You are what you eat, are you? How to interpret the evidence from nutrition epidemiology studies – PART 1
A bit of history

Determinants of dietary intake

Diet and NCDs: the different study types

- Ecological / geographical
- Cross-sectional
- Prospective
- Interventions
How food fed epidemiological methods

A BIT OF HISTORY

Huang Di (2600 BC)

Huang Di asked, “I’ve heard that in the days of old everyone lived one hundred years without showing the usual signs of aging. In our time, however, people age prematurely, living only fifty years. Is this due to a change in the environment, or is it because people have lost the correct way of life?”

Qi Bo replied, “In the past, people practiced the Tao, the Way of Life. They ... **ate a balanced diet at regular times**, arose and retired at regular hours, avoided overstressing their bodies and minds, ... thus, it is not surprising that they lived over one hundred years.”

“These days, people have changed their way of life. They drink wine as it were water,... They **fail to regulate their lifestyle and diet**, and sleep improperly. So it is not surprising that they look old at fifty and die soon after.”
Hippocrates of Cos (400 BC)

Let food be thy medicine: wrongly attributed to him.

On Regimen in Acute Diseases

One must determine by such marks as these, when sweet, strong, and dark wine, hydromel, water and oxymel, should be given in acute diseases. Wherefore the sweet affects the head less than the strong, attacks the brain less, evacuates the bowels more than the other, but induces swelling of the spleen and liver; it does not agree with bilious persons, for it causes them to thirst; it creates flatulence in the upper part of the intestinal canal, but does not disagree with the lower part, as far as regards flatulence; and yet flatulence engendered by sweet wine is not of a transient nature, but rests for a long time in the hypochondria.
James Lind - The first clinical trial (1747)

Of the prevention of the scurvy. Part II.

They all in general had putrid gums, the spots and latitude, with weakness of their knees. They lay together in one place, being a proper apartment for the sick in the fore-hold; and had one diet common to all, viz. water-gruel sweetened with sugar in the morning; fresh mutton-broth often times for dinner; at other times puddings, boiled biscuit with sugar, &c.; and for supper, barley and raisins, rice and currants, figo and wine, or the like. Two of these were ordered each a quart of cyder a-day. Two others took twenty-five guts of elixir vitriol three times a-day, upon an empty stomach; using a gargle strongly acidulated with it for their mouths. Two others took two spoonfuls of vinegar three times a-day, upon an empty stomach; having their gruels and their other food well acidulated with it, as also the gargle for their mouth. Two of the worst patients, with the tendons in the ham rigid, (a symptom none of the rest had), were put under a course of sea-water. Of this they drank half a pint every day, and sometimes more or less as it operated, by way of gentle physic. Two others had each two oranges and one lemon given them every day. These they eat with grease dinels.
“I found that nearly all the deaths had taken place within a short distance of the pump ... With regard to the deaths ... there were sixty-one instances in which I was informed that the deceased persons used to drink the water from Broad Street, either constantly or occasionally...”

“The result of the inquiry then was that there has been no particular outbreak or increase of cholera, in this part of London, except among the persons who were in the habit of drinking water of the above-mentioned pump-well. I had an interview with the Board of Guardians of St. James parish, ... the handle of the pump was removed the following day.”

Case Studies in Public Health. DOI: http://dx.doi.org/10.1016/B978-0-12-804571-8.00017-2
https://en.wikipedia.org/wiki/John_Snow
Determinants of dietary intake
The war in Ukraine is turning "the breadbasket of the world to breadlines" for millions of its people, while devastating countries like Egypt that normally gets 85% of its grain from Ukraine and Lebanon that got 81% in 2020, Beasley said.

Ukraine and Russia produce 30% of the world's wheat supply, 20% of its corn and 75%-80% of the sunflower seed oil. The World Food Program buys 50% of its grain from Ukraine, he said.

As Russia "choke off Ukrainian exports," food prices are skyrocketing, with wheat prices rising between 20% and 50% so far this year, she said.

"We are particularly concerned about countries like Lebanon, Pakistan, Libya, Tunisia, Yemen and Morocco which rely heavily on Ukrainian imports to feed their population," Sherman said.
Trends in caloric availability

Trends in vegetable oil availability

Different types of studies

DIET AND NCDs
A major burden

And many possible markers

Individual foods: beef, fish, bananas, bread, water…
Food categories: meat, dairy, fruit, vegetables…
Nutrients: protein, lipids, vitamins, minerals
Other: AA, flavonoids, phytosterols, polyphenols…
Non-food: additives, pollutants, microplastics, toxins…
Dietary patterns: a priori or a posteriori…
Compliance to dietary guidelines: yes/no, score…
Behaviours: number and timing of meals, fasting, diets…
Ecological correlations

Food balance sheets
production + imports
- exports
- waste
- animal consumption
= food availability

## Ecological temporal correlations

<table>
<thead>
<tr>
<th>Animal products</th>
<th>Total energy</th>
<th>Diseases of the circulatory system</th>
<th>Ischemic heart disease</th>
<th>Cerebrovascular diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>0.265</td>
<td>0.254</td>
<td>0.193</td>
<td>0.266</td>
</tr>
<tr>
<td>Energy</td>
<td>0.388</td>
<td>0.468</td>
<td>0.730</td>
<td>0.373</td>
</tr>
<tr>
<td>Meat</td>
<td>0.357</td>
<td>0.431</td>
<td>0.707</td>
<td>0.335</td>
</tr>
<tr>
<td>Fish</td>
<td>-0.905</td>
<td>-0.908</td>
<td>-0.681</td>
<td>-0.932</td>
</tr>
<tr>
<td>Milk</td>
<td>0.302</td>
<td>0.397</td>
<td>0.534</td>
<td>0.329</td>
</tr>
<tr>
<td>Animal fats</td>
<td>0.567</td>
<td>0.606</td>
<td>0.754</td>
<td>0.543</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vegetal products</th>
<th>Total mortality</th>
<th>Diseases of the circulatory system</th>
<th>Ischemic heart disease</th>
<th>Cerebrovascular diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>-0.479</td>
<td>-0.578</td>
<td>-0.902</td>
<td>-0.460</td>
</tr>
<tr>
<td>Cereals</td>
<td>0.074</td>
<td>-0.001</td>
<td>-0.127</td>
<td>0.041</td>
</tr>
<tr>
<td>Sugar/sweeteners</td>
<td>-0.762</td>
<td>-0.812</td>
<td>-0.952</td>
<td>-0.737</td>
</tr>
<tr>
<td>Vegetable oils</td>
<td>-0.429</td>
<td>-0.479</td>
<td>-0.781</td>
<td>-0.374</td>
</tr>
<tr>
<td>Fruits</td>
<td>0.855</td>
<td>0.874</td>
<td>0.889</td>
<td>0.834</td>
</tr>
<tr>
<td>Vegetables</td>
<td>-0.519</td>
<td>-0.470</td>
<td>-0.125</td>
<td>-0.521</td>
</tr>
<tr>
<td>Alcoholic beverages</td>
<td>0.815</td>
<td>0.838</td>
<td>0.789</td>
<td>0.801</td>
</tr>
</tbody>
</table>

Besson et al. *J Epidemiol* 2013;23:466-473
Geographic associations

SSBs

Obesity

Overlap

Ecological correlations

Easy to perform
Aggregated data available
Hypotheses-making

Wide range in consumption or disease rates needed
*Correlation is not causation*
Prone to confounding
Dietary patterns

- **Hypothesis-oriented or *a priori*: selected beneficial foods
- **Naïve or *a posteriori*: determined by dimension reduction methods (PCA, RRR, cluster analysis)
Cross-sectional studies

<table>
<thead>
<tr>
<th>Major Depressive Disorder Subtypes</th>
<th>Current Atypical OR (95CI)</th>
<th>Current Melancholic OR (95CI)</th>
<th>Current Unspecified OR (95CI)</th>
<th>Remitted Atypical OR (95CI)</th>
<th>Remitted Melancholic OR (95CI)</th>
<th>Remitted Unspecified OR (95CI)</th>
<th>Never Depressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 2</td>
<td></td>
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</tr>
<tr>
<td>Western</td>
<td>1.44 * (1.05, 1.96)</td>
<td>0.64 ** (0.45, 0.90)</td>
<td>1.07 (0.86, 1.34)</td>
<td>1.05 (0.87, 1.26)</td>
<td>0.87 * (0.76, 1.00)</td>
<td>0.98 (0.88, 1.09)</td>
<td>1 (ref.)</td>
</tr>
<tr>
<td>Mediterranean</td>
<td>1.09 (0.82, 1.45)</td>
<td>0.83 (0.62, 1.10)</td>
<td>0.93 (0.76, 1.13)</td>
<td>1.00 (0.85, 1.18)</td>
<td>1.01 (0.89, 1.13)</td>
<td>1.00 (0.91, 1.10)</td>
<td>1 (ref.)</td>
</tr>
<tr>
<td>Sweet-Dairy</td>
<td>0.97 (0.72, 1.32)</td>
<td>1.39 * (1.03, 1.88)</td>
<td>0.97 (0.79, 1.19)</td>
<td>0.94 (0.80, 1.11)</td>
<td>1.03 (0.91, 1.17)</td>
<td>0.99 (0.90, 1.09)</td>
<td>1 (ref.)</td>
</tr>
</tbody>
</table>
Cross-sectional studies

Mostly case-control or association
NO causality
Considerable risk of bias
  • Information/recall
  • Social desirability
  • Sampling
Hypothesis-developping
Should not be disregarded
Prospective studies

Glycemic index (GI)
- Capacity to increase glucose levels after consumption
- High GI: white bread, sugary beverages, potatoes
- Low GI: pulses, pasta

<table>
<thead>
<tr>
<th>Cancer</th>
<th>N cases</th>
<th>Carbohydrate</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>95% CI</th>
<th>95% CI</th>
<th>HR</th>
<th>95% CI</th>
<th>HR</th>
<th>95% CI</th>
<th>HR</th>
<th>95% CI</th>
<th>HR</th>
<th>95% CI</th>
<th>P trend²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tongue</td>
<td>76</td>
<td>High GI</td>
<td>1.075 (0.37-1.53)</td>
<td>0.81 (0.40-1.64)</td>
<td>0.66 (0.31-1.40)</td>
<td>0.59 (0.25-1.36)</td>
<td>0.218</td>
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<tr>
<td></td>
<td></td>
<td>Low GI</td>
<td>1.59 (0.77-3.28)</td>
<td>1.26 (0.58-2.75)</td>
<td>0.99 (0.43-2.30)</td>
<td>1.60 (0.74-3.46)</td>
<td>0.585</td>
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<tr>
<td>Stomach</td>
<td>146</td>
<td>High GI</td>
<td>0.63 (0.38-1.05)</td>
<td>0.68 (0.41-1.14)</td>
<td>0.61 (0.36-1.05)</td>
<td>0.51 (0.27-0.94)</td>
<td>0.045</td>
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<tr>
<td></td>
<td></td>
<td>Low GI</td>
<td>1.18 (0.69-2.03)</td>
<td>1.21 (0.70-2.11)</td>
<td>1.10 (0.62-1.94)</td>
<td>1.36 (0.78-2.37)</td>
<td>0.395</td>
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<tr>
<td>Colon</td>
<td>441</td>
<td>High GI</td>
<td>1.02 (0.74-1.41)</td>
<td>1.29 (0.94-1.77)</td>
<td>1.18 (0.85-1.66)</td>
<td>1.71 (1.19-2.44)</td>
<td>0.004</td>
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<tr>
<td></td>
<td></td>
<td>Low GI</td>
<td>0.94 (0.71-1.25)</td>
<td>0.86 (0.64-1.16)</td>
<td>0.77 (0.56-1.05)</td>
<td>0.75 (0.54-1.03)</td>
<td>0.032</td>
<td></td>
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</tr>
</tbody>
</table>

Sieri et al. Sci Rep 2017;7:9757
Prospective studies

Meta-analysis

- Grouping the information from several prospective studies
- Increased overall sample size, combined effect, heterogeneity, publication bias...

<table>
<thead>
<tr>
<th>Study</th>
<th>Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Americas</strong></td>
<td></td>
</tr>
<tr>
<td>ARIC (USA)</td>
<td>1.00 (0.95, 1.06)</td>
</tr>
<tr>
<td>CARDIA (USA)</td>
<td>0.93 (0.82, 1.05)</td>
</tr>
<tr>
<td>ELSA-Brasil (Brazil)</td>
<td>1.01 (1.00, 1.03)</td>
</tr>
<tr>
<td>MESA (USA)</td>
<td>0.99 (0.94, 1.04)</td>
</tr>
<tr>
<td>PRHHP (Puerto Rico)</td>
<td>0.97 (0.94, 1.01)</td>
</tr>
<tr>
<td>WHI (USA)</td>
<td>1.02 (1.01, 1.03)</td>
</tr>
<tr>
<td>Combined ($I^2 = 44.4%$)</td>
<td>1.01 (0.99, 1.02)</td>
</tr>
<tr>
<td><strong>Eastern Mediterranean</strong></td>
<td></td>
</tr>
<tr>
<td>Golestan (Iran)</td>
<td>1.07 (0.98, 1.18)</td>
</tr>
<tr>
<td><strong>Europe</strong></td>
<td></td>
</tr>
<tr>
<td>COSM/SMC (Sweden)</td>
<td>1.01 (1.00, 1.02)</td>
</tr>
<tr>
<td>EPIC-InterAct France</td>
<td>0.89 (0.77, 1.03)</td>
</tr>
<tr>
<td>EPIC-InterAct Germany</td>
<td>1.49 (1.29, 1.73)</td>
</tr>
<tr>
<td>EPIC-InterAct Italy</td>
<td>1.00 (0.95, 1.06)</td>
</tr>
<tr>
<td>EPIC-InterAct Spain</td>
<td>1.03 (1.00, 1.09)</td>
</tr>
<tr>
<td>EPIC-InterAct Sweden</td>
<td>1.14 (1.07, 1.22)</td>
</tr>
<tr>
<td>EPIC-InterAct UK</td>
<td>1.02 (0.94, 1.12)</td>
</tr>
<tr>
<td>EPIC-InterAct the Netherlands</td>
<td>1.06 (0.91, 1.24)</td>
</tr>
<tr>
<td>FMC (Finland)</td>
<td>0.98 (0.73, 1.32)</td>
</tr>
<tr>
<td>SUN (Spain)</td>
<td>0.96 (0.80, 1.16)</td>
</tr>
<tr>
<td>Whitehall II (UK)</td>
<td>1.10 (1.05, 1.15)</td>
</tr>
<tr>
<td>Combined ($I^2 = 82.3%$)</td>
<td>1.05 (1.01, 1.10)</td>
</tr>
<tr>
<td><strong>Western Pacific</strong></td>
<td></td>
</tr>
<tr>
<td>AusDiab (Australia)</td>
<td>1.07 (0.92, 1.25)</td>
</tr>
<tr>
<td>CKB (China)</td>
<td>1.00 (0.98, 1.01)</td>
</tr>
<tr>
<td>KoGES CAVAS (ROK)</td>
<td>1.06 (0.95, 1.18)</td>
</tr>
<tr>
<td>Combined ($I^2 = 0.0%$)</td>
<td>1.00 (0.98, 1.01)</td>
</tr>
<tr>
<td>Overall ($I^2 = 73.8%$)</td>
<td>1.02 (1.01, 1.04)</td>
</tr>
</tbody>
</table>
Prospective studies

Establish causality
Multiple hypotheses can be tested

Hard to conduct (sample size, follow-up)
Need replication
  • Dietary behaviours
  • Dietary change

Main source of evidence to establish dietary guidelines
Intervention studies

7447 people randomized into:
• Mediterranean diet + nuts
• Mediterranean diet + extra-virgin olive oil (EVOO)
• Low fat diet

Cluster randomization:

- Low salt
- Control
Intervention studies

Very few randomized controlled trials

• Dietary changes hard to sustain in the long term
• Need for large sample sizes
• One hypothesis = one RCT
• Replications needed…
Intervention [studies]

Non-randomized interventions due to changes in

- Policy or legislation
- Economics
- Food availability
- Lifestyle
Life magazine (1997) declared, “The filtration of drinking water plus the use of chlorine is probably the most significant public health advancement of the millennium.”

Similar decreases in cholera and hepatitis A cases.
Switzerland: iodized salt

Conscripts with goiter

- Cantons ayant introduit la prophylaxie par le sel iodé de 1923 à 1930
- Cantons ayant introduit la prophylaxie par le sel iodé de 1936 à 1940

Nicod, Bull World Hlth Org 1953;9:259-73
Finland: North Karelia Project

Vartiainen et al, BMJ 1995;311:589
Cuba

Economic crisis after the fall of Soviet Union

Cuba

Obesity cut by half!

Cuba

Decrease in diabetes, cardiovascular disease, but **not** cancer

Franco et al, Am J Epidemiol;2007;166:1374-80
Poland

Very quick effect:
• 20% decrease in 5 years!
• Never achieved by drugs

Zatonski et al, BMJ 1998;316:1047
Korea

Negative association with:
- Fruit intake
- Fridge ownership
Summary

Dietary intake influenced by multiple factors.
Dietary intake can be assessed via multiple markers.

Diet major determinant of NCDs.

Evidence from prospective studies, few RCTs.