Appendix C. Relative risk (RR) estimates of PC incidence/mortality for drinkers classified using the mid-point method

Table C1

The sample characteristics of the meta-data on pancreatic cancer (PC) incidence/mortality and alcohol consumption and mean hazard ratio (HR) estimates of PC incidence/mortality for moderate drinkers (>4-24 g/day vs "abstainers") by subgroups in 37 cohort studies (145 HR estimates) from 1994 to 2023

Covariates	PC incidence/mortality studies (N=37) ¥				Mean RR & 95% CI ‡‡		
	Study ‡	% ‡	RR ‡	% ‡	RR	95% CI	ttest P
Mean age in years †							
41-55	13	36.11	38	30.89	0.93	0.75 - 1.10	0.1773
56-75	23	63.99	85	69.11	1.07	0.95 - 1.20	ref
Sex							
Men only	22	42.31	54	43.90	1.04	089 - 1.18	0.7614
Women only	21	40.38	40	32.52	1.03	0.86 - 1.21	0.7806
Men and women	9	17.31	29	23.58	1.00	0.80 - 1.20	ref
Countries/regions							
US/CA-Europe-Aus	25	69.44	86	69.92	0.93	0.81 - 1.04	0.0014
Asia (Jap/S-Ko/CN/HK-CN)	11	30.56	37	30.08	1.26	1.09 - 1.43	ref
Follow-up years							
05.00-09.00	15	40.54	52	35.86	0.88	0.73 - 1.04	0.0045
10.50-29.00	22	59.46	93	64.14	1.12	1.00 - 1.23	ref
Baseline conditions ††							
No exclusion	3	8.33	14	11.38	1.23	0.94 - 1.51	0.1411
Exclusion	33	91.67	109	88.62	1.00	0.90 - 1.10	ref
Alcohol use measure							
Quantity-frequency (QF)	30	83.33	94	76.42	1.04	0.93 - 1.15	0.5617
Others	6	16.67	29	23.58	0.96	0.78 - 1.18	ref
Abstainer biases							
Former and occasional	14	37.84	41	28.28	1.13	0.97 - 1.30	0.0408
Former only	20	54.05	93	64.14	0.92	0.81 - 1.04	ref
Neither †††	3	8.11	11	7.59	1.56	1.24 - 1.88	0.0003
Former drinker bias ††††							
No	9	25.00	36	29.27	1.14	0.96 - 1.32	0.1319
Yes	27	75.00	87	70.73	0.98	0.86 - 1.09	ref
Control for smoke in model							
No	8	19.05	36	29.27	1.03	0.85 - 1.21	0.9992
Yes	34	85.95	87	70.73	1.03	0.91 - 1.14	ref
Control for SES †††††							
No	23	63.89	72	58.54	0.94	0.82 - 1.07	0.0367
Yes	13	36.11	51	41.46	1.15	0.99 - 1.30	ref
Control for race							
No	32	88.89	99	80.49	1.03	0.92 - 1.14	0.8611
Yes	4	11.11	24	19.51	1.01	0.79 - 1.23	ref
Control for diet							
No	16	44.44	62	50.41	1.09	0.95 - 1.22	0.2037
Yes	20	55.56	61	49.59	0.96	0.83 - 1.10	ref
Control for exercise							
No	23	63.89	68	55.28	1.01	0.88 - 1.14	0.7214
Yes	13	36.11	55	44.72	1.05	0.91 - 1.19	ref
Control for BMI †††††							
No	4	11.11	7	5.69	1.16	0.76 - 1.57	0.4962
Yes	32	88.89	116	94.31	1.02	0.92 - 1.12	ref
Control for diabetes †††††							
No	9	25.00	15	12.20	1.03	0.75 - 1.30	0.9851
Yes	27	75.00	108	87.80	1.03	0.92 - 1.13	ref
Type of outcome							
Incidence	25	69.44	77	62.60	0.95	0.83 - 1.07	0.0481
Mortality	11	30.56	46	37.40	1.15	0.99 - 1.31	ref

Note: ¥ HR estimates from 37 cohort studies (37 cohorts). † Mean age at study enrollment. †† Control for currently or previously diagnosed pancreatic cancer and/or other illnesses by exclusion or separate analysis. ††† lifetime abstention was strictly defined as zero consumption or never drank one drink and did not include studies with any level of occasional lifetime or past year drinking (e.g. less than 12 drinks or "rarely" or "hardly ever" drinking). †††† Completely or partially biased. ††††† SES=Socioeconomic status and BMI=Body Mass Index. ‡ Number of studies (%) and relative risk estimates (%) for any drinking from the included studies. ‡‡ Unadjusted mean relative risk (RR) and 95% confidence interval (CI) due to any drinking (compared with "abstaining") by subgroups from the included studies.

Table C2. Statistical analysis of mean hazard risk (HR) of mortality or incidence of pancreatic cancer for different categories of drinkers for testing publication bias and heterogeneity of RR estimates from included studies

Drinking categories ¥	N/n †	Mean hazard ratio of PC and 95% CI due to alcohol use ‡			Egger's linear regress for publication bias		Cochran's Q and I^2 tests for heterogeneity	
		HR	95% CI	ttest P	Coeff	ttest P	P (Q statistic)	I^2 (%, 95% CI)
Former drinkers	4/7	1.51	1.14 – 1.89	0.0014	-0.34	=0.6676	>0.05	01.00 (00.00 – 63.49)
Current drinkers (g/day)	37/272	1.12	1.05 – 1.18	0.0001	+0.13	=0.2179	<0.05	35.68 (25.30 – 44.56)
Light-volume (>0-4)	23/37	1.15	1.00 – 1.32	0.0482	+0.47	=0.7835	>0.05	08.76 (00.00 – 48.91)
Low-volume (>4-14)	32/68	0.98	0.86 – 1.10	0.7677	-0.42	=0.0500	<0.05	31.39 (07.19 – 49.27)
Medium-volume (>14-24)	29/56	1.06	0.93 – 1.19	0.3496	-0.15	=0.3742	>0.05	01.00 (00.00 – 21.82)
Increased-volume (>24-44)	29/73	1.19	1.08 – 1.30	0.0004	+0.18	=0.4479	<0.05	36.10 (14.90 – 51.98)
Higher-volume (>44-64)	12/27	1.14	0.95 – 1.33	0.1344	-0.32	=0.2721	>0.05	01.00 (00.00 – 45.77)
Highest-volume (>64)	7/11	1.51	1.24 – 1.84	0.0014	-0.07	=0.9118	>0.05	01.00 (00.00 – 57.17)
Any drinkers	37/279	1.13	1.07 – 1.19	0.0001	+0.17	=0.1140	<0.05	36.22 (25.94 – 45.05)

Note: ¥ Current drinkers classified using the mid-point method to determine mean alcohol consumption. † N= Number of studies (cohorts) and n= Number of risk estimates. ‡ Arithmetic mean hazard ratios without any adjustment.

Table C3. Mean relative risk (RR) estimates for pancreatic cancer (PC) incidence and/or mortality with 95% confidence intervals (CI) with and without adjustment for selected study level covariates

Alcohol drinker categories ¥	N/n †	Model I ‡			Model II ‡‡		
		RR ‡	95% CI	ttest P	RR ‡	95% CI	ttest P
Abstainer	37/78	1.00				1.00	
Current drinkers (g/day)	37/272	1.08	0.94 - 1.25	0.1920	**1.20**	**1.05 - 1.38**	**0.0171**
Light-volume (>0-4)	23/37	1.00	0.94 - 1.07	0.9134	1.12	0.97 - 1.30	0.1207
Low-volume (>4-14)	32/68	0.99	0.94 - 1.04	0.6742	1.10	0.96 - 1.26	0.1841
Medium-volume (>14-24)	29/56	0.97	0.91 - 1.02	0.2383	1.07	0.93 - 1.23	0.3126
Increased-volume (>24-44)	29/73	**1.07**	**1.02 - 1.13**	**0.0125**	**1.19**	**1.04 - 1.37**	**0.0138**
Higher-volume (>44-64)	12/27	**1.11**	**1.03 - 1.19**	**0.0042**	**1.22**	**1.06 - 1.41**	**0.0057**
Highest-volume (>64)	7/11	**1.43**	**1.22 - 1.68**	**0.0001**	**1.58**	**1.29 - 1.93**	**0.0001**
RR change/10 g ↑ ✓	37/272	**1.035**	**1.026-1.044**	**0.0001**	**1.034**	**1.026-1.043**	**0.0001**
Former drinkers	4/7	**1.41**	**1.12 - 1.78**	**0.0042**	**1.49**	**1.16 - 1.91**	**0.0019**
Any drinkers	37/279	1.13	0.98 - 1.30	0.0855	**1.24**	**1.09 - 1.41**	**0.0068**

Note: ¥ Mean daily alcohol use in each category estimated assuming a gamma distribution for population consumption. † N= Number of studies and n= number of risk estimates. ‡ Model I estimates deal with skewed distribution by analyzing natural logged RR, weighting by inverse of variance in each estimate and adjusted for heterogeneity across studies. ‡‡ Model II applies further adjustments for study-level measures of mean cohort age of cohorts/follow-up years (cohort age<56 and follow-up=10+ vs others), former drinker bias strictly defined and less strictly defined (yes or no), study level differences in exclusion of baseline health conditions (exclusion or not), and if BMI controlled (yes or no) in individual studies. ✓ RR change (increased by 2.6%, Model I-II) due to 10 gram increase of pure alcohol intake per day among current drinkers.

Table C4. Mean relative risk (RR) estimates of pancreatic cancer (PC) incidence/mortality with 95% confidence intervals (CI) with and without weighting by estimated study quality and adjustment for selected study level covariates

Alcohol drinker categories ¥	N/n †	Model I ‡			Model II ‡‡		
		RR ‡	95% CI	ttest P	RR ‡	95% CI	ttest P
Abstainer	37/78	1.00			1.00		
Current drinkers (g/day)	37/272	1.08	0.94 - 1.25	0.1920	**1.21**	**1.06 - 1.38**	**0.0142**
Light-volume (>0-4)	23/37	1.00	0.94 - 1.07	0.9134	1.13	0.98 - 1.29	0.0848
Low-volume (>4-14)	32/68	0.99	0.94 - 1.04	0.6742	1.11	0.97 - 1.26	0.1195
Medium-volume (>14-24)	29/56	0.97	0.91 - 1.02	0.2383	1.08	0.95 - 1.13	0.2229
Increased-volume (>24-44)	29/73	**1.07**	**1.02 - 1.13**	**0.0125**	**1.20**	**1.05 - 1.36**	**0.0056**
Higher-volume (>44-64)	12/27	**1.11**	**1.03 - 1.19**	**0.0042**	**1.22**	**1.07 - 1.39**	**0.0033**
Highest-volume (>64)	7/11	**1.43**	**1.22 - 1.68**	**0.0001**	**1.57**	**1.29 - 1.91**	**0.0001**
RR change/10 g ↑ ✓	37/272	**1.035**	**1.026-1.044**	**0.0001**	**1.033**	**1.024-1.041**	**0.0001**
Former drinkers	4/7	**1.41**	**1.12 - 1.78**	**0.0042**	**1.52**	**1.21 - 1.91**	**0.0003**
Any drinkers	37/279	1.13	0.98 - 1.30	0.0855	**1.25**	**1.09 - 1.43**	**0.0063**

Note: ¥ Mean daily alcohol use in each category estimated assuming a gamma distribution for population consumption. † N= Number of studies and n= Number of risk estimates. ‡ Model I estimates deal with skewed distribution by analyzing natural logged RR, weight for precision of RR estimates using the inverse of variance and adjust for heterogeneity across studies. ‡‡ Model II also weights estimates by mean age of cohorts (quality score=+0.4 if mean age<56 years), former drinker bias strictly defined (quality score +04) and less strictly defined (quality score=+0.2), follow-up years (quality score=+0.1 if follow-up year=10+) by giving larger weights; further adjusts for study level differences in exclusion of baseline health conditions (exclusion or not), and if BMI controlled (yes or no) in individual studies. ✓ RR change (increased by 2.6% in Model I, 2.4% in Model II) due to 10 gram increase of pure alcohol intake per day among current drinkers.

Table C5. Mean relative risk (RR) estimate of pancreatic cancer (PC) incidence and mortality by drinking groups and 95% confidence interval (CI) based on 25 cohort studies of PC incidence and 12 cohort studies of PC mortality and alcohol intake in general population between 1986 and 2023

Alcohol drinker categories ¥	N/n †	Model I ‡			Model II ‡‡		
		RR ‡	95% CI	ttest P	RR ‡	95% CI	ttest P
Incidence							
Abstainer	25/46	1.00			1.00		
Current drinkers (g/day)	37/173	1.05	0.97 - 1.14	0.1626	1.07	0.99 - 1.15	0.0881
Light-volume (>0-4)	19/32	0.97	0.91 - 1.03	0.3114	0.99	0.92 - 1.06	0.7066
Low-volume (>4-14)	22/42	1.00	0.95 - 1.06	0.9135	1.02	0.95 - 1.09	0.6126
Medium-volume (>14-24)	20/35	0.96	0.90 - 1.03	0.2538	0.98	0.91 - 1.05	0.5200
Increased-volume (>24-44)	15/25	**1.11**	**1.03 - 1.19**	**0.0086**	**1.12**	**1.03 - 1.22**	**0.0069**
Higher-volume (>44-64)	16/31	**1.12**	**1.04 - 1.20**	**0.0016**	**1.14**	**1.05 - 1.23**	**0.0018**
Highest-volume (>64)	4/8	**1.17**	**1.06 - 1.30**	**0.0020**	**1.18**	**1.07 - 1.31**	**0.0017**
RR change/10 g ↑ ✓	25/173	**1.029**	**1.019-1.039**	**0.0001**	**1.029**	**1.019-1.039**	**0.0001**
Former drinkers	1/1	1.31	0.85 - 2.00	0.2163	1.31	0.85 - 2.00	0.2187
Any drinkers	25/174	1.09	0.99 - 1.19	0.0813	**1.10**	**1.00 - 1.20**	**0.0467**
Mortality							
Abstainer	13/29	1.00			**1.00**		
Current drinkers (g/day)	12/102	**1.13**	**1.05 - 1.22**	**0.0088**	**1.18**	**1.11 - 1.27**	**0.0014**
Light-volume (>0-4)	6/13	1.06	0.88 - 1.28	0.5456	1.13	0.94 - 1.34	0.1881
Low-volume (>4-14)	12/41	1.04	0.86 - 1.24	0.7030	1.08	0.91 - 1.28	0.3793
Medium-volume (>14-24)	3/6	1.25	0.90 - 1.73	0.1725	1.31	0.95 - 1.80	0.0989
Increased-volume (>24-44)	10/21	1.10	0.92 - 1.32	0.2948	1.15	0.96 - 1.37	0.1209
Higher-volume (>44-64)	9/21	1.19	0.99 - 1.43	0.0645	**1.24**	**1.04 - 1.48**	**0.0172**
Highest-volume (>64)	9/21	1.16	0.96 - 1.41	0.1203	**1.22**	**1.01 - 1.47**	**0.0392**
RR change/10 g ↑ ✓	13/102	**1.025**	**1.016-1.034**	**0.0001**	**1.024**	**1.015-1.034**	**0.0001**
Former drinkers	3/6	**1.41**	**1.00 - 1.98**	**0.0487**	**1.39**	**1.02 - 1.88**	**0.0355**
Any drinkers	13/108	**1.17**	**1.06 - 1.29**	**0.0083**	**1.21**	**1.12 - 1.31**	**0.0008**

Note: ¥ Mean daily alcohol use in each category estimated assuming a gamma distribution for population consumption. † N= Number of studies and n= number of risk estimates. ‡ Model I estimates deal with skewed distribution by analyzing natural logged RR, weighting by inverse of variance in each estimate and adjusted for heterogeneity across studies. ‡‡ Model II of studies of PC incidence further adjusts for study-level measures of mean cohort age of cohorts/follow-up years (cohort age<56 and follow-up=10+ vs others), studies with reduced former drinker bias or with former drinker bias; Model II of studies of PC mortality further adjustments for study-level measures of mean cohort age of cohorts/follow-up years (cohort age<56 and follow-up=10+ vs others), studies with reduced former drinker bias or with former drinker bias, study level differences in exclusion of baseline health conditions (exclusion or not), and whether socioeconomic status (SES) and BMI were controlled in individual. ✓ RR if incidence of PC increased by 2.9% and RR of mortality from PC increased by 2.4% (Model II) due to 10 gram increase of pure alcohol intake per day among current drinkers.