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

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

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Short title: Mitigation of COVID-19 by diet

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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 (AT_1R) axis associated with oxidative stress. This leads to insulin resistanceas well as 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 AT_1R axis. Cabbage contains precursors of sulforaphane, the most active natural activator of Nrf2. Fermented vegetables contain many lactobacilli, which are also potent Nrf2 activators. Three examples are given: Kimchi in Korea, westernized foods and the slum paradox. 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.

Key words: COVID-19, diet, sulforaphane, Lactobacillus, Angiotensin converting enzyme 2, kimchi, cabbage, fermented vegetable

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. Several intertwined factors can be proposed: social distancing, health system capacity, age of the population, social lifestyle (gathering of family/friends, social behavior), testing capacity and/or timing and intensity of the first outbreak.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. [2,3]

Diet has been proposed to mitigate COVID-19.[4,5]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. [6]News and social media platforms have implicated dietary supplements in the treatment and prevention of COVID-19 without evidence.[7]

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.

1- 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 [8]. 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 [9]. 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.

3- 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,[3] 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) (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. [10] 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).

4- 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 [3]. 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. [11] 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 [12].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.[13] The impact of the long supply chain of food on health is measurable by an increase in metabolic syndrome and insulin resistance.[14] 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).

5- 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. [15]Indigenous fermented foods such as bread, cheese,vegetables and alcoholic beverages have been prepared and consumed for thousands of years, are strongly linked to culture and tradition, especially in rural households and village communities, and are consumed by hundreds of millions of people.[16]Fermented foods are “foods or beverages made via controlled microbial growth (including lactic acid bacteria (LAB)) and enzymatic conversions of food components.” [17]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 [18].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[19,20]. *Lactobacillus* is also an essential species in the fermentation of sauerkraut, Taiwanese [21], Chinese [22] or other fermented foods[23]. Lactobacilli are among the most common microorganisms found in kefir, a traditional fermented milk beverage [24], milk and milk products [25,26]. During fermentation, LAB synthesize vitamins and minerals, and produce biologically-active peptides with anti-oxidant activity [17,27-31].

Humans possess two protective layers of biodiversity, and the microbiome has been proposed as an important actor of COVID-19 [32]. The environment (outer layer) affects our lifestyle, shaping the microbiome (inner layer). [33] Many fermented foods contain living microorganisms and modulate the intestinal microbiome. [17,31,34-36]

The composition of microbiomes varies in different regions of the world. [37]Gut microbiota has an inter-individual variability due to genetic predisposition and diet. [38]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.[39]

Westernized foods usually lack fermented vegetables and milk-derived products have less biodiversity than traditional ones. Urbanization in western countries was associated with changes in the gut microbiome and with intestinal diversity reduction. [38,40-43] Westernized food in Japan led to changes in the microbiome and in insulin resistance. [44]The gut microbiome of westernized urban Saudis had a lower biodiversity than that of the traditional Bedouin population.[45]Fast food consumption was characterized by reduced Lactobacilli in the microbiome. [46]

The links between gut microbiome, inflammation, obesity and insulin resistance are being observed but further large studies are needed for a definite conclusion. [47-49]

Some COVID-19 patients have intestinal microbial dysbiosis [50] with decreased probiotics such as *Lactobacillus* and *Bifidobacterium* [51]. 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.[18-20,23,30]Lactobacilli are among the most common microorganisms found in milk and milk products [24-26].

6- 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.[52] 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.[53]Lipid metabolism has an important role to play in obesity, in diabetes and its multi-morbidities, and in ageing.[54] 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.[55]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 -therenin-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,[56] which in turn upregulates AT_1R [57]. 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.[58]

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 [59] likely to be associated with insulin resistance [60,61] but also to severe outcomes of COVID-19 (Figure 5A).

7- Anti-oxidant activities of foods linked with COVID-19

Many foods have an antioxidant activity [62-64] and the role of nutrition has been proposed to mitigate COVID-19 [65]. Many antioxidant mechanisms have been proposed, and several foods can interact with transcription factors related to antioxidant effects such as theNuclear factor (erythroid-derived 2)-like 2 (Nrf2).[4]Some processes like fermentation increase the antioxidant activity of milk, cereals, fruit, vegetables, meat and fish.[29]

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.[66] 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.[67]Induction of the antioxidant responsive element and the ROS mediated pathway by Nrf2 reduces the activity of nuclear factor kappa B (NF-κB), [68]whereas NF-κB can modulate Nrf2 transcription and activity, having both positive and negative effects on the target gene expression [69].

Natural compounds derived from plants, vegetables, fungi and micronutrients (e.g. curcumin, sulforaphane, resveratrol and vitamin D) or physical exercise can activate Nrf2.[70,71]However, sulforaphane is the most potent activator of Nrf2.[3,34]"Ancient foods", and particularly those containing *Lactobacillus,* activate Nrf2.[72]

Nrf2 may be involved in diseases associated with insulin-resistance.[60,73-75]Nrf2 activity declines with age, making the elderly more susceptible to oxidative stress-mediated diseases.[76] Nrf2 is involved in the protection against lung [77] or endothelial damage. [78] Nrf2 activating compounds downregulate ACE2 mRNA expression in human liver-derived HepG2 cells.[79]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-κB and activate Nrf2.[80]

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 .[81]The formation of isothiocyanates from glucosinolates depends on plant-intrinsic factors and extrinsic postharvest factors such as industrial processing, domestic preparation, mastication, and digestion.[82]

Sulforaphane [1-isothiocyanato-4-(methylsulfinyl)butane] is an isothiocyanate occurring in a stored form such as glucoraphanin in cruciferous vegetables [83,84].Sulphoraphanes are also found in fermented cabbage [31,85]. 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 [86,87].

Sulforaphane is a clinically relevant nutraceutical compound used for the prevention and treatment of chronic diseases and may be involved in ageing.[88] Along with other natural nutrients, sulforaphane has been suggested to have a therapeutic value for the treatment of coronavirus disease 2019 (COVID-19).[89]

One of the key mechanisms of action of sulforaphane involves the activation of the Nrf2-Keap1 signaling pathway.[90]Sulforaphane is the most effective natural activator of the Nrf2 pathway, and Nrf2 expression and function is vital for sulforaphane-mediated action.[91,92]Sulforaphanes were suggested to be effective in diseases associated with insulin resistance [1,93-95]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 [96]. The redox mechanisms of *Lactobacillus* spp. are involved in the downregulation of ROS-forming enzymes,[97,98]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.[99]

Do lactobacilliprevent 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 [100] 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 [101]. 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) [102].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 [103].

Lactobacillus and Nrf2

Nrf2 may be involved in diseases associated with insulinresistance [73-75]. “Ancient foods”, and particularly those containing *Lactobacillus*, activate Nrf2[72]. The microbiome is highly related to insulin resistance. In mice, several strains of *Lactobacillus* were found to regulate Nrf2 in models of ageing [104], in cardioprotective effects [105], and in non-alcoholic fatty acid liver disease [106]. *Lactobacillus plantarum* CQPC11 - isolated from Sichuan pickled cabbages - antagonizes oxidation and ageing in mice [107]. Lactobacillus protects against ulcerative colitis by modulation of the gut microbiota and Nrf2/Ho-1 pathway [108]. The sugary kefir strain, *Lactobacillus mali* APS1, ameliorates hepatic steatosis by regulation of Nrf2 and the gut microbiota in rats [109]. *In vitro* studies have also found an effect of *Lactobacilli* mediated by Nrf2 [110-112]. Interestingly, the symbiotic combination of prebiotic grape pomace extract and probiotic *Lactobacillus* sp. reduces intestinal inflammatory markers.[113]

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 foundin the intestine of piglets infected by TGEV [114] or PEDV. *Lactobacillus* inhibits PEDV or TGEV effects *in vitro*[115,116].

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. [117]Sulforaphane and LAB both thereforehave 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. [118,119] Nrf2 protects against hallmarks of severe COVID-19. It has anti-fibrotic effects on various organs including the lungs, [120] protects against lung injury and acute respiratory distress syndrome, [121] and endothelial damage[78] . Finally, Nrf2 can block IL-6 in different models of inflammation [122] 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[123] 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.[124]

It is likely that foods with anti-oxidant activity can interact with COVID-19 and that fermented or cruciferou*s* 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.

8- 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 [125]).Kimchi fermented from many vegetables including cabbage has several effects on insulin resistance associated diseases: anti-diabetic properties,[126,127] cardiovascular diseases,[28] dyslipidemia [128] or ageing.[129]Kimchi, when fermented for a long time, reduces insulin intolerance to a greater extent than fresh kimchi,[126] indicating that newly formed products during fermentation are important. In particular, Kimchi from cabbage and Chinese cabbage contains several glucosinolates[130-132] that can be transformed in sulforaphanes either in the plant itself or by the human microbiome.[60] 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. Fermented cassava products (like *gari* and *fufu*) are a major component of the diet of over 800 million people and, in some areas, these products constitute over 50% of the diet.[16]

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[43,133] and may be prone to increasing insulin resistance[44,134] and diseases associated with it, [135] and thereby severe COVID-19.

In the Mediterranean diet, well known for reducing insulin resistance, [136] Nrf2 appears to play an important role. [71,137] The COVID-19 death rate differences in Italian (Figure 2) and Spanish [3]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 [71], active on insulin intolerance. [138] 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.

It is clear that diet is not the only risk factor and should be considered in the context of COVID-19 in a given setting. For example, Nordic/central European people socialize less than the Mediterraneans and simultaneously may consume more fermented vegetables.

8.3. The COVID-19 slum paradox

It was expected that the COVID-19 pandemic will be catastrophic if it reached deprived areas of low- and middle-income countries, in particular informal settlements (slum areas) where social distancing and lockdown are almost impossible to set up. [139]

In the US, highly populated, regional air hub areas, minorities and poverty had an increased risk of COVID-19 related mortality. [140] It was proposed that the inequality might be due to the workforce of essential services, poverty, access to care or air pollution [141]. These are common risk factors in mortality observed in deprived areas of the US. [142] Moreover, in the US and the UK, there are unique health issues facing black, Asian and minority ethnic communities. [143,144] This greater risk of hospitalizations in these populations was not explained by socio-economic or behavioural factors. [145] Social distancing is an important factor to be considered [146] but diet may also be involved.

On the other hand, a recent report of the Municipal Corporation of Greater Mumbai (Public Relation Department, 28-07-2020) found that 57% of subjects tested in the slum area had antibodies against SAR-CoV-2 but only 16% in the non-slum areas. The fatality rate in slum areas was very low (0.05-0.1%). [147] Although precise data are lacking, in Brazilian favelas the spread of COVID-19 is not noticed. [148] Temperature does not seem to be an important factor to contain the pandemic.Fermented foods are popular throughout the world and in many regions they represent a widespread tradition as well as they make a significant contribution to the diet of millions of individuals.[16] This is the case in slum areas and it is possible that fermented foods explain, at least partly, the paradox.

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 mitigate 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 (Figure 6). 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 LABare 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.[149]

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 [150]. 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" [151] and to be ascribed as a disease of the Anthropocene [152]. 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 [153]. 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 [154], allowing SARS-CoV-2 to spread or to be more severe [155]. It is time for mitigation [156].

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References

1. Stafford N. Covid-19: Why Germany's case fatality rate seems so low. BMJ 2020;369:m1395.
2. Bousquet J, Czarlewski W, Blain H, Zuberbier T, Anto J. Rapid Response: Why Germany's case fatality rate seems so low: Is nutrition another possibility. bmj 2020;https://www.bmj.com/content/369/bmj.m1395/rr-12.
3. Bousquet J, Anto JM, Iaccarino G, et al. Is diet partly responsible for differences in COVID-19 death rates between and within countries? Clin Transl Allergy 2020;10:16.
4. Iddir M, Brito A, Dingeo G, et al. Strengthening the Immune System and Reducing Inflammation and Oxidative Stress through Diet and Nutrition: Considerations during the COVID-19 Crisis. Nutrients 2020;12.
5. Cena H, Chieppa M. Coronavirus Disease (COVID-19-SARS-CoV-2) and Nutrition: Is Infection in Italy Suggesting a Connection? Front Immunol 2020;11:944.
6. Infusino F, Marazzato M, Mancone M, et al. Diet Supplementation, Probiotics, and Nutraceuticals in SARS-CoV-2 Infection: A Scoping Review. Nutrients 2020;12.
7. Adams KK, Baker WL, Sobieraj DM. Myth Busters: Dietary Supplements and COVID-19. Ann Pharmacother 2020;54:820-6.
8. Sunyer J, Jarvis D, Pekkanen J, et al. Geographic variations in the effect of atopy on asthma in the European Community Respiratory Health Study. J Allergy Clin Immunol 2004;114:1033-9.
9. Kissler SM, Tedijanto C, Goldstein E, Grad YH, Lipsitch M. Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. Science 2020.
10. Rosenthal PJ, Breman JG, Djimde AA, et al. COVID-19: Shining the Light on Africa. Am J Trop Med Hyg 2020.
11. Fonseca S, Rivas I, Romaguera D, et al. Association between consumption of fermented vegetables and COVID-19 mortality at a country level in Europe MEDRXIV/2020/147025 2020.
12. Fonseca S, Rivas I, Romaguera D, et al. Association between consumption of vegetables and COVID-19 mortality at a country level in Europe. MedRix 2020.
13. Baker P, Friel S. Food systems transformations, ultra-processed food markets and the nutrition transition in Asia. Global Health 2016;12:80.

14. Santulli G, Pascale V, Finelli R, et al. We are What We Eat: Impact of Food from Short Supply Chain on Metabolic Syndrome. J Clin Med 2019;8.
15. Peters A, Krumbholz P, Jager E, et al. Metabolites of lactic acid bacteria present in fermented foods are highly potent agonists of human hydroxycarboxylic acid receptor 3. PLoS Genet 2019;15:e1008145.
16. Azam-Ali S. Fermented fruits and vegetables. A global perspective.1998.
17. Marco ML, Heeney D, Binda S, et al. Health benefits of fermented foods: microbiota and beyond. Curr Opin Biotechnol 2017;44:94-102.
18. Rhee SJ, Lee JE, Lee CH. Importance of lactic acid bacteria in Asian fermented foods. Microb Cell Fact 2011;10 Suppl 1:S5.
19. Patra JK, Das G, Paramithiotis S, Shin HS. Kimchi and Other Widely Consumed Traditional Fermented Foods of Korea: A Review. Front Microbiol 2016;7:1493.
20. Jung JY, Lee SH, Jeon CO. Kimchi microflora: history, current status, and perspectives for industrial kimchi production. Appl Microbiol Biotechnol 2014;98:2385-93.
21. Chen YS, Otoguro M, Lin YH, et al. Lactococcus formosensis sp. nov., a lactic acid bacterium isolated from yan-tsai-shin (fermented broccoli stems). Int J Syst Evol Microbiol 2014;64:146-51.
22. Han X, Yi H, Zhang L, et al. Improvement of fermented Chinese cabbage characteristics by selected starter cultures. J Food Sci 2014;79:M1387-92.
23. Yoon KY, Woodams EE, Hang YD. Production of probiotic cabbage juice by lactic acid bacteria. Bioresour Technol 2006;97:1427-30.
24. Slattery C, Cotter PD, O'Toole PW. Analysis of Health Benefits Conferred by Lactobacillus Species from Kefir. Nutrients 2019;11.
25. Shiby VK, Mishra HN. Fermented milks and milk products as functional foods--a review. Crit Rev Food Sci Nutr 2013;53:482-96.
26. Sanders ME, Merenstein DJ, Reid G, Gibson GR, Rastall RA. Probiotics and prebiotics in intestinal health and disease: from biology to the clinic. Nat Rev Gastroenterol Hepatol 2019;16:605-16.
27. Sanlier N, Gokcen BB, Sezgin AC. Health benefits of fermented foods. Crit Rev Food Sci Nutr 2019;59:506-27.
28. Lavefve L, Marasini D, Carbonero F. Microbial Ecology of Fermented Vegetables and Non-Alcoholic Drinks and Current Knowledge on Their Impact on Human Health. Adv Food Nutr Res 2019;87:147-85.
29. Melini F, Melini V, Luziatelli F, Ficca AG, Ruzzi M. Health-Promoting Components in Fermented Foods: An Up-to-Date Systematic Review. Nutrients 2019;11.
30. Azam M, Mohsin M, Ijaz H, et al. Review - Lactic acid bacteria in traditional fermented Asian foods. Pak J Pharm Sci 2017;30:1803-14.

31. Dimidi E, Cox SR, Rossi M, Whelan K. Fermented Foods: Definitions and Characteristics, Impact on the Gut Microbiota and Effects on Gastrointestinal Health and Disease. Nutrients 2019;11.
32. Riggioni C, Comberiati P, Giovannini M, et al. A compendium answering 150 questions on COVID-19 and SARS-CoV-2. Allergy 2020.
33. Ruokolainen L, Lehtimäki J, Karkman A, Haahtela T. Holistic view on health : two protective layers of biodiversity. Ann Zool Fennici 2017;54:39-49.
34. Septembre-Malaterre A, Remize F, Poucheret P. Fruits and vegetables, as a source of nutritional compounds and phytochemicals: Changes in bioactive compounds during lactic fermentation. Food Res Int 2018;104:86-99.
35. Kok CR, Hutkins R. Yogurt and other fermented foods as sources of health-promoting bacteria. Nutr Rev 2018;76:4-15.
36. De Filippis F, Pasolli E, Ercolini D. The food-gut axis: lactic acid bacteria and their link to food, the gut microbiome and human health. FEMS Microbiol Rev 2020.
37. Mobeen F, Sharma V, Tulika P. Enterotype Variations of the Healthy Human Gut Microbiome in Different Geographical Regions. Bioinformation 2018;14:560-73.
38. Bibbo S, Ianiro G, Giorgio V, et al. The role of diet on gut microbiota composition. Eur Rev Med Pharmacol Sci 2016;20:4742-9.
39. Tian S, Liu X, Lei P, Zhang X, Shan Y. Microbiota: a mediator to transform glucosinolate precursors in cruciferous vegetables to the active isothiocyanates. J Sci Food Agric 2018;98:1255-60.
40. Segata N. Gut Microbiome: Westernization and the Disappearance of Intestinal Diversity. Curr Biol 2015;25:R611-3.
41. Vangay P, Johnson AJ, Ward TL, et al. US Immigration Westernizes the Human Gut Microbiome. Cell 2018;175:962-72 e10.
42. Zuo T, Kamm MA, Colombel JF, Ng SC. Urbanization and the gut microbiota in health and inflammatory bowel disease. Nat Rev Gastroenterol Hepatol 2018;15:440-52.
43. Wilson AS, Koller KR, Ramaboli MC, et al. Diet and the Human Gut Microbiome: An International Review. Dig Dis Sci 2020;65:723-40.
44. Yamashita M, Okubo H, Kobuke K, et al. Alteration of gut microbiota by a Westernized lifestyle and its correlation with insulin resistance in non-diabetic Japanese men. J Diabetes Investig 2019;10:1463-70.
45. Angelakis E, Yasir M, Bachar D, et al. Gut microbiome and dietary patterns in different Saudi populations and monkeys. Sci Rep 2016;6:32191.
46. Mitsou EK, Kakali A, Antonopoulou S, et al. Adherence to the Mediterranean diet is associated with the gut microbiota pattern and gastrointestinal characteristics in an adult population. Br J Nutr 2017;117:1645-55.

47. Saad MJ, Santos A, Prada PO. Linking Gut Microbiota and Inflammation to Obesity and Insulin Resistance. Physiology (Bethesda) 2016;31:283-93.
48. Chen X, Devaraj S. Gut Microbiome in Obesity, Metabolic Syndrome, and Diabetes. Curr Diab Rep 2018;18:129.
49. Lee CJ, Sears CL, Maruthur N. Gut microbiome and its role in obesity and insulin resistance. Ann N Y Acad Sci 2020;1461:37-52.
50. Zuo T, Zhang F, Lui GCY, et al. Alterations in Gut Microbiota of Patients With COVID-19 During Time of Hospitalization. Gastroenterology 2020.
51. Xu K, Cai H, Shen Y, et al. [Management of Corona Virus disease-19 (COVID-19): The Zhejiang Experience]. Zhejiang Da Xue Xue Bao Yi Xue Ban2020;49.
52. Finucane FM, Davenport C. Coronavirus and Obesity: Could Insulin Resistance Mediate the Severity of Covid-19 Infection? Front Public Health 2020;8:184.
53. Guzik TJ, Cosentino F. Epigenetics and Immunometabolism in Diabetes and Aging. Antioxid Redox Signal 2018;29:257-74.
54. Miedema MD, Maziarz M, Biggs ML, et al. Plasma-free fatty acids, fatty acid-binding protein 4, and mortality in older adults (from the Cardiovascular Health Study). Am J Cardiol 2014;114:843-8.
55. Hurrle S, Hsu WH. The etiology of oxidative stress in insulin resistance. Biomed J 2017;40:257-62.
56. Wen H, Gwathmey JK, Xie LH. Oxidative stress-mediated effects of angiotensin II in the cardiovascular system. World J Hypertens 2012;2:34-44.
57. Bhatt SR, Lokhandwala MF, Banday AA. Vascular oxidative stress upregulates angiotensin II type I receptors via mechanisms involving nuclear factor kappa B. Clin Exp Hypertens 2014;36:367-73.
58. Dalan R, Bornstein SR, El-Armouche A, et al. The ACE-2 in COVID-19: Foe or Friend? Horm Metab Res 2020;52:257-63.
59. Sarzani R, Giulietti F, Di Pentima C, Giordano P, Spannella F. Disequilibrium between the Classic Renin-Angiotensin System and Its Opposing Arm in Sars-Cov-2 Related Lung Injury. Am J Physiol Lung Cell Mol Physiol 2020.
60. Bousquet J, Anto J, Czarlewski W, et al. Sulforaphane: from death rate heterogeneity in countries to candidate for prevention of severe COVID-19 Allergy 2020;submitted.
61. Ren H, Yang Y, Wang F, et al. Association of the insulin resistance marker TyG index with the severity and mortality of COVID-19. Cardiovasc Diabetol 2020;19:58.
62. Jain S, Buttar HS, Chintameneni M, Kaur G. Prevention of Cardiovascular Diseases with Anti-Inflammatory and Anti- Oxidant Nutraceuticals and Herbal Products: An Overview of Pre-Clinical and Clinical Studies. Recent Pat Inflamm Allergy Drug Discov 2018;12:145-57.
63. Razmpoosh E, Javadi M, Ejtahed HS, Mirmiran P. Probiotics as beneficial agents in the management of diabetes mellitus: a systematic review. Diabetes Metab Res Rev 2016;32:143-68.

64. Serino A, Salazar G. Protective Role of Polyphenols against Vascular Inflammation, Aging and Cardiovascular Disease. Nutrients 2018;11.
65. Zabetakis I, Lordan R, Norton C, Tsoupras A. COVID-19: The Inflammation Link and the Role of Nutrition in Potential Mitigation. Nutrients 2020;12.
66. Tonelli C, Chio IIC, Tuveson DA. Transcriptional Regulation by Nrf2. Antioxid Redox Signal 2018;29:1727-45.
67. Yamamoto M, Kensler TW, Motohashi H. The KEAP1-NRF2 System: a Thiol-Based Sensor-Effector Apparatus for Maintaining Redox Homeostasis. Physiol Rev 2018;98:1169-203.
68. !!! INVALID CITATION !!! 45.
69. Wardyn JD, Ponsford AH, Sanderson CM. Dissecting molecular cross-talk between Nrf2 and NF-kappaB response pathways. Biochem Soc Trans 2015;43:621-6.
70. Jimenez-Osorio AS, Gonzalez-Reyes S, Pedraza-Chaverri J. Natural Nrf2 activators in diabetes. Clin Chim Acta 2015;448:182-92.
71. Pall ML, Levine S. Nrf2, a master regulator of detoxification and also antioxidant, anti-inflammatory and other cytoprotective mechanisms, is raised by health promoting factors. Sheng Li Xue Bao 2015;67:1-18.
72. Senger DR, Li D, Jaminet SC, Cao S. Activation of the Nrf2 Cell Defense Pathway by Ancient Foods: Disease Prevention by Important Molecules and Microbes Lost from the Modern Western Diet. PLoS One 2016;11:e0148042.
73. Uruno A, Yagishita Y, Yamamoto M. The Keap1-Nrf2 system and diabetes mellitus. Arch Biochem Biophys 2015;566:76-84.
74. Vasileva LV, Savova MS, Amirova KM, Dinkova-Kostova AT, Georgiev MI. Obesity and NRF2-mediated cytoprotection: Where is the missing link? Pharmacol Res 2020;156:104760.
75. Guo Z, Mo Z. Keap1-Nrf2 signaling pathway in angiogenesis and vascular diseases. J Tissue Eng Regen Med 2020;14:869-83.
76. Zhang H, Davies KJA, Forman HJ. Oxidative stress response and Nrf2 signaling in aging. Free Radic Biol Med 2015;88:314-36.
77. Rojo de la Vega M, Dodson M, Gross C, et al. Role of Nrf2 and Autophagy in Acute Lung Injury. Curr Pharmacol Rep 2016;2:91-101.
78. Chen B, Lu Y, Chen Y, Cheng J. The role of Nrf2 in oxidative stress-induced endothelial injuries. J Endocrinol 2015;225:R83-99.
79. McCord JM, Hybertson BM, Cota-Gomez A, Gao B. Nrf2 Activator PB125(R) as a Potential Therapeutic Agent Against COVID-19. bioRxiv 2020.

80. Fang Y, Gao F, Liu Z. Angiotensin-converting enzyme 2 attenuates inflammatory response and oxidative stress in hyperoxic lung injury by regulating NF-kappaB and Nrf2 pathways. QJM 2019;112:914-24.
81. Palliyaguru DL, Yuan JM, Kensler TW, Fahey JW. Isothiocyanates: Translating the Power of Plants to People. Mol Nutr Food Res 2018;62:e1700965.
82. Oliviero T, Verkerk R, Dekker M. Isothiocyanates from Brassica Vegetables-Effects of Processing, Cooking, Mastication, and Digestion. Mol Nutr Food Res 2018;62:e1701069.
83. Vanduchova A, Anzenbacher P, Anzenbacherova E. Isothiocyanate from Broccoli, Sulforaphane, and Its Properties. J Med Food 2019;22:121-6.
84. Quirante-Moya S, Garcia-Ibanez P, Quirante-Moya F, Villano D, Moreno DA. The Role of Brassica Bioactives on Human Health: Are We Studying It the Right Way? Molecules 2020;25.
85. Luang-In V, Deeseenthum S, Udomwong P, Saengha W, Gregori M. Formation of Sulforaphane and Iberin Products from Thai Cabbage Fermented by Myrosinase-Positive Bacteria. Molecules 2018;23.
86. Yagishita Y, Fahey JW, Dinkova-Kostova AT, Kensler TW. Broccoli or Sulforaphane: Is It the Source or Dose That Matters? Molecules 2019;24.
87. Hindson J. Brassica vegetable metabolism by gut microbiota. Nat Rev Gastroenterol Hepatol 2020;17:195.
88. Houghton CA. Sulforaphane: Its "Coming of Age" as a Clinically Relevant Nutraceutical in the Prevention and Treatment of Chronic Disease. Oxid Med Cell Longev 2019;2019:2716870.
89. Horowitz RI, Freeman PR. Three novel prevention, diagnostic, and treatment options for COVID-19 urgently necessitating controlled randomized trials. Med Hypotheses 2020;143:109851.
90. Yang L, Palliyaguru DL, Kensler TW. Frugal chemoprevention: targeting Nrf2 with foods rich in sulforaphane. Semin Oncol 2016;43:146-53.
91. Bai Y, Wang X, Zhao S, Ma C, Cui J, Zheng Y. Sulforaphane Protects against Cardiovascular Disease via Nrf2 Activation. Oxid Med Cell Longev 2015;2015:407580.
92. Zhou S, Wang J, Yin X, et al. Nrf2 expression and function, but not MT expression, is indispensable for sulforaphane-mediated protection against intermittent hypoxia-induced cardiomyopathy in mice. Redox Biol 2018;19:11-21.
93. Xu L, Nagata N, Ota T. Glucoraphanin: a broccoli sprout extract that ameliorates obesity-induced inflammation and insulin resistance. Adipocyte 2018;7:218-25.
94. Teng W, Li Y, Du M, Lei X, Xie S, Ren F. Sulforaphane Prevents Hepatic Insulin Resistance by Blocking Serine Palmitoyltransferase 3-Mediated Ceramide Biosynthesis. Nutrients 2019;11.
95. Sun Y, Zhou S, Guo H, et al. Protective effects of sulforaphane on type 2 diabetes-induced cardiomyopathy via AMPK-mediated activation of lipid metabolic pathways and NRF2 function. Metabolism 2020;102:154002.

96. Perez S, Talens-Visconti R, Rius-Perez S, Finamor I, Sastre J. Redox signaling in the gastrointestinal tract. Free Radic Biol Med 2017;104:75-103.
97. An H, Zhai Z, Yin S, Luo Y, Han B, Hao Y. Coexpression of the superoxide dismutase and the catalase provides remarkable oxidative stress resistance in Lactobacillus rhamnosus. J Agric Food Chem 2011;59:3851-6.
98. Serata M, Iino T, Yasuda E, Sako T. Roles of thioredoxin and thioredoxin reductase in the resistance to oxidative stress in Lactobacillus casei. Microbiology 2012;158:953-62.
99. Kong Y, Olejar KJ, On SLW, Chelikani V. The Potential of Lactobacillus spp. for Modulating Oxidative Stress in the Gastrointestinal Tract. Antioxidants (Basel) 2020;9.
100. Lee E, Jung SR, Lee SY, Lee NK, Paik HD, Lim SI. Lactobacillus plantarum Strain Ln4 Attenuates Diet-Induced Obesity, Insulin Resistance, and Changes in Hepatic mRNA Levels Associated with Glucose and Lipid Metabolism. Nutrients 2018;10.
101. Koutnikova H, Genser B, Monteiro-Sepulveda M, et al. Impact of bacterial probiotics on obesity, diabetes and non-alcoholic fatty liver disease related variables: a systematic review and meta-analysis of randomised controlled trials. BMJ Open 2019;9:e017995.
102. Suzumura EA, Bersch-Ferreira AC, Torreglosa CR, et al. Effects of oral supplementation with probiotics or synbiotics in overweight and obese adults: a systematic review and meta-analyses of randomized trials. Nutr Rev 2019;77:430-50.
103. Barengolts E, Smith ED, Reutrakul S, Tonucci L, Anothaisintawee T. The Effect of Probiotic Yogurt on Glycemic Control in Type 2 Diabetes or Obesity: A Meta-Analysis of Nine Randomized Controlled Trials. Nutrients 2019;11.
104. Li B, Evivie SE, Lu J, et al. Lactobacillus helveticus KLDS1.8701 alleviates d-galactose-induced aging by regulating Nrf-2 and gut microbiota in mice. Food Funct 2018;9:6586-98.
105. Xu H, Wang J, Cai J, et al. Protective Effect of Lactobacillus rhamnosus GG and its Supernatant against Myocardial Dysfunction in Obese Mice Exposed to Intermittent Hypoxia is Associated with the Activation of Nrf2 Pathway. Int J Biol Sci 2019;15:2471-83.
106. Zhao Z, Wang C, Zhang L, et al. Lactobacillus plantarum NA136 improves the non-alcoholic fatty liver disease by modulating the AMPK/Nrf2 pathway. Appl Microbiol Biotechnol 2019;103:5843-50.
107. Qian Y, Zhang J, Zhou X, et al. Lactobacillus plantarum CQPC11 Isolated from Sichuan Pickled Cabbages Antagonizes d-galactose-Induced Oxidation and Aging in Mice. Molecules 2018;23.
108. El-Baz AM, Khodir AE, Adel El-Sokkary MM, Shata A. The protective effect of Lactobacillus versus 5-aminosalicylic acid in ulcerative colitis model by modulation of gut microbiota and Nrf2/Ho-1 pathway. Life Sci 2020;256:117927.

109. Chen YT, Lin YC, Lin JS, Yang NS, Chen MJ. Sugary Kefir Strain Lactobacillus mali APS1 Ameliorated Hepatic Steatosis by Regulation of SIRT-1/Nrf-2 and Gut Microbiota in Rats. Mol Nutr Food Res 2018;62:e1700903.
110. Xu C, Qiao L, Ma L, et al. Biogenic selenium nanoparticles synthesized by Lactobacillus casei ATCC 393 alleviate intestinal epithelial barrier dysfunction caused by oxidative stress via Nrf2 signaling-mediated mitochondrial pathway. Int J Nanomedicine 2019;14:4491-502.
111. Mu G, Li H, Tuo Y, Gao Y, Zhang Y. Antioxidative effect of Lactobacillus plantarum Y44 on 2,2'-azobis(2-methylpropionamidine) dihydrochloride (ABAP)-damaged Caco-2 cells. J Dairy Sci 2019;102:6863-75.
112. Kobatake E, Nakagawa H, Seki T, Miyazaki T. Protective effects and functional mechanisms of Lactobacillus gasseri SBT2055 against oxidative stress. PLoS One 2017;12:e0177106.
113. Pistol GC, Marin DE, Dragomir C, Taranu I. Synbiotic combination of prebiotic grape pomace extract and probiotic Lactobacillus sp. reduced important intestinal inflammatory markers and in-depth signalling mediators in lipopolysaccharide-treated Caco-2 cells. Br J Nutr 2018:1-15.
114. Xia L, Yang Y, Wang J, Jing Y, Yang Q. Impact of TGEV infection on the pig small intestine. Virol J 2018;15:102.
115. Kumar R, Seo BJ, Mun MR, et al. Putative probiotic Lactobacillus spp. from porcine gastrointestinal tract inhibit transmissible gastroenteritis coronavirus and enteric bacterial pathogens. Trop Anim Health Prod 2010;42:1855-60.
116. Zhang X, Li P, Zheng Q, Hou J. Lactobacillus acidophilus S-layer protein-mediated inhibition of PEDV-induced apoptosis of Vero cells. Vet Microbiol 2019;229:159-67.
117. Hassan SM, Jawad MJ, Ahjel SW, et al. The Nrf2 Activator (DMF) and Covid-19: Is there a Possible Role? Med Arch 2020;74:134-8.
118. Romero A, San Hipolito-Luengo A, Villalobos LA, et al. The angiotensin-(1-7)/Mas receptor axis protects from endothelial cell senescence via klotho and Nrf2 activation. Aging Cell 2019;18:e12913.
119. Cai SM, Yang RQ, Li Y, et al. Angiotensin-(1-7) Improves Liver Fibrosis by Regulating the NLRP3 Inflammasome via Redox Balance Modulation. Antioxid Redox Signal 2016;24:795-812.
120. Liu Q, Gao Y, Ci X. Role of Nrf2 and Its Activators in Respiratory Diseases. Oxid Med Cell Longev 2019;2019:7090534.
121. Zhao H, Eguchi S, Alam A, Ma D. The role of nuclear factor-erythroid 2 related factor 2 (Nrf-2) in the protection against lung injury. Am J Physiol Lung Cell Mol Physiol 2017;312:L155-L62.
122. Keleku-Lukwete N, Suzuki M, Yamamoto M. An Overview of the Advantages of KEAP1-NRF2 System Activation During Inflammatory Disease Treatment. Antioxid Redox Signal 2018;29:1746-55.
123. Mitchell F. Vitamin-D and COVID-19: do deficient risk a poorer outcome? Lancet Diabetes Endocrinol 2020;8:570.

124. Hati S, Bhattacharyya S. Impact of Thiol-Disulfide Balance on the Binding of Covid-19 Spike Protein with Angiotensin-Converting Enzyme 2 Receptor. ACS Omega 2020;5:16292-8.
125. Tarvainen M, Fabritius M, Yang B. Determination of vitamin K composition of fermented food. Food Chem 2019;275:515-22.
126. An SY, Lee MS, Jeon JY, et al. Beneficial effects of fresh and fermented kimchi in prediabetic individuals. Ann Nutr Metab 2013;63:111-9.
127. Kim EK, An SY, Lee MS, et al. Fermented kimchi reduces body weight and improves metabolic parameters in overweight and obese patients. Nutr Res 2011;31:436-43.
128. Kim SA, Joung H, Shin S. Dietary pattern, dietary total antioxidant capacity, and dyslipidemia in Korean adults. Nutr J 2019;18:37.
129. Das G, Paramithiotis S, Sundaram Sivamaruthi B, et al. Traditional fermented foods with anti-aging effect: A concentric review. Food Res Int 2020;134:109269.
130. Bousquet J, Anto J, Czarlewski W, et al. Sulforaphane: from death rate heterogeneity in countries to candidate for prevention of severe COVID-19 Allergy 2020;in press.
131. Hong E, Kim GH. GC-MS Analysis of the Extracts from Korean Cabbage (Brassica campestris L. ssp. pekinensis) and Its Seed. Prev Nutr Food Sci 2013;18:218-21.
132. Park CH, Yeo HJ, Park SY, Kim JK, Park SU. Comparative Phytochemical Analyses and Metabolic Profiling of Different Phenotypes of Chinese Cabbage (Brassica Rapa ssp. Pekinensis). Foods 2019;8.
133. Raghuvanshi R, Grayson AG, Schena I, Amanze O, Suwintono K, Quinn RA. Microbial Transformations of Organically Fermented Foods. Metabolites 2019;9.
134. O'Dea K. Westernization and non-insulin-dependent diabetes in Australian Aborigines. Ethn Dis 1991;1:171-87.
135. Kopp W. How Western Diet And Lifestyle Drive The Pandemic Of Obesity And Civilization Diseases. Diabetes Metab Syndr Obes 2019;12:2221-36.
136. Mirabelli M, Chiefari E, Arcidiacono B, et al. Mediterranean Diet Nutrients to Turn the Tide against Insulin Resistance and Related Diseases. Nutrients 2020;12.
137. Martucci M, Ostan R, Biondi F, et al. Mediterranean diet and inflammaging within the hormesis paradigm. Nutr Rev 2017;75:442-55.
138. Darwiche G, Hoglund P, Roth B, et al. An Okinawan-based Nordic diet improves anthropometry, metabolic control, and health-related quality of life in Scandinavian patients with type 2 diabetes: a pilot trial. Food Nutr Res 2016;60:32594.
139. Van Belle S, Affun-Adegbulu C, Soors W, et al. COVID-19 and informal settlements: an urgent call to rethink urban governance. Int J Equity Health 2020;19:81.

140. Correa-Agudelo E, Mersha T, Hernandez A, Branscum AJ, MacKinnon NJ, Cuadros DF. Identification of Vulnerable Populations and Areas at Higher Risk of COVID-19 Related Mortality in the U.S. medRxiv 2020.
141. Abedi V, Olulana O, Avula V, et al. Racial, Economic and Health Inequality and COVID-19 Infection in the United States. medRxiv 2020.
142. Mode NA, Evans MK, Zonderman AB. Race, Neighborhood Economic Status, Income Inequality and Mortality. PLoS One 2016;11:e0154535.
143. Abuelgasim E, Saw LJ, Shirke M, Zeinah M, Harky A. COVID-19: Unique public health issues facing Black, Asian and minority ethnic communities. Curr Probl Cardiol 2020;45:100621.
144. Lassale C, Gaye B, Hamer M, Gale CR, Batty GD. Ethnic disparities in hospitalisation for COVID-19 in England: The role of socioeconomic factors, mental health, and inflammatory and pro-inflammatory factors in a community-based cohort study. Brain Behav Immun 2020.
145. Raisi-Estabragh Z, McCracken C, Bethell MS, et al. Greater risk of severe COVID-19 in Black, Asian and Minority Ethnic populations is not explained by cardiometabolic, socioeconomic or behavioural factors, or by 25(OH)-vitamin D status: study of 1326 cases from the UK Biobank. J Public Health (Oxf) 2020.
146. Rubin D, Huang J, Fisher BT, et al. Association of Social Distancing, Population Density, and Temperature With the Instantaneous Reproduction Number of SARS-CoV-2 in Counties Across the United States. JAMA Netw Open 2020;3:e2016099.
147. SARS-CoV2 seroprevalence study in Mumbai: NTI Asayog-BMC-TIFR study-First round report. Municipal Corporation of greater Mumbai, Public Realtion Department, 28-07-2020 2020;https://www.livemint.com/news/india/mumbai-sero-prevalence-of-57-found-in-slums-and-16-in-residential-societies-11595952896909.html.
148. Pereira RJ, Nascimento G, Gratao LHA, Pimenta RS. The risk of COVID-19 transmission in favelas and slums in Brazil. Public Health 2020;183:42-3.
149. Smith RE. The Effects of Dietary Supplements that Overactivate the Nrf2/ARE System. Curr Med Chem 2020;27:2077-94.
150. Textor J, van der Zander B, Gilthorpe MS, Liskiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. Int J Epidemiol 2016;45:1887-94.
151. Haahtela T, von Hertzen L, Anto JM, et al. Helsinki by nature: The Nature Step to Respiratory Health. Clin Transl Allergy 2019;9:57.
152. O'Callaghan C, Anto J. COVID-19: The Disease of the Anthropocene. Env Res 2020;187:109683.doi: 10.1016/j.envres.2020.. Epub 2020 May 15.
153. Vandana UK, Barlaskar NH, Gulzar ABM, et al. Linking gut microbiota with the human diseases. Bioinformation 2020;16:196-208.

154. McCall LI, Callewaert C, Zhu Q, et al. Home chemical and microbial transitions across urbanization. Nat Microbiol 2020;5:108-15.
155. Haahtela T, Anto J, Bousquet J. Slow Health Catastrophe of Homo urbanicus – Loss of Resilience. Porto Med J 2020.
156. Haahtela T, Valovirta E, Bousquet J, Makela M, Allergy Programme Steering G. The Finnish Allergy Programme 2008-2018 works. Eur Respir J 2017;49.

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
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

+ to ++++: Proposed relative importance

Figure 1:COVID-19 deaths per million inhabitants(from Johns Hopkins Coronavirus Center)

Figure 2: Regional differences of death rates in Italy (from Worldometer)

Figure 3: Regional differences of death rates (May 20) (from *Office fédéral de la santé publique,* Switzerland, Gouvernement français, Lander Bade Wurtenberg))

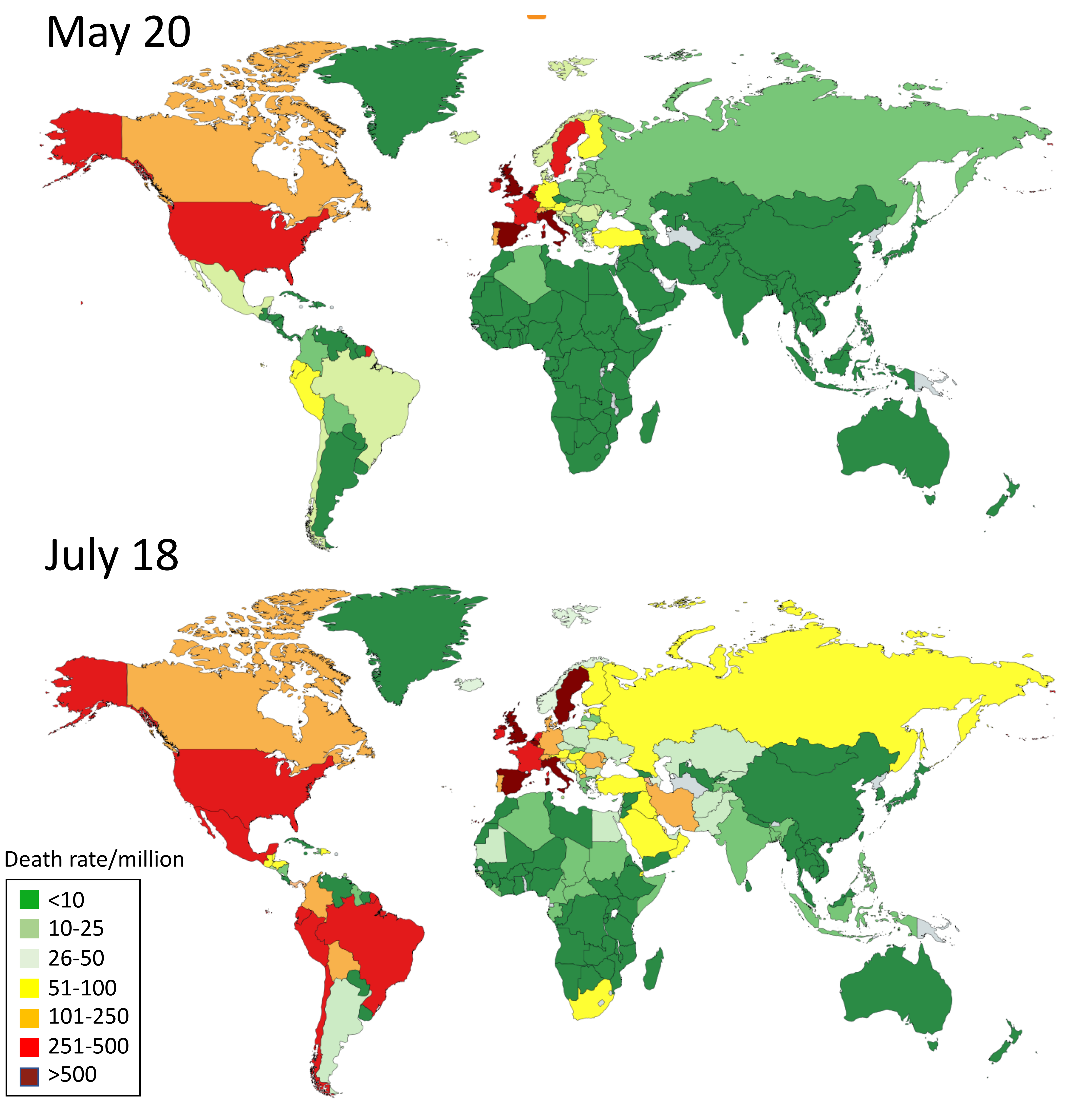
Figure 4: Consumption of head cabbage and COVID-19 death rate at a country level(from Fonseca et al, 12)

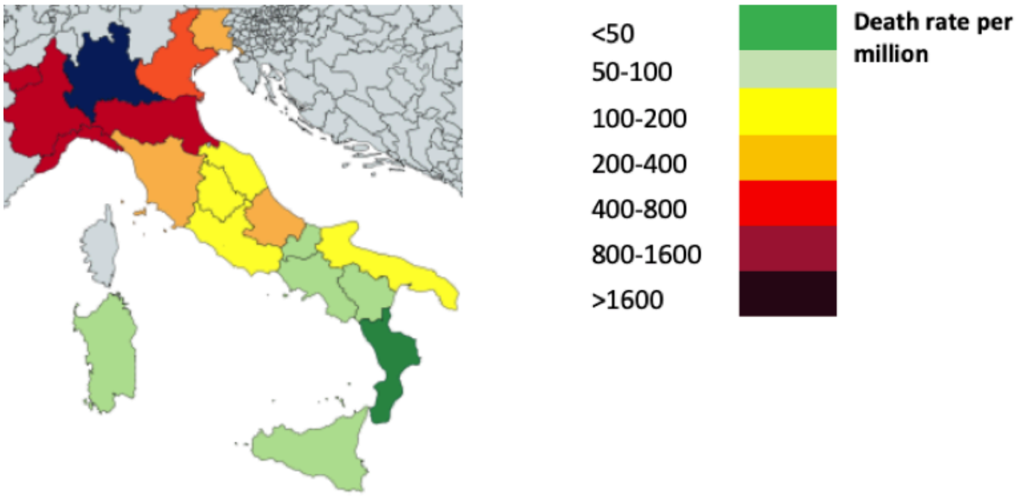
Figure 5: Putative mechanisms of fermented or*Brassica*vegetables against COVID-19

A: Oidative stress induced by SARS-CoV-2 after its binding to ACE2

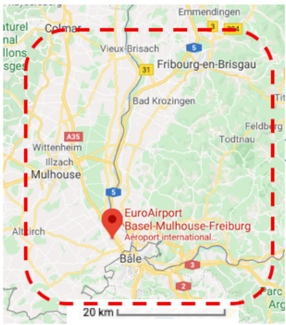
B: Preventive effects of cabbage and fermented vegetables through Nrf2

Figure 6 : Putative role of diet in COVID-19

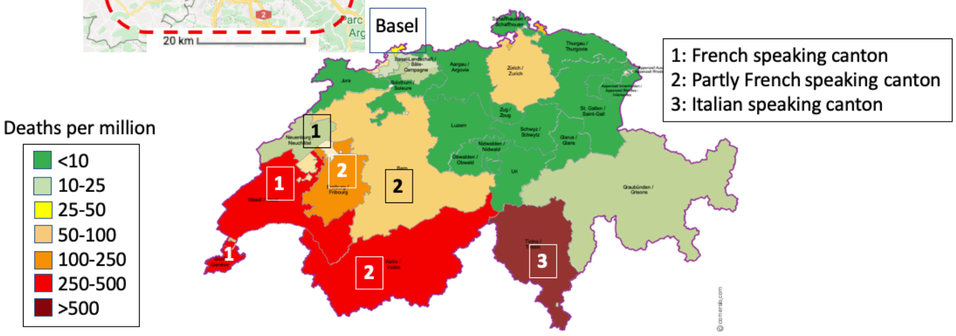

May 20
July 18
Death rate/million
<10
10-25
26-50
51-100
101-250
251-500
>500

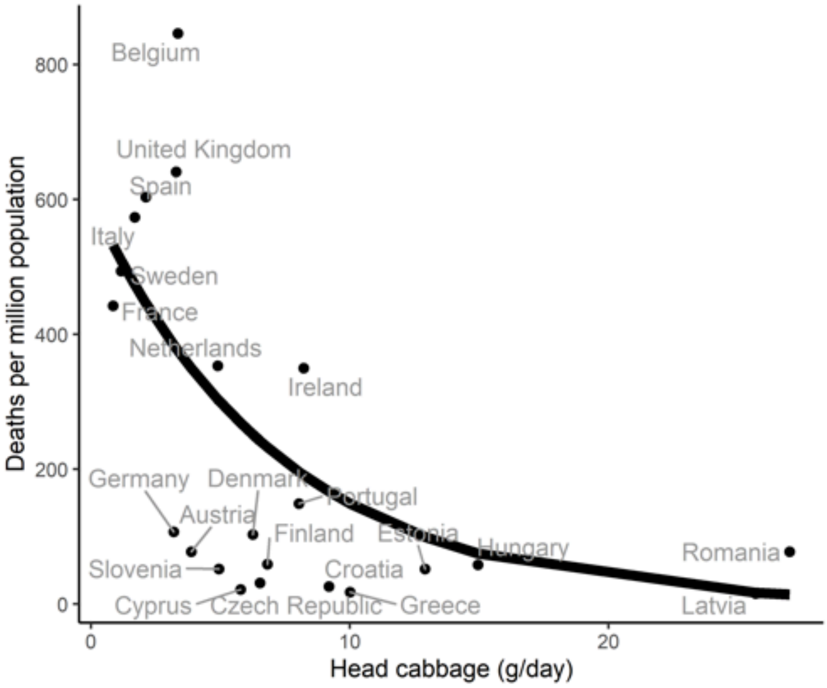

Death rate per million
<50
50-100
100-200
200-400
400-800
800-1600
>1600

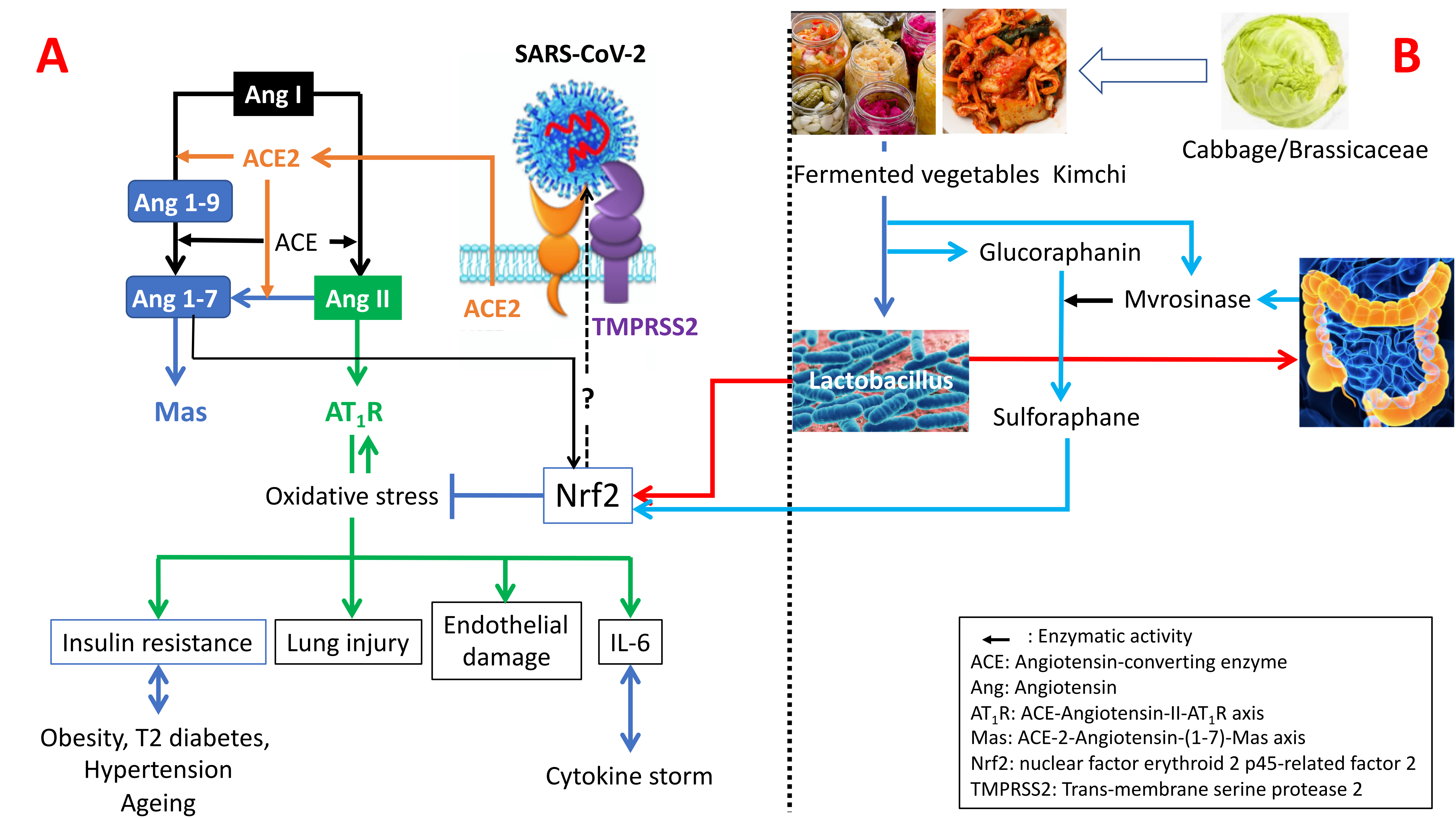
Switzerland



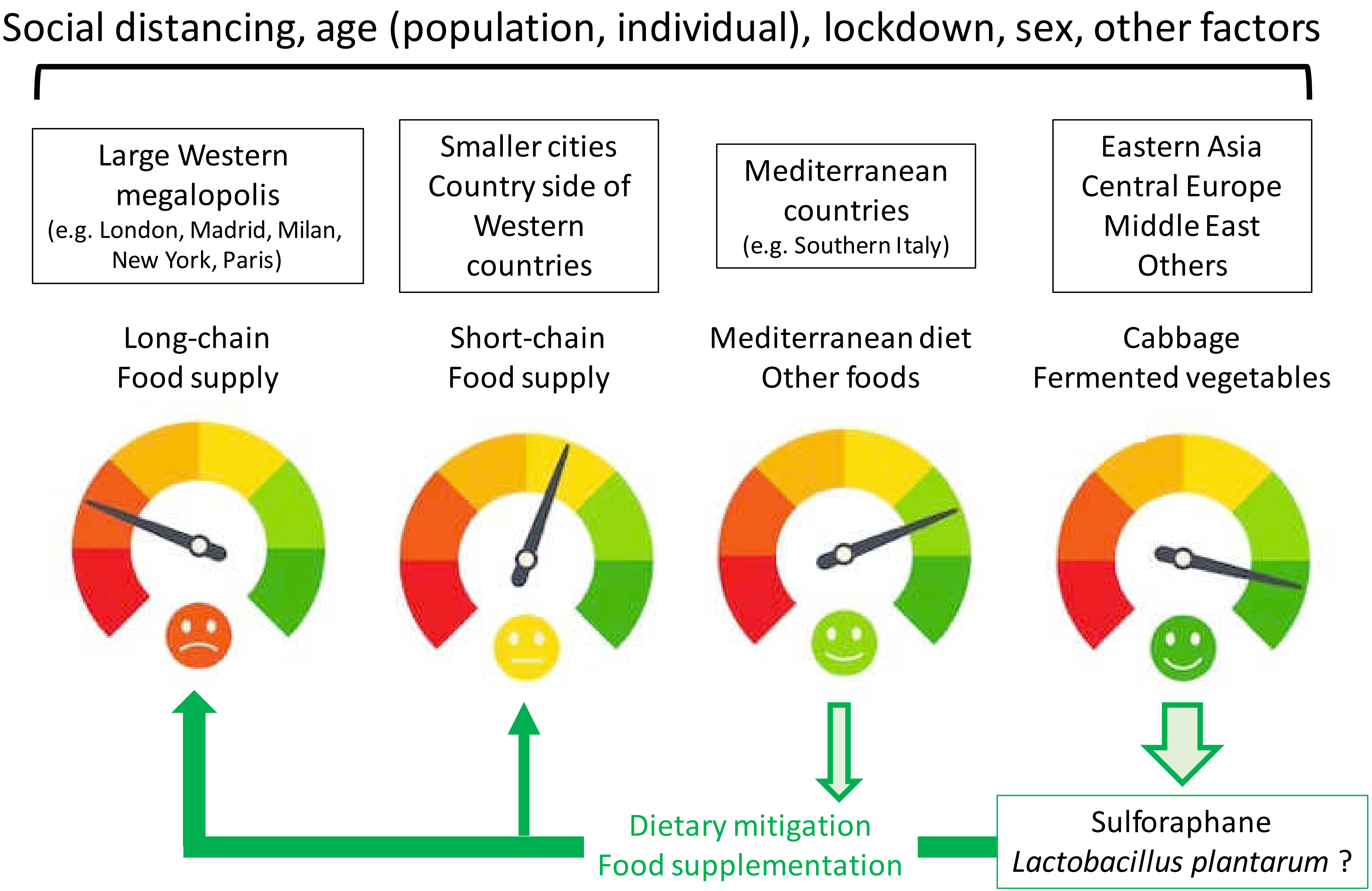
May 20, 2020	Deaths	Population	Deaths/ million
Basel city (Sw)	49	198,000	25
Basel-Lands (Sw)	30	298,000	10
Freiburg (DE)	15	213,000	7
Haut-Rhin (F)	715	765,000	935




Deaths per million population
Head cabbage (g/day)
0
200
400
600
800
0
10
20
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
B
SARS-CoV-2
Ang I
ACE2
Ang 1-9
ACE
Ang 1-7
Ang II
ACE2
TMPRSS2
Mas
AT1R
?
Oxidative stress
Nrf2
Insulin resistance
Lung injury
Endothelial damage
IL-6
Obesity, T2 diabetes,
Hypertension
Ageing
Cytokine storm
Cabbage/Brassicaceae
Fermented vegetables
Kimchi
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


Social distancing, age (population, individual), lockdown, sex, other factors
Large Western megalopolis (e.g. London, Madrid, Milan, New York, Paris)
Smaller cities Country side of Western countries
Mediterranean countries (e.g. Southern Italy)
Eastern Asia Central Europe Middle East Others
Long-chain Food supply
Short-chain Food supply
Mediterranean diet Other foods
Cabbage Fermented vegetables
Dietary mitigation
Food supplementation
Sulforaphane
Lactobacillus plantarum ?