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Alcohol consumption and the risk of pancreatic cancer: A systematic review and meta-analysis of cohort studies

Jinhui Zhao[1], Tim Stockwell[1,2], Timothy S. Naimi[1,3], James M. Clay[1,4], Keegan Lawrence[1], and Adam Sherk[1,5]

[1] Canadian Institute for Substance Use Research, University of Victoria, BC, Canada
[2] Psychology Department, University of Victoria, BC, Canada
[3] School of Medical Sciences, University of Victoria, BC, Canada
[4] Department of Community Health and Epidemiology, Dalhousie University, Nova Scotia, Canada
[5] Canadian Centre on Substance Use and Addiction, Ottawa, ON, Canada

Abstract

Objective: Previous reviews have reported inconsistent relationships between alcohol use and pancreatic cancer (PC). We conducted a meta-analysis of cohort studies to investigate associations between alcohol consumption and PC.

Methods: PubMed and Web of Science were searched for cohort studies of alcohol and PC incidence/mortality up to January 1, 2024. Mixed models were used to model the meta-data and calculate the summarized hazard ratio as relative risk (RR) of PC incidence/mortality. The impact of former drinker misclassification and other study-level covariates were assessed using statistical adjustment, quality weighting and stratification.

Results: Thirty-seven cohort studies provided 279 PC incidence/mortality risk estimates for drinkers versus "non-drinkers". In pooled analyses, there was no significant protection at any level, and significantly increased risk at more than 24g/day. Significant dose-response relationships were observed; e.g., a 2.4% increased risk for each 10g ethanol/day increment in the adjusted model (p=0.0001). Studies with more former drinker bias showed significantly reduced PC risk at more than 14–24g/day and no significant increase in risk for people drinking more than 24–44g/day; neither finding was observed among studies with reduced former drinker bias.

Conclusion: Pancreatic cancer exhibits a dose-response risk relationship with alcohol consumption; consumption of more than 24g/day is associated with 10% to 30% increased risk. Failing to separate former drinkers from lifetime abstainers may yield spurious protective associations at low levels of consumption and may suppress risk estimates at higher levels.

Introduction

Pancreatic cancer (PC; ICD-10: C25; World Health Organization [WHO], 2019) is the seventh leading cause of cancer-related deaths worldwide and the fourth leading cause in developed countries (Soreide et al., 2010). Over decades, epidemiological studies have investigated various PC risk factors including alcohol consumption (Rawla et al., 2019). Alcohol is generally recognized as being associated with PC, along with tobacco smoking, dietary factors, diabetes mellitus, obesity, age, ethnicity, and family history (Rawla et al., 2019). However, there have been inconsistent findings in previously published studies, including several pooled analyses (Genkinger et al., 2009; Lucenteforte et al., 2012; Michaud et al., 2010; Naudin et al., 2025) and meta-analyses (Bagnardi et al., 2015; Choi et al., 2018; Lu et al., 2017; Tramacere et al., 2010) on the association of alcohol consumption with incidence and mortality risk of PC. Some pooled analyses and meta-analyses estimated significantly reduced risk of PC due to low volume alcohol use (Lu et al., 2017; Tramacere et al., 2010) while others found this relationship to be non-significant (Choi et al., 2018; Lucenteforte et al., 2012). All studies consistently found significantly increased risks of PC incidence or mortality for higher levels of consumption (Bagnardi et al., 2015; Genkinger et al., 2009; Lu et al., 2017; Lucenteforte et al., 2012; Tramacere et al., 2010; Wang et al., 2016). However, there are many identifiable weaknesses in these previously published pooled analyses and meta-analyses on PC and alcohol intake.

Correspondence: Dr. Jinhui Zhao, Canadian Institute for Substance Use Research (CISUR), University of Victoria, PO Box 1700 STN CSC, Victoria, BC V8Y 2E4, Canada. Email: zhaoj@uvic.ca
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There is a growing literature critiquing the appearance of J-shaped risk curves in alcohol epidemiology in relation to all-cause mortality (Stockwell et al., 2024; Zhao et al., 2023) and specific conditions (Zhao et al., 2016; 2021), including ischaemic heart disease (World Heart Federation, 2022) and other conditions. Naimi and Chikritzhs (2025) provide a detailed discussion on how purported "abstainers" (such as those who say they never drank but have consumed alcohol previously) and other classification problems distort observational evidence on alcohol and health. A particularly important source of bias arises when former drinkers are misclassified as lifetime abstainers and included in the reference group (Liang & Chikritzhs, 2013). Because former drinkers tend to be systematically less healthy, this misclassification can attenuate risk estimates across all levels of alcohol consumption compared with the affected reference group. We refer to this misclassification as *former drinker bias*. We also assessed *occasional drinker bias*, whereby individuals who reduce their drinking to very low levels are misclassified as abstainers in the reference group.

These classification biases may be further compounded by inadequate control for confounding among individual studies included in subsequent meta-analyses. For example, a previous meta-analysis investigating the alcohol-PC relationship found significantly different results between studies that adjusted for smoking and those that did not (Tramacere et al., 2010). Several others similarly acknowledged that unadjusted confounders in individual studies may have influenced risk estimates but did not account for these potential confounding effects in the pooled analyses (Bagnardi et al., 2015; Choi et al., 2018; Lu et al., 2017; Tramacere et al., 2010). In addition, study-level characteristics may further exacerbate these biases. In particular, the age distribution of study populations may confound or modify observed associations, as studies recruiting older cohorts are more susceptible to selection bias, with abstainer reference groups more likely to include less healthy former drinkers. Consistent with this, higher median ages at recruitment have been associated with apparent protective effects of moderate drinking, reinforcing spurious J-shaped risk curves in pooled analyses (Stockwell et al., 2024; Zeisser et al., 2014; Zhao et al., 2017, 2023).

Taken together, misclassification of drinking status, inadequate control for confounding, and study-level design flaws provide a coherent explanation for the inconsistent findings and apparent protective associations observed in some pooled analyses and meta-analyses of alcohol consumption and pancreatic cancer. These sources of bias are not independent; rather, they may act cumulatively, such that misclassification of abstainers and former drinkers is amplified by residual confounding and age-related selection processes, increasing the likelihood of spurious J-shaped risk curves in pooled estimates.

Consistent with this interpretation, meta-analyses that have explicitly attempted to address these sources of bias, for example by excluding former drinkers from the reference group, restricting analyses to younger cohorts, or improving confounder adjustment, generally do not observe protective associations at low levels of alcohol consumption. Instead, these analyses tend to report null or monotonic associations between alcohol intake and disease risk. (Fillmore et al., 2006; Stockwell et al., 2016, 2024; Zhao et al., 2016, 2017, 2021, 2023).

The aim of this study was to re-evaluate the association between alcohol consumption and PC incidence and mortality by assessing the extent to which classification bias, residual confounding, and study-level characteristics influence pooled risk estimates and the appearance of protective associations at low levels of consumption. To address these limitations in previously published studies and meta-analyses of such associations, we conducted an updated systematic review and meta-analysis, using data available up to January 2024. Specifically, we examined: (a) the association between mean daily alcohol intake and pancreatic cancer incidence and mortality, including dose–response relationships, by pooling hazard ratios (HRs) as relative risks (RRs) from cohort studies with and without adjustment for key study-level confounders; (b) the impact on risk estimates of performing study-level adjustments based on quality criteria, including recruiting younger cohorts, having longer follow-up durations, and addressing former drinker bias; and (c) the extent to which former drinker bias alters observed associations between alcohol consumption and pancreatic cancer risk through stratified analyses.

Methods

Study Design

We undertook a systematic review to find, evaluate and summarize existing research on the associations of PC and alcohol consumption, and performed a meta-analysis to analyze the pooled individual studies on PC and alcohol use identified in the systematic review (Woodward, 2000). Meta-analysis is a powerful research method that statistically combines results from multiple independent studies on the same topic to find more precise estimates, effectively creating a larger, more powerful study to reveal trends, resolve inconsistencies, and provide stronger evidence than any single study. The study protocol was registered in advance on the Open Science Framework (registration https://doi.org/10.17605/OSF.IO/8EAMS; Zhao et al., 2024).

Inclusion and Exclusion Criteria

Inclusion criteria were: (a) cohort studies published in English, including those of non–European origin; (b) original research manuscripts published in peer–reviewed journals that examined the relationship between incidence or mortality of PC and alcohol consumption among human populations in cohort studies; (c) retrospective or prospective (cohort) studies evaluating the relationship between alcohol consumption and incidence or mortality of PC (ICD-10: C25); (d) the mean quantity of alcohol consumed daily in grams of ethanol, with at least two levels of daily alcohol consumption compared with abstinence.

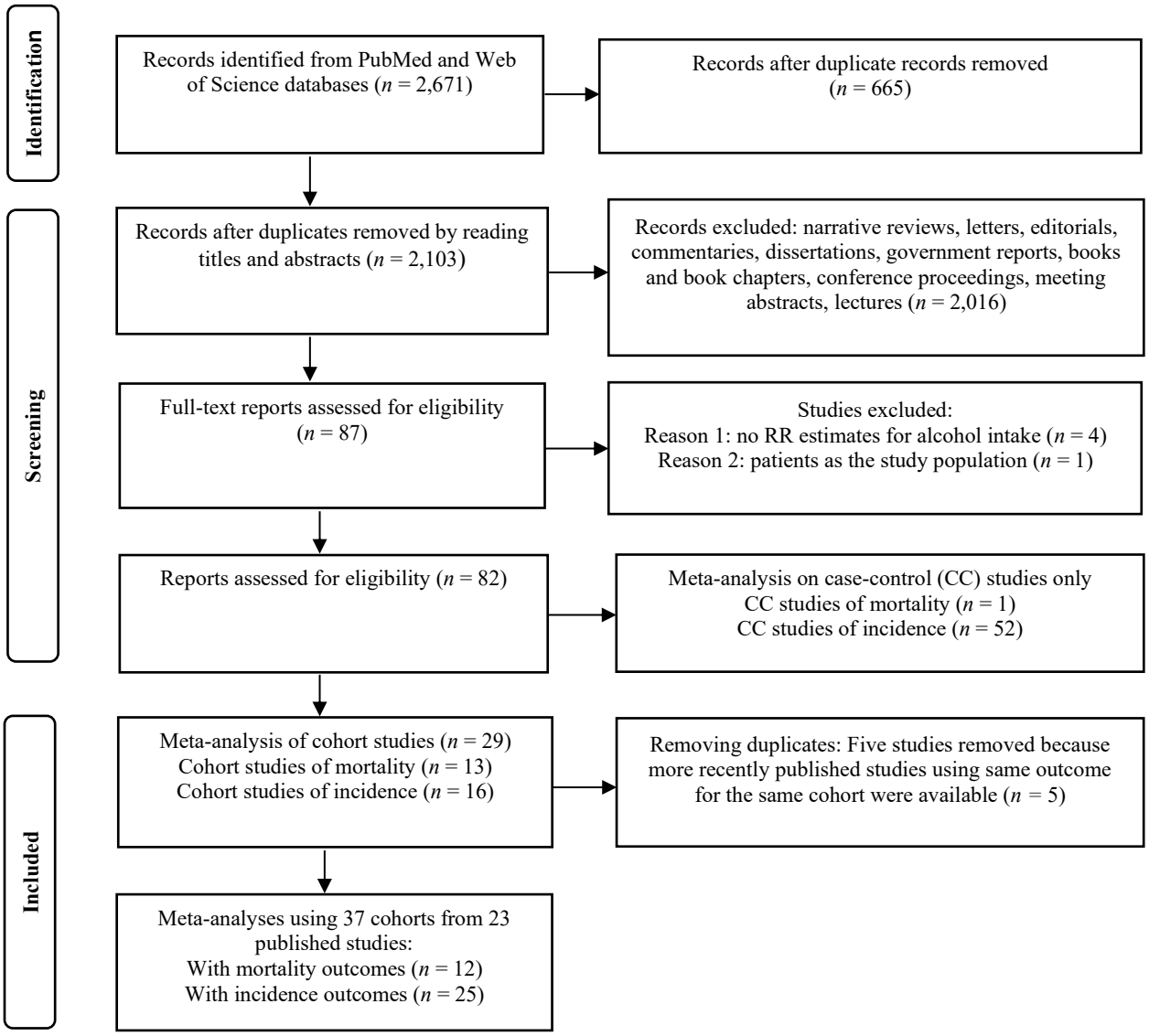
Search Strategy

The systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta–Analyses

(PRISMA) guidelines (Moher et al., 2009). The PubMed and Web of Sciences databases were searched up to January 1, 2024 to capture all relevant published studies. The reference lists of papers meeting the eligibility criteria were also screened for additional potentially relevant papers that may have been missed by our electronic searches. We used the following key words and subject headings to identify relevant articles in electronic databases: [mortality OR death OR incidence] AND [pancreatic cancer OR pancreas cancer OR pancreatic neoplasm OR pancreatic carcinoma OR pancreatic adenocarcinoma OR pancreatic ductal adenocarcinoma] AND [alcohol OR ethanol] AND [case-control OR cohort OR longitudinal].

Figure 1

Flowchart of Systematic Search Process for Studies of Alcohol Intake and Risk of Incidence or Mortality due to Pancreatic Cancer



Study Selection

Two reviewers (KL and JZ) performed the search and read the titles of all the citations and abstracts retrieved from the electronic database searches. We removed all citations that were not focussed on the relationship between alcohol consumption and the incidence or mortality of PC. Further screening of abstracts for eligibility was conducted by the research team. Full-text articles were obtained for all abstracts except for those that clearly did not meet eligibility criteria. The investigators independently evaluated the studies selected to confirm they met inclusion criteria (Figure 1, also Tables A1 and A2 in Appendix A).

Data Extraction and Coding

Three investigators (KL, JC and JZ) independently reviewed all eligible papers to extract and code data from all studies

fulfilling the inclusion criteria, and any disagreements were resolved by discussion with the principal investigators (TS and TN). The coding followed that in the preregistered protocol (Zhao et al., 2024) which was derived from the original Stockwell et al. codebook for meta-analyses of all-cause mortality and alcohol intake (Stockwell et al., 2016) and prepared to identify higher quality studies that were less likely to suffer from lifetime selection biases.

Each study was coded under the supervision of the lead investigators. If multiple reports had been issued from the same dataset, the latest report was coded, unless different sub-populations or outcomes were considered (e.g. males versus females). The coding of all variables in the meta-dataset was double-checked within the investigative group. Data extracted included (a) HR of incidence or mortality of PC due to alcohol intake at various levels of mean daily alcohol consumption; (b) study characteristics, including age and sex of study cohorts at recruitment and follow-up; (c) types of misclassification error present in the abstainer reference group; and (d) type and number of covariates controlled for in individual studies.

Variables

The outcome variables of interest were defined as death from or incidence of PC (ICD-10: C25; WHO, 2019). Hazard ratio (HR) and rate ratio (RR) estimates of incidence/mortality in individual studies were used as the RR estimates. Where studies only reported mortality or incidence rates, these were converted to RR estimates (Woodward, 2000). When *abstainers* or *non-drinkers* were not the reference category in a study and risk for *abstainers* or *non-drinkers* was independently assessed, risk values were recalculated using *abstainers* or *non-drinkers* as the reference group (Fillmore et al., 2006; Stockwell et al., 2016).

The primary exposure variable was average daily level of alcohol consumption in grams of ethanol assessed at baseline, compared with a reference group of variously defined *non-drinkers*. When studies did not define the grams of alcohol per unit or per drink, we converted the alcohol intake into grams based on the country-specific standard drink (International Alliance for Responsible Drinking, 2022; Turner, 1990). We coded the lower and upper bounds for the different categories of drinkers. We converted alcohol intake into grams per day and then generated the mean grams of ethanol per day for each drinking group in the included studies using the gamma distribution of consumption. This approach is more accurate than using the arithmetic midpoint usually employed in meta-analyses of alcohol and health outcomes (Kehoe et al., 2012). To construct a gamma distribution specific to each study's population characteristics, we compiled *per capita* alcohol consumption data by country, sex, and year from the WHO Global Health Observatory (2025). We also performed a sensitivity analysis using the midpoint of low and high cutoff drinking for drinking categories in individual studies with results in Tables C3 and C4 in Appendix C.

We specified lifetime non-drinkers, former drinkers, and current drinkers (Fillmore et al., 2006). *Lifetime abstainers* were initially strictly defined as those who never drank more than 10g ethanol in their lifetime; *former drinkers* were defined as those who drank at least 10g or more ethanol in their lifetime, but were abstaining at study baseline (no studies surveyed the amount of alcohol consumption among former drinkers); and *current drinkers* were defined as those who drank at least one drink over the time periods assessed at baseline in the various studies. Current drinkers were further classified into: *very light drinkers* (> 0–2g/day), *light drinkers* (> 2–4g/day), *low-volume drinkers* (> 4–14g/day), *medium-volume drinkers* (> 14–24g/day), *increased-volume drinkers* (> 24–44g/day), *high-volume drinkers* (> 44–64g/day), and *highest-volume drinkers* (> 64g/day).

Study characteristics were collected: (a) study name, authors and publication date; (b) type of outcome, incidence or mortality; (c) geographic origin, i.e., in which countries individual studies were conducted; and (d) characteristics of study population including age at recruitment or study onset (youngest age, median/mean age, oldest age), sex (male only, females only, or both), years during which the study was conducted, average years of follow-up, health status (no exclusion for existing illness versus excluded for existing illness), and adjustment for potential confounders including smoking status, social economic status (SES), body mass index (BMI), diet, and drinking patterns. When studies assessed the usual or typical drinking amount over a week or a month, it was assumed that individuals in a study who were classified as abstainers by this method and subsequently used as the reference group could include occasional drinkers (i.e., drinkers who typically consumed less than weekly or monthly). We coded a drinking measure as minimally "adequate" if both quantity and frequency (QF) of drinking were assessed over the past 30 days or longer. When multiple independent cohorts were reported within a single publication, each cohort was treated as an independent study and included separately in the meta-analysis.

Studies were coded for whether or not former or occasional drinkers could be misclassified as abstainers. Only three studies met initially strict criteria for excluding former drinkers from abstainers, i.e. abstainers could not include people who previously drank alcohol at even light levels. An additional seven studies were coded as making at least partial efforts to remove former drinkers as they had only loose definitions of lifetime abstention, for example including individuals who reported "almost never" drinking alcohol (e.g., Klatsky et al., 2015) or who did so on less than 12 occasions per year. Misclassification of occasional drinkers as abstainers was coded wherever the reference group included abstainers as well as light or occasional drinkers, e.g., by defining abstainers as people who drank less often than once per day, or per week or per month.

In addition, studies were coded for whether or not any of the following potential confounding variables were included in adjusted models: cohort age, sex, other cancer or pancreatic diseases, other conditions (or excluded at design stage or from analysis), BMI, diabetes (or excluded from analysis), general health (or excluded from analysis), mental health, disability or physical limitations, smoking, marital status, SES, exercise, race, region of residence, weight, former drinking, type of housing, social support, and follow-up duration.

Data Analysis

Exclusions

We first excluded the incidence RR estimates in the studies by Stolzenberg-Solomon et al. (2001), Michaud et al. (2001) and Harnack et al. (1997) as their estimates duplicated those in a more recently published study by Genkinger et al. (2009) which had a longer follow-up period. The mortality risk estimates in Jayasekara et al. (2019) were excluded from the pooled analysis because the incidence risk estimates were included (239 incident cases of PC were diagnosed, of which 228 had died). The incidence risk estimates by Stevens et al. (2009) were excluded because the mortality risk estimates in the Stevens et al. (2009) study were included (separate risk estimates by incident cases and mortality cases) and the incidence risk estimates on the same cohort in the study by Allen et al. (2009) were included.

Tests of Publication Bias and Heterogeneity

Analyses were performed to examine publication bias and heterogeneity of the RR estimates among included studies. Publication bias was assessed through visual inspection of the funnel plot of log-RR of PC incidence/mortality due to alcohol consumption against the inverse standard error of log-RR (Woodward, 2000), the Kendall Rank Correlation Coefficient (Begg & Mazumdar, 1994), and Egger's linear regression method (Egger et al., 1997). We plotted forest graphs of log-RR of PC incidence/mortality for any level drinking to assess heterogeneity among studies (Woodward, 2000). We also assessed between-study heterogeneity of RRs using Cochran's Q (Cochran, 1954) and the I^2 statistic (Higgins & Thompson, 2002). If heterogeneity was detected, mixed effects models (Normand, 1999; Woodward, 2000) were used to obtain the summarized RR estimates adjusted for the effect of heterogeneity. The effects of two studies with large RR estimates (Yi et al., 2010; Zheng et al., 1993) were also investigated by excluding these two studies in multivariable mixed regression models. We conducted bivariate analyses to describe the sample characteristics and estimate mean HRs by study subgroups to identify potential confounders among individual studies.

Multivariable Regression Analysis

Mixed effects regression analyses were performed in which drinking groups and control variables were treated as fixed effects with a random study effect (Normand, 1999; Woodward, 2000). Relative risk estimates of PC by drinking groups were with the basic adjustment and further adjusted for potential confounding effects of study-level covariates. Basic adjustment dealt with skewed distribution and outliers by analyzing natural logged RR (Woodward, 2000), weighting by inverse of variance (IV) in each estimate to adjust for sampling variability (Woodward, 2000) and adjusting for heterogeneity across studies. Covariate-adjustment further controlled for potential confounding effects of study-level covariates which met the inclusion criteria. More details of mixed models can be found in Appendix B.

We also used a quality weighting method by giving larger weights to risk estimates in the studies with the mean age of cohorts younger than 56 years (+0.4), no former drinker bias (+0.4) or reduced former drinker bias (+0.2) and follow-up for at least 10 years (+0.1). The quality weights were incorporated into the sampling weights, i.e., the IV. Other covariates were also adjusted as in Table 3, Model II; results are presented in Table 4, Model II.

Analyses of studies stratified by presence or absence of former drinker bias were performed. Ten studies with absence of former drinker bias included three studies which fully met strict criteria for being free from abstainer bias, and seven studies that made partial attempts to remove former drinker bias. This stratification approach was supported empirically by a significant interaction between level of alcohol use and presence or absence of former drinker bias (F-test $\text{value}_{(df=266)} = 2.68$ and $p = 0.0215$) in the model without any adjustment. We also performed an analysis comparing incidence and mortality studies to examine whether the RR estimates significantly differed by the outcomes (the RR estimates of incidence and mortality in Table C5 in Appendix C) in the included studies.

Models were not stratified by mean age and sex of cohorts as there was no evidence of effect modification for age (F-test $\text{value}_{(df=265)} = 0.49$ and $p = 0.8144$) or sex (F-test $\text{value}_{(df=259)} = 0.32$ and $p = 0.9805$) in basic models. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., 2020) and the SAS PROC MIXED procedure was used to model the meta-data and estimate the summarized RR of PC incidence/mortality due to mean daily alcohol intake (SAS Institute Inc, 2018). All significance tests assumed two-tailed p values or 95% CIs.

Results

Characteristics of Meta-Data

We performed a meta-analysis of 37 cohort analyses contained within 23 published studies on the risk of PC mortality ($n = 12$ studies) and/or incidence ($n = 25$ studies) in relation to levels of average alcohol use. There were 279 estimates of the risk relationship between level of alcohol consumption and PC mortality or incidence from 37 unique cohort analyses contained in 23 studies (Bui et al., 2023; Coughlin et al., 2000; Gapstur et al., 2011; Gaziano et al., 2000; Genkinger et al., 2009; Heinen et al., 2009; Isaksson et al., 2002; Jayasekara et al., 2019; Jiao et al., 2009; Kim et al., 2010; Klatsky et al., 2015; Kono et al., 1986; Lin et al., 2002; Nakamura et al., 2011; Okita et al., 2022; Ozasa, 2007; Pang et al., 2018; Park et al., 2022; Shen et al., 2013; Shibata et al., 1994; Stevens et al., 2009; Yi et al., 2010; Zheng et al., 1993), including 20,786,465 subjects and 65,159 deaths or incidences of PC available for the analysis (Tables A1 and A2 in Appendix A).

Table 1

Sample Characteristics of the Meta-Data on Pancreatic Cancer Incidence/Mortality and Alcohol Use in 37 Cohorts Contained in 29 Studies Published Between 1994 and 2023

Covariates	PC incidence/mortality studies (N=37)[a]				Mean RR & 95% CI[c]		
	Study[b]	%[b]	RR[b]	%[b]	RR	95% CI	t-test P
Mean cohort age (years)[d]							
41-55	13	35.14	86	30.82	1.01	0.90 - 1.11	0.0090
56-75	24	64.86	193	69.18	1.18	1.11 - 1.25	ref
Sex							
Men only	24	44.44	128	45.88	1.17	1.08 - 1.26	0.2451
Women only	21	38.89	81	29.03	1.09	0.98 - 1.21	0.8871
Men and women	9	16.67	70	25.09	1.08	0.96 - 1.20	ref
Countries/regions							
US/CA-Europe-Australia	26	70.27	193	69.18	1.07	0.99 - 1.13	0.0038
Asia (Jap/S-Korea/C/HK-C)	11	29.73	86	30.82	1.26	1.15 - 1.37	ref
Follow-up years							
05.00-09.00	15	40.54	101	36.20	1.01	0.91 - 1.11	0.0045
10.50-29.00	22	59.46	178	63.80	1.19	1.12 - 1.27	ref
Baseline health conditions[e]							
No exclusion	3	8.11	27	9.68	1.32	1.13 - 1.52	0.0389
Exclusion	34	91.89	252	90.32	1.11	1.04 - 1.17	ref
Alcohol use measure							
30+ days QF	30	81.08	215	77.06	1.12	1.05 - 1.19	0.7226
Other	7	18.92	64	22.94	1.15	1.02 - 1.27	ref
Abstainer biases (strict)							
Former and occasional	14	37.84	85	30.47	1.19	1.08 - 1.20	0.0383
Former only	20	54.05	171	61.29	1.05	0.97 - 1.13	ref
Neither[f]	3	8.11	23	8.24	1.46	1.25 - 1.66	0.0004
Former drinker bias (not strict)[g]							
No	10	26.32	88	31.54	1.24	1.14 - 1.35	0.0101
Yes	28	73.68	191	68.46	1.07	1.00 - 1.15	ref
Control for smoking in model							
No	8	18.60	80	28.67	1.07	0.96 - 1.19	ref
Yes	35	81.40	199	71.33	1.15	1.07 - 1.22	0.2900
Control for SES[h]							
No	24	64.86	167	59.86	1.07	0.99 - 1.14	0.0163
Yes	13	35.14	112	40.14	1.22	1.12 - 1.31	ref
Control for race							
No	33	89.19	227	81.36	1.14	1.07 - 1.21	0.3880
Yes	4	10.81	52	18.64	1.07	0.93 - 1.21	ref
Control for diet							
No	17	45.95	145	51.97	1.15	1.07 - 1.24	0.3792
Yes	20	54.05	134	48.03	1.10	1.01 - 1.19	ref
Control for exercise							
No	24	64.86	152	54.48	1.15	1.07 - 1.23	0.4135
Yes	13	35.14	127	45.52	1.10	1.01 - 1.19	ref
Control for BMI[h]							
No	5	13.51	22	7.89	1.44	1.23 - 1.66	0.0028
Yes	32	86.49	257	92.11	1.10	1.04 - 1.16	ref
Control for diabetes							
No	10	27.03	44	15.77	1.22	1.06 - 1.37	0.2063
Yes	27	72.97	235	84.23	1.11	1.04 - 1.18	ref
Type of outcome							
Incidence	25	67.57	174	62.37	1.05	0.98 - 1.13	0.0018
Mortality	12	32.43	105	37.63	1.25	1.15 - 1.35	ref

Notes:

[a]279 relative risk (RR) estimates from 37 cohort analyses contained in 23 cohort studies.

[b]Number of studies (%) and RR estimates (%) for any drinking from the included studies by subgroups.

[c]Unadjusted mean RR and 95% confidence interval (CI) due to any drinking (compared with "abstaining") by subgroups from the included studies.

[d]Mean age at study enrollment.

[e]Control for currently or previously diagnosed pancreatic cancer and/or other illnesses by exclusion or separate analysis.

[f]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).

[g]Completely biased or partially, reduced former drinker bias.

[h]SES=Socioeconomic status and BMI=Body Mass Index.

There were on average five confounders adjusted for in the 37 studies for the RR estimates. Table 1 describes the sample characteristics of the meta-data for all drinkers (the characteristics of moderate drinkers, i.e., drinking between 4g and 24g/day in Table C1 in Appendix C). Three studies (providing 23 risk estimates) were considered to be free from abstainer bias, i.e. had a reference group of strictly defined lifetime abstainers (Kono et al., 1986; Lin et al., 2002; Shen et al., 2013). There were 14 studies (85 risk estimates) with both former and occasional drinker bias (Bui et al., 2023; Coughlin et al., 2000; Gaziano et al., 2000; Isaksson et al., 2002; Jayasekara et al., 2019; Kim et al., 2010; Nakamura et al., 2011; Okita et al., 2022; Ozasa, 2007; Pang et al., 2018; Park et al., 2022; Shibata et al., 1994; Yi et al., 2010; Zheng et al., 1993) and 20 cohorts or sub-studies (171 risk estimates) with former drinker bias but not occasional drinker bias (Allen et al., 2009; Gapstur et al., 2011; Genkinger et al., 2009; Heinen et al., 2009; Jiao et al., 2009; Klatsky et al., 2015; Stevens et al., 2009).

Table 2

Statistical Analysis of Mean Hazard Risk (HR) of Mortality/Incidence of Pancreatic Cancer for Different Categories of Drinkers for Testing Publication Bias and Heterogeneity of RR Estimates from Included Studies

Drinking categories[a]	N/n[b]	Mean hazard ratios and 95% CIs due to alcohol use[c]			Egger's linear regress for publication bias		Cochran's Q and I^2 tests for heterogeneity	
		HR	95% CI	t-test P	Coeff	t-test 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)	25/45	1.09	0.95, 1.24	0.1935	+0.37	=0.0712	>0.05	12.38 [00.00, 39.63]
Low-volume (>4-14)	33/82	1.07	0.96, 1.18	0.1793	-0.12	=0.5144	<0.05	21.92 [00.00, 41.10]
Medium-volume (>14-24)	23/41	0.93	0.78, 1.09	0.4349	-0.25	=0.2669	>0.05	01.00 [00.00, 46.17]
Increased-volume (>24-44)	24/45	1.21	1.06, 1.36	0.0021	+0.20	=0.4058	>0.05	01.00 [00.00, 35.48]
Higher-volume (>44-64)	22/44	1.19	1.04, 1.34	0.0076	-0.09	=0.7530	<0.05	31.95 [01.19, 53.09]
Highest-volume (>64)	9/15	1.42	1.17, 1.68	0.0002	+0.56	=0.1570	>0.05	02.41 [00.00, 27.57]
Any drinkers	37/279	1.13	1.07, 1.19	0.0001	+0.17	=0.1140	<0.05	36.22 [25.94, 45.05]

Notes:
[a]Mean daily alcohol use in each category estimated assuming a gamma distribution for population consumption.
[b]N= Number of studies (cohorts) and n = Number of risk estimates.
[c]Arithmetic mean hazard ratios without any adjustment

Unadjusted mean RR estimates for all study subgroups categorized by sample characteristics showed higher RRs for alcohol consumers as a group versus *abstainers* as defined by the authors of the included studies (Table 1). There were significantly higher RRs in cohorts with mean age 56 years or older versus less than 56 years (1.18 vs 1.01) and in Asian versus Caucasian countries (1.26 vs 1.07). There were significantly higher risks in cohorts followed up for at least 10 years versus fewer (1.19 vs 1.01). Cohorts without exclusion of participants with health conditions at baseline had a significantly higher risk than those with such exclusion (1.32 vs 1.11). Cohorts with former drinker bias at least partially removed had a significantly higher risk than those such bias (1.24 vs 1.07). The studies with no adjustment for BMI had a significantly higher risk than that with adjustment for BMI (1.44 vs 1.10). Studies with mortality outcomes had a significantly higher risks than did the incidence studies (1.25 vs 1.05).

Unadjusted, simple arithmetic mean HRs of PC were significantly higher among former drinkers, current drinkers who drank more than 24g/day, all current drinkers and all former or current drinkers combined (Table 2 and Table C2 in Appendix C). Figure 2 is a forest plot of mean RRs and 95 CI in 37 cohort studies which illustrates the heterogeneity of the RR estimates across all studies. Cochran's Q test showed significant heterogeneity ($p < 0.05$) across all included studies, and the I^2, indicated a moderate degree of heterogeneity ($I^2 = 36.22\%$ and 95% CI[25.94, 45.05]). We thus employed random effect models to estimate pooled RRs accounting for heterogeneity. Figure 3 shows a funnel plot of log-RRs and their inverse standard errors which is symmetrical, i.e. also indicates no publication bias. The *p*-value (0.6397) of the Kendall Tau *b* Correlation Coefficients (0.02) was not statistically significant, suggesting no publication bias, as also indicated by a non-significant Egger's linear regression coefficient (Ps>0.05).

Relative Risk Estimate of Pancreatic Cancer Incidence/Mortality due to Alcohol Intake

Table 3 presents the summarized RR estimates for each drinking group from the meta-analyses of 37 pooled studies containing 279 HR estimates with different levels of

adjustment for study-level covariates. In neither model was the risk of PC significantly increased or decreased for people drinking up to 24g ethanol per day. Risk levels for light and very light drinkers were very close to 1.0 for the Model I. A significantly increased risk of PC was evident in each model for each category of consumption above 24g ethanol per day. These risks were lowest in the basic Standard Model I and highest in the Covariate-adjusted Model II. For example, RR = 1.08 (*t*-test $p = 0.0273$) in Model I, and RR = 1.21 (*t*-test $p = 0.0092$) in Model II for more than 24–44g/day drinkers. Former drinkers had substantial and significantly higher risks of PC incidence/mortality than abstainers in all models e.g. RR = 1.40, $p = 0.0064$ for Model I; RR = 1.49, $p = 0.0019$ for Model II). Significant linear dose-response models (natural log-transformed RR and alcohol intake in grams per day) were fitted showing a 2.6% increase in PC risk for each 10g increment in ethanol per day among current drinkers.

Figure 2

Forest Plot of Relative Risk Estimates And 95% Confidence Intervals for Pancreatic Cancer Incidence/Mortality Comparing Alcohol Consumption and "Abstinence" in 37 Cohort Studies

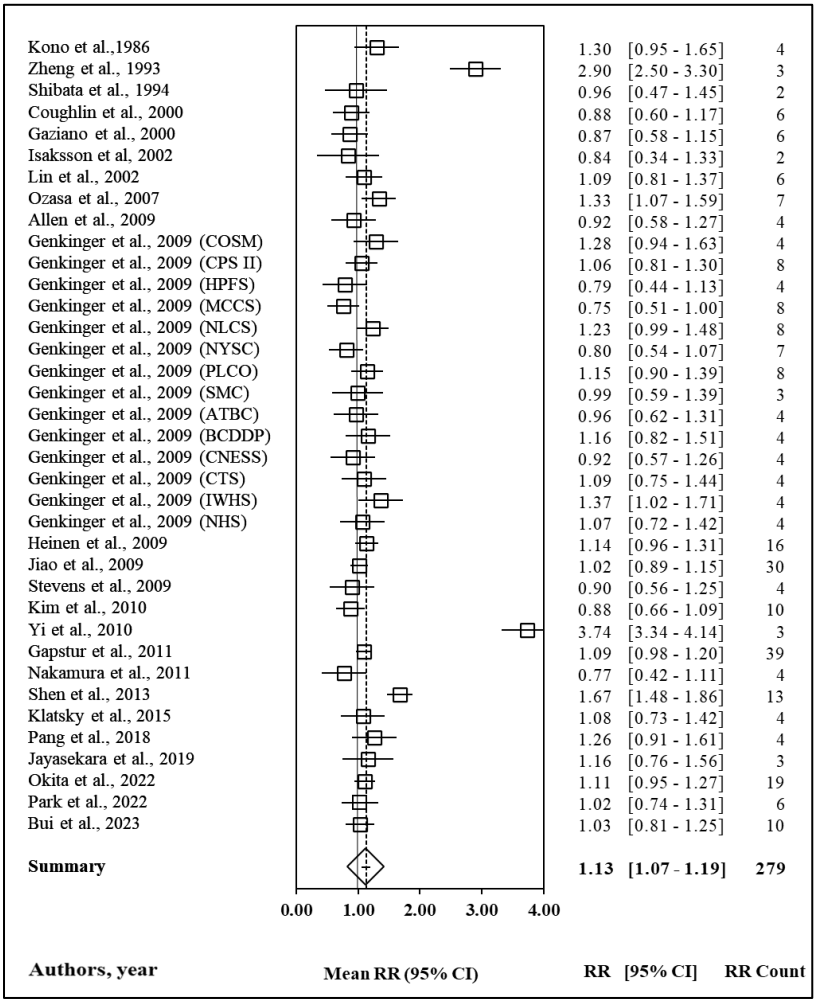


Table 4 and Figure 4 present the Standard Model I alongside a model (Model II) giving larger weights to studies with a mean cohort age younger than 56 years (+0.4), follow-up 10 years or more (+0.1) and no former drinker bias (+0.4 if strictly defined and +0.2 if less strictly defined). This quality-weighted Model II (adjusted for baseline condition exclusion/inclusion and BMI) found markedly increased risk of PC for people drinking up to 24g ethanol per day but significantly increased PC risk at each higher level of consumption. There were also significant linear dose-response models (natural log-transformed RR and alcohol intake in grams per day) fitted to the data within each model indicating increases in PC risk of between 2.4% and 2.5% for each 10g increment in daily ethanol consumption among current drinkers.

Table 5 and Figure 5 compare two models, one of 10 studies with at least partial efforts to exclude former drinker bias and the other of 28 studies all with former drinker bias; in Nakamura et al. (2011), RR for men included in the analysis of 28 studies with former drinker bias and RR for women included in the analysis of 10 studies with reduced former drinker bias. As predicted, there was no evidence of reduced

risk of PC for light- to medium-volume drinkers (up to 24g ethanol per day) among the studies that made some effort to reduce former drinker bias, while significant apparent protection against PC was present for medium level drinkers (more than 14–24g ethanol per day) with RR = 0.89, (p = 0.0096) in the 28 lower-quality studies. Stratified analyses without adjustment for study level covariates showed significantly reduced risk for medium-volume drinkers among the studies with former drinker bias; there were significantly increased risk estimates for all categories of drinkers among the studies with reduced former drinker bias that were slightly higher than for the studies with former drinker bias.

Figure 3

Funnel Plot of Natural Log-Relative Risk Estimates [ln(RR)] for Pancreatic Cancer Incidence/Mortality due to Alcohol Consumption Against Inverse of Standard Error of ln(RR)

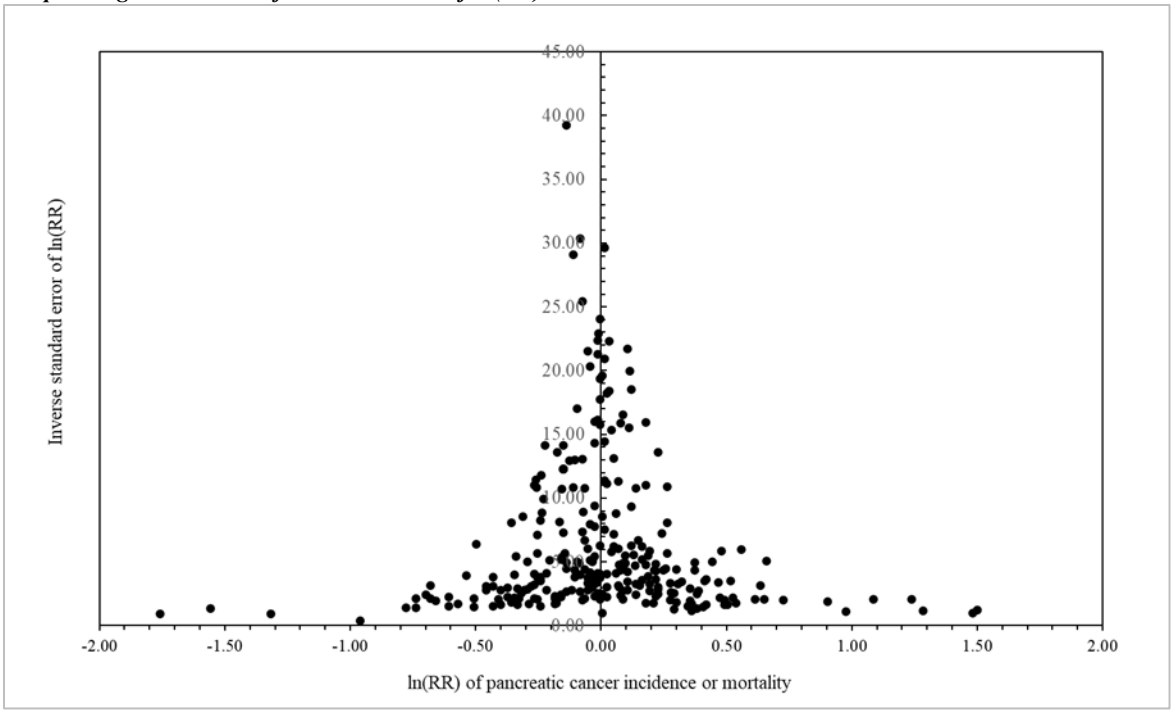


Table 3

Mean Relative Risk Estimates for Pancreatic Cancer Incidence/Mortality With 95% Confidence Intervals With and Without Adjustment for Selected Study Level Covariates

Alcohol drinker categories[a]	N/n[b]	Model I[c]			Model II[d]		
		RR[c]	95% CI	t-test P	RR[c]	95% CI	t-test P
Abstainer	37/78	1.00			1.00		
Current drinkers (g/day)	37/272	1.05	0.97, 1.13	0.1498	**1.18**	**1.10, 1.26**	**0.0015**
Light-volume (>0-4)	25/45	0.99	0.93, 1.07	0.8656	1.12	0.97, 1.29	0.1300
Low-volume (>4-14)	33/82	1.00	0.94, 1.07	0.9065	1.12	0.98, 1.29	0.0988
Medium-volume (>14-24)	23/41	0.97	0.90, 1.05	0.4667	1.09	0.94, 1.26	0.2451
Increased-volume (>24-44)	24/45	**1.08**	**1.01, 1.15**	**0.0273**	**1.21**	**1.05, 1.39**	**0.0092**
Higher-volume (>44-64)	22/44	**1.14**	**1.06, 1.22**	**0.0003**	**1.27**	**1.11, 1.47**	**0.0008**
Highest-volume (>64)	9/15	**1.14**	**1.05, 1.24**	**0.0013**	**1.28**	**1.10, 1.48**	**0.0012**
RR change/10 g ↑[e]	37/272	**1.026**	**1.019, 1.033**	**0.0001**	**1.026**	**1.019, 1.032**	**0.0001**
Former drinkers	4/7	**1.40**	**1.10, 1.78**	**0.0064**	**1.49**	**1.16, 1.92**	**0.0019**
Any drinkers	37/279	1.10	0.98, 1.23	0.1006	**1.22**	**1.11, 1.34**	**0.0021**

Notes:

[a]Mean daily alcohol use in each category estimated assuming a gamma distribution for population consumption.

[b]N = Number of studies and n = number of risk estimates.

[c]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.

[d]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 – reduced former drinker bias (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.

[e]RR change (increased by 2.6%, Model I-II) due to 10g increase of pure alcohol intake per day among current drinkers.

Table 4

Mean Relative Risk Estimates of Pancreatic Cancer Incidence/Mortality With 95% Confidence Intervals With and Without Weighting by Estimated Study Quality and Adjustment for Selected Study Level Covariates

Alcohol drinker categories[a]	N/n[b]	Model I[c]			Model II[d]		
		RR[c]	95% CI	t-test P	RR[c]	95% CI	t-test P
Abstainer	37/78	1.00			1.00		
Current drinkers (g/day)	37/272	1.05	0.97, 1.13	0.1498	**1.18**	**1.10, 1.26**	**0.0015**
Light-volume (>0-4)	25/45	0.99	0.93, 1.07	0.8656	1.12	0.97, 1.29	0.1300
Low-volume (>4-14)	33/82	1.00	0.94, 1.07	0.9065	1.12	0.98, 1.29	0.0988
Medium-volume (>14-24)	23/41	0.97	0.90, 1.05	0.4667	1.09	0.94, 1.26	0.2451
Increased-volume (>24-44)	24/45	**1.08**	**1.01, 1.15**	**0.0273**	**1.21**	**1.05, 1.39**	**0.0092**
Higher-volume (>44-64)	22/44	**1.14**	**1.06, 1.22**	**0.0003**	**1.27**	**1.11, 1.47**	**0.0008**
Highest-volume (>64)	9/15	**1.14**	**1.05, 1.24**	**0.0013**	**1.28**	**1.10, 1.48**	**0.0012**
RR change/10 g ↑[e]	37/272	**1.026**	**1.019, 1.033**	**0.0001**	**1.024**	**1.019, 1.032**	**0.0001**
Former drinkers	4/7	**1.40**	**1.10, 1.78**	**0.0064**	**1.49**	**1.16, 1.92**	**0.0019**
Any drinkers	37/279	1.10	0.98, 1.23	0.1006	**1.22**	**1.11, 1.34**	**0.0021**

Notes:

[a]Mean daily alcohol use in each category estimated assuming a gamma distribution for population consumption.

[b]N = Number of studies and n = number of risk estimates.

[c]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.

[d]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-reduced former drinker bias (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.

[e]RR change (increased by 2.6% in Model I, 2.4% in Model II) due to 10g increase of pure alcohol intake per day among current drinkers.

Figure 4

Plots of Mean Relative Risks of Pancreatic Cancer Incidence/Mortality by Level of Mean Daily Alcohol Use in Pooled Models

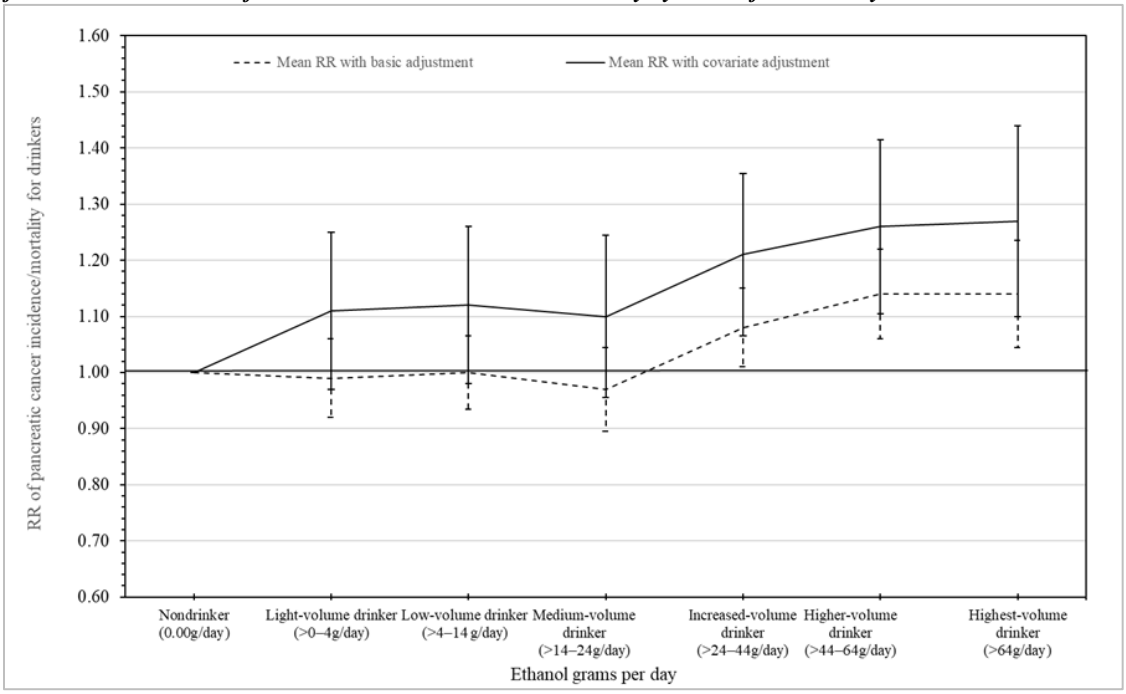


Table 5

Mean Relative Risk Estimates for Pancreatic Cancer Incidence/Mortality With 95% Confidence Intervals With and Without Adjustment for Selected Study Level Covariates by Studies With Reduced Former Drinker Bias and With Former Drinker Bias

Alcohol use categories[a]	Analysis of studies with reduced former drinker bias[b]				Analysis of studies with former drinker bias present [b]			
	N/n[c]	RR[d]	95% CI	t-test P	N/n[c]	RR[d]	95% CI	t-test P
Model I: with basic adjustment[d]								
Abstainer	10/22	1.00			28/52	1.00		
Current drinkers (g/day)	10/81	**1.14**	**1.04, 1.24**	**0.0201**	28/191	1.01	0.86, 1.18	0.8890
Light-low-volume drinker (>0–14)	10/38	1.07	0.98, 1.17	0.2241	26/89	0.98	0.92, 1.04	0.4138
Medium-volume drinker (>14–24)	4/6	1.11	0.99, 1.24	0.1327	19/35	**0.89**	**0.81, 0.97**	**0.0096**
Increased-volume drinker (>24–44)	7/21	**1.15**	**1.05, 1.26**	**0.0091**	17/24	1.08	0.98, 1.19	0.1136
High-volume drinker (>44)	6/16	**1.22**	**1.11, 1.34**	**0.0001**	19/43	**1.10**	**1.02, 1.19**	**0.0094**
RR change/10 gram ↑[e]	10/81	**1.023**	**1.015, 1.031**	**0.0001**	28/191	**1.033**	**1.021, 0.045**	**0.0001**
Former drinkers	4/7	**1.46**	**1.15, 1.86**	**0.0021**	0/0			
Any drinkers	10/88	**1.20**	**1.03, 1.39**	**0.0319**	28/191	1.01	0.86, 1.18	0.8890
Model II: further adjusted for 3 covariates[f]								
Abstainer	10/22	1.00			28/52	1.00		
Current drinkers (g/day)	10/81	**1.29**	**1.19, 1.40**	**0.0019**	28/191	1.08	0.94, 1.13	0.1905
Light-low-volume drinker (>0–14)	10/38	**1.22**	**1.04, 1.42**	**0.0147**	26/89	1.04	0.87, 1.25	0.6686
Medium-volume drinker (>14–24)	4/6	**1.26**	**1.06, 1.49**	**0.0079**	19/35	0.95	0.78, 1.15	0.5854
Increased-volume drinker (>24–44)	7/21	**1.30**	**1.11, 1.53**	**0.0014**	17/24	1.15	0.95, 1.41	0.1589
High-volume drinker (>44)	6/16	**1.39**	**1.18, 1.63**	**0.0001**	19/43	1.17	0.97, 1.42	0.0901
RR change/10 gram ↑[e]	10/81	**1.023**	**1.015, 1.031**	**0.0001**	28/191	**1.032**	**1.021, 1.044**	**0.0001**
Former drinkers	4/7	**1.54**	**1.22, 1.93**	**0.0003**	0/0			
Any drinkers	10/88	**1.34**	**1.21, 1.48**	**0.0014**	28/191	1.08	0.94, 1.13	0.1905

Notes:

[a]Mean daily alcohol use in each category estimated assuming a gamma distribution for population.

[b]See definition of reduced former drinker bias in method section. In Nakamura et al (2011), RR for men included in the analysis of 28 studies with former drinker bias and RR for women included in the analysis of 10 studies with reduced former drinker bias.

[c]N = number of studies (cohorts), and n = number of hazard ratio estimates.

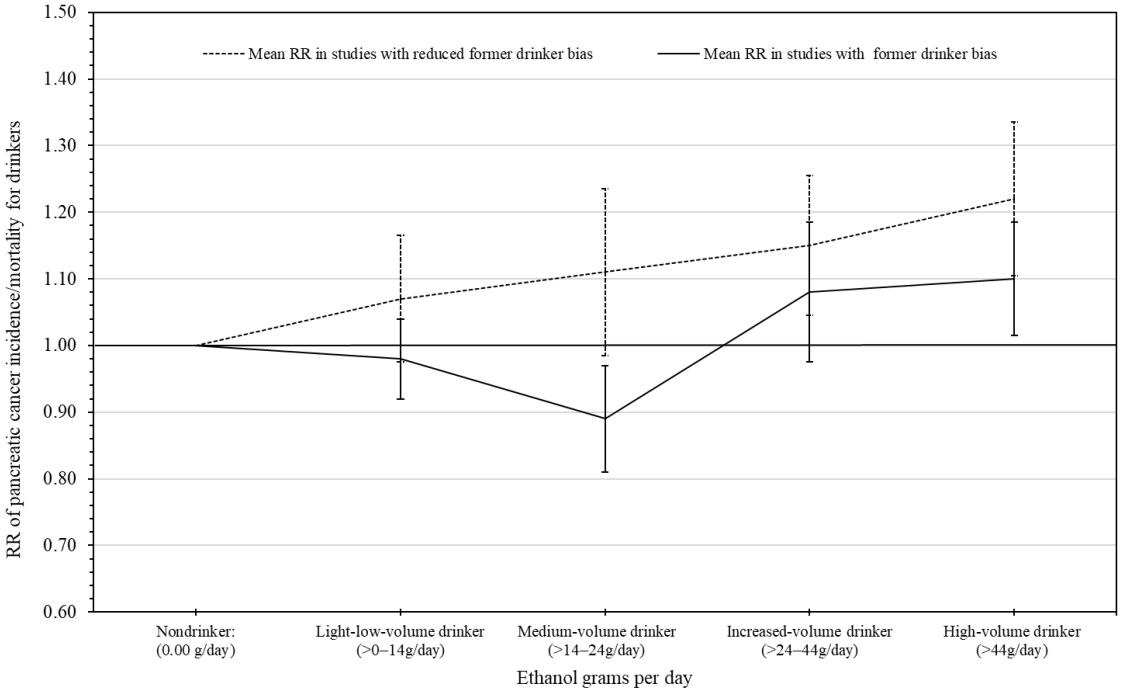
[d]Model I estimates deal with skewed distribution by analyzing natural logged RR, weighting by inverse of variance in each estimate and adjusted for heterogeneity across studies.

[e]RR increased by 2.3% in the analysis of studies with reduced former bias and 3.2% in the analysis of studies with former bias due to 10g increase of pure alcohol intake per day among current drinkers (Model II).

[f]Model II of studies further adjusts for study-level measures of mean cohort age of cohorts/follow-up years (cohort age <56 and follow-up = 10+ vs others), study level differences in exclusion of baseline health conditions (exclusion or not), and if BMI controlled (yes or no) in individual studies.

Figure 5

Plot of Relative Risks of Pancreatic Cancer Incidence/Mortality by Level of Mean Daily Alcohol Use in Models of Studies With Reduced Former Drinker Bias and With Former Drinker Bias



Discussion

In the present study we tested pre-registered hypotheses regarding the impact of selection biases in studies of alcohol use and risk of PC incidence or mortality using a series of meta-analyses of 37 cohort studies. The studies included 279 risk estimates identified by systematic review, collectively spanning 20,786,465 individuals. A major impetus for the study was a lack of consensus in the literature as to whether alcohol use at low to medium levels is associated with reduced, increased, or no change in subsequent PC risk. The study also investigated potential effects of the sample characteristics and covariates, adjusted for in individual studies, on RR estimates using mixed models which adjusted for the potential confounding effects of these study-level covariates.

The major finding was that in our pooled models using several strategies there was a dose-response relationship between alcohol and pancreatic cancer, with a significantly increased risk above 24g/day of ethanol. In addition, in stratified analyses, we explored the role of former drinker misclassification (*former drinker bias*) and found that studies with reduced former drinker bias find no protective effects at low levels of consumption and increased risk associations compared with studies with former drinker bias. This may explain some inconsistencies between previous studies and underlines the importance of both (a) separating former drinkers from lifetime abstainers and (b) ideally reallocating former drinkers within current drinking groups in future studies to create less biased risk estimates.

Alcohol consumption is a recognized cause of acute and chronic pancreatitis (Kristiansen et al., 2008; Li et al., 2008; Samokhvalov et al., 2015; Uomo & Manes, 2007), a known risk factor for PC. Alcohol drinking also may have a direct effect on pancreatic carcinogenesis. Acetaldehyde, the main metabolite of ethanol, is a known carcinogen (International Agency for Research on Cancer [IARC], 1988, 2010) and the induction of pancreatic injury from fatty acid ethyl esters (Criddle et al., 2004; Go et al., 2005) and reactive oxygen species (Seitz & Stickel, 2007) are possible mechanisms, and might explain the association between heavy alcohol drinking and PC. Alcohol-related immunodeficiency and immunosuppression might facilitate carcinogenesis at various organs (Ratna & Mandrekar, 2017; Watson, Borgs, et al., 1994; Watson, Nixon, et al., 1994).

Limitations

Our study has several limitations that must be acknowledged. First, this meta-analysis was based on 37 cohort studies of PC mortality or incidence including 279 risk observations, a relatively small sample, particularly for models in which adjustments were made for study level characteristics. This limitation might have reduced the precision of the RR estimates.

Second, this meta-analysis includes only cohort studies of PC incidence/mortality. The relationship between PC and alcohol intake may differ by type of study design such as case-control studies. Other kinds of selection bias may affect case-control studies, notably the likelihood that individuals will cut down on their alcohol consumption during the

period leading up to a PC diagnosis. The number of confounders of the RR estimates adjusted for varied across 37 studies, ranging from one to 11. Our meta-analysis cannot thus exclude the confounding effects of unavailable or uncontrolled variables in individual studies.

Third, we only assessed mean daily intake of alcohol with no consideration of drinking pattern, e.g., frequency of binge drinking. Very few included studies considered this variable as a predictor of PC risk.

Fourth, we did not consider differential effects from different types of alcoholic beverage. The main ingredient in all alcohol products is ethanol that is metabolized to produce acetaldehyde; both chemicals are designated as group 1 carcinogens (i.e., with sufficient evidence of carcinogenicity in humans) by the IARC (1988).

Fifth, this meta-analysis cannot assess any bias caused by former heavier drinkers who reduced the consumption being misclassified as light or low-volume drinkers. As people age and become unwell, they are more likely to reduce their alcohol consumption and thus may be classified as light or occasional drinkers (Kerr et al., 2002; Shaper et al., 1988). This could explain why our adjusted RR estimates for light- and low-volume drinkers were mostly slightly higher than those for medium-volume drinkers.

Sixth, we did not test for non-linear dose-response relationships which may exist and should be tested in future studies (Rota et al., 2010). Seventh, this study cannot determine whether or not the risk of subtypes of PC due to alcohol intake differed.

Finally, the greatest limitation of our meta-analyses is that we only identified three studies coded as free from both former drinker (strictly defined) and occasional drinker bias, meaning that we compared studies with more or less former drinker bias, but not a robust sample with no former drinker bias. Additionally, no study attempted to reallocate former drinkers into drinking categories according to their prior drinking status (Liang & Chikritzhs, 2013). This leads to reduced risk estimates among drinkers since former drinkers tend to be relatively unhealthy and should rightfully be considered a type of drinker based on intention-to-treat principles. Added to these problems is evidence that even lifetime abstainers may have a disposition towards ill-health from a young age when that ill health cannot be ascribed to a lack of alcohol consumption (Fat & Shelton, 2012). Some have proposed using very light or occasional drinkers as a more appropriate reference group (Naimi & Chikritzhs, 2025). In the present study of PC incidence and/or mortality, risks for very light drinkers were almost identical to those of *abstainers* in most models.

Our baseline models correspond to the conventional meta-analytic approach. We note that each modelling strategy we used, including the conventional approach, has its own strengths and weaknesses. The quality weighting strategy was based on previous theoretical and empirical analyses, but the size of individual weights were determined subjectively by the investigative team; we consider this an exploratory analysis that should be developed more fully in the future. The covariate adjustment strategy used rigorous rules to select study level covariates that were significantly and independently associated with the risk of PC. Adjustment for whether or not a study has a particular characteristic (e.g. type of population) or design characteristic (e.g. whether or not BMI was controlled for) only balance the contributions of each of these types of studies to model estimates; it does not remove the effects of poorly designed studies. The stratified analyses have by necessity reduced power as a function of reduced sample size but they can also eliminate the effects of studies deemed to be of low quality e.g., with regard to former drinker bias.

Conclusion

We conclude that (a) there is a dose-response relationship between level of alcohol use and PC risk in continuous models; (b) this association is significant in categorical models with consumption above 24g ethanol per day (~10–30% increased risk depending on level of consumption and modelling approach); (c) former drinker bias is likely responsible for the appearance of reduced PC risk among lower volume drinkers and also results in suppressed risk estimates at all levels of consumption. The robustness of our findings, coupled with limitations of existing observational studies that may lead to systematic under-estimates of risk, add to other evidence that alcohol is likely causally related to PC. Future studies of alcohol's contribution to risk of cancer and other diseases need to make more rigorous effort to reduce lifetime selection biases (e.g., former drinker bias) to avoid under-estimation of alcohol's contribution to disease incidence and premature mortality at all levels of daily alcohol intake.

Declarations

Ethics Approval and Consent to Participate

Research ethics committee review and approval were not required, as aggregate data were extracted from published studies. Authors of some studies were contacted to clarify relevant information in the studies but no information on individuals in the studies was requested.

Role of the Funding Sources

The study funder had no role in study design, data collection, analysis or interpretation, report preparation and the decision to publish. All authors had full access to all the data and had final responsibility for the decision to submit for publication.

Authors' Contribution

All authors made substantial contributions to conception and design of the study. KL and JZ searched studies from the databases of PubMed and Web of Science and KL, JC and JZ coded the data and created the meta-dataset for the meta-analysis. JZ and TS checked all the included studies and coding. AS and KL generated the gamma-representing alcohol consumption measure among drinkers. JZ, TS and TN analyzed the data and drafted the manuscript. All authors revised the manuscript critically for intellectual content and give final approval of the version to be submitted.

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