 2012;**21**(1):35–43.
14. Grundy SM, Cleeman JJ, Merz CN, Brewer Jr H, Bryan, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;**110**:227–39.
15. Dallman PR. Diagnosis of anemia and iron deficiency: analytic and biological variations of laboratory tests. *Am J Clin Nutr* 1984;**39**(6):937–41.
16. Friedman AJ, Chen Z, Ford P, Johnson CA, Lopez AM, Shander A, et al. Iron deficiency anemia in women across the life span. *J Womens Health (Larchmt)* 2012;**21**(12):1282–9.
17. Yang Y, editor. *Chinese food composition table 2004*. Beijing: Peking University Medical Press; 2005.
18. Boeing H, Bechthold A, Bub A, Ellinger S, Haller D, Kroke A, et al. Critical review: vegetables and fruit in the prevention of chronic diseases. *Eur J Nutr* 2012;**51**(6):637–63.
19. Ruel G, Lapointe A, Pomerleau S, Couture P, Lemieux S, Lamarche B, et al. Evidence that cranberry juice may improve augmentation index in overweight men. *Nutr Res* 2013;**33**(1):41–9.
20. Ruel G, Pomerleau S, Couture P, Lemieux S, Lamarche B, Couillard C. Favourable impact of low-calorie cranberry juice consumption on plasma HDL-cholesterol concentrations in men. *Br J Nutr* 2006;**96**(2):357–64.
21. Wang L, Manson JE, Gaziano JM, Buring JE, Sesso HD. Fruit and vegetable intake and the risk of hypertension in middle-aged and older women. *Am J Hypertens* 2012;**25**(2):180–9.
22. Okarter N, Liu RH. Health benefits of whole grain phytochemicals. *Crit Rev Food Sci Nutr* 2010;**50**(3):193–208.
23. Shi Z, Hu X, Yuan B, Pan X, Dai Y, Holmboe-Ottesen G. Association between dietary patterns and anaemia in adults from Jiangsu Province in Eastern China. *Br J Nutr* 2006;**96**(5):906–12.
24. Ma J, Folsom AR, Melnick SL, Eckfeldt JH, Sharrett AR, Nabulsi AA, et al. Associations of serum and dietary magnesium with cardiovascular disease, hypertension, diabetes, insulin, and carotid arterial wall thickness: the ARIC study. Atherosclerosis Risk in Communities Study. *J Clin Epidemiol* 1995;**48**(7):927–40.
25. Shi Z, Hu X, He K, Yuan B, Garg M. Joint association of magnesium and iron intake with anemia among Chinese adults. *Nutrition* 2008;**24**(10):977–84.
26. Takeda E, Sakamoto K, Yokota K, Shinohara M, Taketani Y, Morita K, et al. Phosphorus supply per capita from food in Japan between 1960 and 1995. *J Nutr Sci Vitaminol (Tokyo)* 2002;**48**(2):102–8.
27. Dixit AA, Azar KM, Gardner CD, Palaniappan LP. Incorporation of whole, ancient grains into a modern Asian Indian diet to reduce the burden of chronic disease. *Nutr Rev* 2011;**69**(8):479–88.
28. Nanri A, Mizoue T, Noda M, Takahashi Y, Kato M, Inoue M, et al. Rice intake and type 2 diabetes in Japanese men and women: the Japan Public Health Center-based Prospective Study. *Am J Clin Nutr* 2010;**92**(6):1468–77.
29. Matsumoto C, Hanson NQ, Tsai MY, Glynn RJ, Gaziano JM, Djousse L. Plasma phospholipid saturated fatty acids and heart failure risk in the physicians' health study. *Clin Nutr* 2013. PMID: 23473794.
30. Subar AF. Developing dietary assessment tools. *J Am Diet Assoc* 2004;**104**(5):769–70.