Exploring the links between Food, Diet and Non-Communicable Disease

Evidence and Controversies

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Almost everything we think we know about the relationship between diet and NCDs remains ambiguous and controversial...
Some comments from US Congressional Hearings in 2015 on the most recent *Dietary Guidelines for Americans*

“We’re concerned that the public at large has lost faith in the process to develop the dietary guidelines which will ultimately decrease the adherence to them with potentially costly effects on public health…”
Kelly (Republican–MS)

“I just want you to understand from my constituents, most of them don’t believe this stuff anymore. You have lost your credibility with a lot of people, and they are just flat-out ignoring this stuff. And so that’s why I say…” Peterson (Democrat–MN)

“…there’s a belief, then, that the people on the committee entered with a bias in some way, shape or form and were searching for the science to back up what they already believed to be true, instead of using the best available science.”
Scott (Republican–GA)
Human nutrition research changed radically in the second half of the 20th century

- Early twentieth century nutrition science was dominated by the identification of essential micronutrients.

- The characterisation of nutrients occurred in the context of major advances in chemistry, biochemistry and physiology.

- Nutrient deficiency conditions (e.g. scurvy, beri beri) lend themselves to investigation using robust experimental methods.
In developed countries NCDs have replaced infectious diseases as the predominant cause of morbidity and mortality

• Since 1945, nutritional deficiencies due to food shortages have become much less common in prosperous countries.

• Massive improvements in public health and clinical practice have led to declines in and morbidity and mortality due to infectious diseases.

• The prevalence of non-infectious diseases such as cardiovascular disease, diabetes and cancer have increased.
The Top 10 Causes of death in USA: 1900 and 2010

Data are from the Centers for Disease Control and Prevention.

The post-war expansion of research into the role of nutrition in the prevention of NCDs reflects increasing prosperity and improved public health.
Death rates due to coronary heart disease (CHD) grew rapidly through the first half of the 20th century.
The role of nutrition in the prevention and management of NCDs is difficult to investigate

- The developmental stages of cardiovascular diseases and cancers take decades.
- Dietary exposures are impossible to measure accurately over long periods of time.
- Residual confounding factors are difficult to control.
- Effect sizes are generally small.
Ideally...
Hypotheses are tested at these levels

In practice, most of our knowledge about diet and disease tends to come from prospective cohort studies.

Hypotheses about causation emerge at these levels

A Hierarchy of Study Designs for Biomedical Research

Systematic Reviews

Randomised Controlled Trials (With hard endpoints)

Randomised Controlled Trials (With intermediate disease biomarkers)

Prospective Cohort Studies

Case-Control Studies

Ecological Studies
Cocoa flavanols: well suited to randomised intervention trials using intermediate biomarkers as the endpoint.

• Cocoa flavanols are well characterised, and can be extracted and administered as supplements.

• The potentially beneficial effects of prolonged supplementation with flavanoids on human vascular endothelium are now well established.

• EFSA has approved a health claim relating to cocoa flavanols “Cocoa flavanols help maintain endothelium-dependent vasodilation, which contributes to normal blood flow”.
A systematic review of randomised controlled trials of the effect of cocoa on blood pressure

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean Difference ( SE )</th>
<th>Cocoa Control Total Weight</th>
<th>Mean Difference ( IV, ) Random, 95% CI</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Murphy 2003</td>
<td>-1.4</td>
<td>13</td>
<td>15</td>
<td>1.5% -1.0 (0.84, 6.84)</td>
</tr>
<tr>
<td>Taiter 2002</td>
<td>-5.0</td>
<td>13</td>
<td>15</td>
<td>3.2% -5.2 (5.5, 9.67)</td>
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<tr>
<td>Engler 2004</td>
<td>1.4</td>
<td>11</td>
<td>10</td>
<td>1.4% 0.8 (68, 10.48)</td>
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<tr>
<td>Fraga 2005</td>
<td>-4.16</td>
<td>14</td>
<td>20</td>
<td>2.2% -4.4 (7.14, 11.86)</td>
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<tr>
<td>Gift 2005a</td>
<td>-6.5</td>
<td>14</td>
<td>15</td>
<td>2.8% -6.9 (10.3, 17.83)</td>
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<tr>
<td>Grazi 2005b</td>
<td>-11.3</td>
<td>20</td>
<td>30</td>
<td>3.1% -11.8 (13.6, 9.44)</td>
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<tr>
<td>Taiter 2007</td>
<td>-2.8</td>
<td>22</td>
<td>22</td>
<td>2.2% -3.1 (5.7, 17.67)</td>
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<tr>
<td>Al-Farsi 2008</td>
<td>-7.1</td>
<td>20</td>
<td>25</td>
<td>2.9% -7.3 (11.3, 23.8)</td>
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<td>Cross 2005</td>
<td>-5.2</td>
<td>24</td>
<td>45</td>
<td>2.2% -5.8 (9.7, 4.54)</td>
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<td>Dario 2008b</td>
<td>-6.1</td>
<td>12</td>
<td>11</td>
<td>1.8% -6.3 (12.88, 0.06)</td>
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<td>Dario 2008c</td>
<td>1.6</td>
<td>11</td>
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<td>1.3% 1.6 (7.32, 10.43)</td>
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<td>Reid 2009</td>
<td>2.6</td>
<td>55</td>
<td>11</td>
<td>0.8% 2.3 (9.14, 15.7)</td>
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<tr>
<td>Silva 2009</td>
<td>0.6</td>
<td>51</td>
<td>20</td>
<td>1.5% 0.6 (8.16, 8.09)</td>
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<td>Biguard 2010</td>
<td>0.25</td>
<td>154</td>
<td>41</td>
<td>2.8% 0.2 (7.27, 2.97)</td>
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<td>Danilo 2010</td>
<td>-5.21</td>
<td>14</td>
<td>12</td>
<td>1.3% -5.7 (12.35, 3.81)</td>
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<tr>
<td>Hsio 2010</td>
<td>-5.12</td>
<td>36</td>
<td>16</td>
<td>1.9% -5.5 (13.31, 13.13)</td>
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<td>Hsio 2011</td>
<td>3.2</td>
<td>72</td>
<td>39</td>
<td>2.7% 3.2 (10.67, 5.77)</td>
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<td>-4.98</td>
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<td>2.8% -4.8 (8.06, 1.96)</td>
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<td>Atzmoos 2012b</td>
<td>-2.45</td>
<td>14</td>
<td>21</td>
<td>2.2% -2.5 (5.19, 0.29)</td>
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<tr>
<td>Gernstedt 2012</td>
<td>-8.7</td>
<td>35</td>
<td>30</td>
<td>2.2% -8.5 (10.69, 0.65)</td>
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<tr>
<td>Khan 2012</td>
<td>2.254</td>
<td>42</td>
<td>42</td>
<td>2.3% 2.0 (1.88, 7.49)</td>
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<tr>
<td>Mapelton 2012</td>
<td>-0.79</td>
<td>12</td>
<td>20</td>
<td>3.0% -0.9 (3.20, 1.62)</td>
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<tr>
<td>Nazzafut 2013</td>
<td>0.342</td>
<td>10</td>
<td>10</td>
<td>1.8% 0.0 (5.67, 6.70)</td>
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<tr>
<td>Sorens 2013</td>
<td>6.191</td>
<td>29</td>
<td>22</td>
<td>2.6% 6.0 (2.56, 7.48)</td>
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<tr>
<td>Ester 2014</td>
<td>-1.507</td>
<td>41</td>
<td>41</td>
<td>2.7% -1.8 (7.31, 13.01)</td>
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<tr>
<td>Iben-Barakar 2014</td>
<td>1.1</td>
<td>24</td>
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<td>Nockels-Richardson 2014</td>
<td>0.7</td>
<td>10</td>
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<td>Sampa 2014b</td>
<td>2.29</td>
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<td>Muziavatoze 2018</td>
<td>-6.1</td>
<td>83</td>
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<td>1.3% -6.5 (7.75, -4.94)</td>
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<tr>
<td>Samov 2015</td>
<td>-4.12</td>
<td>50</td>
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<td>1.6% -4.0 (6.57, -1.49)</td>
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</tbody>
</table>

Total (95% CI): 907 897 100.0% -1.76 (-3.49, -0.43)

Heterogeneity: \( I^2 = 13.99 \), \( T^2 = 3983.57 \), \( df = 38 \ < 0.00001 \), \( P = 0.87 \)
Test for overall effect: \( Z = 2.60 \), \( P < 0.009 \)

Ried et al., Cochrane Database of Systematic Reviews, 2017

Systolic BP (-1.76 mm Hg; p<0.009)

Diastolic BP (-1.76 mm Hg; p<0.001)
A systematic Review of cohort studies on Chocolate Consumption and Risk of Coronary Heart Disease

Yuan et al, Nutrients, 9, 688, 2017
Cocoa appears to lower blood pressure, but does that account for an association between chocolate consumption and cardiovascular disease?

“The evidence is of moderate quality. We were unable to identify any randomised controlled trials that tested the effect of long-term daily use of cocoa products on blood pressure, and there were no trials that measured the health consequences of high blood pressure, such as heart attacks or strokes.”

*Ried et al, Cochrane Database of Systematic Reviews, 2017*

“...the present meta-analysis suggests that chocolate consumption confers reduced risks of CHD, stroke, and diabetes.” “Additional large prospective studies are required to confirm the observed benefits of chocolate in populations...”

*Yuan et al, Nutrients, 9, 688, 2017*
Randomised trials can be conducted in human nutrition research.

The PREDIMED Trial

- A parallel group, multicentre, randomised trial.
- Subjects were men (55-80yrs) and women (60-80yrs) at elevated risk of CVD.
- 7447 participants randomised to three groups (2 MED diet and 1 “low-fat” CONTROL diet).
- MED diet participants were given advice and supplements (1 litre extra-virgin olive oil/wk or 30g mixed nuts/day).
- CONTROL participants received dietary advice only.
- Hard end-points were “combined myocardial infarction, stroke and death from CVD”, and “death from any cause”.

PREDIMED Control and Treatment Diets

Control Group
- Low-fat dairy products
- Bread potatoes and pasta
- Fresh fruit
- Vegetables
- Lean fish
- Vegetable oils
- Baked goods
- Fried snacks
- Red and processed meat
- Visible fat
- Fatty fish
- Spread fats
- Sofrito

Mediterranean Diet Groups
- Extra Virgin olive oil (Supplemented – EVOO group)
- Tree nuts (Supplemented – Nuts group)
- Fresh fruit
- Vegetables
- Fish
- Legumes
- Sofrito
- White meat
- Wine
- Sodas
- Baked goods
- Spread fats
- Red and processed meat

Main Outcome Events

Statistically significant reductions in myocardial infarction, stroke and death from CVD.

No statistically significant reduction in all-cause Mortality.

PREDIMED: Some continuing questions and controversies

• The main finding: The primary endpoint was reduced by 30% and 28% respectively in the olive oil and nuts sub-groups.

• The authors argue that adherence to the Mediterranean diet per se was associated with reduced risk independently of the supplements.

• The study was terminated early (4.8 y) because continued exposure to the control conditions for 6 y was considered potentially damaging.

• The study was not designed or powered to assess effects on total mortality.

In parallel with difficulty of gaining knowledge, the delivery of knowledge is becoming harder.

- There is intense public interest in diet and health but consumers prefer certainty to probability.
- Main stream media favour *simplification* and *exaggeration*.
- Celebrities and other pundits often pursue their own evidence-free agendas.
- The internet generates, amplifies and perpetuates myths about diet and health.
Conclusions

• All scientific knowledge is tentative – our beliefs about nutrition have to be re-examined and updated in the light of emerging evidence. Use Bayesian approaches where appropriate.

• The limitations of observational epidemiology must be acknowledged. Statistically significant associations don’t necessarily prove causality.

• We need more, and better designed, randomised human intervention trials with hard disease endpoints.

• Evidence from both epidemiological studies and intervention trials needs to be underpinned with mechanistic research.