

### *Editorial*

## **Sin of Being Deceived**

### *Urgent Recommendations*

## **Five Don'ts to Prevent COVID-19 and Death (Part 2)**

## **Five Do's to Prevent COVID-19 and Death**

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## Sin of Being Deceived

Translated from the Editorial in Med Check (in Japanese) Nov 2019 : 19 (123) ahead of print

Do you know about Mansaku Itami, a Japanese film director and screenwriter? He is Juzo Itami's father, a Japanese movie actor and director (The Funeral, A Taxing Woman). He died of tuberculosis in 1946, a year after the end of the WWII. The title of this article is taken from his essay "The Problem of War Criminals".

After the world war II, the majority of the Japanese were trying to escape from their responsibilities by justifying themselves that they had participated in the desperate war "because they had been deceived". However, Itami said that being deceived is sin in itself, pointing out that no dictionary had said "those who were deceived are innocent". He also said that people were deceived not only because of a lack of knowledge, but also of weak will.

Med-Check No.85 and No.86 criticize the Japanese Hypertension Guidelines 2019. Physicians who have lost ability to think critically and logically and have no faith are easily deceived into believing in the guideline. They prescribe expensive hypertensives, often leading to polypharmacy. In the words of Itami, it can be said that they are sinners. . Remember the Diovan Scandal. Many doctors were misled by the fake papers, prescribed Diovan and contributed to the total sale of \$ 1 billion per year. They are probably thinking that they were just deceived.

However, doctors are professionals. If they had read the fake papers critically with even a little skepticism, they would not have been

fooled. Dr. Yoshiki Yui, Kyoto University, is the example (see ref Concerns about the Jikei Heart Study. Lancet 2012:379(9824) e48 and Med Check in English No15).

Itami also said if people were not concerned about the fact that they had been deceived, they would be deceived again and again in the future. If this applies to the world of physicians, if they do not mind that they were misled in the Diovan incidence, they would probably be repeatedly deceived.

If physicians who were deceived deeply reflect on themselves, they would not trust the Japanese Hypertension Guidelines 2019 created by the Japanese Society of Hypertension, which has not learnt any lessons from the Diovan case. Instead, they would refer to guidelines created by organizations without conflicts of interest, such as National Institute of Health and Care Excellence (NICE).

When people find out that they have hypertension through medical examination, they simply take medicines prescribed by their doctors. To put it strictly, it can be said that these "patients" are guilty of being fooled.

When you buy something expensive like a car or a house, you would research online or by reading books. Because whether to take a medicine or not is about your or your family's health, you should research more than when you do shopping. It takes little effort to find a reliable source of information with no conflict of interest, such as Med-Check.

To be deceived is sin in itself.

# Urgent Recommendations

## Five Don'ts to prevent COVID-19 and death(Part 2)

Translated from [Med-Check News No.185 \(March 23 2020\)](#)

Med Check Editorial Team

Med Check in English No16 discussed two of the five Don'ts to prevent novel corona virus infection (COVID-19) and death. This article is for the remaining three Don'ts.

Before we get into the main subject, let's take a look at the world trend related to the antipyretic and corticosteroid use discussed in Med Check in English No16.

### Keywords:

COVID-19, ibuprofen, NSAIDs, paracetamol, corticosteroid, SARS-CoV, ACE, ACE2, ACE-I, ARB, immunosuppressants, sleeping pills, glitazones hidden-immunosuppressants

### French Health Minister: Avoid NSAIDs for COVID-19

The Guardian reported on March 13 that the French health minister, Olivier Véran tweeted "The taking of anti-inflammatories [ibuprofen, cortisone ... ] could be a factor in aggravating the infection. In case of fever, take paracetamol. If you are already taking anti-inflammatory drugs, ask your doctor's advice." [1]. A similar statement was made by the UK health authorities [2]. These were also reported in Japan [3] and the information seems to be spreading. Med Check thinks the advice is basically good, but Acetaminophen (paracetamol), which is recommended to use instead, is better than NSAIDs and/or corticosteroid, but unfortunately inappropriate in some situations as we described in Med Check in English No16.

The World Health Organization (WHO) recommended on March 17 that people suffering from COVID-19 symptoms to avoid taking ibuprofen [4]. But soon after that (as of March 22), they updated their statement that they did not recommend avoiding ibuprofen for COVID-19 symptoms [4].

The European Medicine Agency (EMA) also questioned the scientific basis for ibuprofen regulation and said "patients and healthcare professionals can continue using NSAIDs" [5]. However, the EMA has acknowledged that infection due to chickenpox (varicella) and some bacterial infections could be made worse by these medicines (NSAIDs including ibuprofen and ketoprofen). They also say "The product information of many NSAIDs

already contains warnings that their anti-inflammatory effects may hide the symptoms of a worsening infection" [5].

However, a lot of epidemiologic studies and infected animal studies provide evidence that NSAIDs increase mortality and so do corticosteroids (see Med Check in English No16), but WHO and EMA rarely mention these studies. In particular, they never mention the infected animal studies showing increased mortality without exception.

Some researchers criticized the ideas of French minister or UK health authorities [6], but few have criticized them by showing evidence. Even when evidence is presented, it is not strong enough to deny the harm of NSAIDs. For example, Prof. Little (Primary Care Research, University of Southampton) referred to some studies, including practical randomized studies conducted by them. It is a small survey with participants less than 1,000 people and has no power to detect rare complication of encephalopathy. He criticized French minister based on such an inadequate research and pointed out methodological problems in observational studies. He says "The observational evidence is always difficult to interpret due to so called protopathic bias/confounding by indication (i.e. were the NSAIDs prescribed at an early stage of the complications developing and so the NSAIDs use reflects the complications or a more severe illness rather than causing it)"

However, meta-analysis results of three case-control

studies with least bias among 10 studies he referred showed that use of NSAIDs such as ibuprofen is related with increased severe infections by 4 to 6 times [8].

In addition, they never quote the fact that mortality of infected animals is increased by use of NSAIDs and/or corticosteroids as reported in Med Check News No. 184.

### Here is the summary of 5 Don'ts

- 1. Do not use antipyretics to lower fever.** Human body can endure fever at 40-41°C. Because viruses are weak to heat, lowering fever with antipyretics will lead to regrowth of the viruses. In particular, non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided, because they also weaken your defense system. Acetaminophen (paracetamol) is basically harmful, as well.
- 2. Do not use corticosteroids** for the same reasons. Its use in the early phase of infection induce higher mortality.
- 3. Do not use Tamiflu and Xofluza as they suppress immunity.**
- 4. Avoid ACE inhibitor and ARB (angiotensin II receptor blocker) as possible, because they increase ACE2, an enzyme counteracting angiotensin II which acts as a main receptor for SARS-CoV-2 to infect human.** Apart from anticancer drugs, corticosteroids and overt immunosuppressants used for collagen diseases etc., there are many other drugs that reduce your immunity (hidden immunosuppressants). They include antihypertensive drugs especially ARBs and calcium antagonists, sleeping pills, anxiolytics, cholesterol lowering agents, antidiabetics (glitazons, DPP-4 inhibitors, GLP-1 agonists) and PPIs etc. They should be avoided unless they are essential.
- 5. Do not sit up late at night.** A lack of sleep can be the biggest cause of stress that impairs your immunity.

### 3. Do not use Tamiflu or Xofluza for fever

Regarding Tamiflu and Xofluza, please read, the latest information on Med Check in English No 15 (Dec. 2019) <https://www.npojip.org/english/MedCheck/Med%20Check%20Tip-15-2019-12-29.pdf>

which includes two papers:

- 1. Tamiflu: Deaths after Abnormal Behaviour among Teenagers Revisited: Probably related to the removal of contraindications**
- 2. High Risk of Death from Tamiflu and Xofluza: Serious toxicity necessitating suspension of its use**

And others in Med Check in English

<https://www.npojip.org/english/MedCheck/medchecktip.html>: including:

- 3. Cochrane team criticises the ECDC experts' draft advice on oseltamivir use:**

<https://www.npojip.org/english/MedCheck/Med%20Check-TIP%2004-04-05.pdf> (Apr. 2016)

- 4. Critical comments to ECDC by Cochrane team.**

<https://www.npojip.org/english/MedCheck/Suppl%20Critical%20comments%20to%20ECDC%20by%20Cochrane%20team.pdf>

#### 3-1. What will happen if doctors diagnose influenza without test?

In this flu season, flu was not very prevalent due to the unusually warm winter. However, a case has been confirmed in which a medical doctor who conducted a rapid testing for a patient suspected influenza was infected with a novel coronavirus (SARS-CoV-2 or COVID-19 virus), because the patient was found infected with SARS-CV-2 later. Therefore, the Japan Medical Association recommended member doctors against testing even in case with suspected flu and recommended diagnosis based on the clinical symptoms [8].

This measure may be unavoidable and permissible under the current situation where protective equipment for infection prevention is lacking and the risk of infection will increase for doctors in collecting samples and for subsequent other patients.

However, the initial symptoms of the COVID-19 are very similar to those of flu. In China, Tamiflu was used as an anti-influenza agent in about 90% or more patients at the beginning of the epidemic [9,10]

### **3-2. Tamiflu might be prescribed to patients with COVID-19**

Of course, especially in Japan, Tamiflu, Xofluza or other antivirals will be prescribed to patients with COVID-19 if diagnosed influenza.

However, they have no effect on COVID-19. Will they make COVID-19 worse?

### **3-3. Neuraminidase inhibitors such as Tamiflu suppress immunity**

Influenza virus has an enzyme called neuraminidase. Tamiflu, which is still commonly used as anti-influenza virus agents, are called "neuraminidase inhibitors (NIs)" because it interfere with the action of this enzyme of the virus.

Inhalers such as Relenza (zanamivir) and Inavir (laninamivir) or an injection (Rapiacta or peramivir) also belong to the group of "neuraminidase inhibitors (NIs)".

Many people including many physicians believe that neuraminidase inhibitors (NIs) are effective to treat influenza, because they can decrease influenza virus. But this belief is not supported with evidence.

On the contrary, "neuraminidase" is also found in cells throughout the body of animals including humans. It is an essential enzyme to keep cells healthy. When you take Tamiflu, neuraminidase in your body ("endogenous neuraminidase" in medical term) is also inhibited, and immune function will be inhibited. Tamiflu reduce cytokines which is induced to fight influenza virus. Hence symptoms seem lighter, but the healing may be delayed. It has also been confirmed in animals and humans that clinical dose of Tamiflu reduces IgA antibodies of the mucosa in the nose and other respiratory tract for protecting against influenza infection to one-fifth of control (those without Tamiflu).

There is a virus that causes severe respiratory infections in infants called the respiratory syncytial virus (RS virus). This virus has no neuraminidase. Mice challenged by RSV and administration with a clinically compatible dose of Tamiflu showed symptom-relieving effects (decreased weight loss). However, virus increased in the lung of mice.

These are detailed in a review article on "The mechanisms of delayed onset type adverse reactions to oseltamivir" [11]. It is also translated into Japanese [12].

***What happened with these influenza viruses and RS viruses, will happen naturally with the COVID-19***

***Do not use Tamiflu and other NIs as it make the COVID-19 more severe***

### **3-4.No worries: Flu, COVID-19 will be better without drugs**

As described in the previous section, neuraminidase inhibitors, such as Tamiflu, do not reduce the virus but reduce only symptoms as they reduce cytokines which have actions to destroy virus. They simply prevent the body from fighting the virus.

Because anybody has strength to fight against viral infection with their own defense system, drugs are not necessary. They rather interfere the recovery.

Even when you are infected with flu, nothing should be feared

Take this opportunity to develop a habit of not using anti-influenza virus agents.

### **3-5. Xofluza is more toxic than Tamiflu**

Xofluza is the newest anti-influenza virus agent introduced in the clinical setting in Japan. It definitely reduces influenza virus unlike Tamiflu or Relenza. However, it produce resistant virus frequently. Moreover it seems that it could inhibit important human enzymes.

In addition, since intra-intestinal concentration becomes high, intestinal mucosal cell function may be first weakened; subsequently water absorption is interfered, leading to diarrhea. Next, the regeneration of intestinal mucosal cells is inhibited causing injuries, bleeding with melena. In addition, intestinal bacteria can enter the blood stream through injured mucosal membranes and be translocated throughout the body, causing severe systemic infections (bacteremia and sepsis).

During the last influenza season (2018/19), 4.27 million patients with influenza were prescribed with Xofluza. Total 37 death cases were reported by doctors who suspected these deaths may be related to the drug. Mortality rate is at least 1 in 120,000. For those over 60 years of age, mortality rate was 1 in 80,000. There were no reports of deaths among 3 million inhaler users, such as Relenza and Inavir.

The novel coronavirus is transmitted not only from the respiratory tract such as the lungs, but also from the mouth and enters the gastrointestinal tract. If the intestine is injured with Xofluza, intestinal mucosa is easily infected with novel coronaviruses. As described in detail in the next section, the enzyme called ACE2, which acts as a receptor of novel CoV will increase where the tissue is injured. It infects the intestinal mucosal cells, leading to translocation into the blood stream, leading to viremia. It infects various organs of the body attaching ACE2 as the receptor which is present throughout the body, leading to multi-organ failures.

***Do not use Xofluza because it also makes the COVID-19 more severe***

No worries again: Flu, COVID-19 will be better without drugs.

Without Xofluza, you will recover faster overall. Of course, even if you are infected with the novel CoV, it is best to wait to recover naturally.

## **4. There are many other drugs you should avoid**

### **Summary**

The novel coronavirus (CoV) enters the cell with an enzyme called ACE2 as a receptor. This enzyme is found on the surface of almost all cells in the body and increases when the body is injured by sustained excessive stress.

While influenza virus does not infect anything other than the respiratory tract, Novel CoV infects the cells of the intestine, translocates into the blood stream, goes around the body, and infects the cells throughout the body.

It is known that children and adolescents are less likely to be infected or become seriously ill, and that elderly people, especially those aged 70 and older, are more susceptible to infection and illness, and are more likely to become severely ill. In particular, patients with chronic respiratory disease, stroke, high blood pressure, diabetes, and/or heart disease are known to be 3 to 8 times more likely to be severely ill than those without. Smoking also increases the risk by about 3-folds.

People with such chronic diseases or smokers have tissues injured by the sustained stress or directly by

smoking followed by inflammatory reactions to repair. They increase angiotensin II (Ang II), a substance that increases blood pressure. At the same time, an enzyme called ACE2 also increases in order to counteract Ang II.

ARBs (angiotensin II receptor blocker) and ACE (angiotensin converting enzyme) inhibitors further increase ACE2. In addition ARB has immunosuppressive action. Hypertension itself increases the risk of COVID-19 but drugs in addition worsen COVID-19. Actos, an agent for diabetes (glitazones) also increases ACE2.

Apart from anticancer drugs, corticosteroids and overt immunosuppressants used for collagen diseases etc, there are many other drugs that reduce your immunity (hidden immunosuppressants). They include antihypertensive drugs especially ARBs and calcium antagonists, sleeping pills, anxiolytics, cholesterol lowering agents, antidiabetics (glitazons, DPP-4 inhibitors, GLP-1 agonists) and PPIs etc. They should be avoided unless they are essential.

Stop taking cholesterol-lowering agents at any time. It is very safe to discontinue them. However, you should stop some agents carefully. For example, if you want to stop sleeping pills or corticosteroids, please consult your doctor.

### **4-1. The elderly is more susceptible to COVID-19 and more easily deteriorated**

There were 3711 passengers and crew members on the Diamond Princess. Because the population was in close contact, all were tested, and the proportion of infected people and mortality were examined by age and by the presence or absence of symptoms (**Figures 1-A and 1-B**).

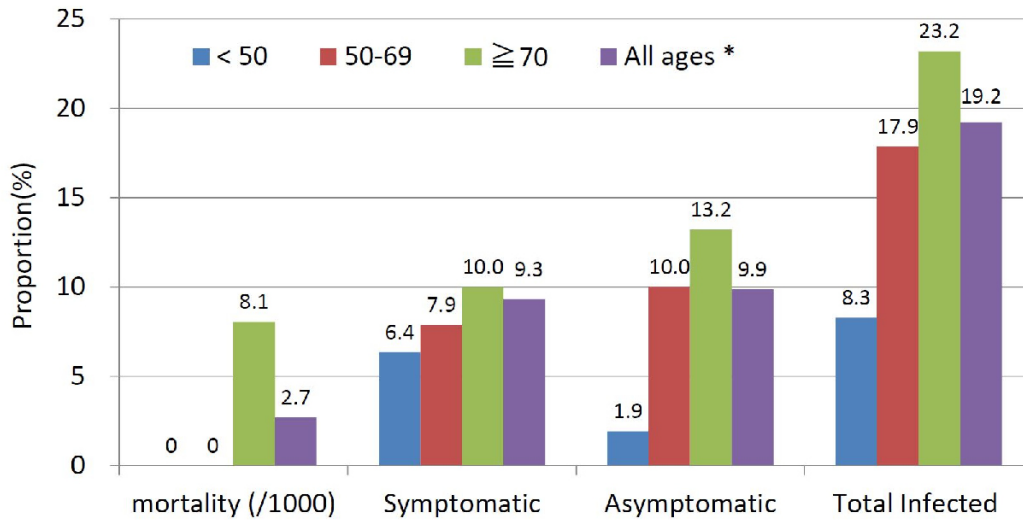
With a little exception of under 20 years of age, the higher the age, the higher the percentage of positive PCR testing in both symptomatic and asymptomatic individuals. Of all 3711 persons aboard of all ages, 712 were positive including asymptomatic as of March 29, and the infection rate was 19.2% overall. Roughly, it indicates that about 20% of the population, including asymptomatic individuals, may have been infected.

### **4-2. Chronic illness increases severity by 3-8 times**

Many reports point out that chronic illnesses are the risk factors which aggravate COVID-19 severe or

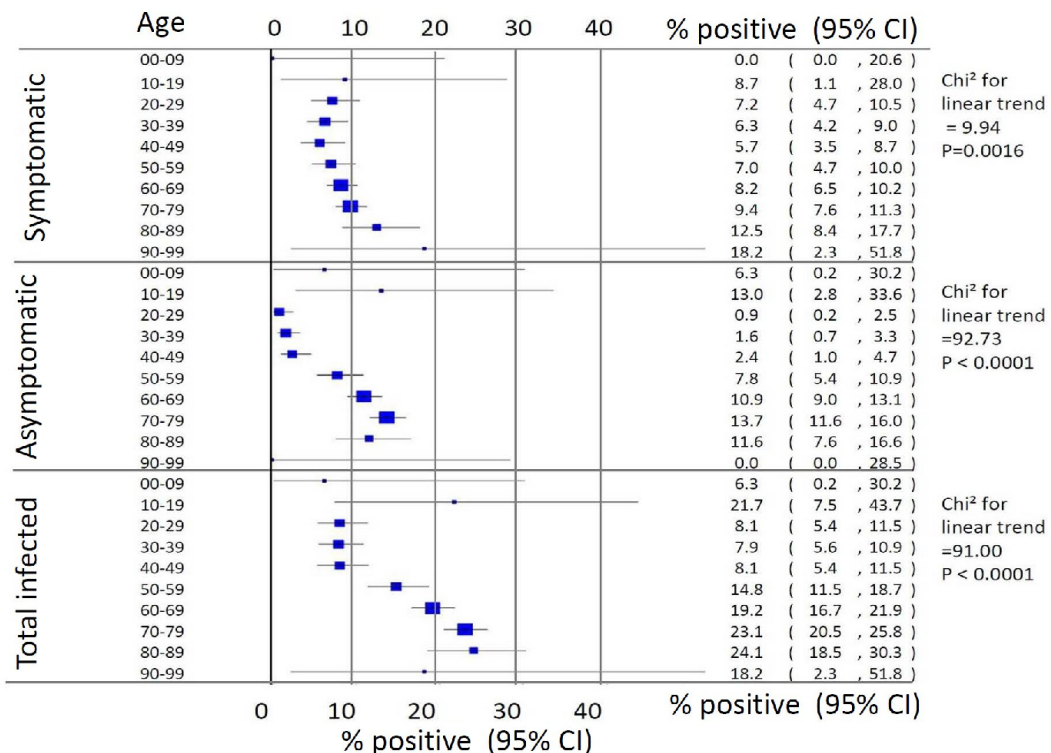
**Figure 1: Percentage of PCR positive among people on Diamond Princess by age and by symptoms.**

**A: By age divided into 3 classes**



Percentage of PCR positive for SARS-CoV-2 is higher in older people: more pronounced in asymptomatic individuals. Overall approximately 20 % of all populations may be infected. Data for all ages\* and mortality are based on the data on March 29, while others are those on Feb 20. Figure was made by Med Check editorial team using data from ref [13-15].

**B. By age every 10 years**



This figure (1-B) shows a little exception that children tend to have a higher percent positive. Although the number is small and the 95% confidence limit is wide, it may be due to the higher activity of children. Plot using data from Ref [13, 14]

increase mortality. So far, we meta-analysed the data for the risk of comorbidity from the six reports [9,10,16-19] up to March 10.

These reports compared patients who were admitted to ICU with those who were not [9,10,18], severe cases with non-severe cases [16], or non-survivors with survivors [16,17,19]. Combined odds ratio was 3.75 (95 % CI:2.73, 5.19)(Figure 2).

The Table shows the results of meta-analysis for various chronic diseases and smoking. Among them, the risk of stroke is particularly high. Is it related to the number of receptors in the brain?

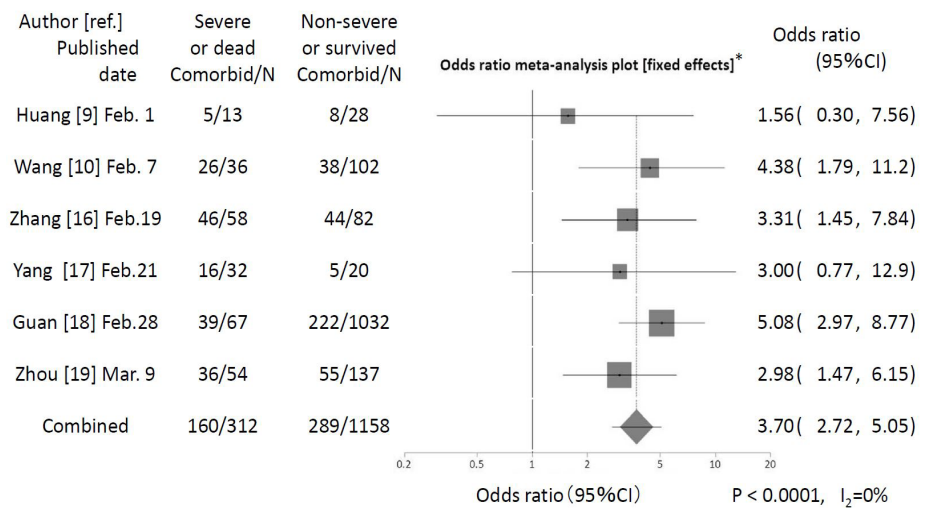
Anyway, note that these odds ratio were derived from the comparison of hospitalized patients and not comparison with non-hospitalized mild cases. If comparison were conducted between severe or deceased patients with non-admitted mild cases, the odds ratio may be much higher.

### 4-3. Virus enters injured tissues attaching ACE2

#### (1) SARS-CoV-2 attach ACE2 to enter the body to systemic dissemination

Not only the novel coronavirus (SARS-CoV-2 or COVID-19 virus) [20-22] and SARS-CoV that emerged in 2003 [23] but also non-SARS-CoV [24] infect the human

**Figure 2: Chronic diseases make illness worse or increase death from COVID-19**



\* By fixed effect (Mantel-Haenszel, Robins-Breslow-Greenland)

body using an enzyme called angiotensin converting enzyme-2 (ACE2).

As we have seen in the previous section, elderly people are more susceptible to COVID-19, especially those with chronic diseases. These may be deeply related. Let's explain how they are related.

The first thing you need to know is that ACE2 is an important enzyme on the cell surface of all tissues throughout the body, including the gut, lungs, brain, liver, kidney, and heart [20-23] (Figure 3).

ACE2 is most commonly found in the small and large intestines, but is found on the cell surface of organs throughout the body, such as the lungs, kidneys, heart, and liver. Furthermore, among leukocytes, ACE2 is present in granulocytes and lymphocytes that are significantly involved in the immune response.

For example, small intestine or colon is the organs with the highest expression of ACE2.

This may be because these organs are vulnerable to injuries with a lot of bacteria inside. ACE2 modulates innate immunity and influences the composition of the gut microbiota [23].

SARS-CoV-2 migrates into the blood, is distributed throughout the body, and could infect every cell of the body [22, 25] (Figure 4).

SARS-CoV-2 could enter into the brain not only through the route

**Table: COVID-19 will be worsened with various chronic diseases and smoking**

Comorbidity	Combined odds ratio						I <sub>2</sub> (%)
	Fixed Effect *			Random effect			
	OR	(95%CI)	P value	OR	(95%CI)	P value	
Any comorbidity	3.75	(2.73, 5.19)	< 0.0001	3.77	(2.77, 5.14)	< 0.0001	0
Hypertension	3.06	(2.18, 4.28)	< 0.0001	3.05	(2.13, 4.36)	< 0.0001	13.4
Diabetes mellitus	3.05	(2.01, 4.61)	< 0.0001	2.61	(1.31, 5.19)	0.0062	60.9
Coronary/Cardiovascular	4.12	(2.38, 7.13)	< 0.0001	3.54	(1.71, 7.32)	< 0.0001	42.0
Chronic pulmonary	3.50	(2.21, 5.53)	< 0.0001	3.32	(2.13, 5.16)	< 0.0001	0
stroke/cerebrovascular	8.17	(3.23, 20.95)	< 0.0001	7.92	(2.88, 17.47)	< 0.0001	0
malignancy	1.21	(0.35, 3.57)	0.787	1.34	(0.50, 3.53)	0.56	0
Smoking	2.80	(1.68, 4.58)	< 0.0001	2.43	(1.14, 5.15)	0.0211	0

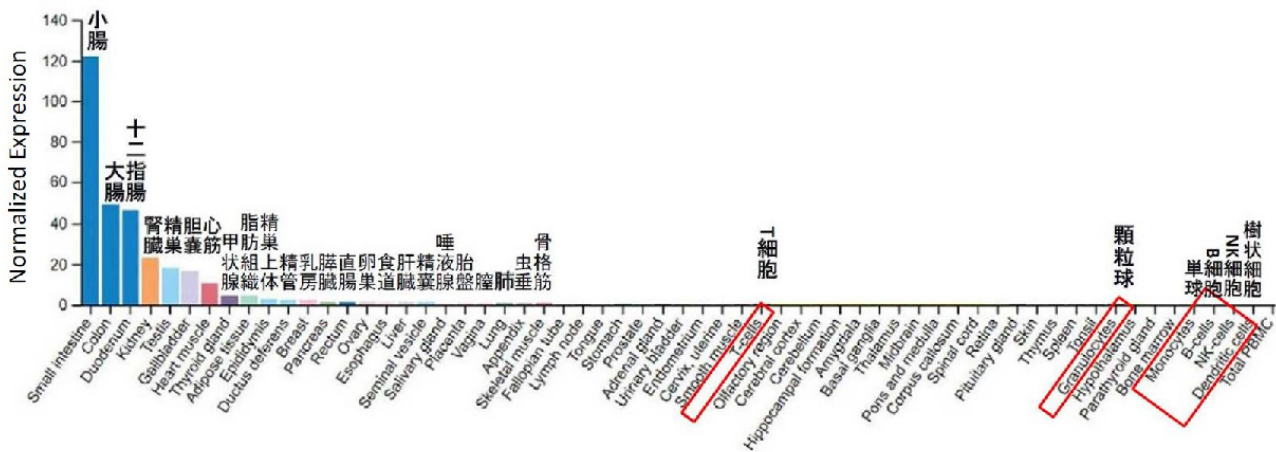
\* Fixed effect by conditional maximum likelihood. Data from Huang[9], Wang[10], Zhang[16], Yang[17], Guan[18] and Zhou [19] were meta-analysed.

Note the higher odds ratio of stroke/cerebrovascular diseases. Smoking is also one of the risk factors.

Note also that these are the results of comparison of all admitted patients. If comparison were conducted between severe or deceased patients with non-admitted patients, the odds ratio may be higher.



**Figure 3: ACE2 is present in almost all cells of various organs**



Expression of ACE2 in human tissues. Data represent Consensus Normalized eXpression levels for 55 tissue types and 6 blood cell types obtained from The Human Protein Atlas ([www.proteinatlas.org](http://www.proteinatlas.org)). Cited from Ref. [20] with little modified by Med Check editorial team. ACE2 is expressed on all surfaces of cells throughout the body and increases when tissue is injured. In this data, the expression of ACE2 in the lung appears to be low, but in another document [21], the expression in the lung is about one third of the large intestine.

via the blood but also directly through the nose [22] (Figure 4).

**(2) Persistent stress with a lack of sleep injure your body**

Excessive stress contracts blood vessels and increases blood pressure, leading to poor supply of blood with oxygen. This situation is called "ischemia". If ischemia continues, the tissue will be damaged.

The injured tissues made during daytime have to be repaired while sleeping at night. However, if the injury during day time is serious and if you don't sleep long enough to repair wounds, injured tissue remains even in the morning. If these situations continue, wounds will build up in weak areas of your body, and the inflammatory response will gradually increase, manifesting as a disease.

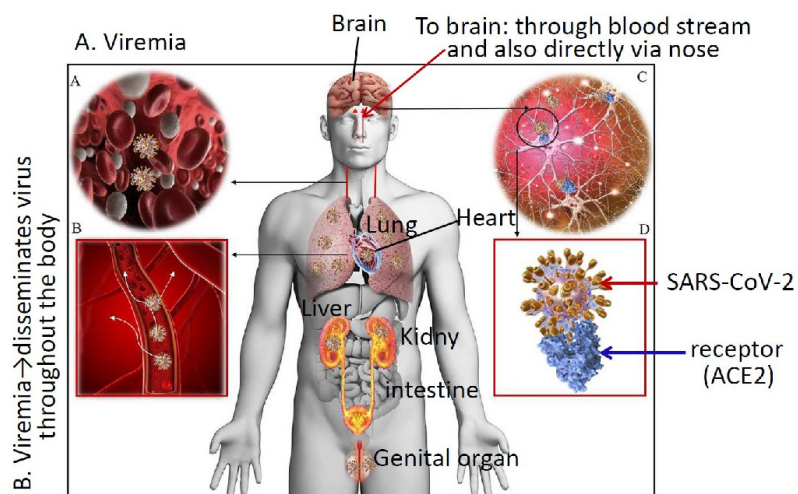
Eczema/dermatitis may be the results of injured skin due to the ischemia derived from persistent excessive stress. Injuries in the bronchi could lead to asthma and chronic obstructive respiratory disease (COPD). The same may be true for colon leading to ulcerative colitis, and for arteries to arteriosclerosis, hypertension, myocardial infarction and

cerebral infarction. If ischemia derived from persistent excessive stress affects your brain dopaminergic nerve, it can cause inflammation in the dopaminergic system leading to depression.

**(3) ACE2 increases when the body is injured**

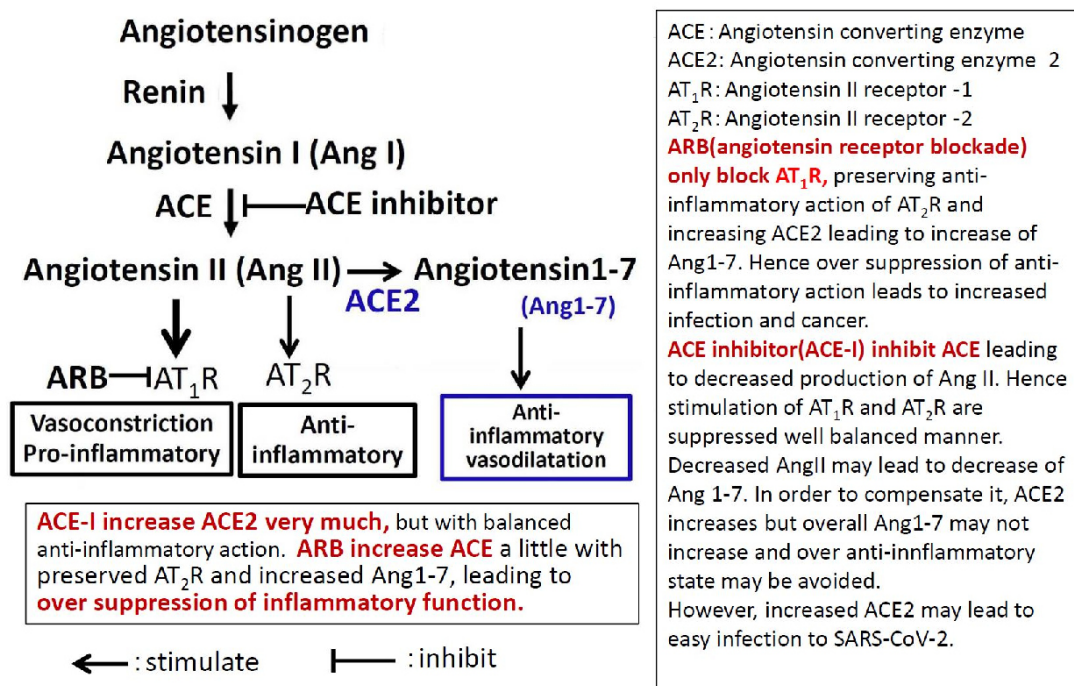
Stress causes a person excited and vasoactive angiotensin II which is converted from inactive angiotensin I by angiotensin converting enzyme (ACE) increases. This angiotensin II works towards making wounds on the body. Our body is well-equipped and brakes to prevent injury induced by excessive angiotensin II. An enzyme called ACE2 is required to make the braking substance (Figure 5). The substance

**Figure 4: SARS-CoV-2 enters into the blood and infects cells throughout the body.**



Cited from Ref. [22] and modified by Med Check Editorial team.

**Figure5: Inflammatory response differently affected by ARB or ACE-I**



acting as a brake is called "angiotensin 1-7".

In addition, when blood pressure becomes high, blood flow becomes faster, and inner surface of the blood vessel have pulsatile shear stress (PSS). Experiments have shown that PSS increases ACE2 as a compensatory response to maintain normal function of cells inside the blood vessels [26].

The main reason why old people rarely infected and deteriorated with non-SARS-CoVs even though they have many receptors (ACE2), may be because they had been frequently exposed with non-SARS-CoVs in their childhood and have immunity to these viruses. However, SARS-CoV-2 is a completely new virus and old people have no immunity to protect against it and they already have a lot of receptors (ACE2) in their body, while younger people have far less ACE2.

**(4) ACE inhibitors and ARBs further increase ACE2**

The liver of the rats that was administered carbon tetrachloride expressed more ACE2 than that of control rats. If rats were pretreated with ACE inhibitors ACE2 increased further compared to rats not receiving ACE inhibitors [27].

Usually mild hypertension does not lead to a serious disease, but SARS-CoV can be as severe as diabetes or heart disease (see Table). This is due to the fact that

hypertension tends to cause intravascular injury due to "shear stress" [26], and the antihypertensive drugs including ACE inhibitor and angiotensin II receptor blocker (ARB) further increase ACE2 [27,28].

Patients with type 1 diabetes and/or with coronary artery disease had more ACE2 than those without [28]. Also, among diabetics, those who take ACE inhibitors or ARBs also had higher ACE2 than those who do not.

**(5) Young people getting ill with COVID-19 have diseases**

If you have complications, ACE2 increases in diseased organs, making it more susceptible to infection and more severe condition with COVID-19.

On the other hand, young adults without complications relatively less infected whether asymptomatic or symptomatic. It is probably because ACE2 has not increased significantly in young adults. Young person having comorbidity may be susceptible to COVID-19 and could get severely ill.

Therefore, those who have no complications do not need to be overly afraid of the COVID-19 if they are aware of what has been said in this article so far.

Of course, in order to avoid infection as much as possible, actions to avoid "closed environment", "crowd" and "close contact" are essential.

#### 4-4. The other Drugs that worsen COVID-19

Substances that reduce inflammation, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, exacerbate any infectious diseases because they diminish the body's function to protect against pathogens, such as viruses.

These agents apparently relieve symptoms transiently, because they stop defense system including fever and induction of cytokines to fight pathogens. However, in the meanwhile, the virus goes deeper into the body and multiplies, causing the body to emit more cytokines and symptoms become more severe. The so-called cytokine storm (storm of cytokines) blows. NSAIDs including ibuprofen and aspirin typically induce cytokine storm injuring endothelial cells all over the body. It induces acute respiratory distress syndrome (ARDS), encephalopathy with liver damage or necrotizing encephalopathy with multi-organ failures.

Lancet's article [29], quoted by the WHO [4] to recommend against ibuprofen in COVID-19 cited the reason why ibuprofen increases ACE2. However, only a single paper was found for the evidence basis on this [30]. Moreover, ibuprofen was not used for infectious diseases in the study[30]. Therefore, causing cytokine storms through hypothermia and anti-inflammatory effects may be far more important than increasing AEC2 for the mechanisms in which NSAIDs worsen COVID-19.

##### (1) Immunosuppressants worsen infections

It is clear that anticancer drugs, corticosteroids and immunosuppressants used for rheumatism and collagen disease exacerbates COVID-19 because they block defense response to the virus.

People with atopic dermatitis may not only use topical steroids, but also immunosuppressants such as tacrolimus (Protopic) ointments. These are very harmful.

We noticed that many clinical trials testing strong immune suppressants are conducted for treatment to reduce severity and/or mortality from COVID-19 [31]. These include methylprednisolone, tocilizumab and baricitinib. They are planned mainly in Italy. But these immunosuppressants increase infection including

tuberculosis. These trials should be stopped, because they may increase severity and death from COVID-19.

##### (2) Beware of the many "hidden immunosuppressants"

Although, we can easily understand that anticancer agents, corticosteroids and overt "immunosuppressants" have immunosuppressive effects, we should be aware of many other agents that suppress immunity even if they are not classified as immunosuppressants.

For more information, please refer to each issue of Med Check (Med Check TIP) in English, Encyclopedia of Drugs You Should avoid(in Japanese), Encyclopedia of "How to Stop Drugs" (in Japanese).

##### 1) Antihypertensive agents:

1. ARB is a typical hidden immunosuppressants (see above). See Figure 5 for a detailed explanation of how immunity is suppressed and how its mechanism differs from ACE inhibitors [32].

2. Calcium antagonists suppress the influx of calcium ions into the cells of vascular smooth muscle, dilate blood vessels and lower blood pressure. However, it is not only smooth muscle that activates cells due to calcium influx. Many immune cells are also activated by calcium influx, such as the action of pancreatic beta-cells that secrete insulin and mast cells and lymphocytes that play an important role in immunity [33]. Therefore, calcium antagonists not only dilate blood vessels and lower blood pressure, but also slow down insulin secretion to develop and exacerbate diabetes. It suppresses immunity, making it more susceptible to infections and cancer.

##### 2) Cholesterol-lowering agents [34-36]

All cholesterol-lowering agents suppress immunity. People with high cholesterol level live longer with better activity of daily life than people with low cholesterol. This is because cholesterol is essential for the function of all cells, including immune cells. Do not lower cholesterol.

In particular, the most commonly used statins not only lower cholesterol, but also suppress immunity through function other than lowering cholesterol. Do not use them. If you are taking cholesterol lowering drugs, you can stop them at any time. There is no inconvenience or harmful effect for you even if you stop them.

##### 3) Sleeping pills and anxiolytics [37-39]

In addition to the most commonly used benzodiazepines (**Note**) such as Ambien (zolpidem), relatively new melatonin derivative ramelteon (trade name Rozerem) and the orexin receptor antagonist suvorexant (Bersomura) also suppress immunity. The quality of sleep obtained with sleeping pills is poor, increasing depression, infectious diseases and cancer, and thus shortening life expectancy. Don't use them. However, in order to discontinue, you must be patient and decrease it very slowly. The same is true for anxiolytics.

**Note:** The so-called "non-benzodiazepines" are classified based on the structure. Because "non-benzodiazepines" or "z-drugs" also act as benzodiazepine receptor agonist, same as the structurally classified benzodiazepines, "Med Check" classify them (z-drugs) as benzodiazepines in terms of mechanism of action.

#### 4) hypoglycemic agent [40-43]

- Actos (glitazone): Carcinogenic and increases ACE2.  
<https://www.npojip.org/english/MedCheck/Med%20Check-TIP%2005-08-08.pdf>
- DPP4 inhibitor
- GLP-1 receptor agonist (Injection)
- SGLT-2 inhibitors

They are also carcinogenic and exacerbate infectious diseases.

#### 5) Drugs for asthma [44]

- Inhaled corticosteroids: Fluticasone is a very strong immunosuppressant.
- Beta agonists (salmeterol, formoterol, salbutamol, etc.) suppress function of immune cells suppressing inflammation. Minimum required should be used.

#### 6) Gastric acid suppressant (also frequently used for reflux esophagitis etc.) [45]

- Proton pump inhibitors (PPI)
- H2 blockers

#### 7) Others: Fluoride [46] also suppress immunity.

## 5. Don't sit up late at night. A lack of sleep is the biggest cause of stress and reduces immunity

When you have a fever, you have to take a rest. When you are not infected, it is important that you exercise moderately during the day time and take enough sleep at night to avoid stress and repair injuries that you had during the day time. A lack of sleep is the greatest stress.

A lack of sleep at night with excessive stress during day time, sympathetic nerves are activated and immunity is suppressed. As a result, blood vessels in various parts of the body contract, resulting in an inadequate supply of oxygen and nutrients. This is "ischemia", which can cause tissue injuries. ACE2 increases in the injured tissues through which SARS-CoV invades your body easily, making your body susceptible to disease and severe condition.

When you sleep, sympathetic nerves are calmed. On the contrary, parasympathetic nerves become active and activate immunity. Injured tissues are healed by immunity while sleeping enough at night, before you get up in the morning. However, if the stress during the day is too strong or the sleep time is too short, the injuries induced during the day time will not be cured and will be carried over to the next day, accumulate and become inflamed in various parts of the body. This is the disease. The cause is common in many diseases even if they occur in different parts of the body.

***Don't sit up late at night! A lack of sleep is the biggest stress.***

***Don't have sleep debt, the main cause of immune suppression***

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# Urgent Recommendations

## Five Do's to prevent COVID-19 and death

Translated from [Med-Check News No.185 \(March 23 2020\)](#)

Med Check Editorial Team

The ongoing epidemic of corona virus infectious disease (COVID-19) is disrupting our daily life. Controversial information is prevailing. "Ibuprofen is harmful/safe" "The SARS-CoV-2 is/not vulnerable to high temperature." "Drinking hot water is/not effective." True information is sometimes treated as false. As we wrote in the No 16 issue of Med Check in English, we are trying to our best to meet such needs as much as possible. In this article, we rather focus on some points based on evidence which are widely misunderstood and will not discuss things which are commonly covered by the media.

### Five Do's (summary)

- 1. Simple mask-wearing is effective. It reduced illness from SARS to one-third, and is more effective than frequent hand-washing (>10/day) that halved it.**
- 2. Mask-wearing is effective because SARS-CoV is vulnerable to high temperature with humidity. It helps your nose and throat keep warm and moisturized.**
- 3. When masks are not available, make it with cloths or handkerchief. They can be washed and used repeatedly.**
- 4. Drink hot drinks such as "kuzuyu (drink made from arrowroot starch). Blowing on and sipping it help warm the throat and the whole body.**
- 5. Get moderate exercise during the day, and have enough sleep at night, but without sleeping pills.**

### Keywords:

COVID-19, SARS, mask-wearing, hand washing, high temperature, humidity, Cochrane review, enough sleep, stress, ischemia

### 1. Simple mask-wearing is effective

The results of the Cochrane review [1] provide the most reliable information as of today on the effect of mask-wearing. It can be accessed for free of charge.

During the SARS epidemic, the association between the onset of SARS and various preventive measures were examined. Jefferson et al [1] reviewed and meta-analyzed these studies. Odds of several interventions such as mask-wearing and hand-washing were compared in patients who developed SARS (cases) and those who did not (controls) after matching sex and age. **Figure 1** shows

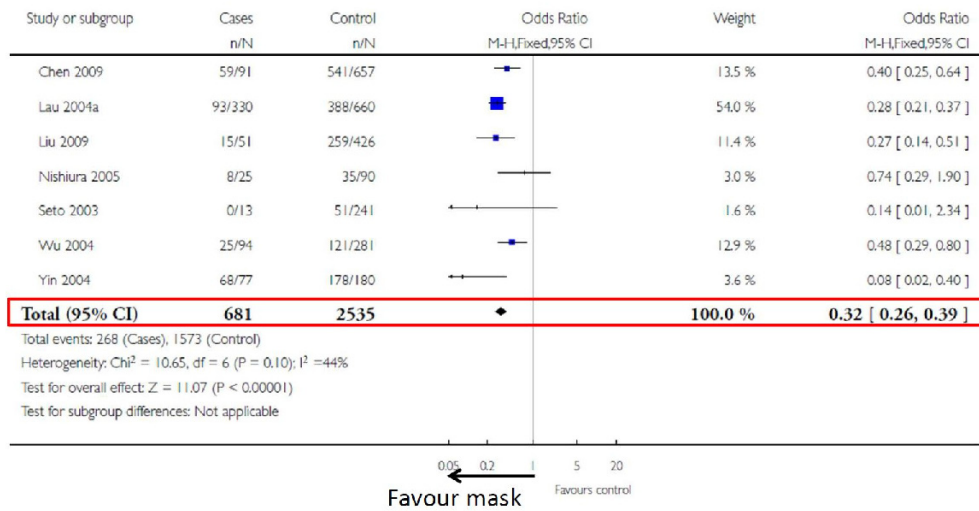
a result for mask-wearing.

Overall odds ratio was 0.32 (95% confidence interval (95%CI): 0.26-0.39,  $p < 0.00001$ ). This suggests that simple mask-wearing reduces the risk of onset to 32 % as a result of 7 studies combined.

With hand-washing for more than 10 times daily, odds ratio for infection with SARS was 0.54 (95% CI:0.44- 0.67,  $p < 0.00001$ ) (**Figure 1B**). This suggests that it only halved the risk. Statistically, mask-wearing is more effective than hand-washing, because upper limit of 95% CI for Mask wearing (0.39) is lower than the lower limit of 95 %CI for hand washing (0.44).

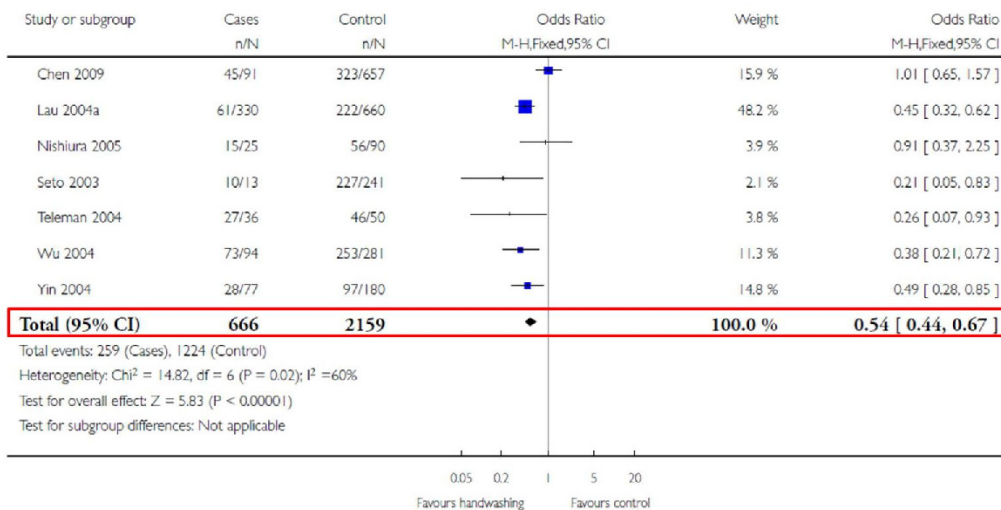
**Figure 1: Effect of physical intervention in SARS Prevention**

**A: Simple Mask-wearing**



How to read the figure 1a above: The data in the top column is based on the report by Chan (2009). In people who did not develop SARS, 541 of 657 persons were wearing masks while in those who developed SARS, only 59 out of 91 were wearing masks. Odds ratio, which was a ratio between odds of mask users/non-users in people with SARS and odds of mask users/non-users in people without SARS, was 0.40. This means that the risk of infection with SARS is reduced to 40% by wearing mask. In the next study by Lau (2004), odds ratio is 0.28 (93/237:388/272). This means that the risk of infection with SARS is reduced to 28% by wearing mask. Based on the combined data from 7 case-control studies (Total), mask-wearing reduced risk for SARS infection to 32% .

**B: Hand washing (>10/day)**



Jefferson T et al. Cochrane Database Syst Rev. 2011 Jul 6; Issue 7[1]

Most experts emphasize the importance of hand-washing. They say that mask-wearing is effective only in preventing the spread of virus from the infected through sneezing and cough, but not really effective in preventing healthy people from being infected. They also recommend disposing and changing masks frequently.

We do not know why, but we have never heard them referring to the result of the Cochrane’s review [1].

N95 respirators are also effective in preventing the onset, and their preventive effect was apparently greater than that of simple masks. However, the difference was not statistically significant, because upper limit of 95% CI for N95 respirators (0.43) is higher than that for Mask wearing (0.39). Rather, because N95 respirators, whose fiber is densely packed, tend to be uncomfortable and irritating to skin [1].

The information from the World Health Organization (WHO) [2] is slightly different from that of Japanese experts. It announced that healthy people do not usually need to wear a mask, but when they have contact with people who are infected or suspected to be infected with SARS-CoV-2, they should wear a mask. Although it does not cite references, it can be said that the WHO has admitted the preventive effect of mask-wearing when personal contact with infected patients is involved.

## 2. Why mask is effective? Higher temperature and humidity

Masks keep the nose and through warm and moisturized.

At the time of writing this article, at 10 a.m. on March 5th, the ambient temperature was 9°C .

RH took the temperature in his mouth just near his throat, and it was 22-23°C without wearing a mask. After putting on a mask, he took the temperature again in the same way, and it was 32-33°C . The difference was about 10°C with and without wearing a mask.

Although he did not measure and compare the moisture in his throat, it would probably be more than 95% with a mask. In winter, both temperature and humidity are low. Especially in areas like Hokkaido, ambient temperature goes below 0°C .

**Figure 2** compares infectivity of SARS-CoV at different temperature [3]. It gradually die at room temperature

(22-25°C) and 33°C , but the speed is slow. The majority of the media labeled the information that “the virus die at 26-27 °C ”as false, claiming that if it is true, the virus should die immediately after they enter human body, but they do not. However, as shown in Figure 2, even at the temperature of 38 °C , they do not die immediately. At room temperature (22-25°C ), at one to two days after the start, titre is reduced to almost 1/10, but it takes 2 to 3 weeks until they are totally lost.

Under low humidity environment, viral viability is decreased at slower rate even at 38°C (**Figure 3**). Viruses survive for a long time under low humidity and low temperature conditions.

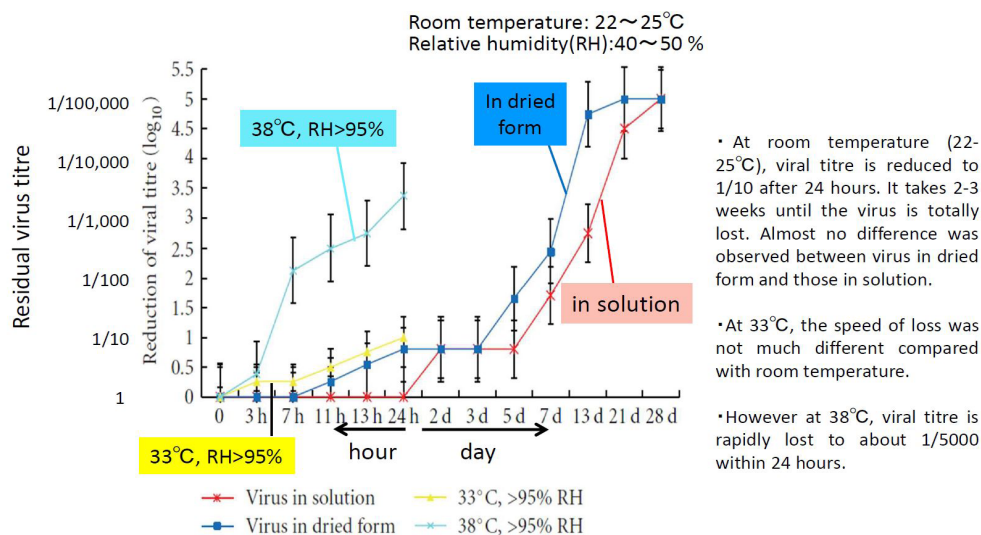
This proves that keeping nose and throat warm and moisturized is extremely important for preventing the growth of viruses at the sites.

Another experiment investigated how much surrogate viruses of SARSCoV, such as transmissible gastroenteritis virus (TGEV) and mouse hepatitis virus (MHV), survive on stainless steel[4](**Figure 4**).

The result showed that the infectious viruses persisted for as long as 28 days at 4 °C and relative humidity (RH) 20%.

However, at 40°C and RH 80%, the levels of the viruses were undetectable after only 6 hours, suggesting that they had actually been all inactivated.

**Figure2: Effect of temperature on SARS-CoV viability**



Cited from Chan Kh et al [3], modified and comments by Med Check team.

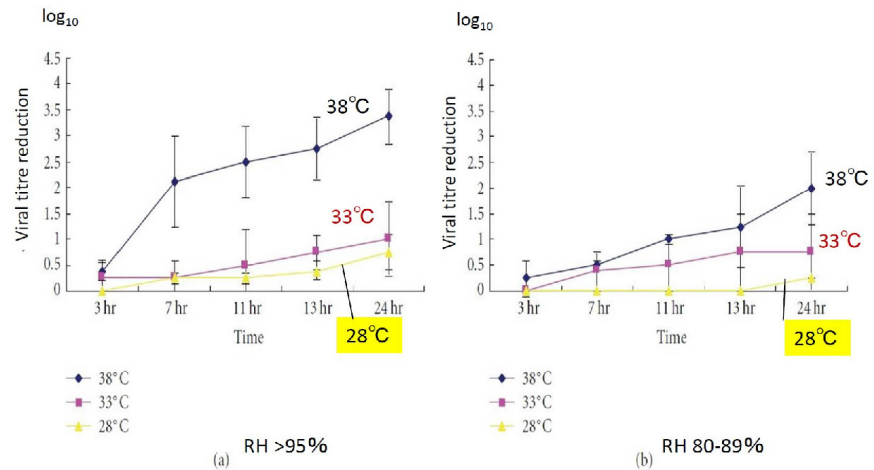


At near room temperature (20 °C) and at RH 20%, viruses decreased to 1/100 after 28 days, while they were undetectable after 1 to 2 weeks when RH was over 50%. This coincides with the result shown in **Figure 2** and **Figure 3**.

In other words, viruses are inactivated much more rapidly at room temperature (26-27 °C) than at 4 °C and at RH 20%. Therefore, the information “viruses die at 26-27 °C” is not simply “wrong”. They just do not die “immediately” under such a condition.

These explain why epidemic of SARS and COVID-19 have occurred in winter, when it is cold and dry. Therefore, it might subside in Japan during rainy season, when it is warm and humid. However, room temperature should not be made too low by air conditioners.

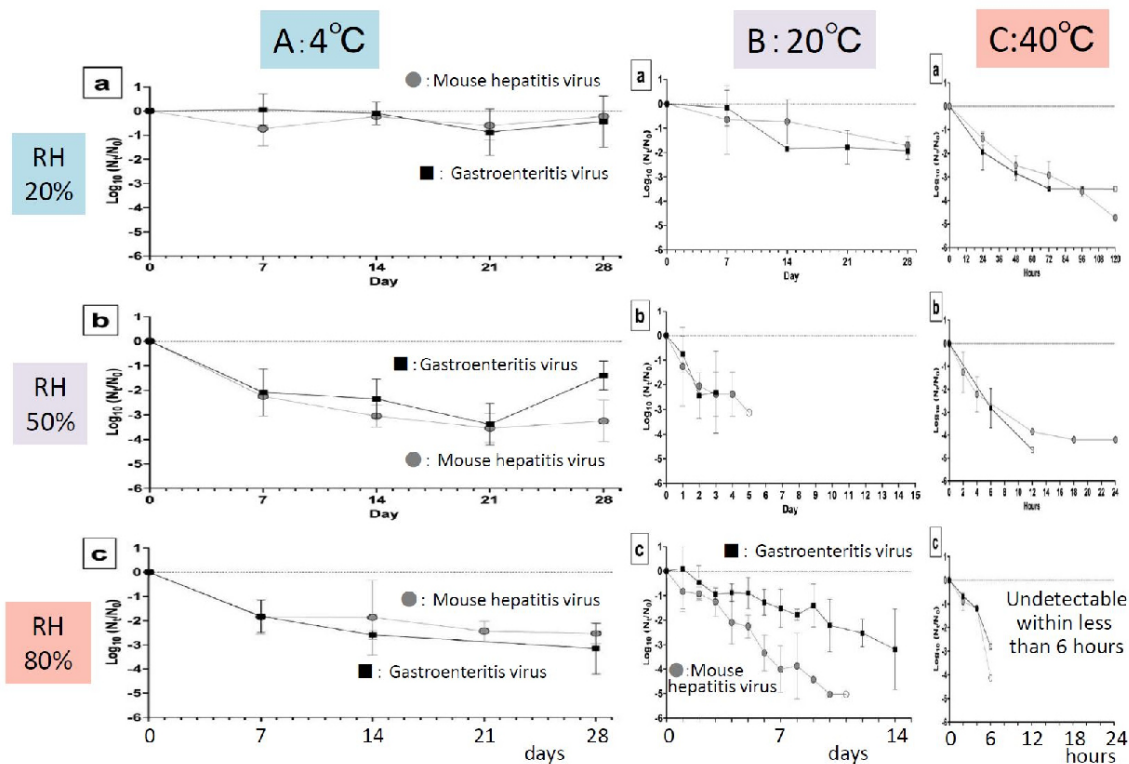
**Figure3: Reduction of SARS-CoV by different temperature and relative humidity**



Cited From Chan Kh et al. Adv Virol 2011;734690 [3]

Mask-wearing keeps nose and throat moisturized (probably over 95%) and keeps the temperature at least at over 30 °C, and is effective. As mentioned earlier, this is why even simple masks are effective. When infected, high fever is expected, but it should not be lowered especially with medicines. This was discussed more in detail in Med Check No 16.

**Figure4: Reduction of viruses by different temperature and relative humidity**



Cited From Casanova LM et al. Appl Environ Microbiol 2010; 76:2712-7 [4]

### **3. If masks are not available, use handkerchief or hand-made masks. They can be washed and used repeatedly.**

Mask shortage is lingering world widely. In order to keep nose and throat warm, not only masks but also covering mouth with handkerchief is very effective. You can find how to make masks with handkerchief at the following website.

<https://news.nifty.com/article/domestic/society/12159-0303m040324/>

[https://m.facebook.com/story.php?story\\_fbid=2828756543847418&id=415021871887576](https://m.facebook.com/story.php?story_fbid=2828756543847418&id=415021871887576)

Hand-washing is also important, but hand-washing for more than 10 times a day is less effective than mask-wearing. Some experts recommend to frequently change masks in a day, but this would aggravate the shortage. Moreover such an advice is unrealistic as they are not available in market.

Even if a small amount of virus that may be on your hands enters nose and mouth, if you can suppress its growth in the body, the onset can be prevented. Masks can be washed and used repeatedly. When washed repeatedly, the metal part of masks might become rusty. If so, drying them under the sun would also kill viruses as they are weak to ultraviolet, and they can be used repeatedly. Spraying alcohol would also be effective in sterilizing masks.

### **4. Sipping hot drink while blowing on it helps warm throat and the whole body.**

Some media report "if viruses really die at 26-27 °C , they should die as they enter the body, but they do not. So this information is false, and drinking hot water is not effective, either". However, this is totally based on misunderstanding.

As mentioned in points 1 and 2 above, corona virus and transmissible gastroenteric virus (TGEV), as well as influenza virus, persist for a long time in a cold and dry environment. On the contrary, they are rapidly inactivated at high humidity and temperature above 38-40 °C , which is like the body temperature when we have fever.

The temperature of hot water which we can drink in big galps is probably more or less around 46-50 °C .

When it is over 55 °C , it would be difficult to drink in big galps. By drinking a hot drink slowly, it will warm throat while passing. It takes time for kuzuyu (drink made with arrowroot starch) to cool down. So prepare it with boiling water, and sip it while blowing on it. This warms and moisturizes throat and the whole body, and also suppresses the growth of viruses which just entered the throat. The most important measure for preventing infection and onset is to keep the body warm including nose and throat.

### **5. Get moderate exercise during the day and enough sleep at night, but do not rely on sleeping pills.**

When you have fever, take a rest. When you are not infected and healthy, get moderate exercise during the day and have enough sleep at night to avoid accumulation of stress. A lack of sleep is the biggest cause of stress.

A lack of sleep with persistent excessive stress activates sympathetic nerve and suppresses immunity, constricting vessels and impeding blood flow. This condition is called ischemia, which injure tissue due to lack of oxygen and nutrition. As viruses easily enter from the injured tissue with excessive expression of a receptor enzyme ACE2, as shown in the previous article (Five Don'ts Part 2), such a condition leads to COVID-19.

At night, sympathetic nerves are calmed down, and parasympathetic nerves become dominant. The injuries created during the day are healed by morning by immunity which is activated during sleep at night. However, if the stress during the day is too intense and/or sleep hour is too short, the injuries cannot be healed during sleep, but is accumulated and develop inflammation, causing disorder at various parts of the body [5,6]. This is how sickness is caused. Different people might develop disorder at different parts of the body, but the cause is very similar.

Most patients who develop severe COVID have some kind of sickness at baseline. For instance, in those with only hypertension, the disease is 2.3 times more likely to become severe, and in those with diabetes and/or heart disease as well as with history of stroke, it is 3-5 times more likely to become severe as shown in the previous article (Five Don'ts Part 2). People with chronic illness

have damaged tissue caused by excessive stress and/or a lack of sleep, and inflammation to heal the injuries. Viruses easily penetrate into the body from the wound or site of inflammation with excessive expression of a receptor enzyme ACE2, leading to be infected easily and aggravated.

Novel corona virus is more contagious than SARS, which spread in 2003, but these two viruses are very similar. SARS-CoV enters the body by binding to ACE2 receptors that are present in any cells. One of the most prominent differences between influenza virus and SARS-CoV or SARS-CoV-2 is that the flu virus infects cells

only in respiratory organs and does not enter blood nor infect other parts of the body while the latter infect not only infect respiratory cells but also digestive system including mouth and gut and enter into blood, circulating the whole body and infecting cells all over the body.

Most children and the youth are usually healthy and have less injured tissues. That is why they are less likely to be infected or develop severe infection. Young people with chronic illness are infected more easily and might become severer than without. Majority of people do not need to be so afraid of novel corona virus as long as they follow the recommendations we described in this series.

### Five Don'ts

1. **Do not use antipyretics** to lower fever. Human body can endure fever at 40-41°C . Because viruses are weak to heat, lowering fever with antipyretics will lead to regrowth of the viruses. In particular, non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided, because they also weaken your defense system. Acetaminophen (paracetamol) is basically harmful, as well.
2. **Do not use corticosteroids** for the same reason. Its use in the early phase of infection induce higher mortality.
3. **Do not use Tamiflu and Xofluza** as they suppress immunity.
4. **Avoid ACE inhibitor and ARB** (angiotensin II receptor blocker) as possible, because they increase ACE2, an enzyme counteracting angiotensin II which acts as a main receptor for SARS-CoV-2 to infect human. Apart from anticancer drugs, corticosteroids and overt immunosuppressants used for collagen diseases etc., there are many other drugs that reduce your immunity (**hidden immunosuppressants**). They include antihypertensive drugs especially ARBs and calcium antagonists, sleeping pills, anxiolytics, cholesterol lowering agents, antidiabetics (glitazons, DPP-4 inhibitors, GLP-1 agonists) and PPIs etc. They should be avoided unless they are essential.
5. **Do not sit up late at night**. A lack of sleep can be the biggest cause of stress that impairs your immunity.

### Five Do's

1. **Simple mask-wearing is effective**. It reduced illness from SARS to one-third, and is more effective than frequent hand-washing (>10/day) that halved it.
2. Mask-wearing is effective because SARS-CoV is vulnerable to high temperature with humidity. It helps your **nose and throat keep warm and moisturized**.
3. When masks are not available, **make it with cloths or handkerchief**. They can be washed and used repeatedly.
4. **Drink hot drinks** such as "kuzuyu (drink made from arrowroot starch). Blowing on and sipping it help warm the throat and the whole body.
5. **Get moderate exercise** during the day, and have **enough sleep** at night, but **without sleeping pills**.

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# MED CHECK

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