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Effects of Initiating Moderate Alcohol Intake on Cardiometabolic Risk in Adults With Type 2 Diabetes

A 2-Year Randomized, Controlled Trial

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Background: Recommendations for moderate alcohol consumption remain controversial, particularly in type 2 diabetes mellitus (T2DM). Long-term randomized, controlled trials (RCTs) are lacking.

Objective: To assess cardiometabolic effects of initiating moderate alcohol intake in persons with T2DM and whether the type of wine matters.

Design: 2-year RCT (CASCADE [CArdiovaSCulAr Diabetes & Ethanol] trial). (ClinicalTrials.gov: NCT00784433)

Setting: Ben-Gurion University of the Negev–Soroka Medical Center and Nuclear Research Center Negev, Israel.

Patients: Alcohol-abstaining adults with well-controlled T2DM.

Intervention: Patients were randomly assigned to 150 mL of mineral water, white wine, or red wine with dinner for 2 years. Wines and mineral water were provided. All groups followed a Mediterranean diet without caloric restriction.

Measurements: Primary outcomes were lipid and glycemic control profiles. Genetic measurements were done, and patients were followed for blood pressure, liver biomarkers, medication use, symptoms, and quality of life.

Results: Of the 224 patients who were randomly assigned, 94% had follow-up data at 1 year and 87% at 2 years. In addition to the changes in the water group (Mediterranean diet only), red wine significantly increased high-density lipoprotein cholesterol (HDL-C) level by 0.05 mmol/L (2.0 mg/dL) (95% CI, 0.04 to 0.06 mmol/L [1.6 to 2.2 mg/dL]; $P < 0.001$) and apolipoprotein(a)$_1$ level by 0.03 g/L (CI, 0.01 to 0.06 g/L; $P = 0.05$) and decreased the total cholesterol–HDL-C ratio by 0.27 (CI, −0.52 to −0.01; $P = 0.039$). Only slow ethanol metabolizers (alcohol dehydrogenase alleles [*ADH1B*1*] carriers) significantly benefited from the effect of both wines on glycemic control (fasting plasma glucose, homeostatic model assessment of insulin resistance, and hemoglobin A_{1c}) compared with fast ethanol metabolizers (persons homozygous for *ADH1B*2*). Across the 3 groups, no material differences were identified in blood pressure, adiposity, liver function, drug therapy, symptoms, or quality of life, except that sleep quality improved in both wine groups compared with the water group ($P = 0.040$). Overall, compared with the changes in the water group, red wine further reduced the number of components of the metabolic syndrome by 0.34 (CI, −0.68 to −0.001; $P = 0.049$).

Limitation: Participants were not blinded to treatment allocation.

Conclusion: This long-term RCT suggests that initiating moderate wine intake, especially red wine, among well-controlled diabetics as part of a healthy diet is apparently safe and modestly decreases cardiometabolic risk. The genetic interactions suggest that ethanol plays an important role in glucose metabolism, and red wine's effects also involve nonalcoholic constituents.

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The risk–benefit balance of moderate alcohol consumption in persons with diabetes is controversial (1, 2). Epidemiologic studies suggest that the incidence of type 2 diabetes mellitus (T2DM) is reduced among moderate alcohol drinkers (3–7). Among healthy persons (8, 9) and diabetic patients (10–12), moderate alcohol consumption is linked to lower cardiovascular and total mortality rates. Yet, whether to recommend initiation of moderate alcohol consumption to patients with T2DM is questionable. The American Diabetes Association (13) leaves moderate alcohol consumption to personal preference. The American Heart Association (14) recommends that alcohol use be discussed by the physician and patient, given the lack of long-term trials that support causal cardioprotective effects (15).

A recent systematic review summarized short-term clinical trials (16) that mostly involved healthy participants and suggested that moderate alcohol consumption is associated with favorable patterns of biomarkers of cardiovascular risk. The effect of moderate alcohol

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EDITORS' NOTES

Context

The long-term benefits and risks of moderate alcohol intake among patients with type 2 diabetes mellitus (T2DM) are unclear.

Contribution

Alcohol-abstaining patients with T2DM were randomly assigned to 150 mL (5 ounces) of red wine, white wine, or mineral water with dinner for 2 years. Primary study outcomes included lipid and glycemic control measures.

Caution

The trial did not include a grape juice control group.

Implication

Moderate alcohol intake, particularly red wine, among patients with T2DM was associated with decreased cardiometabolic risks and no significant adverse events. Genetic typing for alcohol dehydrogenase may identify patients who may benefit clinically from moderate alcohol consumption.

consumption on blood pressure (BP) (17) and adiposity remains controversial (18, 19).

Some studies (20–23) suggest similar beneficial associations for different alcoholic beverages and implicate ethanol as the primary mediator. In contrast, other studies (24–27) propose that red wine may induce superior benefits; whether red wine confers any advantage over white wine is unclear.

After a 3-month feasibility trial (28) in 109 patients with T2DM, we performed the 2-year CASCADE (CArdiovaSCulAr Diabetes & Ethanol) trial among 224 diabetic patients. We hypothesized that initiating moderate wine consumption would improve cardiometabolic risk mainly because of the ethanol component. Therefore, we predicted similar effects of red and white wine. Because of genetic variability in alcohol metabolism, we further hypothesized that the effects of wine on the metabolic variables would vary by *ADH1B* (*rs1229984*) genotype.

METHODS

Design Overview

The 2-year CASCADE trial involved alcohol-abstaining diabetic participants who were randomly assigned in a parallel design (1:1:1) to mineral water, white wine, or red wine (150 mL at dinnertime). Recruitment of participants began in November 2009. Participants who provided informed consent were weighed and measured at baseline and were randomly assigned to a single-phase, 2-year intervention (June 2010 to May 2012). The protocol did not change after trial commencement (earlier modifications are detailed in **Appendix Figure 1** and the **Appendix**, available at www.annals.org). Further, CASCADE was conducted at 2 centers: Ben-Gurion University of the Negev–Soroka Medical Center (BGU–SMC) and Nuclear Research Center Negev (NRCN) in Israel. The study was approved and monitored by the human subjects committees of SMC and BGU, which also cover the NRCN. No financial compensation was provided to participants.

Setting and Participants

During recruitment, we intentionally avoided any emphasis on the alcohol component to correctly identify alcohol abstainers. Candidates were screened by a physician for eligibility. We included men and women aged 40 to 75 years with T2DM diagnosed according to the American Diabetes Association criteria (29). Exclusion criteria were as follows: more than 1 alcoholic drink per week; personal or family history of addiction, smoking, stroke, or myocardial infarction; major surgery within the past 3 months; using more than 2 insulin injections per day or an insulin pump; triglyceride level greater than 4.52 mmol/L (400 mg/dL), hemoglobin A_{1c} (HbA_{1c}) level less than 6.4% or 10% or more; women with first-degree relatives with breast cancer; or pregnant women.

Randomization and Intervention

We performed the randomization (detailed in the **Appendix**) within strata of patients by recruitment site and planned substudies; we used the PROC PLAN procedure in SAS software, version 9.2 (SAS Institute). At NRCN, participants were randomly assigned to receive water or red wine (1:1 ratio). At BGU–SMC, participants in additional substudies were randomly assigned to water or red wine (1:1 ratio) and the remaining participants to water, red wine, or white wine (1:1:3 ratio). The participants were instructed to consume 150 mL (5 ounces) of the randomly assigned beverage with dinner by using a standard 150 mL measuring glass we provided. The randomized beverages were dry red wine (from Golan Heights Winery; 16.9 g of ethanol [14.2% by volume], with 270.1 mg of gallic acid equivalent of total phenols; 120 kcal/150 mL), dry white wine (from Golan Heights Winery; 15.8 g of ethanol [13.3% by volume], with 38.5 mg of gallic acid equivalent of total phenols; 111 kcal/150 mL), or mineral water (from Mey Eden). The red wine had 7-fold higher levels of total phenols and between 4- to 13-fold higher levels of the specific resveratrol group compounds than the white wine. We provided the beverages at no charge for 2 years (mineral water, 18.9 L/mo; white wine, 750 mL/mo [6 bottles]; or red wine, 325 mL/mo [14 bottles]). Patients assigned to consume wine were instructed to initiate drinking gradually over the first month and avoid driving after drinking. The participants were asked to return the empty bottles at each visit to monitor use.

Mediterranean Dietary Guidelines

In an attempt to achieve a comparable healthy diet and provide an incentive to participate, we provided all participants with guidelines to follow a Mediterranean diet as per our previous 2-year DIRECT (Dietary Inter-

Table 1. Baseline Characteristics of the CASCADE Study Population*

Variable	Mineral Water (*n* = 83)	White Wine (*n* = 68)	Red Wine (*n* = 73)	Total (*n* = 224)
Age, *y*	59.1 (6.7)	60.6 (6.8)	59.3 (7.8)	59.7 (7.1)
Men, *%*	65	65	77	69
BMI, *kg/m²*	29.7 (4.0)	30.4 (5.1)	30.0 (4.1)	30.0 (4.4)
Ethanol intake, *g/d*	2.1 (2.6)	2.5 (3.0)	2.5 (3.4)	2.3 (3.0)
Metabolic syndrome components				
HDL-C level				
Total				
mmol/L	1.09 (0.31)	1.11 (0.27)	1.18 (0.33)	1.12 (0.34)
mg/dL	42.1 (12.1)	43.0 (10.6)	45.7 (12.9)	43.5 (13.0)
Men				
mmol/L	1.03 (0.26)	1.04 (0.24)	1.12 (0.32)	1.06 (0.28)
mg/dL	39.7 (10.0)	40.0 (9.4)	43.3 (12.5)	41.1 (10.9)
Women				
mmol/L	1.21 (0.37)	1.25 (0.28)	1.38 (0.30)	1.27 (0.33)
mg/dL	46.6 (14.3)	48.3 (10.9)	53.4 (11.6)	48.9 (12.7)
Triglyceride level				
mmol/L	1.7 (1.3)	1.6 (0.7)	1.5 (0.7)	1.6 (1.0)
mg/dL	150.4 (118.5)	141.0 (65.8)	133.2 (65.7)	141.9 (88.8)
FPG level				
mmol/L	8.3 (2.3)	8.5 (2.1)	8.3 (1.8)	8.3 (2.1)
mg/dL	149.5 (40.6)	153.3 (38.2)	148.9 (32.9)	150.4 (37.3)
BP, *mm Hg*				
Systolic	136.3 (17.4)	136.3 (19.2)	139.7 (19.0)	137.4 (18.5)
Diastolic	77.2 (10.3)	77.4 (11.1)	79.4 (11.1)	78.0 (10.8)
Waist circumference, *cm*				
Total	104.4 (9.7)	105.2 (13.4)	105.3 (9.6)	104.9 (10.9)
Men	104.1 (8.9)	108.5 (13.7)	106.8 (8.4)	106.3 (10.5)
Women	104.8 (11.3)	98.7 (10.4)	100.2 (11.5)	101.7 (11.2)
Mean positive metabolic syndrome criteria (SD), *n*	3.0 (1.2)	3.2 (1.3)	3.0 (1.2)	3.1 (1.2)
Other variables				
Glycemic biomarkers				
HbA_{1c} level, *%*	6.9 (1.1)	6.9 (1.0)	6.8 (0.9)	6.9 (1.0)
Fasting insulin level, *pmol/L*	91 (49)	105 (68)	96 (53)	97 (57)
HOMA-IR score	4.8 (3.4)	5.7 (4.2)	5.0 (3.2)	5.2 (3.6)
Lipid biomarkers				
LDL-C level				
mmol/L	2.43 (0.79)	2.33 (0.80)	2.45 (0.81)	2.41 (0.80)
mg/dL	93.9 (30.5)	90.0 (30.9)	94.7 (31.2)	93.0 (30.8)
Apolipoprotein$(a)_1$ level, *g/L*	1.4 (0.2)	1.4 (0.2)	1.4 (0.2)	1.4 (0.2)
Apolipoprotein$(b)_{100}$ level, *g/L*	0.92 (0.20)	0.90 (0.20)	0.91 (0.20)	0.91 (0.20)
Total cholesterol-HDL-C ratio	4.3 (1.4)	4.0 (1.1)	4.0 (1.2)	4.1 (1.3)
Apolipoprotein$(b)_{100}$–apolipoprotein$(a)_1$ ratio	0.68 (0.19)	0.67 (0.19)	0.64 (0.19)	0.66 (0.19)
Liver function biomarkers				
ALT level, *U/L*	28.6 (4.2)	28.0 (11.5)	30.9 (13.9)	28.8 (13.3)
AST level, *U/L*	24.8 (10.1)	24.35 (10.7)	25.1 (8.4)	24.8 (9.7)
ALP level, *μkat/L*	1.1 (0.3)	1.0 (0.3)	1.1 (0.3)	1.1 (0.3)
Bilirubin level				
μmol/L	8.21 (5.13)	8.03 (5.13)	8.38 (5.11)	8.21 (5.13)
mg/dL	0.48 (0.30)	0.47 (0.30)	0.49 (0.30)	0.48 (0.30)
Genotype				
ADH1B polymorphism, %†				
CC (*ADH1B**1)	27.6	45.0	36.4	35.6
CT (*ADH1B**1*2)	44.7	46.7	37.9	43.1
TT (ADH1B*2, rs1229984)	27.6	8.3	25.8	21.3
Number of different medications in current use, *n (%)*				
Oral glycemic control				
0	19 (22.9)	14 (20.6)	20 (27.4)	53 (23.7)
1	38 (45.8)	33 (48.5)	25 (34.2)	96 (42.9)
2	23 (27.7)	16 (23.5)	21 (28.8)	60 (26.8)
3–4	3 (3.6)	5 (7.4)	7 (9.6)	15 (6.7)
Insulin treatment‡				
0	73 (88.0)	60 (88.2)	63 (86.3)	196 (87.5)
1	10 (12.0)	7 (10.3)	10 (13.7)	27 (12.1)
2	0 (0)	1 (1.5)	0 (0)	1 (0.4)
Lipid-lowering therapy				
0	26 (31.3)	21 (30.9)	26 (35.6)	73 (32.6)
1	49 (59.0)	38 (55.9)	39 (53.4)	126 (56.3)
2	8 (9.6)	9 (13.2)	8 (11.0)	25 (11.2)

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Table 1–Continued

Variable	Mineral Water (*n* = 83)	White Wine (*n* = 68)	Red Wine (*n* = 73)	Total (*n* = 224)
Antihypertensive therapy				
0	37 (44.6)	26 (38.2)	38 (52.1)	101 (45.1)
1	26 (31.3)	29 (42.6)	20 (27.4)	75 (33.5)
2	11 (13.3)	8 (11.8)	8 (11.0)	27 (12.1)
3–4	9 (10.8)	5 (7.4)	7 (9.6)	21 (9.4)
Antiplatelet agents				
0	38 (45.8)	31 (45.6)	36 (49.3)	105 (46.9)
1	42 (50.6)	35 (51.5)	36 (49.3)	113 (50.4)
2	3 (3.6)	2 (2.9)	1 (1.4)	6 (2.7)
Other				
0	52 (62.7)	40 (58.8)	41 (56.2)	133 (59.4)
1	17 (20.5)	16 (23.5)	18 (24.7)	51 (22.8)
2	7 (8.4)	6 (8.8)	9 (12.3)	22 (9.8)
3	5 (6.0)	4 (5.9)	3 (4.1)	12 (5.4)
≥4	2 (2.4)	2 (3.0)	2 (2.8)	6 (2.5)
Distribution of participants by recruitment site, %				
BGU-SMC	64	100	60	74
NRCN	36	0	40	26

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BGU–SMC = Ben-Gurion University of the Negev–Soroka Medical Center; BMI = body mass index; BP = blood pressure; CASCADE = CArdiovaSCulAr Diabetes & Ethanol; FPG = fasting plasma glucose; HbA_{1c} = hemoglobin A_{1c}; HDL-C = high-density lipoprotein cholesterol; HOMA-IR = homeostatic model assessment of insulin resistance; LDL-C = low-density lipoprotein cholesterol; NRCN = Nuclear Research Center Negev.
* 224 participants had type 2 diabetes. Values are means (SDs) unless otherwise indicated. Median time from baseline measurements to randomization was 30 d.
† DNA samples for *ADH1B* analysis were available for only 203 participants.
‡ Injections per day.

vention Randomized Controlled Trial) findings (30). We made no attempt to restrict calories. Group sessions were held for all participants by clinical dietitians at 1-month intervals for the first 3 months and at 3-month intervals thereafter. Wine was not discussed at these meetings.

Outcomes and Follow-up

Primary outcomes were lipid profile variables (high-density lipoprotein cholesterol [HDL-C] level, apolipoprotein(a)$_1$ level, and total cholesterol–HDL-C ratio) and glycemic control (fasting plasma glucose [FPG] level and homeostasis model assessment of insulin resistance [HOMA-IR] score). Secondary outcomes were the other components of the metabolic syndrome (triglyceride levels, BP, and waist circumference) (31), other lipid and glycemic control biomarkers, genetic interaction and safety variables (specific symptoms, medication use, and liver function tests), and quality-of-life indicators. Blood samples were obtained at 0, 6, and 24 months at 8 a.m. after an 8-hour fast; stored at −80 °C; and analyzed at laboratories in Leipzig, Germany, for biomarkers of glycemic control, lipid levels, and liver function (listed in **Table 1**; assay methods are described in the **Appendix**). We calculated the HOMA-IR score according to the following equation (32): insulin (U/mL) × fasting glucose (mmol/L) ÷ 22.5. Participants (33) were weighed without shoes to the nearest 0.1 kg. Waist circumference was measured halfway between the last rib and the iliac crest. Two BP measurements were recorded after resting using an automatic BP monitor (Datascope Accutorr 4 [Datascope]).

Genetic Analysis of Alcohol Dehydrogenase

Genotyping of *ADH1B*1* and *ADH1B*2* (*rs1229984* [www.snpedia.com/index.php/Rs1229984]) (34) was done on a 7300 Real-Time Polymerase Chain Reaction system (Applied Biosystems) using AccuStart Genotyping ToughMix, ROX (Biosearch Technologies), using blood samples from month 6.

Electronic Questionnaires

At 0, 6, and 24 months, participants completed validated (35, 36) electronic questionnaires (30), which collected data on demographics, lifestyle patterns, specific medications and symptoms, and quality of life (**Appendix**) (28). We assessed adherence to the beverage assignment by tracking the returned bottles and having participants complete a specific questionnaire about all alcohol intake within or outside of the protocol. Participants also ranked their degree of adherence to the assigned beverages using a scale of 0% to 100%.

Statistical Analysis

Our primary end points were lipid profile and glycemic control biomarkers. We conducted intention-to-treat analyses, which included all 224 randomly assigned participants; further, we performed the longitudinal analysis (population-averaged generalized estimating equation models) using all available data through the most recent value, with multiple imputation for missing data at later time points. We analyzed all of the data using raw values without transformation. We calculated generalized estimating equation models with exchangeable correlation structure to account for within-subject correlations and Huber–White robust errors (using the "robust" option to the xtgee command

in Stata, version 12 [StataCorp]) adjusted for age, sex, and the use of specific medications (lipid-lowering medications for lipid biomarkers, oral medications for glycemic control biomarkers, and antihypertensive medications for BP). The main results present the changes from baseline in the wine groups compared with the change from baseline in the water group and the corresponding 95% CIs. We did a sensitivity analysis to compare participants who dropped out with those who completed the study; we also analyzed only participants who completed the study. We assessed the changes in sex-specific criteria values of the metabolic syndrome (31) over 24 months.

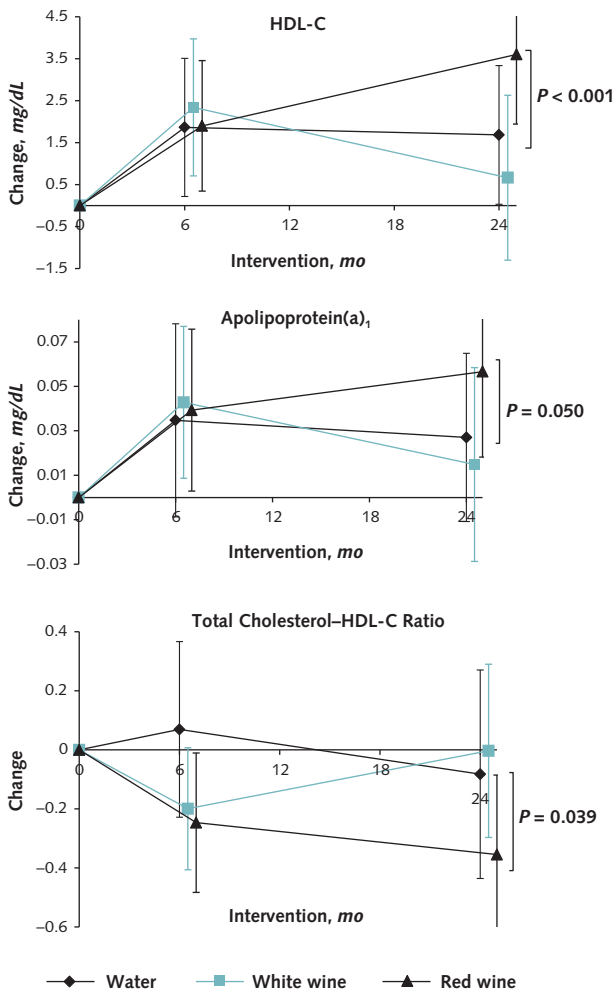
We evaluated the *ADH1B* polymorphism for Hardy–Weinberg equilibrium and tested its effect on biomarker levels. We calculated mean changes in biomarkers within each of the 3 *ADH1B* genotypes for the combined red and white wine groups and the water group, and we tested for interaction between genotype and wine or water groups. For the analysis involving the glycemic variables, BP, and lipid and liver function biomarkers, we pooled data from carriers of either 1 or 2 wild-type alleles (CC and CT) and compared the data with participants who were homozygous for the TT (*rs1229984*) allele based on the biological effect and to enhance statistical power.

On the basis of the results of our pilot study (28), which compared the effects of wine with nonalcoholic beer on glycemic control, we did not perform a formal power calculation for this study. All *P* values were 2-sided. We used Stata software, version 12, and SPSS software, version 19 (IBM), for statistical analyses.

Role of the Funding Source

The European Foundation for the Study of Diabetes provided funding for the study. Beverages were provided by Mey Eden and Golan Heights Winery. These sources were not involved in the design of the study, collection of data, statistical analysis, manuscript preparation or interpretation, or decisions about submission for publication.

Figure 1. Changes in key lipid biomarkers.



The *P* values represent the comparison of 2-y differences in the red wine group versus the water group. Variables are mean changes; bars indicate 95% CIs, and the between-group analyses for differences are for 2 y. At 6 mo, the participants who completed the study were as follows: mineral water, 81; white wine, 62; red wine, 73. After 2 y, 30 participants dropped out (incomplete set of observations). The participants who completed the study were as follows: mineral water, 78; white wine, 52; red wine, 64. To convert HDL-C values to mmol/L, multiply by 0.0259. To convert apolipoprotein(a)$_1$ values to g/L, multiply by 0.01. HDL-C = high-density lipoprotein cholesterol.

RESULTS

Baseline Characteristics

Of the 224 randomly assigned participants, 94% and 87% completed the 12- and 24-month assessments, respectively (mineral water, 94%; white wine, 77%; red wine, 88%; *P* = 0.007 among groups) (**Appendix Figure 1**). Baseline characteristics were distributed similarly across the groups (**Table 1**). The participants (aged 59 years; 69% men; HbA_{1c} level, 6.9%) had an average of 3.1 of 5 criteria of the metabolic syndrome. Most participants were receiving medications for diabetes, hypertension, and hypercholesterolemia. Baseline alcohol intake was 2.3 grams per day (approximately 1 drink per week). The BGU-SMC participants (**Appendix Table 1**, available at www.annals.org) were slightly older, had a smaller proportion of men, and had lower total cholesterol–HDL-C ratio than NRCN participants. All other baseline biomarkers and ethanol consumption were similar.

Adherence

During the trial, participants in the wine groups increased their intake of the specifically assigned wines (approximately 80% consumed daily), and the mineral water group participants remained alcohol abstainers. Beverage adherence, as reflected in the self-reported scale (1% to 100%), was 82%, 85%, and 80% at 6 months and 87%, 84%, and 84% at 2 years for mineral water, white wine, and red wine groups, respectively (**Appendix Figure 2**, available at www.annals.org).

Table 2. Mean 2-y Changes From Baseline in Cardiometabolic Variables in the CASCADE Trial*

Variable	Mineral Water (*n* = 83)	White Wine (*n* = 68)		
	Mean Change (95% CI)	Mean Change (95% CI)	Differences of the Mean Changes vs. Water (95% CI)†	*P* Value
Primary outcomes				
HDL-C level				0.30
mmol/L	0.04 (0.0008 to 0.09)	0.02 (−0.03 to 0.07)	−0.03 (−0.08 to 0.02)	
mg/dL	1.70 (0.03 to 3.30)	0.66 (−1.30 to 2.60)	−1.00 (−3.00 to 0.90)	
Apolipoprotein(a)$_1$ level, *g/L*	0.03 (−0.01 to 0.06)	0.02 (−0.03 to 0.06)	−0.01 (−0.07 to 0.04)	0.65
Total cholesterol–HDL-C ratio	−0.08 (−0.44 to 0.27)	−0.003 (−0.300 to 0.290)	0.08 (−0.08 to 0.23)	0.35
FPG level				0.004
mmol/L	0.57 (−0.03 to 1.18)	−0.4 (−0.9 to 0.1)	−1.0 (−1.6 to −0.3)	
mg/dL	10.30 (−0.63 to 21.20)	−7.1 (−15.7 to 1.6)	−17.2 (−28.9 to −5.5)	
HOMA-IR score	−0.19 (−0.87 to 0.49)	−1.36 (−2.00 to −0.74)	−1.20 (−2.10 to −0.20)	0.019
Secondary outcomes				
Apolipoprotein (b)$_{100}$–apolipoprotein(a)$_1$ ratio	0.01 (−0.03 to 0.04)	0.02 (−0.03 to 0.07)	0.01 (−0.02 to 0.05)	0.47
Triglyceride level				0.004
mmol/L	0.1 (−0.2 to 0.4)	0.02 (−0.1 to 0.2)	−0.09 (−0.2 to −0.03)	
mg/dL	10.4 (−17.8 to 38.7)	1.6 (−13.0 to 16.2)	−7.9 (−13.3 to −2.5)	
LDL-C level				0.59
mmol/L	0.05 (−0.1 to 0.2)	0.1 (−0.1 to 0.4)	0.06 (−0.2 to 0.3)	
mg/dL	2.1 (−5.1 to 9.4)	4.5 (−4.9 to 14.0)	2.2 (−5.9 to 10.4)	
Apolipoprotein(b)$_{100}$ level, *g/L*	0.03 (−0.02 to 0.09)	0.04 (−0.02 to 0.11)	0.01 (−0.05 to 0.07)	0.77
Fasting insulin level, *pmol/L*	−10.42 (−20.14 to −0.49)	−20.1 (−29.9 to −10.4)	−9.72 (−23.61 to 3.75)	0.155
HbA_{1c} level, *%*	0.34 (0.08 to 0.60)	0.27 (0.07 to 0.47)	−0.06 (−0.56 to 0.44)	0.82
Systolic BP, *mm Hg*	−4.80 (−9.70 to 0.14)	1.7 (−3.9 to 7.3)	6.40 (−0.98 to 13.80)	0.089
Diastolic BP, *mm Hg*	−0.9 (−3.8 to 2.1)	−1.3 (−4.8 to 2.1)	−0.40 (−2.50 to 1.70)	0.71
Waist circumference, *cm*	−1.80 (−3.00 to −0.54)	−1.400 (−2.800 to 0.002)	0.39 (−1.40 to 2.20)	0.67
Weight, *kg*	−1.30 (−2.00 to −0.57)	−1.50 (−2.30 to −0.70)	−0.20 (−1.40 to 0.97)	0.74
Number of positive metabolic syndrome criteria	−0.01 (−0.25 to 0.22)	−0.20 (−0.52 to 0.11)	−0.16 (−0.51 to 0.19)	0.38

BP = blood pressure; CASCADE = CArdiovaSCulAr Diabetes & Ethanol; FPG = fasting plasma glucose; HbA_{1c} = hemoglobin A_{1c}; HDL-C = high-density lipoprotein cholesterol; HOMA-IR = homeostatic model assessment of insulin resistance; LDL-C = low-density lipoprotein cholesterol.
* After 2 y of the intervention, 30 participants dropped out and had incomplete sets of observations. The following participants completed the intervention: mineral water (*n* = 78), white wine (*n* = 52), and red wine (*n* = 64).
† Between-group analyses for 2-y differences.

Two-Year Changes

All of the findings are presented as the change from baseline in the wine groups compared with the change from baseline in the water group.

Primary Outcomes

After 2 years (Figure 1 and Table 2), HDL-C levels significantly increased in the red wine group by 0.05 mmol/L (2.0 mg/dL) (95% CI, 0.04 to 0.06 mmol/L [1.6 to 2.2 mg/dL]; $P < 0.001$) compared with the water group. Changes in apolipoprotein(a)$_1$ levels in the red wine group had a similar pattern (0.03 g/L [CI, 0 to 0.06 g/L]; $P = 0.050$) compared with the water group. Beneficial 2-year changes include that the total cholesterol–HDL-C ratio further decreased in the red wine group by 0.27 (CI, −0.52 to −0.01; $P = 0.039$) compared with the water group. The corresponding lipid changes in the white wine group were not significantly different from those in the water group.

Although both wines tended to improve some glucose metabolism components after 2 years, only white wine significantly decreased fasting plasma glucose level by 1.0 mmol/L (−17.2 mg/dL) (CI, −1.60 to −0.3 mmol/L [−28.9 to −5.5 mg/dL]; $P = 0.004$) and HOMA-IR score by 1.2 (CI, −2.1 to −0.2; $P = 0.019$) compared with the water group (Figure 2). Primary outcomes did not vary across the recruitment sites (Appendix Figure 3, available at www.annals.org). The results did not materially differ among participants who completed the trial compared with the entire group (Appendix Figure 1).

Secondary Outcomes

The apolipoprotein(b)$_{100}$-apolipoprotein(a)$_1$ ratio decreased only in the red wine group by 0.03 (CI, −0.06 to 0.00; $P = 0.058$) compared with the water group. Changes in triglyceride levels were more favorable in the white wine group (−0.09 mmol/L [−7.9 mg/dL] [CI, −0.2 to −0.03 mmol/L {−13.3 to −2.5 mg/dL}]; $P = 0.004$) and red wine group (−0.1 mmol/L [−12.0 mg/dL] [CI, −0.3 to −0.02 mmol/L {−22.4 to −1.6 mg/dL}]; $P = 0.023$] than in the water group.

Adiposity and BP

All 3 groups had modest and similar reductions in waist circumference (mean, −1.48 cm) and body weight (mean, −1.4 kg) from baseline. After 2 years of intervention, we found no significant differences in BP among the 3 groups (Table 2).

Table 2–Continued

Red Wine (*n* = 73)		
Mean Change (95% CI)	**Differences of the Mean Changes vs. Water (95% CI)†**	***P* Value**
		<0.001
0.09 (0.05 to 0.14)	0.05 (0.04 to 0.06)	
3.6 (1.9 to 5.3)	2.0 (1.6 to 2.2)	
0.06 (0.02 to 0.10)	0.03 (0 to 0.06)	0.050
−0.36 (−0.62 to −0.09)	−0.27 (−0.52 to −0.01)	0.039
		0.62
0.2 (−0.3 to 0.8)	−0.4 (−1.7 to 1.0)	
4.0 (−5.9 to 13.8)	−6.4 (−31.3 to 18.6)	
−0.98 (−1.70 to −0.30)	−0.77 (−1.70 to 0.17)	0.109
−0.02 (−0.06 to 0.02)	−0.03 (−0.06 to 0)	0.058
		0.023
−0.01 (−0.2 to 0.2)	−0.1 (−0.3 to −0.02)	
−1.3 (−17.5 to 14.9)	−12.0 (−22.4 to −1.6)	
		0.42
0.005 (−0.19 to 0.19)	−0.05 (−0.2 to 0.06)	
0.18 (−7.20 to 7.50)	−1.9 (−6.5 to 2.7)	
0.01 (−0.04 to 0.06)	−0.02 (−0.05 to 0.01)	0.165
−20.1 (−30.6 to −9.7)	−9.7 (−29.2 to 10.4)	0.35
0.12 (−0.08 to 0.32)	−0.22 (−0.64 to 0.20)	0.30
−4.30 (−9.00 to 0.27)	0.48 (−11.00 to 12.00)	0.94
−3.00 (−5.80 to −0.21)	−2.1 (−8.7 to 4.5)	0.54
−1.20 (−2.50 to 0.08)	0.63 (−1.10 to 2.40)	0.48
−1.60 (−2.60 to −0.63)	−0.27 (−1.40 to 0.84)	0.63
−0.40 (−0.60 to −0.17)	−0.34 (−0.68 to 0)	0.049

Genetic Interaction of ADH1B and Wine

Of the 203 participants with available DNA samples, 35.6% were homozygous for the wild-type C allele *ADH1B*1* (CC: "slow ethanol metabolism"), 21.3% were homozygous for *ADH1B*2* (*Arg48His*; *rs1229984*; TT: "fast ethanol metabolism"), and 43.1% were heterozygous (CT), which was consistent with the Hardy–Weinberg equilibrium. We analyzed 2-year genetic data from 173 participants who had DNA samples and had completed the trial. As expected in the water group, changes in biomarkers did not differ across genetic *ADH1B* variants. When the red and white wine groups were combined (Figure 3), however, the improvements in glycemic control were mostly achieved among carriers of *ADH1B*1*. These carriers had favorable significant changes compared with carriers of *ADH1B*2* homozygotes; FPG level was −0.21 mmol/L (−3.8 mg/dL) versus 0.82 mmol/L (14.8 mg/dL; $P = 0.043$), HOMA-IR score was −1.4 versus 0.3 ($P = 0.012$), and HbA_{1c} level was 0.1% versus 0.6% ($P = 0.024$). The test for interaction between genotype and wine or water had a *P* value of less than 0.05.

In contrast to the favorable effect of *ADH1B*1* on glycemic control variables, we found a statistically significant improvement in BP only among the fast metabolizers; homozygotes for *ADH1B*2* (TT; rs1229984) exhibited stronger BP-lowering effects of wine on diastolic ($P = 0.006$) and systolic ($P = 0.059$) BP compared with *ADH1B*1* wild-type C allele carriers. The *ADH1B* polymorphism had no significant effect on changes in lipids induced by wine (mean change in HDL-C level, 0.06 mmol/L [SD, 0.18] [2.2 mg/dL {SD, 7.0}] vs. 0.05 mmol/L [SD, 0.20] [2.0 mg/dL {SD, 7.7}]; change in apolipoprotein(a)$_1$ level, 0.04 g/L [SD, 0. 17] vs. 0.03 g/L [SD, 0.15] of CC vs. TT groups; $P > 0.05$]).

Diet, Quality of Life, Medication Use, and Liver Function Biomarkers

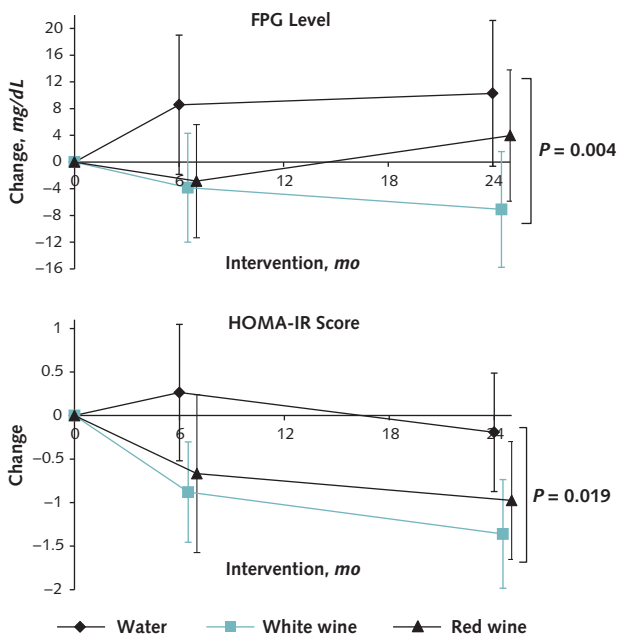
During the trial, the participants had no material changes in energy intake (−36 kcal/d) or energy expenditure (0.78 metabolic equivalents/wk). However, all 3 groups improved their nutrition similarly as expected from the Mediterranean diet (Appendix Figure 4, available at www.annals.org).

We saw no significant wine-related adverse events, symptoms (Appendix Table 2, available at www.annals.org), or changes in quality of life, except that reported sleep quality was significantly improved in both wine groups compared with water ($P = 0.040$).

In all 3 groups, there was no material change in drug therapy according to the use of oral hypoglycemic agents; insulin; or antihypertensive, lipid-lowering, or antiplatelet agents (Appendix Figure 5, available at www.annals.org).

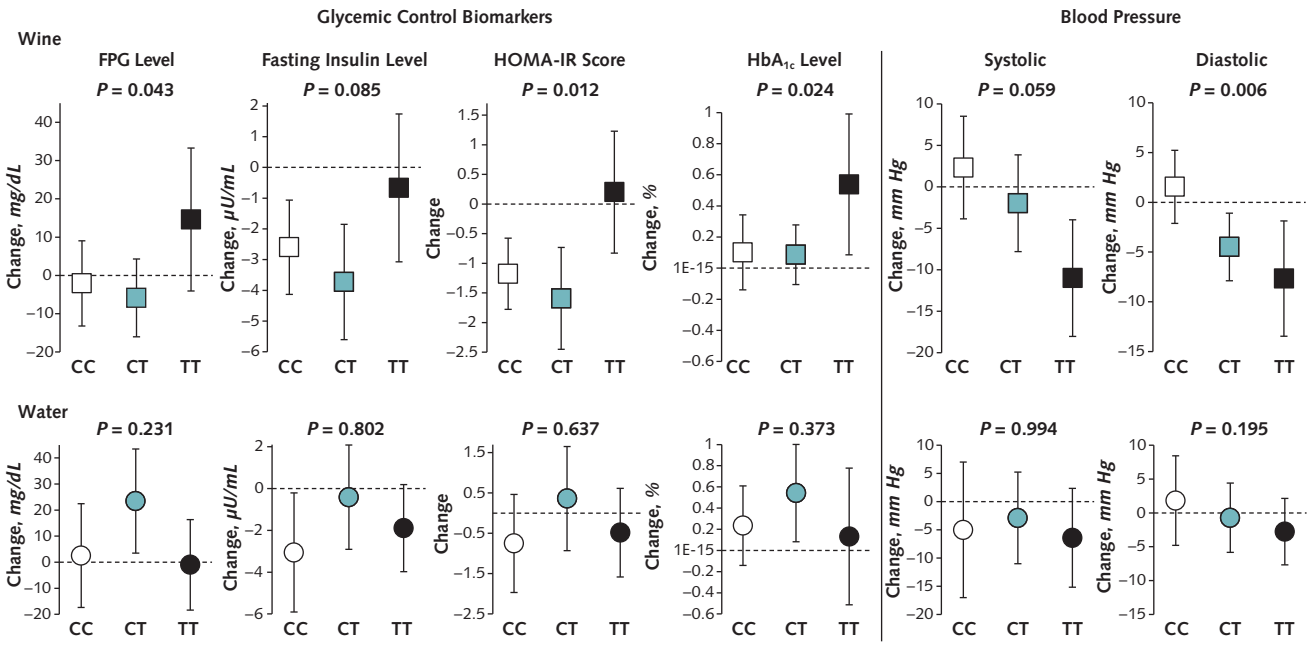
No material changes were seen in liver function tests (alanine aminotransferase, aspartate aminotrans-

Figure 2. Changes in key glycemic control biomarkers.



The *P* values represent the comparison of 2-y differences in the white wine group versus the water group. Variables are mean change; bars indicate 95% CIs, and the between-group analyses for differences are for 2 y. At 6 mo, the participants who completed the study were as follows: mineral water, 81; white wine, 62; red wine, 73. After 2 y, 30 participants dropped out (incomplete set of observations). The participants who completed the study were as follows: mineral water, 78, white wine, 52; red wine, 64. To convert FPG values to mmol/L, multiply by 0.0555. FPG = fasting plasma glucose; HOMA-IR = homeostatic model assessment of insulin resistance.

Figure 3. Effect of long-term consumption of 150 mL of mineral water, white wine, or red wine per day on glycemic control and BP variables in type 2 diabetes mellitus according to genetic variation in *ADH1B*.



The *P* values are for the comparison of the combined genotypes CC (*ADH1B*1* homozygotes; slow alcohol metabolism) and CT (heterozygotes) group versus the TT (*ADH1B*2* homozygotes; fast alcohol metabolism) genotype group. Variables are mean changes; bars indicate 95% CIs, and the between-group analyses for differences are for 2 y. A total of 173 participants with available DNA samples completed the 2-y trial–103 in the combined wine group and 70 in the water group. To convert FPG values to mmol/L, multiply by 0.0555. FPG = fasting plasma glucose; HbA_{1c} = hemoglobin A_{1c}; HOMA-IR = homeostatic model assessment of insulin resistance.

ferase, alkaline phosphatase, or bilirubin) in any of the 3 groups (**Appendix Figure 6**, available at www.annals.org). The *ADH1B* polymorphism had no significant effect on changes in liver enzymes (**Appendix Figure 7**, available at www.annals.org).

Overall Effect on the Metabolic Syndrome

Compared with water, only the red wine group had an overall further significant decrease in the number of variables of the metabolic syndrome by 0.34 (CI, −0.68 to −0.001; $P = 0.049$) (**Table 2**) (**Appendix Figure 8**, available at www.annals.org).

DISCUSSION

There are several clinical implications of this 2-year trial. First, among patients with well-controlled T2DM and a low risk for alcohol abuse, initiating moderate alcohol consumption in the context of a healthy diet is apparently safe and may modestly reduce cardiometabolic risk. Second, red wine may be somewhat superior in improving lipid variables, which indicates the potential synergy of moderate alcohol intake with specific nonalcoholic wine constituents. Third, differential effects on the glycemic control we saw were based on *ADH1B* genetic variants, which indicate that ethanol may play a role in the glycemic effects of the wine intervention. Finally, *ADH1B* variants may assist in identifying patients with T2DM for whom moderate wine consumption may be clinically beneficial.

The study has several limitations. First, study participants were not blinded to group assignment. Second, the gold standard for assessing insulin resistance is the hyperinsulinemic euglycemic clamp (37), but we used fasting insulin and glucose levels to estimate insulin resistance (32). The HOMA-IR score, however, correlates reasonably well with results of clamp studies, including in diabetic patients (38). In addition, change in HDL-C level may not necessarily correlate with HDL functionality (39). Despite the known differences in pharmacokinetics of alcohol by sex (40), we provided similar alcohol doses for both sexes for safety and simplicity. Thus, a 2-glass-per-day regimen among men might have yielded larger changes. We relied on self-reported alcohol intake to assess adherence, but we also monitored use by reviewing returned empty bottles. Finally, we cannot dissect the contribution of nonalcoholic red wine constituents from their combined effect with ethanol.

Strengths of the study include its long duration, use of comprehensive measurements, and high percentage of participants who completed the 2-year follow-up. The nutritional education sessions and free mineral water supply to the control group allowed equal intensity of intervention and enabled assessment of wine-specific effects within the setting of a Mediterranean diet. The CASCADE design benefited from initiating the intervention in a population that generally has low consumption of alcohol (41) and reducing the risk for abuse by including participants older than 40 years

with low addictive risk. Finally, the consistent findings within the groups of glycemic, lipid, liver, BP, and anthropometric variables underscore the robustness of the results.

The differences we saw between red and white wine contrast with our original hypothesis that the beneficial effects of wine are mediated predominantly by alcohol (16, 23). Although our results suggest that the effect of wine on glycemic control was mainly driven by alcohol, a stronger effect of red wine was seen on lipid levels and overall variables of the metabolic syndrome. The provided wines were nearly equal in alcohol and caloric content; however, the levels of total phenols in red wine were 7 times higher. Whether red wine's phenolic compounds (mostly resveratrol and quercetin) (42) render it a uniquely cardioprotective alcoholic beverage is still debated (43–45) because the systemic bioavailability of polyphenols (46) is argued to be low. Differences between red and white wine should be further considered in this context.

The beneficial effect on lipid profile was manifested mostly by increased HDL-C (9.8% increase in the red wine group) and apolipoprotein(a)$_1$ levels. In a recent meta-analysis (16), 30 to 40 g of ethanol per day significantly increased HDL-C levels by 0.09 to 0.10 mmol/L (3.5 to 4 mg/dL) and apolipoprotein(a)$_1$ level by 0.1 g/L; further, triglyceride or low-density lipoprotein cholesterol levels were not affected during short-term (up to 3 months) trials. An 8-week trial in 20 insulin-resistant participants with an alcohol intake of 30 g increased HDL-C levels (47), but this did not occur in a 30-day trial in 18 diabetic patients (48). The increased transport rate of apolipoprotein(a)$_1$ and apolipoprotein(a)$_2$ (49), elevated lipoprotein lipase activity (50), increased cellular cholesterol efflux and its esterification (51), and decreased cholesteryl ester transfer protein activity (52, 53) are some suggested mechanisms for wine's ability to increase HDL-C levels.

The improvement of glycemic control was revealed mainly by changes in FPG level and HOMA-IR score in the white wine group compared with the water group. When alcohol is administered on a short-term basis to diabetic patients, inhibited gluconeogenesis is compensated by increased glycogenolysis and leaves hepatic glucose output unaltered (54). Our earlier 3-month pilot trial (28) showed that FPG level, but not HbA_{1c} or 2-hour postprandial glucose levels, was decreased by wine intervention. In CASCADE, although the hypoglycemic effect was similar within the first 6 months for both the red and white wine groups, white wine had a modest advantage over red wine after 2 years for FPG level; however, this could be a chance finding. The CASCADE participants had well-treated T2DM at baseline, with a satisfactory baseline mean HbA_{1c} level (6.9%). One may speculate that the effect of moderate wine consumption might manifest in decreased HbA_{1c} level only in patients whose metabolic levels are less well-controlled (55).

Class 1 alcohol dehydrogenase contributes to approximately 70% of total hepatic ethanol-oxidizing capacity (56), and a common polymorphism of the *ADH1B* gene, *Arg48His* (*rs1229984*), is associated with greatly enhanced enzymatic activity (56, 57). The gene–alcohol and diabetes risk interaction is controversial in observational studies (58, 59). We found that diabetic patients who were slow alcohol metabolizers had improved glycemic control by initiating moderate wine consumption, which suggests that alcohol may play a role in glucose metabolism. In contrast, diabetic patients who were fast ethanol metabolizers benefited the most from the wine-induced BP-lowering effect, which suggests a mediatory role for ethanol metabolites and potentially explains the inconsistent reports about BP effects on moderate alcohol intake (17). Our results are in accordance with a recent Mendelian randomization analysis of observation studies reporting that carriers of the *ADH1B* (*rs1229984*) had lower BP (2).

Initiation of wine consumption did not alter the number of medications used and did not adversely affect liver function biomarkers or adiposity. The benefit of wine on sleep quality was in accordance with our previous wine trial (28). To our knowledge, CASCADE is the first large, long-term RCT of alcohol, and the results suggest modest beneficial effects of initiating moderate wine consumption among alcohol-abstaining patients older than 40 years with T2DM. These benefits should be weighed against potential risks when translated into clinical practice.

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References

1. **Grønbaek M.** The positive and negative health effects of alcohol-and the public health implications. J Intern Med. 2009;265:407-20. [PMID: 19298457] doi:10.1111/j.1365-2796.2009.02082.x
2. **Holmes MV, Dale CE, Zuccolo L, Silverwood RJ, Guo Y, Ye Z, et al; InterAct Consortium.** Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data. BMJ. 2014;349:g4164. [PMID: 25011450] doi:10.1136/bmj.g4164
3. **Baliunas DO, Taylor BJ, Irving H, Roerecke M, Patra J, Mohapatra S, et al.** Alcohol as a risk factor for type 2 diabetes: A systematic review and meta-analysis. Diabetes Care. 2009;32:2123-32. [PMID: 19875607] doi:10.2337/dc09-0227
4. **Carlsson S, Hammar N, Grill V.** Alcohol consumption and type 2 diabetes Meta-analysis of epidemiological studies indicates a U-shaped relationship. Diabetologia. 2005;48:1051-4. [PMID: 15864527]
5. **Howard AA, Arnsten JH, Gourevitch MN.** Effect of alcohol consumption on diabetes mellitus: a systematic review. Ann Intern Med. 2004;140:211-9. [PMID: 14757619]
6. **Koppes LL, Dekker JM, Hendriks HF, Bouter LM, Heine RJ.** Moderate alcohol consumption lowers the risk of type 2 diabetes: a meta-analysis of prospective observational studies. Diabetes Care. 2005;28:719-25. [PMID: 15735217]
7. **Stampfer MJ, Colditz GA, Willett WC, Manson JE, Arky RA, Hennekens CH, et al.** A prospective study of moderate alcohol drinking and risk of diabetes in women. Am J Epidemiol. 1988;128:549-58. [PMID: 3414660]
8. **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. 1999;319:1523-8. [PMID: 10591709]
9. **Stampfer MJ, Colditz GA, Willett WC, Speizer FE, Hennekens CH.** A prospective study of moderate alcohol consumption and the risk of coronary disease and stroke in women. N Engl J Med. 1988;319:267-73. [PMID: 3393181]
10. **Koppes LL, Dekker JM, Hendriks HF, Bouter LM, Heine RJ.** Meta-analysis of the relationship between alcohol consumption and coronary heart disease and mortality in type 2 diabetic patients. Diabetologia. 2006;49:648-52. [PMID: 16463045]
11. **Solomon CG, Hu FB, Stampfer MJ, Colditz GA, Speizer FE, Rimm EB, et al.** Moderate alcohol consumption and risk of coronary heart disease among women with type 2 diabetes mellitus. Circulation. 2000;102:494-9. [PMID: 10920059]
12. **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. 2001;38:1836-42. [PMID: 11738282]
13. **American Diabetes Association.** Standards of medical care in diabetes–2012. Diabetes Care. 2012;35 Suppl 1:S11-63. [PMID: 22187469] doi:10.2337/dc12-s011
14. **Goldberg IJ, Mosca L, Piano MR, Fisher EA; Nutrition Committee, Council on Epidemiology and Prevention, and Council on Cardiovascular Nursing of the American Heart Association.** AHA Science Advisory: Wine and your heart: a science advisory for healthcare professionals from the Nutrition Committee, Council on Epidemiology and Prevention, and Council on Cardiovascular Nursing of the American Heart Association. Circulation. 2001;103:472-5. [PMID: 11157703]
15. **Ronksley PE, Brien SE, Turner BJ, Mukamal KJ, Ghali WA.** Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. BMJ. 2011;342:d671. [PMID: 21343207] doi:10.1136/bmj.d671
16. **Brien SE, Ronksley PE, Turner BJ, Mukamal KJ, Ghali WA.** Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: systematic review and meta-analysis of interventional studies. BMJ. 2011;342:d636. [PMID: 21343206] doi:10.1136/bmj.d636
17. **Briasoulis A, Agarwal V, Messerli FH.** Alcohol consumption and the risk of hypertension in men and women: a systematic review and meta-analysis. J Clin Hypertens (Greenwich). 2012;14:792-8. [PMID: 23126352] doi:10.1111/jch.12008
18. **Schütze M, Schulz M, Steffen A, Bergmann MM, Kroke A, Lissner L, et al.** Beer consumption and the 'beer belly': scientific basis or common belief? Eur J Clin Nutr. 2009;63:1143-9. [PMID: 19550430] doi:10.1038/ejcn.2009.39
19. **Suter PM.** Is alcohol consumption a risk factor for weight gain and obesity? Crit Rev Clin Lab Sci. 2005;42:197-227. [PMID: 16047538]
20. **Cleophas TJ.** Wine, beer and spirits and the risk of myocardial infarction: a systematic review. Biomed Pharmacother. 1999;53:417-23. [PMID: 10554677]
21. **Hansen AS, Marckmann P, Dragsted LO, Finné Nielsen IL, Nielsen SE, Grønbaek M.** Effect of red wine and red grape extract on blood lipids, haemostatic factors, and other risk factors for cardiovascular disease. Eur J Clin Nutr. 2005;59:449-55. [PMID: 15674304]
22. **Mukamal KJ, Conigrave KM, Mittleman MA, Camargo CA Jr, Stampfer MJ, Willett WC, et al.** Roles of drinking pattern and type of alcohol consumed in coronary heart disease in men. N Engl J Med. 2003;348:109-18. [PMID: 12519921]
23. **Shai I, Rimm EB, Schulze MB, Rifai N, Stampfer MJ, Hu FB.** Moderate alcohol intake and markers of inflammation and endothelial dysfunction among diabetic men. Diabetologia. 2004;47:1760-7. [PMID: 15502925]
24. **Black S.** Clinical and pathologic reports. Newry, UK: Alex Wilkinson; 1819:1-47.
25. **Chiva-Blanch G, Urpi-Sarda M, Llorach R, Rotches-Ribalta M, Guillén M, Casas R, et al.** Differential effects of polyphenols and alcohol of red wine on the expression of adhesion molecules and inflammatory cytokines related to atherosclerosis: a randomized clinical trial. Am J Clin Nutr. 2012;95:326-34. [PMID: 22205309] doi:10.3945/ajcn.111.022889
26. **Estruch R, Sacanella E, Mota F, Chiva-Blanch G, Antúnez E, Casals E, et al.** Moderate consumption of red wine, but not gin, decreases erythrocyte superoxide dismutase activity: a randomised cross-over trial. Nutr Metab Cardiovasc Dis. 2011;21:46-53. [PMID: 19819677] doi:10.1016/j.numecd.2009.07.006
27. **Rimm EB, Klatsky A, Grobbee D, Stampfer MJ.** Review of moderate alcohol consumption and reduced risk of coronary heart disease: is the effect due to beer, wine, or spirits. BMJ. 1996;312:731-6. [PMID: 8605457]
28. **Shai I, Wainstein J, Harman-Boehm I, Raz I, Fraser D, Rudich A, et al.** Glycemic effects of moderate alcohol intake among patients with type 2 diabetes: a multicenter, randomized, clinical intervention trial. Diabetes Care. 2007;30:3011-6. [PMID: 17848609]

29. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 1997;20:1183-97. [PMID: 9203460]
30. **Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, Greenberg I, et al; Dietary Intervention Randomized Controlled Trial (DIRECT) Group.** Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N Engl J Med. 2008;359:229-41. [PMID: 18635428] doi:10.1056/NEJMoa0708681
31. **Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al; International Diabetes Federation Task Force on Epidemiology and Prevention.** Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120:1640-5. [PMID: 19805654] doi:10.1161/CIRCULATIONAHA.109.192644
32. **Neumark YD, Friedlander Y, Durst R, Leitersdorf E, Jaffe D, Ramchandani VA, et al.** Alcohol dehydrogenase polymorphisms influence alcohol-elimination rates in a male Jewish population. Alcohol Clin Exp Res. 2004;28:10-4. [PMID: 14745297]
33. **Shai I, Rosner BA, Shahar DR, Vardi H, Azrad AB, Kanfi A, et al; DEARR study.** Dietary evaluation and attenuation of relative risk: multiple comparisons between blood and urinary biomarkers, food frequency, and 24-hour recall questionnaires: the DEARR study. J Nutr. 2005;135:573-9. [PMID: 15735096]
34. **Chasan-Taber S, Rimm EB, Stampfer MJ, Spiegelman D, Colditz GA, Giovannucci E, et al.** Reproducibility and validity of a self-administered physical activity questionnaire for male health professionals. Epidemiology. 1996;7:81-6. [PMID: 8664406]
35. **Haffner SM, Miettinen H, Stern MP.** The homeostasis model in the San Antonio Heart Study. Diabetes Care. 1997;20:1087-92. [PMID: 9203442]
36. **Golan R, Shelef I, Rudich A, Gepner Y, Shemesh E, Chassidim Y, et al.** Abdominal superficial subcutaneous fat: a putative distinct protective fat subdepot in type 2 diabetes. Diabetes Care. 2012;35:640-7. [PMID: 22344612] doi:10.2337/dc11-1583
37. **DeFronzo RA, Tobin JD, Andres R.** Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol. 1979;237:E214-23. [PMID: 382871]
38. **Katsuki A, Sumida Y, Gabazza EC, Murashima S, Furuta M, Araki-Sasaki R, et al.** Homeostasis model assessment is a reliable indicator of insulin resistance during follow-up of patients with type 2 diabetes. Diabetes Care. 2001;24:362-5. [PMID: 11213893]
39. **Karavia EA, Zvintzou E, Petropoulou PI, Xepapadaki E, Constantinou C, Kypreos KE.** HDL quality and functionality: what can proteins and genes predict? Expert Rev Cardiovasc Ther. 2014;12:521-32. [PMID: 24650316] doi:10.1586/14779072.2014.896741
40. **Baraona E, Abittan CS, Dohmen K, Moretti M, Pozzato G, Chayes ZW, et al.** Gender differences in pharmacokinetics of alcohol. Alcohol Clin Exp Res. 2001;25:502-7. [PMID: 11329488]
41. **Organisation for Economic Co-operation and Development.** Health at a Glance 2011. OCED indicators. OECD Publishing. Accessed at www.oecd.org/els/health-systems/49105858.pdf on 24 August 2015.
42. **Szmitko PE, Verma S.** Antiatherogenic potential of red wine: clinician update. Am J Physiol Heart Circ Physiol. 2005;288:H2023-30. [PMID: 15653767]
43. **Sahebkar A.** Effects of resveratrol supplementation on plasma lipids: a systematic review and meta-analysis of randomized controlled trials. Nutr Rev. 2013;71:822-35. [PMID: 24111838] doi:10.1111/nure.12081
44. **Williamson G, Manach C.** Bioavailability and bioefficacy of polyphenols in humans. II. Review of 93 intervention studies. Am J Clin Nutr. 2005;81:243S-255S. [PMID: 15640487]
45. **Liu Y, Ma W, Zhang P, He S, Huang D.** Effect of resveratrol on blood pressure: a meta-analysis of randomized controlled trials. Clin Nutr. 2015;34:27-34. [PMID: 24731650] doi:10.1016/j.clnu.2014.03.009
46. **Kroon PA, Clifford MN, Crozier A, Day AJ, Donovan JL, Manach C, et al.** How should we assess the effects of exposure to dietary polyphenols in vitro? Am J Clin Nutr. 2004;80:15-21. [PMID: 15213022]
47. **Kim SH, Abbasi F, Lamendola C, Reaven GM.** Effect of moderate alcoholic beverage consumption on insulin sensitivity in insulin-resistant, nondiabetic individuals. Metabolism. 2009;58:387-92. [PMID: 19217456] doi:10.1016/j.metabol.2008.10.013
48. **Bantle AE, Thomas W, Bantle JP.** Metabolic effects of alcohol in the form of wine in persons with type 2 diabetes mellitus. Metabolism. 2008;57:241-5. [PMID: 18191055] doi:10.1016/j.metabol.2007.09.007
49. **De Oliveira E Silva ER, Foster D, McGee Harper M, Seidman CE, Smith JD, Breslow JL, et al.** Alcohol consumption raises HDL cholesterol levels by increasing the transport rate of apolipoproteins A-I and A-II. Circulation. 2000;102:2347-52. [PMID: 11067787]
50. **Nishiwaki M, Ishikawa T, Ito T, Shige H, Tomiyasu K, Nakajima K, et al.** Effects of alcohol on lipoprotein lipase, hepatic lipase, cholesteryl ester transfer protein, and lecithin:cholesterol acyltransferase in high-density lipoprotein cholesterol elevation. Atherosclerosis. 1994;111:99-109. [PMID: 7840818]
51. **van der Gaag MS, van Tol A, Vermunt SH, Scheek LM, Schaafsma G, Hendriks HF.** Alcohol consumption stimulates early steps in reverse cholesterol transport. J Lipid Res. 2001;42:2077-83. [PMID: 11734581]
52. **Savolainen MJ, Hannuksela M, Seppänen S, Kervinen K, Kesäniemi YA.** Increased high-density lipoprotein cholesterol concentration in alcoholics is related to low cholesteryl ester transfer protein activity. Eur J Clin Invest. 1990;20:593-9. [PMID: 2127749]
53. **Hannuksela ML, Rantala M, Kesäniemi YA, Savolainen MJ.** Ethanol-induced redistribution of cholesteryl ester transfer protein (CETP) between lipoproteins. Arterioscler Thromb Vasc Biol. 1996;16:213-21. [PMID: 8620335]
54. **Puhakainen I, Koivisto VA, Yki-Järvinen H.** No reduction in total hepatic glucose output by inhibition of gluconeogenesis with ethanol in NIDDM patients. Diabetes. 1991;40:1319-27. [PMID: 1936594]
55. **Monnier L, Lapinski H, Colette C.** Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). Diabetes Care. 2003;26:881-5. [PMID: 12610053]
56. **Edenberg HJ.** The genetics of alcohol metabolism: role of alcohol dehydrogenase and aldehyde dehydrogenase variants. Alcohol Res Health. 2007;30:5-13. [PMID: 17718394]
57. **Ehrig T, Bosron WF, Li TK.** Alcohol and aldehyde dehydrogenase. Alcohol Alcohol. 1990;25:105-16. [PMID: 2198030]
58. **Beulens JW, Rimm EB, Hendriks HF, Hu FB, Manson JE, Hunter DJ, et al.** Alcohol consumption and type 2 diabetes: influence of genetic variation in alcohol dehydrogenase. Diabetes. 2007;56:2388-94. [PMID: 17563066]
59. **Dakeishi M, Murata K, Sasaki M, Tamura A, Iwata T.** Association of alcohol dehydrogenase 2 and aldehyde dehydrogenase 2 genotypes with fasting plasma glucose levels in Japanese male and female workers. Alcohol Alcohol. 2008;43:143-7. [PMID: 18216179] doi:10.1093/alcalc/agm173

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Appendix

Revisions of the Original Protocol

Modifications of the basic protocol were made between 2008 and 2009 before it was submitted for approval by the institutional review board and before recruitment. The modifications were reported online to the European Foundation for the Study of Diabetes and were as follows:

1. We added dry white wine as an additional intervention group (to address red–white wine differences) and changed the control from dealcoholized red wine to mineral water (as a better control group because it avoids the caloric content of dealcoholized wine).

2. We further excluded smokers and women with family history of breast cancer for safety considerations (to reduce any potential adverse interaction of alcohol with those factors).

3. We added genetic measurements (analysis of *ADH1B* polymorphism) to assess a potential genetic interaction.

4. To simplify the operation, we decided to enroll the patients from 2 centers: BGU–SMC and NRCN. The original plan was to enroll the patients from 3 centers in Israel.

Screening

Participants were recruited by using advertisements for a dietary trial at BGU–SMC and NRCN. Further announcements were made in local press and on radio stations. We intentionally did not emphasize the alcohol component to correctly identify alcohol abstainers. After obtaining informed consent, candidates met with a certified physician (both in the SMC and NRCN clinics) to be screened for inclusion and exclusion criteria and to obtain medical information.

Randomization

The randomization was performed within strata of patients by sites and types of analysis planned for each site group. The 2 sites were NRCN and BGU–SMC. The BGU–SMC site included a subgroup of patients who received additional follow-ups.

Substudies included continuous glucose monitoring, magnetic resonance imaging, and Holter studies. This formed 3 strata: NRCN patients (n = 59); BGU–SMC patients with additional substudy (n = 41); and BGU–SMC patients without additional substudy (n = 124).

The treatments of the first 2 groups were limited to water and red wine with a randomization ratio 1:1 to enhance statistical power to compare these groups within specific substudies. The third group was randomly assigned to 3 treatments—water, red wine, and white wine—with a 1:1:3 ratio to allow for the final ratio of the 3 treatment groups to be 1:1:1. The study population of BGU–SMC included 2 married couples (1 from each stratum). For each couple, the participant with the lower serial number was randomly assigned and the spouses received the same treatment as the randomly assigned spouse.

The randomization was performed by the statisticians from BGU in SAS, version 9.2, using the procedure PROC PLAN.

Electronic Questionnaires

Participants completed electronic questionnaires (at 0, 6, and 24 months) to collect data on demographics, lifestyle patterns, specific medications and symptoms, and quality of life (28). We assessed changes in quality of life by inquiring about the frequency of the following feelings: active, nervous, calm, energetic, depressed, sad, exhausted, and happy. We also assessed changes in hypoglycemia, panic, euphoria, illusions, headaches, bleeding, eye function, diarrhea, body pains, sexual desire, and sleep quality. We assessed adherence to diet by a validated food frequency questionnaire (35) and used a validated questionnaire to assess physical activity (36).

Laboratory Blood Biomarker Methods

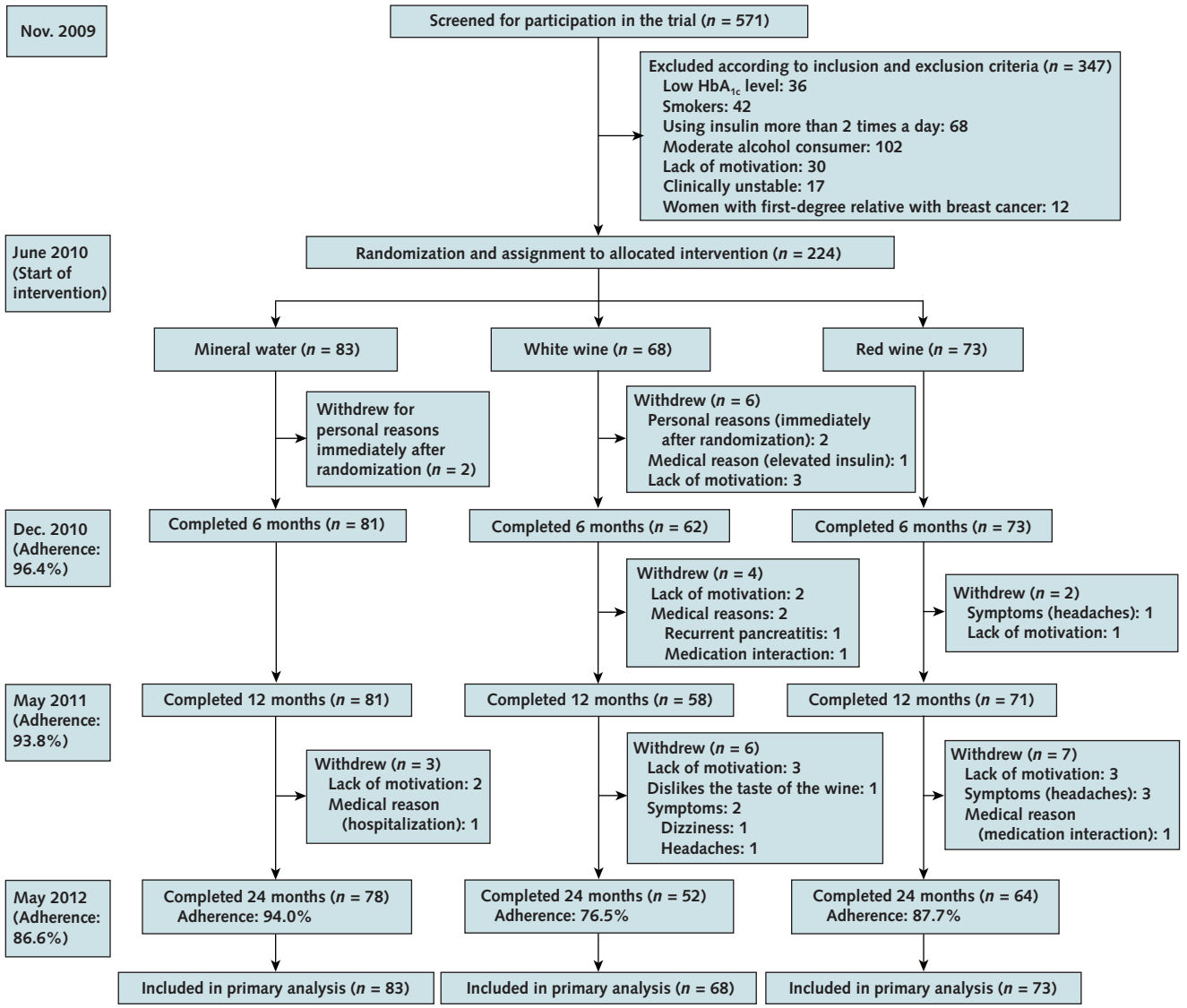
Blood samples were obtained by venipuncture at 8 a.m. after an 8-hour fast at baseline and at 6 and 24 months; samples were stored at −80 °C. Measurements were performed in laboratories in Leipzig, Germany. Fasting plasma glucose level was measured by Roche Glucose Hexokinase, generation 3 (Roche). Glycated hemoglobin (HbA_{1c}) was measured with Tina-quant hemoglobin A_{1c}, generation 3 (Roche). Plasma insulin was measured with the use of an enzyme immunometric assay (Immulite automated analyzer [Diagnostic Products]), with a coefficient of variation (CV) of 2.5%. Serum total cholesterol (CV, 1.3%), HDL-C, low-density lipoprotein cholesterol, and triglycerides (CV, 2.1%) were measured enzymatically with a Cobas 6000 automatic analyzer (Roche). Serum apolipoprotein$(a)_1$ (CV, 1.0% to 4.7%) and apolipoprotein$(b)_{100}$ (CV, 1.1% to 3.1%) were measured by immunoturbidimetric assays (Tina-quant apolipoprotein A-1 and B100, version 2 [Roche]) on a Cobas 6000 automatic analyzer. Liver enzyme and bilirubin were measured with Roche chemicals on the Cobas 6000 (Alkaline Phosphatase acc. to IFCC, generation 2; Alanine Aminotransferase acc. to IFCC with pyridoxal phosphate activation; Aspartate Aminotransferase acc. to IFCC with pyridoxal phosphate activation; Bilirubin Total DPD, generation 2).

Sensitivity Analyses to Evaluate Departures From the Assumption That Data Were Missing at Random

Among the participants who dropped out of the study, baseline characteristics were similar across their assigned intervention groups in demographics, clinical presentation, blood biomarkers, and the use of medications. Comparing those who dropped out with those who completed the study, baseline characteristics in demographics, clinical presentation, blood biomarkers, and the use of medications were similar except that those who dropped out had higher baseline HOMA-IR scores than those who completed the study.

Within each intervention group, baseline characteristics in demographic, clinical presentation, blood biomarkers, and the use of medications were similar between those who dropped out versus completed the study with the exception of the white wine group, in which those who dropped out were younger, had lower baseline HDL-C levels, and used fewer oral glycemic medications than those who completed the study.

Appendix Figure 1. Study flow diagram.



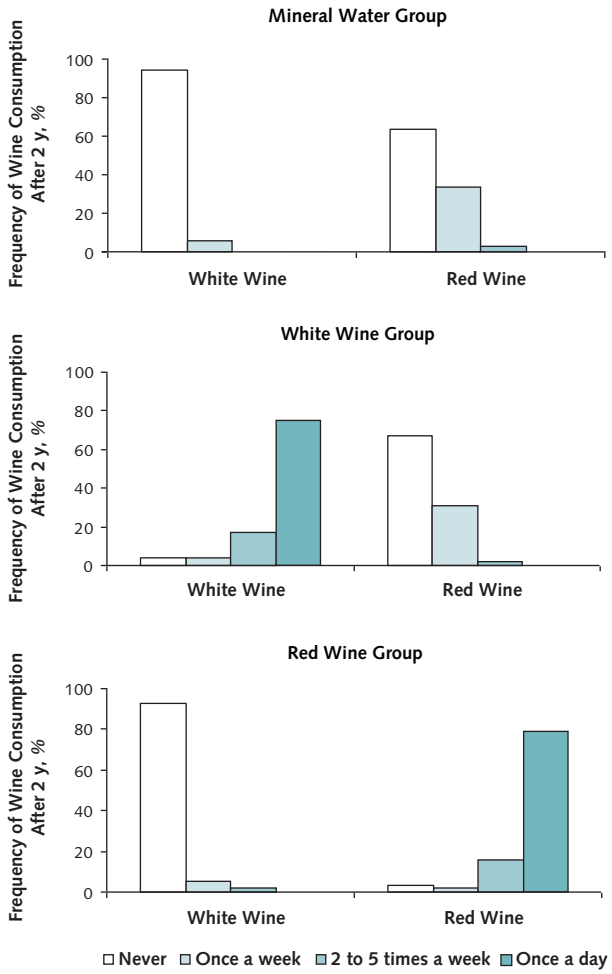
HbA_{1c} = hemoglobin A_{1c}.

Appendix Table 1. Key Demographic and Baseline Characteristics of the CASCADE Study Population, by Center*

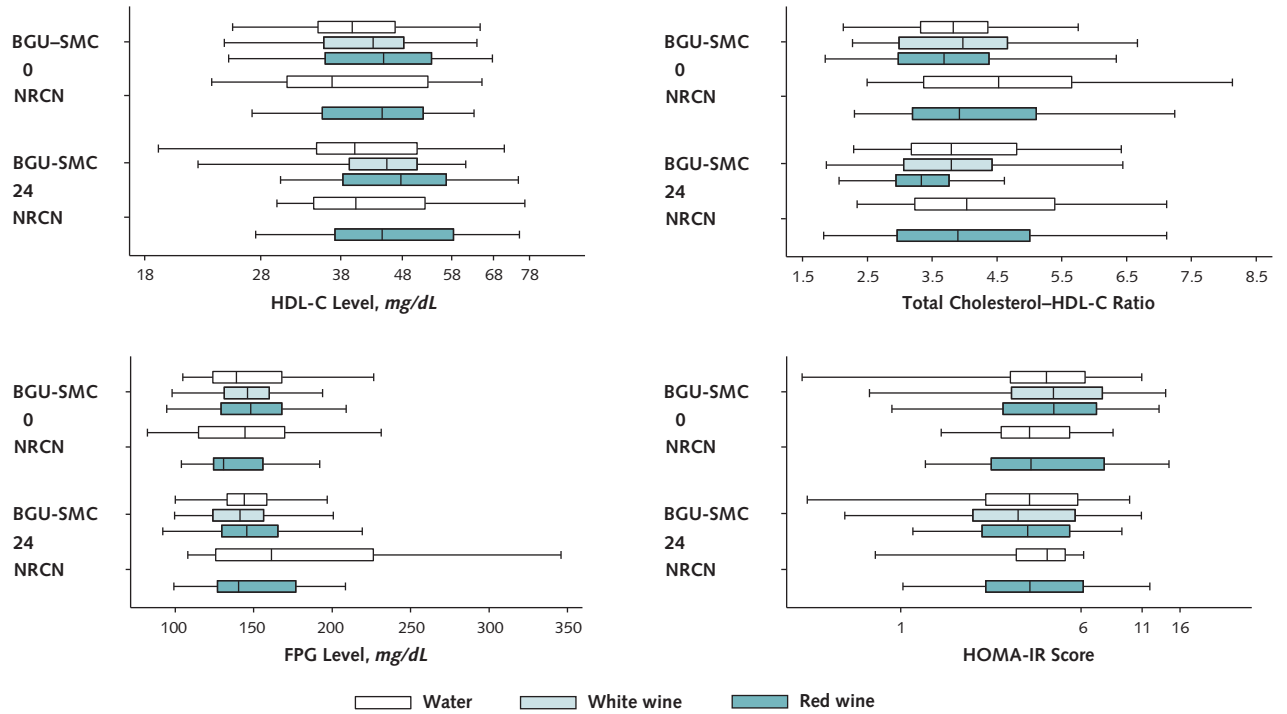
Variable	BGU-SMC				NRCN		
	Mineral Water (*n* = 53)	**White Wine (*n* = 68)**	**Red Wine (*n* = 44)**	**Total (*n* = 165)**	**Mineral Water (*n* = 30)**	**Red Wine (*n* = 29)**	**Total (*n* = 59)**
Age, *y*	60.0 (7.1)	60.6 (6.8)	61.1 (7.5)	60.6 (7.1)	57.4 (5.6)	56.5 (7.4)	57.0 (6.6)
Men, *%*	58	65	66	63	79	93	86
BMI, *kg/m²*	30.3 (4.2)	30.4 (5.1)	29.7 (3.9)	30.2 (4.5)	28.5 (3.6)	30.5 (4.4)	29.5 (4.1)
Ethanol intake, *g/d*	2.2 (2.7)	2.5 (3.0)	1.9 (2.8)	2.3 (2.8)	1.9 (2.6)	3.3 (4.1)	2.6 (3.5)
HDL-C level, *mg/dL*	42.7 (11.8)	43.0 (10.6)	46.0 (12.7)	43.7 (11.6)	40.8 (12.7)	45.1 (13.4)	43.1 (13.1)
Triglyceride level, *mg/dL*	145.0 (130.6)	141.0 (65.8)	128.2 (60.8)	139.0 (91.1)	161.1 (90.8)	140.6 (72.7)	150.5 (81.8)
FPG level, *mg/dL*	147.5 (30.9)	153.3 (38.2)	153.2 (31.7)	151.3 (34.1)	153.8 (56.2)	142.5 (34.2)	147.8 (45.8)
BP, *mm Hg*							
Systolic	138.9 (18.7)	136.3 (19.2)	145.4 (19.4)	139.6 (19.4)	131.0 (13.4)	130.9 (14.8)	131.0 (14.0)
Diastolic	76.9 (11.8)	77.4 (11.2)	80.0 (12.8)	77.9 (11.8)	78.0 (6.9)	78.6 (8.1)	78.3 (7.4)
HbA_{1c} level, %	6.9 (0.88)	6.9 (0.96)	7.0 (0.76)	6.9 (0.88)	6.9 (1.4)	6.7 (1.1)	6.8 (1.2)
Fasting insulin level, *μIU/mL*	13.5 (7.7)	15.1 (9.8)	13.5 (7.3)	14.2 (8.5)	12.2 (5.7)	14.2 (8.3)	13.3 (7.2)
HOMA-IR score	5.0 (3.5)	5.8 (4.2)	5.1 (3.0)	5.3 (3.7)	4.6 (3.3)	5.0 (3.4)	4.8 (3.3)
Total cholesterol–HDL-C ratio	4.1 (1.2)	4.0 (1.1)	3.7 (1.0)	4.0 (1.1)	4.7 (1.5)	4.3 (1.4)	4.5 (1.5)

BGU–SMC = Ben-Gurion University of the Negev–Soroka Medical Center; BMI = body mass index; BP = blood pressure; CASCADE = CArdiova-SCulAr Diabetes & Ethanol; FPG = fasting plasma glucose; HbA_{1c} = hemoglobin A_{1c}; HDL-C = high-density lipoprotein cholesterol; HOMA-IR = homeostatic model assessment of insulin resistance; NRCN = Nuclear Research Center Negev.
* Values are means (SDs). To convert HDL-C values to mmol/L, multiply by 0.0259. To convert FPG values to mmol/L, multiply by 0.0555.

Appendix Figure 2. Adherence to the assigned beverage type after the 2-y intervention.

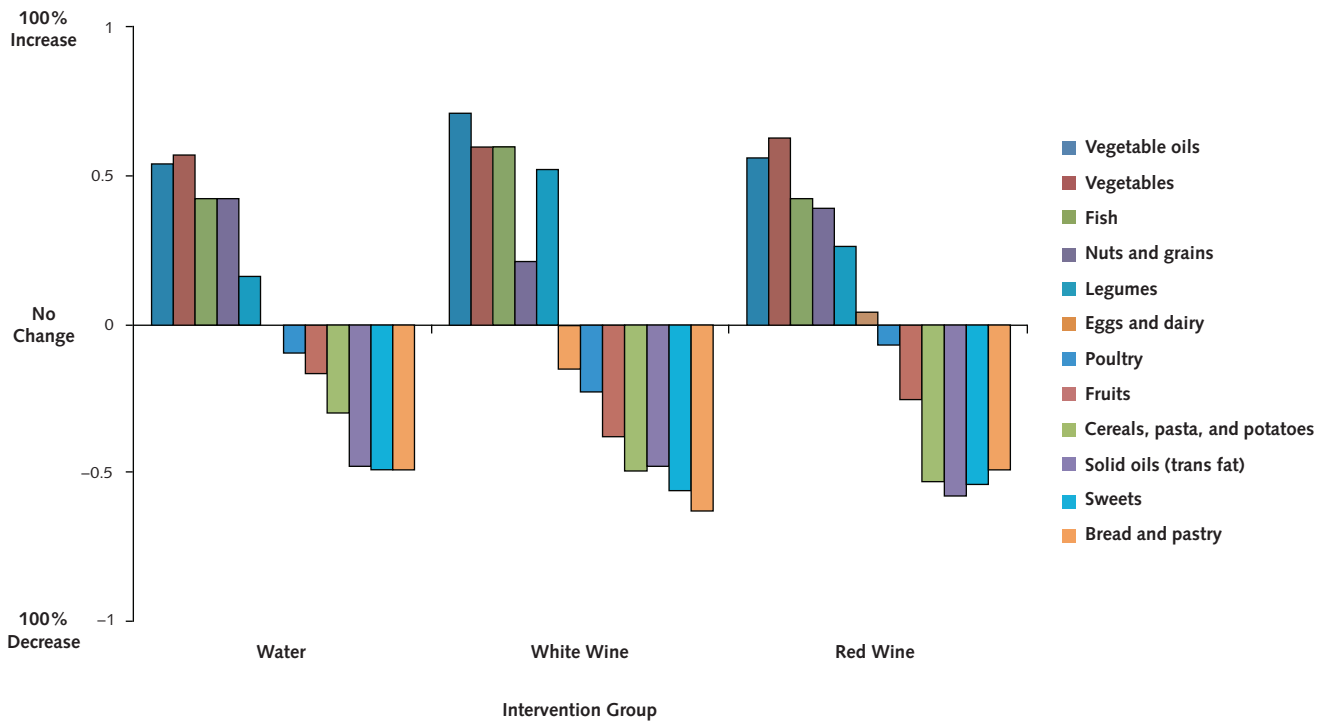


Appendix Figure 3. Baseline and 2-y absolute levels of key variables, by site.



To convert HDL-C values to mmol/L, multiply by 0.0259. To convert FPG values to mmol/L, multiply by 0.0555. BGU-SMC = Ben-Gurion University of the Negev–Soroka Medical Center; HDL-C = high-density lipoprotein cholesterol; HOMA-IR = homeostatic model assessment of insulin resistance; NRCN = Nuclear Research Center Negev.

Appendix Figure 4. 2-y changes in food group consumption.

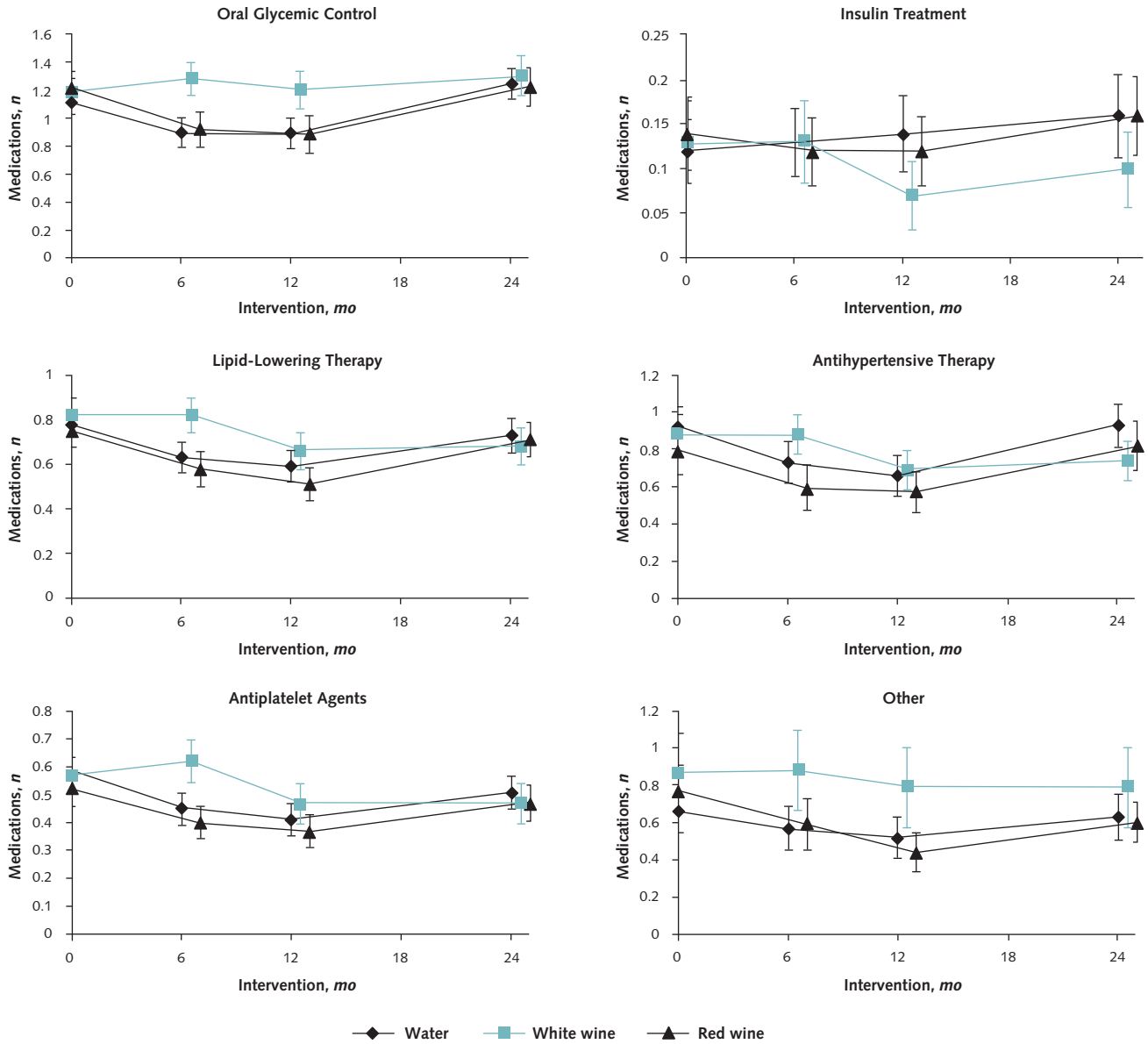


Appendix Table 2. Acute and Adverse Effects*

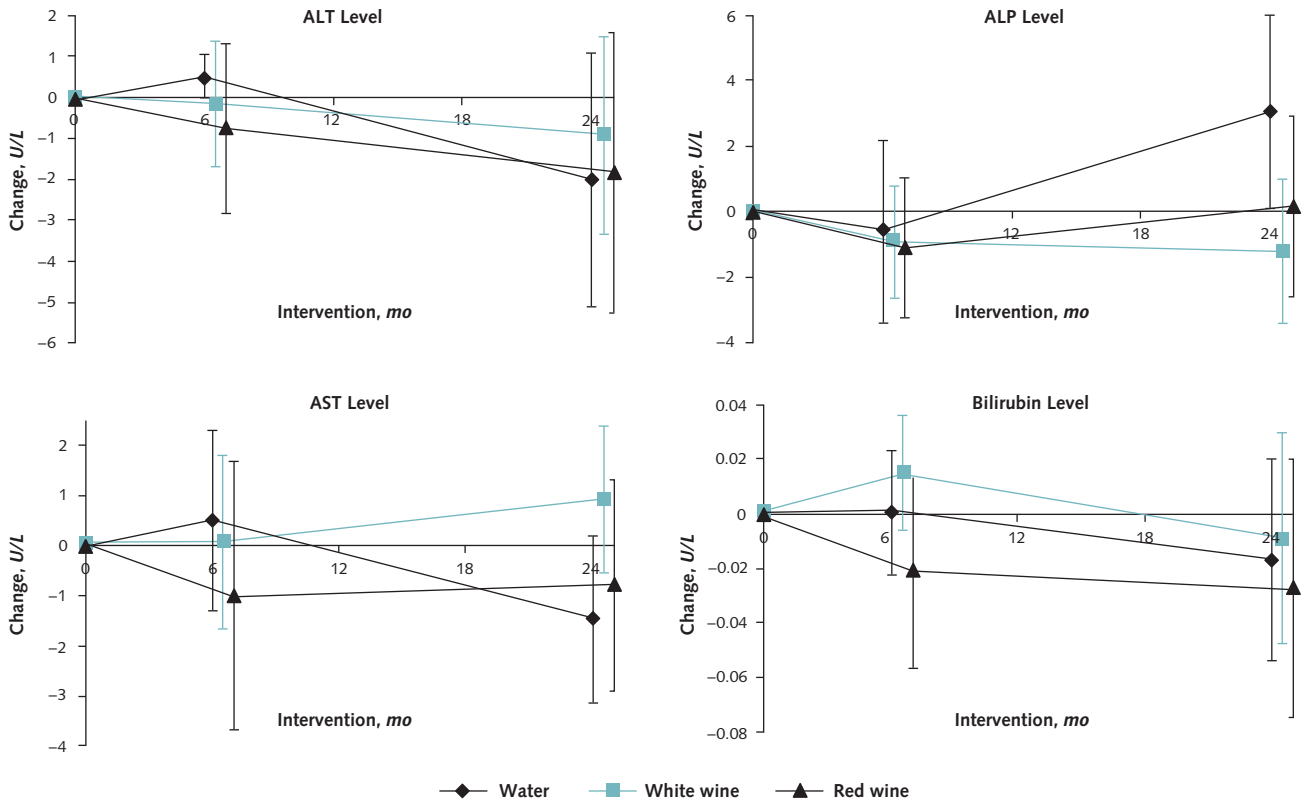
Variable	Water (*n* = 83)	White Wine (*n* = 68)	Red Wine (*n* = 73)
Deaths	0	0	0
Discontinued due to adverse effects			
Total	1	5	5
Headaches	–	1	4
Dizziness	–	1	–
Recurrent pancreatitis	–	1	–
Elevated insulin	–	1	–
Medication interaction	–	1	1
Hospitalization (pulmonary cancer)	1		–
Acute events reported to ethics committee			
Total	6	9	2
MI	2	1	–
Morning motorcycle accident	–	1	–
Breast cancer	–	1	–
Pacemaker implantation	1	–	–
Coronary catheterization	1	–	1
Infectious mononucleosis	–	–	1
Lung cancer	1	–	–
Acute eye inflammation	–	1	–
Arrhythmia	–	2	–
Orthopedic problem	–	1	–
Lung inflammation	–	1	–
Hernia	–	1	–
Bypass surgery	1	–	–

MI = myocardial infarction.
* During the trial, there were no significant differences across the groups in reported symptoms (e.g., bleeding, diarrhea, headaches, illusions, and feeling energetic/calm/exhausted/nervous). Values are numbers.

Appendix Figure 5. Mean changes (95% CIs) in the number of medications during the trial (at 0, 6, 12, and 24 mo) across the assigned intervention groups.



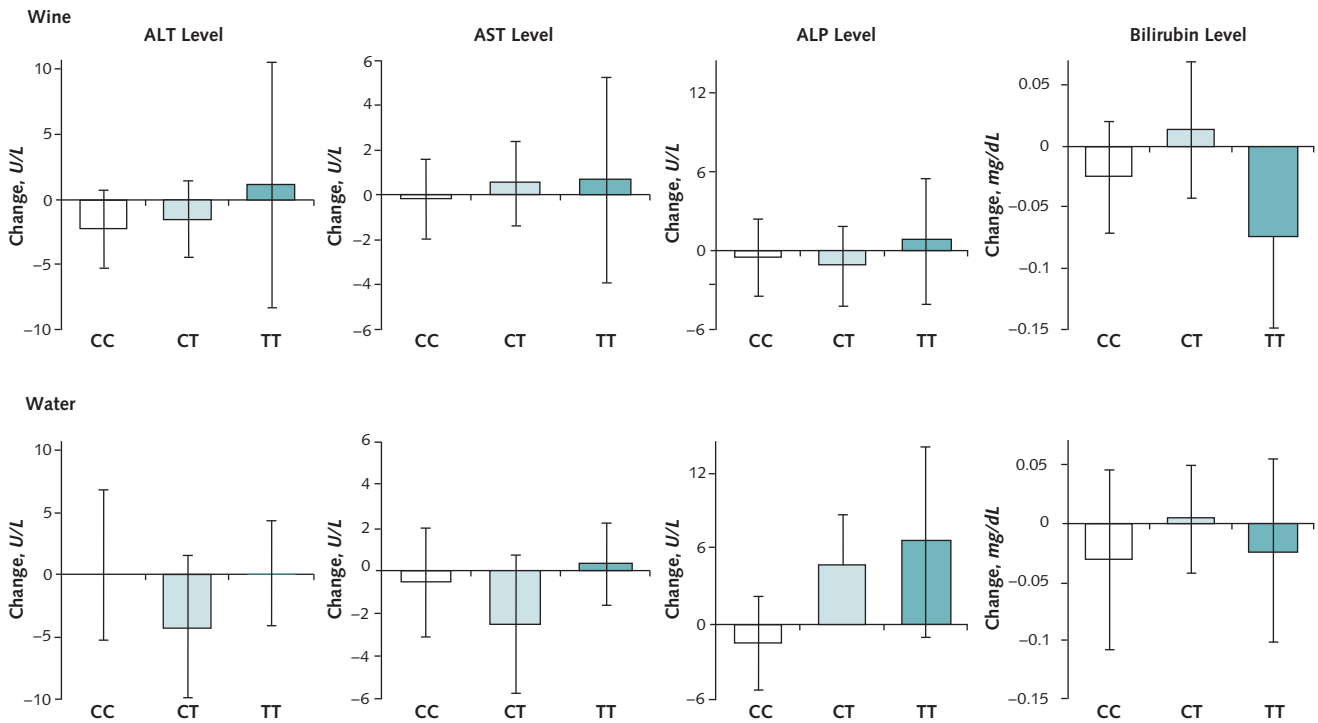
Appendix Figure 6. Changes in liver function biomarkers.



Liver Function Biomarkers	Mineral Water (*n* = 83)	White Wine (*n* = 68)			Red Wine (*n* = 73)		
	Mean Change (95% CI)	Mean Change (95% CI)	Differences of the Mean Changes vs. Water (95% CI)	*P* Value	Mean Change (95% CI)	Differences of the Mean Changes vs. Water (95% CI)	*P* Value
ALT level, *U/L*	−2 (−5.2 to 1.1)	−0.89 (−3.3 to 1.5)	1.1 (−4.1 to 6.3)	0.87	−1.8 (−5.2 to 1.6)	0.20 (−4.8 to 5.2)	1.00
AST level, *U/L*	−1.5 (−3.1 to 0.20)	0.93 (−0.58 to 2.4)	2.4 (−0.62 to 5.4)	0.149	−0.8 (−2.9 to 1.3)	0.67 (−2.2 to 3.6)	0.85
ALP level, *μkat/L*	0.052 (0.002 to 1.000)	−0.020 (−0.058 to 0.017	−0.072 (−0.148 to 0.006)	0.075	0.003 (−0.042 to 0.048)	−0.048 (−0.123 to 0.027)	0.28
Bilirubin level							
μmol/L	−0.34 (−0.86 to 0.34)	−0.17 (−0.86 to 0.51)	0.17 (−1.30 to 1.20)	0.96	−0.51 (−1.20 to 0.34)	−0.17 (−1.20 to 0.86)	0.92
mg/dL	−0.02 (−0.05 to 0.02)	−0.01 (−0.05 to 0.03)	0.01 (−0.06 to 0.07)		−0.03 (−0.07 to 0.02)	−0.01 (−0.07 to 0.05)	

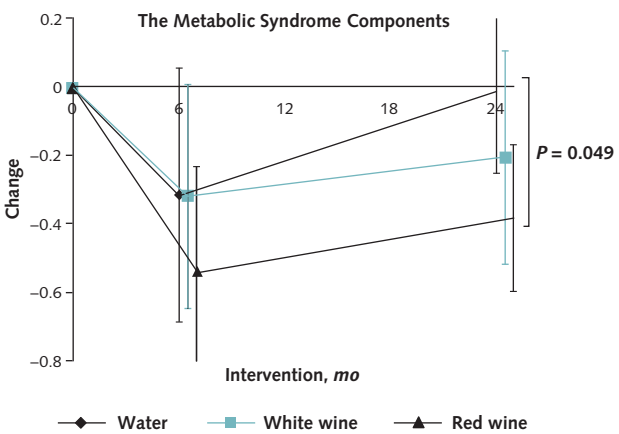
The mean changes from baseline are plotted; bars indicate 95% CIs. At 6 mo, the participants who completed the study were as follows: mineral water, 81; white wine, 62; red wine, 73. After 2 y, we had 30 participants who dropped out; the participants who completed the study were as follows: mineral water, 78; white wine, 52; red wine, 64. ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Appendix Figure 7. 2-y changes in liver function biomarkers according to genetic variation in *ADH1B*.



No significant differences in mean changes from baseline at 2 y were seen between the combined genotypes CC (*ADH1B*1* homozygotes; "slow alcohol metabolism") and CT (heterozygotes) group versus the TT (*ADH1B*2* homozygotes; "fast alcohol metabolism") genotype group for water and wine groups. Bars indicate 95% CIs. A total of 173 participants with available DNA samples completed the 2-y trial–103 in the combined wine group and 70 in the water group. ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Appendix Figure 8. Overall effect of moderate wine consumption on changes in the number of positive criteria of the metabolic syndrome in persons with type 2 diabetes mellitus.



Bars indicate 95% CIs, and the *P* value denotes comparison of 2-y differences in the red wine group versus the water group.