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α-Klotho: the hidden link between dietary inflammatory index and accelerated ageing

Ruiqiang Li[1], Baijing Zhou[1], Xueqing Deng[1], Wenbo Tian[1], Yingyue Huang[1], Jiao Wang[1] and Lin Xu[1,2,3]*

[1]*School of Public Health, Sun Yat-sen University, Guangzhou, People's Republic of China*
[2]*School of Public Health, The University of Hong Kong, Pokfulam, Hong Kong*
[3]*Institute of Applied Health Research, University of Birmingham, Birmingham, UK*

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Abstract

Recent studies suggest an association between greater dietary inflammatory index (DII) and higher biological ageing. As α-Klotho has been considered as a longevity protein, we examined whether α-Klotho plays a role in the association between DII and ageing. We included 3054 participants from the National Health and Nutrition Examination Survey. The associations of DII with biological and phenotypic age were assessed by multivariable linear regression, and the mediating role of α-Klotho was evaluated by mediation analyses. Participants' mean age was 58·0 years (SD 11·0), with a median DII score of 1·85 and interquartile range from 0·44 to 2·79. After adjusting for age, sex, race/ethnicity, BMI, education, marital status, poverty income ratio, serum cotinine, alcohol, physical activity, a higher DII was associated with both older biological age and phenotypic age, with per DII score increment being associated with a 1·01-year increase in biological age (1·01 (95 % CI: 1·005, 1·02)) and 1·01-year increase in phenotypic age (1·01 (1·001, 1·02)). Negative associations of DII with α-Klotho ($\beta = -1{\cdot}01$ pg/ml, 95 % CI: −1·02, −1·006) and α-Klotho with biological age ($\beta = -1{\cdot}07$ years, 95 % CI: −1·13, −1·02) and phenotypic age ($\beta = -1{\cdot}03$ years, 95 % CI: −1·05, −1·01) were found. Furthermore, α-Klotho mediated 10·13 % ($P < 0{\cdot}001$) and 9·61 % ($P < 0{\cdot}001$) of the association of DII with biological and phenotypic age, respectively. Higher DII was associated with older biological and phenotypic age, and the potential detrimental effects could be partly mediated through α-Klotho.

Keywords: **Dietary inflammatory index: α-Klotho: Biological age: Phenotypic age**

Chronological age is a commonly used indicator of ageing. However, it does not fully reflect an individual's functional capacity, health status, or mortality. Biological ageing refers to the process in which organisms gradually lose physiological function and structural integrity within their lifespan[1]. It is a main risk factors for many non-communicable chronic diseases, functional decline and mortality[2]. Phenotypic age serves as a quantifiable indicator of an individual's physiological or health status. There is compelling evidence regarding its positive association with the susceptibility to chronic conditions such as CVD and diabetes[3,4]. Both biological age and phenotypic age are considered to provide a more comprehensive understanding of physical condition and can serve as indicators of the ageing speed[4,5].

Elevated inflammation, which might be affected by various factors including diet, is a significant marker during the ageing process[6,7]. Dietary inflammatory index (DII) is a tool developed to assess the overall inflammatory potential of diet[8]. Dietary patterns that lead to systemic inflammation were associated with chronic diseases such as CVD[9], diabetes[10] and certain cancers[11], potentially resulting in a higher biological age[12]. A recent study based on the 2007–2016 National Health and Nutrition Examination Survey (NHANES) data showed a negative a dose–response relation between DII and serum Klotho concentrations[13], indicating adhering to an anti-inflammatory dietary pattern has potential beneficial effects on ageing.

α-Klotho is a membrane-bound protein encoded by the Klotho gene and serves as an essential antiaging protein[14]. Cytokines, such as tumor necrosis factor-α(TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6), produced during the inflammatory process, as well as reactive oxygen and nitrogen species, may suppress α-Klotho gene expression, leading to a decrease in α-Klotho levels[15]. Inflammatory signalling pathways, such as nuclear factor kappa B (NF-κB) and janus kinase/signal transducer and activator of transcription, might also directly or indirectly reduce the expression of α-Klotho[16]. Therefore, we hypothesised that individuals adhering to anti-inflammation diet

Abbreviations: DII, dietary inflammatory index; NHANES, national health and nutrition examination survey.

* **Corresponding author:** Lin Xu, email xulin27@mail.sysu.edu.cn

would have lower biological age and phenotypic age, and the potential beneficial effects might be mediated through α-Klotho. To investigate this, we analysed data on 3054 participants from the NHANES 2007–2010 wave.

Materials and methods

Study population

Participants of the current study were from the NHANES, which is one of the most authoritative health survey programs in the USA, led by the Centers for Disease Control and Prevention. NHANES adopts a complex multistage sampling design, selecting representative samples from various states across the USA every year, covering populations of all ages, races, sex and regions[17]. The survey includes face-to-face health interviews and health examinations, covering multiple aspects such as physiological measurements, nutrition surveys. All participants provided written consent before the survey. The research protocols were approved by the Research Ethics Review Committee at the National Center for Health Statistics[18]. The study used population data from the 2007–2008 to 2009–2010 cycles. We excluded participants with missing data on the variables of interest such as α-Klotho, age, C-reactive protein and glycated Hb, resulting in a total of 3054 participants (online Supplementary Fig. 1).

Dietary inflammatory index

As per methods used in previous studies[8,19], we used twenty-eight of the forty-five food parameters to calculate the DII scores, including protein, carbohydrates, fibre, total fat, saturated fat acids, MUFA, PUFA, cholesterol, vitamins A, C, D and E, Fe, Mg, Se, Zn, alcohol, riboflavin, thiamin, niacin, folate, vitamins B_{12}, B_6, caffeine, beta-carotene, *n*-3 and *n*-6 PUFA and energy.

The DII was calculated using the following equations:

$$Zscore = [(\text{daily mean intake} - \text{global daily mean intake})/\text{standard deviation}]$$

$$Zscore^1 = Zscore \rightarrow (\text{converted to a percentile score}) \times 2 - 1$$

$$\text{DII} = \sum Zscore^1 \times \text{the inflammatory effect score of each dietary component}[20]$$

Measurement of α-Klotho

Serum samples were received on dry ice and inspected by laboratory reception personnel to ensure the integrity of each package. These samples were then scanned, and the scanned data were cross-referenced with the electronic manifest before being logged into the laboratory information system. All serum samples were stored in a –80°C freezer. Soluble Klotho levels were measured using commercial enzyme-linked immunosorbent assay kits produced by Immunological and Biochemical Laboratory international in Japan. These kits demonstrated a sensitivity of 6 pg/ml. Each study sample underwent repeated measurements, with the Klotho level being determined by averaging the two readings[21]. The precision of the Klotho assay was evaluated by determining the intra-assay and inter-assay coefficients of variation for both recombinant and human samples. The intra-assay precision, which reflects the repeatability within a single assay run, was found to be 3·2 % and 3·9 % for the recombinant Klotho samples and 2·3 % and 3·3 % for the human samples. This indicates a high level of repeatability in the measurements taken during the same assay run. Furthermore, the inter-assay precision, measuring the consistency across different assay runs on separate days, exhibited coefficients of variation values of 2·8 % and 3·5 % for the recombinant samples and 3·8 % and 3·4 % for the human samples. These values are within the acceptable range and demonstrate the stability of the assay across various testing conditions.

Assessment of biological ageing

We used the Klemera–Doubal method algorithm developed by Klaëmmera and Doubal in 2006 to evaluate biological age[22]. Initially, the Klemera–Doubal method algorithm was trained on data from the NHANES in a Caucasian population. The algorithm utilises a combination of eight biomarkers, such as C-reactive protein, serum creatinine, glycated Hb, serum albumin, serum total cholesterol, serum urea nitrogen, serum alkaline phosphatase and systolic blood pressure. Biological age was calculated using the R package (https://github.com/dayoonkwon/BioAge). Furthermore, phenotypic age was assessed based on nine different biomarkers including chronological age, albumin levels, creatinine levels glucose levels, C-reactive protein levels lymphocyte percentage mean cell volume red cell distribution width alkaline phosphatase levels and white blood cell count[23].

$$\text{Phenotypic age} = 141.50 + \frac{\text{Ln}\left[-0.00553 \times \text{Ln}\left(\exp\left(\frac{-1.51714 \times \exp(xb)}{0.0076927}\right)\right)\right]}{0.09165},$$

$xb = -19{\cdot}907 - 0{\cdot}0336 \times \text{Albumin} + 0{\cdot}0095 \times \text{Creatinine} + 0{\cdot}1953 \times \text{Glucose} + 0{\cdot}0954 \times \text{LnCRP} - 0{\cdot}0120 \times \text{Lymphocyte Percent} + 0{\cdot}0268 \times \text{Mean Cell Volume} + 0{\cdot}3306 \times \text{Red Cell Distribution Width} + 0{\cdot}00188 \times \text{Alkaline Phosphatase} + 0{\cdot}0554 \times \text{White Blood Cell Count} + 0{\cdot}0804 \times \text{Chronological Age}$[23]. The specific algorithms and codes for Klemera–Doubal method-biological age and phenotypic age have been published elsewhere[24].

Covariates

Based on literature[25,26] and a directed acyclic graph (online Supplementary Fig. 2), we constructed a multivariable model that considered potential confounders including age, sex, race/ethnicity, BMI, education level, marital status, physical activity, serum cotinine level, poverty income ratio and alcohol intake. BMI was categorised into three groups: underweight/normal (less than 25 kg/m^2), overweight (25–29 kg/m^2) and obesity (≥30 kg/m^2). Education level was categorised as follows: less than 9th grade, 9th–11th grade, high school graduate/general educational development or equivalent, some college/associate degree and college graduate or higher. Marital status included married/living with a partner, widowed/divorced and separated/never married. Alcohol intake was determined based on the question 'Have you had at least twelve drinks of any kind of alcoholic beverage in your entire life?' The poverty income ratio is the ratio of family income to the poverty threshold. The poverty threshold is a standard used by the USA government to

determine if a family is in poverty, based on family size and income level. If the family income is below the poverty threshold, the family is considered to be in poverty. Physical activity was evaluated using a physical activity questionnaire, which included questions such as 'Have you done any vigorous-intensity activities in the past 30 d?' and 'Have you done any moderate-intensity activities in the past 30 d?'.

Statistical analysis

We used sub-sample population weights to yield estimations representative of the entire USA population[27]. Given that the distributions of α-Klotho, biological age and phenotypic age indicators typically exhibit right-skewness, we applied a natural logarithm transformation (ln transformation) to enhance the normality of descriptive and regression analyses. Continuous variables were presented as mean ± SE, while categorical variables were displayed as *n* (%). Differences in DII by demographic characteristics of participants were assessed using χ^2 tests and nonparametric tests.

Multivariable linear regression was used to examine the associations of DII with biological and phenotypic age. DII was analysed as both a continuous and categorical variable by quartiles. To further investigate the impact of covariates on this association, hierarchy models (i.e. crude model, model 1 with adjustment for age, sex, race/ethnicity and model 2 with additional adjustment for BMI, education, marital status, poverty income ratio, serum cotinine, alcohol and physical activity) were used. Multiple testing in regression models was controlled using false discovery rate. We also tested for interaction between DII and sex and performed sex–stratified analysis if significant interaction was found. Furthermore, we employed generalised additive models to examine the association between DII and α-Klotho, as well as markers of biological ageing.

In addition, we conducted mediation analyses to examine the indirect effect of α-Klotho (mediator) on the DII–biological ageing association, yielding the proportion of mediation. Quasi-Bayesian Monte Carlo methods with 1000 simulations were used to calculate the mediating effects of α-Klotho[23]. Direct effect quantifies the impact of DII on biological age and phenotypic age without mediators. Indirect effect indicates the effects of DII on biological age and phenotypic age through mediators.

Results

Demographic characteristics

The mean (SD) age of 3054 participants was 58·04 (11·02) years. 49·21 % were men. The mean (SD) values for α-Klotho, biological age and phenotypic age were 846·82 (304·1) pg/ml, 45·2 (18·2) years and 51·7 (13·8) years, respectively. Participants in the fourth quartile (Q4) group, which exhibited the highest level of pro-inflammatory diet, had lower incomes, a high proportion of women, smokers and drinkers compared with participants in the first quartile (Q1) group characterised by the most anti-inflammatory diet (*P* from 0·001 to 0·049) (Table 1).

Association between dietary inflammatory index and biological and phenotypic age

After adjusting for age, sex, race/ethnicity, BMI, education, marital status, poverty income ratio, serum cotinine, alcohol and physical activity in model 2, the highest DII quartile (*v.* to Q1) was significantly associated with increased biological age (1·01 (95 % CI: 1·005, 1·02) years) and phenotypic age (1·01 (95 % CI: 1·001, 1·02) years) (both $P_{\text{for trend}}<0·05$) (Table 2). After similar adjustment, we found a significant inverse association between DII and α-Klotho ($\beta = -1·01$, 95 % CI: −1·02, −1·006) (online Supplementary Table 1). In addition, higher α-Klotho was associated with lower biological and phenotypic age ($\beta = -1·07$, 95 % CI: −1·13, −1·02 and −1·03, 95 % CI: −1·05, −1·01, respectively) (online Supplementary Table 2). α-Klotho mediated the associations of DII with biological and phenotypic age significantly, with the mediation proportions being 10·13 % and 9·61 % (both *P* values < 0·05), respectively (Fig. 1). Sensitivity analyses generally showed consistent results. DII was positively associated with biological and phenotypic age, whereas negatively associated with α-Klotho levels (online Supplementary Fig. 3).

Sensitivity analysis

In the sensitivity analysis, we enhanced the reliability of our results by excluding individuals with autoimmune disorders, leading to outcomes consistent with our main findings (online Supplementary Table 3). Additionally, a detailed summary of the consumption patterns for the twenty-eight food variables under investigation is available in online Supplementary Table 4. Furthermore, to ensure the comparability of our study cohort with the NHANES dataset, we conducted a thorough demographic comparison, which revealed no significant differences (*P* from 0·06 to 0·51) (online Supplementary Table 5).

Discussion

Our study, for the first time, showed a positive association between DII scores and accelerated biological and phenotypic ageing and quantified the mediating role of α-Klotho in this association. Our findings offer a foundation for future research and interventions aimed at promoting healthier ageing through dietary modifications and a deeper understanding of the molecular mechanisms involving α-Klotho.

As an emerging tool for assessing dietary inflammation, higher DII scores were associated with greater oxidative stress, abnormal cell cycle and DNA damage, which may subsequently lead to acceleration in the ageing process[28–30]. Our results were consistent with previous findings showing a significant positive association between DII scores and both biological age as well as phenotypic age[31,32], indicating a potential link between an anti-inflammatory dietary pattern and healthy ageing. A previous study indicated that a high DII, representing maximum proinflammatory values, was associated with an almost twofold increased risk of accelerated telomere shortening compared with the minimum anti-inflammatory DII values[33].

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Table 1. Basic characteristics of participants

Characteristics	All (*n* 3054)		Dietary inflammatory index (DII)								
			Q1 (*n* 770) (–5·19, 0·44)		Q2 (*n* 766) (0·44, 1·85)		Q3 (*n* 766) (1·85, 2·79)		Q4 (*n* 752) (2,79, 4·23)		
	Mean or *n*	SD or %	Mean or *n*	SD or %	Mean or *n*	SD or %	Mean or *n*	SD or %	Mean or *n*	SD or %	*P* Value
Age (years, Mean, SD)	58·0	11·0	58·3	11·0	58·4	11·1	57·6	10·8	57·8	11·2	0·49
Age (years, *n* (%))											0·61
40–60	1724	56·5	444	57·7	418	54·6	439	57·3	423	56·3	
>60	1330	43·5	326	42·3	348	45·4	327	42·7	329	43·8	
Sex (*n* (%))											**<0·001**
Men	1503	49·2	438	56·9	392	51·2	358	46·7	315	41·9	
Women	1551	50·8	332	43·1	374	48·8	408	53·3	437	58·1	
Race/ethnicity (*n* (%))											0·65
Mexican American	540	17·7	135	17·5	141	18·4	145	18·9	119	15·8	
Other Hispanic	339	11·1	83	10·8	87	11·4	78	10·2	91	12·1	
Non-Hispanic white	1540	50·4	392	50·9	389	50·8	395	51·6	364	48·4	
Non-Hispanic black	540	17·7	134	17·4	129	16·8	125	16·3	152	20·2	
Other/multi-racial	95	3·1	26	3·4	20	2·6	23	3·0	26	3·5	
Education (*n* (%))											**<0·001**
Less than 9th grade	447	14·6	90	11·7	100	13·1	107	14·0	150	19·9	
9th–11th grade	536	17·6	110	14·3	124	16·2	131	17·1	171	22·7	
High school grad/GED or equivalent	700	22·9	162	21·0	158	20·6	209	27·3	171	22·7	
College or AA degree	780	25·5	210	27·3	212	27·7	186	24·3	172	22·9	
College grad or above	591	19·4	198	25·7	172	22·4	133	17·3	88	11·8	
Marital status (*n* (%))											**0·001**
Married/living with partner	1997	65·4	512	66·5	534	69·7	509	66·4	442	58·8	
Widowed/divorced/separated	854	27·9	204	26·5	190	24·8	206	26·9	254	33·8	
Single/never married	203	6·7	54	7·0	42	5·5	51	6·7	56	7·4	
PIR (Mean, SD)	2·6	1·6	2·8	1·6	2·9	1·6	2·6	1·6	2·2	1·5	**<0·001**
Physical activity (*n* (%))											**0·049**
Low	1850	60·6	442	57·4	454	59·3	473	61·7	481	64·0	
High	1204	39·4	328	42·6	312	40·7	293	38·3	271	36·0	
Alcohol (*n* (%))											**0·04**
No	2167	71·0	562	73·0	563	73·5	531	69·3	511	68·0	
Yes	887	29·0	208	27·0	203	26·5	235	30·7	241	32·0	
BMI (kg/m^2, Mean, SD)	29·7	6·4	29·6	6·3	29·5	6·2	29·7	6·4	30·0	6·9	0·46
BMI category (kg/m^2, *n* (%))											0·73
Underweight/normal weight	679	22·2	171	22·2	174	22·7	164	21·4	170	22·6	
Overweight	1150	37·7	291	37·8	287	37·5	306	39·9	266	35·4	
Obese	1225	40·1	308	40·0	305	39·8	296	38·6	316	42·0	
Serum cotinine (ng/ml, *n* (%))											**<0·001**
<0·02	1024	33·5	295	38·3	298	38·9	261	34·1	170	22·6	
0·02–0·28	1012	33·1	271	35·2	250	32·6	260	33·9	231	30·7	
>0·28	1018	33·4	204	26·5	218	28·5	245	32·0	351	46·7	
α-Klotho (pg/ml, Mean, SD)	846·8	304·1	865·8	296·8	839·4	294·5	841·6	302·9	840·3	321·8	0·07
Biological age (years, Mean, SD)	45·2	18·2	43·5	16·6	44·5	19·0	44·6	18·3	48·2	18·6	**<0·001**
Phenotypic age (years, mean, SD)	51·7	13·8	51·4	13·3	51·3	13·4	51·9	13·6	53·3	14·7	**0·03**

PIR, poverty income ratio; Q, quartile.
Continuous variables were presented as mean±standard deviation (SD). Categorical variables were presented as *n* (%). Values in bold font are statistically significant ($P < 0.05$).

Table 2. Association of DII with biological age and phenotypic age

		Crude model		Model 1*		Model 2†	
Outcome	DII (*median (range)*)	*β*	95 % CI	*β*	95 % CI	*β*	95 % CI
Biological age, years	Continuous	**0·02**·	**0·01, 0·03**	**0·02**	**0·01, 0·03**	**0·01**	**0·005, 0·02**
	Category						
	Q1 (–0·87, (<0·44))	Reference		Reference		Reference	
	Q2 (1·23, (0·44–1·85))	–0·02	–0·08, 0·04	–0·01	–0·05, 0·04	–0·01	–0·06, 0·03
	Q3 (2·36, (1·85–2·79))	–0·01	–0·08, 0·06	0·01	–0·05, 0·06	–0·01	–0·06, 0·04
	Q4 (3·23, (>2·79))	0·11	0·05, 0·17	0·11	0·06, 0·16	0·07	0·02, 0·12
P for trend		**<0·001**		**<0·001**		**0·020**	
Phenotypic age, years	Continuous	0·003	–0·004, 0·01	**0·01**	**0·005, 0·013**	**0·01**	**0·004, 0·015**
	Category						
	Q1 (–0·87, (<0·44))	Reference		Reference		Reference	
	Q2 (1·23, (0·44–1·85))	–0·01	–0·05, 0·02	0·001	–0·02, 0·02	–0·002	–0·01, 0·01
	Q3 (2·36, (1·85–2·79))	–0·01	–0·05, 0·02	0·01	–0·01, 0·03	0·004	–0·01, 0·02
	Q4 (3·23, (>2·79))	0·03	–0·01, 0·06	0·06	0·04, 0·08	0·04	0·02, 0·06
P for trend		0·740		**<0·001**		**0·002**	

DII, dietary inflammatory index; FDR, false discovery rate; PIR, poverty income ratio.
* Model 1: adjusted for age, sex and race/ethnicity.
† Model 2: additionally adjusted for BMI, education, marital status, PIR, serum cotinine, alcohol and physical activity.
A natural logarithmic conversion was performed for biological age, phenotypic age.
β: regression coefficients. Values in bold font are statistically significant ($P < 0.05$). All $P_{\text{for trend}}$ were FDR-adjusted.

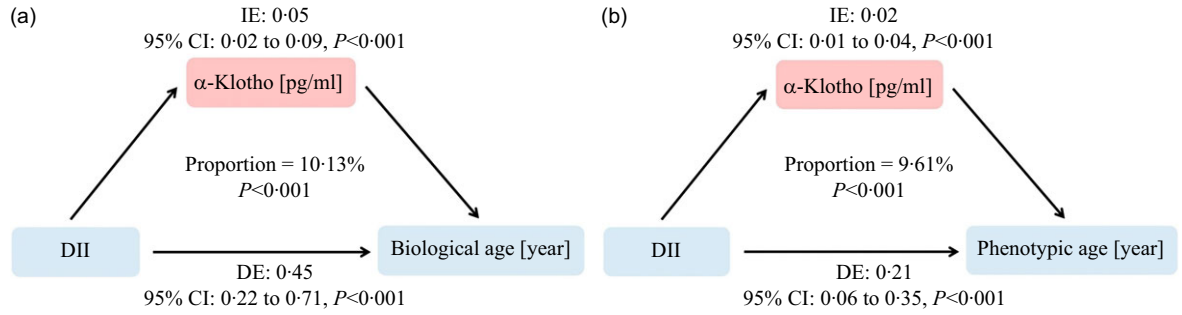

Fig. 1. Proportion of *α*-Klotho-mediated association of DII with biological age (a), phenotypic age (b). Note: (1) Models were adjusted for age, sex, race/ethnicity, BMI, education, marital status, PIR, serum cotinine, alcohol and physical activity. (2DE, direct effect; DII, dietary inflammatory index; IE, indirect effect; PIR, poverty income ratio.

Furthermore, higher DII scores were negatively associated with magnetic resonance imaging markers of brain ageing, such as total grey matter volume and total brain volume[34], suggesting that individuals adopting highly proinflammatory diets may be at risk of brain ageing. In addition, elevated DII scores were positively associated with frailty and an increased risk of mortality within 8 years[35], emphasising the potential impact of DII on overall lifespan. Notably, the association of DII with mortality risk became stronger in those with lower physical activity and high pro-inflammatory food intake, suggesting that lower levels of physical activity may potentiate the accelerated effects of proinflammatory diets on biological ageing[36]. The above evidence suggests that the DII plays a critical role in influencing overall ageing process. Nevertheless, no study to date explored the potential mechanisms underlying the association between DII and biological age using quantitative methods. Our study thus adds to the literature by using mediation analysis to quantify the potential mediating effect through *α*-Klotho. As the mediation proportion via *α*-Klotho was moderate (i.e. 10 %), further studies exploring the other underlying mechanisms are warranted.

Additionally, we found substantially mediating effects of *α*-Klotho on the association between DII and biological/phenotypic ageing. *α*-Klotho is a membrane protein with functions of anti-inflammatory, antioxidant and anti-ageing[31]. Dietary inflammation may inhibit *α*-Klotho expression in the kidneys[37]. Previous studies showed that *α*-Klotho might suppress the production of inflammatory cytokines such as TNF-*α* and IL-6[38]. Moreover, *α*-Klotho may regulate oxidative stress, maintaining cellular stability and slowing ageing[39], as well as gut microbiota, which in turn influences gut health and inflammatory reactions[40]. Additionally, intestinal inflammation could affect the immune and inflammatory responses in the central nervous system through the gut–brain axis, potentially impacting overall health and the ageing process[39,41,42]. Therefore, *α*-Klotho may mediate the association between dietary inflammation and physiological well-being[43].

Our study had several limitations. First, the causal relation between DII and biological/phenotypic ageing could not be established in the current cross-section study. Randomised controlled trials examining the effects of anti-inflammatory dietary patterns on biological/phenotypic age are needed for confirmation. Second, as our study focused on participants aged 40–79 years in the USA, the results might not directly apply to other populations. Another limitation of our study was the use of a reduced set of dietary parameters for calculating the DII. While the DII ideally encompasses forty-five food parameters to

provide a comprehensive measure of diet-related inflammation, our analysis was confined to twenty-eight parameters due to the data availability constraints within the NHANES dataset. Future studies with access to more extensive dietary data could validate and potentially refine our findings, contributing further to our understanding of diet's role in biological and phenotypic ageing. Finally, although we adjusted for various confounding variables, we could not rule out residual confounders, such as sex hormonal and inflammation, that might potentially influence the associations of α-Klotho with biological age or phenotypic age.

Conclusion

A higher DII was associated with older biological and phenotypic age, and the potential detrimental effects could be partly mediated through α-Klotho. Further studies such as randomised controlled trial or Mendelian randomisation are warranted to confirm the causal associations among DII, α-Klotho and the aspects of biological and phenotypic ageing.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The datasets generated and/or analysed during the current study are available in the (NHANES) repository, (https://www.cdc.gov/nchs/nhanes/index.htm).

The study involving human participants underwent a rigorous evaluation and obtained necessary approval from both the National Center for Health Statistics and the Institutional Review Board. Prior to their participation in this research, all patients/participants provided written consent after receiving comprehensive information about the purpose and procedures.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114524001417

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