

Key Findings on Alcohol Consumption and a Variety of Health Outcomes From the Nurses' Health Study

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Objectives. To review critical contributions from the Nurses' Health Study (NHS) on alcohol consumption and health outcomes.

Methods. We performed a narrative review of NHS (1980–2012) and NHS II (1989–2011) publications.

Results. Using detailed information on self-reported alcohol drinking patterns obtained approximately every 4 years combined with extensive information on diet, lifestyle habits, and physician-diagnosed health conditions, NHS investigators have prospectively examined the risks and benefits associated with alcohol consumption. Moderate intake, defined as up to 1 drink a day, is associated with a lower risk of hypertension, myocardial infarction, stroke, sudden cardiac death, gallstones, cognitive decline, and all-cause mortality. However, even moderate intake places women at higher risk for breast cancer and bone fractures, and higher intake increases risk for colon polyps and colon cancer.

Conclusions. Regular alcohol intake has both risks and benefits. In analyses using repeated assessments of alcohol over time and deaths from all causes, women with low to moderate intake and regular frequency (>3 days/week) had the lowest risk of mortality compared with abstainers and women who consumed substantially more than 1 drink per day. (*Am J Public Health.* 2016;106:1586–1591. doi:10.2105/AJPH.2016.303336)

Evaluating the relationship between alcohol intake and long-term health outcomes in observational studies is challenging owing to methodological complexities including nonlinear dose–response associations, the accuracy of the self-reported measurement of alcohol over time, changes in intake owing to health conditions, pharmaceutical contraindications, and age-related reduction in consumption. The Nurses' Health Study (NHS) has been critical in contributing substantially to our understanding of the long-term risks and benefits of light, moderate, and heavy consumption of alcohol in relation to hypertension; diabetes; cardiovascular disease (CVD); colon polyps; cancer of the breast, colon, and ovaries; and several other conditions.

All of our participants are registered nurses who have volunteered for this health study, so the vast majority were moderate

drinkers or did not drink at all, and few participants were heavy drinkers. Therefore, the main focus of our work has been on moderate alcohol consumption. All this work depends on the accuracy of self-reported alcohol consumption from a food frequency questionnaire and several additional questions on drinking patterns, including frequency (days/week), binge drinking, and consuming alcohol with meals. Also, through incorporation of the specific findings of light to

moderate alcohol consumption into an overall healthy lifestyle pattern, we have aimed to quantify the relative importance of alcohol with respect to other known risk or preventive factors for chronic disease.

In this review, we have summarized some of the key findings on alcohol consumption and health outcomes that have been examined using the rich data on NHS participants. For most studies, we used Cox proportional hazards models or conditional logistic regression with risk set sampling to calculate an estimate of the incidence rate ratio (IRR). Two of the studies cited^{1,2} reported odds ratios (ORs) estimated from logistic regression models.

ALCOHOL CONSUMPTION ASSESSMENT

Alcohol consumption was assessed with a 60-item semiquantitative food frequency questionnaire (FFQ) in 1980 and subsequently in 1984, 1986, and every 4 years thereafter with a machine-scannable 131-item FFQ. Initially, the questionnaire asked separately about bottles of beer, glasses of wine, and drinks of spirits. Each drink had 9 frequency response categories ranging from never to 6 or more servings per day over the previous year.

From 1984 to 1990, the FFQ included 4 drink types and common portion sizes: beer

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(1 glass, bottle, or can), red wine (4-ounce glass), white wine (4-ounce glass), and liquor (1 drink or shot). From 1994 onward, the FFQ included 5 alcohol types, adding light beer with the same portion sizes as regular beer. We calculated total alcohol intake by multiplying the average consumption of each beverage by the published alcohol content of the specified portion size on the basis of periodically updated US Department of Agriculture food consumption tables and then summing across beverages.³ Initially, the alcohol content was estimated to be 13.2 grams for a bottle or can of beer, 10.8 grams for a glass of wine, and 15.1 grams for a drink of liquor. Subsequently, this was updated by the US Department of Agriculture to 11.3 grams for a glass of wine; 12.8 grams for a glass, bottle, or can of regular beer and 11.3 grams for light beer; and 14.0 grams for a shot or drink of liquor.

In addition to obtaining information on average alcohol intake, the questionnaires from 1988 onward included questions on drinking frequency, assessed as the usual number of days when alcohol was consumed in a typical week (0, 1–2, 3–4, 5–6, or 7), and heavy episodic drinking, assessed as the largest number of alcoholic drinks consumed in 1 day in a typical month (0, 1–2, 3–5, 6–9, 10–14, or ≥ 15). We did not gather information on whether the participants drank on weekdays or weekends.

On the baseline questionnaire, we asked about “substantial” changes in alcohol intake over the previous 10 years (same, decrease, or increase). Participants were considered former drinkers if they responded that they were nondrinkers at baseline but that their intake decreased substantially over the previous 10 years.

Most previous longitudinal studies obtained information on alcohol intake and other lifestyle characteristics only at baseline and assumed that these behaviors remained constant over decades of follow-up. However, in the NHS, we continue to update this information every 4 years, allowing us to minimize misclassification owing to varying intake over time, accurately characterize the health risks for people whose intake has changed between questionnaire cycles, and examine the behavioral changes following a health diagnosis. This is an important distinction unique to data collected from the NHS.

Early in the development of the FFQ, a subsample of 173 respondents completed 1-week diet records every 3 months for a year to assess the reproducibility and validity of self-reported alcohol intake with the FFQ.⁴ Alcohol intake reported in the four 1-week diet records completed in 1980–1981 was highly correlated with the reported levels in the 1980 (Spearman $r = 0.86$) and 1981 (Spearman $r = 0.90$) FFQs, suggesting that the FFQ assessment of alcohol is reproducible over a 1-year time span. Estimates of average alcohol intake were comparable between the four 1-week diet records (9.0 g/day) and the 1980 (8.2 g/day) and 1981 (9.0 g/day) FFQs.

Some critics have expressed concerns about participants changing their intake during the week of dietary recall to reduce the potential stigma associated with reporting alcohol consumption. Therefore, we also assessed the validity of the self-reported alcohol consumption from the FFQ with serum high-density lipoprotein (HDL) cholesterol levels, a biological marker proven in more than 40 randomized trials to be strongly related to alcohol.⁵ Alcohol intake estimated from the questionnaire (Spearman $r = 0.40$) and diet records (Spearman $r = 0.33$) was correlated with HDL cholesterol. Therefore, the FFQ self-administered questionnaire can provide useful estimates of alcohol intake over an extended period in prospective epidemiologic studies.

HYPERTENSION

Although heavy alcohol consumption has been linked to hypertension, the impact of lower intake levels is less well established. In early analyses, consuming less than 20 grams per day was not associated with incident hypertension, but compared with nondrinkers, the rate was elevated for women consuming 20 to 34 grams per day (about 2–3 drinks; IRR = 1.4; 95% confidence interval [CI] = 1.2, 1.7) and even higher for women consuming 35 or more grams per day (IRR = 1.9; 95% CI = 1.6, 2.2).⁶

In subsequent analyses, we examined the impact of alcohol as part of a healthy lifestyle among middle-aged women. Compared with women reporting no alcohol intake, the rate of incident hypertension

was lowest among those reporting 0.1 to 5.0 grams per day (IRR = 0.88; 95% CI = 0.84, 0.92) or 5.1 to 10.0 grams per day (IRR = 0.84; 95% CI = 0.78, 0.90). There was no association between drinking 10.1 to 15.0 grams per day and the rate of hypertension, but there was an elevated rate among women reporting 30.0 or more grams per day (IRR = 1.61; 95% CI = 1.42, 1.82).⁷

DIABETES

We conducted the first prospective study to examine the association between alcohol consumption and risk for type 2 diabetes. Although alcohol was anecdotally believed to increase diabetes risk, we showed that moderate alcohol intake lowered the risk of type 2 diabetes.⁸ Several studies⁹ have confirmed that there is a U-shaped association between alcohol intake and type 2 diabetes risk, with a nadir of 1 to 2 drinks per day for women, corresponding to a 40% lower risk compared with lifetime abstainers. Drinking 15 or more grams per day attenuated the positive association between glycemic load and type 2 diabetes incidence,¹⁰ potentially by improving insulin sensitivity.

We found that a genotype for slower ethanol metabolism (ADH1C*2) led to higher HDL cholesterol concentrations and a lower rate of myocardial infarction among moderate drinkers.¹¹ However, the ADH1C*2 allele attenuated the inverse association between diabetes and alcohol among women.¹² Additional studies are needed to examine genotype and phenotype associations for the 3 major enzymes (ADH, ALDH, CYP2E) responsible for ethanol metabolism.

CORONARY HEART DISEASE

Although there is consistent evidence across studies that moderate alcohol intake is associated with a lower risk of coronary heart disease (CHD), many critics have attributed these results to uncontrolled confounding and to the contamination of the nondrinker category by former drinkers who stopped drinking alcohol owing to illness (the sick quitter hypothesis). In some of the earliest studies to use the highly detailed updated

information on alcohol consumption and other lifestyle characteristics to examine this association and to address these potential alternative hypotheses, we reported that alcohol consumption lowered the risk of CHD.¹³ Using data on both amount and frequency of alcohol consumption, we gained new insight into the impact of drinking patterns, showing that alcohol intake at least 3 to 4 days per week is associated with a lower risk of myocardial infarction among women, and HDL cholesterol, fibrinogen, and HbA1c accounted for 75% of the association.¹⁴

Even after accounting for other critical lifestyle factors, moderate alcohol intake (0.1–14.9 g/day) was associated with a lower rate of CHD (IRR = 0.77; 95% CI = 0.64, 0.93), and if causal, 12.6% (95% CI = 3.1, 21.8) of all confirmed CHD events could have been prevented if they had all adhered to this optimal level of alcohol intake.¹⁵

The inverse association for moderate alcohol intake and CHD was also evident among women with diabetes. Compared with those reporting no alcohol intake, there was a lower rate of nonfatal or fatal CHD among diabetic women who consumed 0.1 to 4.9 grams per day (IRR = 0.72; 95% CI = 0.54, 0.96) or 5.0 or more grams per day (IRR = 0.45; 95% CI = 0.29, 0.68).¹⁶

To examine the biological mechanisms linking alcohol intake and heart health, we showed that *TaqIB2*, a common polymorphism in the cholesteryl ester transfer protein, modified the association between alcohol intake and HDL cholesterol as well as the risk of CHD.¹⁷ Among noncarriers, the IRR for CHD among women with a usual daily intake of 5 to 14 grams of alcohol was 1.4 (95% CI = 0.6, 3.7) compared with nondrinkers, whereas among B2 carriers the IRR was 0.4 (95% CI = 0.2, 0.8). Other genes associated with lipid metabolism, including lipoprotein lipase, may also modify the association between alcohol and CHD.¹⁸

SUDDEN CARDIAC DEATH

We found a U-shaped association between alcohol intake and the risk of sudden cardiac death. Compared with no alcohol intake, the IRR for sudden cardiac death was 0.64 (95% CI = 0.43, 0.95) for drinking 5.0 to 14.9

grams per day, 0.68 (95% CI = 0.38, 1.23) for drinking 15.0 to 29.9 grams per day, and 1.15 (95% CI = 0.70, 1.87) for drinking 30.0 or more grams per day, with similar results for all beverage types.

By contrast, the inverse association between alcohol intake and nonfatal and fatal CHD was linear, with no evidence of higher risk at higher levels of consumption, although we had limited power to assess heavy drinking.¹⁹

STROKE

It was soon apparent that the same amount of alcohol had a different impact on different cardiovascular events. Compared with nondrinkers, women who consumed moderate amounts of alcohol had a 40% to 60% lower rate of CHD and ischemic stroke, but that same amount resulted in a 3.7-times higher rate of subarachnoid hemorrhage.¹³

In a subsequent analysis with more cases, alcohol had a J-shaped association with the risk of ischemic and hemorrhagic stroke in women, with a lower risk among light drinkers and a higher risk among women who drink 30 or more grams per day.²⁰ Even after accounting for other lifestyle factors, including abstention from cigarette smoking, optimal weight, healthy diet, and daily exercise, moderate alcohol consumption (5–15 g/day) was associated with a lower rate of total stroke (IRR = 0.85; 95% CI = 0.74, 0.98).

COLON POLYPS AND CANCER

Although moderate alcohol intake may lower the risk of diabetes and CVD, habitual drinking is associated with a higher rate of some cancers. Compared with nondrinkers, women who consumed 30 or more grams per day had a 1.79 times (95% CI = 1.02, 3.15) higher odds of hyperplastic polyp of the distal colon and rectum, an indicator of high risk for colorectal carcinoma.¹ Higher intake was also associated with a higher rate of colon cancer, particularly among those with a family history of colorectal cancer.²¹

We and others have reported that high dietary folate, especially in the era before folic acid fortification in the United States,²²

is inversely associated with the risk of colorectal adenoma. Giovannucci et al.²³ hypothesized that a methyl-deplete diet composed of low dietary folate and methionine and high alcohol intake may reduce methyl donors that are required to regulate proto-oncogene expression and thereby cause an elevated risk of premalignant colorectal adenomas. Compared with no alcohol intake, drinking 30 or more grams per day was associated with a 1.84-fold (95% CI = 1.19, 2.86) rate of colorectal adenoma, with similar results across beverage types. A combination of high alcohol and low folate was a particularly strong risk factor for small adenomas.

BREAST CANCER

Because studies examining the link between alcohol and risk of breast cancer were either case-control or cross-sectional studies, there were concerns that results were attributable to recall bias. In the initial analysis of the first 4 years of follow-up and 601 cases, we conducted the first prospective cohort study to evaluate this association,²⁴ and we reported a positive linear relationship, which reached a 60% higher risk among women who consumed more than 1 drink per day than among abstainers. Although this unexpected finding was ridiculed in some circles, it has now been replicated in several subsequent studies. In a pooled analysis of 6 prospective studies, including both NHS cohorts, we observed a 10% higher risk per 10 grams per day increment in alcohol intake.²⁵ In a recent pooled analysis of 20 studies,²⁶ the rate of breast cancer was 32% higher among women who reported drinking 30 or more grams per day than among those reporting no alcohol intake.

Alcohol intake both earlier and later in adult life was independently associated with a modest increase in risk, even at levels as low as 5.0 to 9.9 grams per day (approximately 3–6 drinks/week).²⁷ In an attempt to identify a mechanism underlying this association, Hankinson et al.²⁸ showed that alcohol consumption was positively associated with estrone sulfate concentrations ($r = 0.17$). Women who consumed 30.0 or more grams per day had a 33% higher estrone sulfate level than did nondrinkers. The

modest association between alcohol intake and breast cancer risk among postmenopausal women was not modified by the ADH1C genotype that affects alcohol metabolism.²⁹

OTHER CANCERS

The long follow-up of our cohort has enabled us to study risk factors for other cancers.

We do not have sufficient power to evaluate whether lifestyle choices (e.g., smoking) or genotype may modify the risk of developing these cancers.

TOTAL CANCER

In our most recent investigation of alcohol and cancer,³⁰ we identified all incident cancers (excluding nonadvanced prostate cancers for the half of the study population that was men) during the 30 years of follow-up. Among 88 084 women free of cancer at baseline, we confirmed 19 269 incident cancers, including 9016 cancers from alcohol-related outcomes (i.e., colorectum, breast, oral cavity, pharynx, larynx, liver, and esophagus).

The risk of any cancer increased linearly, with a 4% (95% CI = 0%, 9%) higher risk among women who consumed 5.0 to 14.9 grams per day compared with abstainers, and the highest risk was among those consuming more than 45.0 grams per day (IRR = 1.30; 95% CI = 1.13, 1.50). The associations were slightly stronger for the rate of any alcohol-related cancer. There was no evidence of an association between alcohol intake and other cancers.

BONE DENSITY AND FRACTURES

Chronic alcohol abuse is associated with low bone density and a high risk of fracture. However, moderate alcohol consumption may help to maintain bone density in postmenopausal women by increasing endogenous estrogens or by promoting secretion of calcitonin. In a substudy of participants who completed bone density assessments of the lumbar spine and proximal femur, women

who consumed 10 or more grams per day had higher bone densities at the lumbar spine than did women reporting no alcohol intake, regardless of whether they were current or never users of postmenopausal estrogens.³¹

Even moderate alcohol consumption can lead to poor balance and falls; women with a body mass index less than 21 kilograms per meters² who consumed more than 15 grams per day had a higher risk of forearm and hip fractures (IRR = 1.73; 95% CI = 1.30, 2.29).³²

GALLSTONES

Alcohol has been reported to reduce the risk of gallstones by stimulating gallbladder emptying and reducing stone formation. Other proposed mechanisms include inducing changes in bile concentration and composition that inhibit the absorption of water and electrolytes. In our first analysis, we found that compared with abstinence, alcohol intake of 5 or more grams per day was associated with a 40% (95% CI = 0.4, 0.8) lower rate of symptomatic gallstones incidence.³³ In a subsequent study,³⁴ with 7831 cases of cholecystectomy, we found an inverse linear association with greater alcohol intake. Each 15 grams per day increment in alcohol consumption was associated with a 14% lower rate of gallstones requiring cholecystectomy even after excluding past heavy drinkers.

With the large number of cases, we were also able to explore the impact of drinking patterns, which was of interest because many of the proposed mechanisms suggest that the benefit would be greater if alcohol were consumed in moderation throughout the week rather than only episodically. In addition to the average amount consumed per day, we found that frequency of consumption (in days per week) was inversely associated with risk, with the strongest inverse association among women who drank 7 days a week (IRR = 0.73; 95% CI = 0.63, 0.84). The lower risks of gallstones associated with alcohol intake were apparent for wine, beer, and liquor.

COGNITIVE FUNCTION

In a subset of nurses aged 70 years or older, we used a validated 20- to 30-minute

telephone interview to assess cognitive function.³⁵ Women who consumed less than 15 grams per day had better mean cognitive scores than did nondrinkers, but there was no association between drinking 15 to 30 grams per day and the risk of cognitive impairment or decline.

There were no differences in risk according to beverage type and no interaction with the apolipoprotein E genotype, a strong genetic marker for age-related cognitive dysfunction.

ALCOHOL INTAKE AFTER DIAGNOSIS OF CHRONIC DISEASE

With the aging of the cohort and the concomitant increase in rates of chronic disease, we have ample statistical power to study the impact of modifiable risk factors after a diagnosis of chronic disease to determine if changes in diet and lifestyle can reduce rates of recurrence, other chronic diseases, or total mortality.

Moderate alcohol consumption among women with diabetes was associated with a lower risk of subsequent CHD. In a separate analysis among women who survived an incident myocardial infarction, those who reported diets consistent with the highest quintile of the Alternative Healthy Eating Index 2010 (high-quality diet) had a lower rate of all-cause mortality than did women in the lowest quintile of the diet score (IRR = 0.66; 95% CI = 0.49, 0.88).³⁶ This score included moderate alcohol drinking as a component. After a diagnosis of colorectal cancer, alcohol consumption did not appear to affect prognosis.³⁷

Studying the impact of alcohol intake after a diagnosis of any chronic condition, especially cancer, can be extremely challenging owing to differences in treatment regimens, changes in mental health, and sometimes extreme changes in other lifestyle choices. Thus these results need to be interpreted cautiously and confirmed with other prospective studies with populations from other countries and with different drinking patterns.

OTHER NOTABLE HEALTH CONDITIONS AND DISEASES

We cannot provide a comprehensive review of all of our previous work on alcohol and health risk. However, it is worth noting that the repeated alcohol assessments and long follow-up have allowed us to examine less commonly studied outcomes. For example, long-term moderate alcohol intake was not associated with seizure or epilepsy.³⁸ We also found that moderate alcohol consumption had no substantial adverse effect on renal function in women over an 11-year follow-up period.³⁹

In a cross-sectional study of alcoholic intake and early lens changes, alcohol consumption, especially liquor and wine, was positively related to nuclear opacity, and wine consumption was associated with a lower odds of cortical opacity.² Compared with no alcohol intake, women who reported heavier usual intake (≥ 30 g/day) had a 2-fold (95% CI = 1.2, 3.4) rate of early and dry form age-related macular degeneration.⁴⁰

ALL-CAUSE MORTALITY

As an important component of a healthy lifestyle, we have found that light to moderate alcohol consumption was one of the 5 most important modifiable contributors to lowering the risk of CHD,^{13,41} stroke,²⁰ and total mortality.⁴² Describing alcohol as a component of a healthy diet rather than providing clinical advice only on drinking or not drinking may be the best method to translate our results in a clinical population. We calculated the population-attributable risk for total mortality with 24 years of follow-up and 8882 deaths and categorized women who abstained or who consumed 30.0 or more grams per day as the at-risk group compared with women who consumed 1.0 to 29.9 grams per day.

For comparison with the other most important risk factors, the estimated population-attributable risks for total mortality were 28% for cigarette smoking, 14% for being overweight, 17% for lack of physical activity, 13% for low diet quality, and 7.4% for not drinking a light to moderate amount of alcohol. Compared with moderate alcohol intake, the proportion of

cardiovascular deaths owing to heavy drinking or abstaining was 11.3%, and the proportion of cancer deaths owing to heavy drinking or abstaining was 3.1%.⁴²

Evaluating the risk of all-cause mortality provides one way to evaluate the overall balance of risks and benefits of moderate alcohol consumption. Compared with abstainers, the rate of all-cause mortality was lower among women reporting light (1.5–4.9 g/day; IRR = 0.83; 95% CI = 0.74, 0.93) and moderate (5.0–29.9 g/day; IRR = 0.88; 95% CI = 0.80, 0.98) intake, but the rate was higher among women with higher levels of intake (≥ 30.0 g/day; IRR = 1.19; 95% CI = 1.02, 1.38).⁴³ Similar to our previous analyses, the inverse association between moderate alcohol intake and mortality was strongest among women with risk factors for CVD and those aged 50 years or older.

CONCLUSIONS AND CLINICAL IMPLICATIONS

In general, we found that for the same amount of alcohol consumed per week, there are greater benefits among individuals who drink smaller amounts more frequently than among those who consumed the same amount on only 1 to 2 days per week.

For almost all diseases and health conditions we have summarized, the type of beverage did not strongly modify the risk of chronic disease. Thus, beer, wine, and liquor were all associated with lower CVD risk, but all were associated with higher breast cancer risk.

As noted earlier, most of our work has focused on moderate alcohol consumption. The adverse effects of heavy consumption are well known. Although moderate drinking appears to increase the risk of colon and breast cancer, these risks are more than counterbalanced by the boost in cardiovascular health—especially in middle age and older, when CVD accounts for an increasingly large share of disease and deaths. We still do not have strong enough evidence to suggest that women who are nondrinkers start drinking later in life to reduce their risk of CVD or total mortality, although this would appear to be a reasonable option in the

absence of any contraindication. However, there are many other lifestyle choices documented in the Nurses' Health Study that can substantially reduce a woman's risk of chronic disease without the potential downsides of alcohol.

The *2015–2020 Dietary Guidelines for Americans*⁴⁴ defines moderate alcohol consumption as up to 1 drink per day for women and up to 2 drinks per day for men, where a drink is defined as 12 ounces of beer, 4 ounces of wine, 1.5 ounces of 80-proof spirits, or 1 ounce of 100-proof spirits. Because drinking more alcohol increases dangers, including alcoholism, high blood pressure, obesity, stroke, breast cancer, suicide, and accidents, the American Heart Association suggests that those who drink do so in moderation and consult their doctors about the benefits and risks of consuming alcohol in moderation. **AJPH**

CONTRIBUTORS

E. B. Rimm and E. Mostofsky drafted the article. K. J. Mukamal, E. L. Giovannucci, and M. J. Stampfer provided critical feedback and revisions.

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Note. The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic health care centers, or NIH.

HUMAN PARTICIPANT PROTECTION

This article is a review of published studies, and therefore no institutional review board approval was necessary.

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EDITOR'S NOTE

Because of space restrictions and the large volume of references relevant to the Nurses' Health Study, additional references are provided in a supplement to the online version of this article at <http://www.ajph.org>.