

**Manuscript Title:** Animal and plant protein usual intakes are not adversely associated with all-cause, cardiovascular disease–, or cancer-related mortality risk: an NHANES III analysis

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**Study Headline:** Animal and plant protein foods both have valuable nutritional roles in a healthy eating pattern. Analysis of U.S. dietary intake data shows eating animal-sourced protein foods is not associated with increased all-cause or cardiovascular-related mortality and may even protect against cancer mortality.

**Background:** A large body of research demonstrates that optimal protein intake can improve health and help prevent nutrient deficiencies, which are of increasing concern across vulnerable populations, including children, adolescents, women of child-bearing age, and aging adults. Many of the nutrients found in protein foods, particularly animal-source protein foods, support childhood growth and development; help maintain strength, energy, and vitality for adults; and promote healthy and independent aging.

The Institute of Medicine established Acceptable Macronutrient Distribution Ranges (AMDR) for macronutrients that are associated with reduced risk of chronic disease. The AMDR for protein is 10-35% of total calories for adults, with an intake of 10% of calories from protein as the recommended minimal intake. Research has continued to demonstrate that protein intakes higher than the minimal intake level of the AMDR are beneficial, yet consumers are often hesitant to increase their protein intake with fear of increasing their risk of diseases, such as cardiovascular disease (CVD) or cancer.

To address these concerns and provide a comprehensive analysis of protein intake and mortality, researchers sought to assess United States (U.S.), nationally representative dietary intake data with rigorous methodology and a large study population to examine associations between usual (average) intakes of total, animal, and plant protein and insulin-like growth factor-1 (IGF-1) concentrations with all-cause, cancer and cardiovascular disease related mortality risk in adults.

**Objective:** To analyze data from NHANES III and examine associations between usual intake of total protein, animal-source protein, and plant-source protein and insulin-like growth factor-1 (IGF-1) concentrations with all causes, cancer and CVD mortality risk in adults age 19+ years old.

**Study Design:**

Adult (19 years and older), self-reported dietary intake data (N=15,937; 7,483 men and 8,454 women) from the NHANES III survey (1988-1994) was linked with mortality data (N=3,843 events) through 2006. Usual dietary intakes – or the long-term, average daily intake of a nutrient or food – were estimated for calories, total protein, animal protein, plant protein, total fats, and carbohydrates using both the National Cancer Institute (NCI) method and the multivariate Markov Chain Monte Carlo (MCMC) method, to increase reliability and confidence in the results. The statistical methods accounted for fluctuations in daily protein intake and a deeper assessment that reduced measurement error in protein intake.

Insulin-like Growth Factor 1 (IGF-1), a hormone believed to mediate the potential cancer-promoting effects of protein intake, was measured in a subpopulation of NHANES III participants (n = 5,753) with available mortality data.

Researchers evaluated how usual protein intake and circulating IGF1 levels related to all-cause, cardiovascular, and cancer mortality. Participants were grouped into equal tertiles (3 equal groups) based on protein intake and IGF1 levels, and hazard ratios for mortality were estimated across intake groups. Associations were also examined by different age groups (19+, 19-50, 50-65, 51-70, 66+, and 71+) and gender to identify potential differences between demographic groups.

**Results:**

- Findings from this comprehensive analysis of dietary intake data of U.S. adults 19 years and older shows that eating animal-source protein foods is not associated with increased all-cause (overall) or cardiovascular-related mortality and, importantly, may even protect against cancer mortality.

**Mean usual intakes of macronutrients and IGF-1 in adults 19 years or older in NHANES III**

- Mean usual intakes of macronutrients, including protein, broken out by type, and IGF-1 concentrations are presented in Table 1.
- On average, the study population consumed 2,186 kcal with 49% of calories from carbohydrates, 35% of calories from fat, and 15% of calories from protein, specifically with 10% of calories from animal protein.
  - On average, based on this analysis, US adults are not overconsuming protein but are aligned with the range established in the AMDR for protein.
- At the 33.3<sup>rd</sup>, 50<sup>th</sup> and 66.7<sup>th</sup> percentile of protein intake, 12.6%, 13.2%, and 17.7% of total calories were consumed from protein, respectively; well within the range established in the AMDR for protein intake.

Table 1. Mean usual intakes of protein type by percentiles and IGF-I in US adults ≥19 years old<sup>1</sup>

Variable	N	All		Percentiles of Protein Intake						
		Mean	SE	33.3	SE	50	SE	66.7	SE	P
Total Protein (g)	15,937	82	1	69	1	72	2	97	1	<0.001
Animal Protein (g)	15,937	57	1	46	1	50	2	68	1	<0.001
Plant Protein (g)	15,937	25	1	21	1	22.6	1	29	1	<0.001
Carbohydrates (g)	15,937	266	1	223	1	239	6	307	1	<0.001
Total Fat (g)	15,937	84	1	68	1	74.6	2	99	1	<0.001
Energy (kcal)	15,937	2186	4	1782	2	1915	63	2580	40	<0.001
IGF-1 (ng/ml)	5,753	270	3	219	3	259	3	305	4	<0.001

<sup>1</sup>Sexes combined data from NHANES III; SE - standard error. Usual intakes were determined using the Markov Chain Monte Carlo method.

**Usual animal protein vs plant protein intake and all-cause, CVD and cancer mortality risk**

- No significant associations between usual protein intakes by tertile and all-cause, CVD-related, or cancer mortality risk were reported.

***Protein intake and all-cause mortality risk***

- There were no associations between animal protein (HR=0.99; 95% confidence interval (CI): 0.98-1.01; P=0.29) or plant protein (HR=1.02; 95% CI: 0.95-1.10; P=0.55) intake for all-cause mortality.

***Protein intake and CVD mortality risk***

- Similarly, there were no associations between animal protein (HR=1.02; 95% CI: 0.99-1.04; P=0.14) or plant protein (HR=1.01; 95% CI: 0.91-1.13; P=0.81) intake for CVD mortality.

***Protein intake and cancer mortality risk***

- There was a small inverse (protective) association between animal protein (HR=0.95; 95% CI: 0.91-1.00; P=0.04) intake and cancer mortality, which was not seen with plant protein (HR=1.08; 95% CI: 0.93-1.24; P=0.30) intake.
- The authors report that there are no associations for intakes of total protein, animal protein, and plant protein with all-cause, CVD, and cancer mortality risk when assessed on a 5 or 10 g increment for adults 19 years or older.
- A statistically significant inverse association was found with animal protein intake and cancer mortality for both the 5 g (HR=0.77; 95% CI: 0.61-0.97; p=0.03) and 10 g increment basis (HR=0.60; 95% CI: 0.38-0.95; p=0.03).

- When animal protein and plant protein intakes were both included in hazard models, the results remained the same, suggesting that plant protein intake has a minimal impact on cancer mortality, while animal protein intake may have a protective impact.

### **Impact of age on hazard ratio risk analysis**

- The study population was separated by age into the following groups: 19-65 yr (N=13,296; Mortality N=2,905) and 66 yr and older (N=3,903; mortality N=1,375). No significant associations between usual total protein intakes by age and all-cause, CVD-related, or cancer mortality risk were observed. Similarly, no significant associations between animal or plant protein intake by age with all-cause mortality risk, CVD-related risk, or cancer mortality risk were observed.
- Additionally, a modest but significant protective relationship between usual animal protein intake and cancer mortality in the 50-65 year age group was observed (HR=0.87; 95% CI: 0.76-0.98; P=0.034) but not seen with plant protein (HR=1.05; 95% CI: 0.85-1.31; P=0.64).

### **IGF-1 concentrations and all-cause, CVD and cancer mortality risk**

- Researchers observed no relationship between dietary protein and IGF-1.
- No associations between concentrations of IGF-1 and all-cause mortality (HR=1.00; 95% CI: 0.99-1.00; P=0.81), CVD mortality (HR=0.99; 95% CI: 0.99-1.00; P=0.53) or cancer mortality (HR=1.00; 95% CI: 0.99-1.00; P=0.76).
- Additionally, no association with cancer mortality and IGF-1 concentration (HR=1.00; 95% CI: 0.99-1.00; P=0.87) was observed in the 50-65yr age group.

### **Study Implications:**

- Animal and plant protein foods both play important nutritional roles in a healthy eating pattern.
- The current analysis does not support the hypothesis that animal source-specific protein intake is associated with greater mortality risk, and animal protein intake may have a protective impact on cancer-related deaths.
- The analysis did not show any beneficial mortality-related outcomes with increased plant protein consumption.
- With nutritional guidance advocating for more plant-based foods in proposed healthy dietary patterns, it is important to note that the USDA previously reported that 70% of calories in the average American diet is already from plant-based foods.<sup>1</sup>

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<sup>1</sup> <https://www.ers.usda.gov/data-products/charts-of-note/chart-detail?chartId=81864>