Evaluation of confounding in epidemiologic studies assessing alcohol consumption on the risk of ischemic heart disease

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Abstract

Background: Among different investigators studying the same exposures and outcomes, there may be a lack of consensus about potential confounders that should be considered as matching, adjustment, or stratification variables in observational studies. Concerns have been raised that confounding factors may affect the results obtained for the alcohol-ischemic heart disease relationship, as well as their consistency and reproducibility across different studies. Therefore, we assessed how confounders are defined, operationalized, and discussed across individual studies evaluating alcohol and ischemic heart disease risk.

Methods: For observational studies included in a recent alcohol-ischemic heart disease meta-analysis, we identified all variables adjusted, matched, or stratified for in the largest reported multivariate model (i.e. potential confounders). We recorded how the variables were measured and grouped them into higher-level confounder domains. Abstracts and Discussion sections were then assessed to determine whether authors considered confounding when interpreting their study findings.

Results: 85 of 87 (97.7%) studies reported multivariate analyses for an alcohol-ischemic heart disease relationship. The most common higher-level confounder domains included were smoking (79, 92.9%), age (74, 87.1%), and BMI, height, and/or weight (57, 67.1%). However, no two models adjusted, matched, or stratified for the same higher-level confounder domains. Most (74/87, 85.1%) articles mentioned or alluded to “confounding” in their Abstract or Discussion sections, but only one stated that their main findings were likely to be affected by residual confounding. There were five (5/87, 5.7%) authors that explicitly asked for caution when interpreting results.

Conclusion: There is large variation in the confounders considered across observational studies evaluating alcohol and ischemic heart disease risk and almost all studies spuriously ignore or eventually dismiss confounding in their conclusions. Given that study results and interpretations may be affected by the mix of potential confounders included within multivariate models, efforts are necessary to standardize approaches for selecting and accounting for confounders in observational studies.

Background

Over the past few years, there have been a growing number of studies outlining both harmful and potentially protective effects of alcohol consumption on the risk of various health-related outcomes, including ischemic heart disease.(1–7) Many of these studies, which have gained widespread attention in the media,(8, 9) have the potential to influence consumer behavior and can create uncertainty and false notions regarding healthy or unhealthy practices.(10, 11) The burden of disease from alcohol is undoubtedly high,(8) but there is less clarity about estimates of risk (or even protection) with low levels of consumption.(6–8, 12, 13) Typically, the reported associations between alcohol and health-related outcomes come from observational studies, which have inherent methodological limitations that generate bias and confounding.(14)

Confounding is the bias resulting from the presence of common causes of exposures and outcomes;(15, 16) thus confounders can distort observed exposure-outcome associations.(17, 18) Although there are numerous techniques that can be used to account for confounding in observational research, it is very challenging to completely exclude the impact of unmeasured residual confounding.(16) Furthermore, many potential confounders may be unknown to researchers and can be difficult to identify or measure. Among different investigators studying the same exposures and outcomes, there may be a lack of consensus about potential confounding variables that should be considered as matching (i.e. the selection of comparators or comparison groups with respect to one or more potential confounders), adjustment (i.e. the inclusion of potential confounders in multivariate analyses), or stratification variables (i.e. the fixing of levels of confounders by producing groups (strata) within which confounders do not vary and evaluating associations within stratum of the confounder(s)). As a result, individual studies may evaluate different confounders and/or report on certain subsets of a larger pool of potential variables in published articles.

Recently, the Global Burden or Disease (GBD) 2016 Alcohol Collaborators published a meticulous systematic analysis of alcohol burden across the world, which included separate meta-analyses for 23 health outcomes.(8) Ischemic heart disease was the only outcome with significant evidence for a J-shaped curve,(8) supporting previous claims that lower-volume alcohol intake may be associated with no harm or even protective effects.(9, 19, 20) However, all of these results come from observational studies, where confounders may contribute to both favorable or unfavorable associations.(21) For instance, it has been proposed that some or all of the U-or-J-shaped dose-response trends may be attributable to unmeasurable characteristics that are associated with alcohol consumption and cardiovascular outcomes.(13, 21) While some meta-analyses have suggested that adjusting for common confounders, such as smoking, age, and sex, does not alter the observed effect estimates,(9) others claim that individual studies with adjusted effect estimates have lower (attenuated) protective effects.(19)

Concerns have been raised that confounding factors may affect the results obtained for the alcohol-ischemic heart disease relationship, as well as their consistency and reproducibility across different studies.(20) Therefore, we systematically assessed whether individual observational studies evaluating the impact of alcohol on ischemic heart disease considered the same, similar, or different confounders and how much heterogeneity existed on how these confounders were defined and operationalized in matching, stratifying, or adjusting for them in the analyses. Additionally, we examined how authors of the individual studies considered confounding bias when interpreting their findings.

Methods

Design

Data identification and eligibility

We evaluated the individual studies included in the ischemic heart disease meta-analysis conducted by the GBD 2016 Alcohol Collaborators.(8) We did not perform a separate systematic search because the GBD meta-analysis is recent and comprehensive. Briefly, the GBD authors performed a systematic review of the literature published between 1 January 1950 and 31 December 2016 using PubMed, the Global Health Data Exchange, and the references of previous meta-analyses. Studies were excluded if they: did not report on the association between alcohol use and ischemic heart disease; were not cohort, case-control, or case-crossover studies; did not report a relative measure of risk or cases and non-cases among the exposed and un-exposed; did not report dose-response amounts of alcohol use; and did not have study endpoints that met the case definition used in the GBD 2016 report.(8)

Study characteristics

One author (JDW) manually screened all studies included in the ischemic heart disease meta-analyses performed by the GBD 2016 collaborators, and excluded articles that did not report any information about bivariate or multivariate analyses for an alcohol-ischemic heart disease relationship. For all eligible articles, we then recorded: the first author's name; year of publication; study design (i.e. case-control or cohort); study location (i.e. North America, Europe, Asia, or Other), overall sample size, and name of the journal publishing the study. InCites^{TM} Journal Citation Reports (JCR) was used to determine the 2017 JCR impact factor for each journal. As in previous evaluations, we recorded the most recent impact factor for each journal for consistency, despite the different publication dates of the eligible articles.(22–24)

Confounding variables

For all eligible articles, we screened the Methods and Results sections to identify the adjustment variables (i.e. potential confounders) included in the multivariable models analyzing the impact of alcohol exposure on ischemic heart disease. We recorded how the adjustment variables were measured (e.g. "age continuous" vs. "age categorical") as well as their levels (e.g. age categorical: <50, >50 years). In studies with two or more multivariate models (e.g. a small model adjusted for age vs. a larger model adjusting for all statistically significant factors), we extracted the data from the largest model. We then recorded which variables were used as matching and stratification variables, but were not included as covariates in the multivariable models. However, with the exception of gender, we did not capture whether the analyses were restricted to certain values of specific variables, e.g. based on eligibility criteria. Lastly, all potential variables were then grouped into higher-level confounder domains (e.g. "age continuous" and "age categorical" into "age").

Confounding statements and bias consideration

Following the same protocol as a previous evaluation,(25) we screened the Abstract and Discussion sections of the included studies using six standardized pre-specified questions concerning confounding statements and bias consideration (*Table 1)*..

Table 1. Assessment of consideration of confounding bias in Abstracts and Discussion(25)
1. Do the authors mention confounding using explicitly the terms “confounder(s),” “confounding,” “confound,” or do they allude to it without using those terms, or is confounding not considered at all?
2. Do the authors mention bias using explicitly the term “bias”?
3. Do the authors mention specific confounders that have not been adjusted for? (If yes, what were the reasons? If not, were there unspecified unmeasured confounders without specifically stating which ones?
4. Do the authors state that their main findings are likely, possibly, or unlikely affected by residual confounding?
5. Do the authors state that their findings need to be interpreted with caution due to confounding?
6. Do the authors call for caution or indicate limitations or uncertainty due to possible confounding or other bias in their conclusions?

Analysis

Descriptive statistics were used to characterize eligible articles and their consideration of confounding variables within our higher-level domain categories. Separate “data microarrays” were created to illustrate the confounders that were adjusted for by each article.(26) Figures were created for higher-level confounder domains and articles were ordered in descending order based on the number of confounders considered within studies (x-axis) and times each confounder was considered across studies (y-axis). The figures were color coded to indicate whether each study adjusted, stratified, or matched for each confounder and whether each confounder was considered as a continuous or categorical variable. As suggested during peer review, we also examined the proportion of articles with confounding statements and bias consideration stratified by publication date (before 1990, 1990–1999, 2000–2009, 2010+). All analyses were conducted in R.

Results

Study description

Among the 93 articles referenced by the GBD ischemic heart disease meta-analysis, six were excluded because they did not meet the selection criteria (duplicate (n = 2), non-English language (n = 1), could not be located by a librarian (n = 1), and did not explicitly report results from analyses evaluating the impact of alcohol on ischemic heart disease (n = 2)). Of the 87 remaining eligible articles (*Table S1),* 78 were published in a journal with a 2017 JCR impact factor (median 6.1 (interquartile range [IQR], 4.2–18.9)) (*Table 2)*..

Table 2. Characteristics of 87 observational studies evaluating the impact of alcohol consumption on ischemic heart disease			
	No. (%) Median (Interquartile Range)		
Study characteristics	**Cohort**	**Case-control**	**Total**
Number of studies	70	17	87
Publication year			
<1990	8 (11.4)	2 (11.8)	10 (11.5)
1990-1999	26 (37.1)	5 (19.4)	31 (35.6)
2000-2009	25 (35.7)	8 (47.1)	33 (37.9)
2010+	11 (15.7)	2 (11.8)	13 (14.9)
Location			
North America	33 (47.1)	4 (23.5)	37 (42.5)
Europe	24 (34.3)	9 (52.9)	33 (37.9)
Asia	9 (12.9)	1 (5.9)	10 (11.5)
Other	4 (5.7)	3 (17.7)	7 (8.1)
Population			
All	30 (42.9)	11 (6.5)	41 (47.1)
Males only	33 (47.1)	3 (17.7)	36 (41.4)
Females only	7 (10.0)	3 (17.7)	10 (11.5)
Sample size			
	11957 (4843-49566)	1602 (899-2710)	7735 (2634-36191)

There were 70 (70 of 87, 80.5%) cohort and 17 (17 of 87, 19.5%) case-control studies (*Table 2)*,, which included a median of 11957 (IQR, 4843–49566) and 1602 (IQR, 899–2710) participants, respectively. The majority of the studies were conducted in either North America (37, 42.5%) or Europe (33, 37.9%). Nearly half of the studies included both males and females (41, 47.1%). Two articles did not report results from multivariate regression analyses.

Confounders considered

The largest models in the 85 articles conducting multivariate regression analyses included a median of 9 (IQR, 5–12) adjustment, stratification, and/or matching variables. The vast majority of the 760 total variables were adjustment variables (716, 94.2%); 27 (3.6%) were stratification variables and 17 (2.2%) were matching variables in case-control studies. The 760 variables could be divided into 87 higher-level confounder domains (e.g., “history of angina” and “myocardial infarction” as “heart disease/myocardial infarction/angina”) (*Figure S1)*.. The five most commonly considered higher-level domains in the 85 articles were smoking (79, 92.9%), age (74, 87.1%), BMI, height, and/or weight (57, 67.1%), education (39, 45.9%), and physical activity (35, 41.2%) (*Figure 1).* A total of 33 higher-level domains were only included in one article (*Figure S1);*; 44 were studied at least 3 times. No two articles evaluating the impact of alcohol on ischemic heart disease adjusted, matched, or stratified for the exact same higher-level confounder domains (*Figure 2, Figure S2)*..

Figure 1. The most common higher-level confounder domains considered in 85 observational studies on alcohol and ischemic heart disease risk. Refer to *Figure S1* for a larger data microarray.

Figure 2. A "data microarray" illustrating the higher-level confounder domains considered in 85 observational studies on alcohol and ischemic heart disease risk. Domains are ordered based on how many times they were included in multivariate models. Colors represent whether domains were adjustment, stratification, or matching variables and how they were measured. Refer to *Figure S2* for a larger data microarray.

The 41 articles evaluating both males and females included a total of 391 variables, which could be divided into 65 higher-level confounder domains. The five most commonly considered higher-level domains in the 41 articles were smoking (40, 97.6%), age (35, 85.4%), sex (31, 75.6%), BMI, height, and/or weight (27, 65.9%), and education (23, 56.1%) (*Figure 3, Figure S3).* When limited to the 10 articles evaluating only female participants, there were 126 total variables, which could be divided into 37 higher-level confounder domains. The five most common domains were smoking (10, 100.0%), age (10, 100.0%), BMI, height, and/or weight (10, 100.0%), diabetes and diabetes treatment (9, 90.0%), and hypertensions and hypertension drugs (8, 80.0%). The 34 articles with only male participants contained 243 variables, which could be divided into 58 higher-level confounder domains. The five most common domains were smoking (30, 83.3%), age (29, 80.6%), BMI, height, and/or weight (20, 55.6%), and cholesterol/cholesterol treatment (14, 38.9%).

Figure 3. A "data microarray" illustrating the higher-level confounder domains considered in 85 observational studies on alcohol exposure and ischemic heart disease, stratified by the type of population considered. Domains are ordered based on how many times they were included in multivariate models. Colors represent whether domains were adjustment, stratification, or matching variables and how they were measured. Refer to *Figure S3* for a larger data microarray.

Among the 74 articles with models that included age, one third (24, 32.0%) were categorical variables (*Figure 3)*,, none of which had the exact same age levels. While most (69, 83.1%) of the 83 articles adjusting for smoking included smoking as a categorical variable, only 20 (20 of 69, 29.0%) were measured the exact same way (i.e., never smoking, former smoking, and current smoking). Of the 24 (24 of 65, 36.9%) models that included a measure of BMI as a categorical variable, eight (8 of 24, 33.3%) had cut-off levels that were used in at least one other study (n = 2 articles with <20.0, 20.0–24.9, 25.0–29.9, 30.0–34.9, 35.0+ kg/m^2 and n = 6 articles with <25, 25–29.9, 30+ kg/m^2).

Confounding statements and bias considerations

Across all 87 articles, 56 (64.4%) included a specific mention of confounding bias in their Abstract and/or Discussion sections (*Table 3)*.. While another 18 (20.7%) articles alluded to the concept of confounding, without using any specific terminology, 13 (14.9%) did not mention or allude to confounding in their Abstract and/or Discussion sections. Over half (50, 57.5%) of the articles used the term "bias". Among the

eight mentions of bias that were related to the principle of confounding, three specifically included the words “confounding” or “confound”.

Nearly one-third (26, 29.9%) of the articles included a discussion regarding potential confounders for which there was no adjustment, and authors frequently (16 of 26, 61.5%) stated that these confounders had not been measured (*Table 3).*.

Table 3. Statements of confounding in studies assessing the impact of alcohol on ischemic heart disease		
		Ischemic heart disease
Question		**No. (%, 95% Confidence Interval)**
Total		87 (100)
Term “Confounding” mentioned in Abstract or Discussion		
	Specific	56 (64.4, 54.0-74.7)
	Alluded	18 (20.7, 12.6-29.9)
	No	13 (14.9, 8.0-23.0)
Term “Bias” used in Abstract or Discussion		
	Yes	50 (57.5, 47.1-67.8)
	No	37 (42.5, 32.2-52.9)
Specific mention of non-adjusted confounders		
	Yes	26 (29.9, 20.7-40.2)
	Not measured	16 (69.6, 42.3-80.8)
	Other reasons	5 (21.7, 3.8-34.6)
	No reasons	5 (21.7, 3.8-34.6)
	No	61 (70.1, 59.8-79.3)
Any mention that findings may be affected by confounding?		
	Likely	1 (1.2, 0.0-3.4)
	Possibly	28 (32.2, 23.0-42.5)
	Unlikely	15 (17.2, 9.2-25.3)
	No statement	43 (49.2, 39.1-59.8)
Cautious interpretation needed		
	Yes	5 (5.7, 1.1-11.5)
	No statement	82 (94.3, 88.5-98.9)
Conclusions include any limitations regarding confounding		
	Yes	9 (10.3, 4.6-17.2)
	No	78 (89.7, 82.8-95.4)

Only one article specifically stated that their main findings were likely to be affected by residual confounding. Another 28 (65.1%) reported it was possible and 15 (34.9%) reported it was unlikely that their main findings were to be affected by residual confounding. There were five (5.7%) that explicitly asked for caution when interpreting results (*Table 3).*

Articles published after 2010 were more likely to include a specific mention of confounding (12 of 13, 92.3%), use the term “bias” (11 of 13, 84.6%), and ask for caution when interpreting results (2 of 13, 15.4%) (*Table S2).*

Discussion

Our analysis suggests that there is substantial variation in how adjustment, stratification, and matching confounders are defined, operationalized, and discussed across observational studies evaluating the impact of alcohol consumption on the risk of ischemic heart disease. While the majority of articles accounted for smoking, age, and BMI, these variables were rarely measured the exactly same way, and no two models considered the same higher-level confounder domains. Two-thirds of the articles specifically mentioned confounding bias in their Abstract and/or Discussion sections, but less than 2% claimed that their main findings were likely to be affected by residual confounding. Very few articles called for cautious interpretation due to confounding. Given the lack of standardized approaches for selecting and adjusting for confounders, and the inadequate discussions regarding the importance of confounding, observational studies assessing the impact of alcohol consumption on ischemic heart disease may need to be interpreted with caution.

Most of the largest multivariate models in observational studies evaluating the impact of alcohol on the risk of ischemic heart diseaseaccounted for smoking, age, BMI, and physical activity. Age and smoking are two of the most important risk factors for ischemic heart disease, and studies have regularly found that these variables confound the alcohol-ischemic heart disease relationship.(20) Although evidence on the influence of physical activity and BMI are sparse,(20) a previous evaluation suggested that low BMI and leisure-time physical activity are more common among never-drinkers than among light drinkers.(27) However, the authors noted that the differences were unlikely to be large enough to explain the lower risk observed among light drinkers compared to abstainers.(27) Numerous studies have also indicated that drinking pattern and type of beverage are important confounders.(28) However, we only identified three studies evaluating drinking history in their largest multivariate models. Furthermore, other proposed potential confounders, including cognitive function, dietary habits, and socioeconomic status,(12, 13, 29) were rarely evaluated. Overall, it is unclear whether the lack of consistency across articles reflects the fact that there is little consensus about which variables are potential confounders or the beliefs that the protective effect of alcohol consumption on the risk for cardiovascular disease is independent of how well studies control for confounding.(13) (28, 30, 31)

We also found that articles rarely measured similar adjustment, matching, or stratification variables the same way. For instance, although standard categories for BMI have been proposed in the literature, only one-third of the categorical BMI variables in our sample had the same cut-off levels as at least one other study. These findings build upon previous concerns that it is often difficult to determine how categorical or continuous adjustment variables are treated in analyses.(32, 33) Moreover, different treatment of variables, including incorrect adjustment for continuous confounders, can have an impact on the observed estimates or result in residual confounding.(34)

There are a number of reasons that could explain the variability in the adjustment, stratification, and matching variables. Although it is possible that authors may not be able to measure all potential confounders, and therefore are prevented from considering them in multivariate models, it is more likely

that there is a lack of consensus about what should be considered as matching, adjustment, or stratification variables. Furthermore, researchers may not be reviewing previously published models to determine potentially important confounders. Different studies may have different rigor in measuring some variables, and this can affect whether investigators want to use these variables in their analyses. It is also possible that certain models are preferentially reported or excluded due to biases and potential conflicts of interest, especially if the unreported multivariate models resulted in less desirable results.(26) However, the optimal choice of covariates may be difficult to identify and consensus may be elusive even with the best intentions. While adjusting for a large number of potential confounders is often appropriate and necessary, it can be particularly challenging to differentiate between potential confounders and variables that may be in the path that explains the effect of a risk factor, which should not be adjusted for. Field-wide systematic exposure assessments may help standardize variable adjustments and identify the full range of potential effect estimates due to different modeling considerations (i.e., vibration of effects).(35) Small changes in modelling choices, including exposure and outcome definitions, covariates considered, and statistical methods, can have a major impact on effect estimates observed in observational studies, and can even flip the direction of effects.(35) Furthermore, greater transparency when it comes to the choice, measurement, and impact of potential confounding variables is necessary. Without these efforts, the associations reported in observational studies of alcohol consumption on ischemic heart disease may need to be interpreted with great caution.

Our findings, which suggest that meta-analyses of observational studies evaluating the impact of alcohol consumption on the risk of ischemic heart disease are unlikely to identify effect estimates that have been adjusted for the same variables, are generalizable to other fields. When it comes to performing meta-analyses of observational studies, there are no clear rules regarding the prioritization of adjusted or unadjusted effect estimates. According to the Cochrane Handbook for Systematic Reviews of Interventions, review authors should record both adjusted and unadjusted effect estimates, but “no general recommendation can be made for the selection of which adjustment estimate is preferable.”(36) Instead, review authors are advised to consider the estimates from the models adjusted for the maximum number of covariates, the estimates from the primary models, or the estimates from the models with the largest number of confounders that are identified as important. Previous evaluations suggests that meta-analyses of observational studies evaluating the relationships between type 2 diabetes and cancer and environmental risk factors and dementia often only identify effect estimates from models that consider age and sex, despite a large number of other measurable confounders.(37, 38) Other assessments indicate a lack of consistency among the adjustment variables considered across individuals studies included in meta-analyses.(39–41) To facilitate the inclusion of effect estimates in meta-analyses, the raw data of individual studies should be made available to review authors in order to generate effect estimates across studies using the same or similar confounders. However, raw data are currently rarely available for observational studies.(22, 24) Even if they were available, it is likely that different datasets may vary substantially in what variables they have recorded.

We found that most authors mentioned the concept of confounding, which is consistent with prior evaluations of considerations of confounding in epidemiological studies.(25) However, we found that

authors rarely explicitly state that their main findings should be interpreted with caution due to confounding. This is significantly lower than what has been previously observed among surveyed samples of high-impact observational studies and research focusing on medical interventions.(33, 42) Moving forward, more transparent reporting and discussions regarding the selection of confounders, including the potential impact of residual confounding, are necessary to ensure that observational associations on the relationship between alcohol consumption and ischemic heart disease can be properly interpreted.

This study has a number of potential limitations. First, our sample included 87 observational studies identified by a previous meta-analysis. Therefore, some articles may have been missed and the results may not be generalizable to all observational studies focusing on alcohol-health related outcomes. Although there may have been multiple reports of the same study, different authors evaluating the same data sources could have considered the same or different variables. Second, our study includes articles published between 1981 and 2015, and reporting practices may or may not have changed over time.(42) Our post-hoc analysis suggests that articles published after 2010 were more likely to mention confounding and biases. While these findings may suggest improvements over time, our sample was not designed to assess trends. Third, for each article, we focused only on the covariates included in the largest model. However, it is possible that authors may have considered additional potential confounders that were not eventually included in the largest model. Moreover, some variables included in the largest models may have been considered as predictors worth capturing, instead of potential confounders. However, it is difficult to assess which variables were explicitly deemed to be potential confounders. Fourth, given the different patient populations, it also may not have made sense to adjust for the same characteristics in all studies (e.g., adjusting for sex in a study of only women). This is why we reported separate results for studies that included both genders, only men, and only women. It is possible that some additional confounders beyond gender were dealt with by restriction, i.e. by using eligibility criteria that restricted upfront the study population to have the same value for a potential confounder.

Conclusion

Our evaluation shows that although most authors mention confounding bias when interpreting their study findings, they rarely call for results to be interpreted with caution. However, the high variation in how confounders were defined and handled suggests that the results and their interpretation in these studies may have been affected by definition and handling choices.

Abbreviations

BMI = Body mass index; GBD = Global Burden or Disease

Declarations

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Availability of data and materials: Data will be shared on https://osf.io/zrdx7/ upon publication.
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Supplemental Tables

Table S1. Eligible studies

	Area	Title	Year	Journal
1	Ischemic heart disease	"Moderate alcohol consumption and the risk of sudden cardiac death among US male physicians"	1999	Circulation
2	Ischemic heart disease	"Alcohol intake and the risk of coronary heart disease in the Spanish EPIC cohort study"	2012	Heart
3	Ischemic heart disease	"Alcohol consumption and risk for stroke among Chinese men"	2007	Ann Neurol
4	Ischemic heart disease	"The association of pattern of lifetime alcohol use and cause of death in the European prospective investigation into cancer and nutrition (EPIC) study"	2013	Epidemiology
5	Ischemic heart disease	"Alcohol consumption and the risk of acute myocardial infarction in women. "	1993	J Epidemiol Community Health
6	Ischemic heart disease	"Alcohol, drinking pattern and all-cause, cardiovascular and alcohol-related mortality in Eastern Europe"	2016	Eur J Epidemiol
7	Ischemic heart disease	"Alcohol drinking and mortality among men enrolled in an American Cancer Society prospective study	1990	Epidemiology
8	Ischemic heart disease	"Light-to-moderate alcohol consumption and risk of sudden cardiac death in women"	2010	Heart Rhythm
9	Ischemic heart disease	"Moderate alcohol and decreased cardiovascular mortality in an elderly cohort"	1985	Am Heart J
10	Ischemic heart disease	"Alcohol and mortality in Busselton, Western Australia"	1993	Am J Epidemiol
11	Ischemic heart disease	"Higher usual alcohol consumption was associated with a lower 41-y mortality risk from coronary artery disease in men independent of genetic and common environmental factors: the prospective NHLBI Twin Study"	2015	Am J Clin Nutr
12	Ischemic heart disease	"Alcohol consumption and risk of cardiovascular disease and death in women: potential mediating mechanisms"	2009	Circulation
13	Ischemic heart disease	"Mortality in relation to alcohol consumption: a prospective study among male British doctors."	2005	Int J Epidemiol
14	Ischemic heart disease	"Alcohol drinking pattern and non-fatal myocardial infarction in women"	2007	Addiction
15	Ischemic heart disease	"The association of alcohol consumption with coronary heart disease mortality and cancer incidence varies by smoking history"	2005	J Gen Intern Med
16	Ischemic heart disease	"Type of alcoholic beverage and first acute myocardial infarction: a case-control study in a Mediterranean country"	2003	Clin Cardio

17	Ischemic heart disease	"Coronary heart disease mortality and alcohol consumption in Framingham"	1986	Am J Epidemiol
18	Ischemic heart disease	"Alcohol consumption and mortlity among women"	1995	NEJM
19	Ischemic heart disease	"Association between alcoholic beverage consumption and incidence of coronary heart disease in whites and blacks: the Atherosclerosis Risk in Communities Study"	2004	Am J Epidemiol
20	Ischemic heart disease	"Alcohol consumption and risk of ischemic heart disease in women"	1993	Arch Intern Med
21	Ischemic heart disease	"Light-to-moderate alcohol consumption and mortality in the Physicians' Health Study enrollment cohort"	2000	J Am Coll Cardiol
22	Ischemic heart disease	"Does alcohol protect against ischaemic heart disease in Bulgaria? A case-control study of non-fatal myocardial infarction in Sofia."	2001	Cent Eur J Public Health
23	Ischemic heart disease	"A prospective study of the health effects of alcohol consumption in middle-aged and elderly men. The Honolulu Heart Program"	1994	Circulation
24	Ischemic heart disease	"Alcohol consumption and risk of heart failure: the Atherosclerosis Risk in Communities Study"	2015	Eur Heart J
25	Ischemic heart disease	"Drinking and coronary heart disease: the Albany Study"	1985	Am Heart J
26	Ischemic heart disease	"Type of alcohol consumed and mortality from all causes, coronary heart disease, and cancer"	2000	Ann Intern Med
27	Ischemic heart disease	"Alcohol consumption, drinking pattern and acute myocardial infarction. A case referent study based on the Swedish Twin Register"	1997	J Intern Med
28	Ischemic heart disease	"Alcohol consumption and cardiovascular mortality accounting for possible misclassification of intake: 11-year follow-up of the Melbourne Collaborative Cohort Study"	2007	Addiction
29	Ischemic heart disease	"Alcohol consumption and mortality and hospital admissions in men from the Midspan collaborative cohort study"	2008	Addiction
30	Ischemic heart disease	"Alcohol consumption, Lewis phenotypes, and risk of ischaemic heart disease."	1993	Lancet
31	Ischemic heart	"Established risk factors account for most of the racial differences in cardiovascular disease	2007	PLOS One

	disease	mortality"		
32	Ischemic heart disease	"Genetic variation in alcohol dehydrogenase and the beneficial effect of moderate alcohol consumption on myocardial infarction"	2001	NEJM
33	Ischemic heart disease	"Familial predisposition and susceptibility to the effect of other risk factors for myocardial infarction."	1999	J Epidemiol Community Health
34	Ischemic heart disease	"Alcohol consumption and mortality from stroke and coronary heart disease among Japanese men and women: the Japan collaborative cohort study"	2008	Stroke
35	Ischemic heart disease	"Alcohol consumption, social support, and risk of stroke and coronary heart disease among Japanese men: the JPHC Study"	2009	Alcohol Clin Exp Res
36	Ischemic heart disease	"Alcohol intake and the risk of cardiovascular disease in middle-aged Japanese men"	1995	Stroke
37	Ischemic heart disease	". Alcohol consumption and risk of coronary heart disease"	1991	BMJ
38	Ischemic heart disease	"Alcohol consumption and mortality in Serbia: twenty-year follow-up study. "	2004	Croat Med J
39	Ischemic heart disease	"Alcohol intake, drinking patterns, and risk of nonfatal acute myocardial infarction in Costa Rica"	2005	Am J Clin Nutr
40	Ischemic heart disease	"Alcohol and cardiovascular disease: the Hawaiian experience."	1981	Circulation
41	Ischemic heart disease	" A case-control study of coronary heart disease in Athens, Greece"	1992	Int J Epidemiol
42	Ischemic heart disease	"Alcoholic beverages and myocardial infarction in young men"	1985	Am J Epidemiol
43	Ischemic heart disease	"Mortality in British vegetarians: results from the European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford)."	2009	Am J Clin Nutr
44	Ischemic heart disease	"Alcohol intake and premature coronary heart disease in urban Japanese men"	1998	Am J Epidemiol
45	Ischemic heart disease	"Alcohol consumption and mortality in aging or aged Finnish men"	1989	J Clin Epidemiol
46	Ischemic	"Alcohol intake and nonfatal acute	1991	Am J Cardiol

	heart disease	myocardial infarction in Japan."		
47	Ischemic heart disease	"Alcohol and mortality: a cohort study of male japanese physicians	1986	Int J Epidemiol
48	Ischemic heart disease	"Change in alcohol consumption and risk of death from all causes and from ischaemic heart disease."	1991	BMJ
49	Ischemic heart disease	" Alcohol intake and risk of acute coronary syndrome and mortality in men and women with and without hypertension"	2011	Eur J Epidemiol
50	Ischemic heart disease	"Heavy and nonheavy drinking occasions, all-cause and cardiovascular mortality and hospitalizations: a follow-up study in a population with a low consumption level."	2005	J Stud Alcohol
51	Ischemic heart disease	"Relation between heavy and binge drinking and all-cause and cardiovascular mortality in Novosibirsk, Russia: a prospective cohort study"	2002	Lancet
52	Ischemic heart disease	"Alcohol consumption and cardiovascular disease: differential effects in France and Northern Ireland"	2004	Eur J Cardiovasc
53	Ischemic heart disease	"Alcohol consumption: protection against coronary heart disease and risks to health."	1990	Int J Epidemiol
54	Ischemic heart disease	"Roles of drinking pattern and type of alcohol consumed in coronary heart disease in men"	2003	NEJM
55	Ischemic heart disease	"Alcohol volume, drinking pattern, and cardiovascular disease morbidity and mortality: is there a U-shaped function? "	2001	Am J epidemiol
56	Ischemic heart disease	"The combined influence of leisure-time physical activity and weekly alcohol intake on fatal ischaemic heart disease and all-cause mortality"	2008	Eur Heart J
57	Ischemic heart disease	"Central adiposity and increased risk of coronary artery disease mortality in older women"	1993	Ann Epidemiol
58	Ischemic heart disease	"Alcohol consumption and coronary heart disease morbidity and mortality"	1997	Am J Epidemiol
59	Ischemic heart disease	"Alcohol and mortality in middle-aged men from eastern France. "	1998	Epidemiology
60	Ischemic heart disease	"Prospective study of alcohol consumption and risk of coronary disease in men"	1991	Lancet
61	Ischemic	"Heavy drinking occasions in relation to	2011	Int J Epidemiol

	heart disease	ischaemic heart disease mortality– an 11-22 year follow-up of the 1984 and 1995 US National Alcohol Surveys."		
62	Ischemic heart disease	"Alcohol, mortality and cardiovascular events in a 35 year follow-up of a nationwide representative cohort of 50,000 Swedish conscripts up to age 55"	2012	Alcohol and Alcoholism
63	ischemic heart disease	"Abstention, alcohol use and risk of myocardial infarction in men and women taking account of social support and working conditions: the SHEEP case-control study"	2012	Alcohol and Alcoholism
64	Ischemic heart disease	"Association between alcohol consumption and mortality, myocardial infarction, and stroke in 25 year follow up of 49 618 young Swedish men"	1999	BMJ
65	Ischemic heart disease	"Alcohol consumption and mortality risks in the USA"	2012	Alcohol and Alcoholism
66	Ischemic heart disease	"Myocardial infarction and alcohol consumption: a population-based case-control study"	2007	Nutr Metab Cardiovasc Dis
67	Ischemic heart disease	"Alcohol and exercise in myocardial infarction and sudden coronary death in men and women."	1987	Am J Epidemiol
68	Ischemic heart disease	"No Protective Effect of Alcohol Consumption on Coronary Heart Disease (CHD) in African Americans: Average Volume of Drinking over the Life Course and CHD Morbidity and Mortality in a U.S. National Cohort"	2002	Contemporary Drug Problems
69	Ischemic heart disease	"Alcohol intake and subsequent mortality: findings from the NHANES I Follow-up Study"	1995	J Stud Alcohol
70	Ischemic heart disease	"Alcohol and coronary heart disease: a perspective from the British Regional Heart Study"	1994	Int J Epidemiol
71	Ischemic heart disease	"Alcohol intake and survival in the elderly: a 77 month follow-up in the Dubbo study"	1996	Aust NZ J Med
72	Ischemic heart disease	"A prospective study of moderate alcohol consumption and the risk of coronary disease and stroke in women"	1988	NEJM
73	Ischemic heart disease	"Long-term wine consumption is related to cardiovascular mortality and life expectancy independently of moderate alcohol intake: the Zutphen Study"	2009	J Epidemiol Community Health
74	Ischemic heart disease	"Alcohol use and mortality from coronary heart disease: the role of high-density lipoprotein cholesterol. The Multiple Risk Factor Intervention Trial Research Group"	1992	Ann Intern Med
75	Ischemic heart disease	"Alcohol consumption and sudden coronary death in middle-aged Finnish men"	1987	J intern Med

76	Ischemic heart disease	"Risk factors for non-fatal acute myocardial infarction in Italian women"	2004	Prev Med
77	Ischemic heart disease	"Alcohol consumption and mortality among middle-aged and elderly U.S. adults. "	1997	NEJM
78	Ischemic heart disease	"Alcohol and sudden cardiac death."	1992	Br Heart J
79	Ischemic heart disease	"Alcohol consumption and its contribution to the burden of coronary heart disease in middle-aged and older New Zealanders: a population-based case-control study"	2004	N Z Med J
80	Ischemic heart disease	"Moderate alcohol consumption and heart disease."	2002	Health Rep
81	Ischemic heart disease	" Joint effect of cigarette smoking and alcohol consumption on mortality"	2007	Prev Med
82	Ischemic heart disease	"Alcohol drinking and overall and cause-specific mortality in China: nationally representative prospective study of 220,000 men with 15 years of follow-up"	2012	Int J Epidemiol
83	Ischemic heart disease	"Genetic variation in alcohol dehydrogenase 1C and the beneficial effect of alcohol intake on coronary heart disease risk in the Second Northwick Park Heart Study"	2005	Atherosclerosis
84	Ischemic heart disease	" Follow up study of moderate alcohol intake and mortality among middle aged men in Shanghai, China"	1997	BMJ
85	Ischemic heart disease	"Alcohol consumption and mortality in an American male population: recovering the U-shaped curve–findings from the normative Aging Study"	1992	J Stud Alcohol
86	Ischemic heart disease	"Alcohol consumption, genetic variants in alcohol deydrogenases, and risk of cardiovascular diseases: a prospective study and meta-analysis"	2012	PLOS One
87	Ischemic heart disease	"Alcohol and mortality"	1992	Ann Intern Med

Table S2. Statements of confounding in studies assessing the impact of alcohol on ischemic heart disease by publication year						
Question		**N = 10**	**N = 31**	**N = 33**	**N = 13**	**No. (%, 95% Confidence Interval)**
Total		<1999	1990-1999	2000-2009	2010+	Total
Term “Confounding” mentioned in Abstract or Discussion						
	Specific	6 (60.0)	15 (48.4)	23 (69.7)	12 (92.3)	56 (64.4)
	Alluded	4 (40.0)	7 (22.6)	6 (18.2)	1 (7.7)	18 (20.7)
	No	0 (0.0)	9 (29.0)	4 (12.1)	0 (0.0)	13 (14.9)
Term “Bias” used in Abstract or Discussion						
	Yes	5 (50.0)	16 (51.6)	18 (54.5)	11 (84.6)	50 (57.5)
	No	5 (50.0)	15 (48.4)	15 (45.5)	2 (15.4)	37 (42.5)
Specific mention of non-adjusted confounders						
	Yes	1 (10.0)	4 (12.9)	17 (51.5)	4 (30.8)	26 (29.9)
	No	9 (90.0)	27 (87.1)	16 (48.5)	9 (69.2)	61 (70.1)
Any mention that findings may be affected by confounding?						
	Likely	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)	1 (1.2)
	Possibly	2 (20.0)	4 (12.9)	16 (48.5)	6 (46.2)	28 (32.2)
	Unlikely	2 (20.0)	3 (9.7)	4 (12.1)	6 (46.2)	15 (17.2)
	No statement	6 (60.0)	23 (74.2)	13 (39.4)	1 (7.7)	43 (49.2)
Cautious interpretation needed						
	Yes	1 (10.0)	1 (3.2)	1 (3.0)	2 (15.4)	5 (5.7)
	No statement	9 (10.0)	30 (96.8)	32 (97.0)	11 (84.6)	82 (94.3)
Conclusions include any limitations regarding confounding						
	Yes	1 (10.0)	3 (9.7)	2 (6.1)	3 (23.1)	9 (10.3)
	No	9 (90.0)	28 (90.3)	31 (93.9)	10 (76.9)	78 (89.7)

Figures

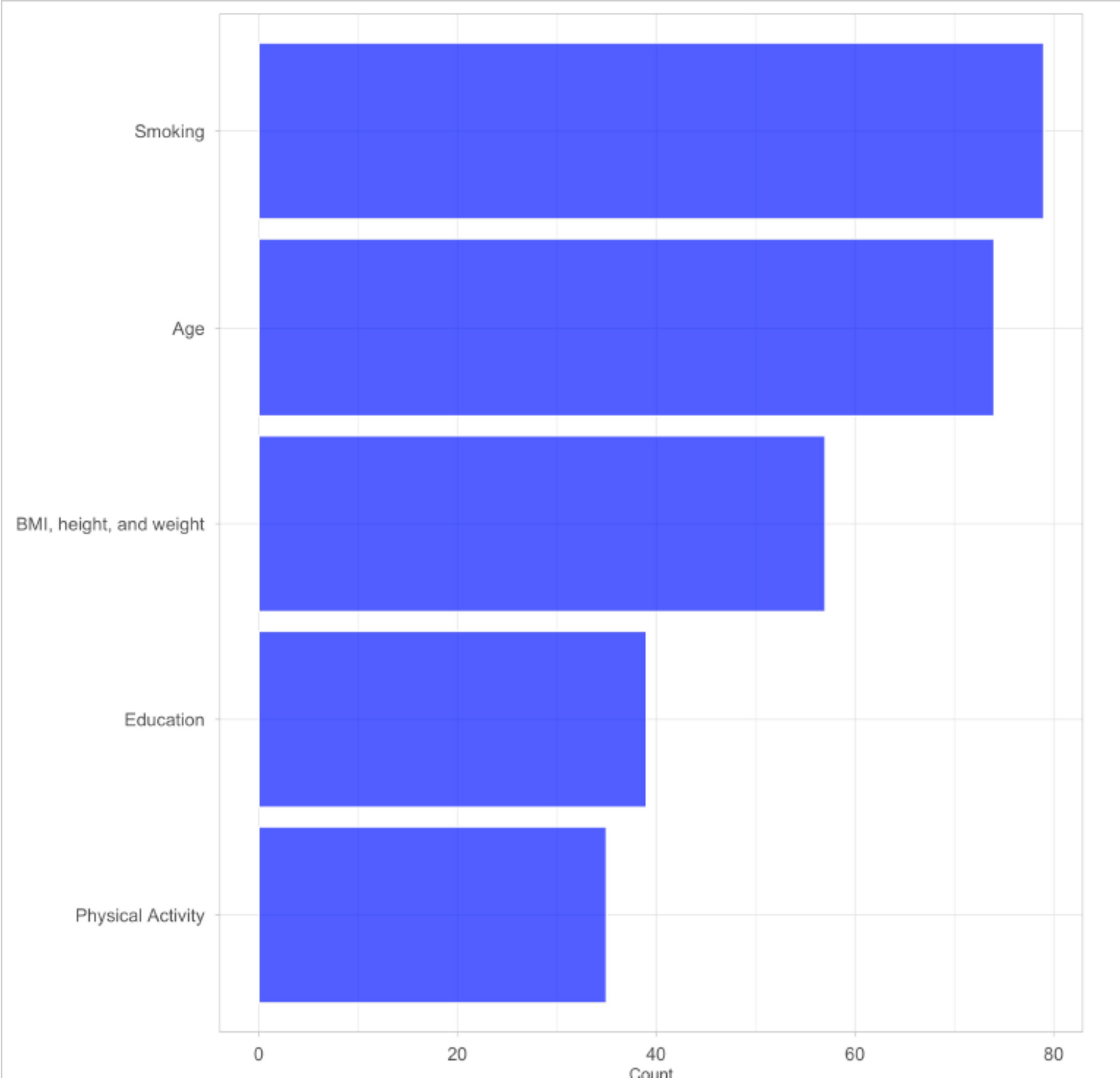

Figure 1

The most common higher-level confounder domains considered in 85 observational studies on alcohol and ischemic heart disease risk. Refer to Figure S1 for a larger data microarray.

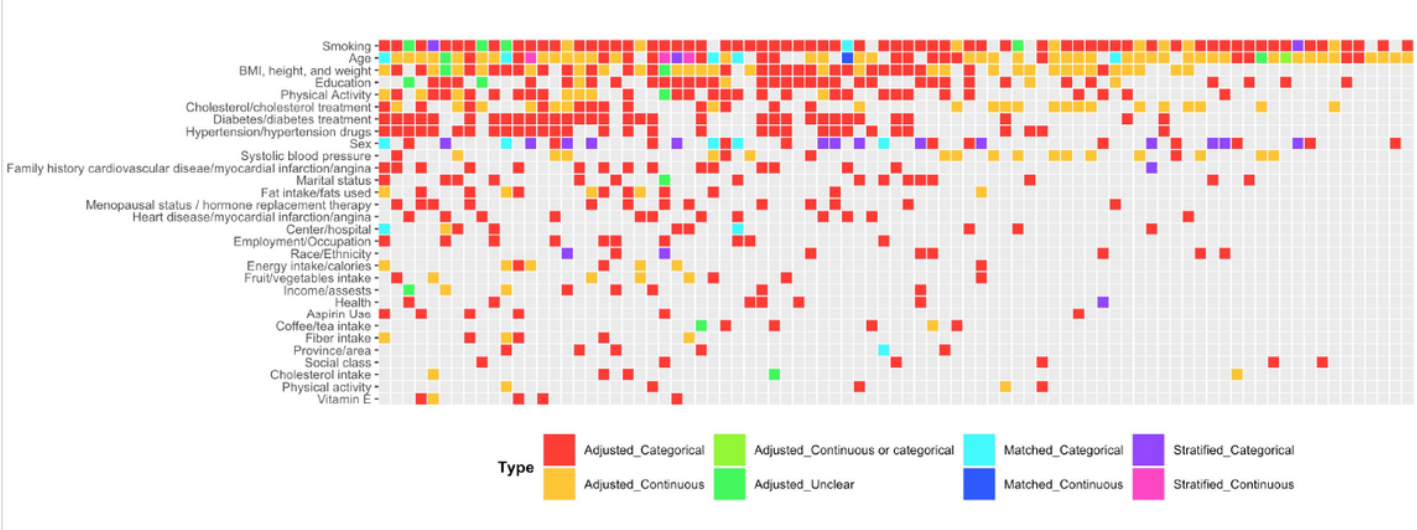

Figure 2

A “data microarray” illustrating the higher-level confounder domains considered in 85 observational studies on alcohol and ischemic heart disease risk. Domains are ordered based on how many times they were included in multivariate models. Colors represent whether domains were adjustment, stratification, or

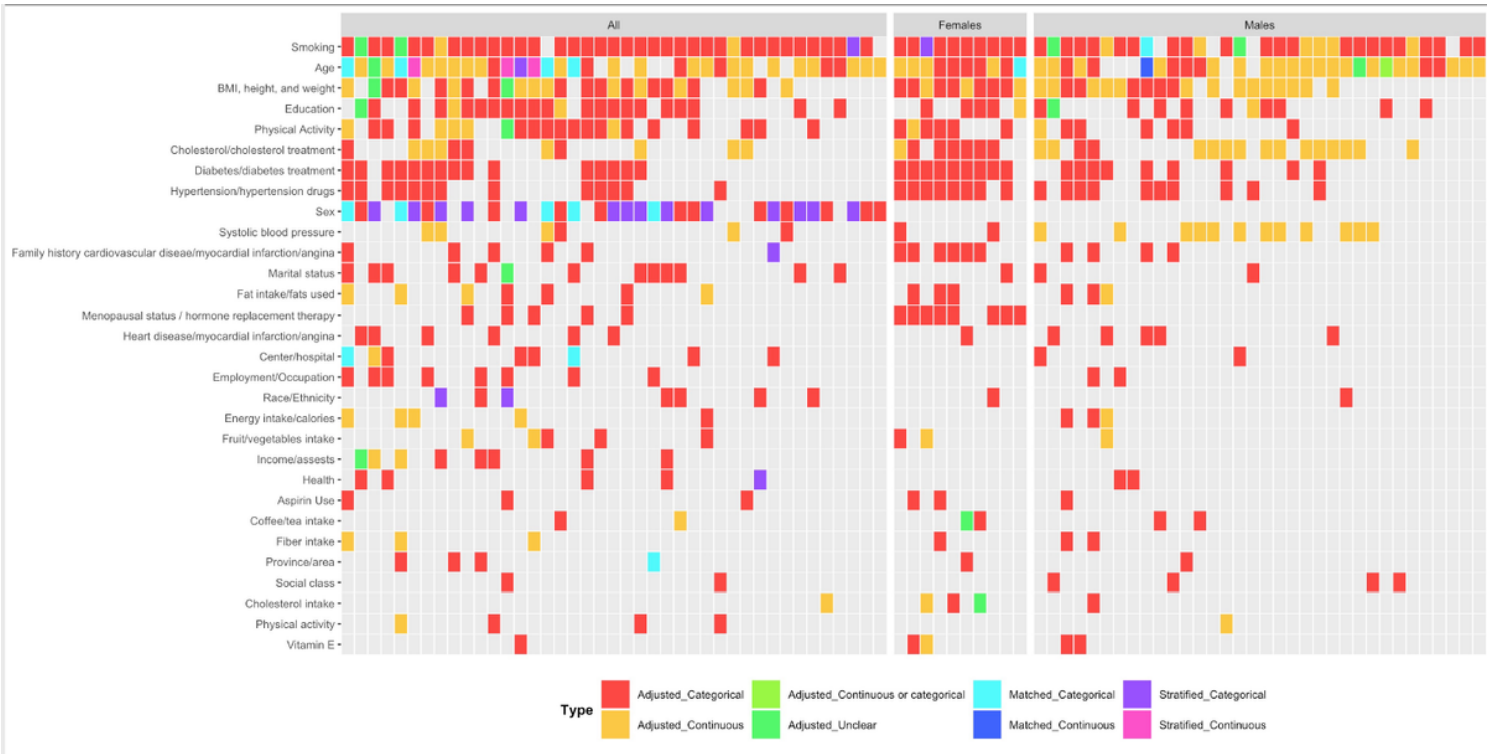

Figure 3

Figure 3. A “data microarray” illustrating the higher-level confounder domains considered in 85 observational studies on alcohol exposure and ischemic heart disease, stratified by the type of population considered. Domains are ordered based on how many times they were included in multivariate models.

Colors represent whether domains were adjustment, stratification, or matching variables and how they were measured. Refer to Figure S3 for a larger data microarray.