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Alcoholic Beverages and Incidence of Dementia: 34-Year Follow-up of the Prospective Population Study of Women in Göteborg

K. Mehlig; I. Skoog; X. Guo; M. Schütze; D. Gustafson; M. Waern; S. Östling; C. Björkelund; L. Lissner

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Abstract and Introduction

Abstract

The objective of this study was to assess the association between different types of alcoholic beverages and 34-year incidence of dementia. Among a random sample of 1,462 women aged 38-60 years and living in Göteborg, Sweden, in 1968-1969, 164 cases of dementia were diagnosed by 2002. At baseline as well as in 1974-1975, 1980-1981, and 1992-1993, the frequency of alcohol intake, as well as other lifestyle and health factors, was recorded and related to dementia with Cox proportional hazard regression, by use of both baseline and updated covariates. Wine was protective for dementia (hazard ratio (HR) = 0.6, 95% confidence interval (CI): 0.4, 0.8) in the updated model, and the association was strongest among women who consumed wine only (HR = 0.3, 95% CI: 0.1, 0.8). After stratification by smoking, the protective association of wine was stronger among smokers. In contrast, consumption of spirits at baseline was associated with slightly increased risk of dementia (HR = 1.5, 95% CI: 1.0, 2.2). Results show that wine and spirits displayed opposing associations with dementia. Because a protective effect was not seen for the other beverages, at least part of the association for wine may be explained by components other than ethanol.

Introduction

There is an increasing literature suggesting a protective effect of moderate alcohol consumption on dementia.^[1-13] It is not fully understood whether different alcoholic beverages, such as beer,

wine, and spirits, are equivalent in this respect. Some studies have shown a protective effect of wine only, which may be due to the level of ethanol, the complex mixture that comprises wine, or the healthier lifestyle ascribed to wine drinkers.^[14,15] Previous studies differ, however, in the gender and age of subjects, the endpoints studied, the definition of moderate intake, the type of beverages studied, and the covariates considered. In particular, the role of smoking^[16-18] and the combined effect of smoking and drinking^[19] in relation to dementia are controversial. Moreover, the use of repeated exposures may modify observed associations in studies of long duration.

The dual purpose of this study is to contrast associations between different alcoholic beverages and dementia, while also comparing results from time-dependent versus baseline models. Our results are derived from a population-based sample of women who were followed for 34 years, during which time the availability of alcohol and the drinking habits changed considerably in Sweden. By use of a time-dependent model, it is possible to measure the importance of alcohol intake at different stages of the study.

Materials and Methods

Participants

The Prospective Population Study of Women in Göteborg, Sweden, started in 1968-1969 with a cross-sectional survey of women aged 38, 46, 50, 54, and 60 years.^[20] To ensure a representative sample of women in Göteborg in 1968, 1,622 women were chosen randomly from the Revenue Office Register, according to their date of birth. Out of these women, 1,462 participated in the health examination, resulting in a participation rate of 90.1 percent. In addition to a physical examination, subjects were asked to complete surveys concerning a variety of demographic, social, lifestyle, and medical factors, including education and socioeconomic status, alcohol consumption, and smoking. The women were later invited for reexaminations in 1974-1975, 1980-1981, 1992-1993, and 2000-2001 with participation rates of 91 percent, 83 percent, 70 percent, and 71 percent, respectively, among those still alive.^[21] Four women who did not respond to the questions about alcohol intake at the baseline examination were excluded from the analysis. In addition to data collected during the health examinations, the National Swedish Death Registry was used to identify the date and cause of death of the remaining 1,458 women, updated through 2002. The study was approved by the ethics committee of Göteborg University, and participants have given informed consent in accordance with the Helsinki Declaration.

Assessment of Alcohol Intake

At each examination, the women were asked about the average intake frequency of three different types of alcoholic drinks, namely, beer, wine, and spirits (table 1). Different frequency categories were assumed to reflect standard "servings" of each beverage. Alcohol exposure reported during the reexamination in 2000-2001 is not considered here, since it occurred after most diagnoses of dementia.

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Table 1. Categories of Consumption of Alcoholic Beverages Asked Separately for Wine, Beer, and Spirits at All Examinations, Göteborg, Sweden, 1968-2002

Label of category	Frequency of alcohol intake
0	Never
1	Earlier, but not during the last 10 years
2	Earlier, but not during the last year
3	Monthly
4	Weekly
5	Several times a week
6	Daily

Assessment of Potential Confounders

At every examination, information on hypertension, body mass index, serum triglycerides, serum cholesterol, medical history, smoking, and leisure-time physical activity was obtained. Hypertension was defined as systolic blood pressure of ≥ 140 mmHg, diastolic blood pressure of ≥ 90 mmHg, or taking antihypertensive medication. Lipids and body mass index were measured in units of millimoles per liter and kilograms per meter squared, respectively. Smoking was defined as present or recent smoking versus never smoking or giving up smoking more than 10 years ago. Leisure-time exercise compared physical activity of at least 4 hours/week with less activity. In 1968-1969, education and socioeconomic status were reported: Education distinguished between compulsory school and higher education, while socioeconomic status was calculated from the maximum of a woman's or her partner's professional ranking (employee/higher employee vs. worker). Supplementary information on incident disorders such as diabetes mellitus, myocardial infarction, or stroke was also obtained from the Swedish Hospital Discharge Register.

Diagnosis of Dementia

Neuropsychiatric examinations were performed in 1974-1975, 1980-1981, and 1992-1993 by psychiatrists and in 2000-2002 by experienced psychiatric nurses. These included a comprehensive psychiatric interview and observation of mental symptoms, as well as extensive batteries of neuropsychiatric tests; from 1992 onward, refer to the papers by Skoog et al.^[22] and Guo et al.^[23] for details. The results of these examinations were combined with close informant interviews, as also described elsewhere.^[22] Diagnoses were made according to criteria from the *Diagnostic and Statistical Manual of Mental Disorders: DSM-III-R*.^[24] Dementia diagnoses for individuals lost to follow-up were based on information from medical records evaluated by geriatric psychiatrists in consensus conferences and from the Swedish Hospital Discharge Registry. Until the last update in 2002, 164 cases of dementia were diagnosed, of which two cases had to be excluded because of missing information on alcohol intake at baseline.

Statistical Analysis

Survival from the 1968-1969 baseline examination to diagnosis of dementia or censoring (until December 31, 2002) was calculated for each individual. We used Cox proportional hazard regression to model the dependence of survival on the exposures and confounding factors. In addition, we studied the influence of exposures and confounding factors on dementia-free survival by using censoring of survival time at either the date of dementia diagnosis or the end of 2002.

Variables describing exposure or possible confounders are likely to change their values from one examination to the next. Exceptions are education and socioeconomic status, collected at baseline only. Within the Cox model with updated covariates, the partial likelihood (PL) is calculated such that the factor for a particular failure time t_i (survival until diagnosis, $i = 1, \dots, 162$) is evaluated by use of the vector of covariates z , which is the most recently measured; if, for instance, a diagnosis is given in $t_i = 1986$,

$$PL = \prod_{i=1}^{162} \frac{\exp[\beta^T z_i(t)]}{\sum_{t_j \geq t_i} \exp[\beta^T z_j(t)]}, \quad t \leq t_i,$$

is evaluated by use of the covariates reported at the second follow-up, z_j ($t = 1980-1981$) (or earlier, if a particular covariate value is missing). Note that the product of failure probabilities includes the cases of dementia only, while the sum in the denominator comprises all survival times until diagnosis or censoring larger or equal to a particular survival time t_i . Maximization of PL as a function of the vector of regression coefficients β gives the effect of each covariate in z . The time-constant Cox model is based upon the covariates evaluated at baseline only, with

$$PL = \prod_{i=1}^{162} \frac{\exp[\beta^T z_i(1968-1969)]}{\sum_{t_j \geq t_i} \exp[\beta^T z_j(1968-1969)]}.$$

Hence, the baseline model measures the long-term effect of covariates, while the updated model is more sensitive to their short-term effect. We therefore compared the results for the updated Cox model with the time-independent or baseline model, which uses the exposure and confounder values measured in 1968-1969 only.

However, since 64 percent of all cases of dementia were diagnosed after 1992, the updated Cox model puts most weight on this examination. To measure the effect of covariates at intermediate examinations, we used covariates updated until 1974-1975 and 1980-1981, respectively. Because the number of diagnoses increased strongly with time in the study, most weight lay on the last update of covariates, while the influence of earlier examinations is weak (one case before 1974-1975, nine cases before 1980-1981).

Only participants with complete baseline information on all three types of alcohol were included in the analysis. If the alcohol intake at a follow-up examination was missing, the value of the

preceding examination was used, and the influence of this replacement was investigated. In the multivariate models, the number of cases and the individuals at risk were reduced because of missing baseline values for cholesterol, socioeconomic status, and education. Five individuals at risk (two cases) were excluded from the time-constant model because of missing values of cholesterol at baseline but were included again in the updated model because of complete information at the follow-up examinations.

For each type of drink, we defined a binary variable for current drinking versus former or never drinking (table 1). The hazard ratio associated with consuming a particular alcoholic beverage, together with the 95 percent confidence interval, is presented, adjusted for all other covariates in the model. In addition, we examined the influence of alcohol consumption (yes/no) irrespective of type of beverage, compared with nonconsumers. Finally, we attempted to isolate the contributions of different beverages by using eight mutually exclusive categories describing the different combinations of drinks.

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Table 1. Categories of Consumption of Alcoholic Beverages Asked Separately for Wine, Beer, and Spirits at All Examinations, Göteborg, Sweden, 1968-2002

Label of category	Frequency of alcohol intake
0	Never
1	Earlier, but not during the last 10 years
2	Earlier, but not during the last year
3	Monthly
4	Weekly
5	Several times a week
6	Daily

To avoid the influence of recent changes in drinking or smoking habits caused by dementia (in which case these variables cannot be used as predictors), we tested the robustness of our results by accepting updated covariates only if they had been measured at least 10 years before diagnosis.

Results

Exposures and Outcomes Over The Study Period

From 1968 to 2002, there were 636 deaths and 162 cases of dementia. In the five age strata (38, 46, 50, 54, and 60 years of age at baseline), the percentage of women still alive at the end of 2002 decreased with increasing age (81 percent, 62 percent, 49 percent, 29 percent, and 5 percent, respectively). The corresponding percentages of women receiving the diagnosis of

dementia were 2 percent, 10 percent, 15 percent, 19 percent, and 16 percent, corresponding to incidence rates of 0.7, 3.3, 5.3, 7.6, and 8.0 events per 1,000 person-years. The average year of diagnosis was 1996 for the youngest cohort and 1992 for the oldest.

Table 2 shows the alcohol consumption and the other covariates from 1968 to 1992. For women with dementia, the results of a particular examination are included only if the examination took place before the date of diagnosis. Although the fraction of smokers decreased over time in the study, the consumption of wine and spirits increased to a maximum in 1980-1981, reflecting the increasing availability of wine and spirits in Sweden.^[25] There was almost no further change in wine consumption until 1992-1993, while a decrease in consumption of hard liquor was observed. Wine and spirits were consumed mainly on a monthly basis, while beer was consumed more frequently (data not shown).

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Table 2. Numbers and Characteristics of Participants at the Four Health Examinations, Göteborg, Sweden, 1968-2002

Examination year	Characteristic	Value(s)
1968-1969	No. of dementia-free participants examined	1,458
	None/beer/wine/spirits (%)	25/68/51/26
	Higher education/socioeconomic status (%)	30/66
	Leisure activity (≥ 4 hours/week) (%)	82
	Smoking (%)	46
	Body mass index (kg/m^2)	24.1
	triglycerides/cholesterol (mmol/liter)	1.22/6.86
	Hypertension (%)	39
	Diabetes/stroke/infarction (%)*	1.0/0.1/0.1
1974-1975	No. of dementia-free participants examined (alive)	1,298 (1,426)
	None/beer/wine/spirits (%)	25/65/59/40
	Leisure activity (≥ 4 hours/week) (%)	77
	Smoking (%)	44
	Body mass index (kg/m^2)	24.6
	triglycerides/cholesterol (mmol/liter)	1.28/6.96
	Hypertension (%)	48
	Diabetes/stroke/infarction (%)*	2.1/0.4/0.7
1980-1981	No. of dementia-free participants examined (alive)	1,146 (1,366)

	None/beer/wine/spirits (%)	21/58/63/50
	Leisure activity (≥ 4 hours/week) (%)	71
	Smoking (%)	40
	Body mass index (kg/m^2)	25.1
	triglycerides/cholesterol (mmol/liter)	1.38/7.08
	Hypertension (%)	67
	Diabetes/stroke/infarction (%)*	3.9/1.0/2.1
1992-1993	No. of dementia-free participants examined (alive)	800 (1,118)
	None/beer/wine/spirits (%)	20/63/64/37
	Leisure activity (≥ 4 hours/week) (%)	77
	Smoking (%)	33
	Body mass index (kg/m^2)	26.3
	triglycerides/cholesterol (mmol/liter)	1.48/6.36
	Hypertension (%)	81
	Diabetes/stroke/infarction (%)*	6.3/5.6/6.5

* Cumulative incidence of diabetes, stroke, and infarction given until 1969, 1975, 1981, and 1992, as the percentage of the baseline population.

Baseline Versus Updated Models

Table 3 gives the hazard ratio for dementia and confidence interval for mutually adjusted, overlapping alcohol exposure categories in the age-adjusted model and the multivariate model. In the age-adjusted baseline model, consumption of spirits was associated with increased risk of dementia, although this association was attenuated in the multivariate model. Wine and beer consumption in the baseline model was not associated with subsequent incidence of dementia, in either the age- or fully adjusted models. In contrast, with models that include updated covariates, wine had a highly significantly protective effect, while the hazard ratios of spirits and beer were attenuated as compared with the baseline models. When considering total intake of any alcoholic beverage (versus none), one sees no significant associations with dementia.

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Table 3. Results for Survival Until Diagnosis of Dementia, Göteborg, Sweden, 1968-2002

Time dependence of	Age-adjusted model*	Multivariate model [†]
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covariate exposure				
	Hazard ratio	95% confidence interval	Hazard ratio	95% confidence interval
Constant covariates (baseline values)				
Wine	0.78	0.54, 1.12	0.82	0.56, 1.19
Beer	1.14	0.79, 1.66	1.21	0.82, 1.80
Spirits	1.59	1.09, 2.30	1.45	0.98, 2.15
Updated covariates (1968-1992)				
Wine	0.58	0.40, 0.85	0.56	0.38, 0.82
Beer	1.12	0.79, 1.57	1.18	0.83, 1.69
Spirits	1.32	0.91, 1.90	1.16	0.80, 1.69

* The hazard ratio and 95% confidence interval are given for the age-adjusted model, including beer, wine, and spirits (162 cases, 1,458 individuals at risk).

† The results for the exposure are given in the multivariate model, which includes education, socioeconomic status, smoking, leisure-time physical activity, body mass index, hypertension, lipids, and history of diabetes, stroke, and infarction (156 cases and 1,406 individuals at risk for the time-dependent model; 154 cases and 1,401 individuals at risk for the constant model).

These models were further tested in a number of ways. Counting former drinkers as drinkers did not change the results in table 3. Next, given that the true as well as the reported value of alcohol intake might be influenced by early stages of disease, we excluded self-reports if given within 10 years before diagnosis. The effect of wine in the updated multivariate model was still protective (hazard ratio (HR) = 0.63, 95 percent confidence interval (CI): 0.43, 0.93), while that of spirits was not (HR = 1.29, 95 percent CI: 0.89, 1.87). Finally, a model that included only participants with complete information until diagnosis or censoring (110 cases, 1,005 individuals at risk) showed an enhanced effect of wine (HR = 0.50, 95 percent CI: 0.32, 0.79) but left the effects of beer and spirits unchanged.

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Table 3. Results for Survival Until Diagnosis of Dementia, Göteborg, Sweden, 1968-2002

Time dependence of covariate exposure	Age-adjusted model*		Multivariate model†	
	Hazard	95% confidence	Hazard	95% confidence

	ratio	interval	ratio	interval
Constant covariates (baseline values)				
Wine	0.78	0.54, 1.12	0.82	0.56, 1.19
Beer	1.14	0.79, 1.66	1.21	0.82, 1.80
Spirits	1.59	1.09, 2.30	1.45	0.98, 2.15
Updated covariates (1968-1992)				
Wine	0.58	0.40, 0.85	0.56	0.38, 0.82
Beer	1.12	0.79, 1.57	1.18	0.83, 1.69
Spirits	1.32	0.91, 1.90	1.16	0.80, 1.69

* The hazard ratio and 95% confidence interval are given for the age-adjusted model, including beer, wine, and spirits (162 cases, 1,458 individuals at risk).

† The results for the exposure are given in the multivariate model, which includes education, socioeconomic status, smoking, leisure-time physical activity, body mass index, hypertension, lipids, and history of diabetes, stroke, and infarction (156 cases and 1,406 individuals at risk for the time-dependent model; 154 cases and 1,401 individuals at risk for the constant model).

The variables beer, wine, and spirits as analyzed so far are overlapping as, for example, wine drinkers may also consume beer and/or spirits, potentially attenuating the observed associations. We attempted to isolate the contributions of specific beverages by replacing the binary variables for use of beer, wine, and spirits by eight mutually exclusive categories describing the different combinations of drinks. In this analysis, we found a risk reduction of almost 70 percent among wine-only drinkers (HR = 0.32, 95 percent CI: 0.12, 0.81) or even more if former drinkers are counted as drinkers (HR = 0.19, 95 percent CI: 0.06, 0.64), using time-dependent covariates. No other disjunctive category showed significant associations with dementia (not shown).

Time-dependent Effects of Wine in Smokers and Nonsmokers

In the multivariate models, smokers got dementia earlier than did nonsmokers (HR = 1.57, 95 percent CI: 1.14, 2.17 in the age-adjusted, updated model; HR = 1.64, 95 percent CI: 1.15, 2.33 in the multivariate-adjusted, updated model; attenuated in the baseline models), which indicates that smoking is an independent risk factor for dementia. On the basis of previous reports of effect modification between smoking and alcohol consumption,^[19] we performed a stratified analysis among those who were current or recent smokers in 1968-1969 (69 cases, 668 individuals at risk) and nonsmokers (87 cases, 789 individuals at risk) separately. Wine drinking was associated with less dementia in smokers (HR = 0.41, 95 percent CI: 0.23, 0.73), but the association was attenuated in nonsmokers (HR = 0.68, 95 percent CI: 0.41, 1.12). Figure 1 illustrates the hazard ratio for dementia associated with consumption of wine and cigarettes within the multivariate model and for consumption of wine among smokers and nonsmokers separately. Although wine always tended to be inversely associated with dementia, it was significant in the whole

population and among smokers from 1980-1981 onward, when over 60 percent of participants reported regular wine consumption.

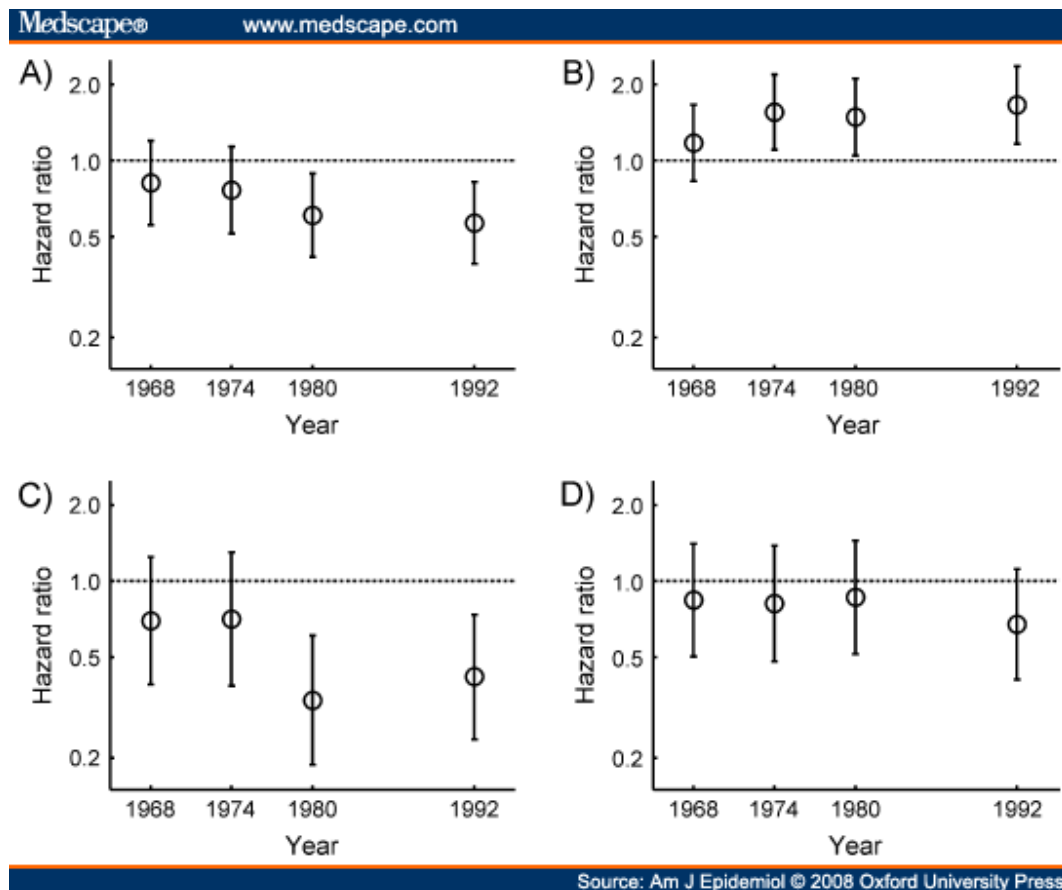


Figure 1. The Hazard Ratio For Dementia In Relation To Current Consumption Of Wine (A) Or Use Of Cigarettes (B), Compared With Abstinence, Within A Multivariate Model, Göteborg, Sweden, 1968-2002. Below, the multivariate model (smoking excluded) is applied to those who reported smoking at baseline (69 cases, 668 individuals at risk) (C) and those who did not (87 cases, 789 individuals at risk) (D) separately. The covariates are updated until the year of examination indicated.

Competing Outcomes: Alcohol and Mortality, Censored for Dementia

In a complementary analysis, we examined the survival time of participants, which was censored at the date of diagnosis of dementia or at the last update at the end of 2002, if they survived. Table 4 gives the results for the Cox model describing mortality censored for dementia. Wine drinking was protectively associated with dementia-free mortality in both the baseline model and the model with updated covariates, although no longer significantly in the multivariate model. Although beer was not associated with dementia, its association with longevity was comparable to that of wine. The use of spirits, on the other hand, tended to shorten the (dementia-free) survival time. Smoking was associated with mortality competing with dementia, in both the baseline (HR = 1.95, 95 percent CI: 1.61, 2.35) and the updated models (HR = 1.68, 95 percent CI: 1.39, 2.03).

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Table 4. Results For Death As An Endpoint Competing With Dementia, Göteborg, Sweden, 1968-2002

Time dependence of covariate exposure	Age-adjusted model*		Multivariate model [†]	
	Hazard ratio	95% confidence interval	Hazard ratio	95% confidence interval
Constant covariates (baseline values)				
Wine	0.81	0.66, 0.98	0.93	0.76, 1.15
Beer	0.73	0.61, 0.89	0.77	0.63, 0.94
Spirits	1.32	1.07, 1.64	1.2	0.96, 1.50
Updated covariates (1968-1992)				
Wine	0.8	0.65, 0.97	0.93	0.75, 1.15
Beer	0.76	0.63, 0.92	0.91	0.75, 1.11
Spirits	1.06	0.86, 1.29	0.9	0.73, 1.10

* The hazard ratio and 95% confidence interval are given for the age-adjusted model, including beer, wine, and spirits (546 cases, 1,458 individuals at risk).

[†] The results for the exposure are given within the multivariate model (510 cases and 1,406 individuals at risk for the time-dependent model; 508 cases and 1,401 individuals at risk for the constant model).

Discussion

Using the Cox model with baseline and updated covariates, we analyzed the long-term and the short-term effects of consumption of different kinds of alcohol on the incidence of dementia in middle-aged women. Although we did not observe an association for intake of alcohol irrespective of type, the protective effect of wine on the one hand and reverse trends for beer and spirits on the other are apparent. A categorical analysis, covering all eight combinations of intake of beer, wine, and/or spirits, showed a robust protective association for exclusive consumption of wine only.

The protective result for wine in the updated model underscores the value of using updated reports of alcohol intake, which may reflect not only the increase of wine drinking between 1968 and 1992 but also the short-term importance of wine intake. Because dementia is a disease of

aging and most cases of dementia were diagnosed about 25 years after the baseline examination, the wine intake reported in 1968-1969 may have lost influence, while the reports given in 1980-1981 showed the strongest impact (figure 1).

When considering mortality (censored for dementia) as an outcome competing with dementia, consumption of wine tended to predict higher longevity. This is an indication that wine drinkers were protected against dementia even though they were likely to reach high ages, and that the protective effect of wine for dementia is not explained by selective mortality.

The attenuation of the positive association between spirits and dementia in the updated model may be partly explained by its equally adverse effect on dementia-free mortality. There is, however, an interaction between consumption of beer and spirits in the updated model, giving rise to a significant excess risk of dementia among those who consumed spirits but not beer (data not shown). This observation is difficult to interpret with the available data and may reflect underlying aspects of beer and liquor consumption, for example, social factors.

A protective association between moderate consumption of wine and dementia or Alzheimer's disease has been found in earlier studies that included both men and women (1, 3, 6, 10). In one study,^[7] a seemingly U-shaped relation between alcohol and dementia turned out to be an inverse relation for women but U-shaped for men. Because women tend not only to drink less but also to prefer wine,^[5,26-28] whereas men often drink higher quantities and prefer beer and spirits, it might be that the protective result for women is a consequence of moderate consumption of wine mainly (as supported by our findings), and the increased risk for high intake in males may reflect consequences of predominantly beer and spirits. The reduced risk of dementia for moderate consumption of alcohol for a female cohort^[11] could be due to predominant consumption of wine rather than other types of alcohol. The same applies to a Swedish study,^[2] finding a significant risk reduction for dementia of 50 percent for moderate intake of alcohol within an 82 percent female cohort. One Finnish report^[8] of an increased risk for dementia with increasing alcohol consumption also stated that the female participants were most likely to be infrequent or nondrinkers, while frequent drinkers were mostly male, and that the most typical drink at that time was beer and distilled liquor, which suggests that, again, the observed increased risk for dementia may be due to overconsumption of spirits or beer within the male population. Our finding that alcohol irrespective of type is not predictive of dementia because of opposite trends of wine and spirits underscores the necessity to differentiate between the types of alcohol as observed in earlier studies. Moreover, it is important that mixed gender studies stratify by gender because different drinking patterns may promote one type (and amount) of alcohol at the expense of the other. The failure to detect differences between types of beverages in the Rotterdam study^[6] might be a consequence of a superposition of male and female cohorts (although adjusted for gender).

The strong difference in the effects of different types of alcoholic beverages seems to suggest that ingredients other than ethanol contribute to a beneficial effect of wine on dementia, such as flavonoids acting as antioxidants^[29] or vasoactive polyphenols,^[30] not typically contained in spirits or beer. In this context, it would be desirable to differentiate red and white wine and to examine dose-response with actual amounts consumed, information which is not available in our study. On the other hand, we observe that wine-only drinkers tend to consume wine less often

than those who also drink other kinds of alcohol. In this way, wine-only drinkers could be viewed as the ones who consume the moderate quantities of ethanol beneficial for health, while the others may consume larger quantities; negative consequences of ethanol may outweigh the positive effects of healthy ingredients. This aspect is, however, difficult to distinguish from the positive effect of a generally healthier lifestyle that is often ascribed to wine drinkers and could include healthy diet, less smoking, physical activity, social contacts, and so on^[31-33] -- factors that are likely to reduce the risk for dementia.

A previous report^[19] of an interaction between smoking and alcohol included as a conclusion that smoking may reduce the risk for dementia among drinkers. In this study, the interactions were significant only for wine and smoking and only if updated until 1980-1981. A stratified analysis, however, showed that the protective association between wine and dementia was very strong in the subgroup of those who smoked at the time of the baseline examination in 1968-1969 (HR = 0.4, 95 percent CI: 0.2, 0.7) and that it was weaker and nonsignificant among the nonsmokers. Contrary to Tyas et al.,^[19] we found that smoking is a risk factor also for drinkers, including those who report use of wine at baseline (HR = 1.7, 95 percent CI: 1.0, 2.8). On the basis of this, one may conjecture that a protective effect of wine may at least partly consist of reducing the adverse effects of smoking, most probably because of ingredients other than ethanol. If, for instance, antioxidants proved to be important, it could be concluded that the existence of free radicals or oxidative stress (increased among smokers) is important in the pathogenesis of dementia.^[34,35] The significance of protection against dementia among smokers could also be a consequence of higher consumption of wine by smokers compared with nonsmokers, which is difficult to estimate because the amount of alcohol intake is unknown.

Among the limitations of this study, the lack of information about the amount of intake of the different alcoholic beverages is the most serious one. Together with the problem of underreporting of alcohol intake and the difficulty to avoid reverse causation, it prevents the investigation of a dose-response relation. Another shortcoming is the lack of knowledge about the type of wine and other dietary sources of antioxidants as well as other sources of free radicals. Despite these limitations, the inverse associations with wine in the various updated models are robust and consistent with earlier research.

In summary, the fact that we do not observe a significant association between total intake of alcoholic beverages and dementia may be a consequence of the opposing trends of wine and spirits described in this article. The relative strength of the association between wine and dementia in smokers compared with nonsmokers is an observation that requires further investigation. This includes subtypes of dementia with Alzheimer's disease and vascular dementia being the most common, which will become increasingly feasible as the cohort ages and the number of incident cases increases. Additionally, it will be important to study the association between alcoholic beverages and dementia in male cohorts, where consumption of beer and spirits is expected to have a higher prevalence than among women.

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Authors and Disclosures

K. Mehlig,¹ I. Skoog,² X. Guo,² M. Schütze,¹ D. Gustafson,² M. Waern,² S. Östling,² C. Björkelund¹ and L. Lissner¹

¹ Department of Public Health and Community Medicine/Primary Health Care, Sahlgrenska Academy at Göteborg University, Göteborg, Sweden

² Neuropsychiatric Epidemiology Unit, Section of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy at Göteborg University, Göteborg, Sweden

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Reprint Address

Kirsten Mehlig, Department of Public Health and Community Medicine/Primary Health Care, Sahlgrenska Academy at Göteborg University, Box 454, SE-405 30 Göteborg, Sweden (e-mail: kirsten.mehlig@gu.se)

Abbreviation Notes

CI = confidence interval; HR = hazard ratio

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