Seafood nutrients and antiviral immunity

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State of The Science

September 17, 2020

To cover

- Introduction to the immune system including anti-viral defence
- Overview of nutrition and immunity (brief)
- Specific micronutrients (vitamin D, zinc, selenium) and (anti-viral) immunity
- Summary & conclusions

Open access Review

BMJ Nutrition, Prevention & Health

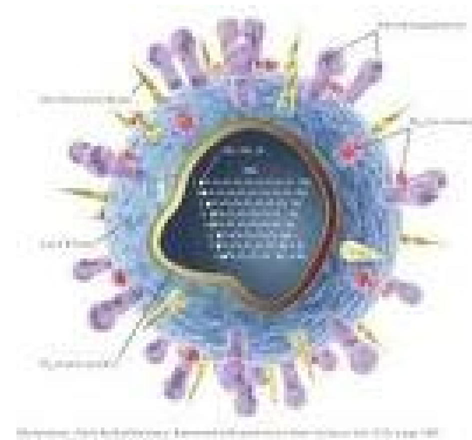
Nutrition, immunity and COVID-19

Philip C Calder

The immune system ….

… is a cell and tissue system that protects the individual from invading pathogens

Viruses



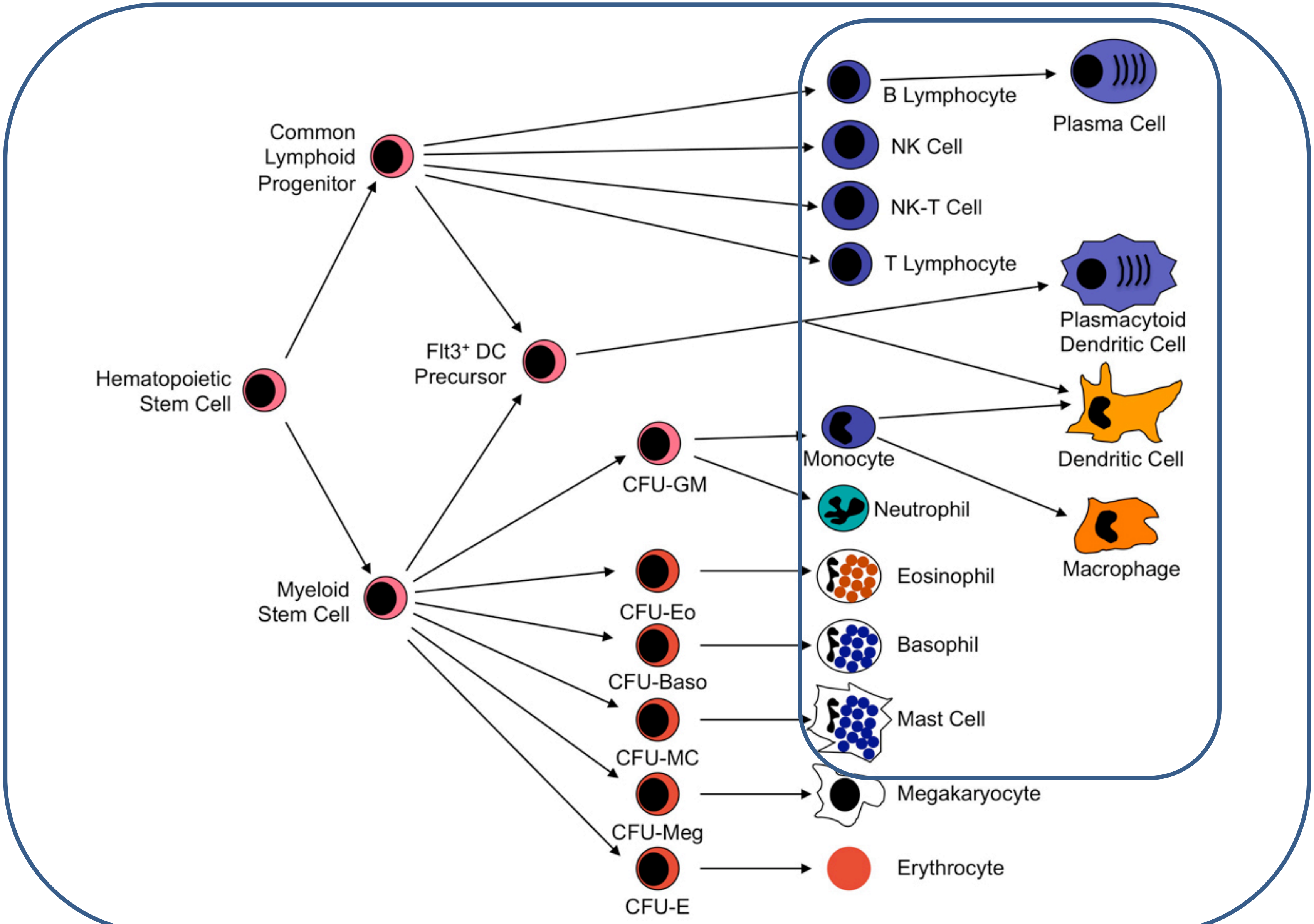
Parasitic worms

Bacteria

Fungi

A well functioning immune system is key to providing robust defence against pathogenic organisms

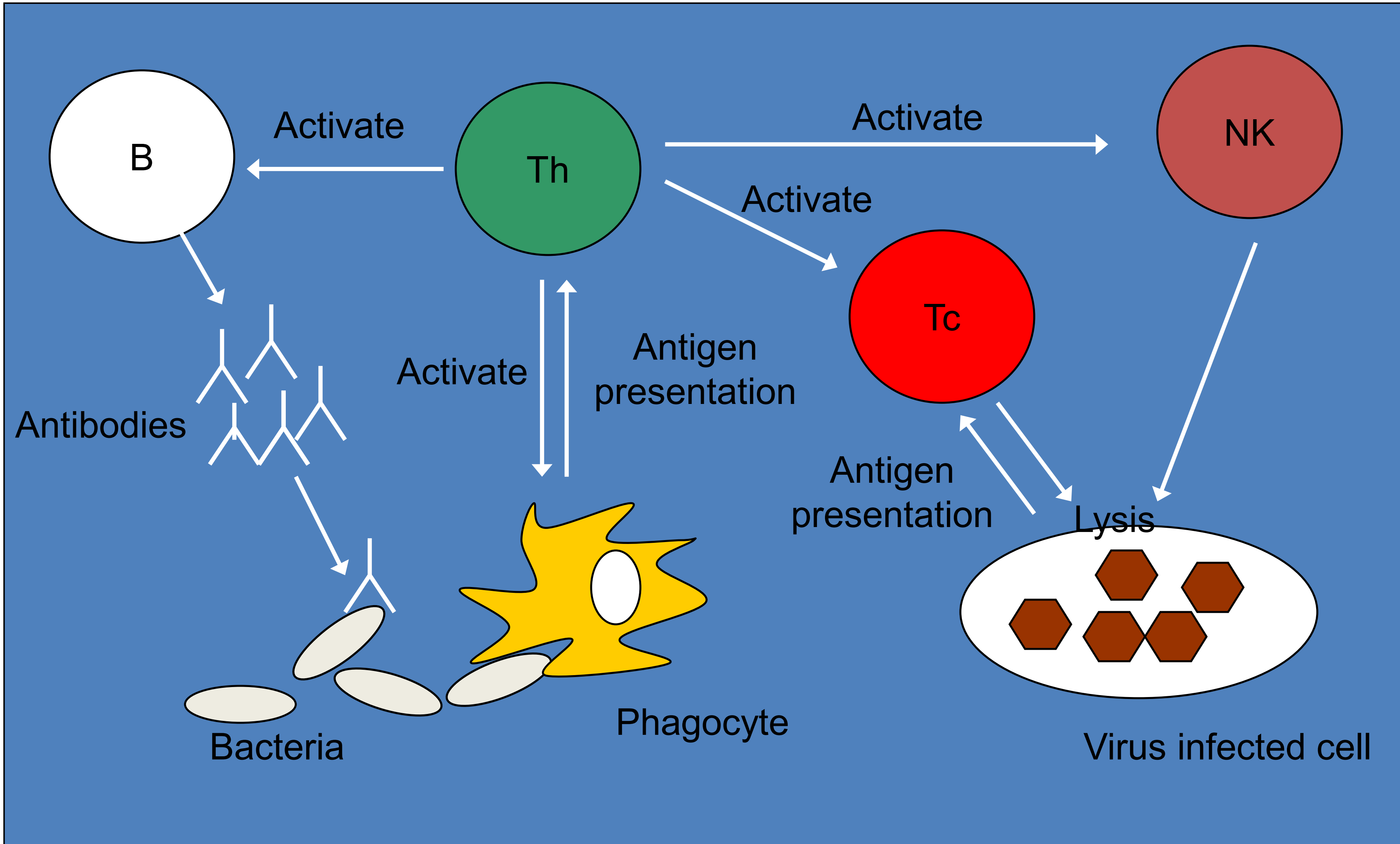
The immune system involves many cell types – each has their own role



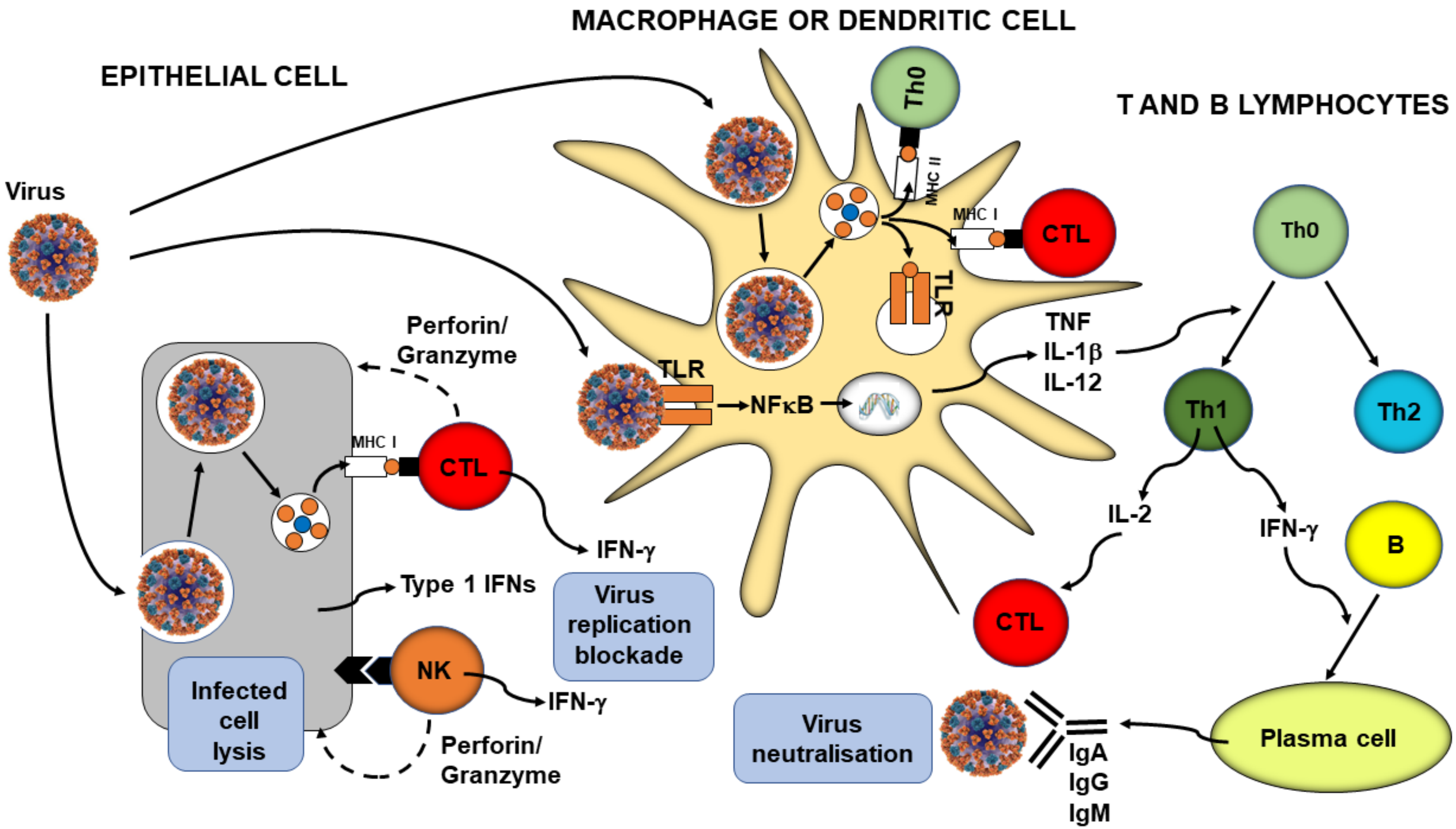
The four general functional features of the immune system

- Exclusion barrier
- Recognition/Identification
- Elimination
- Memory

Interaction amongst immune cells



Anti-viral immunity



Calder (2020) BMJ Nutrition Prevention & Heath 3, e000085

Optimal nutrient supply

$\downarrow$

Optimal nutrient status (& stores)

$\downarrow$

Optimal immune function

Optimal nutrient supply

Optimal nutrient status (& stores)

Optimal immune function

Good defence against pathogens

INADEQUATE nutrient supply

↓

INADEQUATE nutrient status (& stores)

↓

IMPAIRED immune function

↓

IMPAIRED defence against pathogens -> more infections; more severe infections; illness; death

Amongst key nutrients for antiviral immunity are:

Vitamin D

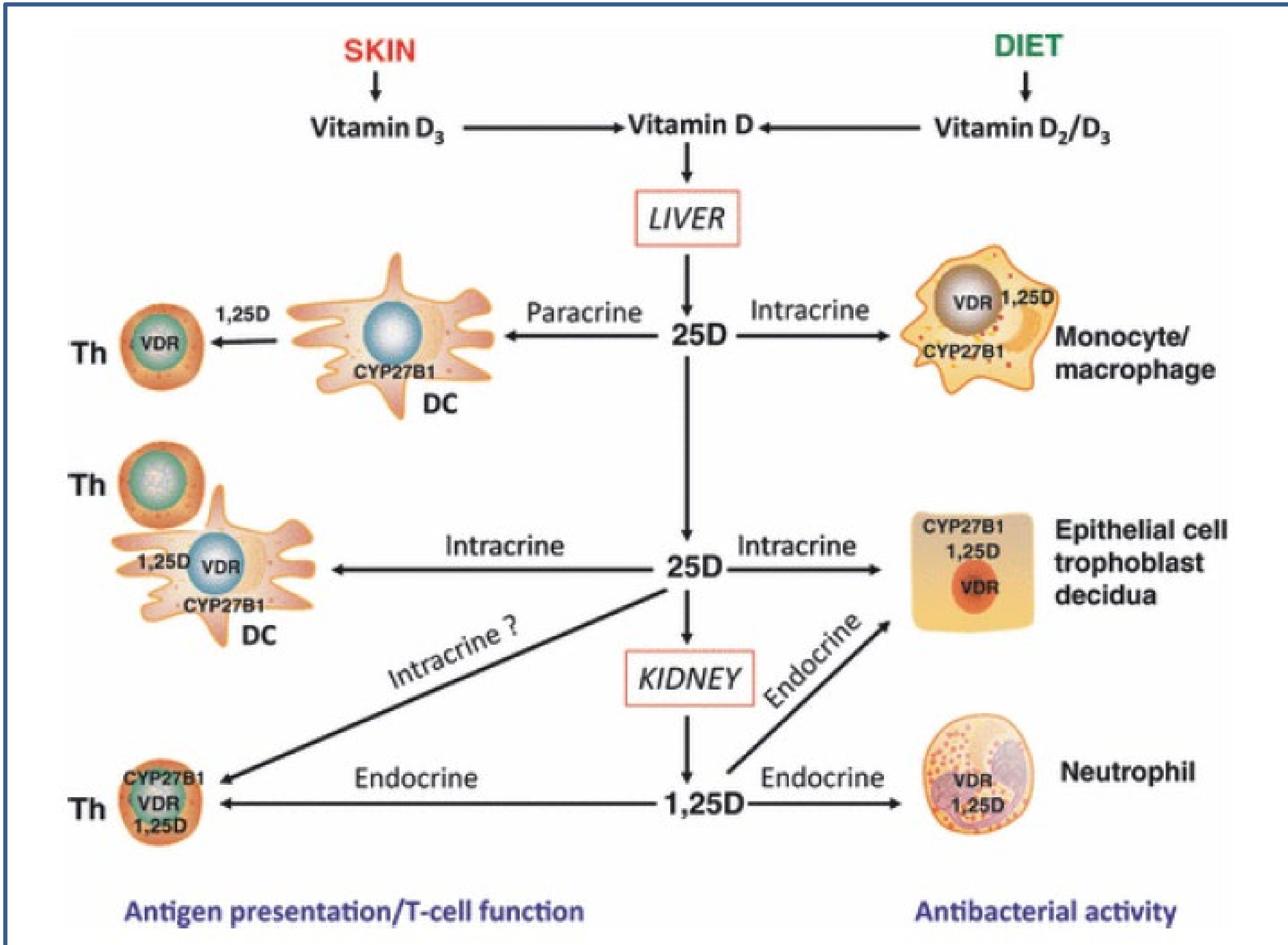
- **important sources: fatty fish; fish oil supplements**

Zn

- **important sources: seafood [oysters, crabs, lobster, fish]**

Se

- **important sources: seafood [oysters, crabs, shrimps, fatty fish]**



Prietl et al. (2013) Nutrients 5, 2502-2521

Vitamin D status has a linear association with seasonal infections and lung function in British adults

Diane J. Berry, Kathryn Hesketh, Chris Power and Elina Hyppönen*

British Journal of Nutrition (2011), **106**, 1433–1440

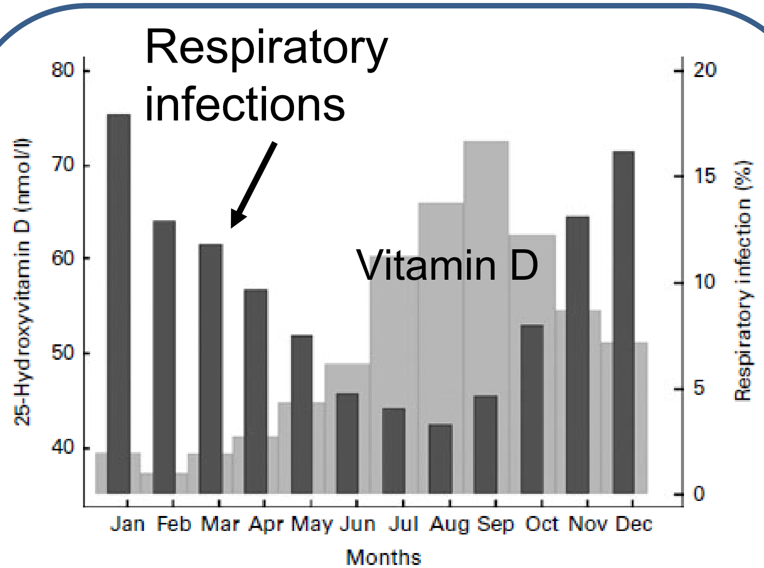


Fig. 1. Geometric mean of 25-hydroxyvitamin D (nmol/l, ▒) concentrations and the prevalence of respiratory infections (■) in the 1958 British birth cohort.

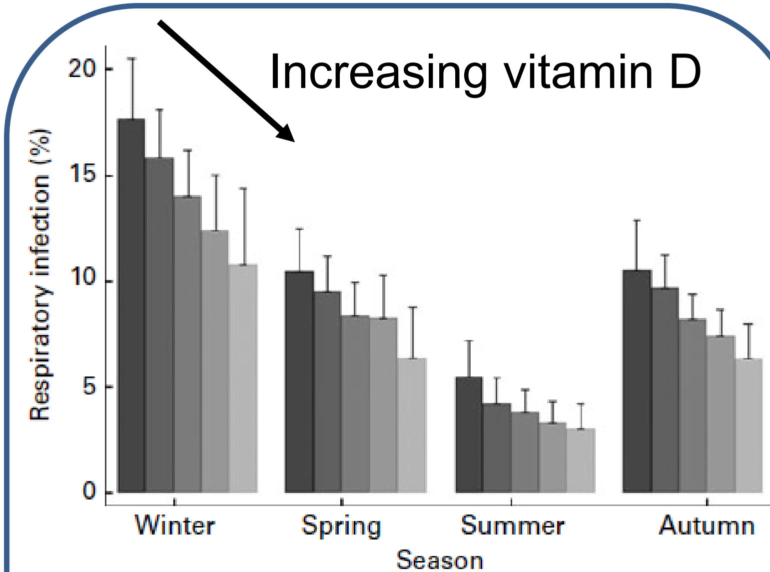


Fig. 2. Prevalence of respiratory infections with 95 % prediction intervals in the 25-hydroxyvitamin D categories of <25 nmol/l (■), 25–49·9 nmol/l (■), 50–74·9 nmol/l (■), 75–99·9 nmol/l (■) and >100 nmol/l (■) as predicted from a logistic regression model adjusted for factors of lifestyle, socio-economic position and adiposity, and season in the 1958 British birth cohort.

But just an association: no “cause and effect”

OPEN ACCESS Freely available online PLOS | ONE

Vitamin D and Respiratory Tract Infections: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Peter Bergman[1,2], Åsa U. Lindh[3], Linda Björkhem-Bergman[4], Jonatan D. Lindh[4]*

June 2013 | Volume 8 | Issue 6 | e65835

- **12 trials**
- **Adults or children**
- **Dose: 300 to 3653 IU/day**
- **7 wk to 3 yr**

40 IU = 1 μg

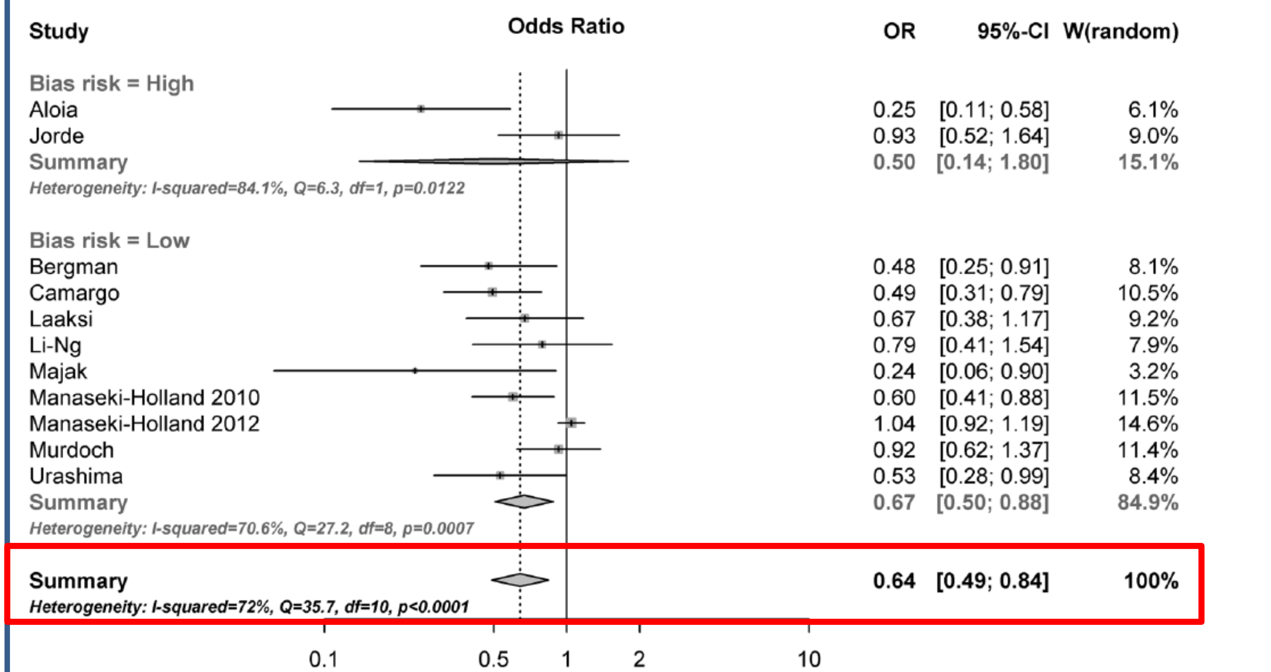


Figure 2. Efficacy of vitamin D for prevention of respiratory tract infections. Error bars indicate 95% confidence intervals.

Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data

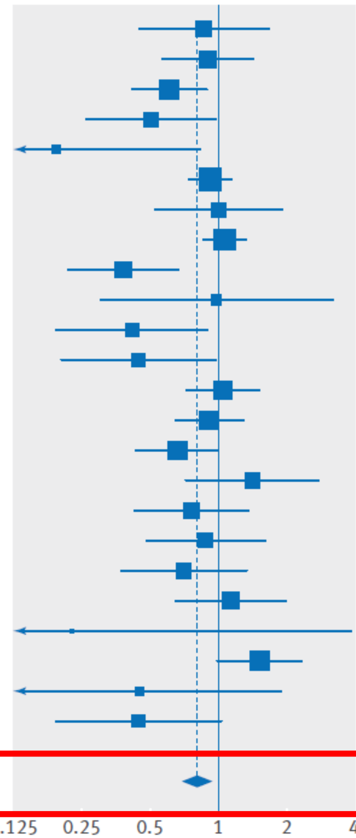
Adrian R Martineau,[1,2] David A Jolliffe,[1] Richard L Hooper,[1] Lauren Greenberg,[1] John F Aloia,[3] Peter Bergman,[4] Gal Dubnov-Raz,[5] Susanna Esposito,[6] Davaasambuu Ganmaa,[7] Adit A Ginde,[8] Emma C Goodall,[9] Cameron C Grant,[10] Christopher J Griffiths,[1,2,11] Wim Janssens,[12] Ilkka Laaksi,[13] Semira Manaseki-Holland,[14] David Mauger,[15] David R Murdoch,[16] Rachel Neale,[17] Judy R Rees,[18] Steve Simpson, Jr[19] Iwona Stelmach,[20] Geeta Trilok Kumar,[21] Mitsuyoshi Urashima,[22] Carlos A Camargo Jr[23]

the bmj | *BMJ* 2017;356:i6583 | doi: 10.1136/bmj.i6583

- **25 trials**
- **N = 11,321**
- **Adults or children**
- **Different approaches to dosing (daily, weekly, bolus, bolus then weekly or daily)**
- **Studies with daily dosing used 7.5 to 100 μg/day**

Study	Proportion with ≥1 ARTI (%): Control	Proportion with ≥1 ARTI (%): Intervention	Weight (%)	Adjusted odds ratio (95% CI)
Li-Ng 2009	33/76 (43.4)	32/81 (39.5)	3.48	0.85 (0.44 to 1.64)
Urashima 2010	69/167 (41.3)	68/167 (40.7)	5.36	0.90 (0.58 to 1.41)
Manaseki-Holland 2010	126/229 (55.0)	97/224 (43.3)	6.12	0.60 (0.41 to 0.88)
Laaksi 2010	54/84 (64.3)	39/80 (48.8)	3.58	0.51 (0.27 to 0.96)
Majak 2011	11/24 (45.8)	4/24 (16.7)	1.00	0.20 (0.05 to 0.82)
Trilok-Kumar 2011	458/1030 (44.5)	438/1034 (42.4)	8.69	0.92 (0.77 to 1.11)
Lehouck 2012	29/89 (32.6)	30/86 (34.9)	3.57	1.00 (0.53 to 1.90)
Manaseki-Holland 2012	245/1505 (16.3)	260/1506 (17.3)	8.58	1.08 (0.89 to 1.30)
Camargo 2012	53/103 (51.5)	44/141 (31.2)	4.36	0.38 (0.22 to 0.65)
Murdoch 2012	155/161 (96.3)	154/161 (95.7)	1.43	0.97 (0.30 to 3.15)
Bergman 2012	39/62 (62.9)	26/62 (41.9)	2.89	0.42 (0.20 to 0.89)
Marchisio 2013	38/58 (65.5)	26/58 (44.8)	2.84	0.44 (0.21 to 0.95)
Rees 2013	276/360 (76.7)	303/399 (75.9)	6.35	1.03 (0.72 to 1.49)
Tran 2014	96/197 (48.7)	185/397 (46.6)	6.60	0.92 (0.65 to 1.30)
Goodall 2014	80/234 (34.2)	70/258 (27.1)	5.94	0.66 (0.45 to 0.98)
Urashima 2014	17/99 (17.2)	32/148 (21.6)	3.41	1.43 (0.73 to 2.78)
Grant 2014	53/80 (66.3)	94/156 (60.3)	4.12	0.77 (0.43 to 1.36)
Martineau 2015 (ViDiCO)	75/118 (63.6)	76/122 (62.3)	3.98	0.87 (0.48 to 1.57)
Martineau 2015 (ViDiAs)	93/125 (74.4)	85/125 (68.0)	3.74	0.71 (0.38 to 1.31)
Martineau 2015 (ViDiFlu)	58/103 (56.3)	83/137 (60.6)	4.38	1.13 (0.66 to 1.95)
Dubnov-Raz 2015	10/11 (90.9)	10/14 (71.4)	0.28	0.23 (0.01 to 3.82)
Denlinger 2016	93/207 (44.9)	110/201 (54.7)	5.86	1.52 (1.02 to 2.28)
Tachimoto 2016	5/35 (14.3)	4/54 (7.4)	1.01	0.45 (0.11 to 1.89)
Ginde 2016	24/52 (46.2)	17/55 (30.9)	2.44	0.44 (0.19 to 1.02)
Simpson 2015	14/16 (87.5)	16/18 (88.9)	0.00	Excluded
Overall: I²=53.3%, P=0.001			100.00	0.80 (0.69 to 0.93)

Adjusted odds ratio (95% CI)



Note: Weights are from random effects analysis

CONCLUSIONS

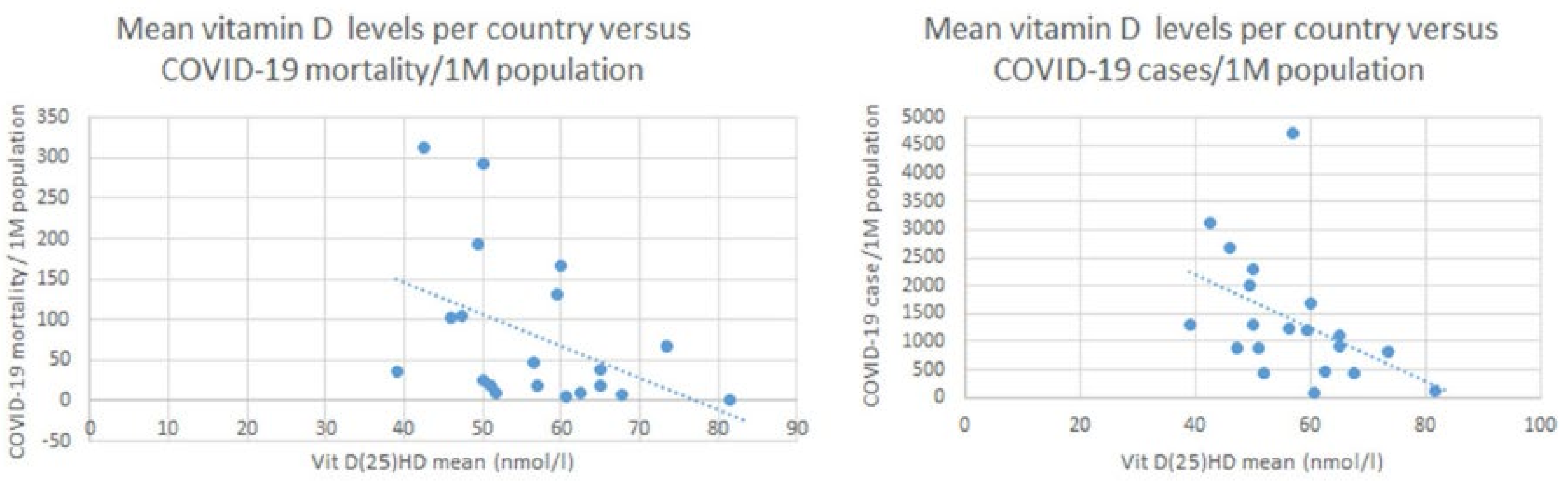
Vitamin D supplementation was safe and it protected against acute respiratory tract infection overall. Patients who were very vitamin D deficient and those not receiving bolus doses experienced the most benefit.

Aging Clinical and Experimental Research
https://doi.org/10.1007/s40520-020-01570-8

SHORT COMMUNICATION

The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality

Petre Cristian Ilie[1] · Simina Stefanescu[2] · Lee Smith[3]



Association – not cause & effect

Low plasma 25(OH) vitamin D level is associated with increased risk of COVID-19 infection: an Israeli population-based study

Eugene Merzon[1,2*], Dmitry Tworowski[3], Alessandro Gorohovski[3], Shlomo Vinker[1,2], Avivit Golan Cohen[1,2], Ilan Green[1,2], Milana Frenkel Morgenstern[3]*

FEBS J. (2020) in press

Table 4: *Multivariate logistic regression analysis of the odds ratio for infection with COVID-19, controlling for multiple conditions*

Variable	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Low vitamin D level**	1.58(1.24- 2.01)	**0.001**	1.50(1.13-1.98)	**0.001**
Age over 50 years	1.51(1.21 1.89)	**0.001**	1.56(1.26- 1.92)	**0.001**
Male	1.42(1.23-1.65)	**0.001**	1.49(1.24-1.79)	**0.001**
Low-medium- SES	2.45(1.99-3.01)	**0.001**	2.13(1.69- 2.68)	**0.001**

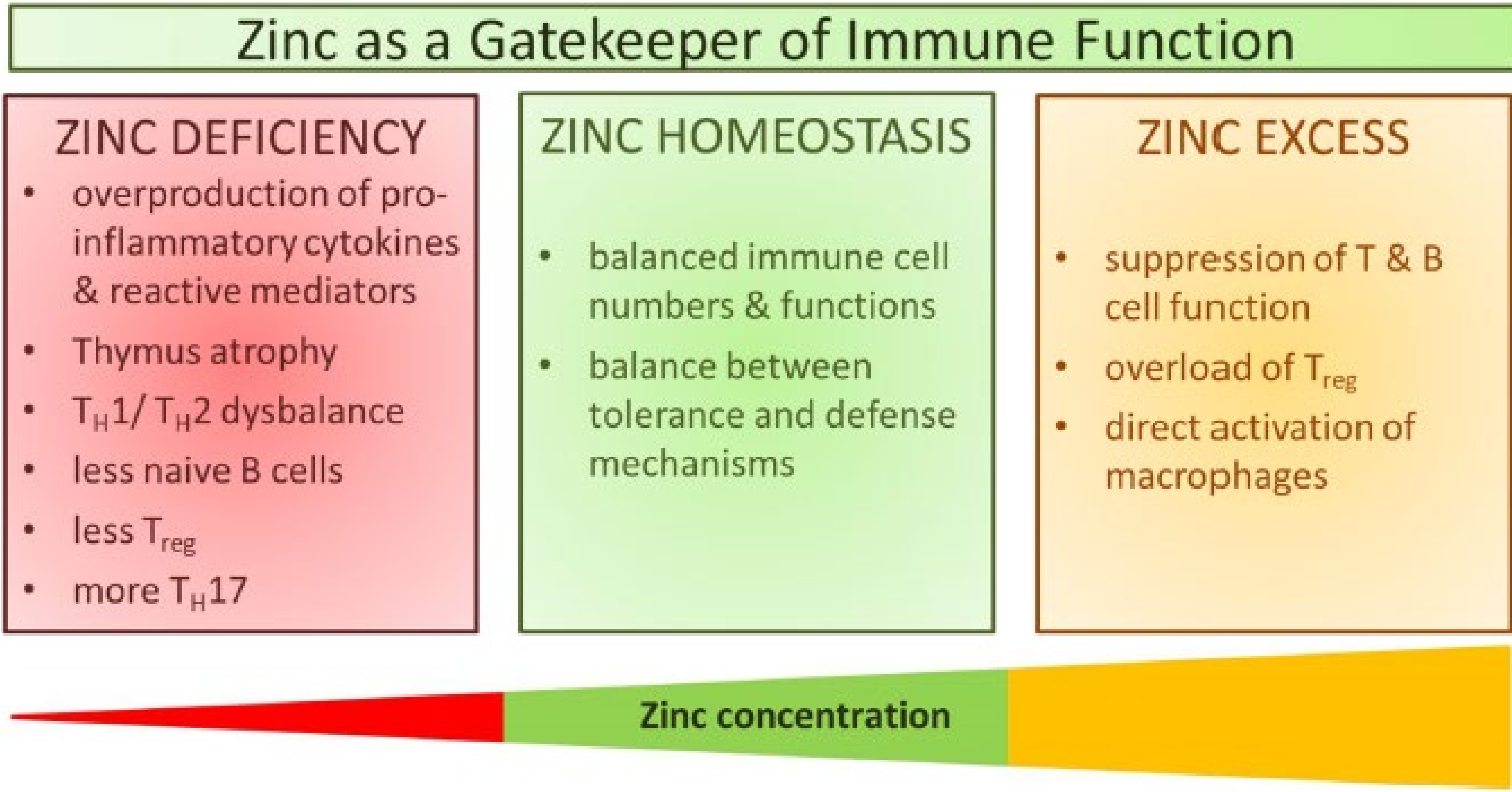
Table 5: *Multivariate logistic regression analysis of the odds ratio for hospitalization of patients with COVID-19, controlling for multiple clinical conditions.*

Variable	Crude OR (95% CI)	P value	Adjusted OR (95% CI) *	P value
Low vitamin D level	2.09(1.01-4.31)	**0.021**	1.95(0.99-4.78)	0.056
Age over 50 years	2.51(1.21-4.89)	**0.001**	**2.71(1.55; 4.78)**	**0.002**

Vitamin D

Zn

Se



Wessels et al. (2017) Nutrients 9, 1286

Am J Med 1981;70:1001-4.

Beneficial effects of oral zinc supplementation on the immune response of old people

Duchateau J, Delepesse G, Vrijens R, Collet H.

Effect of zinc supplementation on serum zinc concentration and T cell proliferation in nursing home elderly: a randomized, double-blind, placebo-controlled trial[1]

Junaidah B Barnett,[2] Maria C Dao,[2] Davidson H Hamer,[2,3,5] Ruth Kandel,[6,7] Gary Brandeis,[4] Dayong Wu,[2] Gerard E Dallal,[2] Paul F Jacques,[2] Robert Schreiber,[6,7] Eunhee Kong,[2] and Simin N Meydani[2]*

Am J Clin Nutr 2016;103:942–51.

- **30 mg/day**
- **3 months**
- **> 65 y**
- **Low zinc status**

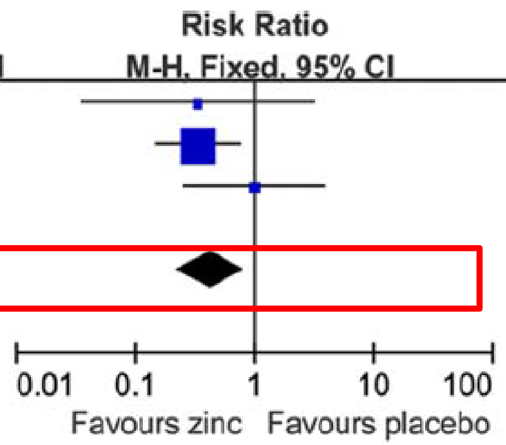
↑ **T-cell proliferation**

Zinc decreases risk of mortality in people with severe pneumonia

Study or Subgroup	zinc Events	zinc Total	placebo Events	placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sempertegui 2014	1	220	3	221	10.7%	0.33 [0.04, 3.19]
Srinivasan 2012	7	176	21	176	75.0%	0.33 [0.15, 0.76]
Wadhwa 2013	4	262	4	263	14.3%	1.00 [0.25, 3.97]
Total (95% CI)		**658**		**660**	**100.0%**	**0.43 [0.22, 0.83]**
Total events	12		28			

Heterogeneity: Chi² = 1.87, df = 2 (P = 0.39); I² = 0%

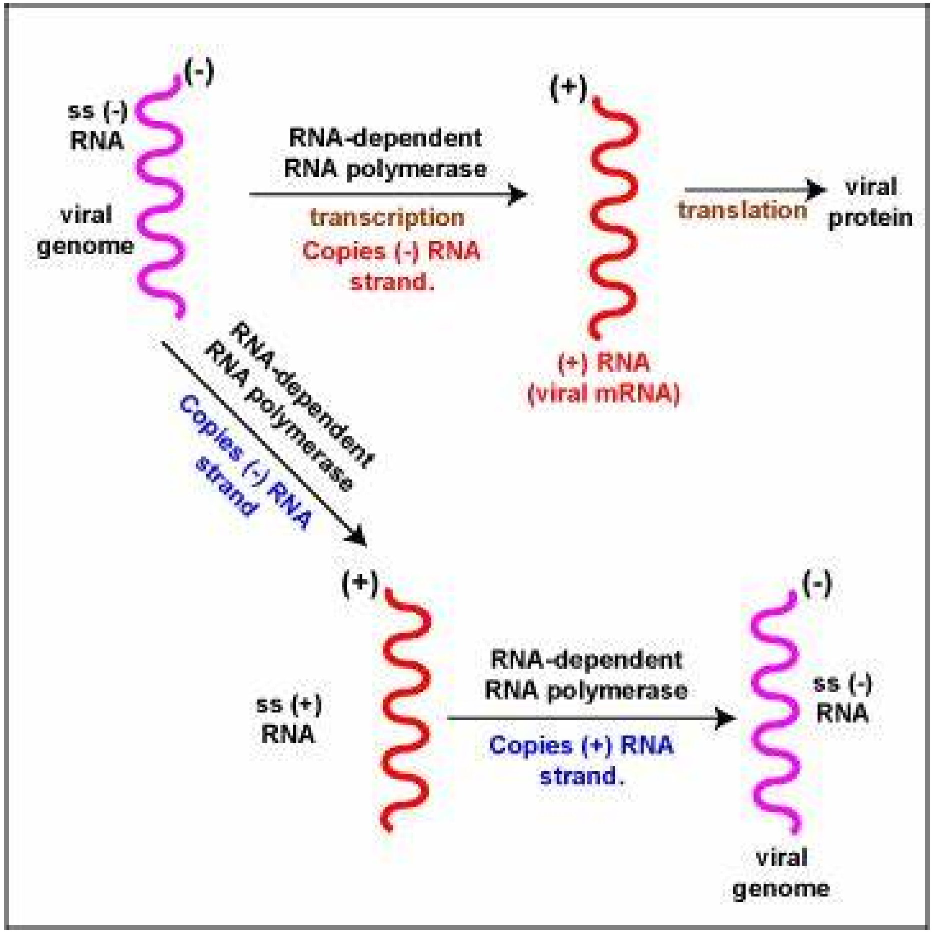
Test for overall effect: Z = 2.51 (P = 0.01)

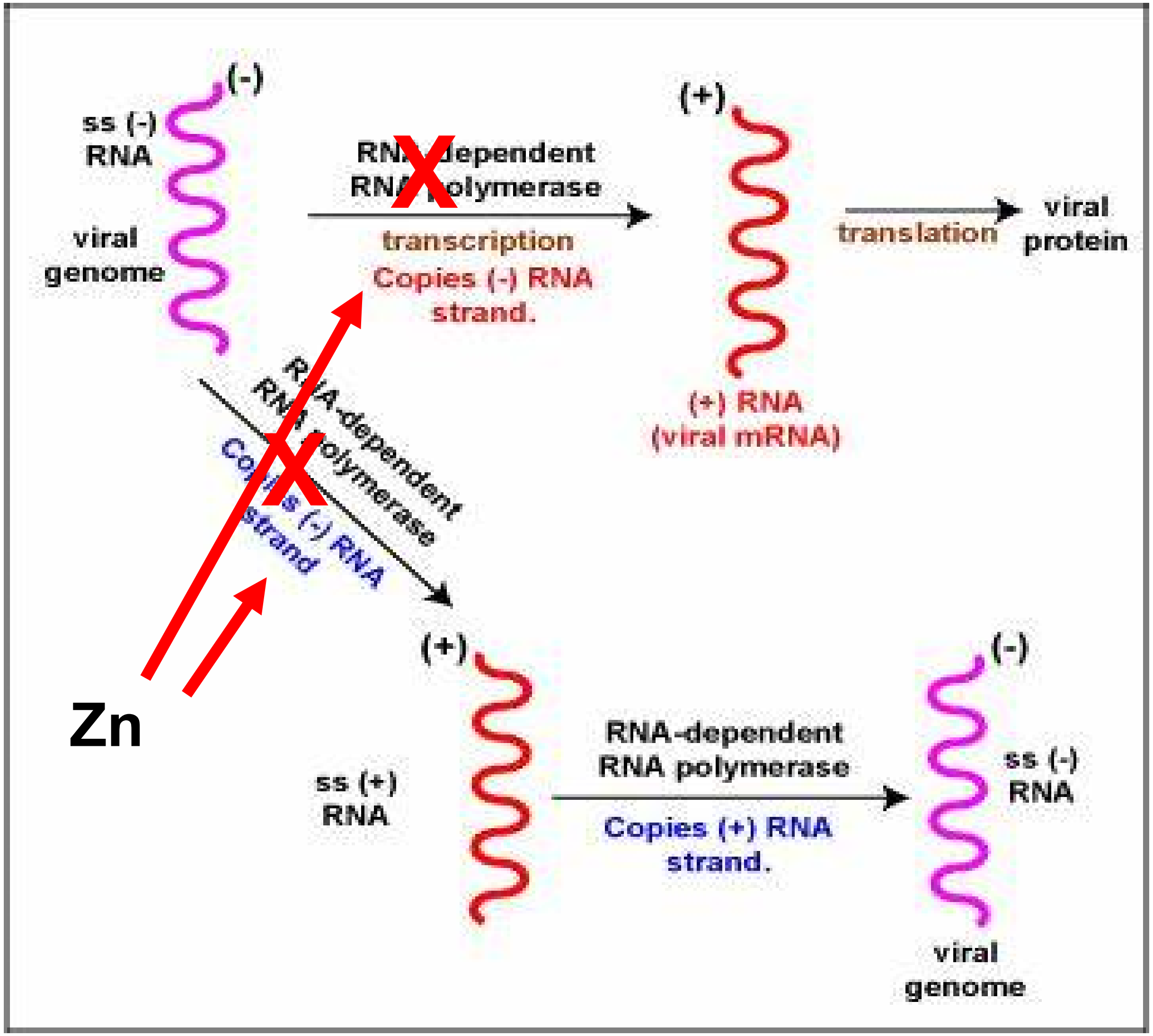


Efficacy of zinc on mortality caused by severe pneumonia.

Wang & Song (2018) Clin. Resp. J. 12, 857-864

Zinc inhibits the activity of an enzyme vital to viral replication (RNA dependent RNA polymerase)



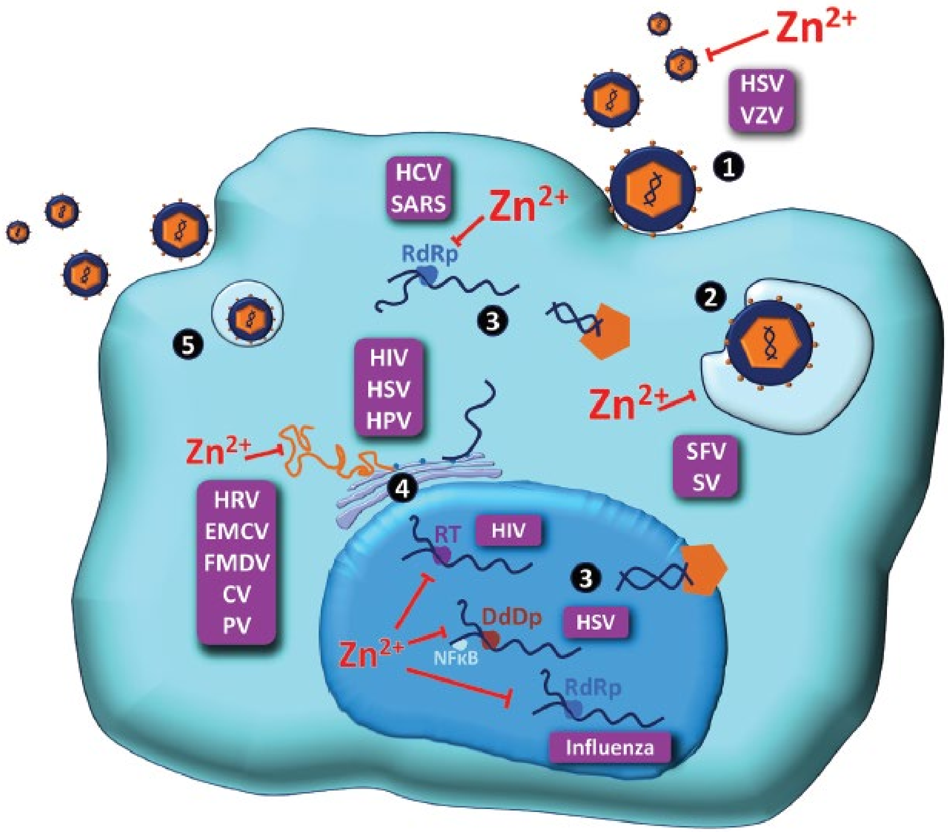


(-)
ss (-) RNA
viral genome
RNA-dependent RNA polymerase
transcription
Copies (-) RNA strand.
(+)
(+) RNA (viral mRNA)
translation
viral protein
RNA-dependent RNA polymerase
Copies (-) RNA strand
(+)
ss (+) RNA
RNA-dependent RNA polymerase
Copies (+) RNA strand.
(-)
ss (-) RNA
viral genome
Zn

The Role of Zinc in Antiviral Immunity

Scott A Read,[1,2] Stephanie Obeid,[3] Chantelle Ahlenstiel,[3] and Golo Ahlenstiel[1,2]

Adv Nutr 2019;10:696–710.



Vitamin D

Zn

Se

Review

Selenium, Selenoproteins, and Immunity

Joseph C. Avery and Peter R. Hoffmann *

Nutrients **2018**, *10*, 1203; doi:10.3390/nu10091203

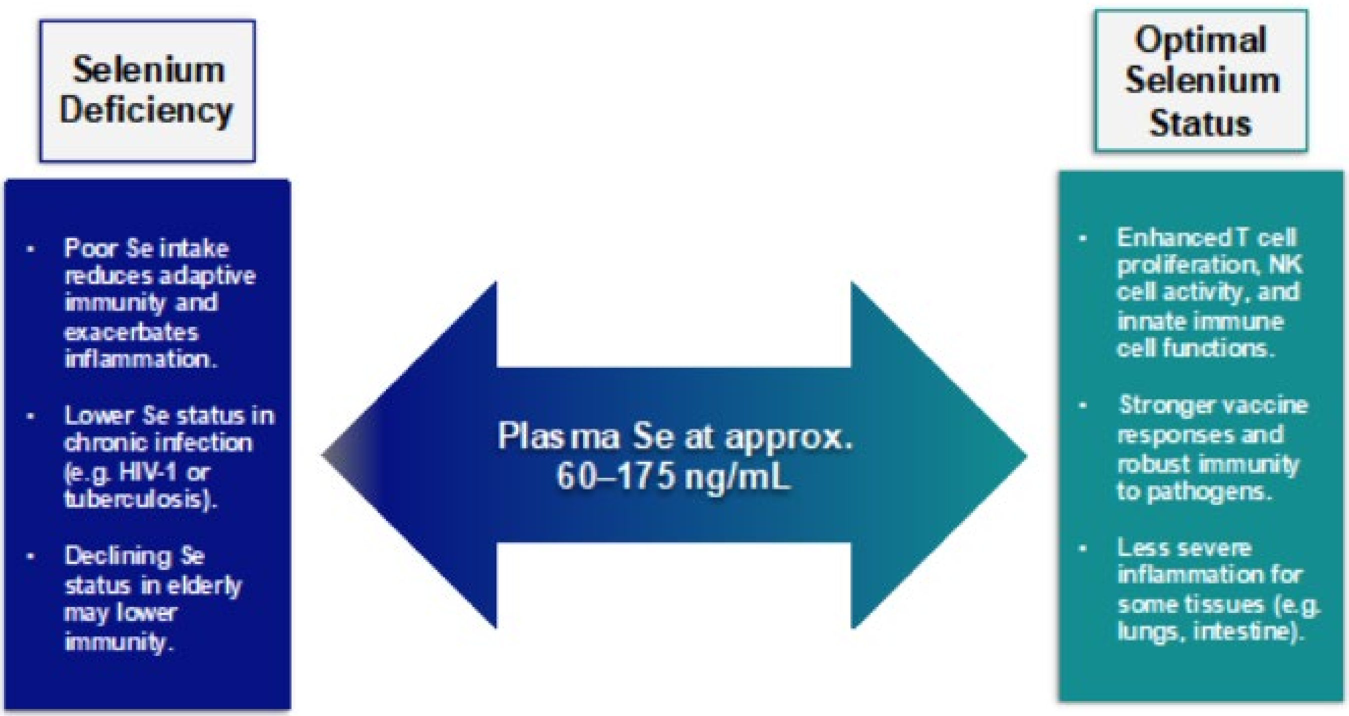


Figure 1. A summary of selenium and immune responses.

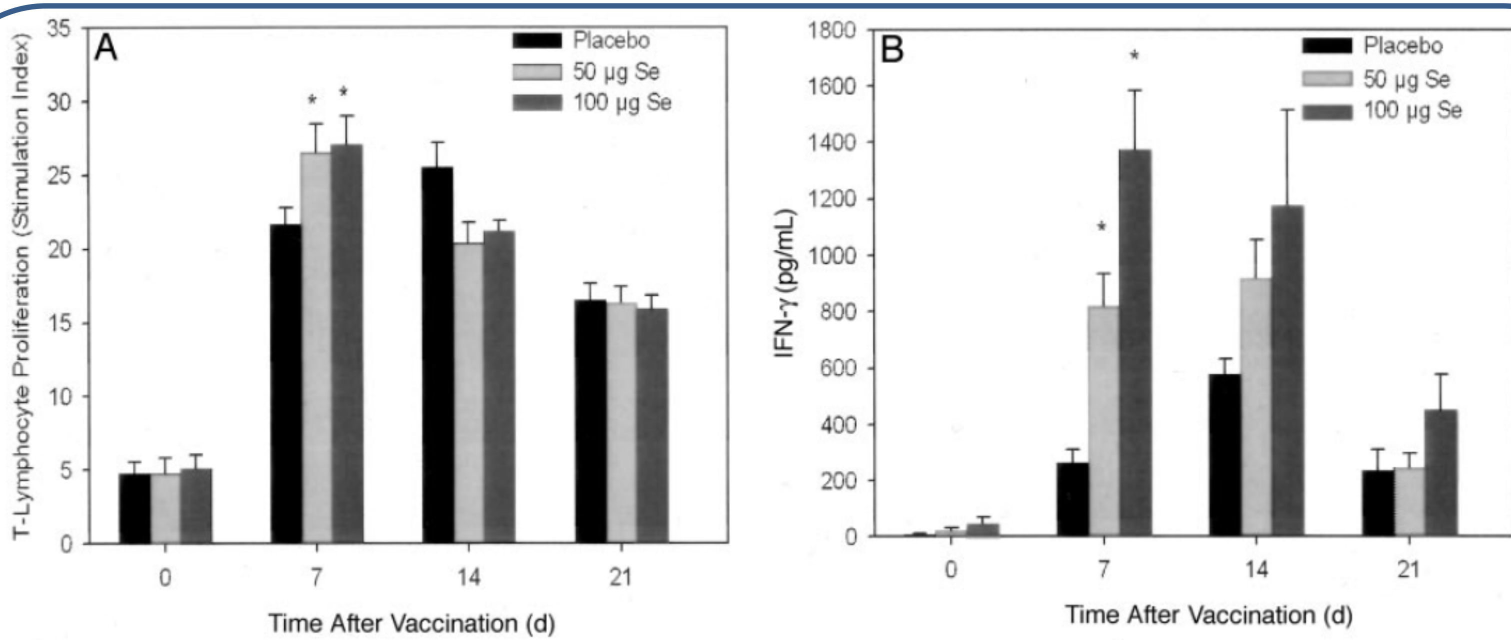
Extensive research in <u>mice</u> has shown that selenium deficiency:

- **Impairs immune responses**
- **Increases susceptibility to viral infection**
- **Permits viruses to mutate (including influenza viruses)**
- **Allows normally weak viruses to become more virulent**

An increase in selenium intake improves immune function and poliovirus handling in adults with marginal selenium status[1–3]

Caroline S Broome, Francis McArdle, Janet AM Kyle, Francis Andrews, Nicola M Lowe, C Anthony Hart, John R Arthur, and Malcolm J Jackson

Am J Clin Nutr 2004;80:154–62.



Selenium increases T cell function in response to polio virus
And increases IFN-γ production

Number of subjects with poliovirus in feces 7, 14, and 21 d after polio vaccination and after supplementation with 50 or 100 μg Se or placebo[1]

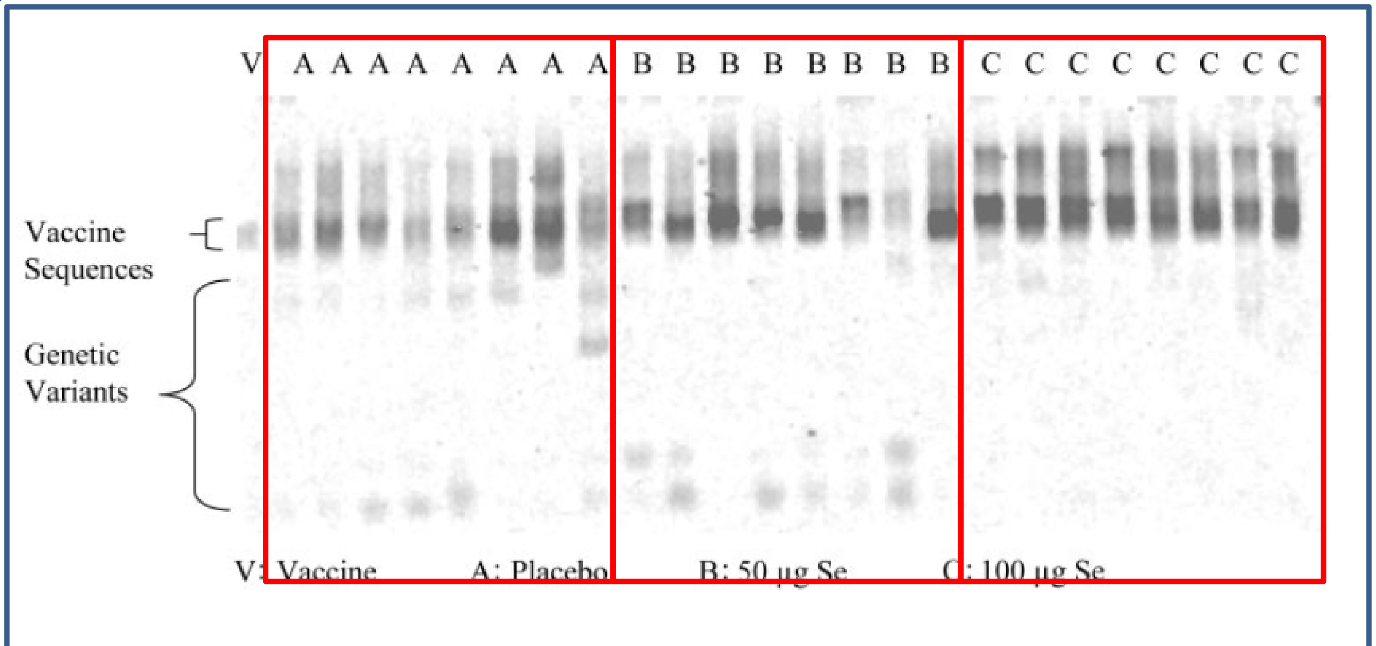
Time after polio vaccination	Placebo (n = 20)	50 μg Se/d (n = 20)	100 μg Se/d (n = 20)
7 d	19	14[2]	10[2]
14 d	19	10[2]	10[2]
21 d	14[2]	9[2]	7[2]

[1] Data were analyzed by using Friedman's test. P for interaction of treatment and day = 0.0001.

[2] Significantly different from placebo, $P < 0.001$.

Se decreases appearance of (oral) polio virus in faeces

=> Se results in better clearance of virus



Fewer mutant viral sequences in faeces

=> Se prevents viral mutations in humans

Association between regional selenium status and reported outcome of COVID-19 cases in China

Jinsong Zhang
Ethan Will Taylor
Kate Bennett
Ramy Saad
Margaret P Rayman

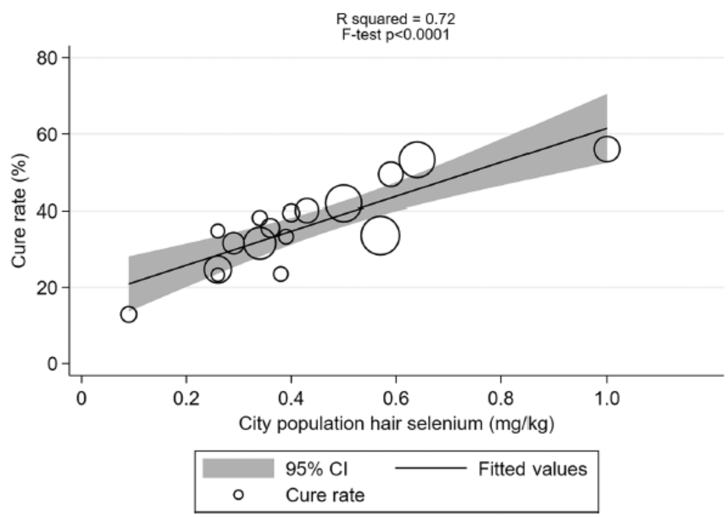
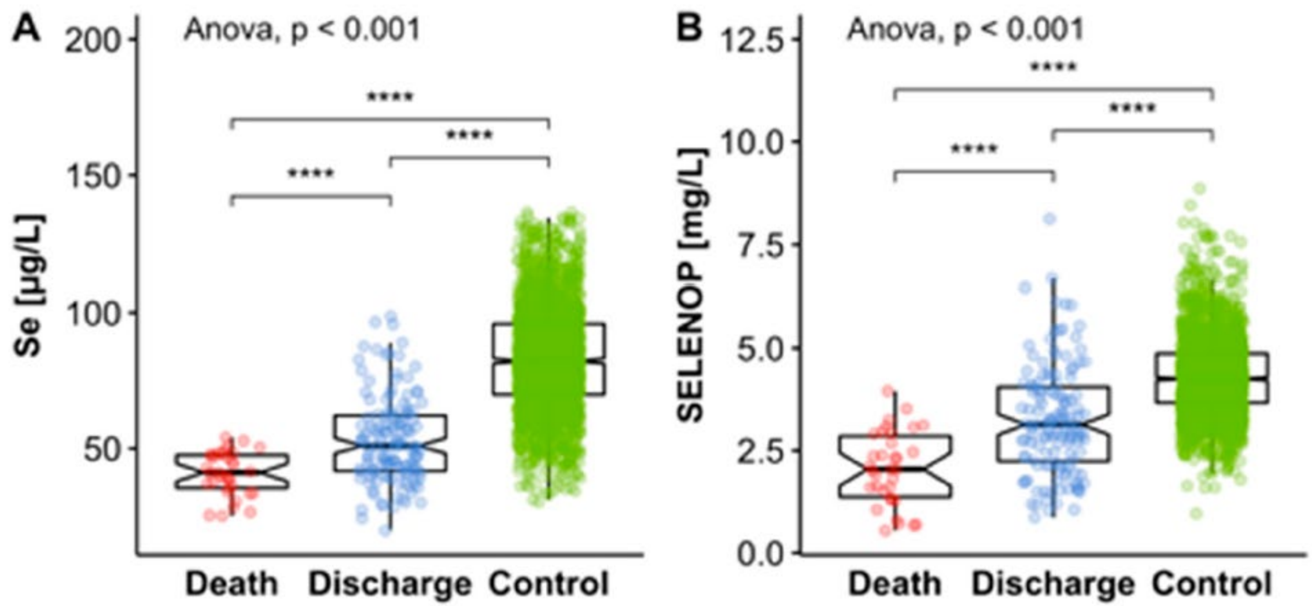


FIGURE 1 Correlation between COVID-19 cure rate in 17 cities outside Hubei, China, on 18 February, 2020 and city population selenium status (hair selenium concentration) analyzed using weighted linear regression (mean ± SD = 35.5 ± 11.1, $R^2 = 0.72$, F test $P < 0.0001$). Each data point represents the cure rate, calculated as the number of cured patients divided by the number of confirmed cases, expressed as a percentage. The size of the marker is proportional to the number of cases.

Am. J. Clin. Nutr. (2020) 111, 1297-1299

Selenium Deficiency Is Associated with Mortality Risk from COVID-19

Arash Moghaddam [1], Raban Arved Heller [2,3], Qian Sun [3], Julian Seelig [3], Asan Cherkezov [1], Linda Seibert [1], Julian Hackler [3], Petra Seemann [3], Joachim Diegmann [1], Maximilian Pilz [4], Manuel Bachmann [1], Waldemar B. Minich [3] and Lutz Schomburg [3,*]



Nutrients (2020) 12, 2098

Summary

- **The immune system is central to protection against infection -> it is complex & there are specific ways in which it deals with viruses**
- **Multiple nutrients play important roles in supporting the immune system – these include vitamin D, zinc & selenium**
- **Vitamin D is important in protecting against (viral) respiratory illness**
- **Zinc seems to have special roles in anti-viral immunity**
- **Selenium also seems to be important and is often overlooked**

Conclusions

- Nothing people can eat will STOP them getting infected (with coronavirus)

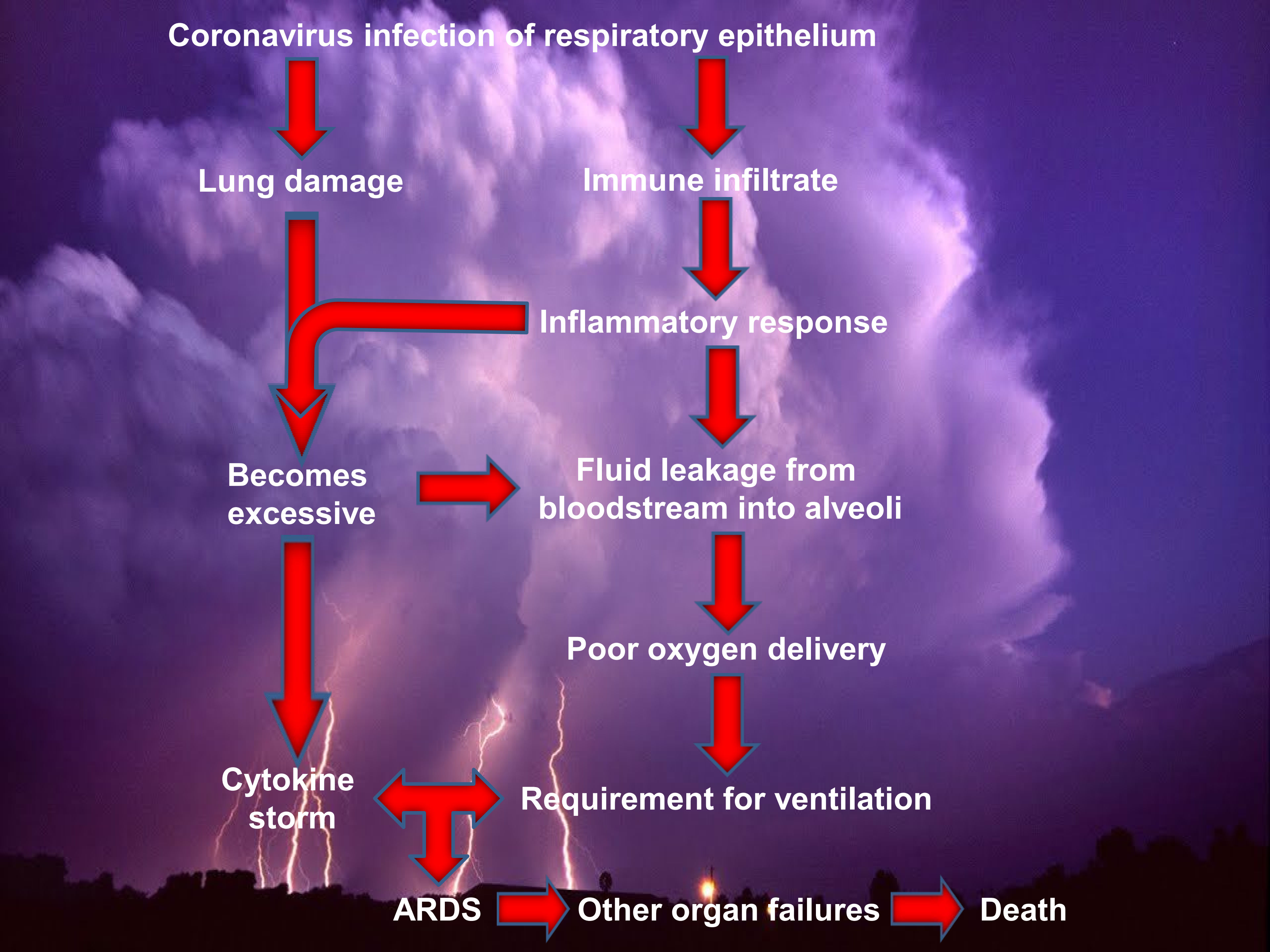
- Good immune defence is vital to combatting infections including with viruses like SARS-CoV2

- Vitamin D, zinc and selenium are all important in supporting the immune system and contribute to anti-viral immunity

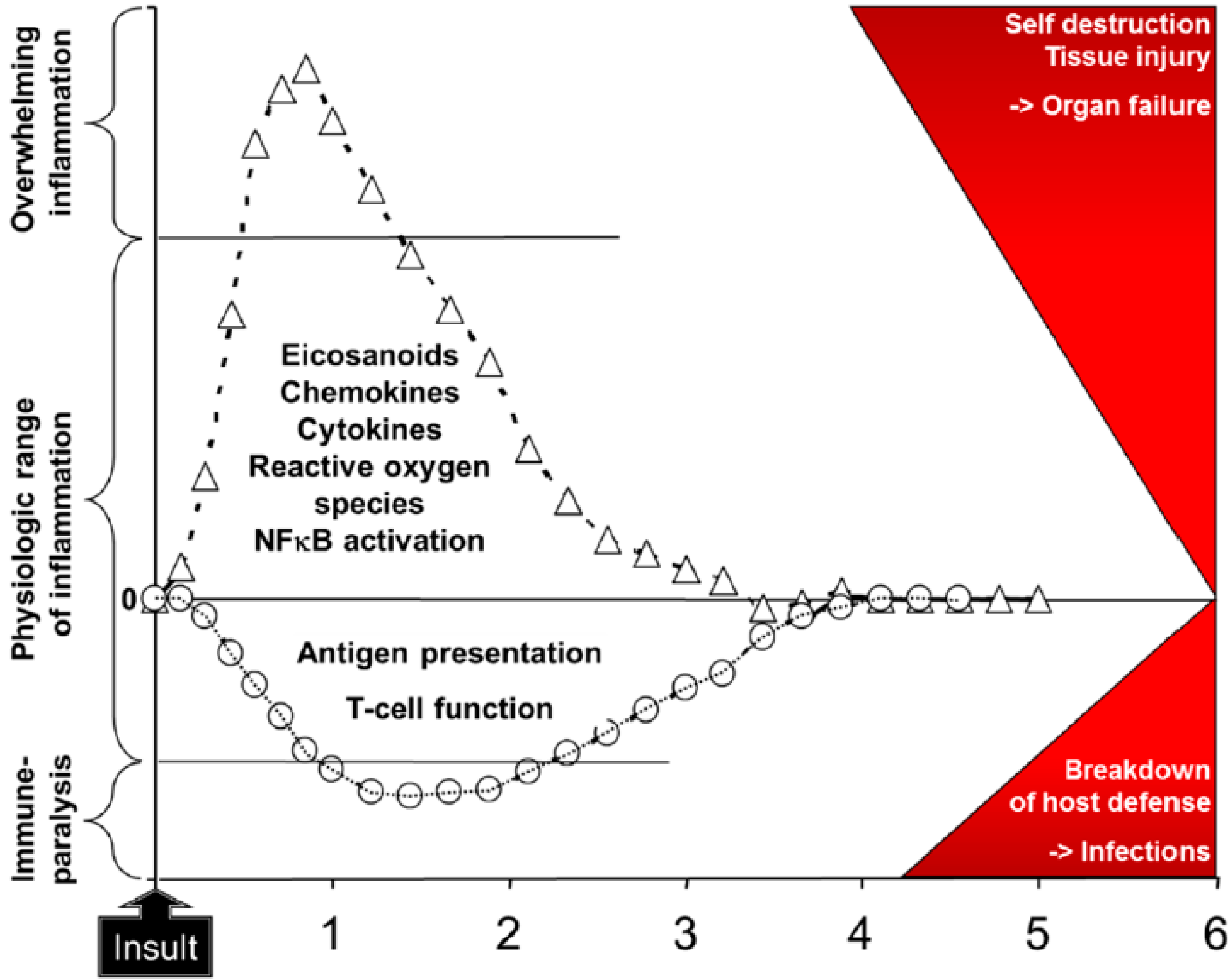
- Seafood is an excellent source of vitamin D, zinc and selenium and its consumption should be encouraged through healthy eating messages

Eat fish!!

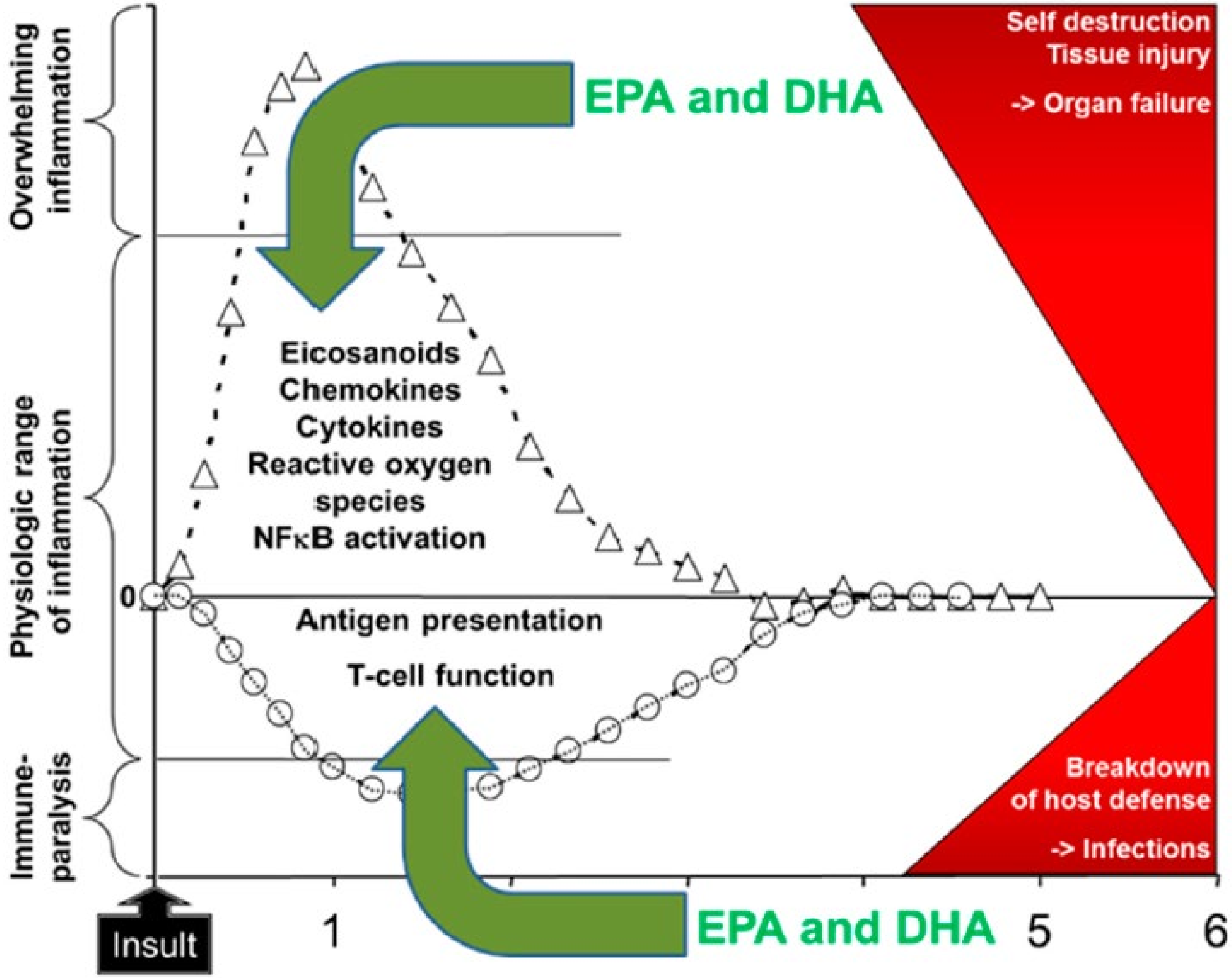
Omega-3 fatty acids & cytokine storm :



Coronavirus infection of respiratory epithelium
Lung damage
Immune infiltrate
Inflammatory response
Becomes excessive
Fluid leakage from bloodstream into alveoli
Poor oxygen delivery
Cytokine storm
Requirement for ventilation
ARDS
Other organ failures
Death



Calder (2020) Marine Drugs 17, 274



Calder (2020) Marine Drugs 17, 274

Cochrane
Library

Cochrane Database of Systematic Reviews

Rich in EPA and DHA (+ other nutrients)

Immunonutrition for acute respiratory distress syndrome (ARDS) in adults (Review)

Dushianthan A, Cusack R, Burgess VA, Grocott MPW, Calder PC

Dushianthan A, Cusack R, Burgess VA, Grocott MPW, Calder PC.
Immunonutrition for acute respiratory distress syndrome (ARDS) in adults.
Cochrane Database of Systematic Reviews 2019, Issue 1. Art. No.: CD012041.
DOI: 10.1002/14651858.CD012041.pub2.

www.cochranelibrary.com

Outcome	Effect	95% CI	P
28 day mortality	0.64	0.49, 0.84	0.0015
ICU LOS (days)	-3.09	-5.19, -0.99	0.004
Ventilator days	-2.24	-3.77, -0.71	0.0042
PaO2/FiO2 at d4	38.88	10.75, 67.02	0.0068
PaO2/FiO2 at d8	23.44	1.73, 45.15	0.034
New organ failure	0.45	0.32, 0.63	< 0.00001

Nutrition 81 (2020) 110900

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Hypothesis

Parenteral fish oil: An adjuvant pharmacotherapy for coronavirus disease 2019?

Raquel S. Torrinhas Ph.D. [a,*], Philip C. Calder Ph.D. [b,c], Gabriela O. Lemos GCert [a], Dan L. Waitzberg Ph.D. [a]

Letter to the Editor

Parenteral Fish-Oil Emulsions in Critically Ill COVID-19 Emulsions

DOI: 10.1002/jpen.1871

Journal of Parenteral and Enteral Nutrition
Volume 00 Number 0
May 2020 1

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Bruce R. Bistrian, MD, PhD

From Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA