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

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38 **Short title: Mitigation of COVID-19 by diet**

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## 46 **Abstract**

47

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

61 **Key words:** COVID-19, diet, sulforaphane, Lactobacillus, Angiotensin converting enzyme 2, kimchi,

62 cabbage, fermented vegetable

## 63 **Abbreviations**

64 ACE: Angiotensin converting enzyme

65 Ang II: Angiotensin II

66 AT<sub>1</sub>R: Angiotensin II receptor type 1

67 COVID-19: Coronavirus 19 disease

68 GI: Gastro-intestinal

69 LAB: Lactic acid bacilli

70 NF-κB: Nuclear factor kappa B

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

72 PEDV: Porcine epidemic diarrhea virus

73 ROS: Reactive oxygen species

74 SARS: Severe acute respiratory syndrome

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

76 TGEV: Transmissible Gastroenteritis Coronavirus Infection

## 80 Introduction

81 A COVID-19 epidemic started in China and then disseminated to other Asian countries before becoming a  
82 pandemic. There is a large variability across countries in both incidence and mortality, and most of the  
83 current debates on COVID-19 focus on the differences between countries. Several intertwined factors can  
84 be proposed: social distancing, health system capacity, age of the population, social lifestyle (gathering of  
85 family/friends, social behavior), testing capacity and/or timing and intensity of the first outbreak. German  
86 fatalities are strikingly low as compared to many European countries. Among the several explanations  
87 proposed, an early and large testing of the population was put forward <sup>1</sup> as well as social distancing.  
88 However, little attention has been given to regional within-country differences that may propose new  
89 hypotheses.

90 It would appear that the pandemic has so far resulted in proportionately fewer deaths in some Central  
91 European countries, the Balkans, China, in most Eastern Asian countries as well as in many Sub-Saharan  
92 African countries. Several reasons can explain this picture. One of them may be the type of diet in these  
93 low mortality countries. <sup>2,3</sup>

94 Diet has been proposed to mitigate COVID-19.<sup>4,5</sup> Some foods or supplements may have a benefit on the  
95 immune response to respiratory viruses. However, to date, there are no specific data available to confirm  
96 the putative benefits of diet supplementation, probiotics, and nutraceuticals in the current COVID-19  
97 pandemic. <sup>6</sup> News and social media platforms have implicated dietary supplements in the treatment and  
98 prevention of COVID-19 without evidence.<sup>7</sup>

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

## 103 1- Biases to be considered

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

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

114 We used mortality per number of inhabitants to assess death rates, as proposed by the European Center for  
115 Disease Prevention and Control (ecdc, <https://www.ecdc.europa.eu/en>), and to report trends with cutoffs at  
116 25, 50, 100 and 250 per million.

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

## 119 **2- Multifactorial origin of the COVID-19 epidemic**

120 Like most diseases, COVID-19 exhibits large geographical variations which frequently remain unexplained  
121 <sup>8</sup>. The COVID-19 epidemic is multifactorial, and factors like climate, population density, age, phenotype  
122 and prevalence of non-communicable diseases are also associated to increased incidence and mortality <sup>9</sup>.  
123 Diet represents only one of the possible causes of the COVID-19 epidemic and its importance needs to be  
124 better assessed. Some risk factors for the COVID-19 epidemics are proposed at the individual and country  
125 levels in Table 1.

## 126 **3- Ecological data on COVID-19 death rates**

127 When comparing death rates, large differences exist between and within countries and the evolution of the  
128 pandemic differs largely between countries (Figure 1). Although there are many pitfalls in analyzing death  
129 rates for COVID-19,<sup>3</sup> the evolution of death rates between May 20 and July 18 shows a dramatic increase  
130 in Latin America and only some increase in European countries, certain African countries, the Middle East,  
131 India, Pakistan and some of the South East Asian countries. However, there is no change in the very low  
132 death rates of Cambodia, China, Japan, Korea, Lao, Malaysia, Taiwan, Vietnam and of many Sub-Saharan  
133 African countries, Australia and New Zealand. This geographical pattern is very unlikely to be totally due  
134 to reporting differences between countries.

135 In some high death-rate countries such as Italy (Figure 2), variations are extremely large from 50 per  
136 million in Calabria to over 1,600 in Lombardia. In Switzerland, the French- and Italian-speaking cantons  
137 have a far higher death rate than the German-speaking ones (*Office fédéral de la santé publique*,  
138 Switzerland) (Figure 3). It may be proposed that the high-death rate cantons were contaminated by French

139 and Italian people. However, the Mulhouse airport serves the region of Basel (Switzerland), the Haut-Rhin  
140 department (France) and the region of Freiburg (Germany). There was a COVID-19 outbreak in the Haut-  
141 Rhin department, in particular in Mulhouse and Colmar. The death rate for COVID-19 (May 20, 2020) was  
142 935 per million inhabitants in France but only 10 to 25 in Switzerland and 7 in Germany. It is important to  
143 consider these regional differences since reporting of deaths is similar within the country and many factors  
144 may be considered.

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

147 The number of deaths is relatively low in Sub-Saharan Africa compared to other regions, and the low  
148 population density (which applies in rural areas but not in megacities such as Cairo or Lagos) or the  
149 differences in health infrastructure are unlikely to be the only explanation.<sup>10</sup> It has been proposed that hot  
150 temperature may reduce COVID-19, but, in Latin American countries, death rates are high (e.g. Brazil,  
151 Ecuador, Peru and Mexico).

#### 152 **4- Is diet partly responsible for differences between and within countries?**

153 Nutrition may play a role in the immune defense against COVID-19 and may explain some of the  
154 differences seen in COVID-19 between and within countries<sup>3</sup>. In this concept paper, raw and fermented  
155 cabbage were proposed to be candidates.

156 To test the potential role of fermented foods in the COVID-19 mortality in Europe, an ecological study, the  
157 European Food Safety Authority (EFSA) Comprehensive European Food Consumption Database, was used  
158 to study the country consumption of fermented vegetables, pickled/marinated vegetables, fermented milk,  
159 yoghurt and fermented sour milk.<sup>11</sup> Of all the variables considered, including confounders, only fermented  
160 vegetables reached statistical significance with the COVID-19 death rate per country. For each g/day  
161 increase in consumption of fermented vegetables of the country, the mortality risk for COVID-19 was  
162 found to decrease by 35.4% (Figure 4).

163 A second ecological study has analyzed cruciferous vegetables (broccoli, cauliflower, head cabbage (white,  
164 red and savoy cabbage), leafy brassica) and compared them with spinach, cucumber, courgette, lettuce and  
165 tomato<sup>12</sup>. Only head cabbage and cucumber reached statistical significance with the COVID-19 death rate  
166 per country. For each g/day increase in the average national consumption of some of the vegetables (head  
167 cabbage and cucumber), the mortality risk for COVID-19 decreased by a factor of 11, to 13.6 %. The  
168 negative ecological association between COVID-19 mortality and consumption of cabbage and cucumber

169 supports the *a priori* hypothesis previously reported. However, these are ecological studies that need to be  
170 further tested.

171 Another diet component potentially relevant in COVID-19 mortality may be the food supply chain and  
172 traditional groceries.<sup>13</sup> The impact of the long supply chain of food on health is measurable by an increase  
173 in metabolic syndrome and insulin resistance.<sup>14</sup> Therefore, areas that are more prone to short supply food  
174 and traditional groceries may have been able to better tolerate COVID-19 with a lower death toll. These  
175 considerations may be partly involved in the lower death rates of Southern Italy compared to the Northern  
176 part (Figure 2).

## 177 **5- Fermented foods, microbiome and lactobacilli**

178 The fermentation process, born as a preservation method in the Neolithic age, enabled humans to eat not-  
179 so-fresh food and to survive.<sup>15</sup> Indigenous fermented foods such as bread, cheese, vegetables and alcoholic  
180 beverages have been prepared and consumed for thousands of years, are strongly linked to culture and  
181 tradition, especially in rural households and village communities, and are consumed by hundreds of  
182 millions of people.<sup>16</sup> Fermented foods are “foods or beverages made via controlled microbial growth  
183 (including lactic acid bacteria (LAB)) and enzymatic conversions of food components.”<sup>17</sup> Not all fermented  
184 foods contain live cultures, as some undergo further processing after fermentation: pasteurization, smoking,  
185 baking, or filtration. These processes kill or remove the live microorganisms in foods such as soy sauces,  
186 bread, most beers and wines as well as chocolate. Live cultures can be found in fermented vegetables and  
187 fermented milk (fermented sour milk, yoghurt, probiotics, etc.).

188 Most traditional foods with live bacteria in the low-death rate countries are based on LAB fermentation  
189 <sup>18</sup>. A number of bacteria are involved in the fermentation of kimchi and other Korean traditional fermented  
190 foods, but LAB - including *Lactobacillus*- are the dominant species in the fermentation process<sup>19,20</sup>.  
191 *Lactobacillus* is also an essential species in the fermentation of sauerkraut, Taiwanese <sup>21</sup>, Chinese <sup>22</sup> or  
192 other fermented foods<sup>23</sup>. Lactobacilli are among the most common microorganisms found in kefir, a  
193 traditional fermented milk beverage <sup>24</sup>, milk and milk products <sup>25,26</sup>. During fermentation, LAB synthesize  
194 vitamins and minerals, and produce biologically-active peptides with anti-oxidant activity <sup>17,27-31</sup>.

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

199 The composition of microbiomes varies in different regions of the world.<sup>37</sup> Gut microbiota has an inter-  
200 individual variability due to genetic predisposition and diet.<sup>38</sup> As part of the gut  
201 microbiome, *Lactobacillus* spp. contributes to its diversity and modulates oxidative stress in the GI tract.  
202 Some foods like cabbage can be fermented by the gut microbiota.<sup>39</sup>

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

209 The links between gut microbiome, inflammation, obesity and insulin resistance are being observed but  
210 further large studies are needed for a definite conclusion.<sup>47-49</sup>

211 Some COVID-19 patients have intestinal microbial dysbiosis<sup>50</sup> with decreased probiotics such  
212 as *Lactobacillus* and *Bifidobacterium*<sup>51</sup>. Many bacteria are involved in the fermentation of vegetables but  
213 most traditional foods with live bacteria in the low-death rate countries are based on LAB fermentation.<sup>18-</sup>  
214 <sup>20,23,30</sup> Lactobacilli are among the most common microorganisms found in milk and milk products<sup>24-26</sup>.

## 215 **6- Angiotensin-converting enzyme 2 (ACE2) and COVID-19**

216 COVID-19 is more severe in older adults and/or patients with comorbidities, such as diabetes, obesity or  
217 hypertension, suggesting a role for insulin resistance.<sup>52</sup> Although differences exist between countries, the  
218 same risk factors for severity were found globally, suggesting common mechanisms. A strong relationship  
219 between hyperglycemia, impaired insulin pathway, and cardiovascular disease in type 2 diabetes is linked  
220 to oxidative stress and inflammation.<sup>53</sup> Lipid metabolism has an important role to play in obesity, in  
221 diabetes and its multi-morbidities, and in ageing.<sup>54</sup> The increased severity of COVID-19 in diabetes,  
222 hypertension, obese or elderly individuals may be related to insulin resistance, with oxidative stress as a  
223 common pathway.<sup>55</sup> Moreover, the severe outcomes of COVID-19 - including lung damage, cytokine storm  
224 or endothelial damage - appear to exist globally, again suggesting common mechanisms.

225 The angiotensin-converting enzyme 2 (ACE2) receptor is part of the dual system -the renin-angiotensin-  
226 system (RAS) - consisting of an ACE-Angiotensin-II-AT<sub>1</sub>R axis and an ACE-2-Angiotensin-(1-7)-Mas  
227 axis. AT<sub>1</sub>R is involved in most of the effects of Ang II, including oxidative stress generation,<sup>56</sup> which in  
228 turn upregulates AT<sub>1</sub>R<sup>57</sup>. In metabolic disorders and with older age, there is an upregulation of the AT<sub>1</sub>R  
229 axis leading to pro-inflammatory, pro-fibrotic effects in the respiratory system, and to insulin resistance.<sup>58</sup>

230 SARS-CoV-2 binds to its receptor ACE2 and exploits it for entry into the cell. The ACE2 downregulation,  
231 as a result of SARS-CoV-2 binding, enhances the AT<sub>1</sub>R axis <sup>59</sup> likely to be associated with insulin  
232 resistance <sup>60,61</sup> but also to severe outcomes of COVID-19 (Figure 5A).

## 233 **7- Anti-oxidant activities of foods linked with COVID-19**

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

### 239 **7-1- Nrf2, a central antioxidant system**

240 Reactive oxygen species (ROS), such as hydrogen peroxide and superoxide anion, exert beneficial and  
241 toxic effects on cellular functions. Nrf2 is a pleiotropic transcription factor at the centre of a complex  
242 regulatory network that protects against oxidative stress and the expression of a wide array of genes  
243 involved in immunity and inflammation, including antiviral actions.<sup>66</sup> Nrf2 activity in response to chemical  
244 insults is regulated by a thiol-rich protein named KEAP1 (Kelch-like ECH-associated protein 1). The  
245 KEAP1-Nrf2 system is the body's dominant defense mechanism against ROS.<sup>67</sup> Induction of the antioxidant  
246 responsive element and the ROS mediated pathway by Nrf2 reduces the activity of nuclear factor kappa B  
247 (NF-κB), <sup>68</sup> whereas NF-κB can modulate Nrf2 transcription and activity, having both positive and negative  
248 effects on the target gene expression <sup>69</sup>.

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

253 Nrf2 may be involved in diseases associated with insulin-resistance.<sup>60,73-75</sup> Nrf2 activity declines with age,  
254 making the elderly more susceptible to oxidative stress-mediated diseases.<sup>76</sup> Nrf2 is involved in the  
255 protection against lung <sup>77</sup> or endothelial damage. <sup>78</sup> Nrf2 activating compounds downregulate ACE2 mRNA  
256 expression in human liver-derived HepG2 cells.<sup>79</sup> Genes encoding cytokines including IL-6 and many  
257 others specifically identified in the "cytokine storm" have been observed in fatal cases of COVID-19. ACE2  
258 can inhibit NF-κB and activate Nrf2.<sup>80</sup>

### 259 **7-2- Sulforaphane, the most potent Nrf2 natural activator**

260 Isothiocyanates are stress-response chemicals formed from glucosinolates in plants often belonging to the  
 261 cruciferous family, and more broadly to the Brassica genus including broccoli, watercress, kale, cabbage,  
 262 collard greens, Brussels sprouts, bok choy, mustard greens and cauliflower.<sup>81</sup> The formation of  
 263 isothiocyanates from glucosinolates depends on plant-intrinsic factors and extrinsic postharvest factors  
 264 such as industrial processing, domestic preparation, mastication, and digestion.<sup>82</sup>

265 Sulforaphane [1-isothiocyanato-4-(methylsulfinyl)butane] is an isothiocyanate occurring in a stored form  
 266 such as glucoraphanin in cruciferous vegetables.<sup>83,84</sup> Sulphoraphanes are also found in fermented cabbage  
 267 <sup>31,85</sup>. Present in the plant as its precursor, glucoraphanin, sulforaphane is formed through the actions of  
 268 myrosinase, a  $\beta$ -thioglucosidase present in either the plant tissue or the mammalian microbiome<sup>86,87</sup>.

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

272 One of the key mechanisms of action of sulforaphane involves the activation of the Nrf2-Keap1 signaling  
 273 pathway.<sup>90</sup> Sulforaphane is the most effective natural activator of the Nrf2 pathway, and Nrf2 expression  
 274 and function is vital for sulforaphane-mediated action.<sup>91,92</sup> Sulforaphanes were suggested to be effective in  
 275 diseases associated with insulin resistance.<sup>1,93-95</sup> It has been proposed that SARS-CoV-2 downregulates  
 276 ACE2 and that there is an increased insulin resistance associated with oxidative stress through the AT<sub>1</sub>R  
 277 pathway. Fermented vegetables and Brassica vegetables release glucoraphanin, converted by the plant or by  
 278 the gut microbiome into sulforaphane, which activates Nrf2 and subsequently reduces insulin intolerance  
 279 (Figure 5B).

### 280 **7-3- Lactic acid bacteria**

#### 281 *Antioxidant activity of Lactobacillus*

282 The gastrointestinal (GI) tract is challenged with oxidative stress induced by a wide array of factors, such  
 283 as exogenous pathogenic microorganisms and dietary aspects. Redox signaling plays a critical role in the  
 284 physiology and pathophysiology of the GI tract.<sup>96</sup> The redox mechanisms of *Lactobacillus* spp. are  
 285 involved in the downregulation of ROS-forming enzymes,<sup>97,98</sup> and redox stress resistance proteins or genes  
 286 differ largely between LAB species. In addition, Nrf-2 and NF- $\kappa$ B are two common transcription factors,  
 287 through which *Lactobacillus* spp. also modulates oxidative stress.<sup>99</sup>

#### 288 *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<sup>100</sup> 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<sup>101</sup>. 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)<sup>102</sup>. 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<sup>103</sup>.

#### *Lactobacillus and Nrf2*

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

#### *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<sup>114</sup> or PEDV. *Lactobacillus* inhibits PEDV or TGEV effects *in vitro*<sup>115,116</sup>.

#### **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<sub>1</sub>R 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

319 reduces insulin intolerance by its potent antioxidant activities. Fermented vegetables contain a high content  
320 of *Lactobacillus* that can activate Nrf2 and impact on the microbiome.<sup>117</sup> Sulforaphane and LAB both  
321 therefore have the ability to reduce insulin resistance.

322 Other putative actions on COVID-19 severity may be postulated. The down-regulation of ACE2 reduces  
323 the Ang-1,7 anti-oxidant activity that was found to activate Nrf2.<sup>118,119</sup> Nrf2 protects against hallmarks of  
324 severe COVID-19. It has anti-fibrotic effects on various organs including the lungs,<sup>120</sup> protects against  
325 lung injury and acute respiratory distress syndrome,<sup>121</sup> and endothelial damage<sup>78</sup>. Finally, Nrf2 can block  
326 IL-6 in different models of inflammation<sup>122</sup> and might play a role in the COVID-19 cytokine storm.

327 These different mechanisms may explain the importance of fermented cabbage in preventing the severity of  
328 COVID-19. It is clear that other nutrients, vitamin D<sup>123</sup> and many different foods act on NRF2 and that  
329 mechanisms other than Nrf2 may be operative.

330 It is not yet known whether sulforaphane and/or LAB may act on the infectivity of SARS-CoV-2. Disulfide  
331 bonds can be formed under oxidizing conditions and play an important role in the folding and stability of  
332 some proteins. The receptor-binding domain of the viral spike proteins and ACE2 have several cysteine  
333 residues. Using molecular dynamics simulations, the binding affinity was significantly impaired when all  
334 of the disulfide bonds of both ACE2 and SARS-CoV/CoV-2 spike proteins were reduced to thiol groups.  
335 This computational finding possibly provides a molecular basis for the differential COVID-19 cellular  
336 recognition due to the oxidative stress.<sup>124</sup>

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

## 342 **8- May dietary modifications change the course of COVID-19?**

### 343 **8-1- Fermented vegetables and Kimchi**

344 It is tempting to propose that countries where traditional LAB-fermented vegetables are largely consumed  
345 are those showing lower COVID-19 death rates and that fermented vegetables represent one possible  
346 preventive approach. Other nutrients are found in these products that may enhance their effect (e.g. vitamin  
347 K<sup>125</sup>). Kimchi fermented from many vegetables including cabbage has several effects on insulin resistance  
348 associated diseases: anti-diabetic properties,<sup>126,127</sup> cardiovascular diseases,<sup>28</sup> dyslipidemia<sup>128</sup> or

349 ageing.<sup>129</sup>Kimchi, when fermented for a long time, reduces insulin intolerance to a greater extent than fresh  
350 kimchi,<sup>126</sup> indicating that newly formed products during fermentation are important. In particular, Kimchi  
351 from cabbage and Chinese cabbage contains several glucosinolates<sup>130-132</sup> that can be transformed in  
352 sulforaphanes either in the plant itself or by the human microbiome.<sup>60</sup> In central European countries, raw  
353 and fermented cabbage is commonly consumed.

354 In Sub-Saharan Africa, people commonly eat fermented foods, mainly cereal-based foods like sorghum,  
355 millet and maize, roots such as cassava, fruits and vegetables. Fermented cassava products  
356 (like *gari* and *fufu*) are a major component of the diet of over 800 million people and, in some areas, these  
357 products constitute over 50% of the diet.<sup>16</sup>

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

## 360 **8-2- Westernized diet**

361 Westernized diets contain a reduced amount of fermented vegetables<sup>43,133</sup> and may be prone to increasing  
362 insulin resistance<sup>44,134</sup> and diseases associated with it,<sup>135</sup> and thereby severe COVID-19.

363 In the Mediterranean diet, well known for reducing insulin resistance,<sup>136</sup> Nrf2 appears to play an important  
364 role.<sup>71,137</sup> The COVID-19 death rate differences in Italian (Figure 2) and Spanish<sup>3</sup> regions suggest a role for  
365 Mediterranean diet and short chain food supply. This also indicates that many foods can have an effect and  
366 that cabbage and fermented foods represent a proof-of-concept. Nrf2 is also involved in the Okinawan-  
367 based diet<sup>71</sup>, active on insulin intolerance.<sup>138</sup> Taken altogether, it is possible that diet is partly involved in  
368 the COVID-19 death clusters found in large Western cities where traditional diet is often replaced by long  
369 chain food supply.

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

## 373 **8.3. The COVID-19 slum paradox**

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

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

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

## 392 **Conclusion**

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

397 Mainstream COVID-19 control strategies including social distancing, confinement and intensive case  
398 finding, testing, tracing and isolating are so far not enough to provide a SARS-CoV-2-free environment and  
399 restore a safe social life. There are hopes for a safe and effective vaccine, but this is unlikely to become  
400 rapidly available. So, there is a need to explore other potentially useful strategies. An area that has not been  
401 sufficiently considered is diet, both as a preventive and/or therapeutically useful intervention, encouraging  
402 people to eat more traditional foods containing fermented vegetables (Figure 6). We have suggested that  
403 fermented vegetables could be associated with a lower COVID-19 mortality due to their potent antioxidant  
404 effect among which sulforaphane and LAB are important. However, many other foods may have a similar  
405 activity. It should be noted that dietary supplements that over-activate Nrf2 may have side-effects.<sup>149</sup>

406

407 Robust evidence from observational studies would be helpful to formally investigate associations between  
408 fermented foods and clinical outcomes in COVID-19. State-of-the-art methods, including the use of DAGs

409 (Directed Acyclic Graphs), may be needed to help assess whether the associations seen are likely to  
410 represent causal relationship <sup>150</sup>. A faster approach would be to develop large clinical trials in the  
411 appropriate populations. Interventions based on diets with a high intake of fermented foods like Kimchi or  
412 other fermented foods are unlikely to present ethical difficulties. Furthermore, the fact that a precise  
413 mechanism has been proposed would facilitate adding reliable biomarkers to the relevant clinical outcomes.  
414 Moreover, new drugs based on the components of these fermented foods may be of interest.

415 If the hypothesis is proved, COVID-19 will be the first infectious disease outbreak associated with a loss of  
416 “nature” <sup>151</sup> and to be ascribed as a disease of the Anthropocene <sup>152</sup>. Imbalance in the gut microbiota is  
417 responsible for the pathogenesis of various disease types including allergy, asthma, rheumatoid arthritis,  
418 different types of cancer, diabetes mellitus, obesity and cardiovascular disease <sup>153</sup>. Fermentation was  
419 introduced during the Neolithic age and was essential for the survival of human kind. When modern life led  
420 to eating reduced amounts of fermented foods, the microbiome drastically changed <sup>154</sup>, allowing SARS-  
421 CoV-2 to spread or to be more severe <sup>155</sup>. It is time for mitigation <sup>156</sup>.

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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<br>++++<br>e.g. Lombardy                                                                                                                                                                                               |
| A | Intensity of social contacts                  | ++               | +++                                                                                                                                                                                                                                         |
| A | Intensity of occupational contacts            | +++              | ++                                                                                                                                                                                                                                          |
| A | Confinement (level)                           | +++              | +++<br>e.g. US versus EU<br>Sweden vs Nordic countries                                                                                                                                                                                      |
| A | Confinement (early measures)                  | +++              | +++<br>e.g. UK versus EU                                                                                                                                                                                                                    |
| A | Climatic conditions (temperature, humidity)   | ?                | ++<br>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                                          | ?                | +<br>The map of COVID-19 deaths in Europe and the low prevalence in Asia and Africa suggest a role for diet                                                                                                                                 |
| B | Food                                          | ++?              | +<br>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                        | ++?              | +<br>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)  | ++?              | ++<br>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 Wurtemberg))

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

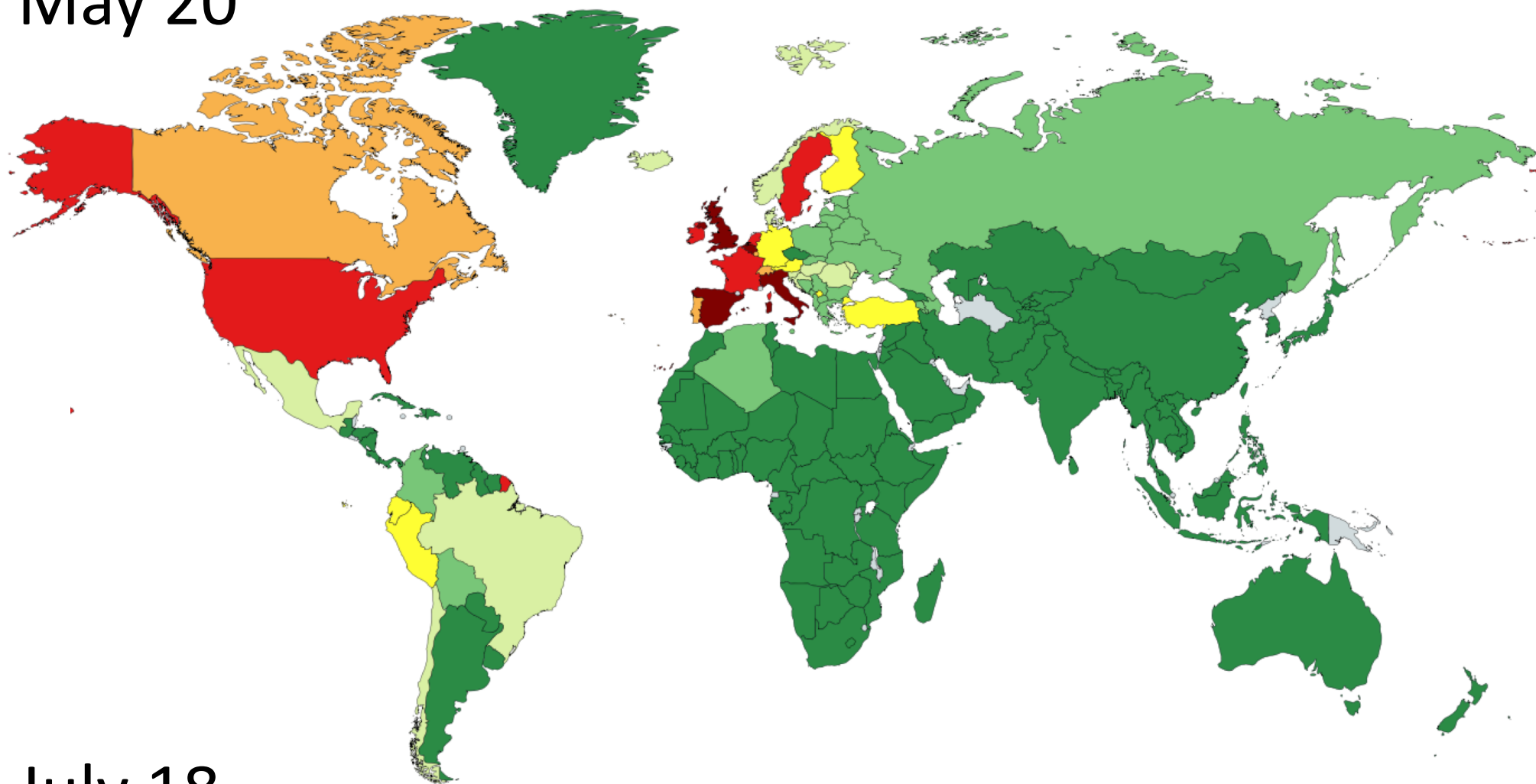
**Figure 5: Putative mechanisms of fermented or Brassica vegetables against COVID-19**

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

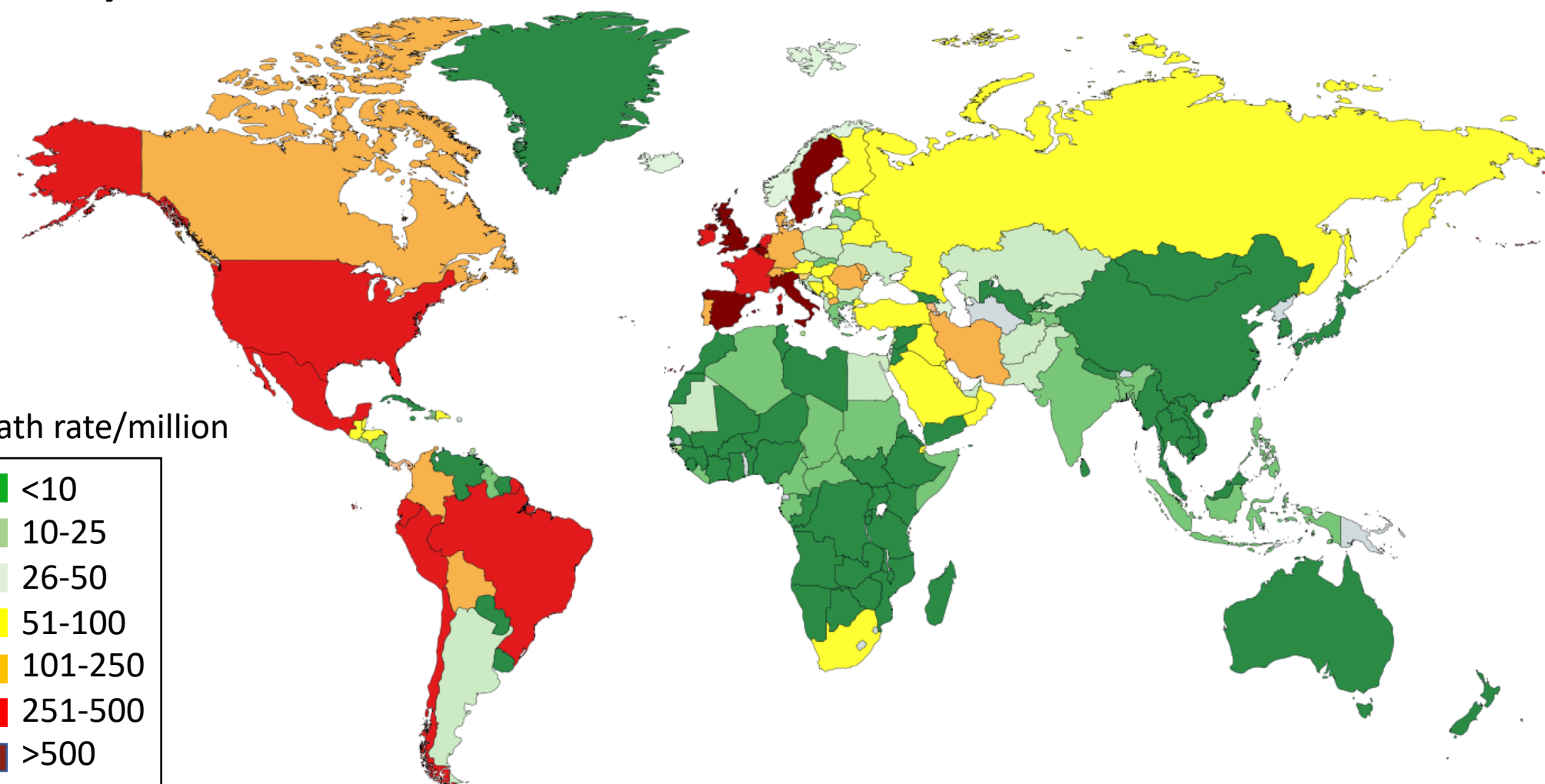
B: Preventive effects of cabbage and fermented vegetables through Nrf2

Figure 6 : Putative role of diet in COVID-19

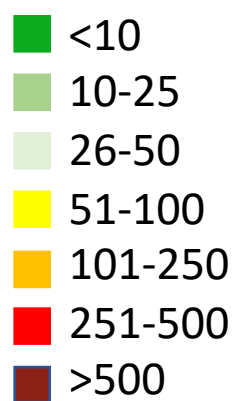
May 20



July 18



Death rate/million



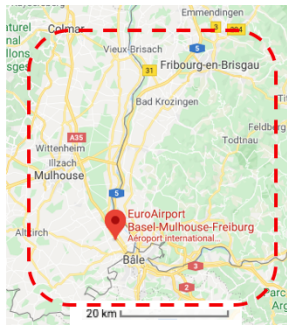


<50  
50-100  
100-200  
200-400  
400-800  
800-1600  
>1600



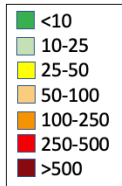
Death rate per  
million

Switzerland

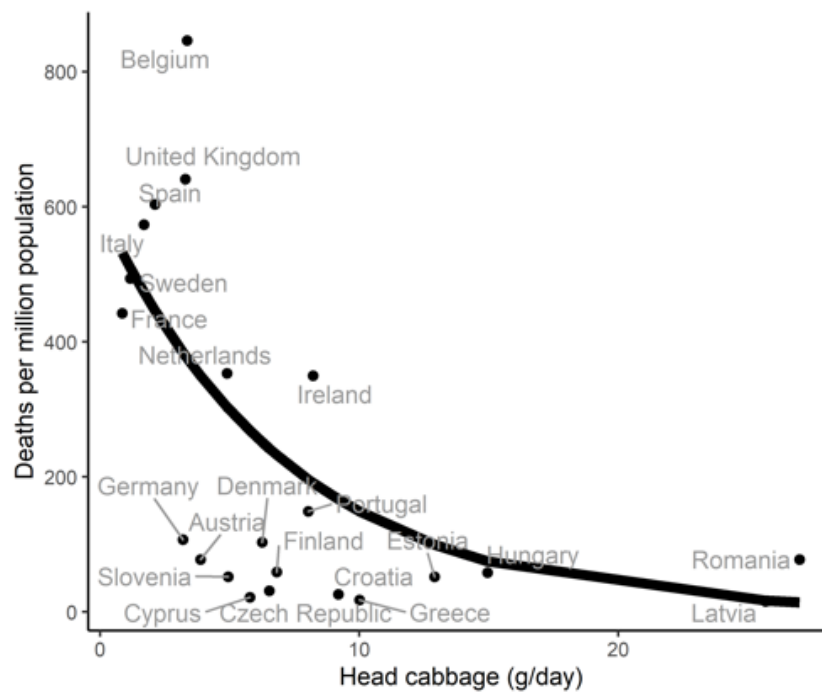


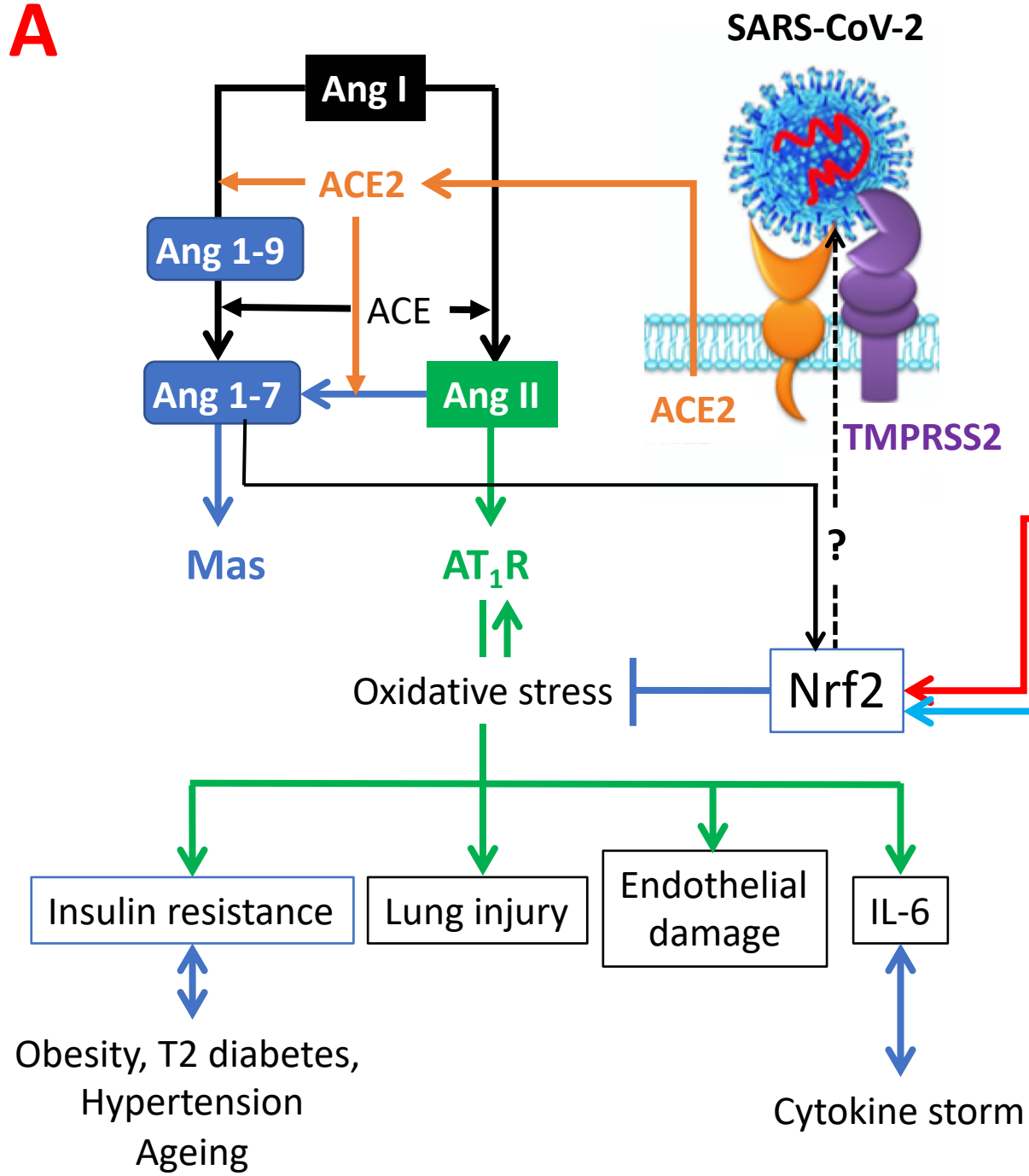
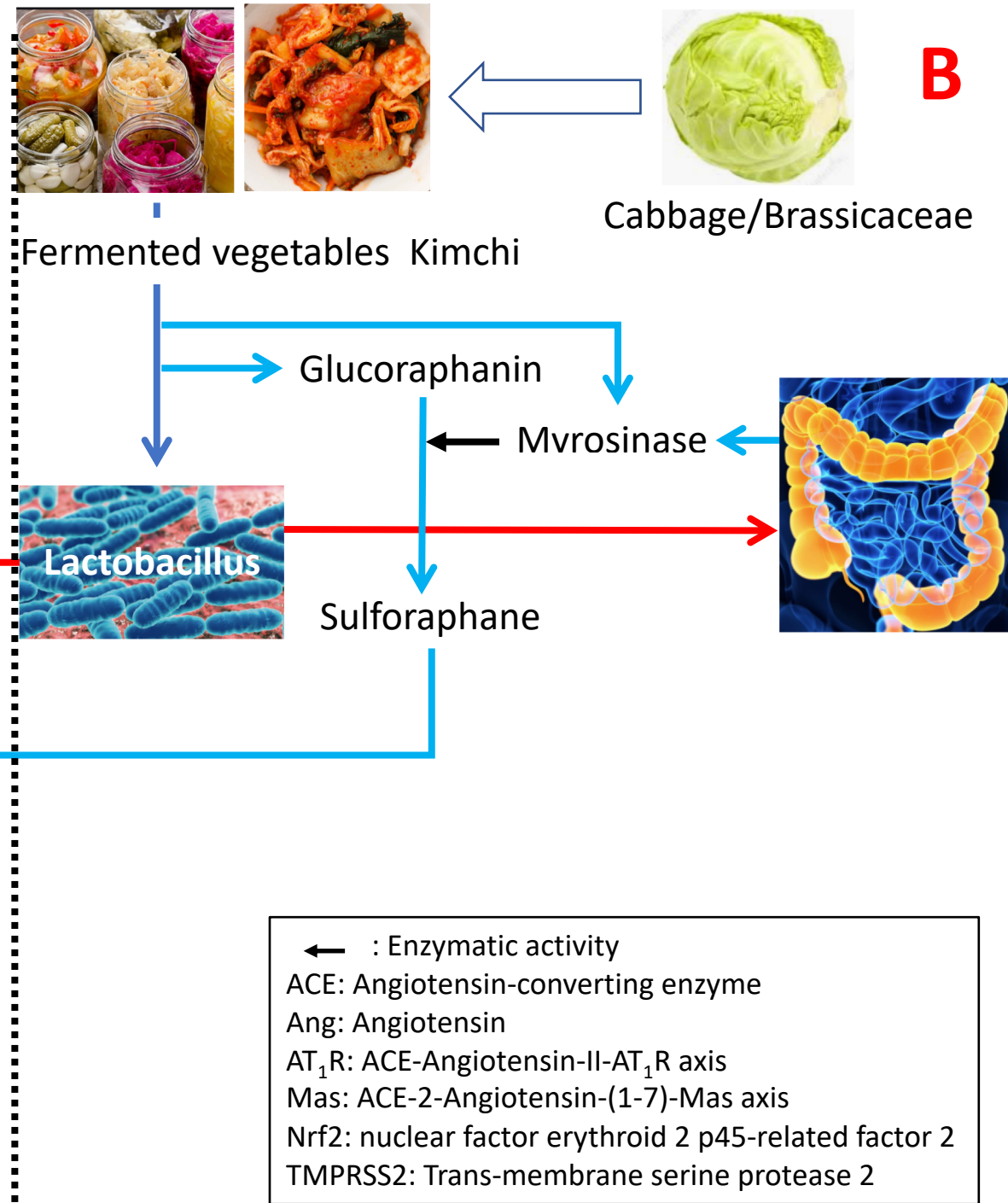
| May 20, 2020     | Deaths | Population | Deaths/<br>million |
|------------------|--------|------------|--------------------|
| Basel city (Sw)  | 49     | 198,000    | 25                 |
| Basel-Lands (Sw) | 30     | 298,000    | 10                 |
| Freiburg (DE)    | 15     | 213,000    | 7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

Deaths per million



- 1: French speaking canton
- 2: Partly French speaking canton
- 3: Italian speaking canton



**A****B**

# Social distancing, age (population, individual), lockdown, sex, other factors

