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Article

Association between Dietary Saturated Fat and Telomere Length: The National Health and Nutrition Examination Survey (NHANES)

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Abstract: This study examines the association between dietary saturated fatty acid (SFA) intake and leukocyte telomere length (LTL) using data from the National Health and Nutrition Examination Survey (NHANES) 1999-2002. Telomeres, protective repeats of DNA at the ends of chromosomes, play a crucial role in cellular aging. Their length is shortened over time and is influenced by various factors, one of which is diet. The present study's objective was to evaluate whether increased SFA consumption is associated with shorter LTL. The analysis, conducted on a large, nationally representative sample of 6646 adults, revealed an inverse association between dietary SFAs and LTL. When examined further, this association was found to be significant in women, but not in men. Serum C-reactive protein (CRP) levels were tested as a potential mediator in this relationship, but no such mediation was found. These findings support the role of dietary factors in modulating cellular aging. However, further research is warranted to elucidate the underlying mechanisms driving the overall association, as well as the gender-specific effects observed.

Keywords: telomere; fats; saturated fat; NHANES

1. Introduction

Telomeres are regions of DNA located at the ends of chromosomes consisting of tandem repeats of the sequence TTAGGG in humans. Their function is to protect the coding sequences of DNA from degradation during cellular division. By acting as a buffer during DNA replication, telomeres are shortened instead of coding sequences. In particular, leukocyte telomere length (LTL) is widely used as a biological measure for assessing cellular aging as well as human aging [1].

Saturated fatty acids (SFAs) are a type of fat molecule that are marked by the absence of carbon-carbon double bonds in their fatty acid chains, meaning they are fully "saturated" with hydrogen atoms. SFAs have a long history of investigation in the field of nutritional science. SFAs have been extensively studied in the scientific literature for their adverse effects on cardiovascular health [2]. However, research in more recent decades has shown mixed results [3–5].

It is well established that dietary patterns are linked to telomere length, especially those associated with oxidative stress or inflammation. [6] For example, the Mediterranean diet, proven to reduce oxidative stress and chronic inflammation, has been found to be positively associated with LTL [7]. Both oxidative stress and inflammation have been demonstrated to shorten LTL [8,9], providing a mechanism through which diet can potentially influence LTL. In fact, dietary SFAs are known to have a marked proinflammatory effect [10,11] and a role in increasing oxidative stress [12,13].

More specifically, dietary SFAs have a potential positive association to levels of several inflammatory biomarkers, one of which is C-reactive protein (CRP) [14]. CRP is an acute-phase inflammatory plasma protein synthesized in hepatocytes in response to elevated levels of certain cytokines [15]. CRP has also linked with LTL in previous research studying NHANES 1999-2002 [16–18].

Several studies have found a link between SFA intake and shorter LTL [19–21], while others have found no link [22,23]. Overall, findings of the current literature are mixed.

The study will attempt to shed light on the relationship between dietary SFA intake and LTL. There is a gap in the literature, as this association has not been assessed in The National Health and Nutrition Examination Survey (NHANES) until now. This is important because NHANES has an

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extremely large and nationally-representative sample size, lending power to statistical conclusions derived from its data. The present inquiry has the largest sample size out of all studies examining the link between dietary SFAs and LTL. The study will also attempt to shed light on the effect modification of gender on the relationship between dietary SFAs and LTL, which has not been sufficiently examined.

The primary objective of the present study is to examine the association between dietary SFA intake and LTL using data from NHANES 1999-2002. Increased consumption of SFAs is hypothesized to be associated with shorter LTL. C-reactive protein (CRP) was tested as a mediator of this association.

2. Materials and Methods

2.1. Study Design and Population

The National Health and Nutrition Examination Survey (NHANES) is a large-scale survey conducted by the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS). The NHANES contains a demographic, dietary, and health-related questionnaire as well as examination and laboratory measurements. Questionnaires were administered in the participant's home, while the physical examination and collection of laboratory samples were conducted in specially equipped mobile examination centers (MECs) [24].

NHANES is a complex survey with a 4-stage sampling design, with each primary sampling unit consisting of multiple counties or one metropolitan statistical area [24]. NHANES samples are weighted to be nationally representative, accounting for nonresponse [24].

NHANES data is typically released in 2-year cycles. Telomere data was only included in the 4-year study period from 1999-2002, and only for individuals 20 years and older. For this study period, NHANES oversampled low-income persons, adolescents 12-19 years, persons over 60 years of age, African Americans and Mexican Americans [24]. Out of 7827 individuals with eligible DNA samples, the current study is composed of 6646 adults aged 20 and over with complete data for all variables detailed below.

The NHANES 1999-2004 data collection protocol was approved by the NCHS Ethics Review Board (Protocol #98-12) [25].

2.2. Dietary Saturated Fat (SFA)

Per the NHANES Dietary Interviewers Procedure Manual [26], a 24-hour dietary recall was performed in the mobile examination center (MEC). Interviews were conducted in person. Measuring guides such as glasses, mugs, bowls, and spoons were provided. A second day of recall was performed via phone interview, although the data has not been publicly released [27]. The present inquiry uses Day 1 MEC interview data.

In order to account for varying total energy intake of individuals, intake of dietary SFAs was indexed as grams of SFAs consumed per 1000 kcal.

2.3. Leukocyte Telomere Length (LTL)

Per NHANES documentation:

> The telomere length assay was performed in the laboratory of Dr. Elizabeth Blackburn at the University of California, San Francisco, using the quantitative polymerase chain reaction (PCR) method to measure telomere length relative to standard reference DNA (T/S ratio), as described in detail elsewhere (Needham et al, 2013; Cawthon, 2002). Each sample was assayed 3 times on 3 different days. The samples were assayed on duplicate wells, resulting in 6 data points. Sample plates were assayed in groups of 3 plates, and no 2 plates were grouped together more than once. Each assay plate contained 96 control wells with 8 control DNA samples. Assay runs with 8 or more invalid control wells were excluded from further analysis (<1% of runs). Control DNA values were used to normalize between-run variability. Runs with more than 4 control DNA values falling outside 2.5 standard deviations from the mean for all assay runs were excluded

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from further analysis (<6% of runs). For each sample, any potential outliers were identified and excluded from the calculations (<2% of samples). The mean and standard deviation of the T/S ratio were then calculated normally. The interassay coefficient of variation was 6.5% [28].

In order to convert from T/S ratio to DNA base pairs, the following formula was used: $3,274 + 2,413 \times (T/S)$ [28].

2.4. Covariates

In the present inquiry, age, gender, race/ethnicity, education, and poverty income ratio (PIR) were selected as demographic covariates. Age was left as a continuous variable during analysis. Race/ethnicity were categorized into 5 responses: Non-Hispanic White, Non-Hispanic Black, Mexican American, Other Race Including Multi-Racial, and Other Hispanic. Education was categorized into 3 responses: Less Than High School, High School Diploma (including GED), and More Than High School. PIR was calculated by dividing household income with the federal poverty threshold for the corresponding household size and served as a measure of socioeconomic status (SES). NHANES recorded the maximum PIR as 5.00 so that all individuals that surpassed this threshold were labeled with a PIR of only 5.00. Six categories were used for PIR as follows: <1.00, 1.00-1.99, 2.00-2.99, 3.00-3.99, 4.00-4.99, and 5.00.

Body mass index (BMI), physical activity, and smoking status were selected as lifestyle covariates. BMI was categorized as follows: Underweight (<18.50), Normal Weight (18.50-24.99), Overweight (25.00-29.99), and Obese (≥30). Physical activity was measured in MET-minutes per week. MET (metabolic equivalent of task)- minutes per week is a measure of energy expenditure. Categories were based on the Physical Activity Guidelines for Americans, which recommends that adults engage in 500-1000 MET-minutes of activity per week [29]. Therefore, the categories were defined as follows: Sedentary (0 MET-minutes/week), Low Activity (0.01-499.99), Recommended Activity (500-1000), and High Activity (≥1000). Smoking status was categorized as Current, Former, or Never.

2.5. Statistical Analysis

NHANES provides 4-year subsample weights specifically for analysis of dietary data in conjunction with mobile examination center (MEC) laboratory and examination data. This is because a greater proportion of MEC exams were scheduled on weekends, meaning that using MEC subsample weights would disproportionately represent dietary intake on weekends [27]. Data for first-stage strata, primary sampling units (PSUs), and sample weights provided by NHANES were used in all statistical analysis to ensure that results were generalizable to the U.S. population.

To describe sample characteristics, weighted percentages of each categorical variable were calculated. Additionally, mean dietary SFA intake and LTL were calculated for each categorical variable.

Multiple linear regression analysis was utilized to test the correlation of dietary SFAs with mean LTL. Three regression models were created that differed in covariate adjustment. Model 1 was age-adjusted. Model 2 was adjusted for demographic covariates as described above. Model 3 was adjusted for demographic and lifestyle covariates. All three models were tested using the overall sample, as well as subsamples of only men and women in order to assess for effect modification through gender. Lastly, mediation through C-reactive protein (CRP) was investigated by applying the Baron and Kenny method [30].

SAS procedure SURVEYFREQ was used to generate weighted percentages, while procedure SURVEYMEANS was used to generate weighted means. Multiple linear regression analysis was performed using procedure SURVEYREG. SAS 9.4 (SAS Institute, Cary, NC, USA) was employed for all statistical analyses. All statistical tests were two-sided. Statistical significance was set when $p<0.05$.

3. Results

The present study sample (n=6646) consisted of 3437 women and 3209 men. The mean ± SE age of the sample was 45.8 ± 0.4 years. The mean leukocyte telomere length (LTL) was 5813 ± 34

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base pairs, and the mean dietary saturated fatty acid (SFA) was 12.0 ± 0.01 g/1000 kcal. The caloric equivalent of 12.0 g of SFA per 1000 kcal is 108 kcal of SFA per 1000 kcal, or 10.8% of total calories. This slightly exceeds the recommendation issued by the Dietary Guidelines for Americans, which advises that adults consume less than 10% of total calories from SFAs [31].

Table 1. Characteristics of the sample (n=6646) by mean LTL and dietary SFA intake

Variable	***N***	**Weighted %**	***SE* of %**	**Mean LTL ± *SE***	**Mean SFA ± *SE***
Gender					
Men	3209	48.7	0.8	5804 ± 32	12.0 ± 0.1
Women	3437	51.3	0.8	5822 ± 38	12.0 ± 0.1
Age[a]					
20–39	2542	40.5	1.2	6033 ± 39	12.0 ± 0.1
40–59	2054	37.2	1.0	5782 ± 40	12.1 ± 0.2
≥60	2140	22.3	0.8	5466 ± 37	11.7 ± 0.1
Ethnicity					
Non–Hispanic White	3448	74.6	1.6	5794 ± 37	12.2 ± 0.1
Non–Hispanic Black	1104	9.3	1.0	5947 ± 51	11.1 ± 0.2
Mexican American	1594	6.9	0.9	5786 ± 39	11.6 ± 0.2
Other Race	159	3.0	0.5	5796 ± 73	10.4 ± 0.8
Other Hispanic	341	6.1	1.4	5885 ± 93	11.6 ± 0.2
Education					
Less Than High School	2135	20.0	1.0	5717 ± 43	11.8 ± 0.2
High School Diploma	1556	26.2	1.0	5781 ± 43	12.4 ± 0.1
More Than High School	2955	53.8	1.6	5865 ± 33	11.8 ± 0.1
Poverty Income Ratio (PIR)					
<1.00	1154	13.6	0.8	5882 ± 41	11.8 ± 0.2
1.00–1.99	1694	20.0	1.3	5754 ± 44	11.7 ± 0.2
2.00–2.99	1086	15.6	0.9	5791 ± 41	12.3 ± 0.2
3.00–3.99	808	13.7	0.8	5860 ± 55	12.3 ± 0.1
4.00–4.99	617	11.3	0.7	5839 ± 50	12.2 ± 0.2
5.00	1287	25.7	1.7	5800 ± 41	11.9 ± 0.2
Body Mass Index (BMI)					
Underweight	92	1.7	0.2	5880 ± 83	11.6 ± 0.7
Normal Weight	1983	32.5	1.0	5892 ± 33	11.7 ± 0.1
Overweight	2431	34.8	1.1	5791 ± 40	11.8 ± 0.1
Obese	2140	30.9	1.2	5752 ± 38	12.5 ± 0.1
Smoking Status					
Never	3429	50.8	1.6	5853 ± 38	11.8 ± 0.1
Former	1783	25.2	1.0	5699 ± 37	12.0 ± 0.1
Current	1434	23.9	1.1	5850 ± 45	12.2 ± 0.2
Physical Activity					
Sedentary	2880	34.9	1.4	5735 ± 40	12.1 ± 0.1
Low Activity	1244	20.2	0.9	5818 ± 38	12.0 ± 0.2
Recommended Activity	776	13.3	0.8	5809 ± 40	12.0 ± 0.2
High Activity	1746	31.6	1.4	5899 ± 34	11.8 ± 0.1

[a] Age left continuous during statistical analysis.

Age was categorized in Table 1 for visualization purposes, but was left continuous for statistical analysis. The correlation between increased age and shortened LTL was significant across the age categories displayed in Table 1 (p<0.0001).

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Table 2. Association of dietary SFA intake with LTL across men and women

	Model 1		Model 2		Model 3	
	$\beta \pm SE$	*p*-value	$\beta \pm SE$	*p*-value	$\beta \pm SE$	*p*-value
Overall	-6.31 ± 1.69	0.0008	-5.96 ± 1.66	0.0012	-5.22 ± 1.70	0.0047
Men	-4.30 ± 2.63	0.11	-4.51 ± 2.59	0.0916	-3.52 ± 2.56	0.18
Women	-8.15 ± 2.63	0.0043	-7.47 ± 2.66	0.0087	-6.84 ± 2.62	0.014

Using the overall sample of adults, all three regression models were significant ($p<0.05$) in finding an inverse relationship between dietary SFAs and LTL. Using Model 3, for every 1 gram increase in SFA intake/1000 kcal, mean LTL was expected to decrease by -5.22 base pairs. In all models, introducing demographic and lifestyle covariates weakened the association tested. However, adjusting for covariates did not alter the significance in the combined sample of men and women.

Gender was found to moderate the association between consumption of SFAs and LTL. When tested across gendered subsamples, all three models showed a significant relationship in women (p=0.014 in Model 3). This finding was not observed in men—an inverse, although statistically insignificant relationship between dietary SFAs and LTL was observed (p=0.18 in Model 3).

Mediation through serum C-reactive protein (CRP) levels was also tested by following the Baron and Kenny method as a preliminary test [30]. Further mediation analysis was not necessary, as no association was found between SFA intake and CRP levels (p=0.5519) using multiple linear regression analysis. Therefore, CRP was found not to be a mediator in the association between consumption of SFAs and LTL.

4. Discussion

The primary aim of the present investigation was to examine the association between dietary saturated fatty acids (SFAs) and mean leukocyte telomere length (LTL) using NHANES data. The study uses the largest sample size (n=6646) out of all prior research studying the correlation between dietary SFAs and LTL.

The current inquiry discovered that in a nationally representative sample of 6646 adults, dietary SFAs were inversely associated with LTL. Further analysis demonstrated that this association was significant in women, but not in men (Table 2).

Dietary SFAs increase inflammation and oxidative stress [10–13], both of which contribute to the shortening of LTL [8,9]. This is the hypothesized mechanism through which SFA is linked to LTL. In particular, C-reactive protein (CRP) is an inflammatory biomarker that has been linked with both dietary SFAs [14] and LTL [16–18].

CRP levels were revealed to not mediate the negative association between SFA intake and LTL. However, this does not mean that other mediator variables are not possible. Some examples are interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), serum amyloid A (SAA), and fibrinogen, all of which are inflammatory biomarkers that have been inversely correlated with LTL [32–36]. CRP was the only inflammatory biomarker measured throughout the NHANES 1999-2002 study period, although fibrinogen was recorded only for the 2001-2002 interval. This warrants future research on the studied association using other biomarkers.

Currently, there is insufficient evidence for any mechanism or explanation for why the negative association between SFA intake and LTL is significant in women but not in men. Men and women consumed the same amount of SFA/1000 kcal (Table 1), meaning that differences in the amount of dietary SFAs consumed is not a possible explanation.

One speculative explanation could be through the differences in fat metabolism between women and men. Blaak suggests gender differences exist in basal lipolysis, catecholamine-stimulated lipolysis, postprandial lipolysis, and exercise-induced lipolysis [37]. However, any number of biological, lifestyle,

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or dietary differences between men and women could potentially influence the association between dietary SFAs and LTL.

Of note, Tiainen et al. [19] conducted a tudy of Finnish adults which concluded that consumption of SFAs was negatively associated with LTL in men, but not in women. This finding is opposite to the gender effect identified in this study. The gender-specific association between SFA intake and LTL must be explored more.

Findings from the present study can inform dietary recommendation and public health guidelines, specifically those that are gender-specific, which are not very prevalent as of today.

The current investigation has several limitations. First, causal effects are only inferred and cannot be determined due to the inherent nature of cross-sectional survey data. Second, NHANES participants performed a self-reported 24-hour dietary recall, which introduces limitations centered around misreporting of dietary data. Unintentional misreporting during dietary recall is undeniable, but there is also the potential for non-random misreporting. Murakami and Livingstone [38] analyzed the dietary assessment of NHANES 2003-2012 and found that prevalence of underreporting and overreporting to be around 25% and 2%. There were higher rates of underreporting in participants that: are women, are older, are non-Hispanic Black, are less educated, have a lower poverty income ratio (PIR), and are overweight or obese. Higher rates of overreporting were associated in participants that: are male, are younger, have a lower PIR, are current smokers, and are underweight. While their sample did not use the same NHANES cycles as the current study, Murakami and Livingstone demonstrated that non-random misreporting bias exists in NHANES dietary recall. Lastly, while the present analysis included 8 covariates, a number of other confounding factors could also explain the relationship between dietary SFAs and LTL.

5. Conclusions

This study investigated the relationship between dietary saturated fatty acid (SFA) intake and leukocyte telomere length (LTL) in NHANES 1999-2002. The findings reveal a significant inverse association between dietary SFAs and LTL in a combined sample of adults. When separated by gender, this association was significant in women, but not in men. Serum C-reactive protein (CRP) levels were not found to mediate this association. These results reinforce the role of dietary factors in cellular aging processes, although further research is needed to understand the underlying mechanisms and implications for dietary recommendations. By utilizing a large, nationally representative sample, this study contributes to the existing body of literature, which has been divided on the link between SFA intake and LTL. In conclusion, the present study supports the original hypothesis that dietary SFAs are associated with decreased LTL.

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