

COVID-19 prevention

What is known about supplements, medications and metabolic risk factors?

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We've noticed that some supermarkets have sold out of high-dose vitamin C, and pharmacists tell us that herbal antiviral supplements and other immunity aids, like Buccaline Berna (an oral vaccine against common bacterial complications of colds and flu) are in high demand. In this fact-sheet we'll answer some of your questions around COVID-19 prevention and risk:

- What is the evidence for supplements in the prevention and treatment of COVID-19?
- What is the evidence around metabolic risk factors?
- Is there any evidence that commonly used medications increase risk?

Initial versus delayed immune response

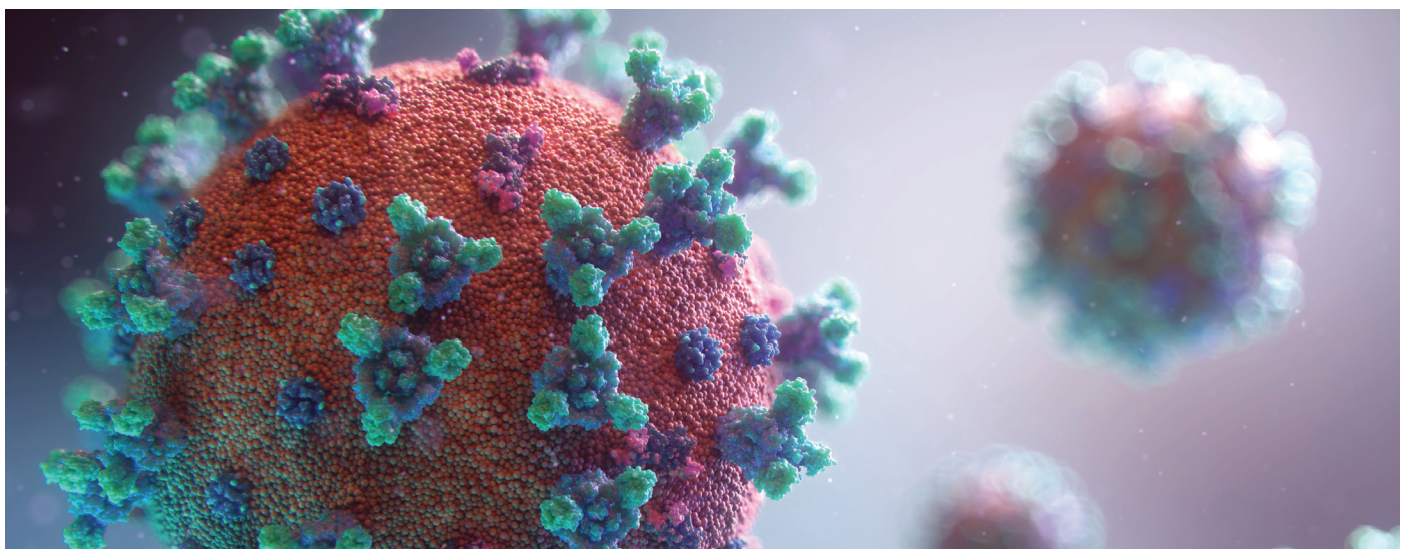
Straight up, it needs to be stated that COVID-19 is a new virus, with some specific features. Not everything that applies to previous colds, flus or pneumonial diseases may apply. So all older

evidence needs to be evaluated carefully. But the pattern so far is characteristic of other pandemics; people with no or light symptoms seem to have had a strong initial immune response and are producing antibodies to COVID-19. Here is a COVID-19 immunological case study of a mild infection, which concludes:

“our study indicates that robust multi-factorial immune responses can be elicited to the newly emerged virus SARS-CoV-2 and, similar to the avian H7N9 disease, early adaptive immune responses might correlate with better clinical outcomes.”

<https://www.nature.com/articles/s41591-020-0819-2.pdf?fbclid=IwAR0Lb6ogephv7nsla-sgkGY>

Life-threatening symptoms seem to involve a problem in the lungs where cells producing pulmonary surfactant (Type II alveolar epithelial cells) are damaged by the virus and reduce normal lung function.



Metabolic risk factors

What is emerging from published data so far is the importance of metabolic risk factors in predicting outcomes. To some extent this is expected, because people with metabolic syndromes have lowered immunity and are taking medications that may potentially increase risk. So to what extent are these associations likely to be causal?

In Wuhan, patients who did not develop Acute Respiratory Distress Syndrome (ARDS) had mean glucose (tested on admission, so random but eating may not have been a priority by then) of 5.40 mmol/l, whereas those who did develop ARDS had a glucose level of 7.40 mmol/l. Blood glucose level in those who developed ARDS was not associated with risk of death.

Those who did not develop ARDS had a mean LDL level of 2.16 mM, vs 1.88 mM in patients who did develop ARDS. P-value for this association was 0.007.

	Did not develop ARDS	Developed ARDS
Glucose	5.40 mmol/l	7.40 mmol/l
LDL	2.16 mM	1.88 mM

Among those who developed ARDS, those who survived had LDL 2.00 mM, vs 1.67 mM in those who died, this was not significant.

<https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2763184>

	Developed ARDS, survived	Developed ARDS, died
LDL	2.00 mM	1.67 mM

Why are these associations likely to be causal? High glucose glycosylates haemoglobin and emerging evidence from virologists is that COVID-19 disrupts haemoglobin for its own purposes and that this is an important feature of COVID-19 pathology, explaining the association (quite apart from the known immunosuppressive effect of high glucose). https://chemrxiv.org/articles/COVID-19_Disease_ORF8_and_Surface_Glycoprotein_Inhibit_Heme_Metabolism_by_Binding_to_Porphyrin/11938173

It is a common epidemiological finding that, "Mortality from cancer and infection was significantly lower among the participants in the highest total cholesterol category" in elderly people.

<https://www.sciencedirect.com/science/article/pii/S0140673697044309>

New research from Glytec, the main supplier of diabetes software in the US, suggests that in-hospital mortality is more than quadrupled in COVID-19 patients with diabetes and hyperglycemia.

"People with diabetes who have not yet been infected with the SARS-CoV-2 virus [which causes COVID-19] should intensify their metabolic control as needed as means of primary prevention of COVID-19 disease," according to expert panel guidance in the *Lancet Diabetes & Endocrinology*.

HDL a marker of respiratory fitness

An emerging risk factor seems to be HDL cholesterol, which has causal links to respiratory fitness, in this pre-print study of cases in three hospitals.

Fasting hypoglycaemia was found in 21.4% of patients in mild 1 (14-day recovery) group with no case of fasting hyperglycaemia. In the mild 2 (30 day recovery) group, 34.1% of the patients had fasting hypoglycaemia, and 2.3% had fasting hyperglycaemia. Compared with mild COVID-19 patients, we found that 24% of severe COVID-19 patients had fasting hyperglycaemia and 4% had fasting hypoglycaemia.

"Patients in the severe group had a lower level of serum total protein (59[58–63] vs. 65[63–70]), serum albumin (36[34–39] vs. 41[37–43]), total cholesterol (3.6[3.3–4.0] vs. 3.8[3.5–4.4]), and HDL-C (0.88[0.81–1.10] vs. 1.05[0.93–1.50]) compared with the mild 1 group."

<https://www.medrxiv.org/content/10.1101/2020.03.24.20042283v1.full.pdf>

The difference in HDL cholesterol is more significant than that in total cholesterol, and is more likely to be causal. Why? Because HDL cholesterol is a marker of respiratory fitness, and ApoA1 is causal in lung health; it is involved

in both the antioxidant protection of lung cells, and the lung's immune function, which relies on "reverse cholesterol transport"-type movement of cholesterol.

"Apolipoprotein A-I (apoA-I) and high-density lipoproteins (HDL) mediate reverse cholesterol transport out of cells. Furthermore, HDL has additional protective functions, which include anti-oxidative, anti-inflammatory, anti-apoptotic, and vasoprotective effects. In contrast, HDL can become dysfunctional with a reduction in both cholesterol efflux and anti-inflammatory properties in the setting of disease or the acute phase response. These paradigms are increasingly being recognized to be active in the pulmonary system, where apoA-I and HDL have protective effects in normal lung health, as well as in a variety of disease states, including acute lung injury (ALI), asthma, chronic obstructive pulmonary disease, lung cancer, pulmonary arterial hypertension, pulmonary fibrosis, and viral pneumonia. Similar to observations in cardiovascular disease, however, HDL may become dysfunctional and contribute to disease pathogenesis in respiratory disorders."

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5030281/>

Lifestyle changes reduce risk of ARDS

Whatever the truth, this is probably not a time to worry about high cholesterol!

<https://bmjopen.bmj.com/content/6/6/e010401So>

We can have a fairly high confidence that people with metabolic diseases who have improved their glucose, HbA1c, and TG/HDL towards normal or near-normal levels by changes in diet, fasting, exercise and so on will be at a reduced risk of ARDS or death from COVID-19 infection. And if their blood pressure has also improved, this may also be protective.

So what we know will definitely help are hand washing, social isolation, and not touching your mouth, eyes, nose. Prioritising sleep, good nutrition, sunlight, stress reduction, and exercise will also help to maximise your immune system's capacity.

There is only limited or moderate evidence for the following:

Medications of concern

ACE inhibitors

The death rate is high in people with hypertension and in other categories likely to be prescribed hypertensives. The ACE inhibitors are a common type of antihypertensive. They inhibit the ACE2 receptor, and this inhibition is thought to cause an increase in expression of the ACE2 receptor. The ACE2 receptor is the main way COVID-19 gets into cells. ACE inhibitors cause or aggravate coughing in some people; in previous epidemiological studies their use is actually associated with lower rates of pneumonia, but this may be because the side effect discourages people with pre-existing respiratory disease from using them. It currently looks as if ACE inhibitors are not as dangerous as first thought, but people who have had ACE inhibitors deprescribed because they were able to lower blood pressure without them have one less thing to worry about. People who still need to take ACE inhibitors for severe hypertension may suffer serious events without them, and shouldn't discontinue their use unless advised by their doctor, but may need to take even more care to avoid infection than the rest of us.

[https://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(20\)30116-8/fulltext](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30116-8/fulltext)

Ibuprofen and paracetamol

The French Health Minister has warned that young people who have developed severe COVID-19 symptoms are more likely to be using Ibuprofen (an NSAID) to control fever. He recommends paracetamol instead, but we need to look at the totality of the evidence – there has been no human RCT of any antipyretic that includes pneumonia mortality data. In animal models of influenza, all NSAIDs increase mortality by 37%.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951171/>

Children given paracetamol with a vaccine had significantly lower antibody concentrations – this is not a desirable result if you are exposed to COVID-19.

<https://www.ncbi.nlm.nih.gov/pubmed/19837254>



So, convenient and popular as these drugs are, it is unclear how beneficial they are for the treatment of COVID-19. We know that if you are already taking these medications, then you should not stop taking them without medical advice. We also know that some fever is beneficial for the immune response against many viral infections, but that a high fever (> 40.6 degrees Celsius) increases the risks of other complications, including brain damage. So a sensible approach might be not to use paracetamol unnecessarily, especially early in the course of infection, and if possible only use it to manage severe fevers.

Statins

There is not a lot of evidence around statins yet, perhaps because almost everyone at high risk is using them. Statins do not decrease, and fibrates increase, ApoA1 levels, which is good news.

Supplements

If you are taking a prescribed medication talk to your doctor or pharmacist about whether any supplements can interact with it.

Vitamin C

High-dose intravenous vitamin C for the symptomatic is now the subject of more than one registered COVID-19 trial, and is included in one of many official protocols from China. A preliminary report appears here.

<http://orthomolecular.org/resources/omns/v16n18.shtml>

We should have published evidence on this soon, but this will not tell us the answer to three other important questions:

- Does oral vitamin C reduce the rate of infections?
- Does it reduce the severity of symptoms in the affected?
- Does self-medication prevent progression to pneumonia?

What evidence there is comes from two Cochrane meta-analyses, one for colds and flu and one for pneumonia.

<https://www.ncbi.nlm.nih.gov/pubmed/23440782>

<https://www.ncbi.nlm.nih.gov/pubmed/23925826>

In these it appears that vitamin C can reduce infection and the risk of pneumonia by a small (but worthwhile) amount. But the studies are few and heterogenous, and the results are inconsistent.

Given these limitations, odds may be 50/50 that the effect seen is a real one. On the other hand, they are intention-to-treat trials, and if the effect is real it may be underestimated (some people forget to take pills). And there is zero evidence for vitamin C making things worse.

There is evidence showing people with pneumonia having lower vitamin C levels, and vitamin C supplements have been shown to reduce recovery time. Vitamin C is an antioxidant that plays a major role in pulmonary defence.

<https://www.ncbi.nlm.nih.gov/pubmed/15139458>

<https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005532.pub3/full>

Vitamin C is best absorbed in a lipospheric form (vitamin C is bound to fat droplets), but these supplements can be expensive, whereas others (non-lipospheric bound) are cheap. All in all, we see no harm, but possible benefit in taking vitamin C. Don't forget about food-based sources though, making sure you consume plenty of vegetables, such as broccoli, green leafy vegetables, peppers, brussel sprouts, potatoes (not too many) and some fruit (kiwifruit, berries, oranges).



Elderberry extracts

Another popular supplement is Sambucol (standardised elderberry juice extract) and pills that usually contain a mixture of elderberry, echinacea, andrographis, olive leaf extract or similar.

These herbal extracts boost the innate immune response. Sceptics are saying, “you cannot tweak your immune system”, but this claim is nonsense. We saw above that paracetamol decreases the response to vaccines – an (adverse) immune tweak. Vaccines not only contain antigenic material that directly stimulates the production of specific antibodies and specific B-cell memory, they also contain adjuvants – compounds that, by stimulating a non-specific innate immunity response, ensure that the antigenic part of the vaccine is noticed and remembered by the B-cells. These adjuvants could be made from certain herbal extracts that have a similar effect if that pathway was cost-effective.

Elderberry extracts have been tested for the prevention of influenza and significantly reduce its severity and duration.

<https://www.ncbi.nlm.nih.gov/pubmed/9395631>

<https://www.ncbi.nlm.nih.gov/pubmed/15080016>

<https://www.ncbi.nlm.nih.gov/pubmed/9395631>

The effect of echinacea on the common cold seems to be weaker and less consistent.

<https://www.ncbi.nlm.nih.gov/pubmed/24554461>

A review of herbal medicines for cough found that andrographis had the best evidence and strongest effect.

<https://www.ncbi.nlm.nih.gov/pubmed/26840418>

Elderberry is relatively expensive, and we do not recommend using immune-stimulating herbal extracts full-time. If they are used, they should be taken immediately before or after a likely exposure, or at the first sign of symptoms or malaise.

Emerging evidence from a Chinese search of medical databases is that elderberry (sambucus) and andrographis are among a list of substances that can reduce expression of the ACE2 receptor, which is the main route of COVID-19 infection. The list makes interesting reading.

<https://www.preprints.org/manuscript/202002.0047/v1>

This kind of computerised drug research has also pinpointed Andrographis in two more recent papers.

<https://www.tandfonline.com/doi/full/10.1080/07391102.2020.1760136>

<https://www.sciencedirect.com/science/article/pii/S2211383520302999>

Micronutrients

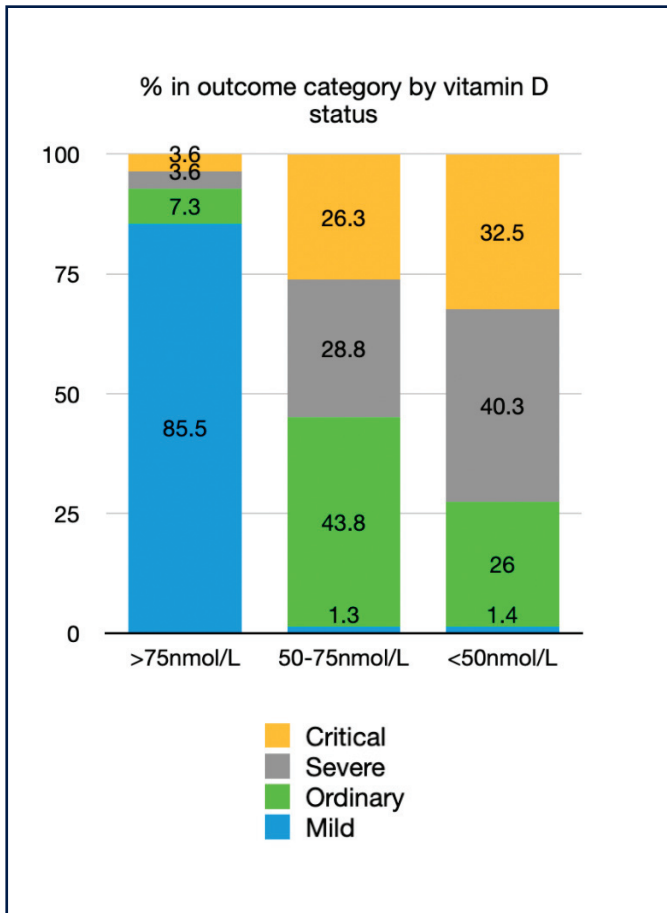
It is known that deficiency of micronutrients weakens the immune response, and retinol, vitamin D, selenium and zinc have been identified as key nutrients for its function that are also common deficiencies.

Retinol is available from animal foods, especially liver and fatty fish, and can be stored in the body long-term.

Vitamin D deficiency is very strongly associated with COVID-19 mortality in Indonesia.

<https://emerginnova.com/patterns-of-covid19-mortality-and-vitamin-d-an-indonesian-study/>





A Philippine study showed that with a deficient vitamin D status (<50nmol/L) the probability of becoming Severe or Critical with Covid-19 was 72.8% against 7.2% with adequate vitamin D (>75nmol/L)

<https://orthomolecular.activehosted.com/index.php?action=social&chash=b73ce398c39f506af761d2277d853a92.164&s=fefd45c21bc3a55252a9c7a67da2b16e>

In the winter months, Vitamin D might be worthwhile supplementing if your stores are low. A recent review of studies show that vitamin D supplementation can prevent against acute respiratory infections, especially if deficient. Vitamin D is best absorbed along with vitamin K, so if you are going to supplement, choose one that contains both Vitamin D3 and K2.

<https://www.ncbi.nlm.nih.gov/pubmed/30675873>

Dexamethasone was the first drug to be proven to give a survival advantage in Covid-19 ICU cases. This is important support because dexamethasone activates the vitamin D receptor and is combined with vitamin D in asthma and prostate cancer protocols.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3196110/>

Zinc and selenium are both essential antioxidant co-factors, which help combat oxidative stress. Zinc is obtained from meat, chicken and seafood, especially oysters. New Zealand soil is low in selenium, which may be a key nutrient in managing COVID-19. Many viruses encode for selenocysteine, making large selenium-sequestering proteins, which protect their genomes from mutation. In low-selenium hosts such viruses are more likely to mutate and become more virulent. Wuhan is a marginal-to-low selenium area, and the theory is that novel viral outbreaks are more likely to begin in such zones.

<https://www.sciencedaily.com/releases/2001/06/010608081506.htm>

We cannot find selenium data for COVID-19 yet, but a pre-2019 coronavirus was found to have 60 selenocysteine residues (60 selenium atoms) per core protein.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC126080/>

A virus using selenium at this rate will depress host immunity and weaken the antioxidant defences of target cells if selenium levels are low. Immune cells require strong innate antioxidant defences because they are generating high levels of ROS (reactive oxygen species).

A new study of Chinese data found that COVID-19 cure rates per region were strongly associated with soil selenium status.

In the city of Enshi in Hubei Province, which has the highest selenium intake in China, the cure rate (percentage of COVID-19 patients declared 'cured') was almost three-times higher than the average for all the other cities in Hubei Province. By contrast, in Heilongjiang Province, where selenium intake

is among the lowest in the world, the death rate from COVID-19 was almost five-times as high as the average of all the other provinces outside of Hubei. Most convincingly, the researchers found that the COVID-19 cure rate was significantly associated with selenium status, as measured by the amount of selenium in hair, in 17 cities outside of Hubei.

<https://doi.org/10.1093/ajcn/nqaa095>

Taking a few Brazil nuts daily can help boost selenium in the body – 4 or 5 a day would be more than enough (the average Brazil nut sold in New Zealand contains 19mcg selenium, and Brazil nuts in that study raised serum selenium levels more than supplements supplying the same amount).

<https://academic.oup.com/ajcn/article/87/2/379/4633360>

N-acetylcysteine (NAC)

Another part of this innate antioxidant system is glutathione, which requires the amino acid cysteine. In supplement form this is given as N-acetylcysteine (NAC). NAC has limited evidence for reducing flu symptoms and may also be of benefit for the common cold.

Lung cell testing of NAC shows results consistent with it preventing 'cytokine storm'.

<https://www.ncbi.nlm.nih.gov/pubmed/19732754/>

Interestingly, both NAC and glutathione are highly effective as antidotes in paracetamol poisoning, which killed 200 people a year in NZ before their introduction. Glutathione is made from amino acids – protein supplies these – and elderly people are known to be at higher risk of having inadequate protein intakes.

A new paper sums up the evidence for nutrients in the treatment of coronaviruses. Some of this is speculative, but it's a good round-up of the relevant literature.

<https://www.sciencedirect.com/science/article/pii/S0033062020300372>



Zinc

There is a little bit of evidence to support inorganic zinc lozenges (not tablets) for shortening the duration of the common cold. Taken at first signs/symptoms zinc may shorten symptom duration. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5418896/>

The 'cytokine storm' concept seems to be irrelevant in Covid-19, which means theoretical objections to adjuvant herbs are lessened.

<https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2767939>