Scientific Research Publishing

Health, 2023, 15, 1096-1115
https://www.scirp.org/journal/health
ISSN Online: 1949-5005
ISSN Print: 1949-4998

Association between Dietary Collagen Consumption and Telomere Length: National Health and Nutrition Examination Survey

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How to cite this paper: Jin, H., Maddela, R.L. and Sinnott, R.A. (2023) Association between Dietary Collagen Consumption and Telomere Length: National Health and Nutrition Examination Survey. *Health*, **15**, 1096-1115.
https://doi.org/10.4236/health.2023.1510075

Received: September 22, 2023
Accepted: October 21, 2023
Published: October 24, 2023

Abstract

Background: Bioactive peptides derived from hydrolyzed collagen have broad physiological functions and beneficial effects on human health, ranging from reducing skin aging to modifying lipid metabolism. Telomere length shortening is an established biomarker of cellular aging. It is not known if collagen consumption is associated with telomere length protection. Our purpose was to investigate the relationship between dietary collagen consumption and telomere length in a nationally representative US adult population. **Methods:** We analyzed the data of 6173 adults aged 20 - 84 from the National Health and Nutrition Examination Survey (NHANES) 1999-2002. Multivariable linear regression and a generalized additive model with smoothing plot were used to assess the association between the total collagen consumption and log-transformed leukocyte telomere length (LTL). **Results:** Compared with the lowest quartile of total collagen (Q1), we found that the second quartile of collagen (Q2) consumption (1.36 - 3.40 g/1000kcal) was positively associated with telomere length (β: 0.017; 95% CI: 0.006, 0.028; P = 0.022) in the females while no association in the males (β: −0.003; 95% CI: −0.019, 0.012; P = 0.678) and overall population (β: 0.008; 95% CI: −0.002, 0.018; P = 0.141). The association in the females is nonlinear with an inflection point of 2.5 g/1000kcal (P for non-linearity: <0.001). **Conclusion:** In conclusion, moderate dietary collagen has a positive and nonlinear association with telomere length in US females, while no significant associations were found in the males and the overall population.

Keywords

Telomere Length, Dietary Collagen, NHANES, Linear Regression

1. Introduction

Telomeres are structures composed of repetitive nucleotide sequences and associated proteins that are located at the ends of the chromosomes. Telomeres play vital roles in protecting the chromosome from nucleolytic degradation, aberrant recombination, and inter-chromosomal fusion [1]. Telomere lengths differ among species and cell types, but are maintained within a defined length distribution in all healthy cells [2]. Reduced telomere length is a biomarker of cellular senescence, genomic instability, and cellular aging, thus is associated with biological aging and aging-related disorders [3]. Telomere length is regulated by both endogenous (genetics, race, and hormones) and exogenous factors (diet, smoking, alcohol consumption, physical activity, etc.) [4]. Telomeres are highly sensitive to oxidative stress [5] [6] [7] and chronic inflammation [8] [9]. Intake of foods with antioxidant and anti-inflammatory properties is associated with longer telomere length [9] [10]. For example, dietary components such as vitamins C and E, polyphenols, curcumin, and omega-3 fatty acids, have been associated with longer telomeres [11] [12].

Collagen and collagen-derived products are widely used in the food, pharmaceutical, and cosmetic industries for their nutritional and functional properties. Collagen is a well-established source of functional peptides that have broad biological activities [13] [14] [15] [16] [17]. Collagen peptides have various beneficial physiological effects, ranging from reducing skin aging [18] [19] [20], promoting wound healing [21], strengthening tendons and ligaments [22], increasing muscle strength [4] [23], and improving bone health [24], to modifying lipid metabolism [25], reducing obesity [26] [27], maintaining blood pressure [28], and preventing atherosclerosis [29]. These beneficial effects have been linked to collagen peptides' antioxidants and anti-inflammatory activity [15] [16] [19] [20] [30], as well as the promotion of the synthesis of new extracellular matrix proteins by collagen peptides [31] [32]. Collagen peptides can increase antioxidant enzyme activity, scavenge free radicals/reactive oxygen species and alleviate oxidative stress [15] [20]. Collagen peptides inhibit the expression of proinflammatory factors (tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, IL-8, inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2)) in an inflammatory disease model [33]. Intramuscular injection of polymerised type I collagen showed an immunomodulatory activity by reducing the excessive inflammatory mediators in COVID-19 cytokine release syndrome [34]. Further, collagen peptides can also regulate the activity of other enzymes such as inhibiting angiotensin-converting enzyme [35], which is a central component of the rennin-angiotensin system that controls blood pressure by regulating the volume of fluids in the body.

Given collagen peptides' prominent antioxidants/anti-inflammatory activities and telomere's sensitivity to oxidative stress and inflammation, here we asked if collagen consumption might affect the telomere length. We therefore assessed the association between dietary collagen and LTL using the large population

based NHANES data. We found that moderate dietary collagen consumption has a positive and nonlinear association with telomere length in US females. To the best of our knowledge, this is the first study investigating the effect of dietary collagen on telomere length.

2. Materials and Methods

2.1. Study Population

We used the data from NHANES 1999-2000 and 2001-2002, because only these 2-year survey cycles include information on LTL from participants aged twenty and beyond. There are in total 7827 individuals having LTL data. The individuals without collagen consumption data (meat and/or seafood consumption) were excluded (n = 323). Other individuals were excluded if: 1) they were ≥85 years old (n = 199); 2) their energy intakes were implausible (male: <600 kcal/day or >8000 kcal/day; female: <600 kcal/day or >6000 kcal/day) (n = 129); 3) with missing values for any of the covariates (n = 1001). Finally, a total of 6173 participants were included in this cross-sectional study.

2.2. Measures

2.2.1. Telomere Length

According to the NHANES, the telomere length assay was performed using the quantitative polymerase chain reaction (PCR) method to measure LTL relative to standard reference DNA (T/S ratio) in the laboratory of Dr. Elizabeth Blackburn at the University of California, San Francisco. The mean T/S ratio values were then converted to base pairs (bp) using the formula: 3274 + 2413* (T/S) [36]. Detailed information can be found in the laboratory section on NHANES website.

2.2.2. Collagen Consumption

NHANES dietary intake was assessed using a single 24-hour dietary recall method, see details at
https://www.cdc.gov/nchs/data/nhanes/nhanes_03_04/DIETARY_MEC.pdf.
Four main food groups source of dietary collagen "Beef, pork, veal, lamb, and game", "Chicken, turkey, and other poultry", "Seafood", and "Frankfurters, sausages, and luncheon meats", were identified using the US Department of Agriculture (USDA) MyPyramid Equivalents Database, version 1.0. Consumption of dietary collagen from each food group was quantified using the method reported by Paul *et al.* [37], in which the average dietary collagen protein (% dry weight) is 5.15% in red meat food group (Beef, pork, veal, lamb and game), 1.4% in poultry group (Chicken, turkey and other poultry), 5.5% in seafood, and 55.43% in the processed meat (Frankfurters, sausages and luncheon meats), respectively. Collagen consumption was expressed as grams consumed per 1000 kcal.

2.2.3. Study Covariates

It has been reported that telomere length is associated with various sociodemo-

graphic and lifestyle factors [4] [38]-[45]. To control the cofounders in our analysis of association between collagen consumption and LTL, we included the following covariates to construct the adjustment model.

Sociodemographic covariates: These included age, gender, race, education, and family income-to-poverty ratio (PIR). Race was grouped as Non-Hispanic White, Non-Hispanic Black, Mexican American, Other Hispanic, and other Race. Self-reported education level was categorized as less than high school, high school, more than high school. PIR is an index of poverty status and was graded into three categories based on the analysis guidelines: ≤1.3, 1.3 - 3.5, and ≥3.5 [46].

Lifestyle covariates: These included smoking status, alcohol intake, physical activity, BMI, and healthy eating index 2015 total score. Smoking was grouped into never, current, and former; alcohol use was defined as never, former, moderate drinkers, and heavy drinkers; physical activity was grouped into sedentary, light, moderate, and heavy. BMI was defined as underweight (<18.5 kg/m^2), normal weight (18.5 - 24.9 kg/m^2), overweight (25.0 - 29.9 kg/m^2), and obese (≥30 kg/m^2). Healthy eating index 2015 (HEI2015) score, the most recent version of the HEI, is a dietary pattern developed by the USDA to measure compliance with national dietary guidelines [47]. The HEI 2015 is scored out of one hundred points and comprises 13 components: total vegetables, greens and beans, total fruits, whole fruit, whole grains, dairy, total protein foods, seafood and plant proteins, fatty acids, sodium, refined grains, saturated fats, added sugars. Different maximum scores and weights were assigned to each component, and the overall thirteen component scores (HEI-2015 scores) were calculated ranging from 0 to 100, with high HEI scores reflecting better diet quality.

CRP: As described by NHANES, the level of serum C-reactive protein (CRP) was measured by the Dade Behring Nephelometer II Analyzer System using latex-enhance nephelometry (Dade Behring Diagnostics Inc., Somerville, NJ). All Protocols followed the standardized guidelines and record accuracy based on CDC reference methods.

2.3. Statistical Analysis

The statistical analysis was performed according to the guidelines of the CDC (https://wwwn.cdc.gov/nchs/nhanes/tutorials/default.aspx). We accounted for masked variance and used the proposed weighting methodology [46]. The outcome variable was the number of LTL, which was natural log-transformed prior to analysis because the data were skewed. The exposure variable was total collagen consumption, expressed as total grams of collagen consumed per 1000 kcal. Continuous variables were expressed as weighted means ± SE. Categorical variables were presented as unweighted frequencies or weighted percentages. The total collagen consumption was categorized based on quartiles (Q1 - Q4) with quartile 1 (Q1) being the referent category. The one-way ANOVA tests (continuous variables) and chi-square tests (categorical variables) were used to compare the population characteristics according to quartiles of collagen consump-

tion. We used multivariable linear regression models to evaluate the association between LTL and total collagen adjusted for multiple potential confounders in overall population as well as in the females and males separately. The collagen was analyzed as quartiles with LTL as the outcome. Four models were applied in the present study. Model 1 was a crude model without adjustment for any potential confounders. Model 2 was adjusted for age, race, education level and PIR. Model 3 was further adjusted for smoking status, alcohol use, physical activity, BMI and HEI2015 score. Model 4 was further adjusted for CRP. In addition, we used a generalized additive model (GAM) and smooth curve fittings to address the nonlinearity of collagen with LTL by male and female, respectively. All GAMs were performed using the R-package mgcv v.1.8-40 [48]. If a non-linear correlation was observed, the piecewise linear regression model was employed to examine the relationship and inflection point between collagen consumption and LTL. Finally, we performed sensitivity analysis to evaluate the robustness of multivariate linear regression results, as well as to test whether the results obtained from the general population also apply to a healthy population. Adults with a prior diagnosis of coronary heart disease, angina, myocardial infarction, stroke, diabetes, congestive heart failure, and cancer were excluded (n = 1354).

All analyses were performed using R (Version 4.0.3). P values less than 0.05 (two-sided) were considered statistically significant.

3. Results

3.1. Baseline Characteristics

Based on 1999-2000 and 2001-2002 NHANES data, among total 6173 participants, 363 (5.9%) reported no meat and/or fish consumption, 3986 (64.6%) reported they consumed "beef, pork, veal, lamb and game", 2482 (40.2%) reported consuming "chicken, turkey, and other poultry", 1165 (18.9%) reported consuming "seafood", 2259 (36.6%) reported consuming "frankfurters, sausages and luncheon meats", respectively (**Figure S1**). Accordingly, average daily collagen consumption (mean ± SE) was 18.1 ± 0.6 g, 8.1 ± 0.3 g/1000kcal per day. Average energy intake was 2239 ± 21 kcal/d. Average telomere length was 5815 ± 35 bp for the entire sample.

The baseline characteristics by quartiles of total collagen are summarized in **Table 1**. Most participants were non-Hispanic White in every quartile (72.85% - 77.66%). Compared to those in the lowest quartile (Q1), males tended to consume more collagen. Participants in the highest quartile were more likely to be non-Hispanic White, having lower education, being current smokers and alcohol users, having heavy physical activity, lower HEI2015 score, higher BMI, and higher total energy intakes. There were marginally significant differences in LTL across collagen quartiles (P = 0.055).

3.2. Association between Total Collagen and Log-Transformed LTL

Table 2 shows the crude and adjusted association between total collagen and

Table 1. Characteristics of the participants (N = 6173).

Characters	Total Collagen Consumption (g/1000kcal)				P value
	Q1 (0 - 1.36) (n = 1583)	Q2 (1.36 - 3.40) (n = 1566)	Q3 (3.40 - 10.45) (n = 1611)	Q4 (10.45 - 153.24) (n = 1413)	
Total Collagen, g/day (mean ± SE)	1.19 ± 0.04	5.14 ± 0.12	14.16 ± 0.33	51.88 ± 1.71	
Age, years	46.11 ± 0.61	45.55 ± 0.54	45.29 ± 0.45	45.3 ± 0.66	0.642
Male, %	39.21	47.74	57.63	54.01	<0.001
Race, %					0.022
Non-Hispanic White	73.41	73.55	72.85	77.66	
Non-Hispanic Black	7.9	9.07	8.88	9.63	
Mexican American	8.15	6.72	8.28	4.08	
Other Hispanic	6.55	6	5.78	5.76	
Other	4	4.66	4.21	2.87	
Education, %					0.03
More than high school	60.75	53.37	53.15	51.6	
High school	21.44	27.84	26.71	28.83	
Less than high school	17.82	18.78	20.14	19.57	
PIR, %					0.533
<1.30	17.03	19.33	20.07	18.56	
1.30 - 3.5	33.56	35.58	35.56	37.15	
≥3.5	49.41	45.09	44.37	44.29	
Smoking status, %					0.035
Never	54.09	50.66	50.21	47.09	
Former	23.23	26.6	26.6	25.34	
Current	22.67	22.74	23.19	27.58	
Alcohol use, %					0.047
Never	15.3	12.73	13.21	9.72	
Former	18.45	15.08	17.05	16.45	
Moderate	58.67	61.91	59.89	64.74	
Heavy	7.58	10.29	9.85	9.1	
Physical activity, %					0.016
Sedentary	22.88	24.79	23.23	22.88	
Light	51.88	49.34	50.02	51.82	
Moderate	21.19	17.77	19.12	16.36	
Heavy	4.05	8.09	7.64	8.94	

Continued

BMI (kg/m²)					0.02
<18.5	2.77	1.17	1.82	1.08	
18.5 - <25	36.6	31.94	29.83	32.06	
25 - <30	32.34	35.63	36.79	34.06	
≥30	28.3	31.26	31.56	32.81	
HEI2015 score					<0.001
Q1	18.79	23.73	22.83	34.59	
Q2	23.13	22.22	25.72	28.95	
Q3	24.88	27.97	25.83	21.36	
Q4	33.2	26.09	25.62	15.1	
CRP					0.59
Q1	25.42	24.96	26.31	24.62	
Q2	27.6	24.12	24.97	25.74	
Q3	22.17	24.93	25.18	25.27	
Q4	24.82	25.99	23.54	24.38	
Energy Intake, kcal	2080.59 ± 35.86	2212.47 ± 42.25	2335.52 ± 41.15	2267.45 ± 34.88	<0.001
Telomere Length, Base Pairs (mean ± SE)	5809 ± 41	5866 ± 41	5789 ± 33	5792 ± 42	0.055

Note: ANOVA was used for continuous variables and Chi-square for categorical variables. PIR, family poverty income ratio; HEI2015 score, healthy eating index 2015 total score; BMI, body mass index; CRP, C-reactive protein.

Table 2. The association between total collagen consumption and log-transformed telomere base pairs by gender.

Models	Quartiles	Female		Male		Overall	
		[β (95% CI)]	P Value	[β (95% CI)]	P Value	[β (95% CI)]	P Value
Model 1							
	Q1	Ref		Ref		Ref	
	Q2	**0.019 (0.007, 0.031)**	**0.004**	−0.007 (−0.022, 0.008)	0.37	0.008 (−0.002, 0.018)	0.161
	Q3	−0.002 (−0.013, 0.009)	0.721	−0.009 (−0.024, 0.006)	0.255	−0.004 (−0.012, 0.004)	0.395
	Q4	0.005 (−0.011, 0.021)	0.556	−0.013 (−0.028, 0.003)	0.132	−0.003 (−0.015, 0.009)	0.678
Model 2							
	Q1	Ref		Ref		Ref	
	Q2	**0.016 (0.004, 0.028)**	**0.017**	−0.004 (−0.019, 0.012)	0.642	0.007 (−0.003, 0.017)	0.172

Continued

	Q3	−0.003 (−0.014, 0.008)	0.603	−0.009 (−0.024, 0.006)	0.271	−0.004 (−0.012, 0.004)	0.329
	Q4	−0.001 (−0.017, 0.015)	0.911	−0.01 (−0.025, 0.006)	0.237	−0.005 (−0.017, 0.007)	0.455
Model 3							
	Q1	Ref		Ref		Ref	
	Q2	**0.017 (0.006, 0.028)**	**0.02**	−0.003 (−0.019, 0.013)	0.733	0.008 (−0.002, 0.018)	0.13
	Q3	−0.003 (−0.013, 0.008)	0.646	−0.007 (−0.022, 0.007)	0.368	−0.003 (−0.011, 0.005)	0.547
	Q4	0.004 (−0.012, 0.021)	0.634	−0.007 (−0.023, 0.009)	0.431	−0.001 (−0.013, 0.011)	0.885
Model 4							
	Q1	Ref		Ref		Ref	
	Q2	**0.017 (0.006, 0.028)**	**0.022**	−0.003 (−0.019, 0.012)	0.678	0.008 (−0.002, 0.018)	0.141
	Q3	−0.002 (−0.013, 0.008)	0.662	−0.007 (−0.022, 0.007)	0.341	−0.003 (−0.011, 0.005)	0.538
	Q4	0.004 (−0.012, 0.021)	0.641	−0.007 (−0.023, 0.009)	0.411	−0.001 (−0.013, 0.011)	0.863

Note: Model 1 was a crude model. Model 2 further adjusted for age, race, education, and family PIR. Model 3 further adjusted for smoking, alcohol use, physical activity, BMI, HEI2015 score. Model 4 additionally adjusted for CRP.

log-transformed LTL (bp) from multivariate linear regression models. The result of the crude model showed a significant positive association between total collagen and LTL, with β of 0.019 (95% CI: 0.007, 0.031; P = 0.004) in the females, but not in the males (β: −0.007; 95% CI: −0.022, 0.008; P = 0.37) and in the overall population (β: 0.008; 95% CI: −0.002, 0.018; P = 0.161) when the second quartile of collagen (Q2) was compared to the first quartile (Q1).

After adjustment for sociodemographic variables (age, race, education level and PIR), the significant positive association in the females was still detected in model 2 (β: 0.016; 95% CI: 0.004, 0.028; P = 0.017). Further, after adjusting for both sociodemographic and lifestyle covariates (*i.e.*, alcohol use, smoking status, physical activity, BMI and HEI2015 score) together, the positive association remained statistically significant as shown in model 3 (β: 0.017; 95% CI: 0.006, 0.028; P = 0.02). Finally, with all the covariates controlled (*i.e.*, additional adding CRP to the model), the result still showed significant association as shown in model 4 (β: 0.017; 95% CI: 0.006, 0.028; P = 0.022). However, no significant associations between total collagen and LTL were observed in the males (model 2: β, −0.004; 95% CI: −0.019, 0.012; P = 0.642), model 3: β, −0.003; 95% CI: −0.019, 0.013; P = 0.733), and model 4: β, −0.003; 95% CI: −0.019, 0.012; P = 0.678) and

in the overall population (model 2: β, 0.007; 95% CI: −0.003, 0.017; P = 0.172), model 3: β, 0.008; 95% CI: −0.002, 0.018; P = 0.13), and model 4: β, 0.008; 95% CI: −0.002, 0.018; P = 0.141).

In contrast, compared with the lowest quartile of total collagen, no significant differences were detected in the third and fourth quartiles of total collagen in the males, females, and combined.

3.3. Identification of Non-Linear Relationship

Results of Table 2 showed a wiggly trend of telomere length from the low collagen quartile to high collagen quartile, *i.e.*, up from Q1 to Q2 then down from Q2 to Q3, suggesting a non-linear relationship between LTL and collagen consumption. GAM is a widely used statistical method in analyzing the more complex and non-linear relationship between the predictor and response variables, therefore we further performed GAM analysis. GAM model with smoothing curve showed that the total collagen and LTL relationship is nonlinear in female (P for non-linearity: <0.001) after multivariable adjustment (Figure 1). No non-linear relationship was observed in male (P for non-linearity = 0.252). Furthermore, piecewise linear regression models were used in the females, and we found an inflection point of 2.5 (g/1000kcal).

3.4. Sensitivity Analysis

We repeated the multivariable linear regression models in the health population by excluding participants having coronary heart disease, angina, myocardial infarction, stroke, diabetes, congestive heart failure and cancer. We found similar results in the sensitivity analysis (Table S1), indicating the above observed associations apply to the healthy population too.

4. Discussion

In this study, we demonstrated a significant positive association between total collagen consumption and LTL in a nationally representative US female population. Multivariable regression analysis revealed that the second quartile of total

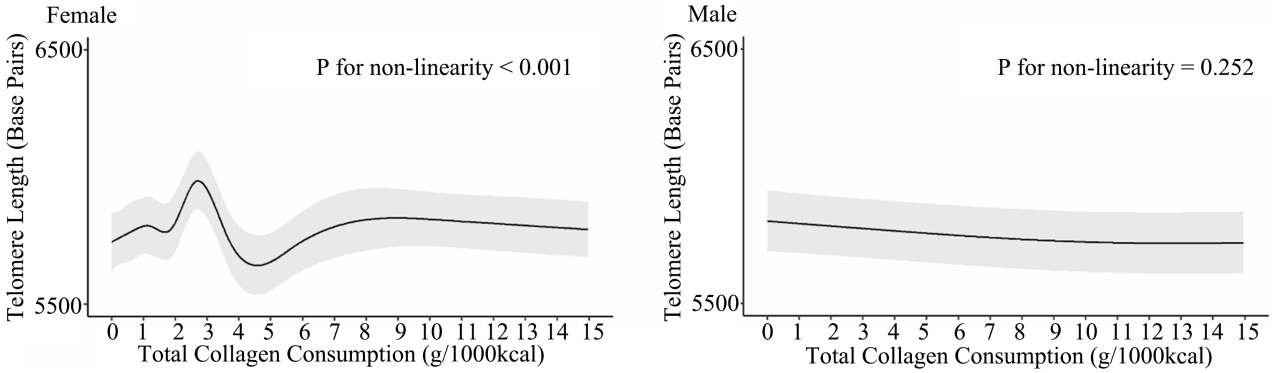

Figure 1. Nonlinear relationship between total collagen consumption and telomere length (base pairs) in the females. Adjusted models adjust for age, race, education, family PIR, smoking status, alcohol, physical activity, BMI, HEI2015 score and CRP.

collagen (Q2), but not in the third (Q3) or the fourth (Q4), was associated with longer LTL compared with the lowest collagen quartile (Q1) in the females. Notably, we found a non-linear association between collagen consumption and LTL, with an inflection point of 2.5 g/1000kcal. Our results from multivariate linear and nonlinear regression analyses suggest that moderate collagen consumption is beneficial but the protective effect against LTL shortening disappear with excessive collagen consumption in the females.

The protective effect of dietary collagen on LTL mostly likely originates from the hydrolyzed collagen hydrolyzation-derived bioactive peptides which are normally buried in the structure of parent proteins and become active after the cleavage of the parent proteins [49]. Orally administered collagen (from food like dietary meat and supplement) is broken down into free amino acids and small oligopeptides (mostly di- and tri-peptide) by our digestive system, which eventually enter the bloodstream and are distributed to the whole body including the skin layers [50] [51] [52]. Collagen peptides have multiple bioactive activities [13] [14] [15] [16] [17]. First, collagen peptides possess antioxidants and anti-inflammation activity. Staggering *in vivo* and *in vitro* studies have showed that collagen peptides can enhance the expression and/or activity of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) thus aid the removal of oxidative toxic intermediates [20] [53] [54] [55] [56] [57]. Collagen peptides of various sequences and lengths, such as those prepared from the fish skin are capable of scavenging free radicals and reactive oxygen species (ROS) [15]. Second, collagen and collagen peptides also show an anti-inflammatory property. It has been reported that short collagen peptides (APD, QA, KA, and WG) originated from Salmo salar skin significantly reduce the expression of proinflammatory factors TNF-α, IL-1β/6/8, NO and cyclooxygenase-2 in an inflammatory disease model [33]. Similarly, intramuscular injection of polymerised type I collagen reduced the excessive inflammatory mediators in COVID-19 cytokine release syndrome [34]. These results are consistent with *in vitro* studies using cultured cells [58] [59]. Third, collagen peptides can regulate the activity of other critical enzymes such as increasing telomerase activity [60] and inhibiting angiotensin-converting enzyme [35]. Collagen peptides' antioxidant and anti-inflammation role may have particular significance in protecting telomere length as telomere is high sensitive to oxidative stress [5] [6] [7] and inflammation [8] [9]. As ROS impedes telomerase activity, which maintains the length of telomeres by addition of guanine-rich repetitive sequences, decreased telomerase activity would impede telomere DNA synthesis and lead to telomere shortening over time. In addition, telomeric DNA is highly enriched in guanine ribonucleotide which forms a G-quadruplexes structure and is sensitive to oxidative stress-induced injury. Guanine base lesion via ROS can result in the destabilization of G-quadruplexes and unfolding of the DNA [61] [62]. The unfolded strand is prone to cellular nucleases cleavage and telomere shortening [63]. Further, excessive ROS also induces DNA single strand break at greater extent at telomeric DNA than other genomic region, eroding the telo-

mere length [64] [65]. The role of collagen peptide in increasing telomerase activity [60] is very interesting and warrants more experimental investigation.

Why does the protective effect against LTL shortening disappear with excessive collagen consumption? We speculate that this might be related to the effects of increasing negative ingredients in the food source of collagen. Among the four NHANES dietary groups, the processed food group (Frankfurters, sausages, and luncheon meats) has very high collagen contents (55.43% dry weight), in sharp contrast with other three food groups (1.4% - 5.5%). The average percentage of daily collagen intake from processed meat was increased from 1.42%-Q1 and 7.70% -Q2 to 33.38%-Q3 and 90.39%-Q4 in the females and similar range in the males (**Table S2**). It is known that the heating and processing of meat produces advanced glycation end products (AGEs) which has an influence on both the inflammation and oxidative stress [66] [67]. Evidence exists that there is a positive association between processed meat intake and markers of oxidative stress and inflammation, including r-glutamyl transferase [68] [69] and C-reactive protein [69] [70]. Many of these processed meats also contain sulfites and other preservatives, which can also trigger inflammation. Indeed, accumulating evidence have showed that intake of ultra-processed food, including processed meat, was associated with shorter LTL [71] [72] [73]. Therefore, the overconsumption of processed meat may mask or counteract the beneficial effects of collagen on LTL. We speculate the lack of effect in the males may also relate to the more unfavorable extrinsic factors including consumption of more processed meat (**Table S2**) and those not included in this study such as stress [74], sleep [75], and consumption of sugar-sweetened beverages [76]. Further studies (such as using collagen supplements) are needed to test the validity of this hypothesis.

The present study has several strengths. To the best of our knowledge, this is the first study to assess the dietary collagen intake in relation to LTL in a nationally representative US population. Second, a broad spectrum of confounding factors, including sociodemographic factors and lifestyle factors as well as CRP have been included in this study. Our findings should be considered generalizable to the US noninstitutionalized population aged 20 to 84. As telomere length is a biomarker for not only the skin aging but also multiple chronic diseases such as cardiovascular diseases, diabetes mellitus, Alzheimer and Parkinson disease, and others [3], our findings have broad clinical and public health implications.

The study has limitations. Due to the cross-sectional nature of the data, our results do not contribute to an understanding of the causal relationship aside from the association. Furthermore, the available NHANES LTL data was based on a single measurement, therefore we cannot examine LTL inter-individual variability over a period of time which may have limited our ability to detect associations. Similarly, collagen consumption was estimated from a 24-hour dietary recall conducted at the time of the survey, which might not reflect collagen intake patterns over the life course. Finally, there is the possibility of unmeasured confounding, although we controlled for many sociodemographic and lifestyle factors in our study. For example, genetic differences may contribute to telo-

meric shortening; psychosocial stress is another important determinant of telomeric shortening.

5. Conclusion

In conclusion, our study based on a nationally representative survey demonstrates a positive and nonlinear association between total collagen consumption and telomere length in the females but not in the males. The current study implies that adult females may benefit from consumption of collagen-rich food in protecting telomere length and slowing biological aging. Further research is still needed to understand how collagen intake relates to telomere length.

Authors' Contributions

H. J., R. L. M. and R. A. S. conceived and designed the study. H. J. analyzed the data. H. J. wrote the manuscript. H. J., R. L. M. and R. A. S. edited the manuscript.

Conflicts of Interest

H. J., R. L. M. and R. A. S. are employed by USANA Health Sciences, Inc. The authors declare no conflicts of interest regarding the publication of this paper.

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Supplemental

Table S1. The association between total collagen consumption and log-transformed telomere base pairs by gender.

Models	Quartiles	Female		Male		Overall	
		[β (95% CI)]	P Value	[β (95% CI)]	P Value	[β (95% CI)]	P Value
Model 1							
	Q1	Ref		Ref		Ref	
	Q2	**0.017 (0.003, 0.031)**	**0.022**	−0.005 (−0.021, 0.012)	0.581	0.008 (−0.004, 0.02)	0.188
	Q3	−0.007 (−0.02, 0.007)	0.359	−0.012 (−0.027, 0.003)	0.13	−0.008 (−0.018, 0.002)	0.086
	Q4	−0.004 (−0.022, 0.015)	0.697	−0.015 (−0.031, 0.001)	0.077	−0.008 (−0.022, 0.006)	0.225
Model 2							
	Q1	Ref		Ref		Ref	
	Q2	**0.014 (0.002, 0.027)**	**0.033**	−0.001 (−0.017, 0.015)	0.925	0.008 (−0.002, 0.018)	0.143
	Q3	−0.006 (−0.019, 0.007)	0.353	−0.011 (−0.026, 0.004)	0.18	−0.007 (−0.017, 0.003)	0.133
	Q4	−0.008 (−0.027, 0.01)	0.399	−0.013 (−0.029, 0.002)	0.115	−0.01 (−0.024, 0.004)	0.16
Model 3							
	Q1	Ref		Ref		Ref	
	Q2	**0.016 (0.004, 0.028)**	**0.032**	0.001 (−0.015, 0.017)	0.884	0.01 (0, 0.02)	0.099
	Q3	−0.006 (−0.019, 0.007)	0.395	−0.009 (−0.024, 0.006)	0.289	−0.005 (−0.015, 0.005)	0.297
	Q4	−0.003 (−0.022, 0.016)	0.772	−0.01 (−0.026, 0.007)	0.287	−0.006 (−0.02, 0.008)	0.436
Model 4							
	Q1	Ref		Ref		Ref	
	Q2	**0.016 (0.004, 0.027)**	**0.035**	0 (−0.016, 0.016)	0.983	0.009 (−0.001, 0.019)	0.113
	Q3	−0.006 (−0.019, 0.007)	0.398	−0.009 (−0.024, 0.005)	0.257	−0.006 (−0.016, 0.004)	0.275
	Q4	−0.003 (−0.022, 0.016)	0.759	−0.011 (−0.027, 0.006)	0.247	−0.006 (−0.02, 0.008)	0.398

Note: Model 1 was a crude model. Model 2 further adjusted for age, race, education, and family PIR. Model 3 further adjusted for smoking, alcohol use, physical activity, BMI, HEI2015 score. Model 4 additionally adjusted for CRP.

Table S2. Average daily total meat and processed meat intake, and percentage of collagen from processed meat according to the quartiles of total collagen by gender.

Quartiles	Female			Male		
	Total meat, oz (mean ± SE)	Processed meat, oz (mean ± SE)	% of collagen from processed meat	Total meat, oz (mean ± SE)	Processed meat, oz (mean ± SE)	% of collagen from processed meat
Q1	1.66 ± 0.09	0.0019 ± 0.0008	1.42	2.36 ± 0.13	0.001 ± 0.0004	0.61
Q2	3.76 ± 0.08	0.0262 ± 0.0034	7.70	5.31 ± 0.17	0.033 ± 0.0048	7.55
Q3	5.29 ± 0.12	0.3151 ± 0.0223	33.38	7.19 ± 0.25	0.4938 ± 0.0437	37.26
Q4	5.08 ± 0.12	2.444 ± 0.0851	90.39	7.72 ± 0.21	3.5373 ± 0.1543	88.36

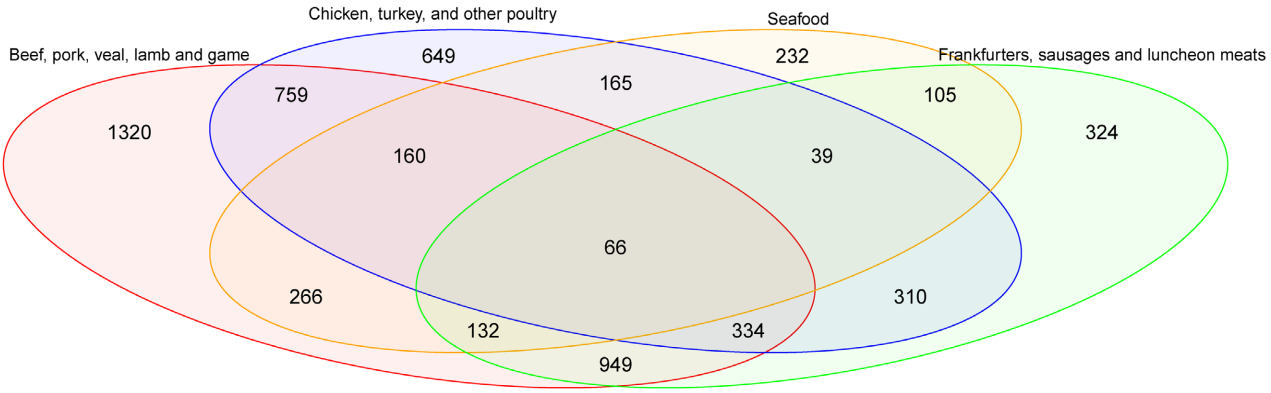

Figure S1. Number of participants of different categories of meat and seafood consumption.