RESEARCH REPORT
HUMAN NUTRITION

Title: Effects of red meat on type 2 diabetes risk factors and markers of chronic inflammation: A systematic review and meta-analysis of randomized controlled trials - **NPB #18-012**

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Industry Summary: Our objective was to summarize the scientific literature pertaining to the effects of red meat intake on diabetes risk factors, including blood markers of glucose, insulin, and chronic inflammation. We conducted a comprehensive literature search of biomedical research databases to collect relevant studies. Eligible studies were those that recruited human participants and randomized them to consume either high or low amounts of red meat and then measured how this dietary manipulation influenced changes in diabetes risk factors over time. Research participants were individuals who were at risk for heart disease or diabetes, but not yet diagnosed with either condition. We assessed 1,172 articles to find 24 articles that met our inclusion criteria. We extracted data from each study on how red meat influenced changes in diabetes risk factors over the course of the study duration. By summarizing the results across all studies, we saw that higher red meat intake did not influence improvements in glycemic control and inflammation that occurred during the studies. Our findings suggest that red meat does not directly influence diabetes risk factors and can be consumed in the context of a healthy eating pattern that helps promote and maintain a healthy body weight.

Key Findings:

- Eating red meat did not affect blood markers of heart disease or type 2 diabetes in the short-term
- There was no benefit of replacing red meat with other animal- or plant-based protein sources to improve blood glucose and inflammation markers
- Most research studies ask participants to consume unprocessed red meat, so more research is needed to understand how processed red meat intake affects blood markers of heart disease and type 2 diabetes
- Red meat should be eaten in a diet that is high in fruits, vegetables, whole grains, and without exceeding calorie needs to decrease risk for type 2 diabetes

Keywords: animal-based protein sources, pork, beef, plant-based protein sources, type 2 diabetes risk factors, adults at risk for cardiometabolic disease

Scientific Abstract: Our objective was to conduct a systematic review and meta-analysis to assess effects of total red meat (TRM) intake on glycemic control and inflammation biomarkers using randomized controlled trials (RCTs) of individuals free from cardiometabolic disease. We hypothesized that higher TRM would negatively influence glycemic control and inflammation based

on positive correlations between TRM and diabetes. We found 24 eligible studies (median duration 8 weeks) from 1,172 articles in PubMed, Cochrane, and CINAHL up to August 2019 that included 1) diet periods differing in TRM, 2) age ≥19 years, 3) males or non-pregnant/lactating females, 4) no diagnosed cardiometabolic disease, and 5) fasting glucose, insulin, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), Hemoglobin A1c (HbA1c), or cytokines including C-reactive protein (CRP). We used 1) repeated measures ANOVA to assess pre to post diet period changes, 2) random-effects meta-analyses to compare pre to post changes between diet periods with ≥ vs <0.5 servings (35g)/day of TRM, and 3) meta-regressions for dose-response relationships. We also grouped diet periods to explore heterogeneity sources including risk of bias using National Heart, Lung, and Blood Institute's Quality Assessment of Controlled Interventions Studies. Glucose, insulin, and HOMA-IR decreased while HbA1c and CRP did not change during TRM or alternative diet periods. There was no difference in change values between diet periods with ≥ vs <0.5 servings/day of TRM [weighted mean difference and 95% CI: 0.040 (-0.049, 0.129) mmol/L glucose, -0.710 (-6.582, 5.162) pmol/L insulin, 0.110 (-0.072, 0.293) HOMA-IR, and 2.424 (-1.460, 6.309) nmol/L CRP] and no dose response relationships (P>0.2). Risk of bias (85% of studies were fair to good) did not influence results. Total red meat consumption, for up to 16 weeks, does not affect biomarkers of glycemic control or inflammation for adults free of, but at risk for, cardiometabolic disease.

Introduction:
Eating high amounts of red and processed meat is often associated with an increased risk of type 2 diabetes in large observational studies. This type of research asks questions about peoples' eating habits at one point in time and then follows up with them years or decades later to see if they were diagnosed with diabetes. In studies like this, it is difficult to determine if high red meat intake is causing diabetes or if there are other factors at play. Eating habits tend to track closely with other health-related lifestyle behaviors. Those people who eat high amounts of red meat also tend to smoke more, exercise less, and have a poorer diet than those who consume less red meat. These unhealthy behaviors are also risk factors for diabetes. Evidence from randomized controlled trials can be used to help us understand if the relationships between higher red meat intake and diabetes risk are causal or if red meat intake is simply a marker of an overall unhealthy lifestyle. Randomized controlled trials assign people to consume either high or low amounts of red meat and then assess their disease risk factors (such as blood glucose) a few weeks or month later. Random assignment of red meat intake helps us eliminate concerns about a person's overall lifestyle influencing the results of our study and always use to infer a cause and effect relationship between red meat intake and disease risk factors. Therefore, our objective was to summarize results of randomized controlled trials in which research participants consumed high vs low amounts of red meat and had their blood glucose, insulin, and markers of chronic inflammation measured at the end of the study. There is currently no comprehensive assessment of results from randomized controlled trials about the effects of consuming total red meat and red meat subtypes, including pork, on type 2 diabetes risk factors or chronic inflammation. This assessment is an important scientific need to inform future Dietary Guidelines Advisory Committees about the effects of red meat intake on these outcomes.

Objectives: To conduct a systematic review and meta-analysis of literature assessing the effects of consuming three 3 oz. servings/week (or ≥0.5 servings/day) of 1) total red meat and 2) red meat subtypes, including pork, on clinically relevant risk factors of type 2 diabetes (i.e. fasting plasma glucose, insulin, and insulin resistance) and markers of chronic inflammation (i.e. plasma cytokines such as interleukin-6 and C-reactive protein).

Materials & Methods: This meta-analysis was registered at PROSPERO, the International Prospective Registrar of Systematic Reviews and followed procedures of Preferred Reporting Items for Systematic Review and Meta-analysis guidelines and the Nutrition Evidence Systematic Review methodology used for evidence synthesis in the 2015 Dietary Guidelines for Americans process. We found 24 eligible studies (median duration 8 weeks) from 1,172 articles in PubMed, Cochrane, and CINAHL up to August 2019. Eligible studies were randomized controlled trials which included at least two diet periods differing in total red meat intake. Research participants had to be males or non-

pregnant/lactating females aged at least 19 years old and had no diagnosed cardiometabolic disease. The outcomes of interest for each study had to include one of the follow: fasting glucose, insulin, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), Hemoglobin A1c (HbA1c), or pro-inflammatory cytokines including C-reactive protein (CRP). "Red meat" and "processed meat" definitions used for this meta-analysis were borrowed from the 2015 Dietary Guidelines for Americans as follows: "all forms of beef, pork, lamb, veal, goat, and non-bird games (e.g. venison, bison, elk)" and "preserved by smoking, curing, salting, and/or the addition of chemical preservatives," respectively. We used repeated measures ANOVA to assess pre to post diet period changes, random-effects meta-analyses to compare pre to post changes between diet periods with ≥ vs <0.5 servings (35g)/day of total red meat, and meta-regressions for dose-response relationships. We also grouped studies to explore sources of variation including population characteristics, prescribed eating pattern, red meat subtype, and study quality.

Results: Of 1172 articles screened, a total of 1094 studies were initially excluded for not meeting inclusion criteria. Of those 1094 studies excluded, 211 were duplicates and 8 were unavailable. Of the 78 full-text articles assessed for eligibility, 19 studies were eligible to be included in the random-effects meta-analyses and an additional 5 studies (for a total of 24) were eligible to be included in the meta-regressions. There were 20 unique RCTs among the 24 identified articles, therefore some RCTs have more than one reference.

Total red meat consumption of all 20 studies ranged from 71 to 238 (median=131) g/day during the red meat diet period. Intervention lengths of all 20 studies ranged from 2 to 24 (median=6) weeks. Seven studies were rated as "good", 10 as "fair", and 3 as "poor". Randomization, allocation, and blinding methods were most often not reported. The "poor" studies generally did not report power analyses for their described primary outcome of interest or were not a priori registered in a clinical trial database.

Glucose, insulin, and HOMA-IR decreased from pre to post in both red meat and alternative diet periods, while HbA1c, CRP, IL-6, and TNF-α did not change. There was no difference in change values between diet periods with ≥ vs <0.5 servings/day of total red meat [weighted mean difference and 95% CI: 0.040 (-0.049, 0.129) mmol/L glucose, -0.710 (-6.582, 5.162) pmol/L insulin, 0.110 (-0.072, 0.293) HOMA-IR, and 2.424 (-1.460, 6.309) nmol/L CRP]. Subgroup analyses did not support a differential effect of consuming ≥ vs <0.5 servings/day of total red meat on glucose, insulin, HOMA-IR, or CRP within groups of studies assessing intentional weight loss, weight maintenance, alternative diet periods which used animal source foods such as fish, poultry, eggs, and/or dairy to replace red meat intake, alternative diet periods which used plant source foods such as soy or carbohydrates to replace red meat intake, basal heart-healthy eating patterns, lean red meat only, unprocessed red meat only, lean unprocessed red meat only, participants that were overweight or obese, or articles graded "good" and "fair" quality. Among comparisons with higher protein eating patterns achieved via replacing carbohydrates with red meat, consuming ≥0.5 servings/day of total red meat decreased insulin concentrations more than consuming <0.5 servings/day of total red meat. Among comparisons with similar macronutrient distributions, consuming ≥0.5 servings/day of total red meat resulted in lesser decreases of HOMA-IR compared to consuming <0.5 servings/day of total red meat.

There was no evidence of a dose-response relationship between total red meat intake and pre to post changes in fasting blood glucose, insulin, HOMA-IR, or CRP. Duration of intervention, group-level mean baseline age, group-level mean baseline body mass index (except glucose), and group-level mean baseline value of outcome variable of interest were not significant covariates for any outcome variable other than glucose and therefore were removed for the presented results.

Discussion: To the best of our knowledge, this is the first meta-analysis of randomized controlled trials assessing effects of total red meat intake on blood markers of type 2 diabetes in adults who are at risk of developing diabetes at a later life stage. We hypothesized that total red meat intake would have a negative impact on these outcomes based on associations between higher red meat intake and diabetes risk from observational research. However, our results showed no effect of total red meat intake on blood markers of diabetes. It is important to note that research participants were asked to consume lean and unprocessed red meat in most of the included studies so evidence regarding effects of eating processed or fatty red meat on these outcomes is lacking. These results support a previous

study from our group which showed no affect of total red meat on blood cholesterol or blood pressures. Overall, red meat intake does not negatively affect blood markers of heart disease and diabetes in the short term. For those who choose to eat red meat, red meat (as with all other protein-rich food sources) should be consumed in the context of a healthy eating pattern high in fruits, vegetables, and whole grains to reduce disease risk.