

Dietary intake of advanced glycation endproducts (AGEs) and changes in body weight in European adults

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Abstract: 301 words

Text: 3473 words

Tables: 3

Supplementary material: 4 Tables and 4 Figures

Acknowledgements:

We thank Petra H. Peeters and Anne M. May from the Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, The Netherlands, for coordinating the EPIC-Panacea study, and all EPIC participants and staff for their contribution to the study.

Funding:

This work was partially financially supported by the World Cancer Research Fund International (WCRF, grant no. 2015/1391, MJ, VK, and HF) and the Fondation de France (FDF, grant no. 00081166, HF, and FDF grant no. 00089811, ALMC).

The coordination of EPIC is financially supported by the European Commission (DG-SANCO) and the International Agency for Research on Cancer. The national cohorts are supported by the following funders: Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Éducation Nationale, Institut National de la Santé et de la Recherche Médicale (INSERM) (France); German Cancer Aid, German Cancer Research Center (DKFZ), Federal Ministry of Education and Research (BMBF) (Germany); the Hellenic Health Foundation (Greece); Associazione Italiana per la Ricerca sul Cancro-AIRC-Italy and National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), Statistics Netherlands (The Netherlands); Health Research Fund (FIS-ISCIII), the Regional Governments of Andalucía, Asturias, Basque Country, Murcia, Navarra, and the Catalan Institute of Oncology (Barcelon), Spain; Cancer Research UK (14136 to EPIC-Norfolk; C570/A16491 and C8221/A19170 to EPIC-Oxford), Medical Research Council (1000143 to EPIC-Norfolk, MR/M012190/1 to EPIC-Oxford) (UK).

List of Abbreviations

AGEs	advanced glycation endproducts
CEL	N ^ε -1- carboxyethyl-lysine
CML	N ^ε -carboxymethyl-lysine
DQ	Dietary questionnaires
DXA	dual-energy X ray absorptiometry
EPIC	European Prospective Investigation into Cancer and nutrition
MG-H1	N ^δ -(5-hydro-5-methyl-4-imidazol-2-yl) ornithines
mrMDS	modified relative Mediterranean Diet Score
PANACEA	Physical Activity, Nutrition, Alcohol, Cessation of smoking, Eating out of home in relation to Anthropometry

1 **Abstract**

2 *Purpose* Advanced glycation endproducts (AGEs) can be formed in foods by the reaction of reducing sugars with
3 proteins, and have been shown to induce insulin resistance and obesity in experimental studies.

4 We examined the association between dietary AGEs intake and changes in body weight in adults over an average
5 of 5 years of follow-up.

6 *Methods* A total of 255,170 participants aged 25-70 years were recruited in 10 European countries (1992-2000)
7 in the PANACEA study (Physical Activity, Nutrition, Alcohol, Cessation of smoking, Eating out of home in
8 relation to Anthropometry), a sub-cohort of the EPIC (European Prospective Investigation into Cancer and
9 Nutrition). Body weight was measured at recruitment and self-reported between 2-11 years later depending on the
10 study center. A reference database for AGEs was used containing UPLC-MS/MS-measured N^ε-(carboxymethyl)-
11 lysine (CML), N^ε-(1-carboxyethyl)-lysine (CEL), and N^δ-(5-hydro-5-methyl-4-imidazolone-2-yl)-ornithine (MG-
12 H1) in 200 common European foods. This reference database was matched to foods and decomposed recipes
13 obtained from country-specific validated dietary questionnaires in EPIC and intake levels of CEL, CML, and MG-
14 H1 were estimated. Associations between dietary AGEs intake and body weight change were estimated separately
15 for each of the three AGEs using multilevel mixed linear regression models with center as random effect and
16 dietary AGEs intake and relevant confounders as fixed effects.

17 *Results* A one-SD increment in CEL intake was associated with 0.111 kg (95% CI 0.087 to 0.135) additional
18 weight gain over 5 years. The corresponding additional weight gain for CML and MG-H1 was 0.065 kg (0.041 to
19 0.089) and 0.034kg (0.012, 0.057), respectively. The top six food groups contributing to AGEs intake, with
20 varying proportions across the AGEs, were cereals/cereal products, meat/processed meat, cakes/biscuits, dairy,
21 sugar and confectionary, and fish/shellfish.

22 *Conclusion* In this study of European adults, higher intakes of AGEs were associated with marginally greater
23 weight gain over an average of 5-years of follow-up.

24 **Keywords** dietary advanced glycation endproducts, weight change, obesity, adults, Europe

25 Introduction

26 In 2016, more than 39% of the world population was affected by overweight or obese (body mass index, BMI \geq
27 25 kg/m²) and it is projected that the prevalence of obesity will increase further in the years to come [1]. This is
28 of concern because the risk of heart disease, stroke, diabetes, and of certain cancers escalates steadily with
29 increasing BMI [2]. Although modest weight loss through changes in diet and physical activity is possible [3],
30 few people manage to maintain these changes in weight over the long term [4]. Prevention of weight gain and
31 obesity are therefore of substantial public health importance.

32 Overweight and obesity arise as consequence of an imbalance between energy intake and expenditure
33 over a prolonged period [5]. Established risk factors contributing to an energy imbalance include high intakes of
34 energy-dense food and low physical activity [6]. However, an ever increasing proportion of people in virtually all
35 regions of the world have access to low-cost, but highly-processed, energy-dense and nutrient-poor food products
36 [7]. That such foods may facilitate overeating has been confirmed in a randomized controlled trial, where a diet
37 composed of ultra-processed foods lead to significantly greater energy intake and weight gain as compared with
38 an unprocessed diet[8]. However, it is currently uncertain what factors trigger overeating of such foods. A by-
39 product of food processing are advanced glycation endproducts (AGEs) [9]. Dietary AGEs are formed, in
40 particular, during heating, by the non-enzymatic reaction of sugars with proteins [10,11]. Major sources of AGEs
41 are foods that undergo dry heat processing to improve flavour and aroma such as crisps, crackers, or cereal
42 products, but also meat and meat-derived products [12]. Well-characterized AGEs are N^ε-carboxymethyl-lysine
43 (CML), N^ε-1-carboxyethyl-lysine (CEL), and N^δ-(5-hydro-5-methyl-4-imidazolone-2-yl) ornithines (MG-H1),
44 which are formed by the reaction of proteins with sugar, sugar-derived intermediates such as methylglyoxal,
45 glyoxal and 3-deoxyglucosone, and with lipid peroxidation products [9,13].

46 Higher AGEs intake may induce weight gain via insulin resistance [14] and hypothalamic inflammation
47 [15]. From animal models and clinical studies in humans, there is evidence that higher exposure to dietary AGEs
48 is associated with impaired insulin sensitivity and weight gain [16-19]. To date there are no prospective data on
49 dietary AGE exposure and weight change available from cohort studies. We, therefore, examined the association
50 of dietary AGEs intake and weight change in a sub-cohort of the EPIC (European Prospective Investigation into
51 Cancer and nutrition) study, the EPIC-Panacea study; PANACEA (Physical Activity, Nutrition, Alcohol,
52 Cessation of smoking, Eating out of home in relation to Anthropometry), where repeated assessments of weight
53 are available.

54

55 Methods

56 **Study population**

57 The EPIC study is an ongoing prospective cohort study across 23 centers in 10 European countries: Denmark,
58 France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom (UK). From
59 1992 to 2000 a total of 521,448 men and women were recruited. In France, Norway, Utrecht (Netherlands) and
60 Naples (Italy), only women were recruited. Individuals were selected from the general population with few
61 exceptions. In France, state-school employees were recruited. The Utrecht and Florence (Italy) centers included
62 women invited for a local population-based breast cancer screening program. Some centers in Italy and Spain
63 included members of local blood donor associations. In Oxford (United Kingdom), one-half of the cohort was
64 recruited from lacto-ovo vegetarians and vegans. The rationale and design of the EPIC has been described in detail
65 elsewhere [20,21]. The EPIC study was approved by the Ethical Review Boards of the IARC and the Institutional
66 Review Board of each participating EPIC center.

67 For the PANACEA study, some of the original 23 centers were combined within countries depending on
68 their follow-up times and/or weight measurement methods, resulting in 16 centers. We excluded pregnant women,
69 participants with missing dietary or lifestyle information, missing data on weight and height or with unreliable
70 anthropometric values at baseline (n=23,713). We further excluded 122,154 individuals with missing weight at
71 follow-up and 2,288 individuals with outlying anthropometry at follow-up: weight change < -5 or > 5 kg/year and
72 BMI at follow up < 16 kg/m². Last, we excluded participants identified as dietary energy over- (n=24,331) or
73 under-reporters (n=93,792) according to Goldberg [22]. This has been shown to reduce BMI-associated bias in
74 energy intake reporting [23], in particular due to underreporting of cakes and cookie consumption [24], which are
75 among the main food groups contributing to AGE intake. More details on follow-up exclusions are given in
76 **Supplemental Figure 1 (Online Resource)** and have been described previously [25,26].

77 After these exclusions, a sample of 70,570 men and 184,600 women with complete and plausible body
78 weight data was available for analyses.

80 **Anthropometric measures and weight change**

81 Two body weight measures were available for each participant: at baseline and after a median follow-up time of
82 5 years [min.: 2 years for Heidelberg (Germany), max.:11 years for Varese (Italy)]. All centers used standardized
83 procedures to measure weight and height at baseline, except, in France, Norway, and Oxford center, where
84 **participants** self-reported their weight. Follow-up weight was self-reported, except for Cambridge (UK) and
85 Doetinchem (The Netherlands) where it was measured [25,26]. The accuracy of self-reported anthropometric
86 measures at baseline and at follow-up was improved with prediction equations derived from **participants** with both

87 measured and self-reported weight at baseline [27]. The main outcome of our study was weight change in kg per
88 5 years, calculated as weight at follow-up minus weight at baseline divided by the follow-up time in years and
89 multiplied by 5 years.

90

91 **Dietary assessment and estimation of AGEs intake**

92 In the EPIC study, usual food intake was assessed **once** at baseline using country-specific validated dietary
93 questionnaires (DQ) [21]. **In brief, three types of DQ were used to assess habitual food consumption of the past**
94 **12 months; a) quantitative DQ were used in northern Italy, Ragusa in Italy, The Netherlands, Germany, Greece,**
95 **Spain, and France, b) semi-quantitative food-frequency questionnaires were used in Denmark, Norway, Naples in**
96 **Italy, and Umeå in Sweden, and c) a combination of semi-quantitative food-frequency questionnaires and 7 to 14**
97 **day food records were used in the UK and Malmö (Sweden). Harmonization of food grouping and portion sizes**
98 **for quantification was carried out centrally at IARC.** To estimate AGEs intake, we used a reference database
99 containing CEL, CML and MG-H1 content values (in mg/100g of food) in over 200 commonly consumed foods
100 [9]. The content values were obtained from European foods measured by ultra-performance liquid
101 chromatography tandem mass-spectrometry [9]. DQ foods from EPIC were then matched to the AGE database by
102 name and, whenever applicable, by their associated descriptors, particularly those pertaining to preparation and/or
103 processing. Generic or multi-ingredient DQ foods were decomposed into more specific foods or ingredients based
104 on country-specific recipes provided by previous EPIC projects [28]. An end-user EPIC AGEs composition
105 database was then generated containing CEL, CML, and MG-H1 content (in mg/100 g) for all DQ foods and
106 recipes. Finally, dietary AGEs intake of these three compounds was calculated (in mg) for the full EPIC cohort
107 by accounting for the reported frequency and quantity of foods consumed by each EPIC participant.

108

109 **Assessment of other covariates**

110 Data on socio-demographic, lifestyle and other factors, including education level, physical activity and smoking
111 history were collected at baseline through validated questionnaires [21].

112

113 **Statistical analyses**

114 Habitual dietary AGEs intake of CEL, CML, and MG-H1 were analysed in separate models both on a continuous
115 scale per 1 standard deviation (SD) /day increment (see below) and by categories, where the energy adjusted
116 dietary AGEs intake was divided by quintiles and the lowest intake placed in the first (reference) category.

117 The association between dietary AGEs intake and body weight change (kg/5 years) was estimated using
118 multilevel mixed linear regression models with center as random effect and dietary AGEs intake and relevant
119 confounders as fixed effects. Models with three different sets of adjustments were fit. The first model (M1) was
120 adjusted for age, sex, and body mass index (BMI) at baseline. Model 2 was further adjusted for total energy intake
121 follow-up time, educational level, levels of physical activity, smoking status at baseline.

122 Model 3 was additionally adjusted for Mediterranean diet, representing healthy dietary habits, using the
123 modified relative Mediterranean Diet Score (mrMDS) [29]. We log (natural)-transformed CEL, CML, and MG-
124 H1 to improve normality and standardized them by dividing each AGE with its standard deviation. Associations
125 with weight change are expressed per 1 SD increment in the log-transformed AGEs intake.

126 Participants with missing values for physical activity (n=3,663, 1.4%), education (n= 3,490, 1.4%) and
127 smoking status (n= 5,138, 2.0%) at baseline were classified in a separate category and included in the models.
128 Model assumptions and fit were checked visually by plotting the residuals against each of the categorical
129 covariates.

130 Because of high inter-correlations between CEL, CML and MG-H1, (*Pearson r* 0.8) we calculated
131 standardized principal components for the three dietary AGEs in order to use them together in one model. This
132 allowed us to investigate independent associations among the three dietary AGEs with weight change.

133 We also conducted center-specific analyses, where respective results were then meta-analyses in random
134 effect models for each AGE [30]. Since the meta-analysed summary estimates were very similar to the pooled
135 analyses, we only present the latter.

136 We tested *a priori* for effect modification by age (categorised as younger than median age <51 and ≥51
137 years), sex, and BMI categories at baseline (<25, 25-30, > 30 kg/m²). This was done by including interaction terms
138 between each potential effect modifier and each individual dietary AGE compound (continuous per 1 SD/day) in
139 the models. *P* values for the interaction term were calculated using *F* tests.

140 We performed a range of sensitivity analyses to assess robustness of our findings and address potential
141 biases (**Supplemental Table 1, Online Resource**). In order to assess whether observed associations were driven
142 by any of the main food sources of AGEs, we adjusted Model 2 in turn for each of the five main food groups
143 contributing to dietary AGEs intake (**Supplemental Table 2, Online Resource**).

144 All statistical analyses were performed with STATA 14.1 (College Station, Texas, USA).

145

146 **Results**

147 *Characteristics of the study population*

148 **Table 1** shows the main characteristics of the study population at baseline in the lowest and highest quintile of
149 each energy adjusted intake of dietary AGE. Participants in the highest quintile of AGEs intake had slightly higher
150 weight gain, were more likely to be women and more likely to be current smoker at baseline. There were some
151 expected differences in consumption of specific food groups, but not with a Mediterranean dietary pattern (Table
152 1).

153 *Main food sources of advanced glycation endproducts*

154 Cereals and cereal products, meat and meat products, fish, cakes and biscuits, and dairy were the main food
155 sources of AGEs (**Supplemental Figures 2-4, Online Resource**). Depending on the AGE compound, the
156 proportion of these main food sources varied to some extent. For example, meat and meat products contributed
157 32% to CEL intake, but only 10% to MG-H1 intake. Cereals and cereal products contributed 38% and 48% to
158 CML intake and MG-H1 intake, respectively.

159

160 *Intake of AGE's and 5-year changes in body weight*

161 Between baseline and the 2nd weight assessment on average five years later, the mean weight increase in the study
162 population was 2.1 kg with large variation between participants (SD 5.0 kg). Body weight changes (kg) over an
163 average of 5 years according to baseline dietary AGEs intake are shown in **Table 2**. After adjustment for total
164 energy intake and potential confounders, each of the three AGEs was positively associated with weight gain.
165 Among the three AGEs, CEL intake was associated with the highest (0.111 kg per 1 SD intake increase/5 years,
166 95% CI 0.087 to 0.135) and MG-H1 intake with the lowest (0.034 kg per 1 SD intake increase/5 years; 95% CI
167 0.012 to 0.057) increase of weight gain in our main model (Model 3). However, associations from model 2
168 remained nearly unchanged after further adjustment in model 3 for Mediterranean diet (Table 2).

169 Analyses by quintiles of each dietary AGEs intake confirmed the findings using intake on a continuous
170 scale, where participants in the highest quintile of CEL, CML, and MG-H1 gained more weight as compared to
171 participants of the lowest quintile (Table 2). The main findings were also robust to a range of sensitivity analyses
172 (Supplemental Table 1, Online Resource). Further adjustment for in turn each of the five main food sources, (meat,
173 fish, cakes, cereals and dairy) also resulted in similar associations with weight change, except after adjustment for
174 meat/meat products, which led to an attenuation by approximately half (Supplemental Table 2, Online Resource).

175 Age and BMI at baseline did not modify associations between CEL, CML, and MG-H1 and weight
176 change. A significant *P* interaction value was obtained between sex and all three AGEs (each *P* interaction <
177 0.001), where the association with weight gain was more pronounced in women than in men. The stratified results
178 in women and men for all three AGEs in Model 3 are shown in **Supplemental Table 3 (Online Resource)**.

179 The results of the combined analysis of the three dietary AGEs with regard to weight change are shown
180 in **Table 3**. Principal component (PC) 1, representing an average high intake of all three AGEs together, showed
181 a positive association with weight gain. The same applied for PC3 reflecting higher intake of CEL. PC2, reflecting
182 a high intake of CML with concurrent low intake of CEL and MG-H1, was not associated with weight change.

183

184 **Discussion**

185 In this prospective analysis, we found that higher dietary intake of AGEs was associated with marginally greater
186 weight gain over an average of 5 years of follow-up in adults from 10 European countries. Observed associations
187 were strongest for CEL, where a high vs. low dietary CEL intake corresponded to a 10% greater body weight
188 increase relative to the population average weight gain. This increase of weight appears trivial at an individual
189 level, but at population level associations were comparable to those observed for high adherence to the
190 Mediterranean diet in the same study population, albeit opposite in direction [31]. Dietary AGEs may be important
191 compounds that lead to energy imbalance and weight gain, and should therefore be studied further in public health
192 research.

193 To date, no prospective epidemiological study has evaluated the relationship between dietary AGEs
194 intake and weight change over time. In vivo models in mice fed with either a high AGE or a low AGE diet, showed
195 a significantly higher weight gain among the high AGE diet groups [17,18], which is congruent with our findings.

196 In a randomized controlled trial, a diet composed of ultra-processed foods lead to significantly greater
197 energy intake and weight gain as compared with an unprocessed diet [8]. The putatively high amounts of AGEs
198 in highly processed foods might be one of the potential components triggering energy overconsumption. However,
199 potential mechanism by which higher dietary intake of AGEs may promote weight gain are not well understood.
200 There is suggestive evidence from experimental models and human intervention studies that higher AGE intake
201 can lead to insulin resistance [32-34]. In a randomized crossover diet-controlled intervention trial with 62
202 volunteers, one month of consuming a high-heat-treated diet, with CML as a marker, induced insulin resistance
203 [32]. Similarly, a double-blind, randomized, crossover trial in 20 participants found that insulin sensitivity
204 increased after a two-week isoenergetic- and macronutrient-matched low-AGE diet, whereas it showed a tendency
205 to decrease after the two-week high-AGE diet [33]. High-normal insulin levels may inhibit lipolysis and promote
206 lipogenesis in adipocytes [14]. A link between AGEs, insulin resistance and weight gain has also been shown in
207 an in vivo study in *Drosophila*, where elevated methylglyoxal, which forms irreversible adducts such as MG-H1
208 in vivo, lead to progressive development of insulin resistance and weight gain [34]. Hypothalamic inflammation
209 might be another pathway whereby higher AGEs intake could promote weight gain. In a rodent study, the

210 combination of an overconsumption of fat and sugar triggered hypothalamic inflammatory responses, mediated
211 by excessive CML and MG-H1 production in hypothalamic neurons [15]. In a hypothalamic inflammatory state,
212 the signaling of two key hormones in energy homeostasis, i.e. insulin and leptin, is compromised, which in turn
213 can trigger an adaptive increase of food intake relative to energy expenditure that favors weight gain [35]. It is of
214 note that we adjusted our analysis for total energy intake, which is recommended in order to reduce bias related
215 to self-reported diet [36]. However, this is not unproblematic in case of weight gain as outcome because of over-
216 adjustment for a mediator. Indeed, as shown in our sensitivity analysis, the magnitude of associations between
217 dietary AGEs intake and weight change more than tripled in models without energy adjustment (Supplemental
218 Table 1).

219 The composition of nutrients, temperature, moisture, and duration of heat exposure are the main
220 parameters that determine the rate of dietary AGEs formation in foods [12]. The formation takes place
221 spontaneously under certain conditions and food preparation methods, like dry-heat cooking at high temperature
222 [37]. In addition, several factors such as composition of the food, presence of pro- or anti-oxidants, availability of
223 water, as well as pH impact on the rate and diversity of AGE formation [38]. It is assumed that the absorption of
224 dietary AGEs into the circulation in humans is about 10% of ingested AGEs, and the renal excretion of the
225 absorbed amount in healthy participants is about 30% [39]. Scheijen et al. showed that higher intake of dietary
226 CML, CEL, and MG-H1 was associated with significantly higher levels of free plasma and urinary CML, CEL,
227 and MG-H1, demonstrating dietary AGEs are indeed absorbed in the human body [40].

228 The main food sources of AGEs with different proportions across the three AGEs were cereals or cereal
229 products, meat and processed meat, cakes and biscuits, dairy, sugar and confectionary, as well as fish and shellfish.
230 Previous studies in the same study population investigated associations between some of these food groups and
231 weight change [41,26,31]. In Vergnaud et al., it was shown that a higher meat consumption was positively
232 associated with weight gain in men and women (per 1 SD higher meat consumption associated with approximately
233 0.25 kg greater weight gain over 5 years) [26]. In our study, meat and meat products contributed to higher CEL
234 intake. Therefore, our findings may in part explain the positive association found in Vergnaud et al. 2010 [26].
235 However, we cannot exclude that higher meat consumption was at least partially driving observed associations
236 between CEL intake and weight gain, because adjustment for meat/processed meat consumption attenuated
237 associations by half (Supplemental Table 2, Online Resource).

238 Several limitations of our study should be pointed out. First only self-reported weight at follow-up was
239 available in most centers. To alleviate this potential source of bias, we applied a prediction equation to improve
240 self-reported weight estimates [27]. Furthermore, in the EPIC-Norfolk study (UK Cambridge center of EPIC) a

241 high correlation between self-reported and measured weight data has been shown ($r=0.97$ in men and $r=0.98$
242 women) [42], likewise the Norway center of EPIC has been presented that self-reported weight and height provide
243 a valid classification of BMI in their cohort of middle-aged Norwegian women, which means that ranking of
244 participants according to self-reported weight was adequate [43]. Moreover, associations with weight gain were
245 strongest in the two centers (Cambridge, UK and Doetinchem, NL) with measured weight at follow-up (data not
246 shown). Second, we were not able to accurately measure changes in body composition (e.g. using dual-energy X
247 ray absorptiometry, DXA); therefore, we had to make the reasonable assumption that encountered weight changes
248 are largely due to changes in body fat mass and not in lean body mass or height [5]. Third, we were not able to
249 elucidate for potential changes in diet during follow-up; yet dimensions of change in weight appear to be more
250 pronounced and more robust if changes in diet can be accounted for [44]. In view of the inherent limitation of all
251 epidemiology studies using self-reported dietary data, measurement error is another drawback. To minimise this
252 bias, adjustments were made for total energy intake, sex, age, dietary patterns and other lifestyle factors notably
253 physical activity and smoking, and for plausibility of dietary energy reporting; the latter has been recently shown
254 in the EPIC-Potsdam sub-study to improve expected associations between intakes of energy-dense foods and BMI
255 [24]. Another limitation might be that given the inevitable correlation between foods and AGEs, residual
256 confounding from other components in the same foods cannot be ruled out. In order to address this potential issue,
257 we in turn adjusted for the five main food groups rich in dietary AGEs and found that the observed associations
258 between dietary AGEs and weight change were to a great extent independent of any single food source.

259 Strengths of our study include its prospective design with a reasonably long follow-up and the large
260 sample size. To the best of our knowledge, it is the first prospective human study confirming evidence from in
261 vivo animal models that higher dietary AGEs intake is associated with weight gain. We used a food-composition
262 table based on state-of-the-art measured AGEs in commonly consumed foods [9]. Nevertheless, to further increase
263 the knowledge about dietary AGEs and their impact on weight change and other health outcomes, it is important
264 to continue the search for, and validation of biomarkers of dietary AGEs intake in the future.

265 We conclude that in this prospective study of adults from 10 European countries representing populations
266 with heterogeneous diets, higher intakes of AGEs were associated with marginally greater weight gain over an
267 average of 5-years of follow-up. Further studies are needed to confirm these findings.

Author contributions:

Heinz Freisling and Mazda Jenab developed the overall research plan; Viktoria Knaze and Reynalda Cordova performed the data matching; Casper G. Schalkwijk provided the AGEs database; Reynalda Cordova conducted the statistical analyses. Vivian Viallon contributed to the statistical analyses; Reynalda Cordova and Heinz Freisling wrote the manuscript; Heinz Freisling supervised the data analysis, reviewed/edited the manuscript, and had primary responsibility for final content; and all authors: contributed substantially to data collection, the interpretation of data and the drafting or critical revision of the manuscript for important intellectual content.

Where authors are identified as personnel of the International Agency for Research on Cancer / World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer / World Health Organization.

Ethics approval

The present study was approved by the ethics committees of the IARC and the individual study centers.

Conflict of Interest Statement

None of the authors declared a conflict of interest.

Data access

Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval. For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at: <http://epic.iarc.fr/access/index.php>.

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Table 1 Main characteristics of the study population according to the lowest (Q1) and highest (Q5) quintile of dietary advanced glycation endproducts (AGEs) intake

	CEL Q1	CEL Q5	CML Q1	CML Q5	MG-H1 Q1	MG-H1 Q5
Dietary AGEs intake (mg/day)	1.2 ± 0.8	3.5 ± 0.7	2.2 ± 0.8	4.4 ± 0.7	7.3 ± 0.6	9.8 ± 0.7
Follow uptime (years)	5.7 ± 2.6	4.9 ± 2.2	5.4 ± 2.3	5.1 ± 2.3	5.4 ± 2.5	5.3 ± 2.1
Weight change (kg/5 years) ¹	1.8 ± 4.5	2.2 ± 5.0	2.0 ± 4.8	2.1 ± 4.9	1.9 ± 4.7	2.2 ± 4.7
Women (%)	70	73	68	75	70	75
Age (years)	53.2 ± 8.6	51.0 ± 9.9	53.1 ± 9.2	51.9 ± 9.8	53.4 ± 8.3	51.2 ± 10.3
BMI at inclusion (kg/m ²)	24.7 ± 3.9	25.2 ± 4.1	25.2 ± 4.1	24.9 ± 3.9	25.0 ± 3.9	24.5 ± 3.8
BMI categories (%)						
< 25 kg/m ²	58	54	54	56	55	61
25 < 30 kg/m ²	33	33	34	33	34	30
> 30 kg/m ²	9	12	12	11	11	9
University degree (%)						
Missing	1.1	1.9	1.4	1.7	1.2	1.6
Physically inactive (%)						
Missing	0.7	1.0	1.6	0.8	0.5	1.6
Smoking status at baseline (%)						
Never	47	56	44	57	46	55
Former	27	25	26	25	26	28
Current	25	17	28	15	26	15
Missing	1.6	2.2	2.5	1.8	1.6	2.2
Previous illness (%) ²						
Missing	7.2	8.8	6.8	10.4	6.6	10.7
Dietary intake						
Total energy intake (kcal/day)	2202 ± 506	2201 ± 413	2193 ± 510	2192 ± 401	2177 ± 487	2183 ± 408
Vegetables (g/day)	225 ± 160	273 ± 142	285 ± 196	206 ± 126	224 ± 162	225 ± 139

Fruits (g/day)	273 ± 212	246 ± 164	293 ± 222	231 ± 157	257 ± 209	242 ± 162
Legumes (g/day)	12 ± 21	24 ± 29	15 ± 23	19 ± 27	9 ± 17	19 ± 29
Meat/products (g/day)	91 ± 55	121 ± 64	98 ± 57	108 ± 61	113 ± 59	93 ± 59
Dairy (g/day)	347 ± 268	338 ± 210	288 ± 223	415 ± 245	342 ± 261	373 ± 225
Fish (g/day)	34 ± 29	44 ± 37	36 ± 34	41 ± 35	38 ± 32	42 ± 39
Egg/egg products (g/day)	19 ± 17	20 ± 18	20 ± 19	19 ± 17	21 ± 18	17 ± 16
Potatoes (g/day)	94 ± 82	96 ± 69	98 ± 80	92 ± 66	95 ± 78	103 ± 75
Cereals/cereal products (g/day)	226 ± 109	235 ± 109	195 ± 82	250 ± 120	184 ± 83	268 ± 109
Sugar/confectionary (g/day)	55 ± 74	36 ± 29	48 ± 71	42 ± 33	55 ± 73	39 ± 30
Cakes/biscuits (g/day)	29 ± 30	52 ± 46	21 ± 20	65 ± 55	28 ± 30	52 ± 45
Added fat (g/day)	30 ± 18	28 ± 18	34 ± 21	25 ± 16	30 ± 18	27 ± 18
Non-alcoholic beverages (g/day)	1187 ± 848	996 ± 693	1185 ± 822	1027 ± 726	1186 ± 813	1141 ± 711
Alcoholic beverages (g/day)	286 ± 412	129 ± 191	305 ± 428	103 ± 152	301 ± 419	115 ± 168
mrMED score units/day	9 ± 3	9 ± 3	9 ± 3	9 ± 3	8 ± 3	9 ± 3

P values for continuous variables (ANOVA) and chi-square tests for categoric variables were all <0.001.

Data are expressed as arithmetic mean ± standard deviation (SD) if not stated otherwise

First quintile corresponds to the lowest and quintile five to the highest intake of energy-adjusted AGEs

BMI body mass index (calculated as weight in kilograms divided by height in meters squared), mrMED modified relative Mediterranean diet score (range 0-18; higher score characterizing a Mediterranean diet)

¹ Calculated as weight at follow-up minus weight at baseline divided by the follow-up time in years and multiplied by 5 years

² Type 2 diabetes, cardiovascular disease, cancer

CEL: N^ε-(1-carboxyethyl)lysine, CML: N^ε-(carboxymethyl)lysine, MG-H1: N^δ-(5-hydro-5-methyl-4-imidazolone-2-yl)-ornithine

Table 2 Difference in body weight gain (kg) over 5 years according to baseline dietary advanced glycation endproducts (AGEs) intake in 255,170 men and women

	CEL	CML	MG-H1
Model 1			
<i>Beta (95%CI) per 1 SD /day</i>	0.089 (0.069, 0.110)	0.052 (0.032, 0.072)	0.021 (0.002, 0.041)
Quintiles of dietary AGEs intake			
Lowest	Reference	Reference	Reference
Q2	0.091 (0.034, 0.149)	0.047 (-0.010, 0.105)	0.052 (-0.006, 0.110)
Q3	0.154 (0.095, 0.212)	0.078 (0.019, 0.136)	0.055 (-0.003, 0.114)
Q4	0.188 (0.128, 0.248)	0.101 (0.041, 0.161)	0.037 (-0.023, 0.096)
Q5	0.221 (0.158, 0.285)	0.116 (0.053, 0.178)	0.066 (0.005, 0.128)
<i>P trend (linear)</i>	<0.001	<0.001	0.098
Model 2			
<i>Beta (95%CI) per (1 SD/day)</i>	0.112 (0.088, 0.137)	0.068 (0.044, 0.092)	0.028 (0.006, 0.051)
Quintiles of dietary AGEs intake			
Lowest	Reference	Reference	Reference
Q2	0.106 (0.047, 0.164)	0.060 (0.002, 0.119)	0.054 (0.004, 0.113)
Q3	0.176 (0.115, 0.236)	0.098 (0.037, 0.158)	0.063 (0.003, 0.124)
Q4	0.222 (0.157, 0.286)	0.129 (0.064, 0.193)	0.046 (-0.017, 0.109)
Q5	0.267 (0.195, 0.340)	0.146 (0.075, 0.218)	0.082 (0.014, 0.150)
<i>P trend (linear)</i>	<0.001	<0.001	0.049
Model 3			
<i>Beta (95%CI) per 1 SD/day</i>	0.111 (0.087, 0.135)	0.065 (0.041, 0.089)	0.034 (0.012, 0.057)
Quintiles of dietary AGEs intake			
Lowest	Reference	Reference	Reference
Q2	0.104 (0.046, 0.163)	0.059 (0.000, 0.117)	0.060 (0.002, 0.119)
Q3	0.173 (0.112, 0.234)	0.094 (0.034, 0.155)	0.072 (0.011, 0.132)
Q4	0.219 (0.154, 0.283)	0.123 (0.059, 0.187)	0.057 (-0.007, 0.120)
Q5	0.264 (0.192, 0.337)	0.138 (0.066, 0.210)	0.098 (0.029, 0.167)
<i>P trend (linear)</i>	<0.001	<0.001	0.016

Multilevel linear mixed models with random effect on the intercept and slope according to center.

Overall mean 5- year weight gain corresponded to 2.1 kg (SD 5.0) and positive beta values indicate more weight gain (kg) over the same period.

Model 1 was adjusted for age, sex and BMI at baseline; Model 2 was further adjusted for follow-up-time in years, total energy intake (kcal/day), educational level, levels of physical activity, smoking status at baseline, and plausibility of dietary energy reporting; Model 3 was further adjusted for modified relative Mediterranean diet score. CEL (mg/day) mean intake \pm standard deviation (SD) within the quintiles of log-transformed CEL: Q1= 1.4 (\pm 0.2), Q2=1.8 (\pm 0.08), Q3=2.2 (\pm 0.1), Q4=2.6 (\pm 0.2), Q5=3.6 (\pm 0.8)

CML (mg/day) mean intake (SD) within the quintiles of log-transformed CML: Q1=2.0 (\pm 0.3), Q2=2.5 (\pm 0.1), Q3=3.0 (\pm 0.2), Q4=3.6 (\pm 0.2), Q5=4.9 (\pm 1.0)

MG-H1 (mg/day) mean intake (SD) within the quintiles of log-transformed MG-H1: Q1=13.2 (\pm 1.2), Q2=17.6 (\pm 1.0), Q3=21.0 (\pm 1.1), Q4=25.4 (\pm 1.5), Q5=36.1 (\pm 8.7)

CEL:N^ε-(1-carboxyethyl)-lysine, CML:N^ε-(carboxymethyl)-lysine, MG-H1: N^δ-(5-hydro-5-methyl-4-imidazolone-2-yl)-ornithine.

Table 3: Difference in body weight gain (kg) over 5 years according to baseline dietary advanced glycation endproducts (AGEs) intake in 255,170 men and women using principal component analysis of the three AGEs

	Model 1		Model 2		Model 3	
	<i>beta per 1 SD/day (95% CI)</i>		<i>beta per 1 SD/day (95% CI)</i>		<i>beta per 1 SD/day (95% CI)</i>	
PC1	0.057	(0.038, 0.077)	0.064	(0.044, 0.083)	0.064	(0.044, 0.083)
Quintiles of PC1						
Lowest	Reference		Reference		Reference	
Q2	0.075	(0.017, 0.132)	0.079	(0.022, 0.137)	0.080	(0.022, 0.138)
Q3	0.097	(0.038, 0.155)	0.104	(0.046, 0.163)	0.150	(0.046, 0.163)
Q4	0.076	(0.017, 0.135)	0.087	(0.028, 0.146)	0.087	(0.028, 0.147)
Q5	0.172	(0.110, 0.233)	0.187	(0.125, 0.248)	0.187	(0.126, 0.249)
<i>P</i> trend (linear)		< 0.001		< 0.001		< 0.001
PC2	-0.011	(-0.032, 0.011)	-0.008	(-0.030, 0.013)	-0.009	(-0.031, 0.013)
Quintiles of PC2						
Lowest	Reference		Reference		Reference	
Q2	-0.004	(-0.065, 0.065)	0.011	(-0.049, 0.072)	0.010	(-0.050, 0.071)
Q3	0.003	(-0.060, 0.066)	0.027	(-0.036, 0.090)	0.025	(-0.038, 0.088)
Q4	-0.029	(-0.093, 0.036)	-0.006	(-0.071, 0.058)	-0.009	(-0.074, 0.056)
Q5	-0.043	(-0.110, 0.024)	-0.029	(-0.096, 0.038)	-0.033	(-0.101, 0.035)
<i>P</i> trend (linear)		0.155		0.332		0.279
PC3	0.112	(0.092, 0.132)	0.103	(0.082, 0.123)	0.101	(0.080, 0.123)
Quintiles of PC3						
Lowest	Reference		Reference		Reference	
Q2	0.125	(0.067, 0.183)	0.105	(0.047, 0.163)	0.103	(0.045, 0.161)
Q3	0.231	(0.172, 0.290)	0.202	(0.143, 0.261)	0.199	(0.139, 0.258)
Q4	0.293	(0.233, 0.353)	0.261	(0.201, 0.321)	0.256	(0.194, 0.318)
Q5	0.285	(0.222, 0.347)	0.260	(0.197, 0.323)	0.253	(0.187, 0.318)
<i>P</i> trend (linear)		< 0.001		< 0.001		< 0.001

Principal component analyses with calculated residuals adjusted for energy intake for each dietary AGE. Non-linear transformation was applied, e.g. log transformation for CEL: N^ε-(1-carboxyethyl)-lysine, CML: N^ε-(carboxymethyl)-lysine, MG-H1: N^β-(5-hydro-5-methyl-4-imidazolone-2-yl)-ornithine in regression model. Model 1 was adjusted for age, sex and body mass index (BMI) at baseline; Model 2 was further adjusted for follow-up-time in years, total energy intake (kcal/day), educational level, levels of physical activity, smoking status at baseline, and plausibility of dietary energy reporting; Model 3 was further adjusted for modified relative Mediterranean diet score. Eigenvalues of the covariance matrix for the three principal components (PCs) are as follows: PC1: 2.38051, PC2: 0.385845 PC3: 0.233649.