Modifiable Risk Factors for Covid 19

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Overview

- Who Gets COVID
- Modifiable Risk Factors
  - Co-morbidities
  - Blood Sugar Control
  - Diet
  - Nutrient Status
  - Environmental Toxins
- The Promise of Antiviral Flavonoids
- Supplementation
- Mathematics of Converting Risk to Protection
- Putting It All Together

Who Gets COVID and Dies From it in United States

	18-29 yo	30-39 yo	40-49 yo	50-64 yo	65-74 yo	75-84 yo	85+ yo
Cases	Ref	1x	1x	1x	1x	1x	1x
Hospitalized	Ref	2x	2x	4x	6x	9x	15x
Death	Ref	4x	10x	35x	95x	230x	600x

Adapted from: Murray M, Pizzorno J, Morello G. *Killer Immunity*. 2022

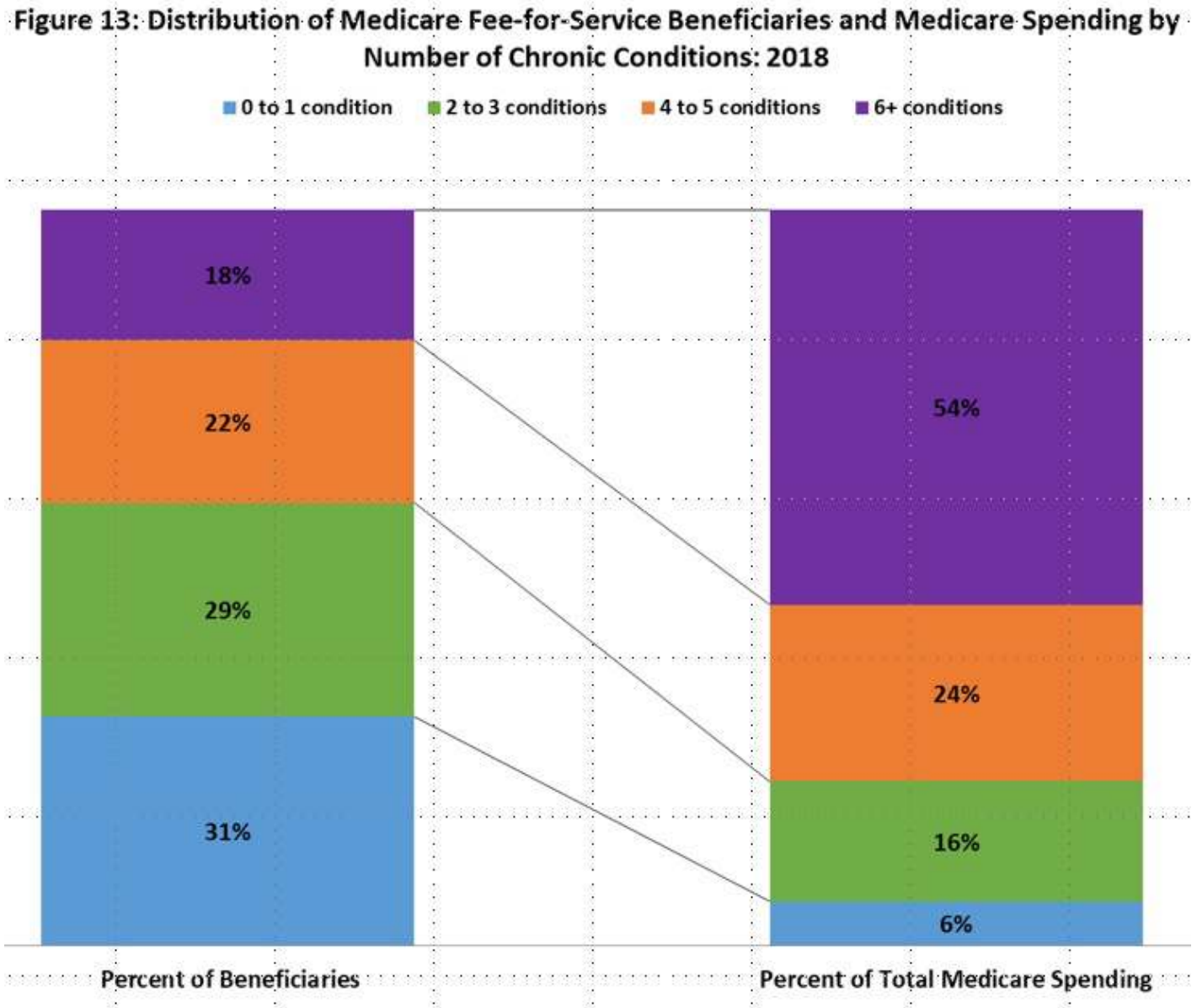
Co-Morbidities!

- 53% of people who die from COVID have **2 or more co-morbidities**
- 75% of vaccinated people who die from COVID have **4 or more co-morbidities**
- US Medicare expenditures mostly for people with **4 or more co-morbidities**

Djaharuddin I, Munawwarah S, Nurulita A, Ilyas M, Tabri NA, Lihawa N. Comorbidities and mortality in COVID-19 patients. *Gac Sanit*. 2021;35 Suppl 2:S530-S532. doi:10.1016/j.gaceta.2021.10.085

People with Multiple Co-Morbidities Account for Most Expenses

- 2018 data
- 6+ comorbidities (14%) account for 54% of costs
- 4 or more comorbidities account for 78% of costs

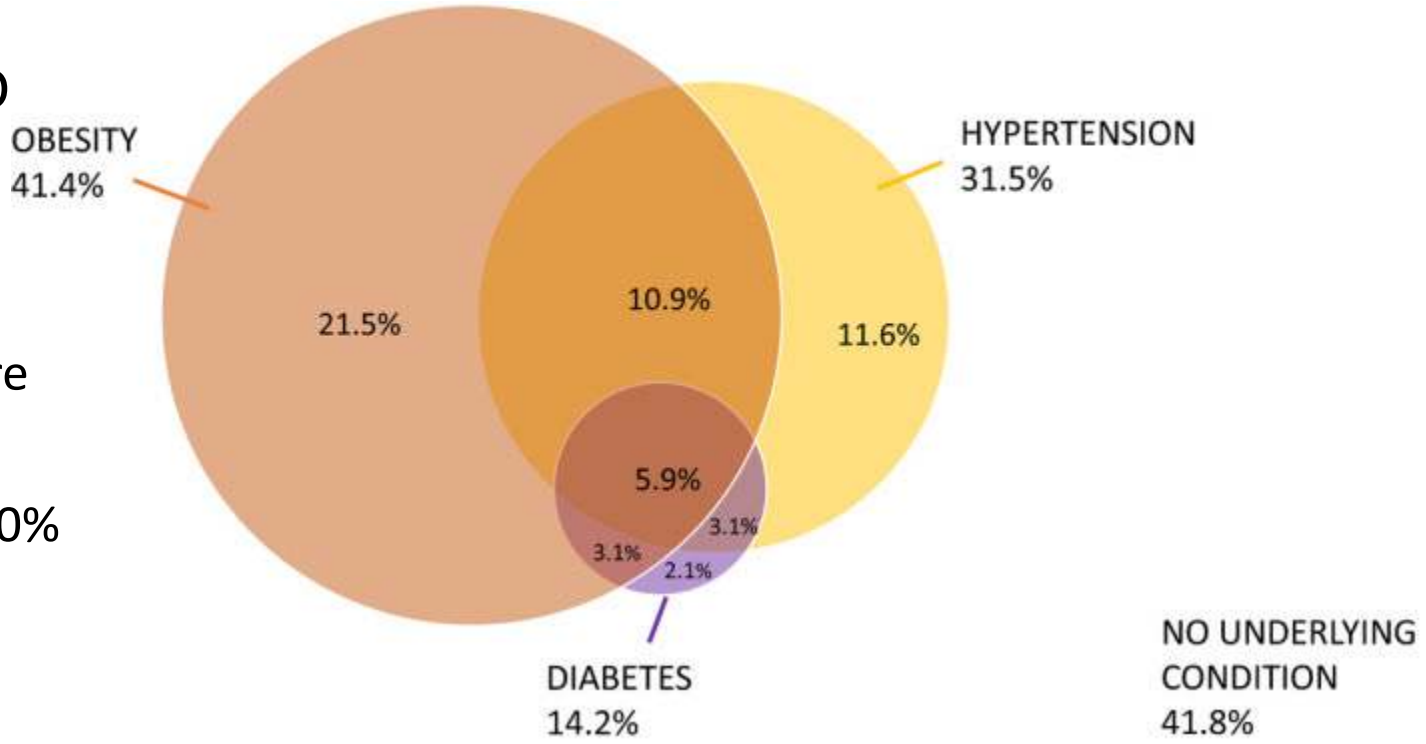


Chartbook and Charts | CMS (accessed 1/15/2022)

Co-Morbidities

Co-Morbidities

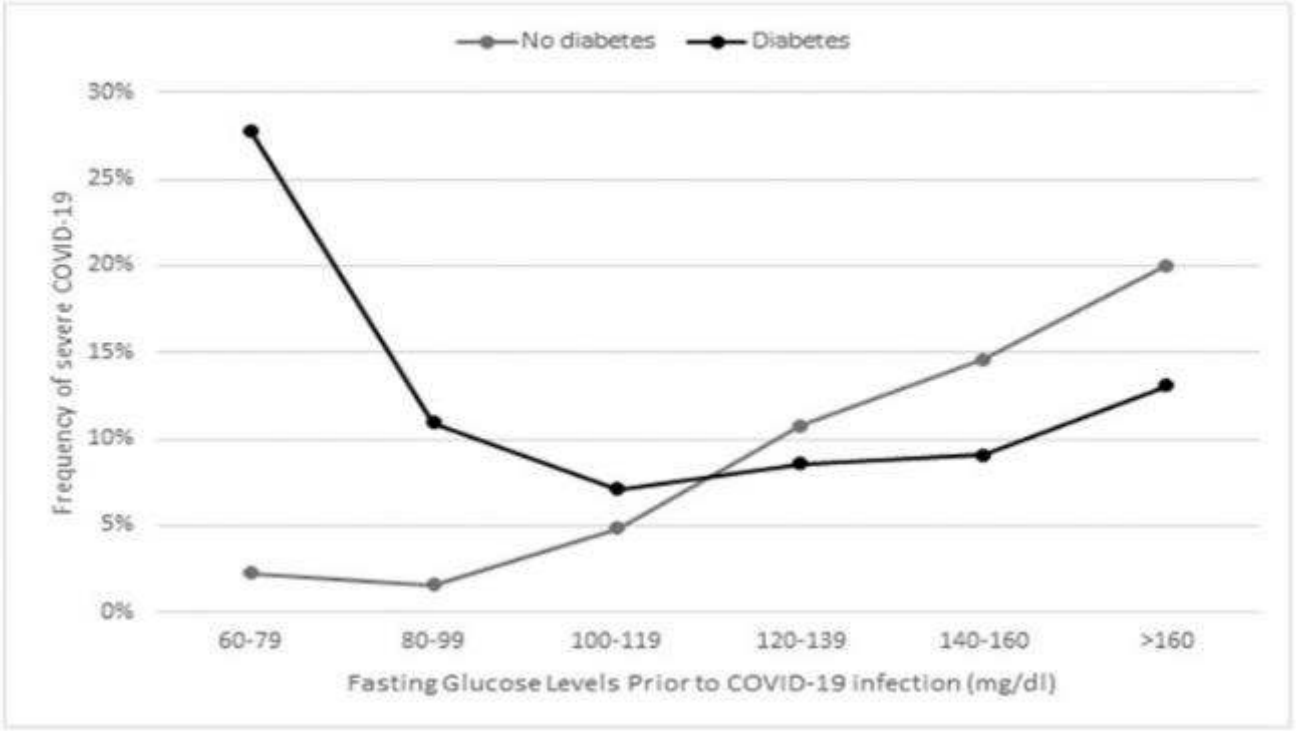
- Virtually everyone who died from COVID has one or more comorbidities.
- 63.5% of COVID hospitalizations attributable to 4 conditions:
  - Diabetes, obesity, hypertension, heart failure
- UK study of 2,217 patients:
  - 1-2 co-morbidities increased risk of death 70%
  - 3 or more had 130% increased risk of death
- Similar numbers from China:
  - 1 co-morbidity increased risk of death 79%
  - Multiple increased risk of death to 159%



O'Hearn M, Liu J, Cudhea F, et al. Coronavirus Disease 2019 Hospitalizations Attributable to Cardiometabolic Conditions in the United States: A Comparative Risk Assessment Analysis. *J Am Heart Assoc*. 2021;10(5):e019259.
Mason KE, Maudsley G, McHale P, et al. Age-Adjusted Associations Between Comorbidity and Outcomes of COVID-19: A Review of the Evidence From the Early Stages of the Pandemic. *Front Public Health*. 2021;9:584182

Blood Sugar Control Hugely Impacts Risk

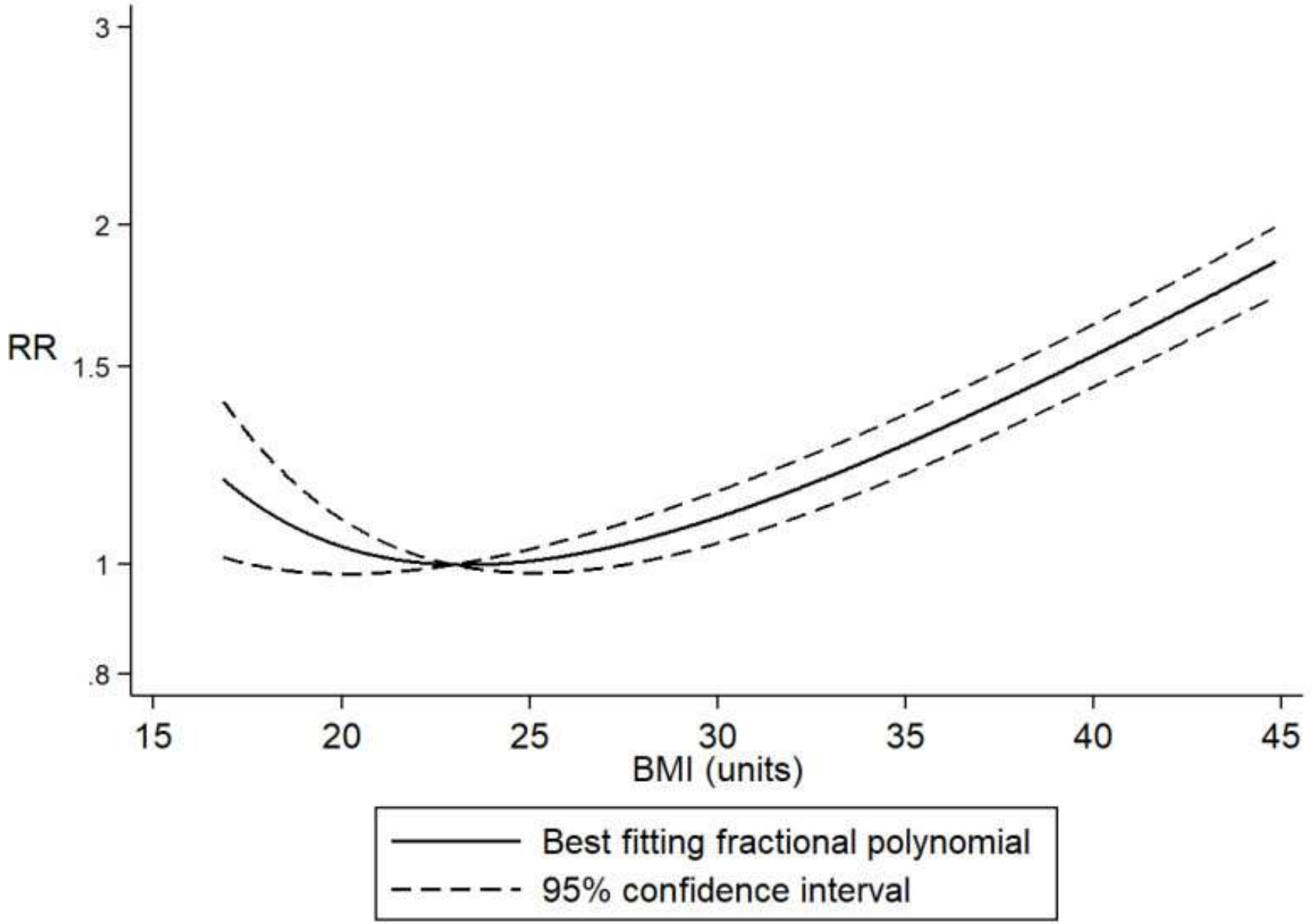
- While most of the research is on overt diabetes, even just poor blood sugar control in non-diabetics increases risk of all aspects of COVID
- For diabetic patients, both high and low glucose levels are risk factors for severe COVID-19
- Blood sugar control critical for COVID resistance



Shauly-Aharonov M, Shafrir A, Paltiel O, et al. Both high and low pre-infection glucose levels associated with increased risk for severe COVID-19: New insights from a population-based study. *PLoS One*. 2021;16(7):e0254847.

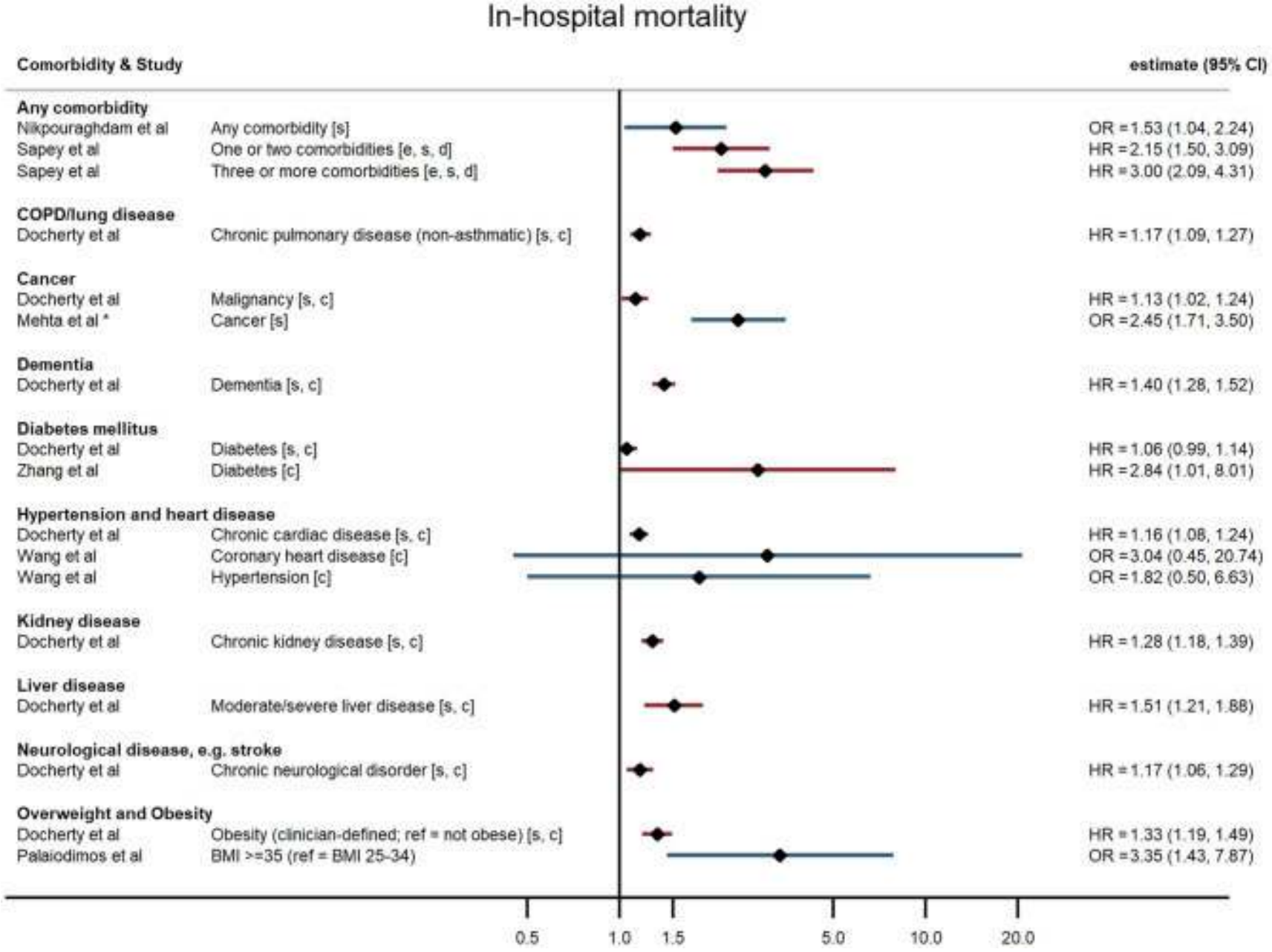
Obesity

- Much of obesity correlation due to insulin resistance
- Strong correlation with inflammation
- Strong correlation with environmental toxins



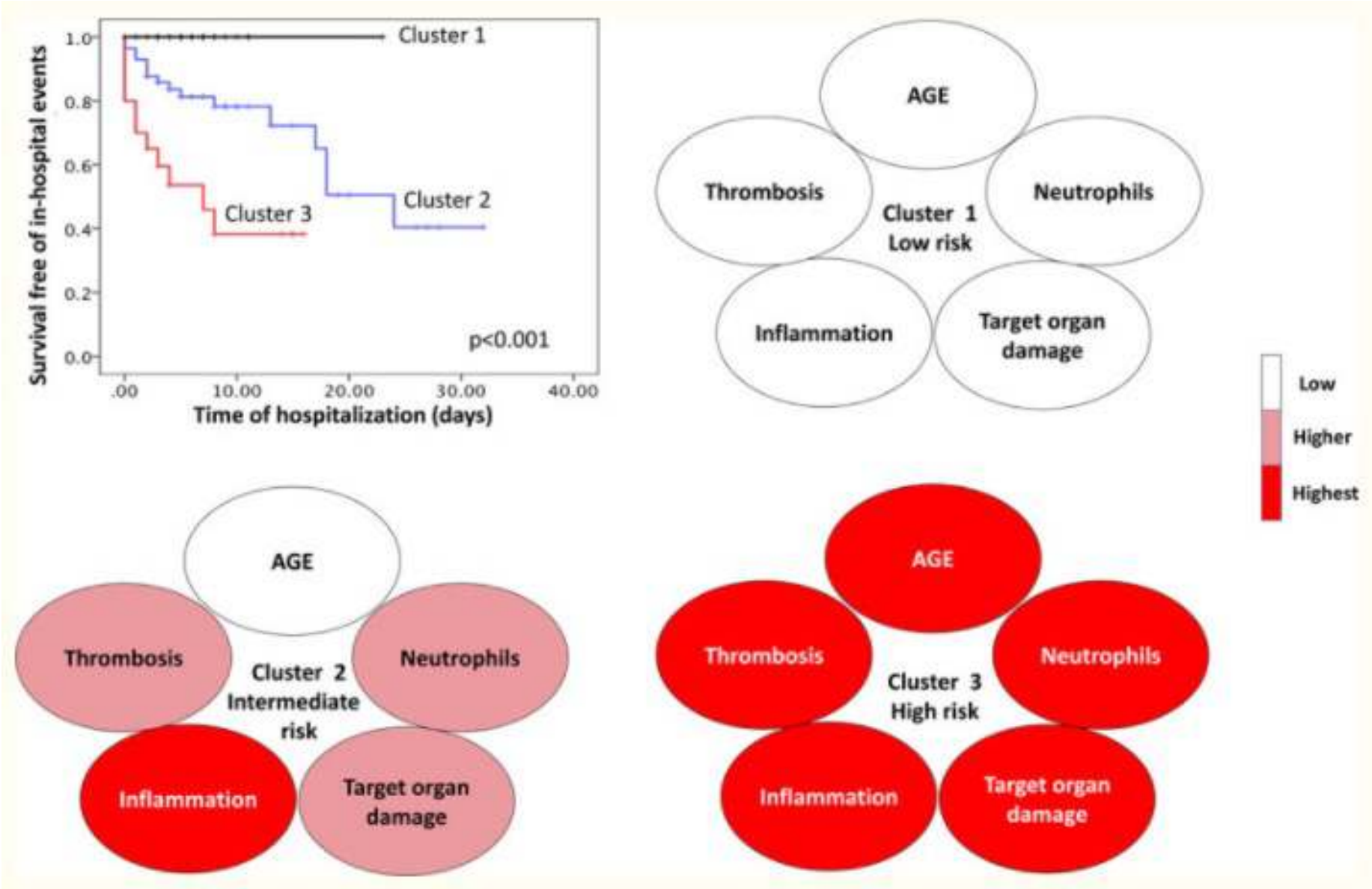
Mahamat-Saleh Y, Fiolet T, Rebeaud ME, et al. Diabetes, hypertension, body mass index, smoking and COVID-19-related mortality: a systematic review and meta-analysis of observational studies. *BMJ Open*. 2021;11(10):e052777.

Hospital Mortality Predictors



Mason KE, Maudsley G, McHale P, Pennington A, Day J, Barr B. Age-Adjusted Associations Between Comorbidity and Outcomes of COVID-19: A Review of the Evidence From the Early Stages of the Pandemic. *Front Public Health*. 2021;9:584182.

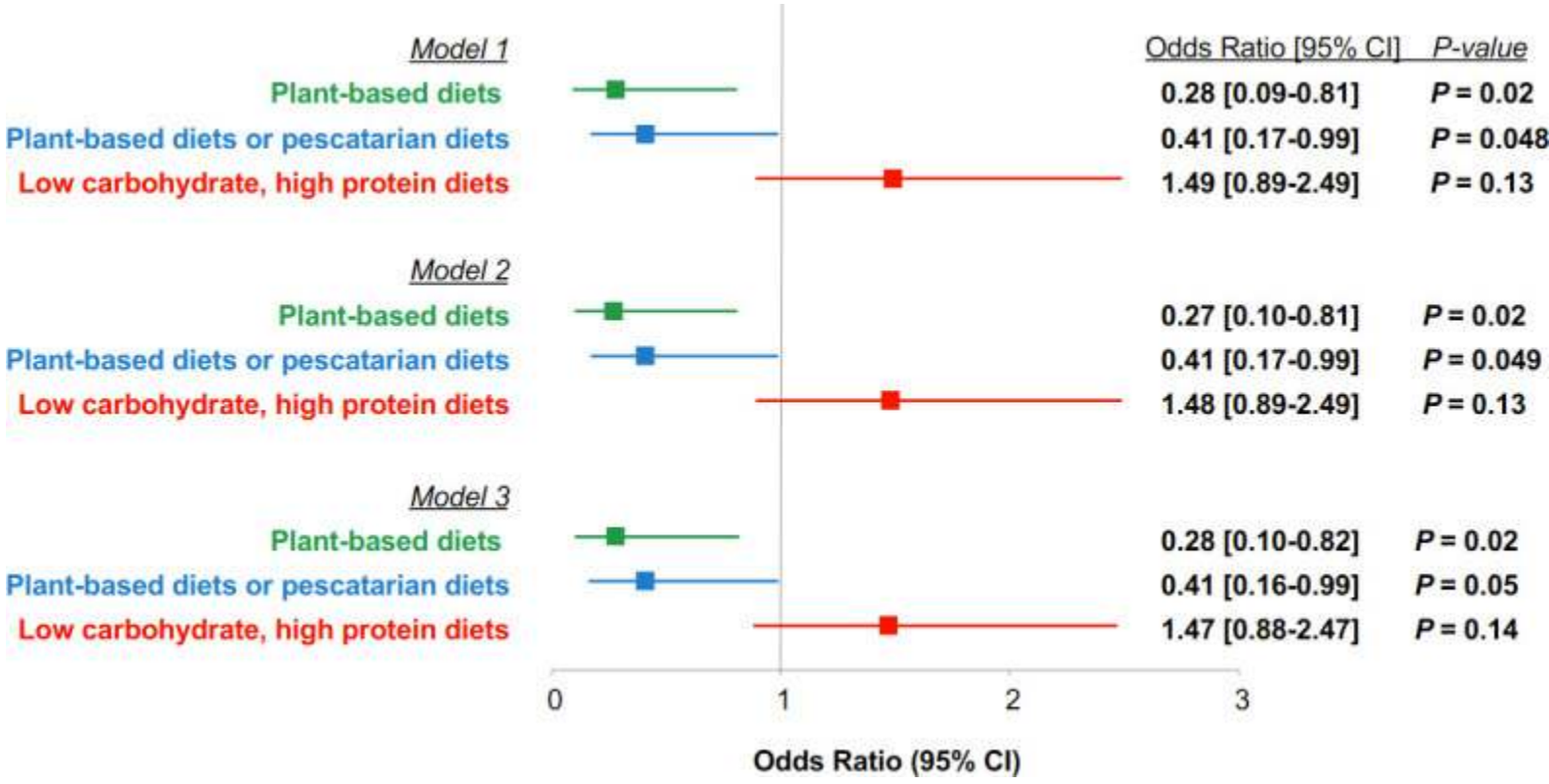
More Risk Factors = More Severe Disease and Increased Death Rate



Ronderos Botero DM, Omar AMS, Sun HK, et al. COVID-19 in the Healthy Patient Population: Demographic and Clinical Phenotypic Characterization and Predictors of In-Hospital Outcomes. *Arterioscler Thromb Vasc Biol*. 2020;40(11):2764-2775

Diet

- 568 cases; 2316 controls
- Self reported diets
- Consistent across different severity criteria
- Model corrections for various potential confounding variables did not affected outcomes



Kim H, Rebholz CM, Hegde S, et al. Plant-based diets, pescatarian diets and COVID-19 severity: a population-based case-control study in six countries. *BMJ Nutr Prev Health*. 2021;4(1):257-266. Published 2021 Jun 7. doi:10.1136/bmjnph-2021-000272

Nutritional Status

Vitamin C and COVID Resistance

Vitamin C	Infect	Severe	LongC	Death	PMIDs	Notes
Blood level		82% <0.4 mg/dL			34243781	94% undetectable vitamin C in ICU
IV C 7 days		ND		ND	33420963	Only benefit was oxygenation & IL6
IV 12 g bid 7 days		ND		ND	33573699	Longer time in hospital
C + Zn		ND		ND	33576820	

ND = No statistical difference

Simon M, Pizzorno J, Katzinger J. Modifiable Risk Factors for SARS-CoV-2. *Integr Med (Encinitas)*. 2021;20(5):8-14.

Omega-3 Fatty Acids and COVID Resistance

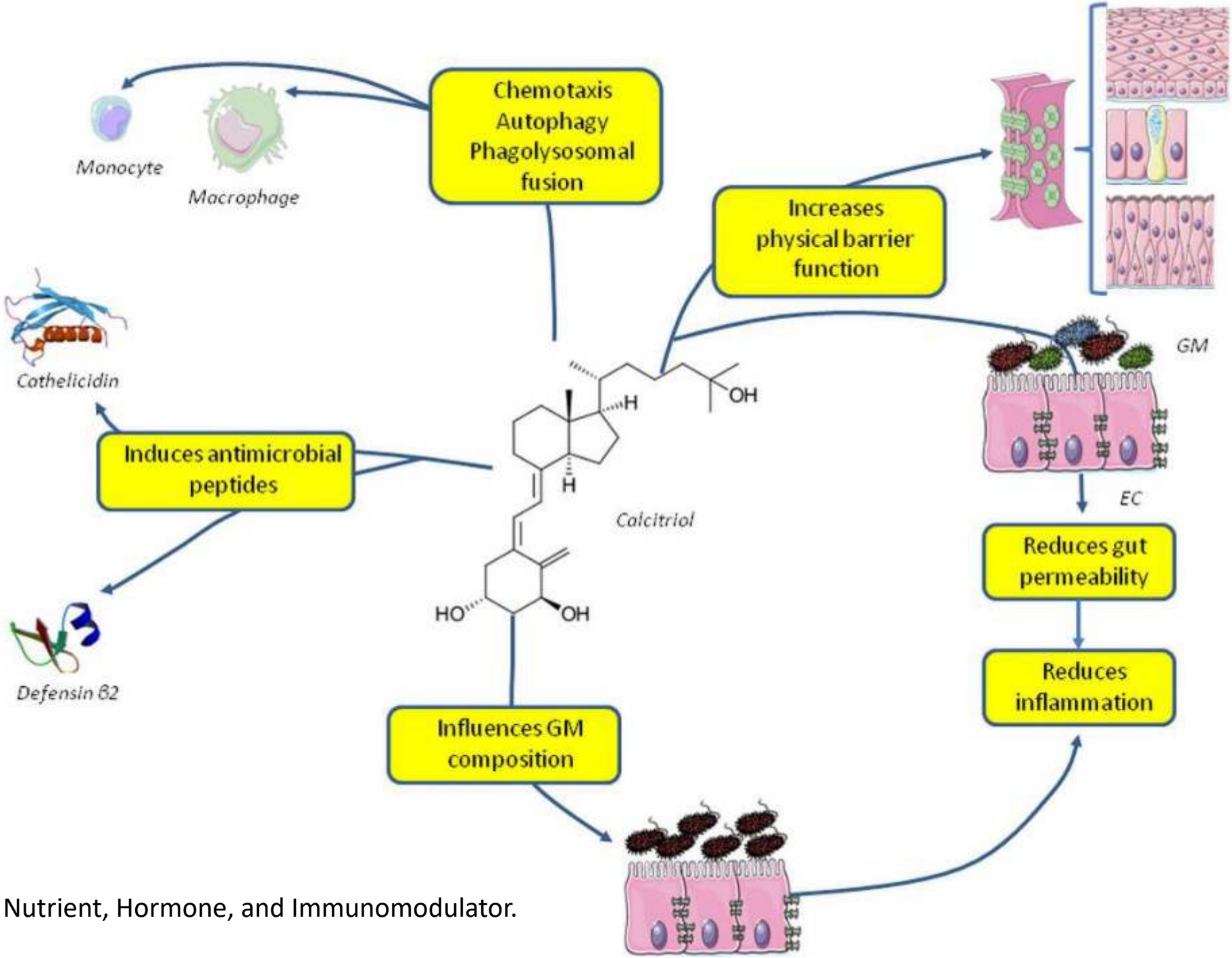
Ω-3	Infect	Severe	LongC	Death	PMIDs	Notes
Deficient		2.2		3.6	34360016	
1000 mg Ω-3 (400 mg EPAs, 200 mg DHAs)/d - 1 mo				0.14	33781275	Survival 21% versus 3% control

Simon M, Pizzorno J, Katzinger J. Modifiable Risk Factors for SARS-CoV-2. *Integr Med (Encinitas)*. 2021;20(5):8-14.

Hard to Overstate Importance of Vitamin D

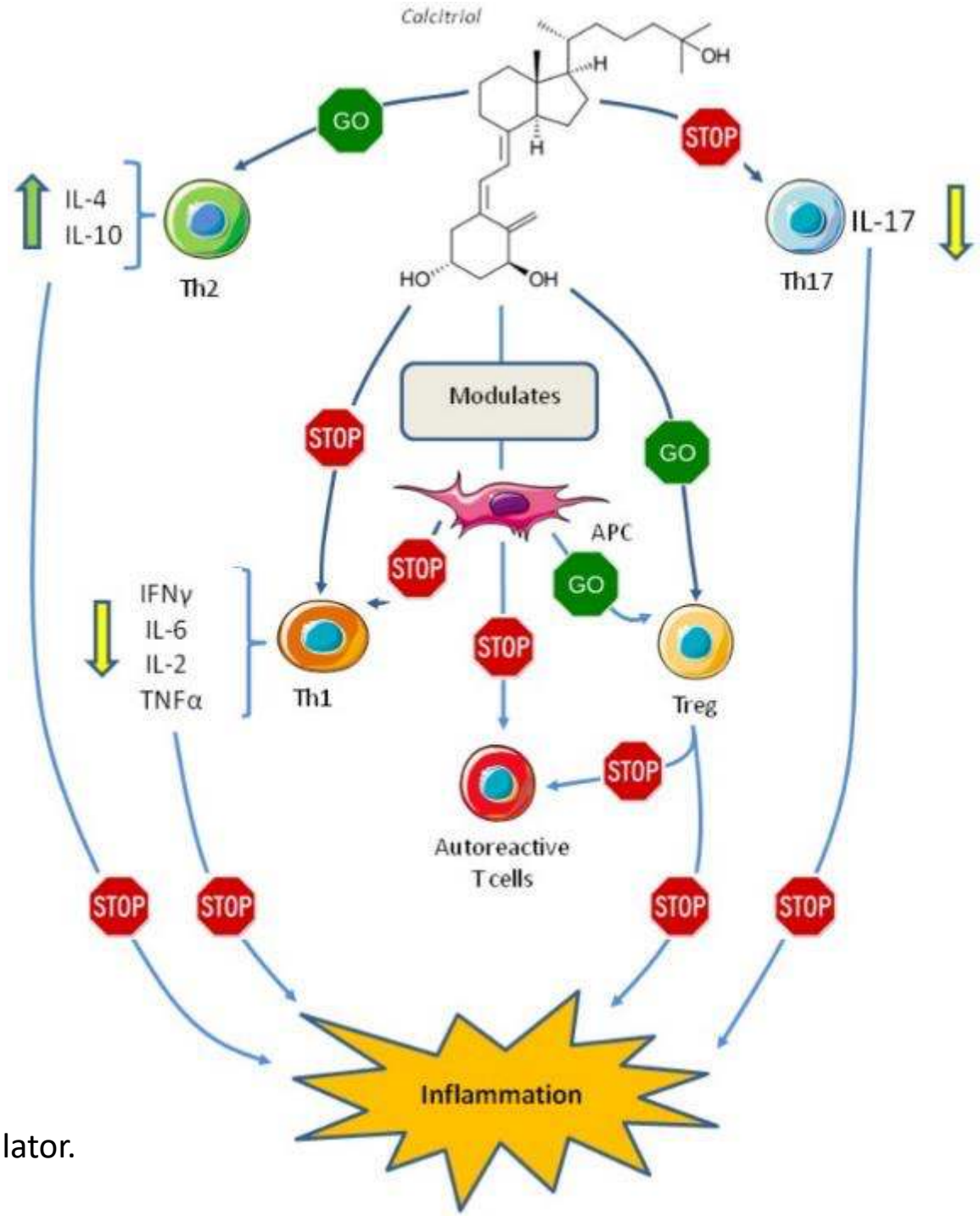
- Immune function
- Inflammation balancing
- Deficiency extremely common

Vitamin D Critical to Many Aspects of Immune Function



Sassi F, Tamone C, D'Amelio P. Vitamin D: Nutrient, Hormone, and Immunomodulator. Nutrients. 2018 Nov 3;10(11)

Vitamin D Critical for Inflammation Balance

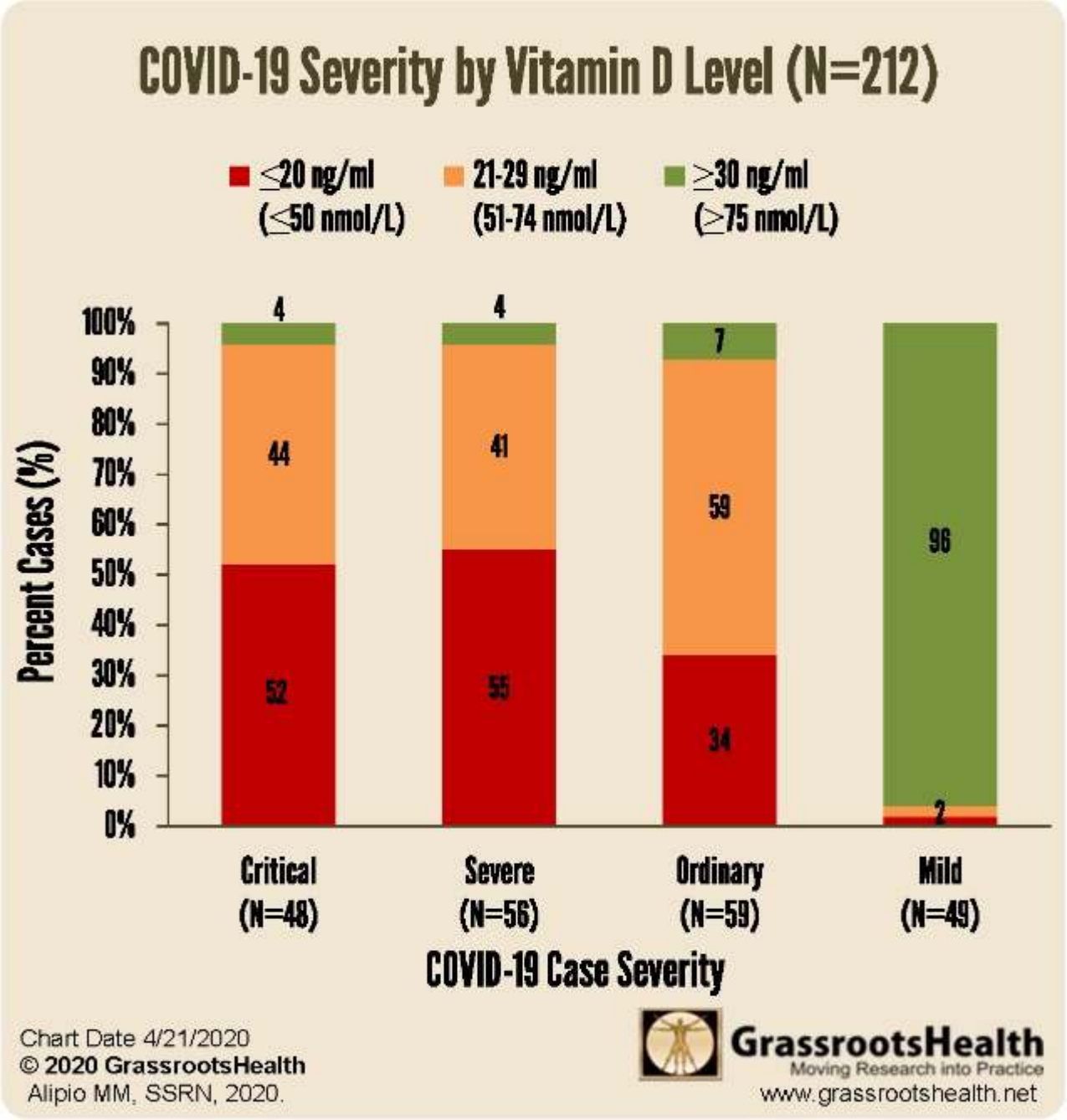


Sassi F, Tamone C, D'Amelio P. Vitamin D: Nutrient, Hormone, and Immunomodulator. Nutrients. 2018 Nov 3;10(11)

Severity Correlates with Deficiency

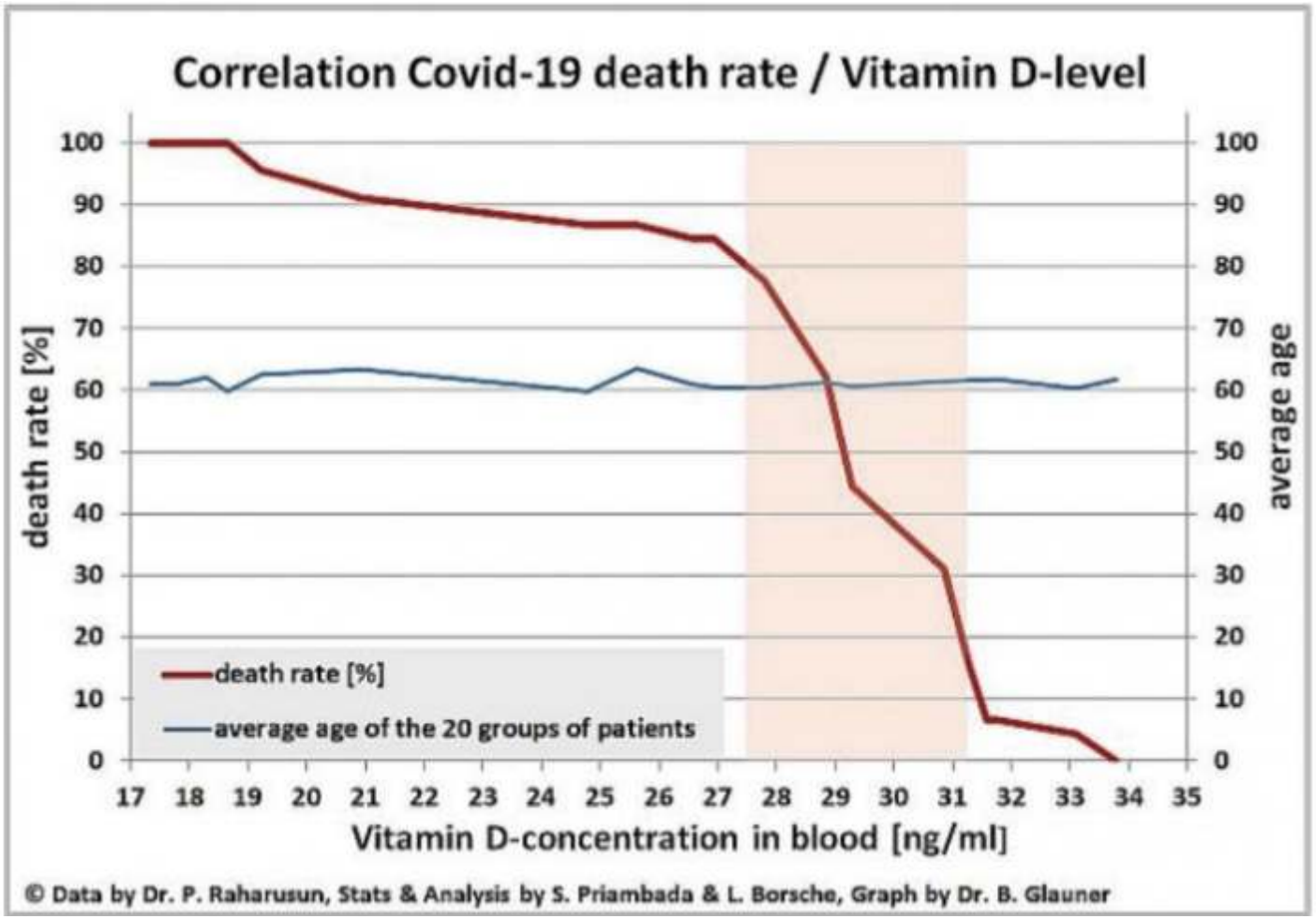
- Optimal: 50-80 ng/ml

No column in optimal range!



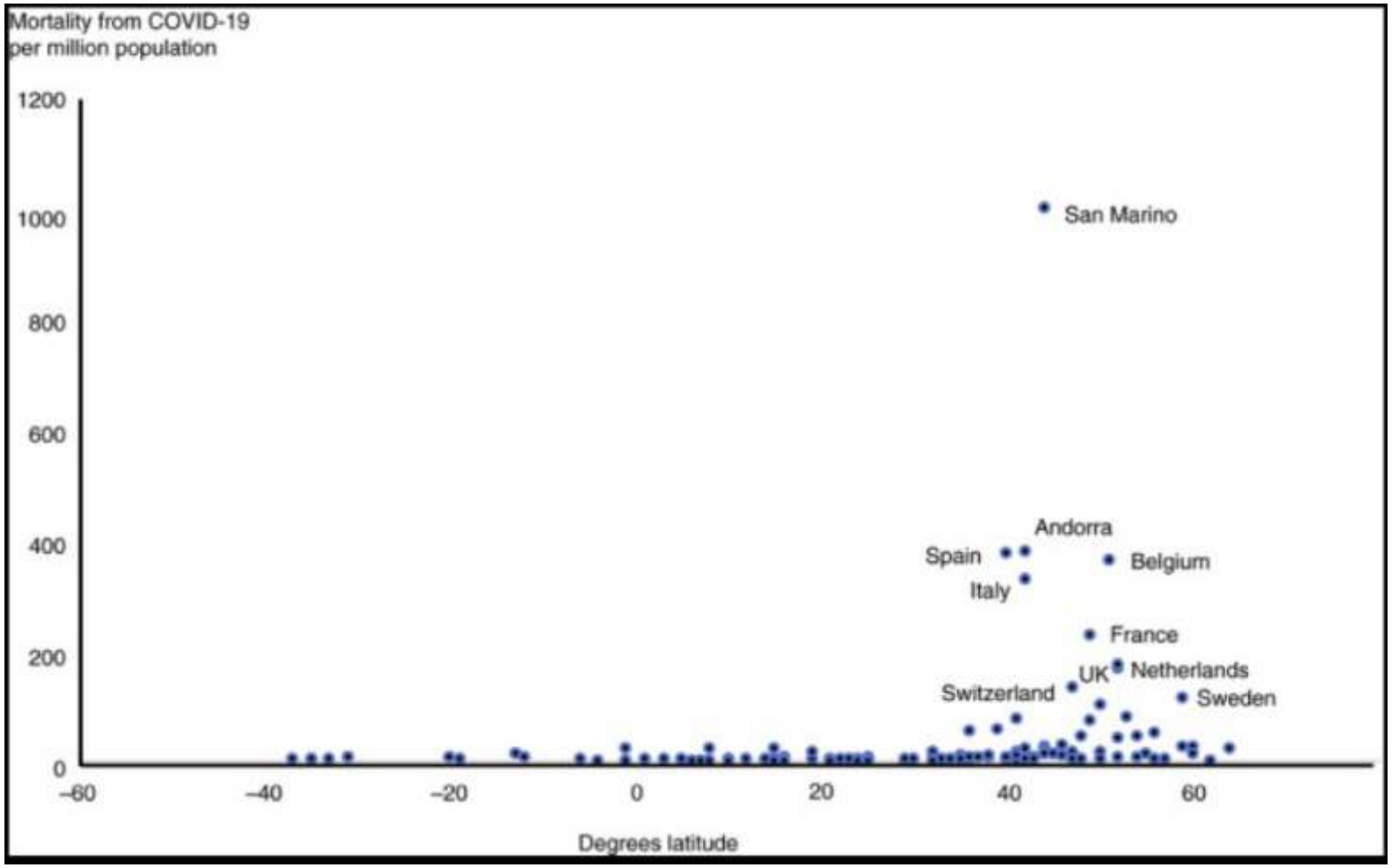
https://www.grassrootshealth.net/blog/first-data-published-covid-19-severity-vitamin-d-levels/ (accessed 2020-06-20)

Vitamin D Critical!!



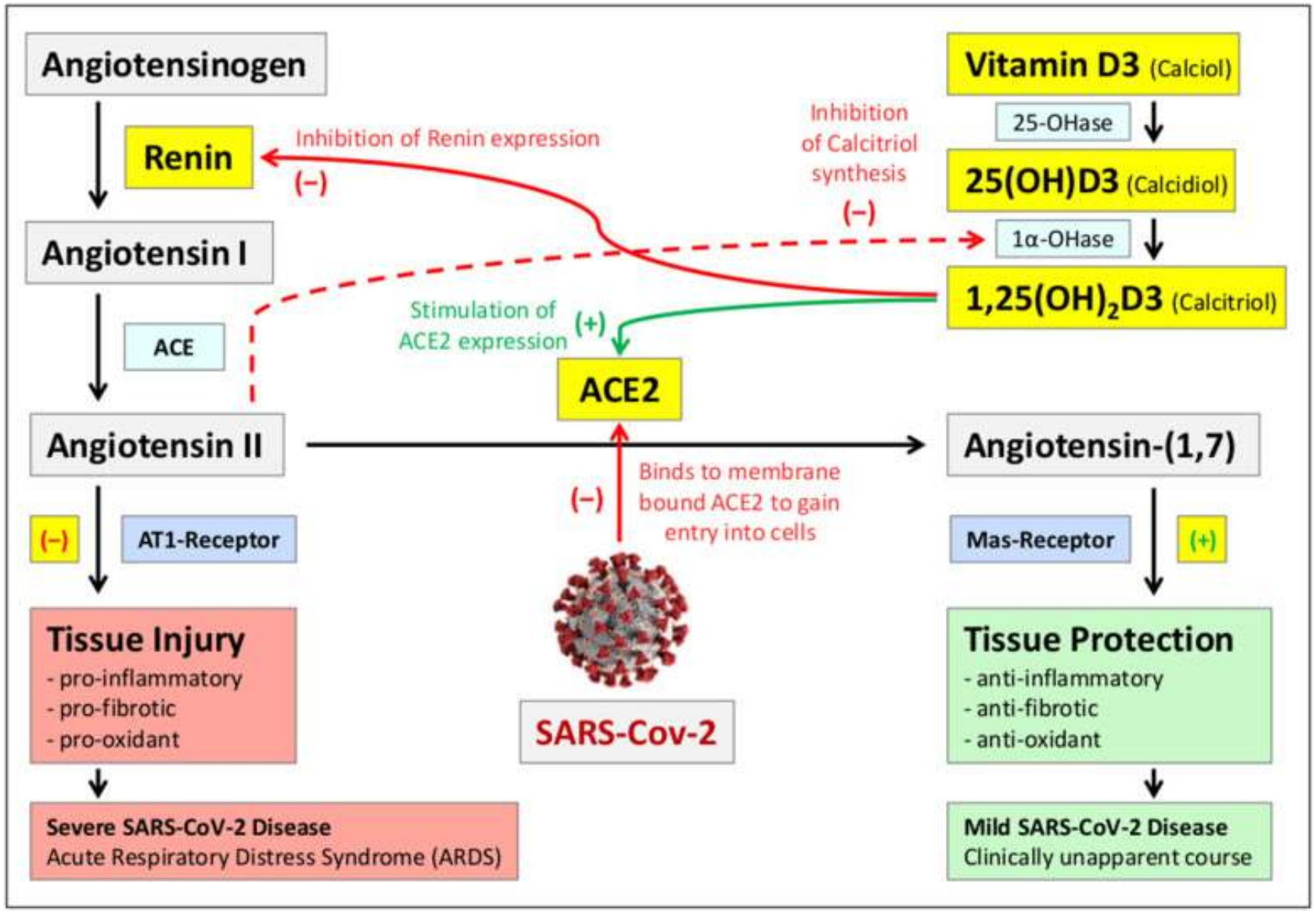
Correlation Between Pandemic & Latitude

- Many possible reasons:
  - Vitamin D
  - UV exposure
  - Higher temperatures
  - Less international travel



Rhodes JM, Subramanian S, Laird E, Kenny RA. Editorial: low population mortality from COVID-19 in countries south of latitude 35 degrees Nort supports vitamin D as a factor determining severity. Aliment Pharmacol Ther. 2020 Jun;51(12):1434-1437 PMID: 32311755

Vitamin D and ACE2



Borsche L, Glauner B, von Mendel J. COVID-19 Mortality Risk Correlates Inversely with Vitamin D3 Status, and a Mortality Rate Close to Zero Could Theoretically Be Achieved at 50 ng/mL 25(OH)D3: Results of a Systematic Review and Meta-Analysis. *Nutrients*. 2021;13(10):3596.

Vitamin D and ACE2

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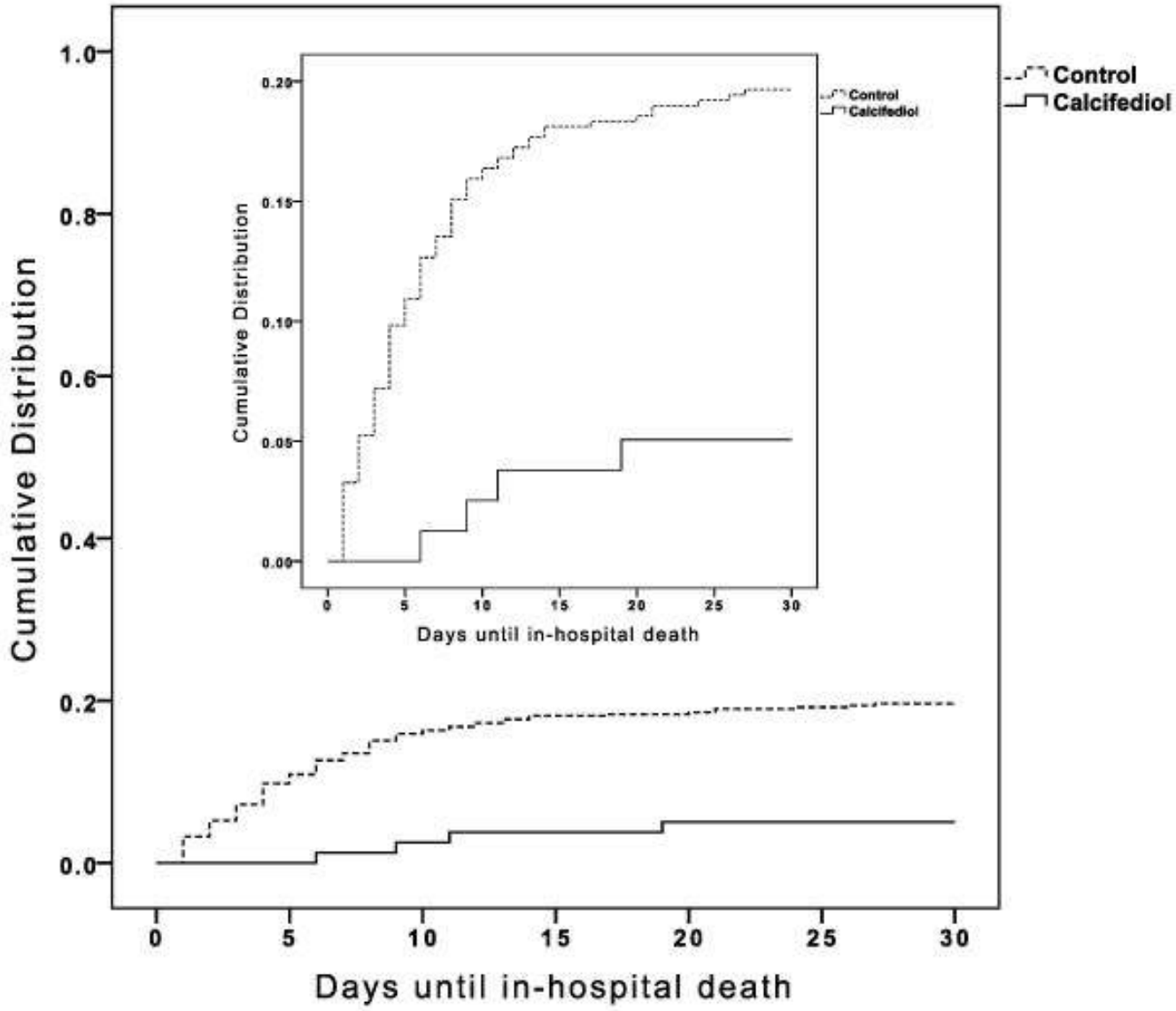
Interaction of vitamin D3 with the renin-angiotensin system (RAS): The renin-angiotensin system (RAS) is an important regulator of blood volume and systemic vascular resistance for the adjustment of blood pressure. The balance between angiotensin II and angiotensin-(1,7) is a critical factor for the proper functioning of the system [87]. Angiotensin-converting enzyme 2 (ACE2) is responsible for converting angiotensin II to angiotensin-(1,7). Angiotensin II primarily triggers vasoconstriction but can also cause inflammation, fibrosis, and oxidative stress in the absence of its counterpart, angiotensin-(1,7). ACE2 is the primary receptor of SARS-CoV-2, which decreases its activity, leading to an increase in angiotensin II levels and a decrease in angiotensin-(1,7) levels. This effect ultimately triggers SARS-CoV-2-induced "acute respiratory distress syndrome" (ARDS) [85,86]. Calcitriol, the active metabolite of vitamin D3, minimizes this effect by inhibiting renin expression and thus angiotensin II synthesis and by stimulating ACE2 expression [88,89], enhancing the conversion of angiotensin II to angiotensin-(1,7). Thus, insufficient vitamin D blood levels lead to the development of severe courses of SARS-CoV-2 disease. In addition, it has been shown that high angiotensin II levels lead to downregulation of the enzyme 1-alpha-hydroxylase [93], which is required for the formation of calcitriol, thereby exacerbating the negative consequences of vitamin D deficiency.

Calcifediol [25(OH)D_3] Effective

- Vitamin D supplementation beneficial, but active form more effective
- Dosage
  - 0.532 mg on entry
  - 0.266 mg on days 3, 7, 14, 21, 28
  - 1 mg = 40,000 IUs



Alcala-Diaz JF, Limia-Perez L, Gomez-Huelgas R, et al. Calcifediol Treatment and Hospital Mortality Due to COVID-19: A Cohort Study. *Nutrients*. 2021;13(6):1760.

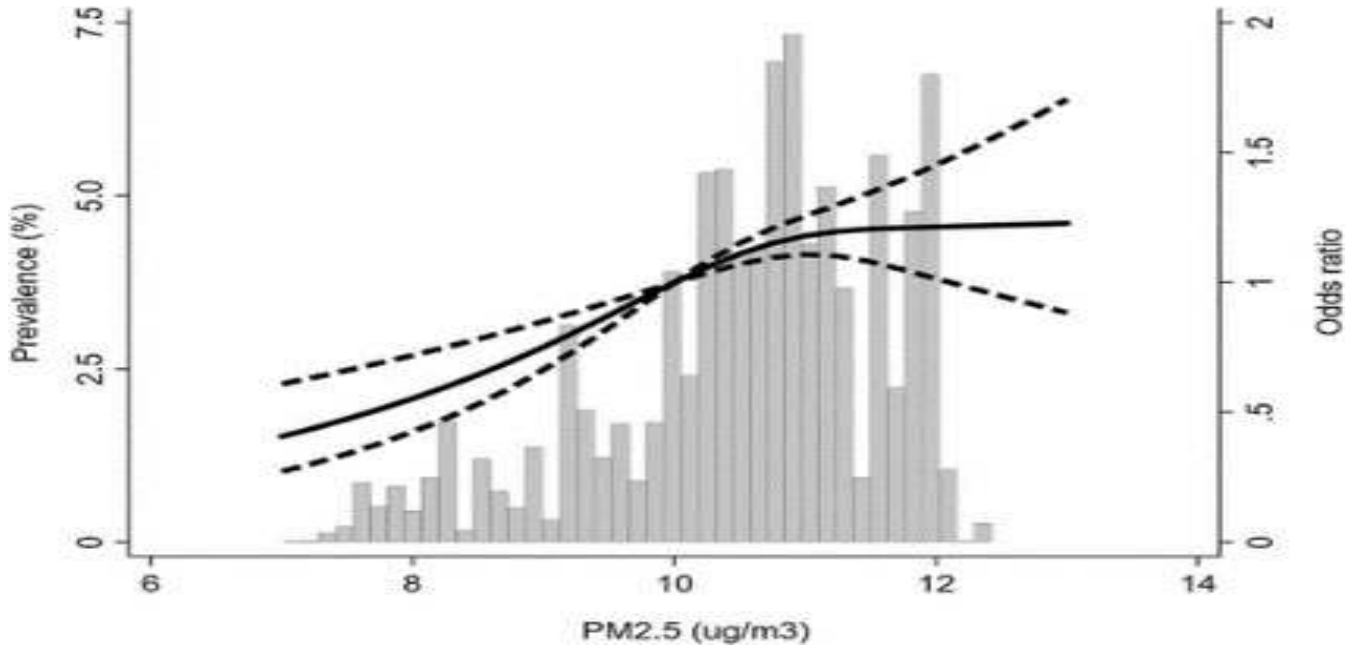
Clinical Application

- Giving vitamin D to seriously ill COVID patients has limited benefit
  - Probably because activation in liver is too slow
- Giving activated vitamin D—25(OH)D_3—very effective

Toxin Exposure

$PM_{2.5}$ Levels Proportional to COVID Risk

- 1 µg/m^3 increase in 10-year annual average PM2.5 associated with 18% higher hospitalization (OR: 1.18).



Mendy A, Wu X, Keller JL, et al. Air pollution and the pandemic: Long-term $PM_{2.5}$ exposure and disease severity in COVID-19 patients. *Respirology*. 2021;26(12):1181-1187.

Air Pollution Increases Many Parameters of COVID-19 Disease

- Except ozone??

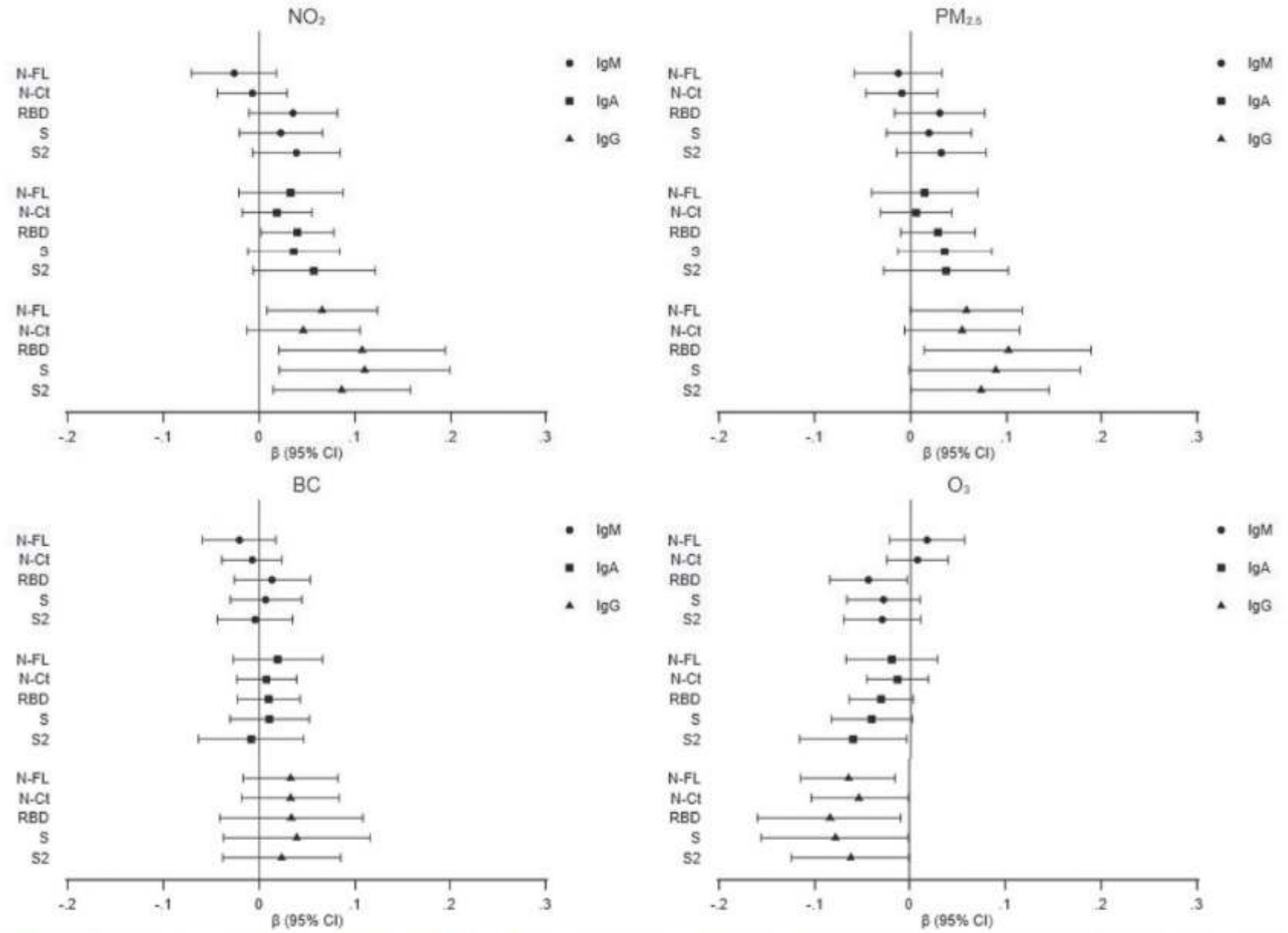


Figure 1. Association of air pollutants—(A) NO_2, (B) $PM_{2.5}$, (C) BC, and (D) O_3)—with levels of IgM, IgA, and IgG against five viral target antigens among participants of the COVICAT study who were seropositive ($n = 743$). Linear regression beta coefficients and 95% CIs were adjusted for potential confounders. The model was adjusted for age, sex, education (less than primary/primary/secondary/university), deprivation index (quintiles), population density, type of survey (online/telephone), and batch. Precise numerical values are shown in Table S6. Note: BC, black carbon; CI, confidence interval; COVICAT, COVID-19 cohort in Catalonia study; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; NCt), nucleocapsid C-terminal region; NFL, nucleocapsid full protein; NO_2, nitrogen dioxide; O_3, ozone; $PM_{2.5}$, fine particulate matter; RBD, receptor-binding domain; S, spike full protein; S2, S2 fragment.

Kogevinas M, Castaño-Vinyals G, Karachaliou M, et al. Ambient Air Pollution in Relation to SARS-CoV-2 Infection, Antibody Response, and COVID-19 Disease: A Cohort Study in Catalonia, Spain (COVICAT Study). *Environ Health Perspect*. 2021;129(11):117003.

Air Filters Work

- Just 2 days in a clean room
- Merv-12 filter
- 33-58% reduction in inflammatory mediators
- Decrease in blood pressure

TABLE 33.3 Reduction in Blood Pressure and Inflammatory Markers After 48 Hours of Residence in a Room with a MERV 12 Filter Unit

Cardiovascular	Biomarkers
Systolic pressure – avg. 2.7 mm Hg drop	IL-1B – 58% reduction
Diastolic pressure – avg. 4.8% mm Hg drop	Soluble CD40 ligand – 55% reduction
Exhaled nitrous oxide – 17% drop	Myeloperoxidase – 33% reduction
	Monocyte chemoattractant protein 1–17.5% reduction

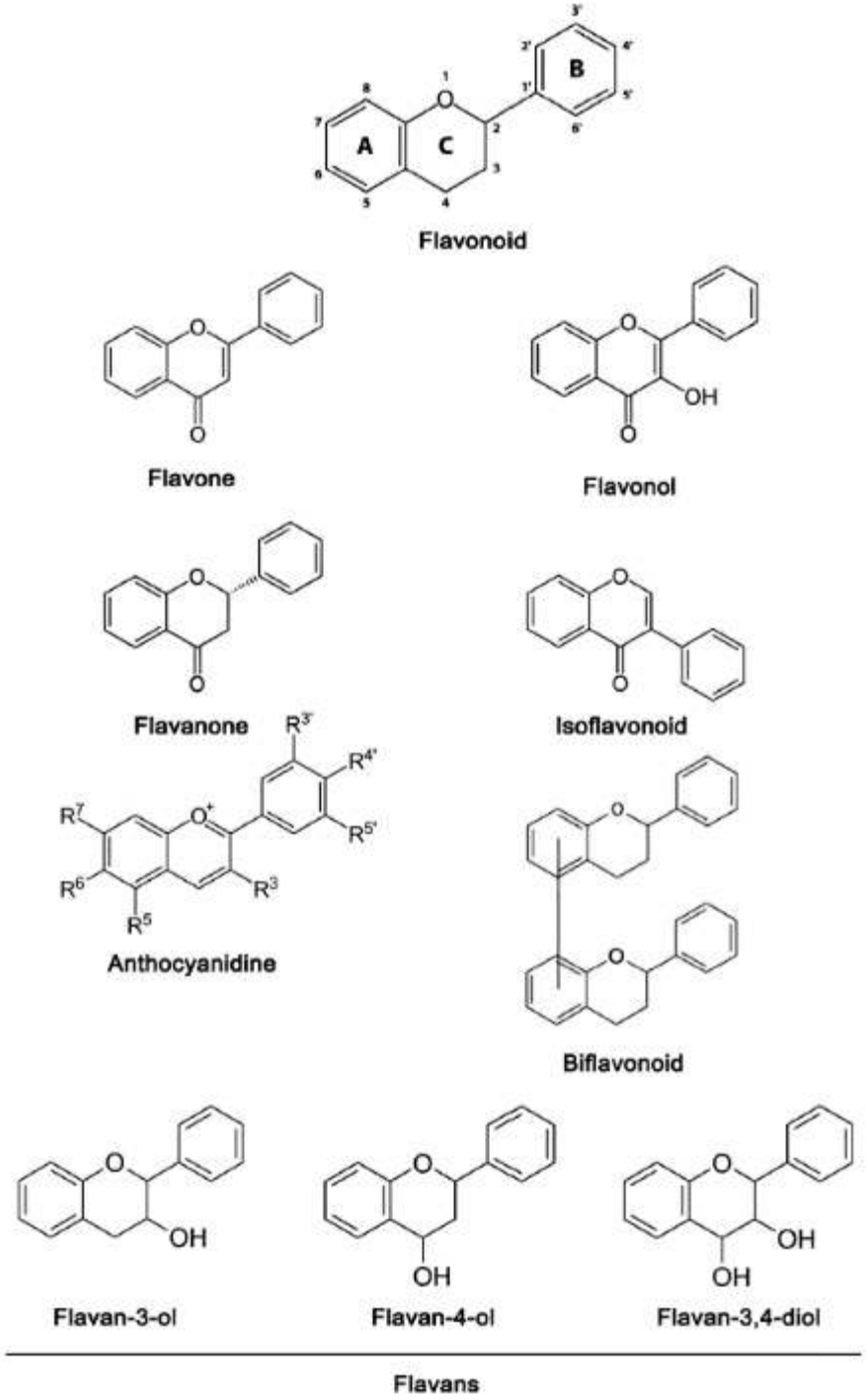
Data from Chen, R., Zhao, A., Chen, H., Zhao, Z., Cai, J., Wang, C., et al. (2015). Cardiopulmonary benefits of reducing indoor particles of outdoor origin: a randomized, double-blind crossover trial of air purifiers. *Journal of the American College of Cardiology, 65*(21), 2279–2287.

From Crinnion W, Pizzorno J. Clinical Environmental Medicine. Elsevier 2019

The Promise of Anti-viral Flavonoids

Flavonoids Defined

- Complex polyphenolic molecules with a core of 2 phenyl rings plus a heterocyclic ring
- Wide range of number of additional rings, substitutions
- Play a major role in the color and taste of foods
- >6, 000 flavonoids that have been structurally identified thus far
- PubMed “flavonoids” with limit “human” produced over 50,000 hits



Zakaryan H, Arabyan E, Oo A, Zandi K. Flavonoids: promising natural compounds against viral infections. Arch Virol. 2017 Sep;162(9):2539-2551. PMID: 28547385

Antiviral Activities

- Many flavonoids have documented antiviral efficacy and several key mechanisms have been identified
  - Directly viricide
  - Block viral binding
  - Block transcription
  - Block co-option of intracellular enzymes required for replication
- Secondary antiviral effects:
  - Zinc ionophores—i.e., facilitate zinc entry into cells where it directly inhibits viral replications

Zakaryan H, Arabyan E, Oo A, Zandi K. Flavonoids: promising natural compounds against viral infections. Arch Virol. 2017 Sep;162(9):2539-2551. PMID: 28547385

Example Viruses Inhibited by Flavonoids

- Avian influenza H5N1 virus
- Human cytomegalovirus (HCMV)
- EBV
- Herpes simplex I and II
- Severe acute respiratory syndrome coronavirus (SARS-CoV)
- Rhesus rotavirus
- Chikungunya virus
- Japanese encephalitis virus (JEV), etc.

Zakaryan H, Arabyan E, Oo A, Zandi K. Flavonoids: promising natural compounds against viral infections. Arch Virol. 2017 Sep;162(9):2539-2551. PMID: 28547385

Example Antiviral Flavonoids

- Apigenin
- Baicalein
- Chrysin
- Hesperidin
- Luteolin
- Myricetin
- Quercetin
- Scutellarein
- Tangeritin
- Wogonin
- 6-hydroxyflavone
- And many, many more.

Zakaryan H, Arabyan E, Oo A, Zandi K. Flavonoids: promising natural compounds against viral infections. Arch Virol. 2017 Sep;162(9):2539-2551. PMID: 28547385

Huge Amount of Direct Research on Flavonoids and SARS-CoV2

- Molecular docking simulations
- In silico modeling
- Cell cultures
- Animal studies
- Human clinical trials

Hypothesis 1

- Much of the problems caused by SARS-CoV2 comes from spike proteins penetrating and damaging the microvasculature
- Flavonoids inhibit spike protein attachment to cells
- Could a person's body level of flavonoids predict:
  - Severity of COVID
  - Risk of Long COVID
  - Risk of ADRs from mRNA vaccines (since they cause the cells to produce spike protein)

Hypothesis 2

- Is the increasing incidence of epidemics and pandemics due to loss of flavonoids from the food supply?

Supplementation

Why a Flavonoid?

- Many flavonoids have documented antiviral efficacy
- Several key mechanisms:
  - Directly viricidal
  - Block viral binding
  - Block transcription
  - Block cooption of intracellular enzymes required for replication, etc.
- Many classes of viruses: e.g., avian influenza H5N1 virus, human cytomegalovirus (HCMV), EBV, Herpes simplex I and II, severe acute respiratory syndrome coronavirus (SARS-CoV), rhesus rotavirus, CHIKV, Japanese encephalitis virus (JEV), etc.

Zakaryan H, Arabyan E, Oo A, Zandi K. Flavonoids: promising natural compounds against viral infections. Arch Virol. 2017 Sep;162(9):2539-2551. doi: 10.1007/s00705-017-3417-y. PMID: 28547385

Antiviral Activity

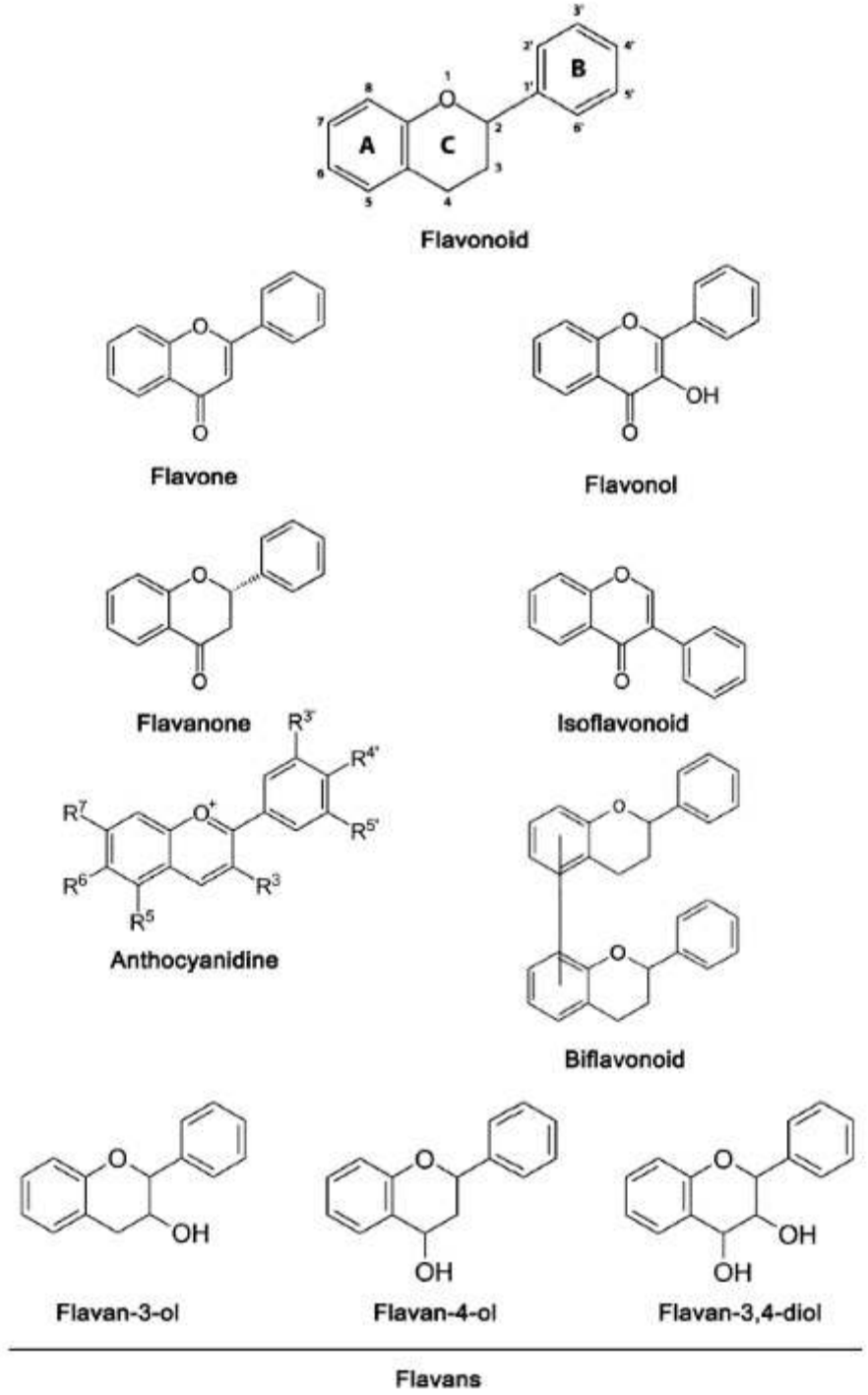
- Examples of antiviral flavonoids: apigenin, baicalein, chrysin, hesperidin, luteolin, myricetin, quercetin, scutellarein, tangeritin, wogonin, 6-hydroxyflavone, etc.
- Flavonoids have been leaving the food supply due to:
  - Growing foods with synthetic chemicals
  - Glyphosate blocking shikimate pathway which produces flavonoids
  - Tilling which disrupts the soil's microbiome

Zakaryan H, Arabyan E, Oo A, Zandi K. Flavonoids: promising natural compounds against viral infections. Arch Virol. 2017 Sep;162(9):2539-2551. doi: 10.1007/s00705-017-3417-y. PMID: 28547385

Pizzorno J. Unimportant Molecules, Unexpected Clinical Consequences. AIC 2021

What Are Flavonoids?

- Connected benzene rings with a wide range of substitutions and additions
- Many are colorful
- >6,000 flavonoids that have been structurally identified
- Huge range of important indirect and direct physiological functions that promote health in many ways



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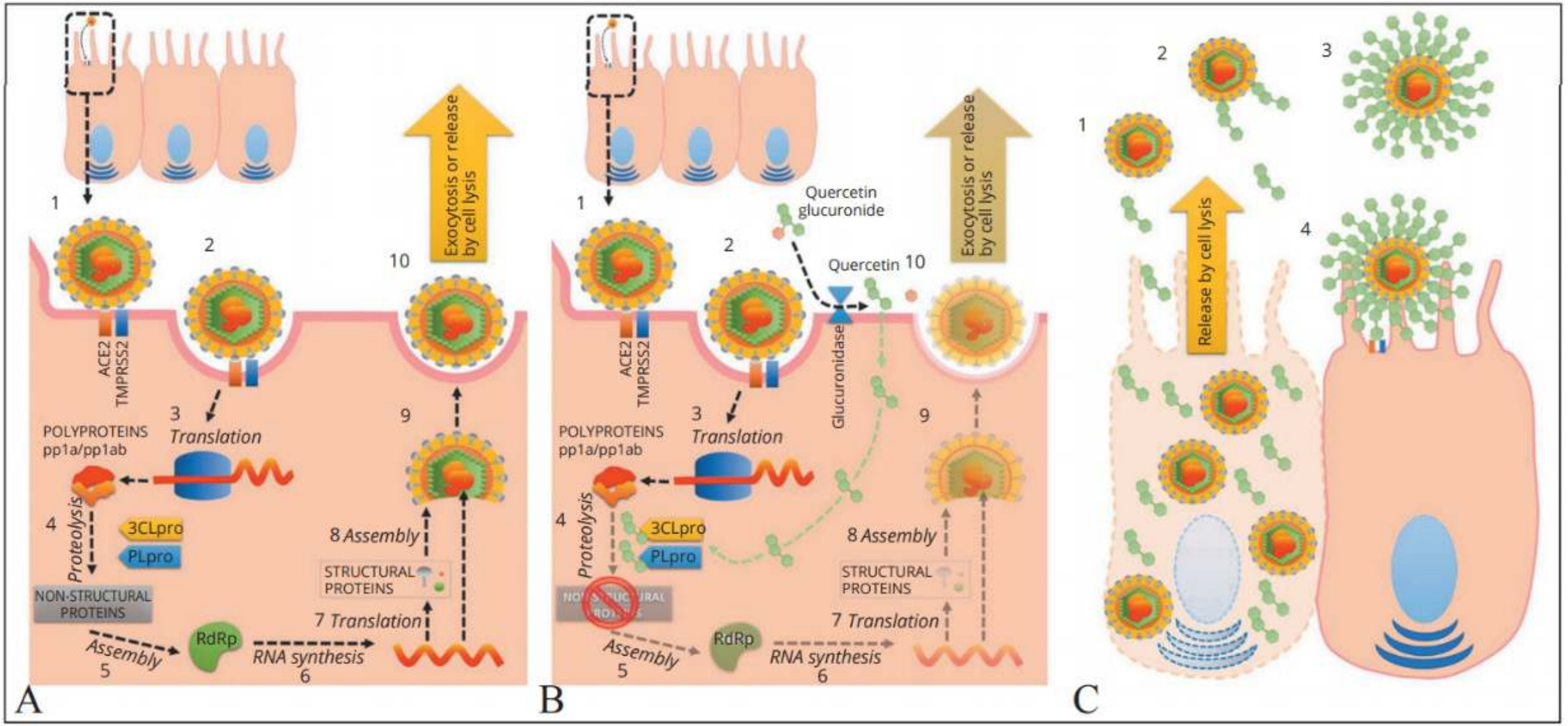
Example Antiviral Flavonoids

Table 2 Antiviral activity of other flavonoids

Flavonoids	Class	Source(s)	Antiviral activity	Other biological activities
Myricetin	Flavonol	Red (grape) wine, leaves of sweet potato (*Ipomoea batatas*), parsley (*Petroselinum crispum*), tea plant (*Camellia sinensis*), and fruits of blueberries (*Vaccinium* genus)	Moloney murine leukemia virus [7], SARS-CoV [63], influenza viruses [77], HIV-1 [103], Rauscher murine leukemia virus [104]	Anticarcinogenic, antioxidant, antithrombotic and anti-inflammatory activity
Hesperetin	Flavanone	Fruits of orange (*Citrus aurantium*), lemon (*Citrus limon*), mandarin (*Citrus reticulata*) and peppermint (*Mentha piperita*)	CHIKV [1], yellow fever virus [12], HSV-1 [61], Sindbis virus [102]	Antioxidant, anti-inflammatory, anti-allergic, hypolipidemic, vasoprotective and anticarcinogenic activity
Chrysin	Flavone	Honeycomb, leaves of passion flowers (*Passiflora caerulea* and *Passiflora incarnata*) and chamomile (*Matricaria chamomilla*)	HSV-1 [111], coxsackie B virus type 3 [117], EV71 [131]	Antioxidant, anticarcenogenic, anti-hypertension, anti-diabetic and antibacterial activity
Galangin	Flavonol	Propolis, leaves of lesser galangal (*Alpinia officinarum*) and rhizome of *Alpina galanga*	Coxsackie B virus type 1 [18], HCV [74], HSV-1 [111]	Antibacterial and anticarcinogenic activity
Morin	Flavonol	Bark, leaves and stem of white mulberry (*Morus alba*), leaves and fruit of Osage orange (*Maclura pomifera*), guava (*Psidium guajava*), and leaves of old fustic (*Maclura tinctoria*)	Canine distemper virus [11], Moloney murine leukemia virus [20], potato virus X [36], equid herpesvirus 1 [41]	Antihypertensive, anti-angiogenic, hepatoprotective, neuroprotectant and anti-inflammatory activity
Tangeretin	Flavone	Peels of tangerine (*Citrus tangerina*), orange (*Citrus aurantium*), lemon (*Citrus limon*), mandarin (*Citrus reticulata*)	RSV [141]	Anticarcinogenic activity
Wogonin	Flavone	Leaves of baical skullcap (*Scutellaria baicalensis*)	HBV [43], influenza H1N1 virus [58]	Anticarcinogenic and anticonvulsant activity
Silymarin	Complex of flavonolignans	Seeds of milk thistle (*Silybum marianum*), artichoke (*Cynara scolymus*), roots of black cohosh (*Actaea racemosa*)	CHIKV [72], influenza A virus [119], HCV [128]	Anticarcinogenic, hepatoprotective and antioxidant activity

Zakaryan H, Arabyan E, Oo A, Zandi K. Flavonoids: promising natural compounds against viral infections. Arch Virol. 2017 Sep;162(9):2539-2551. doi: 10.1007/s00705-017-3417-y. PMID: 28547385

Quercetin Impairs SARS-CoV2



DI Pierro F, Khan A, Bertuccioli A, Maffioli P, Derosa G, Khan S, Khan BA, Nigar R, Ujjan I, Devrajani BR. Quercetin Phytosome® as a potential candidate for managing COVID-19. Minerva Gastroenterol (Torino). 2021 Jun;67(2):190-195. PMID: 33016666.

Study Design

- 30 day, prospective study
- 152 COVID-19 outpatients
  - Half standard of care only
  - Half standard of care plus quercetin
- 500 mg bid liposomal quercetin
  - 400 mg total quercetin/day
  - Open label

Di Pierro, et al. Possible Therapeutic Effects of Adjuvant Quercetin Supplementation Against Early-Stage COVID-19 Infection: A Prospective, Randomized, Controlled, and Open-Label Study Int J Gen Med 2021:14 2359–2366

This is a Preliminary Study

Strengths

- Dr. Di Pierro respected scientist
  - Expert in natural products research
  - >50 articles in PubMed
  - 2020 AIC speaker
- Prospective study
- Adequate enrollment numbers

Weaknesses

- Not published in major journal
- Di Pierro member of Scientific Board of Pharmextracta
- Open label
- The control group had more co-morbidities
  - Sub analysis still showed major benefit

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Outcomes: All Patients

Measure	Control	Intervention	P Value
Hospitalized	28.9%	9.2%	0.002
Days of hospitalization	6.77	1.57	0.001
Needed O_2	19.7%	1.3%	0.01
Admitted to ICU	10.5%	0.0%	0.02
Deaths	3.0%	0.0%	0.04

No reported serious adverse events

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Outcomes: Only Those with No Co-Morbidities

Measure	Control	Intervention	P Value
Hospitalized	22.4%	8.5%	0.08
Days of hospitalization	5.14	1.25	0.01
Needed O_2	12.9%	0	0.005
Admitted to ICU	6.5%	0	0.05
Deaths	6.5%	0	0.05

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Quercetin Improves Many Aspects of COVID

Table 7. Quercetin Decreases Viral Load and Clinical Manifestations of SARS-CoV-2[20]

	Group SC	Group QP	*p*
RT-PCR (positive subjects)			0.0002
At enrollment	21/21 (100%)	21/21 (100%)	
At day 7	19/21 (90.5%)	5/21 (24%)	
At day 14	4/21 (19%)	0/21 (0%)	
At day 21	0/20 (0%)	0/21 (0%)	
Symptoms variation°			0.0118
Healed	4/21 (19%)	12/21 (57%)	
Improved	17/21 (81%)	8/21 (38%)	
Unchanged	0/21 (0%)	1/21 (5%)	
CRP* (mg/L)			n. s.
At enrollment	30.5± 27.9	27.2 ± 27.0	
Day 7	18.1± 22.9	12.3 ± 16.5	
LDH* (U/L)			0.0001
At enrollment	364.9± 139.9	418.6 ± 192.9	
Day 7	327.6± 128.9	270.0 ± 119.6	
Ferritin* (ng/mL)			0.0029
At enrollment	687.8± 879.1	532.7 ± 264.9	
Day 7	557.5± 642.6	319.7 ± 151.6	
D-dimer* (ng/mL)			n. s.
At enrollment	282.0 ± 240.0	211.5 ± 65.7	
Day 7	183.6 ± 111.8	186.3 ± 50.8	
Hospitalized patients	1/21 (4.8%)	0/21 (0%)	n. s.
Patients in ICU	1/21 (4.8%)	0/21 (0%)	n. s.
Deaths	1/21 (4.8%)	0/21 (0%)	n. s.

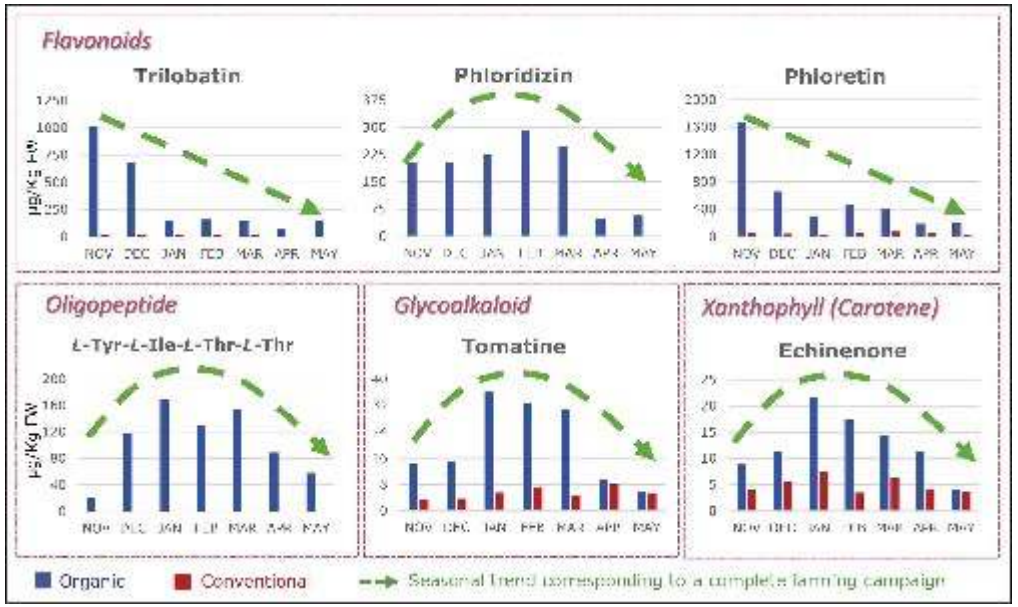
Notes: °Regarding to symptoms, "healed" are those patients who manifest on Day 1 one or more symptoms, but no symptoms on Day 7; "improved" are those patients who show fewer symptoms on Day 7 than on Day 1; "unchanged" are those patients not affected, between the two periods, by variations in their symptoms' frequency. *Values are expressed as mean ± standard deviation.

Abbreviations: SC, standard care; QP, formulated quercetin (+Standard Care); RT-PCR, real-time reverse-transcriptase polymerase chain reaction; LDH, lactate dehydrogenase; ICU, intensive care unit; n. s., not significant.

Di Pierro F, Iqtadar S, Khan A, et al. Potential clinical benefits of quercetin in the early stage of COVID-19: results of a second, pilot, randomized, controlled and open-label clinical trial. Int J Gen Med. 2021;14:2807-2816. doi:10.2147/IJGM.S318949

Growing Foods Chemically Dramatically Lowers Flavonoids

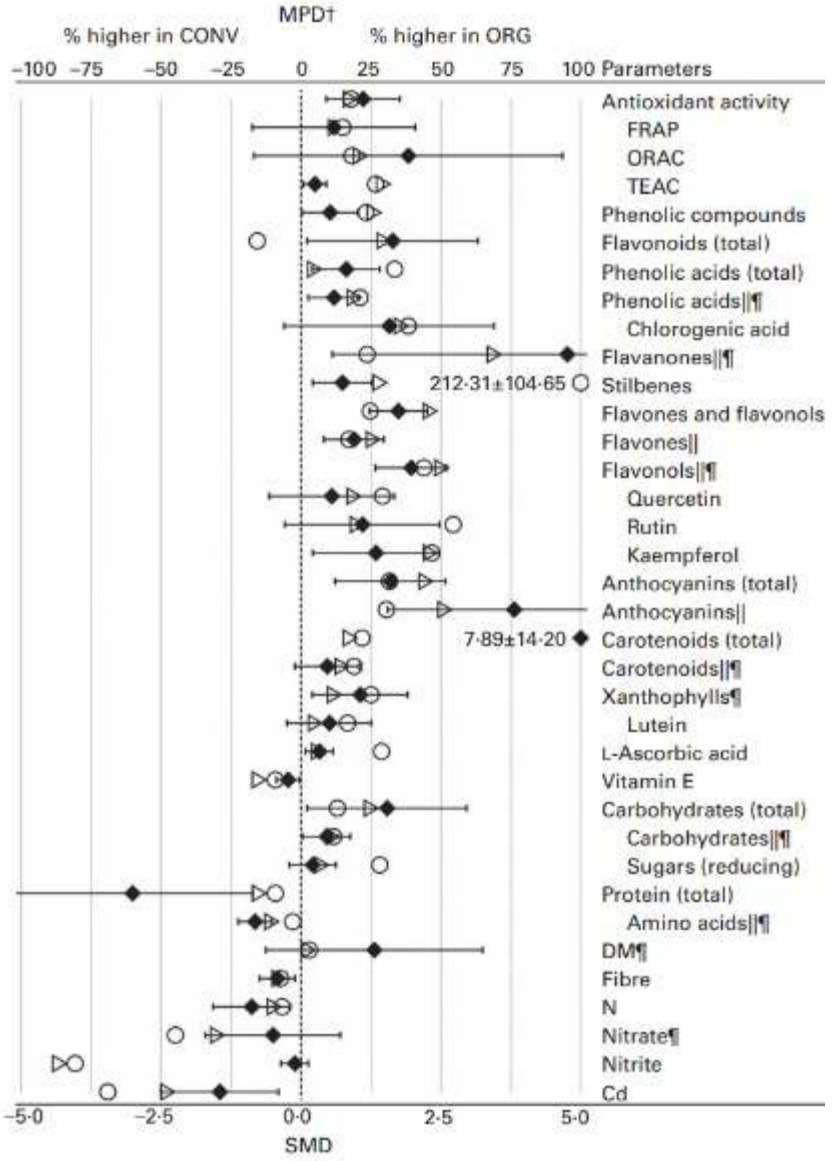
- Tomatoes
- Highly controlled greenhouse
- Shows variation during year
- Dramatic decrease in “unimportant” molecules
- Note: coloring molecules are conserved so food looks normal



Martínez Bueno MJ, Díaz-Galiano FJ, Rajski Ł, et al. A non-targeted metabolomic approach to identify food markers to support discrimination between organic and conventional tomato crops. J Chromatogr A. 2018 Apr 20;1546:66-76 PMID: 29526497

Huge Molecular Differences Between Chemically- and Organically Grown Foods

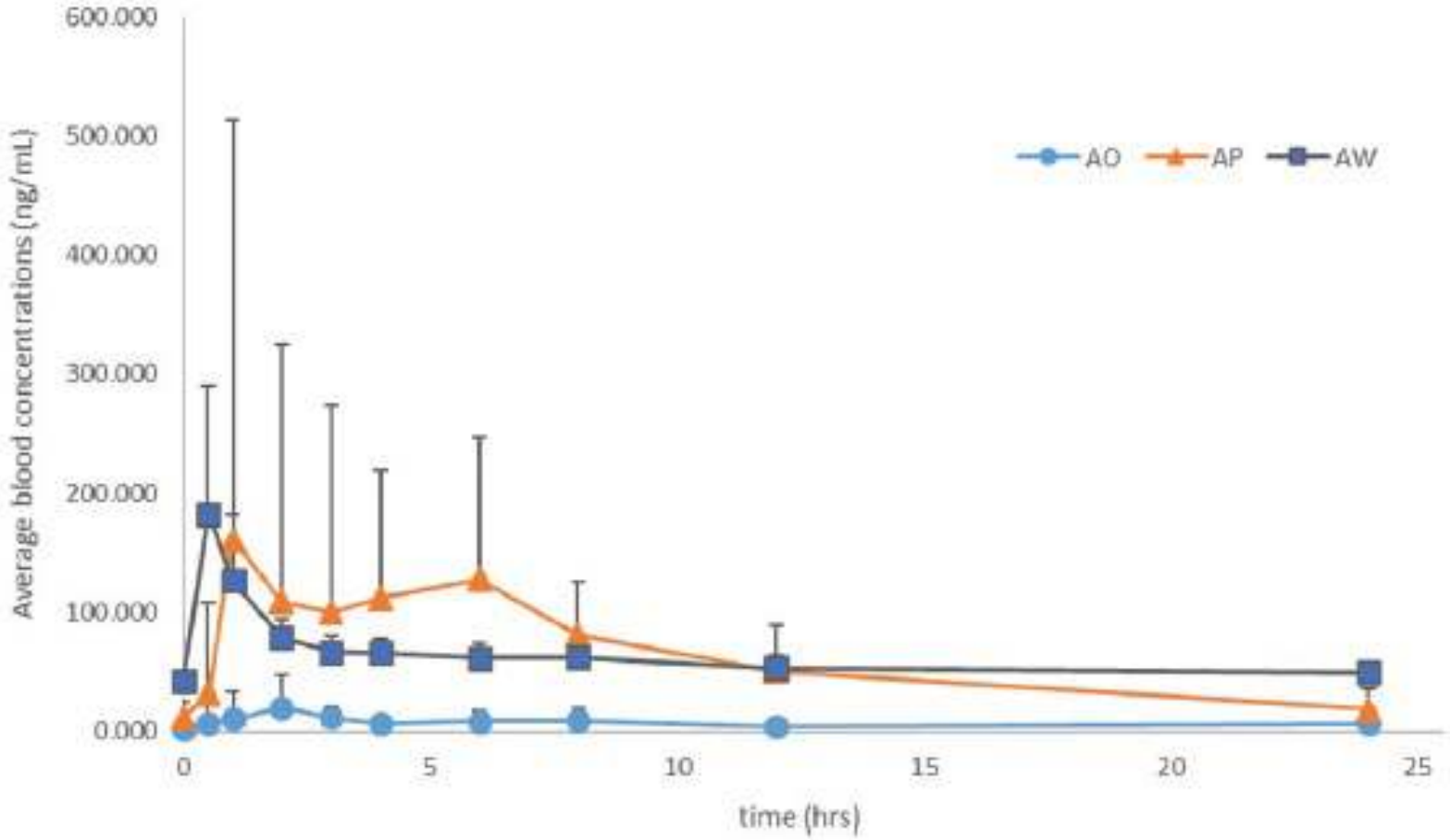
- Metanalysis of 343 studies
- Graph show which has highest % of molecule types
- Organically-grown higher in virtually all the important molecules
- Many of these molecules are anti-viral



Barański M, Srednicka-Tober D, Volakakis N, et al. Higher antioxidant and lower cadmium concentrations and lower incidence of pesticide residues in organically grown crops: a systematic literature review and meta-analyses. Br J Nutr. 2014;112:794-811. PMID: 24968103

Supplementation Critical Due to Sabotage of Food Supply

- Liposomal and LipoMycel much better absorbed



Solnier J, Chang C, Roh K, et al. Quercetin LipoMicel—A Novel Delivery System to Enhance Bioavailability of Quercetin. J Nat Health Prod Res 2021, 3:2; 1–8

Curcumin and COVID Resistance

Curcumin	Infect	Severe	LongC	Death	PMIDs	Notes
160 mg nano-curcumin 14d				0.50	33129099	20% death rate versus 40%

Clinical Takeaways

- Preliminary studies
- Quercetin shown to be safe in many studies
- Liposomal/LipoMycel quercetin is a logical adjunct to standard of care
- Loss of flavonoids from food likely aggravated the pandemic

- Recommendations:
  1. All patients should be advised to consume foods rich in flavonoids
  2. All patients at risk (everyone?) should be prescribed 500 mg/d of liposomal quercetin
  3. Caution if transplant patient on immunosupporessives

Mathematics of Converting Risk to Protection

Probability of an Event: Occurring versus Not-Occurring

- Probability of an event occurring = p
  - Probability of an event not occurring = 1-p
- For example, if there is a 20% chance of rain (p = 0.2), there is an 80% chance of no rain (1-p = 0.8)

Odds Ratio (OR)

- Odds are p/(1-p)
  - Put another way, odds represent the probability of an event happening divided by the probability of the event not happening
- Odds ratio (OR) represents the odds of a certain outcome in one group, divided by the odds of that same outcome in another group
- Example, among passengers on the Titanic
  - 462 women; 308 survived and 154 died
  - 851 men, 142 survived and 709 died
  - The odds of a woman dying were 0.5 (154/308), while for men the odds of dying were about 5 (709/142).
  - When comparing these two groups, the OR for dying was approximately 10 comparing men to women

Converting ORs into Percentages

- For ORs greater than 1, subtract 1 from the OR
- For ORs less than 1, subtract the OR from 1
- For both, multiply by 100 to get a percentage
- From last slide, men had a 400% greater odds of dying, while women had a 90% lower odds.

Calculating Protection

- OR for severe COVID-19 among those with elevated FBG was 1.55 compared to the group without an elevated FBG
  - In other words, there was a 55% increase in odds ([1.55 – 1] × 100) for the group with an elevated FBG.
- The OR for having severe COVID-19 among the group with a normal FBG is 0.645 (1/1.55) compared to those with an elevated FBG
- Therefore, those with a normal FBG had a 35.5% lower odds ([1-0.645] × 100) for severe COVID-19

$\Rightarrow$ **A normal FBG conferes 35.5% protection**

Putting It All Together

Modifiable Factor	Infection		Severe Disease		Death		Reference
	OR	% Protection	OR	% Protection	OR	% Protection	
None of the 4 major cardiometabolic risk factors				64%			O'Hearn et al (2021)
Normal weight (OR for obesity)	2.73	63%	3.81	74%	1.61	38%	Cai et al (2021)
Normal blood sugar (OR for diabetes or elevated FBG levels)			1.55	35%	3.21	69%	Shauly-Aharonov et al (2021); Gregory et al (2021)
Healthy Vitamin D (OR for def)					3.87	74%	De Smet et al (2021)
Healthy Ω-3 fatty acid levels						72%	Zapata et al (2021)
Diet							
Vegan				73%			Kim et al (2021)
Pescatarian				59%			Kim et al (2021)
NOT high protein				74%			Kim et al (2021)
Vitamin D supplementation			0.27	73%			Pal et al (2021)
Quercetin supplementation				68%			Di Pierro et al (2021)

Bayes and Risk

- For **independent** variables, protection is calculated by multiplying the risks (or 1-protection)
- For example, for severe disease
  - No co-morbidities = 64% protection
  - Normal weight = 74% protection
  - Normal blood sugar = 35% protection
  - High plant diet = 73% protection
  - Taking liposomal quercetin = 68% protection
- **IF** all are independent variables, for just these 5 factors, a person's risk of severe disease is: 0.36 * 0.26 * 0.65 * 0.27 * 0.32 = 0.00525
- In other words, 99.5% protection

Conclusion

Everyone Must Increase Their protection from COVID

- Whether vaccinated or not; regardless of strain
- Co-morbidities primary cause of serious disease and death
- Most people significantly deficient in vitamins C and D, omega-3 fatty acids and dietary flavonoids
- Doing everything right dramatically decreases risk of significant infection, serious disease and death
- These strategies are very likely to be equally effective against LongC. However, little significant research at this time