EDITORIAL

Can eating red meat increase the risk of developing Type 2 diabetes?

An Pan[1] Frank B Hu*[2,3,4]

"For the general public, limiting red meat intake, particularly processed red meat, and replacing red meat with healthier dietary choices ... is beneficial for the long-term prevention of diabetes."

The global prevalence of diabetes has doubled in the last 30 years and is predicted to continue to rise at an alarming rate, particularly in developing countries. Recent data suggest that more than 366 million people were living with diabetes in 2011 and the number is projected to grow to 552 million in 2030 [101]. The associated health and financial burdens are enormous [101]. Diet has been widely acknowledged as playing an essential role in the development of diabetes and healthy dietary choices have been recommended to decrease diabetes risk [1]. In many of the widely studied healthy diet indexes that are beneficial for diabetes prevention and management (e.g., the prudent diet pattern, Alternative Healthy Eating Index and the Mediterranean diet), low consumption of red meat is a major component.

Global meat production and consumption have increased rapidly in recent decades, particularly in developing countries [102]. A growing body of evidence suggests that high red meat consumption is related to an elevated risk of Type 2 diabetes. An early report from the Seventh Day Adventists Study found a positive association between total meat intake and risk of Type 2 diabetes [2]; however, it was argued that the study sample had a large proportion of vegetarians and may not represent the general population. Subsequently, a series of studies in the USA and Europe have shown that red meat consumption is clearly a modifiable risk factor for Type 2 diabetes. A very recent meta-analysis summarized data from nine prospective cohort studies and reported that the relative risk (95% CI) for Type 2 diabetes was 1.19 (1.04–1.37) for 100 g/day of unprocessed red meat and 1.51 (1.25–1.83) for 50 g/day of processed red meat [3]. The meta-analysis included over 28,000 incident diabetes cases from more than 442,000 participants followed for between 4 and 28 years [3]. The positive association was also confirmed by another recent publication from the large prospective case-cohort study nested within the European Prospective

"A growing body of evidence suggests that high red meat consumption is related to an elevated risk of Type 2 diabetes."

[1]Saw Swee Hock School of Public Health & Yong Loo Lin School of Medicine, National University of Singapore & National University Health System, 117597, Singapore
[2]Department of Nutrition, Harvard School of Public Health, Boston, MA 02115, USA
[3]Department of Epidemiology, Harvard School of Public Health, Boston, MA 02115, USA
[4]Channing Division of Network Medicine, Department of Medicine, Brigham & Women's Hospital & Harvard Medical School, Boston, MA 02115, USA
*Author for correspondence: Tel.: +1 617 432 0113; Fax: +1 617 432 2435; frank.hu@channing.harvard.edu

Future Medicine part of fsg

Investigation into Cancer and Nutrition study [4]. Therefore, these prospective studies provide consistent and strong evidence that high red meat consumption, particularly processed red meat, is related to an elevated risk of Type 2 diabetes.

A high consumption of red meat is generally accompanied by some other unhealthy lifestyle attributes, including low consumption of whole grains, fruit and vegetables, high prevalence of smoking, less physical activity and high BMI. Therefore, it is critical to measure and adjust those factors in the analysis, as has been commonly done in previous large prospective studies. However, some people have criticized the residual or unmeasured confounding factors in the epidemiological studies. Ideally, whether red meat consumption causes diabetes should be tested in a randomized clinical trial, where two groups of people are allocated by the investigators to eat or not eat (or to eat different amounts of) red meat without other changes to their diet or lifestyle. Practically, this is not feasible or ethical given that a large sample size and long follow-up duration are needed to test the hypothesis. Therefore, we rely on high-quality prospective cohort studies to provide us with the best evidence. One recent publication deserves special attention [5]. Taking advantage of the repeated measures of diet and lifestyle factors in three Harvard cohorts, the Health Professionals Follow-up Study, the Nurses' Health Study and the Nurses' Health Study II, we examined the changes in red meat consumption and subsequent risk of developing Type 2 diabetes [5]. In this comprehensive analysis, compared with people who kept their red meat intake levels constant, individuals who increased red meat consumption by more than 0.5 servings per day in a 4-year period had an almost 50% higher risk of developing Type 2 diabetes in the next 4-year interval and a 30% increased risk in the next 12–16 years. Participants who decreased their red meat intake had no change in diabetes risk in the next 4-year interval, but had a 14% lower risk in the entire follow-up of 12–16 years. This association was independent of baseline red meat consumption and changes in many other lifestyle factors (e.g., physical activity, smoking and overall dietary quality), but partially correlated with bodyweight.

"...increasing red meat intake can have a quick adverse effect on diabetes risk, while decreasing red meat intake has a prolonged benefit."

There are several important implications from this study. First, increasing red meat intake can have a quick adverse effect on diabetes risk, while decreasing red meat intake has a prolonged benefit. The lack of reduced risk in the short term may be explained by high-risk people being more likely to change their lifestyle habits and reduce their red meat intake. Second, consistent with previous findings, the association is stronger for processed red meat than unprocessed red meat, suggesting that ingredients added during the preparation and processing have additional deleterious effects. Third, this 'change-in-risk' analysis approach is, to some extent, a natural experiment, where participants chose to change their diet without interventions from the investigators. Therefore, the results are more generalizable to the real world compared with studies carried out in a well-controlled laboratory or clinical setting. Certainly, the study is observational in nature and is subject to residual confounding and measurement error. However, the measurement error is more likely to underestimate the association. Therefore, this study provides additional robust evidence that limiting red meat intake is beneficial for the prevention of Type 2 diabetes.

There are multiple, complex causes of the association between diabetes risk and regular high red meat intake. Red meat is a major source of saturated fat, cholesterol, animal protein and heme iron. High intake of saturated fat could adversely affect glucose metabolism and insulin resistance [6], although the epidemiological evidence is not entirely consistent [7]. A high intake of cholesterol [8,9] and animal protein [9,10] was also related to an increased risk of Type 2 diabetes in some studies. Recently, studies have consistently shown that higher heme iron intake and increased body iron stores are significantly associated with a greater risk of Type 2 diabetes [11], and the mechanisms include enhanced oxidative stress and detrimental effects on specific tissues and organs, including pancreatic β-cells, liver, fat and muscle [12]. A recent novel study demonstrated that dietary L-carnitine, found in high concentrations in red meat, promotes atherosclerosis through gut-mediated generation of trimethylamine-*N*-oxide [13]. However, whether high intake of dietary L-carnitine also promotes insulin resistance remains unknown, but it is highly possible because atherosclerosis and insulin resistance share several common mechanisms.

Other constituents in red meat, especially processed meat, may also contribute to insulin

resistance and an increased risk of Type 2 diabetes, and these include certain types of preservatives, additives and chemicals arising from meat production, preparation and cooking. Nitrites and nitrates added during meat processing, as well as a variety of heterocyclic amines and polycyclic aromatic hydrocarbons formed during cooking, can be converted into *N*-nitrosamines [14], which are toxic to pancreatic β-cells and increase the risk of diabetes in animal studies [15]. Blood nitrite concentrations in adults have been demonstrated to be associated with endothelial dysfunction [16] and impaired insulin response [17]. Sodium content is much higher in processed red meat and may partially explain the relationship [18]. Advanced glycoxidation end products [19], particularly when cooked at high temperature, may also be involved in the increased risk of Type 2 diabetes. Other additives, such as pink slime (or lean finely textured beef) [103], have raised wide consumer concerns, but their health impacts are still controversial.

The majority of meat products on the market are made from grain-fed farm-raised livestock. Some studies have shown that omega-3 fatty acids and vitamin A and E precursors are somewhat higher in grass-fed, compared with grain-fed beef [20]. However, these differences may be too small to impact upon human health. Whether the heavy use of pesticides, herbicides, fertilizers and antibiotics for beef production has significant long-term health impacts remains unclear. With the increasing demand for organic foods, more studies are needed to evaluate their potential health effects.

In summary, there is convincing evidence that higher red meat consumption is related to an increased risk of Type 2 diabetes. For the general public, limiting red meat intake, particularly processed red meat, and replacing red meat with healthier dietary choices, such as vegetables, legumes, nuts, whole grains, low-fat dairy products, fish and poultry, is beneficial for the long-term prevention of diabetes.

"Other constituents in red meat, especially processed meat, may also contribute to insulin resistance and an increased risk of Type 2 diabetes..."

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1 Salas-Salvado J, Martinez-Gonzalez MA, Bullo M, Ros E. The role of diet in the prevention of Type 2 diabetes. *Nutr. Metab. Cardiovasc. Dis.* 21(Suppl. 2), B32–B48 (2011).

2 Snowdon DA, Phillips RL. Does a vegetarian diet reduce the occurrence of diabetes? *Am. J. Public Health* 75, 507–512 (1985).

3 Pan A, Sun Q, Bernstein AM *et al.* Red meat consumption and risk of Type 2 diabetes: 3 cohorts of US adults and an updated meta-analysis. *Am. J. Clin. Nutr.* 94, 1088–1096 (2011).

4 InterAct Consortium. Association between dietary meat consumption and incident Type 2 diabetes: the EPIC-InterAct study. *Diabetologia* 56, 47–59 (2013).

5 Pan A, Sun Q, Bernstein AM, Manson JE, Willett WC, Hu FB. Changes in red meat consumption and subsequent risk of Type 2 diabetes mellitus: three cohorts of us men and women. *JAMA Intern. Med.* 173(14), 1328–1335 (2013).

6 Manco M, Calvani M, Mingrone G. Effects of dietary fatty acids on insulin sensitivity and secretion. *Diabetes Obes. Metab.* 6, 402–413 (2004).

7 Hu FB, van Dam RM, Liu S. Diet and risk of Type II diabetes: the role of types of fat and carbohydrate. *Diabetologia* 44, 805–817 (2001).

8 Salmeron J, Hu FB, Manson JE *et al.* Dietary fat intake and risk of Type 2 diabetes in women. *Am. J. Clin. Nutr.* 73, 1019–1026 (2001).

9 Song Y, Manson JE, Buring JE, Liu S. A prospective study of red meat consumption and Type 2 diabetes in middle-aged and elderly women: the women's health study. *Diabetes Care* 27, 2108–2115 (2004).

10 Sluijs I, Beulens JW, van der A DL, Spijkerman AM, Grobbee DE, van der Schouw YT. Dietary intake of total, animal, and vegetable protein and risk of Type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition (EPIC)-NL study. *Diabetes Care* 33, 43–48 (2010).

11 Bao W, Rong Y, Rong S, Liu L. Dietary iron intake, body iron stores, and the risk of Type 2 diabetes: a systematic review and meta-analysis. *BMC Med.* 10, 119 (2012).

12 Rajpathak SN, Crandall JP, Wylie-Rosett J, Kabat GC, Rohan TE, Hu FB. The role of iron in Type 2 diabetes in humans. *Biochim. Biophys. Acta* 1790, 671–681 (2009).

13 Koeth RA, Wang Z, Levison BS *et al.* Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat. Med.* 19, 576–585 (2013).

14 Lijinsky W. *N*-nitroso compounds in the diet. *Mutat. Res.* 443, 129–138 (1999).

15 Tong M, Neusner A, Longato L, Lawton M, Wands JR, de la Monte SM. Nitrosamine exposure causes insulin resistance diseases: relevance to Type 2 diabetes mellitus, non-alcoholic steatohepatitis, and Alzheimer's disease. *J. Alzheimers Dis.* 17, 827–844 (2009).

16 Kleinbongard P, Dejam A, Lauer T *et al.* Plasma nitrite concentrations reflect the degree of endothelial dysfunction in humans. *Free Radic. Biol. Med.* 40, 295–302 (2006).

17 Pereira EC, Ferderbar S, Bertolami MC *et al.* Biomarkers of oxidative stress and endothelial dysfunction in glucose intolerance and diabetes mellitus. *Clin. Biochem.* 41, 1454–1460 (2008).

18 Mannisto S, Kontto J, Kataja-Tuomola M, Albanes D, Virtamo J. High processed meat consumption is a risk factor of Type 2 diabetes in the α-Tocopherol, β-carotene Cancer Prevention study. *Br. J. Nutr.* 103, 1817–1822 (2010).

19 Goldberg T, Cai W, Peppa M *et al.* Advanced glycoxidation end products in commonly consumed foods. *J. Am. Diet. Assoc.* 104, 1287–1291 (2004).

20 Daley CA, Abbott A, Doyle PS, Nader GA, Larson S. A review of fatty acid profiles and antioxidant content in grass-fed and grain-fed beef. *Nutr. J.* 9, 10 (2010).

■ Websites

101 International Diabetes Federation. IDF Diabetes Atlas (5th Edition). www.idf.org/diabetesatlas/5e/the-global-burden (Accessed 8 July 2013)

102 World Cancer Research Fund International. Meat consumption patterns – highest in industrialised countries. www.wcrf.org/cancer_statistics/cancer_facts/meat_consumption_patterns.php

103 Red meat and pink slime. http://en.wikipedia.org/wiki/Pink_slime (Accessed 8 July 2013)