Is Dietary Intake of Advanced Glycation End Products Associated with Mortality Among Adults with Diabetes?

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Abstract

Background and Aims—Prior studies suggest a positive association between dietary AGEs and adverse health outcomes but have not well-characterized AGEs intake and its association with mortality in a general adult population in the United States.

Methods and Results—We included 5,474 adults with diabetes from the 2003 to 2018 National Health and Nutrition Examination Survey, a nationally representative sample of the non-institutionalized civilian population in the United States. Concordance to dietary guidelines (Healthy Eating Index 2015 [HEI-2015]) and intake of the AGE Nε-(carboxymethyl)lysine (CML) were estimated using an existing database and two 24-hour food recalls. Multivariable Cox regression evaluated the association between AGEs intake and all-cause mortality. A secondary analysis measured CML, Nε-(1-carboxyethyl)lysine (CEL), and Nδ-(5-hydro-5-methyl-4-imidazolon-2-yl)-ornithine (MGH1) from an alternative database.

Higher AGEs intake was associated with lower concordance to dietary guidelines (Means and standard errors of HEI-2015 score, by quartiles of AGEs intake: Q1=55.2 ± 0.6, Q2=54.1 ± 0.5, Q3=52.1 ± 0.5, Q4=49.0 ± 0.5; p<0.001). There were 743 deaths among 3,884 adults in the mortality analysis (mean follow-up=3.8 years). AGEs intake was not significantly associated with all-cause mortality (Q2 vs. Q1: Hazard Ratio [HR]=0.91 [0.69–1.21], Q3 vs. Q1: HR=0.90 [0.63–1.27], Q4 vs. Q1: HR=1.16 [0.84–1.60]). Results were similar in secondary analyses.

Conclusion—While dietary AGEs intake was associated with concordance to dietary guidelines, it was not significantly associated with all-cause mortality among adults with diabetes. Further research may consider other health outcomes as well as the evaluating specific contribution of dietary AGEs to overall AGEs burden.

Keywords

diabetes; diet; nutrition; mortality; glycotoxins; advanced glycation end products

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Introduction

Advanced glycation end products (AGEs), also referred to as glycotoxins, are a heterogeneous group of compounds associated with oxidative stress and chronic inflammation [1–3]. Although AGEs are formed intracellularly and extracellularly in all tissues and fluids of the human body as a normal part of metabolism, their primary exogenous source is thought to be dietary intake [4, 5]. Specifically, foods that have high fat content and/or are subject to high heat during cooking or processing (e.g. high-heat processed grain products and red meat) tend to be high in AGEs, which are formed from the Maillard reaction when reducing sugars react with amino acids in lipid or protein at high temperatures [6–8]. Consuming too many foods high in AGEs can lead to pathogenic levels of the compounds, and their accumulation can be accelerated in individuals with diabetes due to hyperglycemia and reduced urinary elimination [1, 9].

Dietary approaches to managing diabetes include consuming foods with a lower glycemic index and an overall healthy eating pattern characterized by appropriate energy balance, adequate consumption of fiber, fruits, and vegetables, and limited consumption of saturated and trans fats, processed foods, and sugar-sweetened beverages [10]. Nonetheless, little emphasis is placed on the possible role of dietary AGEs in secondary prevention efforts. In addition to the type of food consumed, parameters relating to the use of heat in processing food (e.g. the use of dry heat, higher temperatures, or increased cooking time) can impact an individual's intake of dietary AGEs. For example, increasing the cooking time of a beef steak from 4 to 8 minutes can nearly double the level of AGEs, and fried, compared to boiled rice can contain between 6 and 66 times the level of AGEs [11]. Therefore, understanding how dietary AGEs impact health may help to better tailor dietary guidance for individuals with diabetes.

To date, studies that have investigated the role of AGEs in diabetes outcomes have been limited by factors such as small sample sizes, unadjusted analyses, focus on patient populations and populations outside the United States (US) [2, 12–16]. This precludes the ability to generalize results to the general US population, where individuals with diabetes may be at particular risk of higher dietary AGEs due to the high-fat and heavily processed Western diet. In addition, existing studies have typically examined the role of serum or plasma AGEs [12–17]. While biomarkers can provide an objective measure of overall AGEs levels, dietary intake can be a more practical indicator as both a modifiable risk factor and potentially major source of AGEs. Here, we aimed to build on existing evidence by using a nationally representative sample of adults with diabetes to 1.) describe the presence and levels of AGEs in the diet; 2.) identify dietary correlates of AGEs; and 3.) better understand the role of AGEs as a risk factor for all-cause mortality.

Subjects, Materials and Methods

Study Population

We used data from the 2003 to 2018 National Health and Nutrition Examination Survey (NHANES), a nationally representative stratified multistage sample of the non-institutionalized U.S. civilian population with data collected in two-year cross-sectional

survey cycles since 1999. NHANES methods and protocols for the questionnaires, laboratory, and examination have been described extensively [18]. Among the 70,718 participants from the 2003 to 2018 survey cycles, we excluded participants who were: under 18 years old (n=28,249), pregnant or lactating (n=968), did not have data on dietary intake (n=9,969), and/or did not have diabetes (n=64,419), which was defined as having either self-report of a diagnosis by a healthcare professional or a glycated hemoglobin (HbA1c) 6.5% (48 mmol/mol). This yielded a final analytic sample of 5,474 adults with diabetes for the descriptive analyses.

For the mortality analysis, participant data were linked to public-use data [19] primarily from the National Death Index and supplemented by other sources including the Social Security Administration and the Centers for Medicare and Medicaid Services. Participants were eligible to be linked to the mortality data if sufficient information on identifying data (e.g. social security number, name, date of birth) was available [20]. Because mortality data on date of death were available up to December 31, 2015, only participants from the 2003 to 2014 survey cycles were followed-up for the mortality analysis (mean=3.8 years follow-up time). Because death information was not available for 1,590 participants, the sample for the mortality analysis included 3,884 individuals.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The NHANES survey protocol was approved by the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS) Ethics Review Board and written informed consent was obtained from all adult participants.

Dietary intake

To assess dietary intake of AGEs, we used the average of data collected from two 24-hour dietary recall interviews, using the Automated Multiple Pass Method of the USDA [21]. The first dietary recall was administered during the in-person examination and the second three to ten days later by telephone. Recalls were administered by trained interviewers fluent in English or Spanish, with translators available for other languages. For each food and beverage reported in the 24-hour recalls, we assigned a value in kilounits per day (kU/day) for the estimated amount of AGEs using a published database of AGEs content of 549 foods via levels of N^e-(carboxymethyl)lysine (CML) measured using an enzyme-linked immunosorbent assay [8]. Type of food preparation method (e.g. boiled, baked, grilled) was matched when data were available in this database. For secondary analyses, AGEs intake was also estimated using a database of 190 foods measuring levels of CML, Nε-(1-carboxyethyl)lysine (CEL), and Nδ-(5-hydro-5-methyl-4-imidazolon-2-yl)-ornithine (MGH1). This database used ultra-performance liquid chromatography tandem mass-spectrometry (UPLC–MS), which may more accurately quantify AGEs [7], although the database had limited information on food preparation methods. For food and beverage items not in the database, we estimated the AGEs intake from an average of similar foods. To examine how dietary AGEs correlate with an overall healthy diet, we calculated the Healthy Eating Index 2015 (HEI-2015) for all participants based on an average of both

dietary recalls [22]. The HEI-2015 measures how well an individual's diet aligns with federal dietary guidelines and includes 13 components that reflect the key recommendations in the 2015–2020 Dietary Guidelines for Americans. Nine "adequacy" components represent food groups whose consumption is encouraged (total fruits, whole fruits, total vegetables, greens and beans, whole grains, total protein foods, seafood and plant proteins, dairy [non-fat fraction], fatty acids). Maximum scores for these components are either 5 or 10, with a higher number indicating higher consumption. Four "moderation" components represent food groups for which there are recommended limits to consumption (refined grains, sodium, added sugars, saturated fats). For these food groups, the maximum score is 10, with a higher number indicating lower consumption. The total HEI-2015 score ranges from 0 to 100, with a higher total HEI-2015 score indicating better alignment with dietary recommendations.

Measurements

We examined dietary intake of AGEs across various demographic and socioeconomic subgroups. Demographic variables included self-reported age (in years), sex (male, female), and race/ethnicity (non-Hispanic White, non-Hispanic Black, Mexican-American, other). Socioeconomic factors included education (less than high school, high school or equivalent, some college or associate's degree, college graduate or above) and poverty-income ratio, an index of income in relation to family need (PIR; <130%, 130–349%, 350%, missing). Cutoffs for PIR were selected a priori based on previously used thresholds as a PIR of less than 130% of the poverty level is the threshold to qualify for federal food assistance benefits (i.e. Supplemental Nutrition Assistance Program [SNAP]), and 350% provides a relatively equal statistical distribution.

We also included variables related to diabetes and overall health, such as HbA1c, smoking status and body mass index (BMI). Smoking status was categorized as never, former, and current. BMI (kg/m^2) was calculated from measured height and weight and classified into standard categories: normal weight (<25 kg/m^2), overweight (25-<30.0 kg/m^2), obesity class I (30-<35.0 kg/m^2), obesity class II (35-<40 kg/m^2), and obesity class III (40 kg/m^2). Variables with missing values (HbA1c [n=174], BMI [n=122], education [n=30], smoking [n=19]) were set to the median value for continuous variables and the largest category for categorical variables. Missing values for PIR (n=470) were set to a missing indicator category.

Statistical Analysis

Sample design variables and weights for the dietary recall were used to produce nationally representative estimates that accounted for the complex survey design, including the stratified multistage cluster sampling. Levels of AGEs were analyzed as quartiles of estimated daily average intake in kU/day. For descriptive analyses evaluating the association between AGEs intake and participant characteristics, medians and interquartile ranges (IQR) were used to describe continuous variables and counts and proportions for categorical variables. For the association between AGEs intake and HEI-2015 scores, means and standard errors were used for each combination of quartile of AGEs intake and HEI-2015 score. An overall F-test was used to test for significantly different HEI-2015 scores between

quartiles of AGEs intake. For the primary analysis on mortality, two multivariable adjusted stratified Cox proportional hazard regression models were conducted. Baseline hazards were stratified by birth cohort to adjust for potential bias from calendar effects and left truncation [23, 24]. Potential confounders were selected a priori based on factors plausibly associated with both AGEs and mortality. The first model adjusted for age (as the time scale), sex, race/ethnicity, and total energy intake. The second model additionally adjusted for education, PIR, smoking status, BMI, HbA1c, and HEI-2015 score. The proportional hazards assumption was verified through visual inspection of Schoenfeld residuals. We used SAS 9.4 (SAS Institute Inc., Cary, NC) and SUDAAN 11 software (Research Triangle Institute, Research Triangle Park, NC) for the statistical analyses. A two-sided p-value<0.05 was used to determine statistical significance.

Results

Overall Sample Characteristics and AGEs Intake

Selected participant characteristics, overall and by quartile of AGEs intake (measured as CML), are shown in Table 1. The median (interquartile range [IQR]) age of all participants was 59.8 (50.4–69.3) and 49.8% (n=2,711) were women. On average, those in the higher quartiles of AGEs intake were more likely to be younger, male, non-Hispanic White, have higher levels of education, higher PIR, higher BMI, and greater overall daily energy intake. Table 2 explores these observations in greater detail, displaying median levels of daily estimated AGEs intake, by participant characteristics. Median intake of AGEs for the entire sample was 13,682 (IQR: 8,727–19,850) kU/day. Although differences in AGEs intake across participant characteristics reflected observations from Table 1, median values of AGEs intake differed the greatest across age groups and gender. While the youngest age group (18–29 years) had a median of 18,318 (13,351–24,080) kU/day of AGEs intake, the estimate for the oldest age group (70 years) was 38% lower at 11,273 (7,436–16,556) kU/day. Among male participants, median intake was 16,123 (10,715–22,673) kU/day, while female participants' median intake was 29% lower at 11,441 (7,385–16,431) kU/day. Supplementary Table 1 shows results from a secondary analysis based on AGEs intake estimated from a database measuring levels of the AGEs CML, CEL, and MGH1 using a UPLC–MS method [7]. Results were similar to Table 2, although estimated AGEs intake differed less across levels of some variables such as age group and BMI.

Association Between AGEs Intake and Mean HEI-2015 Score

Table 3 shows the correlation between quartiles of AGEs intake and dietary quality, as defined by components of the HEI-2015. On average, participants in the lowest quartile of AGEs intake had a higher total HEI-2015 score (mean ± SE: 55.19 ± 0.64) compared to those in the highest quartile (Q4) (49.00 ± 0.52). Participants with a lower mean intake (i.e., lower HEI-2015 scores) of most food groups in the adequacy components (total fruits, whole fruits, total vegetables, greens and beans, fatty acids, whole grains) had a higher mean intake of AGEs. In contrast, participants with a higher mean intake of total protein foods had on average a higher quartiles of AGEs intake. For food groups in the moderation components, participants with higher mean intakes (i.e., lower HEI-2015 scores) of sodium or saturated fats also had on average higher quartiles of AGEs intake, while the observed

trend was reversed for mean intake of added sugars. For the total HEI-2015 score and each individual component, levels of intake were significantly different across quartiles of AGEs intake (overall F-test: $p<0.001$). Supplementary Tables 2–4 show results from a secondary analysis using the alternative database to measure CML, CEL, and MGH1. Here, results were largely similar but trends were less consistent. In particular, correlations between levels of estimated MGH1 intake and components of the HEI-2015 differed from the primary analysis as participants with higher mean intake of some food groups in the adequacy components (greens and beans, whole grains) had higher mean MGH1 intake.

Association Between AGEs Intake and All-cause Mortality

Over a mean follow-up period of 3.8 years through December 31, 2015, there were 743 deaths. Table 4 shows hazard ratios (HR) for the association between quartiles of AGEs intake, measured as CML, and all-cause mortality for the 3,884 participants with available mortality data. In the first model adjusted for age, sex, race/ethnicity, and total caloric intake, AGEs intake was positively but non-significantly associated with mortality when comparing the highest to the lowest quartile (Q2 vs. Q1: HR = 0.93 [0.69–1.24], Q3 vs. Q1: HR = 0.93 [0.65–1.30], Q4 vs. Q1: HR = 1.21 [0.86–1.70]). After further adjustment for education, PIR, smoking status, BMI, HbA1c, and HEI-2015 score (Model 2), results did not substantially change (Q2 vs. Q1: HR = 0.91 [0.69–1.21], Q3 vs. Q1: HR = 0.90 [0.63–1.27], Q4 vs. Q1: HR = 1.16 [0.84–1.60]). Table 5 shows results from a secondary analysis based on AGEs intake estimated from a database measuring levels of CML, CEL, and MGH1 using a UPLC–MS method. Here, results from Model 2 were similar to the primary analysis.

Discussion

As chronically elevated blood glucose, inflammation, and oxidative stress can lead to health complications and premature death among individuals with diabetes [25], understanding dietary intake of AGEs and its associations with health outcomes is particularly important in this population. Among adults with diabetes in a nationally representative sample of the US population, we observed an estimated median daily intake of dietary AGEs of 13,682 kU/day. Few previous studies have estimated AGEs intake using self-reported dietary data, and none to our knowledge have been conducted among adults with diabetes. The estimate from the current study is relatively high compared to previously reported studies, which included a sample of 126 healthy adults aged 18–35 years old in Mexico (median: 10,240 kU/day), 4,080 healthy adults aged 19–70 in Iran (mean: 7,043 kU/day), and 183,548 postmenopausal women in the United States (estimated median: 9,316 kU/day) [26–28]. However, this finding was not unexpected as these estimates were derived from healthier populations and/or in different countries in which average AGEs intake is likely lower due to lower consumption of a highly-processed Western diet [4, 29].

Additionally, we found that a healthy eating pattern, as measured by the HEI-2015, was correlated with lower levels of AGEs. The association between each HEI-2015 component and AGEs intake was generally as expected based on the fat content and typical preparation methods of the foods represented by each component. For example, higher intake of both total and whole fruits showed a linear inverse association with AGEs

intake, reflecting the usual raw consumption and limited fat content of most fruits. The two HEI-2015 components for vegetables (total vegetables, greens and beans) showed a similar association with AGEs intake, although vegetable consumption did not decline as sharply across increasing quartiles of AGEs intake, likely due to a smaller proportion of vegetables consumed raw compared to fruits. In contrast, consumption of foods with high fat content and/or frequently prepared under high temperatures was positively associated with AGEs intake. For example, higher levels of AGEs intake were associated with increased consumption of total protein foods, sodium, and saturated fats. The association between HEI-2015 components and AGEs intake was largely similar for each of the three measured AGEs. For example, intake of both protein components (total protein foods, seafood and plant proteins) was positively associated with intake of CML, CEL, and MGH1. However, intake of fatty acids was negatively associated with CML intake but positively associated with intake of CEL and MGH1. Few prior studies have reported the same evaluation in sufficient detail for valid comparisons. One such study among 255,170 adults in Europe showed largely similar findings - for example with a greater dairy intake for the highest vs. lowest quantile of CML or MGH1 intake, but a weak association with CEL intake [30].

Although the total HEI-2015 score correlated with AGEs intake, dietary quality indices may only partially capture AGEs intake and therefore be insufficient in measuring the overall effect of diet on health outcomes. Dietary quality indices generally measure intake of food groups, macronutrients, and/or micronutrients [31], and do not take into account other factors that can substantially affect AGEs content, such as the method of preparing foods or the interaction between foods [8, 32]. For instance, dietary guidelines suggest limited consumption of sugar-sweetened beverages, which contain negligible levels of AGEs. Additionally, ultra-processed foods typically contain high levels of AGEs due to heat-processing and are associated with adverse health outcomes, but are often not directly incorporated in dietary quality indices [33, 34]. Lastly, some therapeutic diets emphasize glycemic control through a high intake of protein or fat, even though this may increase the AGEs burden in adults with diabetes [8, 35].

Among adults with diabetes, while AGEs intake was not found to be significantly associated with all-cause mortality, this does not eliminate the possibility of an association between dietary AGEs and adverse health outcomes. For example, as a healthy dietary pattern is reported to have a modest association with all-cause mortality [36] and stronger associations with intermediary outcomes such as diabetic retinopathy [37], it is similarly possible that increased intake of dietary AGEs is associated with complications of diabetes as observed in prior studies measuring serum and plasma AGEs [13–16]. On the other hand, it is also possible that dietary AGEs intake is not associated with adverse health outcomes or mortality among adults with diabetes. As AGEs comprise a heterogeneous group of compounds, it is possible that there are specific AGEs which contribute the greatest physiologic effects and any subsequent increased risk of diabetes complications or mortality. Few AGE compounds have been thoroughly studied with the majority of research focusing on CML, methylglyoxal derivatives, pentosidine, and pyrraline. The current study's analysis included CML and CEL, which are both lysine-derived AGEs that differ by a methyl group, with CML being one of the most thoroughly studied and possibly the most abundant in vivo [39]. MGH-1 is also thought to be highly abundant as well as one of the most

highly reactive glycating agents [8, 40]. The bioavailability and biologic activity of the less studied compounds is uncertain. Moreover, melanoidins, formed as the end product of the Maillard reaction, may in fact convey protective health effects in the form of antioxidant and anti-inflammatory activity [41]. Lastly, though existing studies have hypothesized that dietary AGEs are a major source of total AGEs burden and possibly the largest of all endogenous and exogenous sources [4, 5], empirical data are lacking so it remains possible that non-dietary sources or overall AGEs burden is a more relevant risk factor.

Strengths of this study include the nationally representative sample and the specific evaluation of the dietary contribution of AGEs burden. This study also includes limitations. Because this is an observational study, residual confounding may affect the results. Bias may arise from missing data from using a missing indicator or from imputed values in linked mortality data. In addition, AGEs intake was estimated using two 24-hour recalls which may not sufficiently capture the variation in a participant's usual long-term dietary intake compared to other methods such as a food frequency questionnaire, particularly as adherence to dietary management of diabetes may vary. Lastly, the mortality analysis may have been underpowered due to the mean 3.8 years of follow-up, given the modest association between healthy dietary patterns and all-cause mortality [36].

Conclusion

While we observed a significant association between higher AGEs intake and lower concordance to dietary guidelines (i.e. lower HEI-2015 scores), we did not find a significant association between dietary AGEs and all-cause mortality for adults with diabetes. As studies from different lines of evidence collectively suggest a harmful effect, further research might be considered to explain inconsistencies in findings and investigate the role of individual AGE compounds which may convey the greatest risk on adverse health outcomes among adults with diabetes. Assessing both circulating levels and estimated dietary intake within the same sample can also provide evidence on the extent of the biological effects of dietary AGEs relative to other sources of AGEs. Evidence from future studies better characterizing the overall health effects of diet may suggest that dietary guidelines be modified to incorporate indicators of AGEs content.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Availability of data:

NHANES data used in this study are available publicly online at the following sites: https://wwwn.cdc.gov/nchs/nhanes/default.aspx

https://www.cdc.gov/nchs/data-linkage/mortality-public.htm

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Table 1 –

Participant Characteristics, by Quartile of Daily Estimated Advanced Glycation End Products (AGEs) Intake, 2003−2018 (n=5,474)

	All	Dietary AGEs (CML), kU/day[a]			
		Quartile 1 (110–6,874)	Quartile 2 (6,876–11,603)	Quartile 3 (11,618–17,764)	Quartile 4 (17,790–85,719)
Age, years	59.8 (50.4–69.3)	62.4 (52.9–72.4)	62.9 (51.3–71.9)	60.2 (50.7–68.9)	57.0 (48.5–65.6)
Female	2,711 (49.8%)	698 (68.7%)	825 (61.9%)	711 (47.7%)	477 (33.4%)
Race/Ethnicity					
Non-Hispanic White	1,979 (60.9%)	275 (50.3%)	496 (56.8%)	566 (62.7%)	642 (67.5%)
Non-Hispanic Black	1,507 (15.9%)	228 (14.0%)	399 (17.2%)	426 (16.1%)	454 (15.6%)
Mexican-American	1,029 (9.7%)	305 (16.5%)	297 (11.2%)	242 (8.4%)	185 (6.3%)
Other	959 (13.6%)	257 (19.2%)	252 (14.7%)	253 (12.8%)	197 (10.7%)
Education					
Less than high school	1,867 (24.0%)	524 (36.2%)	538 (26.3%)	443 (22.3%)	362 (17.8%)
High school or equivalent	1,288 (25.7%)	215 (25.5%)	345 (26.7%)	366 (26.1%)	362 (24.7%)
Some college/Associate's	1,468 (30.4%)	192 (22.7%)	366 (30.5%)	428 (30.2%)	482 (34.4%)
College degree	851 (19.9%)	134 (15.5%)	195 (16.5%)	250 (21.4%)	272 (23.2%)
Poverty-Income Ratio					
<1.3	1,733 (23.5%)	457 (33.8%)	470 (25.5%)	428 (22.1%)	378 (18.1%)
1.3–3.49	2,061 (36.6%)	309 (30.1%)	574 (39.7%)	611 (39.7%)	567 (34.7%)
3.5	1,210 (33.2%)	169 (25.5%)	270 (27.5%)	326 (31.1%)	445 (43.1%)
Missing	470 (6.8%)	130 (10.7%)	130 (7.3%)	122 (7.1%)	88 (4.1%)
Smoking status					
Never	2,718 (48.3%)	632 (59.2%)	726 (49.3%)	709 (46.9%)	651 (43.4%)
Former	1,874 (35.1%)	294 (25.0%)	524 (36.6%)	519 (34.9%)	537 (39.3%)
Current	882 (16.6%)	139 (15.8%)	194 (14.1%)	259 (18.2%)	290 (17.3%)
Body mass index, kg/m^2					
<24.9 (normal weight)	675 (11.0%)	162 (14.0%)	200 (13.2%)	168 (9.4%)	145 (9.4%)
25–<30.0 (overweight)	1,465 (24.0%)	315 (25.5%)	413 (25.7%)	376 (26.5%)	361 (19.9%)
30–<35.0 (obesity I)	1,647 (29.4%)	323 (28.8%)	451 (31.9%)	459 (29.4%)	414 (27.9%)
35–<40.0 (obesity II)	889 (18.7%)	151 (17.2%)	215 (15.0%)	243 (17.8%)	280 (23.0%)
40 (obesity III)	798 (16.9%)	114 (14.5%)	165 (14.3%)	241 (17.0%)	278 (19.8%)

	All	Dietary AGEs (CML), kU/day[a]			
		Quartile 1 (110–6,874)	Quartile 2 (6,876–11,603)	Quartile 3 (11,618–17,764)	Quartile 4 (17,790–85,719)
HbA1c, %	6.8 (6.3–7.8)	6.8 (6.2–7.6)	6.8 (6.2–7.6)	6.8 (6.3–7.7)	7.0 (6.4–8.1)
Total calories (kcal)/day	1,796 (1,377–2,271)	1,177 (904–1,516)	1,496 (1,215–1,826)	1,825 (1,506–2,164)	2,363 (1,939–2,932)

CML = N^e-(carboxymethyl)lysine

Counts shown are unweighted and variance estimates are adjusted for the complex survey design.

[a]Medians and interquartile ranges are shown for continuous variables.

Table 2 –

Daily Estimated Advanced Glycation End Products (AGEs) Intake, by Participant Characteristics, 2003–2018 (n=5,474)

	Dietary AGEs (CML), kU/day[a]
Overall	13,682 (8,727–19,850)
Overall, per 1,000 kcal	7,682 (5,548–10,023)
Age	
18–29	18,318 (13,351–24,080)
30–39	14,457 (9,888–20,758)
40–49	14,235 (9,439–21,156)
50–59	15,119 (9,392–21,723)
60–69	13,742 (9,069–19,882)
70	11,273 (7,436–16,556)
Gender	
Male	16,123 (10,715–22,673)
Female	11,441 (7,385–16,431)
Race/Ethnicity	
Non-Hispanic White	14,582 (9,612–20,511)
Non-Hispanic Black	13,620 (9,180–19,984)
Mexican-American	10,726 (6,594–16,112)
Other	11,745 (7,320–17,900)
Education	
Less than high school	11,642 (7,008 –17,178)
High school or equivalent	13,631 (8,689–18,949)
Some college/Associate's	14,525 (9,819–20,462)
College degree	15,081 (9,818–21,976)
Poverty-Income Ratio	
<1.3	11,833 (7,122–17,579)
1.3–3.49	13,690 (9,126–19,326)
3.5	15,563 (10,232–22,085)
Missing	11,393 (6,782–15,932)
Smoking status	

	Dietary AGEs (CML), kU/day[a]
Never	13,118 (7,985–18,950)
Former	14,427 (9,805–21,132)
Current	13,980 (9,207–19,738)
Body mass index, kg/m²	
<24.9 (normal weight)	11,745 (7,682–18,548)
25–<30.0 (overweight)	13,002 (8,433–18,053)
30–<35.0 (obesity I)	13,367 (8,474–18,939)
35–<40.0 (obesity II)	15,502 (9,425–22,310)
40 (obesity III)	14,724 (10,214–21,810)
HbA1c, %	
<6%	12,689 (8,037–17,651)
6–6.9%	13,100 (8,448–19,190)
7–7.9%	14,489 (9,100–20,712)
8%	14,759 (9,370–21,239)

CML = N^e-(carboxymethyl)lysine

Counts shown are unweighted and variance estimates are adjusted for the complex survey design.

[a]Medians and interquartile ranges are shown.

Table 3 –

Association Between Quartiles of Advanced Glycation End Products (AGEs) Intake and Mean HEI-2015 Score, 2003–2018 (n=5,474)

HEI-2015 Component	Maximum Possible Score	Dietary AGEs (CML), kU/day [a]				p-value [b]
		Quartile 1 (110–6,874)	Quartile 2 (6,876–11,603)	Quartile 3 (11,618–17,764)	Quartile 4 (17,790–85,719)	
Total Score	100	55.19 ± 0.64	54.06 ± 0.53	52.07 ± 0.49	49.00 ± 0.52	<0.001
Adequacy						
Total fruits	5	2.82 ± 0.10	2.61 ± 0.09	2.25 ± 0.07	1.81 ± 0.07	<0.001
Whole fruits	5	2.70 ± 0.11	2.72 ± 0.09	2.42 ± 0.08	2.00 ± 0.08	<0.001
Total vegetables	5	3.36 ± 0.07	3.29 ± 0.05	3.26 ± 0.06	3.06 ± 0.05	<0.001
Greens and beans	5	1.62 ± 0.09	1.50 ± 0.06	1.45 ± 0.07	1.32 ± 0.08	<0.001
Total protein foods	5	3.81 ± 0.06	4.30 ± 0.03	4.44 ± 0.04	4.56 ± 0.03	<0.001
Seafood and plant proteins	5	2.15 ± 0.09	2.30 ± 0.07	2.33 ± 0.08	2.29 ± 0.09	<0.001
Dairy [c]	10	4.85 ± 0.17	4.99 ± 0.14	4.75 ± 0.09	4.98 ± 0.13	<0.001
Fatty acids	10	5.21 ± 0.14	4.91 ± 0.11	4.90 ± 0.13	4.59 ± 0.11	<0.001
Whole grains	10	3.55 ± 0.17	3.44 ± 0.13	2.87 ± 0.12	2.29 ± 0.10	<0.001
Moderation						
Refined grains	10	5.88 ± 0.17	5.92 ± 0.12	6.12 ± 0.11	5.96 ± 0.12	<0.001
Sodium	10	4.52 ± 0.14	4.18 ± 0.11	3.98 ± 0.14	3.60 ± 0.11	<0.001
Added sugars	10	7.37 ± 0.14	7.51 ± 0.11	7.65 ± 0.10	7.78 ± 0.11	<0.001
Saturated fats	10	7.35 ± 0.13	6.39 ± 0.11	5.65 ± 0.13	4.77 ± 0.12	<0.001

Abbreviations: CML = N^e-(carboxymethyl)lysine; HEI-2015 = Healthy Eating Index 2015.

Variance estimates are adjusted for the complex survey design.

[a] Means and standard errors are shown for HEI-2015 scores. A higher score for "adequacy" components indicates greater consumption of the food group. A higher score for "moderation" components indicates lower consumption of the food group. A higher total score is suggestive of a healthy dietary pattern.

[b] Displayed p-values are from an overall F-test.

[c] Includes only the non-fat fraction of total dairy consumption

Table 4 –

Association Between Quartiles of Advanced Glycation End Products Intake and All-cause Mortality, 2003–2014 (n=3,884)

| | Hazard Ratio (95% Confidence Interval) | |
	Model 1	Model 2
CML - Quartile 1 (ref.)	-	-
CML - Quartile 2	0.93 (0.69–1.24)	0.91 (0.69–1.21)
CML - Quartile 3	0.92 (0.65–1.30)	0.90 (0.63–1.27)
CML - Quartile 4	1.21 (0.86–1.70)	1.16 (0.84–1.60)

Counts shown are unweighted and variance estimates are adjusted for the complex survey design.

Abbreviations: CML = N^e-(carboxymethyl)lysine

Table 5 -

Association Between Quartiles of Advanced Glycation End Products Intake and All-cause Mortality, Alternative Method to Estimate Intake, 2003–2014 (n=3,884)

	Model 1	Model 2
CML		
Quartile 1 (ref.)	-	-
Quartile 2	1.02 (0.79–1.32)	1.02 (0.78–1.33)
Quartile 3	0.97 (0.72–1.32)	0.98 (0.73–1.32)
Quartile 4	1.34 (0.90–2.01)	1.37 (0.93–2.02)
CEL		
Quartile 1 (ref.)	-	-
Quartile 2	1.01 (0.74–1.39)	0.99 (0.72–1.37)
Quartile 3	0.89 (0.66–1.19)	0.87 (0.64–1.19)
Quartile 4	1.25 (0.85–1.82)	1.30 (0.91–1.85)
MGH1		
Quartile 1 (ref.)	-	-
Quartile 2	0.79 (0.60–1.04)	0.77 (0.59–0.99)
Quartile 3	0.65 (0.47–0.90)	0.67 (0.48–0.92)
Quartile 4	1.08 (0.74–1.57)	1.18 (0.83–1.67)

Abbreviations: CML = N^e-(carboxymethyl)lysine; CEL = N^e-(1-carboxyethyl)lysine; MGH1 = N^δ-(5-hydro-5-methyl-4-imidazolon-2-yl)-ornithine