Resveratrol Levels and All-Cause Mortality in Older Community-Dwelling Adults

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**IMPORTANCE** Resveratrol, a polyphenol found in grapes, red wine, chocolate, and certain berries and roots, is considered to have antioxidant, anti-inflammatory, and anticancer effects in humans and is related to longevity in some lower organisms.

**OBJECTIVE** To determine whether resveratrol levels achieved with diet are associated with inflammation, cancer, cardiovascular disease, and mortality in humans.

**DESIGN** Prospective cohort study, the Invecchiare in Chianti (InCHIANTI) Study ("Aging in the Chianti Region"), 1998 to 2009 conducted in 2 villages in the Chianti area in a population-based sample of 783 community-dwelling men and women 65 years or older.

**EXPOSURES** Twenty-four-hour urinary resveratrol metabolites.

**MAIN OUTCOMES AND MEASURES** Primary outcome measure was all-cause mortality. Secondary outcomes were markers of inflammation (serum C-reactive protein [CRP], interleukin [IL]-6, IL-1β, and tumor necrosis factor [TNF]) and prevalent and incident cancer and cardiovascular disease.

**RESULTS** Mean (95% CI) log total urinary resveratrol metabolite concentrations were 7.08 (6.69-7.48) nmol/g of creatinine. During 9 years of follow-up, 268 (34.3%) of the participants died. From the lowest to the highest quartile of baseline total urinary resveratrol metabolites, the proportion of participants who died from all causes was 34.4%, 31.6%, 33.5%, and 37.4%, respectively (P = .67). Participants in the lowest quartile had a hazards ratio for mortality of 0.80 (95% CI, 0.54-1.17) compared with those in the highest quartile of total urinary resveratrol in a multivariable Cox proportional hazards model that adjusted for potential confounders. Resveratrol levels were not significantly associated with serum CRP, IL-6, IL-1β, TNF, prevalent or incident cardiovascular disease, or cancer.

**CONCLUSIONS AND RELEVANCE** In older community-dwelling adults, total urinary resveratrol metabolite concentration was not associated with inflammatory markers, cardiovascular disease, or cancer or predictive of all-cause mortality. Resveratrol levels achieved with a Western diet did not have a substantial influence on health status and mortality risk of the population in this study.
Resveratrol, a polyphenol found in grapes, red wine, peanuts, chocolate, and certain berries and Asian plant roots, has been shown to exert anti-inflammatory effects in vitro and following supplementation in animal models and to increase lifespan and health in mice fed a high-calorie diet. Studies performed in animal models have shown that resveratrol and other chemically related compounds inhibit sirtuin 1 (SIRT1) and mimic the effects of caloric restriction. In 1992, Siemann and Creasy postulated that the cardioprotective effects of red wine could be attributed to resveratrol. The “French paradox,” in which a low incidence of coronary heart disease occurs in the presence of a high dietary intake of cholesterol and saturated fat in France, has been attributed to the regular intake of red wine and in particular, to resveratrol and other polyphenols contained in wine.

Some preliminary evidence also suggests that resveratrol in humans may have anti-inflammatory effects, prevent cancer, diminish arterial stiffness, and improve endothelial reactivity in older women. In a randomized study of 20 healthy adults, plasma concentrations of C-reactive protein (CRP) and tumor necrosis factor (TNF) decreased by about one-third during 6 weeks of supplementation with a plant extract containing resveratrol. In addition, peripheral blood mononuclear cell messenger RNA (mRNA) expression of interleukin (IL)-6 and TNF decreased in the group receiving resveratrol over the same intervention period. In a small crossover trial, a supplement containing resveratrol and polyphenols from muscadine grape suppressed the increase of IL-1β following a high-fat, high-carbohydrate meal. A recent phase 2 study of SRT501, a micronized oral formulation of resveratrol that activates SIRT1, in multiple myeloma patients was halted early owing to a high level of adverse effects and renal failure.

Although resveratrol has attracted a great deal of attention owing to its effects on inflammation, carcinogenesis, and longevity in vitro or in lower organisms, and in trials involving supraphysiologic doses of resveratrol in humans, there is little epidemiologic data to support a link between physiologic levels of resveratrol achieved with the diet alone and health in humans. Some of the challenges in studying resveratrol in humans are the rapid uptake, metabolism, and excretion of resveratrol and the low concentrations found in plasma. Recently, mass spectrometric methods have been developed that allow insights into resveratrol metabolism in humans through the measurement of resveratrol metabolites in urine. We hypothesized that higher urinary concentrations of resveratrol metabolites were associated with reduced risk of all-cause mortality and associated with lower inflammation and lower prevalence and incidence of cardiovascular disease and cancer. To test these hypotheses, we measured urinary metabolites of resveratrol in a population-based cohort study.

Methods

Study Population

The study participants were men and women, 65 years or older, who participated in the Invecchiare in Chianti, “Aging in the Chianti Area” (InCHIANTI) Study, conducted in 2 small towns in Tuscany, Italy. The rationale, design, and data collection methods have been described elsewhere, and the main outcome of this longitudinal study is mobility disability. Briefly, in August 1998, 1270 people 65 years or older were randomly selected from the population registry of Greve in Chianti (population, 11 709) and Bagno a Ripoli (population, 4704), and of 1256 eligible subjects, 1155 (90.1%) agreed to participate. Participants received an extensive description of the study and participated after written, informed consent was obtained. The study protocol complied with the Declaration of Helsinki and was approved by the Italian National Institute of Research and Care on Aging Ethical Committee and by the Institutional Review Board of the Johns Hopkins University School of Medicine. InCHIANTI Study participants were evaluated for a 3-year follow-up visit from 2001 to 2003 (n = 926), a 6-year follow-up visit from 2004 to 2006 (n = 844), and 9-year follow-up visit from 2007 to 2009 (n = 768).

Data Collection and Definition

Data on demographic characteristics, lifestyle factors, and medication use were collected using standardized questionnaires. Smoking history was determined from self-report. Daily alcohol intake, expressed in grams per day, and resveratrol intake, expressed in milligrams per day, were determined at each study visit from participants answers to the European Prospective Investigation into Cancer and Nutrition (EPIC) food frequency questionnaire, which has been validated in the Italian population. Education was recorded as number of years of school.

All participants were examined in a standardized manner by a study geriatrician. Diseases were ascertained according to standard, preestablished criteria and algorithms similar to those used in the Women’s Health and Aging Study for diabetes mellitus, coronary heart disease, chronic heart failure, stroke, and cancer. The algorithm for the diagnosis of diabetes was based on the use of insulin and oral hypoglycemic agents and on responses to a questionnaire administered to the primary care physician of the study participant. Systolic and diastolic blood pressures were calculated as the mean of 3 measures taken with a standard mercury sphygmomanometer during the physical examination. Weight and height were measured using a high-precision mechanical scale. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. The Mini-Mental State Examination (MMSE) was administered at enrollment, and an MMSE score lower than 24 was considered consistent with cognitive impairment. Chronic kidney disease was defined as estimated glomerular filtration rate of less than 60 mL/min/1.73 m² using the 4-variable Chronic Kidney Disease–Epidemiology Collaboration equation of Levey and colleagues.

Mortality data were collected using data from the Mortality General Registry maintained by the Tuscany Region. Analyses include those who refused to participate in the follow-up after baseline and those who moved away but were known to be alive at the time of censoring of this analysis. Causes of death were not available for all participants who died because cause-specific data have not yet been released by the Tuscany re-
dewaldformula.22 Plasmaglucoseconcentrationwasmeasured
protein (LDL) cholesterol level was calculated using the Frie-
protein (HDL) cholesterol concentrations. Low-density lipo-
sersum total cholesterol, triglycerides, and high-density lipo-
enzymatic tests (Roche Diagnostics) were used for measuring
relationship between quartile of total urinary resveratrol metab-
tween alcohol intake and urinary resveratrol metabolites. Cox
Spearmancorrelation was used to examine the relationship be-
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Laboratory Studies
Twenty-four-hour urine samples were collected from partici-
ants at baseline. Urine samples were then aliquoted and im-
mediately stored at −80°C. Of the 1155 adults 65 years or older
who enrolled in the study, 783 had 24-hour urine samples avail-
ble for measurements of resveratrol. Resveratrol conjugates
derived from gut and microbial metabolism were measured in
24-hour urine samples using liquid chromatography-tandem
mass spectrometry (LC-MS/MS).14 Briefly 1 mL of urine with
the internal standard was loaded into a previously equili-
brated Oasis (Waters) HLB (hydrophilic-lipophilic-balanced)
solid-phase extraction 96-well plate (30 mg). Urinary resve-
ratrol metabolites were eluted with acidified methanol solu-
tion and ethyl acetate. After evaporation, the samples were re-
constituted with 100 μL of the mobile phase and then analyzed
by liquid chromatography (PerkinElmer S200) coupled to a
triple-quadrupole mass spectrometer (API3000; Applied Bio-
systems) as described elsewhere.14 The overall time taken per
sample was about 14-minutes, including the cleanup by solid-
phase extraction, optimized runtime by liquid chromatogra-
phy, and mass spectrometry detection.14 Intra-batch and inter-
batch coefficients of variation were less than 10.5% and less
than 10.7%, respectively. Because we were uncertain whether
all the participants collected urine for a full 24-hour period,
all results for urinary resveratrol metabolites were corrected
for creatinine. Urinary creatinine was measured by the modi-
fied Jaffe method,20 and results for 24-hour urinary resve-
ratrol metabolites are reported as nanomoles per gram of cre-
atinine.

Serum CRP, IL-6, IL-1β, and TNF were measured in duplica-
cate by high-sensitivity enzyme-linked immunosorbent as-
says (ELISA) using commercial kits (BioSource Interna-
tional), as described in detail elsewhere.21 Commercial
enzymatic tests (Roche Diagnostics) were used for measuring
serum total cholesterol, triglycerides, and high-density lipo-
protein (HDL) cholesterol concentrations. Low-density lipo-
protein (LDL) cholesterol level was calculated using the Fried-
dewald formula.22 Plasma glucose concentration was measured
by the glucose oxidase method (Beckman Instruments Inc).
Normal, impaired, and diabetic fasting glucose levels were set
at fasting plasma glucose levels of 99 mg/dL or lower, 100 to
125 mg/dL, and higher than 125 mg/dL, respectively.23

Statistical Analysis
Variables are reported as means (SDs) or as percentages. Vari-
ables that were highly skewed (ie, markers of inflammation)
were log-transformed to achieve a normal distribution. Char-
acteristics of subjects were compared across quartiles of uri-
nary resveratrol metabolites using Kruskal-Wallis tests for con-
tinuous variables and χ² tests for categorical variables.
Spearman correlation was used to examine the relationship be-
tween alcohol intake and urinary resveratrol metabolites. Cox
proportional hazards models were used to examine the rela-
tionship between quartile of total urinary resveratrol metab-
olites and all-cause mortality, incident cardiovascular disease,
and incident cancer over 9 years of follow-up. Multivariable
Cox proportional hazards models were adjusted for age, sex,
BMI, and then other variables that were significant in the uni-
ivariate analyses. All analyses were performed using SAS soft-
ware, version 9.1.3 (SAS Institute) with a type I error of 0.05.

Results
Overall, mean (95% CI) log total urinary resveratrol metabo-
lite concentrations were 7.08 (6.69-7.48) nmol/g of creati-
nine. Less than 1% of the study population reported using any
type of nutritional supplement. The characteristics of the par-
ticipants across quartiles of total urinary resveratrol metabo-
lite concentrations are listed in Table 1. There were signifi-
cantly more men in the highest quartiles of total urinary resveratrol metabolites. Alcohol consumption, current smok-
ing, and physical activity were higher among participants in
the highest quartile of total urinary resveratrol metabolites
compared with the lower quartiles. The proportion of partici-
ants with abnormal fasting plasma glucose levels was sig-
nificantly different across quartiles, with the highest propor-
tion of subjects with diabetic fasting glucose levels in the lowest
and highest quartiles. The proportion of participants with cog-
nitive impairment (MMSE score <24) was significantly lower in the participants in the highest quartile of total urinary resve-
ratrol metabolites. There were no significant differences
across the quartiles of total urinary resveratrol metabolite con-
centrations by age, education, BMI, CRP, IL-6, IL-1β, TNF, mean
arterial blood pressure, total cholesterol, HDL cholesterol, LDL
cholesterol, triglycerides, or by prevalence of hypertension,
heart failure, peripheral artery disease, stroke, cancer, and
chronic kidney disease. The prevalence of coronary artery dis-
 ease and diabetes were higher among those in the lowest quar-
tile of total urinary resveratrol metabolites. The Spearman cor-
relation between alcohol consumption in grams per day and
total urinary resveratrol metabolite concentrations was 0.67
(P < .001).

We compared the characteristics of the 782 participants
with resveratrol measurements with the 273 participants who
had no resveratrol measurements at baseline. The partici-
ants with no resveratrol measurements had a significantly
higher proportion with cognitive impairment (MMSE score
<24), stroke, lower physical activity, and mortality compared
with participants who had resveratrol measurements. They also
had lower levels of total cholesterol and higher levels of IL-1β
and TNF compared with the participants who had resveratrol
measurements. There were no significant differences in age,
education, BMI, smoking, chronic disease, or other variables
as, detailed in Table 1 between those with and without resve-
ratrol measurements.

During 9 years of follow-up, 268 (34.2%) of the partici-
ants died. There were no significant differences in the pro-
portion of participants who died across quartiles of total ur-
nary resveratrol metabolite concentrations. The baseline
characteristics of the participants by vital status during fol-
low-up are listed in Table 2. Participants who died were older,
more likely to be male, with lower education, lower BMI, physi-
cally in-active, with diabetic fasting plasma glucose and higher CRP, IL-6, and TNF concentrations, higher mean arterial blood pressure, and lower total, HDL, and LDL cholesterol levels. A higher proportion of those who died had MMSE scores lower than 24, heart failure, peripheral artery disease, stroke, diabetes, and chronic kidney disease. There were no significant differences between participants who died during the study period and those who did not in alcohol intake, current smoking, gut resveratrol metabolites, microbial resveratrol metabolites, total urinary resveratrol metabolites, IL-1β, triglycerides, coronary artery disease, or cancer.

The relationship between total urinary resveratrol metabolites and all-cause mortality was examined using multivariable Cox proportional hazards models (Table 3). Total urinary resveratrol metabolites concentration was not significantly associated with mortality in models adjusting for age, sex, BMI, serum levels of lipids, chronic diseases, and other variables. The relationship between total urinary resveratrol metabolites and mortality did not change in additional models that included markers of inflammation in addition to the covariates used in the final models (data not shown). Sensitivity analyses were conducted to take into consideration mor-

### Table 1. Baseline Characteristics of Study Participants by Quartiles of Total Urinary Resveratrol Metabolites

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>&lt;1554 (n = 195)</th>
<th>1554-4996 (n = 196)</th>
<th>&gt;4996-15 010 (n = 196)</th>
<th>&gt;15 010 (n = 196)</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>75.2 (7.5)</td>
<td>74.3 (7.0)</td>
<td>74.5 (7.0)</td>
<td>73.8 (6.2)</td>
<td>.52</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28.7</td>
<td>33.2</td>
<td>48.2</td>
<td>68.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female</td>
<td>71.3</td>
<td>66.8</td>
<td>51.8</td>
<td>31.3</td>
<td></td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>5.0 (2.6)</td>
<td>5.1 (3.1)</td>
<td>5.6 (3.8)</td>
<td>5.8 (3.4)</td>
<td>.14</td>
</tr>
<tr>
<td>Alcohol intake, mean (SD), g/d</td>
<td>2.4 (5.8)</td>
<td>8.8 (15.9)</td>
<td>16.3 (16.0)</td>
<td>31.1 (24.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Consumes alcohol</td>
<td>37.4</td>
<td>66.8</td>
<td>87.8</td>
<td>99.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>7.7</td>
<td>12.8</td>
<td>8.6</td>
<td>25.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>27.5 (4.2)</td>
<td>27.7 (4.1)</td>
<td>27.5 (3.8)</td>
<td>27.3 (4.0)</td>
<td>.48</td>
</tr>
</tbody>
</table>

**Physical activity**

|                                |                 |                     |                        |                 |                  |
|                                | Inactive        | Low                 | Moderate-high          |                 | .002             |
|                               | 24.6            | 17.9                | 17.9                   | 15.0            |                  |
|                               | 44.6            | 51.3                | 41.8                   | 36.8            |                  |
|                               | 30.8            | 30.8                | 40.3                   | 48.2            |                  |

**Fasting plasma glucose**

|                                |                 |                     |                        |                | .05              |
|                                | Normal          | Impaired            | Diabetic               |                 |                  |
|                               | 72.8            | 15.9                | 11.3                   | 69.7            |                  |

**Log, mean (SD)**

|                                |                 |                     |                        |                | .52              |
|                                | CRP, μg/mL      | IL-1β, pg/mL        | IL-6, pg/mL            | TNF, pg/mL     |                  |
|                               | 1.09 (1.07)     | -2.15 (1.30)        | 1.08 (0.55)            | 1.47 (0.59)    |                  |
|                               | 1.08 (0.98)     | -2.19 (1.14)        | 1.06 (0.50)            | 1.43 (0.52)    |                  |
|                               | 0.97 (1.04)     | -2.24 (1.22)        | 1.16 (0.58)            | 1.45 (0.54)    |                  |
|                               | 0.99 (1.01)     | -2.25 (0.92)        | 1.17 (0.57)            | 1.54 (0.78)    |                  |

**Mean arterial BP, mm Hg**

|                                |                 |                     |                        |                | .78              |
|                                | 105 (11)        | 106 (11)            | 105 (10)               | 106 (12)       |                  |

**Cholesterol, mean (SD), mg/dL**

|                                |                 |                     |                        |                | .28              |
|                                | Total           | HDL                 | LDL                     | Triglycerides  |
|                               | 215 (37)        | 56 (14)             | 133 (31)               | 130 (79)       |                  |
|                               | 223 (41)        | 56 (15)             | 142 (36)               | 132 (63)       |                  |
|                               | 219 (42)        | 55 (16)             | 138 (37)               | 128 (73)       |                  |
|                               | 220 (38)        | 58 (15)             | 138 (34)               | 123 (57)       |                  |

**MMSE score <24**

|                                |                 |                     |                        |                | <.001            |
|                                | 32.8            | 31.1                | 31.0                   | 16.4            |                  |

**Hypertension**

|                                |                 |                     |                        |                | .65              |
|                                | 48.2            | 50.5                | 44.2                   | 47.7            |                  |

**Coronary artery disease**

|                                |                 |                     |                        |                | .03              |
|                                | 6.7             | 1.5                 | 7.1                    | 3.6             |                  |

**Heart failure**

|                                |                 |                     |                        |                | .32              |
|                                | 6.7             | 3.1                 | 4.6                    | 3.6             |                  |

**Peripheral artery disease**

|                                |                 |                     |                        |                | .40              |
|                                | 6.2             | 4.6                 | 4.1                    | 7.7             |                  |

**Stroke**

|                                |                 |                     |                        |                | .53              |
|                                | 4.1             | 3.1                 | 5.6                    | 3.1             |                  |

**Diabetes mellitus**

|                                |                 |                     |                        |                | .02              |
|                                | 15.9            | 10.2                | 9.1                    | 18.5            |                  |

**Cancer**

|                                |                 |                     |                        |                | .30              |
|                                | 7.7             | 6.1                 | 7.6                    | 3.4             |                  |

**Chronic kidney disease**

|                                |                 |                     |                        |                | .07              |
|                                | 27.2            | 23.0                | 20.3                   | 16.4            |                  |

**Died during follow-up, overall**

|                                |                 |                     |                        |                | .67              |
|                                | 34.4            | 31.6                | 33.5                   | 37.4            |                  |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; CRP, C-reactive protein; HDL, high-density lipoprotein; IL, interleukin; LDL, low-density lipoprotein; MMSE, Mini-Mental State Examination<sup>18</sup>; TNF, tumor necrosis factor.

<sup>1</sup>S Conversion factors: To convert ethanol to moles, multiply by 0.0217; total cholesterol, HDL cholesterol, and LDL cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113; CRP to micromoles per liter, multiply by 9.524; IL-6 to micromoles per liter, multiply by 0.131.

<sup>a</sup>Unless otherwise indicated, data are reported as percentage of participants.

<sup>b</sup>Kruskal-Wallis test for continuous variables and χ² test for categorical variables.
tality in the first year following resveratrol measurements, because those who died within the first year may have been ill at the time of resveratrol measurements, and potential effects of excessive alcohol consumption, since resveratrol was strongly associated with alcohol intake, as shown previously. In an alternative analysis, 12 participants who died within 1 year of enrollment were excluded. Total urinary resveratrol metabolites were not significantly related to all-cause mortality in multivariable Cox proportional hazards models adjusting for the same covariates as the models in Table 3 (data not shown).

To corroborate the relationship between urinary resveratrol metabolites and all-cause mortality further, we also examined the relationship of dietary intake of resveratrol with all-cause mortality. In the 783 participants, the mean (95% CI) of log dietary intake of resveratrol in was $-2.42 (-2.55 to -2.28)$ mg/d. The Spearman correlation between dietary intake of resveratrol and total resveratrol metabolites was $0.67 (P < .001)$. The relationship between dietary intake of resveratrol and all-cause mortality was examined using a multivariable Cox proportional hazards model with the same covariates as in the fi-
Table 3. Relationship Between Total Urinary Resveratrol Metabolites and All-Cause Mortality in Separate Multivariable Cox Proportional Hazards Models

<table>
<thead>
<tr>
<th>Covariates in Models</th>
<th>Quartiles of Total Urinary Resveratrol Metabolites, nmol/g creatinine*</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1554</td>
<td>1554–1996</td>
<td>&gt;1996–15 010</td>
<td>&gt;15 010</td>
<td>P Valueb</td>
</tr>
<tr>
<td>Age, sex</td>
<td>0.83 (0.58–1.17)</td>
<td>0.93 (0.67–1.36)</td>
<td>0.73 (0.53–1.05)</td>
<td>1 (Referent)</td>
<td>.55</td>
</tr>
<tr>
<td>Age, sex, education, BMI, physical activity, total cholesterol, HDL cholesterol, MMSE score</td>
<td>0.74 (0.51–1.08)</td>
<td>0.90 (0.62–1.30)</td>
<td>0.71 (0.49–1.02)</td>
<td>1 (Referent)</td>
<td>.30</td>
</tr>
<tr>
<td>Age, sex, education, BMI, physical activity, total cholesterol, HDL cholesterol, MMSE score, mean arterial BP, and chronic diseasesc</td>
<td>0.80 (0.54–1.17)</td>
<td>1.03 (0.70–1.15)</td>
<td>0.94 (0.58–1.22)</td>
<td>1 (Referent)</td>
<td>.43</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; HDL, high-density lipoprotein; MMSE, Mini-Mental State Examination.18

*SI conversion factors: To convert ethanol to moles, multiply by 0.0217; total cholesterol, HDL cholesterol, and LDL cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113; CRP to micromoles per liter, multiply by 0.52, IL-6 to micromoles per liter, multiply by 0.131.

**Unless otherwise indicated, data are reported as hazards ratios (95% CIs) for each quartile of urinary resveratrol metabolites relative to the highest quartile (Referent).

bFor trend across quartiles.

cChronic diseases include coronary heart disease, heart failure, stroke, peripheral artery disease, diabetes, cancer, and chronic kidney disease.

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minimized for 30 days to healthy obese men, did not find significant changes to circulating CRP, IL-6, IL-1β, and IL-18, but there was a reduction in TNF concentrations.30

In the present study of community-dwelling older adults, there were no significant associations between urinary resveratrol metabolites and serum CRP, IL-6, IL-1β, or TNF. A previous study showed that resveratrol supplementation decreased fasting plasma glucose levels in adults with type 2 diabetes33 and in healthy obese men.30 Resveratrol supplementation decreased LDL cholesterol levels in patients recovering from myocardial infarction.32 In 75 patients with cardiovascular disease, supplementation with grape extract for 6 months decreased oxidized LDL and ApoB levels.33 In the present study, there was no significant relationship between urinary resveratrol metabolites and total cholesterol, HDL cholesterol, LDL cholesterol, or triglycerides.

On the other hand, there are trials with resveratrol that reported negative results. A trial of resveratrol-enriched grape extract supplementation for 1 year in hypertensive men with type 2 diabetes mellitus showed no impact of resveratrol on blood pressure, glucose, and lipids, but there was a significant reduction in serum IL-6 and alkaline phosphatase levels and reduction of the expression of proinflammatory cytokines CCL3, IL-1β, and TNF.34 Resveratrol supplementation did not change body composition, resting metabolic rate, plasma lipids, or inflammatory markers in a randomized, double-blind, placebo-controlled trial in nonobese women with normal glucose tolerance.35 In addition, resveratrol did not affect its putative molecular targets, including SIRT1, in either skeletal muscle or adipose tissue. In a randomized, double-blind, placebo-controlled trial, high-dose resveratrol supplementation had no effect on glucose metabolism, insulin sensitivity, resting energy expenditure, or inflammatory markers in obese men.35

Resveratrol is only one of many polyphenols that are found in red wine and grapes. In the present study, urinary resveratrol levels were significantly associated with alcohol intake. The study population is located in the wine-growing Chi-anti region of Tuscany. The moderately high correlation between alcohol intake and urinary resveratrol is most likely attributed to a correlation between wine intake and resveratrol. A previous study has shown that urinary resveratrol levels are a valid biomarker of wine consumption.36 Human studies of the oral absorption of (+)-resveratrol show that the elimination half-life of total resveratrol metabolites is about 6 to 15 hours after oral doses.37 Resveratrol metabolites can be detected in the urine of humans who consume 1 glass of wine per week if the last drink was consumed 3 days previously, or in those who consume 3 glasses of wine per week if the last drink was consumed 5 days previously.25

Conclusions

In conclusion, this prospective study of nearly 800 older community-dwelling adults shows no association between urinary resveratrol metabolites and longevity. This study suggests that dietary resveratrol from Western diets in community-dwelling older adults does not have a substantial influence on inflammation, cardiovascular disease, cancer, or longevity.

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Research  Original Investigation

Resveratrol Unrelated to Mortality in Older Adults