Translation of science into action: the potential role of diet reducing disease risk

Heiner Boeing
Department of Epidemiology

Monday 13th June 2016
In the area of diet and chronic diseases, it is important to understand which lifestyle factors including diet are linked to chronic diseases.

It is also important to investigate which of the dietary factors linked to chronic diseases has which potential to reduce the occurrence of chronic diseases.

Dietary factors with a high potential of influencing the occurrence of diseases should be preferred targets of investigations regarding mechanisms and public health measures.
The Nutrition Societies and its members can be the focal point for

- Collecting the evidence (systematic reviews and meta-analyses) including evaluation by expert groups
- Elucidating the biological mechanisms
- Fostering the methodological developments (techniques, statistical methods)
- Translation of the evidence into actions
- Evaluation and promotion of the selected measures
Collecting the evidence how diet is linked to the disease burden

• Prospective studies (observational and interventive) and their meta-analyses should have a preference against cross-sectional or retrospective study designs when searching the literature for the role of diet for risk of diseases

• It is also important to evaluate the literature how solid is the knowledge regarding mechanisms supporting the epidemiological observations (biological plausability)
A note regarding observational and intervention study designs in research into dietary behaviour

• Dietary recommendations and/or their translation into practice have to address foods. Foods contain usually energy and many other nutritional valuable compounds that are in most instances not the target of the research. Thus, the interpretation of such studies could be biased since the initial research hypothesis is mostly favored.

• Intervention studies with foods are difficult to perform and not easy to interpret. It investigates only one or two interventions and it is unclear whether alternative intervention might have similar or even stronger effects.
• Observational prospective studies have the advantage that exposure can be invested regarding many endpoints (if the study is large enough) and one can investigate many alternatives when diet is concerned
Experiences and examples

• The basis of all collections of the evidence is the results single studies.

• For Europe, the European Prospective Investigation into Cancer and Nutrition (EPIC) played an important role in contributing observational evidence to the dietary field due to their applied methodology, to their size, and to the regional distribution.

• Newer cohort studies with a better and more detailed assessment including the collection of many biomaterials are now underway in many European countries. However, it will take about 5 to 10 further years before they are becoming productive.
European Prospective Investigation into Cancer and Nutrition (EPIC)

• Aim of study: Investigation of disease risk linked with diet and other life style factors
• 23 centres in 10 European countries
• Recruitment between 1992 and 1998
• Prefered age ranges at recruitment: between 40(35)-64 years
• More than 500,000 study participants (50,000 men and 350,000 women)
EPIC-Potsdam-Study

Potsdam: 27,548 study participants (age 35-65 women, 40-65 men)

Study conduct
- Recruitment and basic examinations
- Follow-up
- Re-examination

Basic examination at recruitment
1994-1998

EPIC = European Prospective Investigation into Cancer and Nutrition
EPIC data related to lifestyle and personal history

From questionnaire:
• Tobacco
• Alcohol
• Reproductive history
• Occupation
• Illnesses
• Physical activity
• Socio-economic status

From physical examinations:
• Height
• Weight
• Waist circumference
• Hip circumference
• Sitting height
• Blood pressure
EPIC data on diet

Two dietary measurements:
Dietary questionnaire on usual diet from all 519,978 subjects
• Very detailed, 150 to 300 foods per questionnaire
• To relate diet to disease risk

One day “actual” diet from a 7% sample of subjects (38,000)
• Computerized, 3000 foods and 700 recipes per country
• To calibrate dietary measurements between countries
EPIC Biorespository: Plastic straws for storage of plasma, serum, rbc, and buffy coat
Methodology to address diet and chronic diseases

Dietary and other lifestyle factors assessed at baseline

Hard (and soft) endpoints assessed during follow-up

- Weight change (fat accumulation)
- Type 2 Diabetes
- Myocardial infarction
- Stroke
- Total cancer and individual cancer sites
- Mortality
Study approaches in EPIC

Assessment of risk factors for cancer and mortality
(Full cohort approach and nested case-control studies with biomarkers)

Assessment of risk factors for type 2 Diabetes
Interact-Study (Case-cohort approach with 12,403 cases and 16,154 randomly selected controls)

Assessment of risk factors for MI and stroke
EPIC-Heart and EPIC-CVD (Case-cohort approach with 16,000 cases and 16,154 controls)

Studies on weight gain
Diogenes and PANACEA (Follow-up data analyses)
The German National Cohort (GNC)

18 Study centers
Study design (GNC)

- Prospective population-based cohort study
- 18 study centers
- Participants between 20-69 years old
- Random samples in defined regions
  - **Level 1** \( n=200,000 \) duration: 2.5 h
  - **Level 2** \( n=40,000 \) duration 4 h
  - **Level 3** \( n=\text{variable} \) (additional research projects, external funding)
- **MRI** program, \( n=30,000 \), at 5 sites

The German National Cohort (GNC)
The German National Cohort (GNC)

Pilot phase

Baseline examination

Follow up examination

Questionnaires every 2 – 3 years, combination with secondary data

Utilization for epidemiologic studies

Time schedule
## Examinations and biomaterials

### Cardiovascular system
- Blood pressure and heart rate
- ECG, Electrocardiography
- Vascular Explorer (pulse wave)

### Musculoskeletal system
- Knee, hip, hand joints

### Oral health
- Dental chart

### Sensory organs
- Ophthalmological measurements, hearing test, olfactory test

### Physical activity and fitness
- 7-day accelerometry
- Ergometric test, hand grip strength

### Anthropometry
- Weight, body height, BIA, ultrasound, waist and hip circumferences

### Collection of biosamples
(blood, urine, nasal swabs, saliva, stool)

### Diabetes
- OGTT
- AGE Reader

### Cognitive functions test
- Memory, attention/executive, motor coordination

### Pulmonary function
- Spirometry

---

The German National Cohort (GNC)
Novel dietary assessment strategy: statistical modelling

Individual’s usual intake = Consumption probability * Amount on a consumption day

- **German National Cohort (GNC)**
  - Repeated 24-h food lists (24hFLs)
  - Food frequency questionnaire (FFQ)

- **External source**
  - German National Nutrition Survey II (NVS II)
Dietary components of overall nutritional importance  
(German FBDG)

Fruit and Vegetables
Grain products
Milk and Milkproducts
Red and processed meat, eggs, fish
Oils

Nutrition Cycle of the German Nutrition Society
Not all of the dietary components of the German FBDG will have the potential to reduce risk and are less studied in EPIC (and also other observational cohorts).

The interest in EPIC regarding foods centered on

- Fruit and Vegetables
- Whole grain products (dietary fiber)
- Red and processed meat
Figure 1. Restricted cubic spline and 95% confidence intervals of the nonlinear relation between fruit and vegetable consumption combined (in grams per day) and all-cause mortality, the European Prospective Investigation Into Cancer and Nutrition, 1992–2010.

# Fruit and vegetable quintiles and risk of cancer - EPIC

<table>
<thead>
<tr>
<th>Quintiles of intake of fruit and vegetables (g/d)</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Risk</td>
<td>1</td>
<td>0.95</td>
<td>0.91</td>
<td>0.93</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.92-0.99)</td>
<td>(0.88-0.95)</td>
<td>(0.89-0.97)</td>
<td>(0.85-0.93)</td>
</tr>
</tbody>
</table>

Boffetta et al., JNCI 102, 529-537: 2010
EPIC-Heart study on mortality

Crowe et al., European Heart Journal Advance Access published January 18, 2011

Relative Risk

Portion Fruit and Vegetables / Day

<3 3-4 5-7 >8

IHD Death
### Table 3

Odds ratios (95% CI) for incident diabetes by quartiles of a combined biomarker score of fruit and vegetable intake and by quartiles of plasma vitamin C, beta-carotene and lutein separately: the EPIC-Norfolk Study.

<table>
<thead>
<tr>
<th></th>
<th>Quartiles of the CB-score and plasma vitamin C, beta-carotene and lutein separately</th>
<th>p-trend</th>
<th>Per SD increase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CB-score (mean, SD)</strong></td>
<td>Q1 (reference)</td>
<td>Q2</td>
<td>Q3</td>
</tr>
<tr>
<td>Cases/ total (n)</td>
<td>138/311</td>
<td>102/311</td>
<td>51/311</td>
</tr>
<tr>
<td>Model 1 (95% CI) *</td>
<td>1.00</td>
<td>0.66 (0.47-0.92)</td>
<td>0.28 (0.19-0.41)</td>
</tr>
<tr>
<td>Model 2 (95% CI) †</td>
<td>1.00</td>
<td>0.70 (0.49-1.00)</td>
<td>0.34 (0.23-0.52)</td>
</tr>
<tr>
<td>Model 3 (95% CI) ‡</td>
<td>1.00</td>
<td>0.83 (0.56-1.22)</td>
<td>0.46 (0.30-0.72)</td>
</tr>
<tr>
<td><strong>Vitamin C (mean, SD)</strong></td>
<td>25.6 (9.1)</td>
<td>44.6 (3.4)</td>
<td>56.6 (3.3)</td>
</tr>
<tr>
<td>Cases/ total (n)</td>
<td>132/302</td>
<td>81/300</td>
<td>62/317</td>
</tr>
<tr>
<td>Model 1 (95% CI) *</td>
<td>1.00</td>
<td>0.54 (0.38-0.76)</td>
<td>0.37 (0.25-0.53)</td>
</tr>
<tr>
<td>Model 2 (95% CI) †</td>
<td>1.00</td>
<td>0.59 (0.41-0.85)</td>
<td>0.44 (0.30-0.65)</td>
</tr>
<tr>
<td>Model 3 (95% CI) ‡</td>
<td>1.00</td>
<td>0.63 (0.42-0.95)</td>
<td>0.57 (0.37-0.88)</td>
</tr>
<tr>
<td><strong>Beta-carotene (mean, SD)</strong></td>
<td>8.9 (2.6)</td>
<td>15.5 (1.9)</td>
<td>23.3 (2.7)</td>
</tr>
<tr>
<td>Cases/ total (n)</td>
<td>139/311</td>
<td>88/311</td>
<td>56/311</td>
</tr>
<tr>
<td>Model 1 (95% CI) *</td>
<td>1.00</td>
<td>0.51 (0.36-0.72)</td>
<td>0.28 (0.19-0.41)</td>
</tr>
<tr>
<td>Model 2 (95% CI) †</td>
<td>1.00</td>
<td>0.55 (0.38-0.80)</td>
<td>0.34 (0.23-0.52)</td>
</tr>
<tr>
<td>Model 3 (95% CI) ‡</td>
<td>1.00</td>
<td>0.62 (0.41-0.92)</td>
<td>0.47 (0.30-0.73)</td>
</tr>
<tr>
<td><strong>Lutein (mean, SD)</strong></td>
<td>8.7 (2.0)</td>
<td>13.0 (1.1)</td>
<td>17.2 (1.3)</td>
</tr>
<tr>
<td>Cases/ total (n)</td>
<td>120/311</td>
<td>85/311</td>
<td>66/311</td>
</tr>
<tr>
<td>Model 1 (95% CI) *</td>
<td>1.00</td>
<td>0.55 (0.39-0.78)</td>
<td>0.41 (0.28-0.59)</td>
</tr>
<tr>
<td>Model 2 (95% CI) †</td>
<td>1.00</td>
<td>0.68 (0.47-0.99)</td>
<td>0.53 (0.36-0.79)</td>
</tr>
<tr>
<td>Model 3 (95% CI) ‡</td>
<td>1.00</td>
<td>0.81 (0.54-1.21)</td>
<td>0.73 (0.47-1.11)</td>
</tr>
</tbody>
</table>

Data are ORs (95% CI) estimated using logistic regression.

Total n=1 244 (318 incident diabetes cases and 926 controls).

* Model 1: adjusted for age and sex.

† Model 2: model 1 plus education level, occupational social class, smoking status, physical activity level, family history of diabetes, total energy intake, vitamin supplement use, HDL-cholesterol, and LDL-cholesterol.

‡ Model 3: model 2 plus BMI and waist circumference.

§ The association between plasma vitamin C and T2D was not adjusted for HDL-cholesterol and LDL-cholesterol in model 2 or model 3.

FIGURE 1. Spline model for describing the shape of the association of the intake of fruit and vegetables with weight change. The fifth percentile of fruit and vegetable intake was set as the reference. \( P \) for nonlinearity = 0.72. Adjusted for age (continuous), sex, cohort (dummy variables), years of follow-up (continuous), baseline weight (continuous), baseline height (continuous), change in smoking status (dummy variables), baseline total physical activity (dummy variables), education (dummy variables), alcohol intake (dummy variables), and, in women, postmenopausal status (yes or no) and postmenopausal hormone use (yes or no).
Critical review: vegetables and fruit in the prevention of chronic diseases

Heiner Boeing · Angela Bechthold · Achim Bub · Sabine Ellinger · Dirk Haller · Anja Kroke · Eva Leschik-Bonnet · Manfred J. Müller · Helmut Oberritter · Matthias Schulze · Peter Stehle · Bernhard Watzl

Received: 13 February 2012 / Accepted: 9 May 2012 / Published online: 9 June 2012
© The Author(s) 2012. This article is published with open access at Springerlink.com
Dietary fiber and mortality in EPIC

Intake of dietary fibre and risk of colon cancer

Bingham et al., Lancet, 2003
### Relative risk for colon cancer for quintiles of intake of dietary fiber in EPIC

<table>
<thead>
<tr>
<th>Quintile of intake of dietary fibre (g/d in 24-HDR)</th>
<th>Q1 Männer</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 Männer</td>
<td>18.2</td>
<td>21.0</td>
<td>23.2</td>
<td>25.6</td>
<td>30.1</td>
</tr>
<tr>
<td>Frauen</td>
<td>15.9</td>
<td>17.8</td>
<td>19.4</td>
<td>21.3</td>
<td>24.4</td>
</tr>
<tr>
<td>Relative Risk (n=706)</td>
<td>1</td>
<td>0.95</td>
<td>0.75</td>
<td>0.71</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.75-1.19)</td>
<td>(0.58-0.96)</td>
<td>(0.55-0.94)</td>
<td>(0.54-0.97)</td>
</tr>
<tr>
<td>Relative Risk (n=1118)</td>
<td>1</td>
<td>0.88</td>
<td>0.71</td>
<td>0.68</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.74-1.05)</td>
<td>(0.58-0.86)</td>
<td>(0.55-0.84)</td>
<td>(0.58-0.93)</td>
</tr>
<tr>
<td>Relative Risk n=4517</td>
<td>1</td>
<td>0.98</td>
<td>0.96</td>
<td>0.94</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.89-1.08)</td>
<td>(0.86-1.06)</td>
<td>(0.84-1.05)</td>
<td>(0.72-0.96)</td>
</tr>
</tbody>
</table>

Bingham et al., Lancet 2003, Bingham et al., Cancer Epidemiol Biomarker, 2005, Murphy et al., PLOS One, 2012
Intake of dietary fibre and risk of death of IHD

Grains and Type 2 Diabetes

Fig. 1 Association between cereal fibre, fruit fibre and vegetable fibre consumption and risk of type 2 diabetes in the EPIC-InterAct study (n=26,088). Country-specific HR quartile vs. quartile (95% CIs) were pooled using random effects meta-analysis. HRs were adjusted for sex, smoking status, physical activity, education level, sex-specific alcohol categories, energy, energy-adjusted carbohydrate, magnesium intake, vitamin B1 intake, saturated fatty acids and BMI. The x-axis is on a log scale.
Grains and Type 2 Diabetes (Meta-Analysis)

Fig. 2  Dietary total fibre (a, b) and cereal fibre (c, d) and type 2 diabetes, linear dose–response meta-analyses per 10 g/day (a, c) and non-linear dose–response meta-analyses (b, d). In (a) and (c), the RR of each study is represented by a square, and the size of the square represents the weight of each study to the overall estimate. The 95% CIs are represented by horizontal lines, and the diamond represents the overall estimate and its 95% CI. The x-axis is on a log scale. In (b) and (d), the solid lines represent the best-fitting fractional polynomial, and the dashed lines represent 95% CIs.

InterAct Consortium. Dietary fibre and incidence of type 2 diabetes in eight European countries: the EPIC-InterAct Study and a meta-analysis of prospective studies. Diabetologia. 2015;58:1394-1408
Meat consumption and mortality

<table>
<thead>
<tr>
<th></th>
<th>Observed HR(^a) (95% CI)</th>
<th>Calibrated HR(^a) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red meat (per 100 g)</td>
<td>1.02 (0.98 to 1.06)</td>
<td>1.02 (0.98 to 1.06)</td>
</tr>
<tr>
<td>Processed meat (per 50 g)</td>
<td>1.09 (1.06 to 1.12)</td>
<td>1.18 (1.11 to 1.25)</td>
</tr>
<tr>
<td>Poultry (per 50 g)</td>
<td>0.96 (0.92 to 0.99)</td>
<td>0.95 (0.87 to 1.04)</td>
</tr>
</tbody>
</table>

Figure 1 Nonparametric regression curve for the relation of processed meat intake at recruitment with all-cause mortality, European Prospective Investigation into Cancer and Nutrition (EPIC), 1992-2009. Solid line, effect estimate; dotted lines, 95 percent confidence interval.
Meat consumption and risk for colon cancer - EPIC

Norat et al., JNCI, 2006
Cross over design: Effect of red meat and haem on total N-nitroso compounds excretion

<table>
<thead>
<tr>
<th></th>
<th>n=12</th>
<th>Low red meat</th>
<th>High red meat</th>
<th>vegetarian</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATNC (µg/d)</td>
<td></td>
<td>42.1 ±5.3</td>
<td>190.1 ±21.6</td>
<td>63.3 ± 5.3</td>
</tr>
<tr>
<td>Mean ±SE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>n=9</th>
<th>Low red meat</th>
<th>Haem supplementation</th>
<th>Inorganic iron supplementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATNC (µg/d)</td>
<td></td>
<td>77.5 ±9.0</td>
<td>156.8 ±22.7</td>
<td>60.7 ± 9.5</td>
</tr>
<tr>
<td>Mean ±SE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cross et al., Cancer Res, 2003
Investigations across cancer endpoints: Relative risks by intake of processed and/or red meat in EPIC

Norat et al., JNCI, 2006

Gonzales et al., JNCI 2006

Pala et al, Am J Clin Nutr 2009

Allen et al., Br J Nutr, 2008
Relative Risk by 50 g/d increment

<table>
<thead>
<tr>
<th>Food Type</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total meat</td>
<td>1.08 (1.05, 1.12)</td>
</tr>
<tr>
<td>Red meat</td>
<td>1.10 (1.04, 1.15)</td>
</tr>
<tr>
<td>Processed meat</td>
<td>1.13 (1.04, 1.22)</td>
</tr>
<tr>
<td>Poultry</td>
<td>1.04 (0.91, 1.18)</td>
</tr>
<tr>
<td>Offals</td>
<td>0.99 (0.92, 1.07)</td>
</tr>
<tr>
<td>Meat iron intake (per 1 mg)</td>
<td>1.03 (0.99, 1.07)</td>
</tr>
</tbody>
</table>

Meat consumption and weight gain

Adjusted increase in annual weight change (in g/y) for a 100-kcal increase in meat consumption before and after calibration in the European Prospective Investigation into Cancer and Nutrition ($n = 373,803$)

<table>
<thead>
<tr>
<th></th>
<th>$\beta$</th>
<th>95% CI</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total meat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calibrated data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>13</td>
<td>(-5, 31)</td>
<td>0.15</td>
</tr>
<tr>
<td>M2</td>
<td>71</td>
<td>(47, 95)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>M3</td>
<td>65</td>
<td>(39, 90)</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

$^1$ M1, model 1 (adjusted for sex, age, and an indicator of meat consumption); M2, model 2 (adjusted as in M1 + educational level, physical activity level, smoking status, initial BMI, follow-up time, total energy intake, energy from alcohol, and plausible total energy intake reporting); M3, model 3 (adjusted as in M2 + dietary factors 1 and 2 derived from maximum likelihood factor analysis).
Relative risk for colon cancer at levels of dietary fibre and red meat/processed meat

Norat et al., JNCI, 2006

Hazard Ratios

Red and processed meat

Low Medium High

Low Medium Fiber

Norat et al., JNCI, 2006
Intervention study with meat and whole grains - design

**Figure 2. Diet plan for participants with diet succession: whole grain diet, washout period and red meat diet.**
doi:10.1371/journal.pone.0109606.g002
Table 4. Intervention effects on factors retained after factor analysis (FA) with bands changed due to an intervention and correlations of corresponding factors with measures of obesity (BMI-body mass index, Waist circ.- waist circumference) and sex.

<table>
<thead>
<tr>
<th>FA included changed bands (n = 16)</th>
<th>Intervention effect</th>
<th>Correlations of factors with measures of obesity</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor (Eigenvalue/explained variance)</td>
<td>RM</td>
<td>WG</td>
<td>BMI</td>
</tr>
<tr>
<td>1 (4.3/31.3%)</td>
<td>0.001</td>
<td>0.29</td>
<td>−0.28*</td>
</tr>
<tr>
<td>2 (2.9/30.9%)</td>
<td>0.22</td>
<td>&lt;0.0001</td>
<td>−0.22*</td>
</tr>
<tr>
<td>3 (1.8/19.8%)</td>
<td>0.76</td>
<td>0.22</td>
<td>−0.06</td>
</tr>
<tr>
<td>4 (1.3/12.4%)</td>
<td>0.50</td>
<td>0.009</td>
<td>0.21*</td>
</tr>
<tr>
<td>5 (1.1/12.2%)</td>
<td>0.25</td>
<td>0.70</td>
<td>−0.05</td>
</tr>
</tbody>
</table>

* Correlation significant on level p<0.05.
doi:10.1371/journal.pone.0109606.t004

Biomarkers, meat intake, and type 2 diabetes

<table>
<thead>
<tr>
<th>Selected biomarker</th>
<th>HR (95% CI)</th>
<th>( P_{\text{raw}} )</th>
<th>( P_{\text{FDR}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycine</td>
<td>0.66 (0.57, 0.77)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dicacyl PC 36:4</td>
<td>1.20 (1.07, 1.35)</td>
<td>0.002</td>
<td>0.003</td>
</tr>
<tr>
<td>Dicacyl PC 38:4</td>
<td>1.24 (1.12, 1.38)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lyso-PC 17:0</td>
<td>0.78 (0.68, 0.89)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hydroxy-SM 14:1</td>
<td>0.83 (0.73, 0.94)</td>
<td>0.004</td>
<td>0.007</td>
</tr>
<tr>
<td>Ferritin</td>
<td>1.28 (1.15, 1.42)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\(^1\)Biomarkers were selected based on the mediation criteria 2 and 3—that is, a significant \( P_{\text{FDR}} < 0.05 \) association with total red meat consumption in either men or women and at least a similar trend \( P_{\text{FDR}} < 0.1 \) in the other (criterion 2) and equally directed associations with type 2 diabetes risk (criterion 3). Raw \( P \) values and FDR-controlled \( P \) values (corrected for the 21 tests conducted among all metabolites that fulfilled mediation criterion 2) from a 2-sided Wald-test \( (H_0: \beta = 0) \). FDR, false discovery rate; PC, phosphatidylecholine; SM, sphingomyelin.

\(^2\)Diabetes-HR per SD in serum concentration; the associations of 21 preselected metabolites with type 2 diabetes risk were evaluated in Cox models in the case cohort \( (n = 2681) \) adjusted for total red meat intake, total energy intake (MJ/d), age (years), sex, BMI (in kg/m\(^2\)), sports (h/wk), biking (h/wk), smoking (4 stages: never smoker, former smoker, current smoker <20 units/d, or current heavy smoker >20 units/d), education (4 stages: no vocational training or in training, vocational training, technical school, or technical college or university degree), antihypertensive medication (yes/no), antidyslipidemic medication (yes/no), intake of beverages (alcohol, coffee, sugar-sweetened beverages) (g/d), and intake of whole-grain bread, refined-grain bread, butter, margarine, cabbage, cooked vegetables, mushrooms, potatoes, sauce, and poultry (g/MJ).

Conclusion

• It appears that a cohort study such as EPIC can substantially contribute to identify dietary potentials for prevention
• According to the results of the EPIC - (and other) Studies, some nutritional factors appear to be prime candidates of a healthy diet due to their wide range of endpoints associated with reduced risk
• The search for causal biological mechanisms linked to key aspects of a healthy diet seems to be important
• It remains to see whether other areas of dietary intake have similar impact on disease risk than the prime candidates fruit and vegetables, whole grain products, and meat