Supporting Information

Dietary intake of advanced glycation endproducts (AGEs) and risk of hepatobiliary cancers: a multinational cohort study

Ana-Lucia Mayén; Elom K. Aglago; Viktoria Knaze; Reynalda Cordova; Casper G. Schalkwijk; Karl-Heinz Wagner; Krasimira Aleksandrova; Veronika Fedirko; Pekka Keski-Rahkonen; Michael F. Leitzmann; Verena Katzke; Bernard Srour; Matthias B. Schulze; Giovanna Masala; Vittorio Krogh; Salvatore Panico; Rosario Tumino; Bas Bueno-de-Mesquita; Magritt Brustad; Antonio Agudo; María Dolores Chirlaque López; Pilar Amiano; Bodil Ohlsson; Stina Ramne; Dagfinn Aune; Elisabete Weiderpass; Mazda Jenab; Heinz Freisling

Table of Contents

Supplementary Table 1. Intake of food groups according to tertiles of dietary intake of advanced glycation endproducts (AGEs).

Supplementary Table 2. Hazard ratios (95% confidence intervals) for hepatocellular cancer according to tertiles of dietary intake of advanced glycation endproducts (AGEs).

Supplementary Table 3. Hazard ratios (95% confidence intervals) for hepatobiliary cancer subsites according to tertiles of dietary CML intake.

Supplementary Table 4. Hazard ratios (95% confidence intervals) for hepatobiliary cancer subsites according to tertiles of dietary CEL intake.

Supplementary Table 5. Hazard ratios (95% confidence intervals) for hepatobiliary cancer subsites according to tertiles of dietary MG-H1 intake.

Supplementary Table 6. Sensitivity analyses showing hazard ratios (95% confidence intervals) for hepatocellular carcinoma according to dietary intake of advanced glycation endproducts (AGEs).

Supplementary Table 7. Sensitivity analyses showing hazard ratios (95% confidence intervals) for gallbladder cancer according to dietary intake of advanced glycation endproducts (AGEs).

Supplementary Figure 1. Flowchart for participant inclusion criteria.

Supplementary Figure 2. Food group sources of dietary intake of advanced glycation endproducts in the European Prospective Investigation into Cancer and nutrition (EPIC).

Supplementary Figure 3. Percentage contribution of food groups to CML, CEL and MG-H1 intake in the European Prospective Investigation into Cancer and nutrition (EPIC) study.

Supplementary Figure 4. Subgroup analysis showing hazard ratios (HR) and 95% confidence intervals (CI) for hepatocellular carcinoma according to dietary intake of CEL.

Supplementary Figure 5. Subgroup analysis showing hazard ratios (HR) and 95% confidence intervals (CI) for hepatocellular carcinoma according to dietary intake of CML.

Supplementary Figure 6. Subgroup analysis showing hazard ratios (HR) and 95% confidence intervals (CI) for hepatocellular carcinoma according to dietary intake of MG-H1.

Supplementary Figure 7. Subgroup analysis by country showing hazard ratios (HR) and 95% confidence intervals (CI) for hepatocellular carcinoma according to dietary intake of advanced glycation endproducts (AGEs)

Supplementary Figure 8. Subgroup analysis by country showing hazard ratios (HR) and 95% confidence intervals (CI) for gallbladder cancer according to dietary intake of advanced glycation endproducts (AGEs)

Supplementary Figure 9. Three-knot spline model for associations between energy-adjusted dietary intake of AGEs and risk of gallbladder cancer.

Supplementary Figure 10. Associations between dietary AGEs (per 1 SD increment) and HCC censoring every 2 years of follow-up.

	0	CML	,		CEL			MG-H1	
Food group	T1	T2	Т3	T1	T2	Т3	T1	T2	Т3
(g)									
Red and	89 ± 44	114 ± 50	151 ± 83	84 ± 38	118 ± 57	167 ± 78	96 ± 47	127 ± 75	146 ± 74
processed meat									
Cereals	148 ± 64	233 ± 93	272 ± 133	184 ± 93	237 ± 123	251 ± 113	166 ± 75	238 ± 113	284 ± 128
Dairy	325 ± 294	369 ± 276	371 ± 221	368 ± 271	347 ± 313	331 ± 197	366 ± 324	350 ± 220	323 ± 195
Fish	26 ± 21	36 ± 26	41 ± 34	27 ± 22	32 ± 23	47 ± 36	27 ± 21	37 ± 27	44 ± 35
Potatoes and	127 ± 104	111 ± 103	94 ± 69	126 ± 104	103 ± 102	106 ± 66	126 ± 102	111 ± 104	91 ± 64
other tubers									
Vegetables	150 ± 103	160 ± 86	171 ± 124	151 ± 102	162 ± 109	167 ± 107	152 ± 100	157 ± 110	174 ± 111
Legumes	12 ± 25	12 ± 24	12 ± 32	10 ± 22	13 ± 27	13 ± 33	10 ± 22	14 ± 27	$14\ \pm 34$
Fruits, nuts	220 ± 217	226 ± 159	220 ± 245	235 ± 222	213 ± 170	213 ± 242	211 ± 203	210 ± 172	254 ± 257
and seeds									
Egg and egg	22 ± 20	19 ± 14	17 ± 16	22 ± 19	20 ± 18	17 ± 14	22 ± 19	17 ± 14	18 ± 16
products									
Fat	33 ± 19	31 ± 17	30 ± 16	31 ± 18	33 ± 17	$30\ \pm 18$	30 ± 17	32 ± 18	32 ± 18
Sugar and	70 ± 99	51 ± 68	39 ± 46	64 ± 96	56 ± 76	42 ± 45	68 ± 92	45 ± 49	44 ± 74
confectionary									
Cakes and	18 ± 21	30 ± 25	62 ± 67	21 ± 20	33 ± 32	64 ± 71	19 ± 22	45 ± 44	58 ± 68
biscuits									
Soups,	23 ± 44	42 ± 70	48 ± 70	35 ± 58	39 ± 66	41 ± 69	33 ± 57	39 ± 73	44 ± 62
bouillons	11 . 10		22 . 10		2 0 × 10		14 . 10		01 . 10
Condiments	11 ± 13	20 ± 22	23 ± 19	11 ± 15	20 ± 18	26 ± 21	14 ± 18	22 ± 21	21 ± 18
and sauces									

Supplementary Table 1. Intake of food groups according to tertiles of dietary intake of advanced glycation endproducts (AGEs)¹ in the European Prospective Investigation into Cancer and nutrition, 1992-2000 (n=450,111).

CEL, Nε-[1-carboxyethyl]lysine; CML, Nε-[carboxymethyl]lysine; MG-H1, Nδ-[5-hydro-5-methyl-4-imidazolon-2-yl]-ornithine.

¹Residuals were computed with a linear regression of the ln-transformed intake of AGEs on total energy intake and center.

All values are mean \pm SD.

Supplementary Table 2. Hazard ratios (95% confidence intervals) for hepatocellular cancer according to tertiles of dietary intake of advanced glycation endproducts (AGEs)¹ in the European Prospective Investigation into Cancer and nutrition, 1992-2000 (n=450,111).

		Residuals of AGEs, t	ertiles	
	T1	T2	T3	
			duals of AGEs, tertiles T2 T3 70 76 8 (0.50 - 0.92) 0.71 (0.53 - 0.96) 5 (0.62 - 1.17) 0.88 (0.63 - 1.21) 87 67 9 (0.59 - 1.06) 0.64 (0.47 - 0.87) 5 (0.70 - 1.29) 0.75 (0.54 - 1.04) 68 66 0 (0.44 - 0.81) 0.54 (0.40 - 0.73) 7 (0.56 - 1.07) 0.73 (0.52 - 1.02) xymethyl]lysine; MG-H1, N\delta-[5-hydro-5-methyl-4-in	Ptrend
CML				
Cases, n	109	70	76	
Model 1 ²	1 (Reference)	0.68 (0.50 - 0.92)	0.71 (0.53 - 0.96)	0.025
Model 2 ³	1 (Reference)	0.85 (0.62 - 1.17)	0.88 (0.63 - 1.21)	0.428
CEL				
Cases, n	101	87	67	
Model 1 ²	1 (Reference)	0.79 (0.59 - 1.06)	0.64 (0.47 - 0.87)	0.005
Model 2 ³	1 (Reference)	0.95 (0.70 - 1.29)	0.75 (0.54 - 1.04)	0.085
MG-H1				
Cases, n	121	68	66	
Model 1 ²	1 (Reference)	0.60 (0.44 - 0.81)	0.54 (0.40 - 0.73)	< 0.001
Model 2 ³	1 (Reference)	0.77 (0.56 - 1.07)	0.73 (0.52 - 1.02)	0.068
CEL, Nε-[1-carbox	yethyl]lysine; CML, Na	-[carboxymethyl]lysine; M	G-H1, $\overline{N\delta}$ -[5-hydro-5-methy]	-4-imidazolon-

2yl]-ornithine. T, tertiles. ¹ Residuals were computed with a linear regression of the ln-transformed intake of AGEs on total energy intake and

center.

² Model 1: Energy-adjusted and stratified by sex, center, and age at recruitment in 1-year categories. ³ Model 2: Model 1 and additionally adjusted for educational level, body mass index, physical activity, smoking intensity, lifetime and baseline alcohol intake, coffee intake, self-reported diabetes, and fiber intake.

Supplementary Table 3. Hazard ratios (95% confidence intervals) for hepatobiliary cancer subsites according to tertiles of dietary CML intake¹, European Prospective Investigation into Cancer and nutrition, 1992-2000 (n=450,111).

	Residuals of AGEs, tertiles						
_	T1	T2	T3				
				Ptrend			
CML							
Intrahepatic bile duct	n=36	n=26	n=26				
Model 1	1 (Reference)	0.81 (0.49 - 1.35)	0.78 (0.46 - 1.29)	0.330			
Model 2	1 (Reference)	0.86 (0.51 - 1.45)	0.83 (0.49 - 1.42)	0.503			
Extrahepatic bile duct	n=28	n=30	n=27				
Model 1	1 (Reference)	1.05 (0.62 - 1.77)	0.96 (0.56 - 1.63)	0.868			
Model 2	1 (Reference)	1.09 (0.64 - 1.86)	1.01 (0.57 - 1.77)	0.984			
Gallbladder	n-28	n-27	n-15				
	$\frac{11-20}{1}$	II = 2/	1 40 (0.02 2.40)	0.102			
Model 1	I (Reference)	0.96 (0.56 - 1.63)	1.49 (0.92 - 2.40)	0.103			
Model 2	1 (Reference)	0.92 (0.54 - 1.59)	1.44 (0.88 - 2.36)	0.146			

CML, Nɛ-[carboxymethyl]lysine. T, tertiles.

¹ Residuals were computed with a linear regression of the ln-transformed intake of AGEs on total energy intake and center.

² Model 1: Energy-adjusted and stratified by sex, center, and age at recruitment in 1-year categories.
³ Model 2: Model 1 and additionally adjusted for educational level, body mass index, physical activity, smoking intensity, lifetime and baseline alcohol intake, coffee intake, self-reported diabetes, and fiber intake.

Supplementary Table 4. Hazard ratios (95% confidence intervals) for hepatobiliary cancer
subsites according to tertiles of dietary CEL intake ¹ , European Prospective Investigation into
Cancer and nutrition, 1992-2000 (n=450,111).

	Residuals of AGEs, tertiles				
	T1	T2	T3	Ptrend	
CEL					
Intrahepatic bile duct	n=30	n=32	n=26		
Model 1	1 (Reference)	1.04 (0.63 - 1.72)	0.85 (0.50 - 1.44)	0.536	
Model 2	1 (Reference)	1.08 (0.65 - 1.81)	0.92 (0.53 - 1.58)	0.757	
Extrahepatic bile duct	n=23	n=32	n=30		
Model 1	1 (Reference)	1.27 (0.74 - 2.20)	1.24 (0.71 - 2.15)	0.447	
Model 2	1 (Reference)	1.26 (0.72 - 2.20)	1.27 (0.72 - 2.24)	0.414	
Gallbladder	n=29	n=27	n=44		
Model 1	1 (Reference)	0.99 (0.58 - 1.68)	1.52 (0.95 - 2.44)	0.084	
Model 2	1 (Reference)	0.96 (0.56 - 1.63)	1.43 (0.88 - 2.31)	0.150	

CEL, Nɛ-[1-carboxyethyl]lysine; T, tertiles. ¹ Residuals were computed with a linear regression of the ln-transformed intake of AGEs on total energy intake and

center. ² Model 1: Energy-adjusted and stratified by sex, center, and age at recruitment in 1-year categories. ³ Model 2: Model 1 and additionally adjusted for educational level, body mass index, physical activity, smoking intensity, lifetime and baseline alcohol intake, coffee intake, self-reported diabetes, and fiber intake.

Supplementary Table 5. Hazard ratios (95% confidence intervals) for hepatobiliary cancer subsites according to tertiles of dietary MG-H1 intake¹, European Prospective Investigation into Cancer and nutrition, 1992-2000 (n=450,111).

		Residuals of AGEs, ter	rtiles	
	T1	T2	Τ3	P _{trend}
MG-H1 Intrahepatic bile				
duct	n=35	n=23	n=30	
Model 1	1 (Reference)	0.70 (0.41 - 1.19)	0.88 (0.54 - 1.44)	0.618
Model 2	1 (Reference)	0.78 (0.45 - 1.36)	1.08 (0.63 - 1.84)	0.785
Extrahepatic bile				
duct	n=29	n=26	n=30	
Model 1	1 (Reference)	0.86 (0.50 - 1.47)	0.97 (0.58 - 1.62)	0.901
Model 2	1 (Reference)	0.94 (0.53 - 1.64)	1.15 (0.65 - 2.04)	0.638
Gallbladder	n=25	n=29	n=46	
Model 1	1 (Reference)	1.21 (0.70 - 2.07)	1.73 (1.06 - 2.84)	0.029
Model 2	1 (Reference)	1.22 (0.70 - 2.13)	1.81 (1.07 - 3.06)	0.028
MG-H1 No-[5-hvdro-5-n	nethyl-4-imidazolon-2-v	vll-ornithine T tertiles		

*I*G-H1, Nδ-[5-hydro-5-methyl-4-imidazolon-2-yl]-ornithine. T, tertiles.

¹ Residuals were computed with a linear regression of the ln-transformed intake of AGEs on total energy intake and center.

² Model 1: Energy-adjusted and stratified by sex, center, and age at recruitment in 1-year categories. ³ Model 2: Model 1 and additionally adjusted for educational level, body mass index, physical activity, smoking intensity, lifetime and baseline alcohol intake, coffee intake, self-reported diabetes, and fiber intake.

	N (%)	Tertile (T)1	T2	Т3	Ptrend	AGEs intake per 1 SD increments	Pvalue
CML							
Model 2	450,111 (100)	1 (Reference)	0.85 (0.62 - 1.17)	0.88 (0.63 - 1.21)	0.428	0.87 (0.76 - 0.99)	0.030
Model S1	442,536 (98)	1 (Reference)	0.85 (0.61 - 1.19)	0.91 (0.65 - 1.28)	0.590	0.95 (0.80 - 1.13)	0.572
Model S2	450,111 (100)	1 (Reference)	0.83 (0.60 - 1.13)	0.82 (0.60 - 1.14)	0.242	0.85 (0.74 - 0.96)	0.012
Model S3	309,258 (69)	1 (Reference)	0.82 (0.55 - 1.25)	0.72 (0.48 - 1.10)	0.129	0.84 (0.71 - 0.99)	0.038
Model S4	407,434 (91)	1 (Reference)	0.83 (0.58 - 1.18)	0.86 (0.61 – 1.22)	0.413	$0.90\;(0.78-1.05)$	0.176
Model S5	450,111 (100)	1 (Reference)	0.84 (0.61 - 1.16)	0.86 (0.62 - 1.18)	0.346	0.92 (0.78 - 1.09)	0.335
Model S6	301,987 (67)	1 (Reference)	0.83 (0.57 - 1.23)	0.79 (0.53 - 1.18)	0.252	0.84 (0.71 - 0.99)	0.036
Model S7	$407(79)^2$	1 (Reference)	0.66 (0.36 - 1.21)	0.77 (0.42 - 1.42)	0.400	0.83 (0.63 - 1.10)	0.190
Model S8	$324(53)^2$	1 (Reference)	0.89 (0.44 - 1.81)	0.90 (0.45 - 1.80)	0.764	0.88 (0.64 - 1.22)	0.449
Model S9	$407 (79)^2$	1 (Reference)	0.68 (0.39 - 1.20)	0.75 (0.42 - 1.31)	0.310	0.80 (0.62 - 1.04)	0.094
Model S10	450,111 (100)	1 (Reference)	0.87 (0.63 - 1.20)	0.92 (0.66 - 1.28)	0.612	0.88 (0.77 - 1.00)	0.055
Model S11	450,111 (100)	1 (Reference)	0.86 (0.63 - 1.19)	0.90 (0.65 - 1.24)	0.506	0.87 (0.77 - 1.00)	0.046
Model S12	450,111 (100)	1 (Reference)	0.87 (0.63 - 1.19)	0.92 (0.66 - 1.27)	0.600	0.88 (0.77 - 1.01)	0.061

Supplementary Table 6. <u>Sensitivity analyses</u> showing hazard ratios (95% confidence intervals) for <u>hepatocellular carcinoma</u> according to dietary intake of advanced glycation endproducts (AGEs)¹ in the European Prospective Investigation into Cancer and nutrition, 1992-2000 (n=450,111).

CEL

Model 2	450,111 (100)	1 (Reference)	0.95 (0.70 - 1.29)	0.75 (0.54 - 1.04)	0.085	0.84 (0.74 - 0.96)	0.008
Model S1	442,536 (98)	1 (Reference)	0.96 (0.70 - 1.31)	0.74 (0.52 - 1.04)	0.083	0.86 (0.73 - 1.02)	0.088
Model S2	450,111 (100)	1 (Reference)	0.93 (0.69 - 1.26)	0.72 (0.52 - 1.00)	0.051	0.83 (0.73 - 0.94)	0.005
Model S3	309,258 (69)	1 (Reference)	0.95 (0.64 - 1.41)	0.64 (0.41 - 0.98)	0.042	0.85 (0.72 - 1.00)	0.056
Model S4	407,434 (91)	1 (Reference)	1.01 (0.72 - 1.42)	0.79 (0.55 - 1.14)	0.216	0.85 (0.73 - 0.98)	0.028
Model S5	450,111 (100)	1 (Reference)	0.94 (0.69 - 1.27)	0.73 (0.53 - 1.02)	0.067	0.86 (0.73 - 1.01)	0.070
Model S6	301,987 (67)	1 (Reference)	1.02 (0.71 - 1.46)	0.63 (0.42 - 0.96)	0.032	0.79 (0.67 - 0.93)	0.006
Model S7	$407(79)^2$	1 (Reference)	1.01 (0.56 - 1.81)	0.61 (0.33 - 1.15)	0.128	0.70 (0.53 - 0.92)	0.012
Model S8	$324(53)^2$	1 (Reference)	1.08 (0.55 - 2.12)	0.82 (0.41 - 1.65)	0.575	0.74 (0.54 - 1.01)	0.055
Model S9	$407(79)^2$	1 (Reference)	1.07 (0.62 - 1.84)	0.60 (0.34 - 1.06)	0.078	0.68 (0.53 - 0.88)	0.003
Model S10	450,111 (100)	1 (Reference)	0.97 (0.71 - 1.32)	0.77 (0.55 - 1.07)	0.118	0.85 (0.74 - 0.97)	0.013
Model S11	450,111 (100)	1 (Reference)	0.97 (0.71 - 1.33)	0.78 (0.55 - 1.10)	0.162	0.84 (0.73 - 0.97)	0.019
Model S12 MG-H1	450,111 (100)	1 (Reference)	0.96 (0.71 - 1.30)	0.76 (0.54 - 1.06)	0.102	0.84 (0.74 - 0.96)	0.011
Model 2	450,111 (100)	1 (Reference)	0.77 (0.56 - 1.07)	0.73 (0.52 - 1.02)	0.068	0.84 (0.74 - 0.97)	0.015
Model S1 Model S2	442,536 (98) 450,111 (100)	1 (Reference) 1 (Reference)	0.79 (0.56 - 1.10) 0.77 (0.56 - 1.06)	0.73 (0.51 - 1.04) 0.71 (0.51 - 0.99)	0.082 0.046	0.85 (0.71 - 1.02) 0.85 (0.74 - 0.96)	0.075

0	.0	1	2
~		_	_

Model S3	309,258 (69)	1 (Reference)	0.68 (0.45 - 1.04)	0.65 (0.42 - 1.00)	0.050	0.83 (0.70 - 0.99)	0.033
Model S4	407,434 (91)	1 (Reference)	0.78 (0.54 - 1.11)	0.72 (0.50 - 1.05)	0.084	0.85 (0.74 - 0.99)	0.040
Model S5	450,111 (100)	1 (Reference)	0.76 (0.55 - 1.05)	0.72 (0.51 - 1.00)	0.053	0.84 (0.71 - 1.00)	0.048
Model S6	301,987 (67)	1 (Reference)	0.69 (0.46 - 1.03)	0.69 (0.46 - 1.04)	0.078	0.81 (0.68 - 0.97)	0.021
Model S7	407 (79) ²	1 (Reference)	0.76 (0.42 - 1.37)	0.54 (0.28 - 1.03)	0.059	0.70 (0.52 - 0.94)	0.016
Model S8	$324(53)^2$	1 (Reference)	0.72 (0.36 - 1.43)	0.55 (0.26 - 1.17)	0.122	0.69 (0.49 - 0.97)	0.034
Model S9	407 (79) ²	1 (Reference)	0.66 (0.38 - 1.15)	0.60 (0.33 - 1.07)	0.084	0.71 (0.54 - 0.92)	0.010
Model S10	450,111 (100)	1 (Reference)	0.79 (0.57 - 1.09)	0.75 (0.53 - 1.06)	0.098	0.85 (0.74 - 0.98)	0.025
Model S11	450,111 (100)	1 (Reference)	0.77 (0.56 - 1.07)	0.73 (0.52 - 1.03)	0.073	0.85 (0.74 - 0.97)	0.019
Model S12	450,111 (100)	1 (Reference)	0.79 (0.57 - 1.09)	0.76 (0.53 - 1.08)	0.128	0.85 (0.74 - 0.99)	0.037

CML, Nε-[carboxymethyl]lysine; CEL, Nε-[1-carboxyethyl]lysine; MG-H1, Nδ-[5-hydro-5-methyl-4-imidazolon-2-yl]-ornithine; NA, not available.

¹ Residuals were computed by a linear regression of the ln-transformed intake of AGEs on total energy intake and center.

² Percentage refers to the proportion of cases in the nested case-control dataset (n=202) compared to the number of cases in full cohort (n=255).

Model 2: main model stratified by sex, center and age in 1-year categories, and adjusted for total energy intake, educational level, body mass index, physical activity,

smoking intensity, lifetime and baseline alcohol intake, coffee intake, self-reported diabetes, and fiber intake.

Model S1: model 2 after excluding cancer events that occurred during the first two years of follow-up.

Model S2: model 2 adjusted for the Mediterranean dietary score (mrMDS) instead of fiber intake.

Model S3: model 2 after excluding current smokers.

Model S4: model 2 after excluding subjects reporting heavy drinking at any point in lifetime.

Model S5: model 2 with additional adjustment for under- or over-reporting of total energy intake according to Goldberg.

Model S6: model 2 using a complete case analysis.

Model S7: Odds ratio and 95% confidence interval from conditional logistic regression using the nested case-control dataset with n=204 cases and n=205 matched controls, adjusted for matching factors (incl. sex, age, center), and total energy intake, educational level, body mass index, physical activity, smoking status, alcohol at recruitment, coffee intake, self-reported diabetes, fiber intake, and <u>hepatitis B and C infection status</u>.

Model S8: Odds ratio and 95% confidence interval from conditional logistic regression using the nested case-control dataset excluding those with positive hepatitis B and

C infection status, adjusted for matching factors (incl. sex, age, center), and total energy intake, educational level, body mass index, physical activity, smoking status, alcohol at recruitment, coffee intake, self-reported diabetes, and fiber intake.

Model S9: Odds ratio and 95% confidence interval from conditional logistic regression using the nested case-control dataset with n=204 cases and n=205 matched controls, adjusted for matching factors (incl. sex, age, center), and total energy intake, educational level, body mass index, physical activity, smoking status, alcohol at recruitment, coffee intake, self-reported diabetes, fiber intake, and <u>liver function status</u>: "1" if any was above the clinical threshold (ALT>55 U l-1, AST>34 U l-1, GGT men >64 U l-1, GGT wome>36 U l-1, ALP>150 U l-1, albumin<34 g l-1, total bilirubin>20.5 μ mol l-1; based on the values provided by the laboratory) vs. "0".

Model S10: model 2 with additional adjustment for cake & biscuit intake.

Model S11: model 2 with additional adjustment for red meat & processed meat intake.

Model S12: model 2 with additional adjustment for cereal intake.

	N (%)	Tertile (T)1	T2	Т3	Ptrend	AGEs intake per 1 SD increments	Pvalue
CML		1					
Model 2	450,111 (100)	(Reference)	0.92 (0.54 - 1.59)	1.44 (0.88 - 2.36)	0.146	1.28 (1.05 - 1.56)	0.014
Model S1	442,536 (98)	l (Reference)	0.95 (0.54 - 1.66)	1.45 (0.87 - 2.42)	0.156	1.23 (0.94 - 1.60)	0.130
Model S2	450,111 (100)	l (Reference)	0.94 (0.55 - 1.61)	1.46 (0.89 - 2.39)	0.135	1.29 (1.06 - 1.58)	0.011
Model S3	309,258 (69)	l (Reference)	1.00 (0.52 - 1.89)	1.58 (0.88 - 2.83)	0.127	1.28 (1.02 - 1.62)	0.036
Model S4	407,434 (91)	l (Reference)	1.04 (0.59 - 1.82)	1.51 (0.90 2.52)	0.118	1.28 (1.05 - 1.57)	0.017
Model S5	450,111 (100)	l (Reference)	0.98 (0.57 - 1.69)	1.56 (0.95 - 2.56)	0.080	1.27 (0.99 - 1.64)	0.063
Model S6	301,987 (67)	l (Reference)	1.01 (0.50 - 2.04)	1.56 (0.81 - 3.01)	0.185	1.28 (0.98 - 1.68)	0.075
Model S7	450,111 (100)	1 (Reference)	0.91 (0.53 - 1.56)	1.38 (0.83 - 2.29)	0.213	1.27 (1.03 - 1.55)	0.023
Model S8	450,111 (100)	1 (Reference)	0.96 (0.56 - 1.66)	1.51 (0.92 - 2.49)	0.101	1.31 (1.07 - 1.59)	0.008
Model S9	450,111 (100)	1 (Reference)	0.90 (0.52 - 1.55)	1.34 (0.81 - 2.21)	0.261	1.23 (1.00 - 1.53)	0.055
CEL							
Model 2	450 111 (100)	1 (Reference)	0 96 (0 56 - 1 63)	1 43 (0 88 - 2 31)	0 150	1 17 (0 96 - 1 41)	0 114

Supplementary Table 7. <u>Sensitivity analyses</u> showing hazard ratios (95% confidence intervals) for <u>gallbladder cancer</u> according to dietary intake of advanced glycation endproducts (AGEs)¹ in the European Prospective Investigation into Cancer and nutrition, 1992-2000 (n=450,111).

		1					
Model S1	442,536 (98)	(Reference)	0.96 (0.55 - 1.66)	1.42 (0.86 - 2.35)	0.167	1.21 (0.94 - 1.56)	0.146
Model S2	450,111 (100)	(Reference)	0.96 (0.56 - 1.64)	1.44 (0.89 - 2.34)	0.133	1.17 (0.97 - 1.42)	0.099
Model S3	309,258 (69)	(Reference)	0.86 (0.46 - 1.59)	1.34 (0.77 - 2.32)	0.298	1.15 (0.92 - 1.44)	0.205
Model S4	407,434 (91)	(Reference)	1.01 (0.58 - 1.77)	1.55 (0.94 - 2.56)	0.088	1.20 (0.99 - 1.46)	0.065
Model S5	450,111 (100)	(Reference)	1.01 (0.59 - 1.72)	1.53 (0.94 - 2.48)	0.087	1.25 (0.98 - 1.60)	0.074
Model S6	301,987 (67)	(Reference)	1.14 (0.59 - 2.19)	1.13 (0.59 - 2.16)	0.707	1.09 (0.84 - 1.42)	0.518
Model S7	450,111 (100)	(Reference)	0.94 (0.55 - 1.60)	1.38 (0.85 - 2.25)	0.193	1.15 (0.95 - 1.40)	0.143
Model S8	450,111 (100)	(Reference)	1.05 (0.61 - 1.80)	1.67 (1.01 - 2.77)	0.046	1.26 (1.03 - 1.54)	0.024
Model S9	450,111 (100)	(Reference)	0.94 (0.55 - 1.61)	1.37 (0.85 - 2.24)	0.200	1.14 (0.94 - 1.38)	0.184
MG-H1		1					
Model 2	450,111 (100)	(Reference)	1.22 (0.70 - 2.13)	1.81 (1.07 - 3.06)	0.028	1.27 (1.06 - 1.54)	0.011
Model S1	442,536 (98)	(Reference)	1.23 (0.69 - 2.18)	1.78 (1.03 - 3.08)	0.040	1.34 (1.02 - 1.77)	0.034
Model S2	450,111 (100)	(Reference)	1.22 (0.71 - 2.12)	1.83 (1.10 - 3.06)	0.020	1.28 (1.07 - 1.54)	0.007
Model S3	309,258 (69)	(Reference)	1.00 (0.53 - 1.90)	1.55 (0.85 - 2.83)	0.149	1.25 (1.01 - 1.56)	0.044
Model S4	407,434 (91)	(Reference)	1.36 (0.76 - 2.43)	1.91 (1.10 - 3.33)	0.022	1.28 (1.06 - 1.55)	0.012
Model S5	450,111 (100)	(Reference)	1.28 (0.74 - 2.23)	1.91 (1.13 - 3.24)	0.016	1.39 (1.07 - 1.81)	0.013

		1					
Model S6	301,987 (67)	(Reference)	1.20 (0.61 - 2.34)	1.40 (0.71 - 2.77)	0.330	1.19 (0.91 - 1.56)	0.192
Model S7	450,111 (100)	l (Reference)	1.20 (0.69 - 2.09)	1.75 (1.02 - 2.98)	0.040	1.26 (1.04 - 1.53)	0.016
		1					
Model S8	450,111 (100)	(Reference)	1.23 (0.71 - 2.14)	1.82 (1.08 - 3.09)	0.025	1.28 (1.06 - 1.55)	0.009
Model S9	450,111 (100)	(Reference)	1.18 (0.68 - 2.05)	1.66 (0.96 - 2.87)	0.070	1.23 (1.00 - 1.52)	0.051

CML, Nɛ-[carboxymethyl]lysine; CEL, Nɛ-[1-carboxyethyl]lysine; MG-H1, Nδ-[5-hydro-5-methyl-4-imidazolon-2-yl]-ornithine.

¹ Residuals were computed with a linear regression of the ln-transformed intake of AGEs on total energy intake and center. Model 2: main model stratified by sex, center and age in 1-year categories, and adjusted for total energy intake, educational level, body mass index, physical activity, smoking intensity, lifetime and baseline alcohol intake, coffee intake, self-reported diabetes, and fiber intake.

Model S1: model 2 after excluding cancer events that occurred during the first two years of follow-up.

Model S2: model 2 adjusted for the Mediterranean dietary score (mrMDS) instead of fiber intake.

Model S3: model 2 after excluding current smokers.

Model S4: model 2 after excluding subjects reporting heavy drinking at any point in lifetime.

Model S5: model 2 with additional adjustment for under- or over-reporting of total energy intake according to Goldberg.

Model S6: model 2 using a complete case analysis.

Model S7: model 2 with additional adjustment for cake & biscuit intake.

Model S8: model 2 with additional adjustment for red meat & processed meat intake.

Model S9: model 2 with additional adjustment for cereal intake.

Supplementary Figure 1. Flowchart for participant inclusion criteria.



Supplementary Figure 2. Food group sources of dietary intake of advanced glycation endproducts in the European Prospective Investigation into Cancer and nutrition (EPIC).

CML, Nε-[carboxymethyl]lysine; CEL, Nε-[1-carboxyethyl]lysine; MG-H1, Nδ-[5-hydro-5-methyl-4-imidazolon-2-yl]-ornithine.



Supplementary Figure 3. Percentage contribution of food groups to CML, CEL and MG-H1 intake in the European Prospective Investigation into Cancer and nutrition (EPIC), <u>by</u> <u>geographical region (North: Sweden, Denmark, and Norway; Central: France, the United Kingdom, the Netherlands, and Germany; South: Italy and Spain).</u>

CML, Nε-[carboxymethyl]lysine; CEL, Nε-[1-carboxyethyl]lysine; MG-H1, Nδ-[5-hydro-5-methyl-4-imidazolon-2-yl]-ornithine.





Supplementary Figure 4. Subgroup analysis showing hazard ratios (HR) and 95% confidence intervals (CI) for <u>hepatocellular carcinoma</u> according to dietary intake of advanced glycation endproducts (AGEs)¹ in the European Prospective Investigation into Cancer and nutrition, 1992-2000 (n=450,111).

Cau	Cases	HR(95 %CI)		Pheterogeneity
Male Female	162 93	0.79 (0.67 - 0.93) 0.98 (0.79 - 1.23)	•	0.170
Median age <median >=median</median 	48 207	0.97 (0.71 - 1.34) 0.84 (0.73 - 0.97)		0.947
Lifetime alcohol intake Light drinkers Heavy drinkers	141 55	0.92 (0.77-1.09) 0.68 (0.50-0.92)	-	0.636
Goldberg Underreporters Plausible reporters Overreporters	45 185 25	0.70 (0.51 - 0.96) 0.88 (0.75 - 1.04) 0.97 (0.59 - 1.62)	*	0.270
Diabetes status Non-diabetic Diabetic	195 31	0.87 (0.75 - 1.01) 0.79 (0.51 - 1.23)	•	0.487
BMI <25 =25-<30 >=30	71 105 79	0.80 (0.63 - 1.02) 0.86 (0.70 - 1.07) 1.03 (0.81 - 1.31)	* *	0.890
Smoking Never Former Current	75 79 99	0.90 (0.70 - 1.15) 0.79 (0.62 - 1.00) 0.91 (0.74 - 1.12)	*	0.415
Geographical region Northern Central Southern	109 78 68	0.78 (0.64 - 0.95) 0.79 (0.62 - 0.99) 1.17 (0.85 - 1.61)	• • •	0.687
			0.50 1.0 2.0	

CML

CML, Nɛ-[carboxymethyl]lysine.

¹ Residuals were computed with a linear regression of the ln-transformed intake of AGEs on total energy intake and center.

Geographical region (North: Sweden, Denmark, and Norway; Central: France, the United Kingdom, the Netherlands, and Germany; South: Italy and Spain).

Model 2: main model stratified by sex, center and age in 1-year categories, and adjusted for total energy intake, educational level, body mass index, physical activity, smoking intensity, lifetime and baseline alcohol intake, coffee intake, self-reported diabetes, and fiber intake.

Supplementary Figure 5. Subgroup analysis showing hazard ratios (HR) and 95% confidence intervals (CI) for <u>hepatocellular carcinoma</u> according to dietary intake of advanced glycation endproducts (AGEs)¹ in the European Prospective Investigation into Cancer and nutrition, 1992-2000 (n=450,111).

CEL

0	Cases	HR(95% CI)		Pheterogeneity
Sex	162	0.70 (0.68 0.03)	-	0 272
Female	93	0.89 (0.71 - 1.10)	-	0.212
Median age	40	0.00 (0.70 4.04)	1	0.770
<median< td=""><td>48</td><td>0.96(0.70 - 1.31) 0.81(0.70 0.04)</td><td></td><td>0.770</td></median<>	48	0.96(0.70 - 1.31) 0.81(0.70 0.04)		0.770
2-median	201	0.01 (0.10 - 0.34)		
Lifetime alcohol intake				
Light drinkers	141	0.81 (0.67 - 0.97)	-	0.485
Heavy drinkers	55	0.77 (0.57-1.05)		
Goldberg				
Underreporters	45	0.79 (0.57 - 1.08)		0.269
Plausible reporters	185	0.79 (0.68 - 0.93)	-	
Overreporters	25	0.97 (0.58 - 1.64)	° ∳	
Diabotos status				
Non-diabetic	197	0.84 (0.72 - 0.98)	-	0.308
Diabetic	31	0.81 (0.51 - 1.16)		0.000
RMI				
<25	71	0.85(0.67 - 1.09)		0 994
=25-<30	105	0.81 (0.67 - 1.01)		0.001
>=30	79	0.94 (0.74 - 1.18)	+	
Smoking				
Never	75	0.83 (0.65 - 1.05)		0.332
Former	79	0.87 (0.68 - 1.10)	-	
Current	99	0.82 (0.66 - 1.01)	-=	
Geographical region				
Northern	109	0 85 (0 70 - 1 04)		0 755
Central	78	0.78 (0.62 - 0.97)	-=-	0.100
Southern	68	0.83 (0.63 - 1.10)	-=-	
			0.50 1.0 2.0	

CEL, Nε-[1-carboxyethyl]lysine.

¹ Residuals were computed with a linear regression of the ln-transformed intake of AGEs on total energy intake and center.

Geographical region (North: Sweden, Denmark, and Norway; Central: France, the United Kingdom, the Netherlands, and Germany; South: Italy and Spain).

Model 2: main model stratified by sex, center and age in 1-year categories, and adjusted for total energy intake, educational level, body mass index, physical activity, smoking intensity, lifetime and baseline alcohol intake, coffee intake, self-reported diabetes, and fiber intake.

Supplementary Figure 6. Subgroup analysis showing hazard ratios (HR) and 95% confidence intervals (CI) for <u>hepatocellular carcinoma</u> according to dietary intake of advanced glycation endproducts (AGEs)¹ in the European Prospective Investigation into Cancer and nutrition, 1992-2000 (n=450,111).

	Cases	HR(95% CI)		Pheterogeneity
Sex				
Male	162	0.79 (0.67 - 0.94)	-	0.237
Female	93	0.92 (0.73 - 1.16)	-	
Median age				
<median< td=""><td>48</td><td>0.84 (0.59 - 1.20)</td><td></td><td></td></median<>	48	0.84 (0.59 - 1.20)		
>=median	207	0.84 (0.73 - 0.98)	. ∎-	0.723
Lifetime alcohol intake				
Light drinkers	141	0.81 (0.67 - 0.97)	-	0.991
Heavy drinkers	55	0.81 (0.57 - 1.16)		
Goldberg				
Underreporters	45	0.85 (0.61 - 1.18)		0.746
Plausible reporters	185	0.82 (0.69 - 0.97)	-	
Overreporters	25	1.01 (0.56 - 1.79)	-+	
Diabetes status				
Non-diabetic	195	0.84 (0.72 - 0.99)		
Diabetic	31	0.86 (0.57 - 1.30)		0.170
BMI				
<25	71	0.74 (0.57 - 0.97)		0.882
=25-<30	105	0.87 (0.70 - 1.09)		
>=30	79	1.02 (0.80 - 1.30)	+	
Smoking				
Never	75	0.92(0.72 - 1.19)	-	0.940
Former	79	0.74 (0.58 - 0.95)	- - -	
Current	99	0.90 (0.71 - 1.14)	-	
Geographical region				
Northern	109	0.81 (0.66 - 0.99)		0.997
Central	78	0.80 (0.62 - 1.03)		
Southern	68	0.92 (0.67 - 1.24)		
			0.50 1.0 2.0	

MG-H1

MG-H1, Nδ-[5-hydro-5-methyl-4-imidazolon-2-yl]-ornithine.

¹ Residuals were computed with a linear regression of the ln-transformed intake of AGEs on total energy intake and center.

Geographical region (North: Sweden, Denmark, and Norway; Central: France, the United Kingdom, the Netherlands, and Germany; South: Italy and Spain).

Model 2: main model stratified by sex, center and age in 1-year categories, and adjusted for total energy intake, educational level, body mass index, physical activity, smoking intensity, lifetime and baseline alcohol intake, coffee intake, self-reported diabetes, and fiber intake.

Supplementary Figure 7. Subgroup analysis by country showing hazard ratios (HR) and 95% confidence intervals (CI) for <u>hepatocellular carcinoma</u> according to dietary intake of advanced glycation endproducts $(AGEs)^1$ in the European Prospective Investigation into Cancer and nutrition, 1992-2000 (n=450,111).

				%	
	HCC Cases		HR (95% CI)	Weight	
CML			· · · ·	•	
Denmark	65		0.72 (0.54, 0.96)	7.80	
France & Spain	21		- 1.19 (0.73, 1.95)	2.65	
Italy	50	<u>+</u> ↓	1.20 (0.80, 1.79)	4.04	
Netherlands & Germany	46		0.62 (0.45, 0.85)	6.48	
Sweden & Norway	44		0.84 (0.64, 1.11)	8.31	
UK	29	<u>+</u>	1.04 (0.74, 1.47)	5.39	
Subtotal (I-squared = 54.8%	6, p = 0.050)	\diamond	0.88 (0.71, 1.08)	34.67	
CEL					
Denmark	65	_	0 74 (0 55 1 00)	7 12	
France & Spain	21		0.92 (0.61, 1.38)	3.93	
Italy	50		0.73 (0.49, 1.08)	4.21	
Netherlands & Germany	46		0.67 (0.49, 0.91)	6.89	
Sweden & Norway	44		0.96 (0.73, 1.26)	8.73	
UK	29		0.93 (0.62, 1.39)	4.00	
Subtotal (I-squared = 0.0%,	p = 0.490)	\diamond	0.81 (0.71, 0.93)	34.87	
MG-H1					
Denmark	65		0.74 (0.54, 1.02)	6.27	
France & Spain	21	!	0.94 (0.59, 1.51)	2.87	
Italy	50	\	0.86 (0.58, 1.28)	4.08	
Netherlands & Germany	46		0.76 (0.53, 1.09)	4.96	
Sweden & Norway	44	_ ++	0.85 (0.64, 1.13)	7.96	
UK	29		0.91 (0.62, 1.34)	4.31	
Subtotal (I-squared = 0.0%,	p = 0.939)	\diamond	0.83 (0.72, 0.96)	30.46	
Overall (I-squared = 0.0%,	o = 0.459)	\$	0.83 (0.77, 0.90)	100.00	
NOTE: Weights are from random effects analysis					
			· ·		
		.5 1.5	02		

HR estimates (log-scale)

¹ Residuals were computed with a linear regression of the ln-transformed intake of AGEs on total energy intake and center.

Supplementary Figure 8. Subgroup analysis by country showing hazard ratios (HR) and 95% confidence intervals (CI) for <u>gallbladder cancer</u> according to dietary intake of advanced glycation endproducts (AGEs)¹ in the European Prospective Investigation into Cancer and nutrition, 1992-2000 (n=450,111).

Gallbladder Cases		HR (95% CI)	% Weight		
CML		· · · · ·	-		
Denmark 12		2.09 (1.05, 4.17)	2.75		
France & Spain 17	\	1.02 (0.60, 1.73)	4.66		
Italy 12 —		0.79 (0.37, 1.67)	2.34		
Netherlands & Germany 17 -	i	1.06 (0.54, 2.10)	2.80		
Sweden & Norway 30		1.39 (1.00, 1.94)	11.39		
UK 12		1.65 (1.07, 2.54)	6.93		
Subtotal (I-squared = 15.6% p = 0.314)	\diamond	1.33 (1.05, 1.67)	30.87		
CEL					
Denmark 12	↓↓	2.00 (0.89, 4.48)	2.02		
France & Spain 17 -	_ ◆ <mark> -</mark> ¦	0.83 (0.55, 1.26)	7 38		
Italy 12 -		1 13 (0 56 2 30)	2 60		
Netherlands & Germany 17		1 25 (0 71 2 19)	4 15		
Sweden & Norway 30		1 20 (0 88, 1 63)	13 39		
LIK 12	Li.	1 72 (1 01 2 93)	4 59		
Subtotal (I-squared = 21.1% n = 0.275)		1 21 (0 96, 1 53)	34 12		
	Ť	1.21 (0.00, 1.00)	04.12		
MG-H1					
Denmark 12	↓	1 73 (0 93 3 22)	3 39		
France & Spain 17	_ `	0.93(0.58, 1.49)	5.83		
Italy 12 -		0.00(0.00, 1.10) 0.97(0.47, 2.00)	2.51		
Netherlands & Germany 17		1 47 (0 77 2 80)	3 15		
Sweden & Norway 30		1 33 (0 98, 1 80)	13 70		
lik 12		1.61 (1.03, 2.52)	6 4 3		
Subtotal (Lequared = 0.0% n = 0.492)	6	1 31 (1 08 1 59)	35.00		
Oublotal (1-5quared = 0.070, p = 0.452)	Ť	1.01 (1.00, 1.00)	00.00		
Overall (I-squared = 2.1%, p = 0.430)	\$	1.28 (1.14, 1.44) 1	00.00		
NOTE: Weights are from random effects analysis					
.25 .5	1 2 3 4	D			

HR estimates (log-scale)

¹ Residuals were computed with a linear regression of the ln-transformed intake of AGEs on total energy intake and center.

Supplementary Figure 9. Three-knot spline model for associations between energy-adjusted dietary intake of AGEs and risk of <u>gallbladder cancer</u>.

CML, Nε-[carboxymethyl]lysine; CEL, Nε-[1-carboxyethyl]lysine; MG-H1, Nδ-[5-hydro-5-methyl-4-imidazolon-2-yl]ornithine.

Hazard ratio (HR) and 95% confidence intervals (black dotted lines) from Cox proportional hazard regression stratified by sex, center and age at recruitment (1-year categories), and adjusted for educational level, body mass index, physical activity, smoking intensity, lifetime and baseline alcohol intake, coffee intake, self-reported diabetes, total energy intake and dietary fiber intake.



Supplementary Figure 10. Associations between dietary AGEs (per 1 SD increment) and HCC censoring every 2 years of follow-up. CML, Nɛ-[carboxymethyl]lysine; CEL, Nɛ-[1-carboxyethyl]lysine; MG-H1, Nδ-[5-hydro-5-methyl-4-imidazolon-2-yl]-ornithine.

Hazard ratio (HR) and 95% confidence intervals from Cox proportional hazard regression stratified by sex, center and age at recruitment (1-year categories), and adjusted for total energy intake, educational level, body mass index, physical activity, smoking intensity, lifetime and baseline alcohol intake, coffee intake, self-reported diabetes, and dietary fiber intake. HR represent the highest tertile of CML, CEL or MG-H1 consumption.



Follow up (yrs)