CLINICAL RESEARCH STUDY

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Moderate Alcohol Consumption Is Not Associated with Reduced All-cause Mortality

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ABSTRACT

BACKGROUND: A large body of research suggests that light or moderate alcohol consumption is associated with reduced all-cause mortality. However, concerns remain that the observed relationship is due to selection bias, misclassification of ex-drinkers, or residual confounding.

METHODS: The association between alcohol consumption and all-cause mortality was analyzed using Cox regression. The analysis was performed using data from the Health and Retirement Study, a longitudinal cohort of 24,029 individuals from a nationally representative sample of US adults aged more than 50 years. Drinking level was based on alcohol consumption measured at 3 points over the 4 years before the start of follow-up. Occasional drinkers—those who reported drinking on at least 1 occasion, but always less than once per week—served as the reference category. There was extensive adjustment for sociodemographic variables, health status, and functional status.

RESULTS: During 206,966 person-years of follow up, 7902 individuals died. No level of regular alcohol consumption was associated with reduced all-cause mortality. The hazard ratio and 95% confidence interval in fully adjusted analyses was 1.02 (0.94-1.11) for <7 drinks/week, 1.14 (1.02-1.28) for 7 to <14 drinks/week, 1.13 (0.96-1.35) for 14 to <21 drinks/week, and 1.45 (1.16-1.81) for ≥21 drinks/week.

CONCLUSIONS: Moderate alcohol consumption is not associated with reduced all-cause mortality in older adults. The previously observed association may have been due to residual confounding.

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KEYWORDS: Alcohol; Cohort study; Health and Retirement Study; Mortality

A substantial body of literature suggests that moderate alcohol consumption has health benefits. Meta-analyses have reported an inverse association between moderate alcohol consumption—relative to abstention—and both all-cause mortality[1-3] and cardiovascular disease.[4-6] Given the harmful effects of higher levels of consumption, alcohol appears to have a U- or J-shaped association with adverse health outcomes. Adjustment for a number of confounders, including health-related and sociodemographic factors, attenuates the relationship but does not eliminate it.

Despite this, many continue to question the association because of the possibility of residual confounding and selection bias. In comparison with moderate alcohol consumers, nondrinkers have less favorable levels of 27 of 30 cardiovascular risk factors.[7] Sufficiently adjusting for all of these variables may not be possible. One solution to this problem has been to use occasional drinkers as a reference category instead of abstainers.[8,9] Such individuals drink at levels for which a physiologic effect of alcohol is not plausible, but are likely to be more similar in other characteristics to moderate drinkers than long-term abstainers, thus reducing confounding. Another approach has been to more fully adjust for differences in health status by including functional status in analytic models. Such an approach attenuates the association, but it remains statistically significant.[10]

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A further complication in assessing the association relates to the classification of ex-drinkers. It has long been observed that abstainers include individuals who stopped drinking because of ill health, and such "sick-quitters" are typically excluded from analyses or considered as a separate exposure group.[2,9,11] The original studies that gave rise to the "sick quitter" hypothesis were in middle-aged men,[12,13] whereas more recent studies looking at this question include adults from across the age spectrum.[14,15] This attempt to reduce bias simply creates another selection bias by removing less healthy individuals from the drinking categories.[8] A proposed solution to this problem is to categorize ex-drinkers on the basis of their previous level of consumption, rather than analyzing them separately.[16] Analyses that use an average level of alcohol consumption over time partly achieve this aim and tend to find a weaker protective effect of moderate consumption.[3] Measuring alcohol use over time also has the benefit of providing a more accurate measure of long-term exposure, which is likely to be more etiologically relevant than measurement at a single time point.

The present study evaluates the association between alcohol consumption and all-cause mortality in a large, population-based cohort of middle-aged and older adults. Various strategies to reduce bias are used, including using occasional drinkers as the reference category, measuring alcohol use at several time points, and adjusting for functional status in addition to health and sociodemographic variables.

CLINICAL SIGNIFICANCE

- There is a well-established association between moderate alcohol use and reduced mortality.
- These perceived benefits may limit attempts to reduce excess consumption.
- When adequately controlling for bias, this association is not found.
- Advice on limiting alcohol consumption can be made clearer with these findings.

MATERIALS AND METHODS

Study Population

The analysis used data from the Health and Retirement Study (HRS), a nationally representative cohort study of US adults aged more than 50 years. The study has been described in detail by Sonnega et al.[17] Starting in 1992 (Wave 1), participants were interviewed biennially by telephone or face-to-face. Response rates for the original recruitment waves were 70% to 82%, with 85% of these original participants retained in all subsequent waves. Detailed questioning on alcohol use was first introduced in Wave 3 (1995-1996), and the study population comprised all individuals interviewed at this time point or later who remained alive for the subsequent 2 interview waves (4 years, or 5 years for those interviewed in 1995). The baseline for the present analysis was at the end of this period, at which point follow-up began and continued until Wave 11 (2012). In addition to allowing measurement of alcohol use over time, this minimized the risk that the level of alcohol use was strongly affected by terminal illness, which is a possibility when it is only measured at baseline. The HRS aims to maintain a steady-state size by adding new participants over time, and individuals who joined between Waves 4 and 7 (1998-2004) were also included. **Figure 1** shows the exposure and follow-up periods for participants joining the study in the various waves. A total of 28,083 individuals provided interviews at the first time point, with 24,029 surviving for 4 years and being included in the present analysis.

The HRS is conducted by the Institute for Social Research at the University of Michigan and funded by the National Institute on Aging (U01AG009740) and Social Security Administration. It has received ethical approval from the University of Michigan Institutional Review Board. This secondary analysis is based on fully anonymized, publicly available data (http://hrsonline.isr.umich.edu/). Several exposure variables—income and wealth, and functional and cognitive measures—are taken from the cleaned RAND HRS data file. All other variables are taken from the core HRS files. This analysis uses Early Release data for Wave 11 (HRS 2012 Core, Early V1.0), which have not been cleaned and may contain errors that will be corrected in the Final Public Release version of the dataset.

Outcome

The study outcome was time to death from any cause, with the month and year of the event ascertained from the National Death Index, Social Security Death Index, or contact with proxy respondents.

Primary Exposure

The primary exposure was the average level of alcohol use reported in the 3 interviews over the 4-year period before baseline. In each interview, participants were asked to report their average weekly consumption for the last 3 months. Those who did not respond with "none" or "less than once a week" were asked to report the numbers of days per week they drank and the number of drinks they consumed on those days.

Individuals were classified into 6 mutually exclusive drinking levels. To be classified as a nondrinker over the course of 4 years, participants had to report being abstinent from alcohol at each time point. To be classified as an occasional drinker, participants had to report drinking at least once, but never more than "less than once a week." Those who reported drinking at least 1 drink per week on at least 1 occasion were categorized as regular drinkers and divided into those drinking an average of <7 drinks/week, 7 to <14 drinks/week, 14 to <21 drinks/week, or ≥ 21 drinks/week.

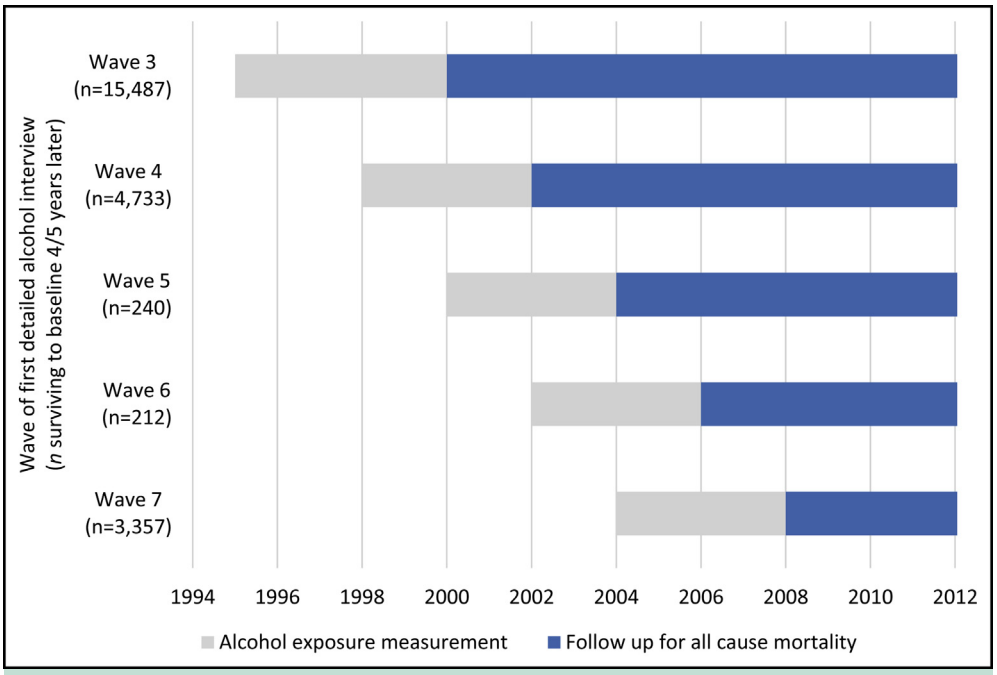

Figure 1 Exposure measurement and follow-up periods for study participants.

Other Exposure Variables

Sociodemographic variables included in the analysis were age, sex, race, whether the participant was born in the United States, religiosity, income quintile, and wealth quintile.

Health-related variables included in the analysis were body mass index (BMI), smoking, binge drinking, and exercise. General measures of health were self-rated health and frequency of healthcare use in the last 2 years. Participants also reported whether they regularly experienced pain, shortness of breath, or fatigue, and if they had ever been diagnosed with diabetes, heart disease, stroke, hypertension, cancer, a chronic lung disease, a psychiatric disorder, or any other disease. There was also adjustment for functional status and cognitive function.

Most potential confounders were measured at the time of the first interview, 4 years before baseline, to reduce the possibility of adjusting for mediators of alcohol's effect on mortality. Age and smoking were measured at baseline, however, and binge drinking was measured as the highest reported frequency during any of the 3 interviews in the 4 years before baseline. Additional details on the exposure variables are provided in the Appendix (online).

Missing Data

Data on the primary exposure were considered missing for 10.0% of the participants, who had not provided information in at least the first interview and the baseline interview (**Appendix Table 1, online**). Data on all sociodemographic variables were complete or near-complete (99.8%). The mean proportion of missing data for the health-related and functional variables was 1.6%.

Any observations that were missing were assumed to be missing at random, and their values were estimated with multiple imputation using chained equations.[18] The imputation model included all exposure variables in the analysis model, in addition to the outcome variable (death) and the Nelson-Aalen estimator of the cumulative hazard.[19] Full details of the imputation process are provided in the Appendix (online).

Statistical Analysis

Extended Cox regression was used to estimate the association between alcohol use during the 4 years before baseline and all-cause mortality. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for each level of alcohol consumption. The proportional hazards assumption was tested by first modeling each variable as time-dependent, using an interaction term with time, in addition to including its main effect. Any interaction terms with a P value $<.05$ were subsequently included in all models that contained the main effect of that variable. The following variables had significant interaction terms and were treated as time-dependent: age, smoking, BMI, exercise, fatigue, cancer, other diseases, and instrumental activities of daily living.

A number of subgroup and sensitivity analyses were performed. Sex-stratified analyses were carried out, given the reported difference in the effects of alcohol on men and women.[2] An analysis was also performed in which abstainers were subclassified into recent abstainers (ex-drinkers but

nondrinkers for the 4 years before baseline) and lifetime abstainers. This distinction was only possible for those who joined HRS between Waves 4 and 7 (n = 8452), when questions about lifetime drinking were first asked.

The use of an average alcohol consumption measure might lead to a heavy drinker who becomes abstinent being classified as a moderate drinker. Therefore, a sensitivity analysis was performed in which the highest level of alcohol consumption at any point during the 4 years was used as the main exposure. In addition, to assess the effect of measuring alcohol consumption at several time points, an analysis was performed in which alcohol use was measured at baseline only.

In any study of older people, there is a risk of selection bias due to "censoring by death" or "health selection."[20,21] When inclusion in a study is conditional on survival until a certain time point, those in higher risk exposure groups may die before study entry, leaving only healthier members in that group and eliminating or reversing the true exposure-outcome association. If the beneficial effects of moderate alcohol consumption were hidden by unhealthy abstainers and occasional drinkers dying before study entry, one would expect to see a more protective effect of moderate alcohol use among younger entrants and a decline in that effect across older age strata. To evaluate whether this bias was present in the study, age-stratified analyses were performed. All statistical analyses were carried out using Stata 13.1 (StataCorp LP, College Station, Tex).

RESULTS

Participant characteristics are provided in **Table 1**. Some 58% of participants were women, and 75% were white; the mean age was 66 years. Some 53% had smoked at some point in their lives. Regular drinkers tended to have fewer comorbidities than nondrinkers and occasional drinkers.

A total of 7902 individuals (32.9%) died during 206,966 person-years of follow up. Among the survivors, 84.5% were interviewed in Wave 11 and followed until the month of their interview in 2012 or 2013. The remainder (15.5%) were censored at the start of 2012, the point at which National Death Index tracking ended.

In a model adjusting only for age and sex, those drinking <7 drinks/week had a reduced mortality risk (HR, 0.90; 95% CI, 0.83-0.97) relative to occasional drinkers (**Table 2**). However, each group of confounders significantly attenuated this apparent protective effect. In a fully adjusted model, no level of regular alcohol use was associated with reduced all-cause mortality. The HR (95% CI) for the lowest risk group of regular consumers, those drinking <7 drinks/week, was 1.02 (0.94-1.11). Among men, it was 1.04 (0.92-1.18), and among women, it was 1.00 (0.90-1.12). In a fully adjusted model using the maximum level of consumption reported over 4 years (**Appendix Table 2, online**), a similar effect measure was seen, with an HR (95% CI) for those reporting drinking no more than 1 to <7 drinks per week at any point of 1.02 (0.94-1.11). When alcohol use was measured only at baseline (**Appendix Table 3, online**), the HR (95% CI) for those drinking 1 to <7 drinks per week was 0.98 (0.89-1.08). Higher levels of consumption (>21 drinks/week) were associated with increased mortality, with an HR (95% CI) of 1.45 (1.16-1.81) (**Table 2**).

Relative to occasional drinkers, the fully adjusted HR (95% CI) for nondrinkers was 1.19 (1.11-1.27) (**Table 2** and **Appendix Table 4, online**). In a subgroup analysis from

Table 1 Participant Characteristics

	Alcohol Consumption Level Over 4 y*						
			Regular Alcohol Consumption (Drinks/Wk)				
	Nondrinker	Occasional Drinker†	<7	7-<14	14-<21	≥21	All Participants‡
N (%)	8,427 (38.9%)	3,856 (17.8%)	6,468 (29.9%)	1,785 (8.3%)	648 (3.0%)	452 (2.1%)	24,029 (100%)
Age, y: mean (SD)	68.1 (11.2)	65.2 (10.6)	64.5 (10.2)	64.8 (10.2)	63.9 (9.6)	62.7 (9.6)	65.9 (10.8)
Female	67.6%	64.7%	54.4%	36.6%	29.0%	18.1%	58.1%
White ethnicity	68.0%	76.2%	81.0%	83.1%	83.3%	80.1%	74.6%
Ever smoker	42.7%	51.4%	58.7%	73.3%	81.5%	84.0%	53.2%
BMI: mean (SD)	27.6 (6.0)	28.1 (5.9)	27.0 (5.1)	26.4 (4.6)	26.5 (5.3)	26.9 (5.3)	27.4 (5.6)
Comorbidities							
Heart disease	15.2%	12.7%	10.3%	10.8%	8.2%	8.9%	12.6%
Diabetes	15.6%	10.3%	7.2%	5.0%	4.6%	7.5%	10.8%
Cancer	6.8%	7.2%	6.6%	7.6%	6.9%	6.6%	6.9%
Difficulty with ≥1 ADL§	18.0%	12.7%	7.2%	6.7%	5.7%	8.4%	12.2%

ADL = activities of daily living; BMI = body mass index; SD = standard deviation.
*Excluding those with missing information for alcohol consumption level (10.0%).
†Those who reported drinking on at least 1 occasion, but always less than once per week.
‡Including those with missing information for alcohol consumption level.
§Activities of daily living were bathing, dressing, eating, transferring, and toileting.

Table 2 Hazard Ratios (95% Confidence Interval) for Association Between Mortality and Alcohol Use Over 4 Years

	Alcohol Consumption Level Over 4 y (Deaths)					
			Regular Alcohol Consumption (Drinks/Wk)			
Covariates Adjusted for	Nondrinker (3528)	Occasional* (1097)	<7 (1587)	7-<14 (539)	14-<21 (192)	≥21 (168)
Age and sex	1.35 (1.26-1.44)	1.00	0.90 (0.83-0.97)	1.05 (0.95-1.17)	1.15 (0.99-1.34)	1.75 (1.49-2.05)
Sociodemographic†	1.24 (1.16-1.33)	1.00	0.96 (0.89-1.03)	1.12 (1.01-1.24)	1.17 (1.01-1.37)	1.66 (1.41-1.94)
Health-related‡	1.23 (1.15-1.32)	1.00	0.99 (0.91-1.08)	1.10 (0.98-1.24)	1.11 (0.94-1.32)	1.45 (1.16-1.81)
Functional status§	1.21 (1.13-1.29)	1.00	0.97 (0.90-1.05)	1.13 (1.02-1.25)	1.20 (1.04-1.40)	1.71 (1.46-2.00)
Fully adjusted	1.19 (1.11-1.27)	1.00	1.02 (0.94-1.11)	1.14 (1.02-1.28)	1.13 (0.93-1.35)	1.45 (1.16-1.81)
Fully adjusted, men	1.21 (1.09-1.35)	1.00	1.04 (0.92-1.18)	1.16 (0.99-1.35)	1.17 (0.94-1.44)	1.53 (1.19-1.96)
Fully adjusted, women	1.16 (1.06-1.27)	1.00	1.00 (0.90-1.12)	1.13 (0.94-1.36)	1.11 (0.81-1.52)	1.59 (0.96-2.64)
Fully adjusted, age <60 y‖	1.28 (1.02-1.62)	1.00	1.02 (0.77-1.34)	1.45 (0.97-2.16)	1.89 (1.12-3.20)	2.47 (1.37-4.45)
Fully adjusted, age 60-69 y‖	1.17 (1.02-1.35)	1.00	0.93 (0.79-1.11)	1.04 (0.81-1.34)	0.81 (0.58-1.14)	1.45 (0.99-2.14)
Fully adjusted, age 70-79 y‖	1.15 (1.01-1.29)	1.00	0.94 (0.82-1.08)	1.04 (0.85-1.26)	1.20 (0.90-1.61)	0.95 (0.64-1.40)
Fully adjusted, age ≥80 y‖	1.26 (1.11-1.42)	1.00	1.19 (1.03-1.37)	1.12 (0.91-1.38)	1.07 (0.75-1.53)	1.68 (0.90-3.13)

*Those who reported drinking on at least 1 occasion, but never more than less than once per week.
†Adjusted for age, sex, income quintile, wealth quintile, whether US born, race, and religiosity.
‡Adjusted for age, sex, smoking, BMI, exercise, binge drinking, self-rated health, frequency of inpatient and emergency department or clinic visits, symptoms (shortness of breath, fatigue, and pain), and diagnoses (cancer, lung disease, psychiatric disease, stroke, hypertension, diabetes, heart disease, and other diseases).
§Adjusted for age, sex, mobility, activities of daily living, instrumental activities of daily living, cognitive level.
‖Age at baseline.

participants who entered the study in later waves and were asked about drinking behavior over their lifetime (Table 3), mortality was significantly elevated for former drinkers who were now abstinent (HR, 1.26; 95% CI, 1.05-1.53), but not for lifetime nondrinkers (HR, 1.16; 95% CI, 0.95-1.43).

The possibility of selection bias due to censoring by death was explored by stratifying the results by age of entry. There was no evidence of a consistent change in alcohol's effects with increasing age (Table 2).

DISCUSSION

This study found no evidence of an association between any level of regular alcohol consumption and reduced all-cause mortality. In terms of participant numbers and deaths, this is the largest study of the alcohol—mortality relationship in which alcohol use was measured at several time points.[3]

Of the various approaches used to minimize bias, it seems that using occasional drinkers as the reference category was the most important. Even when adjusting only for age and sex, the beneficial effect of moderate, regular alcohol consumption was small and similar to that seen in fully adjusted analyses in previous research.[3] After adjustment for confounders, this small effect was eliminated. The increased mortality in abstainers relative to occasional drinkers, despite extensive adjustment for confounders, suggests that residual confounding plays a significant role in explaining the apparent health benefits of alcohol consumption, given the physiologic implausibility that drinking less than 1 drink per week could reduce all-cause mortality by 19%.

Table 3 Hazard Ratios (95% Confidence Interval) for Association Between Mortality and Alcohol Use Over Time, with Abstainers Subdivided

		Alcohol Consumption Level over 4 y					
				Regular Alcohol Consumption (Drinks/Wk)			
Covariates Adjusted for	Lifetime Nondrinker	Former Drinker Now Abstinent	Occasional Drinker*	<7	7-<14	14-<21	≥21
Age and sex	1.12 (0.92-1.36)	1.53 (1.27-1.84)	1.00	0.80 (0.66-0.97)	1.03 (0.81-1.32)	1.22 (0.87-1.70)	1.76 (1.27-2.43)
Fully adjusted†	1.16 (0.95-1.43)	1.26 (1.05-1.53)	1.00	0.99 (0.82-1.21)	1.21 (0.91-1.61)	1.30 (0.88-1.91)	1.49 (0.97-2.29)

*Those who reported drinking on at least 1 occasion, but never more than less than once per week.
†Adjusted for age, sex, income quintile, wealth quintile, whether born in the United States, race, religiosity, smoking, BMI, exercise, binge drinking, self-rated health, frequency of inpatient and emergency department or clinic visits, symptoms (shortness of breath, fatigue, and pain), diagnoses (cancer, lung disease, psychiatric disease, stroke, hypertension, diabetes, heart disease, and other diseases), mobility, activities of daily living, instrumental activities of daily living, and cognitive level.

Comparison with Existing Literature

Two recent studies provide a relatively comprehensive picture of existing knowledge on alcohol use over time and its association with all-cause mortality. Given their methodological differences, their results do not fundamentally contradict those of the present analysis. The first article is a meta-analysis of studies looking at alcohol use over time and all-cause mortality.[3] There was evidence for a small protective effect of alcohol use, with a pooled relative risk of 0.90 (95% CI, 0.81-0.99) for 1 to 29 g of alcohol per day among men. The pooled studies did not measure as many confounders as the present analysis and used abstainers as the reference category, as opposed to occasional drinkers. The second study was published shortly after the search period of the meta-analysis, but represents by far the largest study of the association between long-term alcohol use and mortality, with 380,395 participants and 26,411 deaths.[9] Participants were only questioned about alcohol use at 1 time point, but long-term consumption patterns were ascertained through recall of past drinking levels. They found a protective effect of low levels of alcohol consumption on all-cause mortality, but the effect was limited to those free of disease at baseline (HR, 0.86; 95% CI, 0.74-0.99), approximately age 50 years. Former drinkers who had become unwell were by definition removed from this group, and so the authors suggested that the apparent protective effect could be due to selection bias.

Other studies have called into question the beneficial effects of moderate alcohol consumption. Mendelian randomization studies have found that nondrinking is associated with reduced ischemic heart disease.[22] Meanwhile, research into high-density lipoprotein (HDL) has raised questions about one of the main hypothesized mechanisms of alcohol's protective effect. Alcohol consumption is associated with increased HDL levels,[23,24] which was traditionally believed to protect against cardiovascular disease. However, Mendelian randomization studies[25] and randomized controlled trials[26] have found no evidence of a causal link between high HDL and reduced cardiovascular disease or all-cause mortality.

Study Limitations

The main limitation of this study is that it was restricted to older individuals and lacked detailed information on lifetime consumption patterns. Given that alcohol use declines with age,[27] it is possible that occasional drinkers had been regular drinkers earlier in their lives. However, the lack of a protective effect of moderate alcohol consumption even in those aged less than 60 years provides some reassurance that this was generally not the case. A further limitation is that all exposure information was based on self-report. For alcohol intake, self-reported consumption is generally considered to have acceptable reliability and validity for most research purposes.[28] However, the accuracy of self-reported consumption in HRS has not been specifically investigated. With regard to confounding health variables, a comparison of self-reported HRS data with data derived from medical records found similar incidence rates and risk factor effect sizes for stroke.[29] Although it is not clear if this can be generalized to all self-reported diagnoses in HRS, it at least suggests that such data are unlikely to be significantly biased.

CONCLUSIONS

The analysis reported suggests that the previously observed association between alcohol and reduced mortality does not reflect a causal relationship, and adequate adjustment for potential biases removes any association. Given the considerable evidence base in favor of an association between moderate alcohol consumption and reduced mortality, this finding requires replication in other datasets and population groups.

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APPENDIX

Supplementary material accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.amjmed.2015.10.013.

EXPOSURE VARIABLES: ADDITIONAL INFORMATION

Race was classified as white, Hispanic, black, or other.

Religiosity was measured by asking participants to rate the importance of religion in their life as very important, somewhat important, or not too important.

Binge drinking was classified as the number of times drinking ≥4 drinks/day in the last 3 months.

Exercise was classified as exercising vigorously ≥3 times/week.

Smoking was classified as never, current (<10, 10-19, or ≥20 cigarettes per day), or former (stopped <10, 10-29, or ≥30 years ago).

Self-rated health was measured on a 5-point scale from poor to excellent.

Frequency of healthcare use was measured using the number of inpatient hospital stays in the last 2 years and number of clinic and emergency department visits in the last 2 years.

Functional status was measured in terms of activities of daily living, instrumental activities of daily living, and mobility. Participants were asked if, because of a health or memory problem, they had any difficulty with a series of activities. For activities of daily living, these were bathing, dressing, eating, transferring, and toileting. For instrumental activities of daily living, these were shopping, preparing meals, using the telephone, managing medications, and managing finances. For mobility, these were walking several blocks, walking 1 block, walking across the room, climbing several flights of stairs, and climbing 1 flight of stairs.

Cognitive function was scored using a composite measure, comprising a word recall task and a mental status test.

Imputation of Missing Data

Multiple imputation using chained equations was carried out with the *mi impute chained* command in Stata 13.1 (StataCorp LP, College Station, Tex). In addition to all the variables in the analysis model, the imputation model included a binary variable noting whether the first interview was done by a proxy respondent and the wave in which the participant joined. It also included a 3-category smoking variable (never, former, or current) for which near-complete information was variable (99.1%), as well as the 7-category smoking variable used in the analytic model, for which there was less complete information (89.9%).

Logistic regression was used to estimate binary variables—exercise, cancer, hypertension, diabetes, psychiatric disease, other diseases, pain, shortness of breath, fatigue, and whether US born or not—and predictive mean matching used to estimate all other variables—alcohol consumption, binge drinking, BMI, smoking level, race, religiosity, mobility, activities of daily living, instrumental activities of daily living, cognitive function, number of inpatient admissions, number of clinic or emergency department visits, and self-rated health. In addition, the outcome variable (death) and the Nelson-Aalen estimator of the cumulative hazard were included in the imputation model.

Separate imputations were carried out for men and women using the *by()* option of the *mi impute chained* command; 20 imputations were performed.

A separate multiple imputation, using the same procedure, was performed for the data in **Table 3**, which excluded those interviewed in Wave 3 and divided abstainers into lifetime and recent abstainers.

The time of death was interval censored for a small number of individuals (n = 91, 1.2% of deaths), with information available only for the 1- or 2-year period in which the outcome occurred. In such cases, midpoint imputation was used to estimate the month and year of death.

Appendix Table 1 Proportion of Missing Data for Exposure Variables

Variable	Missing Data (%)
Average alcohol consumption	10.0
Demographic variables	
Age	0
Gender	0
Education level	0
Income quintile*	0
Wealth quintile*	0
US born	0.1
Race	0.02
Religiosity	0.2
Health-related variables	
Smoking	10.1
BMI	1.4
Exercise	0.1
Binge drinking	10.1
Self-rated health	0.04
Inpatient hospital stays	0.35
Clinic and emergency department visits	1.85
Shortness of breath	0.1
Fatigue	0.1
Pain	0.1
Cancer	<0.01
Lung disease	0
Psychiatric disease	0.03
Stroke	<0.01
Hypertension	0.02
Diabetes	0.02
Heart disease	0
Other disease	0.02
Functional status*	
ADL	0.2
Instrumental ADL	0.2
Mobility	0.2
Cognitive function	7.0

ADL = activities of daily living; BMI = body mass index.
*Data for some participants imputed by RAND.

Appendix Table 2 Hazard Ratios (95% Confidence Interval) for Association Between Mortality and Maximum Reported Alcohol Use Over 4 Years

	Maximum Reported Alcohol Consumption Over 4 y (Drinks/Wk)					
Covariates Adjusted for	Nondrinker	<1 (ref)	1-<7	7-<14	14-<21	≥21
Age and sex	1.35 (1.26-1.44)	1.00	0.90 (0.83-0.98)	0.97 (0.87-1.07)	1.03 (0.92-1.16)	1.46 (1.29-1.65)
Fully adjusted*	1.19 (1.11-1.27)	1.00	1.02 (0.94-1.11)	1.11 (0.90-1.24)	1.10 (0.96-1.25)	1.25 (1.06-1.48)
Fully adjusted, men	1.21 (1.09-1.35)	1.00	1.04 (0.92-1.18)	1.09 (0.93-1.27)	1.17 (0.99-1.39)	1.28 (1.05-1.57)
Fully adjusted, women	1.16 (1.06-1.27)	1.00	0.99 (0.89-1.11)	1.16 (0.98-1.37)	0.97 (0.78-1.22)	1.32 (0.94-1.84)

*Adjusted for age, sex, income quintile, wealth quintile, whether US born, race, religiosity, smoking, BMI, exercise, binge drinking, self-rated health, frequency of inpatient and emergency department or clinic visits, symptoms (shortness of breath, fatigue, and pain), diagnoses (cancer, lung disease, psychiatric disease, stroke, hypertension, diabetes, heart disease, and other diseases), mobility, activities of daily living, instrumental activities of daily living, and cognitive level.

Appendix Table 3 Hazard Ratios (95% Confidence Interval) for Association Between Mortality and Alcohol Use Measured at Baseline

	Alcohol Consumption at Baseline (Drinks/Wk)					
Covariates Adjusted for	Nondrinker	<1 (ref)	1-<7	7-<14	14-<21	≥21
Age and sex	1.48 (1.38-1.58)	1.00	0.91 (0.82-1.00)	0.98 (0.87-1.11)	1.19 (1.03-1.38)	1.46 (1.22-1.74)
Fully adjusted*	1.29 (1.20-1.39)	1.00	0.98 (0.89-1.08)	0.96 (0.85-1.09)	1.08 (0.92-1.27)	1.11 (0.89-1.37)
Fully adjusted, men	1.30 (1.17-1.45)	1.00	1.06 (0.93-1.21)	0.97 (0.82-1.15)	1.19 (0.97-1.45)	1.15 (0.90-1.47)
Fully adjusted, women	1.27 (1.15-1.41)	1.00	0.90 (0.77-1.04)	0.98 (0.80-1.21)	0.91 (0.68-1.22)	1.31 (0.80-2.14)

*Adjusted for age, sex, income quintile, wealth quintile, whether US born, race, religiosity, smoking, BMI, exercise, binge drinking, self-rated health, frequency of inpatient and emergency department or clinic visits, symptoms (shortness of breath, fatigue, and pain), diagnoses (cancer, lung disease, psychiatric disease, stroke, hypertension, diabetes, heart disease, and other diseases), mobility, activities of daily living, instrumental activities of daily living, and cognitive level.

Appendix Table 4 Hazard Ratios (95% Confidence Interval) for Association Between Mortality and Alcohol Use Over 4 Years, with Nondrinkers as Reference Category

	Alcohol Consumption Level Over 4 y (Drinks/Wk)					
			Regular Alcohol Consumption (Drinks/Wk)			
Covariates Adjusted for	Nondrinker	Occasional*	<7 (1587)	<7 (1587)	<7 (1587)	<7 (1587)
Age and sex	1.00	0.74 (0.69-0.80)	0.67 (0.63-0.71)	0.78 (0.72-0.86)	0.85 (0.74-0.99)	1.30 (1.12-1.51)
Fully adjusted†	1.00	0.84 (0.79-0.90)	0.86 (0.81-0.92)	0.96 (0.87-1.07)	0.96 (0.81-1.13)	1.22 (0.99-1.51)
Fully adjusted, men	1.00	0.82 (0.74-0.92)	0.86 (0.78-0.94)	0.95 (0.82-1.17)	0.96 (0.79-1.17)	1.26 (0.99-1.59)
Fully adjusted, women	1.00	0.86 (0.79-0.94)	0.86 (0.79-0.95)	0.98 (0.82-1.16)	0.96 (0.70-1.30)	1.37 (0.83-2.27)

*Those who reported drinking on at least 1 occasion, but never more than "less than once a week."

†Adjusted for age, sex, income quintile, wealth quintile, whether US born, race, religiosity, smoking, BMI, exercise, binge drinking, self-rated health, frequency of inpatient and emergency department or clinic visits, symptoms (shortness of breath, fatigue, and pain), diagnoses (cancer, lung disease, psychiatric disease, stroke, hypertension, diabetes, heart disease, and other diseases), mobility, activities of daily living, instrumental activities of daily living, and cognitive level.

Appendix Table 5 Hazard Ratios (95% Confidence Interval) for Association Between Mortality and Alcohol Use During the First 4 Years of Follow-up

	Alcohol Consumption at Baseline (Drinks/Wk)					
Covariates Adjusted for	Nondrinker	<1 (ref)	1-<7	7-<14	14-<21	≥21
Age and sex	1.41 (1.26-1.58)	1.00	0.87 (0.76-0.99)	1.00 (0.84-1.19)	1.10 (0.85-1.43)	1.81 (1.39-2.34)
Fully adjusted*	1.17 (1.04-1.32)	1.00	1.02 (0.89-1.18)	1.16 (0.95-1.42)	1.21 (0.90-1.63)	1.64 (1.15-2.34)
Fully adjusted, men	1.12 (0.94-1.34)	1.00	1.01 (0.83-1.23)	1.05 (0.80-1.36)	1.13 (0.79-1.62)	1.59 (1.06-2.39)
Fully adjusted, women	1.18 (1.01-1.38)	1.00	1.02 (0.83-1.25)	1.33 (0.97-1.82)	1.29 (0.72-2.32)	2.00 (0.81-4.95)

*Adjusted for age, sex, income quintile, wealth quintile, whether US born, race, religiosity, smoking, BMI, exercise, binge drinking, self-rated health, frequency of inpatient and emergency department or clinic visits, symptoms (shortness of breath, fatigue, and pain), diagnoses (cancer, lung disease, psychiatric disease, stroke, hypertension, diabetes, heart disease, and other diseases), mobility, activities of daily living, instrumental activities of daily living, and cognitive level.