High urinary levels of resveratrol metabolites are associated with a reduction in the prevalence of cardiovascular risk factors in high-risk patients

Raul Zamora-Ros\textsuperscript{a,b}, Mireia Urpi-Sardà\textsuperscript{a,c,d}, Rosa M. Lamuela-Raventós\textsuperscript{a,d}, Miguel Ángel Martínez-González\textsuperscript{d,e}, Jordi Salas-Salvadó\textsuperscript{d,f}, Fernando Arós\textsuperscript{d,g}, Montserrat Fitó\textsuperscript{d,h}, José Lapetra\textsuperscript{d,i}, Ramon Estruch\textsuperscript{c,d}, Cristina Andres-Lacueva\textsuperscript{a,j,*}, on behalf of the PREDIMED Study Investigators

\textsuperscript{a} Nutrition and Food Science Department, Xarxa INS, Pharmacy School, University of Barcelona, Spain
\textsuperscript{b} Unit of Nutrition, Environment and Cancer. Cancer Epidemiology Research Programme, Catalan Institute of Oncology (ICO-IDIBELL), Barcelona, Spain
\textsuperscript{c} Department of Internal Medicine, Hospital Clinic, Institut d’Investigació Biomèdica August Pi i Sunyer (IDIBAPS), University of Barcelona, Spain
\textsuperscript{d} CIBER 08/08: Fisiopatología de la Obesidad y la Nutrición and RD06/0045/1003 Alimentación Saludable, Instituto de Salud Carlos III, Spain
\textsuperscript{e} Department of Preventive Medicine and Public Health, School of Medicine, University of Navarra–Clínica Universidad de Navarra, Pamplona, Spain
\textsuperscript{f} Human Nutrition Unit, School of Medicine, IISPV, Universitat Rovira i Virgili, Reus (Tarragona), Spain
\textsuperscript{g} Department of Cardiology, Hospital Traiguerritu, Vitoria, Spain
\textsuperscript{h} Cardiovascular Risk and Nutrition Research Group, Institut Mar d’Investigacions Mèdiques (IMIM), Barcelona, Spain
\textsuperscript{i} Department of Family Medicine, Primary Care Division of Sevilla, San Pablo Health Center, Sevilla, Spain
\textsuperscript{j} Ingenio-CONSOLIDER Program, FUN-C-Food, CSID2007-063, Spain

\textbf{A B S T R A C T}

Moderate wine consumption has been shown to reduce cardiovascular (CV) risk, due to alcohol and polyphenolic compounds, such as resveratrol. We investigated the associations between total urinary resveratrol metabolites (TRMs) as biomarkers of wine and resveratrol consumption and CV risk factors in a large cross-sectional study including high CV risk individuals in Spain. We studied 1000 participants in the PREDIMED Study in whom TRMs were analyzed by LC–MS/MS with a previous solid phase extraction. Multiple linear regression of TRMs (biomarker of wine consumption) improved the mean (95% CI) of HDL [0.168 (0.027–0.309); P = 0.02] and triglyceride [−1.012 (−1.797 to −0.227); P = 0.012] plasma concentrations and heart rate [−0.259 (−0.412 to −0.107); P = 0.001]. Models of TRMs adjusted for alcohol (biomarker of resveratrol intake) decreased fasting blood glucose [−0.533 (−1.034 to −0.033); P = 0.037] and triglyceride [−1.014 (−1.998 to −0.020); P = 0.044] concentrations, and heart rate [−0.277 (−0.467 to −0.087); P = 0.004]. Both resveratrol and wine intake, evaluated as TRMs, were associated with beneficial changes in blood lipid profiles, fasting blood glucose (only resveratrol) and heart rate, suggesting that resveratrol intake via wine consumption might help to decrease CV risk factors.

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1. Introduction

Epidemiological studies show that a regular consumption of moderate amounts of alcoholic beverages is associated with a lower risk of cardiovascular (CV) events. In 2006, a meta-analysis of 34 studies including more than a million subjects and almost 100,000 observed deaths showed lower mortality rates for moderate alcohol consumers compared to that of teetotalers or heavy drinkers [1]. Increasing evidence such as the “French paradox” suggests that red wine provides additional cardioprotection compared with other alcoholic beverages [2,3]. Besides alcohol, wine contains several types of polyphenols that contribute to the differences observed between wine and distillates [4–6]. Among several other wine polyphenols, resveratrol is increasingly recognized as one of the most interesting bioactive components present in wine [7]. Resveratrol (trans-3,4′,5′-trihydroxystilbene) is a natural phytoalexin that occurs in a small number of food sources, including grapes, wines, peanuts, pistachios and berries [8]. Resveratrol protects the vascular walls from oxidation and inflammation, decreasing the risk on cardiovascular disease (CVD) via this mechanism. Resveratrol can directly suppress lipid peroxidation both by copper chelation and by scavenging free radicals [9]. Resveratrol can also indirectly decrease the oxidation of LDL by acting on various enzymatic systems, including nicotinamide adenine dinucleotide-dependent oxidases, hypoxanthine/xanthine oxidase.

Abbreviations: CV, cardiovascular; CVD, cardiovascular disease; HDL, high density lipoprotein; NO, nitric oxide; PREDIMED, Prevención con dieta Mediterránea; SIRT, sirtuin; TRM, total urinary resveratrol metabolites.

* Corresponding author at: Nutrition and Food Science Department-Xarxa INS, Pharmacy School, University of Barcelona, Av. Joan XXIII, s/n, 08028 Barcelona, Spain. Tel.: +34 93 403 48 40; fax: +34 93 403 59 31.

E-mail address: candres@ub.edu (C. Andres-Lacueva).

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lipooxygenase, myeloperoxidase and nitric oxide synthases [10]. Resveratrol can also act as an anti-inflammatory molecule by inhibiting lipooxygenase, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) via its inhibitory effects on nuclear factor κB (NF-κB) [11]. Nowadays, resveratrol is considered to be an important molecule because it can act as a calorie restriction mimic in lower organisms and mice [12]. Resveratrol activates sirtuins (NAD+-dependent deacetylases) whose main function is to improve chances of survival and increase stress resistance in times of adversity. Sirtuins (SIRT) are molecular targets in new approaches for the treatment of diet-induced obesity [13,14] and type 2 diabetes [15], producing beneficial effects on glucose homeostasis and insulin sensitivity [16].

In epidemiological studies, data regarding the intake of foods and dietary components are usually collected using validated food frequency questionnaires, although unhealthy foods such as most alcoholic beverages tend to be typically under-reported [17]. Furthermore, nutritional biomarkers may be a better measure of dietary exposure than self-reported dietary data [17,18]. For this reason, the use of nutritional biomarkers to assess dietary exposure, especially for some particular foods and components believed to be more prone to be affected in self-reports by social desirability bias or other biases, is absolutely necessary. Total urinary resveratrol metabolites (TRMs) have been identified as a biomarker of wine consumption in clinical and epidemiological studies [19,20].

The present study is the first attempt to evaluate the associations between wine or resveratrol consumption and cardiovascular risk factors in a large cross-sectional study including participants at high-CV-risk and using nutritional biomarkers.

2. Methods

2.1. Participants

The rationale, design and objectives of the PREDIMED (Prevenção con Dleta MEDiterránea) study and the criteria and methods for participant selection have been described previously [21,22]. Briefly, this is a large, parallel-group, multi-center, controlled, randomized clinical trial aimed at assessing the effects of the Mediterranean diet on the primary prevention of CVD (www.predimed.es and www.predimed.org). In the present study, we analyzed the baseline data of the first 1000 consecutive admitted participants (479 men and 521 women) recruited from October 2003 to July 2005. All participants gave informed consent to a protocol approved by the local institutional Ethics Committees.

2.2. Questionnaires

Four baseline questionnaires were administered to all participants by personal interview: (a) a questionnaire about lifestyle variables, medical history and all medication taken, including brand name, dose and intake pattern; (b) a 14-item validated questionnaire [23] designed to assess the degree of adherence to the traditional Mediterranean diet; (c) a 137-item validated food frequency questionnaire [24]; and, (d) the validated Spanish version [25] of the Minnesota Leisure-Time Physical Activity Questionnaire. Energy and nutrient intake was calculated from Spanish food composition tables. Trained personnel took anthropometric measurements and blood pressure in triplicate with a validated semi-automatic oscillometer (Omron HEM-705CP, Hoofddorp, The Netherlands).

2.3. Laboratory analyses

Samples of fasting blood and urine were coded and stored at −80 °C until assay. The clinical investigators and laboratory technicians were blinded to clinical data.

Analyses of EDTA plasma were performed by a central laboratory using a Pentra 400 auto analyzer (ABX-Horiba Diagnostics, Montpellier, France). Fasting blood glucose, total cholesterol and triglyceride levels were measured using standard automated enzymatic methods (ABX-Horiba Diagnostics, Montpellier, France). HDL cholesterol was directly determined by accelerator selective detergent methodology (ABX-Horiba Diagnostics, Montpellier, France), and LDL cholesterol was calculated by the Friedewald equation whenever triglycerides were <300 mg/dL. Quality control was performed with the External Quality Assessment UNITY (BIO-RAD, Hercules, California, USA).

Resveratrol metabolites in urine samples were extracted by solid-phase extraction and analyzed by LC–MS/MS as described elsewhere [26]. Briefly, after equilibrating the cartridges (Oasis HLB 60 mg, Waters, Milford, Massachusetts, USA), centrifuged (at 13,000 rpm at 4 °C for 3 min) urine samples (1 mL) were loaded. The cartridges were washed and resveratrol metabolites were eluted with acidified methanol solution and ethyl acetate. The organic extract was evaporated under N2. The samples were redissolved with 100 µL of the initial LC mobile-phase conditions and then analyzed in the LC–MS/MS system. The identification and quantification of resveratrol metabolites in urine were made with an LC system (Perkin-Elmer S200; Norwalk, CT, USA) coupled to a triple quadrupole mass spectrometer (API 3000, Perkin-Elmer Sciex, Concord, ON, Canada) as described elsewhere [26]. Total urinary resveratrol metabolite was calculated as the sum of individual metabolites (trans-resveratrol-3-O-glucuronide, cis-resveratrol-4′-O-glucuronide, cis-resveratrol-3′-O-glucuronide, trans-resveratrol-4′-O-sulfate, trans-resveratrol-3′-O-sulfate, cis-resveratrol-4′-O-sulfate, and cis-resveratrol-3′-O-sulfate) as previously determined as biomarker of consumption [20]. All the results of the urinary resveratrol metabolites were corrected for urine creatinine and were expressed as nmol/g creatinine of morning urine. Urine creatinine was analyzed with the standard Jaffé kinetic method [27].

2.4. Statistical analyses

Descriptive statistics with means (standard deviation) for continuous variables and n (%) for categorical variables were used for the baseline characteristics of the participants. Normal distributions of continuous variables were assessed by the Kolmogorov–Smirnov test. TRM (nmol/g creatinine) levels required a box plot transformation ([(TRM + 0.00001)0.25 − 1]0.25) to improve their adaption to a normal distribution. General linear modeling procedures were performed to estimate adjusted means of CV risk factors according to quartile distribution of TRM.

A multivariable linear regression was fitted to analyze the relationships between Box–Cox transformed TRM and CV risk factors, such as fasting blood glucose, total cholesterol, triglycerides, HDL, LDL, systolic and diastolic blood pressure and heart rate. We controlled potential confounding by age, sex, body weight, smoking status, leisure-time physical activity and medication (acetalsaliclyc acid, ACE inhibitors, antihypertensive drugs, lipid-lowering drugs, insulin, oral hypoglycemic drugs). Since TRM is a biomarker of wine intake [19], we fitted two models with and without alcohol consumption (g alcohol/d) because the results showed two associations: (a) between wine consumption and CV risk factors; and (b) between resveratrol intake and cardiovascular risk factors. All the regression models were tested for outliers, multicollinearity, homoscedasticity, and the normality and independence of errors.
Table 1
Baseline characteristics in participants studied, by TRM quartiles.

<table>
<thead>
<tr>
<th></th>
<th>Total resveratrol metabolite quartiles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q1 (n = 250)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>105 (42.0)</td>
</tr>
<tr>
<td>Age (y) ( ^a )</td>
<td>68.3 (6.1)</td>
</tr>
<tr>
<td>BMI (kg/m(^2)) ( ^b )</td>
<td>29.3 (3.4)</td>
</tr>
<tr>
<td>Sedentary, n (%)</td>
<td>128 (51.2)</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>18 (7.2)</td>
</tr>
<tr>
<td>Alcohol consumption (g/d)</td>
<td>0.49 (2.0)</td>
</tr>
<tr>
<td>Type II diabetes, n (%)</td>
<td>139 (55.6)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>203 (81.2)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>151 (60.4)</td>
</tr>
<tr>
<td>Aspirin, n (%)</td>
<td>58 (23.2)</td>
</tr>
<tr>
<td>Antihypertensive drugs, n (%)</td>
<td>192 (76.8)</td>
</tr>
<tr>
<td>Lipid-lowering drugs, n (%)</td>
<td>102 (40.8)</td>
</tr>
<tr>
<td>Insulin, n (%)</td>
<td>20 (8.0)</td>
</tr>
<tr>
<td>Oral hypoglycemic drugs, n (%)</td>
<td>91 (36.4)</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>124.6 (40.0)</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>212.9 (38.2)</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>54.3 (11.0)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>125.7 (43.3)</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>133.4 (31.7)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>149.9 (18.2)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>84.8 (8.5)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>73.1 (11.6)</td>
</tr>
</tbody>
</table>

\( ^a \) Mean (standard deviation).

\( ^b \) BMI, Body Mass Index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

\( ^c \) Sedentary participants were classified (<200 kcal/week) in leisure-time physical activity.

All statistical tests were two-tailed, and the significance level was \( p < 0.05 \), and were performed using the SPSS Statistical Analysis System v.19.0 (SPSS, Chicago, IL).

3. Results

General baseline characteristics of the study population according to quartiles of TRM are presented in Table 1. The proportion of men, sedentary and smoker participants increased, and type II diabetes mellitus decreased across quartiles of TRM. As expected, alcohol consumption increased across quartiles of TRM, because TRM is a biomarker of wine consumption [20]. However, age, heart rate and oral hypoglycemic drugs decreased across quartiles of TRM.

Multiple linear regression analysis with Box–Cox transformed TRM and without alcohol adjustment is used to assess the relationships between wine consumption and CV risk factors (Table 2). Wine intake was associated with higher concentrations of circulating HDL, lower concentrations of triglycerides and lower heart rate after adjustment for potential confounders except alcohol.

Data on the alcohol-adjusted association of TRMs with cardiovascular risk factors are shown in Table 3. This model is used to evaluate urinary resveratrol excretion as a biomarker of resveratrol intake. Resveratrol intake was directly associated with lower concentrations of fasting blood glucose and triglycerides, and also with lower heart rate. No significant associations were observed between TRM and total cholesterol, HDL, LDL concentrations or blood pressure after controlling for potential confounding variables and alcohol consumption.

4. Discussion

The association between TRM and CV risk factors was investigated in a sample of high-CV-risk participants living in Spain. TRM was used as a biomarker of wine consumption (when the model was not adjusted for alcohol intake) or as a biomarker of resveratrol intake (when the model was additionally adjusted for alcohol intake). This is the first large study to evaluate this hypothesis using objectively measured biomarkers. It was found that moderate wine consumption as well as resveratrol intake were associated with a significant improvement in some recognized CV risk factors.

Besides the adverse effects of alcohol [28] there are a number of studies showing an inverse association between moderate alcohol intake and CVD [29,30]. Several studies have shown that wine and other alcoholic beverages consumption has been related to lipoprotein metabolism, in particular to an increase in plasma

Table 2
Results from multiple linear regression analysis\( ^a \) that evaluated the association between Box–Cox transformed TRM as a biomarker of wine consumption and cardiovascular risk factors, after controlling for various potential confounders.

<table>
<thead>
<tr>
<th></th>
<th>( B ) coefficient</th>
<th>95% confidence interval</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower limit</td>
<td>Upper limit</td>
<td></td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>-0.303</td>
<td>-0.703</td>
<td>0.097</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>0.044</td>
<td>-0.415</td>
<td>0.503</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>0.168</td>
<td>0.027</td>
<td>0.309</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>-1.012</td>
<td>-1.797</td>
<td>-0.227</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>0.033</td>
<td>-0.335</td>
<td>0.401</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>0.085</td>
<td>-0.159</td>
<td>0.289</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>-0.002</td>
<td>-0.156</td>
<td>0.152</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>-0.259</td>
<td>-0.412</td>
<td>-0.107</td>
</tr>
</tbody>
</table>

\( ^a \) All models were adjusted for gender, age, body weight, smoking status, leisure-time physical activity, energy intake and medication.

\( ^b \) SBP, systolic blood pressure; DBP, diastolic blood pressure.
Table 3
Results from multiple linear regression analysis that evaluated the association between Box–Cox transformed TRM as resveratrol intake biomarker and cardiovascular risk factors, after controlling for various potential confoundersa.

<table>
<thead>
<tr>
<th>B coefficient</th>
<th>95% confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower limit</td>
<td>Upper limit</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>0.533</td>
<td>-1.034</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>0.043</td>
<td>-0.534</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>0.050</td>
<td>-0.126</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>-1.014</td>
<td>-1.998</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>0.164</td>
<td>-0.297</td>
</tr>
<tr>
<td>SBPb (mmHg)</td>
<td>-0.024</td>
<td>-0.305</td>
</tr>
<tr>
<td>DBPb (mmHg)</td>
<td>0.061</td>
<td>-0.132</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>-0.277</td>
<td>-0.467</td>
</tr>
</tbody>
</table>

a All models were adjusted for gender, age, body weight, smoking status, energy and alcohol intake, leisure-time physical activity and medication.

b SBP, systolic blood pressure; DBP, diastolic blood pressure.

HDL levels [30,31]. This increase in HDL has been postulated to be the most important protective effect of alcohol against CVD. We also observed that wine consumption was significantly associated with higher HDL and lower triglyceride concentrations, although it was not related to LDL, total cholesterol or fasting blood glucose concentrations. These results are similar to those shown in a review of the effects of alcohol in diabetics [32]. However, in a previous study, blood glucose concentrations in women were inversely associated with the intake of wine, but positively associated with beer and spirit consumption [33]. In the present study, we observed a significant relationship between wine intake and heart rate, although we did not find any association with blood pressure. Excess alcohol intake increases blood pressure [30], although some studies have reported a J-shape dose–response curve [34]. A clinical trial over 4 weeks with a moderate consumption of red wine (300 mL/d and 200 mL/d for men and women respectively) did not show any significant effect of red wine on blood pressure [35]. Our results regarding heart rate are the opposite of those previously reported [36,37], although in another study conducted in Spain, alcohol intake in men (but not in women) was positively associated with heart rate, while wine consumption in men was negatively associated with heart rate (β coefficient = −0.059; P = 0.058); it showed no association in women (β coefficient = −0.093; P = 0.341) [33].

Besides alcohol content, the polyphenol components of wine, especially resveratrol, are active on cardiovascular end points [38]. We found that TRM, as a biomarker of resveratrol intake, was significantly associated with low triglyceride levels, but it showed no association with other blood lipid parameters, such as HDL, LDL and total cholesterol. Recent in vivo studies did not detect any significant effect of resveratrol on serum cholesterol or triglyceride concentrations [39,40]. However, in hypercholesterolemic mice, resveratrol decreases total cholesterol and triglycerides. Moreover, in guinea pigs, grape polyphenol extract, with resveratrol, reduces plasma triglycerides and VLDL but it does not modify LDL, HDL nor total cholesterol [41]. In our study, we did not observe significant associations between resveratrol intake and blood pressure; on the other hand we showed a significant relationship between dietary resveratrol and a lower heart rate. Similar results in blood pressure were obtained in a study of rats, although in the same paper, resveratrol decreased systolic blood pressure in fructose-fed rats [42]. In rats subjected to myocardial ischemia, resveratrol did not modify either blood pressure or heart rate, despite resveratrol preventing myocardial reperfusion ischemia damage through both nitric oxide (NO)–dependent and NO-independent mechanisms [43].

Today the significance of resveratrol is considered to have peaked because of its ability to increase stress resistance and the lifespan of multiple species as a calorie restriction mimetic [12]. A reduction in calorie intake, usually by 30–40%, in rodents, produces a metabolic profile desirable for the prevention of diabetes and diabetic complications [15]. SIRT proteins seem to be mainly responsible for the benefits of calorie restriction [15]. Resveratrol, as an activator of SIR, can decrease blood glucose and improve insulin sensitivity in mice on a high-calorie diet [13]. At a pharmacological dose in streptozotocin-treated rats, red wine polyphenol extract and ethanol both reduced blood glucose [44]. An insulin-like effect of resveratrol has also been described [14,45–47]. But in normal rats it does not reduce blood glucose at 10–50 mg/kg body weight, and it only diminishes blood insulin in high doses (50 mg/kg body weight) [48]. In our study, we found an association between resveratrol and lower blood fasting glucose levels at a nutritional dose. These effects are observed despite low bioavailability and rapid clearance from the circulation [26,49]. It seems that, at low concentrations, resveratrol exhibits biological functions in a SIRT1-dependent manner [14,13,50], whereas at high concentrations it probably does so via a SIRT1-independent pathway [51]. Therefore, the precise mechanisms for the functions of resveratrol have yet to be elucidated [52]. However, low effective concentrations of resveratrol in glucose homeostasis and insulin sensitivity are of great therapeutic importance since lower concentrations mean a higher importance of dietary sources, greater biological safety and lower pharmaceutical cost.

The strength of the present study is the use of nutritional biomarkers to assess the dietary concentrations of wine and resveratrol. Furthermore, this study is interesting because of the relatively large number of participants, the adjustment for several important confounders, and the inclusion of most of the classical cardiovascular risk factors. The limitation of the present study is that the cross-sectional design does not allow us to draw conclusions on causality. Another limitation is that in the model adjusted for alcohol, we analyzed urinary resveratrol as a biomarker of resveratrol intake, although it could also be an indirect biomarker of wine polyphenolic compounds because of it is difficult to separate the effect of resveratrol to the rest of polyphenolic compounds present in wine. Further studies in order to refute or confirm the hypothesis of a protective effect of resveratrol intake on CV risk factors are needed.

5. Conclusions

The results of the present study suggest that wine is related to better plasma lipid profile (higher HDL and lower triglyceride concentrations), and lower heart rate. Resveratrol is associated with beneficial effects on fasting blood glucose, triglycerides and heart rate. We did not observe any association between intake of wine or resveratrol and blood pressure. The association between HDL and wine consumption seems to be due to the total alcohol content. The relationship between wine intake triglycerides or heart rate seems to be mediated by alcohol and the polyphenolic content of wine. The association between resveratrol and fasting blood glucose seems to be alcohol-independent, and to our knowledge
this is the first epidemiological study to show the inverse relationship between resveratrol and fasting blood glucose levels using nutritional biomarkers. We conclude that resveratrol intake via wine consumption is associated with beneficial changes in blood lipids profile, fasting blood glucose and heart rate that may help to decrease CV risk.

Conflict of interest
None declared.

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Appendix A. Other PREDIMED study investigators

School of Pharmacy, University of Barcelona: Rafael Llorach, Montserrat Rabassa, Alex Medina-Remón; Internal Medicine Department, Hospital Clínic, Barcelona: Emilio Sacanella, Ferran Masanés, Rosa Casas, Concha Viñas; University of Navarra-Osasunbidea Primary Care Division: Vicente Extremera, Concepción Arroyo, Luisa García Pérez; Human Nutrition Unit, School of Medicine, Universitat Rovira i Virgili, Reus: Mónica Bollú, Nancy Babio, Josep Basora; Cardiovascular Risk and Nutrition Research Group, Institut Mar d’Investigacions Mèdiques (IMIM), Barcelona: Maria Isabel Covas, Rafael de la Torre, Helmut Schröder; Department of Family Medicine, Primary Care Division of Sevilla: José Manuel Santos, Manuel Ortega-Calvo, Francisco José García, Pilar Román. Department of Cardiology, Hospital Txagorritxu, Vitoria: Itziar Salaverria, Silvia Francisco, Emilio Sanz, Izaskun Felipe, Ainhoa Alonso.

References


