Micronutrient intake and telomere length: findings from the UK Biobank

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Word count abstract/ main text: 252/ 4087

Number of Figures/ Tables: 1/ 3

On-line supplementary material: Yes

Summary

Purpose: To investigate whether micronutrient intake from food as well as the regular uptake of specific vitamins and/or minerals are associated with leucocyte telomere length (LTL).

Methods: This is a cross-sectional study using data from 422,693 UK Biobank participants aged from 40-69 years old, during 2006-2010. LTL was measured as the ratio of telomere repeat number to a single–copy gene and was $\log_e$-transformed and z-standardized (z-LTL). Information concerning supplement use was collected at baseline through the touchscreen assessment, while micronutrient intake from food were self-reported through multiple web-based 24hr recall diaries. The association between micronutrient intake or supplement use and z-LTL was assessed using multivariable linear regression models adjusting for demographic, lifestyle and clinical characteristics.

Results: About 50% (n=131,810) of the participants, with complete data on all covariates, self-reported regular supplement intake. Whilst overall supplement intake was not associated with z-LTL, trends toward shorter z-LTL with regular vitamin B (-0.019 (95% CI: -0.041; 0.002)) and vitamin B9 (-0.027 (-0.054; 0.000)) supplement intake were observed. z-LTL was associated with food intake of pantothenic acid (-0.020 (-0.033; -0.007)), vitamin B6 (-0.015 (-0.027; -0.003)), biotin (0.010 (0.002; 0.018)) and folate (0.016 (0.003; 0.030)). Associations of z-LTL with these micronutrients were differentiated according to supplement intake.

Conclusion: Negative associations equivalent to a year or less of age-related change in LTL between micronutrient intake and LTL were observed. Due to this small effect, the clinical importance of the associations and any relevance to the effects of vitamin and micronutrient intake toward chronic disease prevention remains uncertain.

Keywords: leukocyte telomere length, micronutrients, supplements, vitamins, minerals

Introduction

Telomeres constitute special nucleoprotein structures made of repetitive nucleotide non-coding sequences (TTAGGG) that play a protective role as "caps" on chromosomal ends and prevent genome instability. Telomere length has been proposed as a marker of biological aging, with short length and telomere dysfunction linked with several degenerative diseases [1]. Results from case-control studies suggest an association of telomere attrition with cancer [2] and neurodegenerative diseases including Parkinson's [3] and Alzheimer's disease [4]. Moreover, cross-sectional data from population studies also suggest a linkage between telomere attrition and cardiovascular disease [5] and mortality [6, 7], whilst data from a prospective population-based study highlighted the role of telomere attrition on the pathogenesis of atherosclerosis [8]. Mechanisms of oxidative stress and inflammation have also been implicated in accelerated telomere attrition leading to shorter telomere length [9, 10]. Leucocyte telomere length (LTL) is a complex trait commonly used as a biomarker of telomere dynamics that facilitates the investigation of the associations between telomere length and health outcomes at population level [11].

LTL has been associated with both genetic and environmental factors including lifestyle modifiable characteristics that are linked to the rate of telomere shortening. Shorter telomere length is associated with ageing, smoking [12], alcohol consumption [13] and increased body mass index (BMI) whereas female gender [14] and higher physical exercise levels [15] are related to longer LTL [16]. There is emerging evidence that dietary intake is also associated with LTL [17-19]. Adherence to a health promoting diet rich in vegetables, fruit, grains, fish, and monounsaturated fatty acids (such as the Mediterranean diet) has been reported to play a protective role on telomere integrity and be related to longer LTL [20-22]. Secondary analyses of cross-sectional data of 56 participants, from a case-control study, suggested a significant, but moderate, association between TL and vitamins A, E, C and B9 [23], whilst cross-sectional data from the Helsinki Birth Cohort study (n=1,942) [24] and the National Health and Nutrition Examination Survey (n=10,568) [25] suggested a positive association

between TL and micronutrient intake. Regardless, these results generally rely on population studies with smaller sample sizes than the one utilised in this study. Moreover, results are not always consistent and limited to dietary intake excluding the intake of food supplements [26].

Utilising data from the UK Biobank, we have undertaken a cross-sectional study to comprehensively examine the association between LTL and micronutrient intake from food, and/or supplement intake in a large sample of the UK general adult population. More specifically, we aimed to explore whether regular overall and nutrient-specific supplement intake, and daily micronutrient intake from food were associated with LTL, whilst controlling for well-known determinants of telomere length, which could confound the associations observed including age, sex, lifestyle factors, dietary habits and clinical markers.

Methods

Study design

The UK Biobank (UKB; https://www.ukbiobank.ac.uk/) is a large prospective population-based cohort study of ~500,000 volunteer men and women aged between 40-69 years, recruited between 2006 and 2010 in the United Kingdom. Detailed information regarding the protocol, the procedures and data collected were previously published [27-29]. In brief, participants were asked at baseline to complete an extensive touchscreen questionnaire followed by a brief verbal interview focusing on their lifestyle (including diet), environmental exposures, personal and family medical history. They also had physical measurements and provided samples of blood, urine and saliva, and online 24-hr dietary recalls through the Oxford Web validated questionnaire covering one to four days [30, 31].

Of the initial 474,074 UKB participants with LTL measurement, complete data on basic determinants of LTL were available for 422,693 participants following exclusions for genetically related individuals (randomly excluding one from each pair based on a kinship coefficient of K>0.088, n=33,728),

individuals with either no genetic data or whose samples failed quality control (n=908), participant withdrawal (n=107), and with missing data on ethnicity (n=2,101) or white blood cell count (n= 12,822) (**Figure 1**).

Ethics

Data collection followed the principles of the Declaration of Helsinki and was approved by the North-West Multi-center Research Ethics Committee (reference number 11/NW/0382). All participants provided written informed consent to participate in the UK Biobank and could withdraw at any time.

Leucocyte telomere length (LTL) measurement

LTL was measured on DNA extracted from peripheral blood leukocytes of blood samples collected at baseline. Telomere length was calculated using a validated quantitative PCR method and reported as a ratio of the telomere amplification product (T) to a single-copy gene (S) (T/S ratio) [32]. The measurements were $\log_e$-transformed to approximate the normal distribution and were then transformed to z-standardized values (UKB field code "22192"; z-LTL) to facilitate comparisons with other datasets.

Dietary assessment

At enrollment, all participants completed a short food frequency questionnaire (FFQ) as part of the baseline touchscreen questionnaire [33]. Towards the end of the recruitment phase participants also provided an online 24-hr dietary recall through the Oxford Web validated questionnaire [31, 34]. Subsequent administrations of the web-based questionnaire were completed up to a maximum four separate occasions over approximately a year (Feb 2011 - April 2012) to account for seasonal variation in dietary intake and to provide an estimate of habitual intakes [35].

Micronutrient intake from supplements

During the baseline assessment, participants were also asked about their regular intake of different types of supplements. Specifically, participants were asked whether they regularly consumed any of i) vitamin A, vitamin B, vitamin C, vitamin D, vitamin E, folic acid (vitamin B9), multivitamins (with or without combination of minerals) (UKB field code “6155”), and ii) fish oil (including cod liver oil), glucosamine, calcium, zinc, iron and selenium (“6179”) supplements.

Micronutrient dietary intake

Participants selected all foods and beverages that they consumed over the previous 24 hours from a list of 206 foods and 32 beverages included in the web-questionnaire. Food and nutrient intake was estimated through the "Food portion sizes” (Ministry of Agriculture, Fisheries and Food, 1993) (UKB field“ 100010”) and with the application of the McCance and Widdowson food composition data, taking into account natural content and food fortification [36, 37]. To account for under- or over-reporting, 1,748 (1%) 24-hr dietary assessments with extreme energy intakes (< 800 or > 4200 kcal/day for men; < 600 or > 3500 kcal/day for women) were excluded [38]. When multiple 24hour dietary recalls were available per participant, average intakes were estimated. Since, the difference between the average energy intake of participants with multiple 24-hour recalls and the energy intake of individuals with a single administration was negligible (mean difference (95% confidence interval, CI): 56.6 kcal (33.8; 79.5 kcal)), in the present analysis we also included 53,547 (38%) participants with one 24hour dietary recall to maximize the sample size. We further estimated adherence to a Mediterranean diet through a modified MedDietScore [39], as previously described [40], accounting for food items of the eight food groups collected in UKB (i.e. excluding potatoes, olive oil and legumes). The modified MedDietScore [39, 40] was developed using data from 8 out of the 11 food groups that characterize the Mediterranean dietary pattern. These food groups were collected through the touchscreen questionnaire during recruitment in the UKB, and included fruit, vegetables, fish, poultry, cheese (representing dairy products), red meat and its products, alcohol intake, and bread and cereal intake. To overcome the limitation of not collecting data for potato intake in UKB, bread and cereal type alongside bread and cereal intake were incorporated to

discriminate between non-refined (“brown/ wholemeal/ wholegrain” bread and “bran/ biscuit/ oat/ muesli” cereal) and refined grains (“white” bread and “other (cornflakes/ frosties)” cereal). Participants received scores ranging from '0' to '4' based on their reported frequency consumption of fruit, vegetables, non-refined grains, and dairy products. A score of '0' indicated no consumption, while '4' indicated daily consumption. Intermediate scores ('1' to '3') corresponded to rare, monthly, and weekly consumption, respectively. For participants reporting frequent consumption of refined grains the scores were reversed. For frequency intake of fish, poultry and red meat, that in the Mediterranean Diet is consumed on a weekly basis, a non-monotonic scoring system was followed, assigning a score of “4” for the moderate consumption of fish and poultry and rare consumption of red meat and its products. A non-monotonic function was also used for scoring alcohol intake, with a score of “5” assigned to participants reporting alcohol intake with a consumption up to 28g of ethanol per day (>0mL and <300mL), scores “4” to “1” to a consumption of 28-37.9, 38-47.9, 48-56.9 and 57-66.9g of ethanol per day respectively, and a score of “0” to no consumption or to 67g or more of ethanol per day (700mL). Thus, the potential range of this modified MedDietScore is 0 to 37 [40], instead of 0-55 [39], with higher values indicating greater adherence to the Mediterranean diet.

Statistical Analysis

Data on clinical biomarkers and micronutrient intake were winzorised at the 0.5% and 99.5% percentile values, to reduce extreme outliers, $\log_e$-transformed where necessary after graphically checking their distributions and scaled to the standardized normal distribution. Data are shown as mean (SD) or frequencies (%) for continuous and categorical variables respectively.

Sequential multivariable regression models were used to examine the association between z-LTL, as the response variable, and (i) regular overall supplement intake (derived from UK Biobank fields “6155” and “6179”, classified as “yes/no”; Model (M) 1), (ii) specific category of supplement intake (derived from fields “6155” and “6179”, classified as “no supplement/ vitamins only/ minerals only/

148 vitamins & minerals"; M2), (iii) specific type of supplement intake (all binary responses from fields
149 "6155" and "6179" and specifically: vitamin A (yes/no) , vitamin B (yes/no), vitamin C (yes/no),
150 vitamin D (yes/no), vitamin E (yes/no), folic acid (vitamin B9) (yes/no), multivitamins (yes/no), fish oil
151 (yes/no), glucosamine (yes/no), calcium (yes/no), zinc (yes/no), iron (yes/no) and selenium (yes/no);
152 M3), (iv) the combined effect of vitamins associated with telomere length ($p<0.05$) in M3, namely
153 vitamin B9 and vitamin B (M4), and (v) daily micronutrient intake from food (i.e. vitamin A, vitamin B
154 complex (including separately thiamin, niacin, pantothenic acid, vitamin B6, biotin, folate, vitamin
155 B12, riboflavin), vitamin C, vitamin D, vitamin E, calcium, zinc, iron and selenium; M5). M5 was also
156 stratified according to supplement intake (no (M5a) vs yes (M5b)) to account for the potential
157 interaction of supplement intake with food intake.

158 All models were adjusted for other covariates that were previously shown to be associated with LTL
159 [32], including sociodemographic (i.e. age (UKB field "21003"), sex (males/females; "31"), ethnic
160 background (White, Black, Asian, Chinese, Mixed, and Other; "21000"), educational level (none; O-
161 levels/ CSE/ GCSE that are equivalent to statutory/ compulsory education; A-levels/ non-vocational
162 qualifications/ other professional educational qualifications that are equivalent to advanced
163 education; degree that is equivalent to college or university degree; "6138") and Townsend
164 deprivation index at recruitment with higher scores representing greater levels of deprivation (in
165 quintiles; "189")), anthropometric (i.e. body mass index classification: under and normal weight <25
166 kg/m^2, overweight 25-29.9 kg/m^2 and obese ≥30 kg/m^2 (derived from "21001")), lifestyle (i.e.
167 smoking (never/previous/ current; "20116"), International Physical Activity Questionnaire (IPAQ)
168 activity group (i.e. low/ moderate/ vigorous; "22032") and alcohol intake (5-15g/day (females), 5-
169 30g/day (males)/ <5g/day/ >15g/day (females), >30g/day (males); derived from a combination of
170 participants' self-reported weekly and monthly intake in terms of glasses of alcohol) (18)), and
171 health-related (white blood cell count (WBC; "30000"), low density lipoprotein cholesterol (LDL;
172 "30780"), C-reactive protein (CRP; "30710"), estimated glomerular filtration rate (CKD-EPI; eGFR;
173 "30700"), insomnia (never/ sometimes/ usually; "1200"), fed up feelings (yes/ no; "1960") and self-

reported medically diagnosed diseases including cancer ("2453"), diabetes ("2443"), hypertension and vascular disease (both derived from "6150")). To further control for the confounding effect of the overall diet, models evaluating the association of micronutrient supplement intake and LTL (i.e., M1-M4) were additionally adjusted for UKB participants' overall adherence to Mediterranean diet, whilst models evaluating the association of micronutrient intake from food (i.e., M5) were additionally adjusted for daily energy intake ("26002") [41]. For micronutrient intakes from food found to associate with z-LTL ($p<0.05$) we further investigated quintiles of intake to consider non-linear effects. Results from the regression models are reported as regression coefficients (95% confidence interval, CI).

To facilitate the interpretation, the association of z-LTL with each variable was expressed in terms of age-related change due to LTL, by dividing the regression coefficient for the relevant vitamin intake variable by the absolute value of the regression coefficient for the age-related change in LTL in the UKB sample (i.e., 0.023 per year). All tests were two-sided and the statistical level was set at 0.05. The Bonferroni corrected significance level to account for the seven regression models tested was set at 0.007. Data analyses were performed in Stata (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC).

Results

Participants' flowchart is described in **Figure 1**. Amongst 422,693 non-related UKB participants with complete information on LTL and its key determinants (i.e., age, sex, ethnicity and white blood cell count), complete data on micronutrient intake from food and supplements were available for 343,348 (81%) and 177,990 (42%), respectively (**Figure 1**). Participants with missing data on supplement intake (n=79,345) had on average longer LTL (mean difference (95% CI): 0.026SD (0.018SD; 0.034SD)), were more likely to be women (11.8% (11.4%; 12.2%)), of other than white ethnic background (2.9% more participants of ethnic minorities (2.7%; 3.1%)), and from the most

deprived areas (8.0% (7.6%; 8.3%)), compared to participants with complete data (n=343,348). The pattern was similar when participants with 24hr-recall data (n=177,990) were compared to participants with no 24hr-recalls (n=244,703). Particularly, more participants in the latter group were of other than white ethnic background (2.2% (2.1%; 2.3%)) and from deprived areas (5.6% (5.3%; 5.9%)); but they had on average shorter LTL (-0.066SD (-0.072SD; -0.06SD)) compared to those with available 24hr-recall data. Differences in the distribution of age and WBC were negligible in both cases. Thus, analysis relied on a) 261,204 individuals, with complete data on z-LTL, supplement intake and related co-variates (models M1-M4), and b) 140,099 individuals with complete data on z-LTL, food intake and corresponding co-variates (model M5).

Descriptive statistics of participants' baseline characteristics are shown in **Table 1**. Notwithstanding mutual confounding, participants reporting regular supplement intake (n=131,810) when compared to their counterparts of no intake (n=129,394), have shorter z-LTL, are older, female, and from the least deprived areas. Additionally, supplement consumers tend to follow a healthier lifestyle (i.e., they are of normal weight, vigorously active, abstain from smoking/alcohol and generally adhere to the Mediterranean diet), but they self-reported higher rates of insomnia and medically diagnosed cancer (**Table 1**). Approximately one of every four participants (n=63,588) reported multiple vitamin intake including multivitamin intake, whilst approximately 7% (n=19,048) reported single vitamin intake, with vitamin C being the most common (9,479 (3.63)) and vitamin A (256 (0.10)) the least common single vitamins reported (**Supplementary Table 1**). Regarding mineral and other dietary supplement intake, 17.5% (n=45,780) and 25% (n=66,220) reported multiple and single intake, respectively, with fish oil being the most common (41,301 (15.8)) and selenium being the least common (695 (0.27)) single supplement consumed (**Supplementary Table 1**). Approximately one of every four participants (n=62,826) reported both vitamin and mineral intake (**Supplementary Table 1**).

In the multivariable regression models, overall supplemental intake was not associated with z-LTL (**M1, Table 2**), neither were general types of supplement intake (i.e. vitamins and/ or minerals; **M2,**

Table 2). However, negative associations were observed between vitamin B (beta (95% CI): -0.019 (-0.041; 0.002); p=0.079) and vitamin B9 (-0.027 (-0.054; 0.000); p=0.054), and z-LTL, albeit of small magnitude (i.e., approximately equivalent to 1 year of age-related change in LTL) (**M3, Table 2**). Compared to the overall intake of other vitamins/minerals, the combined intake of vitamin B/B9 was associated with smaller z-LTL (-0.07 (-0.11; -0.03); p=0.001), equivalent to 3 years age-related change in z-LTL (**M4, Supplementary Table 2**)**.**

Overall, we generally observed similar micronutrient intake from food between supplement users (n=72,126) and non-supplement users (n=67,973) (**Supplementary Table 3**). However, the intake of folate, vitamin C and calcium from food was higher among supplement users (mean difference (95% CI): 8.70 (7.50; 9.89) µg/day, 12.2 (11.4; 13.0) mg/day, and 13.9 (10.0; 17.7) mg/day, respectively) compared to non-supplement users (**Supplementary Table 3**). Results from the multivariable regression models for the food intake suggest a negative association of z-LTL with pantothenic acid (-0.020 (-0.033; -0.007); p=0.003) and vitamin B6 (-0.015 (-0.027; -0.003); p=0.014) and a positive association with biotin (0.010 (0.002; 0.018); p=0.010) and folate (0.016 (0.003; 0.030); p=0.019), whilst only the association of z-LTL with pantothenic acid reached Bonferroni significance. In all cases, the magnitude of association was small and equivalent to 1 year or less of age-related change in LTL. The pattern of these associations was different between supplement users and non-users. Particularly, vitamin B6 and folate were associated, in opposing directions, with z-LTL among non-supplement users, whilst pantothenic acid and biotin were associated, in opposing directions, with z-LTL among supplement users (**Table 3**). Evidence of a non-linear association was present for food intake of biotin suggesting a larger difference between the lowest intake quintile compared to the remaining 80% of the data (**Supplementary Figure 1**).

Discussion

We investigated the association between LTL and micronutrient intake, either from supplement and/or food, through cross-sectional data available in the UK Biobank. We observed a null association between LTL and overall supplement intake, however among the different types of supplement intake examined, supplement intake of vitamin B complex had a modest negative association with LTL, that was approximately equivalent to 3 years of age-related change to LTL. While this 3-year change in biological age may appear modest, previous research has demonstrated that even small changes in telomere length can have significant implications for biological aging and age-related disease risk [42]. Associations of LTL with micronutrient intake from food, and particularly with pantothenic and vitamin B6 (both negative), were even smaller and equivalent to 1 year or less of age-related change in LTL, whilst not reaching Bonferrroni significance level.

While the way supplement intake was recorded precluded further investigation of the association between vitamin B complex and LTL, there was detailed information regarding micronutrient intake from food. Dietary pantothenic (vitamin B5) and vitamin B6 intake were negatively associated with LTL, whilst biotin (vitamin B7) and folate (vitamin B9) were positively associated with LTL, although the latter did not reach Bonferroni significance. The opposing associations between these micronutrient intakes from food and LTL could be attributed to the fluctuation in bioavailability and absorption of the micronutrients as well as the potential synergistic or antagonistic interactions with other micronutrients. Any effect dietary micronutrient intake had on LTL was dependent on the use of supplements, with the association of LTL with B6 and folate persisting among non-users and the association of LTL with pantothenic and biotin persisting among users. Notwithstanding the cross-sectional nature of the association, that may result to regular supplement intake among individuals of impaired health (reverse causality), our findings contradict the hypothesis that greater intake of micronutrients is positively associated with telomere maintenance. However, the opposing trend observed in the direction of the association of LTL with supplement intake of vitamin B complex and, particularly, with vitamin B9 is in accordance with the findings of recent animal [43] and offspring [44] studies.

Telomere attrition is a multifaceted process regulated by a combination of cellular and molecular mechanisms, such as oxidative stress, chronic inflammation, and changes in DNA methylation patterns [45,46]. Antioxidant, vitamin, and mineral intake have a positive effect in the replication rate of cells and therefore prevent response to inflammation and reduce the level of oxidative stress in the cells [47,48]. It is, therefore, anticipated that micronutrient intake could impact on telomere length maintenance as regulators of enzymes essential for DNA replication, such as telomerase, contributing to chromosomal stability, repair processes, and overall cellular health [49]. Whilst vitamin B complex, and particularly folate and vitamins B2, B6, and B12, have pivotal roles within the one-carbon metabolism pathways, actively participating in DNA methylation and repair processes essential for maintaining the integrity and stability of chromosomes [50], excessive vitamin and antioxidant intake potentially interfere with normal cellular processes, cell proliferation and the ability to repair DNA damage progressively leading to telomere shortening [51]. Our finding regarding the negative association between vitamin B9 supplement intake and LTL may be, thus, due to the excess folic acid intake, leading to accumulation of folate derivatives which regulate several enzymatic activities and cause DNA attrition [52]. Vitamin B6 intake could also impact on telomere length through mechanisms similar to folate and vitamin B12, regulating DNA methylation via lowering the levels of homocysteine [53]. However, its relationship with telomere length is complex and not fully understood. Although we could speculate that a reversed U-shape association between vitamin B6 and telomere length is possible in accordance with known folate mechanisms, our data failed to support this hypothesis. Pantothenic acid (vitamin B5) is also involved in cellular metabolism through its role in the synthesis of coenzyme A. However, whether its specific role in cellular metabolism influence the mechanisms related with telomere attrition and whether our observed negative association with LTL is in accordance with our hypothesis of excessive intake is yet to be fully elucidated. We could speculate that excessive vitamin B complex intake might disrupt DNA methylation patterns, cell proliferation or other regulatory mechanisms, leading to telomere shortening which can then lead to increased disease risk and lower life expectancy [54].

To our knowledge, this is the first large-scale epidemiological study that comprehensively examines the association between LTL and a variety of micronutrient intake either through supplement or food. We have utilized data from the UK Biobank, a powerful resource that allows adjustment for multiple potential confounders hence minimizing residual confounding, and we have thus examined the association of micronutrient intake with LTL, above and beyond other well-known determinants of LTL. There are no studies of equivalent magnitude with which we can compare our findings directly, whilst the findings from smaller scale epidemiological studies are conflicting suggesting negative association between telomere length, carotenes and tocopherol [55-57] and positive association with serum vitamin A [47] and serum folate [25, 58]. Whilst results from the Framingham Offspring cohort study [59] suggest a negative association between high folic acid intake from both multivitamins and fortified foods and LTL, other studies reveal a protective role of folate on DNA integrity with a positive association between dietary intake or serum folate concentration and LTL [56, 60]. Heterogeneity in the magnitude and the direction of the association between telomere length and the various micronutrients could be attributed to the study design and setting, the method used to measure telomere length, the measurement of micronutrient intake, the population size and the covariates used in the models, with our study providing greater power to detect any association between variation in LTL and micronutrient intake. Even though there is evidence of "healthy volunteer" bias [61], risk factor associations in UK Biobank are accepted to be generalizable [62]. Dietary micronutrient intake data were self-reported through 24hr recall diaries that are prone to recall bias [63]. Regardless, extreme energy intake values were excluded, and regression models were adjusted for energy intake and a number of other personal characteristics to minimize differential misclassification. Participants self-reported whether they regularly consume any vitamins/ minerals without providing any data on their composition. Hence, we cannot investigate dose-response associations between supplement intake and LTL, neither we can disentangle the combined effect of vitamin B supplement intake in the individual components of the complex apart than of B9 albeit we cannot rule out recall bias. Moreover, this is a cross-sectional study and as such

cannot interrogate causal associations between vitamin and mineral intake and telomere length. Lastly, although we utilized multiple 24hr recalls capturing habitual intake and reducing within-person random error, we also considered single administrations to maximize our sample size. Estimations of vitamin and mineral intake based on short-term measurements are expected to suffer from random within-person variation in intake; nevertheless, the large sample size on which this analysis relies upon may succeed in addressing such errors.

Conclusion

In general, we did not observe significant associations between micronutrient intake, either from supplements or food, and LTL. However, negative associations of vitamin B/B9 supplemental intake and pantothenic intake from natural (food) sources with LTL were observed; albeit their small magnitude of the association that may preclude any strong clinical relevance. Regardless, , the pattern of these associations may suggest the presence of complex interactions between micronutrients, individual physiology and the underlying metabolic processes that are yet to be elucidated. While these mechanistic hypotheses provide potential insights, further experimental studies are necessary to better understand the precise molecular pathways and the underlying mechanisms involved in telomere length dynamics, enriched with dose-response clinical trials accounting for years of supplement intake.

Author contributions: VB conceptualised and designed this study; MS, VB performed the data management; MS analysed and interpreted the data, with advice from AN, CPN and VB; VC, CPN and NJS were responsible for data acquisition; VC, CPN, and NJS secured funding for the LTL measurements and oversaw the generation and curation of the LTL measurements; MS, AN and VB drafted the first version of the manuscript. All authors commented on subsequent drafts of the manuscript and critically reviewed it for important intellectual content and gave their final approval to the version to be published.

Conflict of interest: The authors report no conflict of interest in relation to this work.

Funding: This work was funded by the UK Medical Research Council (MRC), Biotechnology and Biological Sciences Research Council and British Heart Foundation (BHF) through MRC grant MR/M012816/1. University of Leicester investigators are supported by the National Institute for Health Research (NIHR) Leicester Cardiovascular Biomedical Research Centre (BRC-1215-20010). CPN is funded by the BHF (SP/16/4/32697).

Acknowledgement: UK Biobank received approval from the North-West Centre for Research Ethics Committee (11/NW/0382). The use of data presented in this paper was approved by the Access Committee of UKB under application number 6077.

Data availability: All data used in this study, including telomere length measurements, are available through application to UK Biobank. Further information on registration to access the data can be found at http://www.ukbiobank.ac.uk/register-apply/.

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