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Association between the dietary antioxidant index and relative telomere length of leucocytes in the Chinese population

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Abstract

Dietary antioxidant indices (DAI) may be potentially associated with relative telomere length (RTL) of leucocytes. This study aimed to investigate the relationship between DAI and RTL. A cross-sectional study involving 1656 participants was conducted. A generalised linear regression model and a restricted cubic spline model were used to assess the correlation of DAI and its components with RTL. Generalised linear regression analysis revealed that DAI ($\beta = 0{\cdot}005$, $P = 0{\cdot}002$) and the intake of its constituents vitamin C ($\beta = 0{\cdot}043$, $P = 0{\cdot}027$), vitamin E ($\beta = 0{\cdot}088$, $P < 0{\cdot}001$), Se ($\beta = 0{\cdot}075$, $P = 0{\cdot}003$), and Zn ($\beta = 0{\cdot}075$, $P = 0{\cdot}023$) were significantly and positively correlated with RTL. Sex-stratified analysis showed that DAI ($\beta = 0{\cdot}006$, $P = 0{\cdot}005$) and its constituents vitamin E ($\beta = 0{\cdot}083$, $P = 0{\cdot}012$), Se ($\beta = 0{\cdot}093$, $P = 0{\cdot}006$), and Zn ($\beta = 0{\cdot}092$, $P = 0{\cdot}034$) were significantly and positively correlated with RTL among females. Meanwhile, among males, only vitamin E intake ($\beta = 0{\cdot}089$, $P = 0{\cdot}013$) was significantly and positively associated with RTL. Restricted cubic spline analysis revealed linear positive associations between DAI and its constituents' (vitamin E, Se and Zn) intake and RTL in the total population. Sex-stratified analysis revealed a linear positive correlation between DAI and its constituents' (vitamin E, Se and Zn) intake and RTL in females. Our study found a significant positive correlation between DAI and RTL, with sex differences.

Keywords: **Dietary antioxidant index: Relative telomere length: Ageing: Dietary intake**

Telomere is a protective structure at the end of a chromosome, consisting of a segment of DNA with a repetitive sequence and an associated protein complex. It plays a key role in cell division, protecting genes at the ends of chromosomes to maintain stability and avoid loss of genetic information[1]. However, as the body ages and certain diseases occur, telomerase is gradually inactivated, leading to a shortening of telomere length[2]. And this may eventually lead to cellular senescence and apoptosis[3]. Therefore, telomere length can be used as a biomarker of cellular ageing and health–disease processes[4].

A large body of evidence demonstrates that the mechanism of telomere length shortening may be related to oxidative stress and inflammation[5]. At the same time, certain nutrients in the diet have potent antioxidant capacity[6,7]. Thus, dietary nutrients with antioxidant capacity may exist to maintain telomere length. The dietary antioxidant index (DAI), which is a metric recommended by Wright *et al.*, allows for a comprehensive evaluation of an individual's dietary intake of multiple antioxidants. These antioxidants include vitamin A, vitamin C, vitamin E, Se, Zn and Mn. A higher score on the DAI represents a

Abbreviations: DAI, Dietary antioxidant index; RTL, relative telomere length.

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richer intake of antioxidants in an individual's diet, which can help minimise the damage caused by oxidative stress[8]. In the existing literature, a single antioxidant element is commonly used to study the relationship between its dietary antioxidant capacity and telomere length. Compared with the assessment of a single antioxidant element, DAI has several advantages. First, it can comprehensively assess the antioxidant capacity of the whole dietary pattern rather than focusing only on the intake of a single antioxidant element, thus more closely resembling the actual dietary situation. Second, DAI can take into account the interaction effects between different foods, thus assessing the antioxidant capacity of the diet more accurately[8]. Considering that some elements in the diet have antioxidant capacity and a proven role in maintaining telomere length[9–14], some association may exist between DAI and telomere length.

Despite theories and findings suggesting that dietary antioxidants are effective in slowing down telomere length shortening, the relationship between DAI and telomere length is currently unknown. Therefore, this study will be the first to use a cross-sectional design to investigate the independent and joint relationship between DAI (including vitamins A, C and E, Se, Zn and Mn) and leucocyte relative telomere length (RTL). The results of the study are expected to provide a theoretical basis for delaying ageing and preventing ageing-related diseases.

Materials and methods

Study population

The study participants were from the towns of Lianhua and Limu in the Hongshui River Basin in Gongcheng Yao Autonomous County, Guangxi, China. This cross-sectional survey was conducted from December 2018 to November 2019. A total of 4356 residents aged 30 years or older participated in this study. The inclusion criteria were as follows: (a) people aged 30 years and older; (b) people living within the study area; (c) people who could provide valid dietary intake data; (d) people who provided valid self-reported personal interview data (including household, sample population and medical statistics questionnaires) and (e) samples with telomere length data. The exclusion criteria were as follows: (a) participants who did not complete the questionnaire or whose covariate information was missing from the questionnaire; (b) those who did not provide validated dietary intake data and (c) those who did not have telomere length measurements. Finally, a total of 1656 subjects were included in this study for analysis. The study procedures were approved by the Medical Ethics Committee of Guilin Medical College (No. 20180702-3) and conducted in accordance with the principles of the Declaration of Helsinki. A written informed consent was provided by each participant.

Assessment of dietary intake

The questionnaire of Wang *et al.*[15], namely, the FFQ, was used to assess dietary intake. Using FFQ is a rational, valid and reliable method for assessing the long-term average intake of 109 common foods[16]. Participants were asked to recall and report the average frequency of consumption and the amount of each consumption over the past year. FFQ was administered using a food album containing dietary items and measurement tools. A standardised portable electronic kitchen scale provided was used to measure the weight of each portion, with the food portion measured in grams and the beverage portion measured in millilitres. The intake of each food item was calculated by multiplying the portion size of each food item by the weight of each food item. The energy and nutrient contents of foods were calculated on the basis of the Chinese Food Composition Table (2019)[17]. The total daily energy intake and dietary vitamins E, C, and A, Se, Zn, and Mn were calculated as follows: daily intake = intake/frequency.

Calculation of the dietary antioxidant index

In this study, DAI was calculated for all subjects by using the measurements recommended by Wright[8]. Six minerals and vitamins (vitamins A, C, and E, Mn, Se, and Zn) from food sources were included to calculate the sum of the standardised *Z*-values of their intake as follows:

$$DAI = \sum_{i=1}^{6} \frac{X_i - \mu_i}{S_i}$$

where Xi is the daily intake of antioxidant i, μi is the mean value of Xi for a particular antioxidant nutrient i consumed by all participants and Si is the standard deviation of μi.

Collection of blood samples and measurement of relative telomere lengths

After the participants fasted for at least 12 h, venous blood was drawn by a professional nurse on the morning of the physical examination and transferred to the Laboratory Department of Gongcheng Yao Autonomous County People's Hospital via cold chain. DNA was extracted using the DNA extraction kit provided by Beijing Adderall Biotechnology Co., Ltd in accordance with the instructions of the kit. The concentration and purity of the DNA samples were detected by UV spectrophotometry. The DNA samples with the ratio of A260/A280 within the range of 1·8–2·0 were regarded as meeting the requirements of quality control. The DNA samples that met these requirements were dispensed into centrifugal tubes with a volume of 1·5 ml and stored in an ultralow temperature refrigerator at –80°C until further analysis. The RTL of leucocytes was determined by measuring the ratio of the number of telomeric repeats (T) to the number of single-copy gene repeats (S) in each DNA sample by using the real-time quantitative PCR (qPCR) method described by Cawthon[18]. RTL is the ratio of the number of telomeric repeats (T) to the number of copies (S) of the single-copy gene (36B4). The forward and reverse primer sequences of telomere gene were 5′-CGGTTTGTTTGGGTTTGGGTTTGGGTTTGGGTTTGGGTT-3′ and 5′-GGCTTGCCTTACCCTTACCCTTACCCTTACCCTTACCCT-3′, respectively. The forward and reverse primer sequences of 36B4 were 5′-CAGCAAGTGGGAAGGTGTAATCC-3′ and 5′-CCCATTCTATCATCAACGGGTACAA-3′, respectively[18]. These primers were purchased from Invitrogen, USA. The DNA of any qualified sample was selected as the standard and diluted to 200, 100, 50, 25, 12·5, 6·25 and

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3·125 ng/μl by using the EB conjugate solution in the Beijing Adderall reagent kit. A concentration of 35 ng/μl was selected as the positive control, and the rest of the DNA samples to be tested were diluted to 25–50 ng/μl with the EB conjugate in the Beijing Adderall kit. The Tel and 36B4 genes were seeded into two corresponding 96-well plates, with two replicate wells set up for each sample. The multiplicity-diluted standard and the samples to be tested were subjected to PCR, a standard curve was established, and the amplification efficiency was calculated. Each 96-well plate was set up with a positive reference sample. Subsequently, Stepone Plus (Application Biosystems, USA) was used to perform quantitative PCR of the Tel and 36B4 genes in the 96-well plates. The total volume of the PCR system was 20 μl, which contained 10 μl PowerUp SYBR Green master mix, 7 μl ribonuclease-free water, 1 μl forward primer, 1 μl reverse primer and 1 μl DNA template. The PCR programme for the Tel genes was 50°C for 2 min and 95°C for 2 min, followed by 40 cycles of 95°C for 15 s and 62°C for 1 min. The PCR programme for the 36B4 genes was 50°C for 2 min and 95°C for 2 min, followed by 40 cycles of 95°C for 15 s, 62°C for 20 s and 72°C for 1 min. This experiment requires that the standard curve correlation coefficient R2 of TEL and 36B4 is ≥0·98 when measured in the range of standard sample dilution concentration x-y. Both amplification efficiencies are required to be greater than 90 %, and the difference in amplification efficiency must be less than 5 % to ensure that the calculated results are accurate and reliable.

The mean RTL was calculated using the $2^{-\Delta\Delta Ct}$ method recommended by Tang[19] as follows. Relative $T/S = 2^{-(\Delta Ct\ \text{Samples to be tested} - \Delta Ct\ \text{positive control})}$, where ΔCt (sample to be tested) is the difference between the CT value of the TEL gene after telomere amplification in the sample to be tested, and the corresponding 36B4 gene CT value and ΔCt (positive control) is the difference between the CT value of the TEL gene after telomere amplification in the DNA telomere of the reference sample of the positive standard and the corresponding 36B4 gene CT value. On this basis, the mean RTL was calculated and used as a measure of telomere length in the samples.

Definition of covariates

Covariates included demographics, lifestyle habits and prevalent diseases. Demographic data investigators conducted face-to-face interviews with the participants by using standardised and structured questionnaires to obtain information, including sex (male or female), age, ethnicity (Han, Yao or other ethnic groups) and educational level (no formal education, 1–6 years, or 7 or more years). Lifestyle habits included alcohol consumption (yes or no), smoking (yes or no) and others. Prevalent diseases included diabetes (yes or no), hypertension (yes or no) and dyslipidaemia (yes or no).

Alcohol consumption was defined as ≥50 g of alcohol per month; smoking was defined as ≥1 cigarette/d; BMI was calculated on the basis of weight and height data as follows: BMI = weight (kg)/height (m^2); and hypertension was defined as systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥90 mmHg or as indicated by current antihypertensive medications[20]. Diabetes mellitus was defined as glycosylated Hb (HbA1c) ≥ 6·5 %, fasting blood glucose ≥ 7·0 mmol/l or taking hypoglycaemic medications[21]. Dyslipidaemia was defined as TC ≥ 5·18 mmol/l, or (and) TG ≥ 1·7 mmol/l, or (and) LDL-cholesterol ≥ 3·37 mmol/l, or (and) HDL-cholesterol < 1·04 mmol/l or taking lipid-lowering drugs[22].

Statistical analysis

A descriptive statistical analysis of the demographics, dietary and lifestyle habits of the study population was carried out by converting DAI into interquartile groups. We used the Kolmogorov–Smirnov test and histogram chart to test the normality of the data. Normally distributed continuous variables were described by mean and standard deviation, and non-normally distributed continuous variables were described by median and interquartile range, and comparisons between groups were made using the one-way ANOVA or the Kruskal–Wallis rank sum test. Frequency (n %) described categorical variables, and between-group comparisons were made by χ^2 test or Fisher's exact probability method. Given that the dietary intake data were positively skewed, they were log10-transformed to reduce bias before analysis.

Generalised linear regression models were used to analyse the correlations between DAI (continuous variables and quartile groups) and its components (vitamins E, C, and A, Se, Zn, and Mn) and RTL. Model I was unadjusted for covariates. Model II added control variables, such as sex, age, ethnicity, BMI, education level, smoking, alcohol consumption and total energy intake, to model I. Model III added control variables, such as diabetes, hypertension and dyslipidaemia, to model II. After controlling for covariates in generalised linear regression model, further sex subgroup analyses were performed. The dose–response relationship between DAI and its components and RTL was explored using restricted cubic spline.

All P-values were two-tailed, and $P < 0·05$ was defined as statistical significance. All analyses were performed using IBM SPSS Statistics version 27 as well as R Studio version 4.2.1.

Results

Demographics

This study included 1656 participants, of whom 62·6 % were female and 37·4 % were male. Table 1 shows the baseline characteristics of the study population stratified in accordance with DAI quartiles. The results showed that the differences in RTL, sex, age, educational level, drinking status, diabetes mellitus, hypertension, dyslipidaemia and BMI were statistically significant ($P < 0·05$).

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Table 2 shows the generalised linear regression model of RTL and DAI. In the fully adjusted model (model III), DAI (continuous values) was significantly positively correlated with RTL ($\beta = 0·005$, 95 % CI (0·002, 0·008), $P = 0·002$), and a significant positive correlation was observed between the highest quartile of DAI and RTL compared with the lowest

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Table 1. Demographic characteristics stratified by quartile of DAI (*n* 1656)

	Total		Quartile 1 (−6·82, −3·35)		Quartile 2 (−3·35, −1·28)		Quartile 3 (−1·28, 2·14)		Quartile 4 (2·14, 54·07)		
DAI	*n* 1656		*n* 414		*n* 414		*n* 414		*n* 414		*P*-overall*
RTL	0·69	0·56, 0·89	0·65	0·55, 0·84	0·69	0·56, 0·87	0·69	0·56, 0·91	0·74	0·58, 0·97	**0·001**†
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	
Sex											**0·003**‡
Male	619	37·38	131	31·64	143	34·54	173	41·79	172	41·55	
Female	1037	62·62	283	68·3	271	65·46	241	58·21	242	58·45	
Age	60·00	50·00, 67·00	64·00	53·00, 69·00	61·00	51·25, 67·75	60·00	49·00, 66·00	53·00	46·00, 63·00	<**0·001**†
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	
Ethnicity											0·054‡
Han	359	21·68	108	26·09	90	21·74	73	17·63	88	21·26	
Yao	1227	74·09	293	70·77	309	74·64	323	78·02	302	72·95	
Others	70	4·23	13	3·14	15	3·62	18	4·35	24	5·80	
Education											<**0·001**‡
No formal educated	256	15·46	109	26·33	69	16·67	42	10·14	36	8·70	
1–6 years	1284	77·54	289	69·81	317	76·57	337	81·40	341	82·37	
7 or more years	116	7·00	16	3·86	28	6·76	35	8·45	37	8·94	
Smoking											0·149‡
No	1354	81·76	341	82·37	349	84·30	324	78·26	340	82·13	
Yes	302	18·24	73	17·63	65	15·70	90	21·74	74	17·87	
Drinking											**0·015**‡
No	1114	67·27	301	72·71	284	68·60	268	64·73	261	63·04	
Yes	542	32·73	113	27·29	130	31·40	146	35·27	153	36·96	
Diabetes											**0·026**‡
No	1443	87·14	349	84·30	353	85·27	375	90·58	366	88·41	
Yes	213	12·86	65	15·70	61	14·73	39	9·42	48	11·59	
Dyslipidaemia											**0·037**‡
No	812	49·03	192	46·38	200	48·31	228	55·07	192	46·38	
Yes	844	50·97	222	53·62	214	51·69	186	44·93	222	53·62	
Hypertension											**0·002**‡
No	890	53·74	195	47·10	214	51·69	241	58·21	240	57·97	
Yes	766	46·26	219	52·90	200	48·31	173	41·79	174	42·03	
BMI (kg/m^2)	22·41	20·29, 24·72	22·21	19·97, 24·43	22·53	20·28, 24·72	22·11	20·23, 24·44	22·79	20·76, 25·27	**0·007**†
Vitamin A (μgRAE/d)	238·53	131·44, 410·11	96·47	58·74, 149·78	191·06	130·16, 256·22	306·39	220·07, 394·31	556·77	419·23, 761·71	<**0·001**†
Vitamin C (mg/d)	51·84	27·05, 93·83	19·52	13·22, 29·04	40·53	27·55, 54·75	68·63	47·61, 89·64	126·62	96·62, 168·54	<**0·001**†
Vitamin E (mg/d)	23·09	14·83, 37·23	13·17	9·05, 18·53	19·82	14·26, 27·34	26·66	19·73, 36·15	46·39	33·21, 64·05	<**0·001**†
Zn (mg/d)	6·68	4·77, 9·33	3·67	2·85, 4·50	5·79	4·94, 6·57	7·73	6·77, 8·79	12·00	10·08, 14·48	<**0·001**†
se (mg/d)	17·45	11·07, 27·30	8·30	5·84, 11·10	14·43	11·46, 17·62	21·70	17·38, 26·53	35·19	27·80, 46·17	<**0·001**†
Mn (mg/d)	3·91	2·84, 5·32	2·30	1·74, 2·83	3·36	2·93, 3·97	4·40	3·80, 5·05	6·81	5·58, 8·09	<0·001†

DAI, dietary antioxidant index; RTL, relative telomere length.
* Statistical significance was set at $P < 0·05$ and marked in bold.
† The Kruskal–Wallis rank sum test was used to compare non-normally distributed data between groups.
‡ The χ^2 test was used to compare categorical variables.

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Table 2. The association between DAI and telomere length

	Model I†			Model II‡			Model III§		
	β	95 % CI	*P**	*β*	95 % CI	*P**	*β*	95 % CI	*P**
All									
DAI (continuity value)	0·007	0·004, 0·009	**<0·001**	0·004	0·002, 0·007	**0·003**	0·005	0·002, 0·008	**0·002**
Quartile 1	Ref			Ref			Ref		
Quartile 2	0·033	−0·008, 0·074	0·111	0·018	−0·022,0·058	0·379	0·018	−0·002,0·058	0·381
Quartile 3	0·042	0·001, 0·083	**0·045**	0·020	−0·021,0·061	0·333	0·020	−0·021, 0·061	0·331
Quartile 4	0·086	0·045, 0·127	**<0·001**	0·050	0·008, 0·092	**0·018**	0·051	0·010, 0·093	**0·016**
$P_{for\ trend}$*	**<0·001**			**0·024**			**0·020**		
Male									
DAI (continuity value)	0·004	0·000, 0·009	**0·040**	0·002	−0·002, 0·007	0·254	0·003	−0·002, 0·007	0·235
Quartile 1	Ref			Ref			Ref		
Quartile 2	0·040	−0·025, 0·105	0·223	0·029	−0·034,0·093	0·364	0·027	−0·036, 0·091	0·398
Quartile 3	0·021	−0·041, 0·083	0·504	0·009	−0·052, 0·071	0·767	0·009	−0·053, 0·070	0·783
Quartile 4	0·076	0·014, 0·139	**0·016**	0·049	−0·013,0·111	0·121	0·049	−0·013, 0·112	0·120
$P_{for\ trend}$*	**0·035**			0·205			0·197		
Female									
DAI (continuity value)	0·009	0·005, 0·013	**<0·001**	0·006	0·002, 0·009	**0·006**	0·006	0·002, 0·010	**0·005**
Quartile 1	Ref			Ref			Ref		
Quartile 2	0·031	−0·020, 0·083	0·234	0·012	−0·040, 0·063	0·657	0·013	−0·038, 0·064	0·609
Quartile 3	0·065	0·011, 0·118	**0·018**	0·029	−0·024, 0·083	0·281	0·030	−0·023, 0·084	0·266
Quartile 4	0·100	0·047, 0·154	**<0·001**	0·045	−0·010, 0·100	0·109	0·047	−0·008, 0·101	0·097
$P_{for\ trend}$*	**<0·001**			0·087			0·079		

DAI, dietary antioxidant index.
* Statistical significance was set at $P < 0·05$ and marked in bold.
† Model I (crude): unadjusted for covariates.
‡ Model II: adjusted for sex, age, ethnicity, BMI, education level, smoking and alcohol consumption.
§ Model III: adjusted for sex, age, ethnicity, BMI, education level, smoking status, alcohol status, diabetes, hypertension and dyslipidaemia.

Table 3. The association between dietary antioxidant index (components) and telomere length

	Model I†			Model II‡			Model III§		
	β	95 % CI	*P**	*β*	95 % CI	*P**	*β*	95 % CI	*P**
All									
Vitamin A	0·060	0·022,0·097	**0·002**	0·028	−0·010, 0·066	0·145	0·029	−0·009, 0·067	0·133
Vitamin C	0·076	0·038, 0·114	**<0·001**	0·041	0·003, 0·079	**0·033**	0·043	0·005, 0·081	**0·027**
Vitamin E	0·130	0·082, 0·178	**<0·001**	0·086	0·037, 0·134	**<0·001**	0·088	0·040,0·137	**<0·001**
Se	0·102	0·053, 0·150	**<0·001**	0·073	0·023, 0·122	**0·004**	0·075	0·025, 0·124	**0·003**
Zn	0·108	0·045, 0·172	**<0·001**	0·071	0·007, 0·136	**0·030**	0·075	0·010, 0·139	**0·023**
Mn	0·108	0·041, 0·175	**0·001**	0·062	−0·005, 0·129	0·072	0·065	−0·002,0·132	0·059
Male									
Vitamin A	0·024	−0·030,0·079	0·385	0·008	−0·046, 0·062	0·781	0·009	−0·045, 0·063	0·756
Vitamin C	0·056	-6·227E-5, 0·112	0·050	0·028	−0·028, 0·083	0·333	0·029	−0·027,0·085	0·304
Vitamin E	0·118	0·047, 0·190	**0·001**	0·089	0·018, 0·160	**0·014**	0·089	0·018, 0·160	**0·013**
Se	0·055	−0·018, 0·129	0·139	0·041	−0·032, 0·114	0·270	0·043	−0·031, 0·116	0·253
Zn	0·078	−0·019, 0·175	0·116	0·029	−0·067, 0·126	0·551	0·032	−0·065, 0·129	0·520
Mn	0·081	−0·021, 0·184	0·120	0·023	−0·078, 0·125	0·653	0·025	−0·077, 0·127	0·628
Female									
Vitamin A	0·089	0·038, 0·139	**<0·001**	0·042	−0·010, 0·093	0·115	0·042	−0·010, 0·094	0·111
Vitamin C	0·090	0·040, 0·139	**<0·001**	0·046	−0·004, 0·096	0·073	0·047	−0·003, 0·098	0·065
Vitamin E	0·140	0·077, 0·203	**<0·001**	0·078	0·013, 0·142	**0·019**	0·083	0·018, 0·147	**0·012**
Se	0·148	0·084, 0·213	**<0·001**	0·092	0·026, 0·157	**0·006**	0·093	0·027, 0·158	**0·006**
Zn	0·161	0·077, 0·245	**<0·001**	0·088	0·003, 0·173	**0·042**	0·092	0·007, 0·177	**0·034**
Mn	0·147	0·060, 0·235	**<0·001**	0·074	−0·014, 0·162	0·101	0·078	−0·010, 0·167	0·082

* Statistical significance was set at $P < 0·05$ and marked in bold.
† Model I (crude): unadjusted for covariates.
‡ Model II: adjusted for sex, age, ethnicity, BMI, education level, smoking and alcohol consumption.
§ Model III: adjusted for sex, age, ethnicity, BMI, education level, smoking status, alcohol status, diabetes, hypertension and dyslipidaemia.

quartile of DAI ($\beta = 0·051$, 95 % CI (0·010, 0·093), $P = 0·016$). The trend test was also significant ($P_{for\ trend} = 0·020$). Sex subgroup analysis showed a significant positive association between DAI and RTL in females in model III ($\beta = 0·006$, 95 % CI (0·002, 0·010), $P = 0·005$). However, no statistical significance was found in the trend test ($P = 0·079$). Moreover, no association was found between DAI and RTL in males, and the trend was not statistically significant ($P = 0·197$).

Table 3 shows the generalised linear regression model between RTL and various dietary antioxidant elements in DAI. In model I, all dietary antioxidants were positively associated with RTL ($P < 0·05$). However, the fully adjusted model (model III)

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only showed positive associations between dietary vitamin C ($\beta = 0{\cdot}043$, 95 % CI (0·005, 0·081), $P = 0{\cdot}027$), vitamin E ($\beta = 0{\cdot}088$, 95 % CI (0·040, 0·137), $P < 0{\cdot}001$), Se ($\beta = 0{\cdot}075$, 95 % CI (0·025, 0·124), $P = 0{\cdot}003$) and Zn ($\beta = 0{\cdot}075$, 95 % CI (0·010, 0·139), $P = 0{\cdot}023$) intakes and RTL. The sex subgroup analyses showed that in model III, dietary vitamin E intake was significantly and positively associated with RTL in males ($\beta = 0{\cdot}089$, 95 % CI (0·018, 0·160), $P = 0{\cdot}013$). In females, dietary vitamin E ($\beta = 0{\cdot}083$, 95 % CI (0·018, 0·147), $P = 0{\cdot}012$), Se ($\beta = 0{\cdot}093$, 95 % CI (0·027, 0·158), $P = 0{\cdot}006$) and Zn ($\beta = 0{\cdot}092$, 95 % CI (0·007, 0·177), $P = 0{\cdot}034$) intakes were significantly and positively associated with RTL.

In addition, restricted cubic spline was further used to estimate the dose–response relationship between DAI and its components and RTL in the total population and sex subgroups, respectively, as shown in Fig. 1 (lists only statistically significant dietary elements). A linear positive correlation was found between DAI and RTL in the total population ($P_{\text{-overall}} = 0{\cdot}0224$, $P_{\text{-non-linear}} = 0{\cdot}8878$) and females ($P_{\text{-overall}} = 0{\cdot}0417$, $P_{\text{-non-linear}} = 0{\cdot}7411$). Among the DAI components, dietary vitamin E ($P_{\text{-overall}} = 0{\cdot}0015$, $P_{\text{-non-linear}} = 0{\cdot}2376$; $P_{\text{-overall}} = 0{\cdot}0336$, $P_{\text{-non-linear}} = 0{\cdot}2972$), Se ($P_{\text{-overall}} = 0{\cdot}0135$, $P_{\text{-non–linear}} = 0{\cdot}3586$; $P_{\text{-overall}} = 0{\cdot}0232$, $P_{\text{-non-linear}} = 0{\cdot}3677$) and Zn ($P_{\text{-overall}} = 0{\cdot}0224$, $P_{\text{-non-linear}} = 0{\cdot}1099$; $P_{\text{-overall}} = 0{\cdot}0432$, $P_{\text{-non-linear}} = 0{\cdot}1646$) intakes were linearly positively correlated with RTL.

Discussion

To our knowledge, this study was the first to explore the association between DAI and RTL. After adjusting for all covariates, DAI (continuous values) showed a positive correlation with RTL. DAI was analysed after categorising it in accordance with interquartile spacing. The results revealed a significant positive correlation between the highest quartile of DAI and RTL compared with the lowest quartile of DAI, that is, the RTL of a diet with a relatively higher intake of DAI was relatively longer. These results suggested a possible antiageing effect of antioxidant dietary metabolites. The results of restricted cubic spline analysis further indicated a linear positive correlation between DAI and RTL. In addition, positive correlations were found between vitamin C, vitamin E, Se, and Zn intakes and RTL.

Consumption of foods high in antioxidants can reduce oxidative stress and free radical damage to the body, thus helping to prevent and treat chronic diseases[8]. Animal experiments have shown that increasing the intake of dietary antioxidants slows down oxidative stress and apoptosis in the liver as well as in the brain, thereby improving psychomotor performance and slowing down the ageing process in aged mice[23,24]. A study investigating the relationship between the total antioxidant capacity of the diet and the risk of non-alcoholic fatty liver disease found that the intake of foods high in antioxidant capacity helped to prevent the onset and progression of non-alcoholic fatty liver disease[25], which has an increased prevalence with age and is considered to be an ageing-related disease[26]. The ageing process is regulated by telomere and mitochondrial function, which are structurally affected by oxidative stress. In a study by Rahmani *et al.*, total dietary antioxidant capacity was used as a proxy for total antioxidant capacity in the diet, which in turn was used to study the association between total antioxidant capacity and ulcerative colitis, and it was found that higher dietary total antioxidant capacity scores were associated with lower odds of ulcerative colitis [27], and that the rapid cellular renewal and oxidative damage observed in ulcerative colitis may accelerate telomere shortening[28]. In summary, intake of foods with higher antioxidant capacity will help to slow down telomere length shortening. The DAI has become a valid indicator for considering the antioxidant properties of a total diet at once[29]. Therefore, the present study used the measure recommended by Wright[8] to calculate the DAI of all the study subjects participating in this study and to investigate the association between DAI and LTL. Unfortunately, however, correlations between RTL and DAI components have only been shown in epidemiologic studies, including vitamin A[30], vitamin C[9,31,32], vitamin E[7,14], Mn[33,34], Se[10,11,35] and Zn[13,36,37]. Comparing the present study with previous studies demonstrated that the levels of vitamin A[31], vitamin C[9] and Zn[12] in the present study were slightly lower than the intermediate levels in other studies. However, the levels of DAI[38] and dietary vitamin E[39], Se[10], and Mn[33] in the present study were slightly higher than those of the corresponding indicators in other studies. A notable detail that while these differences exist, no definitive conclusions could be drawn. These differences may be influenced by various factors, such as different study samples, study design, geographic location and dietary habits. Therefore, further studies are needed to explore these associations in more depth. In the present study, a positive association was found between DAI and RTL, and a significant positive association was observed between the highest quartile of DAI and RTL compared with the lowest quartile of DAI. This finding suggested a high antioxidant dietary pattern, which may slow down the rate of telomere shortening and thus contribute to the prevention of ageing or certain diseases. This finding also validated the protective effect of antioxidants against oxidative damage to cells revealed in earlier studies[40] and could enhance the understanding of the significance of antioxidants.

Numerous studies showed that vitamins have antioxidant properties that neutralise free radical activity and reduce intracellular oxidative stress, thus helping to reduce the extent of oxidative damage to cells and thereby protecting telomere length and stability[32,41]. Kristopher *et al.*[31] found a positive correlation between maternal vitamin C intake and fetal telomere length in a cross-sectional study. Cai *et al.*[9] explored the relationship between dietary vitamin C intake and telomere length by using data from the National Health and Nutrition Examination Survey (NHANES) and found that dietary vitamin C intake was significantly associated with longer telomeres. In an Austrian study on stroke prevention, the plasma concentrations of lutein, zeaxanthin and vitamin C in normal older adults were shown to be associated with a longer telomere length[42]. By examining the relationship between multivitamin use and telomere length in women, Christine *et al.*[43] found that higher dietary intake of vitamin E was associated with longer telomere length in women who did not use multivitamins. Corina *et al.*[14]

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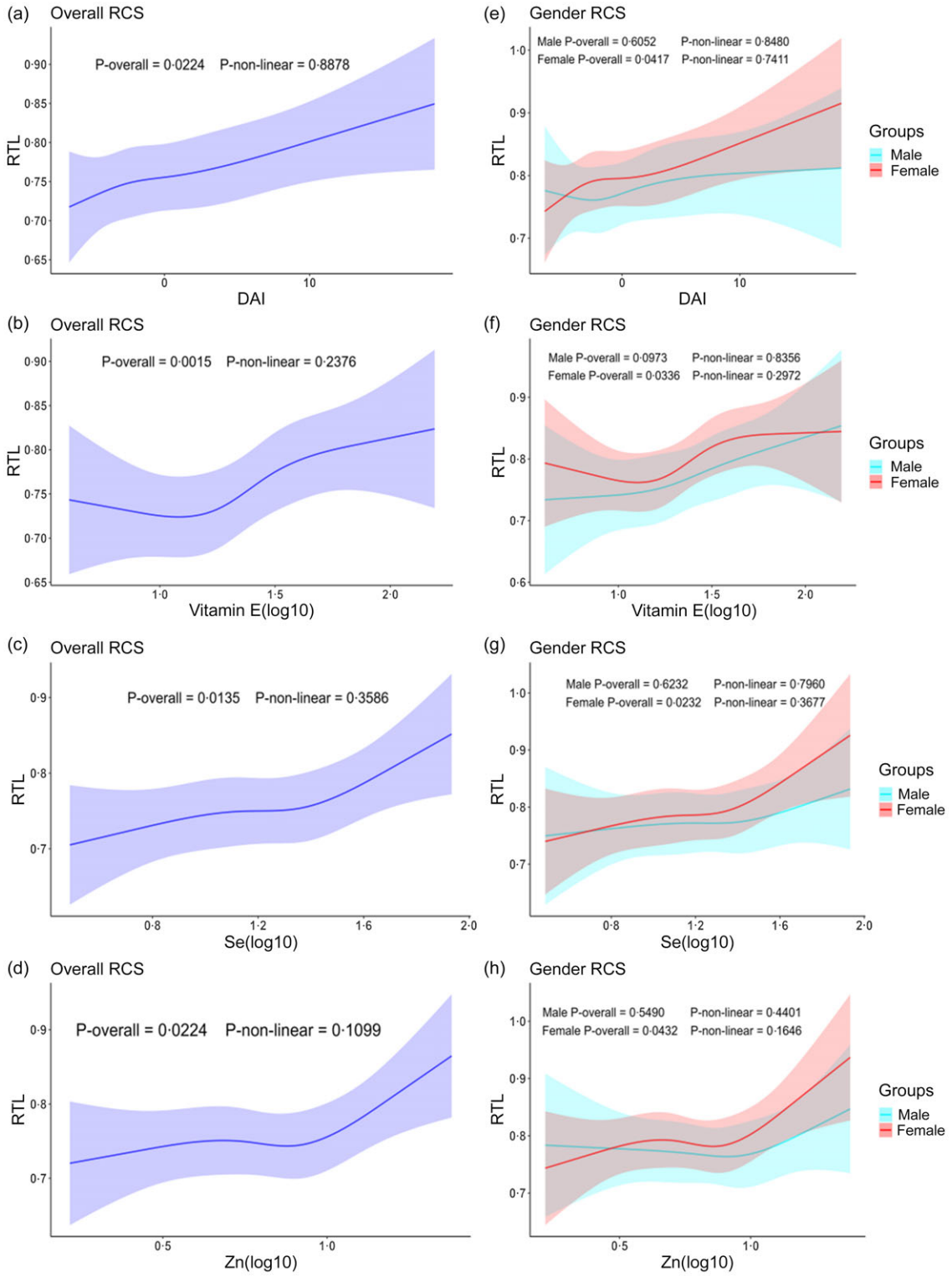

Fig. 1. Dose–response relationship between DAI and log10-transformed dietary vitamin E, selenium, and zinc intakes and RTL. The solid lines and colour ranges represent fitting curves and 95 % CI, respectively. Adjusted for sex, age, ethnicity, BMI, education level, smoking status, alcohol status, diabetes, hypertension and dyslipidaemia. a,b,c,d: both sexes; e,f,g,h: sex subgroups. DAI, dietary antioxidant index; RTL, relative telomere length; RCS, restricted cubic spline.

also demonstrated a longer TL corresponding to higher dietary vitamin E intake. We observed a positive correlation between dietary vitamin C and E intake and both RTL, which is consistent with the findings mentioned above. Vitamin A has a wide range of physiological roles, including immune function, vision, reproduction and cellular communication. Possible mechanisms by which vitamin A affects LTL include its role in immune function, inflammation, and regulation of gene expression and

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epigenetic modifications[44]. We observed no correlation between LTL and dietary vitamin A. This is consistent with the previously reported conclusion that plasma vitamin A concentrations were not associated with LTL in a study of 786 adults[42]. In contrast, a study in the USA based on the NHANES database found a positive correlation between serum vitamin A concentrations and TL[45]. Similarly, in a small-sample study of Japanese female university students by Yuki[30] *et al.*, it was observed that vitamin A intake and TL were positively associated with TL in young Japanese women. The differences in the associations present above may be due to differences in the size of the included study populations (this study: n 1656; other studies: $n \geq 4000$) and the selection of covariates.

Certain trace metal elements may play an influential role in the maintenance of telomere length, especially metals associated with antioxidant effects, which are involved in the activation of various antioxidant enzymes that help scavenge free radicals and reduce oxidative stress in cells[23,46]. Shu *et al.*[10] utilised the NHANES database to assess the relationship between dietary Se intake and telomere length in middle-aged and older adults in the USA and found that increased dietary Se intake was significantly and positively associated with longer telomere length. Gong *et al.*[11] revealed that dietary Se intake was significantly and positively associated with telomere length in a female population with diabetes in the USA. An exploratory study in Norway found that combined supplementation with Se and coenzyme Q10 significantly prevented leucocyte telomere abrasion in older adults[35]. Consistent with the above studies, dietary Se intake was observed to be positively associated with telomere length in the present study. Regarding the association between Zn and telomere length, Liu *et al.*[36] found that Zn helped maintain telomere length in hepatocyte L-02. Moreover, plasma Zn was determined to slow down telomere attrition[37]. The present study similarly showed that dietary Zn intake was significantly and positively associated with RTL. However, some divergent findings were observed regarding the association between Zn and telomere length. Elizabeth *et al.* found that plasma Zn concentration was negatively correlated with telomere length in children[13]. The potential mechanisms underlying the association between Mn and telomere length remain unclear. Mn is an essential component and functions as a cofactor for some antioxidants, such as manganese superoxide dismutase, which plays a crucial role in antioxidant defence[47]. Animal experiments have shown that female rats with higher levels of Mn oxidoreductase have longer telomeres than male rats[48], and high doses of oral Mn resulted in increased glutathione levels[49]. A study of 842 Chinese workers in a coke oven plant by Bai *et al.*[33] found a significant positive correlation between plasma Mn and telomere length. A birth cohort study of 762 mother–neonate pairs in Wuhan, China, reported that the plasma Mn levels in mothers in mid-pregnancy were positively associated with telomere length in newborns[34]. The above findings suggest that Mn has a protective effect on telomere length and the mechanism of this action may be due to its antioxidant potential. It is well known that dietary intake of Mn affects serum levels of Mn. Unfortunately, however, no correlation between dietary Mn intake and telomere length was observed in our study. These conflicting results may be influenced by the different study populations and sources of metallic elements (plasma, urine and diet). Therefore, they need to be further confirmed in prospective studies with larger sample sizes, in different populations, and with different sources of metallic elements.

This study found a positive correlation between DAI and RTL, along with sex differences. A significant positive correlation was also observed between DAI and RTL in females but not in males. Some foreign animal experimental studies showed that oestrogen can protect rats from oxidative stress by inducing antioxidant and longevity-related genes to resist ageing[50]. Higher oestrogen levels may be hypothesised to enhance the antioxidant capacity of cells and work together with dietary antioxidant elements to protect telomeres. Therefore, the association of sex differences between DAI and RTL observed in the present study may be due to the higher oestrogen levels in women than in men, which enhance the antioxidant capacity of cells. The protective effect of antioxidant dietary components on telomeres may vary depending on the difference in oestrogen levels, which may be one of the reasons that no association was observed between DAI and its constituent antioxidant dietary elements and RTL in the males.

This study has several strengths. First, it is the first study to assess the relationship between DAI and RTL in a rural Chinese population. Second, restricted cubic spline was used to characterise the relationship of DAI and its six components with RTL. The results showed a positive correlation between DAI and RTL. However, our study still has some limitations. Firstly, it is a cross-sectional study and, therefore, cannot provide evidence of causality or temporal relationships. Secondly, we did not explore the relationship between serum levels of dietary antioxidants and telomere length. Lastly, our survey lacked important confounding factors such as the use of nutritional supplements, medication usage and physical activity status. These confounding factors are necessary but were not considered in our survey. Similar future studies can provide a deeper understanding of the biological mechanisms by explaining the relationship between serum antioxidant levels and telomere length, as well as better incorporating the confounding factors that require adjustment.

Conclusion

In conclusion, the results of this study confirm the existence of an association between DAI and RTL, but with sex differences. There was a significant positive correlation between DAI and RTL in women, but this correlation was not evident in the male population. This suggests that an antioxidant-rich diet may help maintain telomere length and potentially slow down the ageing process in women. Therefore, this study encourages the female population to try consuming foods rich in dietary antioxidants such as vitamin E, Se and Zn to prolong telomere length and resist ageing. These findings emphasise the importance of a balanced diet and adequate intake of dietary antioxidants to support overall health and slow down the ageing process.

However, most of the previous studies were cross-sectional studies, and more cohort studies and randomised controlled

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trials can be conducted in the future to further explain the physiological mechanisms associated with the relationship between dietary antioxidants and telomere length.

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L. Z.: writing – original draft and writing – review and editing. W. J.: writing – original draft and writing – review and editing. T. Z.: writing – original draft and writing – review and editing. Q. L.: investigation and data curation. J. C.: investigation and data curation. L. L.: methodology and formal analysis. K. T.: methodology and formal analysis. Q. G.: investigation and data curation. S. W.: investigation and data curation. J. R.: investigation and data curation. Y. L.: investigation. Y. J. L.: investigation and data curation. J. C.: investigation and data curation. L. Q.: methodology and formal analysis. C. H.: methodology and formal analysis. X. W.: methodology and formal analysis. Y. L.: conceptualisation. Z. Z.: supervision and project administration. J. Q.: conceptualisation. All authors have read and approved the final manuscript.

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