

HHS Public Access

Author manuscript *Eur J Nutr*. Author manuscript; available in PMC 2018 February 01.

Published in final edited form as:

Eur J Nutr. 2017 February ; 56(1): 295–308. doi:10.1007/s00394-015-1080-1.

No Association between Blood Telomere Length and Longitudinally-Assessed Diet or Adiposity in a Young Adult Filipino Population

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Abstract

Purpose—Telomeres, DNA-protein structures that cap and protect chromosomes, are thought to shorten more rapidly when exposed to chronic inflammation and oxidative stress. Diet and nutritional status may be a source of inflammation and oxidative stress. However, relationships between telomere length (TL) and diet or adiposity have primarily been studied cross-sectionally among older, overweight/obese populations and yielded inconsistent results. Little is known about the relationship between diet or body composition and TL among younger, low- to normal-weight populations. It also remains unclear how cumulative exposure to a specific diet or body

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Conflict of Interest: On behalf of all authors, the corresponding author states that there is no conflict of interest.

composition during the years of growth and development, when telomere attrition is most rapid, may be related to TL in adulthood.

Methods—In a sample of 1,459 young adult Filipinos, we assessed the relationship between blood TL at ages 20.8–22.5 and measures of BMI z-score, waist circumference, and diet collected between the ages of 8.5 and 22.5. TL was measured using monochrome multiplex quantitative PCR, and diet was measured using multiple 24-hour recalls.

Results—We found no associations between blood TL and any of the measures of adiposity or between blood TL and the seven dietary factors examined: processed meats, fried/grilled meats and fish, non-fried fish, coconut oil, fruits and vegetables, bread and bread products, and sugar-sweetened beverages.

Conclusions—Considering the inconsistencies in the literature and our null results, small differences in body composition and consumption of any single pro- or anti-inflammatory dietary component may not by themselves have a meaningful impact on telomere integrity, or the impact may differ across distinct ecological circumstances.

Keywords

telomere length; diet; nutrition; adiposity; nutrition transition

INTRODUCTION

Modern industrialized diets tend to include highly processed animal products, refined grains, and added fats and sugars but often lack adequate fruits and vegetables. Such diets are thought to cause increased risk of chronic noncommunicable diseases and reduced longevity [1–4]. One mechanism via which diet may influence health outcomes is through its potential effects on the length of telomeres, the repeating DNA-protein structures that protect the ends of linear chromosomes from loss of genetic information [5–7]. Telomeres of somatic cells shorten with each cellular replication due to the 'end-replication problem' [6,8], but they may shorten more rapidly if exposed to chronic oxidative stress [9–11] and inflammation [12,13]. Critically short telomere length (TL) leads to cellular senescence and apoptosis [14,15], and TL is thought to play a causal role in aging-related disease processes [16].

Certain dietary factors may contribute to or help protect against oxidative stress and inflammation [17–23] and may thereby influence telomere integrity. For instance, diets high in processed meats, refined grains, and added sugars tend to be associated with increased inflammation, whereas diets higher in fruits, vegetables, fish, and whole grains tend to be related to reduced inflammation [17,20,24–27]. Saturated fats are widely thought to be pro-inflammatory [28–30], though this may only be the case for long-chain saturated fatty acids [31,32]. Also, meats cooked at high temperatures (e.g., fried or grilled) are high in advanced glycation end-products (AGEs), which are thought to contribute to oxidative stress and inflammation [33,34].

In line with the evidence on diet and inflammation, several studies have observed longer blood TL among individuals with higher Alternative Healthy Eating Index scores or higher Mediterranean diet scores [35–38]. Further studies have reported associations between blood

TL and specific foods or nutrients. For example, some studies have reported inverse associations between blood TL and the consumption of all meat [38], red and/or processed meat [39,40], saturated fat [41,42], refined grains [38,43], and non-diet soda [40,44]. Positive associations have been observed between blood TL and consumption of fruits and/or vegetables [38,40,41,45,46] and omega-3 fatty acid supplements [47]. However, findings have not been consistent; in fact, it is more common that studies report null associations between blood TL and consumption of meat [38,43,45,48], saturated fat [37,43,49,50], omega-3 fatty acids or fish [38–41,43,45,48–50], and fruits and vegetables [39,48,50,51].

Notably, many of the populations of the aforementioned studies on diet and TL were, on average, overweight or obese, with the primary exceptions being the few study populations in China and Korea [40,48]. Increased adiposity can be an independent contributor to oxidative stress and inflammation [52,53]. This makes it difficult to clearly separate any direct association between diet and TL from the potential indirect association related to dietary effects on adiposity. Few studies have examined how the relationship between diet and TL may depend on adiposity measures. One study [41] found that associations between blood 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 [54] suggested that salt intake may be related to blood TL in overweight and obese adolescents but not 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 in a pro-inflammatory state, as in the case of chronic caloric excess and overweight or obesity.

TL attrition is most rapid in the pre-adult years, and it has been suggested that these years might be an especially sensitive period in which environmental and lifestyle factors could influence lifelong TL [55]. In particular, we might expect that cumulative exposure to certain dietary factors and adiposity levels during growth and development could have an important impact on TL in adulthood. However, the majority of studies on TL are cross-sectional and conducted among middle-aged and older adult populations. Few studies have explored the relationship between measures of diet or nutritional status and TL among youth. One study reported that estimated levels of total dietary antioxidants were positively associated with blood TL in a sample of 5- to 18-year-olds in Spain, while white bread and dietary glycemic load were both inversely associated with blood TL [43]. That study did not explore whether those associations differed by body composition, though over 60% of the adolescents in that study population was overweight or obese. Another study found that blood TL in normal weight 3- to 9-year-old Australian children was inversely associated with plasma zinc status [56].

A few other studies have explored the relationship between TL and measures of adiposity among younger populations. One study reported an inverse association between blood TL and obesity status among 2- to 17-year-old French children [57], while another found a similar association among 5- to 12-year-old Arab boys but not girls [58]. Among a large sample of 31-year-old Finnish males and females, both body mass index (BMI) and waist-to-hip ratio were found to be inversely associated with blood TL [59], and the inverse

association between BMI and blood TL was found to be stronger at younger ages (<30 years old) than at older ages in a U.S. population aged 8 to 90 years old [60]. In contrast to these studies, however, no associations were found between TL and measures of adiposity in other studies of children [61], adolescents [62], or young adults [49].

Given the inconsistent findings across the literature and the dearth of information on diet, adiposity, and TL from young, non-obese populations, the present study utilizes longitudinal data on diet and body composition measured among Filipinos during the adolescent and early adult years to test whether specific foods and overall nutritional status during years of rapid cellular turnover are associated with blood TL in early adulthood. Still in the midst of a nutrition transition, consumption of meat, soft drinks, and total fat has increased among Filipino populations in recent decades [63–65], and rates of obesity and cardiometabolic disease have, consequently, been rising [65–68]. Thus, this study setting provides a unique opportunity to explore how diet trends in the early stages of the global nutrition transition [69] may be associated with TL. Specifically, we hypothesized that consumption of fried/ grilled meats, processed meats, sugar-sweetened beverages, refined bread and bread products, and coconut oil (the primary cooking oil in the Philippines and a major source of saturated fat) across the adolescent and early adult years would be inversely associated with blood TL but that consumption of non-fried fish and fruits and vegetables would be positively associated with blood TL in young adult Filipinos. Given the dual burden of relatively high prevalence of undernutrition and increasing prevalence of overnutrition in the Philippines [64,65,67,68,70], we hypothesized that the cumulative levels of adiposity across the childhood, adolescent, and early adult years would have a curvilinear association with blood TL. We also predicted that diet-TL associations would depend on overall adiposity levels.

MATERIALS AND METHODS

Study participants

Data came from the Cebu Longitudinal Health and Nutrition Survey (CLHNS) [71,72]. Briefly, this study began in 1983 with the enrolment of 3,327 pregnant women from 17 urban and 16 rural neighborhoods from Cebu, the second largest metropolitan area of the Philippines. Follow-up questionnaires on diet, nutritional status, and demographics were administered in 1991–92, 1994–95, 1998–99, 2002–03, and 2005–06 when the 1983–84 birth cohort was on average 8.5, 11.5, 15.5, 18.7, and 21.5 years old. In 2005, venous blood samples were collected from 1,779 individuals from the 1983–84 birth cohort [73]. Only data from singletons in the cohort were used for the analyses conducted herein. All study protocols were originally reviewed and approved by the Institutional Review Board of University of North Carolina at Chapel Hill. Telomere measurement and analysis using deidentified samples and data were not considered human subject research by Northwestern University's or University of Washington's Institutional Review Boards.

Measurement of TL

Details of the methods used for measuring blood TL can be found elsewhere [73,74]. In brief, DNA was extracted from the blood samples of 1,753 singletons from the 1983–84

birth cohort, and TL (measured as the relative telomere to single copy gene ratio or "T/S ratio") was analyzed using a modified version the monochrome multiplex quantitative polymerase chain reaction (MMqPCR) method [73–75]. The geometric mean intra-assay coefficient of variation was 5.7%, and the correlation of TL between samples that were analyzed on two separate runs was 0.92 (p < 0.0001). Adjustment for well position further increased the precision of the TL measures [74]. TL measured in whole blood, as is most common in studies exploring relationships between diet or adiposity and TL, is generally considered to be exclusively of leukocyte origin. However, because of the possibility of other cellular and non-cellular sources of DNA in the blood [73,76], we refer to TL measured in this way as blood TL rather than leukocyte TL.

Assessment of adiposity

Longitudinal assessment of adiposity was based on BMI z-scores and waist circumference measurements. As BMI is strongly age-dependent during the childhood and adolescent years, BMI z-scores were used instead of BMI to account for age differences of individuals within each survey wave. In order to obtain a more generalizable measure of body mass, World Health Organization reference values for 5- to 19-year-olds, which are used to assess childhood growth worldwide [77–79], were used to estimate BMI z-scores of our population sample using age (in months) and weight and height measurements from 1991, 1994, 1998, 2002 and 2005. A comparable BMI z-score for ages 19 to 23 was obtained using the 19-year-old reference values.

Waist circumference was measured in 1998, 2002, and 2005. Because no generalizable reference exists to estimate waist circumference z-scores, models of waist circumference adjusted for height and age at the time of each waist circumference measurement.

Assessment of diet

Diet during the adolescent and early adult years was assessed using multiple 24-hour recalls administered by trained personnel in 1994, 1998, 2002, and 2005. Surveys were conducted without parental supervision after 1994. One day of intake was recorded in the 1994–95 survey wave, and two days of intake were recorded in subsequent survey years.

Estimates of average total energy intake during each survey year were estimated from 24hour recall data using the 1997 Philippines Food Composition Tables from the Food and Nutrition Research Institute [80], which was periodically updated to include newer food items. Coconut oil consumption was estimated by multiplying the weight of fried or sautéed foods consumed by an absorption factor ranging from 0.025 to 0.17, depending on the kind of food and cooking method [81]. Estimates of daily intake (in grams) of processed meat, fried or broiled/grilled meat, non-fried fish, soft drinks, bread and bread products, and fruits and vegetables were calculated directly from the 24-hour recall data. The processed meat variable represented consumption of processed beef and pork products, including chorizo (local sausages), hot dogs, and other canned meat and meat products. The fried and broiled/ grilled meats and fish variable included beef, poultry, pork, and fish products. The non-fried fish variable included intake of any fresh, smoked, dried, canned, or fermented fish and shellfish consumed raw, boiled, or sautéed; it excluded fried and broiled fish, which, like

fried or broiled meat, tend to be high in AGEs [33]. 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. Estimates of sugar-sweetened beverage intake were based on reports of consuming any kind of soda/soft drink (diet soda consumption is uncommon in Cebu) and non-100% juices.

Statistical analyses

To obtain a measure of cumulative adiposity levels across the juvenile, adolescent, and early adult years that could be used to test linear and quadratic associations with blood TL, BMI z-scores were averaged across the five measurements taken from 1991 to 2005, and waist circumference was averaged across the three available measurements from 1998 to 2005. Women who were pregnant during any of the anthropometric measurement periods (n=113) or who had given birth within six months prior to any of the survey waves (n=68) were excluded.

As with the adiposity measures, kilocalories and each food group of interest (measured in grams) was averaged across the seven 24-hour recalls available for the 1994–2005 years (Table 2). Females and males (n=25) with average kilocalorie values below 500 and 800 or above 3500 and 4000, respectively, were excluded [82].

Multiple linear regression models with robust standard errors were used to test associations between relative blood TL (T/S ratio) and average BMI z-score; average waist circumference; and average intake of processed meat products, grilled/fried meat products, non-fried fish, coconut oil, bread products, fruits and vegetables, and sugar-sweetened beverages. Interactions between dietary factors and average BMI z-score were also tested in the diet-specific models. As age and sex are thought to be the strongest, most consistent predictors of TL [16,55,83–85], each model initially controlled for age (in months at the time of blood collection in 2005), sex, and the interaction between age and sex. Additionally, initial models included ten principal component scores of genome-wide genetic variation that control for potential population structure [86–88]. Fully-adjusted models further controlled for log-transformed average inflation-adjusted household income (collected at birth and again in the five survey waves between 1991 and 2005), smoking status in 2005 (entered as former, current, or never smoker dummy variable categories due to lack of accurate information on pack-years), and average urbanicity score (a scale from 0 to 70 derived from data on population size, population density, communication resources, transportation services, markets, education facilities, and health care services [89]). These additional lifestyle, socioeconomic, and environmental variables were added to the fullyadjusted models because of evidence suggesting that TL may be shorter, on average, among smokers and among those growing up in more adverse socioeconomic circumstances [90-93], as well as evidence of strong relationships between urbanicity and energy density in the Philippines [64,65,89]. In addition to these variables, the models of waist circumference further adjusted for age and height in each measurement period. The diet-related models further adjusted for average kilocalorie consumption across the four survey waves 1994-2005. All age, kilocalorie, height, and waist variables were mean-centered.

Likelihood ratio tests were used to test the combined effect on model fit of adding linear and quadratic terms for average BMI z-score or average waist circumference (Table 5: Models 1A and 1B) and adding BMI z-scores and waist circumference measures from different years (Table 5: Models 2A and 2B) to the fully-adjusted baseline model. The models assessing adiposity-TL associations were run initially on the entire sample and then separately on males and females; we present here just the sex-specific results for the fully-adjusted models.

The models examining diet-TL associations first tested each dietary variable of interest individually in both simple (Table 6: Model 3A) and fully-adjusted models (Table 6: Model 3B). Interactions between each individual dietary variable and average BMI z-score was then tested in the fully-adjusted model (Table 6: Model 3C). Finally, as no significant interactions were found at our adjusted alpha value, all dietary variables of interest were added simultaneously to the fully-adjusted model without interaction terms (Table 6: Model 3D). In the latter model, a likelihood ratio test was used to test the combined effect on model fit of adding all dietary variables to the baseline model, and Wald's tests were used to test the combined effect of 1) processed and grilled/fried animal products; 2) non-fried fish and fruits and vegetables; and 3) bread and bread products and sugar-sweetened beverages.

All models were conducted on the 1,459 (609 females and 850 males) with complete blood TL, BMI, waist circumference, dietary, income, urbanicity, and smoking data (excluding women who were pregnant during or recently prior to any survey wave). With this sample, we had at least 80% power in all models to detect a change in \mathbb{R}^2 as small as 0.01 at Bonferroni-adjusted alpha values of 0.0125 and 0.0071 in the adiposity and dietary models, respectively, to account for the four separate tests of linear and quadratic associations with adiposity measures and the separate tests of seven dietary factors. These adjusted alpha values were used to assess significance, but all p-values reported herein are the raw, unadjusted p-values.

RESULTS

Our study population was 20.8 to 22.5 (mean=21.7) years old in 2005 when blood TL was measured (Table 1). Average household income and urbanicity scores were comparable between males and females, but a substantially greater proportion of males were current or former smokers compared to females.

Overall, the prevalence of underweight was greater than the prevalence of overweight in most years among both males and females (Table 2), though this trend began to reverse in 2005 for males. Given the BMI z-score cutoffs for underweight and overweight of <2 SD and >1 SD, respectively [77], up to 20.4% of males and 18.7% of females were considered underweight in any given year of childhood or adolescence, while no more than 6.4% of males and females were considered in the overweight or obese categories during the younger years. By early adulthood, still 14.9% of males and 33.0% of females were considered underweight (BMI<18.5 kg/m²) but up to 19.3% of males and 14.6% of females could be considered above "normal" weight at the suggested BMI cutoff of 23 kg/m² for Asian populations [94].

Consumption of animal products, processed bread products and sugar-sweetened beverages remained low on average in this population (Table 3). Only about half of the population was consuming at least one serving (85 g or 3 oz) of any kind of meat per day on average. Similarly, only about 60% the population ate the equivalent of one slice of bread on a daily basis. An even smaller proportion of the population (about 10%) was consuming an average of one 8 oz serving of sugar-sweetened beverages on a regular basis. At the same time, consumption of more traditional Filipino foods, other than rice, was also low. A mere 7% and 12% of this population ate an average of one serving (85 g or 3 oz) or more of fish or even a single serving (100 g or 3.5 oz) or more of fruits and vegetables, respectively.

As reported previously for this population [73] and in line with previous studies [76,85], blood TL was, on average, shorter among males ($\beta = -0.036$, p<0.0001) and slightly shorter with each additional month of age ($\beta = -0.0035$, p=0.015) in the simple baseline model (Table 4). The strength of the relationship between age and blood TL was attenuated when variables for average household income, average urbanicity score, and smoking status were added to the baseline model. Average urbanicity score was significantly positively associated with blood TL ($\beta = 0.0028$, p<0.0001), while average log-transformed income was, intriguingly, significantly inversely associated with blood TL ($\beta = -0.027$, p<0.0001). Controlling for these additional variables almost doubled the adjusted R² of the baseline model.

No further substantial changes in the adjusted R^2 were observed when adding our main adiposity or dietary predictors to any of the models (Tables 5 and 6). There was no evidence in our study population of a linear or quadratic association between blood TL and BMI zscores or waist circumference measures in any of the models tested (p-values for all likelihood ratio tests 0.10 without correction for multiple testing) (Table 5). Though the linear and quadratic terms in Model 1B were suggestive of a curvilinear association between blood TL and average waist circumference among males, the likelihood ratio test indicated that the combined effect of the linear and curvilinear terms was not statistically significant, particularly after adjustment for multiple comparisons.

Likewise, there was no evidence that any of the dietary variables examined were associated with blood TL (Table 6). In the simple dietary model (Model 3A), most of the coefficients were in the opposite direction of what we hypothesized, and there were no significant associations (all p-values 0.3 without correction for multiple testing). In the fully-adjusted model (Model 3B), and particularly in the fully-adjusted model that included interactions with average BMI z-score (Model 3C), most of the coefficients were in the hypothesized direction, but still none of the associations in these fully-adjusted models were significant (all p-values 0.08 without correction for multiple testing). Only the interaction between non-fried fish and average BMI z-score approached significance at an unadjusted alpha value (β for interaction = 0.031, p=0.02), but this would not be considered significant after accounting for multiple comparisons. Finally, there was no evidence of a relationship between groups of dietary variables and blood TL in the fully-adjusted model that included all dietary variables together (Model 3D) (all Wald's test p-values 0.68; likelihood ratio test p-value=0.96).

DISCUSSION

This study assessed the association between blood TL and measures of adiposity and proand anti-inflammatory dietary factors among a young, non-Western population. The data used for this study provided a unique opportunity to assess how diet across years of growth, development, and rapid cellular turnover may impact TL of a generally low- to normalweight population. Contrary to expectations, we did not find evidence to support our hypotheses that diet and adiposity levels during the childhood, adolescent, and early adult years are associated with blood TL measured in early adulthood.

The results of the present study contrast with reports of inverse associations between blood TL and obesity status or adiposity measures among children [57] and young adults [59,60], as well as evidence for variable associations between adiposity and blood TL in males and females [58,95]. This could arguably be due to the low proportion of overweight and obese individuals in our sample, at least in comparison to the Finnish sample of young adults in which 49% and 32% of males and females, respectively, were above the 25 kg/m² BMI cutoff for normal weight [59]. Nonetheless, these results are consistent with other studies that reported no associations between adiposity measures and TL among samples of children [61], adolescents [62], and young adults [49], despite substantially higher average BMI levels compared to those in our sample. These results can also be added to the larger body of inconsistent findings between adiposity and TL among adults overall [as reviewed in 85,96], even when considering primarily Western populations in which the prevalence of overweight and obesity is considerably higher than in the Philippines.

Our null findings from the models testing the associations between blood TL and the specific food categories of interest contrast with the one study of adolescents that found significant inverse relationships between blood TL and white bread consumption [43]. They also contrast with several studies among adult populations that reported inverse associations between blood TL and red and/or processed meat [39,40], and soda consumption [40,44] and positive associations between blood TL and consumption of fruit [40,46] and vegetables [38,41,45].

Nonetheless, as few studies reporting significant diet-TL relationships take into account multiple comparisons, the strength of those findings remains unclear. Overall, our null findings are actually in agreement with a greater number of studies that found no association between blood TL and fruits and vegetables assessed together [50,51] or separately [39,43,48] and studies that found no association between fish consumption and blood TL in fully-adjusted models [39,40,43,45,48]. No previous studies explored the relationship between coconut oil and TL. However, considering the saturated fatty acid content of coconut oil, the null results in the present study contrast with the two studies that found no association between total saturated fat intake and blood TL [37,43,49,50]. There are no previous studies exploring the relationship between fried and broiled/grilled animal products and TL with which to compare the results of the present study, but there are several studies that looked at consumption of meat in general and found no statistically significant

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associations with blood TL [43,45,48] or found associations only within specific subpopulations [38].

Given that the nutrition transition was still in a relatively early stage at the time of data collection, particularly in the rural areas of the Philippines [65], it may be that the diet of our study population was not yet particularly pro-inflammatory or that consumption of the proand anti-inflammatory foods investigated was not variable enough across individuals to detect a marked association with blood TL. On the one hand, it was remarkable how consistently low the intake of antioxidant-rich fruits and vegetables was in this young Filipino population compared to reported intake levels of Spanish adolescents [43] and U.S., European, and Chinese adult populations [37,39,41,45,48,50]. On the other hand, consumption of other common "Western" pro-inflammatory foods was also relatively low, with the exception of processed meat, which was consumed at levels comparable to a U.S. adult population in which inverse associations between processed meat and blood TL were found [39]. Despite reports of increased soda consumption in the Philippines in recent decades [63,65], average consumption of sugar-sweetened beverages was still only about a quarter of the levels reported in a U.S. adult population in which a significant inverse association between non-diet soda and blood TL was found [44] and about 10-50% lower than consumption levels of another U.S. adult population [39] and the Spanish adolescent population [43] in which no associations with blood TL were found. Similarly, average consumption of bread and bread products was less than half that of the young Spanish population in which significant associations between white bread and blood TL were reported [43]. Though intake of added oils and fats among this Filipino population was comparable to an elderly Chinese population in which a borderline (albeit sex-specific) inverse association with blood TL was reported [48], coconut oil, the primary source of added fat in the Filipino diet, may actually be relatively anti-inflammatory compared to other saturated or unsaturated fats [31,32]. Moreover, the overall low caloric intake in this population may be protective against inflammation and oxidative stress [97,98]. Caloric intake in the earlier years was about half that of the Spanish adolescents, and at ages 20 to 22 it was lower, on average, than the energy intake of many U.S. and European adult populations in which diet-TL relationships have been assessed [39,41,45,49,50]. In fact, recent studies have demonstrated that this cohort of young Filipinos has, on average, lower levels of inflammatory cytokines than age-matched controls from U.S. and European populations [99,100].

Viewed alongside the generally negative findings in the literature, our data suggest that, at least among younger and low- to normal-weight individuals, differences in adiposity may not have a substantial impact on blood TL. Likewise, individual dietary components may not have a meaningful impact on telomere integrity, at least when caloric consumption and adiposity levels are otherwise low. Though there was little suggestion of an interaction between dietary variables and average BMI z-score, the low proportion of overweight or obese individuals may have limited the ability to detect this.

Some researchers have recently suggested that TL is not the biomarker of cumulative inflammation and oxidative stress that it was previously thought to be and that, compared with biological factors, lifestyle factors play a relatively minor role in determining TL

[16,55,101]. However, given the characteristics of our study sample and several methodological limitations, it remains unclear whether this is an explanation for the null results of the analyses presented here. For example, given the low proportion of overweight individuals and overall low levels of inflammation among this population, any effects of adiposity on inflammation and, thereby, on blood TL may have been too small to detect with our sample size. Similarly, considering the potential synergistic and antagonistic effects of different dietary components [102] and the significant associations between blood TL and both income and level of urbanization in our study sample, it may be that the overall combination of physiological, dietary, lifestyle, and environmental factors matter more than any individual factor. It may also take longer than we originally hypothesized for the cumulative effect of diet and adiposity to become manifest as differences in blood TL. Indeed, a number of studies that found no significant association between TL and individual dietary factors among middle-aged and older adult populations did find significant associations between TL and indices of overall healthy dietary or lifestyle patterns [37,51,103].

Furthermore, given the known potential for measurement error when using qPCR methods [85,101] or attempting to measure the usual diet of either juvenile, adolescent, or adult populations [82,104], we cannot rule out the possibility that statistical noise combined with limited power may have precluded our ability to detect associations in this sample. However, our MMqPCR measure of blood TL is well-validated and shows the expected magnitude of associations with blood TL measured using the gold standard Southern Blot method, as well as with age, sex, maternal blood TL, and paternal age [73,74]. Our sample size is also larger than some other studies that reported associations between TL and diet or adiposity [39,43,45,57,58]. Moreover, the multiple 24-hour recalls across time should have increased the reliability of our dietary measures [105] and should have provided more accurate measures of average dietary intake than the one-time food frequency questionnaires used in almost every other known study on diet and TL.

Additional sources of variability and residual confounding may have come from factors either not measured in this study or not controlled for in the analyses. Had we been able to obtain measures of blood TL at two different time points, we would have been better equipped to distinguish between variability in blood TL caused by inherited and early biological factors versus variability in the actual rate of telomere shortening. Also, it is intriguing that average household income was negatively associated with blood TL in our study sample. These results are not necessarily contradictory to the mixed findings of other studies [106]. However, these findings may indicate that other unmeasured socioeconomic, lifestyle, environmental, and early development factors could be moderating the effect of adiposity and diet on blood TL in our study population, and the effect of those factors may differ across varying ecological circumstances.

In summary, this study found no evidence that individual dietary characteristics or measures of adiposity across the childhood, adolescent, and early adult years are associated with interindividual variability in the blood TL of low- to normal-weight young adult Filipino males and females. 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 measures across childhood and adolescent years among a non-Western population. The null results of this and other studies suggest that small differences in body composition and consumption of any single pro- or antiinflammatory dietary component may not have a meaningful impact on TL, or the impact may differ depending on the broader set of nutritional, lifestyle, and environmental circumstances. Diet and adiposity still undoubtedly play an important role in long-term health and longevity, but telomere attrition may play a relatively minor role, if any, in those specific causal pathways.

Acknowledgments

Partial support for this research came from a National Science Foundation Graduate Research Fellowship (DGE0718145 and DGE1256082) to HJB and Shanahan Endowment Fellowship and *Eunice Kennedy Shriver* National Institute of Child Health and Human Development research infrastructure and training grants (R24 HD042828 and T32 HD007543) to the Center for Studies in Demography and Ecology at the University of Washington. The qPCR laboratory analysis was funded by National Science Foundation (Doctoral Dissertation Improvement Grant BCS-0962282), the Wenner-Gren Foundation (Gr. 8111) and institutional support from Northwestern University. Data and sample collection was funded by the National Institute of Health (grants TW05596, DK078150, RR20649, ES10126, and DK056350). Importantly, we would like to acknowledge the participants and staff of the Cebu Longitudinal Health and Nutrition Survey who made this study possible.

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Sample demographics

		Ma	les (n=850)			Females (n=609)
TL & Demographic Characteristics	Mean	(SD)	(Range)	Mean	(SD)	(Range)
Relative blood TL (T/S ratio)	0.76	(0.16)	(0.20 - 1.27)	0.80	(0.17)	(0.029 - 1.43)
Age, 2005 (years)	21.7	(0.3)	(20.9 - 22.5)	21.7	(0.4)	(20.8 - 22.5)
Average weekly household income, 1983–2005 (Philippine Pesos, inflation-adjusted)	480.7	(366.9)	(68.5 - 3509.3)	499.2	(334.3)	(70.6 - 3490.9)
Average urbanicity score, 1983–2005 a	37.2	(12.6)	(7.8 – 55.7)	37.4	(12.1)	(8.5 – 53.7)
Smoking status, 2005 (%):	%			%		
Never	18.2			67.7		
Former	49.1			5.9		
Current	32.7			26.4		

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Anthropometric characteristics of study sample

		M	iles (n=850)		Fem	ales (n=609)
Anthropometric Measures	Mean	(SD)	(Range)	Mean	(SD)	(Range)
BMI z-score, 1991	-0.8	(0.9)	(-4.9 - 4.3)	-0.8	(0.9)	(-4.4 - 2.6)
% Underweight (<-2 SD)	9.2			7.2		
% Overweight or obese (>1 SD)	2.7			1.5		
BMI z-score, 1994	-1.2	(1.1)	(-4.5 - 3.3)	-1.0	(1.1)	(-4.8 - 2.9)
% Underweight (<-2 SD)	20.4			18.7		
% Overweight or obese (>1 SD)	4.5			5.1		
BMI z-score, 1998	-1.0	(1.1)	(-4.0 - 3.0)	-0.7	(1.0)	(-4.1 - 2.0)
% Underweight (<-2 SD)	16.5			10.2		
% Overweight or obese (>1 SD)	3.3			5.1		
BMI z-score, 2002	-0.9	(1.0)	(-3.9 - 4.0)	-0.6	(1.0)	(-3.6 - 2.8)
% Underweight (<-2 SD)	12.5			6.4		
% Overweight or obese (>1 SD)	4.0			6.4		
BMI z-score, 2005	-0.6	(1.1)	(-3.8 - 3.8)	-0.6	(1.1)	(-3.5 - 3.8)
% Underweight (<-2 SD)	6.8			8.2		
% Overweight or obese (>1 SD)	6.5			7.9		
Average BMI z-score, 1991–2005	-0.9	(6.0)	(-3.3 - 3.7)	-0.7	(6.0)	(-3.2 - 2.0)
BMI (kg/m ²), 2005	21.0	(3.0)	(14.5 - 40.3)	20.1	(3.3)	(13.9 - 41.2)
% <18.5 kg/m ²	14.9			33.0		
% 23.0 kg/m ²	19.3			14.6		
% 25.0 kg/m ²	9.3			8.0		
Waist circumference 1998	64.7	(5.7)	(50.2 - 114.5)	62.9	(5.6)	(50.0 - 93.8)
Waist circumference 2002	68.6	(6.4)	(55.5 - 116.8)	65.6	(6.3)	(51.0 - 97.5)
Waist circumference 2005	72.2	(7.5)	(56.5 - 112.0)	67.5	(1.6)	(53.5 – 112.2)
Average waist circumference, 1998–2005	68.5	(0)	(57.0 - 111.5)	65 3	(5 0)	(54.7 - 96.9)

Dietary characteristics of study sample

		Male	s (n=850)		Fema	les (n=609)
Dietary Variables ^a	Mean	(SD)	(Range)	Mean	(CD)	(Range)
Kilocalories	1943	(547.5)	(810 - 3907)	1423	(439.8)	(556 – 3396)
Meat and poultry (all, g/day)	117.2	(7.6.7)	(0 - 452.0)	89.8	(58.1)	(0 - 380.7)
Processed red meat (g/day)	25.1	(25.3)	(0 - 169.5)	20.7	(21.2)	(0 - 198.6)
Grilled/fried meat & fish (g/day)	90.3	(64.7)	(0 - 568.3)	81.6	(54.0)	(0 - 327.2)
Fish (all, g/day)	46.8	(26.2)	(0 - 155.3)	36.5	(20.6)	(0 - 133.0)
Non-fried fish (g/day)	26.9	(20.4)	(0 - 126.9)	19.8	(15.1)	(0 - 94.6)
Coconut oil (g/day)	9.1	(5.0)	(0 - 28.3)	8.0	(4.4)	(0.4 - 31.7)
Other added oils and fat (g/day)	7.4	(9.9)	(0 - 48.5)	7.0	(5.5)	(0 - 33.3)
Fruit and Vegetables (all, g/day)	55.4	(43.7)	(0 - 325.6)	53.9	(38.3)	(0 - 229.3)
Fruit (g/day)	10.0	(21.7)	(0 - 240.4)	14.4	(22.6)	(0 - 182.1)
Non-root vegetables (g/day)	26.2	(26.7)	(0 - 208.0)	22.4	(19.8)	(0 - 119.4)
Root vegetables & plantains (g/day)	19.2	(23.9)	(0 - 217.7)	17.2	(18.4)	(0 - 103.6)
Rice (g/day)	603.3	(259.8)	(0 - 1591.1)	351.4	(166.8)	(0 - 1033.9)
Bread & bread products (g/day)	52.8	(37.9)	(0 - 252.5)	48.7	(27.3)	(0 - 165.7)
Soft drinks and artificial juices (oz/day)	3.4	(3.4)	(0 - 21.5)	3.5	(3.1)	(0 - 18.9)

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 a Dietary variables are the averages of intakes reported in the 1994, 1998, 2002, and 2005 survey waves.

Baseline regression models (n=1459)

	Simple Baseline Model (Adjuste	ed R ² =0.04)	Fully-Adjusted Baseline Model R ² =0.07)	(Adjusted
	β (95% CI)	р	β (95% CI)	р
Age in 2005 (months)	-0.0035 (-0.0063, -0.00070)	0.015	-0.0021 (-0.0050, 0.00073)	0.15
Sex (male)	-0.036 (-0.053, -0.020)	< 0.0001	-0.043 (-0.063, -0.023)	< 0.0001
Age*sex interaction	-0.0031 (-0.0068, 0.00070)	0.11	-0.0029 (-0.0067, 0.00082)	0.13
Principal component scores (PCS)				
PCS 1	-0.60 (-0.94, -0.26)	0.00	-0.45 (-0.79, -0.11)	0.0090
PCS 2	0.071 (-0.27, 0.42)	0.69	0.088 (-0.25, 0.42)	0.61
PCS 3	0.17 (-0.18, 0.53)	0.34	0.12 (-0.23, 0.47)	0.50
PCS 4	0.088 (-0.26, 0.44)	0.62	0.033 (-0.31, 0.38)	0.85
PCS 5	-0.12 (-0.46, 0.21)	0.47	-0.11 (-0.45, 0.22)	0.50
PCS 6	-0.073 (-0.42, 0.27)	0.68	-0.040 (-0.38, 0.30)	0.82
PCS 7	-0.25 (-0.59, 0.09)	0.16	-0.18 (-0.51, 0.16)	0.30
PCS 8	0.24 (-0.098, 0.58)	0.16	0.22 (-0.10, 0.55)	0.18
PCS 9	0.018 (-0.32, 0.35)	0.92	-0.13 (-0.47, 0.21)	0.44
PCS 10	0.41 (0.065, 0.75)	0.020	0.38 (0.043, 0.71)	0.027
Ln(average income 1983–2005)			-0.027 (-0.041, -0.012)	< 0.0001
Average urbanicity score (1983–2005)			0.0028 (0.0021, 0.0035)	< 0.0001
Smoking status:				
Current smoker			0.012 (-0.010, 0.035)	0.28
Former smoker			0.0094 (-0.011, 0.030)	0.37

Relationship between adiposity measures and blood TL among males and females ^a

	Males (n=850)		Females (n=609)	
	β (95% CI)	р <i>b</i>	β (95% CI)	р <i>b</i>
MODEL 1A				
Average BMI 1991–2005				
Linear term	0.0015 (-0.013, 0.016)	0.84	0.0022 (-0.019, 0.024)	0.84
Quadratic term	-0.0013 (-0.0079, 0.0053)	0.71	0.0078 (-0.0036, 0.019)	0.18
Likelihood Ratio Test		0.82		0.20
MODEL 2A				
BMI z-score 1991	-0.0011 (-0.017, 0.015)	0.90	-0.0025 (-0.024, 0.019)	0.82
BMI z-score 1994	-0.0076 (-0.023, 0.0079)	0.34	0.019 (-0.0032, 0.042)	0.09
BMI z-score 1998	0.00061 (-0.021, 0.019)	0.95	-0.014 (-0.04, 0.013)	0.31
BMI z-score 2002	0.014 (-0.0055, 0.034)	0.16	-0.0078 (-0.036, 0.020)	0.59
BMI z-score 2005	-0.0012 (-0.017, 0.014)	0.88	-0.0055 (-0.029, 0.018)	0.64
Likelihood Ratio Test		0.63		0.35
MODEL 1B				
Average waist circumference 1991–2005 ^b				
Linear term	0.0029 (0.000088, 0.0056)	0.04	-0.0012 (-0.0037, 0.0013)	0.34
Quadratic term	-0.00012 (-0.00022, -0.000017)	0.02	0.00013 (-0.000073, 0.00033)	0.21
Likelihood Ratio Test		0.10		0.37
MODEL 2B				
Waist circumference 1998 ^C	0.0012 (-0.00203, 0.0044)	0.47	-0.00048 (-0.0043, 0.0034)	0.81
Waist circumference 2002 ^C	-0.00085 (-0.0045, 0.0028)	0.64	-0.00081 (-0.0046, 0.0030)	0.68
Waist circumference 2005 ^C	0.00056 (-0.0018, 0.0029)	0.64	0.00038 (-0.0025, 0.0033)	0.80
Likelihood Ratio Test		0.74		0.90

^aAll models control for mean-centered age in 2005 (in months), sex, the interaction between age and sex, log-transformed average inflationadjusted income from 1983 to 2005, average urbanicity score from 1983 to 2005, smoking status (current, former, and never smoker), and ten principal component scores of genome-wide data.

 b All p-values are raw, unadjusted p-values. Significance levels in these models are set at an adjusted alpha value of 0.0125.

^cAll models with waist circumference further controlled for mean-centered height and mean-centered age in each of the measurement periods.

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	MODEL 3A ^a		MODEL 3B b		MODEL 3C ^c		MODEL 3D ^d	
	β (95% CI)	p ^e	β (95% CI)	p ^e	β (95% CI)	p ^e	β (95% CI)	p ^e
Calories (100 kcal)							-0.00089(-0.00032, 0.0014)	0.45
Processed meat (50 g)	0.00048 (-0.017, 0.018)	0.96	-0.0046 (-0.022, 0.013)	0.61	-0.0072 (-0.028, 0.014)	0.51	-0.0025(-0.020, 0.015)	0.78
Interaction with BMI					-0.0038 (-0.021, 0.013)	0.66		
Grilled//fried meat & fish (50 g)	-0.00045 (-0.0087, 0.0078)	0.91	-0.0031 (-0.011, 0.0051)	0.45	-0.0040 (-0.013, 0.0054)	0.37	-0.0032 $(-0.012, 0.0057)$	0.48
Interaction with BMI					-0.0015 (-0.0077, 0.0048)	0.65		
Non-fried fish (50 g)	-0.0023 (-0.026, 0.021)	0.85	$0.0054 \ (-0.018, \ 0.029)$	0.65	0.027 (-0.0031, 0.057)	0.08	0.0042 (-0.020, 0.028)	0.73
Interaction with BMI					0.031 (0.0046, 0.057)	0.02		
Coconut oil (5 g)	0.0021 (-0.0083, 0.013)	0.69	0.001 (-0.0095, 00.011)	0.86	$0.0016 \left(-0.0098, 0.0131\right)$	0.78	0.0028 (-0.0083, 0.014)	0.62
Interaction with BMI					0.0010 (-0.00702, 0.00904)	0.81		
Fruits and vegetables (50 g)	-0.0035 $(-0.013, 0.0060)$	0.47	0.0041 (-0.0054, 0.014)	0.39	0.0020 (-0.0098, 0.0131)	0.77	0.0043 (-0.0053, 0.014)	0.38
Interaction with BMI					-0.0024 (-0.00702, 0.00904)	0.66		
Bread & bread products (50 g)	0.0068 (-0.0059, 0.019)	0.30	0.0019 (-0.011, 0.014)	0.77	$-0.0016 \left(-0.018, 0.015\right)$	0.85	$0.0021 \ (-0.011, \ 0.015)$	0.75
Interaction with BMI					-0.0041(-0.017, 0.0084)	0.52		
Soft drinks and juice (4 oz)	0.0011 (-0.0095, 0.012)	0.84	0.0010 (-0.0095, 00.011)	0.86	-0.00052 (-0.014, 0.013)	0.94	0.0017 (-0.0090, 0.012)	0.75
Interaction with BMI					-0.0020 (-0.012, 0.0080)	0.70		
Wald's Tests								
Processed meat, grilled/fried meat and fish								0.74
Fish and vegetables								0.65
Bread and sweetened beverages								0.89
Likelihood Ratio Test								
Combined dietary factors								0.96

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^aSimple model testing each dietary variable individually only controlling for mean-centered age in 2005 (in months), sex, the interaction between age and sex, ten principal component scores of genomewide data, and mean-centered average kilocalories from 1994 to 2005. ^b Fully-adjusted model testing each dietary variable individually controlling for all in Model 3A in addition to log-transformed average inflation-adjusted income from 1983 to 2005, average urbanicity score from 1983 to 2005, and smoking status (current, former, and never smoker).

^CFully-adjusted model testing interaction between individual dietary variables and average BMI z-score from 1991 to 2005.

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 $d_{\rm Fully-adjusted}$ model testing all dietary variables together in the same model.

 e All p-values are raw, unadjusted p-values. Significance levels in these models are set at an adjusted alpha value of 0.0071.