

Loss of food fermentation in Westernized diet: a risk factor for severe COVID-19?

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To the Editor,

The fermentation process, born as a preservation method in the Neolithic age, enabled humans to eat not-so-fresh food and to survive.¹ Fermented foods are “foods or beverages made via controlled microbial growth (including lactic acid bacteria (LAB)) and enzymatic conversions of food components.”² 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, ...). The westernized diet is lacking many traditional fermented foods.³

The gut microbiota has an inter-individual variability due to genetic predisposition and diet³. Some foods like cabbage can be fermented by the gut microbiota.⁴ The westernized diet has been associated with changes in the gut microbiome.⁵

In this Rostrum, we consider loss of food fermentation either as a reduction of fermented food consumption in the diet or as a change in the microbiome leading to a reduction of fermentation of foods in the gut. This paper is based on the hypothesis that diet may partly explain differences in COVID-19 death rates within and between countries.⁶

Diet and heterogeneity of COVID-19 death rates between and within countries

Large differences exist when assessing death rates between and within countries. Most countries with a very low COVID-19 death rate (Asia, Africa, Central European countries, the Balkans or the Middle East) are well-known to have a diet containing fermented vegetables.

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 country consumption of fermented vegetables, pickled/marinated vegetables, fermented milk,

yoghurt and fermented sour milk.⁷ 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%.

Another diet component potentially relevant in the COVID-19 mortality may be the food supply chain and traditional groceries that may be inferred from death rates in Italian regions (Figure 1B).⁸ The impact of the long supply chain of food on health is measurable by an increase in metabolic syndrome and insulin resistance⁹. 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.

In Switzerland, the French- and Italian-speaking cantons had a far higher death rate than the German-speaking ones (Figure 3) (Office fédéral de la santé publique, *Switzerland*, <https://www.bag.admin.ch/bag/fr/home.html>). 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 (Figure 2).

COVID-19: ACE2 binding and insulin resistance.

The angiotensin-converting enzyme 2 (ACE-2) is part of the dual system, the renin-angiotensin-system (RAS), and includes the ACE-Angiotensin-II-AT₁R axis. AT₁R is involved in most Angiotensin II effects, including oxidative stress generation, pro-inflammatory and pro-fibrotic effects in the respiratory system as well as insulin resistance.^{10,11} SARS-CoV-2 binds¹² and downregulates ACE-2, enhancing the AT₁R axis¹³. It is likely to be associated with insulin resistance.¹⁴

Microbiome, fermented food and lacobacilli.

Humans possess two protective layers of biodiversity, and the microbiome has been proposed as an important actor of COVID-19¹⁵. The environment (outer layer) affects our lifestyle, shaping the microbiome (inner layer).¹⁶ Many fermented foods contain living microorganisms and modulate the intestinal microbiome.^{2,17-20}

The composition of microbiomes varies in different regions of the world.²¹ Urbanization in western countries was associated with changes in the gut microbiome and with intestinal diversity reduction.^{3,5,22-24} Westernized food in Japan led to changes in the microbiome and in insulin resistance.²⁵ The gut microbiome of westernized urban Saudis had a lower biodiversity than that of the traditional Bedouin population.²⁶ Fast food consumption was characterised by reduced Lactobacilli in the microbiome.²⁷

The links between gut microbiome, inflammation, obesity and insulin resistance are being observed but further large studies are needed for a definite conclusion.²⁸⁻³⁰

Some COVID-19 patients have intestinal microbial dysbiosis³¹ with decreased probiotics such as *Lactobacillus* and *Bifidobacterium*³². 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.³³⁻³⁷ Lactobacilli are among the most common microorganisms found in milk and milk products³⁸⁻⁴⁰.

Effect of lactic acid bacteria in insulin resistance and related diseases.

Insulin resistance and Lactobacillus.

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 resistance⁴¹ 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 in particular in insulin resistance⁴². 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)⁴³. 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 both⁴⁴. Nrf2 may be involved in diseases associated with insulin-resistance⁴⁵⁻⁴⁷. “Ancient foods”, and particularly those containing *Lactobacillus*, activate Nrf2⁴⁸. The microbiome is highly related to insulin resistance.

Lactobacillus and Nrf2

In mice, several strains of *Lactobacillus* were found to regulate Nrf2 in models of ageing⁴⁹, cardioprotective effects⁵⁰, and non-alcoholic fatty acid liver disease⁵¹. *Lactobacillus plantarum* CQPC11 - isolated from Sichuan pickled cabbages - antagonizes oxidation and ageing in mice⁵². *Lactobacillus* protects against ulcerative colitis by modulation of the gut microbiota and Nrf2/Ho-1 pathway⁵³. The sugary kefir strain, *Lactobacillus mali*APS1, \soutameliorated ameliorates? hepatic steatosis by regulation of Nrf2 and the gut microbiota in rats⁵⁴. *In vitro* studies have also found an effect of *Lactobacilli* mediated by Nrf2⁵⁵⁻⁵⁷. Interestingly, the synbiotic combination of prebiotic grape pomace extract and probiotic *Lactobacillus* sp. \soutreduced reduces? intestinal inflammatory markers.⁵⁸

Coronavirus disease in animals and lactic acid bacteria.

The porcine epidemic diarrhea virus (PEDV), or Transmissible Gastroenteritis Coronavirus Infection (TGEV), are worldwide-distributed coronaviruses. Low levels of *Lactobacillus* were found in the intestine of piglets infected by TGEV⁵⁹ or PEDV. *Lactobacillus* inhibits PEDV or TGEV effects *in vitro*^{60,61}.

Westernized food and fermented vegetables.

Westernized diets contain a reduced amount of fermented vegetables^{5,62} and may be prone to increasing insulin resistance and thereby severe COVID-19. The transcription factor Nrf2 may be at the centre of the regulatory pathways (Figure 3).

COVID-19 and food fermentation .

Although nutritional epidemiology has been criticized on several fronts - its inability to measure diet accurately and its reliance on observational studies to address etiologic questions⁶³ - there seems to be sufficient evidence to raise several conclusions (to be tested appropriately).

Many factors may play a role in the extension and severity of COVID-19. Diet may represent only one of the possible causes of COVID-19 severity (Table 1). The effects of the microbiome⁶⁴ and diet⁶ on SARS-CoV-2 infection suggest that their role in the gut could be a target for COVID-19 interventions. It is proposed that countries with a large consumption of traditional LAB-fermented vegetables are those showing lower COVID-19 death rates. This hypothesis should be confirmed by experimental studies (Box 1). If certain foods are found to be associated with a prevention of COVID-19 prevalence or severity, it may be of interest to study their LAB composition in order to eventually find some common mechanisms and targets for therapy.

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

		Individual level	Country/region level
A	Contact with a SARS-Cov-2 infected individual	++++	Case zero identified ++++ e.g. Lombardy
A	Intensity of social contacts	++	+++
A	Intensity of occupational contacts	+++	++
A	Confinement (level)	+++	+++ e.g. US versus EU Sweden vs Nordic countries
A	Confinement (early measures)	+++	+++ e.g. UK versus EU

		Individual level	Country/region level
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	?	+
B	Vitamin D	?	+ The map of COVID-19 deaths in Europe and the low prevalence in Asia and Africa suggest a role for diet
B	Diet	?	+ Still unclear
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, 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	++	

Text Box:

Future research areas:

- Mouse models of COVID to investigate the effects of diet, sulforaphane and similar compounds.

- Cellular experiments for the *in depth* investigation of sulforaphane.
- Case control studies.
- Investigation of synergistic effects with other dietary factors and vitamins such as short chain fatty acids, omega 3, vitamin D.
- Identification of the most potent LAB/probiotic strains.
- Multiple omics metabolome analyses of different stages of COVID patients.
- Clinical trials with fermented foods or LABs and other probiotics to prevent severe COVID-19.
- Clinical trials with fermented foods or LABs and other probiotics to reduce severity of COVID-19.

Figure 1: Differences in death rates between Italian regions (July 13, 2020)



Death rate per million

Figure 2: Regional differences of death rates between Switzerland, France and Germany (May 20)

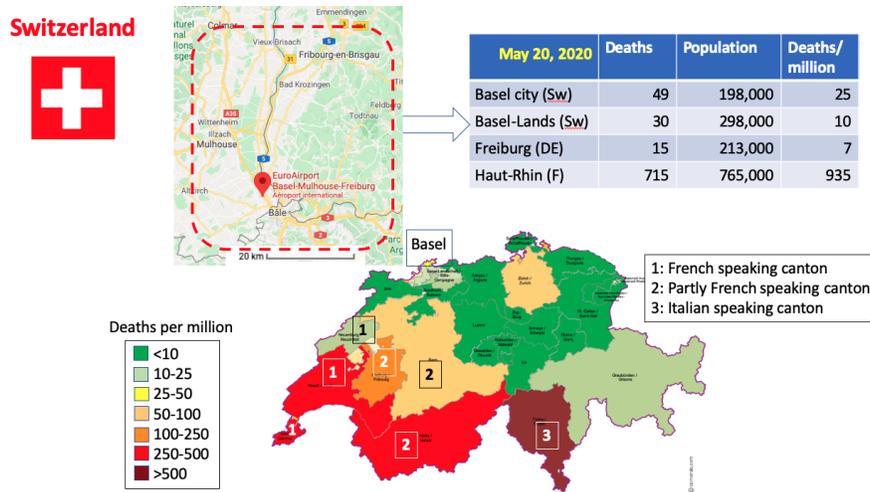
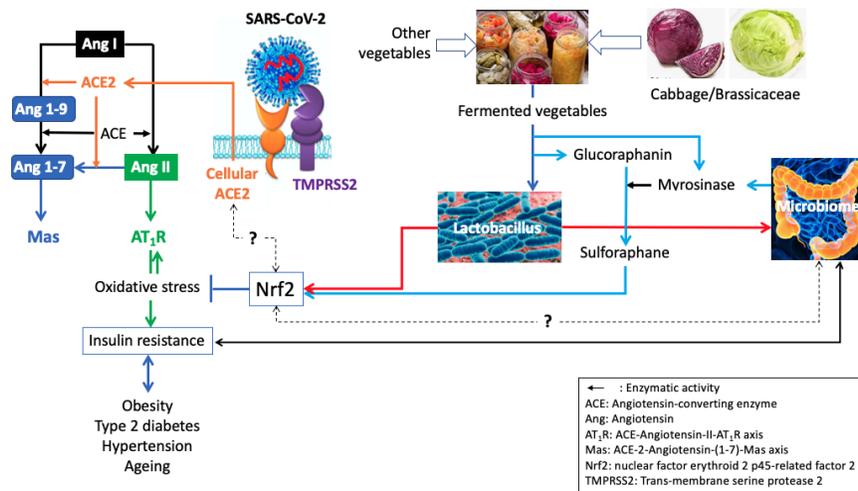


Figure 3: Central role of Nrf2 in the impact of fermented vegetables on COVID-19 severity . SARS-CoV-2 downregulates ACE2, inducing an increased insulin resistance associated with oxidative stress through the AT₁R pathway. Fermented vegetables are often made from Brassica vegetables that release glucoraphanin converted by the plant or by the gut microbiome into sulforaphane which activates Nrf2 and subsequently reduces insulin intolerance. Fermented vegetables have a high content of Lactobacillus that can activate Nrf2 and impact the microbiome.



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