Association between Longitudinally Assessed Dietary Composition and Blood Telomere Length among Young Adult Filipinos

Hilary Jeanne Bethancourt

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Committee Members:

Mario Kratz

Shirley A. A. Beresford

Daniel T. A. Eisenberg

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Abstract

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Hilary Jeanne Bethancourt

Chair of the Supervisory Committee:
Mario Kratz
Department of Epidemiology

Diet and nutrition are known to play a pivotal role in the onset and progression of aging-related diseases, but it remains unclear how diet and nutrition influence aging processes in general. Telomeres, the nucleotide sequences that protect linear chromosome ends from degradation, are considered a biomarker of aging. Evidence that oxidative stress and inflammation can accelerate telomere attrition suggests that nutritional factors may impact telomere length (TL) and, hence, aging by either contributing to or protecting against oxidative and inflammatory processes. However, previous studies have produced inconsistent results on the relationship between TL and diet or nutritional status. Most studies have been cross-sectional and have been conducted among older adult Western populations.

This study aimed to explore the association between longitudinally-assessed diet and adiposity measures and TL among a young Filipino population. Specifically, it tested the hypotheses that 1) processed meats, fried or grilled meats, coconut oil, and non-diet soda are each inversely associated with TL; 2) fish and fruit and vegetable consumption are positively associated with TL; 3) body mass index is associated with TL in a curvilinear fashion; and 4) height-adjusted waist circumference is inversely associated with TL.

Contrary to all hypotheses, the data provided no evidence of an association between TL and any of the dietary factors of interest or either of the measures of adiposity. These results contrast with some previous studies but align with others. The lack of associations may have

been due to the young age of the population, low caloric intake, low consumption of some of the food groups of interest, low levels of adiposity, population differences in anti-inflammatory regulatory networks, and/or methodological and statistical power limitations. Further research with non-Western populations of different ages is warranted in order to elucidate the reasons for inconsistent evidence across studies and populations. Future studies should ideally include multiple longitudinal measurements of diet, body composition, TL, and other markers of biological aging.

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Introduction

Mounting evidence has demonstrated that diet and nutrition play an important role in the onset and progression of many aging-related diseases, including cardiovascular disease, cancer, diabetes, arthritis, and osteoporosis (1, 2). Less is known, however, about how diet and nutrition contribute to the aging process in general. Though there is growing attention on the role of caloric restriction on lifespan (3-6), this has not been well-studied in humans, and the role of specific foods on lifespan have not been thoroughly investigated. Yet, there is reason to believe that certain foods, in additional to nutritional status, could have a direct effect on aging through their influence on oxidative and inflammatory processes (7). Both oxidative stress and inflammation are known to contribute to the cellular and molecular damage that are considered prominent causes of aging (8-10).

Given the long lifespan of humans and the complexity of the aging process, it can be challenging to study the effects of diet on longevity and aging. Recently, however, telomere length (TL) has been suggested as a potential biomarker of aging or, at least, a biomarker of cumulative oxidative stress and inflammation that can contribute to aging (11-14). Telomeres are the nucleotide sequences at the end of linear chromosomes that help maintain genomic stability (15-17). They do this by protecting chromosomes from end-to-end fusion (18) and by serving as buffers (19) against the loss of important genetic information when DNA polymerases fail to fully replicate the 3' end of linear DNA during mitosis (the "end-replication problem") (13, 14, 16, 20). Because telomerase, the specialized ribonucleoprotein enzyme that helps rebuild telomeric DNA and keep telomeres in the protective "capped" state (18) is less active in somatic cells (13, 14, 21), telomeres in somatic cells shorten with each cell division (13, 22, 23). When telomeres reach a critically short length, cells will be more likely to exit the cell cycle, senesce, and eventually enter into apoptosis (cell death) (18, 24). This loss of cellular integrity may be what contributes to aging and disease processes. Shorter age-adjusted TL measured in

peripheral blood cells (25) is purportedly associated with increased risk of cardiovascular disease (26), some cancers (27-29), and mortality (30-32).

TL differs across different tissues, ranging in length from about 4 to 15 kilo-base pairs (14, 33). With each cell division, telomeres generally decrease by about 20-200 base pairs (14, 34), getting shorter, therefore, with chronological age. But only a small portion of this attrition is attributed to the end-replication problem, and the remaining attrition is thought to be a consequence of oxidative stress (34). Telomeres may be more susceptible to damage from oxidative stress due to their high guanine content and limited repair mechanisms (11, 14, 35, 36). Additionally, inflammation is theorized to lead to increased telomere attrition due to its effects on cellular turnover rates (37-39); inflammation can also contribute to increased production of reactive oxygen species (ROS) (14) or vice versa (40). *In vitro* experiments have indicated that oxidative stress can down-regulate telomerase, damage telomeres, and accelerate telomere attrition (11, 36, 41, 42), while antioxidants and anti-inflammatory nutrients, on the other hand, appear to slow telomere attrition rates and be associated with longer TL in cultured cells (7, 11, 14, 41). In fact, TL has consistently been inversely associated with markers of oxidative stress and inflammation in epidemiological studies (33).

The production of ROS and inflammatory cytokines are natural byproducts of cellular metabolism and healthy immune function, respectively (10, 43), and a number of mechanisms have evolved to prevent, mitigate, or repair damage caused by them (43, 44). But certain environmental exposures may contribute to increased production of ROS and inflammatory cytokines that contribute to oxidative stress, chronic inflammation, and cellular damage (10). There is some indication from observational studies (45, 46) and randomized controlled trials (47, 48) that diet can be one of the sources of increased oxidative stress and inflammation, or, conversely, could support the antioxidant defense system and reduction of inflammatory cytokines. Indeed, a number of studies have suggested that overall healthy lifestyle patterns, including maintenance of a healthy diet, normal weight, and adequate physical activity levels,

are associated with longer TL (49-51) and higher telomerase activity (52). Yet it remains unclear to what degree diet, nutrition, and specific food choices have an independent effect on telomere attrition rates. The relationship between specific foods, measures of nutritional status, and TL has only begun to be explored, and existing data have provided inconsistent results (see Appendix A for review of existing studies on diet and TL).

Meat, and red meat in particular, has long received a reputation for contributing to aging-related diseases and mortality (53, 54). Meat is a rich source of iron, which in supplement form contributes to increased free radicals (7) and reduced TL (55). Meat also tends to be high in saturated fatty acids (SFAs), some of which may be pro-inflammatory (56-58). Moreover, meat is one of the major dietary sources of advanced glycation end-products (AGEs) (59). AGEs in meat are increased with cooking at high temperatures (i.e., frying or grilling/broiling) and are known to contribute to oxidative stress, inflammation, and insulin resistance (59, 60). Despite these hypothesized pathways between meat and oxidative stress and inflammation, there is currently no evidence that overall meat consumption is associated with TL (61, 62). However, just as a number of studies have demonstrated that the effect of meat on disease risk can depend on the kind of meat consumed (53, 54), it may not be appropriate to treat all meat equally when assessing its effects on TL either. Only one study has assessed red meat and processed meat separately, and they reported an inverse association with the latter and no association with the former (63). These results line up with evidence that diets high in processed meats tend to be associated with elevated markers of inflammation and oxidative stress in Western populations (64, 65) and that processed meat tends to more strongly associated with cardiovascular disease, diabetes, and overall mortality risk than unprocessed red meats (53, 54, 66). No further studies have explored the relationship between TL and intake of processed meats, and no studies to date have explored the association between TL and consumption of fried or broiled/grilled meats specifically.

Two studies have suggested that SFAs may be inversely associated with TL (67, 68), though these results were not consistent across males and females and were not replicated in other studies (69, 70). Intriguingly, one study suggested that it is the short-to-medium chain SFAs (specifically the 4:0, 6:0, 8:0, and 10:0 SFAs) commonly found in dairy products that was most strongly associated with shorter TL, while, with the exception of 14:0 and 16:0 SFAs, the long-chain SFAs commonly found in meat were not associated with TL (68). The same study reported that, among women who regularly consumed whole fat milk, whole fat cheese, and butter (as opposed to women who consume low-fat versions of these foods), these high-fat dairy products were inversely associated with TL (68). It could be argued that these associations were due to the potential insulinemic effects of dairy rather than to the SFAs (71, 72). However, other analyses have not found associations between dairy product intake and TL, either when separating dairy intake by fat content (63) or looking at all dairy products together (62, 68). It remains unclear, therefore, whether or not observed associations between SFAs and TL may instead just be an artifact of multiple comparisons or residual confounding from other dietary and lifestyle correlates.

Some foods, in contrast, could be protective against telomere attrition. Diets high in fruits and vegetables, for example, have been inversely associated with markers of inflammation and oxidative stress in adolescents (73) and adults (64), potentially because of their high antioxidant and nutrient content (7). Yet, only a few studies to date have provided suggestive evidence of such an association with TL (61, 67), while others have not (62, 63, 70). Likewise, omega-3 fatty acids, though highly susceptible to oxidation ex-vivo, may have some anti-oxidative effects in-vivo (74-76), and appear to also have anti-inflammatory effects (77-79). Blood levels of omega-3 fatty acids were associated with reduced rates of telomere attrition in one prospective observational study (80). Though overall estimates of omega-3 fatty acid intake (67, 69, 70) and fish consumption (61-63) have not been associated with TL in existing studies, a randomized controlled trial involving omega-3 supplementation suggested that absolute intake may not have

as much of an impact on TL as dietary omega-6:omega-3 ratios (76). This may be due to the pro-inflammatory effects of omega-6 fatty acids (56), which was found to be inversely associated with TL in one study (70) but not in others (67, 69).

Obesity and insulin resistance are also associated with increased oxidative stress and inflammation (81, 82). Consequently, foods that may contribute to increased weight gain and metabolic disturbances, such as added sugar in the form of sugar-sweetened beverages, could be hypothesized to influence TL through its effect on body composition and metabolic imbalances (65, 83-86). One longitudinal study, for example, reported greater telomere attrition among individuals with increasing measures of insulin resistance across time (87). Another study found that individuals with type 2 diabetes had shorter TL than their non-diabetic counterparts (88). Yet few studies have looked specifically at TL in relation to foods known to contribute to insulin resistance and type 2 diabetes. Only one study (63) has explored the relationship between TL and consumption of non-diet sodas, a dominant source of added sugar in the diet (84), and found no association.

Furthermore, if obesity and metabolic disturbances influence inflammation and oxidative stress, overconsumption of calories in general would be hypothesized to impact TL. Despite growing evidence that caloric restriction impacts inflammation, oxidative stress, and longevity (3-6, 89, 90), only one study has reported an inverse association between total caloric intake on TL in men only (69), while other studies found no association (62, 63, 70). Studies that have examined the relationships between measures of adiposity (the manifestation of chronic overconsumption) and TL have also reported mixed results. A number of cross-sectional studies with adult populations have reported inverse associations between TL and BMI (70, 91-96) and between TL and waist circumference (70, 91, 94, 96), while other studies reported null associations between TL and BMI (49, 63, 67, 97), waist circumference (49, 63) and waist-hip ratio (67, 91). Some longitudinal studies have even reported an association between

accelerated telomere attrition and BMI (87) and waist-hip circumference ratio (98, 99), while another study found no association between BMI and change in TL across time (95).

Lee et al. (94) reported that the observed association between BMI and TL was stronger among younger individuals (<30 years old), yet other studies with younger populations have been mixed. One study reported that obese males and females (ages 2-17) had shorter TL than their non-obese counterparts. Other analyses among child and adolescent populations reported no difference in TL by obese status among children (100), found an association only in boys (101), or found no linear relationship between TL and BMI or waist circumference (102). Overall, the research on continuous measures of adiposity and TL among younger populations is lacking.

On the other extreme, undernutrition and underweight could potentially be as detrimental as overweight and obesity. Though not to the same degree as overweight, there is a trend toward increased mortality among those with underweight status compared to those with a normal BMI in the U.S. (103). This kind of a trend may be more pronounced in populations where underweight status may be coupled with additional environmental stressors. Moreover, inadequate nutrition could lead to increased susceptibility to infection (3, 104), which could in turn contribute to increased inflammation (105) and, therefore, influence TL. To date, no studies have explored the dynamics of both overweight and underweight status on TL, as most have been conducted among relatively over-nourished populations.

Further studies on the relationship between TL, diet, and nutritional status are needed to resolve some of the inconsistencies and fill in the important gaps across the literature. Such studies are particularly relevant when considering the recent and rapid global shifts toward a diet lacking fruits and vegetables and dominated by unprecedented amounts of industrially-produced and processed animal foods, processed oils, fried foods, refined carbohydrates, and added sugars, particularly in the form of sweetened beverages (106-109). This modern industrialized diet may be advancing cellular aging through its paucity of antioxidant- and

nutrient-rich foods and its abundance of foods that contribute to overnutrition, metabolic disturbances, inflammation, and oxidative stress.

Only one known study to date has explored diet-TL relationships among a non-Western population (62), and this population was elderly (65 years and older). With some of the most rapid dietary shifts occurring in low- to middle-income nations (110), there is a clear need to expand studies to other populations where nutrition dynamics may be quite different than they are in high-income, Western populations. Furthermore, no studies have yet explored how diet over time or during critical years of growth and development may influence TL. Given that cellular turnover and telomere attrition rates are most rapid in the early years of life (111) and that the diets of children in recent decades appear to be more obesogenic than those of their parents (112), the effect of transitioning diets during these critical years on TL deserves greater attention. Finally, the exclusive use of food frequency questionnaires (FFQs) to measure diet in existing studies may fail to capture more subtle diet-TL relationships and may be contributing to the inconsistencies across studies. This dietary assessment tool has been demonstrated to have poor validity (113) and to contribute to null results in other epidemiology studies (114-116). Future investigations need to incorporate more robust methods of dietary assessment.

The objective of the present study, therefore, was to examine relationships between TL and diet and between TL and body composition that remain ambiguous or untested and do so among a young non-Western population using longitudinal dietary (collected by 24-hour recalls) and body composition data. Specifically, this study aimed to examine whether consumption of a more “Westernized”, processed diet and higher body fat during the juvenile, adolescent, and early adult years has observable effects on the TL of young adult Filipino males and females. This study focused on common foods in the Filipino diet that were hypothesized to have the greatest impact on TL: processed meat, fried or broiled/grilled meat, non-fried fish, coconut oil, non-diet soda, and fruits and vegetables.

The diet of the general Filipino population has typically been described as one of rice, fish, and vegetables (117). However, the Filipino diet has in recent decades shifted toward one that may potentially have a more negative impact on TL. Increases in the consumption of total calories, fried foods, processed meat, total fat, and soft drinks, along with concurrent decreases in the intake of fruits and vegetables, have been documented in relation to increasing urbanization and household income among Filipinos (109, 112, 118-120). Higher intake of soda, processed meats, and fried or broiled/grilled meats during childhood and adolescence were hypothesized to be associated with shorter TL among this population. Also, coconut oil, the primary cooking oil used in the Philippines (121), is relatively low in omega-6 fatty acids compared to other vegetable oils (122, 123) but is also high in the medium chain SFAs (124) thought to be associated with shorter TL when consumed in the form of dairy (68). As dairy consumption remains low among adolescents and adults in this population (109, 117), the examination of the association between coconut oil and TL may shed some light on whether medium-chain SFAs are indeed associated with TL when consumed in a form other than dairy. Furthermore, though tropical fish tend to have lower levels of omega-3 fatty acids, a recent analysis showed a dose-response relationship between fish intake and DHA levels in breast milk among Filipino women (125), suggesting a potentially observable association between fish consumption and TL in this population. Finally, as overconsumption of calories in general can lead to excess adiposity and potentially influence pathways that affect telomere attrition (69), this study assessed how excess energy consumption, manifested as adiposity, is associated with TL of young adults.

Hence, this study was designed to specifically test the hypotheses that consumption of processed meat, fried or broiled/grilled meat, coconut oil, and non-diet soda would each be inversely associated with TL and that fish and fruit and vegetable consumption would each be positively associated with TL. This study also tested associations between TL and two measures of adiposity: BMI and height-adjusted waist circumference. Specifically, it tested the

hypotheses that BMI would have a curvilinear association with TL and that waist circumference would have a linear, negative association with TL.

Methods

Study Population and Setting

Data for this study came from the Cebu Longitudinal Health and Nutrition Survey (CLHNS). More specific details on the CLHNS study can be found elsewhere (126-128). In brief, a single-stage cluster-sampling procedure was used in 1983 to randomly select pregnant women among 17 urban and 16 rural administrative units from Cebu, the second largest metropolitan area of the Philippines. Between May 1, 1983 and April 30, 1984, 3080 of the 3327 women originally interviewed (ages 14-47 years old) gave birth to singletons. Frequent surveys on maternal nutrition, sociodemographic characteristics, and infant health and feeding patterns were administered during the mothers' pregnancies and the first two years after parturition. Subsequent surveys to collect information on diet, health history, nutritional status, and physical activity were administered in 1991-92, 1994-95, 1998-99, 2002-03, and 2005-06. In 2005, fasting venous blood samples were collected from 1,779 offspring and 1,893 mothers for DNA extraction (129). This study was based on the telomere data from offspring only. All study protocols were originally reviewed and approved by the Institutional Review Board of University of North Carolina at Chapel Hill. University of Washington's Institutional Review Board does not require additional human subjects approval when using de-identified data.

Measurement of Telomere Length

Methods of telomere measurement for these samples are described in greater detail elsewhere (129). In brief, TL was assayed from the blood samples following procedures for the monochrome multiplex quantitative polymerase chain reaction (qPCR) method (130) with several modifications (129). This method yields a measure of the ratio of the number of

telomere repeat copy number (T) to the length of the single-copy gene copy number (S) that is proportional to the average TL (130, 131). This ratio was normalized by dividing it by a single T/S reference value from controls run in six replicates per plate (129). This normalized ratio produces an estimate of the relative average blood TL that should closely correspond with the measure of terminal restriction fragments used to estimate TL with the gold standard (33) Southern blot method (130). Though TL measured in blood is commonly considered to be exclusively of leukocyte origin, the possibility of other cellular and non-cellular sources of DNA in the blood (129, 132) justify referring to TL in this study as blood TL rather than leukocyte TL.

Telomere length was successfully extracted from 1,753 singleton offspring samples. Approximately 2% (n=36) of the samples with intra-assay coefficients of variation (CVs) above 15% were be dropped from the analysis, leaving 1,717 young adults (900 males and 817 females) with reliable TL estimates (129). The intra-assay geometric mean of the CVs after excluding those >15% was 5.6%, similar to the 5.2% reported by Cawthon (130).

Dietary Assessment and Definition of Dietary Variables

Dietary intake data were collected in this study by trained personnel using 24-hour recalls when the offspring were on average 11.5, 15.5, 18.7, and 21.5 years old. One day of intake was recorded for offspring in the 1994-95 wave, and two days of intake were recorded in subsequent survey years (112). Dietary information was collected directly from offspring with parental supervision (112). Complete dietary information for all survey waves between 1994 and 2005 were available for 1634 of the individuals (777 females and 857 males) with telomere measurements.

Measures of average total energy intake during each survey year were based on previously published measures (112, 119, 133) estimated using the 1997 Philippines Food Composition Tables from the Food and Nutrition Research Institute (134). Estimations of coconut oil were also based on previously published estimates conducted by the CLHNS

research team (121). Individuals did not directly report how much cooking oil they consumed. However, they were asked which oil they generally used when cooking at home, and coconut oil is the primary oil used at establishments outside of the home (135). The CLHNS research team established a method for estimating coconut oil consumption involving multiplying the weight of fried or sautéed food reported in the 24-hour recalls by an "absorption factor" ranging from 0.025 to 0.17, depending on the kind of food and cooking method (135). Using this method, approximately 5 grams of coconut oil were added to every 30-50 grams of fried or sautéed food consumed by individuals who reported cooking with coconut oil or eating outside of the home.

Estimates of consumption of processed meat, fried or broiled/grilled meat, non-fried fish, soft drinks, and fruits and vegetables (grouped together) were calculated in grams, using the raw data and publically available codebooks. Processed meat included processed beef and processed pork products, including bacon, chorizo, hot dogs, ham, salami, and other canned meat and meat products. Fried and broiled/grilled meats included beef, poultry, pork, and other meats (both processed and unprocessed) that were coded as fried or broiled/roasted; it excluded animal parts (e.g., intestines, gizzards, feet, and liver). Total fish consumption was based on recall of consuming any fresh, smoked, dried, canned, or fermented fish and shellfish. It included only raw, boiled, or sautéed fish and excluded fried and broiled fish, which, like fried or broiled meat, tend to be high in AGEs (59). Fruit and vegetable consumption was the combination of all fresh, pickled, or dried vegetables (leafy and non-leafy vegetables and tubers), cooked and raw, combined with fresh, dried, and canned fruits. It excluded fruit juice, coconut, and fruit-based desserts.

Assessment of Adiposity

Weight, height, and subscapular and tricep skinfolds were measured in all five follow-up survey waves. Waist and hip circumferences were measured in the 1998, 2002, and 2005 waves. Recent studies have suggested that the sum of subscapular skinfolds may provide more

valid estimates of body fat than other surrogate measures among children and adolescents (136-139). But they are also more prone to measurement error (140), while BMI, BMI z-scores, waist circumference, and waist circumference-to-height ratios may provide decent approximations of body fat (136, 137, 141) and be less prone to measurement error (140).

For the purpose of this study, BMI z-scores and height-adjusted waist circumference were used as proxies for adiposity, the former potentially representing overall fat mass and the latter representing the central adiposity that may be even more predictive of disease risk (142). BMI z-scores were used to obtain a measure of BMI that could be compared across all juvenile and early adult years; this method also controls for differences in age across individuals at time of anthropometric measurements. Estimation of BMI z-scores was based on reference values for 5- to 19-year olds established by the World Health Organization (143, 144), which, though based more on Western populations (144, 145), are used worldwide (146). As the +1 SD and a +2 SD at 19 years old closely correspond with the international standard adult cut-offs for overweight and obesity of 25 kg/m^2 and 30 kg/m^2, respectively (144, 147, 148), BMI z-score estimates for 20-23 year olds were based on the 19-year-old reference values for males and females.

Covariates of Interest

Older age and male sex are the few factors that are consistently associated with shorter age-adjusted TL in adult populations (33). As TL is comparable among males and females at birth (149), this sex difference appears to be due to higher telomere attrition rates in males (99, 149). Thus, adjustment for age at the time of blood collection, sex, and an interaction between age and sex were included in all models.

Smoking (93), low socioeconomic status (150, 151), and psychological stress (152) have also been associated with shorter TL in some studies. Such findings have not been consistent throughout the literature, and the strength of associations tend to be marginal at best (33, 153).

Nonetheless, as these factors can each influence oxidative stress and inflammation, both smoking status and household income (a surrogate for environmental and psychosocial stressors) were covariates in the statistical models. Smoking status was obtained from 2005 survey data on whether the offspring had ever smoked and whether they still smoked. Total household income was estimated each year based on a series of questions on earnings for any household member over the age of six from employment, agricultural or commercial activities, and other sources. This data was used to calculate an average weekly income in each survey wave that was deflated to 1983 price indices (154).

Statistical Analyses

For the statistical analyses, each food group of interest (measured in grams) was averaged across the two 24-hour recalls for each survey wave, if applicable, and then divided by the average number of kilocalories consumed in each respective year and multiplied by 1000 to get a standardized unit of measurement for each food group: grams/1000 kilocalories, known as nutrient density. These proportions were then averaged across each of the survey waves to obtain a single measure of consumption for each food group.

Total kilocalories were also averaged across the four survey waves. Eighty-three individuals were excluded due to incomplete dietary information across the four time periods. The dietary models were run initially among all individuals with complete dietary information across all four years (n=1632). As seemingly implausible low and high values for caloric intake were recorded for some individuals in some years, the dietary models were run a second time excluding additional individuals (n=132) with caloric intake values in approximately the lowest 1% or 3 SD above the mean of sex-specific kilocalorie distributions in any survey wave. These cut-off values closely corresponded with the recommended cut-points of <500 and >3500 kilocalories for women and <800 and >4000 kilocalories for men (155) but have broader ranges to account for the different nutritional deficits and energy needs of this young, non-Western

population. The exclusion of individuals with extreme caloric intake values did not change the interpretation of any of the results. Thus, only the results of the first analysis are described here; the results of the second analysis are presented in the appendices (Appendix B).

Similarly, BMI z-scores were averaged across the five survey waves from 1991 to 2005 to obtain a single exposure measure that represents adiposity across the juvenile and early adult years. Time points for women who were pregnant during or for more than four months prior to the 2002 or 2005 survey waves were excluded from the calculation of BMI z-score averages. Among non-pregnant women, BMI z-scores did not differ significantly between 2002 and 2005, but they do differ significantly across other years. For that reason, women who were pregnant during or within the year prior to both 2002 and 2005 (n=32) were excluded from the analysis of BMI z-scores altogether, and any females with missing BMI measurements in the 1991-1998 survey waves or in both 2002 and 2005 (n=54) were also excluded. In contrast to females, males on average experienced large differences in BMI z-scores across all survey waves; thus, males with missing BMI measurements in any year (n=41) were excluded from the BMI analysis. Together, this left 1623 individuals (763 females and 860 males) with BMI z-score, TL, and income data.

In contrast to diet and BMI, height-adjusted waist circumference was assessed individually for each year, excluding women who were pregnant during or for more than four months prior to the respective survey waves (n=102 females excluded in 2002 and n=177 females excluded in 2005). This resulted in sample sizes of 1681, 1587, and 1528 in 1998, 2002 and 2005, respectively.

Smoking status entered the models as a categorical dummy variable: never-, prior-, or current smokers. The log-transformed average weekly inflation-adjusted household income across 1994 to 2005 was used in models assessing dietary variables. Although 70 individuals were missing information on household income for one or more of those four years, those same individuals were also missing information on diet. For the BMI model, however, a greater

number of subjects with non-missing BMI averages had missing values for average household income. Consequently, that model adjusted only for log-transformed household income in the year for which there were the fewest missing values (missing n=4): 1994. The waist circumference models adjusted for log-transformed income in each of the respective years. Finally, as a sensitivity analysis to support the use of income variables as a proxy for environmental and psychosocial conditions, models of dietary variables and BMI z-scores were run a second time controlling for the highest level of education attained as of 2005 in place of income. This sensitivity analysis was not run in the waist circumference model, as there was no evidence of an association between educational attainment in 2005 and waist circumference in any year.

For descriptive purposes, chi-squared and one-way ANOVA tests were used to assess univariate differences in demographic and anthropometric characteristics across relative TL (T/S ratio) tertiles. T-tests were used to compare differences in mean energy intake and consumption of major food groups between males and females. One-way ANOVA tests were used to assess differences in dietary characteristics across average BMI z-score categories with the following cut-points: -2, -1, 0, and 1 SD.

For testing the hypotheses, multivariate linear regression with robust standard error estimates was used to test the change in relative TL (T/S ratio), modeled as a continuous linear variable, in relation to the dietary and adiposity measures of interest. All statistical models were planned *a priori*, but covariates were added incrementally in some models to assess changes in beta coefficients and adjusted R^2 values.

To test the association between TL and dietary variables of interest, each dietary variable was first assessed individually, controlling only for average caloric consumption, age (in months) in 2005, sex, and an interaction between age and sex (Model 1). The same model was then run controlling for log-transformed average weekly household income between 1994 and 2005, and smoking status (Model 2). Finally, the model was run with all dietary variables

together (Model 3). Recognizing substantial collinearity due to correlations between food groups of up to 39%, Wald's tests were used to assess the association of all of the hypothesized detrimental foods (soda, meats, coconut oil) and the beneficial foods (fish and fruits and vegetables) together.

To test the association between TL and BMI, TL was regressed on average BMI z-score, entered as both a linear and a quadratic term to account for a potential negative impact of both under- and overnutrition on TL. This model first tested for an interaction between average BMI z-scores and sex (Model 4) and then, for ease of interpretation, was run separately on females (Model 5) and males (Model 6). These models controlled for age (in months) in 2005 and log-transformed income in 1994.

Finally, to test the association between TL and waist circumference, TL was regressed on waist circumference individually in 1998, 2002, and 2005, controlling for height, log-transformed inflation-adjusted income in each of the respective survey years, and age (in months) in 2005. As with the BMI z-score analysis, this model was first run testing an interaction between waist circumference and sex (Models 7a-7c) and then separately for females (Models 8a-8c) and males (Models 9a-9c).

Given the sample size of 1632 in the fully adjusted dietary model (Model 3) and a baseline adjusted R^2 of 0.0227, the dietary analysis had 89% power to detect a difference of 0.01 in the R^2 at the standard alpha-level of 0.05 and 71% power to detect a difference of 0.01 at a Bonferroni-adjusted alpha-level of 0.0083 to account for the multiple comparisons of six different food groups. With the same baseline R^2 and a sample of 1623, the BMI model with both sexes (Model 4) had 92% power at an alpha-level of 0.05 to detect a change of 0.01 in R^2, and it had 82% power to detect such a change at an adjusted alpha-level of 0.0125 to account for the four different tests of adiposity (average BMI z-score and waist circumference in three separate years). Finally, the same 0.01 difference in R^2 could be detected at an adjusted alpha-level of 0.0125 with 91%, 89%, and 88% power in the 1998, 2002, and 2005 waist

circumference models, respectively, given combined male and female sample sizes of 1681, 1587, and 1528 in those respective years.

All analyses were performed using Stata 13. Models were first run without robust standard errors in order to assess model assumptions using the Breusch-Pagan/Cook-Weisberg and White tests for heteroscedasticity and residual and normal quantile-quantile plots. Adjusted R^2 values could also only be obtained from models without robust standard errors. The models were then run a second time with robust standard errors to account for the heteroscedasticity of the residuals in most models. Only the adjusted R^2 and robust standard errors are reported herein.

Results

Offspring were 20.8-22.5 (mean=21.7) years old at the time of the venous blood draw in 2005; there was no significant difference between males and females with respect to age ($p=0.44$) (Table 1). Differences existed between males and females with regard to educational attainment and smoking status. Females had on average one additional year of education by 2005, and were considerably less likely to be current or former smokers. There were no significant differences between sexes with regard to weekly inflation-adjusted household income in any individual survey year or in average income.

There were a number of significant differences between males and females with regard to dietary characteristics (Table 2). Females reported consuming on average more grams of fried/broiled and processed meat, oil, vegetables, fruit, and soda per 1000 kilocalories across the years. Males did consume approximately 500 more calories on average and were obtaining more of their calories from rice and alcohol compared to females. There also appeared to be significant differences in caloric intake and consumption of food groups of interest across different categories of average BMI z-score (Table 3). Though the trends were not particularly

linear, individuals in the upper BMI z-score categories tended to consume more calories; more meats, coconut oil, and soda; less fish; and fewer fruits and vegetables.

Body composition differed between males and females as well (Table 1). Based on the recommended BMI z-score cutoffs for underweight, overweight, and obesity of < -2 SD, >1 SD, and >2 SD, respectively (143), males were more likely than females to be in the extreme categories of underweight and overweight in most years, with the exception of 2005, when a greater proportion of females was underweight compared to males. Females, however, were more likely than males to have a waist-to-height ratio greater than the recommended cutoff of 0.5 (156, 157), particularly in 2002 and 2005.

Relative TL measured in this population with the qPCR method ranged from 0.11 to 1.56 (mean=0.78) (Table 1). Even among this narrow age range, there was a significant decline in relative TL with each additional month in age: β=-0.005 (95%CI:-0.007 to -0.003; p<0.0005); the association between TL and age was strong in both females and males. Though females had, on average, longer TL (β=0.029; 95%CI: 0.013 to 0.045; p=0.001), there was no evidence of an interaction between sex and age (β for interaction=-0.002, p=0.26). Interestingly, inclusion of the interaction term removed the significance of the sex-TL association in the baseline model and in all subsequent models. Nonetheless, despite no indication of a significant interaction between age and sex among this population, the interaction term was kept in all models as part of an *a priori* decision informed by the literature and supported by a visual indication of a slight interaction (Figure 1).

Accounting for only 1.55% of the variance (according to the adjusted R^2 value), age explained the highest, yet still a small, portion of the variation in TL compared to the other covariates. Sex accounted for 0.64% of the variance, and together sex and age and the interaction between the two accounted for 2.25% of the variance among the entire sample and 2.53% of the variance for individuals with complete dietary data. Adding average kilocalories and each of the individual dietary variables of interest one at a time made little difference in the

adjusted R^2 value, and none of the dietary variables was associated with TL in any of the models (Table 4). The Wald's test for assessing the effect of processed meat, fried/broiled meat, coconut oil, and soda together was not significant (p=0.43), nor was the Wald's test for fish and fruit and vegetable consumption together (p=0.61). Additionally, only half of the beta coefficients were in the predicted direction. For example, in line with hypotheses, the beta coefficients for soda and coconut oil intake were negative, while the beta coefficients for fish intake were positive in all models. Contrary to the hypotheses, however, processed meat and fried/broiled meat had a positive beta coefficient and fruits and vegetables had a negative beta coefficient in all models.

As with the dietary variables, the models of BMI and height-adjusted waist circumference demonstrated a lack of association between measures of adiposity and TL. There was no evidence of either a linear or a quadratic association between average BMI z-score and TL in either males or females (Table 5). In fact, the inclusion of the linear and quadratic terms for BMI z-score had no effect on the adjusted R^2. Not surprisingly, the sensitivity analysis using years of education in place of household income in 1994 made no difference in the results (data not shown).

Similarly, there was no evidence of a linear association between waist circumference and TL among males and females for any of the three survey waves assessed (Table 6). There was also no evidence of an interaction between waist circumference and sex. However, the adjusted R^2 did increase with each year and the association between waist circumference and TL approached significance for males in 2005 (p=0.099). Interestingly, the relationship was in the opposite direction (a positive direction) than had been hypothesized. And overall, the direction of association between waist circumference and TL for males was positive in all years and was inconsistent across years for females.

Discussion

This study aimed to assess the association between TL and diet and between TL and adiposity with the objective of better understanding the effect of diet and nutrition on disease and aging processes. The study population was thought to provide a unique opportunity to A) explore relationships between TL and diet and nutritional status in a non-Western population and B) assess longitudinally how diet across years of growth, development, and rapid cellular turnover may impact TL. In line with previous studies and reviews (33), age and sex were the only variables that were consistently associated with TL, even despite a relatively narrow age range. The average decrease of 0.005 in relative T/S ratio for each additional month in age is quite rapid compared to the same reported decrease for every additional year of age among 45 to 84 year-olds in the U.S. (63). Using an estimate of the absolute TL of the reference DNA used to obtain the T/S ratios in these samples, this change of 0.005 was estimated to translate into an average decrease of 13.8 base pairs/month, or approximately 165 base pairs/year. This rate of telomere attrition is greater than the suggested rate of 30-100 base pairs/year in later adulthood (33), and it supports the notion that telomere attrition is more rapid in the earlier years of life (111).

Contrary to all hypotheses, there was no indication of an association between TL and the dietary variables assessed (processed meats, fried/broiled meats, non-diet soda, coconut oil, fruits and vegetables, and fish) or with measures of adiposity (average BMI z-score and height-adjusted waist circumference). These null findings contrast with the one study that reported an inverse association between relative TL and processed meat (63), with two studies that found positive associations between vegetable consumption and TL (61, 67), and one study that found a positive association between fruit consumption and TL (158). However, these null findings are in agreement with three studies that found no association between TL and fruits and vegetables assessed together (70) or separately (62, 63) and three studies that found no association between fish consumption and TL in their fully-adjusted models (61-63).

Furthermore, the association between TL and vegetable consumption reported by Tiainen et al. (67) was not consistent across sexes. No previous studies explored the relationship between coconut oil and TL. However, given the SFA content of coconut oil, the null results in the present study contrast with the two studies that found inverse associations between SFA intake and TL among males (67) and females (68) but agree with the two studies that found no association between SFAs and TL (69, 70). There are no previous studies exploring the effect of fried and broiled/grilled meat on TL with which to compare the results in the present study.

With regard to the null associations between relative TL and measures of adiposity, the results of the present study contrast with the few other studies conducted with children, adolescents, and young adults that report significant inverse associations between TL and obesity status (159), BMI (94), and waist circumference (94). The present results also contrast with studies that provide evidence for varying effects of adiposity on TL depending on sex (96, 101). At the same time, these results are in line with other studies that report null associations between obesity status and TL in children (100), between BMI and TL in adolescents (102), and BMI and TL in young adults (69). The results from many other studies on the association between adiposity and TL among adults have also been inconsistent (33, 160).

There are a number of reasons why the present analyses may have failed to provide evidence for relationships between TL and diet or adiposity measures when a few other studies did. For one, this population was younger than all the other populations in which significant diet-TL relationships were found. In most other studies on this topic (see Appendix A) the populations were at least 30 years old and older. Though senescence can ostensibly begin at any age (161), the cellular damage known to accumulate with age (44) may simply not have been considerable enough among this younger population. Or the internal responses that modulate oxidative and inflammatory processes may still function adequately or not be sufficiently overtaxed at younger ages. As such, perhaps neither inflammatory foods nor foods with anti-oxidative and anti-inflammatory properties make a large enough difference on TL in

younger populations to be observed. In other words, the biological processes that help maintain TL may generally be more robust against environmental insults among younger age groups.

Apart from being young, another reason why foods may not have had much of an impact on this group may have been because of their relatively low energy intake and relatively low levels of adiposity. The average of 1542 and 2198 kilocalories among the young adult females and males, respectively, of this Cebu population in 2005, is lower than energy intake of other populations in which diet-TL relationships have been assessed (61, 67, 69, 70). As expected, the Cebu males and females also had lower BMI (67, 69, 70) and waist circumference (70) than the populations of those other studies where such measures were taken. Even among other study populations where average caloric consumption was not noticeably greater than in Cebu (62, 63, 68), BMI (62, 63, 68) and waist circumference measurements (63) were still noticeable higher than those recorded among this Cebu sample. No known studies have explored interactions between energy intake and food groups, but the few studies that have looked at interactions between dietary factors and BMI have generally found that the effect of certain foods and nutrients may depend on adiposity (67, 162). For example, Tiainen et al. (67) found that the associations between TL and margarine intake among men and vegetable intake among women were significant among overweight and obese individuals but not among their normal-weight counterparts. Another study (162) recently suggested that salt intake may impact TL in overweight and obese adolescents, while a similar association was not found in normal-weight adolescents. In other words, it may be that the body can generally prevent damage caused by the inflammatory and oxidative properties of food, except when the body is already over-stressed, as in the case of chronic caloric excess and obesity.

Alternatively, there may be some genetic, developmental, or environmental factors that influence this population's ability to regulate inflammation and oxidative stress (163). One study, for instance, reported, that this same young adult Cebu population had dramatically lower C-reactive protein (CRP) concentrations compared to age-matched controls from the U.S., despite

relatively high pathogen exposure among the former (163). A later study also demonstrated that this Filipino population has lower levels of the inflammatory cytokine, interleukin-6 (IL-6), and higher levels of the inflammation-inhibiting cytokine, interleukin-10 (IL-10), compared to levels reported among many U.S. and European populations (164). Differences in adiposity only explain some, but not all, of these population differences in markers of inflammation. Though waist circumference was positively associated with CRP levels in Filipino females, and skinfold thickness was positively associated with CRP in Filipino males, these young adult Filipinos still had lower CRP than their U.S. counterparts after controlling for adiposity levels (163).

Apart from any genetic or early developmental factors that may contribute to the lower levels of inflammation among this Cebu population (163, 164), their relatively low calorie diet may be another one of the factors that protects against inflammation, as well as accelerated telomere attrition. Evidence suggests that a reduction in caloric intake of as little as 8% could help reduce oxidative stress and inflammation (89, 104). A large proportion of the individuals in this population could potentially be considered to be consuming a moderately calorically restricted diet, especially if they are modestly physically active. Consequently, many individuals may have simply had reduced diet-induced oxidative stress and inflammation, regardless of the types and amounts of specific foods they consumed.

On the other side of this, however, it is worth noting the number of individuals who were underweight in this population. Not only might these individuals have been undernourished and more susceptible to infection that could impact TL (165), but their underweight status may have also been a proxy for other developmental, environmental, and psychosocial stressors that could further contribute to accelerated telomere attrition (152, 166, 167). It is somewhat surprising, therefore, that there was no indication that a low average BMI z-score was associated with TL given so many who may have been undernourished and potentially more susceptible to infection. Perhaps, therefore, as McDade et al. suggest (168), exposure to

infection, especially if occurring in the critical years of immune function development, actually helps to support more effective anti-inflammatory regulatory networks later in life.

Other reasons for a lack of association between the dietary factors of interest and TL may be related to the relatively low intake of many of the food groups analyzed. For example, the null association between fruit and vegetable consumption and TL was not particularly surprising given the low level of fruit and vegetable consumption among this population. Many countries now recommend consuming at least 400 g of fruits and vegetables a day, with a standard portion estimated around 80 g (169). The averages of 8-11 g/1000 kilocalories of fruit and 28-34 g/1000 kilocalories of vegetables grossly miss this target. In fact, no more than 15 individuals in any given year consumed 400 or more grams of fruits and vegetables. While many of the other populations studied where similar associations were assessed did not necessarily consume an average of 400 g of fruits and vegetables or 5 servings a day, they all consumed substantially more on average than the Cebu population, with greater variation between individuals. Moreover, they may have consumed a greater proportion of raw vegetables. Among the Cebu population, vegetables, when consumed, were mostly consumed in cooked form (primarily boiled or sautéed); less than 2% of the vegetables consumed in any given year were consumed in raw form. There is evidence that cooking lowers the antioxidant content of vegetables (170); and epidemiological studies have indicated that the benefits of raw vegetables on mortality (171) and cancer risk (172) are markedly greater than those of cooked vegetables.

Similarly, meat consumption as a whole was not particularly high. Given a typical serving size of unprocessed meats of 100 g (~3.5 oz.) (53), females and males consumed an average of 0.56 and 0.79 servings/day of unprocessed red meat and poultry. Even in 2005, the ~48 g/1000 kilocalories or 0.8-1.2 servings of unprocessed meat, was still in the mid-range of average meat consumption reported in U.S., European, and Chinese populations (66). Of course, the amount of that meat that was fried or grilled/broiled was even lower. Though there are no studies with which to compare fried and grilled/broiled meat consumption, it is possible

that consumption among the Cebu population was too low to have a substantial effect on TL. The same may be said for fish consumption, which, when considering only non-fried and non-broiled fish, was relatively low compared to the other populations in which no association with TL was found (61-63).

Likewise, the average of 4-5 g/1000 kilocalories of coconut oil in this population may have also been too low to have an observable effect on TL, though this is difficult to compare, as no known studies have explored the effect of coconut oil intake on TL. Yet, even when looking at overall cooking oils and added fats, the 13.7 and 15.7 absolute grams of oil and fats used by females and males in this population, respectively, is considerably lower than the average of 17.7 and 22.7 grams consumed the elderly Chinese females and males in Chan et al.'s study population (62). Thus, while the lack of association on one hand could be inferred to mean that neither coconut oil nor non-dairy, non-meat sources of SFAs are associated with TL, the consumption patterns and lack of associations with other dietary variables makes this an unreliable interpretation.

Soda consumption was also not particularly high when averaged across years or when looking at any particular year. The reason for that was that many people did not report consuming soda, particularly in the early years. Even in the latter years, assuming a serving size of 12 oz. (~340 g), the Cebu population averaged 0.30 to 0.35 servings of soda a day. This number is less than the averages (ranging from 0.39 to 0.48 across TL quartiles) consumed by the multi-ethnic U.S. study population of Nettleton et al. (63). Nonetheless, when looking at the number of individuals who consumed at least one serving of soda a day, up to 109 males and up to 107 females consumed at least 12 oz. of soda a day in the latter years. Even just one serving a day, if consumed regularly, has been estimated to lead to weight gain and increased diabetes risk (173). Slightly higher consumption of sugar-sweetened beverages (~20 oz.) has also been shown to be associated with increased markers of inflammation (174). So, even with

only low to moderate consumption of soda, it is still somewhat remarkable that there was no association with TL.

In contrast to the other food groups examined, it was intriguing that no association was found between TL and processed meat among this population. Given even a more liberal definition (50 g) of a serving of processed meat (53), the Cebu males and females ate on average 0.37-0.46 servings of processed meat a day. This amount is considerably greater than the averages of 0.11 to 0.19 servings across the different quartiles of TL among Nettleton et al.'s study (63), in which a significant association with TL was reported. This amount is also larger than the average intake reported among many populations of other epidemiological studies (66). If there were truly an association between processed meat and TL in the younger years of life, it seems that this analysis should have been able to detect it. Perhaps it is only certain processed meats that have an effect on TL, as Nettleton et al.'s study suggested (63). The use of 24-hour recalls in the present study allowed for a broader definition of processed meat that may have diluted observable effects.

Beyond true potential differences in the lifestyle and anthropometric characteristics of the Cebu population, there are also methodological limitations that could have biased the results of these analyses. All methods of dietary assessment are prone to some degree of error. While multiple 24-hour recalls tend to be considered less biased than the FFQ (albeit still an imperfect method) for dietary measurement (113), the one to two 24-hour recalls per study wave in this population may not have been sufficient to capture the usual diet at any given period of time or to account for potential seasonal fluctuations in diet. Furthermore, the collection of 24-hour recall data from individuals when they were children and adolescent may have been less accurate (175). Even with parental supervision, individuals may have been more likely in those younger years to simply leave out foods, or they may have been even more prone than adults to inaccurately estimate portion sizes (175). It remains unclear, therefore, the degree to which the

extremely low and high values for caloric intake among some individuals in some years were due to inaccurate reporting as opposed to real caloric deficits or surpluses.

Additionally, neither BMI z-scores nor waist circumference, even when controlling for height, are necessarily the best proxies for adiposity in children (137). It may have been worth exploring the relationship between TL and the sum of subscapular and tricep skinfold thickness, which has been more highly correlated with the gold standard dual-energy x-ray anthropometry (DEXA) in children and adolescents (136, 137). But in an effort to avoid too many multiple comparisons, this relationship was not assessed. Further, given that the two measures chosen are still highly correlated with both trunk and total body fat (136, 137) and tend to be less prone to measurement error than skinfold measurements (140), they should have still been able to provide a reasonable proxy with which to observe an association if a true TL-adiposity relationship were to exist in this population.

Furthermore, the method for assaying TL may have introduced another source of variability that could attenuate results (25). Compared to other methods of assaying TL (e.g., Southern Blot), qPCR methods tend to have higher CVs (33). Just a CV of 2% could mean a difference in 100-300 base pairs in telomere length for proliferating human cells that tend to range from 5,000 to 15,000 base pairs (33). The CVs of the present study were quite variable, ranging from 0.12% to 14.99%. Additional sources of variability come from the fact that TL can differ not only across different cells but also within the same cell, and neither qPCR nor other existing methods have the precision to measure TL of a specific chromosome (25). These methodological sources of variability may have decreased the power to detect a significant effect size given the sample size.

Still, other sources of variability and residual confounding may have come from factors either not measured in the study or not controlled for in the analyses. For example, TL is known to be quite variable even among newborns (149), but this was a source of variability that could not be controlled for given lack of data on TL at birth. Other potential factors that could have

influenced relationships between TL, diet, and adiposity may have included rural vs. urban residence, physical activity, environmental sanitary conditions, early childhood conditions, psychosocial stress, use of vitamins/supplements, medication use, and pre-existing health conditions. Some of these factors would potentially artificially inflate associations with some dietary variables, which was not an issue here. But others could have artificially deflated associations with some food groups.

This study also had other limitations with regard to the statistical approach chosen for defining variables and modeling associations. Most obviously, the averaging of dietary variables and BMI z-scores across different periods of growth and development (and potentially changing environments and lifestyles) was not ideal. However, as having only one outcome variable limited the choice of statistical models for dealing with repeat measurements (e.g. generalized estimating equations or generalized linear mixed models), and given the limited prior evidence about a particular critical period or lag time, this was deemed the most appropriate method for using all the available exposure information. Other factors that may have influenced the analyses were the definitions of variables. For example, the indirect estimation of coconut oil intake combined with imprecise estimates of portion size may have led to large over- or under-estimations. Additionally, combining grams of fruits and vegetables together could have influenced study results. Not only do weights in the two different categories mean different things in terms of serving sizes, but it has also been mostly vegetables rather than fruits that have been associated with TL in previous studies (61, 67) and with mortality in other epidemiological studies (171). Still, given such low levels of fruit and vegetable consumption and the hypothesized beneficial antioxidants and nutrients in both food groups, it seemed appropriate to combine the two.

It should be noted that in most other studies that assessed TL-diet associations, adjustments were made in the statistical models for measures of adiposity, most frequently BMI (62, 63, 67-70). Measures of adiposity were not included in the *a priori* models for testing the

TL-diet relationships for two reasons. First, the relationship between TL and measures of adiposity were a separate primary statistical test because it was unclear from the literature that adiposity was associated with TL in this age group. Second, if adiposity were associated with TL, it was hypothesized to be in at least one of the causal pathways between diet and TL, and controlling for it straightaway would, therefore, attenuate any observed associations. Thus, this was one area where the decision to add covariates in an additional exploratory model was based on the results of the predetermined tests. In other words, adjusting for measures of adiposity would have been useful for exploring whether associations between diet and TL existed above and beyond those that existed through pathways of adiposity. But the null results of both the dietary models and the adiposity models suggested that further exploration of this level of association would not be meaningful.

Finally, it is possible that this study simply lacked the power to detect an association between TL and diet or adiposity. Taking into account the multiple comparisons with an adjusted alpha-value, the dietary, BMI, and waist circumference models had 71%, 82%, and 88-91% power to detect a change of 0.01 in the R^2, which would typically be considered to represent a conservatively small effect. However, in these models, the adjusted R^2 didn't increase more than 0.0005, and in many cases actually decreased when the predictors of interest were added to the baseline models. Even the unadjusted R^2 (data not shown) did not change more than 0.002 in any of the models. Notably, the two known factors that influence TL, age and sex, accounted for only 1.6% and 0.6% of the variance, respectively. Part of the reason for the low predictive power of age and sex may be due to the narrow age range and young age, as the gap between males and females is expected to widen with age (149). A coefficient of determination as high as 0.08 (8%) for age has, for example, been reported among populations ranging in age by several decades (95). Still, it may be that, among this young, non-obese, non-Western population, it was unreasonable to expect even an increase of 0.01 in the predictive power of the models when adding dietary factors or adiposity. Other studies have also indicated

that any single dietary or lifestyle factor alone may have a negligible effect on TL but that, when looking at a composite score of dietary patterns or healthy lifestyle characteristics, there are significant associations with TL (49, 50).

Despite the methodological and statistical limitations mentioned above, the strengths of this study still give credit to these null results and suggest that they still provide meaningful information. The longitudinal assessment of dietary and nutritional exposures is something that previous studies have not had. Their use as a life course average mostly prior to the outcome ascertainment is a strength. Additionally, the multiple 24-hour recalls for dietary assessment, despite the limitations mentioned above, may have still been better at capturing usual diet and capturing information about foods not typically included in FFQs. Furthermore, the exploration of understudied (e.g., processed meats and soda) and unexplored (e.g., fried/broiled meats and coconut oil) dietary variables provides a valuable contribution to the literature. Finally, the exploration of TL-diet and TL-adiposity relationships among a younger, non-Western population provides information on the influence of diet during rapid cellular division and physical growth and among a population undergoing nutritional transition (109, 112).

It is important to consider the possibility, therefore, that there simply may be no association between TL and diet or adiposity in young and mostly non-obese individuals. Given the multiple comparisons in other studies, it is possible that some of the significant associations arose by chance alone. Or TL may have simply been correlated with other physiological responses to diet and body composition. This does not necessarily mean there is no relationship between diet and aging, however. The aging process is extremely complex, and TL is now recognized as only one of many hallmarks of aging (9). There are other mechanisms through which cellular and molecular damage and senescence can occur (43, 176, 177). Furthermore, it remains unclear whether shortened telomeres are really a cause, correlate, or consequence of aging and disease, and it has recently been questioned whether TL is really the biomarker of aging that some have proposed it to be (12, 13). A recent review of the evidence

has suggested that TL does not actually meet all of the criteria for a reliable biomarker of aging (25), as it is neither consistently associated with higher risk of mortality nor age-related deterioration of tissue and organ function. TL may also just be an indicator of aging in certain tissues rather than organismal aging (33). Nonetheless, even those who call to question the free radical theory of aging recognize that diet and nutrition influence rates of aging; it may just occur through different pathways or through a combination of pathways (178).

This study will hopefully inspire similar studies in young, non-Western populations, as more research is warranted to shed light on whether the results of this study are due to methodological and statistical issues, whether diet takes more time to influence TL, or whether diet has any causal effect on TL at all. The results from this study suggest that future studies should include multiple measurements of TL to allow for more sophisticated modeling techniques (33) and better assess potential causal relationships between diet, adiposity, and telomere attrition rates. It may be appropriate for future studies to explore both individual food groups and overall dietary patterns, and there is particular need for this in non-Western populations. Furthermore, future studies may also want to further examine specific nutrients that have not been well-explored. For example, recent research suggests that reductions in dietary intake of the amino acid, methionine, may be largely responsible for the beneficial effects of caloric restriction on longevity and health markers (4, 179). Hence, it may be worth looking at overall dietary methionine or protein intake as opposed to consumption of isolated food groups. Finally, as accelerated telomere attrition may be only one potential pathway through which diet and nutrition could contribute to cellular damage and aging, it may be worthwhile to consider TL in combination with other measures of inflammation, oxidative stress, and cellular degeneration.

In summary, this study found no evidence that individual dietary characteristics or measures of adiposity across the childhood, adolescent, and early adult years have a substantial influence on the telomere attrition of the young adult Filipino males and females of Cebu. These results contribute to the existing body of mixed evidence for TL-diet and TL-

adiposity relationships and provide new information regarding specific food groups (e.g. grilled/fried meats and coconut oil) and adiposity across childhood and adolescent years. However, these study results cannot be considered conclusive. Lack of association may have been due to the young age of the population, low calorie intake, low consumption of some of the food groups of interest, low levels of adiposity, population differences in anti-inflammatory regulatory networks, and/or methodological and statistical power limitations. Further research is needed with a variety of Western and non-Western populations of different ages to elucidate the reasons for inconsistent evidence across studies and populations. Future studies should ideally include multiple longitudinal measurements of diet, body composition, TL, and other markers of biological aging.

Tables

Table 1: Demographic and Anthropometric Characteristics by Tertile of Relative Telomere Length (T/S Ratio) and Sex

	ALL			RELATIVE TL (T/S RATIO) TERTILES						p^a
				1		2		3		
				Females (n=242)	Males (n=331)	Females (n=277)	Males (n=295)	Females (n=298)	Males (n=274)	0.003
DEMOGRAPHICS	**N**	**Mean (SD)**	**Range**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	
Relative TL	1717	0.78 (0.17)	(0.11 - 1.56)	0.60 (0.07)	0.60 (0.07)	0.76 (0.04)	0.76 (0.04)	0.98 (0.12)	0.97 (0.11)	
Age, 2005 *(years)*	1717	21.7 (0.3)	(20.8 - 22.5)	21.7 (0.3)	21.7 (0.3)	21.7 (0.4)	21.7 (0.3)	21.6 (0.4)	21.6 (0.4)	<0.0005
Weekly Income, 1994 *(Philippine Pesos, inflation-adjusted)*	1713	496 (478)	(-19 - 11309)	477 (411)	488 (440)	538 (748)	507 (419)	475 (361)	488 (393)	0.27
Average Weekly Income, 1994-2005 *(Philippine Pesos, inflation-adjusted)*	1647	563 (528)	(65 - 10644)	522 (307)	546 (556)	612 (530)	565 (407)	579 (738)	550 (491)	0.26
Years of Education, 2005	1703	10.9 (3.6)	(0 - 23)	11.2 (3.4)	10.4 (3.7)	11.4 (3.1)	10.6 (4.2)	11.6 (3.1)	10.2 (3.8)	0.58
Smoking Status in 2005 (%):	**N**	**%**		**%**	**%**	**%**	**%**	**%**	**%**	0.35
Never	706	40.3		66.5	17.3	63.8	22.3	66.7	15.1	
Former	507	28.9		5.0	51.1	6.9	45.2	6.7	52.2	
Current	528	30.1		28.5	31.6	29.4	32.5	26.6	32.7	
ANTHROPOMETRICS	**N**	**Mean (SD)**	**Range**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**p^a**
BMI Z-score, 1991	1703	-0.8 (0.9)	(-4.9 - 4.3)	-0.9 (0.9)	-0.84 (0.9)	-0.8 (0.8)	-0.8 (1.0)	-0.8 (0.8)	-0.8 (1.0)	0.70
BMI Z-score, 1994	1712	-1.1 (1.1)	(-4.8 - 3.3)	-1.0 (1.0)	-1.17 (1.1)	-1.0 (1.1)	-1.2 (1.2)	-1.0 (1.1)	-1.1 (1.1)	0.85
BMI Z-score, 1998	1689	-0.8 (1.1)	(-4.1 - 3.0)	-0.6 (1.0)	-1.05 (1.1)	-0.6 (1.0)	-1.0 (1.1)	-0.7 (1.0)	-1.0 (1.1)	0.80
BMI Z-score, 2002	1595	-0.8 (1.0)	(-3.9 - 4.0)	-0.6 (0.9)	-0.94 (1.0)	-0.6 (0.9)	-0.9 (1.0)	-0.6 (1.0)	-0.8 (1.1)	0.30
BMI Z-score, 2005	1534	-0.6 (1.1)	(-3.8 - 3.8)	-0.6 (1.0)	-0.6 (1.1)	-0.5 (1.0)	-0.5 (1.1)	-0.6 (1.1)	-0.5 (1.1)	0.79
BMI (kg/m^2), 2005	1534	20.7 (3.1)	(13.9 - 40.3)	19.9 (2.9)	20.93 (3.1)	20.2 (3.2)	21.1 (3.0)	20.1 (3.3)	21.2 (3.2)	0.99
Waist Circumference (cm), 1998	1689	63.9 (5.7)	(50.0 - 114.5)	62.9 (5.2)	64.7 (5.8)	63.4 (5.2)	64.8 (6.2)	62.7 (5.5)	64.9 (5.6)	0.55
Waist Circumference (cm), 2002	1595	67.3 (6.5)	(51.0 - 116.8)	65.0 (5.3)	68.4 (6.3)	65.5 (6.0)	69.2 (7.0)	65.7 (6.3)	68.6 (6.5)	0.31
Waist Circumference (cm), 2005	1532	70.2 (7.8)	(53.5 - 112.0)	67.0 (6.9)	71.8 (7.9)	67.7 (7.3)	72.7 (7.4)	67.5 (7.6)	72.1 (7.3)	0.74
Waist-Height Ratio, 1998	1689	0.4 (0.03)	(0.32 - 0.68)	0.4 (0.03)	0.4 (0.03)	0.4 (0.03)	0.4 (0.04)	0.4 (0.04)	0.4 (0.03)	0.76
Waist-Height Ratio, 2002	1595	0.4 (0.04)	(0.34 - 0.70)	0.4 (0.04)	0.4 (0.04)	0.4 (0.04)	0.4 (0.04)	0.4 (0.04)	0.4 (0.04)	0.40
Waist-Height Ratio, 2005	1532	0.4 (0.05)	(0.35 - 0.71)	0.4 (0.05)	0.4 (0.05)	0.5 (0.05)	0.4 (0.04)	0.5 (0.05)	0.4 (0.04)	0.94

[a] P-value for difference in characteristic across relative TL tertiles.

Table 2: Kilocalories/day and Dietary Intake (g/1000 kilocalories) of Specific Foods by Study Wave

FEMALES (n=777)	1994 Mean (Range)	1998 Mean (Range)	2002 Mean (Range)	2005 Mean (Range)	Average (94-05) Mean (Range)
Kilocalories/day	1152 (186-3735)	1291 (240-3948)	1516 (137-7112)	1542 (201-5138)	1708 (527-4342)
Food/Beverage (g/1000 kcal):					
Unprocessed Meat & Poultry	19 (0-220)	40 (0-236)	46 (0-234)	48 (0-292)	22 (0-82)
Grilled/Fried Meat	11 (0-138)	18 (0-137)	28 (0-203)	33 (0-230)	22 (0-111)
Processed Meat	7 (0-138)	12 (0-125)	15 (0-277)	17 (0-190)	13 (0-76)
Fish	31 (0-222)	23 (0-146)	33 (0-180)	35 (0-335)	31 (0-167)
Added Oils/Fats (all)	7 (0-41)	9 (0-42)	11 (0-47)	11 (0-42)	10 (0-27)
Coconut Oil	3 (0-23)	4 (0-24)	6 (0-29)	6 (0-31)	5 (0-14)
Fruit	16 (0-378)	5 (0-245)	14 (0-324)	10 (0-257)	11 (0-133)
Vegetables:	33 (0-641)	39 (0-439)	32 (0-267)	32 (0-390)	34 (0-272)
Green Vegetables	8 (0-312)	8 (0-226)	6 (0-180)	7 (0-226)	7 (0-93)
Yellow Vegetables	4 (0-114)	4 (0-123)	4 (0-57)	4 (0-137)	4 (0-34)
Root Vegetables	13 (0-381)	17 (0-221)	12 (0-212)	11 (0-192)	13 (0-128)
Fruit and Vegetables	49 (0-763)	44 (0-439)	46 (0-365)	42 (0-390)	45 (0-325)
Rice	226 (0-933)	249 (0-656)	247 (0-691)	258 (0-683)	245 (0-549)
Corn	195 (0-1076)	160 (0-1021)	67 (0-1025)	49 (0-1011)	118 (0-998)
Bread	33 (0-207)	18 (0-154)	21 (0-207)	23 (0-156)	24 (0-95)
Noodles	17 (0-440)	19 (0-248)	22 (0-213)	23 (0-304)	20 (0-127)
Beans	13 (0-201)	11 (0-159)	10 (0-138)	9 (0-180)	11 (0-116)
Soda	15 (0-508)	56 (0-652)	65 (0-778)	77 (0-746)	53 (0-272)
Alcohol	0	0	2 (0-710)	3 (0-329)	1 (0-177)

MALES (n=857)	1994 Mean (Range)	1998 Mean (Range)	2002 Mean (Range)	2005 Mean (Range)	Average (94-05) Mean (Range)	p[a]
Kilocalories/day	1249 (241-4521)	1892 (214-6309)	2076 (225-7046)	2198 (229-8826)	2228 (800-5786)	<0.0005
Food/Beverage (g/1000 kcal):						
Unprocessed Meat & Poultry	30 (0-468)	30 (0-224)	44 (0-269)	49 (0-325)	30 (0-468)	0.005
Grilled/Fried Meat	12 (0-258)	15 (0-137)	24 (0-147)	28 (0-197)	20 (0-98)	0.005
Processed Meat	6 (0-258)	10 (0-124)	13 (0-164)	15 (0-154)	11 (0-74)	0.001
Fish	32 (0-214)	22 (0-215)	31 (0-412)	32 (0-324)	29 (0-133)	0.19
Added Oils/Fats (all)	7 (0-51)	8 (0-40)	9 (0-56)	9 (0-45)	8 (0-24)	<0.0005
Coconut Oil	3 (0-26)	4 (0-17)	5 (0-29)	5 (0-27)	4 (0-13)	<0.0005
Fruit	17 (0-585)	6 (0-193)	4 (0-179)	5 (0-531)	8 (0-168)	<0.0005
Vegetables	30 (0-383)	34 (0-651)	28 (0-386)	22 (0-333)	28 (0-276)	<0.0005
Green Vegetables	9 (0-210)	7 (0-231)	7 (0-254)	4 (0-96)	7 (0-94)	0.37
Yellow Vegetables	4 (0-202)	3 (0-66)	4 (0-85)	2 (0-42)	3 (0-56)	0.001
Root Vegetables	10 (0-298)	18 (0-620)	8 (0-270)	7 (0-144)	11 (0-155)	<0.0005
Fruit and Vegetables	47 (0-683)	40 (0-826)	32 (0-386)	27 (0-617)	37 (0-319)	<0.0005
Rice	225 (0-841)	300 (0-797)	301 (0-686)	334 (0-715)	290 (0-565)	<0.0005
Corn	213 (0-1070)	128 (0-1115)	99 (0-1101)	79 (0-1112)	129 (0-954)	0.21
Bread	33 (0-215)	20 (0-158)	21 (0-193)	14 (0-169)	22 (0-93)	0.04
Noodles	13 (0-436)	19 (0-278)	21 (0-635)	21 (0-236)	18 (0-159)	0.05
Beans	12 (0-236)	10 (0-137)	11 (0-177)	11 (0-165)	11 (0-65)	0.63
Soda	10 (0-710)	48 (0-391)	54 (0-660)	45 (0-945)	39 (0-338)	<0.0005
Alcohol	0	1 (0-312)	8 (0-562)	23 (0-764)	8 (0-251)	<0.0005

[a] P-value for trend in difference between males and females.

Table 3: Dietary Characteristics (Averaged Across 1994 to 2005) by Average BMI Z-Score Category (Averaged Across 1991 to 2005)

	AVERAGE BMI Z-SCORE CATEGORY										
	<-2		≥-2 & <-1		≥-1 & <0		≥0 & <1		≥1		
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	p-value
Kilocalories/day	128	1915 (525)	567	1900 (551)	658	1993 (606)	201	2097 (712)	48	2671 (901)	<0.0005
Processed Meat (g/1000 kcal)	128	12.8 (12.5)	567	11.2 (10.9)	658	11.4 (11.1)	201	13.7 (11.4)	48	13.7 (10.9)	0.0278
Grilled/Fried Meat (g/1000 kcal)	128	22.7 (17.9)	567	19.2 (16.1)	658	20.0 (17.1)	201	25.2 (21.1)	48	37.9 (21.9)	<0.0005
Fish (g/1000 kcal)	128	16.3 (17.2)	567	18.2 (15.6)	658	17.0 (15.4)	201	16.8 (15.1)	48	10.6 (15.0)	0.0207
Coconut Oil (g/1000 kcal)	128	4.9 (2.2)	567	4.6 (2.1)	658	4.7 (2.2)	201	4.9 (2.2)	48	5.6 (2.2)	0.0154
Fruit and Vegetables (g/1000 kcal)	128	41.4 (41.8)	567	41.2 (36.0)	658	42.9 (38.2)	201	34.2 (31.7)	48	25.8 (26.1)	0.0022
Soda (g/1000 kcal	128	45.3 (53.1)	567	43.0 (43.7)	658	44.2 (43.5)	201	53.6 (50.2)	48	66.4 (63.6)	0.0012

Figure 1: Change in Relative Telomere Length (T/S Ratio) by Age and Sex

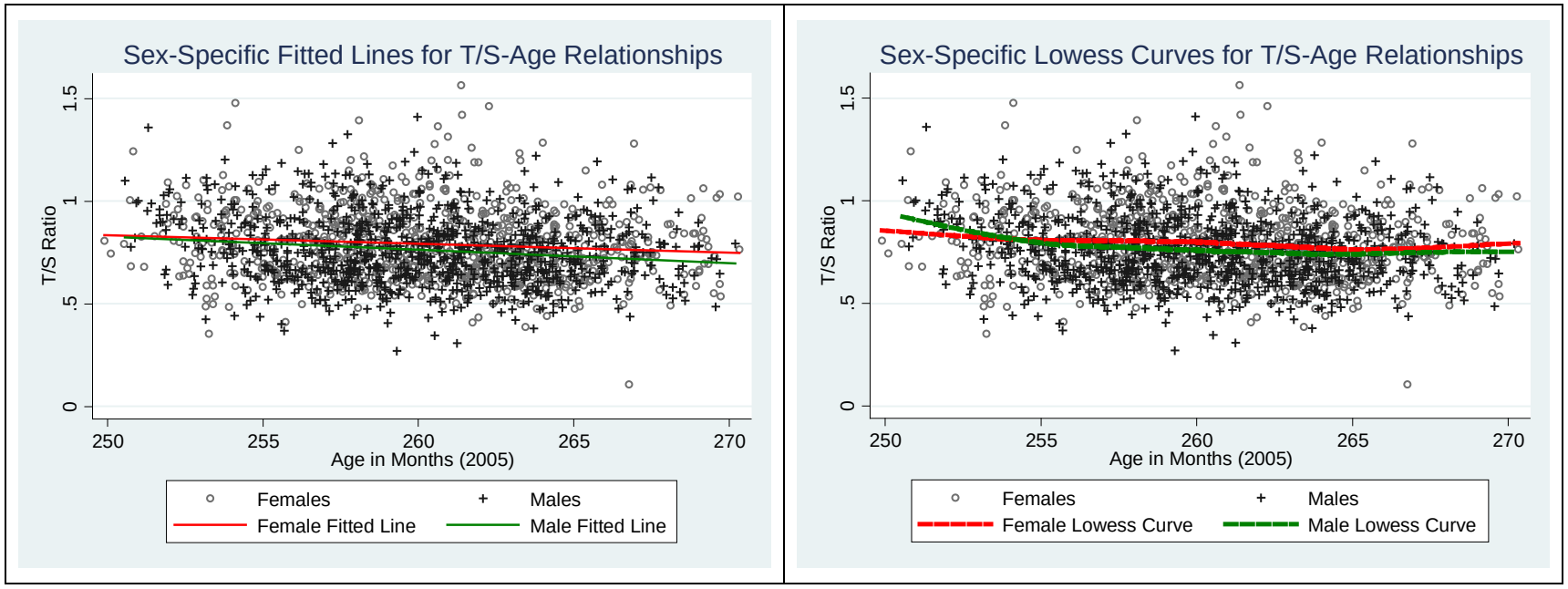

Table 4: Multivariate-Adjusted Results for the Linear Relationship Between Dietary Factors of Interest and Relative Telomere Length (T/S Ratio)

	MODEL 1[a]			MODEL 2[b]			MODEL 3[c]	
	β ± Robust SE	R^2 [d]	p-value	β ± Robust SE	R^2 [e]	p-value	β ± Robust SE	p-value
Processed Meat (g/1000 kcal)	0.00054 ± 0.00038	0.0255	0.155	0.00051 ± 0.00039	0.0236	0.185	0.00054 ± 0.00040	0.176
Grilled/Fried Meat (g/1000 kcal)	0.000074 ± 0.00028	0.0245	0.795	0.000063 ± 0.00030	0.0227	0.832	0.000049 ± 0.00031	0.876
Fish (g/1000 kcal)	0.00014 ± 0.00035	0.0245	0.691	0.00014 ± 0.00035	0.0226	0.694	0.00018 ± 0.00035	0.614
Coconut Oil (g/1000 kcal)	-0.00082 ± 0.0020	0.0245	0.676	-0.0010 ± 0.0021	0.0227	0.600	-0.0015 ± 0.0021	0.475
Fruit and Vegetables (g/1000 kcal)	-0.00011 ± 0.00011	0.0248	0.355	-0.00010 ± 0.00011	0.0229	0.386	-0.00010 ± 0.00012	0.412
Soda (g/1000 kcal)	-0.00011 ± 0.000091	0.0252	0.218	-0.00011 ± 0.000092	0.0234	0.227	-0.00012 ± 0.000093	0.180
Average Kilocalories							0.0000051 ± 0.000009	0.577
Age in 2005 (months)							-0.0046 ± 0.0014	0.001
Sex (male)							0.40 ± 0.52	0.449
Age * sex							-0.0017 ± 0.0020	0.406
Ln(Income 1994-2005)							-0.0017 ± 0.0082	0.840
Smoking Status:								
Current Smoker							0.00080 ± 0.012	0.947
Former Smoker							0.011 ± 0.011	0.318

[a] Model 1: Each food group regressed individually adjusting for average kilocalories, age, sex, and the age-sex interaction (n=1634).
[b] Model 2: Same as Model 1 with further adjustment for income and smoking status (n=1632)
[c] Model 3: All food groups and covariates together in same model (n=1632). The adjusted R^2 for this model was 0.0223.
[d] Baseline adjusted R^2 was 0.0250 when regressing TL on kilocalories, age, sex, and the age-sex interaction.
[e] Baseline adjusted R^2 was 0.0232 when regressing TL on kilocalories, age, sex, the age-sex interaction, income, and smoking status.

Table 5: Multivariate-Adjusted Results for the Linear and Quadratic Relationship Between Average BMI Z-Score and Relative Telomere Length (T/S Ratio)

	Model 4 All (n=1623)		Model 5 Females Only (n=763)[a]		Model 6 Males Only (n=860)[b]	
	β ± SE	p-value	β ± SE	p-value	β ± SE	p-value
Average BMI Z-score (1991-2005)	0.0082 ± 0.012	0.462	0.0079 ± 0.012	0.519	0.0070 ± 0.0074	0.342
Average BMI Z-score^2	0.0080 ± 0.0066	0.183	0.0077 ± 0.0066	0.248	-0.0018 ± 0.0035	0.595
Sex (male)	0.67 ± 0.52	0.208				
Sex*Average BMI Z-score	-0.0015 ± 0.014	0.911				
Sex*Average BMI Z-score^2	-0.0098 ± 0.0074	0.161				
Age in 2005 (months)	-0.0041 ± 0.0015	0.005	-0.0040 ± 0.0015	0.006	-0.0067 ± 0.0014	<0.0005
Sex*Age	-0.0026 ± 0.0057	0.195				
Ln(Income 1994)	-0.00099 ± 0.0058	0.864	0.0026 ± 0.0087	0.769	-0.0038 ± 0.0075	0.61

[a] Excluding years in which females were pregnant during or for four or more months within the year prior to the survey wave.
[b] Excluding males with missing BMI values in any year.

Table 6: Multivariate-Adjusted Results for the Linear Relationship Between Height-Adjusted Waist Circumference and Relative Telomere Length (T/S Ratio)

	Model 7a (1998) Both Sexes (n=1681)		**Model 8a (1998)**[a] Females Only (n=799)		**Model 9a (1998)** Males Only (n=882)	
	β ± SE	**p-value**	**β ± SE**	**p-value**	**β ± SE**	**p-value**
Waist Circumference (cm), 1998	-0.00059 ± 0.0013	0.647	-0.00081 ± 0.0013	0.542	0.0011 ± 0.0011	0.324
Sex (male)	0.50 ± 0.52	0.336				
Waist Circumference*Sex	0.0013 ± 0.0016	0.403				
Height (cm), 1998	0.00074 ± 0.00078	0.341	0.0014 ± 0.0013	0.269	0.00029 ± 0.00099	0.772
Age (months), 2005	-0.0044 ± 0.0014	0.002	-0.0045 ± 0.0014	0.002	-0.0068 ± 0.0014	<0.0005
Age*Sex	-0.0024 ± 0.0020	0.228				
Ln(Income 1998)	0.00092 ± 0.0064	0.885	0.0091 ± 0.0094	0.335	-0.0070 ± 0.0087	0.422
	Model 7b (2002) Both Sexes (n=1587)		**Model 8b (2002)**[b] Females Only (n=701)		**Model 9b (2002)** Males Only (n=886)	
	β ± SE	**p-value**	**β ± SE**	**p-value**	**β ± SE**	**p-value**
Waist Circumference (cm), 2002	0.00055 ± 0.0012	0.65	0.00047 ± 0.0012	0.705	0.0012 ± 0.00088	0.173
Sex (male)	0.67 ± 0.53	0.209				
Waist Circumference*Sex	0.00050 ± 0.0015	0.732				
Height (cm), 2002	0.0013 ± 0.00084	0.114	0.0021 ± 0.0013	0.111	0.00078 ± 0.0011	0.471
Age (months), 2005	-0.0038 ± 0.0015	0.013	-0.0038 ± 0.0015	0.013	-0.0066 ± 0.0014	<0.0005
Age*Sex	-0.0029 ± 0.0020	0.152				
Ln(Income 2002)	-0.0030 ± 0.0060	0.617	-0.0027 ± 0.0093	0.769	-0.0035 ± 0.0079	0.657
	Model 7c (2005) Both Sexes (n=1528)		**Model 8c (2005)**[c] Females Only (n=639)		**Model 9c (2005)** Males Only (n=889)	
	β ± SE	**p-value**	**β ± SE**	**p-value**	**β ± SE**	**p-value**
Waist Circumference (cm), 2005	-0.00020 ± 0.0010	0.843	-0.00037 ± 0.0010	0.718	0.0013 ± 0.00080	0.099
Sex (male)	0.50 ± 0.56	0.366				
Waist Circumference*Sex	0.0013 ± 0.0013	0.311				
Height (cm), 2005	0.0016 ± 0.00084	0.056	0.0032 ± 0.0014	0.019	0.00055 ± 0.0011	0.606
Age (months), 2005	-0.0043 ± 0.0016	0.007	-0.0044 ± 0.0016	0.007	-0.0068 ± 0.0014	<0.0005
Age*Sex	-0.0025 ± 0.0021	0.237				
Ln(Income 2005)	0.0022 ± 0.0052	0.681	0.0044 ± 0.0083	0.599	0.00036 ± 0.0068	0.958

[a] Includes all females for whom data were available for all variables (no pregnancies in this year).
[b] Excludes females who were pregnant during or for ≥4 months within the year prior to the 2002 survey wave.
[c] Excludes females who were pregnant during or for ≥4 months within the year prior to the 2005 survey wave.

Appendix A: Summary of Previous Studies on Diet and Telomere Length

References	Study Design	Subjects	Dietary and TL Assessment and Statistical Methods	Dietary Variables For Which Data are Presented	Covariates in Full Model	Significant Dietary Associations in Full Models
Nettleton et al. 2008 (63)	Cross-sectional	Multi-Ethnic Study of Atherosclerosis (MESA), US, males and females, ages 45-84, n=840	Diet: FFQ TL: qPCR Stats: linear regression; regressed TL on serving/day diff in food	Whole grains, refined grains, fruit, vegetables, non-fried fish, nuts/seeds, high-fat dairy, low-fat dairy, red meat, processed meat, fried foods, non-diet soda, coffee	Age, sex, race/ethnicity, energy intake, education, PA, smoking, study center, BMI, other dietary variables	Each 1 serving/day increase of processed meat was associated with a 0.07 smaller T/S ratio (p=0.006). Assessing different processed meats separately suggested ham, hot dogs, bologna, salami, and lunch meats were the processed meats that accounted for the association.
Cassidy et al. 2010 (70)	Cross-sectional (exploratory analysis)	Nurses' Health Study Participants, US, females only, ages 30-55, n=2284	Diet: FFQ TL: qPCR Stats: quintiles of LTL z-score; linear regression	Energy intake, total protein, total carbohydrates, fiber, cereal fiber, whole grains, SFAs, PUFAs, MUFAs, trans-fats, linolenic acid, linoleic acid, fruits and vegetables, Vit. D, Vit. E	Age, smoking status, postmenopausal HRT, BMI, PA, total energy intake, energy-adjusted protein, PUFAs	Each g/day increase in linoleic acid was associated with a -0.32 difference in TL z-score (p=0.046). Each g/day increase of fiber was associated with a 0.19 increase in TL z -score (p=0.03).
Chan et al. 2010 (62)	Cross-sectional	Chinese men and women, ages 65+, n=2006	Diet: FFQ TL: qPCR Stats: linear regression; TL regressed on 1 SD changes in food group; also looked at TL by quartile of tea and oil/fat consumption	Cereals; meat and poultry; eggs and egg products; fish; milk and milk products; fruits and dried fruits; vegetables; pickled vegetables; legumes, nuts, seeds; dim sum; fast food; fats and oils for cooking; Chinese tea	Age, BMI, energy intake, education, smoking, alcohol, PA, heart disease, diabetes, hypertension; interactions between sex and dietary variables	Each 1 SD increase in ml/day of Chinese tea was associated with a 0.157 increase in T/S ratio among men (p=0.002). Each 1 SD increase in g/day of fats and oils for cooking was associated with a -0.150 decrease in T/S ratio among women (p=0.033). TL did differ significantly across quartiles of tea consumption and oil/fat consumption, but the change across each quartile was not large and was not particularly linear.
Tiainen et al. 2012 (67)	Cross-sectional	Helsinki Birth Cohort, Finland, males and females, ages 57-70, n=1942	Diet: FFQ TL: qPCR Stats: linear regression, separate for males and females; tested for interactions by weight status.	Total fat, SFAs, MUFAs, PUFAs, linoleic acid, linolenic acid, n-3, butter, margarine, oil, vegetables, roots, legumes, fruits, berries, fruit juice	Age, energy intake, BMI, waist-hip ratio, smoking status, education, PA; separate analyses for men and women (and looked at interactions by sex and dietary intake)	Each g/day increase in SFAs was associated with a -0.0004 decrease in T/S ratio among men (p=0.01); margarine was positively associated with TL among overweight men (p=0.03 for interaction by BMI). Each 100 g/day increase in vegetables was associated with a 0.009 increase in T/S ratio among women (p=0.05), particularly overweight women (p=0.004 for interaction by BMI). There was a marginally significant association between fruit consumption and TL among men (p=0.06).

References	Study Design	Subjects	Dietary and TL Assessment and Statistical Methods	Dietary Variables For Which Data are Presented	Covariates in Full Model	Dietary Associations in Full Models
Kark et al. 2012 (69)	Prospective observational study; 10-year follow-up	Jerusalem LRC Prevalence Study, Israel, males and females, ages 28-32 at baseline, n=620	Diet: FFQ (at baseline only) TL: Southern Blot Stats: linear regression; regressing f/u LTL on baseline diet characteristics. Ln transformed diet variables and standardized beta coefficients	Energy intake; protein; carbohydrates; total fat; SFAs; MUFAs; PUFAs; n-3	BMI, PA, smoking, country of origin, baseline TL,	Caloric intake was inversely associated with TL at follow-up in men only (standardized β= -0.157, p=0.002). This relationship persisted when using body weight adjusted caloric intake (β= -0.167, p=0.0007) and when including intake of macronutrients and different fats in the model (as % of energy). This inverse association among men appeared to be restricted to non-smokers (p=0.050 for interaction between calories and smoking). Marginally significant inverse associations were found between MUFAs and PUFAs (as % of energy) and TL (p=0.050 and 0.053)
Marcon et al. 2012 (61)	Cross-sectional	Males and females adults from Tuscany, n=56	Diet: FFQ, TL: Southern Blot Stats: claims to be doing logistic regression but reports beta coefficients for what looks like a linear regression analysis (is not reporting odds ratios)	Cereals, vegetables, fruits, eggs, dairy, oils and butter, meat, fish; micronutrients	Age, sex, and energy intake for models looking at food groups.	Each 100 g/day increase in vegetable intake (particularly root vegetables, peppers and carrots) was associated with a 0.505 increase in mean TL (p=0.013). Of the micronutrients assessed, only beta-carotene was significantly positively correlated with TL, and this was only found among the younger group. There was no association between dietary factors and incidence of having very short TL.
Song et al. 2013 (68)	Cross-sectional	Women's Health Initiative, US, postmenopausal females only (multiracial/multiethnic), n=4029	Diet: FFQ TL: qPCR Stats: linear regression; regressing TL on quartiles of fat and fatty acid intake as percent of energy; TL regressed on quartiles of specific food group intake.	Total fat intake, SFAs (total and separate kinds), MUFAs, PUFAs, and food sources of fat (milk, butter, cheese, and other fat used in cooking or on bread)	Age, race/ethnicity, BMI, smoking, alcohol, diabetes, PA, energy intake, fruit and vegetable intake, Vitamin C, Vitamin E, selenium, beta-carotene	Women in the highest quartile of SFA intake (as % of energy) had shorter TL than women in lower quartiles (p=0.017). Most short and medium chain fatty acids (4:0, 6:0, 8:0, and 10:0 but not 12:0) were inversely associated with TL (p≤0.025 for each). Of the long-chain SFAs, only 14:0 and 16:0 were significantly inversely associated with TL (p=0.020 and 0.031). Among women who drank whole milk, milk intake was inversely associated with TL (p=0.036). Among women who used butter for cooking only, amount of butter was inversely associated with TL (p=0.029). Among women who ate cheese made with whole milk, cheese intake was inversely associated with TL (p=0.038).

References	Study Design	Subjects	Dietary and TL Assessment and Statistical Methods	Dietary Variables For Which Data are Presented	Covariates in Full Model	Dietary Associations in Full Models
Kiecolt-Glaser et al. 2013 (76)	Randomized Controlled Trial	N-3 PUFA RCT, US, men and women, ages 40-85, n=106	Diet: FFQ TL: qPCR Stats: ANOVA and chi-squared to compare treatment groups; linear regression to regress TL on change in plasma fatty acid ratio	Three intervention groups: low-dose (1.25 g/day) n-3 PUFA; high-dose (2.5 g/day) n-3 PUFA; and placebo	Age, sex, and sagittal abdominal diameter	There was a non-significant trend toward an increase in TL in treatment groups. However, a secondary analysis suggested that each one unit decrease in the n-6:n-3 ratio was associated with an average 20 base pair increase in TL (p=0.02).

Abbreviations Key:
PA = physical activity
FFQ = food frequency questionnaire
qPCR = quantitative polymerase chain reaction
TL = telomere length (T/S ratio = a measure of TL)
SFA = saturated fatty acids
MUFA = monounsaturated fatty acids
PUFA = polyunsaturated fatty acids
n-3 = omega-3 fatty acids
n-6 = omega-6 fatty acids

Appendix B: Rerun of Dietary Models Excluding Extreme Low and High Caloric Intakes

Table 2b: Kilocalories/day and Dietary Intake (g/1000 kilocalories) of Specific Foods by Study Wave

FEMALES (n=709) [a]	1994 Mean (Range)	1998 Mean (Range)	2002 Mean (Range)	2005 Mean (Range)	Average (94-05) Mean (Range)
Kilocalories/day	1138 (356-2687)	1285 (409-2887)	1521 (459-3689)	1542 (454-3757)	1371 (531-2816)
Food/Beverage (g/1000 kcal):					
Unprocessed Meat & Poultry	19 (0-220)	26 (0-165)	47 (0-234)	48 (0-292)	23 (0-82)
Grilled/Fried Meat	11 (0-138)	18 (0-137)	28 (0-203)	33 (0-230)	22 (0-111)
Processed Meat	7 (0-138)	12 (0-125)	15 (0-277)	18 (0-190)	13 (0-76)
Fish	17 (0-164)	13 (0-145)	18 (0-142)	19 (0-212)	17 (0-85)
Added Oils/Fats (all)	7 (0-41)	9 (0-42)	11 (0-42)	12 (0-42)	10 (1-27)
Coconut Oil	3 (0-23)	4 (0-18)	6 (0-29)	6 (0-31)	5 (0-14)
Fruit	16 (0-378)	5 (0-245)	14 (0-324)	10 (0-257)	11 (0-133)
Vegetables:	33 (0-641)	38 (0-341)	31 (0-267)	31 (0-313)	33 (0-272)
Green Vegetables	8 (0-312)	8 (0-105)	5 (0-180)	6 (0-226)	7 (0-93)
Yellow Vegetables	4 (0-114)	4 (0-74)	4 (0-57)	4 (0-69)	4 (0-29)
Root Vegetables	13 (0-381)	18 (0-221)	12 (0-212)	11 (0-192)	14 (0-128)
Fruit and Vegetables	48 (0-763)	43 (0-341)	46 (0-365)	42 (0-339)	45 (0-325)
Rice	228 (0-933)	254 (0-656)	247 (0-691)	261 (0-683)	247 (0-549)
Corn	190 (0-1076)	154 (0-1021)	58 (0-1025)	41 (0-998)	111 (0-718)
Bread	34 (0-207)	18 (0-154)	21 (0-207)	23 (0-156)	24 (0-93)
Noodles	17 (0-440)	20 (0-248)	22 (0-213)	23 (0-304)	20 (0-127)
Beans	13 (0-161)	11 (0-159)	11 (0-138)	9 (0-179)	11 (0-116)
Soda	14 (0-496)	56 (0-652)	66 (0-778)	78 (0-599)	53 (0-267)
Alcohol	0	0	2 (0-710)	2 (0-329)	1 (0-177)

[a] Excluding females with caloric intake below 350, 400, 450, and 450 and above 2700, 2900, 3700, and 3800 in 1994, 1998, 2002, and 2005, respectively.

Table 2b (continued)

MALES (n=803) [b]	1994 Mean (Range)	1998 Mean (Range)	2002 Mean (Range)	2005 Mean (Range)	Average (94-05) Mean (Range)	p [a]
Kilocalories/day	1233 (359-3101)	1883 (454-4137)	2039 (509-4707)	2152 (505-4995)	1827 (701-3584)	<0.0005
Food/Beverage (g/1000 kcal):						
Unprocessed Meat & Poultry	19 (0-333)	30 (0-224)	43 (0-269)	48 (0-216)	24 (0-116)	0.038
Grilled/Fried Meat	12 (0-258)	15 (0-137)	23 (0-147)	27 (0-197)	19 (0-98)	0.001
Processed Meat	6 (0-258)	10 (0-124)	13 (0-164)	15 (0-147)	11 (0-74)	0.003
Fish	19 (0-199)	14 (0-193)	17 (0-170)	18 (0-132)	17 (0-107)	0.90
Added Oils/Fats (all)	7 (0-51)	8 (0-40)	9 (0-48)	9 (0-45)	8 (0-24)	<0.0005
Coconut Oil	3 (0-26)	4 (0-17)	5 (0-29)	5 (0-27)	4 (0-13)	<0.0005
Fruit	17 (0-585)	6 (0-193)	5 (0-179)	5 (0-531)	8 (0-168)	0.002
Vegetables	30 (0-383)	34 (0-651)	26 (0-386)	21 (0-333)	28 (0-276)	<0.0005
Green Vegetables	9 (0-210)	7 (0-157)	6 (0-254)	4 (0-96)	6 (0-94)	0.32
Yellow Vegetables	4 (0-202)	3 (0-66)	3 (0-85)	2 (0-42)	3 (0-56)	0.003
Root Vegetables	10 (0-298)	19 (0-620)	9 (0-270)	6 (0-144)	11 (0-155)	0.001
Fruit and Vegetables	47 (0-683)	40 (0-826)	31 (0-386)	26 (0-617)	36 (0-319)	<0.0005
Rice	231 (0-812)	304 (0-797)	306 (0-686)	340 (0-715)	295 (0-565)	<0.0005
Corn	203 (0-1070)	123 (0-1115)	93 (0-1101)	71 (0-1112)	123 (0-954)	0.22
Bread	34 (0-215)	20 (0-158)	21 (0-193)	14 (0-141)	22 (0-93)	0.05
Noodles	13 (0-318)	19 (0-278)	21 (0-635)	21 (0-236)	18 (0-159)	0.04
Beans	13 (0-236)	10 (0-137)	11 (0-177)	11 (0-165)	11 (0-65)	0.43
Soda	9 (0-710)	47 (0-391)	53 (0-660)	45 (0-945)	39 (0-338)	<0.0005
Alcohol	0	1 (0-312)	8 (0-562)	23 (0-764)	8 (0-251)	<0.0005

[b] Excluding males with caloric intake below 350, 450, 500, and 500 and above 3200, 4200, 4800, and 5000 in 1994, 1998, 2002, and 2005, respectively.
[c] P-value for trend in difference between males and females.

Table 3b: Dietary Characteristics (Averaged Across 1994 to 2005) by Average BMI Z-Score Category (Averaged Across 1991 to 2005)*

	AVERAGE BMI Z-SCORE CATEGORY										
	<-2		≥-2 & <-1		≥-1 & <0		≥0 & <1		≥1		
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	p-value
Kilocalories/day	123	1604 (463)	521	1569 (462)	605	1630 (504)	184	1668 (512)	39	1877 (501)	0.0009
Processed Meat (g/1000 kcal)	123	23.0 (17.8)	521	19.0 (15.8)	605	19.6 (16.6)	184	25.1 (21.1)	39	36.1 (18.6)	0.0489
Grilled/Fried Meat (g/1000 kcal)	123	13.1 (12.5)	521	11.5 (10.7)	605	11.4 (10.9)	184	13.7 (11.3)	39	14.2 (11.6)	<0.0005
Fish (g/1000 kcal)	123	4.9 (2.2)	521	4.6 (2.1)	605	4.7 (2.2)	184	5.0 (2.2)	39	5.9 (2.4)	0.0074
Coconut Oil (g/1000 kcal)	123	45.8 (53.7)	521	42.3 (43.1)	605	44.4 (43.9)	184	52.4 (47.8)	39	65.1 (59.7)	0.0027
Fruit and Vegetables (g/1000 kcal)	123	14.7 (13.)	521	17.7 (14.2)	605	16.7 (13.9)	184	16.8 (14.9)	39	10.1 (12.1)	0.0059
Soda (g/1000 kcal	123	39.8 (40.1)	521	40.7 (35.3)	605	42.3 (37.7)	184	33.4 (28.9)	39	26.4 (26.)	0.006

* Excluding females with caloric intake below 350, 400, 450, and 450 and above 2700, 2900, 3700, and 3800 in 1994, 1998, 2002, and 2005, respectively. Excluding males with caloric intake below 350, 450, 500, and 500 and above 3200, 4200, 4800, and 5000 in 1994, 1998, 2002, and 2005, respectively.

Table 4b: Multivariate-Adjusted Results for the Linear Relationship Between Dietary Factors of Interest and Relative Telomere Length (T/S ratio)*

	MODEL 1[a]			MODEL 2[b]			MODEL 3[c]	
	β ± Robust SE	R^2 [d]	p-value	β ± Robust SE	R^2 [e]	p-value	β ± Robust SE	p-value
Processed Meat (g/1000 kcal)	0.00032 ± 0.00040	0.0243	0.420	0.00028 ± 0.00041	0.0243	0.486	0.00031 ± 0.00043	0.472
Grilled/Fried Meat (g/1000 kcal)	0.000060 ± 0.00022	0.0239	0.784	0.000062 ± 0.00022	0.0239	0.776	0.000018 ± 0.00032	0.956
Fish (g/1000 kcal)	0.00013 ± 0.00037	0.0240	0.721	0.00013 ± 0.00037	0.0240	0.725	0.00013 ± 0.00037	0.729
Coconut Oil (g/1000 kcal)	-0.0019 ± 0.0020	0.0244	0.335	-0.0022 ± 0.0020	0.0244	-1.110	-0.0026 ± 0.0021	0.208
Fruit and Vegetables (g/1000 kcal)	-0.00015 ± 0.00012	0.0247	0.201	-0.00014 ± 0.00012	0.0247	0.224	-0.00016 ± 0.00012	0.196
Soda (g/1000 kcal)	-0.000080 ± 0.000096	0.0243	0.407	-0.000077 ± 0.00010	0.0243	-0.790	-0.000092 ± 0.00010	0.347
Average Kilocalories							0.0000084 ± 0.000012	0.491
Age in 2005 (months)							-0.0049 ± 0.0015	0.001
Sex (male)							0.39 ± 0.54	0.468
Age * sex							-0.0016 ± 0.0021	0.429
Ln(Income 1994-2005)							-0.0013 ± 0.0084	0.877
Smoking Status:								
Current Smoker							-0.0011 ± 0.013	0.935
Former Smoker							0.011 ± 0.011	0.307

* Excluding females with caloric intake below 350, 400, 450, and 450 and above 2700, 2900, 3700, and 3800 in 1994, 1998, 2002, and 2005, respectively. Excluding males with caloric intake below 350, 450, 500, and 500 and above 3200, 4200, 4800, and 5000 in 1994, 1998, 2002, and 2005, respectively.

[a] Model 1: Each food group regressed individually adjusting for average kilocalories, age, sex, and the age-sex interaction (n=1612).
[b] Model 2: Same as Model 1 with further adjustment for income and smoking status (n=1510)
[c] Model 3: All food groups and covariates together in same model (n=1510). The adjusted R^2 for this model was 0.0214.
[d] Baseline adjusted R^2 was 0.0245 when regressing TL on kilocalories, age, sex, and the age-sex interaction.
[e] Baseline adjusted R^2 was 0.0227 when regressing TL on kilocalories, age, sex, the age-sex interaction, income, and smoking status.

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