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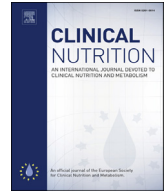
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Covid-19

# Influence of foods and nutrients on COVID-19 recovery: A multivariate analysis of data from 170 countries using a generalized linear model

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## SUMMARY

**Background & aims:** COVID-19 is an emergency public health problem of global importance. This study aimed to investigate the effect of foods and nutrients as complementary approaches on the recovery from COVID-19 in 170 countries, especially considering the complexity of the disease and the current scarcity of active treatments.

**Methods:** A retrospective study was performed using the Kaggle database, which links the consumption of various foods with recovery from COVID-19 in 170 countries, using multivariate analysis based on a generalized linear model.

**Results:** The results showed that certain foods had a positive effect on recovery from COVID-19: eggs, fish and seafood, fruits, meat, milk, starchy roots, stimulants, vegetable products, nuts, vegetable oil and vegetables. In general, consumption of higher levels of proteins and lipids had a positive effect on COVID-19 recovery, whereas high consumption of alcoholic beverages had a negative effect. In developed countries, where hunger had been eradicated, the effect of food on recovery from COVID-19 had a greater magnitude than in countries with a higher global hunger index (GHI), where there was almost no identifiable effect.

**Conclusion:** Several foods had a positive effect on COVID-19 recovery in developed countries, especially food groups with a higher content of lipids, proteins, antioxidants and micronutrients (e.g., selenium and zinc). In countries with extreme poverty (high GHI), foods presented little effect on recovery from COVID-19.

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## 1. Introduction

Coronavirus disease 2019 (COVID-19) was first reported last year in Wuhan, Hubei (China), and the etiologic agent was identified as a new coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The disease has been categorized as a

global pandemic by the World Health Organization (WHO), totaling 114,853,685 confirmed cases and 2,554,694 deaths worldwide by March 4, 2021 [2]. The typical clinical manifestations of COVID-19 include fever, dry cough and fatigue, often with pulmonary involvement. In severe cases of the disease, increases in the levels of cytokines (IL-2, IL-7, IL-10), granulocyte colony stimulating factor (G-CSF), monocyte chemotactic protein (MCP) and TNF- $\alpha$  occur. In this sense, the inflammatory cascade that triggers this cytokine storm appears to be a key factor in the cause of severe acute respiratory syndrome and extra-pulmonary organ failure, demonstrating the importance of the immune system in the progression of this disease [3,4].

In addition, evidence shows that there are certain population groups with higher vulnerability to the disease, especially patients

**Abbreviations:** COVID-19, Coronavirus disease 2019; ARS-CoV-2, severe acute respiratory syndrome coronavirus 2; FAO, Food and Agriculture Organization of the United Nations; IQR, interquartile range; GLM, generalized multivariate linear model.

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with underlying conditions such as chronic non-communicable diseases (e.g., hypertension, type 2 diabetes, ischemic heart disease, chronic obstructive pulmonary disease and cancer). COVID-19 infection severity, worse outcomes and mortality have been associated with age, comorbidities and high body mass index in different countries [5–11]. It is important to highlight that most of the mentioned chronic non-communicable diseases are causally related to food consumption and lifestyle characteristics. Diets rich in carbohydrates, saturated fats and refined sugars contribute to the prevalence of obesity and type 2 diabetes, and may increase the risk of severe COVID-19 and mortality [12]. High consumption of carbohydrates and saturated fats are directly associated with inflammatory conditions, which can compromise health in terms of preventing and overcoming infections. On the other hand, a worse nutritional status is associated with oxidative stress, which negatively affects the immune system. Therefore, a balanced, healthy diet is essential for proper production of antibodies and minimization of oxidative stress and inflammatory status, especially regarding the amount of protein that is sufficient to promote an appropriate immune response [13,14].

Considering that nutritional status has a major impact on the immune system response and on the development of comorbidities considered risk factors for COVID-19, the present study aimed to investigate the effect of the food supply as complementary approaches on recovery from COVID-19 in 170 countries.

## 2. Methods

### 2.1. Study design

The present investigation comprises an observational study with quantitative analysis of cross-sectional data from 170 countries at the population level (Tables S1, S2 and S3).

### 2.2. Datasets

Data were obtained from the public platform Kaggle [15], maintained by the government of the United States of America (USA), which includes the following information from diverse databases:

- The food supply available within each country in 2017 (expressed as a proportion of calories), according to food items and its nutritional contents of macronutrients (expressed as the proportion of proteins, fats and carbohydrates), from the Food and Agriculture Organization of the United Nations (FAO) [16];
- The population from each country, from the Bureau PLB [17];
- The proportion of individuals who recovered from COVID-19 infection in each country (last update 27th January 2021), from the Johns Hopkins Center for Systems Science and Engineering [18] (Table S4), and the fatality rate of COVID-19.

Additionally, information from FAO datasets regarding the food supply according to food items and food groups (in kilograms per capita per year) within each country were incorporated into the database, to address the effect of food consumption on recovery from COVID-19 [16], adjusted by population within each country. Considering that there were no significant changes in food supply in the past four years worldwide (see Figure S1 and Table S5), these data were used in the current scenario of 2020–2021.

A database containing the following variables was also accessed: i) People using at least basic sanitation services (% of the population) in 2017; ii) Prevalence of undernourishment (% of the population) in 2018; iii) Current health expenditure per capita, PPP (current international \$) in 2017, iv) *Gross domestic product* (GDP)

per capita, PPP (current international \$) in 2019; v) Standardized rates of diabetes prevalence (% of population aged 20–79) in 2019. These data were accessed on the World Bank's official website. These variables were used as a control in assessing the influence of food on recovery from COVID-19 [19].

### 2.3. Variables

The dependent variable in the analysis was the COVID-19 recovery rate in each of 170 countries (Table S4). A clinical definition for 'recovered' or 'cured' patients is not specifically available in international guidelines for clinical management of suspected or confirmed COVID-19 and may vary worldwide. Thus, considering the last guidelines from the WHO and the Center of Diseases Control (CDC) in the USA, 'recovery' was defined following the criteria for discharging patients from isolation: (i) Symptomatic cases: 10 days after symptom onset or the receipt of a positive test result if the date of onset cannot be determined, plus at least 24 h without symptoms (including fever and respiratory symptoms) and fever-reducing medications. If a patient presents severe illness from COVID-19, healthcare providers may recommend longer isolation periods after symptoms onset (possibly up to 20 days); (ii) Asymptomatic cases: 10 days after patients testing positive for SARS-CoV-2; (iii) Patients belonging to the following groups are defined as 'recovered' only on the basis of tests: patients hospitalized at any stage of the disease; caregivers in institutions with a population at risk for severe morbidity due to COVID-19 (e.g., nursing homes, institutions caring for geriatric patients, assisted living facilities), patients suffering from suppression of the immune system [20,21].

The independent variables of interest were the proportion of calories, proteins, fats and carbohydrates from alcoholic beverages, animal fats, animal products, cereals, eggs, fish-seafood, fruits, milk, meat, miscellaneous, offal, oil crops, pulses, spices, starchy roots, stimulants, sugar and sweeteners, sugar crops, tree nuts, vegetable oils, vegetables and vegetal products (see the list of foods in each category in Table S2).

The effect of the food supply on recovery from COVID-19 was analyzed considering all countries in a general model, as well as specific models considering countries grouped into regions and categories of the global hunger index (GHI) in 2019 (Table S6):

- Group 1-Developed countries with eradication of hunger: Canada, the United States of America (USA), Japan, South Korea, Australia, New Zealand and some countries in Western Europe (e.g., France, the United Kingdom and Sweden);
- Group 2-Countries in the Americas with a low to moderate global hunger index: countries in Central America, South America and Mexico;
- Group 3-Countries in Europe (e.g., Albania, Ukraine and Russia) and Asia (e.g., Iran, Thailand and China) with a low global hunger index;
- Group 4-Countries with a low, moderate or high global hunger index: all countries in Africa, countries in Oceania (Fiji, French Polynesia, Solomon Islands and Kiribati) and some countries in Asia (e.g., Yemen, Pakistan and Vietnam).

In order to minimize bias in the generalized multivariate linear models (GML) built to assess the influence of food and nutrients on recovery from COVID-19, the following variables were used as control variables: i) People using at least basic sanitation services (% of the population) in 2017; ii) Prevalence of undernourishment (% of population) in 2018; iii) Current health expenditure per capita, PPP (current international \$) in 2017, iv) GDP per capita, PPP (current international \$) in 2019; v) Standardized rates of diabetes

prevalence (% of population aged 20–79) in 2019; vi) Fatality rates of COVID-19.

#### 2.4. Statistical analysis

The statistical analysis included a prior investigation on the distribution of the dependent variable (recovery from COVID-19), testing three different types of probability distribution: the normal distribution, the gamma distribution and the tweedie distribution. Akaike's Information Criterion (AIC) was the parameter adopted for comparison of fit among the distributions tested, considering that lower AIC coefficients indicate better adjustment of the variable to the distribution under assessment [22–26] (Table S7).

The chi-square test adjusted to the GLM was used to assess the main effects of the covariates in recovery from COVID-19, a preliminary step in multivariate analysis. Finally, covariates (food items) with a significant effect on COVID-19 recovery rates were included in the GLM adjusted to the gamma distribution. The effect size of the covariates was based on GLM coefficients ( $\beta$ ) with a 95% confidence interval. Magnitudes of effects ( $\beta$ ) greater than 1 were considered the most substantial.

The statistical analysis was conducted using SPSS software, version 20.0, adopting a level of significance of  $p < 0.05$ .

### 3. Results

The study included 170 countries: 46 (27.05%) from Africa, 35 (20.58%) from the Americas, 38 (22.35%) from Asia, 42 (24.70%) from Europe and the remaining 9 (5.3%) from Oceania (Table S1, supplementary material).

#### 3.1. Probability distribution density function of COVID-19 recovery

Considering the assessment of COVID-19 recovery rates in 170 countries through AIC, the gamma distribution presented the lowest values of AIC coefficients (Table S7); therefore, statistical analyses were performed, adjusting the data for the gamma distribution.

#### 3.2. Food supply and COVID-19 recovery rates

The mean supply of food items available within 170 countries in 2017 are shown in Table S6. Most countries were well supplied with cereals (13.9%–21.1% of the total food supply), fruits (6.4%–11.6%), milk (6.3%–22.8%), starchy roots (4.7%–7.4%) and vegetables (6.7%–33.9%). Countries in Group 1 presented the largest supply of 10 food items (alcoholic beverages, animal fats, meat, milk, miscellaneous, seafood, stimulants, sugar, tree nuts and vegetable oils), whilst countries in Group 2 had the largest supply of fruits, offal, and sugar crops. Countries in Group 3 had the largest supply of eggs, fish-seafood, starchy roots, and vegetables. On the other hand, countries in Group 4 had the largest supply of cereals, oil crops, pulses, and spices.

The high recovery rates of COVID-19 were observed in countries of Group 1 (i.e., countries with eradicated hunger), while countries of Group 4 (i.e., countries with a high global hunger rate) showed the lowest recovery rates of the disease (Table S4). However, Group 4 countries also presented both the lowest prevalence of diabetes mellitus as a comorbidity [6.000 (IQR, 3.8000–9.6500)] and the lowest rates of fatality associated with COVID-19 [0.0018% (IQR, 0.0006–0.0077%)]. In countries from groups 2 and 3, the prevalence of diabetes was 9.1000 (IQR, 7.3000–11.3500) e 6.5000 (IQR, 5.8500–9.1500), respectively, while the fatality rates were 0.0646% (IQR, 0.0118–0.1060), 0.0231% (IQR, 0.0034–0.0821), respectively.

Group 4 countries also had the lowest access to basic healthcare services, with a median percentage of 59.54% (IQR, 36.22%–91.18%), whereas group 1 countries showed the highest rates of 99.26% (IQR, 99.26%–99.89%). Group 3 countries had the second highest rate regarding access to basic healthcare [96.22% (IQR, 96.22%–97.97%)], followed by Group 2 [87.79% (IQR, 83.46%–93.80%)]. The highest rates of undernourishment were found in Groups 2 and 4, with median percentages of 48.20% (25%–69%) and 28% (IQR, 17.20%–47%), respectively. Group 1 countries had the lowest rates of this outcome, with a median percentage of 7% (IQR, 9.0%–15%), while in Group 3 rates were of 26% (IQR, 25%–42.03%).

Regarding the GNP, countries of extreme poverty with a high GHI had the lowest PPP, with a median of \$ 5165 (IQR, 2357.50–10,920), while in developed countries with hunger eradication, per capita income in PPP was the highest, with a median of \$ 51,010 (IQR, 42,402.5–60,850). Group 2 and group 3 countries had a moderate per capita income of \$ 15,140 (IQR, 9770–21,120) and \$ 21,205 (IQR, 14,675–33,447.5), respectively.

#### 3.3. Multivariate analysis of the generalized linear model

The results of multivariate analysis of a GLM adjusted for the gamma distribution in relation to the effects of covariates (food items) on COVID-19 recovery rates considering the 170 countries investigated are presented in Tables 1 and 2. GLM models were estimated using the supply of protein (model 1), lipids (model 2) and carbohydrates (model 3) and the food supply in general (model 4) (Table 1). In addition, GLM models were estimated considering each of the four groups of countries categorized according to the GHI (Table 2).

##### 3.3.1. Effect of food supply and its macronutrients on COVID-19 recovery rates

The multivariate analysis of GLM involving the supply of proteins showed several food items with a significant effect on recovery from COVID-19 (Table 1). In model 1, protein sources (e.g., animal products, eggs, fish-seafood, meat, milk, offal, vegetables) positively impact on patients' recovery ( $p < 0.05$ ). On the other hand, alcoholic beverages had a significant negative effect on the outcome ( $\beta -8.181$  [95% CI -14.290; -2.071],  $p = 0.009$ ), which was also observed in models 3 and 4, confirming the disadvantage of this item consumption. Model 2 revealed that from the 20 analyzed lipid items, 8 (40%) significantly benefit patients (eggs, fish-seafood, meat, milk, offal, tree nuts, vegetable products and vegetable oil). Conversely, no food from the carbohydrates group (model 3) had an impact on the outcome. The general food supply model (model 4) demonstrated that only eggs ( $\beta 33.143$  [95% CI 15.554; 50.732],  $p < 0.0001$ ), fish-seafood ( $\beta 31.526$  [95% CI 14.222; 48.830],  $p < 0.0001$ ), fruits ( $\beta 31.388$  [95% CI 14.199; 48.578],  $p < 0.0001$ ), meat ( $\beta 31.491$  [95% CI 14.211; 48.772],  $p < 0.0001$ ), milk ( $\beta 31.741$  [95% CI 14.444; 49.038],  $p < 0.0001$ ), offal ( $\beta 31.477$  [95% CI 13.944; 48.951],  $p < 0.0001$ ), and vegetable products ( $\beta 23.769$  [95% CI 7.480; 40.057],  $p = 0.004$ ) may contribute to COVID-19 recovery.

##### 3.3.2. Effect of the food supply on COVID-19 recovery rates according to groups of countries

The effect of the food supply on COVID-19 recovery was also assessed according to groups of countries aggregated using the GHI (Table 2). The control variables of the model were: basic sanitation services; prevalence of undernourishment; current health expenditure per capita; domestic general government health expenditure per capita, GDP per capita, GNI per capita, diabetes prevalence and fatality rate.

Results showed that diabetes prevalence was negatively associated with patients' recovery in countries from Groups 1

**Table 1**

Multivariate analysis of a generalized linear model to estimate the effect of the amount of protein consumed (model 1), the amount of lipids consumed (model 2), the amount of carbohydrates consumed (model 3), and the amount of food consumed in general (model 4) on recovery from COVID-19 in 170 countries.

Covariable	Model 1			Model 2			Model 3			Model 4		
	$\beta$	[95%CI]	p	$\beta$	[95%CI]	p	$\beta$	[95%CI]	p	$\beta$	[95%CI]	p
Alcoholic beverages	-8.181	-14.290 - -2.071	0.009	-	-	-	-2.553	-4.937 - -1.831	0.019	-9.750	-15.261 - -4.238	0.001
Animal fats	7.335	-12.344 - 27.015	0.465	-0.553	-2.937 - 1.831	0.649	0.786	-46.057 - 47.628	0.974	-1.674	-9.846 - 6.499	0.688
Animal products	28.664	9.066 - 48.262	0.004	8.250	-5.322 - 21.822	0.233	1.053	-25.157 - 27.263	0.937	-1.771	-10.002 - 6.459	0.673
Cereals	1.900	-11.629 - 15.428	0.783	-0.783	-3.201 - 1.635	0.526	0.753	-7.613 - 9.119	0.860	-1.896	-10.128 - 6.336	0.652
Eggs	33.995	15.299 - 52.692	0.000	29.700	10.010 - 49.390	0.003	1.393	-45.433 - 48.219	0.953	33.143	15.554 - 50.732	0.000
Fish-seafood	33.347	14.746 - 51.948	0.000	28.021	8.517 - 47.526	0.005	0.333	-46.482 - 47.148	0.989	31.526	14.222 - 48.830	0.000
Fruits	2.099	-11.420 - 15.618	0.761	-0.538	-2.967 - 1.891	0.664	1.175	-7.209 - 9.560	0.784	31.388	14.199 - 48.578	0.000
Meat	33.429	14.826 - 52.032	0.000	28.403	8.842 - 47.965	0.004	0.667	-46.167 - 47.500	0.978	31.491	14.211 - 48.772	0.000
Milk	33.501	14.906 - 52.096	0.000	28.660	9.095 - 48.225	0.004	0.733	-46.102 - 47.568	0.976	31.741	14.444 - 49.038	0.000
Miscellaneous	2.562	-10.828 - 15.953	0.708	-1.076	-3.645 - 1.492	0.412	1.785	-6.524 - 10.093	0.674	-1.815	-9.877 - 6.247	0.659
Offal	33.380	14.754 - 52.006	0.000	28.678	8.730 - 48.626	0.005	1.249	-45.788 - 48.286	0.958	31.447	13.944 - 48.951	0.000
Oil crops	1.634	-11.885 - 15.152	0.813	-1.146	-3.531 - 1.238	0.346	0.823	-7.517 - 9.163	0.847	-1.961	-10.070 - 6.148	0.635
Pulses	1.807	-11.717 - 15.331	0.793	-1.049	-3.470 - 1.373	0.396	0.082	-8.203 - 8.366	0.985	-2.454	-10.712 - 5.805	0.560
Spices	2.082	-11.631 - 15.795	0.766	-0.497	-3.362 - 2.367	0.734	1.253	-7.203 - 9.708	0.772	-0.291	-8.451 - 7.870	0.944
Starchy roots	1.829	-11.693 - 15.351	0.791	-0.814	-3.226 - 1.598	0.508	0.445	-7.778 - 8.668	0.916	-1.889	-10.102 - 6.323	0.652
Stimulants	2.158	-11.328 - 15.643	0.754	-0.013	-2.542 - 2.515	0.992	1.229	-7.090 - 9.548	0.772	-2.000	-10.451 - 6.452	0.643
Sugar and sweeteners	2.825	-12.746 - 18.395	0.722	-0.568	-2.963 - 1.828	0.642	-0.568	-2.963 - 1.828	0.642	-1.609	-9.734 - 6.516	0.698
Tree nuts	-0.124	-2.527 - 2.279	0.919	2.413	1.510 - 3.025	0.024	1.036	-7.273 - 9.346	0.807	-0.314	-8.078 - 7.450	0.937
Vegetable products	39.758	17.382 - 62.134	0.000	21.173	6.992 - 35.355	0.003	0.876	-22.821 - 24.574	0.942	23.769	7.480 - 40.057	0.004
Vegetable oil	1.891	-11.692 - 15.474	0.785	5.733	3.162 - 7.696	0.004	0.889	-7.462 - 9.239	0.835	-1.623	-9.786 - 6.541	0.697
Vegetables	32.898	14.260 - 51.536	0.001	-0.767	-3.199 - 1.666	0.537	0.490	-8.047 - 9.028	0.910	-1.798	-9.989 - 6.393	0.667

( $p = 0.031$ ) and 3 ( $p = 0.017$ ). Undernourishment had no effect on the outcome in almost all group countries, except for those in Group 4 (i.e., extreme poverty), where a negative significant impact on COVID-19 recovery was observed ( $\beta -6.611$  [95% CI -11.492; -1.730],  $p = 0.008$ ). Availability of basic sanitation services was an important factor associated with patients' recovery in countries from Group 1 ( $p = 0.010$ ) and Group 4 ( $p < 0.0001$ ).

In countries belonging to Groups 1 and 2, both per capita expenditure on health and GNI per capita had a positive impact on the outcome ( $p$  values  $< 0.05$ ). On the other hand, for countries of Group 4, the GNI per capita in PPP had a negative significant effect on patients' recovery ( $p < 0.001$ ). Group 1 countries were the only ones associated with a positive result regarding GDP per capita in PPP ( $p = 0.006$ ).

The GLM models confirmed that the supply of certain food items had positive effects on recovery from COVID-19 in countries from Groups 1, 2 and 3: eggs, fish-seafood, meat, milk, vegetable products. Vegetables were positively associated with the outcome in all countries. Animal products, fruits and vegetable oils presented a positive result on the outcome only in countries from Groups 1 and 3. In countries from Group 3, offals and tree nuts were positively associated with patients' recovery. Alcohol was the only food item with a negative significant effect on the outcome in countries from Groups 1 and 2.

## 4. Discussion

### 4.1. Effects of the food supply on COVID-19 recovery rates

The results presented in the study show the influence of the food supply on COVID-19 recovery rates, considering diversity and the nutritional content of foods available in the countries studied. Countries in which hunger had been eradicated showed the higher rates of recovery from the disease. Conversely, the regions with reduced effects of the food supply on COVID-19 recovery rates were those from Group 4. This may occur, among other factors, because the increase in oxidative stress induced by dietary deficiencies, especially referring to the supply of antioxidant nutrients, affect individual's immune response, leading to increased susceptibility to viral diseases such as COVID-19 [27]. Therefore, in addition to the

coexistence of chronic diseases, the nutritional status of a patient infected with COVID-19 must also be considered, as nutritional deficiencies can increase the risk of severe infection [27].

Animal food sources presented important contributions to patients' with COVID-19 recovery in the estimated models. They are sources of high caloric content, protein, and essential micro-nutrients. Eggs, milk, meat, and fish had a substantial effect ( $\beta > 1$ ) on the disease recovery in countries from Groups 1, 2 and 3. In these groups, eggs and meat were consumed in greater quantities. The supply of eggs also had significant effect in all countries, being an important source of selenium and preformed vitamin A (retinol) [28,29].

Foods of animal origin are also sources of cholesterol, with eggs being one of the richest foods in this component [30]. Although cholesterol is associated with the development of many diseases, some studies demonstrated that certain levels of cholesterol can increase the body's resistance to infections, acting in this sense to modulate the immune response [31,32]. Milk, meat and dairy products are sources of zinc and retinol [28,33], and, in some countries in Group 1 (Finland, Norway, Sweden, Canada, and USA), dairy products are systematically supplemented with vitamin D [34]. Among the biologically active components of fish, omega-3 polyunsaturated fatty acids (EPA and DHA) are the most studied, being found mainly in oil-rich species [35]. However, fish and seafood also provide vitamin D and selenium, in addition to a balanced amino acid composition [35].

In our model, foods from plant sources had a greater influence on patients' recovery in countries with lower rates of nutritional deficiencies regarding supply of calories. Vegetable oils presented significant contributions in most countries, especially in Groups 1 and 2, where there was a greater consumption of oils, which are mainly composed of unsaturated fatty acids (rapeseed oil, sunflower oil). There was also a large consumption of soybean and olive oils in countries from Group 1 (see tables in supplementary material). The aforementioned vegetable oils are important sources of vitamin E ( $\alpha$ -tocopherol) [36]; soybean and rapeseed oils are particularly important sources of omega-3 unsaturated fatty acids ( $\alpha$ -linolenic acid) [37].

Tree nuts (except for chestnuts) were also important contributors to COVID-19 recovery rates, being one of the most important



**Table 2**  
Coefficients of GLM models for the magnitude of effects of foods consumed on COVID-19 recovery, according to groups of global hunger index.

Covariable	Countries of group 1			Countries of group 2			Countries of group 3			Countries of group 4		
	$\beta$	[95%CI]	p	$\beta$	[95%CI]	p	$\beta$	[95%CI]	p	$\beta$	[95%CI]	p
Fatality rate (%)	-17.825	-31.083--4.567	0.000	-25.788	32.831--18.745	0.000	-13.470	-22.594--4.346	0.000	-8.627	-15.399--6.397	0.435
Prevalence of diabetes (standardized)	-4.159	-7.162--2.480	0.031	-0.067	-0.180--0.047	0.248	-3.009	-5.174--2.156	0.017	0.084	-0.025--0.194	0.131
People using at least basic sanitation services (%)	27.322	6.660--47.985	0.010	2.116	-1.306--5.538	0.226	6.051	-0.111--12.213	0.064	3.571	2.333--4.810	0.000
Prevalence of undernourishment (%)	1.212	-0.369--2.793	0.133	0.422	-1.297--2.142	0.630	-0.466	-2.424--1.492	0.641	-6.611	-11.492--1.730	0.008
GDP per capita	5.710	3.101--7.522	0.006	-0.527	-1.646--0.592	0.356	0.115	-0.653--0.882	0.769	0.625	-0.188--1.439	0.132
GNI per capita*	3.069	2.201--3.938	0.000	3.851	1.827--5.415	0.002	1.272	-0.419--2.963	0.140	-0.876	-3.022--4.773	0.001
Current health expenditure per capita*	3.233	1.832--4.634	0.000	2.669	1.151--5.886	0.007	0.340	-0.137--0.818	0.162	-0.040	-2.860--2.780	0.978
Domestic general government health expenditure per capita*	0.326	-0.908--4.744	0.470	2.344	1.565--5.123	0.001	0.474	-0.374--1.321	0.274	0.022	-2.723--2.766	0.988
Alcoholic beverages	-4.336	-2.064--6.090	0.016	-2.312	-5.034--1.590	0.028	0.039	-0.146--0.224	0.678	-0.023	-0.186--0.140	0.778
Animal fats	-0.683	-2.349--0.982	0.421	3.707	-0.635--8.048	0.670	0.283	-0.880--1.445	0.633	3.171	-0.673--7.016	0.106
Animal products	4.235	1.270--6.342	0.000	0.059	-0.049--0.166	0.286	2.068	1.320--3.167	0.001	-0.012	-0.182--0.159	0.894
Cereals	-0.090	-0.531--0.351	0.690	-	-	-	-0.076	-0.187--0.035	0.179	-0.053	-0.125--0.018	0.143
Eggs	13.234	7.553--20.914	0.000	7.911	3.477--12.699	0.001	9.721	2.312--16.870	0.043	-0.603	-0.818--4.388	0.590
Fish-seafood	8.240	5.714--9.235	0.032	2.611	1.160--3.206	0.003	3.587	2.371--5.197	0.014	0.063	-0.135--0.262	0.531
Fruits	2.013	1.510--0.484	0.039	-0.001	-0.120--0.118	0.987	1.800	1.200--2.244	0.008	0.025	-0.108--0.159	0.709
Meat	5.694	3.769--8.382	0.002	2.002	1.241--3.246	0.009	1.914	1.506--2.090	0.000	0.464	0.129--0.799	0.070
Milk	11.018	8.183--17.146	0.027	2.112	1.517--3.241	0.030	5.096	2.001--7.194	0.005	0.198	0.065--0.332	0.400
Miscellaneous	0.577	-0.162--1.315	0.126	0.348	-2.390--2.348	0.790	0.284	-0.971--1.539	0.658	-0.632	-1.193--0.070	0.270
Offal	-1.299	-7.797--5.199	0.695	0.714	-2.438--3.865	0.657	4.737	2.748--6.725	0.020	-1.658	-4.245--0.929	0.209
Oil crops	-2.653	-4.965--0.341	0.250	-0.745	-1.548--0.058	0.069	-1.506	-3.145--0.133	0.072	-0.180	-0.312--0.048	0.070
Pulses	-2.303	-5.235--0.629	0.124	-0.749	-1.593--0.094	0.082	-3.239	-7.239--1.239	0.900	-0.917	-1.430--0.403	0.068
Spices	-5.904	-32.263--20.456	0.661	-6.233	-9.343--3.122	0.200	-1.274	-3.798--1.251	0.323	1.555	-1.513--4.623	0.321
Starchy roots	0.018	-0.570--0.606	0.952	-0.006	-0.140--0.128	0.929	0.045	-3.247--1.158	0.240	-0.101	-0.142--0.059	0.890
Stimulants	0.636	-1.058--2.330	0.462	0.220	-1.761--2.201	0.828	0.288	0.166--1.410	0.160	1.849	-1.198--4.895	0.234
Sugar and sweeteners	0.261	-0.088--0.610	0.143	-0.197	-0.514--0.121	0.226	0.167	-0.160--0.493	0.317	0.567	0.265--0.869	0.470
Tree nuts	4.160	1.668--5.348	0.170	0.345	-3.151--3.841	0.847	1.927	1.266--2.212	0.005	2.033	-0.416--4.482	0.104
Vegetable oils	3.469	1.927--6.990	0.029	0.025	-1.126--1.176	0.966	2.348	1.292--4.595	0.009	0.245	-1.329--1.725	0.500
Vegetable products	5.160	2.006--7.314	0.042	1.952	1.166--2.490	0.002	3.068	2.167--5.032	0.008	0.350	-1.342--2.361	0.587
Vegetables	15.042	11.290--17.373	0.000	3.095	2.230--5.034	0.014	5.023	3.121--8.075	0.004	6.905	3.084--9.326	0.001

Note: Group 1: Developed countries with hunger eradication; Group 2: Countries on the American continent with a low or moderate global hunger index; Group 3: European and Asian countries with a low global hunger rate; Group 4: Countries with a low, moderate or high global hunger index; \*Values expressed in logarithmic scale.

sources of fats after vegetable oils, with high unsaturated to saturated fat ratios. Walnuts are one of the whole foods with the highest contents of  $\alpha$ -linolenic acid. Nuts are also a source of protein (approximately 25% of energy) and generally have a high content of L-arginine, a precursor amino acid of the endogenous vasodilator nitric oxide (NO). They also provide antioxidants, such as vitamin E and phenolic compounds [38]. Finally, fruits were food items in abundant supply among countries from Groups 1 and 3, characterized by higher consumption of apples and grapes, foods with high polyphenol contents [39,40]. Vegetables comprised the only food group that showed a significant effect on recovery from COVID-19 in countries from all groups. These items are sources of glutathione, an antioxidant tripeptide, in addition to vitamin C, mainly citrus fruits, broccoli, tomatoes and leafy greens [41,42]. In fact, fruit and vegetable intake has already been investigated for potential benefits associated with respiratory and inflammatory conditions [37].

The only food item that had a negative effect on recovery from COVID-19 was alcoholic beverages. In addition to causing liver damage, alcohol consumption has been linked to lung diseases. Alcohol disrupts ciliary function in the upper airways, impairs the function of alveolar macrophages and neutrophils, and weakens epithelial barrier function in the lower airways [43].

#### 4.2. Effects of macro and micronutrient supplies on COVID-19 recovery rates

Overall, proteins and lipids had significant effects on the rates of recovery from COVID-19. Low protein levels can increase the risk of infections associated, for example, with low antibody production [3]. Fatty acids are important in the response to infection because they can significantly alter the immune response, including changes in the organization of cellular lipids and interactions with nuclear receptors. In mice, the consumption of fatty acids has been associated to reduced homeostasis and immune cell functions [3].

A previous study showed that the serum cholesterol level was significantly lower among Chinese patients with COVID-19 [44], and hypolipidemia was associated with the disease severity [44]. Low cholesterol predisposes to infectious diseases because LDL-c participates in the immune system by adhering to and inactivating microorganisms and their toxic products, including viruses [45]. Carbohydrates, which in general showed no effects on recovery from COVID-19, may be associated with the supply of processed carbohydrates and a high glycemic index, which is related to an overload of mitochondrial capacity and increased production of free radicals [3].

On the other hand, many food items rich in selenium, zinc and vitamins (milk, meat, fish, seafood, eggs, vegetables) were positively associated with patients' recovery from COVID-19. Dietary selenium mainly makes up selenoproteins, such as the antioxidant selenoenzymes glutathione peroxidases (GPxs) and thioredoxin reductase (TrxRs), highly expressed in immune cells, such as T lymphocytes and macrophages. The beneficial effects of selenium have been reported almost exclusively for RNA virus infections [46]. Zinc is a dietary trace element critical for the development of immune cells and a cofactor for many enzymes. The deficiency of this micronutrient can contribute to defective immune cell mediation and increased susceptibility to various infections, including pneumonia [27].

Vitamin A is a nutrient widely studied in the field of immune functions. In vitro experiments and animal studies suggest that retinoids are important regulators of differentiation and monocytic function. T cell immunocompetence can be affected by vitamin A deficiency, including lymphopoiesis, distribution, expression of surface molecules and production of cytokines [42]. Vitamin D has

pleiotropic effects on the host's immune pathway and may be involved with pulmonary and alveolar immune function. Evidence suggests that supplementation with vitamin D3, the active form of vitamin D, may decrease susceptibility or improve recovery from infections such as influenza, recurrent pneumonia, and tuberculosis [13,47].

In fact, the seasonality of many viral infections is associated with low concentrations of 25(OH)D, as a result of low doses of UVB due to winter in temperate climates and the rainy season in tropical climates. This is the case of influenza, infection caused by the respiratory syncytial virus and SARS-CoV [48]. Vitamin E, a fat-soluble vitamin, is a potent antioxidant and has the ability to modulate the host's immune functions. Its deficiency impairs humoral and cellular immunity. For some chronic diseases such as hepatitis B, its supplementation is associated with positive outcomes [42].

Finally, vitamin C is best known for its antioxidant properties, being able to eliminate reactive oxygen species, thus protecting cells and tissues in the body against oxidative damage and dysfunction. Additionally, vitamin C plays a role in supporting immune functions. The depletion of this vitamin may be associated with an increasing the severity of infections [49]. A recent study carried out in the USA with 167 patients with sepsis-related ARDS, indicated that administration of ~15 g/day of vitamin C IV for 4 days may decrease patients' mortality [50].

Omega-3 polyunsaturated fatty acids (EPA and DHA) serve as precursors to the production of pro-resolving mediators by macrophages and neutrophils [51]. In fact, EPA is currently being tested in several clinical trials on patients with COVID-19.  $\alpha$ -linolenic acid (ALA) exhibits potent anti-inflammatory properties. In an animal model of lipopolysaccharide-induced acute lung injury, treatment with ALA significantly inhibited the secretion of pro-inflammatory cytokines. In addition, the decrease in the activities of glutathione (GSH) and superoxide dismutase (SOD) caused by the polysaccharide were reversed by treatment with ALA [52].

Overall, our results showed that the consumption of different food items especially proteins, some lipids, antioxidants, and micronutrients may significant benefit COVID-19 recovery. This may be influenced, among others, by countries geographical, socioeconomic, and ecological food cultures. It is possible that in most extreme poverty countries (Group 4), the low socioeconomic conditions are associated with a more difficult access to food - which contributes to malnutrition.

Additionally, factors such as scarcity of basic sanitation services, extremely low expenditure on health per capita and low GDP per capita lead to the onset of several diarrheal and infectious diseases that weaken the population, and make them more vulnerable to malnutrition and opportunistic infections (e.g., pneumonia) [53,54]. In these cases, food may not play the most significant role in COVID-19 recovery as a balanced diet is already unrealistic for most people. The food base in these countries is composed mainly by carbohydrates, being deficient in oils and proteins of animal origin.

Finally, although higher income is often associated with lower rates of malnutrition, its improvement reduces malnutrition by only a small degree. These estimates suggest that countries cannot rely solely on economic growth to reduce malnutrition within an acceptable timeframe [19]. Further socioeconomic, educational, and cultural measures are needed to improve this metric worldwide. It is important to highlight that countries with higher income and greater access to food usually present lower prevalence of undernutrition measured through Body Mass Index (BMI); however, individuals with overweight (BMI  $\geq 25$  kg/m<sup>2</sup>) or obesity (BMI  $\geq 30$  kg/m<sup>2</sup>) may also be malnourished, especially considering absence of additional information on body composition and diagnostic exams. Other studies demonstrated significant evidence on

the impact of an overall poor nutritional status on negative health outcomes of patients infected by COVID-19 [5,7,8].

Our study has some limitations. There are still no standard criteria to define 'recovery' from COVID-19 - given the complexity of the disease and the dynamic of the pandemic, thus, we used the most updated WHO and CDC guidelines. However, one should be aware that these definitions do not consider the sequels resulting from the disease, which may have a long-term effect on patients' quality of life including lung function abnormalities, psychological impairment, depression, reduced exercise capacity and post-traumatic stress disorder [55–58].

Undernourishment has a general concept usually related to low BMI, which represents only one dimension in the measurement of individuals' nutritional status. The definition of undernutrition through estimation of BMI partially represents the concept of malnutrition, which may be biased by other factors like access to food (i.e., food insecurity or malnourished individuals with overweight/obesity considering micronutrients and other diagnostic exams also exist in regions/countries with high food availability) and quality of family/community health environment. Therefore, additional variables that allow further diagnosis of malnutrition among patients with COVID-19 should be considered, according to the proposal of the Global Leadership Initiative on Malnutrition (GLIM), which states that at least one phenotypic criteria (either weight loss, low BMI, or reduced muscle mass like sarcopenia), and at least one etiologic criteria (either reduced food intake or assimilation, or inflammation or disease burden), particularly considering patients' age [59,60] and especially in developed countries should be considered. However, given the lack of data availability on additional dimensions for global diagnosis of malnutrition, it was not possible to estimate further models encompassing multiple variables regarding nutritional status of countries' populations.

The same occurred for additional clinical confounders such as patients' major comorbidities (e.g., prevalence of hypertension, renal insufficiency or chronic obstructive pulmonary disease), whose information was unavailable. Nonetheless, the prevalence patterns of these comorbidities are similar worldwide. Although we used data on food supply from 2017, statistical analyses revealed no important changes in this variable the past four years. For methodological reasons, the variable of basic sanitation services access was only estimated in the model when at least 50% of the population was covered by the service. A cross-sectional design using ecological-level data was selected for our study, which compromises the ability to propose inferences about the longitudinal relationships between exposure (food) and outcome (COVID-19 recovery rates), especially considering the dynamic of the pandemic. We were able to provide important insights on the use of some food items as complementary approaches to COVID-19 management, however, longitudinal studies are necessary to confirm these results.

## 5. Conclusion

The generalized linear models developed in the present study allowed the identification of some macronutrients (lipids and proteins) and micronutrients (selenium, zinc) with a positive significant effect on COVID-19 recovery rates in the 170 countries investigated. The food items with positive effects on recovery rates were eggs, fish-seafood, fruits, meat, milk, vegetable products, vegetables, fruits, and tree nuts. These foods are sources of nutrients that are essential to promote a well-functioning immune system. Higher availability of alcohol had a negative effect on recovery rates. Carbohydrates were found to have no effect in the outcome, which is probably due to the metabolic characteristics of

SARS Cov-2 infection. In developed countries in which hunger had been eradicated, food items had greater effects on recovery from the disease, whereas in countries with a higher global hunger index, food consumption had almost no effect. These findings may be included in guidelines or recommendations for COVID-19 management as complementary approaches to improve patients' recovery, especially considering the complexity of the disease and the current scarcity of further pharmacological treatments.

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## Authors' contributions

Study concepts: AFC, RP, FST, FMS.  
 Study design: AFC, MS, FST, RP, FMS.  
 Data acquisition: AFC, MS, FMS.  
 Statistical analysis: AFC, MS, FMS, DROM.  
 Manuscript preparation: AFC, ROV, BB, MMF, DROM.  
 Manuscript editing: AFC, ROV, BB, MMF, DROM.  
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## Conflict of interest

Not applicable.

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## Appendix A. Supplementary data

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