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Journal

Pediatric Obesity, 18(12)

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Publication Date

2023-12-01

DOI

10.1111/ijpo.13082

Peer reviewed

HHS Public Access

Author manuscript

Pediatr Obes. Author manuscript; available in PMC 2024 December 01.

Published in final edited form as:

Pediatr Obes. 2023 December ; 18(12): e13082. doi:10.1111/ijpo.13082.

Changes in leukocyte telomere length among children with obesity participating in a behavioral weight control program

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Abstract

Objective: To examine changes in Leukocyte telomere length (LTL) during and after a behavioral weight control program for children with obesity.

Methods: We measured LTL among a cohort of 158 children 8 to 12 years of age with a body mass index greater than or equal to the 95th percentile for age and sex. Children were 55% female, 29% white, 52% Latinx, 8% Asian, and 11% Pacific Islander, other or multi-ethnic. All children participated in a six-month, family-based, group behavioral weight control program and were assessed before treatment, after treatment, and one year after the end of treatment. To test the sample population slope of LTL over the intervention and maintenance time periods, we fit spline mixed effect regression models.

Results: LTL increased an average of 0.09 T/S units per year (95% Confidence Interval [CI] 0.04 to 0.13; $P = .0001$) during the weight control program intervention period, followed by an average decline of −0.05 T/S units per year (95% CI −0.08 to −0.03; $P < .0001$) during the one year of follow-up after the completion of the intervention. Among 26 social, psychological, behavioral, and physiological factors we examined, we did not find any predictors of these changes.

Conclusions: LTL increased in response to a behavioral weight control program among children with obesity, suggesting an impact on biological health and cellular aging from participation in a behavioral weight control intervention. LTL may be a useful biomarker for assessing changes in response to behavioral interventions.

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Keywords

Aging; Childhood Obesity; Lifestyle Modifications; Molecular Mechanisms

Introduction

The literature of both observational and genetic determinants of leukocyte telomere length (LTL) show strong correlations with age, and suggest small but consistent associations with chronic disease outcomes, where longer LTL is associated with lower incidence of cardiovascular and metabolic disease.[1 2] While the relationship of LTL with chronic disease risk is not fully understood, the role in molecular aging is clearer.[3] LTL decreases as cells divide, and in so doing contributes to disruptions in physiology at the cellular, organ, and organism level,[3] thus supporting the investigation of LTL as a potential biomarker of future disease risk. The potential value in pediatric populations is that it can be viewed as a short-term measurable precursor of chronic disease risk to help understand the full range of health consequences of interventions during childhood. Supporting this potential utility is the observation that LTL tracks moderately, but not strongly, with a number of other risk factors for chronic non-neoplastic disease, at least among adults.[4] Despite this suggestive evidence, the added value of LTL as a biomarker for disease risk is unclear, particularly among children. Longitudinal data on the dynamic relationship between risk factors and LTL are one piece of evidence needed to understand the utility of LTL as a biomarker. For example, of sixty-three studies of the relationship of BMI and LTL in a recent review, only 13 had LTL measured at two time points.[5] Notably, no studies reviewed had three time points measured, and three timepoints (or ideally more) are necessary to reduce the likelihood that changes in LTL are due to regression to the mean.[6]

For determining the utility of LTL as a measure of risk in response to social, psychological, behavioral, physiological or environmental changes, intervention studies are required with multiple time points of LTL measurement. Intervention studies in adults have shown lengthening of LTL associated with surgically- or mechanically-reduced BMI, but the sample sizes of these studies have been quite small.[7 8] In addition, it is unclear how results from surgical reductions in BMI would compare to effects of behavioral interventions.[9] Prior research among children showed LTL lengthening during an intensive intervention among adolescents age 12 to 16, but with only two time points of LTL, giving less certainty as to the trajectory and the extent to which regression to the mean may explain findings.[10]

The aim of the current analysis is to examine changes of LTL across three timepoints among children with obesity participating in a six-month behavioral weight control program and during the one-year follow-up period. We take advantage of a temporally specific exposure measure where all children received a standardized state-of-the-art 6-month family-based, group, behavioral weight control program and were followed for an additional year of follow-up after the treatment.

Methods

Study sample

Participants were enrolled in the CHANGES trial, a 2-arm parallel group, randomized controlled trial testing the addition of home environment strategies to a family-based, group, behavioral weight control trial for children. All children received the same family-based behavioral weight control program, with children in the treatment group receiving additional home environment strategies. For this study, the treatment and control groups are combined into a single cohort, and we did not examine the impacts of randomization on LTL. All enrolled families received the Stanford Pediatric Weight Control Program, a six-month, family-based group behavioral weight control program based on Epstein's Traffic Light diet and exercise program for children,[11–13] modified to address the needs of the racially-/ethnically- and socioeconomically-diverse population served in our clinical setting.[14,15] It is designed to help children reduce dietary energy density, increase physical activity, reduce screen time and improve parenting practices to reduce weight gain.

To be eligible, children were 8–12 years of age, with body mass index (BMI) greater than or equal to the 95th percentile for age and sex on the U.S. Centers for Disease Control and Prevention (CDC) 2000 BMI references, without medical problems or taking medications affecting weight, medically able to participate in physical activity, able to speak English or Spanish, living within a 25-mile radius of Stanford, not planning to move from the area in the upcoming 18 months, and with no family members with untreated eating disorders in the home. Parents completed signed informed consent for their child and themselves and children signed assent prior to baseline measures and study enrollment. Study recruitment and data collection were conducted between September 11, 2010, and October 15, 2014. We assayed for LTL from frozen (−80 C) whole blood aliquots from 158 children in 2018. The study protocol was approved by the Administrative Panel on Human Subjects in Medical Research at Stanford University.

DNA extraction from Human Blood and Leukocyte Telomere Length assay

DNA purification, using the Qiagen QiaAmp DNA mini kit, was carried out on blood samples. The telomere length measurement assay was adapted from the published original method by Cawthon[15,16] and represents a ratio of two qPCR reactions: *T*elomere over *S*ingle copy gene, (T/S). Using this method, the average +/− standard deviation coefficient of variation (CV) was 2.2 +/− 1.8% (median CV was 1.9% and the interquartile range of the CV was 0.9% - 3.2%). Further details of how samples were handled and the assays are described in the Supplemental Material in accordance with recommendations of the Telomere Research Network Publication Reporting Guidelines.[17]

Statistical analysis

To test the sample population slope of LTL over the intervention (baseline to post-intervention) and maintenance (post-intervention to end of follow-up) time periods, we fit two types of spline mixed effect regression models, one based on a random effect framework, and the other an individual fixed effect framework (SAS (version 9.4), PROC MIXED (SAS/STAT version 15.1)). Conceptually, the first analysis treats the error term

as following a normal distribution, and estimates a population average coefficient. The second model is equivalent to an independent error term for each individual and can be interpreted as estimating a coefficient for each individual. Seven months was chosen as the inflection point, as this captured the timepoint at which most of the participants completed the post-intervention measures. In the random effect model, we controlled for treatment (two categories), gender, Latinx ethnicity, age, parent education and household income (adjusted for household size). In the fixed effect model, the individual is included as a fixed effect. We do not control for BMI nor for puberty in models estimating the effect of the treatment on LTL since the directionality of the relationship with LTL is not clear, and thus BMI may be a mediator of the effects of the intervention on LTL.

Cross sectional models and baseline prediction models

To assess associations between LTL changes and other risk factors measures, a regression model was fit at each time point (baseline, post-intervention, end of follow-up) with LTL modeled as a function of exposure measures. We modeled baseline exposure predicting change in telomere length over the intervention period and separately during the follow up period with change in telomere length over 1 year as the outcome measure. In both models, we controlled for treatment, gender, Latinx ethnicity, age, parent education and household income (adjusted for household size).

Results

The Table shows the characteristics of the sample (n=158), who had LTL measured at any time point. The overall composition of the sample was 55% female, 29% white, 52% Latinx, 8% Asian, and 11% Pacific Islander, other or multi-ethnic. Ascertainment of LTL was 99% at baseline, 82% at post intervention and 75% at follow-up visits. The table shows the large proportion of children with severe obesity (≥120% of the 95th percentile BMI for age and sex), but also the range of income and education for households and the racial/ethnic diversity of the sample.

The Figure presents the results of a random effects spline model fit to examine the changes in LTL over time, with the spline inflection point chosen *a priori* to coincide with the end of the weight control program intervention period, with 88% of our sample (114/130) having their second blood sample obtained <=7 months after baseline. There is a statistically significant rate of increase in LTL during the weight control program intervention period of0.09 T/S units per year (95% CI 0.04 to 0.13; $P = .0001$), followed by a decline during the approximate one year follow-up after the completion of the weight control intervention of −0.05 T/S units per year (95% CI −0.08 to −0.03; $P < .0001$), and a significant difference between the two periods of −0.14 T/S units per year (95% CI −0.20 to −0.08; $P < .0001$). Similar results are found when examining within individual rate of change of 0.08 T/S units per year (95% CI 0.04 to 0.13; $P = .0003$) during the weight loss program intervention period and −0.05 T/S units per year (95% CI −0.08 to −0.03; $P < .0001$) during the follow-up period, and a significant difference in rates between the two periods of −0.14 T/S units per year (95% CI −0.20 to −0.07; $P < .0001$).

As a secondary analysis, we examined predictors of LTL changes over both the intervention and the follow-up period with 26 social (e.g. child school performance, parenting style), psychological (e.g. depressive symptoms), behavioral (e.g. screen time, sugar sweetened beverage consumption) and physiological (e.g. BMI, systolic blood pressure) factors to attempt to understand which modifiable factors may impact LTL trajectories among children with obesity. Results from cross-sectional models are showing in supplemental table S2, and from baseline prediction models in supplemental table S3. We also fit individual fixed effect regression models as within individual analyses which can be interpreted as examining how change in exposures are associated with changes in LTL (shown in supplemental table S4 and supplemental figures S2 and S3). Among these 26 predictors across these several different types of models, we did not find associations with predictors more than would be expected by chance.

Discussion

Increase in LTL During the Behavioral Weight Loss Intervention

There was an increase in LTL during the behavioral pediatric weight control intervention period, and a decrease in LTL during the post-intervention follow-up period. There are three possible explanations of our findings. First, it may be due to chance, but this is addressed through statistical tests and the difference in change of LTL between periods are statistically significant with a p-value of less than 0.0001. Second, there may have been an unmeasured exposure that impacted changes in telomere length that happened to occur during the period of the behavioral weight change intervention. Or third, LTL may increase in response to a six-month behavioral intervention designed to reduce dietary energy density, increase physical activity, reduce screen time and reduce weight gain and decrease during the follow-up period after the intervention ended. We observed an increase in LTL during the behavioral pediatric weight control intervention period, and a decrease in LTL during the post-intervention follow-up period. The significant differences that we observed between the intervention versus follow-up period is suggestive of the substantial relationship between a behavioral weight control intervention program and cellular and immunological level changes among children who are obese.[18] We observed a yearly rate of increase of 0.09 T/S ratio during the intervention period, about half of a standard deviation, and a subsequent decrease of 0.05 T/S during the follow-up period, about one quarter of a standard deviation. The differences between the two time periods argues against regression to the mean as an explanation of these changes. While we can't infer causation from this observational study, these data suggest that LTL may increase in children with obesity in response to a six-month behavioral intervention designed to reduce dietary energy density, increase physical activity, reduce screen time, and reduce weight gain. However, this LTL increase reversed during the follow-up period after the intervention ended.

Our findings of LTL lengthening during the weight control intervention period are consistent with other lifestyle intervention studies with youth who are overweight or obese. These studies have reported an association between an improvement in lifestyle parameters such as dietary quality and physical activity over 2–12 months of follow-up and telomere lengthening and/or maintenance processes.[18,19] It is possible that reductions in biological

stress associated with reduced inflammation in the context of healthier lifestyles could result in attenuated telomere length attrition. Others have theorized that changes in composition of circulating T cell types including increases in naïve T cells with longer telomeres could result in a potential appearance of telomere lengthening.[20] Exercise and other health related behaviors could stimulate an influx in naïve T cells into circulation.

Other longitudinal studies conducted with pre-pubertal children and adolescents have shown observed loss of 0.02 T/S units/year [21] and loss of 0.005 T/S units/year,[22] although these values can't be compared directly to the findings in this study because T/S ratios can vary by study and measurement method. One theory to explain the comparative accelerated loss during the post-intervention follow-up period in our study is the growth and metabolic demands during puberty. Accelerated loss may be due to the competing demands of puberty versus weight loss or maintenance that were present during the follow-up period. These findings are consistent with the metabolic attrition hypothesis.[23] Alternatively, it is possible that the LTL accelerated loss that we saw in our sample of children and adolescents who are obese may also be associated with the additional inflammatory exposures of obesity and metabolic disease compared with other population groups. One theory to explain the comparative accelerated loss during the post-intervention follow-up period in our study is the growth and metabolic demands during puberty. Accelerated loss may be due to the competing demands of puberty versus weight loss or maintenance that were present during the follow-up period. These findings are consistent with the metabolic attrition hypothesis.[21] Alternatively, it is possible that the LTL accelerated loss that we saw in our sample of children and adolescents who were obese may also be associated with the additional inflammatory exposures of obesity and metabolic disease compared with other population groups.

Behavioral, Dietary and Physiological Factors Associated with LTL During the Intervention Period

Another finding was that among 26 social, psychological, behavioral, and physiological measures, changes in only four were associated with LTL change, which is fewer than would be expected by chance alone. The primarily null findings for social, dietary, physiological and behavioral variables run counter to a large literature that has found associations with many of these factors in other observational studies among youth including studies of children with obesity.[20,24] There are three potential reasons for these differences. First, this study was conducted in a sample of children with obesity, and associations may differ in this population. Our population had a high percentage of obesity and severe obesity and a such did not have much heterogeneity in BMI measurements. Second, this study examined the associations using within-individual change of social, psychological, behavioral, and physiological measures, which may not be the same as with fixed characteristics of individuals and is a strength of our analysis using prospective observations over multiple timepoints. Third, the relative absence of null findings in the extant literature may be due to publication bias in the literature, where null results are less likely to be reported and published.[25]

The null associations we found with other cardiovascular biomarkers contrast with prior work in adults, where LTL has been found to be associated with a range of cardiovascular risk factors. In this study, we also found no such associations among children with obesity in contrast with other studies in children that have found associations with obesity and metabolic correlates of obesity including insulin resistance and cardiovascular disease.[24] These null associations between LTL and BMI changes and other risk factor measures suggest that LTL may be a useful unique biomarker of cellular responses to behavioral weight control interventions not captured by other risk factor measures.[22]

Study limitations

Although having LTL measures at three time points is necessary to substantially decrease the likelihood that increasing LTL was due to regression to the mean, more timepoints would be even more beneficial. This was not possible in this study since biological samples were collected at only three time points. A further limitation to this study is the inherent measurement error in the relative qPCR LTL assay. This measurement error is most likely to bias our results towards the null, so is unlikely to be an explanation for the study results.

Conclusion

This is the first study to demonstrate the impact of a behavioral weight control program on children with obesity at the cellular level as manifest with LTL lengthening, and the subsequent LTL loss after the cessation of such a program. Few weight control intervention programs have demonstrated sustained effects once the program terminates and it is possible that LTL loss that follows the intervention period may parallel findings from other interventions.[26 27] While the majority of the pediatric study participants did not yet have obesity-associated metabolic disease such as diabetes mellitus, hypertension or non-alcoholic fatty liver disease, children with obesity are at increased risk for metabolic associated disease as they age into adolescence and adulthood. In adults, shorter LTL is a predictive marker for type 2-diabete mellitus and coronary heart disease.[28–30] As such, the sharp demarcation in the study between the LTL lengthening during the intervention period as compared to loss during the follow-up period supports broadening access to behavioral weight control programs for all children with obesity. Cost-effectiveness analyses of obesity treatment programs often focus on BMI change[31], but as this study suggests, in addition to BMI or other anthropometric changes, behavioral intervention programs may have broader physiological benefits. Ours is the first study to demonstrate the impact of a behavioral weight control program on children with obesity at the cellular level as manifest with LTL lengthening, and the subsequent LTL loss after the cessation of such a program. Few weight control intervention programs have demonstrated sustained effects once the program terminates and it is possible that LTL loss that follows the intervention period may parallel findings from other interventions.[23 24] While the majority of our pediatric study subjects did not yet have obesity-associated metabolic disease such as diabetes mellitus, hypertension and non-alcoholic fatty liver disease, children with obesity are at increased risk for metabolic associated disease as they age into adolescence and adulthood. In adults, shorter LTL is a predictive marker for type 2-diabete mellitus and coronary heart disease.[25–27] As such, the sharp demarcation in our study between the LTL lengthening during the

intervention period versus loss during the follow-up period supports broadening access to behavioral weight control programs for all children with obesity. Cost-effectiveness analyses of obesity treatment programs often focus on BMI change[28], but as our study suggests, in addition to BMI or other anthropometric changes, behavioral intervention programs may have broader physiological benefits.

The null associations we found with other cardiovascular biomarkers are in contrast to prior work in adults, where LTL was found to be associated with a wide range of cardiovascular risk factors.[29] In this study, we found no such associations among children with obesity. One potential explanation for this difference is that it is due to difference in the structure or data or the analysis. The prior work has only examined cross-sectional associations without multiple measures of LTL per individual. An alternative explanation, however, is that there are differences in what LTL captures between children and adults. In children, these null associations between LTL and BMI changes and other risk factor measures would suggest that LTL may be a useful unique biomarker of cellular responses to behavioral weight control interventions not captured by other risk factor measures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank the participants and research personnel who participated in the Stanford CHANGES study, as well as the Stanford Pediatric Weight Control Program coaches and staff.

Professors Rehkopf, Wojcicki, and Robinson conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Ms. Haydel and Mr. Kapphahn performed the statistical analyses and reviewed and revised the manuscript. Professors Robinson and Ms. Haydel supervised the participant recruitment and enrollment, data collection and database management. Professor Lin and Ms. Smith coordinated and supervised the telomere length assays, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Funding:

This collection of data used in this study was supported by the National Heart, Lung, And Blood Institute (NHLBI) of the National Institutes of Health under Award Number R01 HL096015. Telomere analysis was supported by the Stanford Clinical and Translational Science Award (CTSA) to Spectrum (ULI TR001085). The CTSA program is led by the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This work was also supported in part by the Stanford Maternal and Child Health Institute and the Department of Pediatrics at Stanford University.

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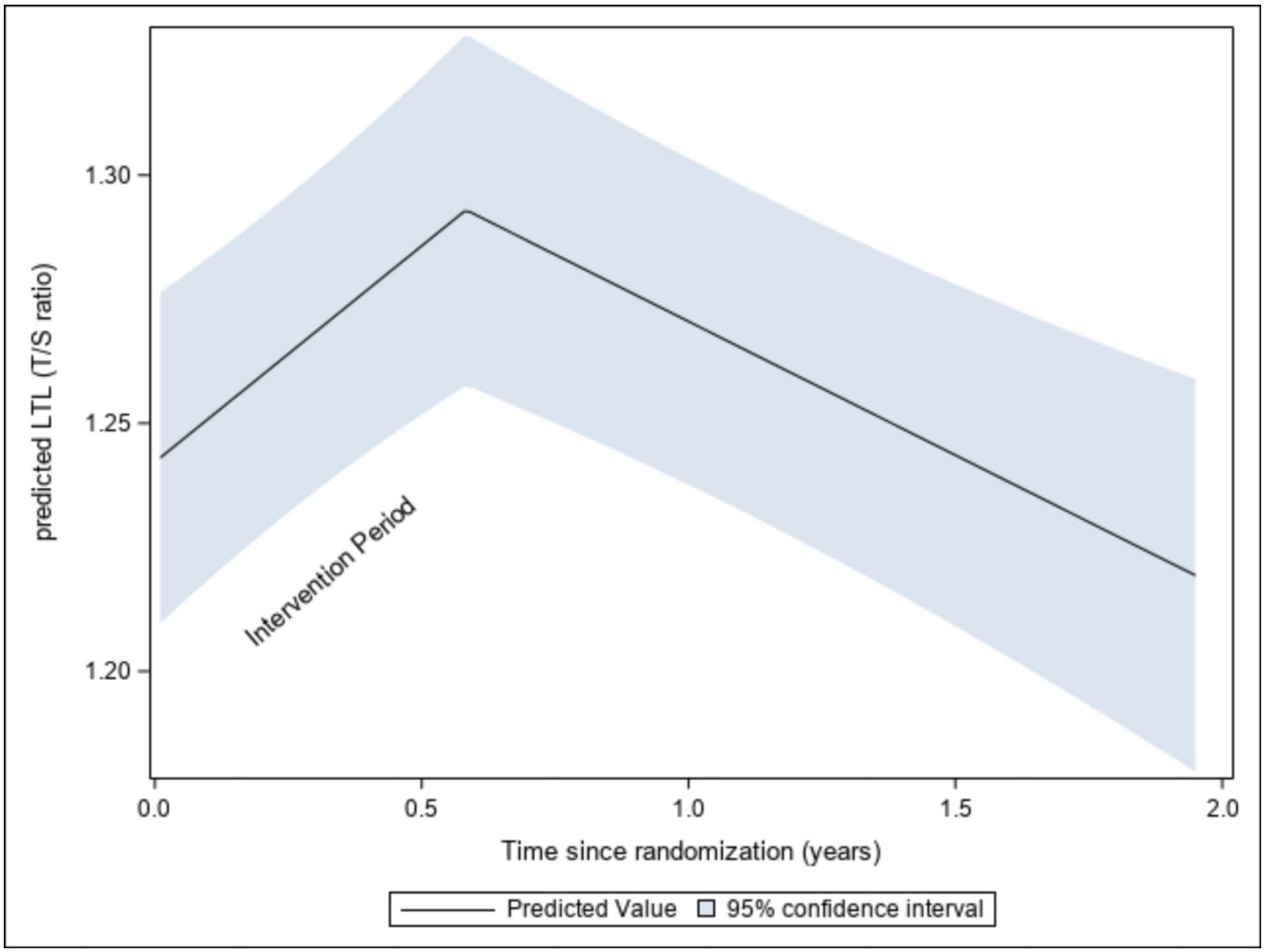

Figure.

Linear spline model-based changes in leukocyte telomere length (T/S ratio) over time. Change per year during weight control intervention period is 0.09 (95% CI 0.04 to 0.13; $P = .0001$), Change per year during follow-up period is −0.05 (95% CI −0.08 to −0.03; $P < .0001$).

Table.

Description of the Study population, 2011–2014.

	Baseline	Post treatment	Follow-up
Sample size	156–158	130–146	119–139
Leukocyte telomere length (T/S ratio), mean (std)	1.2 (0.2)	1.3 (0.2)	1.3 (0.2)
Follow-up time since baseline, (years), mean (std)	n/a	0.57 (0.06)	1.59 (0.07)
Demographics:			
Age in years at BMI measurement, mean (std)	10.5 (1.4)	11.0 (1.4)	12.1 (1.4)
Sex, n (%)			
Female	87 (55.1%)		
Male	71 (44.9%)		
Race/Ethnicity, n (%)			
Latinx	82 (51.9%)		
Asian	12 (7.6%)		
White	46 (29.1%)		
Other (African-American, Pacific Islander, Other and Mixed Race)	18 (11.4%)		
Families who own their own home, n (%)	85 (53.8%)		
Parent/Guardian marital status, n (%)			
Married	112 (70.9%)		
Domestic Partner	17 (10.8%)		
Divorced/Separated or Widowed	22 (13.9%)		
Single – never married	7 (4.4%)		
Maximum household education level, n (%)			
High school graduate or less	41 (25.9%)		
Some college or technical school	27 (17.1%)		
College graduate	43 (27.2%)		
Post grad study	47 (29.7%)		
English spoken at home, n (%)			
Only English	61 (38.6%)		
Mostly English and a little of another language	32 (20.3%)		
About the same amount of English and another language	19 (12.0%)		
Mostly another language and a little English	26 (16.5%)		
Only another language	20 (12.7%)		
Annual total household income, n (%)			
Less than $20,000	30 (19.0%)		
$20,000-$59,999	38 (24.1%)		
$60,000-$139.999	35 (22.2%)		
$140,000-$199,999	24 (15.2%)		
Over $200,000	31 (19.6%)		
Number of adults living in the household, n (%)			

	Baseline	Post treatment	Follow-up
1	11 (7.0%)		
2	116 (73.4%)		
3	15 (9.5%)		
4 or more	16 (10.1%)		
Number of children living in the household, n (%)			
1	30 (19.0%)		
2	72 (45.6%)		
3	40 (25.3%)		
4 or more	16 (10.1%)		
Anthropometric measures:			
Percent over median BMI for age and sex, mean (std)[b]	72.0 (27.5)	63.0 (27.8)	70.0 (31.5)
Prevalence of Severe Obesity, n (%)			
>=120% of the 95th percentile BMI	91 (57.6%)	64 (40.5%)	71 (44.9%)
<120% of the 95th percentile	67 (42.4%)	82 (51.9%)	68 (43.0%)
BMI (kg/m2), mean (std)[c]	29.4 (5.0)	28.3 (5.1)	30.6 (6.0)
Waist circumference (cm), mean (std)[c]	95.7 (12.1)	94.8 (13.1)	99.7 (13.8)
Triceps Skinfold (mm), mean (std)[c]	30.3 (4.1)	27.5 (4.8)	28.6 (4.7)

Table notes: At baseline, Leukocyte Telomere Length (LTL) n=156, anthropometric, survey measures n=158; At post treatment, Leukocyte Telomere Length (LTL) n=130, anthropometric measures n=146; At follow-up, Leukocyte Telomere Length (LTL) n=119, height and weight n=139, waist and skinfold n=137. Percentages don't add to 100% due to rounding.