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## COVID-19-associated stroke risk: Could nutrition and dietary patterns have a contributing role?

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### Abstract

The novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 has created a life-threatening world pandemic. Unfortunately, this disease can be worse in older patients or individuals with comorbidities, having dangerous consequences, including stroke. COVID-19-associated stroke widely increases the risk of death from COVID-19. In addition to the personal hygiene protocols and preventive policies, it has been proven that immune-compromised, oxidative, and pro-coagulant conditions make a person more susceptible to severe COVID-19 complications, such as stroke; one of the most effective and modifiable risk factors is poor nutritional status. Previous literature has shown that healthy dietary patterns, such as the Mediterranean diet, some food groups, and specific micronutrients, reduce the risk of ischemic and hemorrhagic stroke. In this work, for the first time, we hypothesized that a healthy diet could also be a protective/preventive factor against COVID-19-associated stroke risk. In order to prove this hypothesis, it is required to study nutritional intake and dietary patterns in patients suffering from COVID-19-associated stroke. If this hypothesis is proven, the chronic supportive role of a healthy diet in critical situations will be highlighted once again.

**Key Words:** COVID-19; COVID-19-associated stroke; Nutrition; Dietary patterns; Food

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**Core Tip:** The novel coronavirus disease 2019 (COVID-19) can be worse in older patients or individuals with comorbidities, having dangerous consequences, including stroke. COVID-19-associated stroke widely increases the risk of death from COVID-19. Previous literature has shown that healthy dietary patterns, such as the Mediterranean diet, some food groups, and specific micronutrients, reduce the risk of ischemic and hemorrhagic stroke. Recently, healthy nutrition and certain nutrients or nutraceuticals reported to be effective in common relief functions in stroke and COVID-19 pathways. If growing studies confirm our hypothesis, it means that healthy nutrition could be a protective/preventive factor against COVID-19-associated stroke risk.

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## INTRODUCTION

Due to the significance of the current pandemic, many studies have paid attention to its consequent clinical outcomes. Clinical manifestations can astonishingly vary, from asymptomatic to the most life-threatening conditions resulting from cytokine storm<sup>[1,2]</sup>. Currently, the novel coronavirus disease 2019 (COVID-19)-associated stroke is not common and, simultaneously, is one of the most deteriorating consequences of this infection, particularly in those with severe infection<sup>[3,4]</sup>, which is responsible for the mortality of about 40% of affected patients if it occurs<sup>[5,6]</sup>. Stroke, in turn, is the second cause of death and the leading cause of disability<sup>[7]</sup>. Although it is not yet exactly clear whether COVID-19 is a culprit in the co-occurrence of stroke in infected patients<sup>[8]</sup>, studies have shown that the incidence of stroke in COVID-19 patients is about 0.9% to 2.7%<sup>[6,8]</sup>.

COVID-19-associated stroke is often an acute ischemic stroke, while hemorrhagic stroke is also rarely reported, especially in elderly<sup>[5,9]</sup>. Although some studies have reported stroke in young COVID-19 patients<sup>[10]</sup>, a systematic review and meta-summary of the literature have shown a mean age of  $63.4 \pm 13.1$  years and the simultaneous presence of cardiovascular comorbidities<sup>[6]</sup>. Hypertension, diabetes, and inappropriate cholesterol levels are the main comorbidities associated with the severity of COVID-19<sup>[11]</sup>. On the other hand, the available data, indeed, suggest that severe COVID-19 can lead to stroke<sup>[6,9]</sup>. Preventive strategies and available health-promoting protocols based on antiviral therapies, immune modulators, and anticoagulants to reduce the severity of this disease appear to be significant and interesting points to be studied<sup>[12]</sup>. However, lifestyle has always been the most modifiable factor influencing diseases, of which nutrition is a vital part<sup>[13-15]</sup>. The role of healthy nutrition in the prevention and treatment of hypertension, diabetes, and high serum levels of cholesterol, all of which predispose a person to stroke, and most non-communicable diseases has also been proven<sup>[16-18]</sup>. Recently, researchers have discussed immune-modulatory properties and other various effects of healthy nutrition on COVID-19 and its complications<sup>[13-15,19-21]</sup>, among which no attention has been paid to COVID-19-associated stroke.

## HYPOTHESIS

A vast body of evidence-based data from the past to the present has shown that healthy eating can prevent hemorrhagic and ischemic stroke<sup>[22-24]</sup>. Protection against hyper-inflammatory and hypercoagulable states and a pleasant change in metabolites

derived from intestinal microbiota leading to cardiovascular health are the mainstream mechanisms involved<sup>[25]</sup>. Although there is no study concerning nutrition in COVID-19-associated stroke yet, there are growing studies addressing the impact of healthy diets, certain food groups, and some specific nutrients on COVID-19<sup>[13-15,19-21]</sup>. In these studies, healthy nutrition and some nutrients or nutraceuticals are considered mitigators of the disease severity and cytokine storm. On the other hand, some data have shown stroke as the worst event following COVID-19, occurring under cytokine storm and hypercoagulable conditions<sup>[26]</sup>. Altogether, the above-mentioned evidence creates the speculation that people who adhere to a healthy diet and lifestyle may be less likely to have a stroke following COVID-19 affliction.

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## EVALUATION OF THE HYPOTHESIS

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To evaluate our hypothesis, we conducted a comprehensive review by searching both pubmed.gov and scholar.google.com to first understand the association between stroke and COVID-19 and second review the studies in which nutrition has been linked to stroke and COVID-19. The former results are shown in **Table 1**, and the latter in **Table 2**. We also explain them in detail below.

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## COVID-19-ASSOCIATED STROKE RISK

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection enters the target cell *via* the angiotensin-converting enzyme 2 (ACE2) receptor<sup>[12]</sup>. In addition to the lung, this receptor is present in the endothelial cells, heart, kidney, and intestine<sup>[27]</sup>. This is an underlying cause of beyond respiratory manifestations of COVID-19. Once the virus infects the endothelial cells lining blood vessels' beds, inflammatory cells and apoptotic bodies accumulate; this results in vascular endothelial dysfunction, shifting vascular autoregulation to vasoconstriction, and organ ischemia, tissue edema, and pro-coagulant condition consequently<sup>[27,28]</sup>. On the other hand, immune-mediated recruitment of immune cells elevates the inflammatory responses and hyper-inflammatory states, leading to cytokine storm in severe cases. Cytokine storm plays a key role in the pathogenesis of severe COVID-19 manifestations, including acute ischemic stroke caused by hypercoagulable state<sup>[26]</sup>. Similar to other viral syndromes, SARS-CoV-2 is associated with an increased risk of stroke<sup>[29,30]</sup>. Elevated interleukin-6 (IL-6) levels following cytokine storm cause hyperviscosity<sup>[8]</sup>. Thus, besides the mechanisms, including infection-induced hypercoagulability, viral cardiomyopathy and a diffuse hyperinflammatory state<sup>[27,28,31]</sup>, proposed so far for the association between COVID-19 and acute ischemic stroke, a mechanical factor such as dehydration can also increase stroke risk<sup>[8,32]</sup>.

By comparing measured biomarkers in severe COVID-19 patients with moderate cases, a study has shown higher levels of alanine aminotransferase, lactate dehydrogenase, C-reactive protein (commonly known as CRP), ferritin, D-dimer, IL-2R, IL-6, IL-10, and TNF- $\alpha$  in severely infected patients. Furthermore, the total number of T lymphocytes, CD4<sup>+</sup> T cells, and CD8<sup>+</sup> T cells are significantly lower in severe cases than those classified as moderate. Therefore, they have concluded the cytokine storm to be related to disease severity<sup>[33]</sup>. A recently published systematic review further reveals the outstanding presence of raised D-dimer, fibrinogen, and anti-phospholipid antibodies in COVID-19 patients with coincident acute ischemic stroke<sup>[6]</sup>. Thus, the speculation on COVID-19-associated stroke is consistent with previous studies, which have demonstrated well that higher levels of D-dimer significantly associated with older age and pre-existing comorbidities, are related to worse complications and death from COVID-19<sup>[9,34]</sup>. According to a report by Ntaios *et al.*<sup>[35]</sup>, COVID-19-associated ischemic stroke is more severe with poorer outcomes and higher mortality than ischemic strokes unrelated to COVID-19.

Although most studies have discussed ischemic stroke, there are few data to suggest that SARS-CoV-2-induced diffuse endothelial inflammation could also be a mechanism resulting in hemorrhagic stroke<sup>[31]</sup>. On the other hand, as stated, the infection caused by SARS-CoV-2 is mediated by the host cells ACE2 receptors; this, in turn, downregulates the expression of ACE2. Hence, the availability of angiotensin II increases, leading to severe blood pressure fluctuation, especially in patients with a history of hypertension that makes them prone to hemorrhagic stroke<sup>[9]</sup>. Finally, it is hypothesized that therapeutic targeting of protease-activated receptor (commonly referred to as PAR), as a protein engaged in the neuroinflammatory toxicity, may be

**Table 1 Summary of available evidence-based associations between stroke and coronavirus disease 2019**

Ref.	Study design	Sample/ Aim	Main culprits suggested in the occurrence of stroke result from COVID-19 affliction
Bhaskar <i>et al</i> <sup>[26]</sup>	REPROGRAM consortium position paper	An overview of cytokine storm and its implications in COVID-19	(1) Cytokine storm; (2) Thromboembolic events; and (3) Large vessel occlusion
Rothstein <i>et al</i> <sup>[31]</sup>	Retrospective, observational study	844 COVID-19 patients, 28 of them had a stroke	(1) Endothelialitis; (2) Diffuse endothelial inflammation; (3) Infection-induced hypercoagulability; (4) Viral cardiomyopathy; and (5) Diffuse hyperinflammatory state
Valderrama <i>et al</i> <sup>[8]</sup>	Case study	A 52-year-old man with co-occurrence of stroke and COVID-19 infection	(1) Inflammation; (2) Injury to the myocardium; (3) Thrombogenesis; (4) Increased D-dimer levels; (5) Increased interleukin-6 levels; (6) Hyperviscosity; (7) Vascular endothelial damage; (8) Intracerebral hemorrhage; (9) Microthrombosis; and (10) Fibrinogen consumption coagulopathy
Tan <i>et al</i> <sup>[6]</sup>	Systematic review and meta-summary of the literature	A total of 39 studies comprising 135 patients, pooled incidence of co-occurrence of stroke and COVID-19 was 1.2%	(1) Elevated D-dimer; (2) Elevated fibrinogen; and (3) Presence of antiphospholipid antibodies
Wang <i>et al</i> <sup>[9]</sup>	Review article	Summarizing the potential contribution of COVID-19 to hemorrhagic stroke in the elderly and proposing possible mechanisms	(1) Downregulation of ACE2 expression; (2) Increased angiotensin II availability; (3) Severe blood pressure fluctuations; (4) Predisposition to hemorrhagic stroke; (5) Elevated plasma D-dimer levels; (6) Classical inflammatory biomarkers; (7) Viral CNS infections; (8) Cytokine, chemokine, and protease; and (9) Increasing BBB permeability
Ntaios <i>et al</i> <sup>[35]</sup>	Special report	Pooled all patients who were hospitalized with confirmed COVID-19 and AIS in 28 sites from 16 countries	(1) Endotheliopathy; (2) Potentiate the prothrombotic milieu; (3) Immune-mediated platelet activation; (4) Dehydration; and (5) Infection-induced cardiac arrhythmias

ACE2: Angiotensin-converting enzyme 2; AIS: Acute ischemic stroke; BBB: Blood-brain barrier; CNS: Central nervous system; COVID-19: Coronavirus disease 2019.

useful in controlling various complications caused by COVID-19<sup>[32]</sup>.

## DIETARY PATTERNS AND STROKE RISK

According to several national studies, nearly 90% of the stroke burden can be assigned to the modifiable risk factors, including poor diet<sup>[36,37]</sup>. Therefore, a healthy diet is necessary and important as an approved preventive strategy against stroke<sup>[22]</sup>. Many articles are now available, all of which indicate that healthy eating and adherence to the certain dietary patterns, such as the healthy Nordic diet<sup>[23]</sup>, Dietary Approaches to Stop Hypertension (DASH) diet<sup>[22]</sup>, and especially the Mediterranean diet<sup>[24]</sup>, significantly reduce the risk of both ischemic and hemorrhagic strokes. Hansen *et al*<sup>[23]</sup>, in their cohort study with a median follow-up period of 13.5 years identifying 2283 cases of stroke, have found that adherence to a healthy Nordic diet (containing fish, apples, pears, cabbages, root vegetables, rye bread, and oatmeal) has a positive effect on stroke risk so that the higher Healthy Nordic Food Index score is associated with a lower risk of total stroke. Clinical trials have also shown that adherence to a healthy Nordic diet leads to weight loss, decreased blood pressure, and improved serum lipid status<sup>[38-40]</sup>. This diet is rich in potassium and fiber since it contains high amounts of

**Table 2 Summary of available studies related to dietary patterns, some foods, and micronutrients in context of stroke and/or coronavirus disease 2019**

Ref.	Study design	Sample/ Aim	Possible pathways in which nutritional factors may be involved in pathogenesis of stroke and/ or COVID-19-associated stroke
Hansen <i>et al</i> <sup>[23]</sup>	Danish cohort study	Incident cases of stroke among 55338 men and women	(1) Higher Healthy Nordic Food Index score was associated with a lower risk of total stroke; (2) Reduction in blood pressure; (3) Improved blood lipids; (4) Induced weight loss; (5) Lower total and low-density lipoprotein cholesterol; and (6) Increased antioxidant and flavonoid levels
Feng <i>et al</i> <sup>[22]</sup>	Meta-analysis of prospective studies	Included 12 prospective cohort studies comprising a total of 548632 participants	(1) Higher adherence to the DASH diet was related to a reduced risk of developing stroke; (2) Blood pressure-lowering effects; (3) Improved lipid profiles and body weight; (4) Decreased the risk of metabolic syndrome; (5) Improved serum inflammatory biomarkers; (6) Reduced oxidative stress; and (7) Anti-inflammatory and antioxidative effects
Estruch <i>et al</i> <sup>[24]</sup>	Randomized clinical trial	A total of 7447 persons randomly assigned to one of three diets: a Med-diet suppl with extra-virgin olive oil, a Med-diet suppl with mixed nuts, or a control diet	(1) A Med-diet suppl with extra-virgin olive oil or nuts reduced the incidence of major cardiovascular events; (2) High biologic plausibility; (3) Anti-inflammatory and antioxidative effects; (4) Improved endothelial dysfunction; (5) Resistance to vasoreactivity; (6) Insulin sensitivity; and (7) Improved blood lipids
Chiu <i>et al</i> <sup>[47]</sup>	Two prospective cohort studies	Cohort 1, <i>n</i> = 5050; Cohort 2, <i>n</i> = 8302	(1) Taiwanese vegetarian diet is associated with a lower risk of ischemic and hemorrhagic strokes; (2) Shift in the gut microbial community to reduce the production of trimethylamine N-oxide; and (3) Consequent decrease in platelet hyperreactivity and thrombosis
D'Elia <i>et al</i> <sup>[49]</sup>	Meta-analysis	Pooled analysis of 14 cohorts (overall 333250 participants and 10659 events)	(1) An inverse and significant association between K intake and risk of stroke; and (2) Decreased blood pressure
Zhao <i>et al</i> <sup>[50]</sup>	Systematic review and meta-analysis	18 prospective cohort studies on Mg intake and the incidence of stroke	(1) Increasing Mg intake may be a crucial component of stroke prevention that acts in a dose-dependent manner; and (2) Improved cardiovascular health
Iacoviello <i>et al</i> <sup>[51]</sup>	Systematic review	Prospective studies that focused on primary prevention of stroke by nutrition	Nutrients, food groups and dietary patterns are effective in preventing stroke, such as: (1) Vitamin D, dairy calcium, folate (not supplementation), vitamin C, chocolate, coffee, tea, and the regular and moderate alcohol consumption; (2) Calcium and dairy intake are inversely associated with low-grade systemic inflammation; (3) Low-fat dairy and milk consumption decreased the incidence of hypertension; (4) Vitamin D involved in the modulation of the renin-angiotensin system, endothelial function, vascular smooth muscle proliferation, insulin sensitivity, and systemic inflammation; (5) Vitamin C, beta-carotene, and flavonoids are antioxidant compounds and can be reduce blood pressure and improve microvascular function; and (6) Chocolate intake resulted in increased HDL, decreased LDL oxidation, improved endothelial function and reduced blood pressure
Bousquet <i>et al</i> <sup>[52]</sup>	Review article	Role of diet in COVID-19 death rates	(1) Countries where the major daily intake originates from uncooked or fermented kale, cabbages, and fermented dairy products have lower COVID-19 death rates than the others; (2) Mentioned foods known as good sources for anti-ACE activity and rich in antioxidants; and (3) Improving high blood pressure and subsequent hemorrhagic stroke
Kalantar-Zadeh <i>et al</i> <sup>[20]</sup>	Perspective study	Impact of dietary patterns and the commensal microbiome on susceptibility to and severity of COVID-19	(1) A healthy, diverse, and balanced diet based on plants, high fiber, and fermented foods could be a preventative strategy, mitigating harmful effects of SARS-CoV-2; and (2) Probiotics can modulate the immune system, thereby reducing the susceptibility to affliction or morbidity and mortality from COVID-19
Tan <i>et al</i> <sup>[55]</sup>	Prospective observational study	AIS patients, <i>n</i> = 140; Healthy controls, <i>n</i> = 92	(1) Gut-brain axis has been brought to attention; (2) Probiotics and beneficial microbes exert beneficial alterations in the gut microbiome towards producing more SCFAs; (3) There was dysbiosis (low fecal SCFAs level) in AIS patients; and (4) The SCFAs' levels were negatively correlated with stroke severity and prognosis
Zabetakis <i>et al</i> <sup>[14]</sup>	Review article	Speculates on the importance of nutrition as a mitigation strategy to support immune function amid the COVID-19 pandemic	(1) A person's nutritional status, and nutrients and foods' intake, may exert anti-inflammatory and immunomodulatory effects; (2) Nutrients such as vitamin C, vitamin D, and zinc may hold some promise for the treatment of COVID-19; (3) Nutrients with anti-inflammatory, antithrombotic, and antioxidant properties may prevent or attenuate the inflammatory and vascular manifestations associated with COVID-19; and (4) It is vitally important to maintain a healthy diet and lifestyle during the pandemic
Kanki <i>et al</i> <sup>[56]</sup>	Animal study	Adult male C57BL6N mice included in two groups: NCD or HFD	(1) Mice with a HFD have higher levels of endogenous thrombin; (2) Thrombin was considered as a stimulator of PAR-1-based signaling; (3) PAR signaling involved in the neuroinflammatory complications; and (4) HFD mice experience larger infarcts and worse outcomes after stroke induction

Wallace <i>et al</i> <sup>[21]</sup>	Review article	Summary of clinical and prospective cohort studies assessing the relationship of Mg with IL-6, a prominent drug target for treating COVID-19	(1) Nutrition plays an important and safe role in helping mitigate patient morbidity and mortality from COVID-19; (2) Mg participates in the function of many enzymes involved in the severe immune and inflammatory responses that are manifestations of COVID-19; (3) Mg modulates IL-6, NF-κB, and CRP; (4) Mg enhances vitamin D functionality; (5) Mg is essential in preventing the serious consequences of COVID-19; (6) K restores ACE2 functionality; and (7) Hypokalemia is seen in most patients with severe and critical COVID-19
Rhodes <i>et al</i> <sup>[2]</sup>	Perspective study	Review of the evidence relevant to vitamin D and COVID-19	(1) Vitamin D has potential to reduce COVID-19 risk, severity, and mortality; (2) Inflammation and cytokine storm suppression; (3) Inverse modulatory role in the renin-angiotensin system; (4) Downregulating renin and increasing ACE2; and (5) Inverse association between serum level of vitamin D and anti-phospholipid antibodies
Infusino <i>et al</i> <sup>[57]</sup>	Scoping review	Nutraceuticals and supplements studied thus far on COVID-19	(1) Vitamin E, D and C, carotenoids, minerals (Zn, Mn, Cu, and Se), polyphenols, and curcumin have benefit; and (2) Anti-inflammatory, anticoagulant, antioxidant, binding to SARS-CoV-2 target receptor, and antiviral properties

ACE: Angiotensin-converting enzyme; AIS: Acute ischemic stroke; COVID-19: Coronavirus disease 2019; CRP: C-reactive protein; Cu: Copper; DASH: Dietary approaches to stop hypertension; HDL: High density lipoproteins; HFD: High fat diet; IL-6: Interleukin-6; K: Potassium; LDL: Low density lipoproteins; Med-diet: Mediterranean dietary pattern; Mg: Magnesium; Mn: Manganese; NCD: Normal diet; PAR: Protease-activated receptor; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SCFAs: Short-chain fatty acids; Se: Selenium; suppl: supplemented; Zn: Zinc.

fruits and vegetables that are associated with decreased blood pressure. Further, high fiber in whole grains is associated with lower total and low-density lipoprotein cholesterol. On the other hand, abundant flavonoids in apples, kale and broccoli are also related to a reduced risk of stroke<sup>[23]</sup>.

The next most examined dietary approach is the DASH diet, which includes a high intake of fruits, vegetables, whole grains, low-fat dairy, legumes, nuts, low sodium intake, sweetened beverages, and red/processed meat<sup>[22]</sup>. A meta-analysis of prospective studies by Feng *et al*<sup>[22]</sup> has shown that every 4-point increase in the score of adherence to the DASH diet reduces the risk of stroke in a dose-response manner by 4%. This is true for both ischemic and hemorrhagic strokes, although less data is available on the latter. Randomized clinical trials have also shown that adherence to this diet, in addition to lowering blood pressure, can reduce the stroke risk by improving lipid profile, controlling body weight, besides reducing the risk of type 2 diabetes and metabolic syndrome, all of which are important in the pathogenesis of stroke<sup>[41-45]</sup>. Another dietary pattern emphasized to be followed to prevent stroke is the Mediterranean diet. The PREDIMED study<sup>[46]</sup> with 7447 participants has found that adherence to the traditional Mediterranean diet, characterized by high consumption of olive oil, fruits, nuts, vegetables, and cereals, moderate intake of fish and poultry, low intake of dairy products, red meat, and processed/sweetened products, besides moderate consumption of wine, fortified with a mixture of nuts and virgin olive oil for a median of 4.8 years, could reduce the stroke risk by 40% compared to the control. The results of a recent meta-analysis have also shown that any 4-point increase in the score of adherence to the Mediterranean dietary pattern in both the Mediterranean and non-Mediterranean populations are significantly associated with a 14% and 17% reduction in the risk of ischemic and hemorrhagic stroke, respectively<sup>[25]</sup>. Although the Mediterranean dietary pattern, similar to the DASH, is not a low-sodium diet, following this diet high in potassium can probably lead to a reduction in dietary

sodium due to the less consumption of processed foods<sup>[25]</sup>.

A newly published cohort study by Chiu *et al.*<sup>[47]</sup> has demonstrated that a vegetarian diet reduces the risk of ischemic and hemorrhagic stroke, and higher serum levels of vitamin B12 weaken the relationship. Since a vegetarian diet is a meat- and egg-free diet, one of the proposed mechanisms is that the adherence to this diet could reduce substrates of intestinal microbiota to produce trimethylamine N-oxide, thus, reducing the platelet hyperactivation and thrombosis functions, and the risk of stroke, consequently<sup>[47]</sup>. In this study, vitamin B12 deficiency is in favor of a decrease in the incidence of stroke, while other studies are the opposite<sup>[48]</sup>.

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## SOME STUDIED MICRONUTRIENTS OR FOODS AND STROKE RISK

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A meta-analysis study has shown that potassium intake significantly inverses association with stroke risk. It is, therefore, recommended to consume potassium-rich foods to support cardiovascular health and prevent stroke<sup>[49]</sup>. The same relationship in a dose-response manner is true for dietary/supplemental magnesium and total stroke<sup>[50]</sup>. Moreover, stroke studies have rigorously recommended the protective effect of vitamin D on stroke incidence<sup>[51]</sup>. Further, other dietary components recommended in the context of stroke incidence have been listed in their work, among which, other than what we have said thus far, dairy calcium (not supplementation), folate (not supplementation), vitamin C, chocolate, coffee, tea, and the regular and moderate alcohol consumption (not alcohol abuse) are observed<sup>[51]</sup>. Due to controversy and lack of consensus, there is no recommendation for using B12, folate, and B6 to reduce the risk of stroke, and the results are uncertain<sup>[51]</sup>. Hence, more studies are needed in this regard.

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## HOW COULD DIETARY PATTERNS BE ATTRIBUTED TO COVID-19-ASSOCIATED STROKE RISK?

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A study has found that countries where the major daily intake originates from uncooked or fermented kale, cabbages, and fermented dairy products known as good sources for anti-ACE activity and rich in antioxidants have lower COVID-19 death rates than the others<sup>[52]</sup>. ACE converts angiotensin I to angiotensin II, while ACE2 does the opposite in the renin-angiotensin system<sup>[52]</sup>, in addition to being the entry point for SARS-CoV-2 into host cells as mentioned earlier<sup>[12,52]</sup>. Therefore, in the case of infection with SARS-CoV-2, ACE inhibitors may be effective in improving complications such as high blood pressure and subsequent hemorrhagic stroke<sup>[52]</sup>. The blood levels of ACE respond very quickly to food intake. Hence, dietary patterns can affect this enzyme levels; thus, it is suggested that a diet rich in saturated fatty acids increases ACE levels<sup>[52]</sup>.

Meanwhile, many functional foods are listed as ACE inhibitors and antioxidants<sup>[53,54]</sup>. A recent study has discussed that a healthy, diverse, and balanced diet based on plants, high fiber, and fermented foods rich in the beneficial probiotics, such as *Bifidobacteria* and *Lactobacilli* species, could be a preventative strategy, mitigating harmful effects of SARS-CoV-2<sup>[20]</sup>. Probiotics can modulate the immune system by controlling the gut microbiota, thereby reducing the susceptibility to affliction or morbidity and mortality from COVID-19<sup>[20]</sup>. Whereas following a high-fat diet and eating frequent snacks between meals can lead to dysbiosis. Therefore, its frequency should be kept to a minimum and often include fruits and vegetables<sup>[20]</sup>. In this respect, interestingly, Tan *et al.*<sup>[55]</sup> have described that the gut microbiome and the short-chain fatty acids (referred to here as SCFAs) produced by it could regulate brain functions in the path of the gut-brain axis, thus playing a major role in the prevention of stroke. In a study of 140 acute ischemic stroke patients compared with 92 healthy controls, the investigators observed dysbiosis and lower levels of fecal SCFAs in patients with acute ischemic stroke than in controls, finding an inverse relation to stroke severity and prognosis. Therefore, SCFAs are introduced as possible prognostic markers and potential targets for stroke remedy<sup>[55]</sup>.

Furthermore, interestingly, a few recent studies have discussed the Mediterranean diet and COVID-19<sup>[14]</sup>. This dietary pattern is anti-inflammatory; it is rich in bioactive components with anti-inflammatory and antioxidant properties and a variety of vitamins and trace elements but limited in processed foods<sup>[14]</sup>. Mechanisms involved in reducing stroke following adherence to the Mediterranean diet, which may also be

considered for COVID-19–associated stroke, include protection against inflammation, oxidative stress, platelet aggression, endothelial dysfunction, and a beneficial change in metabolites derived from intestinal microbiota that leads to cardiovascular health<sup>[25]</sup>. On the other hand, as one study suggested, therapeutic targeting of PAR could be promising in the management of COVID-19 neuroinflammatory complications<sup>[32]</sup>. In this regard, according to an animal study, mice with a high-fat diet have higher levels of endogenous thrombin compared to those with a normal diet, being considered as a model for stimulation of PAR-1-based signaling. Whereas,  $\beta$ -arrestin-2, unlike thrombin, has a positive effect on this signaling under ischemic stroke condition. High-fat diet mice experience larger infarcts and worse outcomes after stroke induction<sup>[56]</sup>. Therefore, it seems that the role of diet is also prominent in many signaling pathways related to COVID-19 neuroinflammatory complications. Thus, more human studies in this scope are essential.

Apart from nutritional recommendations, due to elevated IL-6 levels followed by a hyperviscosity state<sup>[6]</sup>, it seems necessary to maintain hydration and adequate fluid intake in COVID-19 patients. Altogether, this is important long before and immediately after the COVID-19 pandemic, since long-term and continuous following of these healthy dietary patterns, as said, can prevent or reduce comorbidities; this, in turn, may decrease predisposition to severe COVID-19 and, consequently, its worse complications, such as stroke.

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## HOW COULD SOME MICRONUTRIENTS OR FOODS BE ATTRIBUTED TO COVID-19–ASSOCIATED STROKE RISK?

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Some studies have shown the important role of potassium and magnesium in COVID-19. Since hypokalemia has been observed in most patients with severe and critical COVID-19<sup>[21]</sup>, potassium-rich foods might also play a supportive role in these patients. Magnesium is also important since it participates in the function of many enzymes involved in the severe immune and inflammatory responses that are manifestations of COVID-19. It, due to its modulator role involving IL-6, NF- $\kappa$ B, and CRP, besides its ability to activate and enhance the function of vitamin D, is essential in preventing the serious consequences of COVID-19 and reducing its morbidity and mortality<sup>[21]</sup>. In addition to vitamin D – which has been widely discussed due to potential to reduce COVID-19 risk, severity, and mortality *via* mechanisms including inflammation and cytokine storm suppression, besides the inverse modulatory role in the renin-angiotensin system by downregulating renin and increasing ACE2<sup>[2,21]</sup> – other nutrients, such as vitamins, minerals, and functional foods, have been discussed in the context of COVID-19. All of these components have also been studied separately concerning stroke. However, no study has ever considered them altogether to discuss their association with stroke as a life-threatening complication of COVID-19.

Some studies have shown that the prevalence of vitamin D deficiency is about 70% among patients with the anti-phospholipid syndrome with elevated levels of anti-phospholipid antibodies. Furthermore, antibodies' titers in healthy controls have been found to be lower in the summer season than in other months of the year<sup>[2]</sup>. This is a fascinating common point in parallel with studies that have shown increased levels of anti-phospholipid antibodies in COVID-19–associated stroke cases<sup>[6]</sup>. However, the causal relationship between vitamin D levels or supplementation and serum levels of anti-phospholipid antibodies and thrombotic events has not yet been established<sup>[2]</sup>. Some of the main nutraceuticals and supplements studied thus far on COVID-19 include vitamin E, vitamin D, vitamin C, carotenoids, minerals (Zn, Mn, Cu, and Se), polyphenols, and curcumin. Possible mechanisms of their positive effect on COVID-19 pathways have been proposed as anti-inflammatory, anticoagulant, antioxidant, capable of binding to the SARS-CoV-2 target receptor, and antiviral<sup>[57]</sup>.

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## CONSEQUENCES OF THE HYPOTHESIS

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The present hypothesis stated for the first time in the literature, to our knowledge, proposes a link between a healthy diet and COVID-19–associated stroke risk. Adherence to healthy dietary patterns and more consumption of some foods and nutrients in the recommended daily allowance has always been flagged as a prevention approach in chronic and acute conditions. Here, it is speculated that such a role of healthy nutrition can be highlighted once again in preventing COVID-

19-associated stroke too. Since no study to date has proven this, nutritional intake evaluations or food frequency questionnaire-based studies are strongly recommended in order to elicit uptake of or adherence to certain dietary patterns in COVID-19-associated stroke patients. Also, certain nutrients reported to be effective in common relief functions in stroke and COVID-19 pathways can be prescribed in trials for COVID-19 patients; then, the incidence of stroke among these individuals can be investigated prospectively. If the future data confirm our hypothesis, it means that healthy nutrition could be a protective/preventive factor against COVID-19-associated stroke risk.

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## CONCLUSION

Due to the significance of the current pandemic, many studies have paid attention to its consequent clinical outcomes. COVID-19 can be more severe in older patients or individuals with comorbidities, having dangerous consequences, including stroke. Adherence to healthy dietary patterns and more consumption of some foods and nutrients in the recommended daily allowance has always been emphasized as a prevention approach in chronic and acute conditions. However, it should be noted that the present study did not intend to give dietary advice to definite prevention of COVID-19-associated stroke. It only aimed to review the existing literature to evaluate the hypothesis stating that nutrition could be related to COVID-19 and its associated stroke. As far as we know, nutrition cannot be effective in preventing this crisis in the short time, but it can be found (from examining the history of dietary patterns and nutritional intake in patients with stroke or other serious COVID-19-associated complications) what is the difference between COVID-19 patients without serious complications or even in healthy population (by further nutritional intake evaluations or food frequency questionnaire-based studies). If the future studies confirm the present study's hypothesis (*i.e.* people who adhere to the healthy dietary patterns and habits are less likely to suffer from severe COVID-19-associated complications, such as stroke), the chronic supportive role of a healthy diet in critical situations will be highlighted once again.

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## REFERENCES

- 1 **Pascarella G**, Strumia A, Piliago C, Bruno F, Del Buono R, Costa F, Scarlata S, Agrò FE. COVID-19 diagnosis and management: a comprehensive review. *J Intern Med* 2020; **288**: 192-206 [PMID: 32348588 DOI: 10.1111/joim.13091]
- 2 **Rhodes JM**, Subramanian S, Laird E, Griffin G, Kenny RA. Perspective: Vitamin D deficiency and COVID-19 severity - plausibly linked by latitude, ethnicity, impacts on cytokines, ACE2 and thrombosis. *J Intern Med* 2020 [PMID: 32613681 DOI: 10.1111/joim.13149]
- 3 **Mao L**, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X, Li Y, Hu B. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol* 2020; **77**: 683-690 [PMID: 32275288 DOI: 10.1001/jamaneurol.2020.1127]
- 4 **Helms J**, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, Collange O, Boulay C, Fafi-Kremer S, Ohana M, Anheim M, Meziani F. Neurologic Features in Severe SARS-CoV-2 Infection. *N Engl J Med* 2020; **382**: 2268-2270 [PMID: 32294339 DOI: 10.1056/NEJMc2008597]
- 5 **Qureshi AI**, Abd-Allah F, Al-Senani F, Aytac E, Borhani-Haghighi A, Ciccone A, Gomez CR, Gurkas E, Hsu CY, Jani V, Jiao L, Kobayashi A, Lee J, Liaqat J, Mazighi M, Parthasarathy R, Miran MS, Steiner T, Toyoda K, Ribo M, Gongora-Rivera F, Oliveira-Filho J, Uzun G, Wang Y. Management of acute ischemic stroke in patients with COVID-19 infection: Insights from an international panel. *Am J Emerg Med* 2020; **38**: 1548.e5-1548. e7 [PMID: 32444298 DOI: 10.1016/j.ajem.2020.05.018]
- 6 **Tan YK**, Goh C, Leow AST, Tambyah PA, Ang A, Yap ES, Tu TM, Sharma VK, Yeo LLL, Chan BPL, Tan BYQ. COVID-19 and ischemic stroke: a systematic review and meta-summary of the literature. *J Thromb Thrombolysis* 2020; **50**: 587-595 [PMID: 32661757 DOI: 10.1007/s11239-020-02228-y]
- 7 **Zhao J**, Rudd A, Liu R. Challenges and Potential Solutions of Stroke Care During the Coronavirus Disease 2019 (COVID-19) Outbreak. *Stroke* 2020; **51**: 1356-1357 [PMID: 32228369 DOI: 10.1161/STROKEAHA.120.029701]
- 8 **Valderrama EV**, Humbert K, Lord A, Frontera J, Yaghi S. Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Ischemic Stroke. *Stroke* 2020; **51**: e124-e127 [PMID: 32396456 DOI: 10.1161/STROKEAHA.120.030153]
- 9 **Wang H**, Tang X, Fan H, Luo Y, Song Y, Xu Y, Chen Y. Potential mechanisms of hemorrhagic stroke in elderly COVID-19 patients. *Aging (Albany NY)* 2020; **12**: 10022-10034 [PMID: 32527987]

- DOI: [10.18632/aging.103335](https://doi.org/10.18632/aging.103335)]
- 10 **Oxley TJ**, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, De Leacy RA, Shigematsu T, Ladner TR, Yaeger KA, Skliut M, Weinberger J, Dangayach NS, Bederson JB, Tuhim S, Fifi JT. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. *N Engl J Med* 2020; **382**: e60 [PMID: [32343504](https://pubmed.ncbi.nlm.nih.gov/32343504/) DOI: [10.1056/NEJMc2009787](https://doi.org/10.1056/NEJMc2009787)]
  - 11 **Zaki N**, Alashwal H, Ibrahim S. Association of hypertension, diabetes, stroke, cancer, kidney disease, and high-cholesterol with COVID-19 disease severity and fatality: A systematic review. *Diabetes Metab Syndr* 2020; **14**: 1133-1142 [PMID: [32663789](https://pubmed.ncbi.nlm.nih.gov/32663789/) DOI: [10.1016/j.dsx.2020.07.005](https://doi.org/10.1016/j.dsx.2020.07.005)]
  - 12 **Wiersinga WJ**, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA* 2020; **324**: 782-793 [PMID: [32648899](https://pubmed.ncbi.nlm.nih.gov/32648899/) DOI: [10.1001/jama.2020.12839](https://doi.org/10.1001/jama.2020.12839)]
  - 13 **Laviano A**, Koverech A, Zanetti M. Nutrition support in the time of SARS-CoV-2 (COVID-19). *Nutrition* 2020; **74**: 110834 [PMID: [32276799](https://pubmed.ncbi.nlm.nih.gov/32276799/) DOI: [10.1016/j.nut.2020.110834](https://doi.org/10.1016/j.nut.2020.110834)]
  - 14 **Zabetakis I**, Lordan R, Norton C, Tsoupras A. COVID-19: The Inflammation Link and the Role of Nutrition in Potential Mitigation. *Nutrients* 2020; **12** [PMID: [32438620](https://pubmed.ncbi.nlm.nih.gov/32438620/) DOI: [10.3390/nu12051466](https://doi.org/10.3390/nu12051466)]
  - 15 **Kim SW**, Su KP. Using psychoneuroimmunity against COVID-19. *Brain Behav Immun* 2020; **87**: 4-5 [PMID: [32234338](https://pubmed.ncbi.nlm.nih.gov/32234338/) DOI: [10.1016/j.bbi.2020.03.025](https://doi.org/10.1016/j.bbi.2020.03.025)]
  - 16 **Demasi M**. COVID-19 and metabolic syndrome: could diet be the key? *BMJ Evid Based Med* 2020 [PMID: [32651302](https://pubmed.ncbi.nlm.nih.gov/32651302/) DOI: [10.1136/bmjebm-2020-111451](https://doi.org/10.1136/bmjebm-2020-111451)]
  - 17 **Kastorini CM**, Milionis HJ, Esposito K, Giugliano D, Goudevenos JA, Panagiotakos DB. The effect of Mediterranean diet on metabolic syndrome and its components: a meta-analysis of 50 studies and 534,906 individuals. *J Am Coll Cardiol* 2011; **57**: 1299-1313 [PMID: [21392646](https://pubmed.ncbi.nlm.nih.gov/21392646/) DOI: [10.1016/j.jacc.2010.09.073](https://doi.org/10.1016/j.jacc.2010.09.073)]
  - 18 **Nugent R**, Bertram MY, Jan S, Niessen LW, Sassi F, Jamison DT, Pier EG, Beaglehole R. Investing in non-communicable disease prevention and management to advance the Sustainable Development Goals. *Lancet* 2018; **391**: 2029-2035 [PMID: [29627167](https://pubmed.ncbi.nlm.nih.gov/29627167/) DOI: [10.1016/S0140-6736\(18\)30667-6](https://doi.org/10.1016/S0140-6736(18)30667-6)]
  - 19 **Ciavarella C**, Motta I, Valente S, Pasquinelli G. Pharmacological (or Synthetic) and Nutritional Agonists of PPAR- $\gamma$  as Candidates for Cytokine Storm Modulation in COVID-19 Disease. *Molecules* 2020; **25** [PMID: [32365556](https://pubmed.ncbi.nlm.nih.gov/32365556/) DOI: [10.3390/molecules25092076](https://doi.org/10.3390/molecules25092076)]
  - 20 **Kalantar-Zadeh K**, Ward SA, Kalantar-Zadeh K, El-Omar EM. Considering the Effects of Microbiome and Diet on SARS-CoV-2 Infection: Nanotechnology Roles. *ACS Nano* 2020; **14**: 5179-5182 [PMID: [32356654](https://pubmed.ncbi.nlm.nih.gov/32356654/) DOI: [10.1021/acsnano.0c03402](https://doi.org/10.1021/acsnano.0c03402)]
  - 21 **Wallace TC**. Combating COVID-19 and Building Immune Resilience: A Potential Role for Magnesium Nutrition? *J Am Coll Nutr* 2020; **39**: 685-693 [PMID: [32649272](https://pubmed.ncbi.nlm.nih.gov/32649272/) DOI: [10.1080/07315724.2020.1785971](https://doi.org/10.1080/07315724.2020.1785971)]
  - 22 **Feng Q**, Fan S, Wu Y, Zhou D, Zhao R, Liu M, Song Y. Adherence to the dietary approaches to stop hypertension diet and risk of stroke: A meta-analysis of prospective studies. *Medicine (Baltimore)* 2018; **97**: e12450 [PMID: [30235731](https://pubmed.ncbi.nlm.nih.gov/30235731/) DOI: [10.1097/MD.00000000000012450](https://doi.org/10.1097/MD.00000000000012450)]
  - 23 **Hansen CP**, Overvad K, Kyro C, Olsen A, Tjønneland A, Johnsen SP, Jakobsen MU, Dahm CC. Adherence to a Healthy Nordic Diet and Risk of Stroke: A Danish Cohort Study. *Stroke* 2017; **48**: 259-264 [PMID: [28049735](https://pubmed.ncbi.nlm.nih.gov/28049735/) DOI: [10.1161/STROKEAHA.116.015019](https://doi.org/10.1161/STROKEAHA.116.015019)]
  - 24 **Estruch R**, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventós RM, Serra-Majem L, Pintó X, Basora J, Muñoz MA, Sorlí JV, Martínez JA, Martínez-González MA; PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013; **368**: 1279-1290 [PMID: [23432189](https://pubmed.ncbi.nlm.nih.gov/23432189/) DOI: [10.1056/NEJMoa1200303](https://doi.org/10.1056/NEJMoa1200303)]
  - 25 **Chen GC**, Neelakantan N, Martín-Calvo N, Koh WP, Yuan JM, Bonaccio M, Iacoviello L, Martínez-González MA, Qin LQ, van Dam RM. Adherence to the Mediterranean diet and risk of stroke and stroke subtypes. *Eur J Epidemiol* 2019; **34**: 337-349 [PMID: [30826941](https://pubmed.ncbi.nlm.nih.gov/30826941/) DOI: [10.1007/s10654-019-00504-7](https://doi.org/10.1007/s10654-019-00504-7)]
  - 26 **Bhaskar S**, Sinha A, Banach M, Mittoo S, Weissert R, Kass JS, Rajagopal S, Pai AR, Kutty S. Cytokine Storm in COVID-19-Immunopathological Mechanisms, Clinical Considerations, and Therapeutic Approaches: The REPROGRAM Consortium Position Paper. *Front Immunol* 2020; **11**: 1648 [PMID: [32754159](https://pubmed.ncbi.nlm.nih.gov/32754159/) DOI: [10.3389/fimmu.2020.01648](https://doi.org/10.3389/fimmu.2020.01648)]
  - 27 **Varga Z**, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; **395**: 1417-1418 [PMID: [32325026](https://pubmed.ncbi.nlm.nih.gov/32325026/) DOI: [10.1016/S0140-6736\(20\)30937-5](https://doi.org/10.1016/S0140-6736(20)30937-5)]
  - 28 **Ackermann M**, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, Li WW, Li VW, Mentzer SJ, Jonigk D. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med* 2020; **383**: 120-128 [PMID: [32437596](https://pubmed.ncbi.nlm.nih.gov/32437596/) DOI: [10.1056/NEJMoa2015432](https://doi.org/10.1056/NEJMoa2015432)]
  - 29 **Bova IY**, Bornstein NM, Korczyn AD. Acute infection as a risk factor for ischemic stroke. *Stroke* 1996; **27**: 2204-2206 [PMID: [8969781](https://pubmed.ncbi.nlm.nih.gov/8969781/) DOI: [10.1161/01.str.27.12.2204](https://doi.org/10.1161/01.str.27.12.2204)]
  - 30 **Cowan LT**, Alonso A, Pankow JS, Folsom AR, Rosamond WD, Gottesman RF, Lakshminarayanan K. Hospitalized Infection as a Trigger for Acute Ischemic Stroke: The Atherosclerosis Risk in Communities Study. *Stroke* 2016; **47**: 1612-1617 [PMID: [27165961](https://pubmed.ncbi.nlm.nih.gov/27165961/) DOI: [10.1161/STROKEAHA.116.012890](https://doi.org/10.1161/STROKEAHA.116.012890)]
  - 31 **Rothstein A**, Oldridge O, Schwennesen H, Do D, Cucchiara BL. Acute Cerebrovascular Events in Hospitalized COVID-19 Patients. *Stroke* 2020; **51**: e219-e222 [PMID: [32684145](https://pubmed.ncbi.nlm.nih.gov/32684145/) DOI: [10.1161/STROKEAHA.116.012890](https://doi.org/10.1161/STROKEAHA.116.012890)]

- 10.1161/STROKEAHA.120.030995]
- 32 **Lyden PD.** Stroke, Research and Science in the Time of COVID. *Stroke* 2020; **51**: 2613-2614 [PMID: 32755344 DOI: 10.1161/STROKEAHA.120.031354]
  - 33 **Chen G,** Wu D, Guo W, Cao Y, Huang D, Wang H, Wang T, Zhang X, Chen H, Yu H, Zhang X, Zhang M, Wu S, Song J, Chen T, Han M, Li S, Luo X, Zhao J, Ning Q. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* 2020; **130**: 2620-2629 [PMID: 32217835 DOI: 10.1172/JCI137244]
  - 34 **Thachil J,** Tang N, Gando S, Falanga A, Cattaneo M, Levi M, Clark C, Iba T. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost* 2020; **18**: 1023-1026 [PMID: 32338827 DOI: 10.1111/jth.14810]
  - 35 **Ntaios G,** Michel P, Georgiopoulos G, Guo Y, Li W, Xiong J, Calleja P, Ostos F, González-Ortega G, Fuentes B, Alonso de Leciñana M, Diez-Tejedor E, García-Madrona S, Masjuan J, DeFelipe A, Turc G, Gonçalves B, Domingo V, Dan GA, Vezeteu R, Christensen H, Christensen LM, Meden P, Hajdarevic L, Rodriguez-Lopez A, Díaz-Otero F, García-Pastor A, Gil-Núñez A, Maslias E, Strambo D, Werring DJ, Chandratheva A, Benjamin L, Simister R, Perry R, Beyroui R, Jabbour P, Sweid A, Tjoumakaris S, Cuadrado-Godía E, Campello AR, Roquer J, Moreira T, Mazya MV, Bandini F, Matz K, Iversen HK, González-Duarte A, Tiu C, Ferrari J, Vosko MR, Salzer HJF, Lamprecht B, Dünser MW, Cereda CW, Quintero ABC, Korompoki E, Soriano-Navarro E, Soto-Ramírez LE, Castañeda-Méndez PF, Bay-Sansores D, Arauz A, Cano-Nigenda V, Kristoffersen ES, Tiainen M, Strbian D, Putaala J, Lip GYH. Characteristics and Outcomes in Patients With COVID-19 and Acute Ischemic Stroke: The Global COVID-19 Stroke Registry. *Stroke* 2020; **51**: e254-e258 [PMID: 32787707 DOI: 10.1161/STROKEAHA.120.031208]
  - 36 **Feigin VL,** Roth GA, Naghavi M, Parmar P, Krishnamurthi R, Chugh S, Mensah GA, Norrving B, Shiue I, Ng M, Estep K, Cercy K, Murray CJL, Forouzanfar MH; Global Burden of Diseases, Injuries and Risk Factors Study 2013 and Stroke Experts Writing Group. Global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet Neurol* 2016; **15**: 913-924 [PMID: 27291521 DOI: 10.1016/S1474-4422(16)30073-4]
  - 37 **O'Donnell MJ,** Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, Rangarajan S, Islam S, Pais P, McQueen MJ, Mondo C, Damasceno A, Lopez-Jaramillo P, Hankey GJ, Dans AL, Yusuf K, Truelsen T, Diener HC, Sacco RL, Ryglewicz D, Czlonkowska A, Weimar C, Wang X, Yusuf S; INTERSTROKE investigators. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet* 2010; **376**: 112-123 [PMID: 20561675 DOI: 10.1016/S0140-6736(10)60834-3]
  - 38 **Poulsen SK,** Due A, Jordy AB, Kiens B, Stark KD, Stender S, Holst C, Astrup A, Larsen TM. Health effect of the New Nordic Diet in adults with increased waist circumference: a 6-mo randomized controlled trial. *Am J Clin Nutr* 2014; **99**: 35-45 [PMID: 24257725 DOI: 10.3945/ajcn.113.069393]
  - 39 **Adamsson V,** Reumark A, Fredriksson IB, Hammarström E, Vessby B, Johansson G, Risérus U. Effects of a healthy Nordic diet on cardiovascular risk factors in hypercholesterolaemic subjects: a randomized controlled trial (NORDIET). *J Intern Med* 2011; **269**: 150-159 [PMID: 20964740 DOI: 10.1111/j.1365-2796.2010.02290.x]
  - 40 **Uusitupa M,** Hermansen K, Savolainen MJ, Schwab U, Kolehmainen M, Brader L, Mortensen LS, Cloetens L, Johansson-Persson A, Onning G, Landin-Olsson M, Herzig KH, Hukkanen J, Rosqvist F, Iggman D, Paananen J, Pulkki KJ, Siloaho M, Dragsted L, Barri T, Overvad K, Bach Knudsen KE, Hedemann MS, Arner P, Dahlman I, Borge GI, Baardseth P, Ulven SM, Gunnarsdottir I, Jónsdóttir S, Thorsdóttir I, Orešič M, Poutanen KS, Risérus U, Akesson B. Effects of an isocaloric healthy Nordic diet on insulin sensitivity, lipid profile and inflammation markers in metabolic syndrome -- a randomized study (SYSDIET). *J Intern Med* 2013; **274**: 52-66 [PMID: 23398528 DOI: 10.1111/joim.12044]
  - 41 **Obarzanek E,** Sacks FM, Vollmer WM, Bray GA, Miller ER 3rd, Lin PH, Karanja NM, Most-Windhauser MM, Moore TJ, Swain JF, Bales CW, Proschan MA; DASH Research Group. Effects on blood lipids of a blood pressure-lowering diet: the Dietary Approaches to Stop Hypertension (DASH) Trial. *Am J Clin Nutr* 2001; **74**: 80-89 [PMID: 11451721 DOI: 10.1093/ajcn/74.1.80]
  - 42 **Soltani S,** Shirani F, Chitsazi MJ, Salehi-Abargouei A. The effect of dietary approaches to stop hypertension (DASH) diet on weight and body composition in adults: a systematic review and meta-analysis of randomized controlled clinical trials. *Obes Rev* 2016; **17**: 442-454 [PMID: 26990451 DOI: 10.1111/obr.12391]
  - 43 **Schwingshackl L,** Bogensberger B, Hoffmann G. Diet Quality as Assessed by the Healthy Eating Index, Alternate Healthy Eating Index, Dietary Approaches to Stop Hypertension Score, and Health Outcomes: An Updated Systematic Review and Meta-Analysis of Cohort Studies. *J Acad Nutr Diet* 2018; **118**: 74-100. e11 [PMID: 29111090 DOI: 10.1016/j.jand.2017.08.024]
  - 44 **Pimenta AM,** Toledo E, Rodriguez-Diez MC, Gea A, Lopez-Iracheta R, Shivappa N, Hébert JR, Martínez-González MA. Dietary indexes, food patterns and incidence of metabolic syndrome in a Mediterranean cohort: The SUN project. *Clin Nutr* 2015; **34**: 508-514 [PMID: 24975512 DOI: 10.1016/j.clnu.2014.06.002]
  - 45 **Gupta AK,** Dahlof B, Sever PS, Poulter NR; Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm Investigators. Metabolic syndrome, independent of its components, is a risk factor for stroke and death but not for coronary heart disease among hypertensive patients in the ASCOT-BPLA. *Diabetes Care* 2010; **33**: 1647-1651 [PMID: 20413525 DOI: 10.2337/dc09-2208]

- 46 **Estruch R**, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventós RM, Serra-Majem L, Pintó X, Basora J, Muñoz MA, Sorlí JV, Martínez JA, Fitó M, Gea A, Hernán MA, Martínez-González MA; PREDIMED Study Investigators. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. *N Engl J Med* 2018; **378**: e34 [PMID: 29897866 DOI: 10.1056/NEJMoa1800389]
- 47 **Chiu THT**, Chang HR, Wang LY, Chang CC, Lin MN, Lin CL. Vegetarian diet and incidence of total, ischemic, and hemorrhagic stroke in 2 cohorts in Taiwan. *Neurology* 2020; **94**: e1112-e1121 [PMID: 32102976 DOI: 10.1212/WNL.0000000000009093]
- 48 **Qin X**, Spence JD, Li J, Zhang Y, Li Y, Sun N, Liang M, Song Y, Zhang Y, Wang B, Cheng X, Zhao L, Wang X, Xu X, Huo Y. Interaction of serum vitamin B<sub>12</sub> and folate with *MTHFR* genotypes on risk of ischemic stroke. *Neurology* 2020; **94**: e1126-e1136 [PMID: 31932513 DOI: 10.1212/WNL.0000000000008932]
- 49 **D'Elia L**, Iannotta C, Sabino P, Ippolito R. Potassium-rich diet and risk of stroke: updated meta-analysis. *Nutr Metab Cardiovasc Dis* 2014; **24**: 585-587 [PMID: 24780514 DOI: 10.1016/j.numecd.2014.03.001]
- 50 **Zhao B**, Hu L, Dong Y, Xu J, Wei Y, Yu D, Xu J, Zhang W. The Effect of Magnesium Intake on Stroke Incidence: A Systematic Review and Meta-Analysis With Trial Sequential Analysis. *Front Neurol* 2019; **10**: 852 [PMID: 31447767 DOI: 10.3389/fneur.2019.00852]
- 51 **Iacoviello L**, Bonaccio M, Cairella G, Catani MV, Costanzo S, D'Elia L, Giacco R, Rendina D, Sabino P, Savini I, Strazzullo P; Working Group for Nutrition and Stroke. Diet and primary prevention of stroke: Systematic review and dietary recommendations by the ad hoc Working Group of the Italian Society of Human Nutrition. *Nutr Metab Cardiovasc Dis* 2018; **28**: 309-334 [PMID: 29482962 DOI: 10.1016/j.numecd.2017.12.010]
- 52 **Bousquet J**, Anto JM, Iaccarino G, Czarlewski W, Haahtela T, Anto A, Akdis CA, Blain H, Canonica GW, Cardona V, Cruz AA, Illario M, Ivancevich JC, Jutel M, Klimek L, Kuna P, Laune D, Larenas-Linnemann D, Mullol J, Papadopoulos NG, Pfaar O, Samolinski B, Valiulis A, Yorgancioglu A, Zuberbier T; ARIA group. Is diet partly responsible for differences in COVID-19 death rates between and within countries? *Clin Transl Allergy* 2020; **10**: 16 [PMID: 32499909 DOI: 10.1186/s13601-020-00323-0]
- 53 **Iwaniak A**, Minkiewicz P, Darewicz M. Food-originating ACE inhibitors, including antihypertensive peptides, as preventive food components in blood pressure reduction. *Comprehens Rev Food Sc Food Safety* 2014; **13**: 111-134 [DOI: 10.1111/1541-4337.12051]
- 54 **Ganguly A**, Sharma K, Majumder K. Food-derived bioactive peptides and their role in ameliorating hypertension and associated cardiovascular diseases. *Adv Food Nutr Res* 2019; **89**: 165-207 [PMID: 31351525 DOI: 10.1016/bs.afnr.2019.04.001]
- 55 **Tan C**, Wu Q, Wang H, Gao X, Xu R, Cui Z, Zhu J, Zeng X, Zhou H, He Y, Yin J. Dysbiosis of Gut Microbiota and Short-Chain Fatty Acids in Acute Ischemic Stroke and the Subsequent Risk for Poor Functional Outcomes. *JPEN J Parenter Enteral Nutr* 2020 [PMID: 32473086 DOI: 10.1002/jpen.1861]
- 56 **Kanki H**, Sasaki T, Matsumura S, Yokawa S, Yukami T, Shimamura M, Sakaguchi M, Furuno T, Suzuki T, Mochizuki H.  $\beta$ -arrestin-2 in PAR-1-biased signaling has a crucial role in endothelial function via PDGF- $\beta$  in stroke. *Cell Death Dis* 2019; **10**: 100 [PMID: 30718498 DOI: 10.1038/s41419-019-1375-x]
- 57 **Infusino F**, Marazzato M, Mancone M, Fedele F, Mastroianni CM, Severino P, Ceccarelli G, Santinelli L, Cavarretta E, Marullo AGM, Miraldi F, Carnevale R, Nocella C, Biondi-Zoccai G, Pagnini C, Schiavon S, Pugliese F, Frati G, d'Ettore G. Diet Supplementation, Probiotics, and Nutraceuticals in SARS-CoV-2 Infection: A Scoping Review. *Nutrients* 2020; **12** [PMID: 32521760 DOI: 10.3390/nu12061718]



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