

The Effect of Alcohol Intake on Insulin Sensitivity in Men

A randomized controlled trial

RENATE R. ZILKENS, MPH
VALERIE BURKE, MD
GERALD WATTS, MD, PHD

LAURENCE J. BEILIN, MD
IAN B. PUDDEY, MD

OBJECTIVE — Population data suggest that alcohol consumption may influence the risk of diabetes in a biphasic manner, but this has not been tested by any controlled interventions. The object of this study was to determine whether reducing alcohol intake in moderate-to-heavy drinkers (40–110 g/day) results in improvement in insulin sensitivity.

RESEARCH DESIGN AND METHODS — A 4-week run-in period where subjects maintained their usual drinking pattern was followed by randomization to a two-way cross-over intervention study. In each of two 4-week treatment interventions, subjects either substituted their usual alcohol intake with a 0.9% alcohol beer or maintained their usual alcohol intake. At the end of each 4-week period, insulin sensitivity as determined by the low-dose insulin glucose infusion test and the homeostasis model assessment (HOMA) score, and biomarkers of alcohol consumption (γ -glutamyl transpeptidase [γ -GT] and HDL cholesterol) were measured.

RESULTS — A total of 16 healthy men aged 51.0 ± 2.7 (mean \pm SEM) years with a BMI of 26.4 ± 0.61 kg/m² completed the study. There was a large reduction in alcohol intake (72.4 ± 5.0 vs. 7.9 ± 1.6 g/day, $P < 0.001$) and significant reductions in γ -GT (geometric mean 24.4 units/l [95% CI 19.7–30.2] vs. 18.6 units/l [15.5–22.2], $P < 0.01$) and HDL cholesterol (1.36 ± 0.07 vs. 1.13 ± 0.07 mmol/l, $P < 0.001$). There was no effect of alcohol on insulin sensitivity index (ISI), fasting insulin, glucose, or HOMA score.

CONCLUSIONS — A substantial reduction in alcohol intake from 7.2 to 0.8 standard drinks per day in healthy men did not change insulin sensitivity as measured by ISI or HOMA score.

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Presently, it is difficult to simply define overall effects of alcohol on the insulin-glucose axis. Acutely, alcohol impairs insulin sensitivity in short-term experiments using insulin-glucose clamp techniques (1–5). In contrast, evidence from cross-sectional population-based studies suggests an association between chronic alcohol exposure and

improvement in insulin sensitivity (6), but such studies are rendered inherently weak by the potential for confounding by other variables affecting insulin sensitivity, especially adiposity (7–10). Although there have been no prospective studies evaluating the effect of long-term alcohol use on insulin sensitivity, per se, there have been a number of studies investigat-

ing whether there is any association between alcohol use at baseline and subsequent incidence of type 2 diabetes. Many of these studies found that light (~3–18 g/day) (11–13) to moderate (18–49 g/day) (14–16) alcohol use was associated with a reduced risk for the development of diabetes. Two of these studies (11,13) were hampered due to the very limited number of subjects with moderate to heavy intake (i.e., >20 g/day, equivalent to more than two standard drinks per day). In the prospective Rancho Bernardo Study (17), the upper tertile of drinkers consumed >25 g alcohol/day, whereas in the Atherosclerosis Risk in Communities (ARIC) Study (18), >8% of the male population consumed >36 g alcohol/day. Data from both these studies suggest that levels of alcohol consumption in these men were associated with an increased risk for the development of type 2 diabetes. Taken together, these prospective studies suggest that compared with none or very occasional drinkers, men with a light alcohol intake are more insulin sensitive, whereas men with moderate-to-heavy alcohol intake are more insulin resistant (i.e., a U-shaped relationship).

In contrast, for the women in the Rancho Bernardo study there was no evidence that alcohol use increased the risk of type 2 diabetes (17). In both the Nurses Health study (11) and the ARIC study (18), the association between alcohol consumption and diabetes risk appeared inverse for women (18). For all three studies a significant negative correlation of BMI with alcohol intake led to the conclusion that this may be a major confounding variable in dictating the relations of alcohol intake and incidence of type 2 diabetes in women. Another possible confounding influence in these studies may have been the relative paucity of women reporting a heavy intake of alcohol (i.e., the highest tertile of drinking for women in the Rancho Bernardo study was >17 g/day and the highest quartile of alcohol use in the Nurses Health Study was >15 g/day). An alcohol intervention study in overweight

From the University of Western Australia Department of Medicine, Royal Perth Hospital, Perth, Western Australia, Australia; and the Western Australian Institute for Medical Research, Perth, Western Australia, Australia.

Address correspondence and reprint requests to Ms. Renate Zilkens, University Department of Medicine, GPO Box X2213, Perth, WA 6847 Australia. E-mail: renate@cyllene.uwa.edu.au.

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Abbreviations: ARIC, Atherosclerosis Risk in Communities; CV, coefficient of variation; Ginf, glucose infusion rate; γ -GT, γ -glutamyl transpeptidase; G_{ss} , steady-state blood glucose; HOMA, homeostasis model assessment; ISI, insulin sensitivity index; I_{ss} , steady-state serum insulin; LDIGIT, low-dose insulin and glucose infusion test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

premenopausal women found that chronic moderate red wine consumption (~20 g/day) neither improved nor worsened insulin sensitivity as determined using the intravenous glucose tolerance test (19). In contrast, a more recent study in postmenopausal women reported that drinking 30 g alcohol/day improved insulin sensitivity estimated using fasting insulin, triglycerides, and fat-free mass (20).

On the basis of the current epidemiological evidence for men, we hypothesized that the moderate-to-heavy alcohol use in such subjects would result in reduced insulin sensitivity. To test this hypothesis we undertook a controlled intervention study in healthy predominantly beer-drinking men without preexisting diabetes. The gold standard for the assessment of insulin sensitivity is the hyperinsulinemic-euglycemic clamp technique (21). The continuous low-dose insulin and glucose infusion test (LDIGIT) (22) has previously been validated against this gold standard method and was used together with homeostasis model assessment (HOMA) (23) for assessment of insulin sensitivity during a randomized controlled study, where subjects varied their alcohol intake over intervals of 4 weeks.

RESEARCH DESIGN AND METHODS

Study subjects

Healthy male drinkers aged 20–65 years were sought by advertisement. Subjects were required to be drinking between 40 and 110 g ethanol/day with >60% from beer. Exclusion criteria included smoking within the last 6 months, BMI >30 kg/m², cardiovascular disease, diabetes, blood pressure >160/90 mmHg, or treatment with antihypertensive agents, total cholesterol >7.5 mmol/l, or use of lipid-lowering agents, aspirin, or nonsteroidal anti-inflammatory drugs. All subjects gave written informed consent. The study protocol was approved by the Human Research Ethics Committee of the University of Western Australia.

Study design

The study used a two-period cross-over design. Participants entered a 4-week baseline period during which a consistent pattern of alcohol intake was established, aided by weekly provision of 12 × 375-ml cans of beer (Swan Lager, 4.9% vol/vol

alcohol content; Swan Brewery, Canning Vale, Australia). For the first study period of 4 weeks, subjects were randomized (using random numbers generated with Microsoft Excel 97) to either continue their usual alcohol intake or to reduce their alcohol intake by substituting a low-alcohol beer (0.9% vol/vol, Swan Special Light, a vacuum distillation of normal alcohol beer) of which they were provided 12 × 375-ml cans weekly. During the second study period, subjects swapped over to the alternate-drinking regimen. Participants were encouraged to limit their nonbeer alcohol intake. Alcohol consumption was recorded weekly in 7-day retrospective diaries. At the end of each study period subjects completed a limited food frequency questionnaire (with six categories of frequency from <1 to >6 times/week) and recorded whether they had noticeably altered their level of physical activity. The total intake of absolute alcohol was determined using industry tables of beverage alcohol content. Serum γ -glutamyl transpeptidase (γ -GT) (24) and fasting HDL cholesterol were measured to corroborate changes in self-reported alcohol intake.

Evaluation of insulin sensitivity

The LDIGITs were performed in the morning after an overnight fast at the end of each study phase. A 20-gauge cannula was inserted into a large antecubital vein for the constant 150-min infusion of both insulin (25 mU · kg⁻¹ · h⁻¹) and glucose (4 mg · kg⁻¹ · min⁻¹). Another 20-gauge cannula was placed into an antecubital vein in the contralateral arm to allow for blood sampling at 0, 5, 10, 15, 30, 60, 90, 120, 130, 140, 145, and 150 min. Steady-state blood glucose (G_{ss}) and steady-state serum insulin (I_{ss}) were calculated from the blood samples collected over the last 30 min of the LDIGIT. The insulin sensitivity index (ISI) was calculated as glucose infusion rate (Ginf) divided by I_{ss} and normalizing this ratio to G_{ss} (i.e., $ISI_{LDIGIT} = Ginf / (G_{ss} I_{ss})$) and expressed as ml_(glucose) per kg per min per pmol_(insulin) (22). The estimate of insulin resistance by homeostasis model assessment (HOMA) score was calculated with the following formula: fasting serum insulin (in micro units per liter) × fasting plasma glucose (in millimoles per liter)/22.5 (23,25). Plasma glucose was assayed using the kinetic hexokinase technique (Hitachi 917 Biochemical Analyzer; Hitachi Limited,

Tokyo, Japan) with an interassay coefficient of variation (CV) of 1.6% and intra-assay CV of 1%. Insulin was measured using a chemiluminescent immunometric assay (Immulite 2000 Biochemical Analyzer; Diagnostic Products, Los Angeles, CA) with an interassay CV of 7.6%. Fructosamine was assayed using the COBAS Integra Fructosamine colorimetric reagent system (Roche Diagnostics) with a normal reference range 190–285 μ mol/l and an interassay CV of 2.6%.

Statistics

The data were analyzed using SPSS 11 statistical software (SPSS, Chicago, IL). ANOVA was used to test for treatment order effect. Non-normally distributed data were log transformed. Values are reported as the mean \pm SE except for skewed variables (i.e., ISI, HOMA score, triglycerides, and γ -GT), which are expressed as geometric means with 95% CIs. The method of Hills and Armitage (26) was used to confirm the absence of treatment-period interactions permitting pooling of light alcohol and usual alcohol periods (baseline period omitted) for comparison by paired *t* test for normally distributed data. Univariate linear regression was used to examine associations between alcohol intake and outcome variables. The study had an 80% power to detect a 49% change in ISI at an α of 0.05. Statistical significance was defined as $P < 0.05$. Food frequency categorical data were converted (using category midpoints) before analysis with Wilcoxon's test.

RESULTS— Of the 17 men recruited, 16 completed the alcohol intervention component of the study with one dropout due to a non-study-related issue. Subjects ranged in age from 28 to 65 years (mean 51), were slightly overweight (mean BMI 26.4 \pm 0.6 kg/m²), normotensive, euglycemic, and normolipidemic (Table 1). At baseline, 92% of alcohol was derived from beer, a pattern maintained during intervention. The average drinking history at study entry was 21 \pm 14 years. Substitution of low-alcohol beer was associated with an average decrease in self-reported alcohol intake of 89%, from a mean of 72 \pm 5 to 8 \pm 2 g/day ($P < 0.001$) (Table 1). This is equivalent to a reduction in intake from approximately seven to one standard drink per day (one standard drink = 10 g/day). There was a 24% decrease in the geometric mean of

Table 1—Clinical and metabolic parameters measured at the end of each 4-week alcohol period

	Baseline alcohol intake	Low alcohol intake	Usual alcohol intake
Alcohol intake (g/day)	68.1 ± 4.6	7.9 ± 1.6*	72.4 ± 5.0
Weight (kg)	84.1 ± 1.6	83.0 ± 1.5†	83.9 ± 1.6
HDL cholesterol (mmol/l)	1.35 ± 0.08	1.13 ± 0.07*	1.36 ± 0.07
γ-GT (units/l)	24.4 (20.0–29.8)	18.6 (15.5–22.2)*	24.4 (19.7–30.2)
Fasting glucose (mmol/l)	5.1 ± 0.1	5.0 ± 0.1	5.0 ± 0.1
Fasting insulin (pmol/l)	36 ± 4	34 ± 6	33 ± 3
ISI (ml/kg · min ⁻¹ · pmol/l) × 10 ³	17.7 (13.3–23.7)	18.8 (13.1–26.9)	20.2 (13.8–29.5)
HOMA score	1.05 (0.83–1.33)	0.93 (0.69–1.24)	0.86 (0.58–1.27)
G _{ss} (mmol/l)	5.2 ± 0.1	5.1 ± 0.1	5.0 ± 0.1
I _{ss} (pmol/l)	242 ± 15	244 ± 23	230 ± 22
Fructosamine (μmol/l)	219 ± 4	227 ± 5	223 ± 5

Data are means ± SE and geometric mean (95% CI). Significant differences * $P < 0.001$, † $P < 0.05$ from usual alcohol intake (paired t test low alcohol intake versus usual alcohol intake). $n = 16$ except for ISI, G_{ss}, and I_{ss}, where $n = 12$.

γ-GT in the low compared with the usual alcohol period (18.6 units/l [95% CI 15.5–22.2] vs. 24.4 units/l [19.7–30.2], $P < 0.001$) and a 17% reduction in HDL cholesterol (1.36 ± 0.07 vs. 1.13 ± 0.07 mmol/l, $P < 0.001$). Univariate regression showed that the changes in γ-GT and HDL cholesterol were each associated with the self-reported change in alcohol intake (regression coefficient $B = 0.006$, $SE = 0.002$, and adjusted $R^2 = 0.329$) and ($B = 0.003$, $SE = 0.001$, and adjusted $R^2 = 0.224$), respectively, consistent with compliance with restriction of alcohol intake during the low-alcohol period.

Mean weight was 0.9 kg heavier at the end of the usual alcohol period compared with that at the end of the low-alcohol period (Table 1). During the low-alcohol period, the subjects decreased their alcohol-derived energy intake by 485 kcal/day, whereas the frequency of drinking fruit juice and milk increased by 8 vs. 11 times/month ($P < 0.05$) and 13 vs. 18 times/month ($P < 0.05$), respectively. Weight was the only variable that had a treatment-order effect (i.e., the weight loss was greater for the group that reduced their alcohol intake in weeks 8–12, $P = 0.05$). However, with univariate regression the weight change was still associated with change in self-reported alcohol intake ($B = 0.02$, $SE = 0.01$, and adjusted $R^2 = 0.179$).

Baseline ISI (geometric mean 17.7 [95% CI 13.3–23.7]) was within the normal range of 12–32 previously seen in normal glucose-tolerant men (22). At baseline, mean daily alcohol intake was positively correlated ($P < 0.05$) with fast-

ing insulin ($r = 0.55$) and HOMA score ($r = 0.53$), but these associations were no longer significant after controlling for BMI. Of the 16 men who completed the alcohol intervention, 12 underwent the complete set of three LDIGITs. During all of the LDIGITs, blood glucose levels increased during the first 30 min, declining thereafter, regardless of study phase. Insulin levels increased during the test, achieving plateau at 60 min. Table 1 shows details of the results from the LDIGIT with no statistical differences between alcohol intervention with respect to fasting and steady-state glucose and insulin values, fructosamine levels, HOMA score, or ISI.

CONCLUSIONS— Using a randomized controlled cross-over study design, we have shown that a reduction in daily alcohol intake from seven to one standard drink per day over 4 weeks did not appear to alter the insulin sensitivity of nondiabetic healthy men. The self-reported reduction in alcohol intake was corroborated by a decrease in both γ-GT and HDL cholesterol.

In the prospective Rancho Bernardo Study involving 220 men, those in the highest tertile of drinking (i.e., >25 g alcohol/day) had a significantly higher risk of developing type 2 diabetes compared with the lighter drinkers (17). Even after adjustment for age, BMI, and smoking, alcohol intake was significantly higher in the men who went on to develop type 2 diabetes. Additionally, the relative risk of developing type 2 diabetes in drinkers in the highest tertile was twofold higher in the overweight group of men with a BMI

>26 kg/m². In the more recent and larger prospective ARIC Study involving 5,423 middle-aged men, those who consumed a substantial amount of alcohol (>36 g/day) were 50% more likely, even after adjustment for potential confounders and diabetes risk factors, to develop type 2 diabetes compared with those who drank ≤1.7 g/day (18).

Ethically, it is inappropriate to design an alcohol intervention study using none or occasional drinkers and increase their alcohol intake to moderate-to-heavy levels. We therefore used the alternative model, taking healthy men who were already drinking between 4 and 10 standard drinks per day and restricting their alcohol use for periods of 4 weeks in a randomized controlled cross-over study. The men in our alcohol intervention study were, on average, middle-aged, had a BMI >26 kg/m², and reduced their alcohol intake from an average of 72 g/day to 8 g/day. Our study subjects were similar in age and BMI to the men in the ARIC and Rancho Bernardo study, so we postulated that there would be an improvement in insulin sensitivity with the reduction in alcohol intake.

To our knowledge, there have been three previous reports of alcohol intervention studies investigating the effect of alcohol use on insulin sensitivity (19,20,27). Compared with our study, the men and women in the recent report from the U.K. were considerably younger (aged 21–41 years), thinner (mean BMI 22 kg/m²), had a lower alcohol intake (i.e., 31 g alcohol/day), and were more insulin sensitive with low fasting insulin ~6 pmol/l (27). Additionally, the alcohol

intervention differed in that the subjects either drank 24 g of vodka alcohol daily for 1 week or abstained from alcohol. Using the intravenous glucose tolerance test with minimal model analysis, they also found no difference in insulin sensitivity. In addition the authors reported that they deliberately used the short study period of 1 week to reduce the influence of hepatic enzyme induction and acknowledged that a longer period of alcohol consumption was needed to confirm or refute the epidemiological findings. The second study examined postmenopausal women who drank 0, 15, or 30 g alcohol/day in orange juice for periods of 8 weeks (20). Improvement in insulin sensitivity estimated with a published index of glucose disposal rate corrected for fat-free mass based on fasting insulin and triglyceride levels was seen in the 30-g alcohol/day period. It was a little surprising to find that alcohol caused a reduction in triglycerides in these women, since regular alcohol has usually been associated with higher triglyceride levels. The third study involved 20 overweight (BMI 29.8 kg/m²) premenopausal women and compared the effect of 10 weeks of moderate red wine consumption (~20 g/day) with 10 weeks of alcohol abstinence (19). Chronic moderate wine consumption with the evening meal neither improved nor worsened insulin sensitivity based on the intravenous glucose tolerance test.

In our study, the daily baseline alcohol intake was positively correlated with fasting insulin and HOMA score, measures previously used in larger population studies to reflect insulin sensitivity (28). These associations were, however, lost after controlling for BMI. Using the LDIGIT, a method validated against the hyperinsulinemic-euglycemic clamp approach to assessing insulin sensitivity (22), we did not find the expected improvement in the ISI after a substantial reduction in alcohol intake for 28 days. There are a number of possible explanations for not finding an effect. There may be no effect of reduced alcohol consumption on insulin sensitivity independent of effects mediated by increased abdominal fat. Our baseline data would also be in keeping with this conclusion. However, the possibility that our finding is a false negative needs to be considered. First, we may have been somewhat ambitious in our expectations, since we were powered to detect an improvement of ~50% in the

ISI. In a previous cross-sectional study using the LDIGIT method, the difference between normal-weight impaired glucose tolerant and impaired glucose tolerant ISI was of this order of magnitude (22). Second, if we compare the HOMA scores of our subjects with previous reports, it appears that our subjects were relatively insulin sensitive (23,25,28). The results in our subjects after 4 weeks of substantial reductions in alcohol intake contrast with the reported acute effect of alcohol to cause insulin resistance in short-term experiments (1–5,29). It is possible that with repeated episodes of alcohol ingestion homeostatic mechanisms are involved to maintain normal insulin sensitivity. Third, our study subjects may have not been representative of moderate-to-heavy drinkers that go on to develop type 2 diabetes, since we deliberately selected healthy men with normal blood pressure on no regular medication. Finally, despite the substantial changes seen in γ -GT and HDL cholesterol after 4 weeks of low alcohol intervention, this time frame may have been insufficient to reverse any preexisting insulin resistance.

Our findings cannot be generalized beyond a predominantly healthy beer-drinking male population. The study was also conducted in an ambulatory setting rather than in a metabolic ward, so we were unable to tightly control for background changes in diet and weight that occurred during the switch to low alcohol beer ingestion alone. However, these changes were small, and if there was any effect on insulin sensitivity, the impact of the reported dietary changes and weight loss would have been in opposite directions, reducing the likelihood of any major background confounding influences on our final result.

Moderate alcohol consumption has been associated with lower risk of cardiovascular disease in type 2 diabetes (30–33). It has been recognized that the improvement in HDL cholesterol is the main mechanism behind alcohol's cardioprotective effect, but it has also been suggested that additional cardioprotective mechanisms, such as increases in insulin sensitivity, may also be operating (30,33). A worthwhile focus for future intervention studies into the potential effects of alcohol on insulin sensitivity should be regular drinkers who also have diet-controlled diabetes.

In conclusion, in healthy men, insulin

sensitivity, as measured with the low-dose insulin and glucose infusion test, did not change after a 4-week reduction in daily alcohol intake from seven to one standard drink. If this absence of any short-term effect is also seen in the longer term, it is unlikely that effects of moderate-to-heavy regular consumption on the insulin-glucose axis are of major relevance to the development of type 2 diabetes. These results, however, do not exclude the possibility that part of the mechanism behind the effect of alcohol to impart cardiovascular protection in diabetic populations is through direct actions to improve insulin sensitivity.

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References

1. Yki-Jarvinen H, Nikkila EA: Ethanol decreases glucose utilization in healthy man. *J Clin Endocrinol Metab* 61:941–945, 1985
2. Avogaro A, Fontana P, Valerio A, Trevisan R, Riccio A, Del Prato S, Nosadini R, Tiengo A, Crepaldi G: Alcohol impairs insulin sensitivity in normal subjects. *Diabetes Res* 5:23–27, 1987
3. Shah JH: Alcohol decreases insulin sensitivity in healthy subjects. *Alcohol Alcohol* 23:103–109, 1988
4. Shelmet JJ, Reichard GA, Skutches CL, Hoeldtke RD, Owen OE, Boden G: Ethanol causes acute inhibition of carbohydrate, fat, and protein oxidation and insulin resistance. *J Clin Invest* 81:1137–1145, 1988
5. Boden G, Chen X, DeSantis RA, Kendrick Z: Ethanol inhibits insulin action on lipolysis and on insulin release in elderly men. *Am J Physiol* 265:E197–E202, 1993
6. 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
7. Mayer EJ, Newman B, Quesenberry CP Jr, Friedman GD, Selby JV: Alcohol consumption and insulin concentrations: role of insulin in associations of alcohol intake with high-density lipoprotein cholesterol and triglycerides. *Circulation* 88:2190–2197, 1993
8. Kiechl S, Willeit J, Poewe W, Egger G, Oberhollenzer F, Mugge M, Bonora E: Insulin sensitivity and regular alcohol consumption: large, prospective, cross sectional population study (Bruneck study). *BMJ* 313:1040–1044, 1996

9. Bell RA, Mayer-Davis EJ, Martin MA, D'Agostino RB Jr, Haffner SM: Associations between alcohol consumption and insulin sensitivity and cardiovascular disease risk factors: the Insulin Resistance and Atherosclerosis Study. *Diabetes Care* 23:1630–1636, 2000
10. Facchini F, Chen YD, Reaven GM: Light-to-moderate alcohol intake is associated with enhanced insulin sensitivity. *Diabetes Care* 17:115–119, 1994
11. 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
12. 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
13. 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
14. 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
15. 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
16. 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
17. 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
18. 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
19. Cordain L, Melby CL, Hamamoto AE, O'Neill DS, Cornier MA, Barakat HA, Israel RG, Hill JO: Influence of moderate chronic wine consumption on insulin sensitivity and other correlates of syndrome X in moderately obese women. *Metabolism* 49:1473–1478, 2000
20. 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
21. DeFronzo RA, Tobin JD, Andres R: Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 237:E214–E223, 1979
22. Piatti PM, Monti LD, Caumo A, Santambrogio G, Magni F, Galli-Kienle M, Costa S, Pontiroli AE, Alberti KG, Pozza G: The continuous low dose insulin and glucose infusion test: a simplified and accurate method for the evaluation of insulin sensitivity and insulin secretion in population studies. *J Clin Endocrinol Metab* 80:34–40, 1995
23. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
24. Burke V, Puddey IB, Beilin LJ, Vandongen R, Masarei JR: Changes in markers of alcohol intake in man below 'safe' drinking levels. *Alcohol Alcohol* 27:677–683, 1992
25. Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere M, Monauini T, Muggeo M: Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity. *Diabetes Care* 23:57–63, 2000
26. Hills M, Armitage P: The two-period cross-over clinical trial. *Br J Clin Pharmacol* 8:7–20, 1979
27. Flanagan DE, Pratt E, Murphy J, Vaile JC, Petley GW, Godsland IF, Kerr D: Alcohol consumption alters insulin secretion and cardiac autonomic activity. *Eur J Clin Invest* 32:187–192, 2002
28. Haffner SM, Kennedy E, Gonzalez C, Stern MP, Miettinen H: A prospective analysis of the HOMA model: the Mexico City Diabetes Study. *Diabetes Care* 19:1138–1141, 1996
29. Knip M, Ekman AC, Ekman M, Lepaluoto J, Vakkuri O: Ethanol induces a paradoxical simultaneous increase in circulating concentrations of insulin-like growth factor binding protein-1 and insulin. *Metabolism* 44:1356–1359, 1995
30. Valmadrid CT, Klein R, Moss SE, Klein BE, Cruickshanks KJ: Alcohol intake and the risk of coronary heart disease mortality in persons with older-onset diabetes mellitus. *JAMA* 282:239–246, 1999
31. Solomon CG, Hu FB, Stampfer MJ, Colditz GA, Speizer FE, Rimm EB, Willett WC, Manson JE: Moderate alcohol consumption and risk of coronary heart disease among women with type 2 diabetes mellitus. *Circulation* 102:494–499, 2000
32. Ajani UA, Gaziano JM, Lotufo PA, Liu S, Hennekens CH, Buring JE, Manson JE: Alcohol consumption and risk of coronary heart disease by diabetes status. *Circulation* 102:500–505, 2000
33. Tanasescu M, Hu FB, Willett WC, Stampfer MJ, Rimm EB: Alcohol consumption and risk of coronary heart disease among men with type 2 diabetes mellitus. *J Am Coll Cardiol* 38:1836–1842, 2001