



Full Length Article

Dietary advanced glycation end-products (dAGEs) intake and its relation to sarcopenia and frailty – The Rotterdam Study



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ABSTRACT

Studies on mice have shown a relationship between dietary intake of advanced glycation end-products (dAGEs) and deterioration of musculoskeletal health, but human studies are absent.

We investigated the relationship between dietary intake of carboxymethyllysine (dCML) – an AGE prototype – and risk of sarcopenia at baseline and after 5 years of follow-up and a single evaluation of physical frailty in participants from the population-based Rotterdam Study.

Appendicular lean mass (ALM) was obtained using insight dual-energy X-ray absorptiometry and hand grip strength (HGS) using a hydraulic hand dynamometer. Subjects with both low ALM and weak HGS were classified as having sarcopenia. Frailty (yes/no) was defined by presence of ≥ 3 and pre-frailty by presence of 1 or 2 components namely, exhaustion, weakness, slowness, weight loss or low physical activity. dCML was calculated using a food frequency questionnaire and dAGE databases. Logistic regression analysis was used to evaluate the odds of physical frailty and prevalent sarcopenia at baseline and follow-up and incident sarcopenia.

2782 participants with an age 66.4 ± 9.9 years and dCML intake 3.3 ± 1.3 mg/day, had data on sarcopenia at both time points. Of whom 84 had sarcopenia at baseline and 73 developed sarcopenia at follow-up. We observed an association of one SD increase in dCML intake with prevalent sarcopenia at baseline [odds ratio, OR = 1.27 (1.01–1.59)] and no association of dCML with incident sarcopenia at 5-year follow-up [OR = 1.12 (0.86–1.44)]. For frailty we analyzed 3577 participants, of whom 1972 were pre-frail and 158 were frail. We observed no association of dCML with either pre-frailty [OR = 0.99 (0.91–1.07)] or frailty [OR = 1.01 (0.83–1.22)] when non-frail subjects were used as reference.

Our results show an association of dAGEs with sarcopenia cross-sectionally but not longitudinally where inconclusive findings are observed possibly due to a very low incidence of sarcopenia. There was no association with frailty cross-sectionally.

1. Introduction

The quality of diet has been linked to the risk of both sarcopenia and frailty – two evolving and overlapping concepts in geriatrics [1]. Sarcopenia – muscle insufficiency – is considered to be a precursor or a physical component of frailty. Frailty is defined as a clinical syndrome of increased vulnerability due to diminished strength, endurance, and

reduced physiological function leading to increased dependency [2]. Consumption of Mediterranean diet - a diet rich in whole grain, fruits, vegetables, nuts and low in meat, added sugars – has been shown to reduce the risk of sarcopenia and frailty [3–5]. However, the consumption of processed foods, red meat and saturated fatty acids has been associated with increased risk of frailty and sarcopenia [5–7]. There is growing evidence that western diet rich in sugars and meat contains

Abbreviations: CML, carboxymethyllysine; CEL, carboxyethyllysine; dAGEs, dietary advanced glycation end-products; MGH1, methylglyoxal-derived hydroimidazolone; DQS, Dietary Quality Score; FFQ, food frequency questionnaire; HGS, hand grip strength; ALM, appendicular lean mass; UPLC-MS/MS, ultra performance liquid chromatography - tandem mass spectrometry; ELISA, enzyme linked immunosorbent assay.

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higher levels of advanced glycation end products (AGEs) [8,9]. AGEs comprise a cluster of heterogeneous compounds formed spontaneously when reducing sugars react with an amino group in a so called Maillard reaction both in vivo and in vitro [10]. Accumulation of AGEs in tissues such as blood vessels, bone, muscles, joints has been associated not only with reduced mechanical properties but also to a state of chronic low grade inflammation characteristic of age-related diseases such as cardiovascular disease, osteoporosis, sarcopenia [11,12].

Endogenously, hyperglycemia and reduced renal clearance accelerate AGEs accumulation besides physiological aging [13,14]. Exogenously, smoking and diet are the sources of AGEs [15]. The rate of formation of AGEs in foods is markedly increased during cooking on dry heat at high temperatures and during food processing [16]. An average western diet consists of 75 mg of AGEs per day [17], of which, Carboxymethyllysine (CML) – a prototype AGE – constitutes a major proportion. The absorption of dietary AGEs (dAGEs) is possible when they are either in free form or as small dipeptide molecules while protein bound AGEs act as substrates for gut microbiota altering their composition and induce release of inflammatory mediators into the circulation [17]. In this way, dAGEs consumption may contribute both directly and indirectly to increased inflammatory stress across the tissues promoting chronic diseases [18,19].

Multiple studies using mice models consuming a high fat, high sugar diet contributing to higher AGEs showed negative impact on muscle health [20–22]. Effects observed in skeletal muscle tissue were increased AGEs and lipid accumulation, alteration in fiber type composition and suppression of antioxidant system leading to oxidative stress. In addition, human intervention studies showed a decrease in inflammation markers after consuming a low AGE diet [23]. Although these studies point to a role of dietary AGEs or their precursors in the impairment of muscle function and chronic inflammation, the role of dAGEs intake in humans with sarcopenia and frailty has never been studied.

The aim of our study was to investigate whether intake of dAGEs, estimated with the help of a food frequency questionnaire and primarily a database reporting AGEs content in 190 common Dutch foods, is associated with risk of sarcopenia and frailty in middle age and elderly men and women from the general population.

2. Methods

2.1. Study participants

Participants were included from the Rotterdam Study (RS), a population-based prospective cohort study conducted in the Ommoord district of Rotterdam, the Netherlands. For the detailed design of the study, we refer to a recent update in 2020 [24]. Briefly, the participants were included at three different points in time, namely in 1990, 2000 and 2006 and named in ascending order as RS-I, RS-II and RS-III sub-cohorts based on the year of inclusion, respectively. For RS-I and RS-II, individuals ≥ 55 years and for RS-III, those ≥ 45 years were invited for participation. Participants were followed regularly every 4–6 years. The Rotterdam Study was approved by the institutional review board (Medical Ethics Committee) of Erasmus University Medical Center and by the review board of The Netherlands Ministry of Health, Welfare and Sports. All participants in the present analysis provided written informed consent.

At baseline, 5506 participants had FFQ data on dAGEs after excluding those with abnormal energy intake (< 500 or > 5000 kcal). In this study, we included 4186 participants at baseline from RS-I (5th follow-up visit, $N = 1212$) RS-II (3rd follow-up visit, $N = 1422$) and RS-III (1st baseline visit, $N = 1552$) with data on dAGEs and muscle parameters between year 2006 and 2012. We included 3803 participants at follow-up on the next visit from RS-I (6th follow-up visit, $N = 681$) RS-II (4th follow-up visit, $N = 1062$) and RS-III (2nd follow-up visit, $N = 2060$) with data on muscle parameters and frailty components but not dAGEs between 2010 and 2016. There were some individuals who had

muscle data at baseline but not at follow-up and vice versa. Eventually, 2782 participants had data on muscle parameters at both baseline and follow-up visits and no missing covariates. We excluded all participants with missing data on any of the covariates namely effective glomerular filtration rate (eGFR), body mass index (BMI), diabetes and smoking status (Fig. 1).

2.2. Dietary AGEs assessment

A self-administered semi-quantitative 389-item food frequency questionnaire (FFQ) was filled by the participants between 2008 and 2012 [25]. The employed FFQ collected information on food types consumed, frequency of consumption and serving sizes in the past one month. The FFQ has been validated in two other Dutch populations based on a 9-day dietary record and 4-week dietary history [26,27].

A detailed description of dAGEs calculation for RS participants is provided elsewhere [28]. Briefly, reference amount of AGEs in a particular food item were obtained from two databases. First one is a Dutch database reporting AGEs content, namely CML, carboxymethyllysine (CEL) and methylglyoxal-derived hydroimidazolone (MGH1), content in 190 commonly consumed food items in the Netherlands [9]. Second one is a northern Irish database reporting only CML content in 257 commonly consumed food items in Northern Ireland [29]. Both databases made use of ultra performance liquid chromatography-tandem mass spectrometry technique, UPLC/MS/MS, to quantify protein-bound AGEs. While calculating AGEs intake for our participants based on FFQ, we assumed that usual Dutch cooking temperature, methods and duration were utilized. As an example, daily intake of CML for an individual is calculated as follows: CML content for a food item as reported in AGEs database in mg/100 g is multiplied with the serving size in grams which gives CML content of that food item consumed. All such food items consumed per day are added up to calculate CML intake in mg/day. Hereafter, energy-adjusted daily CML intake was calculated to minimize the effect of total daily energy intake by using the residual method. Briefly, for every participant, we added mean CML intake and the residuals obtained during a linear regression between dAGE intake as dependent variable and total daily energy intake as an independent variable. Similar calculations were performed for CEL and MGH1.

Daily energy intake was calculated from Dutch food composition database (NEVO). A diet quality score (0–14) was calculated based on adherence to the Dutch dietary guidelines with a higher score reflecting a better quality [25].

2.3. Sarcopenia

Sarcopenia was defined using European Working Group on Sarcopenia in Older People (EWGSOP) revised criteria [30] using appendicular lean mass (ALM) and hand grip strength (HGS). ALM and HGS were determined at baseline - the same visit when FFQ was filled and at follow-up with a mean 5.4 years after the first measurement. Subjects with low ALM and weak HGS were classified as sarcopenia, based on timing of measurement as follows - at baseline visit as prevalent sarcopenia (baseline), at follow-up visit as prevalent sarcopenia (follow-up 5 years) and at follow-up new cases from individuals with data at both baseline and follow-up as incident sarcopenia (follow-up 5 years).

In order to obtain ALM, a total body dual energy X-ray absorptiometry incorporating a total body fan-beam densitometer (GE Lunar Corp., Madison, WI, USA) was used. enCORE software was employed to analyze the scans using an algorithm which divides the total body into regions of interest, such as trunk, arms, and legs. Appendicular lean mass (ALM) is computed by summing up the lean mass from the arms and legs. Appendicular skeletal muscle index (ASMI) was defined by dividing appendicular lean mass by squared body height (kg/m^2). Low ALM was defined as $\text{ALM} < 20$ kg or $\text{ASMI} < 7$ kg/m^2 for males and $\text{ALM} < 15$ kg or $\text{ASMI} < 5.5$ kg/m^2 for females.

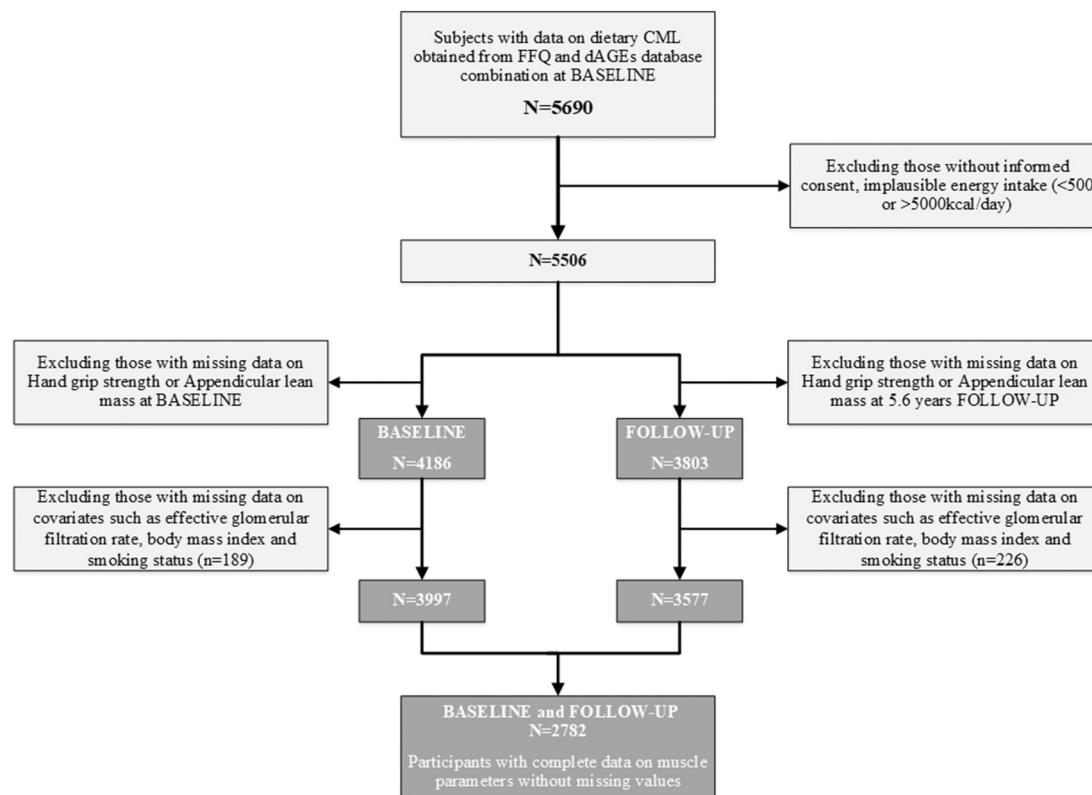


Fig. 1. Flowchart of participant inclusion.

FFQ, food frequency questionnaire; dAGEs, dietary intake of advanced glycation end products.

In order to measure HGS, a hydraulic hand dynamometer (Fabrication Enterprises Inc., White Plains, NY, USA) was used. HGS was measured three times in the nondominant hand and the maximum value out of 3 was recorded. Weak HGS was defined differentially across sexes as weak HGS < 27 kg for men and <16 kg for women.

2.4. Physical frailty

Physical frailty was defined using Fried's criteria [31] as described in detail elsewhere in Rotterdam Study [32]. Physical frailty components were available at a single time point at which dAGEs questionnaire was filled. Briefly, these five components were used to define frailty: 1) weakness reported as weak HGS; 2) slowness reported as slow gait speed (<0.8 m/s) which was evaluated using a 5.79-m long walkway (GAITRite Platinum; CIR systems, Sparta, NJ: 4.88-m active area; 120-Hz sampling rate); 3) weight loss defined as losing 5 % of body weight when compared with previous follow-up visit about 3–5 years earlier; 4) exhaustion reported based on two statements answered as “frequently” or “mostly”, from the Center for Epidemiological Studies Depression (CES-D) scale: (a) I felt that everything I did was an effort; (b) I could not get going [33]; low physical activity defined as ≤14 metabolic equivalent for task (MET) hours per week using an adaptive version of the LASA Study Physical Activity Questionnaire [34]. Briefly, each participant reported the frequency and duration of different activities in the past two weeks. All activities in the questionnaire were assigned a MET value to quantify activity intensity, using a compendium of activity energy cost [35].

Subjects having ≥3 out of 5 components were classified as physically frail, those having 1 or 2 components as being physically pre-frail and those having none of the 5 components as being non-frail.

2.5. Covariates

Height (cm) and weight (kg) were measured in the research center with the individuals in standing position wearing indoor clothing without shoes. Body mass index was computed as weight in kilograms divided by height in meters squared (kg/m^2). Type 2 diabetes mellitus (T2DM) was defined by combining information on fasting blood glucose levels, antidiabetic medication use or self-reported medical history. Smoking status was classified as current, former or never smokers collected through self-report during home interviews. Serum creatinine and serum fasting glucose were measured through automated enzymatic method. Estimated glomerular filtration rate (eGFR) was calculated by the CKD-EPI equation using serum creatinine concentration, age and sex data [36]. Information on educational level was assessed by trained interviewers according to standard Dutch classification based on the UNESCO classification of education [61]. Four categories are: primary education; lower = intermediate general and lower vocational education; intermediate = higher general and intermediate vocational education; and higher = higher vocational education and university.

2.6. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics 25 (version 25.0). Normality of the residuals of the exposure and predictors of interest was determined using histograms and Shapiro-Wilk test. Data are presented as mean ± standard deviation (SD), median (interquartile range, IQR) or as count (percentages) depending on the distribution. Means of continuous variables were compared using independent sample *t*-test or ANOVA, median of continuous variables were compared using Mann-Whitney test and groups of different categorical variables were compared using Chi-square test.

For all our analyses, energy-adjusted dAGEs intake was used as exposure unless specified otherwise. Binary logistic regression and

multinomial logistic regression were used to investigate the associations between dAGEs, prevalent or incident sarcopenia, prevalent physical frailty and their individual components. In our exploratory subgroup analysis, linear regression analysis was used to investigate a relationship between dAGEs and change in ALM or HGS to explore their differential associations with dAGEs intake. Change in ALM or HGS was calculated by subtracting ALM or HGS at follow-up minus ALM or HGS at baseline i.e., a positive value means increase in muscle mass or strength and vice versa. Potential confounders were identified using literature [30,37–39] and a common cause approach.

Throughout our analyses: Model 1 included age, sex, RS-cohorts, Model 2 included in addition diet quality score, daily energy intake, effective glomerular filtration rate (eGFR), smoking status, diabetes status and BMI or body fat percentage/height. Additional adjustment for physical activity and education level did not change the results and were not included our adjusted models due to additional missing data and inclusion led to less powered analyses. We tested for interaction terms between dCML * sex/smoking status/diabetes and eGFR (binary) in the multivariate fully adjusted models. If p-value of interaction was <0.10, stratified analysis was performed.

3. Results

3.1. Descriptive

Table 1 shows the demographic, clinical and muscle related parameters of our study population at baseline (n = 4186). Our population consisted of 43 % males, 13 % subjects with T2DM and 14 % with a eGFR <60 ml/min. Mean age of our population was 68.5 ± 10.6 years, BMI 27.3 ± 4.2 kg/m² and eGFR of 76.5 ± 15.5 ml/min. Total daily energy intake was 2054 (1645; 2528) kcal/day and median physical activity was 40.5 (16.0; 79.9) MET hours/week. 408 (9.7 %) had a low ALM, 986 (23.6 %) had weak HGS and 198 (4.7 %) had prevalent sarcopenia.

A comparison of the total population with subjects who have muscle related data at both baseline and follow-up (n = 2782) showed that at baseline, participants with measurements at both time points were relatively younger (66.4 ± 9.9 vs. 68.5 ± 10.6 years), less subjects with diabetes (11 vs. 14 %), less subjects with eGFR<60 (11 vs. 13 %) and physically active (45.5 (18.3; 84.1) vs. 40.5 (16.0; 79.9) MET h per week). They had lower prevalence of low ALM (7.8 vs. 9.7 %), weak HGS (18.5 vs. 23.6 %) and sarcopenia (3.1 vs. 4.7 %). A comparison of baseline characteristics of subjects lost during follow-up and those who were present at both visits was shown in Supplementary Table 1.

3.2. dAGEs intake and sarcopenia

For our primary analysis, we included 2782 individuals who had complete data on muscle parameters at both baseline and follow-up. 84 (3 %) had prevalent sarcopenia at baseline and 131 (4.7 %) were classified as prevalent sarcopenia at 5-years follow-up. In our adjusted models, one SD increase in dAGEs was associated with sarcopenia at baseline [dCML: Odds ratio (95 % confidence interval), OR = 1.27 (1.01–1.59); dCEL: OR = 1.11 (0.88–1.40) and dMGH1: OR = 0.99 (0.76–1.29)]. After excluding subjects with eGFR<60, there was a higher sarcopenia risk with high dCML intake [dCML: 1.40 (1.10–1.79)]. In our adjusted models, one SD increase in dAGEs was associated with prevalent sarcopenia at 5-year follow-up [dCML: OR = 1.27 (1.05–1.54), dCEL: OR = 1.10 (0.91–1.33); dMGH1: OR = 1.01 (0.98–1.04)]. This association was stronger for subjects with normal renal function, eGFR>60 (see Table 2). All p-value of interaction was >0.10 for dCML with sex/T2DM/smoking. Of note: we performed analysis with prevalent sarcopenia at baseline as well as at follow-up because not all participants with sarcopenia at baseline had sarcopenia at follow-up i.e., sarcopenia reverted in a few. Moreover, around 1000 participants did not overlap between the two time points. Similar results were observed when we performed an analysis including all subjects with prevalent

Table 1

Baseline characteristics of the study population (n = 4186) and those with sarcopenia data at both baseline and follow-up (n = 2782).

	Total baseline population	Baseline population available at follow-up with complete data
Number, N	4186	2782
Carboxymethyl-lysine (CML) intake (mg/day)	3.3 ± 1.3	3.4 ± 1.3
Energy adjusted CML intake	2.41 ± 0.91	2.41 ± 0.90
Carboxyethyl-lysine (CEL) intake (mg/day)	3.1 ± 1.3	3.1 ± 1.3
Energy adjusted CEL intake	2.40 ± 0.90	2.41 ± 0.89
Methylglyoxal-derived hydroimidazolone (MGH1) intake (mg/day)	28.4 ± 11.5	29.2 ± 11.5
Energy adjusted MGH1 intake	28.2 ± 8.0	28.5 ± 8.0
Age (years)	68.5 ± 10.6	66.4 ± 9.9**
Sex (male/n (%))	1797 (43 %)	1244 (43 %)
BMI (kg/m ²)	27.3 ± 4.2	27.3 ± 4.0
RS I/II/III (%)	29/34/37	22/36/42
eGFR (ml/min/1.73 m ²)	76.5 ± 15.5	78.4 ± 14.2
eGFR<60	576 (14 %)	291 (11 %)**
eGFR<60 and diabetes, n (%)	1002 (24 %)	570 (20 %)*
Diabetes, n (%)	543 (13 %)	329 (11 %)*
Diet Quality Score (0–14)	6.9 ± 1.9	7.0 ± 1.9
Never smokers, n (%)	31 %	32 %
Ex-smokers, n (%)	52 %	52 %
Current smokers, n (%)	17 %	15 %
Energy intake (kcal/day)	2054 (1645; 2528)	2094 (1699; 2543)
Physical activity (MET h/week) (n = 3867 and 2732)	40.5 (16.0; 79.9)	45.5 (18.3; 84.1)**
Appendicular lean mass, kg	21.0 ± 4.8	21.3 ± 4.9
Appendicular muscle index, kg/m ²	7.3 ± 1.1	7.4 ± 1.1
Low appendicular lean mass, n (%)	408 (9.7 %)	225 (7.8 %)*
Incident low ALM, n (%)	NA	96 (3.3 %)
Hand grip strength, kg	26.8 ± 9.8	27.7 ± 9.8*
Weak hand grip strength, n (%)	986 (23.6 %)	535 (18.5 %)**
Incident weak HGS, n (%)	NA	327 (11.3 %)
Sarcopenia, n (%)	198 (4.7 %)	89 (3.1 %)*
Incident sarcopenia, n (%)	NA	77 (2.7 %)
Physically pre-frail, n (%)	1972 (47 %)	NA
Physically frail, n (%)	158 (4.1 %)	NA

RS, Rotterdam Study; METh/week, metabolic equivalent task hours per week; kcal/day, kilocalories per day; eGFR, effective glomerular filtration rate; T2DM, Type 2 diabetes mellitus; NA, not applicable.

Data are expressed as mean ± S.D., median (IQR) and number (%).

** p < 0.0001.

* p < 0.05.

sarcopenia at baseline (n = 131/3997) and at 5-years follow-up (n = 147/3577) especially in those with normal renal function (Supplementary Table 2).

After excluding those with prevalent sarcopenia at baseline (n = 84), 73/2698 (2.7 %) were incident cases of sarcopenia at follow-up (i.e., 55 % of those with sarcopenia at 5-year follow-up were new cases). None of the three dAGEs was associated with the risk of incident sarcopenia at 5-year follow-up [dCML: OR = 1.12 (0.86–1.44); dCEL: OR = 1.00 (0.76–1.32), dMGH1: OR = 1.01 (0.98–1.05)].

3.3. dAGEs intake and frailty

1972 (47 %) of included participants were physically pre-frail and 158 (4.1 %) were physically frail in our study population. Table 3 depicts the association of dAGEs with physical frailty and its components as binary variable. In our adjusted model, one SD increase in dAGEs was associated with higher odds of prevalent exhaustion [dCML: OR = 1.18 (1.05–1.31); dCEL: OR = 1.08 (0.97–1.21); dMGH1: OR = 1.02 (1.00–1.03)] but not with any other frailty components. There was also no association between dAGEs and physical frailty [dCML: OR = 1.01

Table 2

Association between one SD increase in dAGEs and odds of prevalent sarcopenia at baseline and at 5-years follow-up and incident sarcopenia at follow-up in all participants available at follow-up.

N = 2782 n/N	Prevalent sarcopenia (baseline)		Prevalent sarcopenia (follow-up 5 years)		Incident sarcopenia (follow-up 5 years)	
	84 (3 %)		131 (4.7 %)		73/2698 (2.6 %)	
	Odds ratio (95 % CI)	p-value	Odds ratio (95 % CI)	p-value	Odds ratio (95 % CI)	p-value
<i>dCML</i>						
Model 1	1.25 (1.00–1.56)	0.05	1.24 (1.03–1.50)	0.02	1.11 (0.84–1.46)	0.46
Model 2	1.27 (1.01–1.59)	0.04	1.27 (1.05–1.54)	0.01	1.12 (0.86–1.44)	0.41
eGFR>60	1.40 (1.10–1.79)	0.006	1.37 (1.11–1.70)	0.003	1.09 (0.79–1.50)	0.61
<i>dCEL</i>						
Model 1	1.04 (0.82–1.31)	0.77	1.05 (0.87–1.26)	0.64	0.96 (0.73–1.28)	0.80
Model 2	1.11 (0.88–1.40)	0.37	1.10 (0.91–1.33)	0.32	1.00 (0.76–1.32)	0.99
eGFR>60	1.10 (0.85–1.42)	0.46	1.13 (0.91–1.41)	0.26	1.06 (0.77–1.44)	0.73
<i>dMGH1</i>						
Model 1	0.98 (0.75–1.28)	0.89	1.01 (0.98–1.04)	0.43	1.01 (0.98–1.05)	0.47
Model 2	0.99 (0.76–1.29)	0.94	1.01 (0.98–1.04)	0.46	1.01 (0.98–1.05)	0.52
eGFR>60	0.99 (0.74–1.33)	0.97	1.02 (0.99–1.04)	0.37	1.02 (0.98–1.06)	0.42

eGFR, effective glomerular filtration rate; d, dietary; CML, carboxymethyl-lysine; CEL, carboxyethyl-lysine; MGH1, methylglyoxal-derived hydroimidazolone.

Model 1 was adjusted for age, sex, RS-cohorts, diet quality score, energy intake. Model 2 was additionally adjusted for diabetes, eGFR, smoking, body fat percentage, height.

dCML * eGFR (binary) all p-value of interaction <0.05 for sarcopenia analysis.

p-value ≤0.05 is considered significant.

Table 3

Binary logistic regression showing association between one SD increase in dietary AGEs and odds of prevalent frailty in all participants.

	N	dCML		dCEL		dMGH1	
		ORs (95 % CI)	p-value	ORs (95 % CI)	p-value	ORs (95 % CI)	p-value
Non-frail and pre-frail participants		Ref.		Ref.			
Physical frailty	3577	1.01 (0.84–1.22)	0.89	0.96 (0.80–1.17)	0.71	1.00 (0.97–1.02)	0.68
Components of physical frailty							
Weakness	3577	1.07 (0.95–1.20)	0.26	0.99 (0.88–1.12)	0.88	1.00 (0.99–1.02)	0.87
Exhaustion	3570	1.18 (1.05–1.31)	0.004	1.08 (0.97–1.21)	0.18	1.02 (1.00–1.03)	0.03
Slow gait speed	2778	0.88 (0.64–1.22)	0.44	0.86 (0.62–1.20)	0.37	1.00 (0.96–1.04)	0.99
Weight loss	3577	0.98 (0.88–1.01)	0.77	1.02 (0.91–1.15)	0.69	1.00 (0.99–1.01)	0.80
Low physical activity	3332	1.02 (0.92–1.13)	0.65	0.99 (0.89–1.10)	0.84	1.00 (0.99–1.01)	0.93

d, dietary; CML, carboxymethyl-lysine; CEL, carboxyethyl-lysine; MGH1, methylglyoxal-derived hydroimidazolone.

Adjusted for age + sex + RS-cohorts + diet quality score + energy intake + diabetes + eGFR + smoking + BMI.

p-value ≤0.05 is considered significant.

(0.84–1.22); dCEL: OR = 0.96(0.80–1.17); dMGH1: OR = 1.00 (0.97–1.02)].

Table 4 shows the results of multinomial logistic regression between dAGEs and physical frailty as ternary variable. One SD increase in dCML was associated neither with pre-frailty [OR = 0.99 (0.91–1.07)] nor with frailty [OR = 1.01 (0.83–1.22)] when non-frail subjects were used as

Table 4

Association between dietary AGEs and multinomial logistic odds for pre-frail and frail participants.

N	Non-frail	Pre-frail		Frail	
		1972		158	
		ORs (95 % CI)	p-value	ORs (95 % CI)	p-value
dCML	Ref.	0.99 (0.91–1.07)	0.77	1.01 (0.83–1.22)	0.95
dCEL	Ref.	1.00 (0.92–1.09)	0.99	0.97 (0.79–1.18)	0.73
dMGH1	Ref.	1.00 (0.99–1.01)	0.68	0.99 (0.97–1.02)	0.63

d, dietary; CML, carboxymethyl-lysine; CEL, carboxyethyl-lysine; MGH1, methylglyoxal-derived hydroimidazolone.

Adjusted for age + sex + RS-cohorts + diet quality score + energy intake + diabetes + eGFR + smoking + BMI.

p-value <0.05 is considered significant.

reference. Neither dCEL nor dMGH1 showed any association with pre-frailty and frailty.

3.4. Subgroup analysis

An exploratory subgroup analysis was performed to explore why dAGEs were associated with prevalent sarcopenia but not with incident. We investigated the associations of dAGEs with individual sarcopenia components namely ALM and HGS to check whether there is a differential association with these components (Table 5 and Supplementary Table 3). A linear regression analysis was performed between dAGEs intake and change in ALM (Δ ALM) and change in HGS (Δ HGS) from baseline to follow-up. One standard deviation increase in dAGEs intake was associated with a negative change in ALM at follow-up [dCML: standardised coefficient, $\beta = -0.056$, 95 % confidence interval (-0.104; -0.008); dCEL: $\beta = -0.039$ (-0.088; 0.10); dMGH1: $\beta = -0.077$ (-0.127; -0.027)]. One standard deviation increase in dAGEs was associated with no change in HGS (a trend towards increase) at follow-up [dCML: $\beta = 0.191$ (-0.026; 0.408); dCEL: $\beta = 0.140$ (-0.076; 0.356); dMGH1: $\beta = 0.191$ (-0.032; 0.414)]. Stratification based on eGFR showed that these associations were mainly influenced by those with normal renal function. Additional adjustment for baseline low ALM or weak HGS did not change the direction but slightly increase the magnitude of effect size (data not shown).

Table 5

Association between one SD increase in dietary AGEs intake and changes in appendicular lean mass (ALM) and hand grip strength (HGS) at follow-up.

N = 2782	CML		CEL		MGH1	
	Standardised coefficient (95 % CI)	p-value	Standardised coefficient (95 % CI)	p-value	Standardised coefficient (95 % CI)	p-value
<i>Change in appendicular lean mass (ΔALM) from baseline to follow-up</i>						
All	-0.056 (-0.104; -0.008)	0.02	-0.039 (-0.088; 0.10)	0.12	-0.077 (-0.127; -0.027)	0.003
eGFR>60	-0.067 (-0.118; -0.016)	0.01	-0.054 (-0.106; -0.001)	0.04	-0.083 (-0.135; -0.030)	0.002
eGFR<60	0.033 (-0.114; 0.179)	0.66	0.04 (-0.100; 0.180)	0.57	-0.039 (-0.205; 0.127)	0.64
<i>Change in hand grip strength (ΔHGS) from baseline to follow-up</i>						
All	0.191 (-0.026-0.408)	0.08	0.140 (-0.076-0.356)	0.20	0.191 (-0.032-0.414)	0.09
eGFR>60	0.136 (-0.099-0.370)	0.26	0.097 (-0.143-0.336)	0.43	0.163 (-0.078-0.404)	0.19
eGFR<60	0.570 (0.021-1.119)	0.04	0.516 (-0.011-1.044)	0.06	0.576 (-0.050-1.202)	0.07

eGFR, effective glomerular filtration rate; CML, carboxymethyl-lysine; CEL, carboxyethyl-lysine; MGH1, methylglyoxal-derived hydroimidazolone.

Adjusted for age + sex + RS-cohorts + diet quality score + energy intake + diabetes + eGFR + smoking + BMI. dCML * eGFR (binary) all p-value of interaction <0.05. p-value \leq 0.05 is considered significant.

4. Discussion

In the present study, we investigated an association between dietary intake of AGEs, namely CML, CEL and MGH1, estimated from FFQ and an AGEs food database and sarcopenia (including ALM and HGS) and physical frailty in middle aged and elderly individuals from a Dutch population based cohort. We observed that higher intake of dAGEs was positively associated with prevalent sarcopenia. However, higher intake of dAGEs was not associated with increased risk of incident sarcopenia at follow-up. Higher intake of dAGEs was associated with a decrease in ALM over time but not with changes in HGS. High consumption of dAGEs showed no relationship to the physical frailty.

Dietary intake of AGEs may deteriorate muscle health and provoke a state of chronic low grade inflammation via several mechanisms although we failed to show a clear association between dAGEs intake and sarcopenia or frailty. Increased crosslinking through AGEs between extracellular matrix proteins not only adds stiffness but also alter structure of the proteins leading to a modification in its function [13]. Binding of AGEs to receptor for AGE (RAGE) on myocytes and endothelial cells in skeletal muscle has been shown to release pro-inflammatory cytokines (including interleukin 6 - IL-6 and tumor necrosis factor alpha - TNF α) via activation of the transcription factor NF- κ B and induce generation of reactive oxygen species [40]. Multiple human intervention studies showed an association of low AGE diet with lower levels of inflammation markers (CRP, IL-6 and TNF α) [41,42]. Chronically raised levels of inflammation markers (IL-6 and TNF α) have been demonstrated in individuals with both sarcopenia and frailty in epidemiological studies [43–45]. Therefore, chronic low-grade systemic inflammation could be the shared link between AGEs and sarcopenia or frailty.

4.1. dAGEs and sarcopenia

We observed that higher intake of dAGEs in those with normal renal function showed a higher prevalence of sarcopenia but no increased risk of incident sarcopenia at follow-up. Regarding AGEs, their increased accumulation in skin and serum has been associated with low muscle mass, weak grip strength and slow walking speed in several epidemiological studies in middle age and elderly, including a study by our group in the RS [46–49]. Absence of an association of dAGEs intake with incident sarcopenia in our study could partially be explained by a very low incidence of sarcopenia (2.7 % at 5 years) which limits statistical power to detect any longitudinal relationship. Also, we observed differential associations of dAGEs with changes in ALM/HGS which may suggest that low intake of dAGEs alone cannot offset age-related HGS decline. In addition, processing food at high temperatures, using dry heat and longer duration of cooking have been shown to substantially increase the quantity of AGEs during food preparation [50,51]. Our

current FFQ does not take any of these factors into account which could have influenced precise calculation of dAGEs and its relationship to muscle strength. Lastly, the possibility of reverse causation cannot be ruled out. A vicious cycle may ignite as sarcopenia increases the risk of poor nutrition i.e., consuming readymade processed meals rich in AGEs while poor nutrition increases the risk of sarcopenia. Future longitudinal studies and employment of dAGEs specific questionnaires should provide a better insight in this relationship.

4.2. dAGEs and frailty

We observed no association between dAGEs intake and physical frailty except for one of the frailty components namely exhaustion which could be a chance finding or due to reverse causation. In line with our findings, a French cohort (n = 423) of \geq 75 years, skin AGEs were neither associated with prevalent nor incident frailty but with increased 4-year risk of exhaustion and low energy expenditure [52]. In contrast, a recent study found an association of skin AGEs with frailty in 250 elderly hospitalized patients (>65 years old) but not with serum protein bound CML and MGH1, assessed through LC-MS/MS [53]. It is worth-remembering that dAGEs consumed as whole proteins undergo proteolysis and are absorbed either as free form or as small peptide bound AGEs while the protein bound AGEs become a substrate for gut microbiota and release inflammatory mediators [54,55]. Whether and to what extent these free AGEs from diet are involved in crosslinking of extracellular matrix proteins or binding to RAGE is not yet completely known [56]. Similarly, to what extent the release of inflammatory mediators via gut microbiota alters endogenous AGEs formation is not yet clear. Thus, in the context of frailty, dAGEs might not share similar characteristics as endogenously formed AGEs. Future research should focus on the effects of dAGEs on inflammation markers and their indirect contribution to the frailty.

4.3. dAGEs and tissue AGEs

Whether dietary consumption of AGE rich foods contribute to increased AGEs accumulation in tissues especially skeletal muscle has been studied on a limited scale. In humans, no direct studies have been performed to evaluate whether dAGEs accumulate in skeletal muscle. In mice, chronic exposure to labelled dAGEs resulted in its accumulation in numerous organs including skeletal muscle [57]. In our previous work, dAGEs have been found to be associated with a small but significant high values of skin AGEs and higher risk of vertebral fractures only in individuals without type 2 diabetes and normal renal function [28,58]. Furthermore, dAGEs have been shown to be correlated with plasma free AGEs (but not protein-bound), inflammation markers and metabolic dysfunction [42,59]. Together, these studies including ours point towards a pathophysiological role of dAGEs in increasing tissue

accumulation of AGEs in the body which may also involve skeletal muscle.

Our study has several strengths. We used a reference database which estimated dAGEs using the state-of-the-art ultra-performance liquid chromatography/tandem mass spectrometry (UPLC/MS/MS) which is considered superior to ELISA [9]. Both FFQ and dAGEs database were primarily intended for Dutch population which points to a reliable representation of dAGEs in our study participants. We derived our participants from Rotterdam Study which is a well characterized population based cohort with a reliable manner of data collection.

Several limitations warrant further discussion. dAGEs assessment was done only at the baseline and any changes in dAGEs intake at the follow-up could not be taken into account. Our FFQ did not include information on cooking duration, quantity of moisture and temperatures used which have been shown to substantially influence the quantity of AGEs formed in food [50,51]. We used CML, CEL and MGH1 as a representative of heterogeneous group of AGEs to generalize our findings while there are already >20 compounds identified as AGEs [60]. Altogether, an exact estimation of dAGEs is not straightforward which may have influenced the precise estimation of intake of AGEs in diet and their association with sarcopenia and frailty. Around 1200 participants did not have a second measurement of either ALM or HGS and were lost to follow-up. These individuals might be more vulnerable (as we showed them to be older, more physically inactive, more often having T2DM and eGFR<60) than those present at both visits. Therefore, we cannot rule out the possibility of survival and selection bias. Lastly, we could not include any inflammation marker as covariates due to its unavailability which would have been an important potential mediator between AGEs and sarcopenia or frailty.

In conclusion, our results suggest a role of dietary intake of AGEs in the pathophysiology of decline in muscle health but no relationship to frailty. However, an association of dAGEs with prevalent sarcopenia but not with incident sarcopenia implicates that this may be an interim association or that there is reverse causality. We call for replication in other independent cohorts. Future research on dAGEs merit inculcation of a FFQ which takes detailed preparation methods into account in addition to the current parameters to increase the accuracy of dAGEs consumption measurements. Well-powered prospective studies are warranted to investigate the role of dAGEs in future risk of sarcopenia and expand our findings.

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CRediT authorship contribution statement

KW and MCZ designed the study. FR, AGU and TV provided essential materials. KW assessed and (statistically) analyzed the data. KW, JC, TL, BE, FR, AGU, TV and MCZ interpreted the results. KW created the figures and tables. KW and MCZ drafted the manuscript. All authors provided

intellectual content to the manuscript. All authors have read and revised the manuscript and approved the final submitted version.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

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