Changes in Alcohol Consumption and Subsequent Risk of Type 2 Diabetes in Men

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OBJECTIVE—The objective of this study was to investigate the association of 4-year changes in alcohol consumption with a subsequent risk of type 2 diabetes.

RESEARCH DESIGN AND METHODS—We prospectively examined 38,031 men from the Health Professionals Follow-Up Study who were free of diagnosed diabetes or cancer in 1990. Alcohol consumption was reported on food frequency questionnaires and updated every 4 years.

RESULTS—A total of 1,905 cases of type 2 diabetes occurred during 428,497 person-years of follow-up. A 7.5 g/day (approximately half a glass) increase in alcohol consumption over 4 years was associated with lower diabetes risk among initial nondrinkers (multivariable hazard ratio [HR] 0.78; 95% CI: 0.60–1.00) and drinkers initially consuming <15 g/day (HR 0.89; 95% CI: 0.83–0.96), but not among men initially drinking ≥15 g/day (HR 0.99; 95% CI: 0.95–1.02; $P_{\text{interaction}} < 0.01$). A similar pattern was observed for levels of total adiponectin and hemoglobin A_{1c}, with a better metabolic profile among abstainers and light drinkers who modestly increased their alcohol intake, compared with men who either drank less or among men who were already moderate drinkers and increased their intake. Likewise, compared with stable light drinkers (0–4.9 g/day), light drinkers who increased their intake to moderate levels (5.0–29.9 g/day) had a significantly lower risk of type 2 diabetes (HR 0.75; 95% CI: 0.62–0.90).

CONCLUSIONS—Increases in alcohol consumption over time were associated with lower risk of type 2 diabetes among initially rare and light drinkers. This lower risk was evident within a 4-year period following increased alcohol intake. ***Diabetes*** **60: 74–79, 2011**

Alcohol consumption has been consistently associated with a reduced risk of type 2 diabetes compared with abstention or excessive consumption (1,2). Most prospective studies measure alcohol consumption at only one point in time which assumes intake is fairly stable over time. However, alcohol consumption is dynamic, especially over longer periods of follow-up (3). Importantly, changes in alcohol consumption over time have been associated with subsequent changes in risk of cardiovascular diseases (4–6) and mortality (7), although some inconsistency exists (8,9). Variability in intake over time thus highlights the constraints of single measures of alcohol consumption.

To our knowledge, no observational studies have examined the association between changes in alcohol consumption over time and future risk of type 2 diabetes, despite the importance of such studies both in assessing the robustness of the alcohol-diabetes association and in addressing a topic of direct clinical importance—what happens when individuals adopt or cease drinking? Short-term randomized trials of alcohol have shown changes in insulin sensitivity and adiponectin concentrations within 6 to 8 weeks, suggesting that changes in subsequent risk of diabetes could plausibly occur with a short latency (10–12). Therefore, we attempted to examine whether initiation of light to moderate alcohol consumption is associated with a lower subsequent risk of type 2 diabetes, and likewise whether a reduction in alcohol consumption is associated with higher type 2 diabetes risk.

To accomplish these aims, we examined men enrolled in the Health Professionals Follow-Up Study (HPFS), an ongoing prospective cohort of men who have repeatedly reported their alcohol consumption over time and in whom validated diagnoses of diabetes have been ascertained for two decades.

RESEARCH DESIGN AND METHODS

The HPFS is a prospective investigation of 51,529 U.S. male health professionals age 40–75 years at baseline in 1986 who returned a mailed questionnaire about diet and medical history. Participants subsequently provided diet, lifestyle, and medical information on biennial questionnaires. We excluded men with missing data on BMI and physical activity at baseline. We also excluded men who had implausible nutritional information (≥70 missing food items or estimated daily energy intake <800 or >4,200 kcal). Furthermore, we excluded men who had died or had been diagnosed with diabetes or cancer (except for those with nonmelanoma skin cancer) before follow-up for these analyses started (i.e., in 1990). After these exclusions, 38,031 participants remained for the analyses.

To assess the association between changes in alcohol intake and biochemical markers of glycemia, we examined a subset of men in this cohort who participated in a nested case-control study of coronary heart disease. In 1994, 18,825 participants provided blood samples. Men who provided samples were somewhat younger, but were otherwise similar to those who did not provide samples. We matched 266 men with incident coronary heart disease until 2000

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and an additional 188 cases from 2000 to 2004 with controls matched for age, date of blood draw, and smoking status on a 1:2 basis, as described previously (13,14). All participants gave written informed consent, and the Harvard School of Public Health Human Subjects Committee Review Board approved the study protocol.

Assessment of alcohol consumption. In 1986, men reported their alcohol consumption on a semiquantitative food frequency questionnaire (FFQ) (15,16) that included separate items for beer, white wine, red wine, and liquor. Participants were asked how often, on average over the previous year, they had consumed each beverage. We calculated total alcohol intake by multiplying the average consumption of each beverage by the published alcohol content of the specified portion size based on periodically updated U.S. Department of Agriculture food composition tables and then summing across beverages (17). The FFQ was administered again every 4 years, with an item for light beer added in 1994. We assessed the validity of self-reported alcohol consumption by comparing estimated alcohol intake from the FFQ with the intake derived from two 7-day dietary records among 127 participants who returned questionnaires in 1986 and 1987 and resided in or near Boston, Massachusetts. The Spearman rank correlation coefficient between alcohol intake estimated from the FFQ and corresponding intake from diet records was 0.86 (18).

Assessment of lifestyle factors. Lifestyle factors were assessed biennially using questionnaires that included questions about BMI, smoking, physical activity, and medical conditions. Participants reported physical activity as the average time engaged in specific activities during the previous year. Reported weights have been shown to correlate well with measured weights (16), and the assessment of physical activity was previously validated (19). We obtained energy intake, coffee consumption, and energy-adjusted intakes of dietary fiber, glycemic load, *trans* fat, and the ratio between polyunsaturated and saturated fat from a semiquantitative FFQ (20). Glycemic load was calculated by multiplying the amount of carbohydrates by the average glycemic index as previously described (21).

Ascertainment of type 2 diabetes. Incident cases of type 2 diabetes were identified by self report and confirmed by a validated supplementary questionnaire detailing symptoms, diagnostic laboratory test results, and diabetes treatment. The diagnosis was confirmed if the participant reported at least one of the following: treatment with insulin or oral hypoglycemic medication, at least one classic symptom (excessive thirst, polyuria, weight loss, or hunger) plus elevated plasma glucose level, or at least two elevated plasma glucose concentrations on two different occasions in the absence of symptoms. Elevated plasma glucose concentration was defined as at least ≥140 mg/dl (≥7.8 mmol/l), plasma glucose ≥200 mg/dl (≥11.1 mmol/l) nonfasting, or plasma glucose ≥200 mg/dl (≥11.1 mmol/l) after ≥2 h during an oral glucose tolerance test before 1998; for cases diagnosed in 1998 and later, the fasting plasma glucose threshold was lowered to ≥126 mg/dl (≥7.0 mmol/l) (22). The validity of self-reported diabetes has been confirmed with medical record reviews in a sample (23).

Measurement of biochemical variables. Blood samples were collected in liquid EDTA tubes, placed on ice packs, stored in styrofoam containers, returned to our laboratory via overnight courier, and centrifuged and aliquoted for storage in liquid nitrogen freezers (−130°C or colder). Plasma total adiponectin concentrations were measured by competitive radio-imunoassay (Linco Research, St. Charles, Mo) for cases and controls ascertained through 2000 (n = 798). Hemoglobin A_{1c} (A1C) concentrations were measured by turbidimetric immunoinhibition for cases and controls through 2004 (n = 1,365).

Statistical analysis. Each individual contributed person-time from the return of the 1990 questionnaire to the date of diagnosis of type 2 diabetes, date of diagnosis of cancer or death, or January 31, 2006, whichever came first. We used Cox proportional hazards models to calculate hazard ratios (HR) and 95% CI. We used change in alcohol consumption updated every 4 years as a time-varying covariable, using an Anderson-Gill data structure (24). Thus, we used the change in alcohol consumption between the 1986 and 1990 questionnaires to determine the risk for type 2 diabetes during the period from 1990 to 1994, the change in alcohol consumption based on the 1990 and 1994 questionnaires for the period from 1994 to 1998, and so on. In these analyses, men contributed person-time only during each 4-year period in which they provided data on alcohol consumption. We skipped contributions of person-time for individuals with missing information on alcohol consumption during follow-up for that specific period. In multivariate models, we adjusted for age (five categories), BMI (eight categories: <23.0, 23.0–23.9, 24.0–24.9, 2.5–26.9, 2.7–28.9, 29.0–30.9, 31.0–34.9, or ≥35.0 kg/m^2), physical activity (quintiles), smoking status (never, former, current 1–14 cigarettes/day, current 15–24 cigarettes/day or current ≥25 cigarettes/day), family history of type 2 diabetes (yes or no), incident and prevalent cardiovascular disease (stroke, myocardial infarction, coronary artery bypass surgery, or angina), hypertension, and hypercholesterolemia, dietary glycemic load, fiber intake, *trans* fat intake, ratio of polyunsaturated to saturated fat (all four in quintiles and energy-adjusted), coffee intake (quintiles), and total energy intake (continuous). All variables were treated as time-varying covariates in our models. Linear trends across (change in) alcohol consumption categories were tested by treating the median value of each category as a continuous variable.

Concentrations of total adiponectin and A1C per 7.5 g/day increment in alcohol intake over 4 years (i.e., 1990–1994) were calculated with a mixed analysis of variance model that included the same terms as the Cox regression model and a term for case-control status with clustering on case-control triads. The models were stratified by alcohol intake in 1990. For these analyses, we excluded men with missing data on alcohol intake and with a history of type 2 diabetes in 1994, leaving 697 and 1,188 men for the adiponectin and A1C analyses, respectively.

RESULTS

In 1990, the first update on alcohol consumption, most subjects (55%) reported only modest changes in alcohol consumption compared with 4 years earlier (Table 1). The median change in alcohol consumption was 0 g/day. No consistent trends were seen in potential confounders among men who decreased or increased their alcohol consumption.

Overall alcohol consumption and risk of type 2 diabetes. During 428,497 person-years of follow-up among 38,031 men, we documented 1,905 cases of newly diagnosed type 2 diabetes. We first examined alcohol consumption in grams per day and risk of diabetes. Compared with abstention, HRs of type 2 diabetes after multivariable adjustment were 1.04 (95% CI: 0.92–1.18) for alcohol consumption of 0.1 to 4.9 g/day, 0.81 (95% CI: 0.69–0.94) for 5 to 9.9 g/day, 0.70 (95% CI: 0.59–0.84) for 10 to 14.9 g/day, 0.71 (95% CI: 0.60–0.84) for 15 to 29.9 g/day, 0.54 (95% CI: 0.44–0.67) for 30 to 49.9 g/day, and 0.50 (95% CI: 0.36–0.69) for alcohol consumption of 50 or more grams per day ($P_{trend} < 0.0001$).

Four-year changes in amount of alcohol intake and risk of type 2 diabetes. The effect of a 7.5 g/day (approximately half a glass) change in alcohol intake on subsequent change in diabetes risk differed between initial alcohol consumption levels ($P_{interaction} < 0.01$) (Table 2). Such an increment had the largest association with risk on men who were initially nondrinkers at the beginning of any 4-year period of change (HR 0.78; 95% CI: 0.60–1.00). This was followed by men who initially consumed <1 glass/day (HR 0.89; 95% CI: 0.83–0.96). A 4-year change in alcohol intake was not associated with subsequent diabetes risk among men who consumed ≥1 glass/day at the beginning of the 4-year period (HR 0.99; 95% CI: 0.95–1.02).

In a sensitivity analysis, we repeated the analysis, excluding men with any missing alcohol data during follow-up. This slightly strengthened the association of changes in alcohol intake with risk among initial nondrinkers (HR 0.71; 95% CI: 0.52–0.98), but had little effect on initial <1 glass/day drinkers (HR 0.89; 95% CI: 0.82–0.96) and ≥1 glass/day drinkers (HR 0.99; 95% CI: 0.95–1.04). To minimize potential bias related to total abstention from alcohol due to poor health, we also excluded all current nondrinkers at the beginning of each follow-up period, with little effect on the HRs (data not shown). Finally, we examined whether changes in BMI and physical activity over time could partially explain the observed relation. We assessed this effect by including levels of BMI and physical activity assessed at both the beginning and end of each 4-year period used to calculate change in alcohol consumption, while retaining all other variables in the model. This did not materially influence our results (results not shown). The association between changes in alcohol consumption

TABLE 1
Characteristics according to 4-year change in alcohol consumption in 1990 stratified by initial intake in 1986 (n = 33,073)*

Initial alcohol consumption (g/day)	Change in alcohol consumption 4 years later (g/day)				
	Moderate to large decrease (≥7.5)	Small to moderate decrease (2.5–7.49)	No change/ relatively stable (±2.49)	Small to moderate increase (2.5–7.49)	Moderate to large increase (≥7.5)
Number drinks/day (0)					
Number (% of total) of participants	—	—	6,868 (20.8%)	309 (0.9%)	170 (0.5%)
Age (years)	—	—	57.8	56.7	59.4
BMI (kg/m^2)	—	—	25.6	25.5	25.7
Weight gain from 1986 to 1990 (lb)	—	—	1.2	1.6	3.0
Alcohol consumption in 1986 (g/day)	—	—	0.0	0.0	0.0
Alcohol consumption in 1990 (g/day)	—	—	0.2	4.1	21.5
Physical activity (METs/week)	—	—	35.8	36.1	38.0
Current smoker (%)	—	—	3.4	3.7	5.0
Family history of diabetes (%)†	—	—	15.9	14.3	11.2
Cardiovascular disease (%)‡	—	—	11.4	13.9	12.9
Hypertension (%)	—	—	25.6	26.3	25.3
Hypercholesterolemia (%)	—	—	28.4	35.9	29.2
<1 drink/day (0.1–14.9)					
Number (% of total) of participants	791 (2.4%)	3,517 (10.6%)	9,321 (28.2%)	2,391 (7.2%)	1,190 (3.6%)
Age (years)	58.9	57.3	57.1	56.7	57.6
BMI (kg/m^2)	25.5	25.5	25.5	25.4	25.7
Weight gain from 1986 to 1990 (lb)	−0.2	1.0	1.3	1.6	1.7
Alcohol consumption in 1986 (g/day)	12.1	8.3	4.9	6.7	8.0
Alcohol consumption in 1990 (g/day)	2.3	3.9	4.7	11.2	24.5
Physical activity (METs/week)	37.8	38.6	36.1	40.3	38.4
Current smoker (%)	5.6	3.5	4.0	4.4	5.4
Family history of diabetes (%)†	14.9	15.6	16.1	15.3	14.5
Cardiovascular disease (%)‡	10.9	11.6	11.3	10.9	10.1
Hypertension (%)	27.0	24.0	23.6	24.2	27.0
Hypercholesterolemia (%)	32.3	30.9	30.7	31.2	33.2
≥1 drink/day (≥15.0 g/day)					
Number (% of total) of participants	3,256 (9.8)	1,498 (4.5)	2,118 (6.4)	665 (2.0)	979 (3.0)
Age (years)	58.7	57.7	58.8	57.7	58.4
BMI (kg/m^2)	25.7	25.4	25.4	25.2	25.6
Weight gain from 1986 to 1990 (lb)	1.1	1.5	1.6	1.5	1.9
Alcohol consumption in 1986 (g/day)	37.9	26.0	30.2	27.7	28.5
Alcohol consumption in 1990 (g/day)	16.4	21.2	30.1	32.2	49.2
Physical activity (METs/week)	39.5	40.2	38.1	39.8	39.7
Current smoker (%)	7.5	5.5	8.6	5.4	9.4
Family history of diabetes (%)†	13.4	15.4	13.7	12.2	13.5
Cardiovascular disease (%)‡	11.4	10.9	10.3	9.5	8.8
Hypertension (%)	31.0	26.5	27.8	24.2	33.8
Hypercholesterolemia (%)	32.4	32.2	31.4	28.2	33.1

*Data are given as mean for continuous variables, except alcohol consumption (median) and percentage for categorical variables and are age-adjusted, except for age. BMI was calculated as the weight in kilograms divided by height in meters squared. MET, metabolic equivalent. Dash indicates data not available. †History of diabetes with onset at age ≥30 years in immediate family. ‡Cardiovascular disease comprises stroke, myocardial infarction, coronary artery bypass surgery, and angina pectoris.

and diabetes risk among the three strata of initial drinkers did not substantially differ by subgroups of BMI. The multivariable-adjusted relative risks for diabetes associated with a 7.5 g/day increase in alcohol among initial nondrinkers, <1 and ≥1 drink/day consumers were 0.66 (95% CI: 0.42–1.04), 0.85 (95% CI: 0.76–0.94) and 0.98 (95% CI: 0.93–1.04) for men with a BMI <28.3 kg/m^2 (median BMI of incident diabetes cases) and 0.86 (95% CI: 0.65–1.14), 0.92 (95% CI: 0.84–1.02) and 0.99 (95% CI: 0.93–1.04) for men with a BMI of ≥28.3 kg/m^2, respectively ($P_{\text{interaction}}$ = 0.48).

Four-year changes in type of drinker and risk of type 2 diabetes. Compared with stable light drinkers (0–4.9 g/day), initial light drinkers who increased their intake to moderate levels (5.0–29.9 g/day) had a significantly lower risk of type 2 diabetes (HR 0.75; 95% CI: 0.62–0.90) (Table 3). Conversely, moderate drinkers who reduced their intake to none or light did not have a lower risk of diabetes (HR 1.09; 95% CI: 0.92–1.30) after multivariable adjustments compared with stable light drinkers. However, stable moderate drinkers had significantly lower risk of diabetes compared with stable light drinkers (HR 0.74; 95% CI: 0.65–0.83). Furthermore, all current moderate alcohol consumption categories were associated with at least a 25% lower risk of type 2 diabetes compared with stable light drinkers, regardless of initial alcohol consumption category ($P_{\text{interaction}}$ = 0.55). No further risk reductions were observed among initial light or moderate drinkers who increased their consumption ≥30.0 g/day. Similar results were obtained when we reanalyzed the data ex-

TABLE 2
Hazard ratios of type 2 diabetes according to updated 4-year changes in alcohol intake stratified by initial intake (n = 38,031)

Initial alcohol consumption (g/day)	Change in alcohol consumption 4 years later (g/day)					
	Moderate to large decrease (≥7.5)	Small to moderate decrease (2.5–7.49)	No change/ relatively stable (± 2.49)	Small to moderate increase (2.5–7.49)	Moderate to large increase (≥7.5)	Per 7.5 g/day increase
Non (0)						
Multivariable-adjusted*	—	—	1.00 [Reference]	0.84 (0.55–1.30)	0.63 (0.35–1.13)	0.78 (0.60–1.00)
Person-years	—	—	89,008	5,170	3,229	
Number of cases	—	—	448	22	13	
<1 drink/day (0.1–14.9)						
Multivariable-adjusted*	1.22 (0.90–1.66)	1.06 (0.89–1.26)	1.00 [Reference]	0.76 (0.63–0.91)	0.84 (0.68–1.03)	0.89 (0.83–0.96)
Person-years	7,446	33,804	113,714	42,162	26,600	
Number of cases	45	165	534	145	112	
≥1 drink/day (≥15.0)						
Multivariable-adjusted*	1.18 (0.91–1.53)	1.14 (0.83–1.56)	1.00 [Reference]	1.04 (0.72–1.51)	0.90 (0.66–1.24)	0.99 (0.95–1.02)
Person-years	33,771	17,464	26,786	11,250	18,093	
Number of cases	155	67	94	40	65	
$P_{interaction}$†						0.004

Dash indicates data not available. *Multivariable-adjusted hazard ratios (95% CIs) were calculated using Cox proportional hazards model and adjusted for age (5 categories), BMI (8 categories), physical activity (quintiles), smoking status (never, former, current 1–14 cigarettes/day, current 15–24 cigarettes/day, or current ≥25 cigarettes/day), family history of type 2 diabetes, incident and prevalent cardiovascular disease (stroke, myocardial infarction, coronary artery bypass surgery, or angina), hypertension, and hypercholesterolemia, dietary glycemic load (quintiles), fiber intake (quintiles), *trans* fat intake (quintiles), ratio of polyunsaturated fat and saturated fat (quintiles; all energy adjusted), coffee intake (quintiles), and total energy intake (continuous). †$P_{interaction}$ value was derived by adding an interaction term between the 7.5 g/day increment in alcohol consumption (continuous) and initial alcohol consumption (categorical) in the multivariate model.

cluding people who abstained from alcohol or who had missing alcohol data during follow-up (data not shown).

Four-year change in amount of alcohol intake and effect on markers of glycemia. To test the robustness of our findings, we next examined the 4-year change in alcohol consumption from 1990–1994 on markers of glycemia collected in 1994, stratified by initial alcohol consumption in 1990 (Table 4). A similar interaction between change in alcohol and baseline alcohol intake as in the main analysis was observed for levels of total adiponectin and A1C among nondiabetic men. For example, a 7.5 g/day increment in alcohol intake, between 1990–1994, was associated with a 1.2 ± 0.3 μg/ml (mean ± SEM) higher total adiponectin level in 1994 among men who were nondrinkers at baseline, a 0.5 ± 0.3 μg/ml higher adiponectin level among <1 glass/day drinkers, and a 0.6 ± 0.3 μg/ml lower level among ≥1 glass/day drinkers at baseline ($P_{interaction}$ = 0.002). For A1C, the inverse association between change in alcohol intake in 1990–1994 and A1C concentration was also strongest among nondrinkers compared with <1 glass/day drinkers and ≥1 glass/day drinkers in 1990 ($P_{interaction}$ = 0.02).

DISCUSSION

In this large prospective cohort study, we found that 4-year changes in alcohol consumption assessed repeatedly over time were followed by subsequent changes in risk of type 2 diabetes. The lower risk associated with an increase in alcohol consumption was dependent on initial drinking levels, with no benefit associated with increased intake among men already drinking moderately. This pattern of lower risk associated with increased alcohol consumption solely among abstainers and light drinkers was

TABLE 3
Hazard ratios of type 2 diabetes according to updated 4-year changes in initial and current drinking category (n = 38,031)

Initial alcohol drinking category (g/day)	Alcohol drinking category 4 years later (g/day)			
	Light (0–4.9)	Moderate (5.0–29.9)	Heavier (≥30.0)	P_{trend}*
Light (0–4.9)				
Multivariable-adjusted†	1.00 [Reference]	0.75 (0.62–0.90)	0.35 (0.11–1.10)	<0.001
Person-years	169,623	31,723	1,127	
Number of cases	875	125	3	
Moderate (5.0–29.9)				
Multivariable-adjusted†	1.09 (0.92–1.30)	0.74 (0.65–0.83)	0.59 (0.45–0.77)	<0.001
Person-years	27,841	134,942	16,050	
Number of cases	159	496	60	
Heavier (≥30.0)				
Multivariable-adjusted†	0.78 (0.44–1.38)	0.67 (0.52–0.88)	0.50 (0.40–0.63)	0.08
Person-years	2,089	15,036	30,067	
Number of cases	12	65	110	

*P_{trend} values were derived from tests of linear trend across increasing categories of alcohol use by treating the median value of each category as a continuous variable. †Hazard ratios (95% CIs) were calculated using Cox proportional hazards model and adjusted for the covariates listed in Table 2.

TABLE 4
Associations of a 7.5 g/day increment in alcohol consumption from 1990–1994 on subsequent total adiponectin and hemoglobin A_{1c} levels, classified by alcohol consumption in 1990

	Mean increment in glycemic marker per 7.5 g/day increase in alcohol consumption from 1990–1994	
Alcohol consumption in 1990 (g/day)	Total adiponectin (μg/ml)	HbA_{1c} (%)
Non (0)		
Mean increment*	1.2 ± 0.3	−0.04 ± 0.02
Number of participants	151	267
<1 drink/day (0.1–14.9)		
Mean increment*	0.5 ± 0.3	−0.02 ± 0.02
Number of participants	355	610
≥1 drink/day (≥15.0)		
Mean increment*	−0.6 ± 0.3	0.01 ± 0.01
Number of participants	191	311
$P_{interaction}$†	0.002	0.02

*Values are mean increments (± SEM) per 7.5 g/day increment in alcohol consumption over 4 years and were calculated with a mixed ANOVA model that included terms for age, BMI, physical activity, smoking status, family history of type 2 diabetes, hypertension, hypercholesterolemia, cardiovascular disease, dietary glycemic load, fiber intake, *trans* fat intake, ratio of polyunsaturated fat and saturated fat (all energy-adjusted), coffee intake, total energy intake, and case-control status. †$P_{interaction}$ value was derived by adding an interaction term between the 7.5 g/day increment of alcohol consumption (continuous), and initial alcohol consumption in 1990 (categorical) in the mixed ANOVA model.

further supported by associations of change in alcohol intake with total adiponectin and A1C.

Our results extend previous epidemiologic studies that have reported an inverse association between moderate alcohol consumption and the longer term risk of type 2 diabetes (1,2). Recent studies have shown that alcohol consumption is associated with lower risk of type 2 diabetes even among low-risk individuals (lean, active nonsmokers) (25,26) and when adjusted for multiple lifestyle factors based on BMI, physical activity level, smoking habits, and diet quality (27–29). Comparisons of different beverage types generally suggest that ethanol rather than the type of alcoholic beverage is responsible for this association (23,30). Furthermore, variation in the *ADH1C* gene, a gene that encodes the alcohol dehydrogenase 1C enzyme that oxidizes ethanol, appears to modify the association between alcohol consumption and type 2 diabetes risk, providing further epidemiologic support for the causal nature of the relationship between alcohol consumption and diabetes risk (31).

The plausibility of these observational results is supported by short-term randomized controlled trials on changes in alcohol consumption (25–30 g/day) (10,11). In these studies, moderate drinking significantly improved insulin sensitivity after 6 to 8 weeks. Also, clinical trials in a variety of populations have shown that alcohol consumption increases adiponectin (11,12,32,33), a hormone secreted by adipose tissue that appears to improve insulin sensitivity. Indeed, adiponectin appears to explain ~25 to 30% of the inverse association between alcohol consumption and type 2 diabetes in women (34) Finally, longer-term randomized trials of 3 to 12 months among diabetic individuals have shown that assignment to alcohol consumption lowers fasting glucose (35) and A1C (36).

These findings from randomized trials suggest that the effects of alcohol intake on glycemia may have a short latency, as they appear within weeks of assignment to alcohol. Our results are consistent with this finding, as the more beneficial metabolic parameters and the lower subsequent risk of diabetes associated with an increase in alcohol consumption were observed in the next follow-up period. Our results further imply that the effect may be transient, as a decrease in consumption was accompanied by a modest increase in risk. Finally, our results highlight that any benefit of alcohol on glycemia and risk of diabetes is restricted to moderate drinking, and increases among those already drinking moderately confer no lower risk.

Several limitations warrant consideration. We relied on self-reported alcohol consumption. However, validation studies in these health professionals comparing self-administered questionnaire with intake assessed by detailed diet records showed correlations above 0.8 and mean and SD values almost identical by the two methods (18). Second, we do not know why men changed their intake. However, we restricted our analysis to men with no history of diabetes and cancer and adjusted for cardiovascular disease, hypertension, and hypercholesterolemia. Third, we do not know when during each 4-year interval the change in alcohol consumption occurred, a limitation that reflects the fact that the administered FFQ specifically queries alcohol consumption in the previous year. Therefore, we cannot definitely evaluate whether the change in intake on type 2 diabetes risk is immediate. We do know, however, that the change in alcohol preceded the diagnosis of diabetes. Fourth, we performed our analysis in male health professionals, and results may therefore not be readily generalizable to other populations. However, within this homogenous group of highly educated men, potential confounding because of social economic status is substantially reduced. Fifth, we could not evaluate changes in beverage types, given the more limited use of any particular beverage compared with total alcohol use. We previously found that all beverage types were inversely associated with type 2 diabetes in this cohort (23). Finally, as with any observational study, unaccounted factors associated with changes in alcohol consumption and risk of type 2 diabetes may introduce an unknown degree of residual confounding, despite the substantial number of potentially confounding factors we included.

In conclusion, in this cohort of male health professionals, increases in alcohol consumption over time were associated with correspondingly lower 4-year risk of type 2 diabetes, although this association was limited to rare and light drinkers at baseline. This suggests that the effect of alcohol consumption on diabetes risk may have a relatively short latency time but may also be transient and reversible. Furthermore, individuals who already consume alcohol in moderation may not further benefit from increased consumption. Although these results may suggest that some individuals should consider adopting regular and moderate intake of alcohol, our findings—even if proven to be causal—are limited to a single outcome of diabetes. Decisions and recommendations about changes in alcohol consumption should, as with alcohol consumption in general, consider the full range of risks and benefits to an individual, including the consistent harms to the individual and society of drinking that exceeds recommended limits.

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M.M.J. contributed to the design of the study, analyzed and interpreted the data, and drafted the first manuscript. S.E.C. contributed to the design of the study and analyzed and interpreted the data. K.J.M. contributed to the design of the study, analyzed and interpreted the data, helped to draft the first manuscript, and supervised the study. F.B.H. acquired data, obtained funding, and supervised the study. H.F.J.H. contributed to the design of the study, obtained funding, and supervised the study. E.B.R. contributed to the design of the study, acquired data, analyzed and interpreted the data, obtained funding, and supervised the study. All authors critically reviewed the manuscript for important intellectual content and approved the final version.

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