Cabbage and fermented vegetables: from death rate heterogeneity in countries to candidates for mitigation strategies of severe COVID-19

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Abstract

Large differences in COVID-19 death rates exist between countries and between regions of the same country. Some very low death rate countries such as Eastern Asia, Central Europe or the Balkans have a common feature of eating large quantities of fermented foods. Although biases exist when examining ecological studies, fermented vegetables or cabbage were associated with low death rates in European countries. SARS-CoV-2 binds to its receptor, the angiotensin converting enzyme 2 (ACE2). As a result of SARS-Cov-2 binding, ACE2 downregulation enhances the angiotensin II receptor type 1 (AT1R) axis associated with oxidative stress. This leads to insulin resistance, lung and endothelial damage, two severe outcomes of COVID-19. The nuclear factor (erythroid-derived 2)-like 2 (Nrf2) is the most potent antioxidant in humans and can block the AT1R axis. Cabbage contains precursors of sulforaphane, the most active natural activator of Nrf2. Fermented vegetables contain many lactobacilli, which are also potent Nrf2 activators. It is proposed that fermented cabbage is a proof-of-concept of dietary manipulations that may enhance Nrf2-associated antioxidant effects helpful in mitigating COVID-19 severity.

Abbreviations

ACE: Angiotensin converting enzyme

Ang II: Angiotensin II

AT_1R: Angiotensin II receptor type 1

COVID-19: Coronavirus 19 disease

GI: Gastro-intestinal

LAB: Lactic acid bacilli

NF-ϰB: Nuclear factor kappa B

Nrf2: Nuclear factor (erythroid-derived 2)-like 2

PEDV: Porcine epidemic diarrhea virus

ROS: Reactive oxygen species

SARS: Severe acute respiratory syndrome

SARS-Cov-2: Severe acute respiratory syndrome coronavirus 2

TGEV: Transmissible Gastroenteritis Coronavirus Infection

Introduction

A COVID-19 epidemic started in China and then disseminated to other Asian countries before becoming a pandemic. There is a large variability across countries in both incidence and mortality, and most of the current debates on COVID-19 focus on the differences between countries. German fatalities are strikingly low as compared to many European countries. Among the several explanations proposed, an early and large testing of the population was put forward [1] as well as social distancing. However, little attention has been given to regional within-country differences that may propose new hypotheses.

It would appear that the pandemic has so far resulted in proportionately fewer deaths in some Central European countries, the Balkans, China, in most Eastern Asian countries as well as in many Sub-Saharan African countries. Several reasons can explain this picture. One of them may be the type of diet in these low mortality countries. [2]

Diet has been proposed to mitigate COVID-19. [3] Some foods or supplements may have a benefit on the immune response to respiratory viruses. However, to date, there are no specific data available to confirm the putative benefits of diet supplementation, probiotics, and nutraceuticals in the current COVID-19 pandemic.[4] News and social media platforms have implicated dietary supplements in the treatment and prevention of COVID-19 without evidence. [5]

In this paper, we discuss country and regional differences in COVID-19 deaths. We attempt to find potential links between foods and differences at the national or regional levels in the aim to propose a common mechanism focusing on oxidative stress that may be relevant in COVID-19 mitigation strategies. We used cabbage and fermented vegetable as a proof-of-concept.

Biases to be considered

According to the Johns Hopkins coronavirus resource center (*https://coronavirus.jhu.edu*), one of the most important ways of measuring the burden of COVID-19 is mortality. However, death rates are assessed differently between countries and there are many biases that are almost impossible to assess. Using the rates of COVID-19 confirmed cases is subject to limitations that are similar to or even worse than the differences in the use of COVID-19 testing.

Differences in the mortality rates depend on health care systems, the reporting method and many unknown factors. Countries throughout the world have reported very different case fatality ratios - the number of deaths divided by the number of confirmed cases - but these numbers cannot be compared easily due to biases. On the other hand, for many countries, the methodology used to report death rates in the different regions is standardized across the country.

We used mortality per number of inhabitants to assess death rates, as proposed by the European Center for Disease Prevention and Control (ecdc, https://www.ecdc.europa.eu/en), and to report trends with cutoffs at 25, 50, 100 and 250 per million.

Our hypothesis is mostly based on ecological data that are hypothesis-generating and that require confirmation by proper studies.

2- Multifactorial origin of the COVID-19 epidemic

Like most diseases, COVID-19 exhibits large geographical variations which frequently remain unexplained [6]. The COVID-19 epidemic is multifactorial, and factors like climate, population density, age, phenotype and prevalence of non-communicable diseases are also associated to increased incidence and mortality[7]. Diet represents only one of the possible causes of the COVID-19 epidemic and its importance needs to be better assessed. Some risk factors for the COVID-19 epidemics are proposed at the individual and country levels in Table 1.

Ecological data on COVID-19 death rates

When comparing death rates, large differences exist between and within countries and the evolution of the pandemic differs largely between countries (Figure 1). Although there are many pitfalls in analyzing death rates for COVID-19, [2] the evolution of death rates between May 20 and July 18 shows a dramatic increase in Latin America and only some increase in European countries, certain African countries, the Middle East, India, Pakistan and some of the South East Asian countries. However, there is no change in the very low death rates of Cambodia, China, Japan, Korea, Lao, Malaysia, Taiwan, Vietnam and of many Sub-Saharan African countries, Australia and New Zealand. This geographical pattern is very unlikely to be totally due to reporting differences between countries.

In some high death-rate countries such as Italy (Figure 2), variations are extremely large from 50 per million in Calabria to over 1,600 in Lombardia. In Switzerland, the French- and Italian-speaking cantons have a far higher death rate than the German-speaking ones (*Office fédéral de la santé publique,*Switzerland*https://www.bag.admin.ch/bag/fr/home.html*) (Figure 3). It may be proposed that the high-death rate cantons were contaminated by French and Italian people. However, the Mulhouse airport serves the region of Basel (Switzerland), the Haut-Rhin department (France) and the region of Freiburg (Germany). There was a COVID-19 outbreak in the Haut-Rhin department, in particular in Mulhouse and Colmar. The death rate for COVID-19 (May 20, 2020) was 935 per million inhabitants in France but only 10 to 25 in Switzerland and 7 in Germany. It is important to consider these regional differences since reporting of deaths is similar within the country and many factors may be considered.

In many Western countries, large cities (e.g. London, Madrid, Milan, New York, Paris) have been the most affected. This seems to be true also for many countries in which the rural areas have much fewer cases.

The number of deaths is relatively low in Sub-Saharan Africa compared to other regions, and the low population density (which applies in rural areas but not in megacities such as Cairo or Lagos) or the differences in health infrastructure are unlikely to be the only explanation.[8] It has been proposed that hot temperature may reduce COVID-19, but, in Latin American countries, death rates are high (e.g. Brazil, Ecuador, Peru and Mexico).

Is diet partly responsible for differences between and within countries?

Nutrition may play a role in the immune defense against COVID-19 and may explain some of the differences seen in COVID-19 between and within countries [2]. In this concept paper, raw and fermented cabbage were proposed to be candidates.

To test the potential role of fermented foods in the COVID-19 mortality in Europe, an ecological study, the European Food Safety Authority (EFSA) Comprehensive European Food Consumption Database, was used to study the country consumption of fermented vegetables, pickled/marinated vegetables, fermented milk, yoghurt and fermented sour milk.[9] Of all the variables considered, including confounders, only fermented vegetables reached statistical significance with the COVID-19 death rate per country. For each g/day increase in consumption of fermented vegetables of the country, the mortality risk for COVID-19 was found to decrease by 35.4% (Figure 4).

A second ecological study has analyzed cruciferous vegetables (broccoli, cauliflower, head cabbage (white, red and savoy cabbage), leafy brassica) and compared them with spinach, cucumber, courgette, lettuce and tomato [10]. Only head cabbage and cucumber reached statistical significance with the COVID-19 death rate per country. For each g/day increase in the average national consumption of some of the vegetables (head cabbage and cucumber), the mortality risk for COVID-19 decreased by a factor of 11, to 13.6 %. The negative ecological association between COVID-19 mortality and consumption of cabbage and cucumber supports the *a priori* hypothesis previously reported. However, these are ecological studies that need to be further tested.

Another diet component potentially relevant in COVID-19 mortality may be the food supply chain and traditional groceries. [11]The impact of the long supply chain of food on health is measurable by an increase in metabolic syndrome and insulin resistance.[12] Therefore, areas that are more prone to short supply food and traditional groceries may have been able to better tolerate COVID-19 with a lower death toll. These considerations may be partly involved in the lower death rates of Southern Italy compared to the Northern part (Figure 2).

Fermented foods, microbiome and lactobacilli

The fermentation process, born as a preservation method in the Neolithic age, enabled humans to eat not-so-fresh food and to survive.[13] Fermented foods are "foods or beverages made via controlled microbial growth (including lactic acid bacteria (LAB)) and enzymatic conversions of food components." [14] Not all fermented foods contain live cultures, as some undergo further processing after fermentation: pasteurization, smoking, baking, or filtration. These processes kill or remove the live microorganisms in foods such as soy sauces, bread, most beers and wines as well as chocolate. Live cultures can be found in fermented vegetables and fermented milk (fermented sour milk, yoghurt, probiotics, etc.).

Most traditional foods with live bacteria in the low-death rate countries are based on LAB fermentation [15]. A number of bacteria are involved in the fermentation of kimchi and other Korean traditional fermented foods, but LAB - including *Lactobacillus* - are the dominant species in the fermentation process[16,17]. *Lactobacillus* is also an essential species in the fermentation of sauerkraut, Taiwanese[18], Chinese [19] or other fermented foods [20]. Lactobacilli are among the most common microorganisms found in kefir, a traditional fermented milk beverage[21], milk and milk products [22,23]. During fermentation, LAB synthesize vitamins and minerals, and produce biologically-active peptides with anti-oxidant activity[14,24-28].

Humans possess two protective layers of biodiversity, and the microbiome has been proposed as an important actor of COVID-19[29]. The environment (outer layer) affects our lifestyle, shaping the microbiome (inner layer). [30]Many fermented foods contain living microorganisms and modulate the intestinal microbiome. [14,28,31-33]

The composition of microbiomes varies in different regions of the world. [34] Gut microbiota has an inter-individual variability due to genetic predisposition and diet. [35]As part of the gut microbiome, *Lactobacillus* spp. contributes to its diversity and modulates oxidative stress in the GI tract. Some foods like cabbage can be fermented by the gut microbiota.[36]

Urbanization in western countries was associated with changes in the gut microbiome and with intestinal diversity reduction. [35,37-40] Westernized food in Japan led to changes in the microbiome and in insulin resistance.[41] The gut microbiome of westernized urban Saudis had a lower biodiversity than that of the traditional Bedouin population.[42] Fast food consumption was characterized by reduced Lactobacilli in the microbiome. [43]

The links between gut microbiome, inflammation, obesity and insulin resistance are being observed but further large studies are needed for a definite conclusion. [44-46]

Some COVID-19 patients have intestinal microbial dysbiosis[47] with decreased probiotics such as *Lactobacillus* and *Bifidobacterium* [48]. Many bacteria are involved in the fermentation of vegetables but most traditional foods with live bacteria in the low-death rate countries are based on LAB fermentation. [15-17,20,27] Lactobacilli are among the most common microorganisms found in milk and milk products[21-23].

Angiotensin-converting enzyme 2 (ACE2) and COVID-19

COVID-19 is more severe in older adults and/or patients with comorbidities, such as diabetes, obesity or hypertension, suggesting a role for insulin resistance.[49] Although differences exist between countries, the same risk factors for severity were found globally, suggesting common mechanisms. A strong relationship between hyperglycemia, impaired insulin pathway, and cardiovascular disease in type 2 diabetes is linked to oxidative stress and inflammation.[50] Lipid metabolism has an important role to play in obesity, in diabetes and its multi-morbidities, and in ageing.[51] The increased severity of COVID-19 in diabetes, hypertension, obese or elderly individuals may be related to insulin resistance, with oxidative stress as a common pathway.[52] Moreover, the severe outcomes of COVID-19 - including lung damage, cytokine storm or endothelial damage - appear to exist globally, again suggesting common mechanisms.

The angiotensin-converting enzyme 2 (ACE2) receptor is part of the dual system – the renin-angiotensin-system (RAS) - consisting of an ACE-Angiotensin-II-AT_1R axis and an ACE-2-Angiotensin-(1-7)-Mas axis. AT_1R is involved in most of the effects of Ang II, including oxidative stress generation,[53] which in turn upregulates AT_1R [54]. In metabolic disorders and with older age, there is an upregulation of the AT_1R axis leading to pro-inflammatory, pro-fibrotic effects in the respiratory system, and to insulin resistance.[55]SARS-CoV-2 binds to its receptor ACE2 and exploits it for entry into the cell. The ACE2 downregulation, as a result of SARS-CoV-2 binding, enhances the AT_1R axis [56] likely to be associated with insulin resistance [57,58] but also to severe outcomes of COVID-19 (Figure 5A).

Anti-oxidant activities of foods linked with COVID-19

Many foods have an antioxidant activity [59-61] and the role of nutrition has been proposed to mitigate COVID-19[62]. Many antioxidant mechanisms have been proposed, and several foods can interact with transcription factors related to antioxidant effects such as the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2). [3] Some processes like fermentation increase the antioxidant activity of milk, cereals, fruit, vegetables, meat and fish. [26]

7-1- Nrf2, a central antioxidant system

Reactive oxygen species (ROS), such as hydrogen peroxide and superoxide anion, exert beneficial and toxic effects on cellular functions. Nrf2 is a pleiotropic transcription factor at the centre of a complex regulatory network that protects against oxidative stress and the expression of a wide array of genes involved in immunity and inflammation, including antiviral actions.[63] Nrf2 activity in response to chemical insults is regulated by a thiol-rich protein named KEAP1 (Kelch-like ECH-associated protein 1). The KEAP1-Nrf2 system is the body's dominant defense mechanism against ROS.[64]Induction of the antioxidant responsive element and the ROS mediated pathway by Nrf2 reduces the activity of nuclear factor kappa B (NF-$\varkappa$B), [65] whereas NF-$\varkappa$B can modulate Nrf2 transcription and activity, having both positive and negative effects on the target gene expression [66].

Natural compounds derived from plants, vegetables, fungi and micronutrients (e.g. curcumin, sulforaphane, resveratrol and vitamin D) or physical exercise can activate Nrf2.[67,68] However, sulforaphane is the most potent activator of Nrf2.[3,34] "Ancient foods", and particularly those containing *Lactobacillus,* activate Nrf2. [69]

Nrf2 may be involved in diseases associated with insulin-resistance.[57,70-72] Nrf2 activity declines with age, making the elderly more susceptible to oxidative stress-mediated diseases.[73] Nrf2 is involved in the protection against lung[74] or endothelial damage. [75] Nrf2 activating compounds downregulate ACE2 mRNA expression in human liver-derived HepG2 cells.[76] Genes encoding cytokines including IL-6 and many others specifically identified in the "cytokine storm" have been observed in fatal cases of COVID-19. ACE2 can inhibit NF-$\varkappa$B and activate Nrf2.[77]

7-2- Sulforaphane, the most potent Nrf2 natural activator

Isothiocyanates are stress-response chemicals formed from glucosinolates in plants often belonging to the cruciferous family, and more broadly to the Brassica genus including broccoli, watercress, kale, cabbage, collard greens, Brussels sprouts, bok choy, mustard greens and cauliflower .[78] The formation of isothiocyanates from glucosinolates depends on plant-intrinsic factors and extrinsic postharvest factors such as industrial processing, domestic preparation, mastication, and digestion. [79]

Sulforaphane [1-isothiocyanato-4-(methylsulfinyl)butane] is an isothiocyanate occurring in a stored form such as glucoraphanin in cruciferous vegetables [80,81]. Sulphoraphanes are also found in fermented cabbage [28,82]. Present in the plant as its precursor, glucoraphanin, sulforaphane is formed through the actions of myrosinase, a β-thioglucosidase present in either the plant tissue or the mammalian microbiome [83,84].

Sulforaphane is a clinically relevant nutraceutical compound used for the prevention and treatment of chronic diseases and may be involved in ageing.[85] Along with other natural nutrients, sulforaphane has been suggested to have a therapeutic value for the treatment of coronavirus disease 2019 (COVID-19).[86]

One of the key mechanisms of action of sulforaphane involves the activation of the Nrf2-Keap1 signaling pathway.[87]Sulforaphane is the most effective natural activator of the Nrf2 pathway, and Nrf2 expression and function is vital for sulforaphane-mediated action.[88,89] Sulforaphanes were suggested to be effective in diseases associated with insulin resistance[1,90-92] It has been proposed that SARS-CoV-2 downregulates ACE2 and that there is an increased insulin resistance associated with oxidative stress through the AT_1R pathway. Fermented vegetables and Brassica vegetables release glucoraphanin, converted by the plant or by the gut microbiome into sulforaphane, which activates Nrf2 and subsequently reduces insulin intolerance (Figure 5B).

7-3- Lactic acid bacteria

Antioxidant activity of Lactobacillus

The gastrointestinal (GI) tract is challenged with oxidative stress induced by a wide array of factors, such as exogenous pathogenic microorganisms and dietary aspects. Redox signaling plays a critical role in the physiology and pathophysiology of the GI tract[93]. The redox mechanisms of *Lactobacillus* spp. are involved in the downregulation of ROS-forming enzymes,[94,95] and redox stress resistance proteins or genes differ largely between LAB species. In addition, Nrf-2 and NF-κB are two common transcription factors, through which *Lactobacillus* spp. also modulates oxidative stress. [96]

Do lactobacilli prevent insulin resistance?

Hundreds of studies have attempted to find an efficacy of LAB on insulin resistance-associated diseases. However, most of them are underpowered or have some methodological flaws. Moreover, not all LAB strains have the same action on insulin resistance [97] and new better designed studies with the appropriate LAB are required. A large meta-analysis found that the intake of probiotics resulted in minor but consistent improvements in several metabolic risk factors in subjects with metabolic diseases, and particularly in insulin resistance[98]. Another recent meta-analysis found that an oral supplementation with probiotics or synbiotics has a small effect in reducing waist circumference but no effect on body weight or body mass index (BMI) [99]. Kefir, a fermented milk product, was not found to be more effective than yoghurt in the glycemic control of obesity, possibly because there are insufficient differences between both [100].

Lactobacillus and Nrf2

Nrf2 may be involved in diseases associated with insulin resistance[70-72]. "Ancient foods", and particularly those containing *Lactobacillus* , activate Nrf2[69]. The microbiome is highly related to insulin resistance. In mice, several strains of *Lactobacillus* were found to regulate Nrf2 in models of ageing [101], in cardioprotective effects[102], and in non-alcoholic fatty acid liver disease[103]. *Lactobacillus plantarum* CQPC11 - isolated from Sichuan pickled cabbages - antagonizes oxidation and ageing in mice[104]. Lactobacillus protects against ulcerative colitis by modulation of the gut microbiota and Nrf2/Ho-1 pathway[105]. The sugary kefir strain, *Lactobacillus mali* APS1, ameliorates hepatic steatosis by regulation of Nrf2 and the gut microbiota in rats [106]. *In vitro* studies have also found an effect of *Lactobacilli* mediated by Nrf2[107-109]. Interestingly, the symbiotic combination of prebiotic grape pomace extract and probiotic *Lactobacillus* sp. reduces intestinal inflammatory markers.[110]

Coronavirus disease in animals and lactic acid bacteria.

The porcine epidemic diarrhea virus (PEDV) and the Transmissible Gastroenteritis Coronavirus Infection (TGEV) are worldwide-distributed coronaviruses. Low levels of *Lactobacillus* were found in the intestine of piglets infected by TGEV [111] or PEDV.*Lactobacillus* inhibits PEDV or TGEV effects *in vitro*[112,113].

7-4- Nrf2 and COVID-19

A putative mechanism may be proposed (Figure 5). SARS-CoV-2 downregulates ACE2 inducing an increased insulin resistance associated with oxidative stress through the AT_1R pathway. This may explain risk factors for severe COVID-19.

Fermented vegetables are often made from cruciferous (Brassica) vegetables that release glucoraphanin converted by the plant or by the gut microbiome into sulforaphane which activates Nrf2 and subsequently reduces insulin intolerance by its potent antioxidant activities. Fermented vegetables contain a high content of *Lactobacillus* that can activate Nrf2 and impact on the microbiome. [114]Sulforaphane and LAB both therefore have the ability to reduce insulin resistance.

Other putative actions on COVID-19 severity may be postulated. The down-regulation of ACE2 reduces the Ang-1,7 anti-oxidant activity that was found to activate Nrf2. [115,116] Nrf2 protects against hallmarks of severe COVID-19. It has anti-fibrotic effects on various organs including the lungs, [117] protects against lung injury and acute respiratory distress syndrome,[118] and endothelial damage, [75] . Finally, Nrf2 can block IL-6 in different models of inflammation[119] and might play a role in the COVID-19 cytokine storm.

These different mechanisms may explain the importance of fermented cabbage in preventing the severity of COVID-19. It is clear that other nutrients, vitamin D [120] and many different foods act on NRF2 and that mechanisms other than Nrf2 may be operative.

It is not yet known whether sulforaphane and/or LAB may act on the infectivity of SARS-CoV-2. Disulfide bonds can be formed under oxidizing conditions and play an important role in the folding and stability of some proteins. The receptor-binding domain of the viral spike proteins and ACE2 have several cysteine residues. Using molecular dynamics simulations, the binding affinity was significantly impaired when all of the disulfide bonds of both ACE2 and SARS-CoV/CoV-2 spike proteins were reduced to thiol groups. This computational finding possibly provides a molecular basis for the differential COVID-19 cellular recognition due to the oxidative stress.[121]

It is likely that foods with anti-oxidant activity can interact with COVID-19 and that fermented or cruciferous vegetables represent one of the possible foods involved. If some foods are found to be associated with a prevention of COVID-19 prevalence or severity, it may be of interest to study their LAB and/or sulforaphane composition in order to eventually find some common mechanisms and targets for therapy.

May dietary modifications change the course of COVID-19?

8-1- Fermented vegetables and Kimchi

It is tempting to propose that countries where traditional LAB-fermented vegetables are largely consumed are those showing lower COVID-19 death rates and that fermented vegetables represent one possible preventive approach. Other nutrients are found in these products that may enhance their effect (e.g. vitamin K [122]). Kimchi fermented from many vegetables including cabbage has several effects on insulin resistance associated diseases: anti-diabetic properties,[123,124] cardiovascular diseases, [25]dyslipidemia [125] or ageing. [126]Kimchi, when fermented for a long time, reduces insulin intolerance to a greater extent than fresh kimchi, [123] indicating that newly formed products during fermentation are important. In particular, Kimchi from cabbage and Chinese cabbage contains several glucosinolates[127-129] that can be transformed in sulforaphanes either in the plant itself or by the human microbiome.[57] In central European countries, raw and fermented cabbage is commonly consumed.

In Sub-Saharan Africa, people commonly eat fermented foods, mainly cereal-based foods like sorghum, millet and maize, roots such as cassava, fruits and vegetables.

It is clear that sauerkraut is consumed in Alsace (France) where a COVID-19 outbreak has been identified, but it is not a regular meal.

8-2- Westernized diet

Westernized diets contain a reduced amount of fermented vegetables[40,130] and may be prone to increasing insulin resistance [41,131] and diseases associated with it,[132] and thereby severe COVID-19.

In the Mediterranean diet, well known for reducing insulin resistance,[133] Nrf2 appears to play an important role.[68,134] The COVID-19 death rate differences in Italian (Figure 2) and Spanish [2] regions suggest a role for Mediterranean diet and short chain food supply. This also indicates that many foods can have an effect and that cabbage and fermented foods represent a proof-of-concept. Nrf2 is also involved in the Okinawan-based diet [68], active on insulin intolerance.[135] Taken altogether, it is possible that diet is partly involved in the COVID-19 death clusters found in large Western cities where traditional diet is often replaced by long chain food supply.

Conclusion

Cabbage contains precursors of sulforaphane, the most active natural activator of Nrf2. Fermented vegetables contain many lactobacilli, also potent Nrf2 activators. It is proposed that fermented cabbage is a proof-of-concept of dietary manipulations that may enhance Nrf2-associated antioxidant effects helpful in mitigating COVID-19 severity.

Mainstream COVID-19 control strategies including social distancing, confinement and intensive case finding, testing, tracing and isolating are so far not enough to provide a SARS-CoV-2-free environment and restore a safe social life. There are hopes for a safe and effective vaccine, but this is unlikely to become rapidly available. So, there is a need to explore other potentially useful strategies. An area that has not been sufficiently considered is diet, both as a preventive and/or therapeutically useful intervention, encouraging people to eat more traditional foods containing fermented vegetables. We have suggested that fermented vegetables could be associated with a lower COVID-19 mortality due to their potent antioxidant effect among which sulforaphane and LAB are important. However, many other foods may have a similar activity. It should be noted that dietary supplements that over-activate Nrf2 may have side-effects.[136]

Robust evidence from observational studies would be helpful to formally investigate associations between fermented foods and clinical outcomes in COVID-19. State-of-the-art methods, including the use of DAGs (Directed Acyclic Graphs), may be needed to help assess whether the associations seen are likely to represent causal relationship[137]. A faster approach would be to develop large clinical trials in the appropriate populations. Interventions based on diets with a high intake of fermented foods like Kimchi or other fermented foods are unlikely to present ethical difficulties. Furthermore, the fact that a precise mechanism has been proposed would facilitate adding reliable biomarkers to the relevant clinical outcomes. Moreover, new drugs based on the components of these fermented foods may be of interest.

If the hypothesis is proved, COVID-19 will be the first infectious disease outbreak associated with a loss of "nature"[138] and to be ascribed as a disease of the Anthropocene [139]. Imbalance in the gut microbiota is responsible for the pathogenesis of various disease types including allergy, asthma, rheumatoid arthritis, different types of cancer, diabetes mellitus, obesity and cardiovascular disease[140]. Fermentation was introduced during the Neolithic age and was essential for the survival of human kind. When modern life led to eating reduced amounts of fermented foods, the microbiome drastically changed [141], allowing SARS-CoV-2 to spread or to be more severe [142]. It is time for mitigation[143].

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Table 1: Possible risk factors for COVID-19 infection explaining geographical differences

		Individual level	Country/region level
A	Contact with a SARS-CoV-2 infected individual	++++	Case zero identified ++++ e.g. Lombardy
A	Intensity of social contacts	++	+++
A	Intensity of occupational contacts	+++	++
A	Confinement (level)	+++	+++ e.g. US versus EU Sweden vs Nordic countries
A	Confinement (early measures)	+++	+++ e.g. UK versus EU
A	Climatic conditions (temperature, humidity)	?	++ Hot and humid temperature may reduce infection but epidemic bursts in Brazil, Peru and Ecuador
A	GDP of a country/region	?	+
A	Vitamin D	?	+
B	Diet	?	+ The map of COVID-19 deaths in Europe and the low prevalence in Asia and Africa suggest a role for diet

		Individual level	Country/region level
B	Food	++?	+ Bibliographic analysis suggests a role for some fermented foods. Raw cabbage can be fermented in the intestine. Kefir is largely used in many low-prevalence countries.
B	Long food chain supply	++?	+ In Italy and Spain, there may be an association with long chain supply. This may be relevant since food quality differs.
B	Traditional fermented food (example of food)	++?	++ This may be a relevant issue. In former Eastern European countries, in the Balkans, in Africa and in many Asian countries with low-COVID-19 prevalence, traditional fermented foods are common (in line with short food chain supply)
B	Air pollution	+?	+?
B	Underserved area	++	++
C	Age	+++	
C	Comorbidities (severity of COVID-19)	+++	++
C	Sex	++	
C	Institutionalized person	++	

A: Risk factors at a country level, B: Environment, nutrition, C: individual level

Figure 1: COVID-19 deaths per million inhabitants (May 20, 2020)

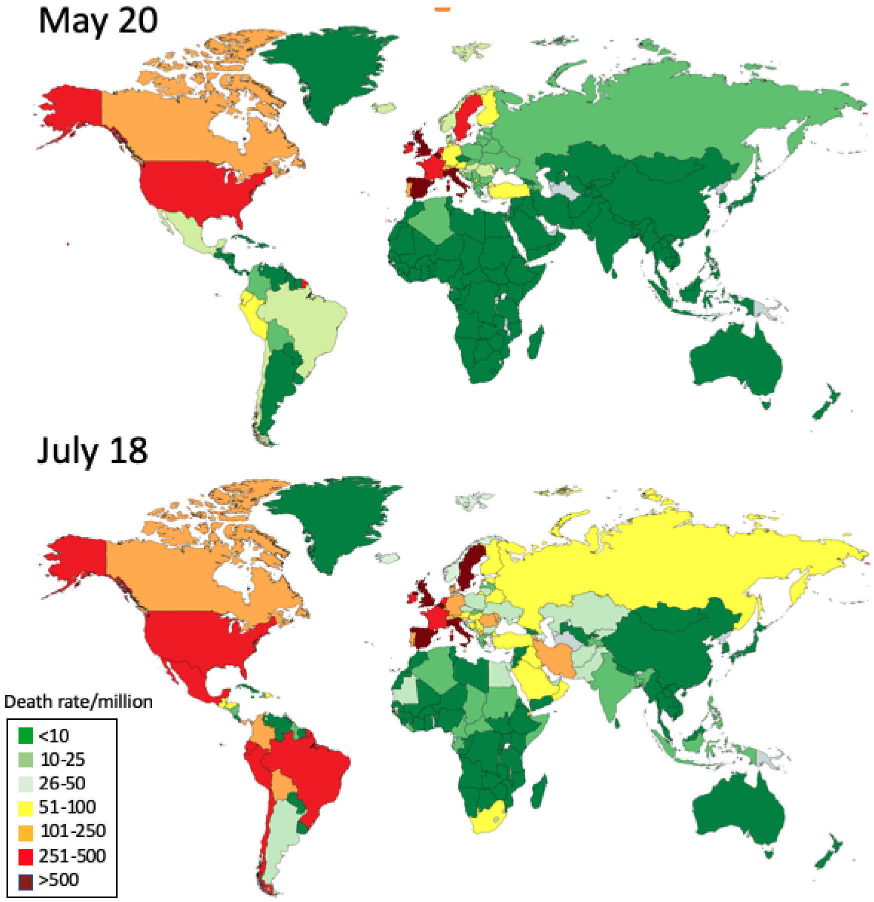


Figure 2: Regional differences of death rates in Italy

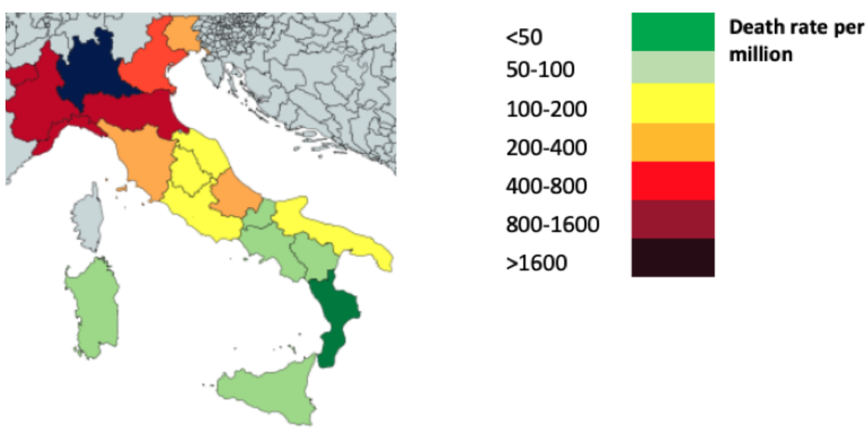


Figure 3: Regional differences of death rates (May 20)

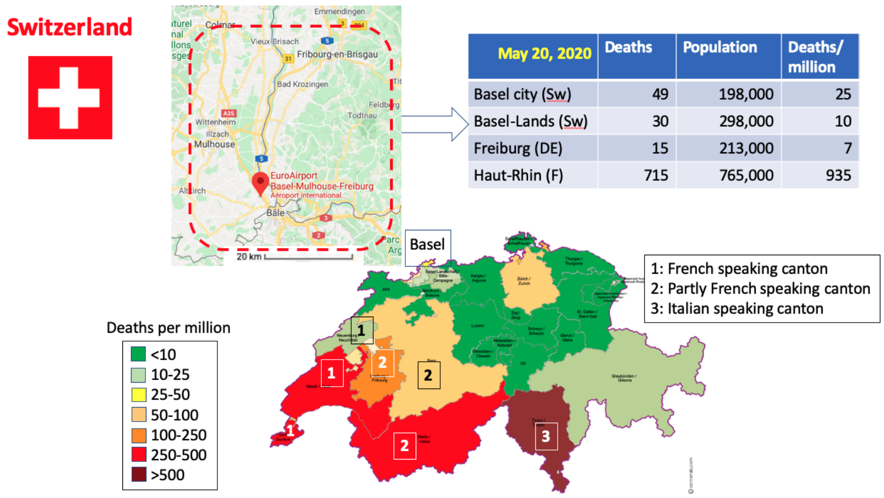


Figure 4: Consumption of head cabbage and COVID-19 death rate at a country level

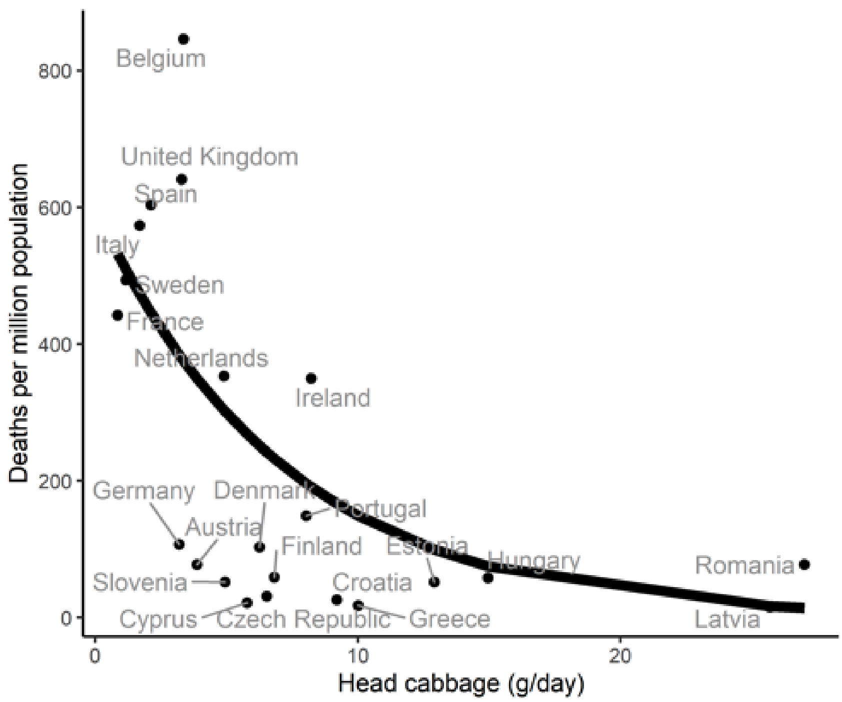
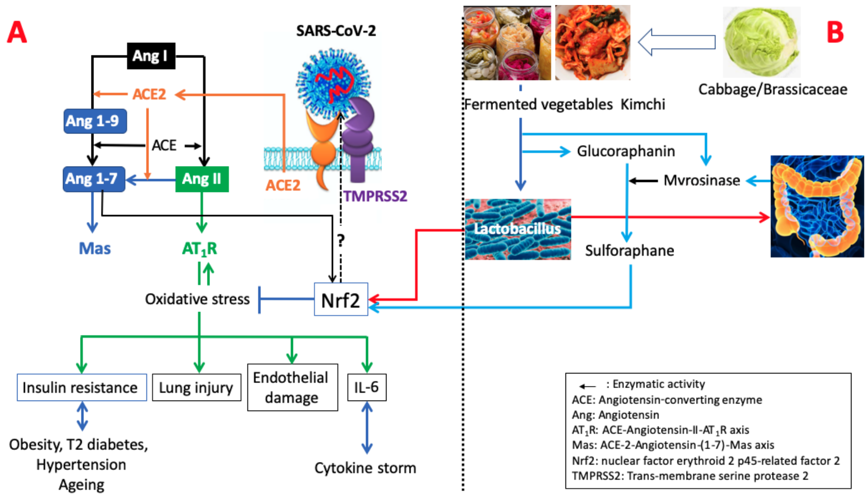
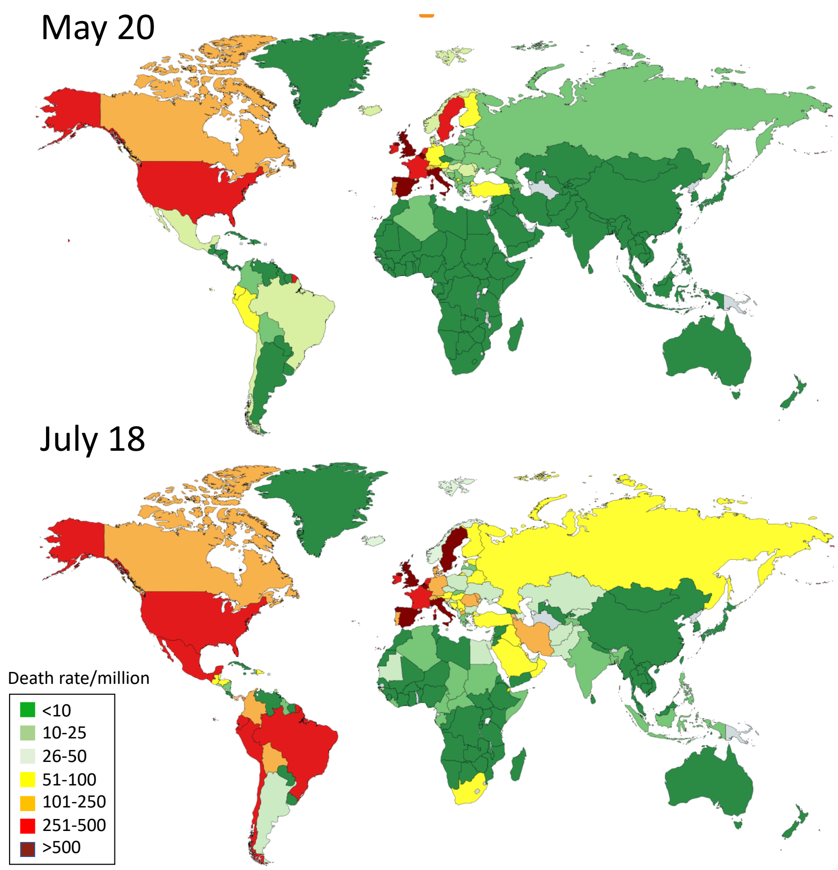
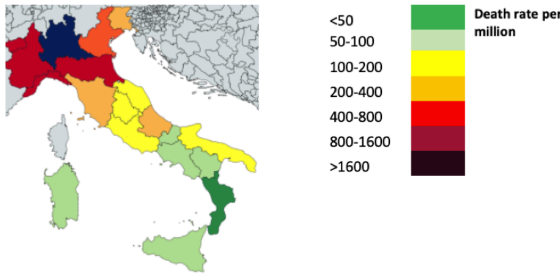


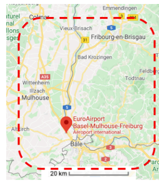
Figure 5: Putative mechanisms of fermented or *Brassica*vegetables against COVID-19


A
Ang I
ACE2
Ang 1-9
ACE
Ang 1-7
Ang II
Mas
AT$_1$R
SARS-CoV-2
ACE2
TMPRSS2
?
Oxidative stress
Nrf2
Insulin resistance
Lung injury
Endothelial damage
IL-6
Obesity, T2 diabetes,
Hypertension
Ageing
Cytokine storm
B
Fermented vegetables Kimchi
Cabbage/Brassicaceae
Glucoraphanin
Mvrosinase
Lactobacillus
Sulforaphane
: Enzymatic activity
ACE: Angiotensin-converting enzyme
Ang: Angiotensin
AT$_1$R: ACE-Angiotensin-II-AT$_1$R axis
Mas: ACE-2-Angiotensin-(1-7)-Mas axis
Nrf2: nuclear factor erythroid 2 p45-related factor 2
TMPRSS2: Trans-membrane serine protease 2

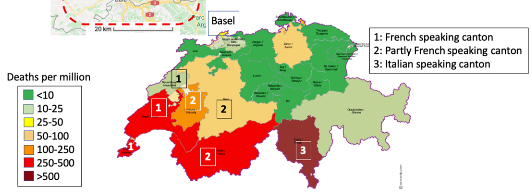

May 20
July 18
Death rate/million
<10
10-25
26-50
51-100
101-250
251-500
>500

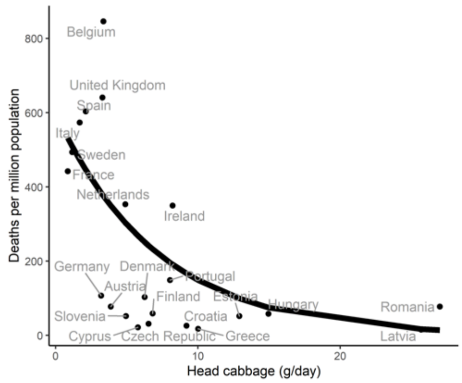

Death rate per million
<50
50-100
100-200
200-400
400-800
800-1600
>1600

Switzerland

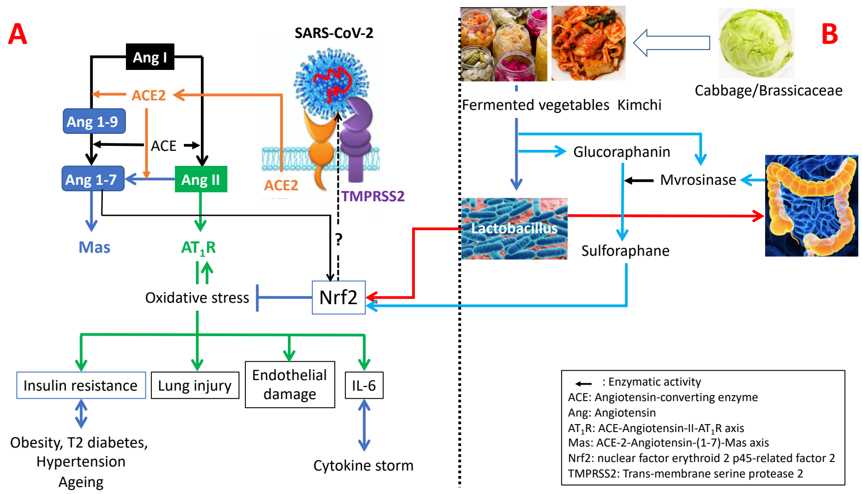


May 20, 2020	Deaths	Population	Deaths/ million
Basel city (Sw)	49	198,000	25
Basel-Lands (Sw)	30	298,000	10
Freiburg (DE)	15	213,000	7
Haut-Rhin (F)	715	765,000	935





Deaths per million population
Head cabbage (g/day)
Belgium
United Kingdom
Spain
Italy
Sweden
France
Netherlands
Ireland
Germany
Denmark
Portugal
Austria
Finland
Estonia
Hungary
Romania
Slovenia
Croatia
Cyprus
Czech Republic
Greece
Latvia


A
Ang I
ACE2
Ang 1-9
ACE
Ang 1-7
Ang II
Mas
AT1R
SARS-CoV-2
ACE2
TMPRSS2
?
Oxidative stress
Nrf2
Insulin resistance
Lung injury
Endothelial damage
IL-6
Obesity, T2 diabetes, Hypertension Ageing
Cytokine storm
B
Fermented vegetables
Kimchi
Cabbage/Brassicaceae
Glucoraphanin
Mvrosinase
Lactobacillus
Sulforaphane
: Enzymatic activity
ACE: Angiotensin-converting enzyme
Ang: Angiotensin
AT1R: ACE-Angiotensin-II-AT1R axis
Mas: ACE-2-Angiotensin-(1-7)-Mas axis
Nrf2: nuclear factor erythroid 2 p45-related factor 2
TMPRSS2: Trans-membrane serine protease 2