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Longitudinal associations of lifetime adiposity with leukocyte telomere length and mitochondrial DNA copy number

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Abstract

Adiposity may cause adverse health outcomes by increasing oxidative stress and systemic inflammation, which can be reflected by altered telomere length (TL) and mitochondrial DNA copy number (mtCN) in peripheral blood leukocytes. However, little is known about the influence of lifetime adiposity on TL and mtCN in later life. This study was performed to investigate the associations of lifetime adiposity with leukocyte TL and mtCN in 9613 participants from the Nurses' Health Study. A group-based trajectory modelling approach was used to create trajectories of body shape from age 5 through 60 years, and a genetic risk score (GRS) was created based on 97 known adiposity susceptibility loci. Associations of body shape trajectories and GRS with

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Authors' contributions

MS and EG were responsible for study design. DH performed statistical analyses and drafted the manuscript. HN, IV, and AC contributed to acquisition of data. AK, ZH, and HS helped to interpret the results and revised the manuscript critically. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

dichotomized TL and mtCN were assessed by logistic regression models. After adjustment for lifestyle and dietary factors, compared with the lean-stable group, the lean-marked increase group had higher odds of having below-median TL (OR = 1.18, 95% CI: 1.04, 1.35; *P* = 0.01), and the medium-marked increase group had higher odds of having below-median mtCN (OR = 1.28, 95% CI:1.00,1.64; *P* = 0.047). There was a suggestive trend toward lower mtCN across the GRS quartiles (*P* for trend = 0.07). In conclusion, telomere attrition may be accelerated by marked weight gain in middle life, whereas mtCN is likely to be reduced persistently by adiposity over the life course. The findings indicate the importance of lifetime weight management to preserve functional telomeres and mitochondria.

Keywords

Adiposity; Telomere; Mitochondrion; Trajectory analysis; Genetic variants

Introduction

The rising prevalence of overweight and obesity in a number of countries has been considered a global pandemic [1]. Between 1980 and 2013, global prevalence of overweight and obesity combined rose by 27.5% for adults and 47.1% for children [2]. Obesity and overweight increase the risk of major chronic diseases, such as diabetes, cardiovascular disorders, and certain types of cancer [3]. An important pathway through which adiposity contributes to these outcomes is by an increase in oxidative stress and systemic inflammation, leading to progressive cellular damage [4].

Both telomeres and mitochondria serve as critical regulators of the ageing process, and are prone to structural damage caused by excessive oxidative stress [5, 6]. Telomeres are repetitive nucleoprotein complexes that protect the ends of linear chromosomes and maintain genomic stability [7]. Telomeres undergo shortening with cell divisions and this erosion can be increased by oxidative stress [8]. Extremely short and dysfunctional telomeres may elicit chromosomal degradation, end-to-end fusion, and atypical recombination, which have been implicated in disease development [9]. Mitochondria are organelles in the cytoplasm of eukaryotic cells with various functions including energy metabolism, free-radical production, calcium homeostasis, and apoptosis [10]. Mitochondrial DNA (mtDNA) is known to be more sensitive to oxidative damage than nuclear DNA due to its lack of protective histones, introns, and efficient DNA repair mechanisms [11]. Increased oxidative stress may lead to altered abundance and compromised functions of mitochondria. Many epidemiologic studies have linked decreased telomere length (TL) and mitochondrial DNA copy number (mtCN) in peripheral blood leukocytes to elevated risk of obesity-related diseases [12–15]. Therefore, alterations in leukocyte TL and mtCN may reflect the cumulative exposure to oxidative stress and underlie the pathogenesis of obesity-related comorbidities.

To date, studies examining the associations of adiposity with leukocyte TL and mtCN have yielded mixed results. A recent meta-analysis of twelve studies including 8010 participants found non-significantly shorter TL in obese individuals compared to those with normal

weight [16]. However, most of the included studies were cross-sectional. Longitudinal studies linking adiposity to TL attrition were sparse with mixed findings [17–20]. More importantly, these studies assessed body mass index (BMI) at only a limited number of time points and were thus unable to capture the long-term effect of adiposity dynamics. For mtCN, epidemiologic evidence about the relationship with adiposity is very limited. Two cross-sectional studies reported an inverse association of mtCN with visceral fat area [21] and waist circumference [22], but not with BMI [22]. In our previous analysis in women from the Nurses' Health Study (NHS), middle-life BMI was associated with lower mtCN [23].

Given that BMI typically increases with age, and obesity during childhood is associated with the persistence of obesity into adulthood [24], a life course perspective is crucial to better understand the pathophysiological impact of adiposity. In this study, we employed two approaches to assess the association of lifetime adiposity with leukocyte TL and mtCN in women from the Nurses' Health Study. First, we characterized the trajectories of body shape from age 5 through 60 years using a group-based modeling approach. This approach respects the continuity of body growth throughout life and classifies individuals into distinct, mutually exclusive groups [25]. Second, given the well-established heritability of BMI, we employed genetic proxies for lifetime adiposity by creating a genetic risk score (GRS) based on 97 common genetic variants that have been robustly associated with higher BMI [26]. This genetic approach also helps to establish causality because the genetic information is not confounded by environmental factors. By linking the early-to-middle-life body shape trajectories and GRS with leukocyte TL and mtCN in later life, our study provides the first evidence regarding the influence of lifetime adiposity on telomere and mitochondrial biology.

Materials and methods

Study population

The Nurses' Health Study (NHS) is a prospective cohort established in 1976 when 121700 female registered nurses aged 30 to 55 years in 11 US states completed and returned a mailed questionnaire. Detailed information on personal characteristics (e.g. lifestyle and dietary factors) and new disease diagnoses has been updated every 2–4 years by questionnaire. From 1989 to 1990, 32826 women provided blood samples and completed a questionnaire (Supplementary Fig. 1, Online Resource). Details of the NHS and blood collection procedure have been described previously [27]. The protocol for this study was approved by the institutional review boards of Brigham and Women's Hospital and Harvard T.H. Chan School Public Health.

The current analysis was restricted to 9061 participants who had available TL data from previous nested case-control studies for cancer, cardiovascular disorders, rheumatoid arthritis, and cognitive disease [28–34], and 4411 participants with available mtCN data from nested case-control studies for skin, lung, and colorectal cancers [35, 36]. After excluding non-Caucasians (n = 346) and those who had a history of diabetes, cardiovascular disease, and cancer at the time of blood collection (n = 697), a total of 9613 participants (n = 8229 for TL and 4007 for mtCN) were included in the final analysis. These participants were

demographically similar to others in the overall NHS cohort in 1990 (Supplementary Table 1, Online Resource).

Assessment of body shape

In 1988, participants were asked to recall their body shape in early and middle life by choosing one of 9 pictorial body diagrams (somatotypes) developed by Stunkard et al [37] that best reflected their body shape at age 5, 10, 20, 30, and 40 (Supplementary Fig. 1, Online Resource). The validity of this measure as a surrogate for adiposity in early life has been assessed among 181 participants aged 71 to 76 in the Third Harvard Growth Study [38]. Comparisons between participants' recalled somatotypes and their measured BMI at similar ages showed Pearson correlation coefficients of 0.60 for age 5, 0.65 for age 10, and 0.66 for age 20 [38].

Body height and weight were inquired at baseline and updated weight was collected via follow-up questionnaires. Recalled weight at age 18 years was obtained in 1980. We used these data to calculate BMI at age 40, 45, 50, 55, and 60. To minimize random variation, we calculated the average BMI within two years for each age. To convert BMI in later life to the same scale as somatotypes, we built a linear regression model for somatotype and BMI at age 40 among women with available data, and then applied the regression coefficients and BMI to impute the somatotype from age 40 to 60. The imputed somatotype was highly correlated with participants' reported somatotype at age 40 ($r = 0.74$) and in 1988 ($r = 0.83$), indicating good performance of our rescaling method.

Trajectory modeling

A group-based trajectory modeling approach was used to identify subgroups that shared a similar trajectory of body shape from age 5 up to 60. This method represents an application of finite mixture modeling to identify relatively homogeneous clusters of developmental trajectories within the population [39]. It fits longitudinal data as a discrete mixture of multiple latent trajectories via maximum likelihood estimation using SAS Proc Traj [40]. In this study, we used a censored normal model with a polynomial function of age. The optimal number of groups and the shapes of trajectories were selected for the best fit to the data using a two-stage approach, as previously described [41]. Finally, we identified that the five-group model with cubic order function of age fit the data best. We then named the trajectory groups to describe their visual patterns: lean-stable, lean-moderate increase, medium-stable, lean-marked increase, and medium-marked increase.

We calculated the posterior predicted probability for each participant of being a member of each of the trajectories. Using ≥ 0.70 as the recommended criteria [42], our model demonstrated excellent performance in classifying individuals into distinct trajectory groups: the average posterior probability for each trajectory group was 0.93, 0.97, 0.90, 0.91, and 0.96.

Covariate assessment

Potential confounders were derived from the questionnaires administrated prior to the time of blood collection. Waist circumference and waist-hip ratio were obtained from the 1986

questionnaire, and information on menopausal status, postmenopausal hormone use, multivitamin use and pack-years of smoking was derived from the 1990 questionnaire. Average level of physical activity was assessed by questionnaires in 1986 and 1988. Average of a summary dietary score, the Alternate Healthy Eating Index (AHEI), was calculated to represent the overall dietary pattern based on individual food intake from food frequency questionnaires (FFQs) in 1980, 1984, 1986, and 1990. Similarly, we also calculated average consumption of alcohol based on these FFQs. The validity and reproducibility of these measures have been reported elsewhere [43].

Measurement of leukocyte TL and mtCN

Genomic DNA was extracted from peripheral blood leukocytes following the QiAmp (Qiagen, Chatsworth, CA) 96-spin blood protocol. DNA concentrations were determined via pico-green quantitation using a Molecular Devices 96-well spectrophotometer.

Relative TL was measured by use of quantitative polymerase chain reaction (qPCR). The average relative TL was calculated as the telomere repeat copy number / a single gene (*36B4*) copy number (T/S) exponentiated ratio [44]. Each sample was assayed in triplicate and quality control samples were interspersed on each plate to assess variability. The coefficients of variation (CVs) for the telomere and single gene assays in the quality control (QC) samples were less than 4%. Although this assay provides a relative measurement of telomere length, T/S ratios correlate well with absolute telomere lengths determined by Southern blot ($r = 0.68$, $P < 0.001$) [44].

Relative mtCN was determined by using qPCR, and the ratio of mitochondrial *ND2* gene copy number to a single gene (a*AluYb8*) copy number (N/S) was calculated [23]. The average relative mtCN was the exponentiated N/S, which is proportional to the average number of mtCN. Each sample was assayed in triplicate and 10% replicate quality control samples were included. The CVs for *ND2* and *AluYb8* assays in the QC samples were less than 1%.

Genotyping and GRS calculation

We included 97 SNPs that are confirmed to be associated with BMI [26]. SNP genotyping and imputation have been described in detail elsewhere [45]. All of the SNPs were genotyped or had high imputation quality ($r^2 \geq 0.8$), as assessed by the MACH software (version 1.0.16, Center for Statistical Genetics, University of Michigan). We calculated a GRS from the 97 SNPs by using an established weighting method. Each SNP genotype was coded as 0, 1, and 2 according to the number of risk alleles (higher BMI-related) and weighted by its relative effect size (β-coefficient) derived from a recent GWAS meta-analysis for BMI [26]. The GRS was calculated by multiplying each β-coefficient by the number of corresponding risk alleles and then summing the products. Each unit of the GRS represented one risk allele, and the GRS could range from 0 to 194, with a higher score indicating greater genetic predisposition to obesity.

Statistical analysis

We calculated z-scores within each of the case-control studies to standardize the distributions of TL and mtCN. Age-adjusted Spearman correlation coefficients (r_S) were computed to examine the relationships of TL and mtCN with somatotypes at age 5 and 10; BMI at age 18, 40, 50, and 60; and BMI change between age 18 and 60. We examined the associations of body shape trajectories with median-dichotomized TL and mtCN z-scores using unconditional logistic regression. We adjusted for age at blood collection, as well as other potential confounding factors, including height, menopausal status, postmenopausal hormone use, physical activity, alcohol consumption, pack-years of smoking, AHEI dietary score, and multivitamin use.

Because 5236 participants (54%) were younger than 60 years at the time of blood collection and their body weight at age 60 was assessed after TL/mtCN measurement, we performed a stratified analysis by age at blood collection (<60, ≥60 years) to examine the sensitivity of our findings to inclusion of these individuals. Given the intricate relationship between smoking and body weight dynamics [46], we also stratified the data by smoking status (ever, never). A likelihood ratio test was performed to assess interaction, by comparing the models with and without product terms between the trajectory groups and the stratified variable.

Similar analyses were performed to examine the association of GRS and individual SNPs with TL and mtCN. To account for multiple testing for individual SNP analysis, we calculated the false discovery rate (FDR) using the Benjamini-Hochberg method. All statistical analyses were conducted by SAS Version 9.4 software (SAS Institute Inc, Cary, NC), and $P < 0{\cdot}05$ was considered statistically significant.

Results

By using the group-based trajectory modeling approach, we identified five heterogeneous trajectories of body fatness from age 5 up to 60 among 9613 women. Fig. 1 shows the estimated mean body shape levels in the five trajectories at each age: 34% (3275) of women maintained a lean and relatively stable body shape throughout life (lean-stable group); 23% (2178) of women started lean and then experienced a moderate increase in body fatness in middle age (lean-moderate increase group); 17% (1593) of women maintained a medium body shape throughout life (medium-stable group); 17% (1689) of women started lean and then gained a substantial amount of weight (lean-marked increase group); and 9% (878) of women started with a medium body shape and then gained more weight over age (medium-marked increase group).

The descriptive characteristics of participants across trajectory groups are shown in Table 1. As expected, the BMI profile throughout adulthood in each group conformed well to the patterns of the identified trajectories, and participants in the heavier trajectories had higher GRS. We also noted that participants in the five trajectories showed distinct lifestyle patterns: those in the lean-stable, lean-moderate increase and medium-stable groups were more physically active and consumed a healthier diet than those in the lean-marked increase and medium-marked increase groups.

In Table 2, after adjustment for age at blood collection, the Spearman correlation analyses showed a statistically significant inverse association of TL z-score with BMI at age 50 (r_S = −0.02) and 60 (r_S = −0.03), as well as BMI change between age 18 and 60 (r_S = −0.03). In contrast, mtCN z-score was inversely associated with body fatness from age 10 up to 60 years (r_S ranged from −0.07 to −0.04). Additionally, we found that age at blood collection was inversely correlated with TL (r_S = −0.09, P < 0.01), and age-adjusted pack-years of smoking was inversely correlated with both TL (r_S = −0.03, P < 0.01) and mtCN (r_S = −0.04, P < 0.01) (data not shown).

We further assessed the associations of body shape trajectories with TL and mtCN in logistic regression models (Table 3). Using the lean-stable group as the reference, the model adjusting for age at blood collection showed that participants in the lean-marked increase group had higher odds of having below-median TL (OR = 1.17, 95% CI: 1.03, 1.33; P = 0.02), and the medium-marked increase group had higher odds of having below-median mtCN (OR = 1.30, 95% CI: 1.02, 1.66; P = 0.03). The observed associations remained statistically significant, after additional adjustment for lifestyle and dietary covariates (OR = 1.18, 95% CI: 1.04, 1.35; P = 0.01 for TL; OR = 1.28, 95% CI: 1.00, 1.64; P = 0.047 for mtCN). However, these associations were attenuated and became statistically nonsignificant after further adjustment for BMI at blood collection (OR = 1.11, 95% CI: 0.94, 1.29; P = 0.21 for TL; OR = 1.04, 95% CI: 0.72, 1.50; P = 0.84 for mtCN).

In stratified analyses by age at blood collection (< 60, ≥ 60 years) and smoking history (never, ever), the association between the lean-marked increase group and shorter TL was statistically significant among never smokers (Supplementary Table 2, Online Resource). In contrast, the association between the medium-marked increase group and lower mtCN did not vary by age or smoking status.

Participants in the current analysis comprised women from previous nested case-control studies of various outcomes. To examine the robustness of our results to the inclusion of participants who were identified as cases in those studies, we performed a sensitivity analysis by restricting the analysis to control participants (n = 4780 for TL and 2589 for mtCN). Similar results were observed (Supplementary Table 3, Online Resource).

Table 4 shows the associations of GRS with TL and mtCN. While we did not find any association for TL, participants with higher GRS showed a trend towards lower mtCN (P for trend = 0.07). Compared with the lowest quartile of GRS, the highest quartile tended to associate with below-median mtCN (OR = 1.24, 95% CI: 0.94, 1.64; P = 0.13). The interaction between GRS and age or smoking was statistically nonsignificant (data not shown). In addition, among 97 SNPs in the GRS, 7 and 6 SNPs were nominally associated with TL and mtCN, respectively (P < 0.05, Supplementary Table 4, Online Resource). However, after correction for multiple testing, none of the associations remained statistically significant with FDR values of > 0.05.

Discussion

To our knowledge, this is the first study to examine the associations of lifetime adiposity with leucocyte TL and mtCN in later life. We used a trajectory-based approach to identify distinct trajectories of body shape in 9613 women from the Nurse's Health study. Compared to participants who were lean throughout the lifetime, those who gained substantial weight (the lean-marked increase group) had shorter TL, and those with persistently higher body fatness (medium-marked increase group) had lower mtCN. To gain insight into causality, we also created a GRS using adult BMI-related genetic variants and, consistent with the trajectory findings, we found an inverse association between GRS and mtCN. Our findings suggest that TL and mtCN reduction may be accelerated by adiposity in different patterns: TL attrition may be predominantly driven by marked weight gain in middle life, whereas mtCN is likely to be reduced persistently by adiposity across the lifespan.

Oxidative stress and systemic inflammation have been implicated in the associations of obesity with TL and mtCN reduction [47, 48]. In childhood, expanding body fat depots induce leptin production, endothelial dysfunction, and glucose impairment, all of which can lead to excessive production of reactive oxygen species (ROS) [49]. With cumulative weight gain in adulthood, systemic oxidative stress would be aggravated, due to insulin resistance and increased production of adipokines and pro-inflammatory cytokines (e.g. IL-6 and TNF-α) [50]. Telomeres and mitochondria are both sensitive to excessive oxidative stress, and reduced TL and mtCN by oxidative damage may contribute to the risk of obesity-related diseases [13, 51]. In fact, tight regulation of TL and mtCN are essential for normal cell function. Even a small but long-term effect on TL or mtCN may lead to severe consequences. Our study demonstrated the associations of adiposity with TL and mtCN reduction from a life course perspective, supporting the axis of adiposity – excessive oxidative stress – TL and mtCN reduction. Moreover, by examining TL and mtCN simultaneously, our study revealed the different patterns in which adiposity influences telomeres and mitochondria.

Multiple studies have investigated the relationship between adiposity and leukocyte TL; however, the results remain elusive. For instance, a cohort study of 622 Finnish men showed the longitudinal association between midlife BMI and TL in later life [17]. Similarly, in an analysis of 7008 U.S. residents from the National Health and Nutrition Examination Survey, higher BMI at age 25 predicted shorter TL at age 30–40 [18]. Nevertheless, a Danish study of 4576 Caucasians and a cohort including 3600 older Germans reported null association of weight change in middle and late life with TL attrition [19, 20]. In addition, the Health and Retirement Study of 2749 middle-aged and older adults found a positive association between baseline BMI and TL 17 years later [52]. Although the reasons for these discrepancies are unclear, studies differ in population characteristics and adiposity measures. Unlike previous studies assessing adiposity at select time points individually, we applied a group-based modeling approach for identification of distinct trajectories of body shape across the lifespan, thus being able to evaluate long-term effects of adiposity. Our data indicate that BMI at older ages was inversely correlated with TL, and marked weight gain in middle life (lean-marked increase group) may expedite telomere attrition. Consistent with our findings, it has been observed that TL is relatively stable from childhood through young adulthood,

and TL shortening predominantly occurs at older ages [53], implying that telomeres are inherently more vulnerable in later life. Moreover, although severe oxidative stress is detrimental to telomeres by causing complete uncapping of telomeric DNA, mild levels of ROS seem to be protective via a pathway increasing telomere repeat additions [54, 55]. Therefore, a delicate balance may be needed to maximize the beneficial effects of certain amount of ROS on telomere maintenance. Individuals who started lean and then gained substantial amount of weight may have progressively increased levels of ROS that may ultimately perturb the balance and induce detrimental effects on telomeres, leading to shorter TL as shown in our study. In addition, we observed that the association between lean-marked increase and TL was stronger among nonsmokers than ever smokers. However, the exact reason remains unknown and future studies are necessary to validate the result.

Previous cross-sectional studies reported that visceral fat area and waist circumference were inversely associated with mtCN [21, 22]. Jokinen et al.'s study with a 12-month follow up suggested that for weight regainers, weight loss may increase mtCN in subcutaneous adipose tissue, while weight regain may reduce mtCN [56]. Our findings extend the knowledge and suggest that higher body fatness over the life course may confer a persistent effect on mtCN reduction. Mitochondria are located in close proximity to sites where ROS are routinely generated, rendering mtDNA particularly susceptible to oxidative attack [57]. Furthermore, unlike nuclear DNA, mtDNA is not protected by histone proteins, introns, and efficient DNA repair mechanisms [11]. At the initial stage when mtDNA was injured by oxidative stress, healthy mitochondria may increase their copy number, to a limited extent, as a feedback mechanism to counterbalance the metabolic defects in impaired mitochondria [48]. Consistently, we observed that participants in the lean-moderate increase (0.04 ± 1.01) and medium-stable (0.04 ± 0.96) groups had almost doubled mtCN than those in the lean-stable (0.02 ± 0.99). However, escalated oxidative stress in the progression of obesity may exhaust the feedback mechanisms and increase the incidence of severe mtDNA damage. To prevent excessive accumulation of oxidative damages, mtDNA degradation would be elicited by a physiologically relevant enzyme system, resulting in the loss of mtCN [58]. This mechanism helps to explain our observation of significantly lower mtCN in women who started with a medium body shape and then gained more weight over age. Of note, we found that adjustment for BMI at blood collection substantially attenuated the association of body shape trajectories with mtCN, whereas the association with TL was minimally affected. This finding further supports the cumulative effect of adiposity on mtCN reduction and the endpoint BMI-independent effect of weight gain on TL attrition.

Our genetic findings provided further support for the influence of lifetime adiposity on mtCN. Many of the variants included in the GRS are within or close to genes that are highly expressed in the central nervous system and may have a persistent effect on the regulation of body mass throughout the life course [26]. Moreover, genetic variants are generally unaffected by environmental factors, and TL and mtCN are unlikely to affect genotypes, thus enabling us to test whether higher BMI precede TL and mtCN reduction. We found no evidence for a causal relationship between genetic obesity variants and TL. This finding is not incompatible with the observed association between the lean-marked increase trajectory and shorter TL, because marked weight gain in middle life is likely to be mainly driven by environmental factors and previous studies did not support a strong association between

genetic variants of adiposity susceptibility and middle-life weight gain [59, 60]. On the other hand, we observed that the higher GRS tended to associate with lower mtCN. Because individuals with more adiposity risk alleles are more likely to be overweight in early life and also to gain further weight as they age [61], the genetic association with mitochondria supports the relationship between the medium-marked increase trajectory and lower mtCN.

The strengths of our study include the prospective design, large sample size, and application of a life course analytic method to examine patterns of body shape across the lifespan, which represents a significant advantage over previous studies that examined body fatness at certain ages. Furthermore, we collected detailed data on lifestyle and dietary factors that allowed us to control for potential confounding. Meanwhile, we created a genetic risk score, a proxy for adiposity exposure independent of environmental confounders, to further investigate the influence of lifetime obesity on telomere and mitochondria. Nevertheless, several limitations need to be acknowledged. First, we assessed TL and mtCN at a single time point, which precluded examination of the changes of TL and mtCN over time. Second, the recalled body shape and self-reported BMI data were subject to measurement error; however, given the prospective study design, any error would likely have attenuated the observed associations. In addition, other obesity indicators such as waist circumference and body fat percentage across the lifespan are useful to confirm our conclusions. Third, the homogeneity of study population limits the generalizability of our findings, although it minimizes the likelihood of residual confounding.

In conclusion, our study demonstrates inverse associations of adiposity with leukocytes TL and mtCN from a life course perspective. Substantial weight gain in middle life may increase late-life TL attrition, whereas higher body fatness and genetic obesity susceptibility may exert a persistent effect on mtCN reduction during the lifetime. These findings highlight the importance of maintaining normal weight over the life course for preservation of functional telomeres and mitochondria.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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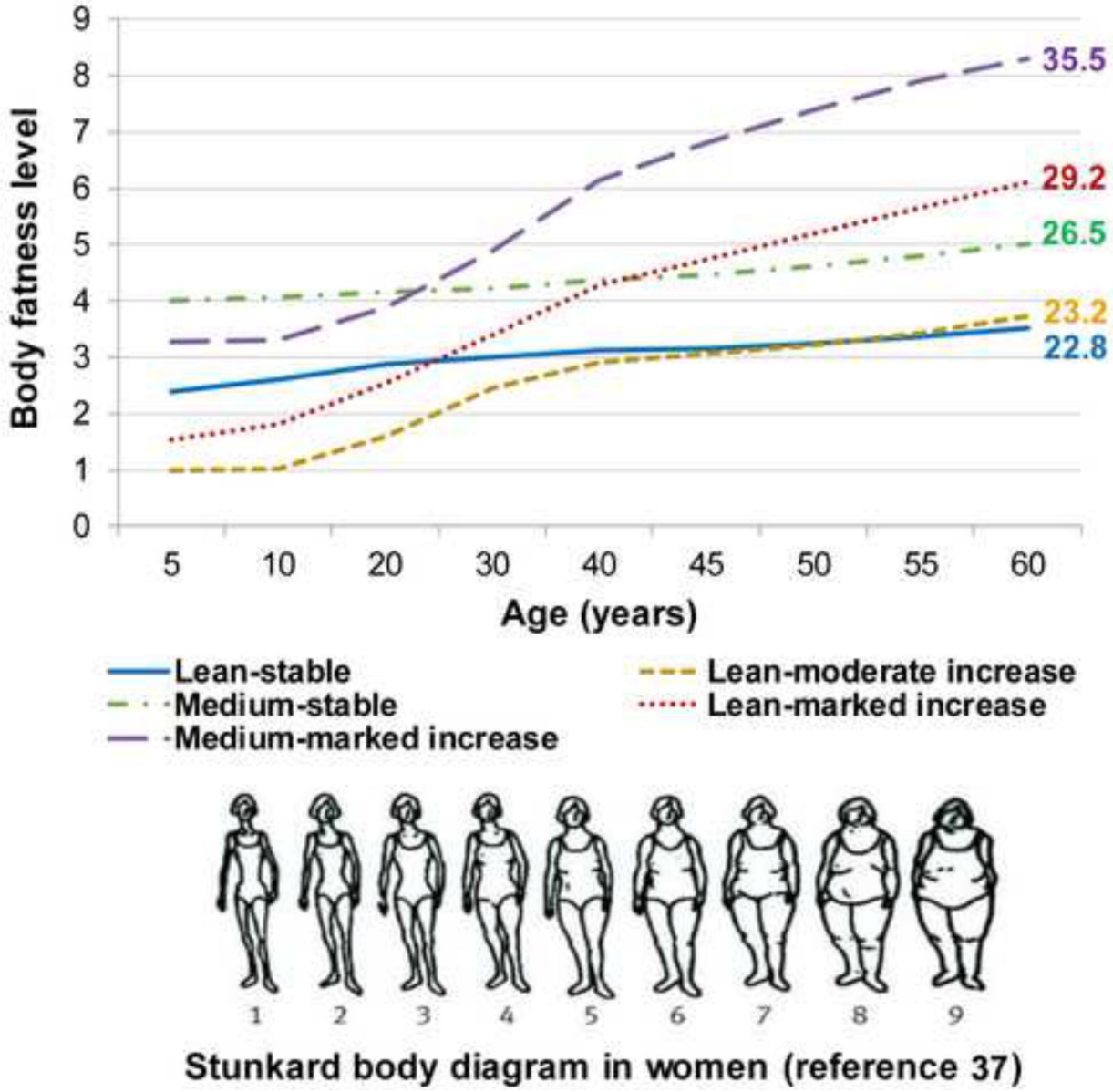

Fig. 1.

Trajectories of body shape by age among 9613 women in the Nurses' Health Study. Mean body mass index at age 60 is shown for each trajectory group

Table 1

Characteristics of 9613 women at blood collection (Nurses' Health Study) according to body shape trajectories[1]

Variable	Lean-stable	Lean-moderate increase	Medium-stable	Lean-marked increase	Medium-marked increase
Participants, n (%)	3275(34)	2178(23)	1593(17)	1689(17)	878(9)
Age at blood collection, years	58.7(6.6)	59.8(6.3)	58.4(6.7)	57.0(6.7)	55.8(6.7)
Genetic risk score[2]	87.3(6.0)	87.3(5.9)	89.3(5.8)	88.5(5.7)	90.0(5.4)
BMI at age 18 (kg/m^2)	20.6(1.9)	19.4(1.8)	23.3(2.8)	21.5(2.4)	24.6(3.5)
BMI at age 40 (kg/m^2)	21.0(1.5)	20.9(1.8)	23.9(1.9)	24.6(1.9)	30.4(3.6)
BMI at age 50 (kg/m^2)	21.9(1.6)	22.1(1.9)	25.4(2.1)	27.2(2.1)	33.7(3.9)
BMI at age 60 (kg/m^2)	22.8(2.1)	23.2(2.3)	26.5(2.6)	29.2(2.5)	35.5(4.2)
Height (inch)	64.6(2.4)	64.7(2.3)	64.6(2.3)	64.3(2.4)	64.3(2.4)
Waist circumference (cm)[3]	74.0(6.8)	75.4(7.8)	81.2(8.1)	87.2(8.9)	99.3(10.7)
Waist/hip ratio[3]	.77(.06)	.78(.09)	.79(.11)	.82(.14)	.84(.11)
Postmenopause (%)	80	80	82	80	80
Current hormone use (%)[4]	47	47	44	35	27
Physical activity (MET-h/wk)[5]	17.3(19.2)	16.0(17.5)	15.0(17.4)	13.5(16.4)	10.7(11.1)
Alcohol consumption (g/d)[5]	8.2(10.8)	7.1(9.5)	6.7(9.9)	5.7(9.2)	3.8(7.4)
Pack-years of smoking	14.8(20.6)	13.3(19.0)	15.2(20.7)	13.8(20.8)	12.8(19.1)
Alternative Healthy Eating Index[5]	45.0(9.1)	43.9(8.8)	45.7(8.8)	43.1(8.2)	41.9(8.2)
Multivitamin use (%)	40	39	39	40	37

[1] All variables are standardized by age at blood collection. Mean (SD) is presented for continuous variables.

[2] Sample size was 1512 in the lean-stable group, 1054 in the lean-moderate increase group, 749 in the medium-stable group, 861 in the lean-marked increase group, and 483 in the medium-marked increase group.

[3] According to the questionnaire in 1986.

[4] Current hormone use was defined in menopausal women.

[5] Average measurements prior to blood collection.

Abbreviations: BMI, body mass index; MET, metabolic equivalent.

Table 2

Age-adjusted Spearman correlations of leukocyte telomere length and mitochondria DNA copy number with body shape/BMI/waist circumference across the lifespan among women in the Nurses' Health Study

	Body shape (age 5)	Body shape (age 10)	BMI (age 18)	BMI (age 40)	BMI (age 50)	BMI (age 60)	BMI change (age 18–60)	Waist circumference (in 1986)
TL z-score								
N	7908	7949	7858	3441	7267	8135	7782	6011
r_s[a]	0.01	0.002	0.005	−0.02	−.02[b]	−.03[c]	−.03[c]	−.03[c]
mtCN z-score								
N	3846	3868	3811	1734	3556	3952	3769	2885
r_s[a]	−0.02	−.04[b]	−.04[b]	−.07[c]	−.04[b]	−.05[c]	−0.03	−.05[c]

[a] Spearman correlation coefficient adjusted for age at blood collection.

[b] $P < 0.05$.

[c] $P < 0.01$.

Abbreviations: BMI, body mass index; TL, telomere length; mtCN, mitochondrial DNA copy number.

Table 3

Associations of body shape trajectories with leukocyte telomere length and mitochondrial DNA copy number among women in the Nurses' Health Study

	Lean-stable	Lean-moderate increase	Medium-stable	Lean-marked increase	Medium-marked increase
TL z-score					
N	2784	1872	1363	1459	751
Mean (SD)[1]	.03(1.02)	.04(1.00)	.01(.97)	−.04(1.02)	.00(1.00)
Age-adjusted OR of lower score (95% CI)[2]	Ref	.96(.85, 1.08)	1.01(.89, 1.15)	1.17(1.03, 1.33)	1.14(.97, 1.34)
P	-	.48	.88	.02	.13
Multivariable-adjusted OR of lower score (95% CI)[3]	Ref	.96(.85, 1.08)	1.02(.89, 1.16)	1.18(1.04, 1.35)	1.15(.97, 1.36)
P	-	.48	.80	.01	.11
mtCN z-score					
N	1358	928	685	695	341
Mean (SD)[1]	.02(.99)	.04(1.01)	.04(.96)	−.01(1.01)	−.21(.93)
Age-adjusted OR of lower score (95% CI)[2]	Ref	.86(.73, 1.02)	.96(.80, 1.15)	1.07(.89, 1.28)	1.30(1.02, 1.66)
P	-	.09	.63	.48	.03
Multivariable-adjusted OR of lower score (95% CI)[3]	Ref	.87(.73, 1.03)	.93(.78, 1.13)	1.06(.88, 1.28)	1.28(1.00, 1.64)
P	-	.10	.47	.51	.047

[1] Standardized by age at blood collection.

[2] Unconditional logistic regression models with adjustment for age at blood collection. TL and mtCN z-score outcomes were dichotomized at the median.

[3] Further adjustment for height (continuous), menopausal status (yes or no), postmenopausal hormone use (never, past, current), physical activity (< 5, 5–11.4, 11.5–21.9, ≥ 22 MET-h/wk), alcohol consumption (< 0.15, 0.15–1.9, 2.0–7.4, ≥ 7.5 g/day), pack-years of smoking (0, 1–15, 16–25, 26–45, > 45 years), AHEI dietary score (< 37.8, 38.8–43.5, 43.6–49.9, > 49.9), and multivitamin use (yes or no).

Abbreviations: SD, standard deviation; OR, odds ratio; CI, confidence interval; Ref, reference; TL, telomere length; mtCN, mitochondrial DNA copy number; MET, metabolic equivalent; AHEI, Alternative Healthy Eating Index.

Table 4

Associations of a genetic risk sore for BMI with leukocyte telomere length and mitochondrial DNA copy number among women in the Nurses' Health Study

	GRS quartile 1	GRS quartile 2	GRS quartile 3	GRS quartile 4	*P* for trend
TL z-score					
N	1035	1034	1037	1049	
Mean (SD)[1]	−.04(.99)	−.01(.95)	−.05(1.03)	.04(1.00)	
OR of lower score (95% CI)[2]	Ref	1.01(.85, 1.20)	.98(.82, 1.17)	.91(.77, 1.08)	.26
P[2]	-	.93	.82	.28	
mtCN z-score					
N	405	392	412	387	
Mean (SD)[1]	.01(.93)	.06(.97)	−.02(1.00)	−.03(.94)	
OR of lower score (95% CI)[2]	Ref	.90(.68, 1.19)	1.08(.82, 1.43)	1.24(.94, 1.64)	.07
P[2]	-	.46	.57	.13	

[1] Standardized by age at blood collection.

[2] Unconditional logistic regression models with adjustment for age at blood collection. TL and mtCN z-score outcomes were dichotomized at the median.

Abbreviations: BMI, body mass index; GRS, genetic risk score; SD, standard deviation; OR, odds ratio; CI, confidence interval; Ref, reference; TL, telomere length; mtCN, mitochondrial DNA copy number.