Moderate Alcohol Consumption Lowers the Risk of Type 2 Diabetes

A meta-analysis of prospective observational studies

LANDO L.J. KOPPES, PHD[1,2]
JACQUELINE M. DEKKER, PHD[1]
HENK F.J. HENDRIKS, PHD[3]
LEX M. BOUTER, PHD[1]
ROBERT J. HEINE, MD, PHD[1,4]

OBJECTIVE — This meta-analysis was undertaken to obtain insight regarding the shape and strength of the relationship between alcohol consumption and the risk of type 2 diabetes, the effects of adjustment for confounders, and the effect of modification by type 2 diabetes definition, sex, and BMI.

RESEARCH DESIGN AND METHODS — The 15 original prospective cohort studies that were included comprise 11,959 incident cases of type 2 diabetes in 369,862 individuals who, on average, were followed for 12 years.

RESULTS — After pooling the data, a U-shaped relationship was found. Compared with nonconsumers, the relative risk (RR) for type 2 diabetes in those who consumed ≤6 g/day alcohol was 0.87 (95% CI 0.79–0.95). For the moderate consumption ranges of 6–12, 12–24, and 24–48 g/day, RRs of 0.70 (0.61–0.79), 0.69 (0.58–0.81), and 0.72 (0.62–0.84) were found, respectively. The risk of type 2 diabetes in heavy drinkers (≥48 g/day) was equal to that in nonconsumers (1.04 [0.84–1.29]). In general, nonsignificant trends for larger RR reduction associated with moderate alcohol consumption were observed for women compared with men, for crude compared with multivariate-adjusted analyses, and for studies that used self-reports instead of testing for type 2 diabetes definition. No differences in RR reductions were found between individuals with low or high BMI.

CONCLUSIONS — The present evidence from observational studies suggests an ~30% reduced risk of type 2 diabetes in moderate alcohol consumers, whereas no risk reduction is observed in consumers of ≥48 g/day.

Diabetes Care 28:719–725, 2005

The prevalence of type 2 diabetes is rising to epidemic proportions. Between 2000 and 2030, a 37% increase in the worldwide prevalence of diabetes is expected (1). Next to the aging of the population, the lack of physical activity and high-energy intake leading to overweight and obesity have been shown to be largely responsible for this epidemic, showing the importance of lifestyle factors for type 2 diabetes risk (2).

Alcohol consumption is a lifestyle factor that also has been suggested to be relevant with respect to the risk of type 2 diabetes. Several studies on the relationship between alcohol consumption and incident type 2 diabetes have been published during the last few years. Two narrative reviews on this topic suggested that moderate alcohol consumption is associated with a decreased incidence of type 2 diabetes but were inconclusive about the magnitude of this decreased incidence and the incidence associated with high levels of alcohol consumption (3,4). Furthermore, these reviews suggested that sex, BMI, and the mode of type 2 diabetes definition (self-report versus objective testing) may be important confounders or modifiers of the relationship. The objective of the present study, therefore, is to perform a meta-analysis on the published data and to calculate pooled estimates with respect to these questions on the relationship between alcohol consumption and the risk of type 2 diabetes.

RESEARCH DESIGN AND METHODS

— Articles included were found through a PubMed search of literature published between 1966 and July 2004. The search resulted in articles that included the text words "(alcohol OR ethanol) AND diabetes AND (inciden* OR (new AND cases))" but that did not include the text word "placebo," or the subject heading "drug therapy." In addition, randomized controlled trials, editorials, letters to the editor, meta-analyses, and review articles were not included. Titles and abstracts of the resulting publications were screened for articles that are possibly of interest for our meta-analysis. The references in these articles and in relevant reviews were checked for additional studies of interest. Included were original peer-reviewed publications on observational cohort or nested case-control studies on the relationship between alcohol consumption and incident type 2 diabetes. Given the presumed nonlinear relationship, a point estimate and an estimate of variability of type 2 diabetes risk needed to be presented for at least two alcohol consumption categories compared with a third reference category (or data should be given from which this could be calculated). Alcohol consumption categories needed to be quantifiable in grams per day.

For studies that reported results from various analyses including more or fewer covariates, the estimates based on the mod-

From the [1]Institute for Research in Extramural Medicine (EMGO Institute), VU University Medical Center, Amsterdam, the Netherlands; the [2]Department of Public and Occupational Health, VU University Medical Center, Amsterdam, the Netherlands; the [3]Department of Nutritional Physiology, TNO Nutrition and Food Research, Zeist, the Netherlands; and the [4]Department of Endocrinology, VU University Medical Center, Amsterdam, the Netherlands.

Address correspondence and reprint requests to Lando L.J. Koppes, PhD, VU University Medical Center, EMGO Institute, Van der Boechorststraat 7, 1081 BT Amsterdam, Netherlands. E-mail: l.koppes@vumc.nl.

Received for publication 30 July 2004 and accepted in revised form 8 November 2004.

el that included the most potential confounders (e.g., age, sex, smoking, physical activity) and that excluded putative intermediate variables (fasting insulin or HDL cholesterol levels) were abstracted.

For studies that only reported ranges of alcohol consumption for the categories used, the mean of the lower and upper limits was used as the average consumption for that range, and 1.5 times the lower limit was assigned as the average consumption in the highest category (where no upper limit was given). The factor 1.5 was based on the information in included studies that reported the average consumption in addition to the lower limit of the highest consumption category. The averages of the consumption ranges that were used in a study were assigned to one of six alcohol categories that were used in this meta-analysis: 0 (reference), <6, 6–12, 12–24, 24–48, and ≥48 g/day. These alcohol categories were chosen because it resulted in about an equal number of independent observations within each stratum. A standard drink contains ~12 g alcohol in the U.S./Canada, 10 g in Europe/Australia, and 21 g in Japan. Stratified analyses were performed because we were unable to find software to perform a meta-regression analysis that takes into account the fact that multiple observations from one study are not independent and that can incorporate the weight (inverse of variance) of the observations properly. Within the strata chosen, multiple observations from a single study were rare.

Odds ratios, relative risks (RRs), and hazard ratios that are used in the original publications were interpreted to reflect RRs. Natural logarithms of the RR estimates for each level of alcohol consumption from the individual studies were used to normalize the data. Natural logarithms of the reported CI limits were used to calculate the standard errors of the log RR estimates of the included studies. If the original study did not use the nonconsumers as a reference, the RRs were recalculated relative to the nondrinkers, assuming equal variance of the RR estimates when using the reported category or the nondrinker category as a reference.

Pooled RR estimates were calculated within each of the alcohol categories. Because the risk estimates differed more across studies than expected from the sampling error within studies, random-effects models were used to combine the reported data from these studies (5). If a study reported more than one RR within one of our six relatively small alcohol categories, one pooled RR was calculated for the study in question per alcohol category before pooling the RRs of the studies in that category.

To examine potential publication bias, separate funnel plots were drawn for the alcohol categories because the method of assessing funnel plot asymmetry assumes one overall RR. In this meta-analysis, however, it was expected that different RRs would be found for different alcohol consumption categories. For each funnel plot, the degree of asymmetry was visually inspected and quantitatively tested with a method modified from Egger et al. (6) that uses the slope instead of the intercept of a fitted regression line.

In addition to the multivariate-adjusted RRs, crude RRs were calculated for studies that reported the number of incident type 2 diabetic cases and noncases (or person-years) per alcohol category. To investigate the effect of confounding, the RRs from these crude data were pooled and compared with the pooled multivariate-adjusted RRs from the same studies. The RRs reported in studies that used self-reports to determine a subject's type 2 diabetes status were compared with the RRs reported in studies that used biochemical testing of type 2 diabetes status. Sex, BMI, and type of beverage have been mentioned as putative modifiers of the relationship between alcohol consumption and the risk of type 2 diabetes. We therefore calculated and compared pooled RRs for men and women. From studies that reported RR estimates for more than one BMI stratum, the RRs reported for the highest strata were pooled and compared with the pooled RRs that are reported for the lowest BMI strata. Modification by type of beverage was not analyzed because only two studies reported alcohol consumption category–specific RR estimates for the different types of beverages (7,8). Student's *t* tests were used to study differences in pooled RRs between the crude and adjusted data, between men and women, and between high and low BMI.

RESULTS — Twenty-eight publications on the relationship between alcohol consumption and the incidence of type 2 diabetes were found after reading titles and abstracts of the 482 hits from the PubMed search and after reference checking. Independent assessment of these publications by L.L.J.K. and J.M.D. with respect to the eligibility for the meta-analysis did not result in disagreement on any publication. For three studies on which multiple reports were published, the most recent publication was included while the others were excluded (9–12). Nine studies were not included because their alcohol consumption data were not quantifiable in grams per day (13–15) or because of incompleteness with respect to alcohol category–specific risk estimates (16–21). The search did not yield any nested case-control study that met the inclusion criteria, whereas 15 relevant cohort studies were identified (7,8,22–34).

Table 1 shows characteristics of the 15 included studies. In total, our meta-analysis comprises 11,959 incident cases of type 2 diabetes in 369,862 individuals who, on average, were followed for 12.0 years. All studies were published in peer-reviewed journals. Four studies included both male and female subjects, eight studies included only men, and three studies only women. In seven studies, all participants were tested for the presence of type 2 diabetes; seven others relied on self-reported diagnoses, while one study used record linkage with national registers. The included studies differed considerably with respect to the number of confounders adjusted for (range 0–15 confounders). In 8 of the 15 studies (7,8, 22,24,29–32), various models including more or fewer confounders were used to calculate the RR of type 2 diabetes for the alcohol categories used. The confounders incorporated in the models that were chosen to be included in this meta-analysis are reported in Table 1.

Figure 1 shows the scatter plot of the RRs of type 2 diabetes by alcohol consumption (abstinence is the reference) as reported in the 15 included studies. Figure 1 indicates considerable heterogeneity between the observations. The areas of the circles differ substantially, indicating that certain estimates add more statistical power than others. The random-effect pooled RRs that are also shown in Fig. 1 indicate a U-shaped relationship between alcohol consumption and the risk of type 2 diabetes. The lowest risks were observed in alcohol drinkers of 6–48 g/day. The risk of type 2 diabetes in drinkers of ≥48 g/day was equal to that of nonconsumers. No publication bias was suspected after visual inspection or statistical

Table 1 —*Characteristics of the included studies*

Reference	Study name, country	Population	Age range at baseline (years)	Sex	No. at risk with follow-up	No. of incident cases of diabetes	Follow-up (years)	Diabetes definition	Confounders adjusted for
Lee et al. (34)	Iowa Women's Health Study, U.S.	Population based	55–69	Women	35,698	1,921	9.3	Baseline and four follow-up self reports	None
Sawada et al. (33)	Tokyo Gas Company Study, Japan	Employees of one company	20–40	Men	4,745	280	13.6	Annual testing	1–6
Carlsson et al. (32)	Finnish Twin Cohort, Finland	Population based	≥18	Men and women	10,856 and 11,664	277 and 297	20.0	Record linkage with national hospital and drug registers	1 and 3
Lee et al. (27)	GGT-study, Korea	Employees of one company	25–55	Men	4,055	83	4.0	Annual testing	None
Nakanishi, Suzuki, and Tatara (28)	Building Company Study, Japan	Office workers of one company	35–59	Men	2,953	370	7.0	Annual testing*	1–4 and 7
Wannamethee et al. (8)	Nurses' Health Study 2, U.S.	Nurses	25–42	Women	109,705	935	10.0	Biennial self-report	1–4 and 7–11
de Vegt et al. (25)	Hoorn Study, the Netherlands	Population based	50–75	Men and women	1,322	131	7.6	Baseline and follow-up testing	1 and 12
Meisinger et al. (28)	MONICA, Germany	Population based	35–74	Men and women	3,052 and 3,114	128 and 85	7.6	Baseline and follow-up self-report	1, 4, and 13
Wannamethee et al. (31)	British Regional Heart Study, U.K.	General practitioners' register	40–59	Men	5,221	198	16.8	Baseline and follow-up self-report	1, 2, 4, 7, 14, and 15
Conigrave et al. (24)	Health Professionals Follow-up Study, U.S.	Health professionals	40–75	Men	46,892	1,571	12.0	Biennial self-report	1–4, 7, 9, 10, and 15–22
Hu et al. (26)	Nurses' Health Study, U.S.	Nurses	30–55	Women	82,393	3,296	16.0	Biennial self-report	1, 3, and 23–25
Kao et al. (7)	ARIC Study, U.S.	Population based	45–64	Men and women	5,423 and 6,838	547 and 569	6.0	Baseline and follow-up testing	1–4, 7, 9, 20, and 26–28
Ajani et al. (22)	Physicians' Health Study, U.S.	Physicians	40–85	Men	20,951	666	12.1	Baseline and follow-up self-report	1–3, 7, 9, and 10
Wei et al. (23)	Cooper Clinic Study, U.S.	Population based	30–79	Men	8,633	149	6.0	Baseline and follow-up testing	1, 3, and 29
Tsumura et al. (30)	Osaka Health Survey, Japan	Employees of one company	35–61	Men	6,362	456	9.7	Biennial testing	1–4, 7, and 30

*Impaired fasting glucose also included in diabetes definition. 1, age; 2, smoking; 3, family history of diabetes; 4, BMI; 5, blood pressure; 6, fitness; 7, physical activity; 8, oral contraceptive use; 9, hypertension; 10, hypercholesterolemia; 11, infertility; 12, sex; 13, survey; 14, social class; 15, preexisting coronary heart disease; 16, dietary glycemic load; 17, fiber; 18, *trans* fat; 19, polyunsaturated fat; 20, energy intake; 21, profession; 22, cancer; 23, time; 24, menopausal status; 25, hormone therapy; 26, waist-to-hip ratio; 27, race; 28, education; 29, years of follow-up; 30, fasting plasma glucose.

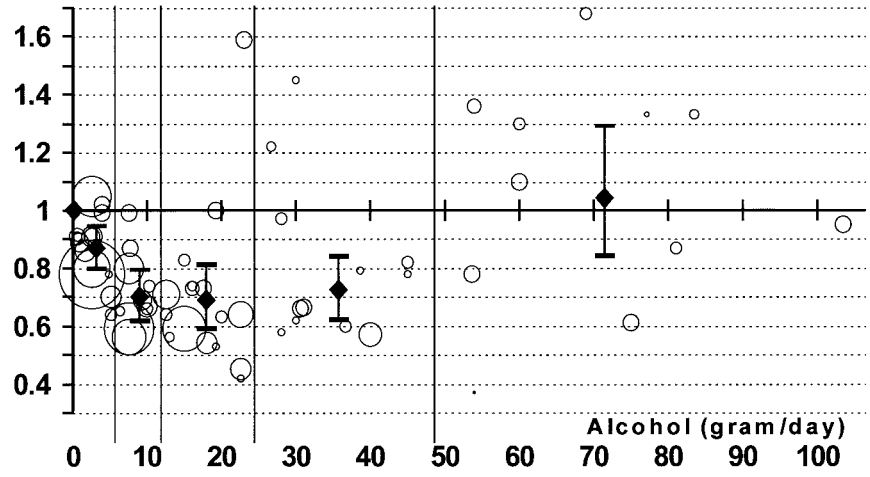

Figure 1—*Scatterplot of the RR estimates of type 2 diabetes reported in the 15 included studies, and the pooled RR estimates with corresponding 95% CIs for five alcohol consumption categories with the nonconsumers as reference category. Each study provides more than one RR estimate. The area of each circle is proportional to the precision of the RR estimate (inverse of its variance).*

testing of the funnel plots drawn for the alcohol consumption categories (graphs not shown).

In 10 of the 15 included studies (7, 8,22–24,26,29–32), the numbers of incident type 2 diabetic cases and noncases (or person-years) were reported per alcohol category in addition to multivariate-adjusted RR estimates. The pooled RRs from these crude data and the pooled multivariate-adjusted RRs are reported in Table 2. The effect of confounding was significant for the lowest alcohol category. Table 2 further indicates that lower RR estimates were found in the studies that used self-reports to assess a subject's type 2 diabetes status (8,22,24,26,28,31,34) than in studies that used glucose testing to define type 2 diabetes (7,23,25,27,29, 30,33).

We further investigated possible modification of the relationship between alcohol consumption and the risk of type 2 diabetes by sex and BMI (Table 2). All but one study (25) gave sex-specific estimates. In women, observations >24 g/day were pooled because only one (imprecise) observation >48 g/day was reported. A significant sex difference was found only for the alcohol consumption range between 6 and 12 g/day. The RRs for women that were found in the other drinking categories were not significantly smaller than those for men. These stratified analyses show that the lower risk of type 2 diabetes of moderate alcohol consumption is significant in both men and women.

Six studies reported results stratified for two or three BMI categories (8,22,26, 29,30,32). The pooled RRs based on these studies show no difference in the RR of type 2 diabetes for low- and high-BMI categories.

CONCLUSIONS — To our knowledge, this is the first meta-analysis on the relationship between alcohol consumption and the risk of type 2 diabetes. It shows a U-shaped relationship with a highly significant ~30% reduced risk of type 2 diabetes in alcohol consumers of 6–48 g/day compared with heavier consumers or abstainers. Fifteen cohort studies on the relationship between alcohol consumption and the risk of type 2 diabetes were retrieved. In the absence of long-term randomized intervention studies, these can be considered the best available evidence.

The lower type 2 diabetes risk in moderate drinkers was consistent over most included studies. Despite this consistency, the risk estimates differed more across studies than was expected from the sampling error within studies. We therefore studied whether multiple adjustment, the type 2 diabetes definition used, and differences between men and women

Table 2 —*RR (95% CI) of type 2 diabetes for alcohol consumption categories for all data, crude and adjusted data, diabetes definition tested and self-reported, men and women, and low and high BMI, with two-sided* **P** *values for differences between subgroups*

	Number of studies	Alcohol consumption categories (g/day)					
		0 (ref.)	<6	6–12	12–24	24–48	>48
All data	15	1	0.87 (0.79–0.95)	0.70 (0.61–0.79)	0.69 (0.58–0.81)	0.72 (0.62–0.84)	1.04 (0.84–1.29)
Crude	10 (w)	1	0.70 (0.59–0.83)	0.59 (0.40–0.89)	0.50 (0.36–0.69)	0.71 (0.59–0.85)	0.98 (0.78–1.23)
Adjusted	10 (w)	1	0.88 (0.80–0.95)	0.73 (0.62–0.86)	0.66 (0.59–0.75)	0.74 (0.63–0.88)	0.93 (0.74–1.18)
P			0.04	0.36	0.12	0.75	0.77
Type 2 diabetes tested	7 (b)	1	0.91 (0.79–1.05)	0.89 (0.72–1.10)	0.86 (0.64–1.15)	0.76 (0.63–0.93)	1.14 (0.89–1.45)
Type 2 diabetes self-reported	7 (b)	1	0.85 (0.75–0.97)	0.65 (0.57–0.73)	0.57 (0.50–0.65)	0.59 (0.49–0.71)	0.88 (0.55–1.39)
P			0.51	0.04	0.03	0.10	0.36
Men	11 (w and b)	1	0.93 (0.82–1.04)	0.80 (0.71–0.90)	0.75 (0.60–0.95)	0.71 (0.60–0.83)	1.06 (0.86–1.32)
Women	6 (w and b)	1	0.81 (0.75–0.88)	0.59 (0.54–0.64)	0.55 (0.47–0.65)	0.78 (0.49–1.23)*	
P			0.14	0.01	0.21		
BMI lowest strata	6 (w)	1	0.76 (0.65–0.88)	0.64 (0.44–0.92)	0.73 (0.53–1.01)	0.85 (0.49–1.46)	1.28 (0.37–4.40)
BMI highest strata	6 (w)	1	0.85 (0.79–0.92)	0.75 (0.63–0.90)	0.67 (0.57–0.78)	0.71 (0.55–0.91)	0.92 (0.73–1.16)
P			0.53	0.45	0.53	0.79	0.65

*The single observation in women in the >48-g/day category is pooled with the observations in the 24- to 48-g/day category. w, within-study comparison; b, between-study comparison.

or individuals with low and high BMI could explain the observed heterogeneity. In most cases, this did not turn out to be the case. Numerous other factors, however, may also have caused the observed heterogeneity, such as differences in alcohol assessment methods, period of follow-up, and all 30 confounders that were adjusted for in some but not all included studies.

A borderline significant difference between the crude and multivariate-adjusted pooled RRs was found for the lowest consumption level. Adjustment for confounders such as age, family history of diabetes, and BMI appears to have some attenuating effect on the estimated RRs. In the seven studies that were based on self-reported type 2 diabetes status, the RRs associated with moderate drinking (6–48 g/day) were 0.57–0.65, whereas in the seven studies that used population testing of type 2 diabetes, the RRs were 0.76–0.89. This difference may be due to the higher frequency of alcohol abstainers attending a general practitioner (35), resulting in relatively more diagnosed cases in this group. The difference may also be caused by a stronger relationship of alcohol consumption with the more severe cases of diabetes that likely are overrepresented in studies relying soley on self-report.

The apparent sex difference was due to the relatively low RRs in the two Nurses' Health Studies and the Iowa Women's Health Study. The trend of lower RRs in women than in men was not found within the three studies that gave results for both men and women (7,28, 32). Possibly, the trend for lower RRs in women than in men is caused by a study-related factor other than sex.

Within-study analyses showed that the reduced risk associated with moderate alcohol consumption was present both in individuals with a relatively low BMI and in those with a relatively high BMI. The alcohol consumption level associated with the lowest type 2 diabetes risk appears to be lower in individuals with a relatively low BMI (6–12 g/day) than in those with a higher BMI (12–24 g/day).

Several studies were not included because their data were not presented in a way that could be used in our meta-analysis. The unadjusted RRs that can be calculated from the Women's Health Study show a convincing decrease in type 2 diabetes risk with the increase in drinking frequency (14). Also in line with the present findings, Hodge et al. (18), Lynch et al. (13), and Watanabe et al. (21) showed trends of a decreased risk of type 2 diabetes associated with alcohol consumption. In three other excluded studies, logistic regression analyses were performed with alcohol as a continuous determinant of type 2 diabetes risk (17,19,20). These studies suggest a positive relationship for men, which is in contrast with the first part but in line with the second part of the U-shaped relationship that was found for men in our meta-analysis.

Our finding of a U-shaped relationship between alcohol consumption and type 2 diabetes risk is analogous with the previously demonstrated relationship with cardiovascular diseases (36,37) and may partly share underlying mechanisms. Moderate alcohol consumption is known to increase HDL cholesterol concentration (38), whereas, at higher consumption levels, body weight, triglyceride concentration, and blood pressure increase (39–42). Another plausible mechanism is through the anti-inflammatory effect of alcohol (43,44). Enhanced insulin sensitivity with lower plasma insulin concentrations is another (and more type 2 diabetes–specific) plausible mechanism because inverse and U-shaped relationships between alcohol consumption and insulin levels have been shown (41). In a recent randomized controlled trial in women without diabetes, alcohol consumption of 30 g/day was shown to have beneficial effects on insulin and triglyceride concentrations (45).

Our study has several potential limitations. First, its quality fully depends on that of the original studies included. Validity threats of those studies are directly inherited. One of these threats is the measurement error that is inevitable when using relatively simple methods to assess alcohol consumption (46). Both differential and nondifferential misclassification of the amount of alcohol consumed at baseline may have resulted in bias. The misclassification, on average, is expected to be an underestimation of the amount of alcohol consumed (47). Therefore, the amount of alcohol consumption associated with the lowest risk of type 2 diabetes in reality may be higher than reported. In addition, one alcohol assessment at baseline may not be a precise representation of the average alcohol amount consumed over the complete time at risk. Because moderate consumers may have changed to abstainers or heavy consumers, and vice versa, it is likely that the magnitude of the U-shaped relationship is underestimated, as is shown to be the case for the relationship between alcohol and mortality (48). In addition, the meta-analysis does not give information on the importance of a stable pattern of alcohol consumption on type 2 diabetes risk. However, as has been demonstrated for coronary heart disease before (49), Conigrave et al. (24) presumed that drinking frequency is inversely associated with type 2 diabetes risk. Because detailed information on the influence of the pattern of consumption, including binge drinking, was missing in all other studies, this remains an important topic for further investigations.

Second, 7 of the 15 studies did not originally use nonconsumers as the reference category. In recalculating the RRs from these studies relative to the category of nonconsumers, the variance had to be reestimated. Since the category of nonconsumers overall comprised 50% more cases of type 2 diabetes than the reference categories that were used in the original publications, it is not likely that we underestimated the variance.

Third, the so-called "sick quitter effect" may have caused bias (individuals with preexisting disease stop drinking and thereby cause the observed lower disease risk in drinkers [50]). However, several large studies investigated this, and the concerns are largely allayed (37). Likewise, the two studies included in the present meta-analysis that reported results for former drinkers and lifetime nonconsumers separately did not find results in accordance with the "sick quitter hypothesis" (7,8).

Fourth, although most original studies adjusted for multiple potential confounders, residual confounding may have resulted in the present findings. A meta-analyses of observational studies has the limitation of all observational data that causal relationships cannot be established, even when experimental work on biological mechanisms is supporting the hypotheses. Only long-term intervention studies can determine the true benefits or adverse effects of alcohol consumption.

With the expectation of >100 million new cases of type 2 diabetes in the coming two decades, and with the prevention of

type 2 diabetes now being recognized as an urgent priority, attaining prevention is the central challenge. There are calculations that 91% of new type 2 diabetic cases could be attributed to the lack of adherence to five lifestyle behaviors, among which is the moderate consumption of alcohol (26).

In conclusion, the present study supports the evidence of a considerably reduced risk of type 2 diabetes associated with moderate but not with heavy alcohol consumption in men and women with low or high BMI.

Acknowledgments— This work was supported by an unconditional grant from the Alcohol Task Force of the European branch of the International Life Sciences Institute (ILSI Europe). Industry members of this task force are Allied Domecq, Brasseries Kronenbourg, Diageo, Heineken, and Moët et Chandon.

The opinions expressed in this article are those of the authors and do not necessarily represent the views of ILSI Europe. We thank Dr. Rob J.P.M. Scholten, Dutch Cochrane Centre, for his assistance with the data analysis.

References

1. Wild S, Roglic G, Green A, Sicree R, King H: Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 27:1047–1053, 2004
2. Zimmet P, Alberti KG, Shaw J: Global and societal implications of the diabetes epidemic. *Nature* 414:782–787, 2001
3. Zilkens RR, Puddey IB: Alcohol and type 2 diabetes: another paradox? *J Cardiovasc Risk* 10:25–30, 2003
4. Howard AA, Arnsten JH, Gourevitch MN: Effect of alcohol consumption on diabetes mellitus. *Ann Intern Med* 140:211–219, 2004
5. DerSimonian R, Laird NM: Meta-analysis in clinical trials. *Control Clin Trials* 7:177–188, 1986
6. Egger M, Davey Smith G, Schneider M, Minder C: Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315:629–634, 1997
7. Kao WH, Puddey IB, Boland LL, Watson RL, Brancati FL: Alcohol consumption and the risk of type 2 diabetes mellitus: Atherosclerosis Risk in Communities study. *Am J Epidemiol* 154:748–757, 2001
8. Wannamethee SG, Camargo CAJ, Manson JE, Willett WC, Rimm EB: Alcohol drinking patterns and risk of type 2 diabetes mellitus among younger women. *Arch Intern Med* 163:1329–1336, 2003
9. Perry IJ, Wannamethee SG, Shaper AG: Prospective study of serum gamma-glutamyltransferase and risk of NIDDM. *Diabetes Care* 21:732–737, 1998
10. Perry IJ, Wannamethee SG, Walker MK, Thomson AG, Whincup PH, Shaper AG: Prospective study of risk factors for development of non-insulin dependent diabetes in middle aged British men. *BMJ* 310: 560–564, 1995
11. Rimm EB, Chan J, Stampfer MJ, Colditz GA, Willett WC: Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. *BMJ* 310:555–559, 1995
12. Stampfer MJ, Colditz GA, Willett WC, Manson JE, Arky RA, Hennekens CH, Speizer FE: A prospective study of moderate alcohol drinking and risk of diabetes in women. *Am J Epidemiol* 128:549–558, 1988
13. Lynch J, Helmrich SP, Lakka TA, Kaplan GA, Cohen RD, Salonen R, Salonen JT: Moderately intense physical activities and high levels of cardiorespiratory fitness reduce the risk of non-insulin-dependent diabetes mellitus in middle-aged men. *Arch Intern Med* 156:1307–1314, 1996
14. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM: C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 286:327–334, 2001
15. Saremi A, Hanson RL, Tulloch-Reid M, Williams DE, Knowler WC: Alcohol consumption predicts hypertension but not diabetes. *J Stud Alcohol* 65:184–190, 2004
16. Fagot-Campagna A, Knowler WC, Narayan KM, Hanson RL, Saaddine J, Howard BV: HDL cholesterol subfractions and risk of developing type 2 diabetes among Pima Indians. *Diabetes Care* 22:271–274, 1999
17. Feskens EJ, Kromhout D: Cardiovascular risk factors and the 25-year incidence of diabetes mellitus in middle-aged men: the Zutphen Study. *Am J Epidemiol* 130: 1101–1108, 1989
18. Hodge AM, Dowse GK, Collins VR, Zimmet PZ: Abnormal glucose tolerance and alcohol consumption in three populations at high risk of non-insulin-dependent diabetes mellitus. *Am J Epidemiol* 137:178–189, 1993
19. Holbrook TL, Barrett-Connor E, Wingard DL: A prospective population-based study of alcohol use and non-insulin-dependent diabetes mellitus. *Am J Epidemiol* 132: 902–909, 1990
20. Monterrosa AE, Haffner SM, Stern MP, Hazuda HP: Sex difference in lifestyle factors predictive of diabetes in Mexican-Americans. *Diabetes Care* 18:448–456, 1995
21. Watanabe M, Barzi F, Neal B, Ueshima H, Miyoshi Y, Okayama A, Choudhury SR: Alcohol consumption and the risk of diabetes by body mass index levels in a cohort of 5,636 Japanese. *Diabetes Res Clin Pract* 57:191–197, 2002
22. Ajani UA, Hennekens CH, Spelsberg A, Manson JE: Alcohol consumption and risk of type 2 diabetes mellitus among US male physicians. *Arch Intern Med* 160: 1025–1030, 2000
23. Wei M, Gibbons LW, Mitchell TL, Kampert JB, Blair SN: Alcohol intake and incidence of type 2 diabetes in men. *Diabetes Care* 23:18–22, 2000
24. Conigrave KM, Hu BF, Camargo CA Jr, Stampfer MJ, Willett WC, Rimm EB: A prospective study of drinking patterns in relation to risk of type 2 diabetes among men. *Diabetes* 50:2390–2395, 2001
25. de Vegt F, Dekker JM, Groeneveld WJ, Nijpels G, Stehouwer CD, Bouter LM, Heine RJ: Moderate alcohol consumption is associated with lower risk for incident diabetes and mortality: the Hoorn Study. *Diabetes Res Clin Pract* 57:53–60, 2002
26. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, Willett WC: Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med* 345: 790–797, 2001
27. Lee DH, Ha MH, Kim JH, Christiani DC, Gross MD, Steffes M, Blomhoff R, Jacobs DR Jr: Gamma-glutamyltransferase and diabetes-a 4 year follow-up study. *Diabetologia* 46:359–364, 2003
28. Meisinger C, Thorand B, Schneider A, Stieber J, Doring A, Lowel H: Sex differences in risk factors for incident type 2 diabetes mellitus: the MONICA Augsburg cohort study. *Arch Intern Med* 162:82–89, 2002
29. Nakanishi N, Suzuki K, Tatara K: Alcohol consumption and risk for development of impaired fasting glucose or type 2 diabetes in middle-aged Japanese men. *Diabetes Care* 26:48–54, 2003
30. Tsumura K, Hayashi T, Suematsu C, Endo G, Fujii S, Okada K: Daily alcohol consumption and the risk of type 2 diabetes in Japanese men: the Osaka Health Survey. *Diabetes Care* 22:1432–1437, 1999
31. Wannamethee SG, Shaper AG, Perry IJ, Alberti KG: Alcohol consumption and the incidence of type II diabetes. *J Epidemiol Community Health* 56:542–548, 2002
32. Carlsson S, Hammar N, Grill V, Kaprio J: Alcohol consumption and the incidence of type 2 diabetes: a 20-year follow-up of the Finnish twin cohort study. *Diabetes Care* 26:2785–2790, 2003
33. Sawada SS, Lee I-M, Muto T, Matuszaki K, Blair SN: Cardiorespiratory fitness and the incidence of type 2 diabetes: prospective study of Japanese men. *Diabetes Care* 26:2918–2922, 2003
34. Lee D-H, Folsom AR, Jacobs DR: Dietary iron intake and type 2 diabetes incidence in postmenopausal women: the Iowa Women's Health Study. *Diabetologia* 47: 185–194, 2004

35. Cryer PC, Jenkins LM, Cook AC, Ditchburn JS, Harris CK, Davis AR, Peters TJ: The use of acute and preventative medical services by a general population: relationship to alcohol consumption. *Addiction* 94:1523–1532, 1999
36. Di Castelnuovo A, Rotondo S, Iacoviello L, Donati MB, De Gaetano G: Meta-analysis of wine and beer consumption in relation to vascular risk. *Circulation* 105: 2836–2844, 2002
37. Maclure M: Demonstration of deductive meta-analysis: ethanol intake and risk of myocardial infarction. *Epidemiol Rev* 15: 328–351, 1993
38. Rimm EB, Williams P, Fosher K, Criqui M, Stampfer MJ: Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. *BMJ* 319:1523–1528, 1999
39. Wannamethee SG, Shaper AG: Alcohol, body weight, and weight gain in middle-aged men. *Am J Clin Nutr* 77:1312–1317, 2003
40. Kato I, Kiyohara Y, Kubo M, Tanizaki Y, Arima H, Iwamoto H, Shinohara N, Nakayama K, Fujishima M: Insulin-mediated effects of alcohol intake on serum lipid levels in a general population: the Hisayama Study. *J Clin Epidemiol* 56: 196–204, 2003
41. Kiechl S, Willeit J, Poewe W, Egger G, Oberhollenzer F, Muggeo M, Bonora E: Insulin sensitivity and regular alcohol consumption: large, prospective, cross sectional population study (Bruneck study). *BMJ* 313:1040–1044, 1996
42. Thadhani R, Camargo CA Jr, Stampfer MJ, Curhan GC, Willett WC, Rimm EB: Prospective study of moderate alcohol consumption and risk of hypertension in young women. *Arch Intern Med* 162:569–574, 2002
43. Imhof A, Froehlich M, Brenner H, Boeing H, Pepys MB, Koenig W: Effect of alcohol consumption on systemic markers of inflammation. *Lancet* 357:763–767, 2001
44. Sierksma A, van der Gaag MS, Kluft C, Hendriks HF: Moderate alcohol consumption reduces plasma C-reactive protein and fibrinogen levels: a randomized, diet-controlled intervention study. *Eur J Clin Nutr* 56:1130–1136, 2002
45. Davies MJ, Baer DJ, Judd JT, Brown ED, Campbell WS, Taylor PR: Effects of moderate alcohol intake on fasting insulin and glucose concentrations and insulin sensitivity in postmenopausal women: a randomized controlled trial. *JAMA* 287: 2559–2562, 2002
46. Koppes LL, Twisk JW, Snel J, Kemper HC: Concurrent validity of alcohol consumption measurement in a 'healthy' population: quantity-frequency questionnaire v. dietary history interview. *Br J Nutr* 88:427–434, 2002
47. Midanik L: The validity of self-reported alcohol consumption and alcohol problems: a literature review. *Br J Addict* 77: 357–382, 1982
48. Gmel G, Gutjahr E, Rehm J: How stable is the risk curve between alcohol and all-cause mortality and what factors influence the shape? A precision-weighted hierarchical meta-analysis. *Eur J Epidemiol* 18:631–642, 2003
49. Mukamal KJ, Conigrave KM, Mittleman MA, Camargo CA Jr, Stampfer MJ, Willett WC, Rimm EB: Roles of drinking pattern and type of alcohol consumed in coronary heart disease in men. *N Engl J Med* 348: 109–118, 2003
50. Wannamethee G, Shaper AG: Men who do not drink: a report from the British Regional Heart Study. *Int J Epidemiol* 17: 307–316, 1988