

ARIC Manuscript Proposal #2974

PC Reviewed: 5/9/2017
SC Reviewed: _____

Status: _____
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Alcohol consumption and risk of type 2 diabetes mellitus

b. Abbreviated Title (Length 26 characters): Alcohol and diabetes

2. Writing Group:

Writing group members: Xintong He, Natalie Daya, Casey M. Rebholz, Mariana Lazo, Elizabeth Selvin; others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _____ **[please confirm with your initials electronically or in writing]**

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3. Timeline: All data are currently available. Analysis begins following approval, and finishes within 1 year from approval of the manuscript proposal.

4. Rationale:

The incidence of type 2 diabetes has increased substantially over the past two decades. Both genetic factors and environmental factors contribute to the risk of type 2 diabetes. As a modifiable behavior, alcohol consumption has been shown to be relevant to diabetes risk. There

is suggestive evidence for a protective effect of moderate alcohol consumption on risk of type 2 diabetes, but this association remains controversial. Investigating how alcohol consumption is associated with incident diabetes can add to our understanding of the development of diabetes, and might be helpful to inform interventions. For example, whether it is reasonable to recommend for or against alcohol consumption of certain alcoholic types of alcoholic beverages, and if so, what is the dose and target subgroup.

Some cohort studies, cross-sectional studies and meta-analyses have shown a U- or J- shaped associations between alcohol consumption and diabetes¹⁻⁴. A previous study of alcohol consumption and diabetes risk in ARIC found no association between moderate alcohol consumption with diabetes risk, while high consumption was associated with elevated diabetes risk, but only in men, and with the harm mainly related to consumption of spirits⁵. This prior study, however, had a short follow-up (maximum 6 years). We now have a much longer follow-up period (over 25 years) and many more events. The additional events will allow us to address long-term risk and allow for more precise comparisons across subtypes of alcohol consumption (frequency, type), and to assess potential risk associations with changes in alcohol consumption patterns over time.

Prior studies suggest that the association of alcohol consumption with diabetes risk may differ by gender, race and/or obesity status. A systematic review of 38 prospective cohort studies found a protective effect of moderate alcohol consumption but this was confined to women, and there is no risk reduction in studies sampled an Asian population region⁶. A nested case-cohort study found that moderate drinking was associated with decreased diabetes risk in women but not men⁷. A cohort study found that the protective effect only exists in men⁸. A meta-analysis, in contrast, has shown a U-shaped association in both sexes¹. Some studies indicated that the protective effect might also differ by body mass index. A cross-sectional study found that the protective effect only existed in individuals who were classified as being normal weight or overweight, but not among individuals classified as being obese⁹. A cohort study also showed that the protective effect of moderate drinking only exists in normal-weight people⁴. Another study found stronger association among overweight people than normal-weight people⁷. Different alcoholic types of alcoholic beverage may also have different effect. A cohort study showed that the protective effect is particularly of wine and beer². Other cohort studies found that the protective effect is primarily linked to wine^{8,10}. The protective effect does not differ by types of alcoholic beverage in another study¹¹. The literature is also inconsistent for associations of binge drinking with diabetes^{8,12}.

The purpose of our study is to prospectively explore the association between alcohol consumption and incident diabetes in the ARIC population – we will examine types of alcoholic beverage, episodic drinking, and changes in drinking status. We will also examine potential differences by sex, race and body mass index.

5. Main Hypothesis/Study Questions:

This study will prospectively assess the association between alcohol consumption and the risk of type 2 diabetes in the ARIC cohort. The key study questions are as follows:

Question 1: What are the associations between alcohol consumption status (never, former, and current) and amount of weekly alcohol consumption among current drinkers with the risk of diabetes?

Question 2: Does the association between alcohol consumption with risk of type 2 diabetes differ by the type of beverage consumed? Are there differences by sex or body mass index?

Question 3: What is the association between heavy episodic drinking and risk of type 2 diabetes?

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study design:

A prospective cohort study, with ARIC visit 1 as baseline.

Exclusion:

We will exclude individuals with diabetes at baseline (see definition below), individuals with ethnicity other than black or white, and those with missing information on baseline diabetes status, baseline alcohol consumption or adjustment variables mentioned below. Baseline diabetes will be defined by any of the following: (1) baseline fasting glucose more than 126 mg/dL; (2) baseline non-fasting glucose more than 200 mg/dL; (3) self-reported diabetes or use of diabetes medication.

Exposure:

The main exposure of interest will be alcohol consumption. Information on alcohol consumption status and average quantity of alcohol consumption (by type) among current drinkers was obtained during the ARIC visits. We will categorize baseline alcohol consumption into 5 groups according to the following questions: “Do you presently drink alcoholic beverages?” and “Have you ever consumed alcoholic beverages?” We will define never-drinkers as people answering no to both questions, former-drinkers as people answering no to the first question and yes to the second, and current drinkers as people answering yes to the first question. The following questions are asked among current drinkers. “How many glasses of wine do you usually have per week (4-ounce glasses)?”, “How many bottles or cans of beer do you usually have per week (12-ounce bottles or cans)?” and “How many drinks of hard liquor do you usually have per week (1.5-ounce shots)?”. We will further categorize current drinkers into 3 groups (light, moderate or heavy-drinkers) according to these three questions, by the weekly ethanol consumption, where 4 ounces of wine = 10.8 g of ethanol, 12 ounces of beer = 13.2 g of ethanol, and 1.5 ounces of spirits = 15.1 g of ethanol. Heavy drinking is typically defined differently in males and females, with a cut point of 15 drinks per week for males and 8 drinks per week for females by CDC¹³. Moderate drinking is defined as up to one drink per day for women and up to two drinks per day for men, according to the U.S. Dietary Guidelines for Americans¹³. Therefore, different cut points are applied in males and females. The 5 categories will include never-drinkers, former-drinkers, and three categories of current-drinkers (for males, < 7 drinks/week, 7 – 14 drinks/week, and \geq 14 drinks/week; for females, < 1 drinks/week, 1 – 7 drinks/week, and \geq 7 drinks/week). Different cut points might be applied to better assess the association. Another exposure is episodic drinking, which is only measured at visit 3, which is defined as ever drinking 5 or more drinks per day. Additionally, we will assess continuous alcohol consumption among current

drinkers as grams per week. We will also consider type of alcoholic beverage consumed, which is assessed at every visit.

The table below shows the alcohol related variables available at each visit in ARIC data:

Variable	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Ethanol intake (g/week)	X	X	X	X	X
Type and amount	X	X	X	X	X
Episodic drinking			X		

Outcome:

The outcome of interest will be incident type 2 diabetes. For the primary analysis, incident type 2 diabetes will be defined as meeting any one of the following criteria: (1) fasting glucose more than 126 mg/dL; (2) non-fasting glucose more than 200 mg/dL; (3) current use of diabetic medication or self-reported diagnosis of type 2 diabetes. The time of incident diabetes will be assigned to the corresponding visit or AFU (annual follow-up) time.

For the sensitivity analysis, we will compare visit-based diabetes definition to the self-reported diabetes definition, since there are no glucose measurements between visit 4 and visit 5. At each visit, the visit-based diabetes definition will be fasting glucose more than 126 mg/dL or non-fasting glucose more than 200 mg/dL. Self-reported diabetes will be doctor diagnosis or medication use at visits or AFU.

Adjustment variables:

Baseline variables: age, sex, race-center, total energy intake (potential confounder, since people with high total energy intake may drink more, and meanwhile may at a higher risk of diabetes), baseline fasting-glucose, family history of diabetes (binary: yes or no), education (three categories), physical activity, hypertension (binary), HDL, total cholesterol, smoking status (packing years), and baseline body mass index which will have three categories: normal-weight ($< 25 \text{ kg/m}^2$), overweight (between 25 kg/m^2 to 30 kg/m^2), and obese ($\geq 30 \text{ kg/m}^2$).

Time-varying variable: body mass index (three categories as above) at each visit.

Statistical analysis:

We will examine associations overall and stratified by sex. Two-sided values of $p > 0.05$ will be considered significant.

- (1) To assess the associations between alcohol consumption (current/former/never) and amount of alcohol consumption in current drinkers (three categories of doses) with the risk of type 2 diabetes, we will use person-years and time-to-event approaches. We will use multivariable Poisson regression to compare incidence rates of diabetes among different alcohol consumption groups, and multivariable Cox proportional hazard model to compare the hazard of diabetes among the groups (if the proportional hazard assumption holds), adjusting for potential confounders. Never-drinkers will be the reference group. The first model will only adjust for age, race, education, family history of diabetes, smoking, and total energy intake, which are not thought to be in the causal pathway. The second model will further adjust for physical activity, body mass index (time-varying), hypertension history, HDL, and total cholesterol. The third model will further adjust for baseline fasting glucose. In all the

above regression models, the 5 alcohol consumption groups will be analyzed as indicator variables.

- (2) We will assess whether body mass index is an effect modifier on the association between alcohol consumption and risk of diabetes, by stratification analysis and regression, and to assess whether body mass index is a potential mediator. Firstly, we will compare hazard of diabetes among different alcohol consumption groups as in (1), stratify by sex and baseline body mass index (three categories), and test whether hazard ratios differ by body mass index groups, in males and females respectively. Secondly, for Cox regression analysis, we will add interaction terms of alcohol consumption groups and time-varying body mass index (three categories) in each of the models in (1), and examine whether the coefficients of the interaction terms are significantly different from 0. In this regression, missing body mass index values will be carried forward from the last visit. To assess whether body mass index is a possible mediator, we will control for BMI in the Cox models as a time-varying variable to see if it attenuates hazard ratios between alcohol and incident diabetes. Since body mass index is a risk factor of diabetes, to assess mediation we will also examine whether change in body mass index during follow-up is associated with alcohol consumption.
- (3) To compare the associations between different types of alcoholic beverage at baseline visit with later incident diabetes, we will assess hazard of diabetes among never-drinkers and people predominantly drinking one type of alcoholic beverage, with never-drinkers as reference. People predominantly drinking one type of beverage are defined when a certain type of beverage accounts for more than two thirds of total alcohol consumption of that person, calculating from the three questions they answered, as mentioned before. Since the sample size might be small for people predominantly drinking one type of beverage, we will classify them as two categories (light to moderate drinkers and heavy drinkers) for each types of alcoholic beverage, using a cut point of 80 g/week. We will compare hazard ratios of “light to moderate to never” and “heavy to never” for the three types of beverage, respectively, to see whether the association between alcohol amount and incident diabetes differ by types of alcoholic beverage.
- (4) To assess the dose effect of alcohol as a continuous variable among current drinkers, we will use restricted cubic splines in the Cox proportional hazard models to more flexibly model the association between baseline weekly alcohol consumption (as a continuous variable, gram per week) and incident diabetes, adjusting for three different sets of potential confounders as above.
- (5) We will explore the association between episodic drinking and incident diabetes by Cox proportional hazard model (if proportional hazard assumption holds), adjusting for the same sets of variables above. We will classify participants into 4 groups (never-drinkers, former-drinkers, current drinkers with episodic drinking, and current drinkers without episodic drinking) at visit 3, and compare the hazard of incident diabetes from visit 3. If we find a narrow range of weekly ethanol intake among episodic drinkers, we will further compare the hazard between episodic drinkers versus non-episodic current drinkers with a similar range of weekly ethanol consumption.

Secondary analysis:

- (1) If there are enough participants changing drinking patterns, we will assess the association between drinking pattern and future diabetes risk. We will categorize participants into three

categories (decreasing drinking, constant drinking and increasing drinking) by the first two visits, and compare the future hazard with visit 2 as the baseline.

- (2) We will also investigate the association between average cumulative amount of alcohol consumption with risk of diabetes. Average cumulative amount of alcohol consumption will be defined as the average weekly alcohol intake from visit 1 to the last visit before incident diabetes or censoring. For participants with missing data of alcohol consumption at certain visits, we will average the amount only from visits with the data.
- (3) To test whether race is an effect modifier, we will stratify by sex and race (having 4 subgroups) in the Cox regression analysis of hazard of the 5 alcohol consumption groups, to see whether the association (hazard ratios) differ by race, within males and females respectively.
- (4) We will exclude more participants at baseline to explore reverse causation. To address the problem that people with health issues may drink less, which will make drinking seems protective, a sensitivity analysis will be conducted to further exclude baseline chronic diseases including chronic lung disease and cancer.
- (5) Since there are no glucose-based measurements since visit 4 until visit 5, we will test the difference of using visit-based diabetes and using self-reported diabetes in the first two analyses mentioned in the above part (statistical analysis).
- (6) Since smoking might be a substantial confounder of the association between alcohol consumption with diabetes risk, we will examine the hazard ratio as in (1) further stratified by baseline smoking status (current, former and never), or restrict the analysis in non-smokers.

Limitations:

- (1) Potential limitations of this study include recall and/or reporting bias regarding self-report alcohol consumption that may result in misclassification of the exposure.
- (2) Analyses in subgroups and for types of alcoholic beverage may have limited power to detect moderate association.
- (3) Very high alcohol consumption is low in this population and thus, we may have limited ability to examine associations in this group.

7.a. Will the data be used for non-CVD analysis in this manuscript? ___ Yes ___X___ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ___ Yes ___ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ___ Yes ___X___ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ___ Yes ___ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: <http://www.cscce.unc.edu/ARIC/search.php>

Yes No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

(1) Alcohol Consumption as a Risk Factor for Non-Insulin Dependent Diabetes Mellitus #474

Published and based on 6 years of follow-up:

Kao W H L, Puddey I B, Boland L L, et al. Alcohol consumption and the risk of type 2 diabetes mellitus: atherosclerosis risk in communities study[J]. American Journal of Epidemiology, 2001, 154(8): 748-757.

(2) Alcohol consumption and myocardial biomarkers #2442

(3) Alcohol consumption and incident CHD, CVD and total mortality #449

(4) Alcohol consumption and left atrial size and function #2229

(5) Alcohol consumption and incident hypertension #451

(6) Alcohol consumption and risk of heart failure #2247

(7) The Association Between Alcohol Consumption and Incident Atrial Fibrillation: The Atherosclerosis Risk in Communities (ARIC) Study. #2459

(8) Alcohol consumption and risk of congestive heart failure #922

Alcohol consumption and Cardiac Structure and Function #2231

(9) Association of Obesity, Smoking and Alcohol Consumption with Ischemic Stroke in Atrial Fibrillation: The ARIC Study #2290

(10) Effect of Alcohol Consumption (and Type of Alcoholic Beverage Consumed) on Lipid Levels: The ARIC Study #1187

(11) Longitudinal Association of Alcohol Consumption and Cognition #410

(12) The relationship between ischemic stroke incidence and alcohol consumption #904

(13) Association between alcohol consumption and cognitive impairment: The ARIC Neurocognitive Study #2195

(14) Does smoking modify the relationship between alcohol consumption and risk of coronary heart disease (CHD)? #743

(15) Cigarette Smoking, Coffee and Alcohol Consumption in relation to Parkinson's Disease in Atherosclerosis Risk in Community Cohort #1176BB

(16) Alcohol & Wall Thickness #073

(17) Cross-sectional association of alcohol and cognition #408

(18) Correlation of Amount and Type of Alcohol Intake on MRI Changes in the Brain #404

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes No

11.b. If yes, is the proposal

- A. primarily the result of an ancillary study (list number* _____)**
 B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____)

*ancillary studies are listed by number at <http://www.csc.unc.edu/aric/forms/>

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from <http://publicaccess.nih.gov/> are posted in <http://www.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript Yes No.

References

1. Baliunas D O, Taylor B J, Irving H, et al. Alcohol as a risk factor for type 2 diabetes[J]. Diabetes care, 2009, 32(11): 2123-2132.
2. Koloverou E, Panagiotakos D B, Pitsavos C, et al. Effects of alcohol consumption and the metabolic syndrome on 10-year incidence of diabetes: the ATTICA study[J]. Diabetes & metabolism, 2015, 41(2): 152-159.
3. Liu C, Yu Z, Li H, et al. Associations of alcohol consumption with diabetes mellitus and impaired fasting glycemia among middle-aged and elderly Chinese[J]. BMC public health, 2010, 10(1): 713.
4. Hozawa A, Okamura T, Tanaka T, et al. Relation of Gamma-glutamyltransferase and alcohol drinking with incident diabetes: the HIPOP-OHP study[J]. Journal of atherosclerosis and thrombosis, 2010, 17(2): 195-202.
5. Kao W H L, Puddey I B, Boland L L, et al. Alcohol consumption and the risk of type 2 diabetes mellitus: atherosclerosis risk in communities study[J]. American Journal of Epidemiology, 2001, 154(8): 748-757.
6. Knott C, Bell S, Britton A. Alcohol consumption and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis of more than 1.9 million individuals from 38 observational studies[J]. Diabetes Care, 2015, 38(9): 1804-1812.

7. Beulens J W J, van der Schouw Y T, Bergmann M M, et al. Alcohol consumption and risk of type 2 diabetes in European men and women: influence of types of alcoholic beverage and body sizeThe EPIC–InterAct study[J]. *Journal of internal medicine*, 2012, 272(4): 358-370.
8. Rasouli B, Ahlbom A, Andersson T, et al. Alcohol consumption is associated with reduced risk of Type 2 diabetes and autoimmune diabetes in adults: results from the Nord - Trøndelag health study[J]. *Diabetic Medicine*, 2013, 30(1): 56-64.
9. Metcalf P A, Scragg R K R, Jackson R. Light to moderate alcohol consumption is protective for type 2 diabetes mellitus in normal weight and overweight individuals but not the obese[J]. *Journal of obesity*, 2014, 2014.
10. Hodge A M, English D R, O'dea K, et al. Alcohol intake, consumption pattern and types of alcoholic beverage, and the risk of Type 2 diabetes[J]. *Diabetic Medicine*, 2006, 23(6): 690-697.
11. Djoussé L, Biggs M L, Mukamal K J, et al. Alcohol consumption and type 2 diabetes among older adults: the Cardiovascular Health Study[J]. *Obesity*, 2007, 15(7): 1758-1765.
12. Cullmann M, Hilding A, Östenson C G. Alcohol consumption and risk of pre - diabetes and type 2 diabetes development in a Swedish population[J]. *Diabetic Medicine*, 2012, 29(4): 441-452.
13. <https://www.cdc.gov/alcohol/faqs.htm> Accessed 4/14/17