Seafood nutrients and antiviral immunity

Philip Calder
Professor of Nutritional Immunology
University of Southampton
Southampton
United Kingdom
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
Nutrition, immunity and COVID-19
The immune system ....

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

- **B cells**
  - Activate
  - Antibodies
  - Bacteria

- **Th (T helper)**
  - Activate
  - Antigen presentation

- **NK (Natural Killer)**
  - Activate

- **Tc (T cytotoxic)**
  - Activate
  - Antigen presentation
  - Lysis
  - Virus infected cell

- **Phagocyte**
  - Activate

Cells and interactions are shown in a diagram with arrows indicating the activation and antigen presentation processes.
Optimal nutrient supply

Optimal nutrient status (& stores)

Optimal immune function
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]
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


But just an association: no “cause and effect”
### Vitamin D and Respiratory Tract Infections: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Peter Bergman, Åsa U. Lindh, Linda Björkhem-Bergman, Jonatan D. Lindh

June 2013 | Volume 8 | Issue 6 | e65835

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

#### Table 1. Odds Ratios for Vitamin D and Respiratory Tract Infections

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio</th>
<th>95%-CI</th>
<th>W(random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bias risk = High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aloia</td>
<td>0.25 [0.11; 0.58]</td>
<td>6.1%</td>
<td></td>
</tr>
<tr>
<td>Jorde</td>
<td>0.93 [0.52; 1.64]</td>
<td>9.0%</td>
<td></td>
</tr>
<tr>
<td>Summary</td>
<td>0.50 [0.14; 1.80]</td>
<td>15.1%</td>
<td></td>
</tr>
<tr>
<td>Bias risk = Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bergman</td>
<td>0.48 [0.25; 0.91]</td>
<td>8.1%</td>
<td></td>
</tr>
<tr>
<td>Camargo</td>
<td>0.49 [0.31; 0.79]</td>
<td>10.5%</td>
<td></td>
</tr>
<tr>
<td>Laaksi</td>
<td>0.67 [0.38; 1.17]</td>
<td>9.2%</td>
<td></td>
</tr>
<tr>
<td>Li-Ng</td>
<td>0.79 [0.41; 1.54]</td>
<td>7.9%</td>
<td></td>
</tr>
<tr>
<td>Majak</td>
<td>0.24 [0.06; 0.90]</td>
<td>3.2%</td>
<td></td>
</tr>
<tr>
<td>Manaseki-Holland 2010</td>
<td>0.60 [0.41; 0.88]</td>
<td>11.5%</td>
<td></td>
</tr>
<tr>
<td>Manaseki-Holland 2012</td>
<td>1.04 [0.92; 1.19]</td>
<td>14.6%</td>
<td></td>
</tr>
<tr>
<td>Murdoch</td>
<td>0.92 [0.62; 1.37]</td>
<td>11.4%</td>
<td></td>
</tr>
<tr>
<td>Urasihama</td>
<td>0.53 [0.28; 0.99]</td>
<td>8.4%</td>
<td></td>
</tr>
<tr>
<td>Summary</td>
<td>0.67 [0.50; 0.88]</td>
<td>84.9%</td>
<td></td>
</tr>
</tbody>
</table>

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

40 IU = 1 µg
• 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
<table>
<thead>
<tr>
<th>Study</th>
<th>Proportion with ≥1 ARTI (%)</th>
<th>Adjusted odds ratio (95% CI)</th>
<th>Weight (%)</th>
<th>Adjusted odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li-Ng 2009</td>
<td>33/76 (43.4)</td>
<td>32/81 (39.5)</td>
<td>3.48</td>
<td>0.85 (0.44 to 1.64)</td>
</tr>
<tr>
<td>Urashima 2010</td>
<td>69/167 (41.3)</td>
<td>68/167 (40.7)</td>
<td>5.36</td>
<td>0.90 (0.58 to 1.41)</td>
</tr>
<tr>
<td>Manaseki-Holland 2010</td>
<td>126/229 (55.0)</td>
<td>97/224 (43.3)</td>
<td>6.12</td>
<td>0.60 (0.41 to 0.88)</td>
</tr>
<tr>
<td>Laakso 2010</td>
<td>56/84 (64.3)</td>
<td>39/80 (48.8)</td>
<td>3.58</td>
<td>0.51 (0.27 to 0.96)</td>
</tr>
<tr>
<td>Majak 2011</td>
<td>11/24 (45.8)</td>
<td>4/24 (16.7)</td>
<td>1.00</td>
<td>0.20 (0.05 to 0.82)</td>
</tr>
<tr>
<td>Trilok-Kumar 2011</td>
<td>458/1030 (44.5)</td>
<td>438/1034 (42.4)</td>
<td>8.69</td>
<td>0.92 (0.77 to 1.11)</td>
</tr>
<tr>
<td>Lehouck 2012</td>
<td>29/89 (32.6)</td>
<td>30/86 (34.9)</td>
<td>3.57</td>
<td>1.00 (0.53 to 1.90)</td>
</tr>
<tr>
<td>Manaseki-Holland 2012</td>
<td>245/1505 (16.3)</td>
<td>260/1506 (17.3)</td>
<td>8.58</td>
<td>1.08 (0.89 to 1.30)</td>
</tr>
<tr>
<td>Camargo 2012</td>
<td>53/103 (51.5)</td>
<td>44/141 (31.2)</td>
<td>4.36</td>
<td>0.38 (0.22 to 0.65)</td>
</tr>
<tr>
<td>Murdoch 2012</td>
<td>155/161 (96.3)</td>
<td>154/161 (95.7)</td>
<td>1.43</td>
<td>0.97 (0.30 to 3.15)</td>
</tr>
<tr>
<td>Bergman 2012</td>
<td>39/62 (62.9)</td>
<td>26/62 (41.9)</td>
<td>2.89</td>
<td>0.42 (0.20 to 0.89)</td>
</tr>
<tr>
<td>Marchisio 2013</td>
<td>38/58 (65.5)</td>
<td>26/58 (44.8)</td>
<td>2.84</td>
<td>0.44 (0.21 to 0.95)</td>
</tr>
<tr>
<td>Rees 2013</td>
<td>276/360 (76.7)</td>
<td>303/399 (75.9)</td>
<td>6.35</td>
<td>1.03 (0.72 to 1.49)</td>
</tr>
<tr>
<td>Tran 2014</td>
<td>96/197 (48.7)</td>
<td>185/397 (46.6)</td>
<td>6.60</td>
<td>0.92 (0.65 to 1.30)</td>
</tr>
<tr>
<td>Goodall 2014</td>
<td>80/234 (34.2)</td>
<td>70/258 (27.1)</td>
<td>5.94</td>
<td>0.66 (0.45 to 0.98)</td>
</tr>
<tr>
<td>Urashima 2014</td>
<td>17/99 (17.2)</td>
<td>32/168 (21.6)</td>
<td>3.41</td>
<td>1.43 (0.73 to 2.78)</td>
</tr>
<tr>
<td>Grant 2014</td>
<td>53/80 (66.3)</td>
<td>94/156 (60.3)</td>
<td>4.12</td>
<td>0.77 (0.43 to 1.36)</td>
</tr>
<tr>
<td>Martineau 2015 VIDICO</td>
<td>75/118 (63.6)</td>
<td>76/122 (62.3)</td>
<td>3.98</td>
<td>0.87 (0.48 to 1.57)</td>
</tr>
<tr>
<td>Martineau 2015 VidiAs</td>
<td>93/125 (74.4)</td>
<td>85/125 (68.0)</td>
<td>3.74</td>
<td>0.71 (0.38 to 1.31)</td>
</tr>
<tr>
<td>Martineau 2015 VidiFlu</td>
<td>58/103 (56.3)</td>
<td>83/137 (60.6)</td>
<td>4.38</td>
<td>1.13 (0.66 to 1.95)</td>
</tr>
<tr>
<td>Dubnov-Raz 2015</td>
<td>10/11 (90.9)</td>
<td>10/14 (71.4)</td>
<td>0.28</td>
<td>0.23 (0.01 to 3.82)</td>
</tr>
<tr>
<td>Denlinger 2016</td>
<td>93/207 (44.9)</td>
<td>110/201 (54.7)</td>
<td>5.86</td>
<td>1.52 (1.02 to 2.28)</td>
</tr>
<tr>
<td>Tachimoto 2016</td>
<td>5/35 (14.3)</td>
<td>4/54 (7.4)</td>
<td>1.01</td>
<td>0.45 (0.11 to 1.89)</td>
</tr>
<tr>
<td>Ginde 2016</td>
<td>26/52 (46.2)</td>
<td>17/55 (30.9)</td>
<td>2.44</td>
<td>0.44 (0.19 to 1.02)</td>
</tr>
<tr>
<td>Simpson 2015</td>
<td>15/58 (26.3)</td>
<td>15/58 (26.3)</td>
<td>0.00</td>
<td>Excluded</td>
</tr>
</tbody>
</table>

Overall: I²= 53.3%, P< 0.001

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

Petre Cristian Ilie¹ · Simina Stefanescu² · Lee Smith³

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\textsuperscript{1,2*}, Dmitry Tworowski\textsuperscript{3}, Alessandro Gorohovski\textsuperscript{3}, Shlomo Vinker\textsuperscript{1,2}, Avivit Golan Cohen\textsuperscript{1,2}, Ilan Green\textsuperscript{1,2}, Milana Frenkel Morgenstern\textsuperscript{3*}

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

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

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude OR (95% CI)</th>
<th>P value</th>
<th>Adjusted OR (95% CI) *</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low vitamin D level</td>
<td>2.09(1.01-4.31)</td>
<td>0.021</td>
<td>1.95(0.99-4.78)</td>
<td>0.056</td>
</tr>
<tr>
<td>Age over 50 years</td>
<td>2.51(1.21-4.89)</td>
<td>0.001</td>
<td>2.71(1.55; 4.78)</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Vitamin D

Zn

Se
Zinc as a Gatekeeper of Immune Function

**ZINC DEFICIENCY**
- overproduction of pro-inflammatory cytokines & reactive mediators
- Thymus atrophy
- $T_{H1}/T_{H2}$ dysbalance
- less naive B cells
- less $T_{reg}$
- more $T_{H17}$

**ZINC HOMEOSTASIS**
- balanced immune cell numbers & functions
- balance between tolerance and defense mechanisms

**ZINC EXCESS**
- suppression of T & B cell function
- overload of $T_{reg}$
- direct activation of macrophages

---

Wessels et al. (2017) Nutrients 9, 1286
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


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

T-cell proliferation
Zinc decreases risk of mortality in people with severe pneumonia.

Efficacy of zinc on mortality caused by severe pneumonia.

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

viral genome

ss (-) RNA

RNA-dependent RNA polymerase

transcription

Copies (-) RNA strand.

(+)

RNA-dependent RNA polymerase

translation

viral protein

(+)

RNA (viral mRNA)

ss (+) RNA

viral genome

Copies (+) RNA strand.

(-)
The Role of Zinc in Antiviral Immunity

Scott A Read,¹,² Stephanie Obeid,³ Chantelle Ahlenstiel,³ and Golo Ahlenstiel¹,²

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 **mice** 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\textsuperscript{1–3}


Selenium increases T cell function in response to polio virus And increases IFN-\(\gamma\) production
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.
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,*
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
    - Fluid leakage from bloodstream into alveoli
      - Poor oxygen delivery
        - Requirement for ventilation
          - Cytokine storm
            - Becomes excessive
              - ARDS
                - Other organ failures
                  - Death
Calder (2020) Marine Drugs 17, 274
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
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Effect</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 day mortality</td>
<td>0.64</td>
<td>0.49, 0.84</td>
<td>0.0015</td>
</tr>
<tr>
<td>ICU LOS (days)</td>
<td>-3.09</td>
<td>-5.19, -0.99</td>
<td>0.004</td>
</tr>
<tr>
<td>Ventilator days</td>
<td>-2.24</td>
<td>-3.77, -0.71</td>
<td>0.0042</td>
</tr>
<tr>
<td>PaO2/FiO2 at d4</td>
<td>38.88</td>
<td>10.75, 67.02</td>
<td>0.0068</td>
</tr>
<tr>
<td>PaO2/FiO2 at d8</td>
<td>23.44</td>
<td>1.73, 45.15</td>
<td>0.034</td>
</tr>
<tr>
<td>New organ failure</td>
<td>0.45</td>
<td>0.32, 0.63</td>
<td>&lt; 0.00001</td>
</tr>
</tbody>
</table>
Hypothesis

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

Raquel S. Torrinhas Ph.D. a,*, Philip C. Calder Ph.D. b,*, 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

Bruce R. Bistrian, MD, PhD

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