The Effect of Alcohol Consumption on Insulin Sensitivity and Glycemic Status: A Systematic Review and Meta-analysis of Intervention Studies

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OBJECTIVE

Moderate alcohol consumption is associated with a reduced risk of type 2 diabetes. This reduced risk might be explained by improved insulin sensitivity or improved glycemic status, but results of intervention studies on this relation are inconsistent. The purpose of this study was to conduct a systematic review and meta-analysis of intervention studies investigating the effect of alcohol consumption on insulin sensitivity and glycemic status.

RESEARCH DESIGN AND METHODS

PubMed and Embase were searched up to August 2014. Intervention studies on the effect of alcohol consumption on biological markers of insulin sensitivity or glycemic status of at least 2 weeks' duration were included. Investigators extracted data on study characteristics, outcome measures, and methodological quality.

RESULTS

Fourteen intervention studies were included in a meta-analysis of six glycemic end points. Alcohol consumption did not influence estimated insulin sensitivity (standardized mean difference [SMD] 0.08 [−0.09 to 0.24]) or fasting glucose (SMD 0.07 [−0.11 to 0.24]) but reduced HbA_{1c} (SMD −0.62 [−1.01 to −0.23]) and fasting insulin concentrations (SMD −0.19 [−0.35 to −0.02]) compared with the control condition. Alcohol consumption among women reduced fasting insulin (SMD −0.23 [−0.41 to −0.04]) and tended to improve insulin sensitivity (SMD 0.16 [−0.04 to 0.37]) but not among men. Results were similar after excluding studies with high alcohol dosages (>40 g/day) and were not influenced by dosage and duration of the intervention.

CONCLUSIONS

Although the studies had small sample sizes and were of short duration, the current evidence suggests that moderate alcohol consumption may decrease fasting insulin and HbA_{1c} concentrations among nondiabetic subjects. Alcohol consumption might improve insulin sensitivity among women but did not do so overall.

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META-ANALYSIS

Moderate alcohol consumption, compared with abstaining and heavy drinking, is related to a reduced risk of type 2 diabetes (1,2). Although the risk is reduced with moderate alcohol consumption in both men and women, the association may differ for men and women. In a meta-analysis, consumption of 24 g alcohol/day reduced the risk of type 2 diabetes by 40% among women, whereas consumption of 22 g alcohol/day reduced the risk by 13% among men (1).

The association of alcohol consumption with type 2 diabetes may be explained by increased insulin sensitivity, anti-inflammatory effects, or effects of adiponectin (3). Several intervention studies have examined the effect of moderate alcohol consumption on these potential underlying pathways. A meta-analysis of intervention studies by Brien et al. (4) showed that alcohol consumption significantly increased adiponectin levels but did not affect inflammatory factors. Unfortunately, the effect of alcohol consumption on insulin sensitivity has not been summarized quantitatively. A review of cross-sectional studies by Hulthe and Fagerberg (5) suggested a positive association between moderate alcohol consumption and insulin sensitivity, although the three intervention studies included in their review did not show an effect (6–8). Several other intervention studies also reported inconsistent results (9,10). Consequently, consensus is lacking about the effect of moderate alcohol consumption on insulin sensitivity. Therefore, we aimed to conduct a systematic review and meta-analysis of intervention studies investigating the effect of alcohol consumption on insulin sensitivity and other relevant glycemic measures.

RESEARCH DESIGN AND METHODS

This study was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews) Statement guidelines for the reporting of systematic reviews and meta-analysis of intervention studies. The PRISMA checklist and the protocol for this study are provided in the Supplementary Data.

Data Sources and Searches

A literature search was conducted in PubMed MEDLINE and Embase for relevant intervention studies published up to August 2014. A prespecified search string including search terms on alcohol, consumption, and glycemic measures was used for PubMed and Embase (Supplementary Data). References and related citations of articles were screened to identify other relevant articles. The exposure of interest was (moderate) alcohol consumption and the primary outcome measure, insulin sensitivity. All estimates of insulin sensitivity were included, which were indices from direct measures (e.g., hyperinsulinemic-euglycemic glucose clamp [HEGC]) and indirect measures of insulin sensitivity (e.g., the frequently sampled intravenous glucose tolerance test [FSIVGTT] and oral glucose tolerance test [OGTT]). HOMA of insulin resistance (HOMA-IR) was also included, which is based on fasting insulin and glucose levels and, therefore, primarily reflects hepatic insulin resistance (11). Other relevant outcome measures taken into account were fasting insulin, fasting glucose, and hemoglobin A_{1c} (HbA_{1c}). HbA_{1c} reflects average plasma glucose levels over the past 8–12 weeks and is therefore used as a measure of glycemic status (12).

Study Selection

Relevant studies were selected by two researchers (A.L.J.H., J.W.J.B.) during a multiphase process on the basis of the following inclusion criteria: trials with an alcohol intervention, relevant outcome measures as previously described, intervention period of at least 2 weeks, and written in English or Dutch. We excluded studies of individuals with (a history of) alcoholism or heavy drinkers (individuals consuming $\geq$60 g alcohol for at least 1 day per week) and animal studies. No publication date or status restrictions were imposed. In the first phase, titles of all retrieved studies were screened to select articles with a relevant subject; the abstracts of these articles were judged on relevance in the next phase. If judged relevant, the full text was studied in the third phase to determine whether the article was eligible for inclusion. When discrepancies occurred about the inclusion of a particular article, a third author (K.J.M. or I.C.S.) was consulted.

Data Extraction and Quality Assessment

From the included studies, sample size, participant characteristics, inclusion and exclusion criteria, study design, duration of intervention, and specific outcome measures were extracted on a prespecified form. Detailed information about the alcohol intervention (e.g., dosage, type, frequency, duration) was described. If a study did not report the grams of alcohol per unit, this was calculated based on the amount in milliliters given to the subjects and the alcohol volume of the beverage [g alcohol = (mL $\times$ %v/v) $\times$ 0.8, where %v/v is the percentage of alcohol volume per total volume]. Authors of included articles were contacted if further information was required (13–15).

To assess the quality of the studies, aspects such as randomization procedures, compliance with the intervention, and dropout rates were extracted. Randomization and the inclusion of an alcohol-free control group were regarded as the most important criteria to decide whether a study had sufficient quality. If these criteria were not met, the studies were excluded from further meta-analyses. Because randomization of crossover studies may be less important than randomization of parallel studies, we also conducted a sensitivity analysis including nonrandomized crossover studies. Because blinding of participants to the alcohol intervention is of uncertain effectiveness, this criterion was not regarded as essential for inclusion. To assess the quality of the included studies, the 5-point Jadad scale was used (16).

Data Synthesis and Analysis

The mean and SD of the outcome variables at the end of the alcohol intervention period and control period were extracted from the articles. If SEs were reported, we used the equation SD = SE $\times$ square root of the number of subjects. The mean effects of the various studies measuring the insulin sensitivity index (ISI), HOMA-IR, insulin, glucose, or HbA_{1c} were pooled in a meta-analysis and shown in a forest plot. To combine the studies measuring ISI and HOMA-IR in one meta-analysis, the inverted HOMA-IR (1/HOMA-IR) was calculated using the delta method.

Heterogeneity between studies was tested using χ^2 and I^2 statistics. If χ^2 and I^2 showed no evidence for heterogeneity ($I^2 < 30\%$) (17), analyses were conducted using the inverse variance fixed-effects model for pooling the studies. Otherwise, the DerSimonian and Laird random-effects model was used. The mean outcomes for insulin, glucose, and insulin sensitivity were assessed using different methods and needed to be

standardized. Therefore, Cohen *d* was used to calculate the standardized mean difference (SMD), which is the mean difference between the intervention and control group divided by the pooled SD.

In sensitivity analyses, the effect of moderate alcohol consumption on the reported outcomes was determined by excluding studies with high alcohol dosages (>40 g/day). Furthermore, if more than one intervention arm was tested in a study, we combined the outcomes (17). Additionally, analyses were performed excluding studies potentially causing heterogeneity to determine their effect on the results.

In a meta-regression, the influences of alcohol dosage and duration of the intervention on the results were tested. The influence of type of alcoholic beverage was not assessed due to too few studies to stratify by alcoholic beverage. Because only two studies used the gold standard HEGC to estimate insulin sensitivity (11), we tested with a meta-regression whether the effect of alcohol on insulin sensitivity differed between these studies.

Because the association of alcohol consumption with type 2 diabetes differs for men and women, we conducted sex-stratified analyses. Effect modification by sex was tested in a meta-regression for insulin sensitivity.

Potential publication bias was examined by visual inspection of the funnel plot and by the Egger and Begg statistical tests. In case evidence of publication bias was found, we used the trim and fill method by Duval and Tweedie (18) to calculate a pooled SMD based on filled data to adjust for publication bias. The level of significance was set at $P < 0.05$. Analyses were performed with the STATA meta-procedure (Stata 10.0).

RESULTS

In total, 4,991 titles were found through the database searches and 24 through additional methods (Supplementary Fig. 1). After screening of titles and abstracts, 46 articles remained eligible and the full text was assessed. Finally, 22 articles met criteria for inclusion in the qualitative synthesis.

Study Characteristics

Descriptive data of the included studies are summarized in Table 1. Of the 22 studies, 15 used a crossover design and 7 a parallel design. The intervention duration of the studies ranged from 2 to 12 weeks, with an average duration of 5.6 weeks for ISI, 4.2 weeks for HOMA-IR, 7.2 weeks for insulin, 5.9 weeks for glucose, and 4.3 weeks for HbA_{1c}. Two studies did not use an alcohol-free control group (14,19). The dosage of alcohol varied from 10 to 70 g/day of which one study used >40 g/day (20). ISI was measured by six studies, of which two used the gold standard HEGC (10,21) and four used indirect measures of insulin sensitivity (based on OGTT, FSIVGTT, or fasting levels) (8,9,22,23). HOMA-IR was measured by four studies (15,24–26). Seven studies were performed by the same institute (10,21–26), but they were treated as independent because they included different subjects.

Quality Assessment

The results of the quality assessment are shown in Supplementary Table 1. Of the 22 studies included in the qualitative synthesis, 4 did not report the measurement of compliance to the intervention (9,14,20,27). Blinding of the researcher was not reported or not conducted in any of the studies. Dropout rates were described in 18 studies. The studies scored between 1 and 3 points on the Jadad scale (range 0–5). Of the 22 studies, 2 were excluded from the meta-analysis because they did not include an alcohol-free control group (14,19), and 4 were excluded because they did not have a randomized design (13,28–30). Because only two studies included subjects with type 2 diabetes, these studies were excluded as well (31,32). One study included both healthy and type 2 diabetic subjects, and from this study, only data from healthy subjects were included (15). Overall, 14 studies were included in the meta-analysis (Table 1 and Supplementary Table 1).

Meta-analysis

The number of included studies in the analysis was 7 for ISI, 5 for HOMA-IR, 9 for insulin, 10 for glucose, and 3 for HbA_{1c}. The forest plots on insulin sensitivity and glycemic status are shown in Figs. 1–3.

Pooled analysis showed no difference in ISI after a period of alcohol consumption compared with no alcohol consumption (SMD 0.06 [−0.13 to 0.26], $P = 0.53$, test for heterogeneity $P = 0.76$, $I^2 = 0\%$). For HOMA-IR, both the χ^2 ($P < 0.01$) and I^2 (97%) statistics demonstrated heterogeneity. In a random-effects model, the pooled SMD was 0.35 [−0.90 to 1.59], indicating no effect of alcohol consumption on HOMA-IR ($P = 0.59$). Similar results were observed when studies measuring ISI and HOMA-IR were combined (SMD −0.12 [−0.61 to 0.39], $P = 0.65$). A random-effects model was used because heterogeneity was present ($P < 0.01$, $I^2 = 91\%$). The funnel plot indicated that the results of the intervention arms (i.e., red wine, gin) of Chiva-Blanch et al. (15) were largely responsible for this heterogeneity. Exclusion of this study resulted in an SMD of 0.08 (−0.09 to 0.24, $P = 0.35$), with no evidence of heterogeneity ($P = 0.90$, $I^2 = 0\%$). Sex-stratified analysis showed different effects in men and women ($P_{sex} = 0.018$) (Fig. 1). Alcohol consumption tended to increase insulin sensitivity in women (SMD 0.16 [−0.04 to 0.37], $P = 0.12$) but not in men (SMD −0.30 [−1.23 to 0.64], $P = 0.54$). In men, heterogeneity was present ($P < 0.01$, $I^2 = 95\%$), and exclusion of the study by Chiva-Blanch et al. resulted in a pooled SMD of −0.07 (−0.34 to 0.20, $P = 0.61$). However, after exclusion of Chiva-Blanch et al., the pooled SMDs in men and women were no longer significantly different ($P = 0.18$).

Fasting insulin concentrations were lower after alcohol consumption compared with abstinence, as shown by a pooled SMD of −0.19 (−0.35 to −0.02, $P = 0.03$) and the test for heterogeneity ($P = 0.92$, $I^2 = 0\%$). Sex-stratified analysis showed that alcohol consumption decreased insulin concentrations in women (SMD −0.23 [−0.41 to −0.04], $P = 0.02$). Only two studies measured insulin concentrations in men, showing a decrease in insulin levels (SMD −0.13 [−0.62 to 0.36], $P = 0.59$) (Fig. 2*A*).

For fasting glucose concentrations, the pooled SMD was 0.07 [−0.11 to 0.24], indicating no effect of alcohol consumption on glucose concentration among individuals without diabetes ($P = 0.45$, $P_{heterogeneity} = 0.94$, $I^2 = 0\%$). Similar results were observed when men and women were analyzed separately (Fig. 2*B*). In women, the SMD was 0.01 (−0.20 to 0.21, $P = 0.94$); in men, the SMD was 0.14 (−0.24 to 0.53, $P = 0.48$).

For HbA_{1c}, a random-effects model was used because the I^2 statistic indicated evidence for some heterogeneity ($I^2 = 30\%$). The pooled SMD was −0.62 (−1.01 to −0.23), showing lower HbA_{1c}

Table 1—Characteristics of studies included in this systematic review and meta-analysis on the effect of alcohol consumption on insulin sensitivity

Study reference	Design	Participants	Participant characteristics	Intervention	Alcohol dosage (g/day)	Intervention period (weeks)	Outcome measure	In meta-analysis
Bantle 2008 (31)	Randomized crossover	17 diabetic men and women	Age 64 (45–82) years BMI 31.7 (21.3–41.2) kg/m^2	Abstinence or white/red wine during dinner	18	4	Insulin, glucose, HbA_{1c}	No*
Beulens 2006 (21)	Randomized crossover	17 healthy men with waist circumference >94 cm	Age 53 (9) years BMI 29.1 (4.2) kg/m^2 Insulin 10.7 (5.6) units/L	Red wine or dealcoholized red wine with dinner	40	4	ISI (HEGC)	Yes
Beulens 2007 (23)	Randomized crossover	19 healthy lean or overweight men	Lean: Age 21 (2) years BMI 21.4 (2.0) kg/m^2 Insulin 4.7 (1.2) units/L Overweight: Age 28 (6) years BMI 30.1 (3.4) kg/m^2 Insulin 11.0 (5.4) units/L	Whisky or mineral water	32	4	ISI (OGTT), HbA_{1c}	Yes
Beulens 2008 (22)	Randomized crossover	20 healthy lean or overweight men	Lean: Age 19 (2) years BMI 20.1 (1.0) kg/m^2 Overweight: Age 21 (2) years BMI 31.3 (3.9) kg/m^2	Beer or alcohol-free beer during dinner	40	3	ISI (OGTT)	Yes
Bhathena 1995 (27)	Randomized crossover	37 healthy premenopausal women	Age 30 (7) years BMI 24.4 (4.6) kg/m^2	Ethanol mixed with fruit juice or soft drink after dinner	30	12	Insulin	Yes
Cesena 2011 (28)	Parallel (one arm)	42 healthy men and women	Age 46 (9) years BMI 25.1 (2.8) kg/m^2	Abstinence or red wine during dinner	24	2	Glucose	No†
Chiva-Blanch 2013 (15)	Randomized crossover	52 healthy and 15 diabetic men	Age 60 (8) years BMI 29.6 (3.9) kg/m^2	Gin, red wine, or dealcoholized red wine	30	4	HOMA-IR, insulin, glucose	Yes
Contaldo 1989 (20)	Randomized crossover	8 healthy men	BMI 25.4 (1.4) kg/m^2	Abstinence or red wine during dinner	75	2	Insulin, glucose	Yes
Cordain 1997 (13)	Randomized crossover	14 healthy men	Age 32 (9) years	Abstinence or wine	28	6	Insulin, glucose	No†
Cordain 2000 (8)	Randomized crossover	20 sedentary and overweight premenopausal women	BMI 29.8 (2.2) kg/m^2 Insulin 8.6 (3.3) units/L	Abstinence or red wine	20	10	ISI (FSIVGTT), insulin, glucose	Yes
Davies 2002 (9)	Randomized crossover	51 healthy postmenopausal women	Age 60 (8) years BMI 27.4 (5.7) kg/m^2 Insulin 6.5 (5.7) units/L	Alcohol or isocaloric beverage	15 or 30	8	ISI (MFFM), insulin, glucose	Yes
Flechtner-Mors 2004 (52)	Randomized parallel	40 overweight men and women	Age 48 (11) years BMI 34.2 (6.4) kg/m^2	Grape juice or white wine during meals	17	12	Insulin, glucose	Yes

Continued on p. 727

Table 1—Continued

Study reference	Design	Participants	Participant characteristics	Intervention	Alcohol dosage (g/day)	Intervention period (weeks)	Outcome measure	In meta-analysis
Joosten 2008 (24)	Randomized crossover	36 healthy postmenopausal women	Age 57 (4) years BMI 25.4 (3.3) kg/m^2 Insulin 37.4 (12.6) pmol/L	White wine or white grape juice daily during dinner	25	6	HOMA-IR, insulin, glucose, HbA_{1c}	Yes
Joosten 2011 and 2014 (25,26)	Randomized crossover	24 healthy premenopausal women	Age 24 (4) years BMI 22.2 (1.6) kg/m^2 Insulin 41.7 (16.0) pmol/L	Beer or alcohol-free beer during dinner	26	3	HOMA-IR, insulin, glucose, HbA_{1c}	Yes
Joosten 2012 and 2014 (53,26)	Randomized crossover	24 healthy men	Age 26 (3) years BMI 24 (3) kg/m^2	Vodka and orange juice or orange juice during dinner	30	4	HOMA-IR, insulin, glucose	Yes
Kim 2009 (29)	Parallel	20 nondiabetic, insulin-resistant men and women	Age 54 (7) years BMI 32 (5) kg/m^2	Abstinence or vodka or red wine during dinner	30	8	Steady-state plasma glucose, glucose	No†
Lavy 1994 (14)	Randomized parallel	20 healthy men	—	Red or white wine	40	2	Glucose	No‡
Queipo-Ortuño 2012 (33)	Randomized crossover	10 healthy men	Age 48 (2) years BMI 27.6 (3.2) kg/m^2	Gin, red wine, or dealcoholized red wine	30	3	Glucose	Yes
Romeo 2008 (30)	Parallel (one arm)	57 healthy women and men	Women: Age 38 (9) years BMI 24.4 (3.5) kg/m^2 Men: Age 35 (6) years BMI 25.5 (2.4) kg/m^2	Abstinence or beer during the meal	11 (women), 22 (men)	4	Glucose	No†
Shai 2007 (32)	Randomized parallel (multicenter)	91 diabetic men and women	Age 62 (6) years BMI 30.1 (4.6) kg/m^2	Wine or nonalcoholic beer during dinner	13	12	Glucose, HbA_{1c}	No*
Sierksma 2004 (10)	Randomized crossover	23 healthy men	Age 52 (5) years BMI 26.7 (3.0) kg/m^2 Insulin 8.9 (8.8) units/L	Whisky or tap water during dinner	40	2.5	ISI (HEGC)	Yes
Zheng 2012 (19)	Randomized parallel	45 healthy men and women	TFL: Age 24 (2) years BMI 21.3 (1.6) kg/m^2 TCL: Age 24 (1) years BMI 21.1 (2.2) kg/m^2	TFL or TCL	10	4	HOMA-IR, insulin, glucose	No‡

Data are mean (SD) or (range) unless otherwise indicated. MFFM, whole-body glucose disposal rate normalized to fat-free mass; TCL, traditional Chinese liquor; TFL, tea-flavor liquor. Reason for exclusion from meta-analysis: *participants with type 2 diabetes, †no randomized design, ‡no control group.

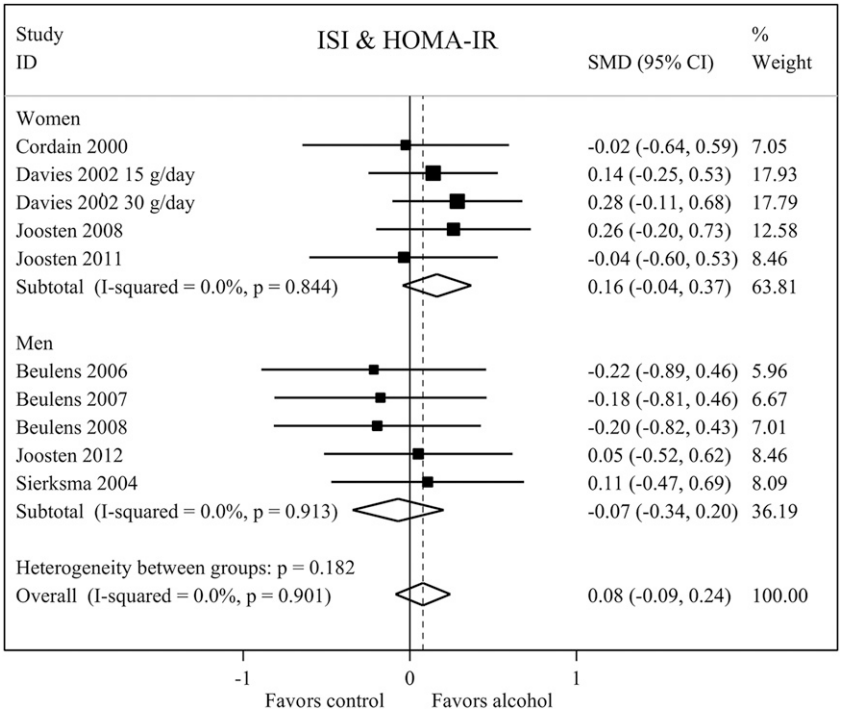

Figure 1—Forest plot of meta-analysis of the effect of alcohol consumption on insulin sensitivity. Data are pooled SMDs with 95% CIs and are calculated with exclusion of the results of the two study arms of Chiva-Blanch et al. (15) because they induced heterogeneity.

concentrations after alcohol consumption compared with no alcohol consumption ($P < 0.01$) (Fig. 3).

Sensitivity Analyses and Meta-regression

Only the study by Contaldo et al. (20) used a high alcohol dosage (70 g/day) and measured insulin and glucose concentrations. Exclusion of this study from the meta-analysis resulted in generally similar results for insulin (SMD −0.18 [−0.36 to −0.01]) and glucose (SMD 0.06 [−0.12 to 0.23]).

Combining the two intervention arms of the studies by Davies et al. (9) with 15 and 30 g alcohol/day and those of Queipo-Ortuño et al. (33) with red wine and gin resulted in generally similar outcomes. The pooled SMD for insulin sensitivity (ISI and HOMA-IR) was 0.06 (−0.11 to 0.24) overall and 0.15 (−0.08 to 0.38) in women. For insulin, SMD was −0.18 (−0.38 to −0.01) overall and −0.22 (−0.43 to −0.02) in women. Including the nonrandomized crossover study by Cordain et al. (13) resulted in generally similar results for insulin (SMD −0.17 [−0.33 to 0.00]) and glucose (SMD 0.08 [−0.09 to 0.25]).

The meta-regression showed no influence of duration (all $P_{trend} > 0.60$) and/or alcohol dosage (all $P_{trend} > 0.67$) on the pooled SMD of ISI and HOMA-IR and of insulin and glucose. Additionally, the meta-regression showed no differences between results from the studies using the HEGC to measured insulin sensitivity and the other studies (SMD −0.03 for HEGC studies vs. 0.09 for other studies, $P = 0.64$).

Publication Bias

Results of the Egger and Begg tests showed publication bias for the outcomes of ISI, ISI and HOMA-IR, and glucose (Supplementary Table 2). Visual inspection of the funnel plots showed some asymmetry, which was due to missing results in favor of alcohol treatment from smaller studies (Supplementary Fig. 2). For ISI and HOMA-IR, we

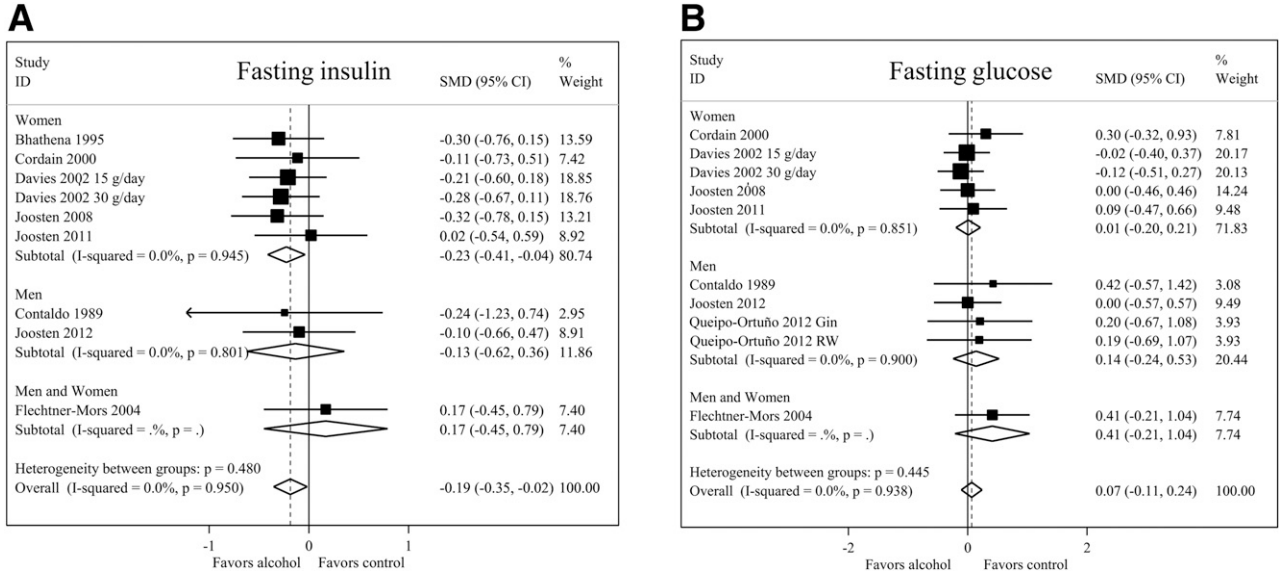

Figure 2—Forest plots of meta-analysis of the effect of alcohol consumption on fasting insulin (*A*) and fasting glucose (*B*). Data are pooled SMDs with 95% CIs. RW, red wine.

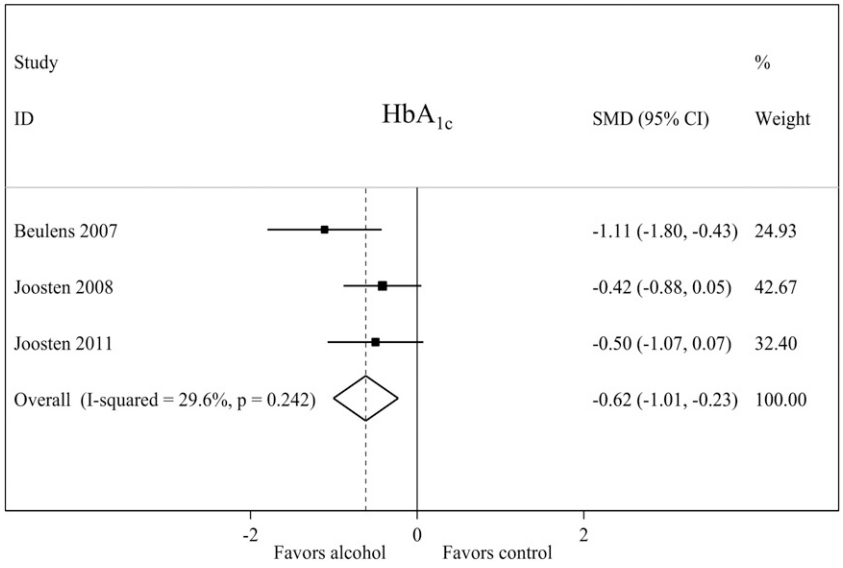

Figure 3—Forest plot of meta-analysis of the effect of alcohol consumption on HbA_{1c}. Data are pooled SMDs with 95% CIs.

calculated an adjusted pooled SMD by using the trim and fill approach by Duval and Tweedie (18). This resulted in four extra study estimates (linear method used) and an adjusted pooled SMD of 0.17 (0.02–0.31, *P* = 0.03). The trim and fill method shows that without publication bias, the pooled SMD would probably indicate a positive effect of alcohol consumption on insulin sensitivity, whereas the unadjusted SMD did not show an effect (SMD 0.08 [−0.09 to 0.24], *P* = 0.35). The adjusted results and funnel plot are shown in Supplementary Table 2 and Supplementary Fig. 2.

CONCLUSIONS

This meta-analysis shows that moderate alcohol consumption did not affect estimates of insulin sensitivity or fasting glucose levels, but it decreased fasting insulin concentrations and HbA_{1c}. Sex-stratified analysis suggested that moderate alcohol consumption may improve insulin sensitivity and decrease fasting insulin concentrations in women but not in men. The meta-regression suggested no influence of dosage and duration on the results. However, the number of studies may have been too low to detect influences by dosage and duration.

Comparison With Other Studies

The primary finding that alcohol consumption does not influence insulin sensitivity concords with the intervention studies included in the review of Hulthe and Fagerberg (5). This is in contrast with observational studies suggesting a significant association between moderate alcohol consumption and improved insulin sensitivity (34,35). However, the results of these studies might be biased through residual confounding because of their observational nature. Moreover, in contrast to intervention studies, observational studies are not designed to detect a causal relationship. On the other hand, we cannot exclude the possibility that the intervention studies in this review had an insufficient sample size or too short a duration to detect an effect of alcohol consumption on insulin sensitivity (10,21,23,24).

We found lower fasting insulin levels after alcohol consumption. This finding agrees with the inverse relation between alcohol consumption and insulin levels observed in observational studies (36–39). However, in the DESIR (Data from an Epidemiological Study on the Insulin Resistance syndrome) cohort, a longitudinal study, no relation between the average or a change in alcohol consumption and fasting insulin levels was found, but this may be a result of the inclusion of subjects with type 2 diabetes (40). Fasting insulin level is a surrogate marker of insulin sensitivity in healthy subjects, with lower insulin levels indicating higher insulin sensitivity (11,41). Conversely, low insulin levels are a common phenomenon in subjects with type 2 diabetes due to impaired insulin secretion by β-cells. Because we excluded studies in subjects with type 2 diabetes, the results of lower fasting insulin levels may indicate higher insulin sensitivity. Additionally, we observed no change in glucose levels by alcohol consumption, and lower insulin levels coinciding with unchanged glucose levels suggest an improved insulin sensitivity.

The current meta-analysis suggests that men and women might respond differently to a period of alcohol consumption with regard to insulin sensitivity. Subgroup analysis showed that the effect of alcohol consumption on insulin sensitivity was only present among women, but the pooled effects in men and women were not significantly different. These results generally concord with observational studies showing a larger risk reduction of moderate alcohol consumption on risk of type 2 diabetes in women than in men (40% vs. 13%) (1) and with the study by Beulens et al. (42). The studies included in the review by Hulthe and Fagerberg (5), which were mainly cross-sectional, did not find sex differences in alcohol effects.

We observed lower levels of HbA_{1c} in subjects consuming moderate amounts of alcohol compared with abstainers. This has also been shown in several observational studies (39,43,44). Alcohol may decrease HbA_{1c} by suppressing the acute rise in blood glucose after a meal and increasing the early insulin response (45). This would result in lower glucose concentrations over time and, thus, lower HbA_{1c} concentrations. Unfortunately, the underlying mechanism of glycemic control by alcohol is not clearly understood.

Strengths and Weaknesses of the Study

A major strength of this meta-analysis is the inclusion of studies with a randomized controlled design and the inclusion of several complementary end points, providing a comprehensive overview of the evidence on this topic. There are also limitations that warrant consideration. As in any meta-analysis, the strength of the current study is largely determined by the quality and number of the included studies. The results of the quality assessment show that the larger part of the included studies did

not report or did not take into account some important aspects, such as blinding. Nevertheless, randomization and the inclusion of an alcohol-free control group were the most important quality factors for this review, and only six studies did not satisfy those criteria. Compliance was measured in most studies (17 of 22) but was only reported in 13. However, of these 13 studies, 11 reported good or excellent compliance, suggesting that low compliance did not influence the results of the studies. Second, the analysis of several different outcomes resulted in inclusion of a small number of studies for certain end points, such as HbA_{1c}. Third, only two studies used the gold standard HEGC to estimate insulin sensitivity (11). Because this may lead to inconsistency in the results, we standardized the results of the different studies using Cohen *d*. However, the results from the studies using HEGC were similar to the other intervention studies, and no significant heterogeneity was present except for the combined meta-analysis of ISI and HOMA-IR. This was due to the study of Chiva-Blanch et al. (15), who reported a relatively small variation in HOMA-IR, causing a relatively large SMD. Exclusion of this study removed heterogeneity without changing the effect. Fourth, because most studies used a crossover design, a carryover effect might have influenced the outcomes. Another limitation was the short duration and small sample sizes of the included studies. The average duration of 5.4 weeks may not have been long enough to show detectable differences in insulin sensitivity or glucose status. In addition, effects may change after longer-term intake of alcohol. Therefore, the short-term nature of the included studies does not allow us to draw conclusions on longer-term alcohol consumption.

It is important to note evidence for publication bias for certain outcomes in the current study. The publication bias unexpectedly suggests that smaller studies with positive results are missing. After adjustment for publication bias using the trim and fill method, even a significant increase in insulin sensitivity by alcohol consumption was shown. However, statistical tests for publication bias may yield biased results with small numbers of studies and are prone to heterogeneity (17).

Finally, the results of this research may not be generalizable to all healthy subjects because the selected studies included mainly light to moderate alcohol consumers. Therefore, the period of abstaining from alcohol might also be seen as an intervention, and subjects might have responded differently than alcohol abstainers.

Implications

To draw implications from the current research, the findings need to be placed in a clinical context. In this meta-analysis, we observed that alcohol consumption decreased fasting insulin levels by 0.19, which translates to an ~11% decrease in insulin (−20 pmol/L) in people with impaired glucose tolerance, as calculated from data of the Diabetes Prevention Program study (46), and a 13% decrease in insulin (−5.2 pmol/L) in normoglycemic people, as calculated from data of the Multiethnic Study of Atherosclerosis (MESA) (47). For comparison, metformin treatment results in a 14% decrease in fasting insulin levels and a 40% lower risk of diabetes versus a control group (48). An 11% reduction of fasting insulin levels after alcohol consumption would result in an ~30% reduced risk of diabetes, which is in line with the 40% risk reduction observed among women.

The reduced HbA_{1c} concentration found in the current study by alcohol consumption (SMD −0.62) is equal to a 5% reduction in HbA_{1c} concentration in both the MESA and the Diabetes Prevention Program studies (from 5.4% [36 mmol/mol] to 5.1% [33 mmol/mol] and from 5.9% [41 mmol/mol] to 5.6% [38 mmol/mol], respectively) (46,49). The Diabetes Prevention Program study showed that 4 years of metformin medication and a lifestyle intervention both resulted in a reduction in HbA_{1c} of ~3% (50). Because type 2 diabetes is characterized by hyperglycemia, HbA_{1c} could be seen as a surrogate end point of the disease rather than an intermediate factor in the pathway toward type 2 diabetes. The World Health Organization indeed suggests that a level >6.5% (48 mmol/mol) be used as a cutoff point for diagnosing diabetes (51). In this respect, the current results for HbA_{1c} match with the reduced risk of type 2 diabetes with moderate alcohol consumption. Results of alcohol intake on HbA_{1c} should be carefully interpreted because we included only three intervention studies in the analysis. However, the results suggest that drinking a moderate amount of alcohol is not harmful with regard to insulin sensitivity and glycemic status in healthy adults without type 2 diabetes.

Conclusion

This systematic review and meta-analysis showed that moderate alcohol consumption decreased fasting insulin and HbA_{1c} concentrations among nondiabetic subjects. Alcohol consumption might improve insulin sensitivity among women but did not do so overall. These results may partly explain the lower risk of type 2 diabetes with moderate alcohol consumption found in observational studies. However, more intervention studies with a longer intervention period are necessary to confirm the results.

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