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Shorter Preschool, Leukocyte Telomere Length is Associated with Obesity at Age 9 in Latino Children

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Abstract

Objective—To determine the potential role of leukocyte telomere length as a biomarker for development of childhood obesity in a low-income Latino population.

Methods—A birth cohort of Latino children (N=201) in San Francisco (May 2006-May 2007) was followed until age 9 and assessed annually for obesity and dietary intake. Leukocyte telomere length was measured at 4 and 5 years (n=102) and assessed as a predictor for obesity at age 9 adjusting for known risk factors. Leukocyte telomere length at age 4 and 5 was evaluated as possible mediator of the relationship between excessive sugar-sweetened beverage consumption and obesity at age 9.

Results—Shorter leukocyte telomere length in preschoolers was associated with obesity at age 9 (adjusted odds ratio 0.35, 95% confidence interval 0.13-0.94) after adjustment for known risk

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

AUTHORSHIP

TWK and JMW wrote the manuscript and conducted the analyses of the data. JMW and EE conceived the study. EB and JL designed and conducted the telomere length measurements. TWK, JMW, DFJ, VBC, and KM interpreted the results. EE, EB, JL, DFJ, VBC, and KM revised the manuscript. All authors read and approved the final manuscript.

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factors. Telomere length mediated 10% of the relationship between excessive sugar-sweetened beverage consumption and obesity.

Conclusion—Shorter leukocyte telomere length may be an indicator of future obesity risk in high-risk populations, as it is particularly sensitive to damage from oxidative stress exposure including those from sugar-sweetened beverages.

Keywords

childhood obesity; leukocyte telomere length; Latinos; sugar-sweetened beverage; middle childhood

BACKGROUND

Latino children have a higher obesity rate than non-Latino whites in the United States [1], with increased risk for non-fatty liver disease, diabetes mellitus, and chronic obesity [2]. The ability to predict obesity, particularly those at risk for associated co-morbidities could make it possible to target high-risk children and intervene early. Obesity in early childhood is a good predictor of future obesity risk, but there is a need for predictors for later metabolic disease development. Leukocyte telomere length has been found to predict onset of cardiometabolic diseases in adults, specifically diabetes mellitus and cardiovascular disease [3–5], however telomere length has been minimally studied in children and to our knowledge, no studies have evaluated the relationship between telomere length and future obesity risk in high-risk Latino children.

Telomeres and Chronic Inflammation

Telomeres are specialized nucleoprotein structures at the end of the chromosomes in eukaryote cells. They stabilize the chromosomes and prevent the loss of genetic material at cell division. With each division cycle, telomeres shorten by approximately 100-200 base pairs [6]. The loss of telomere length is not constant throughout life with most of the loss occurring before age 4, with attrition rates of 1 kilobase per year. Between age 4 and young adulthood the telomere length attrition plateaus and throughout adult life there is gradual telomere attrition [7, 8]. Inflammation contributes to telomere shortening as the guanine-rich telomeric sequence is highly sensitive to damage from oxidation. High levels of oxidation species in systemic inflammation including obesity and metabolic disease contribute to accelerated telomere attrition [9].

Telomere Length, Obesity and Metabolic Disease

Obesity and other chronic diseases are systemic chronic inflammatory states [10]. Studies in adults suggest an inverse association between body mass index (BMI) and leukocyte telomere length [11]. Two meta-analyses demonstrate a negative correlation between adult BMI and leukocyte telomere length, but with significant heterogeneity, in part due to the co-morbidities that often occur with obesity in adults [12, 13]. Few studies explore the relationships between leukocyte telomere length and obesity in children and those that do examine the relationship using cross-sectional data [14–16], which does not provide any clues on the possibility of telomere length serving as an associated factor for future disease.

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As adult studies suggest that shorter telomere length is sensitive to the inflammatory processes associated with metabolic disease [17, 18], and shorter telomere length and associated inflammatory cytokine production may result in onset of type 2 diabetes mellitus, and coronary heart disease [17, 18], we sought to better understand the relationship between leukocyte telomere length in the preschool years and future school aged obesity including chronic obesity in high-risk Latino children during the time period with metabolic disease first surfaces.

METHODS

Study Population

A cohort of 201 pregnant Latina women were recruited in 2006-7 in the prenatal clinics at two San Francisco hospitals (University of California, San Francisco Medical Center and San Francisco General Hospital) during the second and third trimesters of pregnancy. The recruitment including inclusion and exclusion criteria has been described in previous publications [8, 10, 19, 20]. Briefly, the women recruited were mostly foreign-born (93%) with Spanish as their primary language and almost all were part of the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) program. A high percentage of mothers (61%) cited Mexico as their country of birth with the remainder originating from Central America. The Institutional Review Board and Committee on Human Research at the University of California, San Francisco, approved the study. The mothers gave written consent for their participation and their children's participation.

Procedures

Predictor - Telomere Length Measurements—Telomere length was measured in subset of our cohort at age 4 and/or 5 (n=102) from genomic DNA in dried blood spots collected via finger prick. The quantification of telomere length was ascertained using a quantitative polymerase chain reaction, and DNA extraction was done with QIAamp DNA Investigator Kit (catalog number 56504; QIAGEN). The assay for telomere length measurement was adapted from the original published method by Cawthon, R.M. [21] as presented by Lin, J et al. [22]. The average coefficient of variation for this study was 4.8% [8]. Telomere length is expressed as the T:S, the ratio of a telomeric product to a single-copy gene product.

Child Characteristics—After recruitment, mothers and children were followed up at delivery, 4-6 weeks, 6 months, 12 months and annually thereafter. At each study visit, child's weight and height/length were assessed as previously described [8, 10, 19, 20]. We also assessed consumption of sugar-sweetened beverages (sodas, colas, kool-aid, Hi-C) at each visit and excessive consumption of sugar-sweetened beverages was defined as ≥ 4 times weekly.

Outcomes – Weight Status—Using CDC growth curves [23], childhood overweight and obesity was defined as BMI ≥ 85^{th} percentile, obesity as BMI ≥ 95^{th} percentile and underweight as BMI ≤ 5^{th} percentile. Chronic childhood obesity was defined as being obese at both 4 or 5 and 9 years and not being chronically obese was defined as not being obese at

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either. Weight gain between 4 or 5 and 9 years was defined as having a child change from normal to overweight or obese BMI grouping or change from overweight to obese. No weight gain was defined as staying normal or overweight at both time points. Weight loss was defined as being obese at 4 or 5 years, but not at 9 years and no weight loss was staying obese from 4 or 5 to 9 years.

Statistical Analyses

Bivariate analysis was performed using t-tests, chi-squared test or Fischer's exact test for calculations where cell sizes were less than or equal to 5 to evaluate the relationship between weight status at 9 years (overweight, obese, chronic obesity, weight gain, and weight loss) and known risk factors for obesity at age 4 and 5 in our population [19, 20] as well as telomere length at 4 and 5 years and telomere length attrition from 4 to 5 years. We used repeat measures of telomere length to increase our sample size as some children were measured at 4 years and not at 5 years (n=22 out of 91 measured at 4 years) and vice versa (n=11 out of 80 measured at 5 years). Because of repeat measures of telomere length (T/S) for a subset of the children, inferences were based on robust standard errors to account for the within-individual correlation as previously described [8]. Excessive sugar-sweetened beverage consumption's association with weight status at 9 years was evaluated at age 2, 3, 4, and 5.

Multivariable logistic regression models were used to investigate the relationship between telomere length and childhood obesity at age 9 adjusting for known risk and protective factors for obesity including exclusive breastfeeding and maternal characteristics such as high pre-pregnancy BMI, high age and low education level. Subsequent analyses assessed the relationship between accelerated telomere shortening between age 4 and 5 and obesity at age 9. Interaction between excessive sugar-sweetened beverage consumption at age 5 and telomere length at age 4 and 5 was assessed. Additional regression analyses were conducted to examine the role of telomere length at age 4 or 5 as potential mediator of the effect on relationship between sugar sweetened beverage consumption and obesity at age 9. These analyses were based on methods for a causal mediation analysis using the medeff function which can handle binary outcomes [24] and are summarized as the estimated percentage of the effect of excessive consumption of sugar-sweetened beverages as explained by telomere length. The analyses were conducted using Stata software (version 12; StataCorp LP).

RESULTS

Telomere Length and Weight Status

Among the 201 children recruited, 143 children (71%) were followed-up at 9 years, and 102 (51%) had telomere length measured. Among the 102 children, 91 (89%) were measured at 4 years, 80 (78%) at 5 years and 69 (68%) were measured at both 4 and 5 years. Two children were excluded because the exact time of measurement was missing. Of the 102 children who had telomere length ascertained and were followed up at 9 years the prevalence of overweight was 59% (60/102), the prevalence of obesity 42% (42/102), the prevalence of chronic obesity was 36% (36/102), and the prevalence of weight loss and weight gain between age 4 or 5 and 9 was 4% (4/102) and 13% (13/102), respectively. Excessive intake

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of sugar-sweetened beverages increased from 4.6% (3/63) at age 2, to 10% (7/70) and 8.5% (6/71) at age 3 and 4 respectively. Excessive sugar sweetened beverage consumption was much higher at age 5 (21.2%; 21/99) and at age 9 (17.3%; 3/75). The demographics and family characteristics of the children with telomere length measured did not differ from where telomere length was not assessed including gender (p=0.4), birthweight (p=0.9), exclusive breastfeeding at 4-6 weeks (p=0.9), maternal pre-pregnancy BMI (p=0.9), maternal age at birth (p=0.6), excessive sugar-sweetened beverage intake at age 5 (p=0.9) and maternal education (p=0.06).

Overweight or Obese at 9 Years—There was no difference in telomere length at 4 and 5 years for children who were overweight or obese compared with normal weight children (p=0.82; Table 1). Change in telomere length from age 4 to 5 was also not significantly different between normal weight and overweight and obese children (p=0.59; Table 1). Excessive sugar-sweetened beverage consumption at age 2,3,4, and 5 did also not differ between normal weight and overweight and obese children (p=0.65, p=0.31, p=1.00, and p=0.21; Table 1)

Obese at 9 Years—There was no association in telomere length measured at 4 and 5 years and obesity although our findings approached statistical significance with obese children having shorter telomeres than non- obese ones (1.8±0.04 vs. 1.9±0.05, p=0.07; Table 1). We found no difference between telomere attrition rate from 4 to 5 years and obesity in children at 9 years of age (p=0.31). Excessive consumption of sugar-sweetened beverages at 5 years was higher in children who were obese at 9 years compared to those not obese (31% versus 14%, p=0.04). Meanwhile, there was no association between excessive consumption of sugar-sweetened beverages at age2, 3 and 4 and obesity at age 9 (p=0.39, p=0.17 and p=0.28) (Table 1).

Chronic Obesity, Weight Gain and Weight Loss—There was no difference in telomere length at 4 and 5 years and chronic obesity (p=0.10), weight gain from 4 and 5 to 9 years (p=0.91) and weight loss from 4 and 5 to 9 years (p=0.81; Table 1). The change in telomere length between 4 and 5 years also did not differ significantly for chronic obesity (p=0.30), weight gain (p=0.74) and weight loss (p=0.74). Telomere length measured at age 4 was not associated with weight changes including weight gain (p=0.98) and weight loss (p=0.42; Table 1). There was also no association between telomere length at 5 years and the association with weight gain (p=0.75) or weight loss (p=0.30; Table 1). The percentage of children with excessive sugar-sweetened beverage consumption at 2, 3, 4, and 5 years was not impacted by chronic obesity (p=0.65, p=0.11, p=0.68, and p=0.14), weight gain (p=0.56, p=1.00, p=1.00, and p=0.23) or weight loss (p=0.20, p=0.49, p=1.00, and p=0.56). (Table 1)

Multivariable Regression and Mediation

We conducted multivariate analyses of the relationship between telomere length at 4 and 5 years and obesity at 9 years adjusting for variables that were previously associated with obesity in our cohort including child gender, birthweight, exclusive breastfeeding at 4-6 weeks, maternal pre-pregnancy BMI, maternal age, and maternal education [19, 20]. Shorter telomere length was associated with obesity at 9 years (odds ratio (OR) 0.35, 95%

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confidence interval (CI) 0.13-0.94) (Table 2). None of the adjusting variables including birthweight (95%CI 0.74-5.05), gender (95%CI 0.35-2.00), exclusive breastfeeding (95%CI 0.38-2.51), maternal pre-pregnancy BMI (95%CI 0.99-1.17), maternal age (95%CI 0.87-1.05) or education (95%CI 0.13-1.93) were significantly associated with obesity at 9 years (Table 2). As a sensitivity analysis, we looked at telomere length measured at 4 and separately at 5 years and neither of them reached association (OR 0.37, 95%CI 0.29-1.8 and OR 0.21, 95%CI 0.03-1.5) adjusting for known risk factors.

In the second multivariate model, which included excessive consumption of sugar-sweetened beverages at 5 years of age, we found that higher maternal education at inclusion was protective against obesity (OR 0.29, 95% CI 0.08-0.99) and excessive consumption of sugar-sweetened beverages at 5 years (OR 3.9, 95% CI 1.06-14.45) was associated with obesity at 9 years. Telomere length (OR 0.36, 95%CI 0.11-1.15) and maternal pre-pregnancy BMI (95%CI 0.99-1.18) neared statistical significance while birthweight (95%CI 0.83-6.52), gender (95%CI 0.31-2.00), exclusive breastfeeding (95%CI 0.42-3.27), and maternal age (95%CI 0.86-1.04) were not associated with obesity at 9 years (Table 3). We found no interaction between excessive sugar-sweetened beverage consumption at 5 years and telomere length at age 4 and 5 in relation to obesity outcome (p=0.35).

A casual mediation analysis showed that combined telomere length at 4 and 5 years accounted for 10% of the effect excessive consumption of sugar-sweetened beverages at 5 years (≥ 4 times weekly) had on obesity at 9 years.

DISCUSSION

Significance of Our Study

Our study found that leukocyte telomere length at age 4 and 5 years was associated with obesity at 9 years as was reduced maternal education level after adjustment for known risk factors for this cohort [19, 20]. Of the subset of children who were obese at 9 years, the prevalence of chronic obesity was 76%, possibly indicating increased risk for future metabolic disease development in this subset. It is the first study to assess leukocyte telomere length in preschoolers and the link with obesity at 9 years in low-income, urban Latino children. Our finding suggests that telomere length could play an important role as an associated factor of later childhood obesity. Adult studies have suggested that leukocyte telomere length might also act as a predictor of metabolic disease in adults, specifically diabetes mellitus, cardiovascular disease and non-fatty liver disease [3–5, 18]. Shorter telomere length may serve as a marker of future development of obesity and concomitant metabolic disease as telomeres may be initially impacted by inflammatory processes prior to weight gain [16, 25, 26].

Weight Gain

Adult weight gain has been shown to be a risk factor for telomere length shortening in multiple studies [11, 27], although we found no association between leukocyte telomere length at age 4 and 5 and weight gain from 5 to 9 years in contrast with the association between telomere length at age 4 and 5 and obesity at age 9. However, the number of

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children who changed weight categories from normal weight to obese or overweight and from overweight to obese was small (n=13).

We did find a near association between telomere length at age 4 and 5 and chronic obesity (p=0.10; Table 1) suggesting that shorter telomere length may set the stage for the cumulative impact of inflammatory process which ultimately result in metabolic disease. A high percentage of children in our cohort who were obese were chronically obese (76%). Previous studies that looked at the association between shorter telomere length and childhood obesity have been cross-sectional with divergent findings in European and Arab children [14, 15]. As children have less obesity-associated metabolic disease compared with adults, differences in obesity phenotype and disease pathology may explain differential impacts on telomere shortening processes. Telomere length may be a better marker for incident weight gain as shorter leukocyte telomeres may facilitate the inflammatory cascade that results in obesity and more importantly metabolic disease. Meanwhile, there was no association between obesity at age 4 and 5 and shorter telomere length as we have shown in our previous work [10] suggesting that the relationship between obesity and shorter telomere length may not always be a concurrent process.

Weight Loss and Telomere Length Change

We did not find any difference in telomere length in those who lost weight in contrast with other studies [16, 26] compared to those who did not lose weight, although the number of children who lost weight in the cohort was low (n=4).

Excessive Sugar-Sweetened Beverage Consumption

Childhood obesity has been linked with consumption of sugar-sweetened beverages [28] similar to our findings. Shorter telomeres in adults have been found to be associated with higher consumption in our previous work [29]. Our findings indicates that sugar-sweetened beverage consumption may affect telomere length loss and obesity as children age. Regular consumption of sugar-sweetened beverages might influence metabolic disease development through accelerated cell aging. This is supported by our previous work which found that excessive sugar-sweetened beverage consumption at 4 years and daily consumption of 100% fruit juice at age 3 were shown to be associated with shorter telomere length 4 and 5 [10]. Our mediation analysis suggested that telomere length might be an important intermediary variable to understand in the trajectory from sugar sweetened beverage consumption to obesity.

Limitations and Further Directions

A limitation of our study was the small sample size (N=102) and also the restriction to one population group. Future studies should include a larger sample size of children and be conducted in multi-ethnic cohorts. Another limitation was that the only data we had on a poor diet was sugar-sweetened beverage consumption, other relevant variables such as total energy intake should be included in future studies. Furthermore, we had only two measurements of leukocyte telomere length at age 4 and 5 years over a short time period. Repeated measurements at earlier time points as early as birth or 1 year might be predictive

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of obesity at 9 years and make it possible to intervene even earlier to prevent childhood obesity development, as behavior changes are long and slow.

Conclusion

Our study showed that telomere length in preschoolers was associated with obesity at 9 years. We hypothesize that sugar-sweetened beverage consumption may shorten telomere length resulting in a cascade of negative impacts from oxidative stress exposures including increased risk for obesity and chronic obesity. Future studies should investigate the role of leukocyte telomere length as a predictive biomarker for childhood obesity and metabolic disease development.

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Table 1

Telomere length (T:S), sugar-sweetened beverage consumption and weight status in Latino children at 9 years of age (N=102) (San Francisco included from birth between 2006–7)

	Over-weight at 9 years (60/102)	**Not over-weight at 9 years**	**P**	**Obese at 9 years (43/102)**	**Not obese at 9 years**	**p**	**Chronic obesity[8] (36/90)**	**No chronic obesity**	**P**	**Weight gain[9] (13/54)**	**No weight gain**	**p**	**Weight loss[10] (4/40)**	**No weight loss**	**P**
Telomere length at 4 years (T:S) (mean ± SD)	1.80 ± 0.34	1.77 ± 0.39	0.71	1.71 ± 0.28	1.84 ± 0.41	0.16	1.74 ± 0.28	1.84 ± 0.41	0.23	1.81 ± 0.29	1.81 ± 0.39	0.98	1.88 ± 0.27	1.74 ± 0.28	0.42
Telomere length at 5 years (T:S) (mean ± SD)	1.94 ± 0.28	2.02 ± 0.40	0.27	1.90 ± 0.25	2.02 ± 0.38	0.11	1.90 ± 0.26	2.04 ± 0.38	0.08	1.99 ± 0.27	2.03 ± 0.37	0.75	1.73 ± 0.16	1.90 ± 0.26	0.30
Telomere length at 4 and 5 years (mean ± SE)	1.87 ± 0.04	1.88 ± 0.06	0.82	**1.81 ± 0.04**	**1.92 ± 0.05**	**0.07**	1.82 ± 0.04	1.93 ± 0.05	0.10	1.89 ± 0.07	1.91 ± 0.06	0.91	1.81 ± 0.09	1.83 ± 0.04	0.81
Change in telomere length from 4 to 5 years in months (T:S) (mean ± SD)	0.05 ± 0.21	0.02 ± 0.03	0.59	0.06 ± 0.30	0.01 ± 0.03	0.31	0.07 ± 0.33	0.04 ± 0.03	0.30	0.01 ± 0.02	0.02 ± 0.03	0.74	−0.01 ± 0.03	0.07 ± 0.33	0.74
Excessive sugar-sweetened beverages intake at 5 years (≥4 times a week), n/T (%)	15/59 (25)	6/40 (15)	0.21	**13/42 (31)**	**8/57 (14)**	**0.04**	10/36 (28)	8/53 (15)	0.14	4/13 (31)	6/41 (15)	0.23[11]	0/4 (0)	10/36 (28)	0.56[4]

[8] Chronic obesity is defined as obesity at both age 5 and 9 years and no chronic obesity is defined as not being obese at either.

[9] Weight gain between 5 and 9 years is defined as going from normal to overweight or obese and going from overweight to obese. No weight gain is defined as staying normal or overweight at both time points

[10] Weight loss is defined as being obese at 5 years, but not at 9 years and no weight loss is staying obese from 5 to 9 years

[11] Fischer's exact test

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Table 2

Multivariable logistic regression of telomere length as a predictor for obesity at 9 years excluding sugar-sweetened beverages (n=93, total number of observations = 156) (San Francisco included from birth between 2006–7)

Variable	Odds ratio	95% confidence interval
Birthweight (kg)	1.93	0.74–5.05
Gender (male)	0.83	0.35–2.00
Telomere length measurements at 4 and 5 years (T:S)	**0.35**	**0.13–0.94**
Exclusive breastfeeding at 4–6 weeks	0.97	0.38–2.51
Maternal pre-pregnancy BMI (kg/m^2)	1.07	0.99–1.17
Maternal age (years)	0.95	0.87–1.05
Education(≥high school diploma)	0.49	0.13–1.86

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Table 3

Multivariable logistic regression of telomere length as a predictor for obesity at 9 years including sugar-sweetened beverages (n=90, total number of observations = 153) (San Francisco included from birth between 2006–7)

Variable	Odds ratio	95% confidence interval
Birthweight (kg)	2.33	0.83–6.52
Gender (male)	0.79	0.31–2.00
Telomere length measurements at 4 and 5 years (T:S)	0.36	0.11–1.15
Exclusive breastfeeding at 4–6 weeks	1.19	0.42–3.27
Maternal pre-pregnancy BMI (kg/m^2)	1.08	0.99–1.18
Maternal age (years)	0.95	0.86–1.04
Education(≥high school diploma)	**0.29**	**0.08–0.99**
Sugar-sweetened beverages at 5 years ≥4 or more time a week	**3.91**	**1.06–14.45**