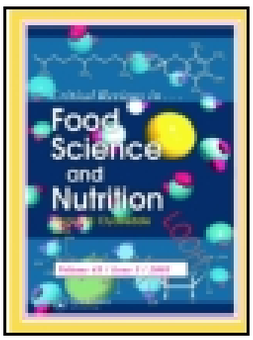

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Red meat, diseases and healthy alternatives: A critical review

Cem Ekmekcioglu[1,*], Peter Wallne[1], Michael Kundi[1], Ulli Weisz[2], Willi Haas[2], Hans-Peter Hutter[1]

[1]Institute of Environmental Health, Centre for Public Health, Medical University of Vienna

[2]Institute of Social Ecology, IFF Vienna, Alpen-Adria University Klagenfurt

[*]**Corresponding author and request for reprints:** Cem Ekmekcioglu, MD, Institute of Environmental Health, Centre for Public Health, Medical University Vienna, Kinderspitalgasse 15, A-1090 Vienna, Austria, Phone.: +43-1-40160-34927, email: cem.ekmekcioglu@meduniwien.ac.at

Abstract

Meat is an important food for human nutrition, by especially providing high quality protein and also some essential micronutrients, in front iron, zinc and vitamin B_{12}. On the other hand a high intake of red and processed meat is associated with an increased risk for diseases, especially type II diabetes and colorectal cancer, as several epidemiological studies and meta-analyses have shown. This review summarizes meta-analyses of publications studying the association between red and processed meat intake and diabetes, cardiovascular diseases, colorectal and other cancers, and all- cause mortality. Various potential mechanisms involved in the increased disease risk are discussed. Furthermore the beneficial effects of healthy alternatives for meat, like fish, nuts, vegetables and fruits, pulses and legumes, whole grains, and dairy products, are reviewed by including selected papers and recent meta-analyses.

Key words

red meat; processed meat; disease; diabetes; cancer; cardiovascular disease; mortality; healthy foods

1. Nutritional value of meat in brief

Meat is an important source of several indispensible nutrients which are essential for optimal health throughout human life. Meat is especially rich in proteins with a high biological value. Meat supplies all of the essential amino acids with no limiting amino acids (Williams, 2007) including high levels of the essential amino acids lysine and methionine which are found in relatively lower concentrations in most cereals (lysine) or legumes (methione), respectively (Bender, 1992; Elango et al., 2009).

Furthermore meat is also a rich source of essential micronutrients like especially iron, zinc, and B-vitamins (Pereira and Vicente, 2013; Wyness et al., 2011). In industrialized countries, the intakes of B-vitamins in general meet the dietary requirements for most of the population groups. However, meat, fish and to some extent also animal products like milk are the only foods providing significant amounts of Vitamin B_{12}, which has a special relevance for clinical and nutritional medicine (Wyness et al., 2011).

Also iron supply from meat is important. Iron is found in many foods with animal foods providing iron in the heme-form from haemoglobin and myoglobins whereas plant derived foods consist of non-heme iron. In contrast to non-heme iron heme-iron is highly bioavailable and well absorbed in the intestinal tract as an intact molecule by enterocytes (Hallberg and Hulthen, 2000). In the diet of people in the European Union meat delivers about 47% of Vitamin B_{12} and 16 to 20% of iron (Westhoek et al., 2011).

In addition to iron meat contains also substantial amounts of zinc, and beef and lamb can be classified according to EU health claims legislation as a rich source and pork as a source of zinc (Wyness et al., 2011).

Finally in addition to saturated fat meat is also a noteworthy source of monounsaturated (especially oleic acid) and long chain polyunsaturated fatty acids (PUFAs) and can contribute up to 20% of long chain omega-3 polyunsaturated fatty acid intake (Russo, 2009). In this regard meat contains relevant amounts of linoleic acid, an omega-6 fatty acid and alpha-linolenic acid, an omega-3 fatty acid. However the content of EPA and DHA, which have cardioprotective and health promoting effects (Calder and Yaqoob, 2009), is low in meat but high in fish. The profile of meat fatty acids will also vary in dependence on the proportions of lean and fat present. For example, lean meat is relatively higher in PUFAs and lower in saturated fatty acids (Wyness et al., 2011).

2. Red and processed meat intake and risk for diseases

By providing proteins with a high biological value and some essential micronutrients meat has an important impact on our health. However nowadays people in the industrialized world eat too much meat and processed meat, a trend which negatively affects our health, as many studies in the last decades have presented. It becomes more and more evident that a higher consumption of red meat and processed meat is associated with a higher risk for the most important non-communicable diseases, in front diabetes, gastrointestinal cancer and cardiovascular disease (Aune et al., 2009; Larsson and Wolk, 2006; Micha et al., 2010). For example, most recently the International Agency for Research on Cancer (IARC), the cancer agency of the World Health

Organization, has classified processed meat as carcinogenic to humans and red meat as probably carcinogenic to humans (WHO, 2015).

Meanwhile several meta-analyses of primarily prospective cohort studies were conducted to evaluate and confirm the association between meat, processed meat and these and other diseases (Aune et al., 2009; Feskens et al., 2013; Micha et al., 2010).

In some cases the meta-analyses also include case control and cross sectional studies which are more susceptible to recall and selection biases, especially dietary recall bias, than a cohort design (Xu et al., 2013). Furthermore, a general problem of observational studies is heterogeneity, which may stem from different factors including study design, sample size, demographic factors, intake unit or serving sizes and various confounders. All of these factors could limit the interpretation of the association between meat and diseases (critically discussed in Klurfeld, 2015). In addition residual confounding may be relevant to some degree, especially in the case of dietary habits. Individuals with high intakes of red meat and processed meat may practice a general unhealthy life style with for example smoking, eating less vegetables, fruits and whole grains, being less physical active and so on. All of these factors may increase the risk for different diseases.

This review summarizes meta-analyses which have investigated the risk for diabetes, cardiovascular disease (CVD), colorectal and other cancers, and all-cause mortality associated with the intake of red and processed meat. Potential mechanisms involved in the higher disease risk are discussed. Furthermore, by considering recent meta-analyses, health promoting effects of other foods are discussed, which might be alternatives for meat.

2.1 Diabetes

Refering to The International Diabetes Federation (International Diabetes Federation, 2015) in the year 2015 415 million people in the world had diabetes and this estimate is projected to increase to 642 million by 2040. In the European Union, type 2 diabetes and impaired glucose tolerance are one of the major public health concerns (Valensi et al., 2005).

The association between red and processed meat and risk of type 2 diabetes has been investigated in several cohort studies and summarised in a handfull of meta-analyses.

A literature search was performed in the databases Pubmed, Scopus and Embase with the search terms „meat and (diabetes or diabetic) and meta-analysis“ from publications between 2005 and July 2015. Papers were restricted to English publications. Risk ratios, incidence rate ratios or odds ratios (relative risks) had to be available with 95% confidence intervals. Only publications including red meat and/or processed meat were considered. 8 publications were selected from the search. From these 2 were excluded since they were no meta-analyses leaving 6 studies with 2 of them being abstracts (Table 1). All of the meta-analyses included cohort studies. Calculations were performed on high vs. low and/or dose response analyses (per serving/gram increase in red meat or processed meat), respectively. The summary of the relative risks for red meat and processed from the selected meta-analyses are shown in Table 1. All of the meta-analyses showed a higher relative risk in the high vs. low and dose-response analyses, respectively. Relative risks were in the range of 1.13 to 1.21 for red meat and 1.19 to 1.82 for processed meat, respectively. However heterogeneity was relatively high, with indicated I^2 values between 36% and 94.3%.

Potential mechanisms linking meat intake to diabetes risk

Meat is a energy dense food and epidemiologic data from observational studies suggest that red meat is linked to obesity and increased waist circumference, both which are established risk factors for type 2 diabetes (Halkjaer et al., 2009; Newby et al., 2003). In this regard vegetarians for example show lower body weights than meat-eaters (Berkow and Barnard, 2006).

A recent systematic review including eight studies and 9 comparisons regarding meat and weight showed that there was a positive relationship with weight gain, body-mass index, or waist circumference in six of the studies (Fogelholm et al., 2012). This was confirmed in a more recent meta-analysis showing that compared to a low consumption, a high intake of red and processed meats are associated with higher odds ratio for higher BMI and waist circumference (Rouhani et al., 2014).

In addition to a higher risk of obesity dietary advanced glycation and lipoxidation endproducts, which exert pro-oxidative and pro-inflammatory effects, may also be mechanistically involved in the higher diabetes risk by meat and meat products (White and Collinson, 2013).

Meat contains heme iron, which is highly bioavailable and therefore represents a good dietary iron source for the body. However although iron is essential for health, free iron has strong pro-oxidant capabilities catalysing several reactions which result in the production of reactive oxygen species and therefore high (free) iron levels in the body and cells may favor cellular oxidative stress (Rajpathak et al., 2009). This can lead to tissue damage, among others also in the pancreatic beta cells. An increased iron status, as usually measured by serum ferritin, has a positive association with the risk of type 2 diabetes as shown in several studies (Basuli et al.,

2014). A summary of meta-analyses also showed a link between high heme-iron intake and type 2 diabetes risk (White and Collinson, 2013).

Another factor may be nitrosamines, which may cause insulin resistance in rats (Tong et al., 2009). Furthermore blood nitrite concentrations in adults have been related to impaired insulin response (Virtanen et al., 1994). Nitrosamine can be build in the stomach or within the food product by interaction of amino products by nitrites and nitrates, which are used frequently in the preservation of processed meat.

Meat is a rich source of saturated fatty acids (SFA) and cholesterol which could increase insulin resistance (Feskens et al., 2013). A correlation between an increased intake of SFA and decreased insulin sensitivity has been shown in several cross-sectional studies (Kim et al., 2015; Riccardi et al., 2004) with four of eight epidemiological studies demonstrating a relationship between a high SFA intake and risk of T2DM independently of body mass index (Kim et al., 2015).

2.2 Cardiovascular diseases

Several studies have demonstrated that individuals who consume a vegetarian diet for a longer time span tend to have lower levels of cardiovascular risk factors, such as blood pressure, fasting plasma glucose and total cholesterol and also lower risks for CVD and mortality (summarized in (McEvoy et al., 2012)). Furthermore subgroup analysis of individuals from the EPIC-Oxford study showed that vegetarians, especially vegans, have a lower prevalence of hypertension and lower systolic and diastolic blood pressures than meat eaters (Appleby et al., 2002).

On the other hand several prospective studies described a positive association between (red) and processed meat intake and CVD (Ashaye et al., 2011; Kontogianni et al., 2008; Steffen et al., 2005). For example in a large cohort study of US Americans which were prospectively followed during 10 years both red and processed meats were associated with an increased risk of CVD-mortality for men and women in the highest quintile of red and processed meat intakes (Sinha et al., 2009).

A literature search was performed in Pubmed, Scopus and Embase with the search terms „meat and (cardiovascular or myocardial or coronary or stroke or heart or cardiac) and meta-analysis“from publications between 2005 and July 2015. Papers were restricted to English publications. Risk ratios, incidence rate ratios or odds ratios (relative risks) had to be available with 95% confidence intervals. Only publications including red meat and/or processed meat were considered. 7 publications were selected from the search. From these 3 were excluded since they were no meta-analyses or meta-analyses exclusively studying mortality leaving 4 studies and 5 comparisons (Table 2). All of the meta-analyses included mainly cohort studies. Calculations were performed on high vs. low and/or dose response analyses (per serving/gram increase in red meat or processed meat), respectively.

The summary of the relative risks for red meat and processed meat from the selected meta-analyses are shown in Table 2. For processed meat all of the meta-analyses showed a higher relative risk for coronary heart disease (CHD) and stroke in the high vs. low and dose-response analyses, respectively. However for red meat relative risks for CHD and stroke were lower (range between 1.00 to 1.23). Available I^2 values indicated low heterogeneity.

Potential mechanisms linking meat intake to cardiovascular risk

Meat is a source of saturated fatty acids and cholesterol and since many years a positive association between saturated fatty acids (SFAs), blood cholesterol and risk for CHD is suggested. It has been proposed that eating foods with high levels of SFAs and cholesterol may raise the risk of CHD (Stradling et al., 2013). However, recent systematic reviews of cohort studies have not found statistically significant associations between SFA and cardiovascular endpoints (Siri-Tarino et al., 2010; Skeaff and Miller, 2009).

Nonetheless, fat quality plays an important role and replacing saturated with unsaturated fats appears to be beneficial regarding cardiovascular health, although not all studies did show a risk benefit (Schwingshackl and Hoffmann, 2014).

In addition to SFAs and cholesterol high intakes of *trans* fatty acids have been demonstrated to adversely effect the ratio of low density lipoprotein (LDL)-cholesterol to HDL-cholesterol (Lichtenstein, 2014), which is established risk factor for CHD. Ruminant meat, beef and lamb, contain some *trans* fatty acids, whereas pork and chicken contain less. However, a recent meta-analysis did not find an adverse effects of ruminant *trans* fatty acids up to 4.19% of daily energy intake on the ratios of LDL to HDL (Gayet-Boyer et al., 2014).

Regarding dietary cholesterol and cardiovascular risk the results are unequal and studies heterogenous to draw any conclusions as summarised in a recent meta-analysis of prospective studies (Berger et al., 2015).

In addition to fat the higher sodium in processed meats could potentially contribute to an increased risk for CVDs. On average, processed meats contains about 400% more sodium per 50 gram servings than red meat (Micha et al., 2012). The association between dietary sodium/salt intake and blood pressure has been known since nearly a century (summarized in (Ekmekcioglu et al., 2013)) and recent meta-analyses of randomized trials have proven that modest reductions in dietary sodium intake are associated with significant reductions in blood pressure in both normotensives and especially hypertensives (Graudal et al., 2011; He and MacGregor, 2002). Furthermore, reducing salt intake reduces cardiovascular morbidity and mortality. Meta-analyses calculated a reduced risk in the range of approximately 10-20% reduction in cardiovascular events (He and MacGregor, 2011; Strazzullo et al., 2009).

Meat is a rich source of biovailable heme-iron and since more than 2 decades an association between high iron stores and CVD has been proposed in several studies ((Salonen et al., 1992; Sullivan, 1989); reviewed in (Basuli et al., 2014)) although the results were not consistent (Friedrich et al., 2009). Equivalent to the diabetes risk a plausible mechanism undelying the association may be the ability of iron to generate reactive oxygen species and therefore induce oxidative stress.

Regarding intake of dietary intake of heme iron and CVD several studies are available. A recent meta-analysis included thirteen studies with 252 164 participants and 15 040 CVDs cases (Fang et al., 2015). The results showed that heme iron intake was significantly associated with increased risk of CVD, with each 1 mg/day increment bearing a RR of 1.07.

2.3 Colorectal cancer

The gastrointestinal tract is exposed to food ingredients nearly permanently throughout ones life. Therefore an association between food and gastrointestinal cancer is comprehensible. Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women worldwide (World Cancer Research Fund International, 2012). Furthermore CRC is the number one cause of cancer mortality in European nonsmokers (Ferlay et al., 2013). CRC occurs more frequently in Western countries with a high red meat intake; in contrast, CRC is less frequent in countries where meat intake is low (Bingham and Riboli, 2004; Corpet, 2011).

For meanwhile many years probable to convincing epidemiological evidence has been established regarding the intake of red and processed red meat intake and colorectal cancer risk (Chan et al., 2011; Johnson et al., 2013; Reedy et al., 2010). The 2007 expert report of the WCRF and the AICR for example (World Cancer Research Fund and American Institute for Cancer Research, 2007) concluded that there was convincing evidence that physical activity decreased the risk of CRC and that intake of red meat, processed meat, alcoholic drinks (men), body fatness and abdominal fatness increased the risk of CRC. Most recently the International Agency for Research on Cancer (IARC) classified the consumption of processed meat as “carcinogenic to humans (Group 1) and red meat as “probably carcinogenic to humans” (Group 2A) after evaluating more than 800 epidemiological studies (Bouvard et al., 2015; WHO, 2015). It was calculated that for each serving (50g) of processed meat per day the risk of colorectal cancer increased by 18%. Considering that many people consume relevant amounts of red and processed meat worldwide these risks are of important relevance for public health.

A literature search was performed in Pubmed, Scopus and Embase with the search terms „meat and (cancer or neoplasm) and (colon or rectal or colorectal) and meta-analysis“ from publications between 2005 and July 2015. Papers were restricted to English publications. Risk ratios, incidence rate ratios or odds ratios (relative risks) had to be available with 95% confidence intervals. Only publications including red meat and/or processed meat were considered. 17 publications were selected from the search. From these 8 were excluded since they were no meta-analyses or only restricted to Asian populations or meta-analysis exclusively studying colorectal adenomas or a meta-analysis studying only poultry leaving 9 studies (Table 2). Mainly cohort studies were included with one exception where only case-control studies were analysed (Sadri and Mahjub, 2006). Calculations were performed on high vs. low and/or dose response analyses (per serving/gram increase in red meat or processed meat), respectively.

The summary of the relative risks for red meat and processed from the selected meta-analyses are shown in Table 3. For red and processed meat all of the meta-analyses showed a higher relative risk in the high vs. low and dose-response analyses, respectively. Relative risks were in the range of 1.05 to 2.20 for red meat and 1.09 to 1.20 for processed meat, respectively. One outlier was the meta-analysis by Sadri and Mahjub (Sadri and Mahjub, 2006) only including case-control studies, which do not provide true relative risks and where the causal inference is less robust (Wang and Attia, 2010). Available I^2 values indicated low heterogeneity.

Potential mechanisms linking meat intake to colorectal cancer risk

Various plausible mechanisms through which ingredients from red and processed red meat can favor CRC development have been put forward (Corpet, 2011; Demeyer et al., 2015). Potential

mechanisms which may explain why red meat intake may be a risk factor for colorectal carcinogenesis include in particular meat related mutagens heterocyclic amines, polycyclic aromatic hydrocarbons (PAH) and *N*-nitroso compounds (summarized in (Demeyer et al., 2015)). Cooking process seems to play an important role with f. ex. a considerable reduction in PAH levels in meat can be achieved by avoiding the pyrolysis of fat that droping into the cooking flames (Alexander et al., 2008; Demeyer et al., 2015). Furthermore removal of charred and blackened stuff from the surface of broiled meat and fish on the dish (Sugimura, 1997) can also reduce PAH and heterocyclic amine levels.

Furthermore also heme iron has been implicated in the development of CRC (summarized in (Demeyer et al., 2015)). The mechanism may be lipid peroxidation (Bastide et al., 2015) with the generation of radicals and toxic malondialdehyde and also formation of N-nitroso compounds in the gut by heme iron (Abid et al., 2014).

In general, it can be assumed that a high intake of red and processed meat is accompanied by a lower intake of whole grains, vegetables and fruits, which might be protective against cancer but also CVDs (see section 4).

2.4 All-cause mortality

Previous large scaled studies demonstrated an association between meat intake and higher risk for mortality. For example in the National Institues of Health-AARP study cohort over half a million people aged 50-71y were prospectively followed. More than 71 000 deaths during 10 years of follow-up occured and red meat intake was associated with an increase for overall mortality by 31% for men and 36% for women for the highest vs. lowest intake quintiles. Every

specific cause of death was also significantly increased, including cancer, CVD, injuries and sudden deaths. Furthermore, the consumption of white meat, which was defined as poultry or fish, was inversely associated with total and cancer mortality (Sinha et al., 2009).

A subsequent prospective study in 2 cohorts consisting of 37 698 men and 83 644 women also found an increased risk for total, CVD and cancer mortality for a 1-serving-per-day increase in unprocessed or processed red meat (Pan et al., 2012).

The results from the EPIC cohort of 448 568 men and women regarding meat and mortality showed that after adjustment for various confounders, a high vs. low consumption of red meat was related to higher all-cause mortality (HR = 1.14) and the association was stronger for processed meat (HR = 1.44) (Rohrmann et al., 2013).

Finally, also a recent study in more than 74 000 Swedish men and women found that compared with no consumption, consumption of red meat > 100 g/d was increasingly associated with shorter survival---up to 2 y for participants consuming an average of 300 g/d (Bellavia et al., 2014).

A literature search was performed in Pubmed, Scopus and Embase with the search terms „meat and (mortality or survival or death) and meta-analysis" from publications between 2005 and July 2015.

Papers were restricted to English publications. Risk ratios, incidence rate ratios or odds ratios (relative risks) had to be available with 95% confidence intervals. Only publications including red meat and/or processed meat were considered. 4 publications were selected and included from

the search (Table 4). All of the meta-analyses included cohort studies. Calculations were performed on high vs. low and/or dose response analyses (per serving/gram increase in red meat or processed meat), respectively.

The summary of the relative risks for red meat and processed from the selected meta-analyses are shown in Table 4. For red and processed meat all of the meta-analyses showed a higher relative risk in the high vs. low and dose-response analyses, respectively. Relative risks were in the range of 1.04 to 1.17 for red meat and 1.15 to 1.25 for processed meat, respectively. Available I^2 values indicated a high degree of heterogeneity.

2.5 Other cancers

In addition to colorectal cancer also the risk for other cancers is associated with a higher intake of red (processed) meat (Table 5). A Pubmed search with the terms „meat and meta-analysis“ from 2005 until June 2015 revealed several meta-analyses showing in general harmful associations of high red (processed) meat intake and various cancers.

27 meta-analyses including various types of cancers were selected from the Pubmed search. The summary of the relative risks for red meat and processed from the selected meta-analyses are shown in Table 5.

For dietary red meat, except for 3 meta-analyses (Alexander et al., 2010b; Lee et al., 2008; Wei et al., 2015) all of the meta-analyses showed a higher relative risk in the high vs. low and dose-response analyses, respectively. High relative risks were especially found for esophagheal and gastric cancers, respectively with relative risks ranging from 1.17 to 1.73.

For processed meat all of the meta-analyses showed a higher relative risk in the high vs. low and dose-response analyses, respectively. High relative risks were especially found for esophageal and gastric cancers, respectively with relative risks ranging from 1.15 to 1.64.

Available I^2 values indicated a variable degree of heterogeneity from 0% to 85.9%

3. Meat intake recommendations

Due to the association of a high intake of red and processed meat and various diseases many governmental and non-governmental health and nutrition agencies have recommended restriction of red and/or processed meat intake. The World Cancer Research Fund and the American Institute of Cancer Research recommend to limit the intake of red meat and avoid processed meat. The public health goal is that on a population level the average consumption of red meat should be no more than 300 grams per week, very little if any of which to be processed. People who eat red meat should consume less than 500 g a week, very little if any to be processed (The World Cancer Research Fund and American Institute of Cancer Research). For cancer prevention the WHO (WHO/FAO, 2003) recommends to moderate consumption of preserved meat (e.g. sausages, salami, bacon, ham).

The German Society of Nutrition recommends to not eat more than 300-600 g/week meat and processed meat (DGE, website). Furthermore they state that regarding health aspects white meat is rated better than red meat. The Austrian Society of Nutrition and the Austrian Ministry for Health recommend to eat not more than 300 - 450g low fat meat and processed meat per week (Bundesministerium für Gesundheit).

Within Europe, the EPIC study reported high variation in meat intake amongst the European countries/centres participating in this study. The lowest meat intakes were reported in Greece and the highest meat intakes in Spain. Red meat intake ranged from 24--57 g/d in women and 40--121 g/d in men within the ten countries participating (Linseisen et al., 2002).

In the European Nutrition and Health report the mean availability for red meat or processed meat for persons in Austria was 65g/d or 92g/d, respectively. The total meat availability was 182 g/d (Elmadfa, 2009). So about half of the meat availability was by processed meat.

4. Healthy foods and risk for diseases

Since many institutions recommend to reduce he intake of red meat and processed meat healthy alternatives should be provided to especially compensate for potential critical nutrients but also at least partly for energy. This section summarizes health effects of other foods on diabetes, CVDs, colorectal cancer and overal mortality. Due to the huge literature available only selected papers and results from recent meta-analyses were considered.

4.1 Fish

Fish is a primary source of the essential omega-3 fatty acids DHA and EPA, which are not only important for neurological development but also possess anti-inflammatory, vasculo-protective, and possibly also anti-arrhythmic effects (Lee and Lip, 2003). Therefore fish and fish oil including omega-3-fatty acids have a protective effect regarding CVDs. This finding was supported impressively by the GISSI Prevention trial in patients surviving from recent myocardial infarctions. In these high risk group 1 g/d fish oil supplements significantly lowered

the rates of the primary endpoint (death, nonfatal MI, or stroke) over 3.5 years (GISSI-Prevenzione Investigators, 1999).

In an early systemic review of prospective cohort studies it was shown that 40 - 60g fish per day is optimal and associated with a significant risk reduction of 40-60% for coronary heart disease mortality in high risk populations (Marckmann and Gronbaek, 1999).

A recent meta-analysis showed that among prospective cohort studies, more than ≥4 times per week fish consumption was associated with a 21% reduction in acute coronary syndrome. Furthermore, in dose-response analysis, each additional 100 g serving of fish per week was associated with a 5% reduced risk (Leung Yinko et al., 2014).

Furthermore a fish intake in the range of 2-4 servings a week reduces the relative risk for cerebrovascular disease in the extent of 6% compared to ≤ 1 servings a week as shown in meta-analysis of cohort studies. Relative risk for intakes of ≥ 5 servings a week versus 1 serving a week was 0.88 (Chowdhury et al., 2012).

In contrast to CVDs fish consumption seems to be not protective against type 2 diabetes (Zhou et al., 2012). On the contrary a meta-analysis of 9 cohort studies found a pooled RR of 1.146 for high vs. low fish intake (Zhou et al., 2012). This may derive from environmental contaminants such as dioxins (Lee et al., 2006) and methyl mercury, which might raise T2DM risk (Mozaffarian and Rimm, 2006). Another meta-analysis showed no risk effect of fish on diabetes (Zhang et al., 2013).

Regarding colorectal cancer a meta-analysis found that fish consumption decreased the risk of colorectal cancer by 12% (summary OR: 0.88) (Wu et al., 2012). A more recent meta-analysis calculated that fish consumption was associated with reduced risk of colorectal cancer with a RR of 0.93 (Yu et al., 2014).

Regarding mortality a recent meta-analysis of 12 prospective cohort studies analysed that compared with the lowest category, the highest category of fish intake was associated with an approx. 6% significantly lower risk of all-cause mortality (Zhao et al., 2015). The dose-response analysis showed a nonlinear relationship between fish consumption and all-cause mortality. Compared with never consumers, intake of 60g of fish per day was associated with a 12% reduction.

However, it should also be remarked that dietary recommendations regarding fish consumption often neglect a variety of critical issues, e.g. the problem of overfishing (Oken et al., 2012). Also the social and economic effects of recommended fish consumption should be taken into account (Institute of Medicine and National Research Council, 2015).

4.2 Nuts

Nuts are rich in vegetable protein, dietary fiber, antioxidant vitamins, certain minerals (eg, magnesium and potassium), and phytochemicals (especially flavonoids) (Afshin et al., 2014; Mozaffarian et al., 2011). Furthermore nuts have a low content of saturated fatty acids and high levels of monounsaturated fatty acids, such as especially oleic acid, as well as a variable amounts of PUFAs, especially the plant derived α-linolenic acid, which, among others, can be found in high concentrations in walnuts (Brufau et al., 2006).

Nut consumption was shown to reduce total cholesterol, LDL-cholesterol, and the LDL-to-HDL ratio in a pooled analysis of 25 intervention trials (Sabate et al., 2010). In this regard prospective epidemiological studies have consistently demonstrated that a frequent consumption of nuts reduces CHD risk (Kelly and Sabate, 2006). The largest of these studies was the American Nurse's Health Study, which followed-up 86 016 women for 14 years (Hu et al., 1998). After multivariate adjustment it was shown that frequent (> 5 units/week) nut consumption was associated with a 35% lower risk for total coronary heart disease compared to women who never or rarely ate nuts.

A meta-analysis from 2006 of 4 prospective cohorts reported an inverse association between nut consumption and fatal ischaemic heart disease (IHD) (Kelly and Sabate, 2006). A recent meta-analysis including cohort and randomized controlled studies also showed that the consumption of nuts was inversely associated with fatal IHD (RR per 4 weekly 28.4-g servings: 0.76), nonfatal IHD (RR: 0.78), and diabetes (RR: 0.87) but not stroke (Afshin et al., 2014).

Regular nut consumption, especially pistachios and mixed nuts, also lowers blood pressure in persons with type 2 diabetes as shown in a recent meta-analysis (Mohammadifard et al., 2015).

Regarding diabetes recent meta-analyses did not find a beneficial or harmful effect of nut consumption on diabetes risk (Guo et al., 2015b; Wu et al., 2015a).

Regarding colorectal cancer a recent meta-analytic calculation showed a RR of 0.76 for the highest category of nut consumption compared to the lowest category (Wu et al., 2015a).

Regarding mortality different meta-analyses were published. By pooling 6 studies Grosso et al. (Grosso et al., 2015) for example showed that high vs. low nut consumption was associated with a 23% lower risk for all-cause mortality. Earlier meta-analyses found a 20% (Bao et al., 2013; Luo et al., 2014a) risk reduction for overal mortality in frequent nut eaters compared to rare or no nut eaters.

Since nuts are energy dense foods with a high fat content concerns can arise whether regular eating of nuts could lead to unwarranted weight gain. However this seems to be not the case as for example a recent meta-analysis, which included 31 clinical trials, showed that diets including nuts did not increase body weight, body mass index or waist circumference compared to control diets (Flores-Mateo et al., 2013).

4.3 Vegetables and fruits

The important role of vegetables and fruits on human health are out of question. Several studies have shown positve effects of these food groups on various non-communicable diseases (Slavin and Lloyd, 2012). Therefore various institutions around the globe recommend to eat daily fruits and vegetables (Montagnese et al., 2015). The positive effects of fruits and vegetables derive from their concentration of health promoting ingredients such as vitamins, especially vitamins C and A; minerals, including magnesium and potassium; various phytochemicals, and dietary fiber.

The positive effect of fruits and vegetables on CVDs, diabetes, colorectal cancer, and mortality were analysed in several meta-analyses. An extensive critical review from 2012, which was initiated by The German Nutrition Society, summarized evidenced based the positive effects of fruits and vegetables on human health. A convincing evidence was found for hypertension, CHD,

and stroke, that increasing the consumption of vegetables and fruit reduces the risk of disease. Furthermore the authors concluded probable evidence that the risk of cancer in general is inversely associated with the consumption of vegetables and fruit. Furthermore increased consumption of vegetables and fruit may prevent body weight gain with possible evidence (Boeing et al., 2012).

Regarding stroke a more recent meta-analysis found that the multivariable relative risk of stroke for the highest versus lowest category of total fruits and vegetables consumption was 0.79, and 0.77 for fruits or 0.86 for vegetables consumption, respectively (Hu et al., 2014b). A linear dose--response relationship showed that the risk of stroke was reduced by 32% and 11% for every 200 g per day increase in the intake of fruits and vegetables, respectively.

Regarding diabetes a meta-analysis by Carter et al. showed that greater intake of green leafy vegetables is associated with a 14% reduction in risk of type 2 diabetes (Carter et al., 2010). However no significant benefits on incidence of type 2 diabetes were detected with increased consumption of vegetables in general, fruit, or fruit and vegetables combined. A recent meta-analysis showed a small effect of vegetables and fruits on diabetes risk (Wu et al., 2015b).

Regarding colorectal cancer an earlier meta-analysis, which included 14 prospective studies with follow-ups of 6--20 years, showed that an intake of fruit and vegetables is associated with a non-significant reduction (6-9%) in the risk of CRC. However eating fruit and vegetables was significantly associated with a reduced risk of distal cancer (Park et al., 2005). Another meta-analysis by Aune et al. (Aune et al., 2011b) which included 19 prospective studies found summary relative risks for the highest vs the lowest intake of 0.92 for fruit and vegetables

combined, 0.90 for fruit, and 0.91 for vegetables. The inverse associations appeared to be restricted to colon cancer and the greatest risk reduction was observed when intake increased from very low levels of intake.

Regarding mortality a recent meta-analysis of prospective cohort studies showed that higher consumption of fruit and vegetables was significantly associated with a lower risk of all cause mortality. A threshold of about five servings of fruit and vegetables a day was detected, after which the risk of all cause mortality did not reduce further (Wang et al., 2014).

4.4 Pulses and Legumes

Legumes contain important phytochemicals which are beneficial for health and protect against several diseases, including CHD and diabetes (Bouchenak and Lamri-Senhadji, 2013; Rebello et al., 2014). Furthermore legumes are rich in fibre, a good source of protein, and contain relevant amounts of B vitamins as well as essential minerals, such as iron, calcium and potassium.

Several studies showed beneficial effects of legumes on CVD and risk factors, and the metabolic syndrome. For example consumption of five cups per week of pulses (yellow peas, chickpeas, navy beans, and lentils) over 8 weeks in an *ad libitum* diet reduced the risk factors of the metabolic syndrome (Mollard et al., 2012). In a meta-analysis including 11 clinical trials, the intake of nonsoy legumes reduced total cholesterol, LDL cholesterol, and triglycerides by 7%, 6%, and 17%, respectively, without significant changes in body weight (Anderson and Major, 2002).

Short-term studies have demonstrated that legume consumption lowers blood glucose and insulin responses and increases insulin sensitivity when compared with white bread or pasta (summarized in (Rebello et al., 2014)). Furthermore a meta-analysis of randomized controlled trials showed that pulses alone, or as part of a low GI or high fibre diet improved markers of glycaemic control, such as glycosylated haemoglobin (HbA1c) and fructosamine (Sievenpiper et al., 2009). However, a recent meta-analysis, which pooled 2 prospective cohorts, did not find a significant association between legume consumption and incident diabetes (Afshin et al., 2014).

On the other hand, regarding CVD, the latter meta-analysis provided evidence that the consumption of 4 weekly 100g servings of legumes was associated with 14% lower risk of ischaemic heart disease (Afshin et al., 2014). Also blood pressure is reduced by dietary intake of pulses as shown in a meta-analysis including 8 isocaloric trials with 554 participants with or without hypertension (Jayalath et al., 2014).

Finally, a higher intake of legumes also reduces colorectal cancer risk as shown in a recent meta-analysis including 14 cohort studies (RR = 0.91) (Zhu et al., 2015).

4.5 Whole grains

Whole grains are rich in in vitamins, minerals and phytochemicals but especially also fiber, which may improve insulin sensitivity and glucose metabolism. For example intake of especially cereal fiber, and only non-significantly fruit or vegetable fiber, has been associated with reduced type 2 diabetes risk in a meta-analysis of prospective studies (Schulze et al., 2007).

In this regard several studies and meta-analyses have shown that whole grain intake reduces diabetes risk (de Munter et al., 2007; Montonen et al., 2003; Sun et al., 2010; Ye et al., 2012). For example a meta-analysis of sixteen cohort studies found relative risk per 3 servings per day of whole grains of 0.68 while the relative risk for refined grains was 0.95 (Aune et al., 2013b).

Furthermore a high whole grain intake might also have a positive impact on overweight and obesity, which also may explain the protective effects on type 2 diabetes. However a meta-analysis of randomized controlled studies of whole-grain intake compared with controls in adults did not revealed any effect on body weight with a small beneficial effect on body fat (Pol et al., 2013).

Regarding colorectal cancer a recent meta-analysis including 25 prospective studies concluded that a high intake of dietary fibre, in particular cereal fibre and whole grains, is associated with a reduced risk of colorectal cancer. For whole grains the summary relative risk for colorectal cancer with an increment of three servings daily (90 g/day) of whole grains was 0.83 with no evidence of heterogeneity (Aune et al., 2011a).

In addition to diabetes and cancer whole grains might also reduce the risk for CVD. A recent meta-analysis for example calculated risk ratio of 0.84 for CVD per 7 g/day increase in fibre from cereal sources (Threapleton et al., 2013).

4.6 Dairy products

Dairy products are not only important for bone health but might be protective against certain diseases, including diabetes. For example a recent meta-analysis including seventeen cohort

studies suggested that there is a significant inverse association between intakes of dairy products, low-fat dairy products, and cheese and risk of type 2 diabetes (Aune et al., 2013a). The risk reductions were in the magnitude of 7-22% dependent on the amount and kind of the dairy product. The highest reduction was analysed for 200 g/d of yogurt.

These results were confirmed in another similar meta-analysis concluding that a modest increase in daily intake of dairy products such as low fat dairy, cheese and yogurt may contribute to the prevention of type 2 diabetes (Gao et al., 2013).

Regarding CVD another dose-response meta-analysis suggested that milk may be marginally significant inversely associated with overall risk of CVD (RR 0.94 per 200 mL/d) but not associated with all-cause mortality (Soedamah-Muthu et al., 2011). Another meta-analysis did also found no significant effect of dairy products on all-cause mortality (O'Sullivan et al., 2013). Furthermore a meta-analysis including 18 separate results from 15 prospective cohort studies found that total dairy (RR 0.88), low-fat dairy (RR 0.91), fermented milk (RR 0.80) and cheese (RR 0.94) were significantly associated with a reduced risk of stroke. On the other hand whole/high-fat dairy, nonfermented milk, butter and cream were not significantly associated with risk of stroke (Hu et al., 2014a).

Regarding colorectal cancer there was also a beneficial effect of dairy intake as demonstrated by a meta-analysis of 19 cohort studies showing a risk reduction of 19% for 400g/d consumption of dairy products (Aune et al., 2012). These results were confirmed in a more recent meta-analysis showing that in men consuming nonfermented milk (highest intake category in average 525

g/day) the overall relative risk of colon cancer was 0.74 (95% confidence interval 0.60-0.91) (Ralston et al., 2014). No effects were seen in women.

5. Conclusions

Meat is and will be an important food for human nutrition. Meat is a valuable source of high quality protein and some micronutrients, especially iron, zinc and vitamin B_{12}.

However a high intake of red and especially processed meat is detrimental to health as a huge number of epidemiological studies and associated meta-analyses have shown in the last decades. The increased risk is shown in particular for diabetes and colorectal cancer but also for total mortality and cardiovascular diseases. Relating to disease risk white meat is often rated better than red meat, for example regarding mortality (Sinha et al., 2009) or diabetes risk (Feskens et al., 2013).

Concurrently to the reduction of (red) meat intake the consumption of healthy foods, in front whole grains, vegetables, and legumes should be increased (Figure). Fish is also important as a substantial source of iron, zinc and omega-3-fatty acids and could serve as a healthy alternative. For example it was shown that replacement of one serving of red meat or processed red meat with one serving of nuts, low-fat dairy products, or whole grains was associated with a lower risk of type 2 diabetes (Pan et al., 2011). The risk reduction was higher for replacement of processed red meat compared to red meat. Risk reductions were also calculated for replacement with fish or poultry.

Although it is now quite evident that a reduction of a high intake of red meat is favaroble regarding disease risk it should also be mentioned that a considerable reduction of meat intake might be associated with a suboptimal supply with selected nutrients, especially in vulnerable populations. Critical could be for example iron in women in childbearing age, iron and zinc in children during the period of growth, or protein and vitamin B_{12} in older persons. Compensation could be achieved by for example including fish, dairy, eggs and legumes to the diet.

Finally, several papers in the last years calculated scenarios showing that reducing the intake of (red) meat and optimising diets is not only beneficial to human health but, through a reduction of greenhouse gas emissions, also for our climate (Tilman and Clark, 2014; Yip et al., 2013).This would be an important environmental co-benefit of a reduction of meat intake with a high impact for our future.

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Table 1. Meta-Analyses of studies analysing the association between dietary red meat or processed meat and risk for diabetes

Reference	**Relative Risk highest vs. lowest intake**	**95% CI**	**I^2 in %**		**Relative Risk per serving**	**95% CI**	**I^2 in %**
Dietary red meat							
Aune et al. 2009 (Aune et al., 2009)	1.21	1.07 -- 1.38	58.5%		1.20 (per 120 g/d)	1.04 -- 1.38	68.3%
Micha et al. 2010 (Micha et al., 2010)					1.16 (per 100 g/d)	0.92 -- 1.46	
Pan et al. 2011 (Pan et al., 2011)					1.19 (per 100g/d)	1.04 -- 1.37	93.3%

Feskens et al. 2013 (Feskens et al., 2013)					1.13 (per 100 g)	1.03 -- 1.23	36%
Tamez et al. 2013 (Tamez et al., 2013)					1.13 (per 100 g/d)	1.08 -- 1.17	
Bylsma et al. 2015 (Bylsma et al., 2015)	1.18	1.10 -- 1.26	64.08%				
Dietary processed meat							
Aune et al. 2009 (Aune et al., 2009)	1.41	1.25 -- 1.60	53.2%		1.57 (per 50 g/d)	1.28 -- 1.93	74.0%
Micha et al. 2010 (Micha et al., 2010)					1.19 (per 50 g/d)	1.11 -- 1.27	
Pan et al. 2011 (Pan et al., 2011)					1.51 (per 50 g/d)	1.25 -- 1.83	94.3%

Feskens et al. 2013 (Feskens et al., 2013)					1.32 (per 50 g)	1.19 -- 1.48	89%
Tamez et al. 2013 (Tamez et al., 2013)					1.35 (per 50 g/d) 1.82 (per 100 g/d)	1.24 -- 1.55 1.64 -- 2.02	

Table 2. Meta-Analyses of studies analysing the association between dietary red meat or processed meat and risk of CHD or stroke

Reference	**Relative Risk highest vs. lowest intake**	**95% CI**	**I^2 in %**		**Relative Risk per serving**	**95% CI**	**I^2 in %**
Dietary red meat							
Mente et al. 2009 [1] (Mente et al., 2009)	1.23	0.98 -- 1.49					
Micha et al. 2010 [1] (Micha et al., 2010)					1.00 (per 100 g/d)	0.81 -- 1.23	
Micha et al. 2010 [2] (Micha et al., 2010)					1.17 (per 100 g/d)	0.40 -- 3.43	
Kaluza et al.					1.11 (per 100	1.06 --	0.0%

2012 [2] (Kaluza et al., 2012)					to 120 g/d red and total meat)	1.16	
Chen et al. 2013 [2] (Chen et al., 2013)	1.09	1.01 -- 1.18	0.0%		1.13 (per 100 g/d)	1.03 -- 1.23	
Dietary processed meat							
Micha et al. 2010 [1] (Micha et al., 2010)					1.42 (per 50 g/d)	1.07 -- 1.89	
Micha et al. 2010 [2] (Micha et al., 2010)					1.14 (per 50 g/d)	0.94 -- 1.39	
Kaluza et al. 2012 [2] (Kaluza et al., 2012)					1.13 (per 50 g/d)	1.03 -- 1.24	37.8%
Chen et al. 2013 [2] (Chen et al., 2013)	1.14	1.05 -- 1.25	23.0%		1.11 (per 50 g/d)	1.02 -- 1.20	

[1]**risk of CHD**

[2]**risk of stroke**

Table 3. Meta-Analyses of studies analysing the association between dietary red meat or processed meat and risk of colorectal cancer

Reference	**Relative Risk highest vs. lowest intake**	**95% CI**	**I^2 in %**		**Relative Risk per serving**	**95% CI**	**I^2 in %**
Dietary red meat							
Larsson and Wolk 2006 (Larsson and Wolk, 2006)	1.28	1.15 -- 1.42	0%		1.28 (per 120 g/d)	1.18 -- 1.39	0%
Sadri and Mahjub 2006 (Sadri and Mahjub, 2006)	2.20	1.86 -- 4.08					
Huxley et al. 2009 (Huxley et	1.21	1.13 -- 1.29					

al., 2009)							
Smolinska and Paluszkiewicz 2010 (Smolinska and Paluszkiewicz, 2010)					1.21 (RR of colon CA; per 50 g/d)	1.07 -- 1.37	
Alexander et al. 2011 (Alexander et al., 2011)	1.12	1.04 -- 1.21			1.05 (per 70 g)	0.97 -- 1.13	
Chan et al. 2011 (Chan et al., 2011)	1.10	1.00 -- 1.21	22%		1.17 (per 100 g/d)	1.05 -- 1.31	0%
Johnson et al. 2013 (Johnson et al., 2013)					1.13 (per 5 servings/week)	1.09 -- 1.16	
Alexander et al. 2015 (Alexander et al., 2015)	1.11	1.03 -- 1.19	33.6%				

Dietary processed meat							
Larsson and Wolk 2006 (Larsson and Wolk, 2006)	1.20	1.11 -- 1.31	0%		1.09 (per 30g/d)	1.05 -- 1.13	0%
Huxley et al. 2009 (Huxley et al., 2009)	1.19	1.12 -- 1.27					
Alexander et al. 2010 (Alexander et al., 2010a)	1.16	1.10 -- 1.23			1.10 (per 30 g)	1.05 -- 1.15	
Chan et al. 2011 (Chan et al., 2011)	1.17	1.09 -- 1.25	6%		1.18 (per 50 g/d)	1.10 -- 1.28	12%
Johnson et al. 2013 (Johnson et al., 2013)					1.09 (per 5 servings/week)	0.93 -- 1.25	

Table 4. Meta-Analyses of studies analysing the association between dietary red meat or processed meat and risk of all-cause mortality

Reference	**Relative Risk highest vs. lowest intake**	**95% CI**	**I^2 in %**		**Relative Risk per serving**	**95% CI**	**I^2 in %**
Dietary red meat							
O'Sullivan et al. 2013 (O'Sullivan et al., 2013)	1.17	1.08 -- 1.27	85%				
Abete et al. 2014 (Abete et al., 2014)	1.09	0.94 -- 1.28	95.4%		1.04 (per 100 g/d)	0.92 -- 1.17	95%
Larsson and Orsini 2014 (Larsson and Orsini, 2014)	1.10	0.98 -- 1.22	83%		1.09 (per 100 g/d)	0.997 -- 1.20	

Wang et al. 2015 (Wang et al., 2015)	1.05	0.93 -- 1.19	90.2%				
Dietary processed meat							
O'Sullivan et al. 2013 (O'Sullivan et al., 2013)	1.21	1.16 -- 1.28	62%				
Abete et al. 2014 (Abete et al., 2014)	1.22	1.16 -- 1.29	44.4%		1.25 (per 50 g/d)	1.07 -- 1.45	95.7%
Larsson and Orsini 2014 (Larsson and Orsini, 2014)	1.23	1.17 -- 1.28	57%		1.22 (60 g/d vs.10 g/d)	1.13 -- 1.31	
Wang et al. 2015 (Wang et al., 2015)					1.15 (per 50 g/d)	1.11-- 1.19	75%

Table 5. Meta-Analyses of studies analysing the association between dietary red meat or processed meat and risk of other cancers

Reference	**Disease**	**Relative Risk highest vs. lowest intake**	**95% CI**	**I^2 in %**	**Relative Risk per serving**	**95% CI**	**I^2 in %**
Wang and Jiang 2012 (Wang and Jiang, 2012)	Bladder cancer	1.17	1.02 -- 1.34	53.7%			
Li et al. 2014 (Li et al., 2014)	Bladder cancer	1.15	0.97 -- 1.35	73.5%			
Taylor et al. 2009 (Taylor et al., 2009)	Breast Cancer	1.24	1.08 -- 1.42				
Alexander et al. 2010	Breast cancer	1.02 (fixed effects	0.98 --		1.04 (per 100 g) 1.12 (per	1.00 --	

(Alexander et al., 2010c)		model) 1.07 (random effects model)	1.07 0.98 -- 1.17		100 g)	1.07 1.03 -- 1.23	
Guo et al. 2015 (Guo et al., 2015a)	Breast cancer	1.10	1.02 -- 1.19	62.2%	1.11 (per 120 g/d)	1.05 -- 1.16	
Bandera et al. 2007 (Bandera et al., 2007)	Endometrial cancer	1.48	1.22 -- 1.80	49.8%	1.51 (per 100 g/d)	1.19 -- 1.93	44.0%
Choi et al. 2013 (Choi et al., 2013)	Esophageal cancer	1.38	1.17 -- 1.64	67.1%			
Huang et al. 2013 (Huang et al., 2013)	Esophageal cancer	1.31	1.05 -- 1.64	18.9%	1.45 (per 100 g/d)	1.09 -- 1.93	61.8%
Qu et al. 2013 (Qu et	Esophageal cancer	1.57	1.26 --	56%			

al., 2013)			1.95				
Salehi et al. 2013 (Salehi et al., 2013)	Esophageal cancer	1.40	1.09 -- 1.81				
Zhu et al. 2014 (Zhu et al., 2014)	Esophageal cancer	1.55	1.22 -- 1.96	63.6%			
Bonequi et al. 2013 (Bonequi et al., 2013)	Gastric cancer	1.73 (odds ratio)	1.20 -- 2.51	64.5%			
Zhu et al. 2013 (Zhu et al., 2013)	Gastric cancer	1.45	1.22 -- 1.73	76.4%			
Song et al. 2014 (Song et al., 2014)	Gastric cancer	1.37	1.18 -- 1.59	67.6%	1.17 (per 100 g/d)	1.05 -- 1.32	73.8%
Wei et al. 2015 (Wei et	Glioma	0.89	0.71 --	0.0%			

al., 2015)			1.12				
Luo et al. 2014 (Luo et al., 2014b)	Hepatocellular carcinoma	1.10	0.85 -- 1.42	61.1%			
Alexander and Cushing 2009 (Alexander and Cushing, 2009)	Kidney cancer	1.12	0.98 -- 1.29				
Yang et al. 2012 (Yang et al., 2012)	Lung cancer	1.34	1.18 -- 1.52	63.9%			
Xue et al. 2014 (Xue et al., 2014)	Lung cancer	1.44	1.29 -- 1.61	77.0%			
Fallahzadeh et al. 2014 (Fallahzadeh	Non-Hodgkin Lymphona	1.10 (odds ratio)	1.02 --	59.4%			

et al., 2014)			1.19				
Xu et al. 2014 (Xu et al., 2014)	Oral cavity - oropharynx cancer	1.05	0.66 -- 1.66	49.4%			
Kolahdooz et al. 2010 (Kolahdooz et al., 2010)	Ovarian cancer	1.16	1.02 -- 1.32				
Wallin et al. 2011 (Wallin et al. 2011)	Ovarian cancer				1.02 (per 100 g/week)	0.99 -- 1.04	0%
Larsson et al. 2012 (Larsson and Wolk, 2012)	Pancreatic cancer				1.13 (per 120 g/d)	0.93 -- 1.39	69.8%
Alexander et al. 2010 (Alexander et al., 2010b)	Prostate cancer	1.00	0.96 -- 1.05		1.00 (per 100 g/d)	0.95 -- 1.05	

Lee et al. 2008 (Lee et al., 2008)	Renal cell cancer				0.99 (≥80g/d ⇔ 4 serv/w) 1.00 (2 servings/week)	0.85 -- 1.16 0.95 -- 1.06	
Wang and Jiang 2012 (Wang and Jiang, 2012)	Bladder cancer	1.10	1.00 -- 1.21	3.5%			
Li et al. 2014 (Li et al., 2014)	Bladder cancer	1.22	1.04 -- 1.43	64.9%			
Alexander et al. 2010 (Alexander et al., 2010c)	Breast cancer	1.00 (fixed effects SRRE) 1.08 (rand. effects SRRE)	0.98 -- 1.01 1.01 -- 1.16		1.03 (per 30 g) 1.06 (per 30 g)	1.00 -- 1.16 0.99 -- 1.14	
Guo et al.	Breast cancer	1.08	1.01	58.3%	1.09 (per 50	1.03	

2015 (Guo et al., 2015a)			-- 1.15		g/d)	-- 1.16	
Bandera et al. 2007 (Bandera et al., 2007)	Endometrial cancer						
Choi et al. 2013 (Choi et al., 2013)	Esophageal cancer	1.32	1.08 -- 1.62	58.4%			
Huang et al. 2013 (Huang et a. 2013)	Esophageal cancer	1.41	1.09 -- 1.83	39.4%	1.37 (per 50 g/d)	1.03 -- 1.81	71%
Qu et al. 2013 (Qu et al., 2013)	Esophageal cancer	1.55	1.22 -- 1.97	45.3%			
Salehi et al. 2013 (Salehi et al., 2013)	Esophageal cancer	1.41	1.13 -- 1.76	62%			
Zhu et al.	Esophageal	1.33	1.04	61.5%			

2014 (Zhu et al., 2014)	cancer		-- 1.69				
Larsson et al. 2006 (Larsson et al., 2006)	Gastric cancer	1.63 (12 cc-studies) 1.24 (7 cohort-studies)	1.31 -- 2.01 0.98 -- 1.56	42.4% 53.8%	1.38 (30 g/d;9 cc-stud.) 1.15 (30 g/d;6 coh.-stud.)	1.19 -- 1.60 1.04 -- 1.27	28.6% 0%
Bonequi et al. 2013 (Bonequi et al., 2013)	Gastric cancer	1.64 (odds ratio)	1.08 -- 2.45	64.5%			
Zhu et al. 2013 (Zhu et al., 2013)	Gastric cancer	1.45	1.26 -- 1.65	61.0%			
Wei et al. 2015 (Wei et al., 2015)	Glioma	1.25	1.08 -- 1.45	22.4%			
Luo et al. 2014 (Luo et	Hepatocellular	1.01 (fixed effects	0.79 --	42.9%			

al., 2014b)	carcinoma	model)	1.28				
Alexander and Cushing 2009 (Alexander and Cushing, 2009)	Kidney cancer	1.07	0.94 -- 1.23				
Yang et al. 2012 (Yang et al., 2012)	Lung cancer	1.06	0.90 -- 1.25	79.5%			
Xue et al. 2014 (Xue et al., 2014)	Lung cancer	1.23	1.10 -- 1.37	75.7%			
Fallahzadeh et al. 2014 (Fallahzadeh et al., 2014)	Non-Hodgkin Lymphona	1.17 (odds ratio)	1.06 -- 1.29	45.3%			
Xu et al. 2014 (Xu et	Oral cavity - oropharynx	1.91	1.19 --	85.9%			

al., 2014)	cancer		3.06				
Kolahdooz et al. 2010 (Kolahdooz et al., 2010)	Ovarian cancer	1.20	1.07 -- 1.34				
Wallin et al. 2011 (Wallin et al. 2011)	Ovarian cancer				1.05 (per 100 g/week)	0.98 -- 1.14	0%
Larsson and Wolk, 2012 (Larsson and Wolk, 2012)	Pancreatic cancer				1.19 (per 50 g/d)	1.04 -- 1.36	0%
Alexander et al. 2010 (Alexander et al., 2010b)	Prostate cancer	1.05	0.99 -- 1.12		1.02 (per 30 g)	1.00 -- 1.04	
Lee et al. 2008 (Lee et al., 2008)	Renal cell cancer				1.21 (≥27 g/d ⇔ 1 serv/d) 1.01 (2	0.97 -- 1.51 0.97	

					servings/week)	-- 1.51	

Figure. Association between different foods and risk for diabetes (A), cardiovascular diseases (B), colorectal cancer (C), and all-cause mortality (D) based on available meta-analyses (up to July 2015). → = increases risk = reduces risk ----- = no or small effect or no meta-analyses available