

Supplemental materials:

Supplemental Table 1

Characteristics of 10,100 participant at Atherosclerosis Risk in Communities (ARIC) Study Visit 4 (1996-1998) and incidence rate (95% confidence interval) of dementia by categories of aspartate aminotransferase

	Aspartate aminotransferase (U/L)					
	10th percentile (8-15)	10-20th percentile (16-17)	2nd quintile (18-19)	3rd quintile (20-21)	4th quintile (22-26)	5th quintile (≥27)
N	672	1230	1784	1874	2519	2021
Age, years, mean (SD)	62.9 (5.8)	62.7 (5.7)	63.2 (5.6)	63.7 (5.6)	63.4 (5.6)	63.1 (5.6)
Female, N (%)	439 (65.3)	813 (66.1)	1050 (58.9)	1078 (57.5)	1245 (49.4)	928 (45.9)
Race-Center, N (%)						
NC/white	183 (27.2)	320 (26.0)	414 (23.2)	410 (21.9)	569 (22.6)	390 (19.3)
NC/black	21 (3.1)	35 (2.8)	54 (3.0)	43 (2.3)	39 (1.5)	34 (1.7)
MI/black	200 (29.8)	279 (22.7)	353 (19.8)	338 (18.0)	414 (16.4)	362 (17.9)
MN/white	87 (12.9)	239 (19.4)	451 (25.3)	543 (29.0)	819 (32.5)	692 (34.2)
MD/white	181 (26.9)	357 (29.0)	512 (28.7)	540 (28.8)	678 (26.9)	543 (26.9)
Education, N (%)						
<High school	182 (27.1)	261 (21.2)	352 (19.7)	353 (18.8)	436 (17.3)	339 (16.8)
High school or vocational school	295 (43.9)	509 (41.4)	807 (45.2)	783 (41.8)	1033 (41.0)	842 (41.7)

College, graduate, or professional school	195 (29.0)	460 (37.4)	625 (35.0)	738 (39.4)	1050 (41.7)	840 (41.6)
APOE e4 status, N (%)	191 (28.4)	377 (30.7)	559 (31.3)	539 (28.8)	760 (30.2)	605 (29.9)
Alcohol Use, N (%)						
Current	250 (37.9)	535 (43.7)	837 (47.0)	913 (49.0)	1330 (53.1)	1102 (54.8)
Former	252 (38.2)	396 (32.4)	557 (31.3)	537 (28.8)	708 (28.3)	562 (28.0)
Never	158 (23.9)	293 (23.9)	386 (21.7)	414 (22.2)	468 (18.7)	346 (17.2)
Smoking, N (%)						
Current	184 (27.9)	265 (21.7)	308 (17.3)	246 (13.2)	250 (10.0)	211 (10.5)
Former	242 (36.7)	468 (38.2)	722 (40.6)	826 (44.3)	1204 (48.0)	960 (47.8)
Never	234 (35.5)	491 (40.1)	747 (42.0)	792 (42.5)	1053 (42.0)	839 (41.7)
BMI, kg/m2, mean (SD)	30.2 (6.6)	29.4 (6.1)	29.0 (5.5)	28.5 (5.5)	28.5 (5.2)	29.0 (5.4)
Underweight, N (%)	6 (0.9)	3 (0.2)	5 (0.3)	18 (1.0)	20 (0.8)	15 (0.7)
SBP, mmHg, mean (SD)	127.4 (20.2)	127.4 (19.1)	126.5 (18.6)	127.6 (18.8)	127.6 (18.7)	128.2 (18.4)
DBP, mmHg, mean (SD)	69.5 (11.2)	69.9 (10.5)	70.8 (9.9)	70.8 (10.2)	71.5 (9.9)	72.1 (10.4)
Hypertension, N (%)	353 (52.8)	565 (46.0)	826 (46.5)	878 (47.2)	1170 (46.6)	973 (48.3)
Total cholesterol, mmol/L, mean (SD)	5.1 (0.9)	5.2 (0.9)	5.2 (0.9)	5.3 (1.0)	5.2 (1.0)	5.2 (1.0)

HDL, mmol/L, mean (SD)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	1.2 (0.4)
Diabetes, N (%)	201 (30.1)	259 (21.1)	303 (17.0)	261 (14.0)	357 (14.2)	357 (17.8)
Hypoglycemia, N (%)	2 (0.3)	3 (0.2)	3 (0.2)	2 (0.1)	7 (0.3)	6 (0.3)
Incidence rate of Dementia*	11.9 (10.1-14.1)	10.4 (9.2-11.9)	11.1 (10.0-12.3)	12.3 (11.2-13.5)	11.5 (10.6-12.5)	12.0 (11.0-13.2)

Values are Count (Proportion), mean (SD), or incidence rate (95% confidence interval)

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein cholesterol

Dementia was ascertained by an expert adjudication panel at scheduled visits, telephone or informant interviews, or ICD-9 codes

Underweight was defined as BMI <18.5 kg/m². Hypoglycemia was defined as fasting glucose <70 mg/dL

* Per 1,000 person-year, estimated by Poisson regression with continuous variables centered at the mean

Supplemental Table 2

Subgroup hazard ratios (95% confidence interval) of incident dementia by categories of aspartate aminotransferase measured at Atherosclerosis Risk in Communities (ARIC) Study Visit 4

(N=10,100)

	Aspartate aminotransferase (U/L)						P value for interaction
	10th percentile (8-15)	10-20th percentile (16-17)	2nd quintile (18-19)	3rd quintile (20-21)	4th quintile (22-26)	5th quintile (≥27)	
Age							0.425
<65	1.08 (0.77-1.52)	1.11 (0.85-1.44)	1 (Ref.)	0.96 (0.75-1.23)	0.85 (0.67-1.07)	0.98 (0.77-1.23)	
≥65	1.36 (1.04-1.79)*	1.00 (0.79-1.27)	1 (Ref.)	1.07 (0.88-1.30)	1.04 (0.87-1.25)	1.23 (1.01-1.49)*	
Sex							0.095
Male	1.61 (1.13-2.28)*	1.40 (1.05-1.87)*	1 (Ref.)	1.08 (0.85-1.38)	1.02 (0.82-1.28)	1.16 (0.92-1.46)	
Female	1.07 (0.82-1.40)	0.88 (0.71-1.11)	1 (Ref.)	0.96 (0.79-1.16)	0.92 (0.77-1.12)	1.11 (0.91-1.36)	
Race							0.364
White	1.32 (1.02-1.71)*	1.03 (0.83-1.27)	1 (Ref.)	1.01 (0.84-1.20)	0.90 (0.76-1.06)	1.14 (0.96-1.35)	
Black	1.10 (0.75-1.62)	1.08 (0.78-1.49)	1 (Ref.)	1.06 (0.79-1.42)	1.15 (0.87-1.53)	1.08 (0.80-1.47)	
APOE							0.838
No	1.15 (0.87-1.52)	1.05 (0.83-1.34)	1 (Ref.)	1.06 (0.87-1.30)	1.01 (0.83-1.23)	1.14 (0.93-1.40)	
Yes	1.31 (0.94-1.82)	1.02 (0.78-1.33)	1 (Ref.)	0.95 (0.76-1.19)	0.89 (0.72-1.10)	1.12 (0.90-1.40)	

Current alcohol use

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No	1.18 (0.92-1.52)	0.91 (0.73-1.14)	1 (Ref.)	0.93 (0.77-1.12)	0.89 (0.74-1.06)	1.10 (0.90-1.33)
Yes	1.26 (0.84-1.89)	1.28 (0.96-1.72)	1 (Ref.)	1.16 (0.90-1.48)	1.09 (0.87-1.38)	1.21 (0.95-1.53)

Diabetes

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No	1.17 (0.90-1.52)	0.89 (0.72-1.10)	1 (Ref.)	1.03 (0.87-1.22)	0.97 (0.82-1.13)	1.16 (0.99-1.38)
Yes	1.19 (0.80-1.77)	1.38 (0.97-1.95)	1 (Ref.)	0.95 (0.66-1.37)	0.97 (0.70-1.35)	0.99 (0.71-1.39)

Dementia was ascertained by an expert adjudication panel at scheduled visits, telephone or informant interviews, or ICD-9 codes.

All models were adjusted for age, gender, race-center, education, APOE e4 status. No interaction term was tested for alcohol use and diabetes with aspartate aminotransferase categories.

* Statistically significance at P<0.05

Supplemental Table 3

Hazard ratios (95% confidence interval) of incident dementia by categories of alanine aminotransferase and aspartate aminotransferase measured at Atherosclerosis Risk in Communities (ARIC) Study Visit 4 (N=9,460, fasting for 8 hours and more)

Alanine aminotransferase (U/L)						
	10th percentile (5-10)	10-20th percentile (11-12)	2nd quintile (13-14)	3rd quintile (15-17)	4th quintile (18-22)	5th quintile (≥23)
	N=604	N=1227	N=1587	N=2177	N=1888	N=2157
Model 1	1.34 (1.08-1.67)*	1.17 (0.99-1.40)	1 (Ref.)	1.05 (0.90-1.22)	1.12 (0.96-1.31)	1.18 (1.01-1.38)*
Model 2	1.31 (1.05-1.63)*	1.15 (0.97-1.37)	1 (Ref.)	1.03 (0.88-1.20)	1.08 (0.92-1.26)	1.11 (0.95-1.30)
Model 3	1.30 (1.04-1.62)*	1.13 (0.95-1.35)	1 (Ref.)	1.03 (0.89-1.20)	1.08 (0.93-1.27)	1.13 (0.96-1.32)

Aspartate aminotransferase (U/L)						
	10th percentile (8-15)	10-20th percentile (16-17)	2nd quintile (18-19)	3rd quintile (20-21)	4th quintile (22-26)	5th quintile (≥27)
	N=614	N=1157	N=1705	N=1805	N=2430	N=1929
Model 1	1.23 (0.98-1.53)	1.01 (0.84-1.22)	1 (Ref.)	1.02 (0.88-1.20)	0.95 (0.82-1.10)	1.14 (0.98-1.33)
Model 2	1.17 (0.94-1.46)	0.99 (0.83-1.20)	1 (Ref.)	1.03 (0.88-1.20)	0.95 (0.82-1.10)	1.13 (0.97-1.32)
Model 3	1.16 (0.93-1.45)	0.99 (0.82-1.19)	1 (Ref.)	1.04 (0.89-1.21)	0.96 (0.83-1.11)	1.16 (0.99-1.35)

Dementia was ascertained by an expert adjudication panel at scheduled visits, telephone or informant interviews, or ICD-9 codes

Model 1 (Primary model): age, gender, race-center, education, APOE e4 status

Model 2: + alcohol use, diabetes

Model 3: + smoking, body mass index, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol

* Statistically significance at $P < 0.05$

Supplemental Table 4

Hazard ratios (95% confidence interval) of incident dementia by categories of alanine aminotransferase and aspartate aminotransferase measured at Atherosclerosis Risk in Communities (ARIC) Study Visit 4 accounting for alcohol use and body weight (N=10,100)

	Alanine aminotransferase (U/L)					
	10th percentile (5-10)	10-20th percentile (11-12)	2nd quintile (13-14)	3rd quintile (15-17)	4th quintile (18-22)	5th quintile (≥23)
	N=644	N=1281	N=1649	N=2279	N=1981	N=2266
Model 1	1.34 (1.08-1.65)*	1.16 (0.98-1.38)	1 (Ref.)	1.05 (0.91-1.22)	1.15 (0.98-1.34)	1.19 (1.02-1.39)*
Model 2	1.32 (1.06-1.64)*	1.15 (0.97-1.37)	1 (Ref.)	1.05 (0.90-1.21)	1.15 (0.98-1.34)	1.20 (1.03-1.41)*
Model 3	1.34 (1.08-1.66)*	1.17 (0.98-1.38)	1 (Ref.)	1.05 (0.90-1.21)	1.14 (0.97-1.32)	1.17 (1.00-1.36)*
Model 4	1.34 (1.08-1.65)*	1.16 (0.98-1.38)	1 (Ref.)	1.05 (0.90-1.22)	1.14 (0.98-1.33)	1.18 (1.01-1.38)*

	Aspartate aminotransferase (U/L)					
	10th percentile (8-15)	10-20th percentile (16-17)	2nd quintile (18-19)	3rd quintile (20-21)	4th quintile (22-26)	5th quintile (≥27)
	N=672	N=1230	N=1784	N=1874	N=2519	N=2021
Model 1	1.22 (0.99-1.51)	1.04 (0.87-1.24)	1 (Ref.)	1.01 (0.87-1.17)	0.96 (0.83-1.11)	1.13 (0.97-1.31)
Model 2	1.23 (1.00-1.53)	1.05 (0.87-1.25)	1 (Ref.)	1.01 (0.87-1.17)	0.96 (0.83-1.11)	1.15 (0.99-1.34)
Model 3	1.22 (0.98-1.51)	1.04 (0.87-1.25)	1 (Ref.)	1.01 (0.87-1.18)	0.96 (0.83-1.10)	1.12 (0.96-1.30)
Model 4	1.22 (0.98-1.51)	1.04 (0.87-1.24)	1 (Ref.)	1.01 (0.87-1.17)	0.96 (0.83-1.11)	1.12 (0.97-1.31)

Dementia was ascertained by an expert adjudication panel at scheduled visits, telephone or informant interviews, or ICD-9 codes

Model 1 (Primary model): age, gender, race-center, education, APOE e4 status

Model 2: Model 1 + alcohol use, total weekly alcohol consumption, years since stop drinking, cumulative drinking years before stop drinking, and total weekly alcohol consumption before stop drinking

Model 3: Model 1 + body mass index category

Model 4: Model 1 + body mass index

* Statistically significance at $P < 0.05$

Supplemental Table 5

Hazard ratios (95% confidence interval) of incident dementia by categories of alanine aminotransferase and aspartate aminotransferase measured at Atherosclerosis Risk in Communities (ARIC) Study Visit 4 (N=10,883, including 783 individuals with AST:ALT ratio ≥ 2)

Alanine aminotransferase (U/L)						
	10th percentile (4-10)	10-20th percentile (11-12)	2nd quintile (13-14)	3rd quintile (15-17)	4th quintile (18-22)	5th quintile (≥ 23)
	N=639	N=1132	N=2492	N=1636	N=2684	N=2300
Model 1	1.39 (1.15-1.67)*	1.15 (0.98-1.35)	1 (Ref.)	0.98 (0.85-1.13)	1.09 (0.96-1.23)	1.14 (0.99-1.31)
Model 2	1.38 (1.14-1.67)*	1.14 (0.97-1.34)	1 (Ref.)	0.97 (0.84-1.12)	1.04 (0.92-1.18)	1.07 (0.94-1.23)
Model 3	1.38 (1.14-1.67)*	1.15 (0.97-1.35)	1 (Ref.)	0.98 (0.85-1.13)	1.06 (0.93-1.20)	1.10 (0.95-1.26)

Aspartate aminotransferase (U/L)						
	10th percentile (8-15)	10-20th percentile (16-17)	2nd quintile (18-19)	3rd quintile (20-21)	4th quintile (22-26)	5th quintile (≥ 27)
	N=711	N=1319	N=1913	N=2000	N=2685	N=2255
Model 1	1.18 (0.96-1.45)	1.07 (0.90-1.27)	1 (Ref.)	1.02 (0.88-1.17)	0.96 (0.84-1.10)	1.16 (1.00-1.33)*
Model 2	1.11 (0.90-1.37)	1.04 (0.88-1.24)	1 (Ref.)	1.02 (0.88-1.18)	0.96 (0.84-1.10)	1.16 (1.00-1.33)*
Model 3	1.10 (0.89-1.36)	1.04 (0.88-1.23)	1 (Ref.)	1.03 (0.89-1.19)	0.97 (0.84-1.11)	1.18 (1.03-1.36)*

Dementia was ascertained by an expert adjudication panel at scheduled visits, telephone or informant interviews, or ICD-9 codes

Model 1 (Primary model): age, gender, race-center, education, APOE e4 status

Model 2: + alcohol use, diabetes

Model 3: + smoking, body mass index, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol

* Statistically significance at $P < 0.05$

Supplemental Table 6

Hazard ratios (95% confidence interval) of level 1 dementia by categories of alanine aminotransferase and aspartate aminotransferase measured at Atherosclerosis Risk in Communities

(ARIC) Study Visit 4 (N=5,384, separate stabilized weights for death and non-death drop-out)

Alanine aminotransferase (U/L)						
	10th percentile (5-10)	10-20th percentile (11-12)	2nd quintile (13-14)	3rd quintile (15-17)	4th quintile (18-22)	5th quintile (≥23)
	N=306	N=673	N=895	N=1246	N=1094	N=1260
Model 1	2.01 (0.97-4.18)	1.24 (0.71-2.18)	1 (Ref.)	1.38 (0.77-2.46)	1.44 (0.78-2.68)	1.08 (0.58-1.99)
Model 2	2.13 (1.12-4.03)*	1.39 (0.76-2.55)	1 (Ref.)	1.43 (0.79-2.60)	1.42 (0.78-2.57)	1.06 (0.57-1.98)
Model 3	2.12 (1.18-3.78)*	1.36 (0.72-2.58)	1 (Ref.)	1.48 (0.84-2.61)	1.37 (0.80-2.35)	1.07 (0.60-1.93)

Aspartate aminotransferase (U/L)						
	10th percentile (8-15)	10-20th percentile (16-17)	2nd quintile (18-19)	3rd quintile (20-21)	4th quintile (22-26)	5th quintile (≥27)
	N=301	N=650	N=989	N=1029	N=1425	N=1080
Model 1	0.85 (0.43-1.69)	0.79 (0.41-1.53)	1 (Ref.)	0.72 (0.37-1.39)	0.53 (0.29-0.97)*	0.60 (0.31-1.15)
Model 2	0.78 (0.39-1.55)	0.84 (0.52-1.36)	1 (Ref.)	0.83 (0.47-1.44)	0.56 (0.33-0.93)*	0.64 (0.39-1.05)
Model 3	0.73 (0.37-1.47)	0.83 (0.52-1.34)	1 (Ref.)	0.86 (0.50-1.47)	0.61 (0.38-0.96)*	0.69 (0.43-1.10)

Level 1 dementia was ascertained by an expert adjudication panel at scheduled visits

Variables included to estimate the probability of death and non-death drop-out: age, gender, race-center, education, APOE e4 status, alcohol use, diabetes, smoking, body mass index, blood

pressure, total cholesterol, high-density lipoprotein cholesterol, suspect dementia status, global cognition factor score, comorbidity (coronary heart disease, heart failure, stroke), auxiliary variables from annual follow-up interviews (an indicator of a report by proxy, self-reported poor health, number of hospitalizations), and interactions between variables.

Model 1 (Primary model): age, gender, race-center, education, APOE e4 status

Model 2: + alcohol use, diabetes

Model 3: + smoking, body mass index, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol

* Statistically significance at $P < 0.05$